17 October 2019
EMA/CHMP/613823/2019
Committee for Medicinal Products for Human Use (CHMP)

CHMP assessment report on group of an extension of marketing authorisation and an extension of indication variation

Kalydeco

International non-proprietary name: ivacaftor

Procedure No. EMEA/H/C/002494/X/0075/G

Note

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

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List of abbreviations

ADR	adverse drug reaction
AE	adverse event
ALT	alanine transaminase
AUC	area under the concentration versus time curve
AUC0-∞	AUC from the time of dosing extrapolated to infinity
AUCss	AUC at steady-state
AUC0-tlast	AUC from the time of dosing to the last measurable concentration
BA	bioavailability
BMI	body mass index
CDC	Centers for Disease Control and Prevention
CF	cystic fibrosis
CFQ-R	Cystic Fibrosis Questionnaire-Revised
CFTR	CF transmembrane conductance regulator gene
CFTR	CF transmembrane conductance regulator protein
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CL	clearance
CL/F	apparent clearance
Cmax	maximum observed concentration
Cmin	minimum observed concentration
Cmin,ss	Cmin at steady-state
CQAs	Critical Quality Attributes
CYP	cytochrome P450
DDI	drug-drug interaction
DSL	Design Space Limits
ECG	electrocardiogram
EEA	European Economic Area
EMA	European Medicines Agency
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
FE-1	fecal elastase-1
FEF25%-75%	forced expiratory flow 25%-75%
FEV0.5	forced expiratory volume in 0.5 seconds
FRC	functional residual capacity
FVC	forced vital capacity
GLSMR	geometric least squares means ratio
GMP	Good Manufacturing Practices
IA2R	Interim Analysis 2 Report
IPC	In-Process Control
IPFT	infant pulmonary function tests
IQR	interquartile range
IRT	immunoreactive trypsin and/or trypsinogen
IVA	ivacaftor
LCI	lung clearance index
MIAH	Manufacturer and Importer Authorisation Holder
Max	maximum

Min	minimum
n	size of subsample
N	total sample size
ND	not determined
NOR	Normal Operating Range
OE	ophthalmologic examination
P	probability
PD	pharmacodynamic, pharmacodynamics
PDCO	European Medicines Agency Pediatric Committee
PEx	pulmonary exacerbation
Ph.Eur.	European Pharmacopoeia
PIP	pediatric investigation plan
PK	pharmacokinetic, pharmacokinetics
ppFEV1	percent predicted forced expiratory volume in 1 second
PT	Preferred Term
q12h	every 12 hours
qd	daily
Q/F	apparent inter-compartmental clearance
QbD	Quality by Design
QP	Qualified Person
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SDD	Spray Dried Dispersion
SLS	Sodium Lauryl Sulfate
SOC	System Organ Class
TEZ	tezacaftor
UK	United Kingdom
ULN	upper limit of normal
US	United States
Vc/F	apparent central volume
Vp/F	apparent peripheral volume
WR	written request

1. Background information on the procedure

1.1. Submission of the dossier

Vertex Pharmaceuticals (Ireland) Limited submitted on 21 November 2018 a group of variation(s) consisting of an extension of the marketing authorisation and the following variation(s):

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

The MAH applied for an addition of a new strength of 25 mg granules in sachet in the treatment of cystic fibrosis in children aged 6 to less than 12 months old.

In addition, the MAH proposed updates to sections 4.2, 4.4, 4.5, 4.8, 5.1, 5.2 and 5.3 of the SmPC, and the PL for the 150 mg film-coated tablet presentations to bring it in line with the new dosage form (25 mg granules), which supports the extension of indication for children aged 6 to 12 months old.

Furthermore, the MAH took the opportunity to implement minor updates to the Product Information.

The RMP (version 8.4) is updated in accordance.

Moreover, the PI is brought in line with the latest QRD template version 10.1.

The legal basis for this application refers to:

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

Kalydeco, was designated as an orphan medicinal product (EU/3/08/556) on 08 July 2007 in the following indication: Treatment of cystic fibrosis.

The new indication, which is the subject of this application, falls within the above mentioned orphan designation.

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0353/2018 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0353/2018 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

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

Protocol assistance

The MAH did not seek Protocol assistance at the CHMP.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Maria Concepcion Prieto Yerro

The application was received by the EMA on	21 November 2018
The procedure started on	28 December 2018
The Rapporteur's first Assessment Report was circulated to all CHMP members on	3 April 2019
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	26 March 2019
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	11 April 2019
The CHMP agreed on the consolidated List of Questions to be sent to the MAH during the meeting on	26 April 2019
The MAH submitted the responses to the CHMP consolidated List of Questions on	24 May 2019
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	22 July 2019
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	11 July 2019
The CHMP agreed on a list of outstanding issues in writing to be sent to the MAH on	25 July 2019
The MAH submitted the responses to the CHMP List of Outstanding Issues on	17 September 2019
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	8 October 2019
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 Kalydeco on	17 October 2019
The CHMP adopted a report on similarity of Bronchitol (mannitol), TOBI Podhaler (tobramycin inhalation powder), Cayston (aztreonam lysinate inhalation use) and Symkevi (tezacaftor/ivacaftor) on (Appendix 1)	17 October 2019

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Cystic Fibrosis (CF) is an autosomal recessive disease with serious, chronically debilitating morbidities and high premature mortality, and at present, there is no fully satisfactory 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.

2.1.2. Epidemiology

CF affects approximately 44,000 individuals in the EU (ECFS Patient Registry, 2016 Annual Data Report) and is considered an orphan disease. Approximately half of the individuals affected by CF are less than 18 years of age. Data from the mentioned registry corresponding to 2016 show that in some countries there is no newborn screening, and that in others, in the five years previous to 2016, almost all the CF patients underwent newborn screening. In total, 72% of all children of 5 years old or younger registered in the ECFSPR in 2016 underwent newborn screening; however, this estimate reflects the fact that not all the countries perform newborn screening. The mean age at diagnosis (in years) was 4.14 with approximately half of the patients diagnosed before the age of 0.34 years (around 4 months).

The F508del is the most frequent mutation in the CF patients. The G551D- CFTR mutation is present in 1198 alleles (1.40%) and the country with the highest allele prevalence is Ireland (8.78%). The allelic frequency is less for other non-G551D gating mutations.

2.1.3. Aetiology and pathogenesis

The underlying cause of CF, a defect 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.

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. More than 1900 mutations in the CFTR gene have been identified.

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.

CF causing mutations can be divided into 2 groups based on the extent of loss of chloride transport caused by the mutation. A complete or near complete loss of CFTR chloride transport is referred to as "minimal function" of CFTR. A less complete loss of CFTR-mediated chloride transport is referred to as "residual function" of CFTR.

2.1.4. Clinical presentation, diagnosis

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.

The diagnosis of CF is usually based on a clinical picture compatible with the disease, and it is confirmed by laboratory evidence of abnormal CFTR protein function (a positive sweat test) or by genotyping analysis. Loss of lung function is the major cause of morbidity and mortality in patients with CF. However, at very young ages clinically apparent lung disease may be absent although lung structural changes may be already present and progressing. In children with CF, pancreatic insufficiency and poor nutritional status are the most significant clinical manifestations of the disease. It is anticipated that ivacaftor treatment in this age range may contribute to slowing disease progression at older ages and to the prevention of the negative consequences of CF, such as compromised lung and pancreatic function, impaired nutritional status, development of cystic fibrosis-related diabetes or liver disease. Overall, validated endpoints that may help to substantiate whether this is the case are lacking but published 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.

2.1.5. Management

The majority of CF therapies target the symptoms of the disease such as nutritional supplements, antibiotics, and mucolytics. CFTR modulators are small molecules that target the functional defect of the mutated CFTR protein and therefore they are not intended as a replacement for or an alternative to any of the current non-modulator therapies. The goal of therapy is to maintain and restore respiratory function.

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.

About the product

Kalydeco tablets are indicated for the treatment of patients with cystic fibrosis (CF) aged 6 years and older and weighing 25 kg or more who have one of the following gating (class III) mutations in the CFTR gene: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N or S549R.

Kalydeco tablets are also indicated for the treatment of patients with cystic fibrosis (CF) aged 18 years and older who have an R117H mutation in the CFTR gene.

Kalydeco tablets are also indicated in a combination regimen with tezacaftor 100 mg/ivacaftor 150 mg tablets for the treatment of patients with cystic fibrosis (CF) aged 12 years and older who are homozygous for the F508del mutation or who are heterozygous for the F508del mutation and have one of the following

mutations in the CFTR gene: P67L, R117C, L206W, R352Q, A455E, D579G, 711+3A→G, S945L, S977F, R1070W, D1152H, 2789+5G→A, 3272 26A→G, and 3849+10kbC→T.

Kalydeco granules are indicated for the treatment of children with cystic fibrosis (CF) aged 12 months and older and weighing 7 kg to less than 25 kg who have one of the following gating (class III) mutations in the CFTR gene: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N or S549R.

This extension of the marketing authorisation intends to support an indication expansion for Kalydeco (ivacaftor, IVA) for the treatment of cystic fibrosis in patients 6 to <12 months of age who have at least 1 of the mutations in the *CFTR* gene that are currently indicated for Kalydeco.

Ivacaftor is a potentiator of the CFTR protein, i.e., *in vitro* ivacaftor increases CFTR channel gating to enhance chloride transport in specified gating mutations with reduced channel-open probability compared to normal CFTR.

Type of Application and aspects on development

Study 124 is included in the IVA pediatric investigational plan (PIP) in the EU, and European Medicines Agency Paediatric Committee (PDCO) agreed the open-label extension Study 126 would be captured in the Kalydeco Risk Management Plan. A Type B meeting with the FDA was held on 05 May 2017, and an EMA/Rapporteur presubmission meeting was held on 29 March 2017; Vertex discussed with the FDA and the EMA Rapporteur the proposed clinical development of Kalydeco in patients 0 to <24 months of age, and the submission plan for the age groups <12 months to support the filing for an indication extension based on interim analysis of PK and safety data from 5 patients from each age cohort. In the US, Kalydeco was approved for the treatment of children aged 12 to <24 months on 15 August 2018 and Kalydeco was approved for treatment of children aged 6 to < 12 months on 29 April 2019. .

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as granules in sachet containing 25 mg of ivacaftor as active substance. This new strength is being introduced to support an indication expansion for Kalydeco for the treatment of cystic fibrosis (CF) in infants aged at least 6 months, toddlers and children weighting 5 kg to less than 25 kg who have at least 1 of the mutations in the *CFTR* gene that are currently indicated for Kalydeco.

Other ingredients are: colloidal anhydrous silica, croscarmellose sodium, hypromellose acetate succinate, lactose monohydrate, magnesium stearate, mannitol, sucralose and sodium lauryl sulfate (E487).

The product is available in packaged in a biaxially oriented polyethylene terephthalate/polyethylene/foil/polyethylene (BOPET/PE/Foil/PE) sachet.

2.2.2. Active substance

The active substance and its spray-dried dispersion (SDD) used to manufacture ivacaftor 25 mg granules in sachet, are identical to those used to manufacture the already approved Kalydeco 150 mg tablets and Kalydeco 50 mg and 75 mg granules in sachet. Therefore, no information on the active substance and the SDD has been submitted within this line extension application.

2.2.3. Finished medicinal product

Description of the product and Pharmaceutical development

The finished product is an immediate release granule dosage form for oral administration. The ivacaftor granules have a diameter of 2.0 mm, a target thickness of 2.1 mm and a target weight of 6.87 mg. Each granule contains a target of 1.92 mg of ivacaftor, which is previously formulated as an amorphous SDD intermediate.

The granules are filled by count into the primary container closure (sachet) to achieve the targeted strength of ivacaftor per packet. Each sachet is equivalent to one unit dose (25 mg, 50 mg or 75 mg).

For administration, the contents of the packet are emptied and mixed with soft food.

The composition of the ivacaftor granules is provided in Table 1.

Table 1.Composition of Ivacaftor Granules

Component		*Quality Standard*	*Component Function*
Ivacaftor SDD	Ivacaftor drug substance	3.2.S.4.1	Active
	Hypromellose acetate succinate	USP/NF[a]	Stabilizer
	Sodium lauryl sulfate (SLS)	Ph.Eur.	Surfactant
Lactose monohydrate		Ph.Eur.	Filler
Mannitol		Ph.Eur.	Filler
Sucralose		Ph.Eur.	Sweetener
Croscarmellose sodium		Ph.Eur.	Disintegrant
Colloidal silicon dioxide		Ph.Eur.	Glidant
Magnesium stearate		Ph.Eur.	Lubricant
Total		---	---
Minitablets per Packet[b]		---	---

[a] *HPMCAS meets USP/NF specifications. No Ph. Eur. Monograph exists.*

All excipients 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 and in paragraph 2.1.1 of this report.

As indicated above, the active substance and SDD used in the ivacaftor granules 25 mg, 50 mg and 75 mg and the ivacaftor tablet 150 mg are identical.

Most of the pharmaceutical development relevant for Kalydeco 25 mg granules was performed for Kalydeco 150 mg film-coated tablets and Kalydeco 50 mg and 75 mg granules. All the three granule formulations (25 mg, 50 mg and 75 mg strengths) are proportional and manufactured from the same drug product bulk by filling different amounts into the sachets.

The dissolution medium and the dissolution conditions (Apparatus 2 –paddles) are the same as for the 50 mg and 75 mg granules strengths. The dissolution profiles and rates are shown to be independent of granule strength. As shown for the 50 mg and 75 mg granules strengths, the dissolution method is able to discriminate against granule formulations with different bioavailability (prototype formulation and

Phase 3 granules), different degree of ivacaftor crystallinity, compression pressure and spray-dried dispersion bulk density.

The container closure system for ivacaftor granules is a Biaxially Oriented Polyethylene Terephthalate/Polyethylene/Foil/Polyethylene (BOPET/PE/Foil/PE) sachet. The material complies with Ph.Eur. requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process of Kalydeco 25 mg granules is identical to the one of Kalydeco 50 mg and 75 mg granules, with the exception of the filling step (different number of granules are filled per sachet to achieve the different strengths).

Briefly, the manufacturing process consist of manufacture of the ivacaftor SDD -which comprises mixture preparation, spray drying and secondary drying-, followed by blending, compression, and filling.

The manufacture of a SDD is a non-standard method of manufacture. Since this step of the manufacturing process is common to the approved Kalydeco 150 mg tablets, the MAH had extensive experience and provided validation data from commercial scale.

Design spaces were proposed for the following steps of the manufacturing process of the medicinal product: spray drying, secondary drying, blending and compression. The robustness of the process was verified during validation at commercial scale. The available development data, the proposed control strategy and batch analysis data from commercial scale batches fully support the proposed design spaces.

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

Product specification

The finished product release specifications, are identical to those for the 50 mg and 75 mg granules and include appropriate tests for this kind of dosage form: appearance, identification (IR), assay (HPLC), degradation products (HPLC), uniformity of dosage units (Ph. Eur.), dissolution (Ph. Eur.), physical form (XRPD), water content (Karl Fischer) and microbial limits (Ph. Eur.)

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

The potential presence of elemental impurities in ivacaftor granules was assessed according to the ICH Q3D Guideline for Elemental Impurities using a risk based approach. The risk assessment considered the potential contributions from the ivacaftor drug substance and SDD (including solvents, reagents, excipients, and equipment), water, granule excipients, and manufacturing equipment to determine the overall contribution of elemental impurities to the ivacaftor granules.

The elemental impurities intentionally added in the ivacaftor drug substance manufacturing process are controlled according to ICH Q3D requirements.

The risk assessment of the content of Class 1 and Class 2A elemental impurities (as defined in ICH Q3D) in the ivacaftor drug substance and SDD demonstrated that the risk of elemental impurities in these materials is low. All granule excipients were also shown to comply with ICH Q3D requirements in the granules. Testing of representative batches including three commercial batches of drug substance and

SDD from each manufacturer confirmed that the contents of Class 1 and Class 2A elemental impurities are consistently below 30% of the ICH Q3D Option 1 limits.

This risk assessment and confirmatory testing demonstrates that the risk of elemental impurities in the ivacaftor granules is low and the product will consistently meet the ICH Q3D requirements. Therefore, no additional controls on elemental impurities are required.

Batch analysis results were provided for four commercial scale batches of 25 mg granules (three from one manufacturer and one from a second manufacturer) confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

The stability studies provided in this application were initiated and presented as part of the application for the approved 50 mg and 75 mg granules strengths. A bracketing approach was followed.

Specifically, stability data from three commercial scale batches of each of the bracketing strengths (25 mg and 100 mg) manufactured at one of the proposed manufacturing sites and stored for up to 48 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided.

Supportive stability data from three commercial scale batches manufactured at another commercial manufacturing site and stored for 3 months at long term and accelerated conditions were also provided.

The batches of Kalydeco 25 mg granules in sachet are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

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

All results met the acceptance criteria for the attributes evaluated. The stability data show that the finished product is stable when packaged in the configuration proposed for commercial distribution under all storage conditions.

Photostability per ICH Q1B, Option 2, was not performed with ivacaftor granules as the commercial container closure is light protective.

In-use stability in food was also evaluated to confirm that stability and release of ivacaftor are preserved when mixed with food prior to administration. Applesauce, carrot puree, yogurt, infant formula and water were selected as representative foods as they are commonly available, patient friendly, and demonstrated acceptable sensory attributes.

Chemical and physical stability of granules mixed with food was evaluated by testing assay and degradation products, dissolution, and physical form.

Sachets of 25 and 100 mg were mixed with food and tested after 1-hour contact time at room temperature.

All results met the acceptance criteria for the attributes evaluated.

The XRPD profile with infant formula was determined to be due to the formation of a co-crystal with ivacaftor and triglycerides. This was confirmed by spectroscopic analysis and by ultimately comparing the XRPD pattern to those of a series of well characterized pure cocrystals. Comparable dissolution profiles in quality control and simulated intestinal media, and similar solubility of the triglycerides co-crystals to the ivacaftor SDD, suggest that formation of an ivacaftor-triglyceride co-crystal in food will not have an impact on ivacaftor bioavailability. Overall, the results of the in-use stability in food show that all results meet the acceptance criteria.

Based on available stability data, the proposed shelf-life of 36 months with no storage conditions as stated in the SmPC (section 6.3) are acceptable.

Adventitious agents

It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

2.2.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the 25 mg granules has been presented in a satisfactory manner. Most of the pharmaceutical development relevant for Kalydeco 25 mg granules was performed for Kalydeco 150 mg film-coated tablets and Kalydeco 50 mg and 75 mg granules. All the three granule formulations (25 mg, 50 mg and 75 mg strengths) are proportional and manufactured from the same drug product bulk by filling different amounts.

The MAH has applied QbD principles in the development of the finished product and their 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.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

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

2.2.6. Recommendations for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

This is a Line Extension Application to the Kalydeco (Ivacaftor) Marketing Authorisation, in order to request the addition of a new pharmaceutical strength of one of the existing pharmaceutical forms, that is 25 mg granules in sachet, which is proposed to support an Extension of Indication to children aged 6 to less than 12 months old who have one of the currently approved gating mutations in the CFTR gene: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N or S549R.

Apart from the Environmental Risk Assessment (ERA), no new clinical data have been submitted in this application.

2.3.2. Ecotoxicity/environmental risk assessment

An updated ivacaftor ERA (VX-770: Kalydeco Monotherapy and in combination with VX-809 or VX-661 Environmental Phase I and II Risk Assessment) was provided in Module 1.6.1 in procedure EMEA/H/C/002494/II/63/G (supportive Type II variation for tezacaftor/ivacaftor combination regimen indication), which is resumed in the following table. The report provided a revised F_{pen} based on the prevalence of relevant CFTR mutations that ivacaftor is prescribed for in Kalydeco, Orkambi and Symkevi. The F_{pen} was refined by mutation only and was not restricted by age, thereby incorporating the proposed Kalydeco monotherapy indication extension.

The Phase II Tier B assessments of ivacaftor are ongoing and the Applicant states that the final ivacaftor ERA (Kalydeco monotherapy) will be available and submitted to the European Medicines Agency at a later stage.

