26 April 2023
EMA/222339/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Orkambi

International non-proprietary name: lumacaftor / ivacaftor

Procedure No. EMEA/H/C/003954/X/0078/G

Note

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

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Table of contents

List of abbreviations

Abbreviation	Term
ADI	acceptable daily intake
AE	adverse event
AIFA	Italian Medicines Agency
ALT	Alanine transaminase
AST	Aspartate transaminase
ATC	anatomic class
AUC	area under the plasma concentration versus time curve
BA	Bioavailability
BCS	Biopharmaceutics Classification System
BQL	below the quantifiable limit
BMI	body mass index
BOPET/PE/Foil/PE	biaxially-oriented polyethylene terephthalate/polyethylene/foil/polyethylene
BW	body weight
CF	cystic fibrosis
CFTR	CF transmembrane conductance regulator protein
CHMP	Committee for Medicinal Products for Human Use
CMP	Continuous Manufacturing Process
CI	confidence interval
Cl^-	chloride ion
CL/F	Apparent clearance
CK	creatine kinase
CQAs	Critical Quality Attributes
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
CV	coefficient of variation
DIOS	distal intestinal obstruction syndrome
EC	European Commission
EC50	concentration at which effect is at half the maximum
EC90	concentration at which effect is 90% of the maximum
EMA	European Medicines Agency
F508del	*cystic fibrosis transmembrane conductance regulator gene mutation with an in-frame deletion of a phenylalanine codon corresponding to position 508 of the wild type protein*
FDC	Fixed dose combination
G551D	cystic fibrosis transmembrane conductance regulator missense gene mutation that results in the replacement of a glycine residue at position 551 of cystic fibrosis
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GPCR	G protein-coupled receptors
HPLC	high performance liquid chromatography
HPMCAS	Health-related quality of life
HRQOL	hypromellose acetate succinate
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IIV	inter-individual variability
IPCs	In Process Controls
iPFT	infant pulmonary function testing
IR	Infrared
IVA	ivacaftor
k_a	first-order absorption rate constant
K_i	inhibition constant
LCI	lung clearance index
LDPE	Low Density Polyethylene
MAA	marketing authorisation applicant
MBW	multiple breath washout
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation	Term
mRNA	messenger RNA
MTD	maximum tolerated dose
NA	not applicable
NCA	Non compartmental analysis
NOAEL	no observed adverse effect level
OR	odds ratio
PAES	Post-authorisation efficacy studies
PCS	potentially clinically significant
pcVPCs	pharmacodynamic(s)
PD	prediction-corrected VPCs
PDCO	Paediatric Committee (EMA)
PEx	Pulmonary exacerbation
P-gp	permeability-glycoprotein
Ph. Eur.	European Pharmacopoeia
PIP	Paediatric Investigational Plan
PK	Pharmacokinetic(s)
PK/PD	pharmacokinetic/pharmacodynamic
$ppFEV_1$	percent predicted FEV1
PT	preferred term
QbD	apparent intercompartmental clearance
Q/F	Quality by design
QT	QT interval
QTPP	quality target product profile
RSE	relative standard error
RTRT	Real Time Release Testing
SAE	serious adverse event
SDD	spray-dried dispersion
SmPC	Summary of Product Characteristics
SOC	system organ class
VPCs	visual predictive checks

1. Background information on the procedure

1.1. Submission of the dossier

Vertex Pharmaceuticals (Ireland) Limited submitted on 27 May 2022 a group of variation(s) consisting of an extension of the marketing authorisation and the following variation(s):

Variation(s) requested		**Type**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

Extension application to add a new strength of 75 mg of lumacaftor and 94 mg of ivacaftor fixed dose combination granules, grouped with a type II variation (C.I.6.a).

C.I.6: Extension of indication to include treatment of cystic fibrosis for children aged 1 to less than 2 years old of age who are homozygous for the F508del mutation in the CFTR gene, based on final results from study 122, a 2-part study of CF subjects 1 to <2 years of age homozygous for F508del. As a consequence, sections 4.1, 4.2, 4.5, 4.6, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 11.2 of the RMP has also been submitted.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

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

1.3. Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0506/2020 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0506/2020 not yet completed as some measures were deferred.

1.4. Information relating to orphan market exclusivity

1.4.1. 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.

1.5. Scientific advice

The MAH did not seek Scientific advice at the CHMP.

1.6. Steps taken for the assessment of the product

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

Rapporteur: Armando Genazzani Co-Rapporteur: Finbarr Leacy

The Rapporteur appointed by the PRAC was: Rhea Fitzgerald

The application was received by the EMA on	27 May 2022
The procedure started on	16 June 2022

The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	8 September 2022
The CHMP Co-Rapporteur's critique was circulated to all CHMP and PRAC members on	9 September 2023
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	13 September 2022
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	29 September 2022
The CHMP agreed on the consolidated List of Questions to be sent to the MAH during the meeting on	13 October 2022
The MAH submitted the responses to the CHMP consolidated List of Questions on	17 December 2022
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	26 January 2023
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	13 September 2022
The CHMP agreed on a list of outstanding issues to be sent to the MAH on	23 February 2023
The MAH submitted the responses to the CHMP List of Outstanding Issues on	24 March 2023
The CHMP Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	13 April 2023
The CHMP Rapporteur circulated the updated Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	21 April 2023
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	26 April 2023
The CHMP adopted a report on similarity of Orkambi with Kalydeco, Tobi Podhaler, Kaftrio and Symkevi on (see Appendix on similarity)	26 April 2023

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

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. Cystic fibrosis is caused by mutations in the CF transmembrane conductance regulator (*CFTR*) gene that result in absent or deficient function of the CFTR protein at the cell surface. The CFTR protein is an epithelial chloride channel responsible for aiding in the regulation of salt and water absorption and secretion. The

failure to regulate chloride transport in these organs results in the multisystem pathology associated with CF.

In people with CF, loss of chloride transport due to defects in the CFTR protein result in the accumulation of thick, sticky mucus in the bronchi of the lungs, loss of exocrine pancreatic function, impaired intestinal absorption, reproductive dysfunction, and elevated sweat chloride concentration. Lung disease is the primary cause of morbidity and mortality in people with CF.

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

This line extension application is for an age adapted dosage strength and includes an extension of indication to children 1 year and older, from the currently approved target population 2 years and older. The same genotypic subpopulation of cystic fibrosis (homozygous for the F508del mutation in the CFTR gene) is indicated. The line extension proposes an additional dosage strength of oral granules for children 1 to<2 years: LUM 75-mg/IVA 94-mg granules in sachet.

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 and two FDC granules strengths in sachet: LUM 100 mg/IVA 125 mg and LUM 150 mg/IVA 188 mg.

2.1.2. Epidemiology

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.

Since the introduction and continued advances of newborn and antenatal screening, many patients with CF are identified through a positive screening test and subsequently diagnosed within the first year of life. Approximately 60% of patients with CF in the EU and 83% of patients with CF in the UK are diagnosed by 1 year of age. In the US, more than 80% of patients with CF are diagnosed by 2 years of age. CF clearly affects the paediatric population, as approximately half of the total CF patient population in the US, EU, Australia, and Canada are less than 18 years of age.

Orkambi is currently approved in the EU for the treatment of CF patients 2 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 vitamins. Treatment 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 (tezacaftor/ivacaftor, TEZ/IVA) and Kaftrio (elexacaftor/tezacaftor/ivacaftor, ELX/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, Symkevi and Kaftrio as part of fixed dose combinations) is a potentiator, the active substance lumacaftor, tezacaftor and elexacaftor are correctors (present in the fixed dose combinations).

2.2. 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 claimed indication is:

Orkambi granules are indicated for the treatment of cystic fibrosis (CF) in patients aged 1 year and older who are homozygous for the F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene (see sections 4.2, 4.4, and 5.1).

For the proposed use in paediatric patients aged 1 to less than 2 years, the age- and weight-adapted dosing is proposed as follows:

Age	**Weight**	**Strength**	**Dose (every 12 hours)**	
			Morning	**Evening**
1 to <2 years	7 kg to <9 kg	lumacaftor 75 mg/ivacaftor 94 mg	1 sachet	1 sachet
	9 kg to <14 kg	lumacaftor 100 mg/ivacaftor 125 mg	1 sachet	1 sachet
	≥14 kg	lumacaftor 150 mg/ivacaftor 188 mg	1 sachet	1 sachet

2.3. Type of Application and aspects on development

The line extension is supported by a new FDC strength 75/94 mg of Orkambi oral granules, to extend use in the paediatric population from the current 2 years or older to younger children i.e. 1 to <2 years. The line extension dossier is supported by a Phase 3, 2-part, open-label, multicentre study in subjects 1 to <2 years of age with CF, homozygous for F508del, to assess pharmacokinetics (PK) parameters.

2.4. Quality aspects

2.4.1. Introduction

This application concerns a line extension of the currently authorised Orkambi 200 mg/125 mg and 100 mg/125 mg film-coated tablets and Orkambi 100 mg/125 mg and 150 mg/188 mg granules in sachet, to introduce a new product strength: Orkambi 75 mg/94 mg granules in sachet and extend the current indication to patients 1 to < 2 years of age.

The finished product is presented as granules in sachet containing 75 mg of lumacaftor and 94 mg of ivacaftor.

Other ingredients are microcrystalline cellulose, croscarmellose sodium, hypromellose acetate succinate (HPMCAS), povidone (K30) and sodium laurilsulfate.

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

2.4.2. Active Substance

Orkambi is a fixed-dose combination (FDC) of two active substances which International Non-proprietary Names are lumacaftor and ivacaftor. This FDC lumacaftor/ivacaftor is already approved in the European Union for Orkambi (100 mg/125 mg and, 200 mg/125 mg, film-coated tablets (EU/1/15/1059/005 and EU/1/15/1059/001, respectively), and Orkambi 100 mg/125 mg and 150 mg/188 mg granules in sachet (EU/1/15/1059/006 and EU/1/15/1059/007, respectively). No new data regarding the active substances have been provided to support this line extension application.

2.4.3. Finished Medicinal Product

2.4.3.1. Description of the product and pharmaceutical development

The finished product is presented as granules in sachet for oral administration containing 75 mg of lumacaftor and 94 mg of ivacaftor.

The composition of the new lower dosage strength (75 mg/94 mg) and the authorised granules strengths is the same in terms of both active substances (lumacaftor and ivacaftor) and excipients content. In fact, the same bulk granules are packed in sachets at a different granule fill mass to manufacture the three granule strengths. As in the authorised presentations, lumacaftor active substance is provided as a crystalline solid while ivacaftor active substance as an amorphous spray-dried dispersion (SDD) intermediate.

The new dosage strength is determined by the fill weight of the fixed-ratio granules that are heat-sealed in foil laminate sachets. For the administration, the granules are emptied from the sachets and mixed with a small amount of soft food for oral administration (details regarding the administration are reported in the SmPC).

The two active substances, lumacaftor and ivacaftor, have a very low solubility in water (< 1µg/mL) and the insufficient physical stability of amorphous ivacaftor in aqueous media, do not allow neither a solution nor a suspension formulation of the lumacaftor/ivacaftor FDC. Consequently, a granule dosage form for oral administration was developed for ease of administration to paediatric patients. The granules are emptied from the sachet and mixed with a small amount of soft food or liquid.

All excipients are already used in existing Orkambi presentations. They are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC. No compatibility studies for lumacaftor/ivacaftor FDC granules have been conducted for this line extension application.

In order to evaluate the sensory attributes of the oral granules, the MAH conducted a sensory study (Study 013) with adult trained panellists. The study was conducted with lumacaftor active substance, ivacaftor Spray Dried Dispersion (SDD) and 75 mg/125 mg lumacaftor/ivacaftor granules with excipients. This was described in the line extension EMEA/H/C/003954/X/0034/G which introduced the 100/125 mg or 150/188 mg granules. Briefly, the results of the study indicated that the lumacaftor/ivacaftor FDC granules show a moderate intensity bitterness profile due overall to the ivacaftor SDD. After mixing of lumacaftor/ivacaftor FDC granules with small amounts (about 5mL) of soft foods (carrot puree, plain non-fat yogurt and applesauce) for oral administration, there was a significant reduction of the bitterness and an improvement of the overall sensory profile of the finished product. The water showed only a slight reduction of the bad taste. Based on the obtained results of the taste study, the conclusion was that the lumacaftor/ivacaftor FDC granules dosed with soft foods have an acceptable palatability (see further information under the stability section). After that, the acceptability of the lumacaftor/ivacaftor FDC granules was confirmed in two pivotal Phase 3 studies: Study 115 where were tested lumacaftor/ivacaftor (100 mg/125 mg and 150 mg/188 mg) FDC granules and Study 122 for lumacaftor 75 mg/ivacaftor 94 mg.

The pharmaceutical development of lumacaftor/ivacaftor FDC granules contains QbD elements. The quality target product profile (QTPP) of granules is shown in

Table 1.

Table 1 Quality Target Product Profile

Safe and efficacious
Bioavailable
Oral administration
Immediate release fixed-dose combination granules of 75 mg lumacaftor / 94 mg ivacaftor, 100 mg lumacaftor / 125 mg ivacaftor and 150 mg lumacaftor / 188 mg ivacaftor
At least 24 month shelf life at room temperature packaged in sachets

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

The manufacturing development has been evaluated through the use of risk assessment and design of experiments to identify the critical product quality attributes and critical process parameters. The critical process parameters have been adequately identified.

The lumacaftor/ivacaftor FDC granules CQAs and their impact on quality, safety, and/or efficacy are provided in Table 2.

Table 2 Critical Quality Attributes

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 [a]	Ensures safety of the drug product

Dissolution is a critical quality attribute (CQA) of lumacaftor/ivacaftor FDC immediate release granules. In Phase 3 clinical study, three different doses strengths of FDC granules (lumacaftor/ivacaftor 75 mg/94 mg, 100 mg/125 mg and 150 mg/188 m), were tested. Two independent *in-vitro* dissolution methods were developed for testing the lumacaftor/ivacaftor tablets. Taking into account that the paediatric FDC granules have the same composition as the intragranular ingredients of the paediatric FDC tablets, the applicability of the FDC paediatric tablet dissolution methods were evaluated for use in the FDC granules. This was assessed as part of EMEA/H/C/003954/X/0034/G which concluded that 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, including the 75 mg/94 mg strength. In addition, with available *in vivo* data, the clinical relevance of both dissolution methods was established.

The primary packaging is in a 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.

2.4.3.2. Manufacture of the product and process controls

With this line extension submission, the MAH is adding a new bulk granule manufacturing site and a new primary packaging/sachet filling site for the new 75 mg of lumacaftor and 94 mg of ivacaftor granule strength. To add these sites for the already authorised granule strengths the MAH should submit the relevant variation application.

Lumacaftor/ivacaftor bulk granules are manufactured using a continuous manufacturing process and utilize the same operations used for the authorised lumacaftor/ivacaftor paediatric tablet and granules

strengths. In fact, the same fixed-ratio granules formulation is used for all FDC granule strength formulation (lumacaftor/ivacaftor 75 mg/94 mg, 100 mg/125 mg and 150 mg/180mg); each product is filled at a different target granule fill mass.

The Quality Target Product profile (QTPP) and the Critical Quality Attributes (CQAs) are the same for the three strengths. The MAH states that the bulk granule content (% w/w) composition, manufacturing and packaging process and equipment used at the manufacturing sites are the same for lumacaftor/ivacaftor (75 mg/94 mg, 100 mg/125 mg and 150 mg/188 mg) FDC granules finished product.(to note as indicated above, the MAH should submit a variation to register the new manufacturing site for the 100 mg/125 mg and 150 mg/180 mg strengths).The manufacturing process for Lumacaftor/Ivacaftor FDC Granules includes sieving of ivacaftor SDD and lumacaftor active substance with intragranular excipients, blending, granulation, drying, milling and sachet packaging.

As described in the CHMP AR for the existing granule strengths, Vertex used Quality by Design (QbD) in product and process development of the lumacaftor/ivacaftor FDC granules.

In this line extension application the MAH wishes to a manufacturing site for bulk granules. he proposed granule manufacturing process at this new siteand its development has been acceptably described and the. design spaces developed justified

The MAH states that after manufacturing, the excess bulk lumacaftor/ivacaftor FDC granules manufactured are packed in a container The storage time and conditions have been supported by bulk granules stability studies from two batches However, even if the bulk granules packaging seems to be more moisture protective than the sachet packaging, the sachet stability data provided by the MAH can be considered as bulk granules supportive stability data only and does not substitute the requirement to provide the bulk stability data in compliance with EMA/Quality of Medicines Q&A: Part 2. Consequently, the MAH is required to commit to provide bulk granules stability data (minimum of two batches) from commercial scale batches for each bulk granules manufacturing site, in compliance with *EMA/Quality of Medicines Q&A, Part 2 – section 5*, post-approval (REC1).

Process validation is complete at the existing and the newly proposed manufacturing site For sachet filling/primary packaging process validation is complete at one of the sites butis still on-going at another and no 75 mg/94 mg granules will be placed on the market from that second site until process validation is complete. 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.

2.4.3.3. Product specification

The finished product release and shelf-life specifications are the same as for the already authorised FDC lumacaftor/ivacaftor bulk granule dosage strengths (105 mg/125 mg and 150 mg/188 mg) and include appropriate tests for this kind of dosage form.

The potential presence of elemental impurities in the lumacaftor/ivacaftor FDC granules was assessed as part of EMEA/H/C/003954/X/0034/G 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 were adequately described and appropriately validated in accordance with the ICH guidelines as part of EMEA/H/C/003954/X/0034/G. Satisfactory information regarding the reference standards used for assay testing has been presented.

A risk assessment was performed to verify the potential presence of nitrosamines in lumacaftor/ivacaftor FDC granules, in compliance with EMA/369136/2020 (procedure number: EMEA/H/A-5(3)/1490). The MAH has provided a risk evaluation about the presence of nitrosamine(s) impurities in both active substances (lumacaftor and ivacaftor), finished product intermediate, finished product, and sachet packaging processes. Based on the information provided, it is accepted that there is no risk of nitrosamine impurities in the granules. Therefore, no specific control measures are deemed necessary.

The analytical methods used are the same used for the authorised 100 mg/125 mg and 150 mg/188 mg granules. They 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 eight commercial scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

2.4.3.4. Stability of the product

As indicated above, the three dosage strengths of lumacaftor/ivacaftor FDC granules are packaged from bulk granules of the same composition and have the same packaging configuration. Consequently, the information obtained from the 100 mg/125 mg and 150 mg/188 mg FDC granules dosage strengths can be applied to the 75 mg/94 mg strength. The proposed shelf-life of 36 months without any special storage condition is supported by the following available data:

- 48 months under long-term conditions (25°C/60% RH ± 5% RH) and 6 months under accelerated conditions (40°C/75%RH ± 5% RH) stability data from 3 primary stability batches of 100 mg/125 mg FDC granules and 3 primary stability batches of 150 mg/188 mg FDC granules stored in the commercial container closure system (foil laminated sachet);
- 24 months under long-term and 6 months under accelerated conditions from three primary stability batches of 75 mg/94 mg dosage strength in the commercial packaging (foil laminated sachet);
- 12 months of long-term and three months of accelerated conditions stability data from a fourth additional primary stability batch of 75 mg/94 mg dosage strength in the commercial configuration (foil laminated sachet) and manufactured using the tighter in-process controls for the sachet filling (see details below).

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.

Lumacaftor/ivacaftor FDC granules in its commercial packaging (foil laminate sachet) was shown to be stable under the tested storage conditions. The six primary stability batches of 100 mg/125 mg and 150 mg/188 mg FDC granules met the commercial specifications at all time points through 48 months at both long-term (25°/60% RH) and accelerated (40°C/75% RH) storage conditions. The obtained stability data from the primary stability batches of the new 75 mg/94 mg FDC granules met the commercial established specifications at all times, except for one of the batches which showed an out of specification for lumacaftor assay limit below 95.0-105.0% at long term condition. The MAH indicated that this was due to a lower sachet fill weight for this specific batch and not related to a

change during stability. No changes were observed in any of the other attributes tested. As consequence the MAH implemented a tighter process controls in the sachet filling process to reduce the batch variability and to ensure conformance to the assay specification at release and at shelf-life. . An additional 75 mg/94 mg batch was manufactured with this narrower sachet fill weight IPC acceptance criteria and placed on stability. All stability data from this batch met the proposed specification.

Taking into account that the laminate foil container closure system is a light protective packaging, the no photostability test as per ICHQ1B guideline, Option 2, was conducted with lumacaftor/ivacaftor granules. This is acceptable.

In-use stability studies to verify the chemical and physical stability of granules mixed with more common foods that could be used to administrate the granules were assessed as part of the previous line extension introducing the 100 mg/125 mg and 150 mg/188 mg FDC granules (EMEA/H/C/003954/X/0034/G). The conclusions from that study are also applicable to the 75 mg/94 mg FDC granules and support the instructions included in the SmPC: '" The entire content of each sachet of granules should be mixed with one teaspoon (5 mL) of age-appropriate soft food or liquid and the mixture completely consumed. Some examples of soft foods or liquids include puréed fruits or vegetables, flavoured yogurt, applesauce, water, milk, breast milk, infant formula or juice. Food or liquid should be at room temperature or below. Once mixed, the product has been shown to be stable for one hour, and therefore should be ingested during this period".

Based on available stability data, the proposed shelf-life of 36 months without any special storage condition as stated in the SmPC (section 6.3) are acceptable.

2.4.3.5. Adventitious agents

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

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the 75 mg/94 mg granules has been presented in a satisfactory manner. The applicant has applied QbD principles in the development of the finished product and its manufacturing process. Design spaces have been proposed for several steps in the manufacture of the finished product. The design spaces have been adequately verified. 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.

