15 November 2018
EMA/843650/2018
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Orkambi

International non-proprietary name: lumacaftor / ivacaftor

Procedure No. EMEA/H/C/003954/X/0034/G

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

BOPET	biaxially-oriented polyethyleneterephthalate
CQA	Critical Quality Attribute
FBD	Fluid bed drying
FDC	Fixed dose combination
FeSSIF	Fed State Simulated Intestinal Fluid
HPLC	High performance liquid chromatography
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IG	intra-granular
IR	Infrared
KF	Karl Fischer titration
PE	Polyethylene
Ph. Eur.	European Pharmacopoeia
QbD	Quality by design
RH	Relative Humidity
SDD	spray-dried dispersion
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

1. Background information on the procedure

1.1. Submission of the dossier

Vertex Pharmaceuticals (Europe) Ltd. submitted on 12 February 2018 a group of variation(s) consisting of extensions of the marketing authorisation concerning and two new strengths and a new pharmaceutical form grouped with the following variation:

Variation(s) requested		Type
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	I, II and III

The MAH applied for an addition of a new pharmaceutical form (granules) and an addition of two new strengths (100/125 mg and 150/188 mg) for paediatric use (2 to 5 years).

In addition, the MAH updated sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.3, 6.3 and 6.4 of the SmPC of the tablets formulation to bring it in line with the safety updates proposed with the new paediatric granules formulation and its extension for use in 2-5 years old. Annex II, the PL and RMP v5.4 have been updated accordingly.

Annex II, the PL and RMP v5.4 have been updated accordingly.

The legal basis for this application refers to:

Article 7.2 of Commission Regulation (EC) No 1234/2008 – Group of variations

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) PIP P/0005/2018 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0005/2018 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.

Scientific Advice

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

1.2. Steps taken for the assessment of the product

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

Rapporteur: Nithyanandan Nagercoil Co-Rapporteur: Daniela Melchiorri

The application was received by the EMA on	12 February 2018
The procedure started on	1 March 2018
The Rapporteur's first Assessment Report was circulated to all CHMP members on	23 May 2018
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	22 May 2018
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	29 May 2018
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	14 June 2018
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	28 June 2018
The MAH submitted the responses to the CHMP consolidated List of Questions on	20 July 2018
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	21 August 2018
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	29 May 2018
The CHMP agreed on a list of outstanding issues in writing to be sent to the MAH on	20 September 2018
The MAH submitted the responses to the CHMP List of Outstanding Issues on	16 October 2018
The PRAC Rapporteur circulated the Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	25 October 2018
The CHMP Rapporteur circulated the Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	31 October 2018
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	31 October 2018
The CHMP Rapporteur circulated an Updated Assessment Report to all CHMP members on	8 November 2018

The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Orkambi on	15 November 2018
The CHMP adopted a report on similarity of Bronchitol, Kalydeco, Cayston, Tobi Pohaler and Symkevi on	15 November 2018

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Orkambi is currently 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. This line extension application is for an age adapted formulation and includes an extension of indication to children 2 years and older, from the currently approved target population 6 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 two fixed dose combination (FDC) tablet strengths: LUM 200-mg/IVA 125-mg FDC tablet and LUM 100-mg/IVA 125-mg FDC tablet. Both are for oral administration, given as 2 tablets daily every 12 hours.

The line extension proposes an additional presentation of oral granules for children 2-5y. Two strengths are proposed: 100 mg/125 mg granules in sachet and 150 mg/188 mg granules in sachet.

2.1.2. Epidemiology

Cystic fibrosis 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. 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 currently approved in the EU for the treatment of CF patients 6 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. Aetiology and pathogenesis

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 non-functional 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.

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. 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.

2.1.4. 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 younger 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.

2.1.5. Management

Current CF treatments include CFTR modulators and enzyme supplements, mucolytics, antibiotics, and vitaminsTreatment guidelines recommend CFTR modulator and non-modulator medications concomitantly administered to maintain and improve lung function, reduce the risk of infections and exacerbations, and improve quality of life. CF is caused by mutations in the CF transmembrane conductance regulator (CFTR) gene that affect the production of the CFTR protein. Drugs that target the underlying defect in the CFTR protein, CFTR modulators, target specific defects caused by mutations in the CFTR gene and thus treat the underlying cause of the disease. The main goal of therapy is to maintain and restore respiratory function. There are two main types of modulators, potentiators and correctors. Potentiators recover the function of the CFTR protein at the apical surface of epithelial cells that is disrupted in class III and IV genetic mutations, while correctors improve intracellular processing of the CFTR protein, increasing surface expression, in class II mutations. A third type is production correctors or read-through agents, which promote transcription of CFTR in class I mutations.

Kalydeco (ivacaftor, IVA), Orkambi (lumacaftor/ivacaftor, LUM/IVA) and Symkevi (texacaftor/ivacaftor, TEZ/IVA) are the CFTR modulators approved for specific age groups of CF patients with specific mutations. Ivacaftor (in Kalydeco as mono-component and in Orkambi and Symkevi as part of fixed dose combinations) is a potentiator, the active substance lumacaftor and tezacaftor are correctors (present in the fixed dose combinations).

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.

Ivacaftor is a potentiator of the CF transmembrane conductance regulator (CFTR) 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.

The line extension is supported by a new FDC of Orkambi in a new presentation: oral granules, to extend use in the paediatric population from the current 6 years or older to younger children i.e. 2 -5 years. The line extension dossier is supported by three clinical (uncontrolled) studies and population PK.

The claimed indication is:

Orkambi granules are indicated for the treatment of cystic fibrosis (CF) in children aged 2 years and older who are homozygous for the F508del mutation in the CFTR gene (see sections 4.2, 4.4 and 5.1).

The approved indication is:

Orkambi granules are indicated for the treatment of cystic fibrosis (CF) in children aged 2 years and older who are homozygous for the F508del mutation in the CFTR gene (see sections 4.2, 4.4 and 5.1).

The applicant has had one CHMP protocol assistance procedure dated 26 February 2015 on clinical aspects. The purpose was to seek the CHMP's input and concurrence on the planned clinical development plan for subjects 6 through 11 years of age to support a future application to extend the Marketing Authorization for LUM/IVA combination therapy to include patients with CF 6 years of age and older who are homozygous for the F508del-CFTR mutation.

2.2. Quality aspects

2.2.1. Introduction

This is a centralised line extension application of the currently authorised Orkambi 200mg/125 mg and 100mg/125mg lumacaftor/ivacaftor fixed-dose combination (FDC) coated tablets for the addition of a new dosage form, oral granules, in two strengths supporting the extension of the currently approved indication, to children 2-5 year old.

The finished product is presented as granules in a sachet containing 100/125 mg or 150/188 mg of lumacaftor/ivacaftor as active substances to enable weight-based dosing.

Other ingredients are: hypromellose acetate succinate, sodium lauryl sulfate, croscarmellose sodium and microcrystalline cellulose and povidone (K30).

The product is available in a foil laminate [biaxially-oriented polyethyleneterephthalate/polyethylene/ foil/polyethylene (BOPET/ PE/Foil/PE)] sachet, as described in section 6.5 of the SmPC.

2.2.2. Active Substance

The active substances lumacaftor and ivacaftor used to manufacture the granules are the same used to manufacture the currently approved FDC tablets. As a result, no new information has been provided within this line extension application.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

The finished product consists of granules in a sachet for oral administration. The granules are a FDC product of the active ingredients lumacaftor and ivacaftor in a single oral dosage form. The same fixed-ratio granule formulation is used for both granule strengths of 100 mg lumacaftor /125 mg ivacaftor and 150 mg lumacaftor /188 mg ivacaftor. The two strengths are determined by the fill weight of the fixed-ratio granules which are heat-sealed in foil laminated sachets. For administration, the granules are emptied from the sachets and mixed with a small amount of soft food for oral administration.

The composition of the lumacaftor/ivacaftor FDC granules has been presented. Lumacaftor active substance is provided as a crystalline solid. Ivacaftor active substance is provided as an amorphous spray-dried dispersion (SDD) intermediate.

Lumacaftor active substance is provided as a crystalline solid. Ivacaftor active substance is provided as an amorphous spray dried dispersion (SDD) intermediate. No new data regarding the active substances or ivacaftor SDD is provided with this line extension application.

The lumacaftor/ivacaftor fix-dosed combination (FDC) granules contain excipients used in the commercial lumacaftor/ivacaftor FDC tablets, 100/125 mg and 200/125 mg. Therefore, no additional compatibility studies were conducted for the granules. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no excipients from animal origin or novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

As for the FDC tablets, finished product and manufacturing process development were conducted under a Quality by Design (QbD) paradigm.

The quality target product profile (QTPP) of the lumacaftor/ivacaftor FDC granules was to obtain, bioavailable, safe and efficacious immediate release fixed-dose combination granules of 100 mg lumacaftor / 125 mg ivacaftor and 150 mg lumacaftor / 188 mg ivacaftor for oral administration having at least 24 month shelf life at room temperature packaged in sachets.

Due to the low aqueous solubilities of lumacaftor and ivacaftor (< 1µg/mL) and the insufficient physical stability of amorphous ivacaftor in aqueous media, neither a solution nor a suspension formulation of lumacaftor/ivacaftor fixed dose combination (FDC) was feasible. Therefore, a granule dosage form was developed for ease of administration to paediatric patients.

Potential critical quality attributes (CQAs) for the lumacaftor active substance, ivacaftor SDD and the lumacaftor/ivacaftor FDC granules have been described.

The lumacaftor/ivacaftor FDC granules CQAs and their impact on quality, safety, and/or efficacy is summarized in Table 3.

Table 1. CQAs of lumacaftor/ivacaftor FDC granules

Critical Quality Attribute	**Impact on Quality, Safety and/or Efficacy**
Appearance	Provides a visual indicator of product quality
Identification (lumacaftor) Identification (ivacaftor)	Assurance that the correct active ingredients were used in the drug product processing for quality, safety, and/or efficacy
Assay (lumacaftor) Assay (ivacaftor)	Required to be maintained at a given level to ensure efficacy and safety
Degradation Products	Degradation products can impact assay/potency and potentially safety
Dissolution (lumacaftor) Dissolution (ivacaftor)	Impacts the rate of drug release
Uniformity of Dosage Units (lumacaftor) Uniformity of Dosage Units (ivacaftor)	Ensures uniform dose across the batch
Physical Form (lumacaftor) Physical Form (ivacaftor)	Affects bioavailability

Microbial Limits	Ensures safety of the drug product
Elemental Impurities	Ensures safety of the drug product
Residual Solvents	Ensures safety of the drug product

An initial risk assessment was performed on the incoming materials, process and lumacaftor/ivacaftor FDC granules to determine which materials and process steps could potentially impact the CQAs. Risk assessment, prior knowledge, and screening experiments are used to design multivariate experiments that evaluate main effects and interactions.

Data from QbD studies were analyzed to determine the design space that ensures all CQAs are within acceptance limits. The process knowledge gained throughout QbD development formed the basis of the overall product control strategies for active substance and finished product. The control strategy includes control of input material attributes, critical process parameters, in-process controls, and product specifications.

A summary of the manufacturing process design space for the lumacaftor/ivacaftor FDC granules finished product was presented.

For oral administration, the granules are emptied from the sachets and mixed with a small amount of soft food or liquid.

A summary of formulations used throughout clinical development has been provided. They included 75 mg lumacaftor / 125 mg ivacaftor FDC granules in amber glass vials (used in Phase 1 studies), 100 mg lumacaftor / 125 mg ivacaftor and 150 mg lumacaftor / 188 mg ivacaftor FDC granules in capsules (used in phases 1 and 3) or sachets (used in phase 3 studies).

In order to evaluate the sensory attributes of the oral granules, a human sensory study with adults was conducted with lumacaftor active substance, ivacaftor SDD and lumacaftor/ ivacaftor FDC granules. They were dosed alone and after mixing with small amounts of soft foods or liquids for administration. As the formulation is intended for paediatric patients, soft foods (carrot puree, yogurt and applesauce) that are commonly administered to young children were tested. Results indicated that the FDC granules showed a moderate intensity bitterness profile that was attributed primarily to the ivacaftor SDD. Mixing the lumacaftor/ivacaftor FDC granules with small amounts (~5mL) of soft foods (carrot puree, plain non-fat yogurt and applesauce) for oral administration significantly reduced the bitterness and improved the overall sensory profile of the finished product. Water provided only a slight reduction in negative attributes. Based on the results of the sensory study, it was concluded that the lumacaftor/ivacaftor FDC granules dosed with soft foods have acceptable palatability.This was confirmed in a pivotal Phase 3 study.

Dissolution is a critical quality attribute (CQA) of the FDC immediate release granules, verifying that the desired release profiles of the active ingredients are maintained.

Two independent *in vitro* dissolution methods were developed for testing the lumacaftor/ivacaftor FDC tablets, one for each active ingredient. Since the paediatric FDC granules have the same composition as the intragranular component of the paediatric FDC tablets, the applicability of the FDC paediatric tablet dissolution methods were assessed for use in the FDC granules. Based on previous knowledge from the paediatric FDC tablet process, only potentially critical process parameters and product attributes that are unique to the FDC granules were assessed for dissolution, including the following:

• ivacaftor spray dried dispersion (SDD) bulk density

• granule particle size

• granule water content

• stability changes under stressed conditions

Both dissolution methods have shown discriminating ability against meaningful manufacturing variations and are considered suitable for their intended use as the primary release and stability quality control methods for lumacaftor/ivacaftor FDC granules. In addition, with available *in vivo* data, the clinical relevance of both dissolution methods has been established.

The primary packaging is foil laminate [biaxially-oriented polyethylene terephthalate/polyethylene/ foil/polyethylene (BOPET/ PE/Foil/PE)] sachet. The material complies with Ph. Eur. and EC requirements. 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

As indicated above, the composition and the manufacturing process of the lumacaftor/ivacaftor FDC bulk granules is the same as the manufacturing process of the lumacaftor/ivacaftor FDC granules used in the commercial 100 mg lumacaftor / 125 mg ivacaftor FDC tablets. The novelty in the proposed product is the packaging into sachets. The lumacaftor active substance is provided as a crystalline, jet-milled material and the ivacaftor active substance is provided as an amorphous spray-dried dispersion (SDD). The same fixed-ratio granule formulation is used for both granule strengths of 100 mg lumacaftor / 125 mg ivacaftor and 150 mg lumacaftor / 188 mg ivacaftor. The two strengths are determined by the fill weight of the fixed-ratio granules which are heat-sealed in foil laminated sachets

The process consists of incoming material screening, intra-granular (IG) blending, twin-screw wet granulation (TSWG), fluid bed drying (FBD) and milling. The IG blending is performed in a non-continuous batch mode, while TSWG, FBD and milling are performed in a continuous mode. The sachet packaging process to manufacture the finished lumacaftor / ivacaftor FDC granules finished product is a single unit operation using a sachet filler system.

The process is considered to be a standard manufacturing process.

The manufacturing process, equipment, formula and site are common to the Orkambi paediatric tablets. As such, the process is sufficiently validated until the bulk granules are obtained. The filling process is new and, as such, will be conducted before marketing in line with the process validation scheme provided. Major steps of the manufacturing process have been validated by a number of studies. Overall, it has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

As indicated above a design space comprising several unit operations has been developed. The available development data, the proposed control strategy and batch analysis data from commercial scale batches fully support the proposed design space.

Product specification

The finished product release specifications shown in Table 5 include appropriate tests for this kind of dosage form: appearance, identification (IR), assay (HPLC), degradation products (HPLC), dissolution (Ph. Eur., HPLC), water content (KF), uniformity of dosage units (HPLC), granules particle size (laser diffraction), microbial limits (TAMC, TYMC, E. coli) (Ph. Eur.).

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

Physical form at release is effectively controlled via limits on the incoming lumacaftor active substance and ivacaftor SDD and process controls. It has been demonstrated that the manufacture processing conditions, including short periods of water contact (wet granulation), temperature elevation (drying) and mechanical impacts (milling), do not change the physical form of lumacaftor and ivacaftor SDD. Physical form is a critical quality attribute for the FDC granules to ensure bioavailability; however, lumacaftor and ivacaftor SDD are physically stable during manufacture of the FDC granules. All samples were tested for physical form during QbD experiments and did not show lumacaftor Form II or crystalline ivacaftor. To date, all batches manufactured for clinical use and formal stability conform to the expected physical form on release. The physical form of lumacaftor and ivacaftor has also been demonstrated on stability by ICH stability studies and a forced crystallization study; therefore, physical form testing for FDC granules has been omitted from the specification.

The potential presence of elemental impurities in the lumacaftor/ivacaftor FDC granules was assessed according to the ICH Q3D Guideline for Elemental Impurities using a risk based approach. The risk assessment considered the potential inputs from both lumacaftor and ivacaftor active substances and ivacaftor SDD (including solvents, reagents, excipients, and equipment), water, excipients, manufacturing equipment and container closure systems to determine the overall content of elemental impurities in the lumacaftor / ivacaftor FDC granules. This risk assessment and confirmatory testing demonstrates that the risk of elemental impurities in the lumacaftor / ivacaftor granules is low and the product will consistently meet the ICH Q3D requirements. Therefore, no additional controls on elemental impurities are required.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay testing has been presented.

Batch analysis results are provided for 5 commercial scale batches of each strength confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data from three commercial scale batches of each strength of finished product stored for up to 12 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches of Orkambi 100/125 mg or 150/188 mg granules are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for appearance, assay, degradation products, dissolution, water content and physical form. Microbial limits (TAMC, TYMC and *E. coli*) and water activity were tested on batches stored at 30 ºC / 75% RH. The analytical procedures used are stability indicating.