Table 2

Substance (INN/Invented Name): Ivacaftor			
CAS-number (if available): 873054-44-5			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	>4.7	Potential PBT: Y
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	>4.7	
	BCF	not available	B/not B
Persistence	ready biodegradability	not available	
	DegT50	$DT_{50,\ system}$ = 1233/261 d (sandy silt loam sediment / sand sediment)	DT_{50} values corrected to 12°C. Conclusion: vP
Toxicity	NOEC algae NOEC crustacea NOEC fish	≥54.7 0.0031 ≥1000	T
	CMR	not investigated	potentially T
PBT-statement :	PBT assessment cannot be finalised.		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$	0.026	µg/L	> 0.01 threshold: Y; based on refined Fpen, Fpen refinement currently not acceptable.
Other concerns (e.g. chemical class)			N
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption	OECD 106	K_{oc} =2710; 1970; 5900 L/kg	
Ready Biodegradability Test	OECD 301	not available	study not required
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50water}$ 1.7/4.4 d at 20°C $DT_{50water}$ 3.6/9.4 d at 12°C $DT_{50sediment}$ 1329/208 d at 20°C $DT_{50sediment}$ 2836/444 d at 12°C $DT_{50total\ system}$ 581/123 d at 20°C	Significant shifting to sediment observed. Ivacaftor is very persistent in sediment

		$DT_{50total\ system}$ 1233/261 d at 12°C % shifting to sediment >10%			
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD 201	NOEC	≥54.7	µg/L	growth rate
Daphnia sp. Reproduction Test	OECD 211	NOEC	3.1 p.m.	µg/L	
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC	p.m.	µg/L	report not available
Activated Sludge, Respiration Inhibition Test	OECD 209	EC10	>1000	µg/L	respiration
Phase IIb Studies					
Bioaccumulation/*Species*	OECD 305	BCF	not available	L/kg	%lipids:
Aerobic and anaerobic transformation in soil	OECD 307	DT50 $\%CO_2$	p.m.	d	report not available
Soil Micro-organisms: Nitrogen Transformation Test	OECD 216	NOEC	≥0.046	mg/ kg	endpoint potentially insufficient to exclude a risk to soil micro-organisms.
Terrestrial Plants, Growth Test	OECD 208	NOEC	≥1818	mg/ kg	
Earthworm, Acute Toxicity Tests/*Eisenia fetida*	OECD 207	NOEC	≥417	mg/ kg	
Collembola, Reproduction Test/*Folsomia candida*	ISO 11267	NOEC	≥690	mg/ kg	
Sediment dwelling organism/*Species*		NOEC	not available	mg/ kg	normalised to 10% o.c.

2.3.3. Discussion on non-clinical aspects

No new non-clinical data have been submitted in this application, which is considered acceptable apart from the studies of updated ERA. The ERA for ivacaftor is being revised, with new experimental studies conducted and planned to assess the impact of ivacaftor in the environment which will be submitted in due course. Final ivacaftor ERA will refer to monotherapy medicinal products (Kalydeco 150 mg film-coated tablets and Kalydeco 25 mg, 50 mg and 75 mg granules) and to combination therapy (Orkambi 100 mg/125 mg film-coated tablets and Orkambi 200 mg/125 mg film-coated tablets, Symkevi 100 mg/150 mg film coated tablets). This is accepted by the CHMP.

2.3.4. Conclusion on the non-clinical aspects

The data submitted in the non-clinical part of the dossier are acceptable for this type of application.

2.4. Clinical aspects

2.4.1. Introduction

GCP

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

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

- Tabular overview of clinical studies

Type of Study	Study Identifier/ Location	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Subjects/ Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Phase 3 Safety, PK, and Efficacy	VX15-770-124 Module 5.3.5.2	Part A: To evaluate the safety and PK of IVA treatment Part B: To evaluate the safety, PK, PD, efficacy, and acceptability/palatability of IVA treatment	Nonrandomized, open-label, multiple-dose	IVA 25-, 50-, or75-mg granules; 25, 50, or 75 mg q12h; PO	Part A: 6 subjects Part B: 11 subjects male and female subjects <12 months of age and have a *CFTR* gating mutation (Cohorts 2 and 6)	Part A: Days 1 through 3, and morning dose on Day 4 Part B: 24 weeks	Ongoing Cohort 1 and Cohort 5 are complete; (subjects 12 to <24 months of age) Cohort 2 and Cohort 6 are complete; (subjects 6 to <12 months of age)
Phase 3 Safety, PD and Efficacy	VX15-770-126 Module 5.3.5.2	IVA Arm: To evaluate the safety of long-term IVA treatment in subjects with CF who are <24 months of age at treatment initiation and have a *CFTR* gating mutation To evaluate the PD of long-term IVA treatment in subjects with CF who are <24 months of age at treatment initiation and have *CFTR* gating mutation To evaluate the efficacy of long-term IVA treatment in subjects with CF who are <24 months of age at treatment initiation and have *CFTR* gating mutation Observational Arm: To evaluate long-term safety after discontinuation of IVA treatment in subjects with CF who were <24 months of age at treatment initiation and have a *CFTR* gating	Open-label, 2-arm	25-, 50-, or 75-mg granules, and others (to be determined based on safety and PK data from study 770-124, age and weight); PO	Approximately 75 male and female subjects who are < 24 months of age and have a *CFTR* gating mutation on at least 1 allele	IVA Arm: 128 weeks Observational Arm: 104 weeks	Ongoing

2.4.2. Pharmacokinetics

The pharmacokinetics of ivacaftor in the target age group from 6 to less than 12 months of age was investigated in Study 124 which is an ongoing, two-part study, with part A assessing mainly PK and part B (24 weeks) assessing safety and efficacy. In Part A, ivacaftor 25 mg (children aged 6 to less than 12 months and weighing 5 to < 7 kg) or 50 mg (children aged 6 to less than 12 months and weighing 7 to < 14 kg) as granules was administered twice daily for a total of 7 doses to obtain steady-state concentrations. The proposed dosing recommendations in section 4.2 of the SmPC would theoretically allow dosing children aged 6 to less than 12 months and weighing ≥ 14 kg to less than 25 Kg with ivacaftor 75 mg BID. A 14-kg body weight is above the 97th percentile for the oldest children in the age range from 6 to less than 12 months according to the WHO weight-for-age growth charts. Although CF is commonly associated with undernutrition, the proportion of overweight and obese individuals is increasing.

In Study 124, ivacaftor granules were mixed with approximately 1 teaspoon (5 mL) of appropriate liquid or soft food and administered with an age-appropriate fat-containing meal or snack. This method of administration is in line with the recommendations to administer ivacaftor 150 mg tablets. This is endorsed as the magnitude of food effect for the final granule formulation is similar to that of the 150-mg tablet when administered with a high-fat meal relative to fasted conditions. In Part B, the dose could be adjusted if needed based on Part A results but all subjects received 50 mg BID.

PK data was available from both parts, from Part A/Cohort 2 (6 subjects, 24 PK observations) and from Part B/Cohort 6 (11 subjects, 82 PK observations) as well. Cohorts 2 and 6 enrolled patients who are six to less than twelve months of age. In Cohort 2, 1 subject received 25 mg IVA q12h. In the 50-mg IVA q12h group, there were 5 subjects. In Part B, a total of 11 subjects were enrolled (including 3 subjects

who participated also in Part A). At Day 1, all subjects weighed 7 to <14 kg (range: 7.8 to 10.7 kg) and therefore received IVA 50 mg q12h.

Plasma concentrations of IVA and metabolites, M1-IVA and M6-IVA, were analysed by descriptive statistics. PK analysis of IVA for comparison of IVA disposition to that of adults was conducted as described within the Population PK report (Report O290) via nonlinear mixed effects modeling with the nonlinear mixed effects modelling (NONMEM) software.

Analytical methods: The analytical method validations for the determination of M1, and M6 in K2EDTA and K3EDTA were already assessed in prior procedures. There were three analytical methods used in the clinical studies that were already assessed in the previous assessment reports. The results of the cross-validation and transfers experiments determined that data were comparable between the three laboratories where data on plasma concentrations were generated. All original samples analyzed within the 446 days demonstrated long-term storage stability in human plasma containing K2EDTA at -80 ºC ± 10 ºC.

The in-study validation for each analyte shows acceptable calibration standards and QCs and the reasons for the reanalysis of samples are acceptable for each analytes (above ULOQ and one sample due to unacceptable internal standard response) for VRT-842917. The ISR was performed in a total of 31 samples for each analyte. For the samples reanalysed, the ISR was acceptable as 90.3% (28 samples out of 31 samples) of the samples reanalysed were within the acceptance range (± 20%).

*Bioavailability and food effect:*A new dose strength, i.e., ivacaftor 25 mg granules is proposed to dose children aged 6 to less than 12 months and weighing at least 5 kg to less than 7 kg. The comparative bioavailability and food effect have been investigated with the 150 mg dose (2x75 mg) in studies 012 and 015 (assessed in EMEA/H/C/002494/X/0034/G). The conclusions regarding bioavailability and food effect can be extrapolated to the 25 mg strength because the formulations are qualitatively identical, quantitatively proportional, the same manufacturing method is used, and ivacaftor PK is linear. In addition, the dissolution profiles of both strengths should be similar. A question has been included in the quality part of this report in this respect. These investigations were conducted with the highest strengths/doses (worst case scenario) as required in the guideline on the investigation of bioequivalence and the guideline on interactions.

As the magnitude of food effect for the final granule formulation is similar to that of the 150-mg tablet when administered with a high-fat meal relative to fasted conditions, the proposed dosage and administration recommendations for the granule formulation are the same as for the film-coated tablets, i.e., they are to be administered with fat-containing food, the same as Kalydeco 150-mg tablets.

Pharmacokinetics in the target paediatric population: The doses for the 6 to <12 month cohort in Study 124 were selected based on simulations conducted using a previously developed population PK model that included data from subjects 1 through 5 years of age. The primary objective of Part A/Cohort 2 of study 124 was to evaluate the PK of ivacaftor and metabolites M1-IVA and M6-IVA at the doses selected in infants and toddlers with cystic fibrosis who were <24 months of age at treatment initiation and have a *CFTR* gating mutation.

Ivacaftor metabolite concentrations were determined but they are not incorporated in the model or their values further discussed with respect to those of older age groups. Plots of observed plasma concentrations of metabolites M1 and M6 over time in children aged 6 to less than 12 months were provided and compared to those of adult subjects and children aged 6 to less than 12 years old dosed with ivacaftor 150 mg BID. While the observed M1 plasma concentrations are mostly within the range of values that have been observed in adults and children, for M6 2 infants had observed plasma concentrations higher than 6000 ng/ml (almost the double of the concentrations observed in the remaining infants

enrolled in Part A/Cohort 2) which are above the range of values observed in these two older age groups. No remarkable adverse events were reported for these two infants.

Ivacaftor metabolites are not included in the pop-PK model given that prior attempts to develop an integrated population PK model were not successful as parameter estimates for the metabolite models were not physiologically reasonable and with unrealistic relationships between body size and volume of distribution. Therefore, the pop-PK analysis only characterise ivacaftor exposure as the key driver of efficacy. This has been accepted for prior procedures. Regarding the consequences of possible genetic polymorphisms, at the time of assessment of MAA of Symkevi, the MAH committed to characterise post-authorisation the systemic exposure to ivacaftor and tezacaftor in subjects with the variant *CYP3A4*22* in comparison with wild-type *CYP3A4*. A study has been completed assessing the systemic exposure to ivacaftor and tezacaftor in subjects with the variant *CYP3A4*22* in comparison with subjects with 2 copies of the wild-type *CYP3A4* allele. No subjects were homozygous for *CYP3A4*22* and therefore it cannot be excluded that exposure in such patients is increased to a larger extent than in the heterozygous population. The lack of data in this population is reflected in section 5.2 of the Kalydeco SmPC.

The MAH has calculated the intra-subject variability of the granules based on the residual variability of the cross-over study 015, where healthy adult volunteers were enrolled. The real intra-subject variability could not be estimated because the design is not a replicate design. However, the residual variability is an acceptable alternative. The estimated intra-subject variability expressed as coefficient of variation (CV, %) was 15%, 15%, and 24% for $AUC_{0-\infty}$, $AUC_{0-tlast}$, and C_{max} respectively. The MAH was also requested to estimate the intra-subject and inter-subject variability in the target paediatric population and provide the percent coefficient variation (%CV) for Cmin,ss and AUC,ss in children aged 6 to less than 12 months based on the pop-PK analysis. This has been done based (apparently) on Model 2 (see further below). Inter and intrasubject variability in AUCss was 46% and 20% respectively, while for Cmin,ss these values were 60% and 23%. The MAH was requested to explain how these low values of intra-individual variability have been calculated. It has been clarified that they were calculated using model-predicted exposures from empirical Bayes estimates (EBEs). Due to the small sample size and the limited availability of blood samples in these young subjects the values (both inter- and intra-subject variability) should be viewed with caution.

Population-PK analysis: Plasma concentrations of IVA and metabolites, M1-IVA and M6-IVA, were analysed by descriptive statistics but PK analysis of IVA for comparison of IVA disposition to that of adults was conducted via nonlinear mixed effects modelling. The population PK model supporting dosing recommendations for children aged at least 6 months to less than 12 months includes data from paediatric patients (from less to 18 years down to 3 months of age). This pop-PK modelling and simulation study with PK paediatric-only data was initially developed to support dosing recommendations of ivacaftor for children aged 12 to less than 24 months. The PK data set consisted at that time of 197 subjects (which already included data from the 6 children aged 6 to less than 12 months enrolled in Part A/Cohort 2). This model has been updated with data from the 11 subjects enrolled in Part B/Cohort 6 as well as with data from 6 subjects enrolled in Part A, Cohort 3 (aged 3 to less than 6 months).

A two-compartment model with zero-order delivery to the absorption compartment and subsequent first-order absorption was chosen as the ivacaftor structural model, with weight as an allometric function affecting the disposition parameters. After the initial fitting, an attempt of model refinement was made which included testing different models. Covariate models to account for age, sex, patient status (healthy volunteers versus patients with cystic fibrosis), and non-white race did not explain the variability in ivacaftor PK in a meaningful manner in adults and paediatric subjects two years of age and older. Race was not expected to have any impact due to the fact that all children were White. Most of them were female. Therefore, only body weight (with fixed allometric relationships) and age as a marker of maturation were considered as covariates for the analysis.

A model to describe the effects of age on ivacaftor clearance was investigated by incorporating a maturation function driven by post-menstrual age (PMA) which did not improve the fit of the model. As a consequence, this effect was not retained into the model and dosing recommendations proposed for section 4.2 of the SmPC (including in case of moderate hepatic impairment as well as in case of concomitant administration with moderate or strong CYP3A4 inhibitors) are weight-based for children weighing at least 5 kg to less than 25 kg (for which the corresponding ages are approximately 2 months to 8 years of a healthy same-age population of reference). However, neither numerical nor graphical information was initially submitted to show how the different models tested performed. The MAH was requested to provide a list of all models tested as well as the rationale for the model development procedure, including the numerical and graphical evaluation that supported the MAH's choice of the final model. Information on the models tested was discussed in response to the major objection and data regarding the process followed in report O290 (the initial pop-PK report submitted supporting current dosing recommendations) were provided. A summary table including the model description and the objective function value of each of the models tested as well as diagnostic plots with the loess smooth lines when applicable and stratified by body weight and age have been provided. The data provided support to the choice of the model with fixed exponent allometric scaling, and no maturation among the models initially tested and prior to the update with PK data from children less than 6 months of age (see further below). The diagnostic plot of ETA1-CL/F versus Age including the loess smooth line shows a trend on Cl/F over the studied age range (i.e., decreasing clearance with increasing age which was an unexpected finding).

Model-based predicted ivacaftor Cmin,ss and AUC,ss values in six to eleven month old subjects for the 50 mg dose group were similar to those of adults administered 150 mg BID ivacaftor. There was only one subject weighing less than 7 kg who was administered ivacaftor 25 mg BID for 4 days and even though the predicted exposure for this patient was within the adult range too, the influence of CYP3A maturation on ivacaftor clearance could not be excluded based on these very limited data from younger patients. Additional data were requested by CHMP for patients under 7 kg to evaluate the adequacy of the population pharmacokinetic model in estimating individual PK parameters for subjects under 7 kg of bodyweight. In addition, model-based simulations also showed that some patients aged 6 to less than 12 months and weighting at least 7 to less than 14 kg could have AUCss values exceeding the maximum observed AUC values in adults (approximately 30000 ng/mL•h) when dosed at 50 mg. This was also of concern considering that dosing recommendations for children with (moderate or severe) hepatic impairment or receiving concomitant treatment with moderate or strong CYP3A4 inhibitors are based on the conclusion from the initially developed population PK modelling and simulation analysis that there was minimal or no influence of CYP3A maturation on ivacaftor clearance. As a consequence, the MAH was requested to update the pop-PK model with the available PK data of children treated in study 124 (including children below 6 months of age and/or weighing less than 5 kg as Study 124 is ongoing enrolling younger age cohorts) and based on this updated model, to simulate the exposure of different dosing regimens per age and bodyweight groups (including, but not limited to, the dose of 25 mg for children aged 6 to less than 12 months of age and weighing ≥ 7 kg to less than 14 kg and for children weighing less than 7 kg) to compare the exposure distributions for each individual age and bodyweight group.

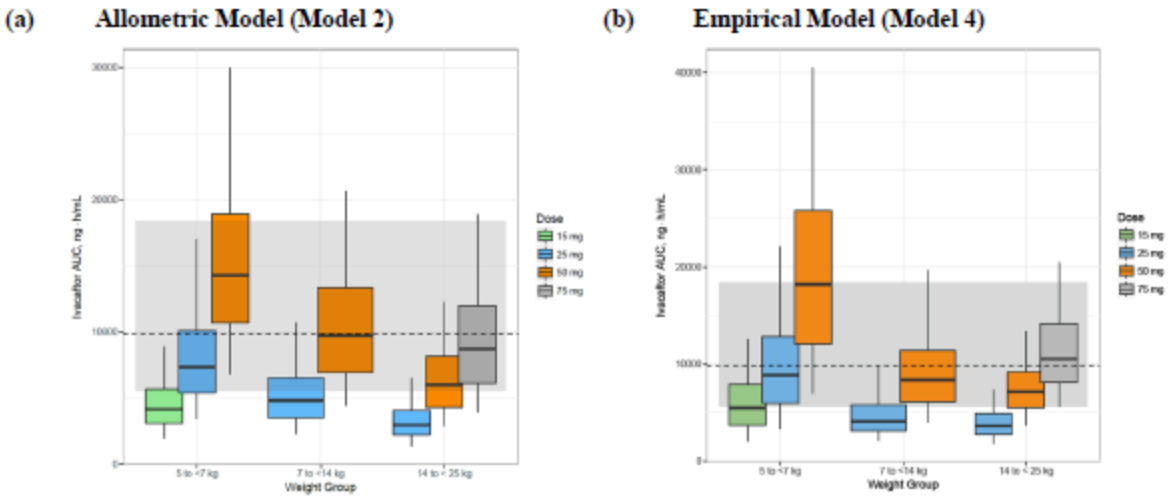
In response to the Major Objection, the MAH updated the pop-PK model above discussed with data from 6 subjects aged 3 to <6 months of age enrolled in Cohort 3 (Part A of study 124). Three of these infants received ivacaftor 25 mg BID (body weight below 7 kg) and the remaining 3 received 50 mg BID. Their body weight and length range from 5.3 to 8.1 kg and from 59.0 to 68.1 cm, respectively. Their weight-for-length z-scores and percentiles ranged from -2.83 to 0.73 and from 0 to 77 respectively. A child who received 25 mg IVA presented plasma concentrations of ivacaftor and metabolite M1 well above the maximum observed concentrations in the remaining children in this cohort, with values at least two

times higher. Plasma concentrations of M6-IVA were the highest observed ones. The weight-for length z-score and percentile was -2.83 and 0 respectively, which is indicative of wasting.

Not only was the prior model (fixed exponent allometric scaling, and no maturation, Model 1) updated with the above mentioned PK data (Model 2, a two-compartment disposition with allometric scaling on body weight and no maturation), but also some additional models were run by the MAH, i.e. Model 3 which implemented a maturation function driven by post-menstrual age and Model 4 which implemented an empirical Emax structure for weight effect and a maturation function. Regarding Model 4, it is stated that this model was run with and without maturation effect but no details were provided on the model without maturation effect. This was done and a fifth model (M5) was discussed which is an empirical model (as Model 4) without maturation. This model performed worse than Model 4 in terms of the objective function value, precision of the estimated parameters and predictions. A base model, which includes no age (maturation) or weight effects was also run to have a base model with the same data set (Model 1b) used in the previous mentioned models (Model 2-Model 5).