At the time of the CHMP opinion, there was a minor unresolved quality issue having no impact on the Benefit/Risk ratio of the product, which pertained to the requirement to provide confirmatory bulk granules stability data from a minimum of two commercial scale batches for each bulk granule manufacturing site. This point is put forward and agreed as recommendation for future quality development.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

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

2.4.6. Recommendation(s) for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

The MAH should provide confirmatory bulk granules stability data from a minimum of two commercial scale batches for each bulk granule manufacturing site (REC1).

2.5. Non-clinical aspects

2.5.1. Introduction

No new non-clinical studies have been submitted in this application.

2.5.2. Ecotoxicity/environmental risk assessment

With the renewal EMEA/H/003954/R/0056 finalised in November 2020, the complete ERA for both lumacaftor and ivacaftor in Orkambi (fixed dose combination, lumacaftor/ivacaftor) was agreed. The conclusions were that both ivacaftor (VX-770) and lumacaftor (VX-809) are unlikely to represent a risk to the environment.

The present submission encompasses the extension of the indication for Orkambi granules in sachet for children aged 1 to less than 2 years who are homozygous for the F508del mutation in the CFTR gene.

The MAH highlighted that the ERA report dated 11 September 2019 already included patients 1 to <2 years of age since the calculations performed for the initial environmental risk assessment accounted for the entire population of CF patients (irrespective of age), so no updated ERA in relation to the line extension has been provided. This is considered acceptable.

2.5.3. Discussion on non-clinical aspects

It is agreed that no updated report is considered necessary since the calculation for the initial ERA already included patients 1 to <2 years of age.

2.5.4. Conclusion on the non-clinical aspects

No new non-clinical data have been submitted in this application, which is considered acceptable by the CHMP.

The extended indication does not lead to a significant increase in environmental exposure further to the use of Orkambi as it was already part of the environmental risk assessment.

Considering the above data, Orkambi is not expected to pose a risk to the environment.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

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**

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	Study Status; Type of Report
Phase 3 Safety, PK, and Efficacy	VX16-809-122 (Module 5.3.5.2)	**Part A** Primary Objective Evaluate the PK of LUM and IVA in subjects 1 to <2 years of age with CF, homozygous for F508del Secondary Objectives • Evaluate the safety of LUM/IVA in subjects 1 to <2 years of age with CF, homozygous for F508del • Evaluate the PK of metabolites of LUM and IVA in subjects 1 to <2 years of age with CF, homozygous for F508del **Part B** Primary Objective Evaluate the safety of LUM/IVA in subjects 1 to <2 years of age with CF, homozygous for F508del Secondary Objectives • Evaluate the PD of LUM/IVA in subjects 1 to <2 years of age with CF, homozygous for F508del • Evaluate the PK of LUM and IVA and their respective metabolites in subjects 1 to <2 years of age with CF, homozygous for F508del	Open-label, 2-part, multicenter	**LUM/IVA (fixed-dose):** LUM 75-mg/94-mg IVA granules; LUM 100-mg/125-mg IVA granules; LUM 150-mg/188-mg IVA granules **Part A:** • LUM 75-mg/IVA 94-mg granules q12h (subjects 7 to <10 kg at screening/) • LUM 100-mg/ IVA 125-mg granules q12h (subjects 10 to <14 kg at screening) • LUM 150-mg/ IVA 188-mg granules q12h (subjects ≥14 kg at screening) **Part B:** • LUM 75-mg/IVA 94-mg granules q12h (subjects 7 to <9 kg at screening/) • LUM 100-mg/ IVA 125-mg granules q12h (subjects 9 to <14 kg at screening) • LUM 150-mg/ IVA 188-mg granules q12h (subjects ≥14 kg at screening) Oral administration	**Part A:** 14 subjects **Part B:** 46 subjects Of the enrolled subjects, 1 subject participated in the optional LCI Substudy Male and female subjects 1 to <2 years of age with CF, homozygous for F508del	**Part A** Approximately 15 days **Part B** Approximately 24 weeks	Completed; Full

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

The proposed extension of indication is based on results from Study 122, a Phase 3, 2-part, open-label, multicentre study in subjects 1 to <2 years of age with CF, homozygous for F508del. Study 122 was designed to assess pharmacokinetics (PK) in Part A and safety in Part B.

The extrapolation of benefit to this age group is further supported by pharmacodynamic (PD) data from Study 122 Part B.

Study 122 is a phase 3, 2-part, Open-label Study to Evaluate the Safety and Pharmacokinetics of Lumacaftor/Ivacaftor in Subjects 1 to Less Than 2 Years of Age With Cystic Fibrosis, Homozygous for F508del.

Part A was designed to evaluate the PK and safety of LUM/IVA over 15 days of dosing. The evaluation of LUM/IVA as multiple doses allowed for the assessment of the time-dependent induction effect of LUM on the metabolism of IVA. The duration of dosing in Part A was selected to evaluate the PK and safety endpoints when the induction effect of LUM on the metabolism of IVA was anticipated to have reached steady state.

Part B was designed to evaluate the safety of LUM/IVA dosing over 24 weeks in this paediatric CF population. In addition, the PD effects and PK of multiple doses of LUM/IVA over 24 weeks of dosing were evaluated, and a 2-week Washout Period was included in order to evaluate the off-drug PD response.

For both Parts A and B, LUM/IVA granules were administered orally every 12 hours (q12h).

The doses and weight bounds in Study 122 were selected to achieve the target exposures observed previously to be safe and efficacious in adult subjects. After completion of Part A Cohort 1 (18 to <24 months), Part A Cohort 1 PK and safety results were reviewed and the popPK models were updated to determine the dosing regimen for Part A Cohort 2 (12 to <18 months of age) and subjects 18 to <24 months of age in Part B.

The updated popPK models supported a new lower dose of L75/I94 q12h for subjects weighing 7 to <10 kg at screening for Part A Cohort 2.

After completion of Part A Cohort 2 (12 to <18 months), Part A Cohort 2 PK and safety results and a subset of PK and safety data from subjects 18 to <24 months of age through Week 12 in Part B was reviewed. The popPK models were updated again to include Part A Cohort 2 data and the available Part B data. The updated models supported an adjustment to the weight bound between the L75/I94 and L100/I125 q12h dose from 10 kg to 9 kg.

The PK Set contained data for all subjects who received at least 1 dose of study drug, which included 7 subjects in Part A Cohort 1, 7 subjects in Part A Cohort 2, and 46 subjects in Part B.

Results

Part A

PK concentrations for LUM and M28-LUM are presented in the table below:

Table 3 Summary of Plasma concentrations for Lum and M28-LUM, PK Set, Part A

			Day 1	Day 8	Day 15		
Dose (mg)	Baseline Weight	Statistic	$C_{3\text{-}4h}$ (ng/mL)	C_{trough} (ng/mL)	C_{trough} (ng/mL)	C_{2h} (ng/mL)	$C_{3\text{-}4h}$ (ng/mL)
LUM							
L75/I94 q12h	7 to <10 kg	N	7	7	5	7	7
		Mean	14600	12000	8380	16000	16600
		SD	5560	8880	7790	8400	9590
L100/I125 q12h	10 to <14 kg	N	7	6	6	5	5
		Mean	12600	12800	10500	13100	13900
		SD	7190	3900	3070	6790	5800
M28-LUM							
L75/I94 q12h	7 to <10 kg	N	7	7	5	7	7
		Mean	252	1410	1460	1380	1420
		SD	128	791	1060	877	870
L100/I125 q12h	10 to <14 kg	N	7	6	6	5	5
		Mean	192	1470	1370	1130	1240
		SD	106	365	468	300	506

Source: Table 14.4.1.1
LUM: lumacaftor; N: total number of values; PK: pharmacokinetic; q12h: every 12 hours

The mean LUM Ctrough values were comparable between Day 8 and Day 15, which suggests that steady state for LUM was achieved by Day 8. The mean LUM C3-4h was comparable on Day 1 and Day 15, showing minimal accumulation of LUM from Day 1 to Day 15.

The trend for M28-LUM Ctrough was similar to that of the parent and suggests that steady state for M28-LUM was achieved by Day 8. The mean M28-LUM C3-4h increased from 252 ng/mL on Day 1 to 1420 ng/mL on Day 15 for the L75/I94 q12h group and from 192 ng/mL to 1240 ng/mL on Day 15 for the L100/I125 q12h group, which shows an accumulation of M28-LUM from Day 1 to Day 15.

The mean LUM and M28-LUM concentrations at each timepoint were comparable between the 2 dosing groups.

PK concentrations for **IVA, M1-IVA, and M6-IVA** are presented in the table below:

Table 4 Summary of Plasma Concentrations for IVA, MI-IVA, and M6-IVA, PK Set, Part A

			Day 1	Day 8	Day 15		
Dose (mg)	Baseline Weight	Statistic	$C_{3\text{-}4h}$ (ng/mL)	C_{trough} (ng/mL)	C_{trough} (ng/mL)	C_{2h} (ng/mL)	$C_{3\text{-}4h}$ (ng/mL)
IVA							
L75/I94 q12h	7 to <10 kg	N	7	7	5	7	7
		Mean	1620	169	78.9	824	718
		SD	648	75.5	19.1	448	352
L100/I125 q12h	10 to <14 kg	N	7	6	6	5	5
		Mean	1320	185	120	346	496
		SD	804	101	60.5	225	268
MI-IVA							
L75/I94 q12h	7 to <10 kg	N	7	7	5	7	7
		Mean	3010	606	284	1710	2120
		SD	1150	298	70.2	863	781
L100/I125 q12h	10 to <14 kg	N	7	6	6	5	5
		Mean	2450	842	604	944	1630
		SD	1690	527	394	598	881
M6-IVA							
L75/I94 q12h	7 to <10 kg	N	7	7	5	7	7
		Mean	1520	2380	1460	1650	3530
		SD	1050	843	763	535	1660
L100/I125 q12h	10 to <14 kg	N	7	6	6	5	5
		Mean	934	3290	2800	2720	3210
		SD	903	1830	2300	2010	1880

Source: Table 14.4.1.1
IVA: ivacaftor; N: total number of values; PK: pharmacokinetic; q12h: every 12 hours

The mean IVA C3-4h was higher on Day 1 and decreased on Day 15 to 718 ng/mL for the L75/I94 q12h group and 496 ng/mL for the L100/I125 q12h group. The trend for M1-IVA C3-4h was similar to that of the parent. Unlike the parent and M1-IVA results, the mean M6-IVA C3-4h increased from Day 1 to Day 15, which shows an accumulation of M6-IVA.

Ctrough of IVA, M1-IVA and M6-IVA were all higher on Day 8 than Day 15.

Part B

PK concentrations for LUM and M28-LUM are presented in the table below:

Table 5 Summary of PK Concentrations for LUM and M28-LUM (PK Set, Part B)

			Day 15	Week 4	Week 12	Week 24	
Dose (mg)	Baseline Weight	Statistic	C_{trough} (ng/mL)	C_{trough} (ng/mL)	C_{trough} (ng/mL)	Conc (ng/mL)	$C_{trough,ave}$ (ng/mL)
LUM							
L75/I94 q12h	7 to <9 kg	N	1	1	1	1	1
		Mean	13500	21900	12100	11200	15800
		SD	NR	NR	NR	NR	NR
L100/I125 q12h	9 to <14 kg	N	43	43	41	35	44
		Mean	9030	9370	9160	8930	9300
		SD	4390	5030	4400	5310	3990
L150/I188 q12h	≥14 kg	N	1	1	1	1	1
		Mean	887	1000	566	288	818
		SD	NR	NR	NR	NR	NR
M28-LUM							
L75/I94 q12h	7 to <9 kg	N	1	1	1	1	1
		Mean	1460	1570	1740	1870	1590
		SD	NR	NR	NR	NR	NR
L100/I125 q12h	9 to <14 kg	N	43	43	41	35	44
		Mean	1260	1340	1440	1470	1350
		SD	528	579	599	548	544
L150/I188 q12h	≥14 kg	N	1	1	1	1	1
		Mean	786	602	501	569	630
		SD	NR	NR	NR	NR	NR

Sources: Tables 14.4.1.2 and 14.4.1.3
LUM: lumacaftor; N: total number of values; NR: not reported; PK: pharmacokinetic; q12h: every 12 hours
Notes: The Week 24 PK sample was taken at the same time as other blood collections. $C_{trough,ave}$ is the average of Day 15, Weeks 4, and 12.

The mean LUM Ctrough was comparable between the Day 15, Week 4, and Week 12 Visits in the L100/I125 q12h and L150/I188 q12h groups. This suggests that steady state for LUM was achieved by Day 15. The trend for M28-LUM Ctrough was similar to that of the parent. The LUM Ctrough in the L75/I94 q12h group appeared to be more variable across study visits than that observed in the

L100/I125 q12h group, likely because only 1 subject was dosed in the L75/I94 q12h group in Part B so a trend cannot be established.

For the purpose of cross-study comparisons between this study and the pivotal Phase 3 study in subjects aged 2 through 5 years old with CF, Ctrough,ave was calculated to provide composite values of approximate trough concentrations.

PopPK analysis

An updated popPK analyses of lumacaftor (LUM, also known as VX-809) in combination with ivacaftor (IVA, also known as VX-770) was provided in report (R231). R231 popPK analyses were conducted to support the dose selection and the overall clinical development for LUM/IVA. The analyses described in this report are a continuation of previous analyses for this age group (R230) and were used to support the dose selection for LUM/IVA in 12 to <24 months of age in CF subjects. R231 popPK analyses documents the final popPK modelling and simulations of LUM and IVA in CF subjects 12 to less than 24 months of age based on the final data from Study VX16-809-122. According to the MAH, these results support the dose selection for Orkambi (LUM/IVA combination therapy) in subjects 12 to <24 months of age with cystic fibrosis (CF) homozygous for the *F508del* mutation.

Specific objectives of this analysis are:

• to evaluate the previously developed popPK model (Report R230) of LUM when co-administered with IVA in CF subjects aged 12 months through 11 years of age using the final PK dataset from Study 122;

• to evaluate the previously developed popPK model (Report R230) of IVA when coadministered with LUM in CF subjects aged 12 months through 11 years of age using the final PK dataset from Study 122 and taking into account its increased metabolism due to CYP3A induction by LUM;

• to simulate the exposures of LUM and IVA with the studied dosing regimen in Part B of Study 122;

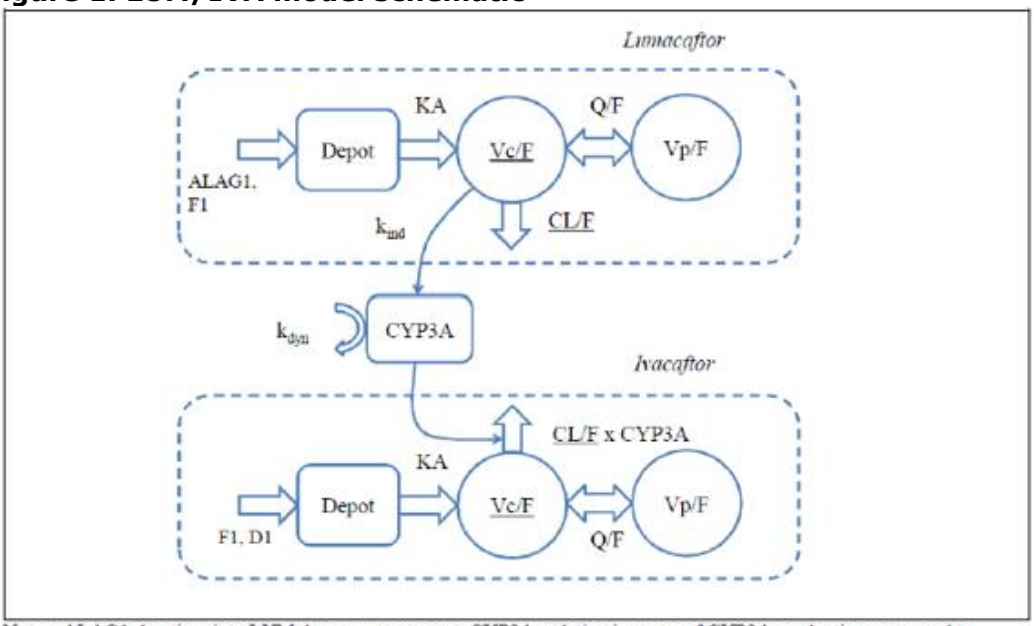
• to summarize the exposures of LUM and IVA in CF subjects aged 12 to less than 24 months in Part B of Study 122; and

• to support the dose selection for CF subjects 12 to less than 24 months of age taking LUM/IVA combination therapy.

Models described in Report R230 were used as a starting point to evaluate the effect of age and weight on the exposures of LUM and IVA.

Figure 1 below show the schematic of the PK model for LUM/IVA:

Figure 1. LUM/IVA model schematic



Notes: ALAG1: lag time into LUM depot compartment; CYP3A: relative increase of CYP3A production compared to homeostasis; D1: zero order duration; F1: relative bioavailability for granulation formulation; KA: first-order absorption; K_{dyn}: dynamic response rate of CYP3A production and degradation; K_{ind}: degree of LUM induction of CYP3A; V_c/F: central volume; V_p/F: peripheral volume; CL/F: (central) clearance; Q/F: intercompartmental clearance; Depot refers to the depot compartments; IIV was included onto V_c/F and CL/F.

LUMACAFTOR

The LUM dataset included a total of 1602 observations for 287 unique subjects with 3 observations excluded from the analysis.

The final LUM dataset used for model development included 1599 LUM plasma concentration measurements from 287 CF subjects, including 62 LUM plasma concentration measurements from 14 unique 12 to <24 months CF subjects in Part A and 259 LUM plasma concentration measurements from 46 unique 12 to <24 months CF subjects in Part B.

PK profiles at steady-state stratified by age and dose groups show that the concentration profiles of the newest data added (12 to <24 months) are comparable to the other age groups, noting that there is only 1 subject 12 to <24 months administered the LUM 150 mg/IVA 188 mg q12h dosing regimen.

Baseline weight and baseline age were correlated covariates with a strong correlation between weight and age within this paediatric population.

The LUM final model is a linear, two-compartment popPK model with first-order absorption, zero-order infusion duration, absorption lag, inter-individual variability (IIV) on CL/F and Vc/F, proportional error, and the following covariate effects:

- Estimated allometric exponents (weight effect) on clearances (CL/F and Q/F) and volumes (Vc/F and Vp/F); and
- Fixed effect of fast maturation rate on CL/F.

Shrinkage estimates for the IIV effects were 10% for CL/F and 42% for Vc/F, indicating that ETA-based diagnostics were more reliable for CL/F than Vc/F (i.e., shrinkage was less than 30%).

According to the MAH, the final model provided an adequate description of the LUM concentration data.

No significant trends were observed on the IIV versus categorical covariates, noting that there were only 3 subjects in the <9kg weight group. Graphical presentation of the covariate effects of age and weight on the IIV values for CL/F and Vc/F, showed that there were no significant trends observed in

the final model. Distribution of quantiles for random effects indicated that the IIVs were normally distributed. Evaluation of the random effect terms in the model showed a significant correlation between CL/F and Vc/F, as expected given the nature of the OMEGA matrix.

The precision of the model parameter estimates was obtained from the successful covariance step in NONMEM with the default setting. With exception of KA (relative standard error (RSE)=40%), all PK parameters were well estimated (RSE <12%) for the final data set (including subjects 12 months through 11 years of age). RSE for KA is inflated due to the fact that its value is close to 1 and was log transformed for purposes of estimation (with log(1)=0). The 95% confidence interval for KA was reasonably narrow [0.6-0.9], confirming that KA was reasonably estimated. The PK parameters (CL/F, Vc/F, Q/F, Vp/F, KA, and D1) are for a 70-kg CF patient receiving LUM in the tablet formulation.

IVACAFTOR

The IVA dataset included a total of 1588 observations for 287 unique subjects. 9 observations were excluded from the analysis, including 3 BLQ entries and 2 records prior to the first dose.

The final IVA dataset used for model development included 1579 IVA plasma concentration measurements from 287 CF subjects, including 62 IVA plasma concentration measurements from 14 unique 12 to <24 months CF subjects in Part A and 258 IVA plasma concentration measurements from 46 unique 12 to <24 months CF subjects in Part B. Overall, the percentage of BLQ observations was small: 3 out of 1588 observations, or <0.01%.

Overall, plots show that the concentration profiles of the newest data added (12 to <24 months) are comparable to the other age groups, noting that there is only 1 subject 12 to <24 months administered the LUM 150 mg/IVA 188 mg q12h dosing regimen.

Covariates were identical between LUM and IVA, the matrix-plot showing the distributions and correlation of the continuous covariates most relevant to the IVA exposures matched those for LUM.

The schematic of the final model structure was unchanged from that of Report R230. The IVA final model is a linear, two-compartment popPK model with first-order absorption, zero-order infusion duration, IIVs on CL/F and Vc/F, proportional error, induction delay, and the following covariate effects: estimated allometric exponent (weight effect) on clearances (CL/F and Q/F) and volumes (Vc/F and Vp/F); and fixed effect of fast maturation rate on CL/F.

Shrinkage estimates for the IIV effects were 8% for CL/F and 43% for Vc/F, indicating that ETA-based diagnostics were more reliable for CL/F than Vc/F (i.e., shrinkage was less than 30%).

According to the MAH the final model provided an adequate description of the IVA concentration data.

No significant trends were observed on the IIV versus categorical covariates, noting that there were only 3 subjects in the <9kg weight group. Graphical presentation of the covariate effects of age and weight on the IIV values for CL/F and Vc/F showed that there were no significant trends observed in the final model.

Distribution of quantiles for random effects indicated that the IIVs were generally normally distributed. Evaluation of the random effect terms in the model showed a significant correlation between CL/F and Vc/F, as expected given the nature of the OMEGA matrix.