The stability data show that the finished product is stable when packaged in the configuration proposed for commercial distribution under all storage conditions. All results met the acceptance criteria for the attributes evaluated. The X-ray powder diffraction data from all of the formal stability studies confirm the presence of lumacaftor Form I, absence of lumacaftor Form II and crystalline ivacaftor at all test points under all storage conditions.

Photostability as per ICH Q1B, Option 2, was not performed with lumacaftor / ivacaftor granules as the commercial container closure is light protective. This is accepted since from the photostability testing of the tables it was confirmed that they are stable.

In addition, in-use stability studies were conducted to establish stability of granules mixed with common foods that might be used for administration.

Chemical and physical stability of granules mixed with small volumes (~5 mL) of selected liquids and soft foods were evaluated by testing assay and degradation products, dissolution, and physical form. The test results at 1 hour after mixing the FDC granules with water, apple juice, applesauce, carrot puree, fat free yogurt, infant formula and chocolate pudding demonstrated acceptable chemical stability. No change in dissolution was observed after mixing the FDC granules with the selected liquid, vegetable puree and fat containing foods, i.e., apple sauce, carrot puree, and whole milk yogurt. No physical form change of lumacaftor active substance or ivacaftor SDD was observed for FDC granules mixed with fat free foods. However, mixing FDC granules with fat containing foods (e.g., infant formula and chocolate pudding) showed formation of ivacaftor:triglyceride cocrystals. Ivacaftor SDD is known to form co-crystals with triglycerides when mixed with fat-containing foods. However, co-crystals prepared had solubilities in Fed State Simulated Intestinal Fluid (FeSSIF) at 37°C comparable to the solubility of the ivacaftor SDD present in the granules, indicating that the ivacaftor triglyceride co-crystals are expected to have equivalent bioavailability to ivacaftor SDD. In addition, phase 3 studies included fat containing foods in the food selection for administration.

Based on available stability data, the proposed shelf-life of 2 years in the intended container closure system as stated in the SmPC (section 6.3) are acceptable. Once mixed, the mixture has been shown to be stable for one hour.

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 finished product has been presented in a satisfactory manner. This line extension is based on data that has been submitted for the approved 100 / 125 mg FDC tablets and any changes relevant to the granules has been provided as replacement, additions or revised documents. The applicant has applied QbD principles in the development of the finished product and their manufacturing process. Design spaces have been proposed for several manufacturing steps. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

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

2.2.6. Recommendation(s) for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

The MAH has made reference to previous clinical development of lumacaftor, ivacaftor and in combination, which were supported by appropriate pharmacology, pharmacokinetic/pharmacodynamic, metabolism and toxicology studies, submitted as part of the original Marketing Authorisation Application for Orkambi and for the clinical development and registration for Kalydeco. As these non-clinical data have been previously assessed and approved, they were not discussed in detail here. However, nonclinical safety data from toxicity studies were previously submitted to support the proposed indication extension of Orkambi in the 6- through 11-year-old age group (EMEA/H/C/003954/X/0020). These studies also support the current proposed indication aimed at CF patients 2 to 5 years of age and were included in this assessment for completeness.

2.3.2. Pharmacology

Not applicable

2.3.3. Pharmacokinetics

Not applicable

2.3.4. Toxicology

In the juvenile rat study, lumacaftor at 500 mg/kg/day was associated with mortality in one male animal on post-natal day 10. Macroscopic and microscopic effects observed 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 no observed adverse effect level. The exposure to lumacaftor observed at this dose represents an approximate 5-fold safety factor to that seen in subjects aged 2 to 5 years in clinical study 115. The results of the juvenile toxicity 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 in this regard. The SmPC for the proposed products is considered to be acceptable.

2.3.5. Ecotoxicity/environmental risk assessment

An environmental risk assessment (ERA) was submitted for ivacaftor.

A Phase I estimation of exposure showed that an evaluation of the persistence, bioaccumulation and toxicity (PBT) of VX-770 was required (log octanol-water partition coefficient >4.5). These studies were conducted under Phase II Tier A and B. The outcome of the Phase II Tier A environmental effects assessment in algae, daphnia, fish and microorganisms confirmed that VX-770 is unlikely to represent a risk to surface water, groundwater or to microorganisms. However, a bioaccumulation study in fish has yet to be finalised.

The outcome of the Phase II Tier B terrestrial effects assessment in microorganisms, plants, earthworms and Collembola confirmed that VX-770 is unlikely to represent a risk to the terrestrial environment.

A final lumacaftor ERA will be provided in March 2019 once all the studies with lumacaftor are completed, as some studies assessing the impact of lumacaftor on the environment are still ongoing.

2.3.6. Discussion on non-clinical aspects

No new issues have been identified from a non-clinical perspective and juvenile data suitably supports this application. A definitive assessment on the potential risk of ivacaftor and lumacaftor to the environment cannot be made at this time as data from ongoing studies will to be submitted in 2019.

2.3.7. Conclusion on the non-clinical aspects

As a result of the above considerations, the lack of available data does not allow to conclude definitively on the potential risk of ivacaftor and lumacaftor to the environment following approval of this line extension. The MAH has, however, already made a commitment to perform the required studies as part of an agreed follow-up measure, which is acceptable.

Overall, the available nonclinical data on lumacaftor and ivacaftor support the proposed use in children above the age of 2 years.

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 115

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

Phase 3 Safety, PK, and PD	VX15-809-115 (Module 5.3.5.1)	**Part A** Primary Objective Evaluate the PK of LUM and IVA and their respective metabolites in subjects aged 2 through 5 years with CF, homozygous for *F508del* Secondary Objective Evaluate the safety of LUM/IVA in subjects aged 2 through 5 years with CF, homozygous for *F508del*	Open-label, 2-part, multicenter	**LUM/IVA (fixed-dose)**: LUM/IVA granules • LUM 100-mg/IVA 125-mg granules q12h (subjects <14 kg at screeing) • LUM 150-mg/IVA 188-mg granules q12h (subjects ≥14 kg at screening)	**Part A** 12 subjects **Part B** 60 subjects Of the enrolled subjects, 37 subjects participated in the optional LCI Substudy	**Part A** Approximately 15 days **Part B** Approximately 24 weeks

Study 013

Phase 1 Taste Profiling	VX13-809-013 (Module 5.3.5.4)	Objective Evaluate the flavor (basic tastes, aroma, texture, and mouthfeel) of LUM/IVA granule formulation and optionally improve the palatability of the drug product.	Open-label	**LUM:** 75-mg granule powder **IVA:** 125-mg granule powder **LUM/IVA:** L75/I125 mg granule powder	7 subjects Male and female healthy subjects 25 through 80 years of age	Single tastings across 3 days

Study 014

Type of Study	**Study Identifier/ Location of Report**	**Objective(s) of the Study**	**Study Design and Type of Control**	**Test Product(s) (Formulation); Dosage Regimen; Route of Administration**	**Number of Subjects Dosed/ Healthy Subjects or Diagnosis of Patients**	**Duration of Treatment**
Phase 1 BA	VX15-809-014 (Module 5.3.1.2)	Primary Objective Evaluate the relative bioavailability of the granule formulation compared to the tablet formulation of LUM/IVA in the fed condition as a single LUM 100-mg/IVA 125-mg dose Secondary Objectives • Evaluate the food effect on the granule formulation as a single LUM 100-mg/IVA 125-mg dose • Evaluate the dose proportionality of the granule formulation between LUM 100-mg/IVA 125-mg and LUM 150-mg/IVA 188-mg doses in the fed condition • Assess the safety and tolerability of LUM 100 mg/IVA 125 mg and LUM 150 mg/IVA 188 mg in healthy adult subjects	Open-label, randomized, single-dose, 4-sequence, 4-period, crossover (Williams Design)	**LUM/IVA (fixed-dose)** 100-mg LUM/125-mg IVA tablet, LUM/IVA granules • LUM 100 mg/IVA 125 mg (tablet) • LUM 100 mg/IVA 125 mg (granules in capsules) • LUM 150 mg/IVA 188 mg (granules in capsules) Oral administration	16 subjects Healthy adult male and female subjects aged 18 to 55 years, inclusive	Single dose on 4 dosing occasions

2.4.2. Pharmacokinetics

Orkambi (lumacaftor/ivacaftor; LUM/IVA) 200mg/125mg film-coated tablet was approved in the EU on 19 November 2015 for the following indication: treatment of CF in patients aged 12 years and older who are homozygous for the F508del mutation in the CFTR gene. Orkambi 100mg/125mg film-coated tablet was further approved in the EU on 8 January 2018 for the following indication extension: treatment of CF in patients aged 6 years and older who are homozygous for the F508del mutation in the CFTR gene.

The new proposed strength and dosage form are as follows:

Orkambi (Lumacaftor/Ivacaftor) 100 mg/125 mg granules in sachet

Orkambi (Lumacaftor/Ivacaftor) 150 mg/188 mg granules in sachet

The indication proposed for the above is as follows:

Orkambi granules are indicated for the treatment of cystic fibrosis (CF) in children aged 2 years and older who are homozygous for the F508del mutation in the CFTR gene.

This line extension application is for the addition of a new dosage form, granules, in 2 strengths supporting an extension of indication, i.e. extension of the currently approved age range to include 2-5 years. The new

proposed strength and dosage form i.e. Orkambi (Lumacaftor/Ivacaftor) 100 mg/125 mg granules in sachet and 150 mg/188 mg granules in sachet have a posology as proposed below:

• One sachet of 100-mg/125-mg of LUM/IVA every 12 hours for patients weighing less than 14 kg

• One sachet of 150-mg/188-mg of LUM/IVA every 12 hours for patients weighing 14 kg or greater

PK modelling informed the altered ratio of LUM:IVA in the new strength granules 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. The posology and dosing have been reflected in the SmPC.

PK data to support the line extension are mainly derived from two clinical studies (study 115, an open label uncontrolled 24 week study in children 2-5y; and study 014, an uncontrolled bioavailability study in healthy adults) together with a Population PK analysis the objective of which was to compare observed, and predict population, data for LUM and IVA exposures in 2-5 year old patients compared with patients 12 years and older. In study 115 , LUM/IVA were given to 2-5 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. PK studies were conducted in the fed state, due to the increase in bioavailability of Orkambi with food, as recommended in the SmPC.

For Study 115 part A, the PK concentrations of LUM and M28-LUM were similar between day 1 and day 15. IVA and M1-IVA C3-4h concentrations were reduced between day 1 and day 15 whereas M6-IVA concentrations were increased. The trough concentrations of IVA, M1-IVA and M6-IVA were variable between day 8 and day 15.

For Study 115 part B, the LUM PK trough concentrations and at C2-6h were all comparable between the CF subjects < 14 kg and ≥ 14 kg. However, mean IVA concentrations appeared to be 30% lower at W24 compared to day 15. It was also noted that the CV% of IVA and its metabolite concentrations was high (approaching 100% at several time points). Therefore, the MAH was asked to discuss the high interindividual variability in IVA concentrations and its impact on efficacy/safety. In their response, the MAH justified the high variability in IVA and IVA metabolites concentration by similarity in the variability between Study 115 and the other Phase 3 studies in other age groups. Therefore, it is agreed that the variability is unlikely to impact clinical efficacy or safety in study 115 population.

The PK parameters of the granule formulation were similar to the tablet formulation. The Cmax of the both components are lower for the granules than the tablets, the AUC for IVA is similar for both the tablet and granule formulations, for Lumacaftor it is somewhat lower for the granules. No information on PK-PD relationships have been provided in this submission. . The MAH was asked to justify why the lower Cmax and AUC (for LUM) will not influence the efficacy. The MAH indicated that LUM/IVA exposure range in Studies 011, 109, and 115 is not sufficient for a conclusive PK/PD analysis. Additionally, sweat chloride measure showed no exposure response trend confirming the lack of an exposure response profile for sweat chloride. The applicant's justification was accepted.

Food significantly increases the bioavailability of LUM/IVA from the granules. It is indicated in Sec 4.2 of the proposed SmPC that the granules be administered in the fed state and this is agreed.

LUM and IVA exposures ($AUC_{0-\infty}$ and Cmax) were dose proportional between LUM 100-mg/IVA 125-mg and LUM 150-mg/IVA 188-mg doses.

The MAH used a population PK approach to characterise the exposure for LUM and IVA in the CF subjects within 2-5 years of age. The MAH pooled the results of 3 studies (study 115, study 109 and study 011) while fitting the data to the previously described 2-compartmental models for LUM and IVA accounting for the reduction in IVA Cl due to CYP3A induction by LUM. Cl was estimated to be 1.7 L/hr for LUM and 17.36 for IVA (without induction). The MAH used the model to predict the AUC0-12h exposures which appeared comparable for LUM between the 2-5 and other age groups (6-11, 12-17 and ≥18). However, IVA exposure appeared 1.4 to 1.7 fold higher in the 2-5 age group compared to the ≥18 age group. The MAH confirmed that the increase in the median of IVA AUCs in the target paediatric population is not expected to change the clinical outcomes as small variations in AUC do not appear to have a significant influence on observed sweat chloride. Additionally, the median IVA AUCs in the 2 to <5 years paediatric population were generally comparable to 6 to <11 years population and 2- to 4-fold lower than that observed in 2 to <12 years subjects for IVA monotherapy, which showed to be safe in this paediatric population. This is considered adequate.

The current recommendations for impaired renal function are adequate for the new formulation in the 2-5 year old age group.

Moderate and severe hepatic impairment is rare in children 2 – 5 years of age with CF but does occur. 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. The table with recommendations for dose modifications in hepatic impairment in section 4.2 of the SmPC has been suitably amended. The MAH has provided simulations in the age group 2-5 for the effect of dose adjustment in on LUM and IVA exposures in moderate hepatic impairment. The simulation showed that a reduction of the dose to q24h maintained the exposure for LUM and IVA within the 90% CI of adult exposures, although LUM lower quartile in 2-5 CF subjects <14 kg was below the lower limit of the adult 90% CI. The MAH was asked to discuss LUM lower exposure in those subjects. The MAH acknowledged the low LUM exposure in CF subjects who are 2 to 5 years of age and who weigh <14 kg and conducted additional dose simulations to propose a new regimen to better match the LUM exposures in adults. The new simulation results showed that 25% dose reduction achieved LUM/IVA exposures which best matches to the efficacious exposures of LUM/IVA in adults. The MAH hence proposed an amended dose recommendation for this subgroup and this has been adequately reflected in the SmPC changes, section 4.2. This is acceptable to the CHMP.

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. No Patients with CF over the age of 5 were included in the studies accompanying this submission.

As CYP3A maturation is complete before 2 years of age, recommendations for LUM/IVA dose adjustments for patients 2-5 years of age in the setting of CYP3A inhibition are based on those for patients 12 years and older. The SmPC recommendations as proposed for the CF subjects 2-5 years are acceptable.

2.4.3. Pharmacodynamics

Relevant to the current line extension application, study 115 evaluated a range of PD endpoints in CF patients 2-5 years of age administered with Orkambi granules formulation. In particular, study 115 part B 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 Week 24. The mean absolute change from baseline in sweat chloride at Week 24 was -31.7 mmol/L (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 2-5 years age group at the proposed posology. However, the effect of treatment on biomarkers such as sweat chloride that directly measure CFTR function, can be considered only as intermediate proof of efficacy (the report from the Workshop on Endpoints in Cystic Fibrosis clinical trials (EMA/769571/2012). The same report also indicates that the effect of the CFTR modifiers on the sweat gland may not necessarily reflects the effect on other organs.

2.4.4. Discussion on clinical pharmacology

In Study 115, BMI, weight and stature increased from baseline over 24 weeks in the 2-5y old subjects. While this could be consistent with improved pancreatic function and therefore improved nutritional status, the effect on treatment on these parameters is also confounded by growth that would occur between the ages 2-5y. This will be followed in post-authorisation phase.

Limited spirometry endpoints were evaluated in this study and no notable changes observed. The guideline on clinical development of medicinal products for the treatment of cystic fibrosis EMEA/CHMP/EWP/9147/2008-corr* (22 October 2009) recommends FEV1 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, FEV1 may not be sufficiently sensitive to detect a treatment effect. Given that lung function may not have deteriorated and FEV1 is difficult to measure in children in this age group, the limited results are not interpretable. The report from the workshop 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 non-significant decline (reflecting improvement) in LCI2.5 from baseline through to 24 weeks (mean change from baseline -0.58 (P = 0.0559) and a statistically significant benefit in the >14kg group. The clinical relevance is however not established.

IRT is a sensitive marker of pancreatic insufficiency. There was a statistically significant decline in IRT levels through week 24 with a variable but non-significant increase after the 2 weeks wash out. This is usually used a test for neonatal screening, the significance and implication of the findings on clinically relevant outcomes needs to be discussed.

FE-1 was low at baseline in most patients indicating exocrine pancreatic insufficiency. There was a statistically significant improvement in FE1 levels at week 24 with a variable but non-significant decline after the 2 weeks wash out. Again, while this test is used to measure exocrine pancreatic insufficiency, the significance and implication of the findings on clinically relevant outcomes remains unclear.

The results taken together imply that the directionality of the PD endpoints does suggest a positive PD effect for most end points. Overall, the exploratory PD data from study 115 part B provide support that Orkambi at the proposed posology acts in a manner consistent with the primary pharmacology.

2.4.5. Conclusions on clinical pharmacology

The clinical pharmacology of Orkambi in the new formulation in the age range proposed in the line extension is supported by the PD endpoints in Study 115.