Selected diagnostic plots and model-based simulations have been provided for each of the 5 models discussed in responses to the CHMP. Based on all the presented diagnostic plots stratified by body weight and age, including VPCs and corrected VPCs as well as precision in parameter estimates, it can be concluded that Model 4 fits the data for children 6 to less than 12 months of age reasonably well.

Given the young age of children enrolled in Cohorts 2 and Cohorts 6 of study 124 and the involvement of CYP3A4 in the metabolism of ivacaftor (and metabolite M1), Cl/F and Vc/F values were plotted vs. age and weight. As previously said, the plot showing CL versus age showed a trend of apparent decrease of clearance with increasing age from 6 months up to 6 years which was unexpected. The diagnostic plots of ETA 1 vs. weight and age presented in response to the day 180 MO confirm that Model 4 is the one producing the best fit. It is therefore concluded that all data provided support the inclusion of both maturation and weight effects in the empirical model (Model 4) to capture trends in CL/F over the full age range and provide the best goodness of fit. Simulations of expected exposures for different dosing regimens per body weight bands for children aged 6 to less than 12 months were generated based on Model 2 and Model 4 including a dose of 15 mg for children weighing less than 7 kg as requested (see Figure below) showing that this dose may result in underexposure which is more pronounced when Model 2 is used.



AUC: area under the concentration versus time curve; AUC_{0-12hr}: area under the concentration versus time curve (from the time of dosing to 12 hours); IVA: ivacaftor; NHANES: National Health and Nutrition Examination Survey

Note: Shaded area represents 5th and 95th percentiles of exposures in adults. Dashed lines represent median of the adults. Simulation of AUC for all age groups (including adults) was performed using the population parameter estimates excluding inter-occasion variability and residual variability. Weights and ages were randomly sampled from NHANES for each weight and dose group.[2] This simulation provides an appropriate comparison of the central tendency in AUC between these groups.

Figure 1 Simulation of IVA AUC0-12hr at Steady-State for the Different Dosing Regimens for the Paediatric Population 6 to <12 Months of Age

Overall, these predictions are reassuring for the proposed doses of 25 mg, 50 mg, and 75 mg BID for children weighing at least 5 kg to less than 7 kg, for those weighing 7 kg to less than 14 kg and for those in the weight band from ≥ 14 kg to less than 25 kg, respectively when considering that simulations of exposures resulting from these regimens are consistent to those of older subjects and are not anticipated to exceed the maximum observed AUC values in adults (approximately 30000 ng/mL × h).

No attempt has been made during simulations to explore the effect of moderate hepatic impairment or the coadministration of ivacaftor with CYP3A4 moderate or strong inhibitors on the predicted ivacaftor exposures. Even though it has been concluded that the inclusion of both maturation and weight effects in the empirical model (Model 4) best captures the trend in CL/F over the full age range and provide the best goodness of fit, this has no impact on dosing recommendations with respect to the initial proposal. The simulations based on Model 2 (fixed exponent allometric scaling, no maturation) and Model 4 (empirical with maturation effect) would lead to the same dosing recommendations as currently proposed. The main difference seems to be that in the lighter children the predicted ivacaftor exposures are higher when Model 4 is used. Overall, it appears that the contribution of the maturation effect on CL is not as relevant as that of body weight.

Special populations: Of the covariates tested in the pop-PK study including PK data from children aged 6 to less than 12 months of age enrolled in Cohort 2/Part A and Cohort 6/Part B of Study 124 only body weight (with fixed allometric relationships) and age as a marker of maturation were considered as covariates for the analysis. A maturation function driven by post-menstrual age (PMA) was implemented in the pop-PK model to account for CYP3A4 maturation but as the fit of the model did not improve the effect of age was not retained in the final model on which these simulations were based. As sated above, even though it has been concluded that the inclusion of both maturation and weight effects in the empirical model (Model 4) best captures the trend observed in CL/F over the full age range and provide the best goodness of fit, this has no impact on dosing recommendations with respect to the initial

proposal. Therefore, the same dosing recommendations as initially proposed are kept on the basis that the systemic exposure for the 6 to <12 month population is accurately predicted by the updated model and consistent with exposures in older age groups including adults. Additionally, the MAH state that post-marketing experience to date in all age groups has not identified any issues with the current recommended guidance for patients with hepatic impairment.

The recommended dose for patients 6 to <12 months with moderate hepatic impairment is similar to the recommendation for patients 12 months to <6 years old with moderate hepatic impairment, but is adjusted for the smaller size of the 6 to <12 month old patients:

- 6 to <12 months and ≥5 to <7 kg: one 25-mg sachet/packet of granules qd
- 6 to <12 months and ≥7 to <14 kg: one 50-mg sachet/packet of granules qd

For patients with mild hepatic impairment, no dose adjustment is needed while in children with severe hepatic impairment use of IVA is not recommended unless the benefits outweigh the risks. In such case, the starting dose should be 1 sachet/packet of granules qd or less frequently. Dosing intervals should be modified according to the clinical response and tolerability which are basically the same recommendations as for older paediatric subjects and adults.

At the present time and even taken into account the current acceptance of the proposed posology for infants aged 6 to less than 12 months without hepatic damage, some concerns remain regarding the use of ivacaftor at the proposed doses in subjects with hepatic impairment as this was an exclusion criterion. Upon request, the MAH included a warning in section 4.4 of the SmPC to highlight that there are no safety data in children aged 6 to less than 12 months of age with moderate or severe hepatic impairment when treated with ivacaftor as recommended in section 4.2 of the SmPC. The MAH clarified however that the available post-marketing data in patients with hepatic impairment treated with ivacaftor as recommended in the SmPC were reassuring.

For subjects with mild or moderate renal impairment no dose adjustment is needed as there was minimal elimination of ivacaftor and its metabolites in urine in a mass balance study. Caution is recommended in case of severe renal impairment or end-stage renal disease. This seems acceptable. The median (range) gestational age at delivery of infants enrolled in Part B/Cohort 6 was 39.0 weeks (37, 41), i.e., all of them were born at term. Given that these children were at least 6 months of age at enrolment in Cohort 2 and Cohort 6 it can be assumed that at that time renal maturation is advanced.

Interactions: The recommended IVA dose for patients 6 to <12 months is 25 mg (5 to <7 kg) and 50 mg (7 to <14 kg) twice weekly during concomitant dosing with strong CYP3A inhibitors and 25 mg (5 to <7 kg) and 50 mg (7 to <14 kg) once daily during concomitant dosing with moderate CYP3A inhibitors.

The basis for such recommendations is the same as described above, i.e., the impact of CYP maturation on IVA disposition in this age group is minimal. The fact that both, the age and the weight should be taken into account, does not have any impact on the dosing recommendations on the same basis as explained above, i.e., that the systemic exposure for the 6 to <12 month population is accurately predicted by the updated model and consistent with exposures in older age groups including adults. Upon request of the CHMP, the MAH included a warning in section 4.4 of the SmPC to highlight that there are no safety data in children aged 6 to less than 12 months of age when treated with ivacaftor as recommended in section 4.2 of the SmPC given that the prior (within a defined time frame) or concomitant use of CYP3A4 inhibitors was an exclusion criterion.

It has also been clarified that IVA and its metabolites are BCRP substrates. While the co-administration of BCRP inhibitors is not expected to alter the exposure of IVA and M1-IVA meaningfully due to their high intrinsic permeability and elimination via CYP3A catalysed metabolism, plasma concentrations of M6-IVA may be increased due to its low passive permeability and potential transporter-mediated clearance.

However, the MAH states that the potential increase in M6-IVA exposures with BCRP inhibitors (such as cyclosporin) is not expected to be clinically relevant as available literature suggest that BCRP inhibition can potentially increase exposures of sensitive substrates by approximately 2- to 3-fold, which is within the ~2- to 5-fold exposure range seen in subjects in the IVA Phase 3 studies. This information is included in the SmPC of Kalydeco. Hepatic BCRP is expressed early during human development and does not undergo major relevant developmental changes after term birth.

Exposure relevant for safety evaluation: The highest ivacaftor exposure that has been observed in the paediatric population corresponds to children aged 6 to less than 12 years of age who were dosed with 150 mg BID. The predicted mean (SD) AUC,ss and Cmin,ss in this age group is 20000 (8330) ng•h/mL and 1240 (594) ng/ml, respectively. This level of exposure was demonstrated to be safe and efficacious in this age group in clinical trials. Age (maturation) is not relevant for children aged 6 years and older patients as CYP3A4 maturation is complete. However, the degree of uncertainty in children aged 6 to less than 12 months of age is greater as the conclusions of Model 4 suggest that both body weight and age should be taken into consideration. The simulations based on Model 2 (fixed exponent allometric scaling, no maturation) and Model 4 (empirical with maturation effect) would lead to the same dosing recommendations as currently proposed. The main difference seems to be that in the lighter children the predicted ivacaftor exposures are higher when Model 4 is used for simulations of predicted exposure. In study 003 (moderate hepatic impairment), the $AUC_{0-\infty}$ for total and unbound ivacaftor was approximately 2-fold higher in subjects with moderate hepatic impairment than in matched healthy subjects. Total and unbound $AUC_{0-\infty}$ of ivacaftor metabolites, M1 and M6 were approximately 1.5- to 1.7-fold higher in moderate hepatic impairment subjects than in matched healthy subjects. Co-administration with ketoconazole, a strong CYP3A inhibitor, increased ivacaftor AUC by 8.5-fold and increased M1 to a lesser extent than ivacaftor.

2.4.3. Pharmacodynamics

No new data have been provided regarding the mechanism of action and primary/secondary pharmacology and this is acceptable for this type of application. The pharmacodynamic profile of Kalydeco is already well described.

2.4.4. Discussion on clinical pharmacology

No new data have been provided regarding the mechanism of action and primary/secondary pharmacology. This is considered acceptable to the CHMP since the pharmacology of ivacaftor is well known. The underlying cause of CF and the mechanism of action of ivacaftor are the same regardless of the age of the subjects with cystic fibrosis considered. In vitro data on the pre-specified CFTR gating mutations covered by this extension of the indication have been discussed in the frame of previous procedures. No attempts have been done to implement PD markers such as sweat chloride in the population model given the limited number of children enrolled in Part B (n=11) with only 6 children having completed data, i.e., baseline and Week 24 data. A request was made to incorporate sweat chloride data at the time of assessment of the extension of the indication to children aged 12 to less than 24 months but there was insufficient information to develop a linear or nonlinear exposure-response model. This was however accepted by CHMP and therefore no request in this sense is made in the present procedure. Dose finding is therefore based on targeting the adult dose that has been shown to be efficacious in the pivotal studies in older paediatric subjects and adult subjects. This is acceptable but the initial population PK model selected to support dosing recommendations for children below 12 months of age did not take into account any influence of CYP3A4 maturation on ivacaftor clearance. Given that only a single child in Part A/Cohort 2 had been dosed with 25 mg BID, the MAH was requested to update the model with PK data of younger children (below 6 months of age and/or below 5 kg of body weight) and to further discuss the potential influence of CYP3A4 maturation on ivacaftor clearance. This request was

fulfilled and additional models were developed and discussed. Of these, an empirical model with maturation function is the one that best describes the observed PK data in infants aged 6 to less than 12 months of age. In spite of the fact that both maturation (age) and body weight should be taken into account, the contribution of each one seems to be different with body weight apparently being most relevant. The simulations based on Model 2 (fixed exponent allometric scaling, no maturation) and Model 4 (empirical with maturation effect) would lead to the same dosing recommendations as currently proposed. The main difference seems to be that in the lighter children the predicted ivacaftor exposures are higher when Model 4 is used. Therefore, it is considered that this issue is solved. However, concerns still remain regarding dosing recommendations for infants aged 6 to less than 12 months with hepatic impairment or receiving concomitant administration with moderate or strong CYP3A4 inhibitors and thus, the MAH was requested to add a cautionary sentence in section 4.4 of the SmPC to highlight that no safety data are available in infants aged 6 to less than 12 months of age in the above situations. This is considered adequate to the CHMP. In addition, the section 4.5 of the SmPC of Kalydeco was also updated with the information on its potential to interact with transporters. In vitro studies showed that ivacaftor is not a substrate for OATP1B1 or OATP1B3. Ivacaftor and its metabolites are substrates of BCRP in vitro. Due to its high intrinsic permeability and low likelihood of being excreted intact, co-administration of BCRP inhibitors is not expected to alter exposure of ivacaftor and M1 IVA, while any potential changes in M6 IVA exposures are not expected to be clinically relevant.

2.4.5. Conclusions on clinical pharmacology

The conclusion of the updated pop-PK modelling is that CYP34 maturation has an effect on ivacaftor clearance. In spite of this, dose is weight-based given that the influence of age on ivacaftor clearance appears limited in the group of children aged 6 to less than 12 months of age when compared to body weight. This effect of age will continue to be assessed in children below 6 months of age. The SmPC of Kalydeco has been updated with the relevant information for the prescriber.

2.5. Clinical efficacy

2.5.1. Dose response study and main study

Study VX15-770-124

A Phase 3, 2-Part, Open-label Study to Evaluate the Safety, Pharmacokinetics, and Pharmacodynamics of Ivacaftor in Subjects With Cystic Fibrosis Who Are Less Than 24 Months of Age at Treatment Initiation and Have a CFTR Gating Mutation

Methods

Study 124 is an ongoing Phase 3, 2-part, open-label study of orally administered IVA in subjects with CF who were <24 months of age at treatment initiation (Day 1) and have a *CFTR* gating mutation or *R117H* (currently in the US only) on at least 1 allele. The present analysis of data from study 124 corresponds to the Interim Analysis 2 Report which includes all data from subjects 6 to less than 12 months of age who completed Cohort 2/Part A and/or Cohort 6/Part B (through 24 weeks of treatment).

Study 124 is a two-part study. Part A was designed to evaluate the safety and PK of multiple-dose administration of IVA over 4 days of dosing, and to confirm (or adjust if necessary) the doses for Part B. Part B was designed to evaluate the safety, PK, PD, and efficacy of IVA in subjects over 24 weeks. The study is ongoing as younger subjects are being enrolled in subsequent descending age cohorts of the study following PK and safety assessments for each age cohort, as follows:

- Cohort 1: subjects aged 12 to <24 months

- Cohort 2: subjects aged 6 to <12 months
- Cohort 3: subjects aged 3 to <6 months
- Cohort 4: subjects aged 0 to <3 months

Subjects will be enrolled in Part B sequentially in the following cohorts based on age at Day 1 of Part B:

- Cohort 5: subjects aged 12 to <24 months
- Cohort 6: subjects aged 6 to <12 months
- Cohort 7: subjects aged 0 to <6 months

During the treatment periods of Parts A and B, 25 mg (for subjects 5 to <7 kg on Day 1), 50 mg (for subjects 7 to <14 kg on Day 1), or 75 mg (for subjects ≥14 to <25 kg on Day 1) IVA was to be administered every 12 hours (q12h). Part A consisted of a Screening Period (Day -28 to Day -1), a Treatment Period (Day 1 to Day 5), a Follow-up Telephone Call (Day 14), and a Follow-up Ophthalmologic Examination (OE, 8 weeks after the last dose). Part B consisted of a Screening Period (Day -28 to Day -1), a Treatment Period (Day 1 to Week 24), a Follow-up Visit (4 weeks after the last dose), and a Follow-up OE (24 weeks after the last dose). Figure below shows the basic study design.

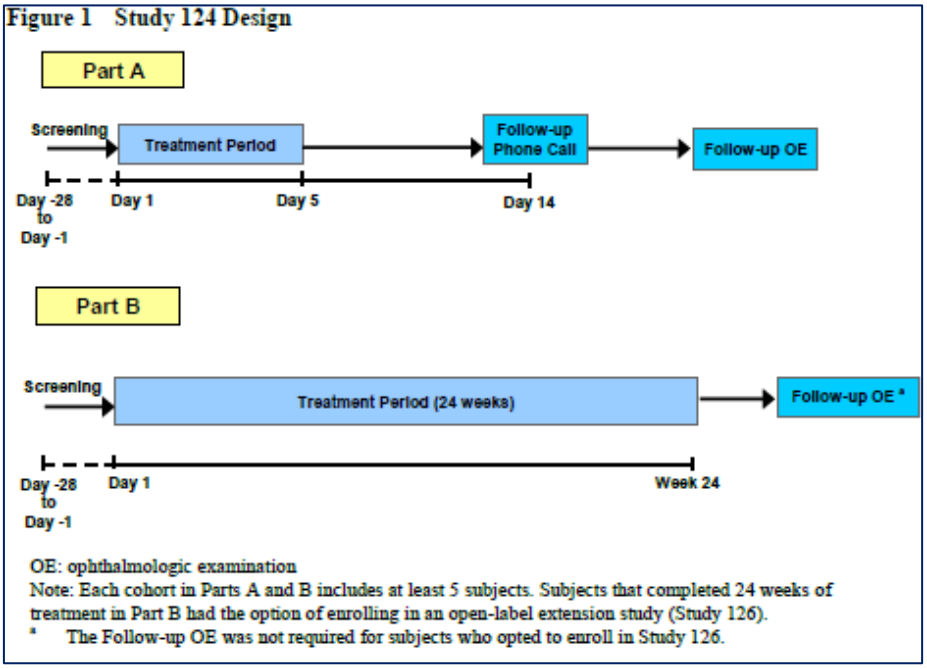


Figure 2 Schematic of study design

All subjects who completed 24 weeks of study drug treatment in Part B were eligible to enrol in the open-label treatment arm of an extension study (Study 126). Subjects who completed 24 weeks of study drug treatment who did not enrol in the treatment arm of Study 126 were required to complete the Follow-up Visit (4 weeks ± 7 days after the last dose of study drug) and were eligible to enrol in the observational arm of Study 126.

Study Participants

Key inclusion criteria

- Male or female with confirmed diagnosis of CF, defined as a sweat chloride value ≥60 mmol/L by quantitative pilocarpine iontophoresis OR 2 CF-causing mutations.

- Must have had 1 of the following 9 CFTR mutations on at least 1 allele: *G551D, G178R, S549N, S549R, G551S, G1244E, S1251N, S1255P,* or *G1349D*. Subjects who had an *R117H-CFTR* mutation were eligible in regions where IVA is approved for use in subjects 2 through 5 years of age with an *R117H-CFTR* mutation.
- Aged 0 to <24 months at Day 1; subjects who completed Part A who were ≥24 months of age on Day 1 in Part B were not eligible to enrol in Part B.
- For Cohorts 4 and 7 only, gestational age ≥38 weeks.
- Weight at screening within the weight limits as defined for the study drug dose levels

Key exclusion criteria

- History of any illness or condition that, in the opinion of the investigator, might have confounded the results of the study or posed an additional risk in administering study drug to the subject
- An acute upper or lower respiratory infection, or PEx, or changes in therapy (including antibiotics) for pulmonary disease within 4 weeks before Day 1
- Colonization with organisms associated with a more rapid decline in pulmonary status (e.g., *Burkholderia cenocepacia, Burkholderia dolosa*, and *Mycobacterium abscessus*) at screening.
- Abnormal liver function at screening or any prior history of clinically relevant elevated (>2 × upper limit of normal [ULN]) serum aspartate transaminase (AST), serum alanine transaminase (ALT), or bilirubin (excluding newborn hyperbilirubinemia)
- Any clinically significant "non-CF-related" illness within 2 weeks before Day 1. "Illness" was defined as an acute (serious or non-serious) condition (e.g., gastroenteritis)
- Use of any moderate or strong inducers or inhibitors of CYP3A within 2 weeks before Day 1
- Presence of a lens opacity or cataract identified at the screening OE (excluding those considered congenital and non-progressive, such as a suture cataract)

Treatments

In Part A, IVA was administered every 12 hours (q12h) for 3 days with the last dose of study drug being administered the morning dose on Day 4 (7 total doses) to obtain steady-state concentrations of IVA. In Part B, at each study visit, the IVA dose for each subject was reassessed based on body weight and adjusted if necessary. For Cohorts 2 and 6, IVA granules were administered orally at a dosage of 25, 50 or 75 mg q12h based on weight. In Part A, doses administered from the evening dose on Day 1 through the evening dose on Day 3 were administered q12h at home, and the Day 1 and Day 4 morning dose was administered in the clinic. On Day 1 of Part B, subjects received a single dose of 25, 50 mg or 75 mg IVA, or other suitable starting dose based on PK data from Part A (by weight) in the clinic. At each study visit, the IVA dose for each subject was reassessed based on body weight and adjusted if necessary. For Cohort 6, all subjects received 50 mg IVA based on their weight for the duration of the 24-week treatment period. Each dose of granules was mixed with approximately 1 teaspoon (5 mL) of appropriate liquid or soft food and administered with an age-appropriate fat-containing meal or snack.