The precision of the model parameter estimates was obtained from the successful covariance step in NONMEM with the default setting. Except for kenz (84.2%), all fixed-effect PK parameters were well estimated (RSE <22%) for the final data set (including subjects 12 months through 11 years of age).

Median IVA CL/F for this population was 5.54 L/h in the absence of LUM induction, and 25 L/h in the presence of LUM.

The visual predictive checks (VPCs) were based on 500 simulated replicates of the model analysis dataset. Since 4 different doses were administered in this population, both VPCs and prediction-corrected VPCs (pcVPCs) were performed. Some deviations were observed in higher weight groups (14 to <24 kg and ≥24 kg), primarily in the 2.5th and 97.5th percentiles. Also, there was not sufficient data in the lightest (<9kg) subgroup to adequately assess model predictions other than the median. Overall, the VPCs indicated that the LUM final model captured the observed data at steady state reasonably well, especially for the central tendencies and the population of interest (12 to <24 months).

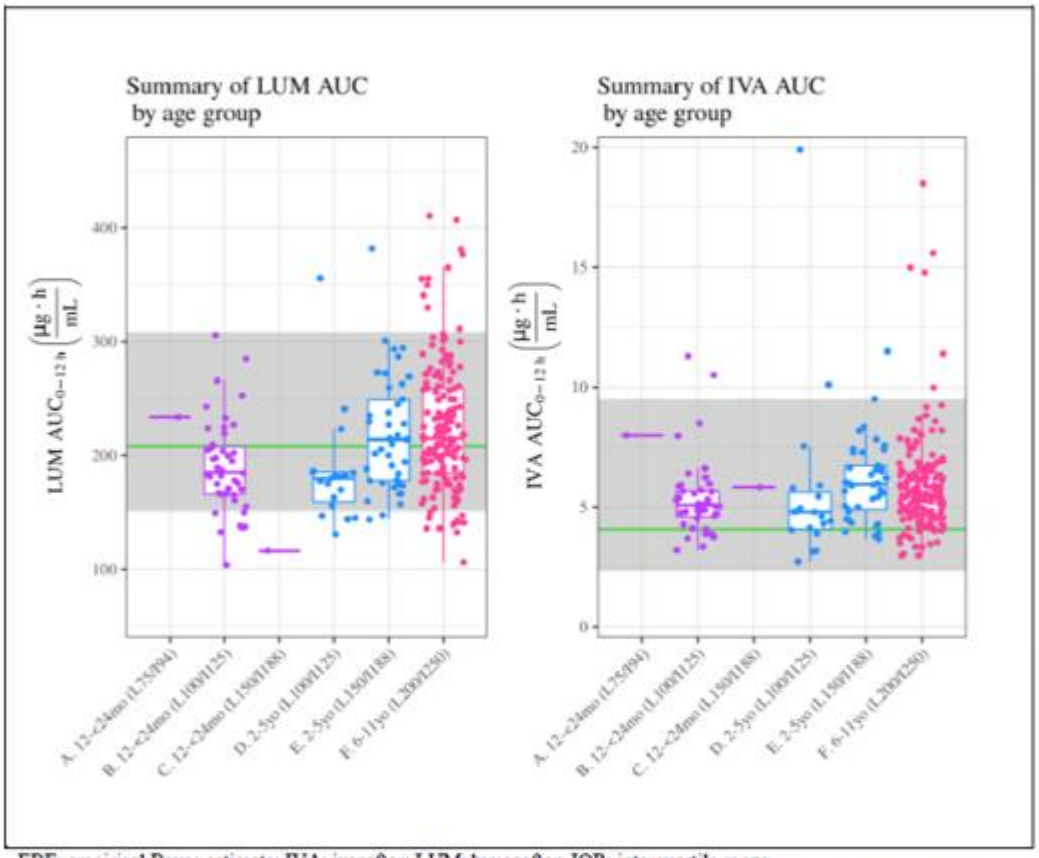
Altogether, these model diagnostics demonstrated that the popPK model for LUM was consistent with the observed data.

Figure 2 below shows the steady-state exposures for LUM and IVA AUC's, derived from EBEs simulations for the different age and weight groups.

The studied dosing regimen was:

- LUM 75 mg/IVA 94 mg q12h for subjects weighing 7 to <9 kg;
- LUM 100 mg /IVA 125 mg q12h for subjects weighing 9 to <14 kg; and
- LUM 150 mg /IVA 188 mg q12h for subjects weighing ≥14 kg

Figure 2 Summary of LUM (Left) and IVA (Right) Steady-State AUC by Age and Dose Groups



EBE: empirical Bayes estimate; IVA: ivacaftor; LUM: lumacaftor; IQR: interquartile range
Notes: Green horizontal line represents the median of the adult values and the gray shaded area indicates the 5th and 95th percentiles of the adult values. Boxplots: median is represented by a horizontal line, and the IQR is represented by a box. The whiskers mark the largest and smallest values within 1.5 × IQR. Dots represent individual EBE values.

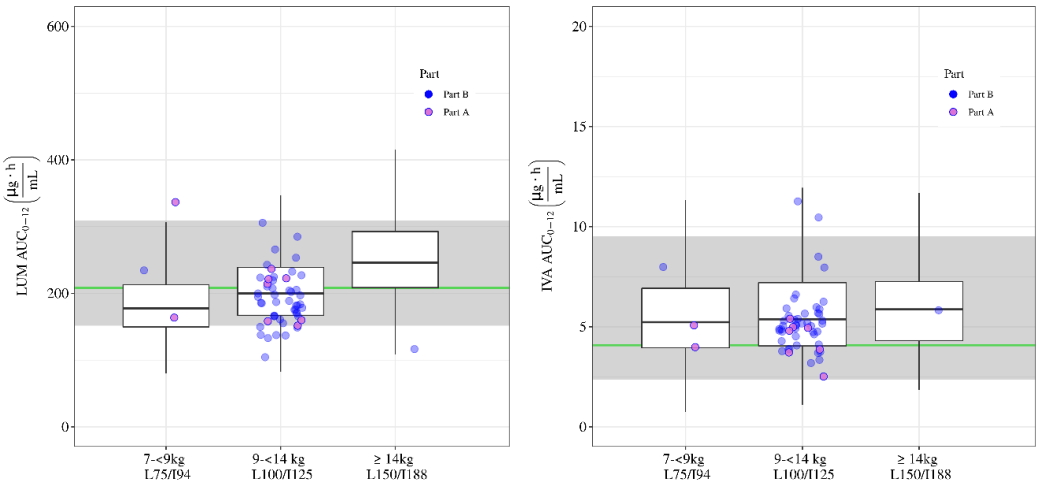
Overall, in subjects 12 to <24 months of age, the majority of LUM and IVA exposures were within the exposure range for subjects ≥18 years of age (gray shaded region) for each dose group.

Further available data in children < 9 kg:

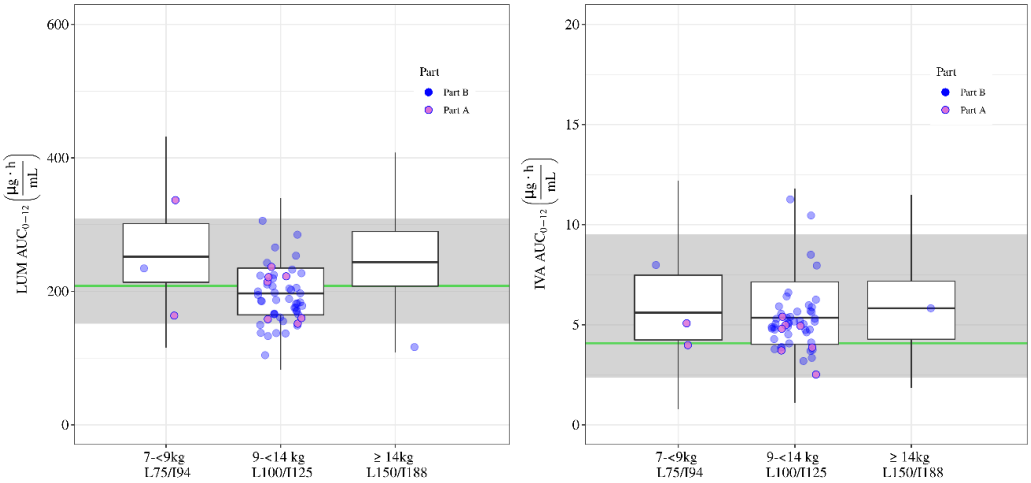
All available PK data for LUM/IVA in children weighing 7 to <9 kg were previously incorporated in the popPK models presented in Report R231. These data included 2 subjects in Part A and 1 subject in Part B, resulting in 3 total subjects in the weight group. The Part A data were not displayed in the final model outputs because the model outputs focused on Part B pharmacokinetic (PK) exposures. Data from the 2 children aged 1 to <2 years weighing 7 to <9 kg dosed in Part A are added to Figure 3 Panel A for the final models presented in Report R231.

Figure 3 **Predicted LUM (Left) and IVA (Right) $AUC_{0\text{-}12h}$ at Steady State for CF Subjects 12 to <24 Months of Age: Final Report R231 Models (Panel A) Versus Models With an Empirical Weight Adjustment for <9 kg Subjects (Panel B)**

Panel A: Final Report R231 Models



Panel B: Models With an Empirical Weight Adjustment for <9 kg Subjects



$AUC_{0\text{-}12}$ or $AUC_{0\text{-}12h}$: area under the concentration versus time curve from 0 to 12 hours; CF: cystic fibrosis; IQR: interquartile range; IVA: ivacaftor; LUM: lumacaftor; q12h: every 12 hours; WHO: World Health Organization

Notes: Individual data points representing predicted $AUC_{0\text{-}12h}$ are shown for subjects 12 to <24 months of age from Study 122 Part A (pink circles) and Part B (blue circles). Dose of LUM/IVA (L/I) given q12h is provided below each weight bound. Boxplots present exposures from simulated subjects based on the WHO growth charts. The median is represented by a horizontal line, and the IQR is represented by a box. The whiskers represent the largest and smallest values within 1.5 × IQR. Gray area in the left panels represents the 5th to 95th percentiles of LUM $AUC_{0\text{-}12h}$ exposures in the adult population receiving LUM 400 mg q12h.

For the lowest weight group (7-<9 kg), the predictions from the popPK model are generally consistent with the observed IVA PK exposures from the 3 subjects, whereas the LUM PK predictions are lower than the observed LUM PK exposures from these subjects 1 to <2 years of age weighing 7 to <9 kg, probably due to high variability in PK.

New analyses have been added to the modelling provided in the initial line extension submission for patients 1 to <2 years of age. These analyses evaluated if alternative models (i.e., different maturation functions or weight adjustments) might better fit the available data and whether or not those models support the proposed dosing regimen.

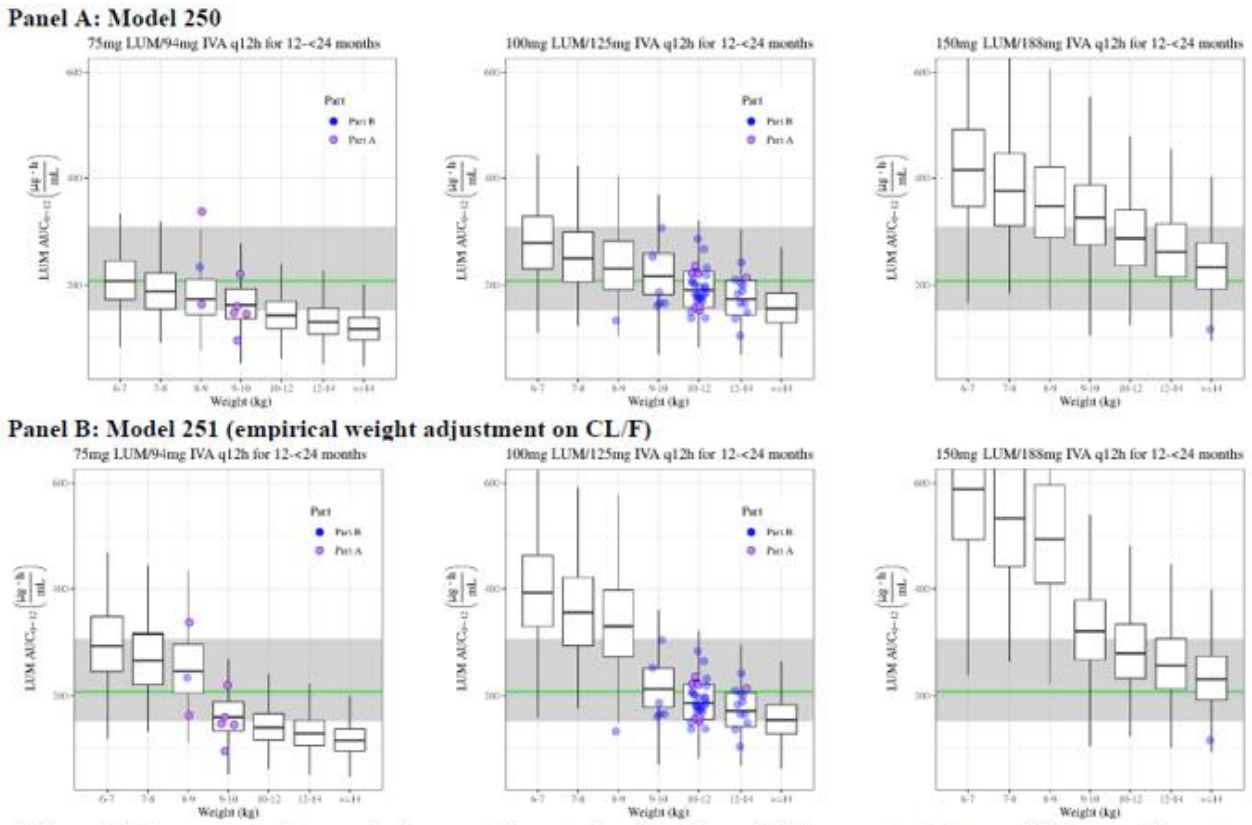
The results of this modelling demonstrated that:

1) Data from LUM/IVA treatment in subjects 1 to <2 years of age supports that ontogeny does not impact PK for this age group, suggesting that full CYP maturation is achieved by approximately 1 year of age. This is consistent with a fast maturation rate, as reported in the literature. The differences between the model predictions and the observed data for the 7 to <9 kg weight group (observed when plotted against weight but not against age) are not attributable to maturation effects not captured by the PK models.
2) The differences between the model predictions and the observed data for the 7 to <9 kg weight group were tried to be corrected with an empirical adjustment to the submitted models, although there is no physiological rationale for such an adjustment.
   In comparison to the final models from Report R231, this adjustment was shown to improve the OFV by 5.5 points for LUM and 2.4 points for IVA. Diagnostic plots for both the random effects of CL/F versus binned weight group improved for both LUM and IVA. Conditional weighted residuals (CWRES) plots stratified by weight group also improved for both LUM and IVA. Subsequently, the updated models (with weight empirical adjustment) were used to simulate the proposed dosing regimen for CF subjects 1 to <2 years of age as a sensitivity analysis to explore the impact of these adjustments on the predicted exposures for subjects weighing 7 to <9 kg. Similar to the predicted exposures from Report R231, the majority of the predicted exposures from the updated models for subjects weighing 7 to <9 kg were within the adult exposure range previously shown to be safe and efficacious (Figure 3).

According to the MAH, while empirical weight adjustments improved the diagnostics for both the LUM and IVA models, it is difficult to justify inclusion of these adjustments for several key reasons. First, the OFV improvements were modest at best, with neither adjustment being significant at the P<0.01 level. Second, there is no physiological rationale for why subjects weighing 7 to <9 kg would have additional altered clearance compared to heavier subjects beyond the effect of allometric scaling, especially as this altered clearance is not attributable to maturation. Furthermore, this adjustment introduces an unrealistic step-change in predicted LUM exposures upon crossing the 9 kg threshold as shown in Panel B of Figure 4.

The most reasonable explanation for the observed exposures for the 3 subjects in the 7 to <9 kg weight group is that these subjects are generally within the variability expected due to weight effects for the originally submitted models.

Figure 4 **LUM Simulated Steady-State $AUC_{0\text{-}12h}$ by Weight: Model 250 (Panel A) Versus Model 251 (Panel B)**



$AUC_{0\text{-}12}$ or $AUC_{0\text{-}12h}$: area under the concentration versus time curve from 0 to 12 hours; CL/F: apparent oral clearance; IQR: interquartile range; IVA: ivacaftor; LUM: lumacaftor; q12h: every 12 hours; WHO: World Health Organization

3) The most reasonable explanation for the differences between the model predictions and the observed data for the 7 to <9 kg weight group is that the PK are consistent with the submitted models, and the observed data are generally within the expected variability in PK for this weight group. This conclusion is supported by an assessment of the model predictability of steady-state AUC versus weight.

2.6.2.2. Pharmacodynamics

Please refer to section 2.6.5 Clinical efficacy for the evaluation of PD endpoints.

2.6.3. Discussion on clinical pharmacology

Study 122 is a phase 3, 2-part, Open-label Study to Evaluate the Safety and Pharmacokinetics of Lumacaftor/Ivacaftor in Subjects 1 to Less Than 2 Years of Age With Cystic Fibrosis, Homozygous for F508del consisting of two parts:

Part A to evaluate the PK and safety of LUM/IVA over 15 days of dosing.

Part B to evaluate the safety of LUM/IVA dosing over 24 weeks in this paediatric CF population.

The PK Set contained data for all subjects who received at least 1 dose of study drug, which included 7 subjects in Part A Cohort 1 (12 to <24 months), 7 subjects in Part A Cohort 2 (12 to <18 months), and 46 subjects in Part B (1-2 years).

Previously developed popPK modeling (Report P187 and Report Q052) were used to conduct simulations to determine the weight bounds that would achieve LUM and IVA exposures similar to the exposures observed in adult CF subjects in Part B of study 122. Report R230 included data from Part A from both Cohorts (18 to <24 months and 12 to <18 months) and a data cut through week 4 from

Part B of Study 122 (12 to <24 months). R231 Population PK study report is a continuation of the analysis presented in Report R230, and includes the final data from Study 122 Part B (all subjects 12 to <24 months through week 24). According to the MAH, simulations from PopPK R231 support the dose selection for Orkambi (LUM/IVA combination therapy) in subjects 12 to <24 months of age with cystic fibrosis (CF) homozygous for the *F508del* mutation.

In the final model R231 maturation effect has been considered consistent with a fast maturation rate, whereby according to the MAH the full maturation is achieved around 1 year of age. However, no data supporting this assumption was provided and literature data on ontogeny functions show that differences may exist (Lang et al., 2020 and Wildt et al., 1999). Therefore, the MAH was asked to better justify the assumption of a fast maturation in this age range. The MAH explained that the effect of maturation has been explored in the initial model R230, in which fast and slow maturation rates were analysed, but only the fast maturation effect was included in the model R231. In order to support the fast maturation rate in both R230 and R231 models, the MAH used maturation parameters fixed to values reported in the literature for gentamicin. The CHMP noted that gentamicin is mainly renally cleared with a negligible impact of hepatic elimination thus, questioning the adequacy of this substrate for the fast metabolism hypothesis also considering that data from literature (de Wildt et al, 1999) suggests that CYP3A4 approximately reaches 50% of adult levels between 6 and 12 months of age. Overall, data seems to suggest that weight has major impact on the PK variability as compared to age and therefore the issue was not further pursued by the CHMP.

Applying the corrected cut off of 7 to <**9** kg to phase A of study 122 (modified after a preliminary revision of data), only two subjects (8.9 kg and 8.1 kg both of 12 months of age) were enrolled. Thus, overall, only three patients (of which 2 in the phase A and 1 in the phase B of the study) in the above mentioned range have been studied. The predictive performance of the population pharmacokinetic models was considered hampered by the CHMP due to the limited number of patients in the lower weight subset. The MAH was asked to present any other available PK data for lumacaftor/ivacaftor in children weighing less than 9 kg, applying a full extrapolation to the under 9 kg subgroup and to define a bodyweight cut-off for the paediatric patient population >12 months of age.

In response, the MAH confirmed that there are no additional LUM/IVA data in children weighting 7 to <9kg. Only 3 children aged 1 to <2 years weighing 7 to <9 kg have been treated in the Study 122 (2 in Part A and 1 in Part B) and submitted the final model outputs showing also the 2 patients in Part A, previously excluded. The IVA exposure of these 2 patients is lower than that observed for the patient in Part B, however falls within the exposure in adults. For LUM, one patient in Part A showed lower exposure of that in Part B and falls within the adult exposure, while the other one showed higher exposure of that in Part B and falls outside the adult exposure.

In order to verify if this variability in exposure could be explained by a difference in weight, the MAH submitted further analyses with an empirical adjustment of weight on CL/F using the model R231. This adjustment slightly improves the OFV, diagnostic plots and CWRES for patients <9 kg, however, although the predicted exposure is still contained in that of adults, it is not possible to verify if the empirical adjustment of weight should be retained in the model (predicted exposures for subjects 7 to <9 kg cannot be considered reliable since it is based/verified only on three patients weighing 8-9 kg). Uncertainties remain regarding the unexplained variability in subjects weighting 7-9 kg difficult to be elucidated on the basis of only scarce observed data (3 patients).

Despite this consideration strictly related to PK variability in the younger patients and despite the very small numbers recruited for this age brackets (particularly for those in the 7-9kg weight bracket), considering the sufficiently known efficacy of LUM/IVA, and the relatively manageable safety profile to restrict use to those children over 9 kg is in effect delaying the start of treatment that would seem to be overly cautious. Therefore the CHMP agreed that further cut-off weight was not necessary. In

addition a study is planned in children aged from birth to 1 year (Study 19) the MAH will collect PK data in this study and submit them with an update of a popPK model when available, in agreement with the CHMP request.