2.5. Clinical efficacy

Study 115 was a Phase 3, 2-part, open-label study in CF subjects 2 through 5 years of age, homozygous for *F508del.* Part A was designed to evaluate the pharmacokinetics (PK) and safety of LUM/IVA administered for 15 days. A review of safety, tolerability, and available PK data was completed after Part A completion, to determine the dose(s) to be evaluated in Part B.

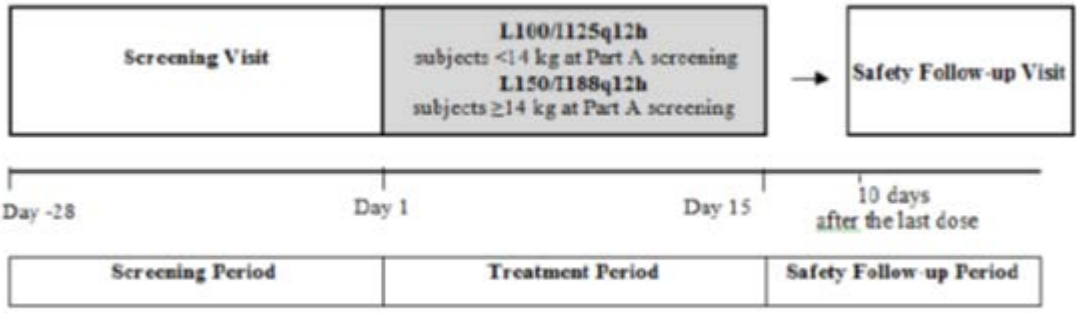
Part B was designed to evaluate the safety of LUM/IVA administered for 24 weeks.

Moreover, the following PD parameters related to efficacy were assessed in Study 115 Part B: (1) sweat chloride, (2) body mass index (BMI) and BMI z-score, (3) weight and weight z-score, (4) stature and statue z-score, (5) pulmonary exacerbations (PExs) and hospitalizations, (6) fecal elastase-1 (FE-1) levels, (7) immunoreactive trypsinogen (IRT), (8) microbiology cultures, (9) spirometry, and (10) lung clearance index (LCI; optional substudy).

Methods

Schematic of Study 115 Design

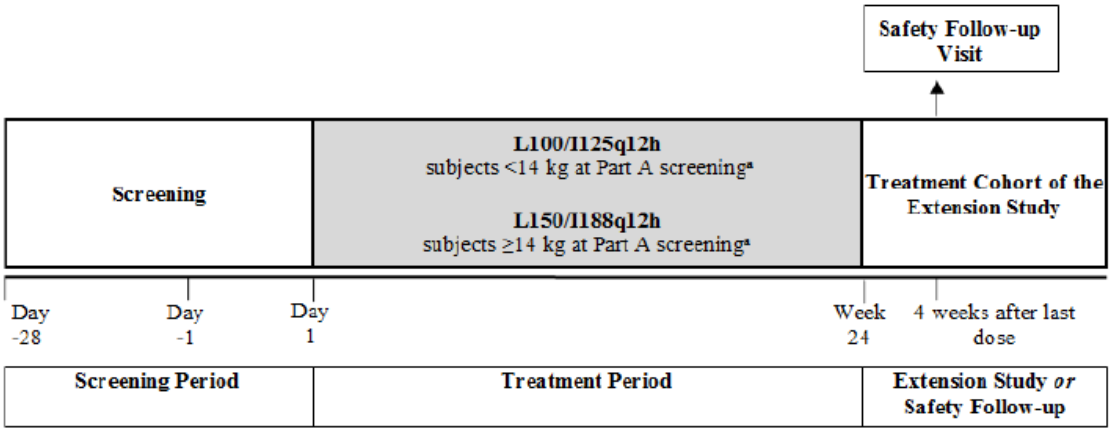
Part A



IVA: ivacaftor; LUM: lumacaftor

Notes: Approximately 12 subjects were planned for enrollment. Assuming a 10% dropout rate, approximately 10 subjects were expected to complete Part A. Approximately half of the subjects were originally planned to complete the study in each of the following weight groups: <14 kg and ≥14 kg at screening. No dose adjustments were made during the Treatment Period. On Day 15, only the morning dose of LUM/IVA was administered.

Part B



ETT: Early Termination of Treatment; IVA: ivacaftor; LCI: lung clearance index; LUM: lumacaftor
Notes: Approximately 56 subjects were planned for enrollment. Assuming a 10% dropout rate, approximately 50 subjects were expected to complete Part B; at least 10 subjects were planned to be <3 years of age. Subjects had to be ≥3 years of age for enrollment in the optional LCI substudy.
a Subjects who prematurely discontinued LUM/IVA were asked to complete the ETT Visit, to remain on study, and to complete the study assessments from the time of LUM/IVA discontinuation through the Week 24 Visit and the Safety Follow-up Visit, if applicable. The Safety Follow-up Visit was not required for subjects who permanently discontinued LUM/IVA before or at the Week 16 Visit if they returned for the Week 24 Visit or for subjects who continued onto commercially available LUM/IVA by prescription of a physician within 2 weeks (± 4 days) of completing LUM/IVA at Week 24 or at the ETT Visit.

Study Participants

Male and female subjects 2 through 5 years of age with CF, homozygous for *F508del:*

1. Subject's legally appointed and authorized representative (e.g., parent or legal guardian) signed and dated an ICF, and the subject signed and dated an assent form (if applicable).
2. Subject's legally appointed and authorized representative (e.g., parent or legal guardian) was willing and able to comply with scheduled visits, treatment plan, study restrictions, laboratory tests, and other study procedures.
3. Subjects (males and females) were between 2 and 5 years of age, inclusive, on the date of informed consent (and assent, if applicable) for the relevant study part.

4. Subjects who weighed ≥8 kg without shoes and wearing light clothing at the Screening Visit.
5. Subjects with confirmed diagnosis of CFat the Screening Visit. CF was defined as follows:
2 CF-causing mutations (all as documented in the subject's medical record) AND chronic sinopulmonary disease OR gastrointestinal/nutritional abnormalities;
6. Subjects who were homozygous for *F508del* (genotype confirmed at the Screening Visit). If the *CFTR* screening genotype result was not received before Day -1, a previous *CFTR* genotype laboratory report could be used to establish eligibility.
7. Subjects with stable CF disease as deemed by the investigator at the Screening Visit.
8. Subjects who were willing to remain on a stable CF medication regimen through Day 15 (Part A) or through the Safety Follow-up Visit (Part B), if applicable.

Treatments

Test treatment:

Dose rationale: The doses chosen for Study 115 were based on simulations conducted using a previously developed population PK model with data from CF subjects 6 through 11 years of age. The plasma concentration versus time data from Part A was intended to inform the appropriateness or necessary adjustment of planned doses for Part B. A population PK model with allometric scaling of clearance and volume of distribution as a function of weight was used to project exposures of LUM and IVA for comparison with clinical experiences with both drugs and to select doses to be evaluated in the study population. The IVA model was coupled to the LUM model to account for the induction of CYP3A by LUM, which increases the metabolism of IVA. The population PK model was based on data obtained from subjects 6 years of age and older across the LUM and IVA combination development program. No safety issues were identified in prior clinical or nonclinical studies that would preclude the dosing regimen proposed for the current protocol.

Rationale for LUM Dose

LUM exposure projections for subjects 2 through 5 years of age were based on available data from Studies 103, 104, and 011. In the LUM/IVA combination program, the dose regimen of LUM 400 mg/IVA 250 mg every 12 hours (q12h) was used in the Phase 3 studies (Study 103 and Study 104) for subjects 12 years of age and older. In the Phase 3 Study 011, the dose regimen of LUM 200 mg/IVA 250 mg q12h was used for subjects 6 through 11 years of age. For subjects 2 through 5 years of age who weigh <14 kg, oral administration of LUM 100 mg was projected to yield a mean AUCss of 201 µg·h/mL. For subjects 2 through 5 years of age who weigh ≥14 kg, oral administration of LUM 150 mg was projected to yield a mean AUCss of 238 µg·h/mL. Based on these simulations, the LUM doses selected for Part A were expected to

yield exposures that were comparable to those of subjects 6 years of age and older (i.e.,203 µg·h/mL), which were shown to be safe and well tolerated in combination with IVA.

Rationale for IVA Dose

IVA as a single agent was previously investigated and approved for use in paediatric patients with CF 2 to less than 6 years of age with select mutations; the weight-based IVA exposures were from the Phase 3 study (Study 770-108).

In the LUM/IVA combination program, due to the induction effect of LUM on the metabolism of IVA, the IVA exposures are lower than that of the IVA monotherapy.

For subjects 2 through 5 years of age who weigh <14 kg, oral administration of IVA 125 mg in combination with LUM was projected to yield a mean AUCss of 5.49 µg·h/mL. For subjects 2 through 5 years of age who weigh ≥14 kg, oral administration of IVA 188 mg in combination with LUM was projected to yield a mean AUCss of 5.71 µg·h/mL. Based on these simulations, the IVA doses selected for Part A were expected to yield IVA exposures that were comparable to subjects 6 years of age and older and within prior clinical experience with IVA alone (10.5 µg·h/mL for subjects <14 kg and 11.3 µg·h/mL for subjects ≥14 kg).

Dose used:

Subjects weighing <14 kg at screening

LUM 100 mg/IVA 125 mg every 12 hours (q12h) (1 capsule [Part A;q12h] or 1 stick pack [Part B;q12h) was administered orally.

Subjects weighing ≥14 kg at screening

LUM 150 mg/IVA 188 mg q12h (2 capsules [Part A;q12h] or 1 stick pack [Part B;q12h]) was administered orally LUM/IVA was administered within 30 minutes of consumption of fat-containing food Duration of treatment:

Part A: Up to 15 days

Part B: up to 24 weeks

Objectives

Primary Objectives

Part A: To evaluate the pharmacokinetics (PK) of lumacaftor (LUM) and ivacaftor (IVA) and their respective metabolites in subjects aged 2 through 5 years with cystic fibrosis (CF), homozygous for F508del

Part B: To evaluate the safety of LUM/IVA combination therapy in subjects aged 2 through 5 years with CF, homozygous for F508del

Secondary Objectives

Part A: To evaluate the safety of LUM/IVA combination therapy in subjects aged 2 through 5 years with CF, homozygous for F508del

Part B:

- To evaluate the pharmacodynamics (PD) of LUM/IVA combination therapy in subjects aged 2 through 5 years with CF, homozygous for F508del
- To evaluate the off-drug PD response after the Washout Period
- To evaluate the PK of LUM and IVA and their respective metabolites in subjects aged 2 through 5 years with CF, homozygous for F508del

Outcomes/endpoints

Study 115 Endpoints

Endpoints	Study 115 Part A	Study 115 Part B
Primary	PK parameters of LUM and IVA	Safety and tolerability assessments based on AEs, clinical laboratory values (serum chemistry, hematology, coagulation studies, and urinalysis), standard 12-lead ECGs, vital signs, pulse oximetry, ophthalmological examinations, and spirometry
Secondary	• PK parameters of the metabolites of LUM and IVA • Safety and tolerability assessments based on AEs, clinical laboratory values (serum chemistry, hematology, coagulation studies, and urinalysis), standard 12-lead ECGs, vital signs, pulse oximetry, and spirometry	**PD endpoints:** • Absolute change from baseline in sweat chloride at Week 24 • Absolute change in sweat chloride from Week 24 at Week 26 • Absolute change from baseline in BMI and BMI-for-age z-score at Week 24 • Absolute change from baseline in weight and weight-for-age z-score at Week 24 • Absolute change from baseline in stature and stature-for-age z-score at Week 24 • Absolute change from baseline in $LCI_{2.5}$ at Week 24 • Absolute change from baseline in $LCI_{5.0}$ at Week 24 • Time-to-first pulmonary exacerbation through Week 24 • Number of pulmonary exacerbations through Week 24 • Number of CF-related hospitalizations through Week 24 • Absolute change in FE-1 levels from baseline at Week 24 • Absolute change in serum levels of IRT from baseline through Week 24 • Change in microbiology cultures from baseline at Week 24 • Absolute change from baseline in $ppFEV_1$ at Week 24 **Other endpoints:** • Acceptability/palatability of LUM/IVA granules at Day 1 • PK parameters of LUM, IVA, and their respective metabolites

Source: VX15-809-115/Appendix 16.1.1/Protocol Version 3.0
AEs: adverse events; BMI: body mass index; CF: cystic fibrosis; FE-1: fecal elastase 1; IRT: immunoreactive trypsinogen; IVA: ivacaftor; LCI: lung clearance index; LUM: lumacaftor; PD: pharmacodynamics; PK: pharmacokinetic; $ppFEV_1$: percent predicted forced expiratory volume in 1 second

Sample size

No formal sample size calculations were performed for Part A or Part B.

Randomisation

This was an open-label study.

Blinding (masking)

This was an open label study.

Statistical methods

Approximately 12 subjects were planned for enrolment in Part A; 12 were enrolled. Approximately 56 subjects were planned for enrolment in Part B; 60 were enrolled.

Results

Participant flow

Subjects in Part B were enrolled at 20 sites in North America. Subject disposition is summarized in table below. Sixty subjects were enrolled and received at least 1 dose of LUM/IVA; 56 (93.3%) subjects completed LUM/IVA treatment, and 57 (95.0%) subjects completed the study. Three subjects in the L150/I188q12h group prematurely discontinued from both LUM/IVA treatment and the study because of AEs of LFT elevations. One subject in the L100/I125q12h group prematurely discontinued LUM/IVA treatment 1 month early due to a miscommunication (classified as “other” reason); this subject completed the study. All 57 subjects who completed the study, including the subject who prematurely discontinued study treatment, rolled over into a 2-year extension study (Study 116). Thirty-seven subjects (5 in the L100/I125q12h group and 32 in the L150/I188q12h group) participated in the LCI Substudy.

Subject Disposition (All Subjects Set, Part B)

Disposition/Reason	n (%)[a] L100/I125q12h N = 19	L150/I188q12h N = 41	Total N = 60
All Subjects Set[b]	19	41	60
Safety Set[c]	19	41	60
Full Analysis Set[d]	19 (100.0)	41 (100.0)	60 (100.0)
Enrolled but never dosed	0	0	0
Completed LUM/IVA treatment	18 (94.7)	38 (92.7)	56 (93.3)
Prematurely discontinued treatment	1 (5.3)	3 (7.3)	4 (6.7)
Reason for LUM/IVA LUM/IVA discontinuation			
AE	0	3 (7.3)	3 (5.0)
Other[e]	1 (5.3)	0	1 (1.7)
Last completed on-treatment scheduled visit			
Day 1	0	0	0
Day 3	0	0	0
Day 15	0	1 (2.4)	1 (1.7)
Week 4	0	2 (4.9)	2 (3.3)
Week 8	0	0	0
Week 12	0	0	0
Week 16	1 (5.3)	0	1 (1.7)
Week 20	0	0	0
Week 24	0	0	0
Completed study[f]	19 (100.0)	38 (92.7)	57 (95.0)
Prematurely discontinued study	0	3 (7.3)	3 (5.0)
Reason for study discontinuation			
AE	0	3 (7.3)	3 (5.0)
Rollover to extension study	19 (100.0)	38 (92.7)	57 (95.0)

Source: Table 14.1.1.1b

AE: adverse event; IVA: ivacaftor; LUM: lumacaftor; N: total sample size; n: size of subsample; q12h: every 12 hours

[a] Percentages were calculated relative to the number of subjects in the Safety Set.

[b] The All Subjects Set included all subjects who provided informed consent (and assent, if applicable) and enrolled or dosed in Part B.

[c] The Safety Set included all subjects who received at least 1 dose of LUM/IVA in Part B.

[d] The Full Analysis Set included all subjects enrolled in Part B who were exposed to any amount of LUM/IVA in Part B.

[e] "Other" did not include subject refused further dosing (not due to AE), lost to follow-up, death, did not meet eligibility criteria, noncompliance with study drug, other noncompliance, physician decision, requires prohibited medication, or study termination by sponsor (i.e., no subjects discontinued from LUM/IVA treatment for these reasons).

[f] The completed study category included subjects who completed the Safety Follow-up Visit, if applicable.

Recruitment

Subject Demographics (Safety Set, Part B)

Characteristic	L100/I125q12h N = 19	L150/I188q12h N = 41	Total N = 60
Sex, n (%)			
Male	10 (52.6)	21 (51.2)	31 (51.7)
Female	9 (47.4)	20 (48.8)	29 (48.3)
Age at baseline (months)			
N	19	41	60
Mean (SD)	31.6 (5.05)	49.9 (10.63)	44.1 (12.57)
SE	1.16	1.66	1.62
Median	30.0	49.0	43.5
Min, max	24, 40	25, 69	24, 69
Age group			
<3 years	14 (73.7)	5 (12.2)	19 (31.7)
≥3 years	5 (26.3)	36 (87.8)	41 (68.3)
Ethnicity, n (%)			
Hispanic or Latino	1 (5.3)	2 (4.9)	3 (5.0)
Not Hispanic or Latino	18 (94.7)	39 (95.1)	57 (95.0)
Race, n (%)			
White	18 (94.7)	41 (100.0)	59 (98.3)
Other[a]	1 (5.3)	0	1 (1.7)

Source: Table 14.1.2.1b
N: total sample size; n: size of subsample; q12h: every 12 hours
Note: Percentages were calculated relative to the number of subjects in the Safety Set.
[a] "Other" did not include Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, or not collected per local regulations categories.