Objectives

Part A

Primary

• To evaluate the safety of ivacaftor (IVA)

• To evaluate the pharmacokinetics (PK) of IVA and metabolites hydroxymethyl-ivacaftor (M1-IVA) and ivacaftor carboxylate (M6-IVA)

Part B

Primary

• To evaluate the safety of IVA

Secondary

• To evaluate the PK of IVA and metabolites M1-IVA and M6-IVA

• To evaluate the pharmacodynamics (PD) of IVA

Tertiary

• To evaluate the efficacy of IVA

• To evaluate the acceptability/palatability of IVA granules

Outcomes/endpoints

Assessment of the safety of IVA treatment in subjects with CF who are less than 2 years of age and have a CFTR gating mutation was a primary objective of Parts A and B. For PK endpoints, refer to PK section.

Primary safety endpoints:

• AEs

• Clinical laboratory values (hematology and serum chemistry)

• OEs

• Physical examinations

• Standard 12-lead ECGs

• Vital signs

Pharmacodynamic endpoint (Part B only): sweat chloride test (measured as absolute change from baseline)

Tertiary and exploratory efficacy endpoints (Part B only):

- Absolute change from baseline for the following:
    - Weight
    - Length
    - Weight-for-length
    - Weight-for-age z-score
    - Length-for-age z-score
    - Weight-for-length-for-age z-score
    - Lung clearance index (LCI) at qualified study sites (based on training and availability of mass spectrometry Multiple Breath Washout [MBW] analysis). (Note: MBW was optional and performed only on subjects for whom additional or separate informed consent was obtained)

- Functional residual capacity (FRC) from plethysmography and forced expiratory flow 25% to 75% (FEF25%-75%), forced expiratory volume in 0.5 seconds (FEV0.5), and forced vital capacity (FVC) from the raised-volume rapid thoracoabdominal compression (RVRTC) only at qualified sites. (Note: these tests were optional and were to be performed only on subjects for whom additional or separate informed consent was obtained for the procedures. Only 1 site was identified globally).
- Markers of pancreatic function and inflammation, i.e., Faecal elastase-1 (FE-1) and Immunoreactive trypsin and/or trypsinogen (IRT) (Note: the assay used in study 108 [in children aged 2 to less than 6 years with pre-specified *CFTR* gating mutations], which was discontinued by the manufacturer, only measured trypsinogen whereas the assay used in Study 124 measures both trypsin and trypsinogen resulting in a broader quantification window). In addition, although lipase and amylase levels were collected as part of safety assessments, the results were included under efficacy because they are useful indicators of pancreatic inflammation.
- Markers of intestinal inflammation (faecal calprotectin)
- Qualitative microbiology cultures

- Pulmonary exacerbations (PEx)
- CF-related hospitalizations
- Acceptability/palatability of ivacaftor granules

Randomisation

Not applicable, as this was a single-treatment-arm study and an open-label study.

Statistical methods

Study 124 is still ongoing. The sample size was based on the availability of the subject population and PK analysis considerations, and not on any statistical consideration. Therefore, the study is not powered to detect a significant treatment effect. Continuous variables (analysed as the absolute change from baseline to the post-baseline value) and categorical variables were summarized by standard descriptive statistics. Incomplete/missing data were not imputed, unless specified otherwise.

Three analysis set were defined as follows:

- The All Subjects Set was defined separately for Parts A and B as all subjects who were eligible for study enrolment or received at least 1 dose of study drug. This analysis set was used for all individual subject data listings and the disposition summary table.
- The Full Analysis Set (FAS) for Part B was defined as all subjects who were eligible for study enrolment and received at least 1 dose of study drug.
- The Safety Set was defined separately for Parts A and B as all subjects who received at least 1 dose of study drug. The Safety Set was used for all safety analyses, with subjects analyzed according to the treatment they received, unless specified otherwise.

Results

Participant flow

PART A: Six subjects were enrolled, 5 subjects were in the IVA 50 mg group and 1 subject was in the IVA 25 mg group. All 6 subjects completed 4 days of treatment, 3 subjects continued into part B.

PART B: Subject disposition for Part B/Cohort 6 is presented in below. A total of 11 subjects were enrolled and included in the Safety Set. All 11 subjects completed the 24 weeks of treatment and rolled over into Study 126.

Table 3 Study 124 PART B/Cohort 6: Subject Disposition

Table 2 Study 124 Part B/Cohort 6: Subject Disposition

Disposition	IVA 50 mg n (%)
All Subjects Set	11 (100.0)
Safety Set	11 (100.0)
Full Analysis Set	11 (100.0)
Last treatment period visit/week completed	
Week 24	11 (100.0)
Completed study drug treatment	11 (100.0)

Source: Study 124 IA2R/Table 10-5
FAS: Full Analysis Set; IVA: ivacaftor; n: size of subsample
Notes: Percentages were calculated relative to the number of subjects in the FAS. All Subjects Set was defined as all subjects who were eligible for study enrollment or received at least 1 dose of study drug. Safety Set was defined as all subjects who received at least 1 dose of study drug. FAS was defined as all subjects who were eligible for study enrollment and received at least 1 dose of study drug.

Recruitment

The study recruitment started in March 2016 and is ongoing.

Conduct of the study

Protocol deviations: There were 3 protocol deviations in 3 subjects that were identified as important protocol deviations (IPDs). After review of these deviations, it was determined that 2 of the 3 deviations did not compromise interpretation of the study results or significantly affect the subject's rights, safety, or well-being, as summarised below:

- One subject was deemed eligible based on normal LFTs at the Screening Visit. The subject received first study dose of IVA 50-mg in February 2018. On May 2018, the site was alerted to an historical ALT elevation of 160 U/L (ALT >3 to ≤5 × ULN) that occurred in November 2017, which would have met exclusion criterion 4 (AST and ALT levels were normal). This LFT elevation was reviewed by the principal investigator (PI) and was considered not clinically relevant to the study. No LFT elevations were observed during the 24-week treatment period. The sponsor determined that there had not been any safety concerns while the subject had been receiving IVA and this IPD did not affect interpretation of study results.
- Other two protocol deviations were related to study procedures and assessments and were considered not to compromise interpretation of the study results or significantly affect the subject's rights, safety, or well-being.

Baseline data

PART A

Demographics: In the 50-mg group, the mean age of the 5 subjects was 8 months (range: 6 to 10 months). All 6 subjects were White and of non-Hispanic or Latino ethnicity. The majority of subjects had the *G551D* mutation. The most prevalent genotype was *G551D/F508del*.

Baseline characteristics: The mean (SD) and median (Min, Max) values of weight-for-age z-scores were -0.48 (0.65) and -0.46 (-1.42, 0.43) respectively. These figures for weight-for-age percentiles were 34.1 (21.1) and 32.1 (8, 66). Regarding length-for-age z-scores, the mean (SD) and median (Min, Max) baseline values were 0.80 (0.63) and 0.97 (-0.33, 1.42) respectively while the percentile values were 75.8 (20.4) and 83.3 (37, 92). Mean (SD) and median (Min, Max) values of weight-for-length z-scores were -1.14 (0.51) and -1.21 (-1.70, -0.34) respectively while the percentile values were 15.2 (12.2) and 11.2 (4, 37) respectively. The table below shows the baseline data on anthropometric characteristics of infants enrolled in Part A/Cohort 2 by dosing group.

Table 4 Baseline Characteristics, Safety Set, Part A/Cohort 2

Characteristic	[redacted]	IVA 50 mg N = 5	Total N = 6
Weight (Kg)			
n		5	6
Mean (SD)		7.9 (0.6)	7.7 (0.6)
Median		7.9	7.7
Min, Max		7.1, 8.8	6.7, 8.8
Weight-for-age Z-score			
n		5	6
Mean (SD)		-0.39 (0.68)	-0.48 (0.65)
Median		-0.41	-0.46
Min, Max		-1.42, 0.43	-1.42, 0.43
Weight-for-age (Percentile)			
n		5	6
Mean (SD)		37.3 (21.8)	34.1 (21.1)
Median		34.0	32.1
Min, Max		8, 66	8, 66
Length (cm)			
n		5	6
Mean (SD)		71.9 (2.4)	71.2 (2.7)
Median		71.0	70.7
Min, Max		69.9, 76.0	67.8, 76.0
Length-for-age Z-score			
n		5	6
Mean (SD)		0.85 (0.69)	0.80 (0.63)
Median		1.09	0.97
Min, Max		-0.33, 1.42	-0.33, 1.42
Length-for-age (Percentile)			
n		5	6
Mean (SD)		76.9 (22.6)	75.8 (20.4)
Median		86.1	83.3
Min, Max		37, 92	37, 92
Weight-for-length Z-score			
n		5	6
Mean (SD)		-1.05 (0.51)	-1.14 (0.51)
Median		-1.20	-1.21
Min, Max		-1.70, -0.34	-1.70, -0.34
Weight-for-length (Percentile)			
n		5	6
Mean (SD)		17.0 (12.6)	15.2 (12.2)
Median		11.6	11.2
Min, Max		4, 37	4, 37

PART B

Tables 3 and 4 below show the demographic and disease characteristics of infants enrolled in Part B/Cohort 6 of Study 124.

Demographics: At Day 1, all subjects weighed 7 to <14 kg (range: 7.8 to 10.7 kg) and therefore received IVA 50 mg q12hdll.11 subjects were White, and the majority (90.9%) were of non-Hispanic or Latino ethnicity; ethnicity was not reported for 1 subject. The majority of subjects had a *G551D* mutation. The most prevalent genotype was *G551D/F508del* .

Table 5 Subject Demographics, Safety Set, Part B/Cohort 6

Characteristic	IVA 50 mg N = 11
Sex, n (%)	
Male	[redacted]
Female	
Age at Screening (Months)	
n	11
Mean (SD)	8.4 (1.43)
Median	8.0
Min, max	6, 11
Age at Baseline/Day 1 (Months)	
n	11
Mean (SD)	9.0 (1.34)
Median	9.0
Min, Max	7, 11
Ethnicity, n (%)	
Not Hispanic or Latino	10 (90.9)
Not collected per local regulations	1 (9.1)
Race, n (%)	
White	11 (100.0)
Geographical Region, n (%)	
North America	7 (63.6)
Europe	3 (27.3)
Australia	1 (9.1)
Genotype, n (%)	
G551D/DELF508	[redacted]
G551D/S108F ($TG_{12}T_5S108F$)	
G178R/DELF508	

Source: Table 14.1.2.b6
IVA: ivacaftor; n: size of subsample; N: total sample size
Notes: Percentages are calculated relative to the number of subjects in the Safety Set.

Baseline characteristics

Table 6 Baseline Characteristics, Safety Set, Part B/Cohort 6

Characteristic	IVA 50 mg N = 11
Weight (kg)	
n	11
Mean (SD)	8.9 (1.0)
Median	8.6
Min, max	7.8. 10.7
Length (cm)	
n	11
Mean (SD)	72.5 (2.6)
Median	72.0
Min, max	68.4, 78.0
Weight-for-length (percentile)	
n	11
Mean (SD)	54.7 (27.8)
Median	56.7
Min, max	7, 90
BMI (kg/m^2)	
n	11
Mean (SD)	16.83 (1.24)
Median	16.78
Min, max	14.40, 18.65
Weight-for-age z-score	
n	11
Mean (SD)	0.37 (0.71)
Median	0.71
Min, max	-0.76, 1.24
Length-for-age z-score	
n	11
Mean (SD)	0.63 (0.62)
Median	0.69
Min, max	-0.67, 1.61
Weight-for-length-for-age z-score	
n	11
Mean (SD)	0.13 (0.85)
Median	0.17
Min, max	-1.48, 1.26

Source: Table 14.1.3.1.b6

BMI: body mass index; IVA: ivacaftor; n: size of subsample; N: total sample size; WHO: World Health Organization

Notes: All results displayed are baseline results. Baseline was defined as the most recent non-missing measurement before the first dose of study drug. Z-scores are calculated using WHO Child Growth Standards for children 0 to 24 months of age.

Medical history

Table 7 Medical History That Occurred in At Least 2 Subjects, Safety Set, Part B/Cohort 6

Condition (Preferred Term)	IVA 50 mg N = 11 n (%)
CF lung	10 (90.9)
Pancreatic failure	10 (90.9)
Gastroesophageal reflux disease	5 (45.5)
Constipation	3 (27.3)
Teething	3 (27.3)
Cough	2 (18.2)
Staphylococcus test positive	2 (18.2)
Weight gain poor	2 (18.2)

Source: Table 14.1.4.b6
CF: cystic fibrosis; IVA: ivacaftor; n: size of subsample; N: total sample size; PT: Preferred Term
Notes: A subject with multiple events within a PT was counted only once within the PT. Medical history events were coded with MedDRA Version 21.0.

Prior and concomitant medication: The most commonly reported concomitant medications were pancreatin (72.7%), sodium chloride (63.3%), amoxicillin (45.5%), and paracetamol (45.5%). Pancreatic enzyme replacement therapy (pancreatin or pancrelipase) was reported for 9 (81.8%) subjects.

Numbers analysed

The PK Set contained data for all subjects who received at least 1 dose of study drug. All efficacy analyses were conducted using the Safety Set, which included 11 subjects who received at least 1 dose of study drug in Part B/Cohort 6.

Outcomes and estimation

Sweat chloride: The absolute changes from baseline were calculated at each time point for those subjects in Part B/Cohort 6 that had both a baseline value and a value at that time point. One subject had a missing baseline sample because of insufficient sweat sample volume. For this subject, historical sweat chloride values were used for baseline. Five subjects did not have sweat chloride measurements at Week 24: for 2 subjects, measurements were not collected, and for 3 subjects, sweat sample volumes were insufficient. The mean (SD) sweat chloride level at baseline was 101.5 (9.8) mmol/L (n=11). Treatment with IVA led to rapid reductions in sweat chloride concentrations at Week 2 that were sustained to Week 24. The mean (SD) absolute change from baseline in sweat chloride was -52.6 (16.4) mmol/L (n = 9) at Week 2 and -58.6 (16.5) mmol/L (n = 6) at Week 24. Mean absolute changes from baseline in sweat chloride concentration are summarized below.

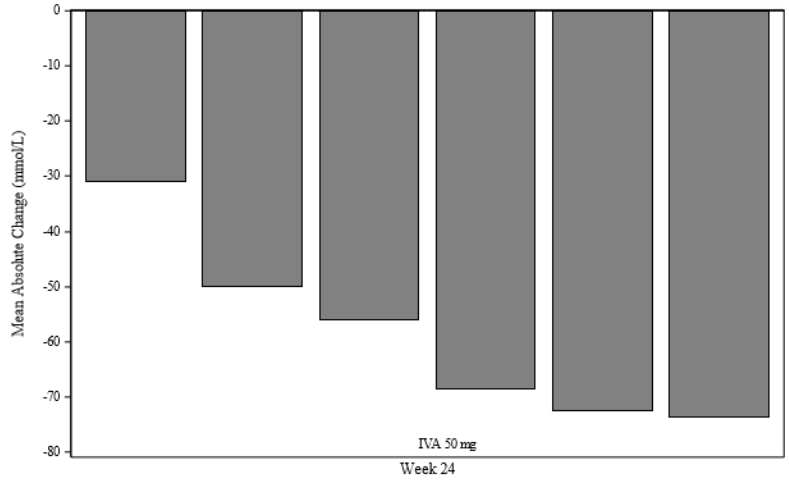
Table 8 Absolute Changes from Baseline in Sweat Chloride (mmol/L), FAS, Part B/Cohort 6

		IVA 50 mg N = 11	
Visit	Statistic	Sweat Chloride (mmol/L)	Absolute Change From Baseline at Visit (mmol/L)
Baseline	n	11	NA
	Mean (SD)	101.5 (9.8)	NA
	Median	106.0	NA
	Min, max	85.5, 111.5	NA
Week 2	n	9	9
	Mean (SD)	48.9 (16.8)	-52.6 (16.4)
	Median	46.0	-47.5
	Min, max	29.0, 81.5	-77.0, -30.0
Week 12	n	7	7
	Mean (SD)	43.2 (26.2)	-57.1 (20.2)
	Median	30.0	-62.5
	Min, max	25.5, 85.5	-79.0, -25.5
Week 24	n	6	6
	Mean (SD)	43.1 (19.8)	-58.6 (16.5)
	Median	38.8	-62.3
	Min, max	24.0, 80.5	-73.5, -31.0

Source: Table 14.2.1.1.b6
FAS: Full Analysis Set; IVA: ivacaftor; n: size of subsample; N: total sample size; NA: not applicable
Notes: Baseline was defined as the most recent measurement before the first dose of study drug in Part B. Subjects shown in dose group according to their Day 1 dose in Part B.

Four (36.4%) subjects had at least 1 on-treatment sweat chloride value ≤30 mmol/L. At Week 24, 3 subjects had a sweat chloride value <35 mmol/L, including 1 subject who had a sweat chloride value <30 mmol/L which is the diagnostic cut-off for normal sweat chloride. To evaluate individual subject response to IVA, a waterfall plot showing the absolute change from baseline in sweat chloride at Week 24 for subjects with baseline and Week 24 results is presented in below. Sweat chloride concentration decreased in all of these subjects: changes ranged from 31.0 to 73.5 mmol/L.

Table 9 Waterfall Plot of Mean Absolute Change From Baseline at Week 24 in Sweat Chloride, FAS, Part B/Cohort 6



Source: Figure 14.2.1.1.2.b6
FAS: Full Analysis Set; IVA: ivacaftor
Note: Only subjects who had both baseline and Week 24 sweat chloride values are included in this figure. All of these subjects had the *G551D/F508del* genotype.

Nutritional status: *Weight, Weight-for-age Z-score, and Weight-for-age Percentile*

Mean absolute changes from baseline in weight-for-age z-scores are shown in table below.

Table 10 Absolute Changes From Baseline in Weight-for-age Z-score, FAS, Part B/Cohort 6

		IVA 50 mg N = 11	
Visit	**Statistic**	**Weight-for-age Z-score**	**Absolute Change From Baseline at Visit**
Baseline	n	11	NA
	Mean (SD)	0.37 (0.71)	NA
	Median	0.71	NA
	Min, max	-0.76, 1.24	NA
Week 2	n	11	11
	Mean (SD)	0.40 (0.70)	0.03 (0.14)
	Median	0.67	-0.02
	Min, max	-0.66, 1.21	-0.20, 0.28
Week 12	n	11	11
	Mean (SD)	0.61 (0.71)	0.24 (0.31)
	Median	0.84	0.17
	Min, max	-0.59, 1.43	-0.11, 1.03
Week 24	n	11	11
	Mean (SD)	0.73 (0.75)	0.36 (0.54)
	Median	0.72	0.45
	Min, max	-0.52, 1.71	-0.29, 1.63

Source: Table 14.2.2.1.b6

FAS: Full Analysis Set; IVA: ivacaftor; n: size of subsample; N: total sample size; NA: not applicable; WHO: World Health Organization

Notes: Baseline was defined as the most recent measurement before the first dose of study drug in Part B. Z-scores were calculated using WHO Child Growth Standards for children 0 to 24 months of age. Subjects shown in dose group according to their Day 1 dose in Part B.

Eleven infants were enrolled in Part B/Cohort 6. Median (range) weight-for-age z-score and percentile at baseline were 0.53 (-0.18, 1.24) and 65.9 (43, 89), respectively for some infants. These values for other infants were as follows: 0.71 (-0.76, 1.05) and 76.1 (22, 85). The median (range) change from baseline at week 24 in the z-score and percentile was for some infants 1.05 (0.48, 1.63) and 28.2 (6, 50) respectively. For other infants these values were as follows: 0.26 (-0.29, 0.70) and 10.3 (-8, 18). Mean (SD) weight at baseline was 8.9 (1.0) kg. The mean absolute change (SD) from baseline at Week 24 was 1.8 (0.7) kg. At Week 24, mean (SD) weight was 10.7 (1.1) kg.

Length, Length-for-age Z-score, and Length-for-age Percentile: Mean absolute changes from baseline in length-for-age z-score are summarized below.