Overall, exposures for both, LUM and IVA in Study 122 were within the exposure range for subjects ⩾ 18 years of age. The median AUC0-12h value for LUM in all 12 to <24 month subjects (185 µg • h/mL,) was close to the adult median. The median IVA exposure for all 12 to <24 months subjects (5.12 µg·h/mL) was slightly higher than the median IVA exposure in adult subjects, but it was comparable to IVA exposures from other paediatric age groups and well below the median exposure in subjects 12 to <24 months of age (8.9 µg·h/mL) receiving the IVA monotherapy dose of 50 mg q12h (Report N364). Mean LUM and IVA exposure by age group have been updated in section 5.2 of the SmPC.

Overall, the simulation results for LUM and IVA indicate that the studied regimen is appropriate for this age group.

Special population:

Since the effect of maturation observed in subjects 1 to <2 years of age was considered minimal and LUM and IVA exposures under the proposed dose regimens are predicted to be similar for subjects 1 to <2 years of age and subjects 2 through 5 years of age, the impact of hepatic impairment on the exposures for subjects 1 to <2 years of age are expected to be similar to that predicted for 2 through 5 years of age. Thus, the same dose adjustments are proposed for both age groups. Section 4.2 of the SmPC has been updated with recommendations also for 1 to <2 years subgroup, this was considered acceptable by the CHMP.

As the effect of maturation observed in subjects 1 to <2 years of age was considered minimal, recommendations for LUM/IVA dose adjustments for CF patients 1 to <2 years of age in the setting of CYP3A inhibition are consistent with those for CF patients from 2 through 5 years of age. Thus, the same recommendations are added in section 4.2 of the SmPC.

2.6.4. Conclusions on clinical pharmacology

Although some uncertainties remain on the modelling analysis pertaining to the age brackets 7-9 kg, these issues strictly related to PK are overcome by the sufficiently known efficacy and manageable safety profile of LUM/IVA. In addition the MAH committed to further develop and submit an update of the popPK model as new PK data become available from studies in younger cohorts.

The CHMP considered that the clinical pharmacology package was sufficient to support the following dosing recommendations in patients 1 to <2 years of age:

Dosing recommendations in patients aged 1 to <2 years

Age	Weight	Strength	Dose (every 12 hours)	
			Morning	Evening
1 to <2 years	7 kg to <9 kg	lumacaftor 75 mg/ivacaftor 94 mg	1 sachet	1 sachet
	9 kg to <14 kg	lumacaftor 100 mg/ivacaftor 125 mg	1 sachet	1 sachet
	≥14 kg	lumacaftor 150 mg/ivacaftor 188 mg	1 sachet	1 sachet

2.6.5. Clinical efficacy

Efficacy in the 1 to <2-years group is extrapolated from data from older populations of subjects. The main study in children 1 to <2 years, evaluated the Safety and Pharmacokinetics of Lumacaftor/Ivacaftor in patients With Cystic Fibrosis, Homozygous for F508del. PD data were assessed as a secondary objective in the second part of the study.

2.6.5.1. Main study

Study 122: A Phase 3, 2-part, Open-label Study to Evaluate the Safety and Pharmacokinetics of Lumacaftor/Ivacaftor in Subjects 1 to Less Than 2 Years of Age With Cystic Fibrosis, Homozygous for F508del.

Part A was designed to evaluate the PK and safety of LUM/IVA over 15 days of dosing. The evaluation of LUM/IVA as multiple doses allowed for the assessment of the time-dependent induction effect of LUM on the metabolism of IVA. The duration of dosing in Part A was selected to evaluate the PK and safety endpoints when the induction effect of LUM on the metabolism of IVA was anticipated to have reached steady state.

Part B was designed to evaluate the safety of LUM/IVA dosing over 24 weeks in this paediatric CF population. In addition, the PD effects and PK of multiple doses of LUM/IVA over 24 weeks of dosing were evaluated, and a 2-week Washout Period was included in order to evaluate the off-drug PD response.

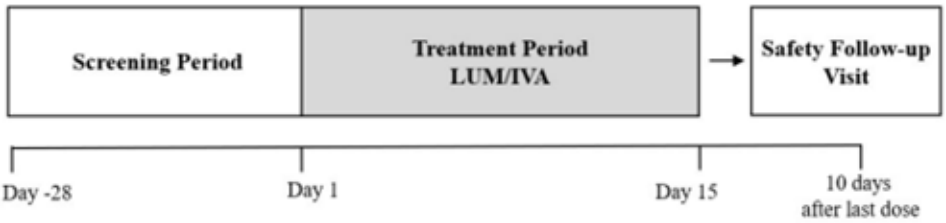
Part A

Two cohorts were enrolled sequentially in the following order:

- **Cohort 1**: subjects aged 18 to <24 months
- **Cohort 2**: subjects aged 12 to <18 months

A review of safety, tolerability, and available PK data was completed after each cohort to confirm the doses and weight bounds for Cohort 2 and Part B.

Figure 5 Part A Study Design



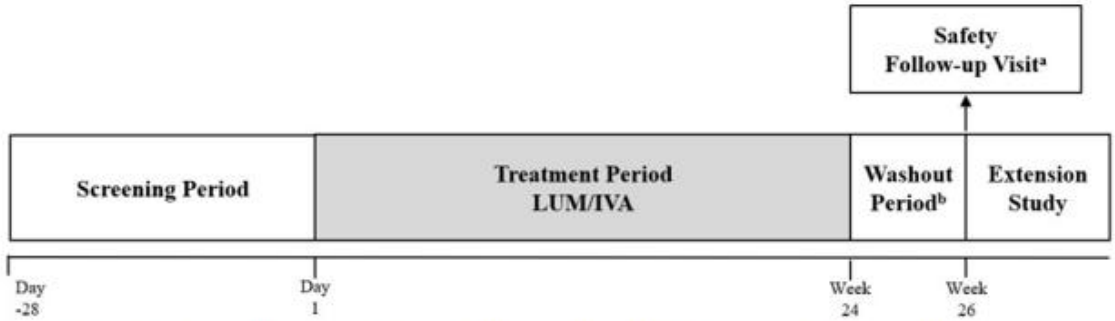
Source: Based on Appendix 16.1.1/Protocol Version 1.0/Figure 9-1 and Protocol Version 2.0/Figure 9-1
LUM/IVA: lumacaftor/ivacaftor

Part B

Subjects who completed Part B treatment could enroll in an optional open-label extension study (if they met the eligibility criteria for that study).

A lung clearance index (LCI) Substudy was conducted at 1 site.

Figure 6 Part B Study Design



Source: Based on Appendix 16.1.1/Protocol Version 1.0/Figure 9-2 and Protocol Version 2.0/Figure 9-2
LUM/IVA: lumacaftor/ivacaftor

[a] The Safety Follow-up Visit was scheduled to occur 2 weeks (± 4 days) after the last dose. For subjects who enrolled in the optional open-label extension study, this visit was the Day 1 Visit of the extension study.

[b] During the 2-week Washout Period (Week 24 to Safety Follow-up Visit [or Week 26 (± 4 days)], subjects did not receive LUM/IVA treatment.

Methods

- **Study Participants**

Main inclusion criteria

- Weight at the Screening Visit must have been within the weight limits as defined for the study drug dose levels or according to the dosing guidelines
- Subjects with confirmed diagnosis of CF at the Screening Visit. CF was defined as:
    - 2 CF-causing mutations (all as documented in the subject's medical record)
        - Subjects must have been homozygous for F508del (genotype confirmed at the Screening Visit): If a genotype test had been performed previously and was documented in the subject's medical record, the subject was not required to be tested for CFTR genotype at screening, but the subject's eligibility must have been approved by the Vertex medical monitor. If a historic genotype result was not available at the Screening Visit or if the historic genotype result was not approved by the Vertex medical monitor, the subject was tested for CFTR

genotype at the Screening Visit, and the results must have been reviewed before the first dose. Note: Newborn screening genotype results were not sufficient for eligibility.

AND (1 of the 2 criteria below)

- chronic sinopulmonary disease **OR** gastrointestinal/nutritional abnormalities

OR

- a SwCl value ≥60 mmol/L by quantitative pilocarpine iontophoresis as documented in the subject's medical record OR from the SwCl test result obtained at the Screening Visit. If an eligible historical SwCl result was documented in the subject's medical record, that result alone (and not the Screening Visit result) may have been used to determine eligibility.

- Subjects with stable CF disease as deemed by the investigator at the Screening Visit.

Main exclusion criteria

- History of any comorbidity reviewed at the Screening Visit that, in the opinion of the investigator, might have confounded the results of the study or posed an additional risk in administering LUM/IVA to the subject. For example, a history of cirrhosis with portal hypertension.
- Any clinically significant laboratory abnormalities at the Screening Visit
- Any of the following abnormal laboratory values at the Screening Visit: • Hemoglobin 9.5 g/dL ·Alanine transaminase (ALT), aspartate transaminase (AST), or total bilirubin 2 × upper limit of normal (ULN) • Chronic kidney disease of Stage 3 (estimated glomerular filtration rate [eGFR] <60 mL/min/1.73 m2 calculated by the Bedside Schwartz equation) based on the normal range for eGFR in this age group (62 to 191 mL/min/1.73 m2)
- An acute upper or lower respiratory infection, PEx, or changes in therapy (including antibiotics) for pulmonary disease within 28 days before Day 1 (first dose of LUM/IVA).
- A standard 12-lead ECG demonstrating QTc >450 msec at the Screening Visit. If QTc exceeded 450 msec at the Screening Visit, the ECG should have been repeated 2 more times during the Screening Period, and the average of the 3 QTc values should have been used to determine the subject's eligibility.
- History of solid organ or hematological transplantation.
- Ongoing or prior participation in an investigational drug study (including studies investigating LUM and/or IVA) within 30 days of the Screening Visit. • A Washout Period of 5 terminal half-lives of the previous investigational study drug, or 30 days, whichever was longer, must have elapsed before the Screening Visit. • The duration of the elapsed time may have been longer if required by local regulations.
- Use of restricted medication or food within specified duration before the first dose of LUM/IVA as defined in Appendix 16.1.1/Protocol Version 2.0/Section 9.4.
- History of cataract/lens opacity or evidence of cataract/lens opacity determined to be clinically significant by a licensed ophthalmologist during the OE at the Screening Visit. The Screening Visit OE did not need to be repeated if there was documentation of an examination meeting protocol criteria that was conducted within 3 months before the Screening Visit

- **Treatments**

LUM/IVA was administered to each Part A cohort or in Part B in accordance with the weight-based dosing regimens summarized in Table 6.

Table 6 Study 122 Doses

Study Part/Cohort (Age Group)	Weight Range at Screening	Dosing Regimen
Part A Cohort 1 (18 to <24 months)	10 to <14 kg	L100/I125 q12h
	≥14 kg	L150/I188 q12h
Part A Cohort 2 (12 to <18 months)	7 to <10 kg	L75/I94 q12h
	10 to <14 kg	L100/I125 q12h
	≥14 kg	L150/I188 q12h
Part B (12 to <24 months)	7 to <9 kg[a]	L75/I94 q12h
	9[a] to <14 kg	L100/I125 q12h
	≥14 kg	L150/I188 q12h

Sources: Appendix 16.1.1/Protocol Version 2.0/Figure 9-1 and Figure 9-2; Justification for Dose Selection Memorandum 2

PK: pharmacokinetics; popPK: population PK; q12h: every 12 hours

[a] During Part B, a review of safety and PK data in Part A (Cohorts 1 and 2) and a subset of subjects in Part B was completed and incorporated into the popPK models. The updated popPK models supported a decrease in the upper weight bound for the L75/I94 dose and the lower weight bound for the L100/I125 dose from 10 kg to 9 kg.

LUM/IVA was to be administered within 30 minutes of consumption of fat-containing food such as a standard CF high-fat, high-calorie meal or snack by the subject according to guidelines.

LUM/IVA was supplied as granules in a stick pack; details are shown in Table 7Table 7.

Table 7 Study Drug Information

Drug Name	Formulation/ Route	Batch/Lot Number	Packaging (Formulation Strength)	Storage Condition
LUM/IVA	Granules/ Oral	W051450 W051451	Supplied as 75-mg LUM/94-mg IVA granules in 1 stick pack	Store at ≤25°C (77°F) with excursions to 30°C (86°F)
LUM/IVA	Granules/ Oral	W040284 W043806 W051090	Supplied as 100-mg LUM/125-mg IVA granules in 1 stick pack	Store at ≤25°C (77°F) with excursions to 30°C (86°F)
LUM/IVA	Granules/ Oral	W040396 W043805 W051092	Supplied as 150-mg LUM/188-mg IVA granules in 1 stick pack	Store at ≤25°C (77°F) with excursions to 30°C (86°F)

Source: Appendix 16.1.6 and Appendix 16.1.1/Protocol Version 2.0/Table 10-1

IVA: ivacaftor; LUM: lumacaftor

Part B: The duration of 24 weeks provides an adequate assessment of safety in this population.

- **Objectives**

Primary Objectives

Part A

To evaluate the PK of LUM/IVA in subjects 1 to <2 years of age with CF, homozygous for F508del

Part B

To evaluate the safety of LUM/IVA in subjects 1 to <2 years of age with CF, homozygous for F508del

Secondary Objectives

Part A

- To evaluate the safety of LUM/IVA in subjects 1 to <2 years of age with CF, homozygous for F508del
- To evaluate the PK of the metabolites of LUM and IVA in subjects 1 to <2 years of age with CF, homozygous for F508del

Part B

- To evaluate the pharmacodynamics (PD) of LUM/IVA in subjects 1 to <2 years of age with CF, homozygous for F508del
- To evaluate the PK of LUM and IVA and their respective metabolites in subjects 1 to <2 years of age with CF, homozygous for F508del

Outcomes/endpoints

Part A

Pharmacokinetic assessments: Plasma concentrations of LUM, M28-LUM, IVA, M1-IVA, and M6-IVA.

Part B

PD endpoints are reported in the Table 8 below:

Table 8 Study 122 Part B: PD/Efficacy Endpoints and Statistical Analysis Methods

Endpoint (Data Set/Analysis Set)	Method of Analysis
Secondary PD Endpoints	
Absolute change from baseline in SwCl at Week 24 (FAS)	Descriptive summary statistics, 95% CI
Additional PD Endpoints	
Absolute change in SwCl from Week 24 at Week 26 (FAS)	Descriptive summary statistics, 95% CI
Absolute change from baseline in weight-for-length z-score, BMI-for-age z-score, BMI, weight-for-age z-score, weight, length-for-age z-score, and length at Week 24 (FAS)	Descriptive summary statistics, 95% CI
Absolute change from baseline in FE-1 levels at Week 24 (FAS)	Descriptive summary statistics, 95% CI
Absolute change from baseline in serum IRT levels at Week 24 (FAS)	Descriptive summary statistics, 95% CI
Absolute change from baseline in fecal calprotectin levels at Week 24 (FAS)	Descriptive summary statistics, 95% CI
Number of PEx and CF-related hospitalizations through Week 24 (FAS)	Summary of number of events through Week 24 (inclusive) normalized by the time spent in the study
Change from baseline in microbiology cultures at Week 24 (FAS)	Descriptive summary statistics
Absolute change from baseline in LCI at Week 24 (LCI Substudy Set)	Individual subject data listing
Acceptability/palatability of LUM/IVA granules at Day 1 (FAS)	Descriptive summary statistics

Source: Appendix 16.1.1/Protocol Version 2.0 and Appendix 16.1.9/SAP Version 2.0
BMI: body mass index; CF: cystic fibrosis; FAS: Full Analysis Set; FE-1: fecal elastase-1; IRT: immunoreactive trypsin; IVA: ivacaftor; LCI: lung clearance index; LUM: lumacaftor; PD: pharmacodynamics; SwCl: sweat chloride

Lipase and amylase were collected as part of safety assessments. The results are discussed with the other PD assessments relating to pancreatic function because they are useful indicators of pancreatic inflammation/injury. Only descriptive analysis of safety was performed.

- **Sample size**

Part A Approximately 10 subjects were planned for enrollment. No formal sample size calculations were performed. The number of subjects in Part A is common in clinical pharmacology studies and was considered sufficient to achieve the PK objectives of Part A.

Part B Approximately 30 subjects were planned for enrollment. Assuming a 10% dropout rate, approximately 27 subjects were to complete Part B. No formal sample size calculations were performed. The number of subjects in Part B was deemed adequate to meet the primary safety objective.

- **Randomisation and Blinding (masking)**

N/A

- **Statistical methods**

Analysis Sets

The analysis sets were defined separately for Parts A and B.

All Subjects Set was defined as all subjects who signed informed consent and enrolled, or were dosed, in Part A or Part B respectively. This analysis set was used for all individual subject data listings and the disposition summary table, unless specified otherwise.

Safety Set for Part A included all subjects who received at least 1 dose of study drug in Part A. The Part A safety analyses were based on the Safety Set overall and by cohort, unless otherwise specified.

Safety Set for Part B included all subjects who received at least 1 dose of study drug in Part B. The Part B safety analyses were based on the Safety Set overall, unless otherwise specified.

Full Analysis Set (FAS, Part B only) included all enrolled subjects in Part B who were exposed to any amount of study drug in Part B. PD analyses (except LCI) were based on the FAS.

LCI Substudy Set (Part B only) included all subjects who signed informed consent to the optional LCI Substudy in Part B and enrolled and dosed in Part B. LCI-related analyses were based on the LCI Substudy Set.

Results

- **Participant flow**

A total of 46 subjects were enrolled and received at least 1 dose of study drug in Part B; subjects 18 to <24 months of age (N = 25) were enrolled first, followed by enrolment of subjects 12 to <18 months of age (N = 21). Subject disposition data are presented in Table 9.

Table 9 Subject Disposition, All Subjects Set, Part B

Disposition	Total n (%)
All Subjects Set	47
Safety Set (dosed)	46
Full Analysis Set (enrolled and dosed)	46
Enrolled but not dosed[a]	1
Completed treatment	45 (97.8)
Discontinued treatment	1 (2.2)
Reason for discontinuation of treatment	
AE	1 (2.2)
Completed study	43 (93.5)
Discontinued study	3 (6.5)
Reason for discontinuation from study	
AE	1 (2.2)
Withdrawal of consent (not due to AE)	1 (2.2)
Other	1 (2.2)
Rolled over to extension study	
Yes	40 (87.0%)
No	6 (13.0%)

Source: Table 14.1.1b
AE: adverse event; n: size of subsample;
Notes: The All Subjects Set included all subjects who signed informed consent and enrolled, or dosed, in Part B. The Safety Set included all subjects who received at least 1 dose of study drug in Part B. The Full Analysis Set included all enrolled subjects who were exposed to any amount of study drug in Part B. Percentages were calculated relative to the number of subjects in the Safety Set. Number of subjects who completed study includes those who completed the Safety Follow-up Visit, as applicable.
[a] This subject turned 2 years of age by Day 1 and did not meet eligibility requirements (Section 10.2.6).

- **Recruitment**

Study initiation: 07 September 2018 (date first eligible subject in Cohort 1 signed the informed consent form for Part A)

Study completion: 29 October 2021 (date last subject completed the last visit in Part B)

- **Conduct of the study**

In Version 2.0 (04 December 2019), the following key changes were included:

- Updated the planned dosing regimen based on the PK results from Part A Cohort 1 as follows:
  - Added a lower dose of LUM 75 mg/IVA 94 mg for subjects who weighed 7 to <10 kg at screening for Part A and Part B.
  - Updated the lower weight bound from 8 kg to 10 kg for the LUM 100 mg/IVA 125 mg dose in Part B.
- Added the additional endpoint for absolute change from baseline in weight-for-length z-score at Week 24 for Part B.

In addition, 2 Justification for Dose Selection Memoranda were implemented to communicate updated dosing regimens after review of available PK data and the updated popPK models, as summarized in Table 10.

Table 10 Updates to Dosing regimen During Study Conduct

Memorandum or Protocol Version	Updates to Dosing Regimen	Affected Cohorts/Parts	Updated Dosing Regimen	
			Doses	Weight at Screening
Justification for Dose Selection Memorandum 1[a]	Updated the lower weight bound for the L100/I125 dose from 8 kg to 10 kg	Part B (subjects 18 to <24mo)	L100/I125 q12h L150/I188 q12h	10 to <14 kg ≥14 kg
Protocol Version 2.0[a]	• Added a lower dose of L75/I94 for subjects 7 to <10 kg • Updated the lower weight bound for the L100/I125 dose from 8 kg to 10 kg (for Part B)	Part A Cohort 2; Part B (subjects 18 to <24mo)	L75/I94 q12h L100/I125 q12h L150/I188 q12h	7 to <10 kg 10 to <14 kg ≥14 kg
Justification for Dose Selection Memorandum 2[b]	Updated the weight bound between L75/I94 and L100/I125 from 10 kg to 9 kg	Part B (subjects 12 to <24mo)	L75/I94 q12h L100/I125 q12h L150/I188 q12h	7 to <9 kg 9 to <14 kg ≥14 kg

Source: Appendix 16.1.1/Protocol Version 2.0/Figure 9-1 and Figure 9-2; Justification for Dose Selection Memorandum 1 and 2

I: ivacaftor; L: lumacaftor; mo: months old; q12h: once every 12 hours

[a] Updated dosing regimen was based on a review of the safety and PK data from Cohort 1 Part A and incorporation of the PK data into the popPK models.

[b] Updated dosing regimen was based on a review of safety and PK data in Part A (Cohorts 1 and 2) and a subset of subjects in Part B (subjects 18 to <24 months old through Week 12) and incorporation of the PK data into the popPK models.