Conduct of the study

Amendment 1: Version 1.0 of the protocol, dated 03 March 2016, was amended to Version 2.0, dated 01 August 2016, to add a Washout Period to evaluate the off-drug PD response in Part B. In addition, the inclusion criterion of ppFEV1 ≥40 was removed from Parts A and B to avoid excluding subjects who were otherwise eligible but unable to perform spirometry given their age. Additional important changes in Part B included making the LCI assessment optional and adding serial post-dose vital sign assessments on Day 1 for respiratory AE monitoring.

Amendment 2: Version 2.0 of the protocol, dated 01 August 2016, was amended to Version 3.0, dated 13 April 2017, to include prescription of a SAB for subjects in Part B (if not already prescribed). The prescription ensured constant availability of bronchodilator therapy based on a request from the PDCO as part of the PIP for this product.

Baseline data

Baseline Characteristics (Safety Set, Part B)

Characteristic	L100/I125q12h N = 19	L150/I188q12h N = 41	Total N = 60
Weight (kg)			
n	19	41	60
Mean (SD)	12.7 (1.0)	17.1 (2.3)	15.7 (2.8)
SE	0.2	0.4	0.4
Median	12.8	16.4	15.6
Min, max	9.4, 13.9	14.1, 23.9	9.4, 23.9
Weight group, n (%)			
<14 kg	19 (100.0)	0	19 (31.7)
≥14 kg	0	41 (100.0)	41 (68.3)
Stature (cm)			
n	19	41	60
Mean (SD)	89.1 (3.4)	103.4 (6.1)	98.8 (8.6)
SE	0.8	1.0	1.1
Median	89.1	102.8	99.2
Min, max	82.4, 96.0	92.9, 116.6	82.4, 116.6
BMI (kg/m^2)			
n	19	41	60
Mean (SD)	15.99 (1.07)	15.98 (1.03)	15.98 (1.03)
SE	0.25	0.16	0.13
Median	15.63	15.86	15.85
Min, max	13.84, 17.62	13.14, 17.92	13.14, 17.92
Weight z-score			
n	19	41	60
Mean (SD)	-0.70 (0.64)	0.21 (0.71)	-0.08 (0.80)
SE	0.15	0.11	0.10
Median	-0.66	0.22	-0.08
Min, max	-2.61, 0.10	-1.29, 1.60	-2.61, 1.60
Stature z-score			
n	19	41	60
Mean (SD)	-0.84 (0.72)	0.09 (0.87)	-0.20 (0.93)
SE	0.16	0.14	0.12
Median	-0.95	0.03	-0.13
Min, max	-2.41, 0.39	-2.21, 1.50	-2.41, 1.50
BMI z-score			
n	19	41	60
Mean (SD)	-0.10 (0.85)	0.30 (0.76)	0.17 (0.80)
SE	0.20	0.12	0.10
Median	-0.27	0.32	0.29
Min, max	-2.17, 1.10	-2.16, 1.50	-2.17, 1.50

Sweat chloride (mmol/L)			
n	19	37	56
Mean (SD)	105.5 (8.0)	106.0 (7.2)	105.8 (7.4)
SE	1.8	1.2	1.0
Median	104.3	106.5	106.0
Min, max	84.0, 120.0	89.0, 121.3	84.0, 121.3
FEV_1 (L)			
n	1	16	17
Mean (SD)	0.65 (--)	0.86 (0.16)	0.85 (0.17)
SE	--	0.04	0.04
Median	0.65	0.87	0.84
Min, max	0.65, 0.65	0.62, 1.18	0.62, 1.18
Percent predicted FEV_1 (percentage points)			
n	1	16	17
Mean (SD)	95.6 (--)	83.1 (10.8)	83.8 (10.9)
SE	--	2.7	2.6
Median	95.6	81.3	81.8
Min, max	95.6, 95.6	62.6, 105.7	62.6, 105.7

Source: Table 14.1.3.1b

BMI: body mass index; FEV_1: forced expiratory volume in 1 second; GLI: Global Lung Initiative; N: total sample size; n: size of subsample; pp: percent predicted; q12h: every 12 hours

Note: Spirometry was only done for subjects ≥3 years age at screening. Baseline for sweat chloride was defined as the average of the values at screening and the pretreatment measurement on Day 1. Baseline for the other variables was defined as the most recent non-missing measurement before the first dose of LUM/IVA in the study. The pp values were calculated using the Quanjer GLI-2012 Regression Equations and Lookup Tables.

Numbers analysed

Analysis Populations (Parts A and B)

Population (definition)	L100/I125q12h	L150/I188q12h	Total
Part A			
All Subjects Set (gave informed consent[a] and enrolled or dosed)	4	8	12
Safety Set Part (received at least 1 dose of LUM/IVA)	4	8	12
Part B			
All Subjects Set (gave informed consent[a] enrolled or dosed)	19	41	60
Safety Set (received at least 1 dose of LUM/IVA)	19	41	60
Full Analysis Set (exposed to any amount of LUM/IVA)	19	41	60
LCI Substudy Set (consented to LCI substudy and enrolled and dosed)	5	32	37

Sources: Table 14.1.1a, Table 14.1.1.1b, and Table 14.1.1.2b

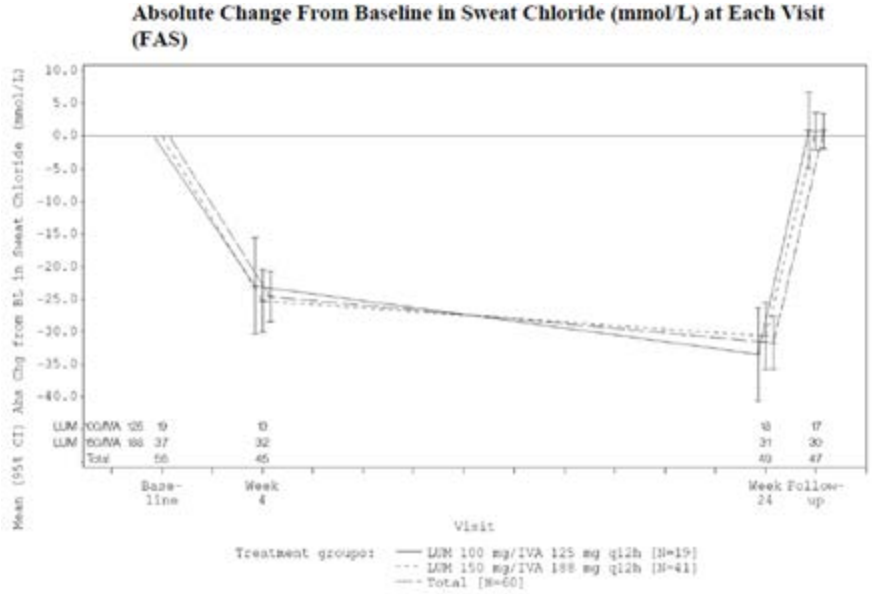
IVA: ivacaftor; LCI: lung clearance index; LUM: lumacaftor; q12h: every 12 hours

[a] And gave assent, if applicable

Outcomes and estimation

Sweat chloride concentration: There was a statistically significant improvement (i.e., a reduction) in sweat chloride concentration in the overall population after LUM/IVA treatment, with a mean absolute change from baseline at Week 24 of -31.7 mmol/L ($P<0.0001$), see figure below.

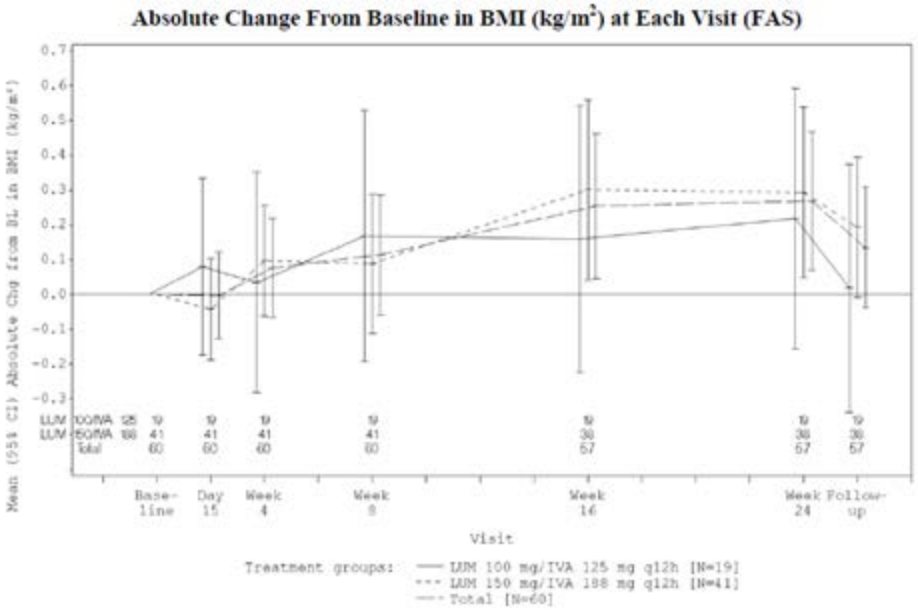
The improvement in sweat chloride concentration was reversed after a 2-week Washout Period without LUM/IVA treatment. The mean absolute change in sweat chloride concentration from Week 24 at Week 26 was 33.0 mmol/L (P<0.0001) in the overall population.



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 2 – 5 years age group at the proposed posology. However, the effect of treatment on biomarkers such as sweat chloride that directly measure CFTR function, can be considered as intermediate proof of efficacy (the report from the Workshop on Endpoints in Cystic Fibrosis clinical trials (EMA/769571/2012). The same report also indicates that the effect of the CFTR modifiers on the sweat gland may not necessarily reflects the effect on other organs.

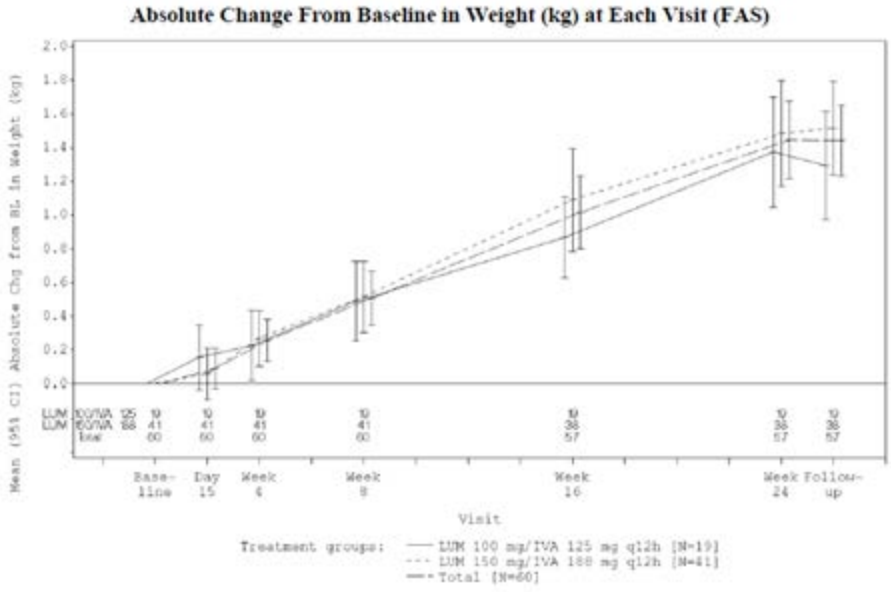
BMI, weight and stature: After treatment with LUM/IVA, the overall population showed a statistically significant improvement in parameters related to BMI, weight, and stature at Week 24:

BMI: mean absolute change from baseline of 0.27 kg/m2 (P = 0.0091)

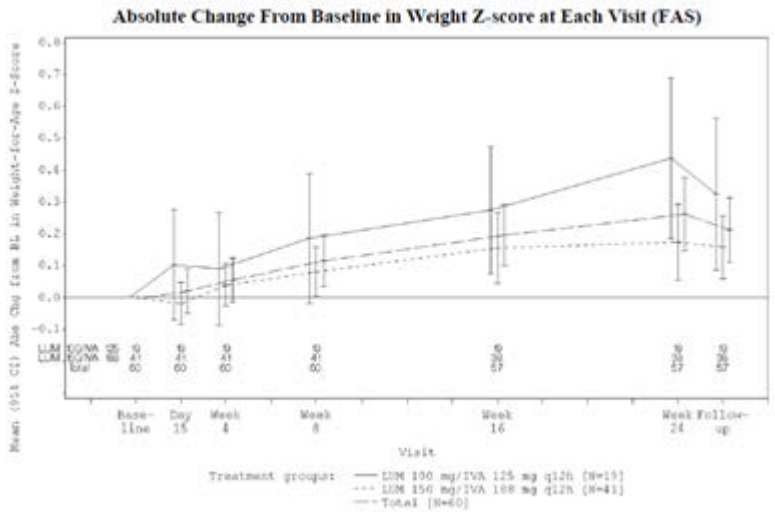


BMI-for-age z-score: mean absolute change from baseline of 0.29 (*P* = 0.0003)

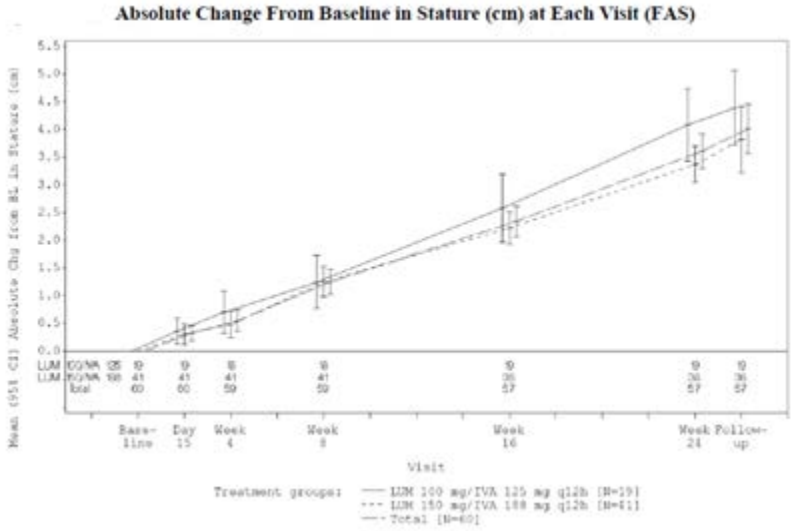
Weight: mean absolute change from baseline of 1.4 kg (*P*<0.0001)



o Weight-for-age z-score: mean absolute change from baseline of 0.26 (*P*<0.0001)



Stature: mean absolute change from baseline of 3.6 cm (*P*<0.0001).



Stature-for-age z-score: mean absolute change from baseline of 0.09 (*P* = 0.0104).

Through Week 24, 18 (30.0%) subjects had PEx events. The normalized number of PExs (event rate per patient year) was 0.90 for PExs and 0.20 for CF-related hospitalizations. The time to first PEx was based on a Kaplan-Meier analysis, subjects had an event-free probability (95% CI) of 0.695 (0.561, 0.796) at Week 24

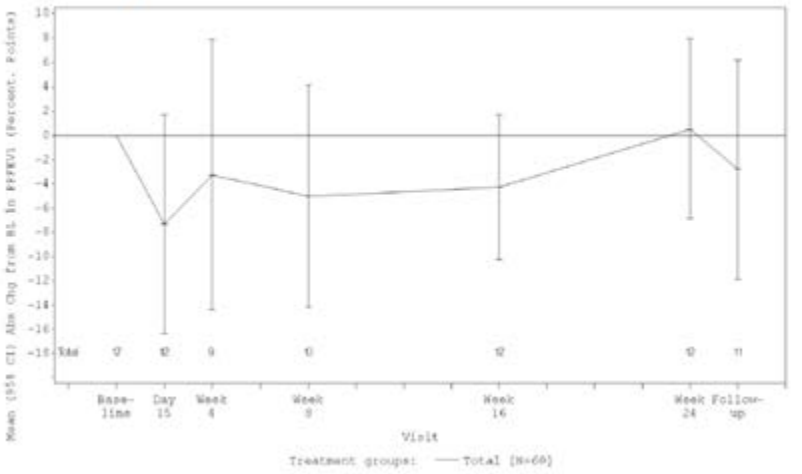
After treatment with LUM/IVA, the overall population showed a statistically significant improvement in FE-1at week 24 and IRT through Week 24, suggesting the potential of LUM/IVA to improve pancreatic function

o FE-1: mean absolute change from baseline of 52.6 µg/g (*P* = 0.0012). FE-1 levels <15 µg/g were observed in 43 (89.6%) subjects with data at baseline. At the Follow-up Visit, after the 2-week Washout Period, the improvement in FE-1 decreased both overall and for several individual subjects, with a mean absolute change from baseline of 13.5 µg/g (*P* = 0.1781).

No notable changes from baseline were observed in microbiology cultures at Week 24. For all bacterial species tested, the majority of subjects had a negative culture result at both time points.

No notable changes from baseline were observed in ppFEV1 at Week 24. Limited data were available due to the difficulty of obtaining spirometry measurements in young children (12 subjects had both a baseline and a Week 24 measurement available).