Table 11 Absolute Changes From Baseline in Length-for-age Z-score, FAS, Part B/Cohort 6

		IVA 50 mg N = 11	
Visit	Statistic	Length-for-age Z-score	Absolute Change From Baseline at Visit
Baseline	n	11	NA
	Mean (SD)	0.63 (0.62)	NA
	Median	0.69	NA
	Min, max	-0.67, 1.61	NA
Week 2	n	11	11
	Mean (SD)	0.59 (0.64)	-0.03 (0.56)
	Median	0.72	0.04
	Min, max	-0.24, 1.78	-1.54, 0.47
Week 12	n	10	10
	Mean (SD)	0.81 (0.69)	0.26 (0.35)
	Median	0.77	0.27
	Min, max	-0.47, 1.99	-0.53, 0.87
Week 24	n	11	11
	Mean (SD)	0.89 (1.20)	0.27 (1.34)
	Median	0.75	0.25
	Min, max	-0.50, 3.79	-1.81, 3.38

Source: Table 14.2.2.1.b6

FAS: Full Analysis Set; IVA: ivacaftor; n: size of subsample; N: total sample size; NA: not applicable; WHO: World Health Organization

Notes: Baseline was defined as the most recent measurement before the first dose of study drug in Part B. Z-scores were calculated using WHO Child Growth Standards for children 0 to 24 months of age. Subjects shown in dose group according to their Day 1 dose in Part B.

Eleven infants were enrolled in Part B/Cohort 6. Median (range) length-for-age z-score and percentile at baseline were 1.03 (0.46, 1.61) and 81.2 (68, 95), respectively for some infants. These values for other infants were as follows: 0.69 (-0.67, 1.38) and 75.4 (25, 92). The median (range) change from baseline at week 24 in the z-score and percentile was for some infants -0.48 (-0.69, -0.27) and -11.2 (-12, -10) respectively. For other infants these values were as follows: 0.41 (-1.81, 3.38) and 10.8 (-58, 41). Mean (SD) length at baseline was 72.5 (2.6) cm. The mean absolute change (SD) from baseline at Week 24 was 7.7 (3.5) cm. At Week 24, mean (SD) length was 80.2 (4.4) cm.

Weight-for-length, Weight-for-length-for-age Z-score, and Weight-for-length-for-age Percentile: Mean absolute changes from baseline in weight-for-length-for-age z-score are shown here:

Table 12 Absolute Changes From Baseline in Weight-for-length-for-age Z-score, FAS, Part B/Cohort 6

		IVA 50 mg N = 11	
Visit	Statistic	Weight-for-length-for-age Z-score	Absolute Change From Baseline at Visit
Baseline	n	11	NA
	Mean (SD)	0.13 (0.85)	NA
	Median	0.17	NA
	Min, max	-1.48, 1.26	NA
Week 2	n	11	11
	Mean (SD)	0.20 (0.89)	0.07 (0.42)
	Median	0.48	0.07
	Min, max	-1.36, 1.35	-0.49, 0.92
Week 12	n	10	10
	Mean (SD)	0.24 (0.98)	0.11 (0.52)
	Median	0.44	0.09
	Min, max	-1.40, 1.73	-0.73, 1.25
Week 24	n	11	11
	Mean (SD)	0.40 (1.25)	0.26 (1.30)
	Median	-0.15	0.35
	Min, max	-1.04, 2.16	-2.04, 2.22

Source: Table 14.2.2.1.b6

FAS: Full Analysis Set; IVA: ivacaftor; n: size of subsample; N: total sample size; NA: not applicable; WHO: World Health Organization

Notes: Baseline was defined as the most recent measurement before the first dose of study drug in Part B. Z-scores were calculated using WHO Child Growth Standards for children 0 to 24 months of age. Subjects shown in dose group according to their Day 1 dose in Part B.

Eleven infants were enrolled in Part B/Cohort 6. Median (range) weight-for-length Z-score and percentile at baseline were 0.11 (-0.48, 0.71) and 53.8 (32, 76), respectively for some infants. These values for other infants were as follows: 0.17 (-1.48, 1.26) and 56.7 (7, 90). The median (range) change from baseline at week 24 in the z-score and percentile was for some infants 1.63 (1.04, 2.22) and 42.2 (20, 64), respectively. For other infants these values were as follows: 0.02 (-2.04, 1.99) and 0.8 (-69, 42).

Exocrine pancreatic function and inflammation:

Faecal elastase-1 (FE-1): Mean FE-1 at Week 24 (291.3 µg/g) was increased compared to baseline (119.6 µg/g). The mean (SD) absolute change from baseline (n=10) was 53.3 (61.5) µg/g at Week 2 and 159.3 (154.4) µg/g at Week 24 (n=9). Mean absolute changes from baseline in FE-1 are shown in the below table.

Table 13 Absolute Change From Baseline in Faecal Elastase-1 (µg/g), FAS, Part B/Cohort 6

		IVA 50 mg N = 11	
Visit	Statistic	FE-1 (µg/g)	Absolute Change From Baseline at Visit (µg/g)
Baseline	n	10	NA
	Mean (SD)	119.6 (199.1)	NA
	Median	19.3	NA
	Min, max	8, 500	NA
Week 2	n	11	10
	Mean (SD)	202.6 (203.0)	53.3 (61.5)
	Median	92.0	41.8
	Min, max	8, 500	-7, 192
Week 12	n	10	9
	Mean (SD)	287.1 (189.8)	184.8 (180.7)
	Median	313.0	232.5
	Min, max	8, 500	-24, 493
[illegible]	[illegible]	[illegible]	[illegible]
Week 24	n	9	9
	Mean (SD)	291.3 (170.5)	159.3 (154.4)
	Median	290.0	126.0
	Min, max	8, 500	0, 424

Source: Table 14.2.2.7.1.b6

FAS: Full Analysis Set; FE-1: fecal elastase-1; IVA: ivacaftor; n: size of subsample; N: total sample size; NA: not applicable

Note: Baseline was defined as the most recent measurement before the first dose of study drug in Part B. Reported values of <15 µg/g were replaced by 7.5 µg/g. Reported values of >500 µg/g were replaced by 500 µg/g.

Nine subjects had FE-1 values at baseline and at Week 24 and 2 of them were pancreatic sufficient (FE-1 values > 200 µg/g at baseline) and remained with values above this cut-off throughout the 24 weeks of treatment. The mean (SD) FE-1 values at baseline for the 7 subjects with exocrine pancreatic insufficiency was 28.6 (30.6) µg/g. At week 24, the mean (SD) FE-1 value was 231.6 (141.8) µg/g. The mean (SD) absolute change from baseline at week 24 was 203.1 (147.3) µg/g. Five of the 7 subjects with FE-1 values ≤200 µg/g at baseline had FE-1 values >200 µg/g at Week 24. Two of these 7 subjects remained with values ≤ 200 µg/g at Week 24. For none of the subjects who were exocrine pancreatic insufficient a value of FE-1 above the cut-off of 500 µg/g was observed which was seen in the two subjects who were pancreatic sufficient at baseline.

Immuno-reactive trypsin and/or trypsinogen (IRT): The mean (SD) absolute change from baseline to Week 24 in IRT was -406.2 (363.3) ng/mL. The absolute change from baseline was only calculated at each time point for those subjects who had a baseline value. At week 24 the mean absolute change from baseline in IRT could be calculated for 9 children. Mean absolute changes from baseline in IRT are shown here:

Table 14 Absolute Change From Baseline in IRT (ng/mL), FAS, Part B/Cohort 6

		IVA 50 mg N = 11	
Visit	Statistic	IRT (ng/mL)	Absolute Change From Baseline at Visit (ng/mL)
Baseline	n	9	NA
	Mean (SD)	1120.6 (238.2)	NA
	Median	1200.0	NA
	Min, max	485.4, 1200.0	NA
Week 2	n	10	8
	Mean (SD)	805.1 (387.7)	-344.4 (337.9)
	Median	863.5	-245.6
	Min, max	188.6, 1200.0	-877.8, 0.0
Week 12	n	11	9
	Mean (SD)	855.9 (357.9)	-341.1 (291.9)
	Median	788.6	-411.4
	Min, max	245.0, 1200.0	-810.9, 0.0
Week 24	n	9	7
	Mean (SD)	753.2 (363.6)	-406.2 (363.3)
	Median	737.3	-211.8
	Min, max	358.0, 1200.0	-830.3, 0.0

Source: Table 14.2.2.9.b6

FAS: Full Analysis Set; IRT: immunoreactive trypsin and/or trypsinogen; IVA: ivacaftor; n: size of subsample; N: total sample size; NA: not applicable

Note: Baseline was defined as the most recent measurement before the first dose of study drug in Part B. Reported values of <14 ng/mL were replaced by 7 ng/mL. Reported values of >1200 ng/mL were replaced by 1200 ng/mL.

Six subjects in Cohort 6 had both baseline and Week 24 data for IRT. All 6 subjects who had these values were pancreatic insufficient at baseline (FE-1 < 200 µg/g). The mean (SD) absolute change from baseline at week 24 in IRT using the Cisbio assay (range of detection from 8.0 to 1200 ng/ml) was -450.6 (376.7) ng/ml. Median change (Min, Max) was -480.4 (-830.3, 0.0) ng/ml.

Lipase, total amylase: Serum lipase and amylase levels were collected as part of safety assessments in Parts A and B. Only data from Part B/Cohort 6 are reported. The range of reference of lipase levels is method-dependent. The specific assay used in Study 124 was an enzymatic colour rate assay. The normal range of this assay considered in Study 124 is 4 to 23 U/L (aged <12 months) and 4 to 31 U/L (aged ≥12 months). Ten infants enrolled in cohort 6 of Study 124 had lipase levels at both baseline and at week 24. The mean (SD) change from baseline at week 24 in lipase levels in subjects with pancreatic insufficiency (n=8) was -90.50 (75.04) with a median (range) change of -100.00 (-203.0, 23.0) U/L. For those with lipase levels elevated at baseline (n=10, mean [SD] 362.90 [281.18] U/L), the mean (SD) change from baseline at week 24 was -265.40 (287.06) with a median (range) of -137.50 (-885.0, 23.0) U/L. The mean baseline value in children with elevated values is 362.90 U/L which is almost 16 times higher than the upper limit of the normal range (23 U/L). The maximum value at baseline was 983.0 U/L (22 times higher than the upper limit of the normal range). These values are of concern but the all subjects with elevations in lipase at baseline were asymptomatic.

Regarding amylase (total amylase), the normal range of serum amylase considered in Study 124 is 6 to 44 U/L (aged <12 months) and 8 to 79 U/L (aged ≥12 months). The assay used in Study 124 uses as substrate 2-chloro-4-nitrophenyl-α-D-maltotrioside (CNPG3) and gives a direct measurement of α-amylase activity in the sample.

Ten infants enrolled in cohort 6 of Study 124 had total amylase levels at both baseline and at week 24. The mean (SD) change from baseline at week 24 in amylase levels in subjects with pancreatic insufficiency (n=8) was -7.8 (31.1) U/L with a median (range) change of -6.5 (-58, 52) U/L. For those with amylase levels elevated at baseline (n=8, mean [SD] 92.0 [34.4] U/L), the mean (SD) change from baseline at week 24 was -28.5 (40.9) U/L with a median (range) of -37.0 (-76, 52) U/L. The mean baseline value in children with elevated values is 92.0 U/L which is 2 times higher than the upper limit of the normal range (44 U/L). The maximum value at baseline was 145 U/L (3 times higher than the upper limit of the normal range).

Faecal calprotectin (FC): Nine infants had values of FC at both baseline and week 24. Out of these 9 infants, 7 had exocrine pancreatic insufficiency (EPI). At baseline, the mean (SD) values of FC was 128.80 (97.73) µg/g with a median (range) value of 81.90 (50.8, 272.6) µg/g. The mean (SD) absolute change from baseline at week 24 in FC in subjects with EPI was -44.21 (146.90) µg/g with a median (range) value of -50.60 (-256.3, 155.4) µg/g. In infants with pancreatic sufficiency (n=2) a mean absolute decrease of -56.70 µg/g was observed.

Efficacy endpoints related to lung disease:

- One subject had LCI assessed. The absolute change from baseline at Week 24 was -0.84. LCI values were 7.47 at Day 1 (baseline) and 6.63 at Week 24.
- One subject had Infant Pulmonary Function Tests (IPFTs) performed. For this subject, only Functional Residual Capacity (FRC) values were available at both baseline and Week 24. The absolute change in FRC from baseline at Week 24 was 77.60 mL. FRC was 163.90 mL at baseline and 241.50 mL at Week 24.
- There were no identifiable trends in qualitative microbiology oropharyngeal culture outcomes.
    - Of 11 subjects, 9 had paired samples for evaluation of *Burkholderia, H. influenzae*, methicillin-susceptible *Staphylococcus aureus* (MSSA), methicillin-resistant *S. aureus* (MRSA)*, and P. aeruginosa* at baseline and Week 24.
        - One subject had a positive *P. aeruginosa* non-mucoid culture at baseline; this subject had a negative culture at Week 24.
        - Two subjects had positive MSSA cultures at baseline; both had positive cultures at Week 24.
        - Five subjects had positive *H. influenzae* cultures at baseline; 2 had negative cultures at Week 24, and 3 had positive cultures at Week 24.
        - One subject had a negative *H. influenzae* culture at baseline and a positive culture at Week 24.
        - No cases of MRSA or *Burkholderia* were observed over the treatment period.
- Two definitions of PEx were used for analyses because there is no consensus definition for PEx in younger pediatric patients.
    - Definition 1: 7 subjects (63.6%) had a total of 10 PEx. The observed event rate per year is 1.95.
    - Definition 2: 3 subjects (27.3%) had a total of 4 PEx. The observed event rate per year is 0.78.
    - One subject had 1 CF-related hospitalization (event rate/year = 0.20).

- A palatability assessment of ivacaftor granules was performed at the Day 1 Visit of Part B. All subjects fully consumed the dose. The majority of subjects (8 [72.7%]) liked the food with ivacaftor granules (either very much or a little). Overall, the mean study drug compliance was 99.3%, and 100% of subjects were ≥80% compliant with study drug.

Ancillary analyses

Not applicable

Summary of main study

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

Table 15 Summary of Efficacy for Study VX15-770-124

Title: A Phase 3, 2-Part, Open-label Study to Evaluate the Safety, Pharmacokinetics, and Pharmacodynamics of Ivacaftor in Subjects With Cystic Fibrosis Who Are Less Than 24 Months of Age at Treatment Initiation and Have a CFTR Gating Mutation		
Study identifier	VX15-770-124	
Design	phase 3, two-part, open-label	
	Duration of main phase:	Part A: Day 1 - Day5, follow-up phone call at Day 14, follow-up for ocular examination 8 weeks after last dose Part B: Day 1-week24, rollover to Study 126 OR follow-up 4 weeks after last dose and follow-up for ocular examination 24 weeks after last dose
	Duration of Run-in phase:	N/A
	Duration of Extension phase:	96-week open-label extension study 126
Hypothesis	N/A	
Treatments groups	Part A: Ivacaftor 25 mg BID for children from 6 to < 12 months old and weighing 5 to less than 7 kg Ivacaftor 50 mg BID for children from 6 to < 12 months old and weighing 7 to less than 14 kg Part B: dose adjusted based on Part A if needed	PART A (Cohort 2): ivacaftor 25 mg BID, n=1; ivacaftor 50 mg, N=5, duration: 4 days PART B (Cohort 6): ivacaftor 50 mg, N=11, duration: 24 weeks

Endpoints and definitions	Primary endpoint	Safety (Part A and Part B) and PK (Part A) in subjects with cystic fibrosis (CF) who are 6 to <12 months of age at treatment initiation and have a pre-specified *CFTR* gating mutation	
	Secondary endpoint (Part B)	Sweat chloride (SC)	Absolute change from baseline at week 24 (mmol/L)
	Tertiary endpoints (Part B): - Measures of nutritional status	- Weight, length, weight-for-length; weight-for-age Z-score, length-for-age Z-score, and weight-for-length-for-age Z-score and percentile	Absolute change from baseline at Week 24
	- Markers of pancreatic exocrine function	- FE-1 (µg/g), IRT (ng/ml), lipase (U/L), and total amylase (U/L)	
	- Markers of intestinal inflammation	- Faecal calprotectin (µg/g)	
Database lock	Study is ongoing in infants less than 6 months of age/End of Interim Analysis 2: 26 July 2018 (date last subject in Cohort 6 completed Part B Week 24 Visit)		

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	ivacaftor	
	Number of subject	11	
	Absolute change from baseline in SC; mean (SD), mmol/L	-58.6 (16.5) n=6	
	Absolute change from baseline in weight-for-age Z-score; mean (SD), units	0.36 (0.54) (n=11)	
	Absolute change from baseline in length-for-age Z-score, mean (SD), units	0.27 (1.34) (n=11)	
	Absolute change from baseline in weight-for-length-for-age Z-score; mean (SD), units	0.26 (1.30) (n=11)	
	Absolute change from baseline in FE-1; mean (SD), (µg/g),	203.1 (147.3) (n=7)	
	Absolute change from baseline in IRT (Cisbio assay);mean (SD), (ng/ml)	-450.6 (376.7) (n=6)	
	Absolute change from baseline in lipase; mean (SD), (U/L)	-90.50 (75.04) (n= 8)	

	Absolute change from baseline in total amylase; mean (SD), (U/L)	-7.8 (31.1) (n=8)		
	Absolute change from baseline in FC; mean (SD), (µg/g),	-44.21 (146.90) (n=7)		
Notes	The study is currently ongoing			
Analysis description	Summary statistics provided of changes from baseline at Week 24 for continuous variables based on the observed data for subjects with both baseline and Week 24 data for the variable of interest. Change from baseline in FE-1, IRT, lipase, total amylase, and FC restricted to subjects with exocrine pancreatic insufficiency at baseline.			

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

Mean absolute changes from baseline of selected efficacy endpoints from placebo-controlled Studies 102, 103, and 111 and from open-label studies of subjects with a gating mutation ≥2 through 5 years of age (Study 108), and subjects with a gating mutation 12 to <24 months of age (Study 124, Cohort 5) are shown below. Results from these previous studies provide context for the efficacy results of subjects 6 to <12 months of age in Cohort 6 of Study 124. In both placebo-controlled and open-label studies, treatment with IVA led to improvement in CFTR function.

Table 16 Mean Absolute Change From Baseline (SD) for Selected Efficacy Endpoints After 24 Weeks of IVA Treatment in Subjects 12 Months of Age and Older (Studies 102, 103, 111, and 108 and Study 124, Cohort 5)

Analysis	Study 102 *G551D* Subjects ≥12 Years	Study 103 *G551D* Subjects 6 to 11 Years	Study 111 Non-*G551D* Gating Mutation Subjects ≥6 Years	Study 108 Gating Mutation Subjects 2 to 5 Years	Study 124 Cohort 5 Gating Mutation Subjects 12 to <24 Months
CFTR function					
Sweat chloride (mmol/L)	-52.2 (16.92)	-58.6 (21.74)	-59.2 (32.57)	-46.9 (26.19)	-73.5 (17.5)
Nutritional status					
Weight (kg)	3.0 (3.60)	3.8 (2.18)	3.8 (1.90)	1.4 (0.56)	1.4 (0.6)
Weight-for-age z-score (unit)	0.36 (0.309)	0.30 (0.255)	0.41 (0.193)	0.20 (0.251)	0.15 (0.42)
BMI (kg/m^2)	0.93 (1.145)	1.11 (0.920)	1.26 (0.759)	0.32 (0.538)	ND
BMI-for-age z-score (unit)	0.36 (0.324)	0.33 (0.364)	0.42 (0.276)	0.37 (0.424)	ND
Stature (cm)[a]	0.5 (1.21)	3.3 (1.11)	2.7 (1.34)	3.3 (1.17)	6.1 (1.6)
Stature-for-age z-score (unit)[a]	ND	ND	0.12 (0.13)	-0.01 (0.33)	0.28 (0.60)
Weight-for-length (percentile)	ND	ND	ND	ND	1.5 (17.1)
Weight-for-length-for-age z-score (unit)	ND	ND	ND	ND	0.07 (0.65)
Lung function					
$ppFEV_1$ (percentage point)	11.1 (8.92)	13.2 (13.51)	13.5 (10.18)	1.8 (17.81)[b]	ND
Pancreatic function					
FE-1 (µg/g)	ND	ND	ND	99.8 (138.35)	164.7 (151.9)
IRT (ng/mL)	ND	ND	ND	-20.70 (23.991)[c]	-647.1 (339.3)[b]

Sources: Module 2.5 Pediatric Addendum/Tables 8, 9, 19, and 20, Study 102/Table 14.3.7, Study 103/Table 14.3.7, Study 111/Table 14.2.4.1.1ole, Study 108/Table 14.2.2.7b, and Module 2.7.3 Study 124 12 to 24 months Addendum/Table 6

BMI: body mass index; FE-1: fecal elastase-1; IRT: immunoreactive trypsin and/or trypsinogen; IVA: ivacaftor; ND: not determined; $ppFEV_1$: percent predicted forced expiratory volume in 1 second

Notes: Descriptive statistics are provided for all parameters. All mean absolute changes are within-group changes from baseline.