- **Baseline data**

Table 11 Subject Demographics, Safety Set, Part B

Characteristic	Total N = 46
Sex, n (%)	
Male	22 (47.8)
Female	24 (52.2)

Table 12 Subject Demographics, Safety Set, Part B

Characteristic	Total N = 46
Age at baseline (months)	
n	46
Mean (SD)	18.1 (3.5)
Median	18.5
Min, max	12, 23
Age group at baseline	
12 to <18 months	21 (45.7)
18 to <24 months	25 (54.3)
Race, n (%)	
White	36 (78.3)
Black or African American	1 (2.2)
Asian	1 (2.2)
American Indian or Alaska Native	3 (6.5)
Native Hawaiian or Other Pacific Islander	1 (2.2)
Not collected per local regulations	7 (15.2)
Other	1 (2.2)
Ethnicity, n (%)	
Hispanic or Latino	2 (4.3)
Not Hispanic or Latino	37 (80.4)
Not collected per local regulations	7 (15.2)

Source: Table 14.1.2b
n: size of subsample; N: total sample size
Notes: Age at baseline was defined as age at Day 1. If a subject was reported to have multiple races, then the subject was counted under each reported race. Percentages are calculated relative to the number of subjects in the Safety Set.

Table 13 Baseline Characteristics, Safety Set, Part B

Characteristic	Total N = 46
Dosing group at enrollment	
LUM 75 mg/IVA 94 mg q12h	1 (2.2)
LUM 100 mg/IVA 125 mg q12h	44 (95.7)
LUM 150 mg/IVA 188 mg q12h	1 (2.2)
Weight (kg)	
n	46
Mean (SD)	11.3 (1.3)
Median	11.4
Min, max	8.6, 15.2

Table 14 Baseline Characteristics, Safety Set, Part B

Characteristic	Total N = 46
Length (cm)	
n	46
Mean (SD)	81.1 (4.1)
Median	81.2
Min, max	71.2, 89.0
BMI (kg/m^2)	
n	46
Mean (SD)	17.17 (1.22)
Median	17.04
Min, max	14.78, 20.94
Weight-for-age z-score	
n	46
Mean (SD)	0.46 (0.79)
Median	0.51
Min, max	-0.85, 3.01
Length-for-age z-score	
n	46
Mean (SD)	-0.25 (0.97)
Median	-0.19
Min, max	-2.95, 1.55
Weight-for-length-for-age z-score	
n	46
Mean (SD)	0.79 (0.77)
Median	0.68
Min, max	-0.57, 3.22

Source: Table 14.1.3b

BMI: body mass index; IVA: ivacaftor; LUM: lumacaftor; n: size of subsample; N: total sample size; q12h: every 12 hours

Notes: Baseline was defined as the most recent non-missing measurement before the first dose of study drug in Part B. Dosing group at enrollment was based on weight at screening. Percentages are calculated relative to the number of subjects in the Safety Set. BMI: Body Mass Index = Weight/(Length × Length) (kg/m^2).

Table 15 Medical History That Occurred in At Least 20% Subjects Overall, Safety Set, Part B

Condition (Preferred Term)	Total N = 46 n (%)
Subjects with any medical history	46 (100.0)
Pancreatic failure	46 (100.0)
CF lung[a]	44 (95.7)
Gastrooesophageal reflux disease	11 (23.9)

Source: Table 14.1.4b
CF: cystic fibrosis; n: size of subsample; N: total sample size; PT: Preferred Term
Notes: A subject with multiple conditions within a PT was counted only once within the PT. Medical history events were coded with MedDRA Version 24.1.
[a] CF lung indicates clinical manifestation of CF lung disease. Age of onset of CF lung disease varies.

Concomitant medications

The most commonly reported concomitant medications were pancreatin (67.4%), salbutamol (60.9%), sodium chloride (58.7%), dornase alfa (54.3%), multivitamins (34.8%), pancrelipase (32.6%), and paracetamol (32.6%).

Prior medication (only up to 10% of subjects)

Table 16 Prior Medications by Preferred Name safety Set Part B

Preferred Name	Total N = 46 n (%)
Subjects with any prior medication	46 (100.0)
PANCREATIN	30 (65.2)
SALBUTAMOL	27 (58.7)
SODIUM CHLORIDE	27 (58.7)
DORNASE ALFA	21 (45.7)
ASCORBIC ACID;BETACAROTENE;BIOTIN;CALCIUM PANTOTHENATE; COLECALCIFEROL;CYANOCOBALAMIN;FOLIC ACID;NICOTINAMIDE; PHYTOMENADIONE;PYRIDOXINE HYDROCHLORIDE;RETINOL PALMITATE;RIBOFLAVIN;THIAMINE MONONITRATE;TOCOPHEROL; ZINC ASCORBATE	16 (34.8)
PANCRELIPASE	15 (32.6)
VITAMINS NOS	12 (26.1)
BETACAROTENE;BIOTIN;CALCIUM PANTOTHENATE;COLECALCIFEROL; CYANOCOBALAMIN;DL-SELENOMETHIONINE;FOLIC ACID; NICOTINAMIDE;PHYTOMENADIONE;PYRIDOXINE HYDROCHLORIDE; RIBOFLAVIN;SODIUM ASCORBATE;THIAMINE MONONITRATE; TOCOPHEROL;TOCOPHEROLS MIXED;UBIDECARENONE;ZINC SULFATE	11 (23.9)
COLECALCIFEROL	10 (21.7)
MACROGOL 3350	9 (19.6)
SALBUTAMOL SULFATE	6 (13.0)
VITAMIN D NOS	6 (13.0)
OMEPRAZOLE	5 (10.9)
PARACETAMOL	5 (10.9)

- **Numbers analysed**

14 subjects in part A and 46 in part B

- **Outcomes and estimation**

PD data provides information used to support efficacy of IVA/LUM.

Primary endpoint: n/a

Secondary endpoint

Absolute Change in SwCl at week 24

Change from baseline through Week 24: this was an additional prespecified analysis

It was defined as the average of SwCl measurements at Week 4, Week 12, and Week 24.

Table 17 Absolute Change From Baseline in Sweat Chloride (mmol/L) by Visit, FAS, Part B

		Total N = 46	
Visit	Statistic	Sweat Chloride (mmol/L)	Absolute Change From Baseline at Visit (mmol/L)
Baseline	n	35	--
	Mean (SD)	104.2 (7.7)	--
	Median	105.0	--
	Min, max	87.0, 117.0	--
	95% CI	(101.5, 106.8)	--
Week 4	n	38	32
	Mean (SD)	72.9 (12.5)	-30.4 (13.2)
	Median	72.0	-28.3
	Min, max	42.5, 100.0	-56.0, -8.5
	95% CI	(68.8, 77.0)	(-35.1, -25.6)
Week 12	n	38	33
	Mean (SD)	69.7 (15.9)	-32.3 (17.2)
	Median	71.3	-30.0
	Min, max	45.0, 104.5	-60.5, 1.5
	95% CI	(64.5, 74.9)	(-38.4, -26.2)

Table 18 Absolute Change From Baseline in Sweat Chloride (mmol/L) by Visit, FAS, Part B

		Total N = 46	
Visit	Statistic	Sweat Chloride (mmol/L)	Absolute Change From Baseline at Visit (mmol/L)
Week 24[a]	n	29	24
	Mean (SD)	73.1 (13.9)	-29.1 (13.5)
	Median	75.0	-29.8
	Min, max	41.0, 99.0	-51.5, -3.0
	95% CI	(67.8, 78.4)	(-34.8, -23.4)
Through Week 24[b]	n	42	35
	Mean (SD)	71.9 (11.8)	-31.3 (13.0)
	Median	71.8	-29.0
	Min, max	49.0, 98.0	-53.7, -8.8
	95% CI	(68.2, 75.6)	(-35.8, -26.9)
Week 26[c]	n	27	25
	Mean (SD)	100.8 (9.7)	-3.5 (11.8)
	Median	99.5	-5.0
	Min, max	81.0, 130.0	-20.5, 28.0
	95% CI	(96.9, 104.6)	(-8.3, 1.4)
Change from Week 24 at Week 26[b]	n	--	21
	Mean (SD)	--	27.3 (11.1)
	Median	--	28.5
	Min, max	--	10.5, 51.0
	95% CI	--	(22.3, 32.3)

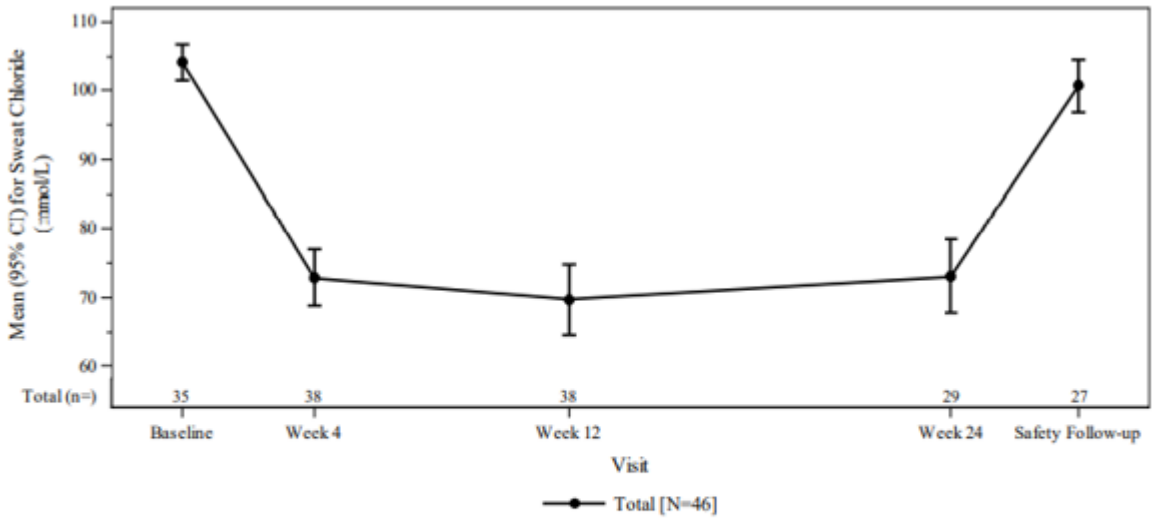
Sources: Tables 14.2.1.1b and 14.2.1.2b
FAS: Full Analysis Set; n: size of subsample; N: total sample size; SwCl: sweat chloride
Notes: Baseline SwCl was defined as the average of the values at screening and the pretreatment measurement on Day 1. If only 1 pre-first dose measurement was available, that measurement was considered the baseline. The absolute changes from baseline in SwCl were calculated at each time point for subjects in Part B that had both a baseline value and a value at that time point. The 95% CI are based on the t-distribution.

[a] Absolute change from baseline in SwCl at Week 24 was a secondary endpoint.

[b] Absolute change in SwCl from Week 24 at Week 26 was an additional endpoint. Absolute change from baseline in SwCl through Week 24 was an additional analysis. . Through Week 24 was defined as the average of SwCl measurements at Week 4, Week 12, and Week 24.

[c] The Week 26 Visit was also the Safety Follow-up Visit.

Figure 7 Mean (95% CI) for Sweat Chloride (mmol/L) at Each Visit,FAS, Part B



Source: Figure 14.2.1.1b
FAS: Full Analysis Set; SwCl: sweat chloride
Notes: Baseline sweat chloride was defined as the average of the values at screening and the pretreatment measurement on Day 1. If only 1 pre-first dose measurement was available, that measurement was considered the baseline. Analysis included both on-treatment measurements and measurements after treatment discontinuation (Washout Period). The 95% CI are based on the t-distribution.

Absolute Change From Baseline in BMI, Weight, Length, Associated Z-scores, and Weight-for-length Z-score at Week 24

Table 19 Absolute Change From Baseline in Growth Parameters at Week 24, FAS, Part B

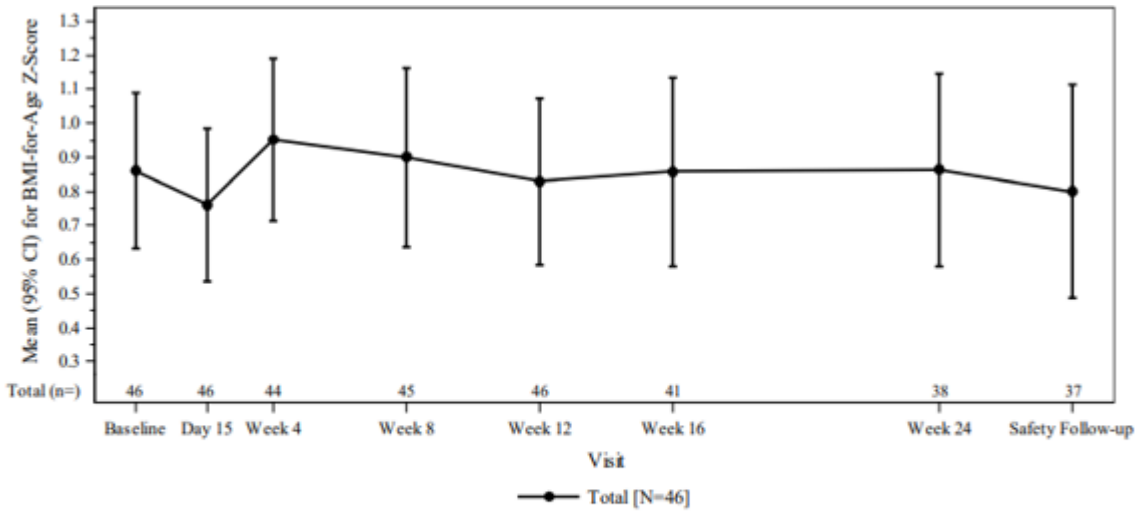
Parameter Statistic	Total N = 46 Baseline	Absolute Change From Baseline at Week 24
BMI-for-age Z-score		
n	46	38
Mean (SD)	0.86 (0.77)	0.04 (0.55)
Median	0.75	0.05
Min, max	-0.52, 3.07	-1.02, 1.35
95% CI	(0.63, 1.09)	(-0.14, 0.22)
BMI (kg/m²)		
n	46	38
Mean (SD)	17.17 (1.22)	-0.20 (0.84)
Median	17.04	-0.23
Min, max	14.78, 20.94	-1.91, 1.64
95% CI	(16.81, 17.54)	(-0.47, 0.08)
Weight-for-length Z-score		
n	46	38
Mean (SD)	0.79 (0.77)	0.04 (0.53)
Median	0.68	0.07
Min, max	-0.57, 3.22	-1.02, 1.26
95% CI	(0.56, 1.01)	(-0.13, 0.22)
Weight-for-age Z-score		
n	46	38
Mean (SD)	0.46 (0.79)	0.06 (0.33)
Median	0.51	0.04
Min, max	-0.85, 3.01	-0.50, 0.96
95% CI	(0.23, 0.70)	(-0.05, 0.17)

Table 20 Absolute Change From Baseline in Growth Parameters at Week 24, FAS, Part B

Parameter Statistic	Total N = 46 Baseline	Total N = 46 Absolute Change From Baseline at Week 24
Weight (kg)		
n	46	38
Mean (SD)	11.3 (1.3)	1.3 (0.6)
Median	11.4	1.3
Min, max	8.6, 15.2	0.5, 3.5
95% CI	(10.9, 11.7)	(1.1, 1.5)
Length-for-age Z-score		
n	46	38
Mean (SD)	-0.25 (0.97)	0.07 (0.52)
Median	-0.19	0.04
Min, max	-2.95, 1.55	-0.99, 1.21
95% CI	(-0.54, 0.03)	(-0.11, 0.24)
Length (cm)		
n	46	38
Mean (SD)	81.1 (4.1)	5.1 (1.7)
Median	81.2	5.1
Min, max	71.2, 89.0	2.0, 9.4
95% CI	(79.9, 82.4)	(4.5, 5.7)

Source: Tables 14.2.2.1.1b, 14.2.2.1.2b, 14.2.2.1.3b, 14.2.2.2.1b, 14.2.2.2.2b, 14.2.2.3.1b, and 14.2.2.3.2b
BMI: body mass index; FAS: Full Analysis Set; n: size of subsample; N: total sample size
Notes: Baseline was defined as the most recent non-missing measurement before the first dose of study drug in Part B. BMI = Weight/(Height × Height) (kg/m^2). Z-scores were calculated using World Health Organization (WHO) Child Growth Standards for children 0 to 24 months of age. The 95% CI are based on the t-distribution.

Figure 8 Mean (95% CI) for BMI-for-age Z-score at Each Visit, FAS, Part B

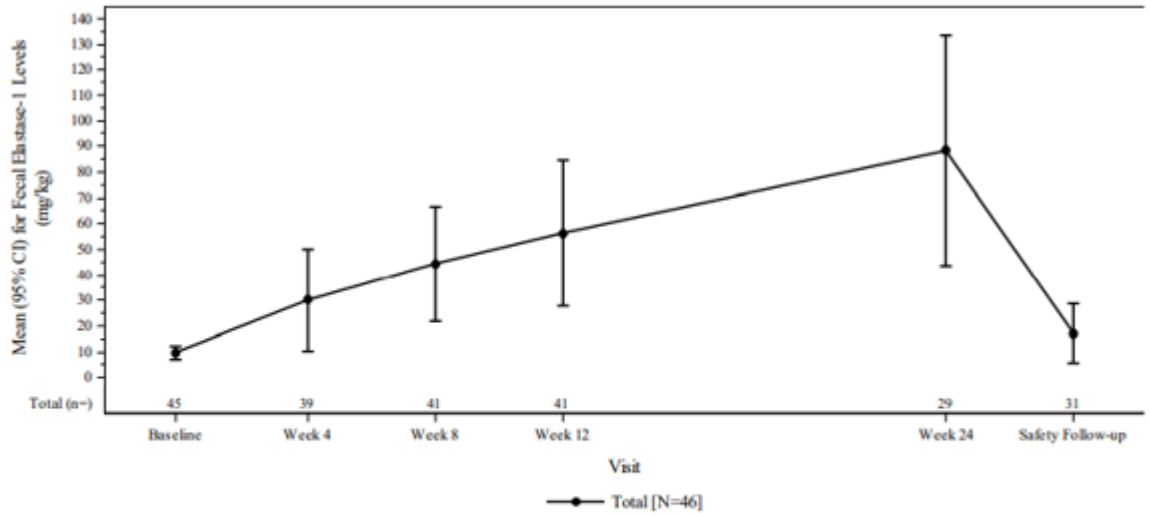


Source: Figure 14.2.2.1.2b
BMI: body mass index; FAS: Full Analysis Set; n: size of subsample; N: total sample size
Notes: Baseline was defined as the most recent non-missing measurement before the first dose of study drug in Part B. Analysis included both on-treatment measurements and measurements after treatment discontinuation (Washout Period). The 95% CI are based on the t-distribution.

Markers of Pancreatic Function and Inflammation

Absolute Change From Baseline in FE-1 Levels at Week 24.

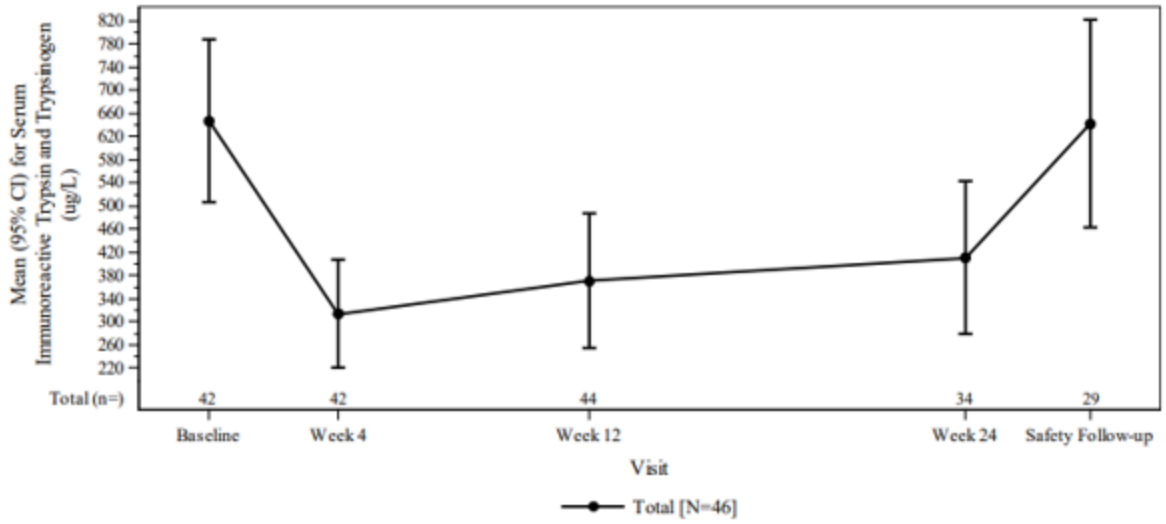
Figure 9 Mean (95% CI) for FE-1 at Each Visit, FAS, Part B



Source: Figure 14.2.3.1b
FAS: Full Analysis Set; FE-1: fecal elastase-1; n: size of subsample; N: total sample size
Notes: Baseline was defined as the most recent non-missing measurement before the first dose of study drug in Part B. Analysis included both on-treatment measurements and measurements after treatment discontinuation (Washout Period). The 95% CI are based on the t-distribution.