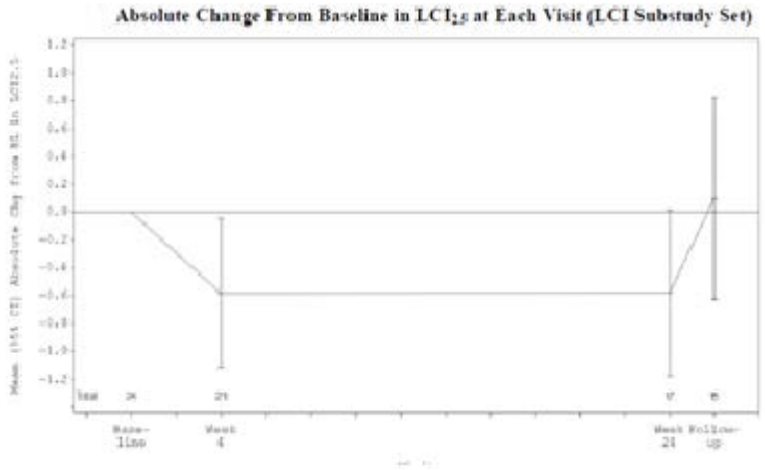
Absolute Change From Baseline in ppFEV$_1$ (Percentage Points) at Each Visit (FAS)



The guideline on clinical development of medicinal products for the treatment of cystic fibrosis EMEA/CHMP/EWP/9147/2008-corr* (22 October 2009) recommends FEV1 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, FEV1 may not be sufficiently sensitive to detect a treatment effect. Given that lung function may not have deteriorated and FEV1 is difficult to measure in children in this age group, the results are not interpretable.

In acceptability and palatability assessments, when consuming food containing LUM/IVA mixture, 17.9% of subjects “liked it very much” and 12.5% “liked it a little.” Overall, 58 (96.7%) subjects were ≥80% compliant with LUM/IVA dosing in Part B.

In the LCI Sub study, the overall population had a mean change from baseline in LCI2.5 at Week 24 of -0.58 (*P* = 0.0559). The LCI5.0 showed no meaningful change from baseline during the treatment period. In the higher weight group (older subjects), the change from baseline in LCI2.5 was -0.76 (P = 0.0322). The LCI5.0 fluctuated over time and showed no meaningful change from baseline during the treatment period. The mean (SD) absolute change from baseline in LCI5.0 was -0.06 (0.66) in the overall population at Week 24 (P = 0.7235).



Ancillary analyses

Not applicable

Summary of main study

No primary efficacy end points were identified. Efficacy was extrapolated from trials in older age groups. A number of PD endpoints were studied in Study 115 part B.

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

Not applicable.

Clinical studies in special populations

Not applicable.

Supportive studies

Study 114, relative BA of L100/I125 as a granule formulation versus the tablet formulation, the effect of food on the BA of L100/I125 as a granule formulation, and the dose proportionality of the granule formulation. The L100/I125 tablet used in Study 014 is the same formulation used in patients 6 through 11 years of age. The L100/I125 and L150/I188 granule formulation used in Studies 014 and 115 is intended for commercialization for treatment of the 2- through 5-year-old population;

Study 116, ongoing, open-label, rollover study to evaluate the long-term safety of LUM/IVA in subjects who participated in Study 115. Efficacy of LUM/IVA was not an objective of Study 115; given the same underlying pathophysiology of CF and feedback from regulatory authorities, efficacy in this age group was extrapolated from data from the placebo-controlled, Phase 3 study in CF subjects 6 through 11 years of age (Study 109) and placebo-controlled, Phase 3 studies in CF subjects 12 years of age and older (Studies 103 and 104). PD outcomes supporting efficacy in this age range were observed.

2.5.1. Discussion on clinical efficacy

Design and conduct of clinical studies

The application for the extension of the indication of Orkambi to children aged 2 to 5 years is based on a single study 115, a Phase 3, two-part, open-label study to evaluate the safety, pharmacokinetics and pharmacodynamics of Orkambi in the patient population target of the present variation procedure. Efficacy was extrapolated from trials in older age groups.

Children recruited in Study 115, although by an indirect comparison with European CF registries, can be considered as a cohort sufficiently representative of European young children with CF. It is of note that: i) the mean BMI was 15.98 kg/m2 which corresponds approximately to 25% of healthy subjects in this range (10.25th percentile) if CDC reference growth charts were used to evaluate growth rate in enrolled patients, and the mean BMI z-score was 0.17 which corresponds to ~ 50th percentile; ii) the mean baseline sweat chloride concentration was 105.8 mmol/L, well above the threshold of 60 mmol/L considered for inclusion in the trial; iii) all subjects tested at baseline had FE-1 levels <200 µg/g and therefore were pancreatic insufficient; iv) children in this age range typically have difficulty performing spirometry assessments, only 1 subject in the L100/I125q12h group and 16 subjects in the L150/I188q12h group were able to complete spirometry testing at baseline; overall, the mean percent predicted forced expiratory volume in 1 second (ppFEV1) in these subjects was 83.8, indicating normal lung function; v) In a subset of CF collaborative patients ≥3 years of age at screening, LCI was used as a surrogate exploratory endpoint to measure lung ventilation inhomogeneity. However, only very few patients (4 in the lower dose group and 20 in the higher dose group) had LCI values measured at baseline and moreover the baseline mean, median and range of all LCI values were all in the physiological value for age; vi) microbiologcial clinical data at baseline of enrolled 2-5 years old CF patients largely overlapped with those reported in available CF registries. Due to the limited follow up and limited number of expected infective events in the 2-5 years patient population, thanks to the availability of newborn screening programs, it was not expected to detect any meaningful change between baseline and week 24 treatment.

The most common medical history conditions were pancreatic failure (83.3%), GERD (43.3%) and CF lung (38.3%). Administered background symptomatic treatments, reflected those commonly prescribed in EU patients with clinical manifestations of CF, with the exception of dornase alfa (71.7%), the most common administered medication after Salbutamol (78.3%). Several randomised and observational epidemiological data (Konstan MW et al. J Cyst Fibros 2012; 11:78-83. Yang C et al 2016; Cochrane Database Syst Rev. 2016; 4:CD001127) suggest that dornase alfa, a recombinant deoxyribonuclease that improves mucus clearance in the lung, has the potential to alter the course of CF by decreasing the rate of lung function decline and the risk of exacerbations when administered early in children. Thus, the concomitant therapy with dornase alfa may have impacted on several secondary PD endpoints. In the absence of a control group, it is thus difficult to disentangle the effect of LUM/IVA from that of dornase alfa on pulmonary exacerbations and number of hospitalizations, as well as on absolute change of ppFEV1, also considering the lack of clinical knowledge on the effect of dornase alfa in early treatment of paediatric EU patients with CF.

Efficacy data and additional analyses

Study 115 part B 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 Week 24. The mean absolute change from baseline in sweat chloride at Week 24 was -31.7 mmol/L (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 2-5 years age group at the proposed posology. However, the effect of treatment on biomarkers such as sweat chloride that directly measure CFTR function, could be considered as intermediate proof of efficacy for very young children (see report from the Workshop on Endpoints in Cystic Fibrosis clinical trials (EMA/769571/2012). The same report also indicates that the effect of the CFTR modifiers on the sweat gland may not necessarily reflects the effect on other organs.

In Study 115, BMI, weight and stature increased from baseline over 24 weeks in the 2-5 years old subjects. While this could be consistent with improved pancreatic function and therefore improved nutritional status, the effect on treatment on these parameters is also confounded by growth that would occur between the ages 2-5 years. The company was requested to provide a comparison with an age matched untreated CF cohort to support interpretation of the results. The MAH presented the requested analyses, however questions remain on the treatment effects of Orkambi on growth parameters given the confounding from natural growth and the absence of a comparator.

Limited spirometry endpoints were evaluated in this study and no notable changes observed. The guideline on clinical development of medicinal products for the treatment of cystic fibrosis EMEA/CHMP/EWP/9147/2008-corr* (22 October 2009) recommends FEV1 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, FEV1 may not be sufficiently sensitive to detect a treatment effect. Given that lung function may not have deteriorated and FEV1 is difficult to measure in children in this age group, further post-marketing data will be needed. The MAH will initiate a post-authorisation efficacy study.

The report from the workshop 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 non-significant decline (reflecting improvement) in $LCI_{2.5}$ from baseline through to 24 weeks (mean change from baseline -0.58 (P = 0.0559) and a statistically significant benefit in the >14kg group. Data provided on this surrogate give sufficient assurance on efficacy, however, considering the invalidated status of this surrogate confirmation on clinical parameters needs to be given post authorisation. Given that there was no meaningful change in LCI5.0, (a change in LCI 2.5 in those >14kg only) and that changes in FEV1 have not been measured, the agreed post-authorisation efficacy study will need to be evaluated once results are available.

The Pex rate per patient year and related hospitalisations is noted. However, this is difficult to interpret meaningfully in a within-group analysis. The MAH was required to discuss this and present a comparison with an appropriately selected age matched untreated CF cohort. The MAH stated that although the data on PEx are available via CF registries, significant differences in the event definitions between the CF registry and this clinical study would preclude meaningful and appropriate comparisons of the estimates from these 2 sources, and therefore does not believe a matched cohort from registries would provide additional information. Given the absence of a consensus definition for PEx in clinical trials in this population, the following definition was used in trial 115 for the analysis of PExs: New or changed treatment with oral, inhaled, or IV antibiotics AND fulfillment of 1 criterion from List A of sinopulmonary signs or 2 criteria from List B of sinopulmonary symptoms, within the period 3 days before antibiotic start date through antibiotic stop date. 3/19 patients (15.8%) in the LUM 100 mg/ IVA 125 mg q12h group had 5 events of pulmonary exacerbations through week 24 (event rate per patient year 0.54), while in the LUM 150 mg/ IVA 188 mg q12h group 15/41 (36.6%) had 20 pulmonary exacerbations (event rate per patient year 1.07). Of these, one patient in the LUM 100 mg/ IVA 125 mg q12h group and 3

patients in the LUM 150 mg/ IVA 188 mg q12h group required hospitalization. In the absence of a control group, it is difficult to evaluate whether this is the expected number of events in this patient population. Furthermore, the interpretation of data of time-to-first pulmonary exacerbation is hampered by the small number of patients. In general, very few events are expected in this young population of CF patients.

IRT is a sensitive marker of pancreatic insufficiency. Trypsinogen is a protein produced by the pancreas that can be detected in the blood via the immunoreactive trypsinogen (IRT) assay and is used in clinical practice as a neonatal screening test for CF, wherein elevated levels are associated with pancreatic inflammation. Changes from baseline have been observed in immunoreactive trypsinogen through Week 24 (the overall mean (SD) absolute change from baseline was -130.2 ng/mL P < 0.0001). It is accepted that low IRT concentrations correlate with clinical and biochemical evidence of malabsorption, and might be considered a marker of pancreatic function. However, no compelling evidence from the literature is available to support IRT as specific indicator of pancreatic function and thus available data do not allow to adequately evaluate the clinical relevance of the observed change in immunoreactive trypsinogen from baseline.

Absolute change from baseline in percent predicted forced expiratory volume in 1 second (ppFEV1)

Assessment of changes in ppFEV1, the recommended primary endpoint to be used for registration studies as outlined in the CHMP guideline on the clinical development of medicinal products for the treatment of cystic fibrosis (EMEA/CHMP/EWP/9147/2008), is not feasible in children from birth through 5 years of age because FEV1 involves spirometry, which can only be performed in children 6 years of age and older. In addition, spirometry parameters are not sufficiently sensitive to detect early manifestations of lung disease in young children with CF or for assessing drug effects. Given to low disease progression, longer longitudinal observations in younger patients are needed to guide interpretation of test results.

Lung Clearance Index (LCI)

Treatment with LUM/IVA resulted in a statistical improvement (i.e., a reduction) in LCI2.5, with a mean (SD) absolute change from baseline of -0.58 (1.16) in the overall population at Week 24 (P = 0.0559).

The LCI5.0 fluctuated over time and showed no meaningful change from baseline during the treatment period, the mean (SD) absolute change from baseline in LCI5.0 was -0.06 (0.66) in the overall population at Week 24 (P = 0.7235).

Due to both technical limitations in the assay performance in patients under six years of age, as well as to incomplete knowledge of the range of LCI in CF people of very young age and age matched healthy control subjects, it is not possible to disentangle treatment effect from variability due to asymptomatic disease. Longer longitudinal observations in young patients in whom lung disease progression is very low may help to guide test result interpretation.

During the procedure, the MAH provided the requested efficacy data from the ongoing Studies 116 (enrolling 2-5 years old patients from study 115) and 110 (long term open label study enrolling 6-11 years old subjects coming from studies 109 and 011B).

Efficacy data for Study 116: an interim efficacy analysis was performed by the MAH to provide this response. With regard to change in ppFEV1, no conclusion can be drawn as the numbers in are small. The levels in sweat chloride at week 48 is similar to that observed at week 24, though a small numerically declining trend is noted. A similar trend is observed for growth parameter (BMI, weight for age, and height for age) Z scores.

The present interim analysis data does not allow a clear conclusion, but is considered sufficient at the time. While sweat chloride and levels growth parameters Z scores, are somewhat similar at week 48 to those at week

24, a small numerical decline is noted. Further data over time are required from this study and the PAES (with an untreated control group) to confirm changes in these parameters and clinical benefit for this patient group over time, is required.

Efficacy data for Study 110: The MAH has provided the results with the appropriate baseline (i.e. end of the parent study). Overall, the results for Study 110 is similar. Results at week 48 on treatment are similar to those seen at week 24, with a numerical decline noted. As above, additional data are awaited after study closure in 2019 before firm conclusions can be drawn.

The results so far from both these efficacy studies seem to indicate an overall maintenance of measured parameters, albeit with a somewhat numerically declining trend. Additional data are awaited after closure of both studies in 2019 before further conclusions can be drawn.

Exploratory PD data from study 115 part B provide support that the new FDC of Orkambi at the proposed posology acts in a manner consistent with the primary pharmacology and the benefit-risk of the combination is positive in the given age group. Further data will be collected in post-authorisation phase. Therefore, the CHMP requested that the MAH conducts a PAES for patients 2- to 5-years-old at initiation of Orkambi to provide the additional data. In addition to the proposed PAES study described here, data from the ongoing safety Studies 809-108 (PASS) and 809-116 will be provided.

The research question that the PAES study should allow to confirm whether children with CF homozygous for f508del-CFTR (F/F) and who are treated with Orkambi early in life will have less advanced disease when they become older compared to those who were never treated with Orkambi (or other CFTR modulator) or who initiated treatment with Orkambi at a later age.

The objectives of the PAES study should be:

- to evaluate disease progression in children with CF homozygous for f508del-CFTR (F/F) and who initiate Orkambi treatment between the ages of 2 through 5 years in comparison to a concurrent matched cohort of children with CF who have never received Orkambi (or other CFTR modulator) treatment. Thus, a matched concurrent untreated cohort of 2-5 year CF patients homozygous for F508del-CFTR (F/F) – in addition to the longitudinal historical cohort - should be foreseen in the study protocol;
- to describe disease progression in children with CF homozygous for f508del-CFTR (F/F) and who initiate Orkambi treatment between the ages of 2 through 5 years compared with children from Study 110 who initiated Orkambi treatment between the ages of 6 through 11 years. This in addition to the comparison with an historical cohort as proposed by the MAH.
- to evaluate the safety outcomes among children with CF homozygous for f508del-CFTR (F/F) and who initiate Orkambi treatment between the ages of 2 through 5 years. In order to allow evaluating long term effectiveness and safety of Orkambi in young children the study should follow patients for up to 6 years after the end of the enrolment period. The primary outcomes of interest in this study should be measures of nutritional status and pulmonary exacerbations (PEs) leading to hospitalization.

The CHMP strongly recommended that the protocol for this PAES is developed in discussion with the CHMP SAWP, to which the MAH agreed.

2.5.2. Conclusions on the clinical efficacy

An extrapolation exercise of efficacy based on efficacy data from older age groups was conducted. PK studies have been done in the proposed age group and these do not rise any concerns. While the extrapolation is in principle acceptable, there are some uncertainties given the size of the effect for Orkambi in adults.

During the evaluation, the MAH submitted also the requested efficacy data from Studies 116 and 110. The results so far from both these efficacy studies seem to indicate an overall maintenance or measured parameters, albeit with a somewhat numerically declining trended. Additional data are awaited after closure of both studies in 2019 before further conclusions can be drawn.

Therefore a PAES study needs to be undertaken to confirm the extrapolation. The MAH commits to conducting such PAES for patients 2- to 5-years-old at initiation of Orkambi to provide the additional data that CHMP is requesting in this patient population. The study protocol is strongly recommended to be designed based on a CHMP scientific advice. The MAH agreed to that. In addition to the proposed PAES study described here, data from the ongoing safety Studies 809-108 (PASS) and 809-116 will be provided.

The CHMP considers the following measures necessary to address issues related to efficacy:

Post-Authorisation Efficacy Study (PAES) Based on an agreed protocol, the Applicant should conduct a long-term effectiveness study to compare disease progression among children with CF homozygous for F508del-CFTR and are aged 2 through 5 years at the time of Orkambi treatment initiation versus disease progression among concurrent matched cohort of children with CF who have never received Orkambi treatment, in addition to a longitudinal historical cohort.	Interim Analysis: December 2022 Final Report: December 2025

2.6. Clinical safety

Patient exposure

The mean exposure for the 12 subjects in Part A was 14.4 daysand for the 60 subjects in Part B the mean exposure was 28.5. These exposures were in children 2-5 years old, see tables below.

Summary of Exposure (Safety Set, Part A)

	L100/I125q12h N = 4	L150/I188q12h N = 8	Total N = 12
Exposure duration (days)			
n	4	8	12
Mean (SD)	16.0 (1.15)	13.6 (4.31)	14.4 (3.68)
SE	0.58	1.52	1.06
Median	16.0	15.0	15.0
Min, max	15, 17	3, 16	3, 17

Source: Table 14.1.7a
IVA: ivacaftor; LUM: lumacaftor; N: total sample size; n: size of subsample; q12h: every 12 hours
Note: Duration of LUM/IVA exposure (days) = last dose date − first dose date + 1, regardless of any interruptions in dosing.