[a] At 2 years of age and older, if children can stand unassisted and follow directions, stature was measured as height; otherwise, stature was measured as length.

[b] Spirometry assessments are not reliably feasible in this age group. Only 20 subjects in this 2- through 5-year old patient population could provide baseline and post-treatment spirometry values, and the results showed considerable variability.

[c] Different assays for IRT were used in Studies 108 and 124. In Study 108, the DiaSorin assay was used. In Study 124, the Cisbio assay was used.

Clinical studies in special populations

Not applicable.

Supportive study(ies)

Not applicable.

2.5.2. Discussion on clinical efficacy

Design and conduct of clinical studies

The extension of the indication of Kalydeco to children with CF aged 6 to less 12 months who have a pre-specified *CFTR* gating mutation in at least an allele of the *CFTR* gene is based on a report (Interim Analysis 2 Report) that describes PK, safety and efficacy data from children enrolled in Cohort 2 (Part A) and Cohort 6 (Part B) of study 124 which is an ongoing (as it continues to enrol children below 6 months of age) open-label, two-part study in infants and toddlers less than 2 years. In Part A, which is intended to assess PK and safety, subjects received ivacaftor granules based on body weight (25, 50 or 75 mg BID) for 4 days. During Part B, ivacaftor doses (adjusted if needed based on results of Part A) are administered for 24 weeks which allows detecting short-term safety and efficacy. Cohorts 2 and 6 only enrolled children aged 6 to less than 12 months. All subjects who completed 24 weeks of treatment in Part B are eligible to enrol in an uncontrolled extension study (Study 126) which will provide 96 weeks of ivacaftor treatment.

In study 124, ivacaftor granules were administered orally every 12 hours at the following doses after mixing with approximately 1 teaspoon (5 mL) of appropriate liquid or soft food and administered with an age-appropriate fat-containing meal or snack: • 25 mg for subjects weighing 5 to <7 kg, • 50 mg for subjects weighing 7 to <14 kg, • 75 mg for subjects weighing ≥14 to <25 kg. At each study visit in Part B, the dose for each subject was adjusted based on body weight if necessary. Based on the data provided at week 24 none of the subjects enrolled in Cohort 6/Part B received a dose of 75 mg BID as the maximum body weight observed at week 24 was 12.8 kg.

No formal dose-response studies were conducted, 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. This is acceptable as well as the general approach of the modelling and simulation study which used allometric scaling of clearance and volume of distribution and implemented in the model a maturation function driven by post-menstrual age to account for maturational changes in clearance. However, the latter was not kept in the initial selected model (as model fit did not improve) and only body weight was retained as the covariate that explains variability in ivacaftor PK in a meaningful manner. The MAH was requested to update the model with the available PK data of children below 6 months of age. This was done and one of the models (Model 4) developed included a maturation function and was the one producing the best fit of the data in spite of which it was not considered appropriate by the MAH. Additional CHMP questions were raised in this respect, and finally it has been agreed that Model 4 (model with empirical effect of body weight on Cl and a maturation effect that depends on PMA) is the one that best fits the data. The simulations provided based on this model indicate that the proposed dosing recommendations are reasonable as most infants aged 6 to less than 12 months would present an exposure similar to that in adults while less than 5% of them could present an exposure higher than that observed in adults.

Lack of randomisation/placebo control arm of study 124 is justified on the basis of extrapolation of efficacy (from adults and older children) as the underlying cause of CF and the mechanism of action of ivacaftor are the same regardless of the age of the subjects with cystic fibrosis considered. From this perspective pharmacokinetics and safety of ivacaftor were selected as appropriate primary endpoints for study 124 with PD and efficacy endpoints being secondary and tertiary endpoints respectively. The main uncertainties in relation to extrapolation of efficacy are related to the heterogeneity of target organs and the progression of the disease over time which lead to clinical manifestations that vary according to age and require efficacy endpoints tailored to the age of the population considered.

The diagnosis of CF is confirmed by laboratory evidence of abnormal CFTR protein function (a positive sweat test) or by genotyping analysis. The need for the presence of clinical features compatible with the diagnosis of cystic fibrosis (which is the main criterion for the diagnosis) was not a requisite. This seems reasonable taking into account that at young ages clinically apparent lung disease may be absent although lung structural changes may be already present and progressing. In children with CF, pancreatic insufficiency and poor nutritional status are the most significant clinical manifestations of the disease. It is anticipated that ivacaftor treatment in this age range may contribute to slowing disease progression at older ages and to the prevention of the negative consequences of CF, such as compromised lung and pancreatic function, impaired nutritional status, development of cystic fibrosis-related diabetes or liver disease. A robust demonstration in this respect is hampered by the lack of appropriate endpoints and by the length of the follow-up that would be required. The PASS study requested at the time of MA of Kalydeco ("enrolling" children aged 6 and older patients) in which long-term safety and effectiveness measures were assessed showed that in the UK and US registries where this study was conducted, ivacaftor-treated patients had a lower prevalence of CF-related complications and select microorganisms and had better preserved lung function. There are a number of limitations in relation to the design of the PASS study (such as this was primarily a safety study) but the data are overall encouraging.

In Part A, a single child received 25 mg BID while in Part B all children received 50 mg BID which is somehow expected if it is considered that according to the WHO weight-for-age growth charts 5 kg (the lower limit of body weight considered) is below the third percentile for both boys and girls at the age of 6 months. The 2016 annual report of the European Cystic Fibrosis Society Patient Registry shows that the median z-score of weight-for-age in the age group from birth to 4 years is -0.2, i.e., close to the median of a healthy population of reference (CDC 2000 reference charts used by the registry to compute z-scores for weight, height, and BMI). In the 2018 Annual Report of the UK Cystic Fibrosis Patient Registry females aged 1 year had a median (IQR) weight percentile of 53.3 (25.2-72.9) while in males of the same age these figures were 61.9 (35.4-84.9). There seems to be a systematic lower weight in females compared to males that is more evident at older ages. This justifies that results of body weight-for-age z-scores etc. are provided separately by sex even acknowledging that in Part B a small number of male subjects were enrolled. In Part B (24 weeks of duration), safety, PD (sweat chloride), and efficacy variables (nutritional status, markers of exocrine pancreatic function, markers of intestinal inflammation, pulmonary function tests and microbiology) were evaluated. Efficacy evaluation was tertiary objective in this study.

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. In addition, spirometry is not sufficiently sensitive to detect early manifestations of lung disease in young children with cystic fibrosis and for assessing response to treatment. In study 124, assessment of lung clearance index (LCI) is planned but only for subjects whose parents/legal tutors specifically consent. Lung clearance index (LCI) is not (yet) a validated endpoint and the change (decrease) reflecting a treatment effect that is clinically relevant has not been identified. However, its use is encouraged in young children. Similarly, study 124 includes the assessment of Infant Pulmonary Function Tests (IPFT) such as plethysmography only for those children whose parents/legal representatives specifically consent to the procedure.

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. For infants and young children, the aim of nutritional interventions is to achieve the 50th percentile of weight and length for a healthy same-age population up to age of two years (Turck D, Braegger CP, Colombo C et al. 2016). Weight-for-age, length-for-age, and weight-for-length-for-age z-scores were assessed in study 124. However, the interpretation of the absolute change from baseline in the anthropometric parameters is limited, not only by the lack of a control group but also by the nutritional interventions (including PERT)

that are put in place in children diagnosed following newborn screening. Furthermore, interpretation of such data in the absence of information about daily intake and appetite of these children is challenging. Of note, this information is particularly easy to collect in this age range.

Markers of exocrine pancreatic function such as faecal elastase-1 (FE-1) and serum immune reactive trypsinogen (IRT) seem particularly relevant for these young children as in the presence of 2-CF causing mutations belonging to class I, II, or III exocrine pancreatic insufficiency (EPI) is usually well established very soon after birth. These endpoints hold the potential to address whether EPI can be prevented or improved (as FE-1 in the range of EPI is present soon after birth). The lack of a control, group is, however, a drawback for their interpretation, in particular in case of IRT where very high levels are presented at birth that decrease over time. Although different patterns of decrease have been observed, this decrease occurs across a number of years. In prior procedures, the MAH argued that decreases of IRT in response to ivacaftor were seen more rapid than the usual decrease seen due to the underlying disease. A number of additional uncertainties were related to the assay used to determine IRT which is critical as a number of factors may affect the values of IRT and their interpretation. In Study 124 the Cisbio assay was used which is a radioimmunoassay that is specific for trypsin, trypsinogen, and the enzyme's inhibited forms, and has a range of detection from 8.0 to 1200 ng/mL. In healthy adult subjects the serum trypsin concentration ranges from 140 to 400 ng/mL (median 200 ng/mL). In children aged 6 to 12 months a cut-off value(s) or a range of reference of normal values is not addressed but it is likely that this is age-dependent. In newborn screening programs in Europe, a fixed cut-off of 60 to 90 ng/mL (median 65) or a floating cut-off ranging from the 99.0th to 99.5th percentiles of all samples tested by a laboratory was used to determine the abnormal range. 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. In a study performed by Gleghorm G et al (1985), lipase was significantly elevated in infants with CF who were younger than 1 year, irrespective of pancreatic function (sufficient or insufficient). After the first year of life, lipase values declined toward normal. When compared to the rate of decline of trypsinogen (also determined in the same study), lipase decline was greater, i.e., 67% of lipase values were within or below the normal range by 3 years, whereas 67% of trypsinogen values continued to be elevated. As for total amylase, also limited evidence seems to exist.

The overall conclusion from the MAH is that values below the normal range for amylase and lipase appear to correlate with pancreatic insufficiency and normal or above normal values with preservation of pancreatic function. While collecting and reporting values of lipase and (preferably) pancreatic isoamylase is endorsed, the fact remains that there is very sparse evidence about the course of lipase and amylase levels in subjects with cystic fibrosis.

Faecal calprotectin (FC) is a non-CF specific inflammatory marker which is known to be elevated in patients with CF, particularly in pancreatic insufficient (PI) patients (Garg M et al 2017). The study by Garg (2013) included a sample of patients with cystic fibrosis and healthy controls in the age range from 0 to 10 years. FC levels are usually low in infants with cystic fibrosis during the first year of life and increase afterwards until the age of four years. As a consequence of distinctive age-related variations in the values, careful interpretation of levels of FC is required in children under four years of age. From > 4 to 10 years, FC was consistently higher in CF patients compared with healthy controls. In Study 124 the assay used to determine FC was a commercial immunoassay for which the normal range of reference quoted ranges from 15.625 to 162.9 µg/g with an upper assay range until 2000 µg/g. However, this assay has been mainly assessed in subjects with inflammatory bowel disease.

The sample size of study 124 was based on the availability of the subject population and PK analysis considerations, and not on any statistical consideration. Therefore, the study is not powered to detect a significant treatment effect. Continuous variables (analysed as the absolute change from baseline to the pos-baseline value) and categorical variables were summarized by standard descriptive statistics.

Incomplete/missing data were not imputed. The difficulties to measure certain variables (e.g. sweat chloride) in these young children are acknowledged by the CHMP.

Efficacy data and additional analyses

In Part A, 6 infants were enrolled. Their mean age (SD) was 7.7 (1.86) months. All 6 subjects were White and of non-Hispanic or Latino ethnicity. The majority of subjects had the *G551D* mutation, and 1 subject had the *R117H* mutation. The most prevalent genotype was *G551D/F508del* (5 out of the 6 subjects). Complete set of anthropometric parameters as z-scores and percentiles were provided by the MAH upon request for children enrolled in Part A. For the overall population of infants enrolled in Part A/Cohort 2, both the mean and median values of weight-for age z-scores and percentiles show that these children are below the median value of weight expected in a healthy same-age population of reference but still above the cut-off of -2 which would be indicative of underweight. Weight-for-age, however, fails to distinguish between short children of adequate body weight and tall, thin children. The mean and median values of length-for-age z-scores and percentiles show normal values (e.g., median mean length-for-age percentile of 75.8) which is somehow striking when considering that most children with cystic fibrosis usually present with worse values of stature than of body weight. Regarding weight-for-length z-scores and percentiles which may be indicative of wasting (i.e., children too light for their height), the median values (-1.21 and 11.2 respectively) indicate that these children are below the expected median values of a healthy same-age population of reference, with some of them close to -2 (with values below -2 indicative of wasting). Wasting or thinness indicates in most cases a recent and severe process of weight loss, which is often associated with acute starvation and/or severe disease. However, wasting may also be the result of a chronic unfavourable condition.

In part B, 11 infants were enrolled (three of them from Part A) and all of them received ivacaftor 50 mg BID given that at Day 1 as all subjects weighted 7 to <14 kg (range: 7.8 to 10.7 kg). The mean (SD) age at baseline was 9.0 (1.34) months. All 11 subjects were White. The majority of subjects had a *G551D* mutation. One subject had a *G178R* mutation. The most prevalent genotype was *G551D/F508del*.

The median (min, max) weight- and length-for-age z-scores were 0.71 (-0.76, 1.24) and 0.69 (-0.67, 1.61) respectively. The median (min, max) weight-for-length-for-age z-score was 0.17 (-1.48, 1.26) while the median (min, max) weight-for-length percentile was 56.7 (7, 90) which is in clear contrast with the median values observed in Part A (-1.21 and 11.2 respectively). Clarification was requested from the MAH in this respect given the difference in anthropometric parameters between children enrolled in Part A/Cohort 2 and those in Part B/Cohort 6 with the latter overall having better anthropometric parameters at baseline likely reflecting a more preserved nutritional status except for the above mentioned strikingly higher length-for-age z-score and percentile in Part A/ Cohort 2 which suggests that children enrolled in Part A were tall and thin as compared to children enrolled in Part B. In their response, the MAH stated that at baseline subjects enrolled in Part B were slightly older than subjects enrolled in Part A (median age at baseline Part A: 7.0 months, Part B: 9.0 months) and had grown in size contributing to the higher median weight-for- length percentile at baseline. Even if the numerical differences in weight-for-length percentiles between Part A and Part B are acknowledged, these are considered not to be relevant to the core purpose of Part A, which was to characterize the PK and establish appropriate dosing for Part B. The MAH was requested to further discuss this issue. The baseline demographic and disease characteristics of the 3 infants who continued in Part B and of those who did not do it were provided and the reason(s) for not being enrolled in Part B clarified. Two infants from Part A/Cohort 2 were not enrolled in Part B/Cohort 6 due to their age at Day 1 of Study 124 while the family of the 3rd child elected to screen for the extension study 126. In addition, this subject apparently was about to age out of eligibility for Part B. The 3 infants who enrolled in Part B were younger. In terms of weight-for-length percentiles, children who did not enrol in Part B had overall lower values than the ones of infants who did (as expected) but no systematic differences are observed in these two groups of children.

The MAH concludes that nutritional parameters were normal at baseline. None of the z-scores discussed are below -2 which would be indicative of growth problems. However, it appears that even within the normality, not all of the children enrolled were in a similar situation at baseline.

Median (range) baseline sweat chloride was 101.5 (85.5, 111.5) mmol/l (n=11). Regarding FE-1 and IRT, mean (SD) baseline values were 119.6 (199.1) µg/g (n=10) and 1120.6 (238.2) ng/ml (n=9) respectively.

Data provided regarding the medical history of the patients enrolled in Part B shows that almost all patients (10/11) had CF lung disease and/or pancreatic insufficiency.

Children in study 124 continued to receive their usual, prescribed CF therapy in addition to ivacaftor. The most commonly reported concomitant medications were pancreatin (72.7%), sodium chloride (63.3%), amoxicillin (45.5%), and paracetamol (45.5%). Pancreatic enzyme replacement therapy (pancreatin or pancrelipase) was reported for 9 (81.8%) subjects. Ten subjects are reported to have pancreatic failure while only 9 seem to be receiving pancreatic enzyme replacement therapy.

Sweat chloride

The mean (SD) sweat chloride level at baseline was 101.5 (9.8) mmol/L (n=11). Treatment with ivacaftor led to rapid reductions in sweat chloride concentrations at Week 2 that were sustained to Week 24. The mean (SD) absolute change from baseline in sweat chloride was -52.6 (16.4) mmol/L at Week 2 and -58.6 (16.5) mmol/L (n = 6) at Week 24. Four (36.4%) subjects had at least 1 on-treatment sweat chloride value ≤30 mmol/L. At Week 24, 3 subjects had a sweat chloride value <35 mmol/L, including 1 subject who had a sweat chloride value <30 mmol/L which is the diagnostic cut-off for normal sweat chloride.

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

Weight, Weight-for-age z-score, and Weight-for-age Percentile

Five infants enrolled in Part B had a weight-for-age Z-score between 0 and -1 SDS at baseline which is shown by a minimum value of -0.76. At week 24 some children were still below 0 SDS as shown by a minimum value of -0.52 but the mean weight-for-age Z-score increased from 0.37 at baseline to 0.73 at Week 24 (mean [SD] absolute change from baseline 0.36 [0.54]).

Only a small number of male infants were enrolled in Cohort 6. The median (range) absolute change in weight-for-age z-score and percentile from baseline at week 24 was 1.05 (0.48, 1.63) and 28.2 (6, 50) respectively. These figures for some infants were as follows: 0.26 (-0.29, 0.70) and 10.3 (-8, 18) respectively. The MAH was requested to clarify an apparently anomalous result seen in one of the subjects in the other group for which the mean weight-for-age percentile changed at week 24 with a mean change in body weight. In this case, the median weight-for-length percentile at week 24, i.e. indicative of possible risk of overweight. These values were confirmed and therefore this is expected to have an impact on the calculation of the mean values that are included in section 5.1 of the SmPC.

Mean (SD) weight at baseline was 8.9 (1.0) kg. The mean absolute change (SD) from baseline at Week 24 was 1.8 (0.7) kg. At Week 24, mean (SD) weight was 10.7 (1.1) kg which according to the WHO growth charts of weight-for-age percentiles would correspond to a value above the 85th percentile for the age range from 6 months to less than 12 months.

Length, Length-for-age z-score, and Length-for-age Percentile

Regarding mean absolute changes from baseline in length-for-age Z-scores, 4 children enrolled in Part B had a length Z-score between 0 and -1 SDS which is shown by a minimum value of -0.67. At week 24 some children were still below 0 SDS as shown by a minimum value of -1.81 but the mean length-for-age

Z-score increased from 0.63 at baseline to 0.89 at Week 24 (mean [SD] absolute change from baseline 0.27 [1.34]).

The above data have been also provided as percentiles and by sex. As said, only a small number of male patients were enrolled in Cohort 6. The median (range) change from baseline at week 24 in the z-score and percentile was for some infants -0.48 (-0.69, -0.27) and -11.2 (-12, -10) respectively. For other infants these values were as follows: 0.41 (-1.81, 3.38) and 10.8 (-58, 41).

Mean (SD) length at baseline was 72.5 (2.6) cm. The mean absolute change (SD) from baseline at Week 24 was 7.7 (3.5) cm. At Week 24, mean (SD) length was 80.2 (4.4) cm which according to the WHO growth charts of length-for-age percentiles would correspond to a value around the 97th percentile for the age range from 6 months to less than 12 months. This is quite an anomalous value even considering that it is a mean value. It has been clarified that the length of one subject was very likely overestimated at week 24 as the change from baseline at week 24 was 10.7 cm.