Absolute Change From Baseline in Serum IRT Levels at Week 24

Figure 10 Mean (95% CI) for Serum IRT Levels at Each Visit, FAS, Part B

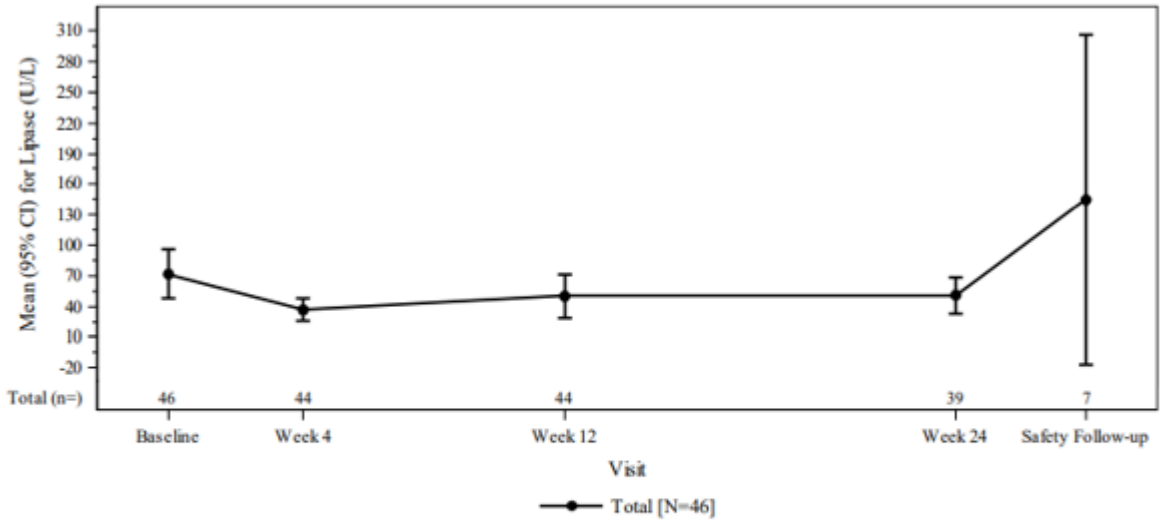


Source: Figure 14.2.5.1b
FAS: Full Analysis Set; IRT immunoreactive trypsin and trypsinogen; n: size of subsample; N: total sample size
Notes: Baseline was defined as the most recent non-missing measurement before the first dose of study drug in Part B. Analysis included both on-treatment measurements and measurements after treatment discontinuation (Washout Period). The 95% CI are based on the t-distribution.

Lipase and Amylase Lipase and amylase levels were collected as part of the safety assessments. The results are discussed with the other PD assessments relating to pancreatic function because they are useful indicators of pancreatic inflammation/injury.

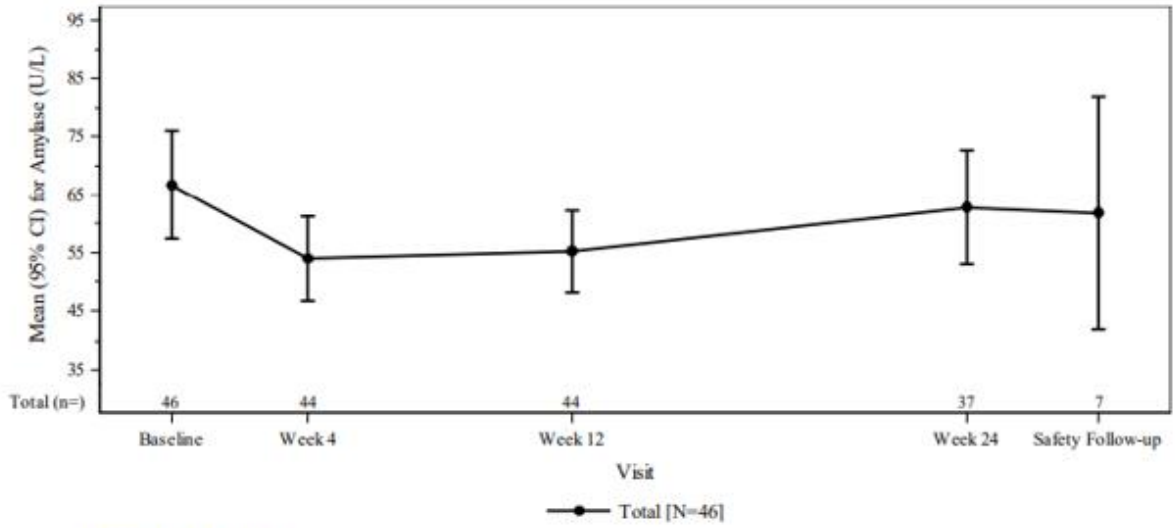
Both total amylase and pancreatic amylase levels were assessed.

Figure 11 Mean (95% CI) for Lipase Levels at Each Visit, Safety Set, Part B



Source: Figure 14.3.4.2.1b
n: size of subsample; N: total sample size
Notes: Baseline was defined as the most recent non-missing measurement before the first dose of study drug in Part B. Analysis included both on-treatment measurements and measurements after treatment discontinuation (Washout Period). The 95% CI are based on the t-distribution.

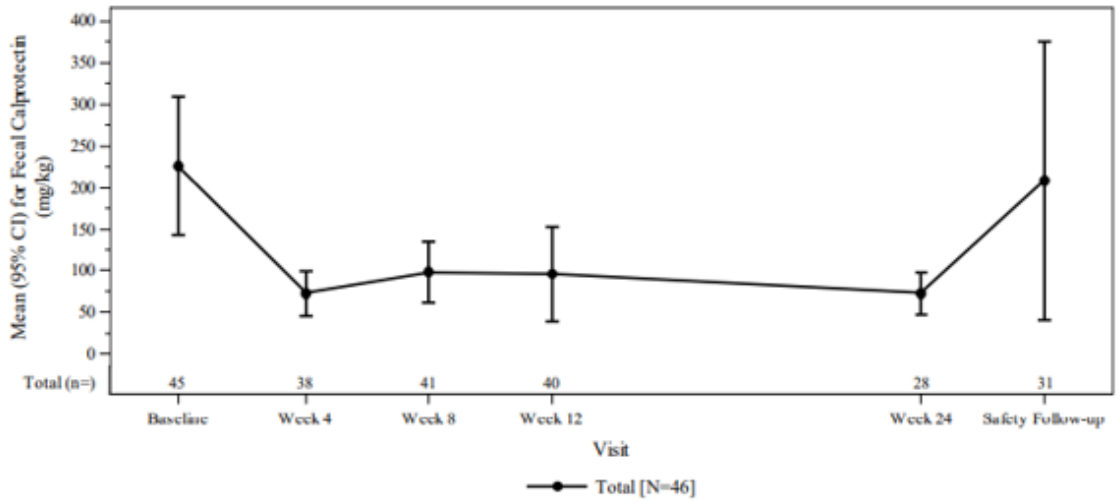
Figure 12 Mean (95% CI) for Total Amylase Levels at Each Visit, Safety Set, Part B



Source: Figure 14.3.4.1.1b
n: size of subsample; N: total sample size
Notes: Baseline was defined as the most recent non-missing measurement before the first dose of study drug in Part B. Analysis included both on-treatment measurements and measurements after treatment discontinuation (Washout Period). The 95% CI are based on the t-distribution.

Absolute Change From Baseline in Fecal Calprotectin Levels at Week 24

Figure 13 Mean (95% CI) for Fecal Calprotectin (mg/Kg) at Each Visit, FAS, Part B



Source: Figure 14.2.4.1b
n: size of subsample; N: total sample size
Notes: Baseline was defined as the most recent non-missing measurement before the first dose of study drug in Part B. Analysis included both on-treatment measurements and measurements after treatment discontinuation (Washout Period). The 95% CI are based on the t-distribution.

Number of PEx and CF-related Hospitalizations Through Week 24

Table 21 Number of PEx and CF-related Hospitalizations Through Week 24, FAS, Part B

Category	Total N = 46
Number of PEx through Week 24	
Number of subjects with events, n (%)	9 (19.6)
Total number of events	15
Total number of days (years) on study	7806 (23.2)
Number of PEx through Week 24, normalized by total number of years on study (rate per patient-year)	
Mean (SD)	0.6 (1.5)
Median	0.0
Min, max	0.0, 6.0

Table 22 Number of PEx and CF-related Hospitalizations Through Week 24, FAS, Part B

Category	Total N = 46
Number of CF-related hospitalizations through Week 24	
Number of subjects with events, n (%)	3 (6.5)
Total number of events	4
Total number of days (years) on study	7806 (23.2)
Number of CF-related hospitalizations through Week 24, normalized by total number of years on study (rate per patient-year)	
Mean (SD)	0.2 (0.7)
Median	0.0
Min, max	0.0, 4.0

Source: Table 14.2.6b

CF: cystic fibrosis; FAS: Full Analysis Set; n: size of subsample; N: total sample size; PEx: pulmonary exacerbations

Notes: Total number of days on study = Sum of (number of days on study across all subjects in the FAS, where number of days on study = Week 24 date - first dose date in Part B + 1 for each subject. Number of PEx/CF-related hospitalizations through Week 24, normalized by the total number of years on study = number of events / total number of years on study, for each subject. Total number of years on study = total number of days on study / 336. A subject with no events has 0 events/patient-year after normalization.

Change From Baseline in Microbiology Cultures at Week 24

Samples were tested for the following bacterial species: Burkholderia, Haemophilus influenzae, methicillin-resistant Staphylococcus aureus, methicillin-susceptible Staphylococcus aureus, mucoid Pseudomonas aeruginosa, non-mucoid Pseudomonas aeruginosa, small colony variant Pseudomonas aeruginosa, and Stenotrophomonas maltophilia.

Overall, no notable changes in microbiology cultures were observed between baseline and Week 24. The most commonly isolated organism was methicillin-susceptible S. aureus; between 33.3% and 38.9% of subjects had positive cultures for methicillin-susceptible S. aureus over the study duration.

Absolute Change From Baseline in LCI at Week 24

This was a substudy, however only 1 subject for 1 measurement was enrolled therefore no conclusion could be made.

Acceptability/Palatability of LUM/IVA Granules at Day 1

Table 23 Summary of Acceptability/Palatability at Day 1, FAS, Part B

	Total N = 46 n (%)	
Reaction of Subject[a]	Food Only	Food With Study Drug
Liked it very much	27 (58.7)	17 (37.0)
Liked it a little	12 (26.1)	5 (10.9)
Not sure	4 (8.7)	12 (26.1)
Disliked it a little	0	7 (15.2)
Disliked it very much	2 (4.3)	4 (8.7)

Source: Table 14.2.8b

FAS: Full Analysis Set; n: size of subsample; N: total sample size

[a] Reaction of the subject was assessed by the investigator in consultation with the subject's parent/legal guardian according to the 5-point facial hedonic scale.

- **Summary of main results**

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

Table 24 Summary of results for trial VX16-809-122

Title: A Phase 3, 2-part, Open-label Study to Evaluate the Safety and Pharmacokinetics of Lumacaftor/ Ivacaftor in Subjects 1 to Less Than 2 Years of Age With Cystic Fibrosis, Homozygous for F508del			
Study identifier	Study VX16-809-122		
Design	Phase 3, 2-part, open-label, multicenter study evaluating the PK, safety, and PD of multiple doses of LUM/IVA in subjects 1 to <2 years of age		
	Duration of main phase:		Part A: 2 weeks Part B: 24 weeks
Hypothesis	Evaluate the Safety and Pharmacokinetics of Lumacaftor/Ivacaftor		
Treatments groups	Part A Cohort 1 subjects aged 18 to <24 months		LUM/IVA 7 patients
	Part A Cohort 2 subjects aged 12 to <18 months		LUM/IVA 7 patients
	Part B		LUM/IVA 46 patients
Endpoints and definitions	Primary endpoint	Part A: PK Part B: safety	
	Secondary endpoint	SwCl is a direct in vivo PD measure of CFTR function	Absolute change from baseline at week 24
	Other endpoints	Markers of pancreatic exocrine function Markers of intestinal inflammation	FE-1, IRT, lipase, total amylase, pancreatic amylase Fecal calprotectin Absolute change from baseline at Week 24
Database lock	<date>		

Results and Analysis		
Analysis description	**Primary Analysis**	
Analysis population and time point description	Full Analysis Set (FAS) and Safety Set	
Descriptive statistics and estimate variability	Treatment group	LUM/IVA
	Absolute change from baseline in SwCl; mean, (mmol/L)	-29.1 (95% CI -34.8, -23.4)
	Absolute change from baseline in FE-1 levels; mean (SD), (mg/kg),	73.1 (112.6)
	Absolute change from baseline in IRT levels; mean (SD), (µg/L)	-295.5 (329.9)
	Absolute change from baseline in lipase; mean (SD), (U/L)	-26.77 (53.92)
	Absolute change from baseline in total amylase; mean (SD), (U/L)	-4.6 (27.5)
	Absolute change from baseline in pancreatic amylase; mean (SD), (U/L)	-2.1 (5.3)
	Absolute change in fecal calprotectin, mean (SD) mg/kg.	-106.63 (186.98)
Notes	n/a	

2.6.5.2. Clinical studies in special populations

N/A

2.6.5.3. In vitro biomarker test for patient selection for efficacy

N/A

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

N/A

2.6.5.5. Supportive study

N/A

2.6.6. Discussion on clinical efficacy

Design and conduct of clinical studies

This variation concerns the extension of the indication of Orkambi (lumacaftor/ivacaftor) to also include children with CF who are homozygous for delta 508 from age 1- 2 years.

A new granule preparation is added to dose the lighter children within this proposed new age group, 1 year to 2 years. The additional new strength granule preparation 75/94 mg is intended to dose children aged 1-2 years who weight 7-9kg. The already approved 100/125mg and 150/188mg granule preparations are proposed to dose children aged 1-2 years who weight 9 to <14kg and ≥14kg respectively.

A dose-response study was not performed, but dose finding was supported by population PK analysis aimed at targeting a similar systemic exposure as that of older paediatric and adult subjects that has been shown to be efficacious. The simulations provided based on this model indicate that the proposed dosing recommendations are reasonable as children aged 1 to less than 2 years would present an exposure similar to that in adults. See section 2.6.3 Discussion on clinical pharmacology.

The proposed indication extension is based on results from Study 122, a Phase 3, 2-part, open-label, multicentre study in subjects 1 to <2 years of age with CF, homozygous for F508del. **Part A** was designed to evaluate the safety and PK of LUM/IVA over a treatment period of 15 days. Enrolment was sequential: Cohort 1 (subjects 18 to <24 months of age [N = 7]) and Cohort 2 (subjects 12 to <18 months of age [N = 7]). Safety, tolerability, and available PK data from Part A were reviewed to determine the dose(s) to be evaluated in Part A Cohort 2 and Part B.

Part B was designed to evaluate the safety, PK, and pharmacodynamic (PD) of LUM/IVA over 24 weeks of treatment.

The MAH therefore does not present controlled, randomised data for this age group, and instead provides open label, uncontrolled data for this age group. Given the lack of controlled data for this age group, the MAH is also relying on a PK and PD (primarily sweat chloride) bridge to the randomised controlled data from older age groups. Overall, this approach can in principle be considered acceptable given:

1. the challenges in recruiting very young children to clinical trials

2. practical difficulties in reliably and accurately carrying out respiratory based disease assessment in children under the age of 6 years

3. lack of consensus on the magnitude of clinically relevant effect on the various markers of CF severity in younger children

4. recognition that definite efficacy improvement is difficult to demonstrate in a very young population with relatively mild disease at baseline.

5. recognition that the same disease process applies in children age 1-2 years as in older children and adults with CF.

Of note a similar approach was used to extend the indication to the age 2-5 year old age group, where the applicant also presented a small, open label study in that age group and drew a PK/PD bridge to the data from older children/adults. For the 6-11 year old age group, a randomised placebo controlled trial was provided, using LCI2.5 as the primary EP- and this demonstrated a small LS mean treatment difference of -1.09 (95%CI, -1.43, -0.75) P<0.0001 for the absolute change through week 24.

Efficacy/PD data was collected from Study 122 Part B. In addition, the MAH proposes that efficacy in the 1-2 years old age group can be extrapolated from the placebo controlled phase 3 data from older populations.

The majority of subjects completed the study (93.5%) only 3 subjects discontinued due to the AE occurrence (severity not specified), withdrawal of consent (not due to AE), and other reason. 87% of patients rolled over the extension study.

In Part B, 46 subjects received at least 1 dose of study drug, 97.8% completed study drug treatment and 93.5% completed the study.

Baseline characteristics and concomitant medication use reflect a typical population of CF patients. Subjects were balanced between males and females, the majority being White. The median age at baseline was 18.5 months (range: 12 to 23 months). Median of weight for age z score was 0.51 and length for age z score -0.19. All subjects had pancreatic failure, 95.7% clinical manifestation of CF lung disease and roughly 24% gastroesophageal reflux. Concomitant medication use was typical of a CF population in this age group.

Inclusion and exclusion criteria were adequate.

LUM/IVA was administered to each Part A cohort or in Part B in accordance with the weight-based dosing regimens. See section 2.6.3. Discussion on clinical pharmacology.

Change in percent predict FEV1 (the recommended primary endpoint to be used for registration studies as outlined in the EMA CF guideline, EMEA/CHMP/EWP/9147/2008) is not feasible in children from birth through 5 years of age because FEV1 involves spirometry, which cannot be performed by young children as forced manoeuvres are needed. Therefore FEV1 was not assessed in study 122. Instead the following additional PD assessments related to efficacy were evaluated in Part B: (1) body mass index (BMI) and BMI-for-age z-score, (2) weight, weight-for-age z-score, and weight-for-length z-score, (3) length and length-for-age z-score, (4) pulmonary exacerbations (PEx) and CF-related hospitalizations, (5) fecal elastase-1 (FE-1) levels, (6) immunoreactive trypsinogen (IRT) levels, (7) microbiology cultures, (8) fecal calprotectin levels, and (9) multiple-breath washout (MBW) (optional LCI substudy). Part B included a 2-week Washout Period to evaluate off-drug PD response.

Efficacy data and additional analyses

Primary objectives of the study were PK and safety and are described in the dedicated sections. Secondary objectives were PD markers which are those commonly used in CF studies and PK endpoints. These PD markers are used as supportive of clinical benefit.

Absolute change from baseline in SwCl at week 24 was a secondary PD endpoint in Study 122 Part B. SwCl is a direct in vivo PD measure of CFTR function. The mean (SD) SwCl at baseline was 104.2 (7.7) mmol/L. LUM/IVA treatment resulted in a substantial improvement (reduction) in SwCl as shown by the mean (SD) absolute change from baseline at week 24: -29.1 (13.5) mmol/L (95% CI -34.8, -23.4). The decline in mean sweat chloride to ~ 75 mmol/L value was still at a higher value than normal range (< 30 mmol/L). The magnitude of improvement in SwCl after 24 weeks of treatment was consistent with that observed in other studies including CF subjects with a different age range and treated with LUM/IVA. Although no patient achieved normalisation of SwCl, the MAH provided reference to natural history data to justify that improvement in CFTR function by 10-20%, in patients homozygous for F508del, would be expected to result in clinically meaningful benefit.

SwCl decline at week 24 was very similar to that observed at earlier time points (i.e. week 4 and 12) suggesting that the maximum effect was displayed early, and it remained stable/not increasing over time. This is likely related to the mechanism of action of the drug consisting of restoration of the biochemical defect by the combined corrector/potentiator action of LUM/IVA. At the Follow-up (Week 26), after the 2-week Washout Period, the SwCl concentration returned to approximately baseline, with a mean (SD) absolute change from baseline at Week 26 of -3.5 (11.8) mmol/L (95% CI: -8.3, 1.4) supporting that the effect is due to LUM/IVA. SwCl results have been reflected in section 5.1 of the SmPC.

The mean change in sweat chloride is within the range of the decrease seen in older children and adult patients.

Nutritional status has a significant effect on pulmonary disease progression and survival in patients with cystic fibrosis. As a consequence, the nutritional status of children with CF is closely followed. Other secondary endpoints were related to growth parameters (weight-for-length z-score and BMI, weight, length, and their associated z-scores). These values were normal at baseline and remained stable over 24 weeks of LUM/IVA treatment.

Z-scores for growth parameters were in the normal range at baseline. A slight increase, absolute change from baseline, was noted at week 24 for parameters such as median weight (of 1.3 kg) and length (of 5.1 cm). The observed changes in this age range (1-2 y) across a 6 month period seem limited, hence it is difficult to dissect the improvement due to growth and/or an amelioration of nutritional status from improved pancreatic function due to LUM/IVA treatment.

The pancreas is one of the earliest organs affected in CF patients who are homozygous for the F508del mutation, a high fraction of whom develop pancreatic insufficiency. Therefore others endpoints related to markers of pancreatic exocrine function were evaluated. These endpoints hold the potential to address whether exocrine pancreatic insufficiency can be prevented or improved.

Fecal elastase (FE-1) is a diagnostic measure of pancreatic exocrine sufficiency, with a lack of elastase output in stool being considered indicative of pancreatic insufficiency (<200 µg/g). Rescue of pancreatic function will result in an increase in FE-1 levels. The mean (SD) FE-1 level at baseline was 9.7 (8.1) mg/kg therefore below the threshold of 200 µg/g (equivalent to 200 mg/kg) established for pancreatic insufficiency. The mean (SD) absolute change FE-1 at Week 24 was 73.1 (112.6) mg/kg showing an increase corresponding to an improvement although below the 200 mg/kg cut-off. A subgroup of 4 out of the 28 (14.3%) subjects with both baseline and Week 24 values had FE-1 values ≥200 mg/kg at Week 24 therefore achieving a level above the pancreatic function insufficiency cut-off.

Evaluation of Immunoreactive trypsinogen (IRT) is used in clinical practice as part of newborn screening for CF wherein elevated levels at birth are associated with disease. Over time, however, patients with CF show a longitudinal decline in IRT with nondetectable levels observed around 5 years of age, indicating a loss of pancreatic tissue. A decrease in serum IRT levels was observed by Week 4 and remained below baseline over the 24 weeks of LUM/IVA treatment. The mean (SD) absolute change in serum IRT from baseline was -295.5 (329.9) µg/L (95% CI: -416.6, -174.5) at Week 24, suggesting improvement in pancreatic inflammation/injury with LUM/IVA treatment.