Summary of Exposure (Safety Set, Part B)

	L100/I125q12h N = 19	L150/I188q12h N = 41	Total N = 60
Total exposure (subject-years)	9.4	19.1	28.5
Exposure duration (days)			
n	19	41	60
Mean (SD)	165.8 (7.11)	156.9 (37.27)	159.7 (31.22)
SE	1.63	5.82	4.03
Median	168.0	168.0	168.0
Min, max	138, 171	23, 174	23, 174
Exposure duration by interval, n (%)			
>0 to ≤2 weeks	0	0	0
>2 to ≤4 weeks	0	3 (7.3)	3 (5.0)
>4 to ≤8 weeks	0	0	0
>8 to ≤16 weeks	0	0	0
>16 to ≤24 weeks	18 (94.7)	30 (73.2)	48 (80.0)
>24 weeks	1 (5.3)	8 (19.5)	9 (15.0)

Source: Table 14.1.7b
IVA: ivacaftor; LUM: lumacaftor; N: total sample size; n: size of subsample; q12h: every 12 hours
Note: Duration of LUM/IVA exposure (days) = last dose date – first dose date + 1, regardless of any interruptions in dosing.

Adverse events

Part A

A total of 10 (83.3%) subjects had at least 1 AE and 6 (50.0%) subjects had at least 1 AE considered related to LUM/IVA (related [8.3%] or possibly related [41.7%], as determined by the investigator),. The majority of subjects had AEs that were considered mild (9 subjects [75.0%]) in severity. No subjects had severe or life-threatening AEs. One (8.3%) subject had an AE that led to LUM/IVA discontinuation.

AEs by SOC and PT (Safety Set, Part A)

System Organ Class Preferred Term	n (%) L100/I125q12h N = 4	 L150/I188q12h N = 8	 Total N = 12
Subjects with any AEs	4 (100.0)	6 (75.0)	10 (83.3)
Respiratory, thoracic, and mediastinal disorders	2 (50.0)	4 (50.0)	6 (50.0)
Cough	2 (50.0)	3 (37.5)	5 (41.7)
Rhinorrhoea	0	2 (25.0)	2 (16.7)
Nasal congestion	1 (25.0)	0	1 (8.3)
Gastrointestinal disorders	4 (100.0)	0	4 (33.3)
Faeces soft	2 (50.0)	0	2 (16.7)
Vomiting	2 (50.0)	0	2 (16.7)
Faeces discoloured	1 (25.0)	0	1 (8.3)
Flatulence	1 (25.0)	0	1 (8.3)
Infections and infestations	0	2 (25.0)	2 (16.7)
Infective pulmonary exacerbation of cystic fibrosis	0	1 (12.5)	1 (8.3)
Lice infestation	0	1 (12.5)	1 (8.3)
Lower respiratory tract infection viral	0	1 (12.5)	1 (8.3)
Investigations	0	1 (12.5)	1 (8.3)
Respiratory rate increased	0	1 (12.5)	1 (8.3)
Skin and subcutaneous tissue disorders	1 (25.0)	0	1 (8.3)
Hyperhidrosis	1 (25.0)	0	1 (8.3)

Source: Table 14.3.1.2a

AE: adverse event; N: total sample size; n: size of subsample; PT: Preferred Term; q12h: every 12 hours; SOC: System Organ Class

Notes: MedDRA version 20.0 was used. A subject with multiple events within a category was counted only once in that category. The table is sorted in descending order of the total column by SOC and by PT within each SOC.

Part B

A total of 59 (98.3%) subjects had at least 1 AE. As depicted in table below, the most common AE relationship was possibly related to LUM/IVA (as determined by the investigator). A total of 29 (48.3%) subjects had at least 1 AE considered related to LUM/IVA (related [3.3%] or possibly related [45.0%], as determined by the investigator). The majority of subjects had AEs that were considered mild (29 subjects [48.3%]) or moderate (25 subjects [41.7%]) in severity A total of 5 (8.3%) subjects had severe AEs. No subjects had life-threatening AEs. Three (5.0%) subjects had at least 1 AE that led to LUM/IVA discontinuation. Three (5.0%) subjects had at least 1 AE that led to LUM/IVA interruption. (2 had elevated transaminases and 1 had constipation).

Overview of AEs (Safety Set, Part B)

Category	n (%) L100/I125q12h N = 19	L150/I188q12h N = 41	Total N = 60
Number of AEs (total)	131	236	367
Subjects with any AEs	19 (100.0)	40 (97.6)	59 (98.3)
Subjects with Grade 3/4 AEs	2 (10.5)	3 (7.3)	5 (8.3)
Subjects with AEs by relationship			
Not related	1 (5.3)	8 (19.5)	9 (15.0)
Unlikely related	6 (31.6)	15 (36.6)	21 (35.0)
Possibly related	11 (57.9)	16 (39.0)	27 (45.0)
Related	1 (5.3)	1 (2.4)	2 (3.3)
Subjects with AEs by maximum severity			
Mild	7 (36.8)	22 (53.7)	29 (48.3)
Moderate	10 (52.6)	15 (36.6)	25 (41.7)
Severe	2 (10.5)	3 (7.3)	5 (8.3)
Life-threatening	0	0	0
Subjects with AEs leading to LUM/IVA discontinuation	0	3 (7.3)	3 (5.0)
Subjects with AEs leading to LUM/IVA interruption	2 (10.5)	1 (2.4)	3 (5.0)
Subjects with SAEs	2 (10.5)	2 (4.9)	4 (6.7)
Subjects with related SAEs	1 (5.3)	0	1 (1.7)
Subjects with AEs leading to death	0	0	0

Source: Table 14.3.1.1b

AE: adverse event; IVA: ivacaftor; LUM: lumacaftor; N: total sample size; n: size of subsample; q12h: every 12 hours; SAE: serious adverse event

Notes: MedDRA version 20.0 was used. When summarizing the number of events, a subject with multiple events within a category was counted multiple times in that category. When summarizing the number and percentage of subjects, a subject with multiple events within a category was counted only once in that category. Related SAEs included related and possibly related events.

Serious adverse event / deaths / other significant events

Part A

The majority of subjects had AEs that were considered mild (9 subjects [75.0%]) in severity. One (8.3%) subject had an AE of respiratory rate increased that was of moderate severity; this AE also led to LUM/IVA discontinuation. No subjects had severe or life-threatening (i.e., Grade 3 or 4) AEs.

Part B

The majority of subjects had AEs that were considered mild (29 subjects [48.3%]) or moderate (25 subjects [41.7%]) in severity. A total of 5 (8.3%) subjects had severe AEs. The majority of severe events resolved and were considered possibly related to LUM/IVA. One (1.7%) subject each had severe events of gastroenteritis viral and constipation, both of which were SAEs. One (1.7%) subject had severe events of ALT, AST, and GGT increased that led to LUM/IVA discontinuation. An additional 1 (1.7%) subject each had severe events of ALT increased and infective PEx of CF, the latter of which was an SAE. No life-threatening (Grade 4) AEs occurred.

There were no deaths in study 115.

Adverse events of special interest (AESIs)

AESIs were not evaluated in Part A.

Part B

AESIs were defined as AEs related to elevated transaminases, respiratory symptoms, and respiratory events. The AESI category of respiratory events comprises PTs for respiratory symptoms and reactive airway.

AESI of Elevated Transaminases: A total of 8 (13.3%) subjects had AESIs of elevated transaminases. By PT, ALT increased occurred in 8 (13.3%) subjects and AST increased occurred in 6 (10.0%) subjects. The majority of AESIs of elevated transaminases were mild (5 of 8 subjects) or moderate (1 of 8 subjects) in severity. Two subjects had AESIs of elevated transaminases that were severe. No life-threatening AESIs of elevated transaminases occurred. Two (3.3%) subjects had AESIs of elevated transaminases that led to LUM/IVA interruption. Three (5.0%) subjects discontinued treatment due to an AESI of elevated transaminases. No serious AESIs of elevated transaminases occurred, and all transaminase elevations returned to baseline at subsequent visits. Among the 8 subjects with AESIs of elevated transaminases, the median time-to-onset of the first AESI was 29.0 days overall, and the mean (SD) duration of events was 39.2 (40.6) days.

AESI of Respiratory Symptoms: A total of 3 (5.0%) subjects had AESIs of respiratory symptoms. By PT, dyspnea occurred in 3 (5.0%) subjects and respiration abnormal occurred in 1 (1.7%) subject. All AESIs of respiratory symptoms were mild (2 of 3 subjects) or moderate (1 of 3 subjects) in severity. No subjects had AESIs of respiratory symptoms that led to interruption or discontinuation of treatment. No subject had a serious AESI of respiratory symptoms. Among the 3 subjects with AESIs of respiratory events, the median time-to-onset of the first AESI was 2.0 days, and the mean (SD) duration of events was 2.3 (1.9) days.

AESI of Respiratory Events: A total of 6 (10.0%) subjects had AESIs of respiratory events. In addition to the subjects with respiratory symptoms described in Section 12.2.4.4 (dyspnoea and respiration abnormal), other respiratory events of wheezing occurred in 3 (5.0%) subjects. All AESIs of respiratory events were mild (3 of 6 subjects) or moderate (3 of 6 subjects) in severity. No subjects had AESIs of respiratory events that led to interruption or discontinuation of treatment. No subject had a serious AESI of respiratory events. Among the 6 subjects with AESIs of respiratory events, the median time-to-onset of the first AESI was 9 days, and the mean (SD) duration of events was 6.1 (7.2) days.

Laboratory findings

Mandatory Liver Function Testing

It was strongly recommended that subjects with new treatment-emergent ALT or AST elevations of ≥3 × ULN and clinical symptoms be followed closely, including repeated confirmatory testing performed by the central laboratory within 48 to 72 hours of the initial finding and subsequent close monitoring of ALT and AST levels, as clinically indicated. LUM/IVA administration was interrupted immediately if any of the following criteria were met: ALT or AST ≥8 × ULN, ALT or AST ≥5 × ULN for more than 2 weeks, ALT or AST ≥3 × ULN in association with total bilirubin ≥2 × ULN and/or clinical jaundice. Resumption of Study Drug was allowed if a convincing alternative aetiology was identified.

Evaluation of Each Laboratory Parameter

Part A

Mean values were variable and showed no clinically notable trends over time. There were no clinically notable trends or safety concerns identified in these chemistry parameters. No subjects had LFT results that met threshold criteria. A total of 3 (27.3%) subjects had a ≥30% change from baseline in creatinine; the only other

chemistry finding occurred in 1 subject. There were no AEs related to chemistry findings, including LFT results, in Part A.

Part B

LFT Results

Mean ALT and AST concentrations showed transient elevations at Week 4 and returned to baseline values by Week 8. At Week 4, the mean ALT concentration was 52.4 U/L (normal reference range: 5 to 30 U/L) and the mean AST concentration was 61.7 U/L (normal reference range: 0 to 55 U/L). At other time points, concentrations were within or slightly above normal. Mean GGT concentration was relatively stable with no consistent pattern of change. Mean ALP and bilirubin concentrations stabilized below baseline from Day 15 onward; the mean ALP concentration (but not bilirubin) returned to baseline at the Follow-up Visit. No subjects had elevations in total bilirubin or ALP. The percentage of subjects with an ALT or AST elevation was 15.0% at the >3 × ULN threshold, 11.7% at the >5 × ULN threshold, and 8.3% at the >8 × ULN threshold.

Renal function, creatinine

A total of 18 (30.0%) subjects had a ≥30% change from baseline in creatinine, and 1 (1.7%) subject had a ≥ 100% change from baseline in creatinine; all other chemistry findings occurred in 4 subjects or fewer. There were no clinically notable trends or safety concerns identified in other chemistry parameters.

Vital Signs

No clinically notable trends were observed

Safety in special populations

Not applicable.

Safety related to drug-drug interactions and other interactions

No new data have been presented in the application.

Discontinuation due to adverse events

Part A

Of the 12 subjects in Part A, 1 (8.3%) subject had an AE that led to LUM/IVA discontinuation. The subject had an AE of respiratory rate increased that was considered moderate in severity and possibly related to LUM/IVA and that resolved without treatment after 4 days.

Part B

A total of 3 (5.0%) subjects had AEs that led to LUM/IVA discontinuation, all of which were LFT elevations that were considered possibly related to LUM/IVA.

AEs That Led to Interruption of Study Drug

There were no AEs that led to LUM/IVA interruption in Study 115 Part A. Three (5.0%) subjects had AEs that led to LUM/IVA interruption. By PT, ALT increased and AST increased each occurred in 2 (3.3%) subjects, and constipation occurred in 1 (1.7%) subject. All AEs that led to LUM/IVA interruption had an outcome of resolved.

Post marketing experience

There is no post marketing experience with the use of Orkambi in the subpopulation of children aged 2-5years.

2.6.1. Discussion on clinical safety

The only relevant safety data for this extension of indication originate from study 115, which enrolled CF children aged 2 and 5 years of age inclusive, with confirmed diagnosis of CF, homozygous for F508del, either symptomatic or with a sweat chloride value ≥ 60 mmol/L. In addition, safety data from 16 adults included in the Phase 1 bioavailability study (study 014) as well as 4 included in the taste profiling study were also presented, although the relevance of these data is limited as these were healthy adults. As a consequence, the main discussion on safety data focuses on study 115.

In part A of study 115, 4 subjects received the L100/I125q12h dose and 8 subjects received the L150/I188q12h dose; the mean LUM/IVA exposure was 14.4 days. In part B of the study 19 subjects received the L100/I125q12h dose and 41 subjects received the L150/I188q12h dose; the mean LUM/IVA exposure was 159.7 days. In the LCI substudy set, 5 subjects received the L100/I125q12h dose and 32 subjects received the L150/I188q12h dose. Thus, only limited data in the 2-5 year patient population, with only short term exposure (up to 6 months) are available to characterize safety profile of the drug in this patient population. Therefore, the CHMP requested that the MAH performs a long-term effectiveness study, to compare disease progression among children with CF homozygous for *F508del-CFTR* and are aged 2 through 5 years at the time of Orkambi treatment initiation versus disease progression among concurrent matched cohort of children with CF who have never received Orkambi treatment, in addition to a longitudinal historical cohort. This has been agreed.

Part A of study 115: All subjects (4/4) in the L100/I125q12h dose and 6/9 subjects in the L100/I125q12h dose, reported at least an AE, indicating that safety issues start very soon after treatment. In total 10 patients in Part A reported a total of 20 AEs (11 events occurred in subjects receiving the lower dose and 9 events in subjects receiving the higher dose). One subject receiving L150/I188q12h dose discontinued LUM/IVA due to an AE of respiratory rate increased, moderate in severity and possibly related to LUM/IVA that resolved without treatment. All other AEs were mild in severity. No SAE occurred. Cough (5 events), rhinorrhoea, faeces soft and vomiting (2 events each) were the most frequent events that occurred in Part A of the study, while all other events were single occurrences. Among the single occurrences of AEs, there was one event each of faeces discoloured and hyperhidrosis, both occurring in patients in the L100/I125q12h group and both considered drug related by the investigator.

Part B of study 115: Almost all patients reported at least an AE (19/19 in the L100/I125q12h dose and 40/41 subjects in the L100/I125q12h dose group). By preferred term, adverse events with an incidence ≥10% were cough, vomiting, pyrexia, rhinorrhea, nasal congestion, upper respiratory tract infection, ALT increased, ear infection, constipation , diarrhoea and AST increased. The most common related AEs (≥5% incidence overall) were cough, ALT increased, AST increased, nasal congestion and vomiting. Overall, the AEs were mostly consistent with common manifestations of CF disease or with common illnesses in subjects 2 through 5 years of age. A total of 4 (6.7%) subjects had at least 1 SAE in Part B of study 115. Two (3.3%) subjects had SAEs of infective PEx (Pulmonary Exacerbation) of CF, which is a common manifestation of CF disease, and 1 (1.7%) subject each had SAEs of gastroenteritis viral and constipation, both severe in intensity. The SAE of constipation was considered related (possibly related, as determined by the investigator) to LUM/IVA and led to LUM/IVA interruption. All SAEs resolved. 3/19 subjects (16%) in the L100/I125q12h dose and 2/41 subjects (5%) in the L100/I125q12h dose group reported an AE of Pseudomonas test positive.

Even though the limited number of enrolled subjects, particularly in the low dose group (n=19) must be considered in the interpretation of data, the frequency of subjects with Serious Adverse events (2/19, 10.5%: gastroenteritis viral and constipation) was higher in the group of subjects weighing less than 14 kg compared with the group >14 kg (2/41, 4.9%, two events of pulmonary exacerbations), as well as the frequency of subjects with AEs leading to LUM/IVA interruption (2 events, 10.5% transaminase increased and constipation vs 1 event, 2.4%, transaminase increased).

Among AESI, AEs of elevated transaminases (8/60, 13%, frequency category very common) and permanent treatment discontinuation due to AEs of elevated transaminases (5%) as well as the maximum transaminase levels (ALT or AST elevation >3 × ULN: 15.0%; >5 × ULN threshold: 11.7% at the, and >8 × ULN threshold: 8.3%), occurred with higher frequency in the 2-5 years old age subjects compared to the 6-12 years age category. Two subjects had AESIs of elevated transaminases that were severe. Two subjects (3.3%) had AESIs of elevated transaminases that led to LUM/IVA interruption and three subjects (5%) discontinued treatment due to an AESI of elevated transaminases. Among the 8 subjects with AESIs of elevated transaminases, the median time-to-onset of the first AESI was 29.0 days overall, and the mean (SD) duration of events was 39.2 (40.6) days. Exclusion criteria excluded subjects having at baseline >2UNL of transaminases. The current 4.4 section of the SmPC reports information about the occurrence of transaminases and/or bilirubin increase in patients with CF receiving LUM/IVA and different risk minimization measures as well as dose adjustment are reported to minimise hepatobiliary toxicity and related events. Although these measures could apply to the 2-5 age group as well a more adequate information was added in the relevant SmPC sections (including section 4.4) to inform the prescriber that AEs of elevated transaminases have been observed with higher frequency in this younger age group, as compared to the 6-12 years age category.