Weight-for-length-for-age z-score and Weight-for-length-for-age Percentile

Regarding mean absolute changes from baseline in weight-for-length-for-age Z-score, 5 children enrolled in Part B had a weight-for-length-for-age Z-score between 0 and -2 SDS at baseline which is shown by a minimum value of -1.48. At week 24 some children were below -2 SDS as shown by a minimum value of -2.04 but the mean weight-for-length-for-age Z-score increased from 0.13 at baseline to 0.40 at Week 24 (mean [SD] absolute change from baseline 0.26 [1.3]). Based on the maximum value of 2.16 observed at week 24 it would appear that some children are overweight (i.e., weight-for-length-for-age Z-score > 2 SDS). Weight-for-length-for-age Z-scores and percentiles have been provided also by sex. The median (range) change from baseline at week 24 in the z-score and percentile was for the male infants 1.63 (1.04, 2.22) and 42.2 (20, 64), respectively. For female infants these values were as follows: 0.02 (-2.04, 1.99) and 0.8 (-69, 42). The interpretation of the anthropometric data is not that easy in the absence of additional information such as assessment of daily intake, appetite etc. The maximum weight-for-length-for-age z-score at week 24 shows that some children are overweight (i.e., Z-score above + 2 SDS) while others remain below the target of the 50th percentile (that would correspond to a 0 Z-score in a population normally distributed). The MAH was requested to clarify the distribution of the eleven children enrolled in Part B according to their weight-for-length-for-age Z-scores and percentiles at baseline and at week 24. The MAH states that the data are well distributed across the possible range of percentiles at baseline and at Week 24. Overall, the baseline dataset includes infants with weight-for-length z-scores which range from values close to -2 to +1.26 which are still considered within the normal range. However, the lowest value at baseline is closed to the cut-off indicative of wasting (below -2) while the highest one at week 24 is indicative of overweight (i.e., 2.16). The influence of these extreme values is noted when calculating mean and median values. Mean (SD) values are included in section 5.1 of the SmPC for both cohort 5 (12 to less than 24 months) and cohort 6 (6 to less than 12 months) which should be viewed with some caution for the reasons mentioned. For completeness median (main, max) values will also be included. As Study 124 is ongoing further refinement of the data described in section 5.1 of the SmPC will be done as applicable at the time the final results of the study are submitted.

Although CF is commonly associated with undernutrition, the proportion of overweight and obese individuals is increasing. Increased weight does not necessarily correlate with better lung function as high fat mass but low lean body (muscle) mass predicts in fact poor CF disease prognosis. Therefore, body composition needs to be assessed in all overweight/obese patients as well as in those underweight. Serum/plasmatic markers such as blood count, iron status (transferrin), serum prealbumin etc. are also used to assess the nutritional status.

Faecal elastase-1 (FE-1)

Out of the 9 subjects with FE-1 data at baseline and at week 24, 7 subjects were pancreatic insufficient. The mean (SD) FE-1 values at baseline for these 7 subjects was 28.6 (30.6) µg/g. At week 24, the mean (SD) FE-1 value was 231.6 (141.8) µg/g. The mean (SD) absolute change from baseline at week 24 was 203.1 (147.3) µg/g. Five of them had FE-1 values >200 µg/g at Week 24 while the other two had an FE-1 value ≤200 µg/g. None of these subjects had a post-baseline FE-1 value FE-1 ≥500 µg/g. Two subjects who were pancreatic sufficient at baseline reached a value above 500 µg/g and none of them became insufficient during treatment with ivacaftor.

Immunoreactive trypsin and/or trypsinogen (IRT)

Six subjects in cohort 6 had both baseline and Week 24 data for IRT and a baseline FE-1 value. All 6 subjects who had these values were pancreatic insufficient at baseline (FE-1 < 200 µg/g). The mean (SD) absolute change from baseline at week 24 in IRT using the Cisbio assay (range of detection from 8.0 to 1200 ng/ml) was -450.6 (376.7) ng/ml. Median change (Min. Max) was -480.4 (-830.3, 0.0) ng/ml.

IRT is elevated immediately after birth in neonates with CF as a marker for pancreatic ductal congestion and reflects leakage from the exocrine cells to the blood. This is accompanied by fibrosis and ongoing loss of exocrine tissue. IRT levels are therefore expected to decline with age naturally and this may confound the effect of ivacaftor. However, the rapid (observed at week 2) and steep decline after starting ivacaftor suggests a treatment effect and, supports the hypothesis that early intervention with ivacaftor can improve pancreatic function in young children mainly if this accompanied for consistent trends in other biomarkers of gastrointestinal function and inflammation.

Lipase, total amylase

Ten infants enrolled in cohort 6 of Study 124 had lipase levels at both baseline and at week 24. The mean (SD) change from baseline at week 24 in lipase levels in subjects with pancreatic insufficiency (n=8) was -90.50 (75.04) with a median (range) change of -100.00 (-203.0, 23.0) U/L. For those with lipase levels elevated at baseline (n=10, mean [SD] 362.90 [281.18] U/L), the mean (SD) change from baseline at week 24 was -265.40 (287.06) with a median (range) of -137.50 (-885.0, 23.0) U/L. The mean baseline value in children with elevated values is 362.90 U/L which is almost 16 times higher than the upper limit of the normal range (23 U/L). The maximum value at baseline was 983.0 U/L (22 times higher than the upper limit of the normal range). These values are of concern but all subjects with elevations in lipase at baseline were asymptomatic. While the mean values show reasonable decreases, there is a maximum value of decrease of -885.0 U/L which is assumed to be the one observed in the subject with a baseline value of 983.0 U/L.

Ten infants enrolled in cohort 6 of Study 124 had total amylase levels at both baseline and at week 24. The mean (SD) change from baseline at week 24 in amylase levels in subjects with pancreatic insufficiency (n=8) was -7.8 (31.1) U/L with a median (range) change of -6.5 (-58, 52) U/L. For those with amylase levels elevated at baseline (n=8, mean [SD] 92.0 [34.4] U/L), the mean (SD) change from baseline at week 24 was -28.5 (40.9) U/L with a median (range) of -37.0 (-76, 52) U/L. The mean baseline value in children with elevated values is 92.0 U/L which is 2 times higher than normal (44 U/L). The maximum value at baseline was 145 U/L (3 times higher than normal).

Reductions in both (mean) serum lipase and total amylase levels were observed over the 24 weeks of treatment with ivacaftor. As in the case of IRT, the rapid (observed at week 2) and substantial decline in the levels of these enzymes may suggest that treatment with ivacaftor reduces pancreatic inflammation in these young subjects. While the use of the pancreatic isoamylase is preferred, it would appear that overall these results are in line with those of FE-1 and IRT. However, there are sparse data about the values of lipase and amylase that could be expected in subjects with cystic fibrosis as compared to normal subjects. Therefore, these data are not included in section 5.1 of the SmPC.

Faecal calprotectin (FC)

At baseline most subjects (9 of 11) were within the normal range provided by the reference lab which ranged from 15.625 to 162.9 µg/g while the cut-off value described and used in the study by Garg et al (2017) and Ellemuler et al (2018) was 50 µg/g. Nine infants had values of FC at both baseline and week 24. Out of these 9 infants, 7 had exocrine pancreatic insufficiency (EPI). At baseline, their mean (SD) value of FC was 128.80 (97.73) µg/g with a median (range) value of 81.90 (50.8, 272.6) µg/g. These values for the two subjects with pancreatic sufficiency were 95.40 (12.59) µg/g and 95.40 (86.5, 104.3) µg/g. There seems to be some contradictory findings regarding whether the values of FC differ from patients with exocrine pancreatic insufficiency versus those seen in subjects with exocrine pancreatic sufficiency. The mean (SD) absolute change from baseline at week 24 in FC in subjects with EPI was -44.21 (146.90) µg/g with a median (range) value of -50.60 (-256.3, 155.4) µg/g. In infants with pancreatic sufficiency (n=2) a mean absolute decrease of -56.70 µg/g was observed. While it may be difficult in the absence of a control arm to conclude whether the decrease observed in FC can be directly attributed to ivacaftor, results in FC when taken together with those observed for other biomarkers of gastrointestinal function such as faecal elastase-1 and IRT give support to the potential of ivacaftor as a drug that decreases gastrointestinal inflammation. However, as previously said, due to distinctive age-related variations, careful interpretation of the levels of FC is required in children under four years of age. In addition, there seems to be some contradictory findings regarding whether the values of FC differ from patients with exocrine pancreatic insufficiency versus those seen in subjects with exocrine pancreatic sufficiency.

The pattern seen in FE-1, IRT, lipase, and FC suggests that indeed ivacaftor is able to improve pancreatic exocrine function. It is of limit that the assay used to determine IRT in children aged 2 to less than 6 years of age (study 108) is not the same as the one used in study 124 as the values cannot be directly compared. These variables are usually analysed as a change from baseline to the end of the study. Intuitively these are better (or in addition) presented as the percent of subjects who show at baseline an altered value and reach at week 24 values within the normal range. Responder's analyses have not been provided by the MAH on the basis that the small sample size of Cohort 6 would not allow for a precise analysis. This is accepted for the current procedure. However, it can be anticipated that this question may be raised at the time of final results from Study 124 are submitted.

Pulmonary function (LCI and IPFTs)

Lung Clearance index and IPFT were performed in a subject each. Regarding LCI, the absolute change from baseline at Week 24 was -0.84. LCI values were 7.47 at Day 1 (baseline) and 6.63 at Week 24. As for IPTF, only FRC values were available at both baseline and Week 24. The absolute change in FRC from baseline at Week 24 was 77.60 mL. FRC was 163.90 mL at baseline and 241.50 mL at Week 24. Whether this is consequence of the treatment with ivacafor cannot be properly assessed. Percent predicted values should be used as children are expected to increase lung volumes with growth. The result in LCI is as expected although of limited magnitude which may be partially explained for the young age of this cohort of children.

Pulmonary exacerbations (PEx)/Microbiology

Two definitions of PEx were used for analyses because there is no consensus definition for PEx in younger paediatric patients. Under definition 1 (less restrictive), 7 subjects (63.6%) had a total of 10 PEx. The observed event rate per year is 1.95. Under definition 2, 3 subjects (27.3%) had a total of 4 PEx (event rate per year is 0.78). A single subjects had 1 CF-related hospitalization (event rate/year = 0.20). No definitive conclusions can be drawn regarding the effect on pulmonary exacerbations (which occurred at an event rate per year which was similar to that seen in infants aged 12 to less than 24 months) or microbiology (qualitative microbiology oropharyngeal culture). No cases of MRSA or *Burkholderia* were observed over the treatment period.

Acceptability and palatability assessment

A palatability assessment of ivacaftor granules was performed at the Day 1 Visit of Part B. All subjects fully consumed the dose. The majority of subjects (8 [72.7%]) liked the food with ivacaftor granules (either very much or a little). A single time point of assessment seems insufficient and very likely this endpoint should have been assessed at additional visits but there is a lack of structured guidance to formally assess acceptability and palatability. Overall, the mean study drug compliance was 99.3%, and 100% of subjects were ≥80% compliant with study drug.

The present interim analysis of data from study 124 focuses on children aged 6 to less than 12 months of age. The MAH was requested to compare the results in this age group to those of children in the age group from 12 to less than 24 months and from 2 to less than 6 years of age. As further analyses (by sex and by exocrine pancreatic function) have been requested for Cohort 6 in study 124, and only partially for Cohort 5 (12 to less than 24 months of age), the same was requested for children under 6 years old, i.e., anthropometric parameters (Z-scores and percentiles) by sex and markers of pancreatic inflammation (FE-1 and IRT) restricted to subjects with exocrine pancreatic insufficiency. Overall, the same trend as for younger children in Study 124 is observed at baseline (i.e., female girls had overall less preserved nutritional status than male children based on weight-for-age z-scores and percentiles). The mean (SD) absolute change in weight-for-age z-scores and percentiles were 0.27 (0.16) and 7.6 (5.3) respectively in female patients (n=6). In male patients (n=27), these figures were as follows: -0.12 (0.83) and 6.0 (7.6) respectively. Regarding, height-for-age z-scores and percentiles, the mean (SD) absolute change from baseline at week 24 in female children was -0.27 (0.36) and -8.5 (11.6) respectively. In male children the following mean (SD) changes were obtained: 0.05 (0.30) and 2.5 (7.7) respectively. Overall these changes are of limited magnitude for both female and male children, in particular when height is considered.

Regarding faecal elastase-1, in study 108 26 patients with exocrine pancreatic insufficiency (EPI) had both baseline and week 24 values. The mean (SD) value of FE-1 was 9.8 (9.3) µg/g. The mean (SD) absolute change from baseline was 103.7 (139.6) µg/g with a median (range) value of 103.7 (0, 451) µg/g. Therefore, also an increase of FE-1 was seen for some patients but not for all of them. The mean (SD) baseline value of FE-1 in subjects with EPI enrolled in Cohort 6 of Study 124 was 25.9 (29.3) µg/g with median (range) value of 7.5 (8, 85) µg/g. The mean (SD) absolute change from baseline at week 24 was 203.1 (147.3) µg/g with a median (range) value of 236.0 (0, 424) µg/g. Overall, infants in Study 124 seem to experience changes of higher magnitude than older children which may perhaps be ascribed to the cumulative pancreatic damage caused by CF. As for IRT, in children enrolled in Study 108 with EPI and for whom values of IRT were available at both baseline and week 24 (n=20), the mean (SD) absolute change from baseline at Week 24 was -17.8 (24.3) ng/ml. The magnitude of the change cannot be compared to that seen in Cohort 5 (12 months to less than 24 months) and Cohort 6 (6 to less than 12 months) of Study 124 due to differences of the assay used in both studies.

A final CSR will be provided for Study 124 when completed, which will include a global analysis of safety and efficacy data from all age cohorts. The PI will adequately be updated if needed.

2.5.3. Conclusions on the clinical efficacy

The second interim analysis of Study 124 provides PK, safety, PD (sweat chloride) and some efficacy data (tertiary endpoints) of the treatment with ivacaftor in infants aged 6 to less than 12 months with at least a pre-specified gating mutation in an allele of the *CFTR* gene. Study 124 is an uncontrolled study and this raises uncertainty about the interpretation of the efficacy endpoints, as for some of them many confounders may a play a role. The most robust result is that seen on sweat chloride (mean absolute change from baseline of -58.6 mmol/L) which is in the range of values seen in the pivotal trials of ivacaftor in older patients. This provides support for extrapolation of efficacy even though this is just a biomarker of CFTR activity. Similarly, the increase in FE-1 observed at Week 24 in children with well-established

exocrine pancreatic insufficiency seems very relevant but how this translates into quality of life and nutritional status would require a prolonged follow-up which cannot be addressed in the frame of a relatively short-term registration clinical trial such as Study 124. Additional data have been provided for some biomarkers of gastrointestinal function and inflammation that point out in the same direction as faecal elastase-1. Whilst the submitted data is considered sufficient to conclude on efficacy in the claimed population, further data are needed to interpret the results of biomarkers such as faecal calprotectin, lipase and amylase. This is the reason not to reflect them in section 5.1 of the SmPC at this time. As Study 124 is ongoing further refinement of the data described in section 5.1 of the SmPC will be done as applicable at the time when data from all cohorts are available. It would have been very helpful to put the data of the present study into context with data coming from disease-registries, an issue that has been repeatedly requested but never accomplished. For subjects aged 2 to less than 6 years of age, a PAES, which was agreed in a previous procedure, is ongoing aimed at assessing whether starting treatment at the age of two years may have an impact on disease progression. The same request was done for children below 2 years of age. However, the MAH argued that the number of available children in this age range would make the study unfeasible. This was accepted by CHMP. Overall, although some clarity would still be desirable about certain aspects as above mentioned, it is considered that from a clinical point, sufficient data and argumentation has been provided.

2.6. Clinical safety

Patient exposure

In Part A/Cohort 2, 1 subject received 25 mg IVA, and 5 subjects received 50 mg IVA. All subjects completed the 5-day treatment period (4 days of IVA treatment). In Part B/Cohort 6, all 11 subjects received 50 mg IVA, and all 11 completed the study. The mean (SD) exposure to study drug was 24.3 (0.55) weeks (range: 23 to 25 weeks). All 11 subjects enrolled into Study 126 and therefore did not have the Follow-up Visit, per protocol.

Demographics and Baseline Characteristics of Study Population

Part A/Cohort 2: One subject weighed 6.7 kg at baseline and therefore received IVA 25-mg q12h. Five subjects weighed 7 to <14 kg (mean: 7.9 kg, range: 7.1 to 8.8 kg) at baseline and therefore received IVA 50-mg q12h. In the 50-mg group, the mean age was 8 months (range: 6 to 10 months). The mean age of all 6 subjects was 7.7 months (range: 6 to 10 months). All subjects were White and of non-Hispanic or Latino ethnicity. Nutritional parameters (weight, length, and weight-for-length percentiles) were normal at baseline.

Part B/Cohort 6: All 11 subjects weighed >7 to <14 kg at Day 1 and throughout the treatment period (mean weight at baseline: 8.9 kg, range: 7.8 to 10.7 kg) and therefore received IVA 50 mg q12h throughout the treatment period. The mean age at baseline was 9 months (range: 7 to 11 months). All subjects were White and all, but 1, were of non-Hispanic or Latino ethnicity; ethnicity was not reported for the 1 subject. Nutritional parameters (weight, length, weight-for-age z-score, length-for-age z-score, weight-for-length-for-age z-scores, and weight-for-length percentiles) were normal at baseline.

Adverse events

Part A/Cohort 2. Key safety findings were as follows:

- Four (66.7%) of the 6 subjects had AEs: the subject in the 25 mg group and 3 subjects (60.0%) in the 50 mg group. No AEs occurred in more than 1 subject.

- All AEs were mild in severity except for 1 event of vomiting, assessed as moderate in severity. All AEs were considered unlikely related or not related to study drug except for 1 event each of constipation, vomiting, and sleep disorder, which were considered possibly related to study drug.
- There were no deaths, serious AEs (SAEs), treatment interruptions or discontinuations.
- There were no notable adverse trends in clinical laboratory assessments, vital signs, or ECG parameters.

Part B/Cohort 6. The safety data in this study are consistent with previous studies in subjects 12 months of age and older. Key safety findings were as follows:

- Ten (90.9%) of the 11 subjects had AEs.
- Most AEs were typical for patients with CF of this age group. The most commonly reported AEs (>20% of subjects) included cough, nasal congestion, rhinorrhea, pyrexia, and vomiting.
- The majority of subjects had AEs that were mild or moderate in severity, and considered unlikely related or not related to study drug. There were 2 severe AEs (1 AE each of viral rash and respiratory tract infection viral) that were also SAEs. There were no life-threatening AEs.
- Three (27.3%) subjects had a total of 3 SAEs. The 3 SAEs were viral rash, cough, and respiratory tract infection viral. All were considered unlikely or unrelated to study drug.
- One (9.1%) subject had an AE of rash that led to treatment interruption.
- There were no deaths or treatment discontinuations due to AEs.
- One (9.1%) subject had alanine transaminase (ALT) elevation >3 × to ≤5 × upper limit of normal (ULN) at Week 24 which was not associated with bilirubin elevation. The subject remained on study drug in the extension study 126 and the transaminase elevation resolved.
- No subjects had total bilirubin levels above the normal range.
- No treatment-emergent cataracts (lens opacities) were observed.
- There were no notable adverse trends in other clinical laboratory assessments, vital signs, or ECG parameters

Table below summarizes the above information.

Table 17 Overview of Adverse Events, Safety Set, Part B/Cohort 6

Category	IVA 50 mg N = 11
Subjects with any AEs, n (%)	10 (90.9)
Subjects with related AEs, n (%)	2 (18.2)
Subjects with AEs leading to treatment discontinuation, n (%)	0
Subjects with AEs leading to treatment interruption, n (%)	1 (9.1)
Subjects with SAEs, n (%)	3 (27.3)
Subjects with AEs leading to death, n (%)	0

Source: Study 124 IA2R/Table 14.3.1.1.b6
AE: adverse event; IVA: ivacaftor; n: size of subsample; N: total sample size; SAE: serious adverse event
Notes: When summarizing number and percent of subjects, a subject with multiple events within a category was counted only once in that category. Related AEs included related, possibly related, and missing categories.

The incidence of AEs that occurred in 2 or more subjects is shown in table below. The most common AEs were cough, nasal congestion, rhinorrhea, pyrexia, and vomiting. These AEs are generally typical for patients with CF in this age group.