Even though total amylase and lipase are collected for safety purposes, they are presented under efficacy assessment as both are thought to be also markers of pancreatic inflammation. Limited evidence has been provided showing the course of serum lipase levels in young infants with cystic fibrosis. An evaluation of the classical markers of exocrine function such as lipase and amylase was performed. Lipase levels were elevated at baseline (the mean (SD) lipase at baseline was 71.26 (81.05) U/L (normal range: 4 to 31 U/L). The mean (SD) absolute change from baseline at Week 24 was -26.77 (53.92) U/L. The decrease started early (by week 4) and was maintained through week 24.

Total amylase levels were normal at baseline (mean (SD) at baseline was 66.7 (31.7) U/L (normal range: 8 to 79 U/L). Pancreatic amylase levels at baseline were below the lower limit of normal at baseline (the mean (SD) pancreatic amylase level at baseline was 10.7 (7.9) U/L (normal range: 13 to 53 U/L). The mean (SD) absolute change from baseline at Week 24 was -4.6 (27.5) U/L for total amylase and -2.1 (5.3) U/L for pancreatic amylase, respectively. Therefore LUM/IVA treatment was accompanied by a decrease of pancreatic enzymes reflecting a better pancreatic function.

Although different markers of pancreatic function have been used overall supporting an improvement of the exocrine pancreatic function, longer data are needed to confirm the actual impact on pancreatic function.

Intestinal inflammation is a feature of CF and fecal calprotectin has been shown to be increased in paediatric patients with CF potentially contributing to suboptimal growth in this population. However, specificities related to the age range 1-2 years of age need to be considered. A study conducted from Garg M et al. compared fecal calprotectin levels in CF and healthy children (HC) 0-10 years old. At birth, calprotectin levels in CF children were significantly lower than HC suggesting the gut environment in CF is altered from the early years of life. By four years of age, this trend reverses and calprotectin is consistently higher in CF patients compared with HC due to intestinal inflammation, indicating that calprotectin has potential use as a gastrointestinal endpoint in older children. Hence this data suggests age-dependency and careful interpretation of fecal calprotectin is required in children under four years with CF (Garg M et al., Journal of Cystic Fibrosis Volume 16, Issue 5, September 2017).

At baseline mean (SD) fecal calprotectin was 226.06 (279.26) mg/kg, higher than the commonly used cut off of > 50 mg/kg. The mean (SD) absolute change from baseline at Week 24 was -106.63 (186.98) mg/kg (95% CI: -180.60, -32.66). Starting from Week 4 a decrease was observed, and sustained over the 24 weeks. Overall, a decrease in fecal calprotectin levels was shown reflecting amelioration of intestinal inflammation.

CF PEx are a compilation of patient signs and symptoms that often result in the need for aggressive treatment, including the use of intravenous antibiotics that may require hospitalization. PEx are the major cause of morbidity and decreased quality of life for CF patients. Pulmonary exacerbations [PEx]) and CF related hospitalization are considered in this section as indirect measure of efficacy. 9 (19.6%) subjects had PEx and 15 events were reported; 3 (6.5%) subjects undergone hospitalization and 4 events were reported. The event rate per patient-year was 0.6 for PEx and 0.2 for CF-related hospitalizations.

Overall, data coming from PD markers are supportive of LUM/IVA clinical efficacy in the age range 1-2 years.

In the Study 122 no specific endpoints assessing pulmonary function have been included due to the difficulties in performing assessment in this age range. A substudy aimed at assessing LCI assessment included only one subject therefore not informative. The MAH was asked to comment further on the reasons why the LCI/Multiple breath washout substudy did not happen, and the feasibility of this assessment in this age group. The MAH explained that the lung clearance index sub-study was optional in Study 122 as this modality was not available in all sites, and this endpoint was exploratory only. The MAH has sufficiently explained why there were no LCI data collected in the Study.

2.6.7. Conclusions on the clinical efficacy

Overall, it is agreed that a relevant PD effect (indirectly with a PD/Sweat Chloride secondary endpoint), has been demonstrated in the open label Study 122 in CF patients homozygous for F509del-CFTR aged 1-2 years administered with the new FDC combination granule preparations of Orkambi at the proposed weight based posologies.

The data presented in this application supporting the approval in the paediatric patients aged from 1 to 2 years of age are based on a safety PK study with PD parameters provided as secondary endpoints. The number of patients included is also limited which can be acceptable. However, in view of the above and considering that clinical efficacy data were not collected the MAH was asked to extend the ongoing PAES study (2-5 years of age) to recruit also children aged 1-2 years. The MAH agreed on this extension anticipating that the study endpoints will be the same as the protocol for 2-5 years of age and that a protocol will be submitted by end of June 2023.

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 1 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

2.6.8. Clinical safety

2.6.8.1. Patient exposure

Part A: All subjects (14) received at least 1 dose of study drug in the Part A Treatment Period, with a mean (SD) exposure of 14.2 (4.2) days.

Part B: 46 subjects received at least 1 dose of study drug, with a mean (SD) exposure of 166.5 (16.3) days (see Table 25).

Table 25 Study 122 Part B: Summary of Exposure, Safety Set

	Total N = 46
Total exposure (subject-years)	22.8
Exposure duration (days)	
n	46
Mean (SD)	166.5 (16.3)
SE	2.4
Median	168.5
Min, max	60, 175
Exposure duration by interval, n (%)	
>0 to ≤2 weeks	0
>2 to ≤4 weeks	0
>4 to ≤8 weeks	0
>8 to ≤16 weeks	1 (2.2)
>16 to ≤24 weeks	22 (47.8)
>24 weeks	23 (50.0)

Source: Study 122 CSR/Table 14.1.7b
N: total sample size; n: size of subsample
Notes: Total exposure (subject-years) = Sum of (study drug exposure in subject-years across all subjects in the Part B Safety Set), where 1 subject-year is defined as 1 subject with 48 weeks of treatment. Duration of study drug exposure (days) = last dose date - first dose date in Part B + 1 day, regardless of any interruptions in dosing. Duration of study drug exposure (weeks) = Duration of study drug exposure (days)/7; 1 week = 7 days.

2.6.8.2. Adverse events

Treatment-emergent AEs will hereafter be referred to as AEs.

PART A

Overview of AEs

Table 26 Overview of AEs, Safety Set, Part A

Category	Cohort 1 N = 7 n (%)	Cohort 2 N = 7 n (%)	Total N = 14 n (%)
Number of AEs	13	11	24
Subjects with any AEs	6 (85.7)	6 (85.7)	12 (85.7)
Subjects with AEs by strongest relationship			
Not related	0	4 (57.1)	4 (28.6)
Unlikely related	3 (42.9)	1 (14.3)	4 (28.6)
Possibly related	2 (28.6)	1 (14.3)	3 (21.4)
Related	1 (14.3)	0	1 (7.1)
Subjects with AEs by maximum severity			
Mild	4 (57.1)	4 (57.1)	8 (57.1)
Moderate	2 (28.6)	2 (28.6)	4 (28.6)
Severe	0	0	0
Life-threatening	0	0	0
Subjects with AEs leading to treatment discontinuation	1 (14.3)	0	1 (7.1)
Subjects with AEs leading to drug interruption	0	0	0
Subjects with SAEs	0	0	0
Subjects with related AEs	3 (42.9)	1 (14.3)	4 (28.6)
Subjects with Grade 3/4 AEs	0	0	0
Subjects with related SAEs	0	0	0
Subjects with AE leading to death	0	0	0

Source: Table 14.3.1.1a

AE: adverse event; n: size of subsample; N: total sample size; SAE: serious adverse event

Notes: Cohort 1 included subjects 18 to <24 months of age; Cohort 2 included subjects 12 to <18 months of age. When summarizing number of events, a subject with multiple events within a category was counted multiple times in that category. When summarizing number and percentage of subjects, a subject with multiple events within a category was counted only once in that category. When summarizing number of subjects with related (serious) AEs, AEs with relationship of related, possibly related, and missing were counted. Subjects with Grade 3/4 TEAEs included the 'Severe' and 'Life Threatening' categories. If subjects only had one event with missing severity, then the subject was summarized in the "Missing" category. "Missing" was not displayed in the table if no subjects fall into this category.

Table 27 AEs Occurring in ≥ 2 Subjects Overall by PT, Safety Set, Part A

Preferred Term	Cohort 1 N = 7 n (%)	Cohort 2 N = 7 n (%)	Total N = 14 n (%)
Subjects with any AEs	6 (85.7)	6 (85.7)	12 (85.7)
Rhinorrhoea	3 (42.9)	2 (28.6)	5 (35.7)
Cough	3 (42.9)	1 (14.3)	4 (28.6)
Rash	2 (28.6)	1 (14.3)	3 (21.4)
Influenza	0	2 (28.6)	2 (14.3)

Source: Table 14.3.1.3a

AE: adverse event; n: size of subsample; N: total sample size; PT: Preferred Term

Notes: Cohort 1 included subjects 18 to <24 months of age; Cohort 2 included subjects 12 to <18 months of age. Events were coded with MedDRA Version 24.1. A subject with multiple events within a category (Any or PT) was counted only once in that category.

SEVERITY All AEs were mild (57.1%) or moderate (28.6%) in severity (Table 26). There were no Grade 3 or Grade 4 AEs.

RELATIONSHIP One (7.1%) subject had an AE that was assessed by the investigator as related to study drug; 3 (21.4%) subjects had an AE that was assessed by the investigator as possibly related to study drug.

PART B

Overview of AEs

Table 28 Overview of AEs, Safety Set, Part A

Category	Total N = 46 n (%)
Number of AEs	197
Subjects with any AEs	44 (95.7)
Subjects with AEs by strongest relationship	
Not related	15 (32.6)
Unlikely related	13 (28.3)
Possibly related	14 (30.4)
Related	2 (4.3)
Subjects with AEs by maximum severity	
Mild	24 (52.2)
Moderate	18 (39.1)
Severe	2 (4.3)
Life-threatening	0
Subjects with AEs leading to treatment discontinuation	1 (2.2)
Subjects with AEs leading to drug interruption	2 (4.3)
Subjects with SAEs	5 (10.9)
Subjects with related AEs	16 (34.8)
Subjects with Grade 3/4 AEs	2 (4.3)
Subjects with related SAEs	1 (2.2)
Subjects with AEs leading to death	0

Source: Table 14.3.1.1b

AE: adverse event; n: size of subsample; N: total sample size; SAE: serious adverse event

Notes: When summarizing number of events, a subject with multiple events within a category was counted multiple times in that category. When summarizing number and percentage of subjects, a subject with multiple events within a category was counted only once in that category. An AE with relationship missing was counted as Related. When summarizing number of subjects with related (serious) AEs, AEs with relationship of related, possibly related, and missing were counted. Subjects with Grade 3/4 AEs included the 'Severe' and 'Life Threatening' categories. If subjects only had 1 event with missing severity, then the subject was summarized in the "Missing" category. "Missing" was not displayed in the table if no subjects fell into this category.

The table below summarizes AEs occurring in ≥10% of subjects by preferred term (PT).

Table 29 AEs Occurring in At Least ≥ 10% of Subjects by PT, Safety Set, Part B

Preferred Term	Total N = 46 n (%)
Subjects with any AEs	44 (95.7)
Cough	16 (34.8)
Infective pulmonary exacerbation of cystic fibrosis	10 (21.7)
Pyrexia	10 (21.7)
Vomiting	8 (17.4)
Upper respiratory tract infection	6 (13.0)
Constipation	5 (10.9)
Ear infection	5 (10.9)
Pseudomonas test positive	5 (10.9)
Rhinorrhoea	5 (10.9)
Viral upper respiratory tract infection	5 (10.9)

Source: Table 14.3.1.3b
AE: adverse event; n: size of subsample; N: total sample size; PT: Preferred Term
Notes: Events were coded with MedDRA Version 24.1. A subject with multiple events within a category (Any or PT) was counted only once in that category.

AEs by Severity The majority of subjects had AEs that were mild (52.2%) or moderate (39.1%) in severity. Two (4.3%) subjects had AEs considered severe in intensity. One subject had severe AEs of ALT increased and AST increased that resulted in treatment discontinuation and were considered related to study drug. The second subject had a severe AE of infective pulmonary exacerbations (PEx) of CF, which was considered unlikely related to study drug and resolved with treatment. No life-threatening (i.e., Grade 4) AEs occurred.

AEs by Relationship Two (4.3%) subjects had AEs that were assessed by the investigator as related to study drug: 1 subject had an SAE of distal intestinal obstruction syndrome (DIOS) and 1 subject had severe AEs of ALT increased and AST increased.

14 (30.4%) subjects had AEs considered to be possibly related to study drug and 28 (60.9%) subjects had AEs considered to be unlikely related or not related to study drug.

By PT, the most common AEs assessed by the investigator as being related or possibly related (≥5% incidence overall) to study drug were constipation, vomiting, and cough (6.5% subjects each).

AESI

Adverse Events of Special Interest AESIs were defined as AEs of elevated transaminases, respiratory events, and respiratory symptoms.

Table 30 Study 122 Part B: AESI Categories

AESI Category	Grouped PTs
Elevated transaminases	ALT abnormal, ALT increased, AST abnormal, AST increased, transaminases abnormal, transaminases increased, LFT abnormal, LFT increased, hypertransaminasemia, hepatic enzyme increased, hepatic enzyme abnormal
Respiratory symptoms	Chest discomfort, dyspnea, respiration abnormal
Respiratory event	Asthma, bronchial hyperreactivity, bronchospasm, chest discomfort, dyspnea, respiration abnormal, wheezing

Source: Study 122 CSR/Appendix 16.1.9/SAP Version 2.0
AESI: adverse event of special interest; ALT: alanine transaminase; AST: aspartate transaminase; LFT: liver function test; PT: Preferred Term

Elevated Transaminases: Four (8.7%) subjects had an AESI of elevated transaminases. None were serious, and the majority of events were mild or moderate in severity. One (2.2%) subject had AEs of ALT and AST increased that were assessed by the investigator to be severe in intensity and resulted in treatment discontinuation. The remaining subjects did not have study drug interrupted. The mean time-to-onset of first event was 98 days. There was only 1 event with a duration, which was 61 days.

Dyspnoea: There was 1 (2.2%) subject who had an AE of dyspnoea that led to treatment interruption. Dyspnoea is an event that is included in both categories of respiratory event AESIs and respiratory symptom AESIs.

2.6.8.3. Serious adverse event/deaths/other significant events

Part A

There were no AEs leading to death nor SAEs.

Part B

There were no AEs leading to death.

Five (10.9%) subjects had SAEs: 3 subjects had SAEs of infective PEx of CF, 1 subject had an SAE of post procedural fever, and 1 subject had an SAE of DIOS. All SAEs were assessed by the investigator to be moderate or mild in severity. One SAE (DIOS) was assessed by the investigator to be related to study drug and treatment was interrupted. The other SAEs were assessed by the investigator to be not related or unlikely related to study drug, and these SAEs did not lead to study drug interruption or discontinuation.

2.6.8.4. Laboratory findings

Part A

No clinically relevant trends were observed in chemistry parameters.

No subjects had ALT or AST >3 × ULN, nor total bilirubin >2 × ULN.

Hematology No clinically relevant trends were observed in hematology parameters. No subjects had AEs related to hematology findings.

Vital Signs No clinically relevant trends were observed for blood pressure (BP), pulse rate, temperature, or respiratory rate. No subjects had AEs related to vital signs findings.

Part B

Liver tests

Table 31 Threshold Analysis of LFT Chemistry Parameters, Safety Set, Part B

Parameter Threshold Analysis Criteria, n/N1 (%)	Total N = 46
ALT	
>3 × ULN	5/46 (10.9)
>5 × ULN	2/46 (4.3)
>8 × ULN	1/46 (2.2)
AST	
>3 × ULN	2/46 (4.3)
>5 × ULN	0/46
>8 × ULN	0/46
ALT or AST	
ALT >3 × ULN or AST >3 × ULN	5/46 (10.9)
ALT >5 × ULN or AST >5 × ULN	2/46 (4.3)
ALT >8 × ULN or AST >8 × ULN	1/46 (2.2)
ALP	
>1.5 × ULN	1/46 (2.2)
Total Bilirubin	
>1.5 × to ≤2 × ULN	0/46
>2 × ULN	0/46

Source: Table 14.3.4.3b

ALP: alkaline phosphatase; ALT: alanine transaminase; AST: aspartate transaminase; LFT: liver function test; n: size of subsample; N: total sample size; ULN: upper limit of normal

Notes: The number of subjects with a value meeting the parameter criteria category during the TE period is represented as "n". "N1" was the number of subjects with at least 1 post-baseline assessment. Percentage was n/N1. A subject with multiple events was only counted once in the most severe category for mutually exclusive criteria with different cutoffs.

Other Clinical Chemistry Parameters

No clinically relevant trends were observed in other chemistry parameters. Two (4.3%) subjects had AEs related to other chemistry findings (excluding LFT) results. One subject had an AE of blood creatine phosphokinase increased and 1 subject had an AE of lipase increased. Neither AE was serious or led to treatment interruption or discontinuation. Both AEs resolved without treatment.

Hematology No clinically relevant trends were observed in hematology parameters. One subject had an AE of neutropenia that was considered mild in severity; the AE was not serious and did not lead to treatment interruption or discontinuation. The AE of neutropenia resolved without treatment.

Vital Signs No clinically relevant trends were observed for BP, pulse rate, temperature, or respiratory rate. No subjects had AEs related to vital signs findings.

- Blood Pressure: Mean changes in BP fluctuated over the course of the study, but there were no clinically meaningful changes from baseline. Mean (SD) absolute change from baseline at Week 24 was 1.9 (18.7) for SBP and -0.5 (13.3) for DBP. There were no AEs of blood pressure increased. Values ≥95th percentile occurred at least twice in 44 (95.7%) subjects for SBP and in all 46 (100%) subjects for DBP. The percentages of subjects with SBP and DBP values ≥95th percentile showed no pattern of increase over time when evaluated by visit.
- Pulse Oximetry: No clinically relevant trends were observed for pulse oximetry. No subjects had AEs related to pulse oximetry findings.
- Electrocardiograms: No clinically relevant trends were identified in changes in ECG findings. No subjects had AEs related to ECG findings.

No subjects had cataracts.

2.6.8.5. In vitro biomarker test for patient selection for safety

Not applicable

2.6.8.6. Safety in special populations

Not applicable

2.6.8.7. Immunological events

Not applicable

2.6.8.8. Safety related to drug-drug interactions and other interactions

Not applicable

2.6.8.9. Discontinuation due to adverse events

Part A

No AEs leading to treatment interruption were reported. One subject (Cohort 1) had an AE of rash that led to treatment discontinuation. The AE was assessed by the investigator to be moderate in severity and possibly related to study drug. The AE resolved without treatment.

Part B

One (2.2%) subject had AEs (ALT increased and AST increased) leading to treatment discontinuation. Both AEs were assessed by the investigator to be severe in intensity and related to study drug.

Two (4.3%) subjects had AEs that led to treatment interruption. One subject had an SAE of Distal intestinal obstruction syndrome (DIOS) that was assessed by the investigator to be moderate in severity and related to study drug. Study drug was interrupted, and the event resolved with treatment. One subject had an AE of dyspnoea that was assessed by the investigator to be moderate in severity and possibly related to study drug. Study drug was interrupted, and the event resolved with treatment.

2.6.8.10. Post marketing experience

Since the International Birth Date of 02 July 2015, it is estimated that 24,168 patients (representing 45,998 patient-years) have been treated with commercial LUM/IVA cumulatively as of 19 May 2021. The benefit-risk profile of LUM/IVA remains favourable.

2.6.9. Discussion on clinical safety

Safety was the primary objective of Part B and a secondary objective of Part A of study 122. In part A, 14 subjects were enrolled, the mean (SD) LUM/IVA exposure was 14.2 (4.2) days. In part B, 46 subjects received at least one dose of study drug, the mean (SD) exposure was of 166.5 (16.3) days.

LUM/IVA safety data from clinical trials and post marketing are available from CF subjects >2 years. Although specificities related to the age range 1-2 years should be considered the overall safety data set coming from older CF subjects is considered supportive.

Overview of AEs: in **part A** 85.7% subjects had at least 1 AE. All AEs were mild or moderate in severity. There were no deaths or serious AEs. One subject had an AE assessed as related to study drug; one subject discontinued LUM/IVA due to an AE. An AE of rash was reported in 3 subjects. All AEs of rash were non-serious and did not require treatment. One subject had an AE of rash that led to treatment discontinuation. For all subjects, the AEs of rash resolved.

In **part B** forty-four (95.7%) subjects had at least 1 AE, and 16 (34.8%) subjects had at least 1 AE considered related to LUM/IVA (related [4.3%] or possibly related [30.4%], as determined by the investigator). The majority of subjects had AEs that were considered mild (24 [52.2%] subjects) or

moderate (18 [39.1%] subjects) in severity. 2 (4.3%) subjects had severe AEs. No subjects had life-threatening AEs. There were no deaths. Five (10.9%) subjects had SAE. Of these 3 were PEx reported in CF subjects.

One (2.2%) subject discontinued LUM/IVA due to an AE; 2 (4.3%) subjects interrupted LUM/IVA due to an AE, one was a SAE of DIOS assessed as related to study drug. DIOS is described in CF subjects in approximately 10% of CF patients after lung transplantation (J Gastrointest Surg 2009 Aug;13(8):1448-53).

With reference to AESI, 8.7% of subjects had elevated transaminases.

10.9% of subjects had ALT or AST >3 × ULN, 2 (4.3%) subjects had ALT or AST >5 × ULN, and 1 (2.2%) subject had ALT or AST >8 × ULN over the duration of the study. None of these events was serious, one was severe leading to treatment discontinuation. Hepatobiliary adverse reactions including increase of transaminases is already included in the SmPC sections 4.4 and 4.8 (common ADR). A short description of these ADRs for patients 1 to less than 2 years has been added in section 4.8 of the SmPC.