The AESI respiratory events (asthma, bronchial hyper-reactivity, bronchospasm, chest discomfort, dyspnoea, respiration abnormal, wheezing) occurred in 6 (10.0%) of subjects. All AESIs of respiratory events were mild (3 of 6 subjects) or moderate (3 of 6 subjects) in severity, with a median time-to-onset of the first AESI of 9 days, and a mean (SD) duration of events of 6.1 (7.2) days. No subjects had AESIs of respiratory events that led to interruption or discontinuation of treatment. No subject had a serious AESI of respiratory events.

As regards to other categorical changes in chemistry laboratory values, in Part A in the L100/I125q12h dose group, 3/7 subjects had a ≥30% change from baseline of creatinine and 1/7 subjects had potassium increase >=5.5 mmol/L. Similarly, in Part B of the study: A total of 18 (30.0%) subjects had a ≥30% change from baseline in creatinine, and 1 (1.7%) subject receiving L100/I125q12h dose had a ≥100% change from baseline in creatinine; potassium >=5.5 mmol/L occurred in 3 (5%) subjects. This information appears new as compared with known safety profile. In the MAH's view the observed increases in potassium levels and creatinine are likely due to normal variability seen during the study. None of observed the potassium or creatinine increases were persistent throughout the study, but were rather increases observed at single time points. None of these subjects required study dose interruption or discontinuation due to potassium elevations or creatinine increase. Overall, it is acknowledged that available data do not allow any conclusion on an effect of LUM/IVA on kidney function in the 2-5 years age range but this issue will be monitored in ongoing long term safety studies and in the PAES. The SmPC states 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.

Blood pressure increase is a known ADR of LUM/IVA (frequency category uncommon in the current SmPC), and a warning on the need to monitor periodically blood pressure in all patients during treatment is present in section 4.4 of the SmPC. Even though no subject in Study 115 had AE related to increased blood pressure, a high percentage of subjects had SBP and DBP values ≥99th percentile, particularly in the group of children weighing less than 14 kg (SBP: 10/19, 52.6% and 15/ 41, 36.6%; DBP: 9/19, 47.4% and 12/41, 29.3% in the

L100/I125q12h dose and in the L150/I188q12h dose group respectively). The SmPC already includes a warning/precaution of blood pressure increase and recommends blood pressure monitoring when receiving Orkambi treatment regardless of age group or weight and thus no additional changes are deemed necessary at this time. The issue of the effect of LUM/IVA on blood pressure in the age range 2-5 years will continued to be monitored in the ongoing long term safety study.

In Part A of the study, a postdose heart rate (HR) decrease was observed. The greatest mean change from baseline in the overall population was -13.4 bpm at 4 hours postdose on Day 1; postdose changes were minimal on Day 15. Similarly, in Part B of Study 115, a postdose HR decrease was observed. The mean change from baseline in the overall population was -8.5 bpm at 4 hours postdose on Day 1; other postdose time points were not assessed. Clinical relevance of heart rate decrease is classified as missing information in the RMP.

In Part A of the study 2/4 subjects in the L100/I125q12h dose group had a QTcF increase ≥30 to ≤60 msec. 7/10 subjects with normal ECG at baseline and 1/1 subject with abnormal ECG at baseline had a post baseline abnormal ECG evaluation classified as clinically insignificant.

In Part B of study 115, a total of 5 (8.3%) subjects had an HR of ≥120 bpm with an increase from baseline of ≥20 bpm, and 11 (18.3%) subjects had a QTcF increase from baseline of ≥30 to ≤60 msec. No subject had a QTcF increase from baseline of >60 msec or an absolute value of ≥500 msec. All AEs related to ECG parameters or in the SOC of cardiac disorders (2 in total) were mild in severity, were not considered serious, and did not lead to LUM/IVA interruption or discontinuation.

Overall, it is noted that the follow-up in the conducted studies is only 6-month and long term data are needed in order to better define the safety profile of Orkambi. The MAH agreed that the long term safety data can be provided by the MAH from the PAES. From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.6.2. Conclusions on the clinical safety

The safety profile of Orkambi in this age group seems generally the same as that reported for older subjects. However, in the youngest group some AEs, i.e. transaminases increase, has been observed more frequently than in older patients. This information is adequately reflected in the SmPC.

Moreover, the follow-up is limited to a 6-month time period. Further safety data with drug exposure longer than 6 months are needed. The MAH agreed that the long term safety data safety data will also be provided by the MAH from the PAES besides data from the ongoing safety Studies 809-108 (PASS), Study 110 and 809-116. The MAH hence commits to conducting a PAES for patients 2- to 5-years-old at initiation of Orkambi (see section on clinical efficacy).

2.7. Risk Management Plan

Safety concerns

Important identified risks	• Respiratory events • Blood pressure increase • Hepatobiliary events
Important potential risks	• 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 2 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 LUM and/or IVA • Potential environmental risk

CFTR: cystic fibrosis transmembrane conductance regulator; CYP3A: cytochrome P450 - enzyme subfamily 3A; LUM/IVA: LUM in combination with IVA; P-gp: permeability glycoprotein; ppFEV$_1$: forced expiratory volume in 1 second

Pharmacovigilance plan

Planned and Ongoing Post-authorisation Studies in the Pharmacovigilance Plan				
Study/Status	**Summary of Objectives**	**Safety Concerns Addressed**	**Milestones**	**Due Dates**
Category 1 – Imposed mandatory additional PV activities which are Conditions of the MA (key to benefit risk)				
Study 108/ Started	To evaluate the utilisation patterns and long-term effects 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	Annual Reports	Annual Reports Due: December 2017/ 2018/ 2019/ 2020 Final Report: December 2021
Category 2 – Imposed mandatory additional PV activities which are Specific Obligations in the context of a conditional MA under exceptional circumstances (key to benefit risk)				
None				
Category 3 – Required additional PV activities (by the competent authority)				
Study 110/ Started	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	Final Report	August 2019
Study 116/ Started	To evaluate the long-term safety of LUM/IVA in	• Respiratory events • Blood pressure increase	Final Report	December 2019

Planned and Ongoing Post-authorisation Studies in the Pharmacovigilance Plan				
Study / Status	**Summary of Objectives**	**Safety Concerns Addressed**	**Milestones**	**Due Dates**
	subjects aged 2 years and older with CF	• Hepatobiliary events • Cataracts • Cardiac arrhythmias • Long-term safety • Clinical relevance of heart rate decrease		
Nonclinical Studies/ Started	To evaluate the potential environmental risk of LUM and IVA	• Potential environmental risk	Final Report	March 2019

CF: cystic fibrosis; LUM/IVA: LUM in combination with IVA; $ppFEV_1$: percent predicted forced expiratory volume per 1 second

Risk minimisation measures

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Respiratory Events	**Routine risk minimisation measure:** SmPC Section 4.4 and PL Section 2 where advice is given for additional monitoring in patients with $ppFEV_1$ <40. SmPC Section 4.8 PL Section 4 **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection** Prescription only **Additional PV activities:** • Study 110 • Study 116
BP Increase	**Routine risk minimisation measure:** SmPC Section 4.4 and PL Section 2 where advice is given for periodic monitoring of BP. SmPC Section 4.8 PL Section 4 **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection** Prescription only **Additional PV activities:** • Study 108 (PASS) • Study 110 • Study 116
Hepatobiliary Events	**Routine risk minimisation measure:** SmPC Section 4.4 and PL Section 2 where advice is given on monitoring LFTs. Recommendations weighing benefit-risk in patients with advance liver disease before LUM/IVA initiation are included in SmPC Section 4.4 SmPC Section 4.2, 4.4, and 5.2 and PL Section 3 where advice is given on dose adjustment based on severity of hepatic impairment. SmPC Section 4.8 PL Section 4 **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection** Prescription only **Additional PV activities:** • Study 108 (PASS) • Study 110 • Study 116

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Concomitant use of LUM/IVA with strong CYP3A inhibitors or inducers	**Routine risk minimisation measure:** SmPC Sections 4.2 and 4.5 where advice is given on dose reduction when Orkambi is initiated or re-initiated while taking strong CYP3A inhibitors. SmPC Sections 4.4 and 4.5 where advice is given that coadministration of Orkambi with strong CYP3A inducers is not recommended. PL Section 2 **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection** Prescription only **Additional PV activities:** None
Concomitant use of LUM/IVA with sensitive CYP3A substrates and CYP3A substrates with a narrow therapeutic index	**Routine risk minimisation measure:** SmPC Sections 4.4 where advice is given that coadministration with certain CYP3A substrates is not recommended SmPC Section 4.5 where advice is given that coadministration with certain CYP3A substrates may result in reduced exposure of the substrate medications. PL Section 2 **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection** Prescription only **Additional PV activities:** None
Cataracts	**Routine risk minimisation measure:** SmPC Section 4.4 and PL Section 2 where advice is given on baseline and follow-up ophthalmological examinations in paediatric patients. SmPC Section 5.3 **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection** Prescription only **Additional PV activities:** • Study 110 • Study 116
Cardiac arrhythmias	**Routine risk minimisation measure:** SmPC Sections 5.3 **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection** Prescription only **Additional PV activities:** • Study 108 (PASS) • Study 110 • Study 116
Off-label use in children less than 2 years of age or in patients who are not homozygous for *F508del-CFTR* mutation	**Routine risk minimisation measure:** SmPC Section 4.1 and PL Section 1 where the Orkambi indication is described. SmPC Section 4.2 where advice is given on genotyping. SmPC Section 4.4 and PL Section 2 where advice is given that Orkambi should not be used in patients with CF who have certain genotypes. **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection** Prescription only **Additional PV activities:** Study 108 (PASS)

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Use in pregnant and lactating women	**Routine risk minimisation measure:** SmPC Section 4.6 and PL Section 2 where advice is given on the use of Orkambi during pregnancy and breastfeeding. SmPC Section 5.3 **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection** Prescription only Pregnancy follow-up form **Additional PV activities:** Study 108 (PASS)
Patients with $ppFEV_1 < 40$	**Routine risk minimisation measure:** SmPC Section 4.4 and PL Section 2 where advice is given on additional monitoring in patients with $ppFEV_1$ <40 during initiation of therapy. SmPC Sections 4.8 and 5.1 **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection** Prescription only **Additional PV activities:** • Study 108 (PASS)
Long-term safety	**Routine risk minimisation measure:** SmPC Sections 4.8 and 5.1 **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection** Prescription only **Additional PV activities:** • Study 108 (PASS) • Study 110 • Study 116
Safety in patients with cardiac disease	**Routine risk minimisation measure:** SmPC Section 5.3 **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection** Prescription only **Additional PV activities:** Study 108 (PASS)
Use in patients with organ transplant	**Routine risk minimisation measure:** SmPC Section 4.4 and PL Section 2 where advice is given that Orkambi use in this population is not recommended. SmPC Section 4.5 and PL Section 2 provide a list of immunosuppressants (used after organ transplant) with which concomitant use of Orkambi is not recommended. **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection** Prescription only **Additional PV activities:** • Study 108 (PASS)
Clinical relevance of heart rate decrease	**Routine risk minimisation measure:** SmPC Section 5.1 **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection** Prescription only **Additional PV activities:** • Study 110 • Study 116
Effect of LUM/IVA on P-gp substrates	**Routine risk minimisation measure:** SmPC in Section 4.5 and PL Section 2 where advice is given to use caution and appropriate dose adjustments during coadministration with P-gp substrates, such as digoxin. **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection** Prescription only **Additional PV activities:** None

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Clinical relevance of interaction potential between transporters and LUM and/or IVA	**Routine risk minimisation measure:** SmPC Sections 4.5 and 5.2 **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection** Prescription only **Additional PV activities:** None
Potential environmental risk	**Routine risk minimisation measure:** SmPC Section 6.6 and PL Section 5 where advice is given to dispose of Orkambi according to local requirements. **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection** Prescription only **Additional PV activities:** Nonclinical environmental risk assessment studies

BP: blood pressure; *CFTR*: cystic fibrosis transmembrane conductance regulator; CYP3A: cytochrome P450 - enzyme subfamily 3A; LUM/IVA: LUM in combination with IVA; P-gp: permeability glycoprotein; PL: Patient Leaflet; ppFEV$_1$: percent predicted forced expiratory volume in 1 second; SmPC: Summary of Product Characteristics

Conclusion

The CHMP and PRAC considered that the risk management plan version 5.4 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

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Orkambi film coated tablets and kalydeco granules in sachet. The bridging report submitted by the MAH has been found acceptable.

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 has a PASS imposed as a condition to the marketing authorisation.

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

The current line extension application is for an extension of indication to children 2-5 years old, from the currently approved target population of cystic fibrosis patients 6 years and older, homozygous for F508del-CFTR. Orkambi (lumacaftor/ivacaftor; LUM/IVA) 200mg/125mg film-coated tablet was approved in the EU on 19 November 2015 for the following indication: treatment of CF in patients aged 12 years and older who are homozygous for the F508del mutation in the CFTR gene. Orkambi 100mg/125mg film-coated tablet was further approved in the EU on 8 January 2018 for the following indication extension: treatment of CF in patients aged 6 years and older who are homozygous for the F508del mutation in the CFTR gene.

This line extension proposes a new formulation, i.e. granules in the following strengths:

- Orkambi (Lumacaftor/Ivacaftor) 100 mg/125 mg granules in sachet
- Orkambi (Lumacaftor/Ivacaftor) 150 mg/188 mg granules in sachet

The dose regimens proposed vary by weight of the child, with a cut off at 14 kg. The aim of therapy is to modify the course of the disease due to correction/improvement in chloride channel function. Changes in ppFEV1, the recommended primary endpoint to be used for registration studies as outlined in the CHMP guideline, EMEA/CHMP/EWP/9147/2008, are not easily and reliably registered in children from birth through 5 years of age because spirometry can only be performed in children > 6 years of age and spirometry parameters are not sufficiently sensitive to detect early manifestations of lung disease in young children with CF. Lung Clearance Index (LCI) has been proposed as a surrogate exploratory endpoint to measure lung ventilation inhomogeneity in recruited collaborative children who were ≥3 years of age, as a potentially more sensitive measurement than ppFEV1during the early stages of lung disease progression. A strong linear correlation has been noted between LCI and FEV1 in collaborative patients, in several studies (Mulligan M et al 2017. Ir Med J; 110:629). However, technical difficulties have been registered in patients under six years of age (Saunders C et al 2017. Curr Med Res Opin; 33: 613-620). Only limited comparative data of normal range of LCI in CF people and age matched healthy control subjects are available in very young people (O'Neill K et al.2016.Chest;150:1323-1332; Horsley AR et al 2008. Thorax; 63:135-140), and even more importantly, no consensus has been reached at present, in the literature, regarding the minimal clinically important differences in the LCI endpoint. Longer longitudinal observations in younger patients in whom lung disease progression is very low would be needed to guide test result interpretation. Exocrine pancreatic insufficiency and poor nutritional status are among the most significant clinical manifestations of CF in infants. These factors often lead to poor growth with subsequent growth delay, poorer cognitive development, and other clinical comorbidities such as decreased lung function and survival. Malnourishment is associated with worsening in lung function in children with CF and is an independent predictor of mortality in this population. Data in the literature suggest that early therapeutic intervention is beneficial to young children with CF; studies have demonstrated benefits such as improved measures of growth, nutrition, and lung disease through early intervention in children diagnosed by newborn screening.

3.1.2. Available therapies and unmet medical need

There are no specific targeted therapies for F508del (class II mutation) CF children aged <6 years old. At present these patients with CF and clinical manifestations receive mainly supportive therapies for controlling exocrine pancreatic insufficiency (EPI) and lung disease. There is thus a recognised unmet clinical need for new effective therapies able to interfere with CF progression, prolong survival and improve patients' quality of life. Lumacaftor (LUM, a CFTR corrector) has been developed in combination with ivacaftor (IVA, a CFTR potentiator) as a fixed dose combination (FDC) 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 CF patients 6 years and older homozygous for F508del-CFTR.

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. In the EU the targeted therapy with Kalydeco (containing ivacaftor, one of the two active components of Orkambi) has been recently authorized in children with CF aged 2 years and older and weighing less than 25 kg who have specific CFTR gating defects (class III mutations). The extension of indication in children aged 2 to 5 years old was granted for Kalydeco based on extrapolation of efficacy from older patients and on the assumption that early initiation with a targeted therapy would result in a better disease control and possibly prolonged survival of CF patients. However, long-term effectiveness and safety of Kalydeco when administered to the 2-5 years CF patient population are currently under investigation in a post-authorization efficacy study (PAES) using the US Cystic Fibrosis Foundation (CFF) registry and the UK Cystic Fibrosis registry-based data capture as described in the RMP and outlined in Annex II of the marketing authorisation.

Symkevi is indicated in a combination regimen with ivacaftor 150 mg tablets for the treatment of patients with cystic fibrosis (CF) aged 12 years and older who are homozygous for the F508del mutation or who are heterozygous for the F508del mutation and have one of the following mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene: P67L, R117C, L206W, R352Q, A455E, D579G, 711+3A→G, S945L, S977F, R1070W, D1152H, 2789+5G→A, 3272-26A→G, and 3849+10kbC→T.