1 (2.2%) subject had an AE of dyspnoea that led to treatment interruption. Respiratory adverse reactions including dyspnoea are already included in the sections 4.4 and 4.8 of the SmPC.

Laboratory findings: in part B one (2.2%) subject had an alkaline phosphatase (ALP) level >1.5 × ULN during the study, the AE was not serious and did not lead to treatment interruption or discontinuation. No subjects had total bilirubin >2 × ULN. This information has been added in section 4.8 of the SmPC, in addition, hepatobiliary adverse reactions are already included in the SmPC sections 4.4, 4.8 (common ADR).

One AE of blood creatine phosphokinase increase was reported, this is an ADR common in frequency and already reported in the section 4.8 of the SmPC.

Mean changes in blood pressure fluctuated over the course of the study, but there were no clinically meaningful changes from baseline. Effect on blood pressure is also reported in the SmPC sections 4.4 and 4.8 (common ADR).

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

However the safety data exposure in total is relatively small in this age group. This period is too small to adequately characterise the safety profile when used in children aged 1-2 years. Long-term safety data will be collected in study 124. Study 124, a Category 3 PASS, is an open-label extension of Study 122 that includes rollover subjects who participated in Study 122 Part B and subjects who did not participate in Study 122 Part B and were 12 to <24 months of age at Study 124 Day 1. The objective of this study is to evaluate safety and tolerability of long-term LUM/IVA treatment patients aged 12 to <24 months at treatment initiation. The MAH has added this Category 3 PASS as an additional pharmacovigilance activity. Study outcomes include the important identified risk (respiratory events) and important potential risk (cataracts) of the RMP. Results will be submitted in July 2024.

2.6.10. Conclusions on the clinical safety

Overall, the findings from open label Study 122, support the use of LUM/IVA in subjects 1 through 2 years of age with CF, homozygous for F508del. The safety profile described from this small study is consistent with that reported in CF subjects of other age-ranges; no new safety concerns were identified.

Additional, long-term safety data will be collected for this age group in study 124 (Category 3 study) .

2.7. Risk Management Plan

2.7.1. Safety concerns

Important identified risks	• Respiratory events
Important potential risks	• Cataracts
Missing information	• Use in pregnant and lactating women • Use in patients with organ transplant

2.7.2. 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 that are Conditions of the MA (key to benefit risk)				
None				
Category 2 – Imposed mandatory additional PV activities that 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 124 Ongoing	To evaluate the long-term safety and tolerability of LUM/IVA in subjects 12 to <24 months at treatment initiation with CF	•Respiratory events •Cataracts	Final report	July 2024

CF: cystic fibrosis; LUM/IVA: LUM in combination with IVA; MA: marketing authorization; PV: pharmacovigilance

2.7.3. 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 Prescription only **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection** None **Additional PV activities:** Study 124
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 Prescription only **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection** None **Additional PV activities:** Study 124
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 Prescription only **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection** Pregnancy follow-up form **Additional PV activities:** None

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
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. Prescription only **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection** None **Additional PV activities:** None

PL: Package Leaflet; ppFEV$_1$: percent predicted forced expiratory volume in 1 second; PV: pharmacovigilance; SmPC: Summary of Product Characteristics

2.7.4. Conclusion

The CHMP considered that the risk management plan version 11.4 is acceptable.

However, it is noted that there are no further pharmacovigilance activities ongoing or planned to investigate the use of Orkambi in pregnant and lactating women, or the use of Orkambi in patients with organ transplant. Therefore, the MAH is asked to re-evaluate the summary of safety concerns at the next regulatory opportunity, with a view to potentially removing these two remaining areas of missing information from the safety specification.

2.8. Pharmacovigilance

2.8.1. 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.

2.8.2. 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

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

- Readability testing was previously conducted for the Orkambi 100 mg/125 mg and 150 mg/188 mg granules package leaflet and reviewed during the initial paediatric line extension, procedure EMEA/H/C/003954/X/0034/G.
- Updates made to the package leaflets are minimal, and the structure and guidance for

caregivers remains aligned to the principles agreed on in procedure EMEA/H/C/003954/X/0034/G.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The proposed indication expansion for Orkambi is for the treatment of CF in patients 1 to 2 years of age.

The underlying cause of cystic fibrosis (CF), a loss of CFTR function that arises from a mutation in the gene encoding the CFTR protein, has adverse effects that can be observed in newborns and continue to progress through adulthood. The CFTR protein is an epithelial chloride channel that aids in regulating salt and water absorption and secretion in various tissues. This function is defective in patients with CF due to a loss of cell surface expression and/or function of CFTR protein. The failure of mutated CFTR protein to regulate chloride transport results in the multisystem pathology associated with CF. Since the introduction and continued advances of newborn and antenatal screening, many patients with CF are identified through a positive screening test and subsequently diagnosed within the first year of life. Approximately 60% of patients with CF in the EU and 83% of patients with CF in the UK are diagnosed by 1 year of age.

In the US, more than 80% of patients with CF are diagnosed by 2 years of age.CF clearly affects the paediatric population, as approximately half of the total CF patient population in the US, EU, Australia, and Canada are less than 18 years of age. Even before the widespread adoption of newborn screening, the majority of patients with CF were diagnosed in infancy or early childhood due to manifestations of the disease. In patients with severe genotypes (e.g., F508del/F508del), pancreatic destruction leading to pancreatic exocrine insufficiency begins in utero, and lung involvement is manifested by pulmonary inflammation and infection that begins shortly after birth. Loss of lung function is the major cause of morbidity and mortality in patients with CF. Infants with CF as young as 1 month show the presence of lung disease. Airway inflammation signals the beginning of the destructive cycles of chronic inflammation, infection, and irreversible lung damage that are characteristic of CF lung disease.

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 are associated with other clinical comorbidities such as decreased lung function and survival. Malnourishment is associated with worsening lung function in children with CF and is an independent predictor of mortality in this population. Notably, 11.5% of children with CF fall below the US CDC's tenth percentile for weight and 9.8% of children fall below the CDC's fifth percentile for height. Additionally, increased energy expenditure and appetite suppression due to lung disease contribute to poor somatic growth and poor nutritional status in young patients with CF.

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. LUM/IVA targets the underlying mechanisms of disease, thus treatment with LUM/IVA at a young age could postpone or even prevent the onset of clinical manifestations of CF, such as CF lung disease and impaired exocrine pancreatic function.

3.1.2. Available therapies and unmet medical need

There is currently no cure available for CF. Hence, the goals of current CF therapies are to slow or reverse disease progression, manage symptoms and complications such as pancreatic insufficiency and respiratory infections, and improve quality of life. The majority of CF therapies currently available, including nutritional supplements, antibiotics, and mucolytics, target the downstream consequences and symptoms of the disease. CFTR modulators (i.e., correctors and potentiators) target the underlying cause of CF with the potential to alter the course of the disease. Kalydeco (IVA) and Orkambi (LUM/IVA) are the only CFTR modulators approved for CF patients 2 through 5 years of age. Kalydeco is approved for CF patients 4 months of age and older for certain genotypes. At this time, there is no approved CFTR modulator therapy available for CF patients homozygous for F508del aged <2 years of age, therefore the unmet need exists.

3.1.3. Main clinical studies

Study 122 is a Phase 3, 2-part, Open-label Study to Evaluate the Safety and Pharmacokinetics of Lumacaftor/Ivacaftor in Subjects 1 to Less Than 2 Years of Age With Cystic Fibrosis, Homozygous for F508del.

Part A was designed to evaluate the safety and PK of LUM/IVA over a treatment period of 15 days. Two cohorts were enrolled sequentially in Part A: Cohort 1 (subjects 18 to <24 months of age [N = 7]) and Cohort 2 (subjects 12 to <18 months of age [N = 7]). Safety, tolerability, and available PK data from Part A were reviewed to determine the dose(s) to be evaluated in Part A Cohort 2 and Part B.

Part B was designed to evaluate the safety, PK, and pharmacodynamic (PD) of LUM/IVA over 24 weeks of treatment. A total of 46 subjects were enrolled and dosed in Part B; subjects 18 to <24 months of age [N = 25] were enrolled first, followed by enrollment of subjects 12 to <18 months of age [N = 21]. For Part B, the primary endpoint was safety and tolerability; the secondary endpoints were absolute change from baseline in SwCl at Week 24 and PK parameters of LUM, IVA, and their respective metabolites. The following additional PD assessments related to efficacy were evaluated in Part B: (1) body mass index (BMI) and BMI-for-age z-score, (2) weight, weight-for-age z-score, and weight-for-length z-score, (3) length and length-for-age z-score, (4) pulmonary exacerbations (PEx) and CF-related hospitalizations, (5) fecal elastase-1 (FE-1) levels, (6) immunoreactive trypsinogen (IRT) levels, (7) microbiology cultures, (8) fecal calprotectin levels, and (9) multiple-breath washout (MBW) (optional LCI substudy). Part B included a 2-week Washout Period to evaluate off-drug PD response.

3.2. Favourable effects

Dose finding was supported by population PK analysis aimed at targeting a similar systemic exposure as that of older paediatric and adult subjects that has been shown to be efficacious. PK data collected during the study 122 showed that subjects 12 to <24 months of age > 9 kg reached comparable exposure with older paediatric values and adult values, supporting the proposed dosing recommendations.

This extension of indication to very young CF children, aged 1 to 2 years old, is based on extrapolation of Orkambi efficacy from older children and adults to the younger children enrolled in study 122. Therefore PD markers commonly used in CF studies were assessed to support clinical efficacy.

Absolute change from baseline in SwCl at week 24 was a secondary PD endpoint in Study 122 Part B. SwCl is a direct *in vivo* PD measure of CFTR function. An absolute change from baseline at Week 24 in SwCl was observed (the mean (SD) absolute change from baseline at week 24 was -29.1 (13.5)

mmol/L (95% CI -34.8, -23.4). The maximum effect was displayed early (week 4) and it remained stable/not increasing over time.

A decline in mean sweat chloride to ~ 75 mmol/L value was seen. This result is similar to that seen in other studies including CF subjects with a different age range and treated with LUM/IVA. Natural history data support that improvement in CFTR function by 10-20%, in patients homozygous for F508del, would be expected to result in clinically meaningful benefit. The mean change in sweat chloride is within the range of the decrease seen in older children and adult patients.

Growth parameters (weight-for-length z-score and BMI, weight, length, and their associated z-scores) were normal at baseline and remained stable over the 24 weeks of treatment.

Z-scores for growth parameters were in the normal range at baseline. A slight increase, absolute change from baseline, was noted at week 24 for parameters such as median weight (of 1.3 kg) and length (of 5.1 cm).

Other endpoints related to markers of pancreatic exocrine function have been evaluated.

The mean (SD) fecal elastase (FE-1) level at baseline was below the threshold of 200 µg/g (equivalent to 200 mg/kg) established for pancreatic insufficiency. At Week 24 an increase corresponding to an improvement was detected (73.1 (112.6) mg/kg) although below the 200 mg/kg cut-off. A subgroup of 4 out of the 28 (14.3%) subjects with both baseline and Week 24 values had FE-1 values ≥200 mg/kg at Week 24 therefore achieving a level above the pancreatic function insufficiency cut-off.

A decrease in serum Immunoreactive trypsinogen (IRT) levels was observed by Week 4, and remained below baseline over the 24 weeks of LUM/IVA treatment. The mean (SD) absolute change in serum IRT from baseline was -295.5 (329.9) µg/L (95% CI: -416.6, -174.5) at Week 24, suggesting improvement in pancreatic inflammation/injury with LUM/IVA treatment.

An evaluation of the classical markers of exocrine function such as lipase and amylase was performed and a decrease of pancreatic enzymes reflecting a better pancreatic function was noted.

At baseline mean (SD) fecal calprotectin was 226.06 (279.26) mg/kg, higher than the commonly used cut off of > 50 mg/kg. Overall, a decrease (the mean (SD) absolute change from baseline at Week 24 was -106.63 (186.98) mg/kg (95% CI: -180.60, -32.66) in fecal calprotectin levels was observed reflecting amelioration of intestinal inflammation. Starting from Week 4 a decrease was observed and sustained over the 24 weeks.

9 (19.6%) subjects had PEx and 15 events were reported; 3 (6.5%) subjects undergone hospitalization and 4 events were reported. The event rate per patient-year was 0.6 for PEx and 0.2 for CF-related hospitalizations.

Overall, data are considered supportive of efficacy and are consistent with the known Orkambi profile.

3.3. Uncertainties and limitations about favourable effects

Uncertainties pertain on PK in subjects weighting less than 9 kg due to a relative lack of PK data (only 3 patients weighing less than 9 kg were enrolled). However, considering the known efficacy of LUM/IVA, restricting the use to those children over 9 kg was considered by the CHMP to be overly cautious. In addition, the MAH will collect PK data in Study 19 in infants and will submit these data to the CHMP to reconfirm the accuracy of the PK model.

No clinical efficacy endpoints were included in the Safety, PK Study 122, instead PD parameters were collected as secondary objective.

The decline in mean sweat chloride to ~ 75 mmol/L remain substantially higher than normal range for sweat chloride (< 30 mmol/L). Although no patients achieved normalisation of sweat chloride, the MAH

provided references from natural history data to justify that improvement in CFTR function by 10-20%, in patients homozygous for F508del, would be expected to result in clinically meaningful benefit. The magnitude of improvement in SwCl was consistent with that observed in older children and adults.

Other secondary endpoints were related to growth parameters (weight-for-length z-score and BMI, weight, length, and their associated z-scores). The observed changes in this age range (1-2 y) across a 6 month period seem limited, hence it is difficult to dissect the improvement due to growth and/or an amelioration of nutritional status from improved pancreatic function due to LUM/IVA treatment.

A series of others endpoints related to markers of pancreatic exocrine function have been evaluated. Results, overall supported an improvement of the exocrine pancreatic function, however longer data are needed to confirm the actual impact on pancreatic function.

In the study no specific endpoints assessing pulmonary function have been included due to the difficulties in performing assessment in this age range. A substudy aimed at assessing LCI assessment was planned, however this study was optional and the endpoint only exploratory. Only one subject was included, results are therefore not informative.

Overall, the level of evidence submitted to support efficacy in the patients aged 1 to less than 2 years is limited by the lack of a control arm, the sample size of the study, the duration of treatment and the uncertainty on whether the pharmacodynamic improvements observed are maintained.

Additionally no clinical efficacy data in patients age 1 to 2 years old were provided. Thus, the MAH agreed to extend the ongoing PAES study (2-5 years of age) to recruit also children aged 1-2 years to gain more information on Orkambi efficacy in children aged 12-24 months.

3.4. Unfavourable effects

The safety profile described from study 122 is generally consistent with that reported in CF subjects of other age-ranges; no new safety concerns were identified.

In **part A** all AEs were mild or moderate in severity. There were no deaths or serious AEs. One subject had an AE assessed as related to LUM/IVA; one subject discontinued LUM/IVA due to an AE.

Rash was reported in 3 subjects. All AEs of rash were non-serious and did not require treatment. One subject had an AE of rash that led to treatment discontinuation. For all subjects, the AEs of rash resolved.

In **part B** the majority of subjects had AEs that were considered mild (24 [52.2%] subjects) or moderate (18 [39.1%] subjects) in severity. 2 (4.3%) subjects had severe AEs. No subjects had life-threatening AEs. There were no deaths. Five (10.9%) subjects had an SAE. Of these 3 were PEx reported in CF subjects.

One (2.2%) subject discontinued LUM/IVA due to an AE; 2 (4.3%) subjects interrupted LUM/IVA due to an AE one was a SAE of DIOS assessed as related to study drug.

In part B: 8.7% of subjects had elevated transaminases: 10.9% of subjects had ALT or AST >3 × ULN, 4.3% subjects had ALT or AST >5 × ULN, and 2.2% subject had ALT or AST >8 × ULN over the duration of the study. None of these events was serious, one was severe leading to treatment discontinuation. Hepatobiliary adverse reactions including increase of transaminases is already included in the SmPC sections 4.4 and 4.8 (common ADR).

2.2% of subjects had dyspnoea that led to treatment interruption. All respiratory adverse reactions including dyspnoea are already included in the sections 4.4 and 4.8 of the SmPC.

One AE of blood creatine phosphokinase increase was reported, this is an ADR common in frequency and reported in the section 4.8 of the SmPC.

Mean changes in blood pressure fluctuated over the course of the study, with no clinically meaningful changes from baseline. Effect on blood pressure is already reported in the SmPC sections 4.4 and 4.8.

3.5. Uncertainties and limitations about unfavourable effects

From study 122 no new safety concerns have been identified for CF subjects 1-2 years old. The safety outcomes were generally consistent with the background profile in patients with CF and the established safety profile of LUM/IVA, and do not raise any new signals.

However the safety data exposure in total is small in this age group and the duration of follow-up very limited to adequately characterise the safety profile when used in children aged 1-2 years. 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 extending the PAES to address relevant uncertainties. Additional long-term safety data will also be collected in study 124. Study 124, a Category 3 PASS, is an open-label extension of Study 122 that includes rollover subjects who participated in Study 122 Part B and subjects who did not participate in Study 122 Part B and were 12 to <24 months of age at Study 124 Day 1. The objective of this study is to evaluate safety and tolerability of long-term LUM/IVA treatment patients aged 12 to <24 months at treatment initiation.

3.6. Effects Table

Table 32 Effects Table for Orkambi in 1-2 years old CF patients homozygous for F508del-CFTR

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
SwCl (secondary endpoint)	SwCl is a direct in vivo PD measure of CFTR function	mmol/L	mean (SD) absolute change from baseline at week 24 was -29.1 (13.5) (95% CI -34.8, -23.4).	N/A	The decline is at a still higher value than normal range (< 30 mmol/L). / improvement in CFTR function by 10-20%, in patients homozygous for F508del, would be expected to result in clinically meaningful benefit.	Study 122
Unfavourable Effects						
elevated transaminases	It is an AESI of Orkambi included in 4.4 and 4.8 of SmPC		Part B: 8.7% of subjects had elevated transaminases	N/A	Known AESI of the drug/not long term data in this age	Study 122

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Dyspnoea Safety was primary endpoint)	It is an AESI of Orkambi included in 4.4 and 4.8 of SmPC		2.2% of subjects had dyspnoea that led to treatment interruption	N/A	Known AESI of the drug/not long term data in this age	Study 122

Abbreviations: SwCl: sweat chloride

Notes: only the secondary endpoint is added, the so-called other endpoints are not in the table please see the AR

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Available data from study 122 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 1 to 2 years old, is also based on the extrapolation of Orkambi efficacy from older children and adults to the younger children enrolled in study 122. Therefore the PD parameters are acceptable to assume a similar clinical benefit for younger children. The clinical relevance of some parameters may not be fully ascertained in the patient population of 1 to 2 years, but it can be agreed that efficacy is being extrapolated from trials in older children. However, considering to the limited PD data provided, the lack of clinical data in the children aged 1 to 2 years old, and given that the disease is usually less sever in younger children with little deterioration in lung function, further data are expected to be generated in the PAES.

Only a few PK data have been submitted for patients in the 7-9 kg weight brackets, adding some uncertainties related to PK variability in this weight group. To confirm the accuracy of the PK model for this weight group further PK data will be submitted by the MAH when available.

The safety profile did not show new safety concerns as compared to the safety profile of LUM/IVA coming from CF subjects from other trials and post marketing. Only a small number of children were exposed for 24 weeks, thus a complete characterisation of the safety profile of LUM/IVA in this age group is not possible at present. Therefore, further safety data with drug exposure longer than 24 weeks are needed and will be generated in the imposed PAES and in the PASS.

3.7.2. Balance of benefits and risks

Available data from study 122 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 CF children, aged 1 to less than 2 years old. These 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 uncertainties linked to the uncontrolled study and the small number of patients with PD parameters and the lack of clinical efficacy data further clinical study data are expected to be generated post authorization with the extension of the PAES to children 1 to 2 years of age. In addition further long-term safety data will be generated by the PASS planned by the MAH.

3.8. Conclusions

The overall benefit/risk balance of Orkambi is positive, subject to the conditions stated in section

'Recommendations'.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Orkambi is not similar to Kalydeco, TOBI Podhaler, Symkevi and Kaftrio within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000. See appendix on similarity.

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 75 mg / 94 mg, granules in sachet is favourable in the following indication(s):

Orkambi granules are indicated for the treatment of cystic fibrosis (CF) in patients aged 1 year and older who are homozygous for the F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene (see sections 4.2, 4.4, and 5.1).

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 Marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

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

- **Obligation to conduct post-authorisation measures**

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

Description	**Due date**
Post-Authorisation Efficacy Study (PAES)	Interim Analysis:

Description	Due date
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 1 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.	December 2022 Final Report: December 2025

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0506/2020 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

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.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II, IIIA, IIIB and A
X.02.III	Annex I_2.(c) Change or addition of a new strength/potency	Line Extension	I, IIIA, IIIB and A

Extension application to add a new strength of 75 mg of lumacaftor and 94 mg of ivacaftor fixed dose combination granules, grouped with a type II variation (C.I.6.a).

Extension of indication to include treatment of cystic fibrosis for children aged 1 to less than 2 years old of age who are homozygous for the F508del mutation in the CFTR gene, based on final results from study 122, a 2-part study of CF subjects 1 to <2 years of age homozygous for F508del. As a consequence, sections 4.1, 4.2, 4.5, 4.6, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Annex II has also been updated. In addition, the MAH took the opportunity to implement minor updates in the Product Information. Version 11.4 of the RMP has also been approved.

5. Appendix

5.1. CHMP AR on similarity dated 26 April 2023