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 FDC of Orkambi granules submitted with the line extension could fulfil an unmet need in the extended target population 2-5 years as evidence of clinical benefit in this age group has been provided.

3.1.3. Main clinical studies

This extension of indication of Orkambi to homozygous F508del CF children aged 2 to 5 years is based on a single study 115, a Phase 3, two-part, open-label study to evaluate the safety, pharmacokinetics and pharmacodynamics of Orkambi in the patient population target of the present variation procedure. No dedicated efficacy study has been submitted in support of the present extension of indication, and the demonstration of efficacy relies on the extrapolation from older subjects, on the base of the claim of disease similarity across age groups. The Concept paper on the need for revision of the Guideline on the Clinical Development of medicinal products for the treatment of Cystic Fybrosis identifies, among issues to be addressed, the feasibility of

extrapolating between different age groups and definition of clinical endpoints suitable for young children. Based on this extrapolation approach, Kalydeco (ivacaftor), indicated for the treatment of Cystic Fibrosis in patients with CFTR mutation that causes a CFTR gating defect, received in November 2015 an extension of indication in the 2 to less than 6 years age range.

Study 115 was a Phase 3, 2-part, open-label, multicentre study in subjects 2 through 5 years of age with CF, homozygous for F508del. Part A evaluated the PK and safety of LUM/IVA administered for 15 days. Safety, tolerability, and available PK data from Part A were reviewed to determine the dose(s) to be evaluated in Part B. No primary efficacy end points were identified as efficacy was extrapolated from trials in older age groups.

The following clinical endpoints were assessed 24 weeks after treatment initiation: Sweat chloride, body mass index (BMI), BMI-for-age z-score, weight, weight-for-age z-score, stature, stature-for-age z-score, pulmonary exacerbations (PExs), CF-related hospitalizations, faecal elastase-1 (FE-1), immunoreactive trypsinogen (IRT), qualitative microbiology cultures, spirometry (subjects ≥3 years of age at screening of Parts A and B), acceptability and palatability of LUM/IVA granules, lung clearance index (LCI) (subjects ≥3 years of age at screening of Part B who consented and assented to the optional LCI Sub study).

There was no comparison group. Analyses included change from baseline at 24 weeks and in some endpoints, effects of discontinuation of treatment at week 24, measured at week 26. In study 115, Part B, 60 subjects (19 subjects in the L100/I125q12h and 41 subjects in the L150/I188q12h) were enrolled, 3 subjects (5.0%) discontinued due to adverse events, and one subject discontinued prematurely due to miscommunication with previous study coordinator; all other subjects completed the 24 weeks treatment period. All 57 subjects who completed the study, including the subject who prematurely discontinued study treatment, rolled over into a 2-year extension study (Study 116). Thirty-seven subjects participated in the LCI Substudy. Children recruited in Study 115, although by an indirect comparison with European CF registries, can be considered as a cohort sufficiently representative of European young children with CF.

The major deficiencies of study 115 is the lack of a placebo control arm, together with the limited duration (only 6 months) given the slow disease progression in the 2-5 years age range compared with older ages. Acceptance of this study design to support the extension of indication in very young CF children, aged 2 to 5 years old, is made on the basis that extrapolation of Orkambi efficacy from older children and adults to the younger children enrolled in study 115.

3.2. Favourable effects

There was a statistically significant improvement (i.e., a reduction) in sweat chloride concentration in the overall population after LUM/IVA treatment, with a mean absolute change from baseline at Week 24 of -31.7 mmol/L (P<0.0001). The improvement in sweat chloride concentration was reversed after a 2-week Washout Period without LUM/IVA treatment. The mean absolute change in sweat chloride concentration from Week 24 at Week 26 was 33.0 mmol/L (P<0.0001) in the overall population.

After treatment with LUM/IVA, the overall population showed a statistically significant improvement in parameters related to BMI, weight, and stature at Week 24:

- BMI: mean absolute change from baseline of 0.27 kg/m2 (P = 0.0091)
- BMI-for-age z-score: mean absolute change from baseline of 0.29 (P = 0.0003)
- Weight: mean absolute change from baseline of 1.4 kg (P<0.0001)
- Weight-for-age z-score: mean absolute change from baseline of 0.26 (P<0.0001)

- Stature: mean absolute change from baseline of 3.6 cm (P<0.0001)
- Stature-for-age z-score: mean absolute change from baseline of 0.09 (P = 0.0104)

Through Week 24, 18 (30.0%) subjects had PEx events. The normalized number of PExs (event rate per patient year) was 0.90 for PExs and0.20 for CF-related hospitalizations.

After treatment with LUM/IVA, the overall population showed a statistically significant improvement in FE-1 at Week 24 and IRT through Week 24, suggesting the potential of LUM/IVA to improve pancreatic function:

- FE-1: mean absolute change from baseline of 52.6 µg/g (P = 0.0012)
- IRT: mean absolute change from baseline of -130.2 ng/mL (P < 0.0001)

No notable changes from baseline were observed in microbiology cultures at Week 24. For all bacterial species tested, the majority of subjects had a negative culture result at both time points.

No notable changes from baseline were observed in ppFEV1 at Week 24. Limited data were available due to the difficulty of obtaining spirometry measurements in young children (12 subjects had both a baseline and a Week 24 measurement available).

In acceptability and palatability assessments, when consuming food containing LUM/IVA mixture, 17.9% of subjects "liked it very much" and 12.5% "liked it a little." Overall, 58 (96.7%) subjects were ≥80% compliant with LUM/IVA dosing in Part B.

In the LCI Sub study, the overall population had a mean change from baseline in LCI2.5 at Week 24 of -0.58 (P = 0.0559). The LCI5.0 showed no meaningful change from baseline during the treatment period.

3.3. Uncertainties and limitations about favourable effects

The main uncertainty is related to the clinically relevance of the PD endpoints seen in Study 115. While these may be statistically significant, the clinical significance of the change and its relationship to clinical outcomes needs to be clearly demonstrated. It is acknowledged that robust outcomes like FEV are difficult to measure in small children. Also, lung function is relatively well maintained in small children with CF. No reliable assessment of treatment effect on pulmonary function is possible based on the provided data. Changes in ppFEV1, the recommended primary endpoint in CF studies, are both not easily evaluable as well as not sufficiently sensitive in this age group. Moreover, the use of the Lung Clearance Index (LCI) is hampered by both technical limitations in the assay performance in patients under six years of age, as well as to incomplete knowledge of the range of LCI in CF people of very young age and age matched healthy control subjects. Thus it is difficult to disentangle treatment effect from variability due to asymptomatic disease. The results of a within group analysis are harder to interpret than if a counterfactual group had been included, even though in case of some outcomes, a degree of deterioration is seen on discontinuation of treatment. While this is supportive in ascribing benefit of treatment, the clinical relevance of the magnitude of change from baseline to week 24 and from 24 to 26 has not been fully justified. During the evaluation procedure, additional data from ongoing studies 116 and 110 were provided that in general suggesting sweat chloride level at week 48 is similar to that observed at week 24, though a small numerically declining trend is noted. A similar trend is observed with for growth parameter (BMI, weight for age, and height for age) Z scores. Additional data are awaited after closure of both studies in 2019 and from the PAES to which the MAH committed.

3.4. Unfavourable effects

The 24-week, un controlled Study 115 (part B) showed that administration of LUM/IVA was overall safe and well tolerated for up to 24 weeks in subjects 2-5 years of age. The common AEs observed were mostly manifestations of CF disease. No new safety concerns were identified compared with subjects age 6 years and older. The Cumulative exposure of children 2-5 years old in these studies was 26.5 years. The most common AE relationship was possibly related to LUM/IVA (as determined by the investigator). A total of 29 (48.3%) subjects had at least 1 AE considered related to LUM/IVA (related [3.3%] or possibly related [45.0%], as determined by the investigator). The majority of subjects had AEs that were considered mild (29 subjects [48.3%]) or moderate (25 subjects [41.7%]) in severity A total of 5 (8.3%) subjects had severe AEs. Three (5.0%) subjects had at least 1 AE that led to LUM/IVA discontinuation and three (5.0%) subjects had at least 1 AE that led to LUM/IVA interruption (2 had elevated transaminases and 1 had constipation). Four (6.7%) subjects had SAEs.

Elevated transaminases: A total of 8 (13.3%) subjects had AESIs of elevated transaminases. The ALT increased occurred in 8 (13.3%) subjects and AST increased occurred in 6 (10.0%) subjects. The majority of AESIs of elevated transaminases were mild (5 of 8 subjects) or moderate (1 of 8 subjects) in severity. Two subjects had AESIs of elevated transaminases that were severe. No life-threatening AESIs of elevated transaminases occurred.

Respiratory symptoms: A total of 3 (5.0%) subjects had AESIs of respiratory symptoms. Dyspnoea occurred in 3 (5.0%) subjects and respiration abnormal occurred in 1 (1.7%) subject. All AESIs of respiratory symptoms were mild (2 of 3 subjects) or moderate (1 of 3 subjects) in severity. Serial spirometry assessments were obtained on Day 1 to evaluate postdose FEV1, and a postdose decline was observed. Because of the difficulty of performing spirometry in young children, limited data were available and showed substantial variability. Based on data from 10 subjects with postdose evaluations at 2 and/or 4 hours, and taking the lowest postdose measurement per subject, the mean change from predose ppFEV1 was -13.7 percentage points. This decline in ppFEV1 was generally asymptomatic, with few respiratory AESIs observed on Day 1, and not associated with any meaningful change in respiratory rate or pulse oximetry.

The deficiencies of study 115 is the lack of a placebo control arm, together with the limited duration (only 6 months) given the slow disease progression in the 2-5 years age range compared with older ages. Acceptance of this study design to support the extension of indication in very young CF children, aged 2 to 5 years old, is made on the basis that extrapolation of Orkambi efficacy from older children and adults to the younger children enrolled in study 115.

3.5. Uncertainties and limitations about unfavourable effects

The safety data exposure in total is relatively small in this age group (60 participants over 6 months). This period is too small to adequately characterise the safety profile when used in 2-5y olds. The safety profile is considered sufficiently characterized for marketing authorisation but it is considered important to generate further post authorisation efficacy and safety data by means of a PAES to address relevant uncertainties. Further data are expected to be generated by the ongoing clinical programme being conducted by the MAH and by the imposed PAES study to which the MAH committed.

3.6. Effects Table

Effects Table for Orkambi line extension in 2 – 5 year old CF patients homozygous for F508del-CFTR .

Effect	Short Description	Unit	Treatment	Control	Uncertainties / Strength of evidence	
Favourable Effects						
Mean reduction in sweat chloride	Treatment difference baseline to week 24 p < 0.0001	mmol /L	LUM 150 / IVA 125 mg q12h LUM 150 / IVA 188 mg q12h	Nil	Pharmacodynamic marker but recommended by CHMP.	
Numerical improvement from baseline in BMI, height and weight	Change from baseline. Clinically small but statistically significant		LUM 150 / IVA 125 mg q12h LUM 150 / IVA 188 mg q12h	Nil	These endpoints are likely to be relatively insensitive to revelation of treatment benefit in patients at a relatively early stage of disease. Absence of control group makes interpretation difficult. Confounded by growth occurring naturally between 2-5y	
Pulm exacerabtions per patient year and hospitalisations reported	Numerical figures reported		LUM 150 / IVA 125 mg q12h LUM 150 / IVA 188 mg q12h	Nil	No interpretation is possible in the absence of a comparator. Also lung function usually does not deteriorate significantly at this age	
Decline in Fecal elastase and Immunoreactive trypsinogen	Both markers of pancreatic insufficiency Small changes seen, statistically significant but not clinically significant	µg/g, ng/mL	LUM 150 / IVA 125 mg q12h LUM 150 / IVA 188 mg q12h	Nil	Magnitude of change not likely to be clinically relevant. Absence of comparator group makes interpretation difficult	
Absolute change in PPFEV1 – limited data	Very limited data as difficult to measure in small children. No interpretation possible	%	LUM 150 / IVA 125 mg q12h LUM 150 / IVA 188 mg q12h	Nil	Not interpretable	
Absolute change in LCI 2.5 and LCI 5.0 Inconsistent	Data from a sub group- limited. LCI 5 – inconsistent. LCI 2.5 changed less favourably in children <14kg	-	LUM 150 / IVA 125 mg q12h LUM 150 / IVA 188 mg q12h	Nil	Recommended by EMA workshop report EMA/769571/2012, but lacks an established clinically relevant magnitude of benefit. Inconsistent results here. Not clinically correlated.	

Effect	Short Description	Unit	Treatment	Control	Uncertainties / Strength of evidence	
Unfavourable Effects						
Transaminase elevation	13% overall, in 5% led treatment discontinuation	%	LUM 150 / IVA 125 mg q12h LUM 150 / IVA 188 mg q12h	nil	Occurred with higher freq than in 6-11y olds	
Frequency of SAE and AE in children <14 kg	SAE-2/19 AE leading to treatment interruption - 2		LUM 150 / IVA 125 mg q12h LUM 150 / IVA 188 mg q12h	nil	Indicates a possibly less favourable safety profile in younger children Overall safety data is available only for a very short period of exposure	

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Cystic fibrosis represents an area with a high-unmet medical need for specific targeted therapies. Studies performed in CF children diagnosed by newborn screening suggest that early intervention is associated with an improvement in nutritional status and lung disease.

Available data from study 115 show a consistent positive trend in the amelioration of PD parameters (i.e. change from baseline in sweat chloride, FE-1 level, IRT) following Orkambi treatment. This extension of indication to very young CF children, aged 2 to 5 years old, is made on the basis of the extrapolation of Orkambi efficacy from older children and adults to the younger children enrolled in study 115. Therefore the PD parameters are acceptable to assume a similar clinical benefit for younger children. This uncontrolled study showed a statistical improvement in PD parameters. The clinical relevance of some parameters may not be fully ascertained, but efficacy is being extrapolated from other trials. It is understood that lung function parameters are difficult to assess in young children and a full efficacy study may not be feasible and hence extrapolation from older age groups has been applied. However, given that the disease is usually less sever in younger children and that there is little deterioration in lung function, further data are expected to be generated in the imposed long term prospective study.

The safety data set in the 2-5 year CF patient population is limited both in terms of number of exposed children as well as in terms of follow-up, and a complete characterisation of the safety profile of Orkambi in this age group is thus not possible at present. Therefore, further safety data with drug exposure longer than 6 months are needed and will be generated in the imposed PAES. It is important to consider that there are no treatments approved for this age group in homozygous the F508del patients and therefore, the proposed product fills a treatment gap.

3.7.2. Balance of benefits and risks

No confirmatory clinical efficacy studies have been provided. However this acceptable given that this is an extrapolation of efficacy based on efficacy data from older age groups. PK studies have been done in the

proposed age group and do not give rise to concerns. Available data from study 115 show a consistent positive trend in the amelioration of PD parameters (i.e. change from baseline in sweat chloride, FE-1 level, IRT) following Orkambi treatment in very young CF children, aged 2 to 5 years old. This results give sufficient certainty that extrapolation of Orkambi efficacy to this patient population can be applied based on data from older children and adults. However, taking into consideration the unvalidated status of the PD biomarker and some uncertainties given the size of the effect for Orkambi in adults, further clinical study data are expected to be generated post authorization in the imposed long term prospective study. This study is expected to provide verification of the impact of Orkambi treatment on clinical outcomes (including long term safety) and disease progression and to confirm current efficacy and safety assumptions. To fulfil this expectation the study will answer whether children with CF homozygous for f508del-CFTR (F/F) and who are treated with Orkambi early in life will have less advanced disease when they become older compared to those who were never treated with Orkambi (or other CFTR modulator) or who initiated treatment with Orkambi at a later age.

3.8. Conclusions

The overall B/R of Orkambi in the proposed indication is positive.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Orkambi (lumacaftor/ivacaftor) is not similar to Bronchitol (mannitol), Cayston (aztreonam), TOBI Podhaler (tobramycin) Kalydeco (ivacaftor) and Symkevi (tezacafor/Ivacaftor) within the meaning of Article 3 of Commission Regulation (EC) No. 847/200.
See appendix 1.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of, Orkambi 100 mg/125 mg and 150 mg/188 mg granules is favourable in the following indication:

Orkambi granules are indicated for the treatment of cystic fibrosis (CF) in children aged 2 years and older who are homozygous for the F508del mutation in the CFTR gene.

The CHMP therefore recommends the extension(s) 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 complete post-authorisation measures

The MAH shall complete the below measures:

Description	Due Date
Post-Authorization Safety Study (PASS) 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
Post-Authorisation Efficacy Study (PAES) Based on an agreed protocol, the Applicant should conduct a long-term effectiveness study to compare disease progression among children with CF homozygous for *F508del-CFTR* and are aged 2 through 5 years at the time of Orkambi treatment initiation versus disease progression among concurrent matched cohort of children with CF who have never received Orkambi treatment, in addition to a longitudinal historical cohort.	Interim Analysis: December 2022 Final Report: December 2025

In addition, CHMP recommends the variation to the terms of the marketing authorisation concerning the following change(s):

Variations requested		Type	Annexes affected
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I, II and III

Update of sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.3, 6.3 and 6.4 of the SmPC of the tablets formulation to bring it in line with the safety updates proposed with the new paediatric granules formulation and its extension for use in 2-5 years old. Annex II, the PL and RMP v5.4 have been updated accordingly.