Table 18 Adverse Events Occurring in At Least 2 Subjects by System Organ Class and Preferred Term, Safety Set, Part B/Cohort 6

System Organ Class[a] Preferred Term	IVA 50 mg N = 11 n (%)
Subjects with any AEs	**10 (90.9)**
Infections and infestations	**9 (81.8)**
Ear infection	2 (18.2)
Hand-foot-and-mouth disease	2 (18.2)
Otitis media	2 (18.2)
Tonsillitis	2 (18.2)
Viral Upper respiratory tract infection	2 (18.2)
Respiratory, thoracic, and mediastinal disorders	**7 (63.6)**
Cough	7 (63.6)
Nasal congestion	4 (36.4)
Rhinorrhoea	4 (36.4)
Gastrointestinal disorders	**6 (54.5)**
Vomiting	3 (27.3)
Skin and subcutaneous tissue disorders	**5 (45.5)**
Dermatitis diaper	2 (18.2)
General disorders and administration site conditions	**3 (27.3)**
Pyrexia	3 (27.3)

Source: Study 124 IA2R/Table 14.3.1.2.b6
AE: adverse event; IVA: ivacaftor; n: size of subsample; N: total sample size; PT: Preferred Term; SOC: System Organ Class
[a] A subject with multiple events within a category (Any, SOC, or PT) was counted only once in that category. The table was sorted in descending order by SOC, and by PT within each SOC.

The majority of subjects had AEs that were mild or moderate in severity. There were no AEs that were considered life-threatening. Two subjects (18.2%) had AEs that were considered severe (respiratory tract infection viral and viral rash). These 2 AEs were also SAEs and narratives have been provided. Of the 10 subjects who had AEs, 2 subjects had an AE considered related to study drug (both were considered possibly related) by the investigator (vomiting, ALT increased). One (9.1%) subject had an AE of rash that led to treatment interruption. There were no AEs that led to permanent treatment discontinuation.

Serious adverse event/deaths/other significant events

There were no deaths or AEs that led to treatment discontinuation. Three (27.3%) subjects had a total of 3 SAEs. One subject had an SAE of viral rash (suspected eczema coxsackium); 1 subject had an SAE of cough; and 1 subject had an SAE of viral respiratory tract infection. All of the SAEs (viral rash, cough, and respiratory tract infection viral) were considered by the investigator to be unlikely related or not related to study drug. This is acceptable to the CHMP.

Laboratory findings

Liver Function Test Results: Fluctuations from baseline in mean LFT measurements throughout the 24-week treatment period were not considered clinically significant. The maximum on-treatment LFT results are presented in the table below. The majority of subjects had maximum on-treatment ALT or

aspartate transaminase (AST) ≤2 × ULN. One subject had an ALT elevation >3 × to ≤5 × ULN at Week 24. The subject enrolled in Study 126 and remained on study drug without interruption. The ALT elevation was resolved by the Week 2 Visit of Study 126. No subjects had AST and/or ALT elevations >5 x ULN. No subjects had total bilirubin levels above the ULN.

Table 19 Maximum On-treatment Liver Function Test Results, Safety Set, Part B/Cohort 6

Maximum On-treatment Result	IVA 50 mg N = 11 n (%)
ALT or AST	
>2 × to ≤3 × ULN	0
>3 × to ≤5 × ULN	1 (9.1)
>5 × to ≤8 × ULN	0
>8 × ULN	0
Bilirubin	
>2 × ULN	0

Source: Study 124 IA2R/Table 14.3.4.3.1.b6
ALT: alanine transaminase; AST: aspartate transaminase; IVA: ivacaftor; LFT: liver function test; N: total sample size; n: size of subsample; ULN: upper limit of normal
Notes: The categorized result was the maximum of all post-baseline, on-treatment LFT assessments. The denominator was the number of subjects with at least 1 post-baseline assessment.

Lipase and Amylase: Mean (SD) serum lipase at baseline was elevated at 331.36 (286.52) U/L (normal range: 4 to 23 U/L [ages <12 months] and 4 to 31 U/L [ages ≥12 months]). The mean (SD) lipase level decreased to 90.45 (63.76) U/L at Week 24. Mean (SD) serum amylase at baseline was 76.1 (39.8) U/L (normal range: 6 to 44 U/L [ages <12 months] and 8 to 79 U/L [ages ≥12 months]). The mean (SD) amylase level decreased to 54.2 (29.0) U/L at Week 24. All subjects with elevations in serum lipase and/or amylase at baseline were asymptomatic.

Electrocardiograms: No clinically important trends were identified in ECG results. All subjects had a maximum QTcF interval of ≤450 msec during study treatment. No subjects had an increase in QTcF of >30 to ≤60 msec. There were no ECG results that were considered by the investigator to be AEs.

Safety in special populations

The proposed dose of IVA granules for patients 6 to <12 months is 25 mg for patients weighing 5 to <7 kg and 50 mg for patients weighing 7 to <14 kg, administered q12h with fat-containing food.

Based on the results of Phase 1 Study 013 in adult subjects with moderate hepatic impairment, the following IVA dose adjustments have been recommended in patients with moderate hepatic impairment:

- ≥6 years: one 150 mg tablet qd
- 12 months to <6 years and ≥14 kg: one 75-mg sachet/packet of granules qd
- 12 months to <6 years and 7 to <14 kg: one 50-mg sachet/packet of granules qd

Although moderate hepatic impairment is relatively rare in children <24 months with CF, such a level of liver disease may occur. The recommended dose for patients 6 to <12 months with moderate hepatic impairment is similar to the recommendation (but adjusted for the smaller size of these patients) for patients 1 to <6 years old with moderate hepatic impairment:

- 6 to <12 months and ≥5 to <7 kg: one 25-mg sachet/packet of granules qd
- 6 to <12 months and ≥7 to <14 kg: one 50-mg sachet/packet of granules qd

Studies have not been conducted in patients with severe hepatic impairment (Child-Pugh Class C), but exposure is expected to be higher than in patients with moderate hepatic impairment. The use of IVA in patients with severe hepatic impairment is therefore not recommended unless the benefits outweigh the risks. In such case, the starting dose should be 1 sachet/packet of granules qd or less frequently. Dosing intervals should be modified according to the clinical response and tolerability. In addition, no safety data are available in infants aged 6 to less than 12 months of age with moderate hepatic impairment treated with ivacaftor.

Safety related to drug-drug interactions and other interactions

A reduction in the IVA dose is recommended for coadministration with strong or moderate CYP3A inhibitors. The recommended IVA dose in patients ≥6 years of age is 150 mg twice weekly with strong CYP3A inhibitors and 150 mg daily (qd) with moderate CYP3A inhibitors. The recommended IVA dose for patients 1 to <6 years of age is 50 mg (7 to <14 kg) or 75 mg (≥14 kg) twice weekly during concomitant dosing with strong CYP3A inhibitors and 50 mg (<7 to 14 kg) or 75 mg (≥14 kg) qd during concomitant dosing with moderate CYP3A inhibitors.

It is expected that during the course of their treatment with IVA, patients 6 to <12 months may receive therapeutic agents that include strong and moderate CYP3A inhibitors. Dose adjustments for IVA in patients 6 to <12 months in the setting of CYP3A inhibition were extrapolated from that of older patients. The population PK analyses support that changes in IVA disposition can be accounted for by changes in body weight and that the impact of CYP maturation on IVA disposition in this age group are minimal. The recommended IVA dose for patients 6 to <12 months is 25 mg (5 to <7 kg) and 50 mg (7 to <14 kg) twice weekly during concomitant dosing with strong CYP3A inhibitors and 25 mg (5 to <7 kg) and 50 mg (7 to <14 kg) qd during concomitant dosing with moderate CYP3A inhibitors.

There were no unique findings due to age to suggest a safety concern related to drug-drug interactions (DDI) or other interactions in subjects 6 to <12 months of age. There were no AEs identified caused by DDI in Study 124. The DDI profile in children 6 to <12 months of age is expected to be the same as that in older subjects based on:

- the population PK analyses which support that changes in IVA disposition can be accounted for by changes in body weight and that the impact of CYP maturation on IVA disposition in this age group are minimal, and
- IVA exposures in subjects 6 to <12 months of age were comparable to exposures in adults.

Discontinuation due to adverse events

Part A/Cohort 2: There were no deaths, SAEs, treatment interruptions, or discontinuations.

Part B/Cohort 6: There were no deaths or treatment discontinuations due to AEs. One (9.1%) subject had an AE of rash that led to treatment interruption.

Post marketing experience

IVA is approved in Australia, Brazil, Canada, EU, Israel, New Zealand, Switzerland, and the US. Cumulatively, 6,993 patients (representing 12,416 person-years) have received at least 1 dose of IVA during the period from the Development International Birth Date of IVA (31 January 2012) to 23 January 2018. No new safety concerns have been identified based on ongoing postmarketing surveillance data; data have been consistent with those from the clinical studies and the established safety profile of IVA. Although Kalydeco was approved (29 April 2019) in the USA for patients with CF 6 to <12 months of age no post-marketing data for this age group are available yet.

2.6.1. Discussion on clinical safety

The safety database in the target paediatric population is limited in terms of size and drug exposure. Only safety data from 17 children between 6 and 12 months of age from study 124 are available and only 11 out of them received 50 mg q12h for approximately 24 weeks. This precludes the CHMP from fully characterising the safety profile from a quantitative point of view as only frequent adverse reactions could be detected. However, based on the available data coming from the interim analysis 2 of study 124, ivacaftor seems well tolerated with reported AEs that are consistent with those observed in older children. The most common AEs were cough, pyrexia, vomiting and upper respiratory tract infection and most of them were mild or moderate in severity. There were no deaths or treatment discontinuations due to AEs. There were no safety concerns in clinical laboratory or ECG parameters. A patient from cohort 6 had ALT elevation >3 x to ≤5 x ULN but continued on treatment and the levels normalised at week 2 of study 126. No patients presented increases of AST/ALT higher than 5 x to ≤ 8 x ULN or 8 x ULN. None had elevations of bilirubin >2 x ULN. Overall, these data are reassuring. Furthermore, CYP3A4 maturation may occur at a different pace in subjects of the same age. In addition to that, there are a number of CYP3A4 variants for which the rates of non-expressers in the general population are relatively high. There are no safety data in these situations as prior (within 2 weeks of Day 1 of study 124) or concomitant treatment with moderate or strong CYP3A4 inhibitors was not allowed in study 124 as it was the case for children with moderate alterations in liver function tests (>2 × ULN) which is striking as non-specific biochemical abnormalities in liver function tests (ALT, AST, and GGT) are very common during the first years of life in children with CF. The MAH states that the DDI profile in children 6 to <12 months of age is expected to be the same as that in older subjects based on pop-PK modelling results and that there were no unique findings due to age to suggest a safety concern related to DDI or other interactions in Study 124 subjects. As for children with hepatic impairment, safety monitoring is thought to be an appropriate measure to mitigate this risk. Dosing recommendations in these special situations are driven by the fact that the initially selected pop-PK models did not identify maturation (age) as a relevant covariate to be taken into account. Upon request this issue was further explored and it has been concluded that both body weight and age are relevant covariates to be taken into account when dosing infants in the age range from 6 to less than 12 months. However, the effect of body weight seems more relevant in this age range than that of the age. Therefore, the MAH was requested to include a cautionary statement in section 4.4 of the SmPC to highlight that there are no safety data in children aged 6 to less than 12 months of age with moderate hepatic impairment when treated with ivacaftor at the proposed doses. This was also the case for the concomitant administration with moderate and strong CYP3A4 inhibitors.

The extension study 126 is expected to provide safety data for an additional period of 96 weeks. No safety data from this study have been presented in the current submission but it was clarified that children from Cohort 6 enrolled in the extension study had not experienced any serious adverse events at data cut-off date 13 August 2018. The final CSR of study 126 will be completed in 2022. At the cut-off data 09 April 2019, 28 subjects out of 36 in this study rolled over from study 124. Most of them, were 12 to < 24 months of age (n=20) and 4 were ≥ 24 months. The MAH stated that no new safety concerns had been identified at that time and this is reassuring.

Immunological events had not been specifically addressed by the MAH in the initial submission. The MAH has updated the information with the available data and has clarified that, in all, four cases of rash were reported, two from cohort 5 and two from cohort 6. There was no need to change the dose in three of the cases and in only one case the treatment was interrupted and resumed. No other immunological events have been identified by the MAH.

2.6.2. Conclusions on the clinical safety

The small sample size, the lack of placebo control and the relative short duration of study 124 make it

difficult to perform a comprehensive safety evaluation of ivacaftor in children with CF aged 6 to less than 12 months. However, the available data suggest that the safety profile in the target paediatric population is similar to that seen in older children. The safety data beyond 24 weeks are expected to be supported with the data coming from the extension study 126 in which no new adverse reactions have been identified until the cut-off data of 09 April 2019. Maturation of CYP3A4 was not shown in the initially selected pop-PK models to have an influence on ivacaftor clearance. Upon request of the CHMP, this issue was further explored and it has been concluded that both body weight and age are relevant covariates to be taken into account when dosing infants in the age range from 6 to less than 12 months. However, the effect of body weight seems more relevant in this age range than that of the age and therefore the dosing recommendations as proposed by the MAH are acceptable.

Dosing recommendations for children with moderate hepatic impairment and for the concomitant use with CYP4A4 inhibitors initially raised some concern, particularly in the case of concomitant administration with strong CYP3A4 inhibitors as ivacaftor AUC may be increased by 8.5-fold and M1 to a lesser extent. In this respect, the MAH was requested to include a warning in section 4.4 of the SmPC to highlight that there are no safety data in children aged 6 months to less than 12 months of age with moderate hepatic impairment. This was also the case for the concomitant administration with moderate or strong CYP3A4 inhibitors. The MAH also clarified that the final CSR of study 126 will be completed in 2022. At the cut-off data 09 April 2019, 28 subjects out of 63 (including de novo patients) rolled over from study 124 to study 126. Most of them, were 12 to < 24 months of age (n=20) and 4 were $\geqslant$ 24 months. The MAH confirmed that no new safety concerns had been identified by then which is reassuring.

2.7. Risk Management Plan

Safety concerns

Important identified risks	• None
Important potential risks	• Hepatotoxicity • Cataract • Concomitant use of IVA with strong CYP3A inhibitors or inducers
Missing information	• Use in pregnant and lactating women • Indicated use in children aged less than 6 years

CYP: cytochrome P450; IVA: ivacaftor

Pharmacovigilance plan

Study/Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 1 – Imposed mandatory additional PV activities which are Conditions of the MA (key to benefit risk)				
None				
Category 2 – Imposed mandatory additional PV activities which are Specific Obligations in the context of a conditional MA under exceptional circumstances (key to benefit risk)				
None				
Category 3 – Required additional PV activities (by the competent authority)				
Study 126 Ongoing	<u>IVA Arm</u> In subjects with CF who are <24 months of age at treatment initiation and have an approved IVA-responsive mutation: • To evaluate the safety of long-term IVA treatment • To evaluate the PD of long-term IVA treatment • To evaluate the efficacy of long-term IVA treatment <u>Observational Arm</u> To evaluate long-term safety after discontinuation of IVA treatment in subjects with CF who were <24 months of age at treatment initiation and have an approved IVA-responsive mutation	• Hepatotoxicity • Cataract • Use in children aged 12 to <24 months old at initiation	Final Report	March 2022

CF: cystic fibrosis; IVA: ivacaftor; PD: pharmacodynamics
Note: Study 126 addresses a subpopulation of the Missing Information of "Indicated use in children aged less than 6 years."

Risk minimisation measures

Safety concerns	**Risk Minimisation Measures**	**Pharmacovigilance Activities**
Hepatotoxicity	**Routine risk minimisation measure:** SmPC Section 4.4 where advice is given on monitoring LFTs. SmPC Section 4.8 PL Section 4 **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection** Prescription only **Additional PV activities:** Study 126
Cataract	**Routine risk minimisation measure:** SmPC Section 4.4 where advice is given on recommended ophthalmological examinations SmPC Section 5.3 PL Section 2 **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection** Prescription only **Additional PV activities:** Study 126
Concomitant use of IVA with strong CYP3A inhibitors or inducers	**Routine risk minimisation measure:** SmPC Section 4.2 where dose reductions are recommended when co-administered with a strong inhibitor of CYP3A. SmPC Section 4.4	**Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection** Prescription only **Additional PV activities:**

	PL Section 2 **Additional risk minimisation measures:** None	None
Use in pregnant and lactating women	**Routine risk minimisation measure:** SmPC Section 4.6 where advice is given on to use Kalydeco during pregnancy only if clearly needed and during breastfeeding if the potential benefit outweighs the potential risks. PL Section 2 **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection** Prescription only Pregnancy follow-up form **Additional PV activities:** None
Indicated use in children aged less than 6 years	**Routine risk minimisation measure:** SmPC Section 4.2 where the posology is described SmPC Sections 4.8 and 5.2 PL Section 2 **Additional risk minimisation measures:** No risk minimisation measures	**Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection** Prescription only **Additional PV activities:** Study 126

Conclusion

The CHMP and PRAC considered that the risk management plan version 8.4 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

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

Periodic Safety Update Reports submission requirements

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

2.9. Product information

2.9.1. User consultation

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:

The CHMP considered that the submitted variation, for application for Kalydeco (ivacaftor) 25 mg granules in sachet and to extent the indication to include patients of 6 to less than 12 months, does not

involve a relevant impact on the readability of the PIL. Therefore, the company's justification not to undertake further consultation with target patient groups, is considered acceptable

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Kalydeco granules are currently authorised for children with cystic fibrosis aged 12 months and older and weighing ≥ 7 kg to less than 25 kg. The aim of the present procedure is the extension of the indication of Kalydeco granules to children with cystic fibrosis aged at least 6 months of age and weighing at least 5 kg, as follows: " Kalydeco granules are indicated for the treatment of infants aged at least 6 months, toddlers and children weighing 5 kg to less than 25 kg with cystic fibrosis (CF) who have one of the following gating (class III) mutations in the CFTR gene: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N or S549R (see sections 4.4 and 5.1).". The current application involves an additional strength: Kalydeco 25 mg granules in a sachet. Dosing recommendations are as follows: Infants aged at least 6 months, toddlers, children, adolescents and adults should be dosed according to Table below.

Dosing recommendations for patients aged 6 months and older

Weight	Dose	Total daily dose
≥5 kg to < 7 kg	25 mg granules taken orally every 12 hours with fat containing food	50 mg
≥ 7 kg to < 14 kg	50 mg granules taken orally every 12 hours with fat containing food	100 mg
≥ 14 kg to < 25 kg	75 mg granules taken orally every 12 hours with fat containing food	150 mg
≥ 25 kg	See Kalydeco tablets SmPC for further details.	

CF greatly affects the paediatric population, as approximately half of the total population with CF is <18 years of age. Pancreatic destruction leading to pancreatic exocrine insufficiency begins early in life, and lung involvement is manifested by pulmonary inflammation and infection that begins shortly after birth. There are published data that support that early treatment (e.g., early nutritional support, including pancreatic enzyme replacement therapy and other measures) improves the outcome of children with cystic fibrosis. There is therefore an expectation that by treating young children early in life with CFTR modulators such as ivacaftor this may have an impact on disease progression and prolong survival.

3.1.2. Available therapies and unmet medical need

There is currently no fully effective cure for CF. The majority of CF therapies available including nutritional supplements, antibiotics, and mucolytics target the downstream consequences and symptoms of the disease. The CFTR modulators such as ivacaftor are small molecules that target the functional defect of the mutant CFTR protein. They are not intended as a replacement for or an alternative to any of the current non-modulator therapies and therefore are to be administered on top of the standard of care. These CFTR modulators are not a cure for CF and must be taken chronically for the patient to maintain treatment benefits.

Kalydeco is currently approved in the EU for the treatment of patients aged at least 12 months of age with the certain CFTR gating mutations.

3.1.3. Main clinical studies

The extension of the indication of Kalydeco to children with CF aged 6 to less 12 months who have a pre-specified CFTR gating mutation in at least an allele of the CFTR gene is based on a report (Interim Analysis 2 Report) that describes PK, safety and efficacy data from children enrolled in Cohort 2 (Part A) and Cohort 6 (Part B) of study 124. Study 124 is ongoing (as it continues to enrol children below 6 months of age) open-label, two-part study in neonates, infants and toddlers less than 2 years. In Part A, which is intended to assess the PK and safety, the current study protocol plans that subjects receive ivacaftor granules based on body weight (25, 50 or 75 mg BID) for 4 days. During Part B, ivacaftor doses (adjusted if needed based on results of Part A) are administered for 24 weeks which allows assessing short-term safety (primary endpoint) and efficacy (tertiary endpoint). Cohorts 2 and 6 only enrolled children aged 6 to less than 12 months. All subjects who completed 24 weeks of treatment in Part B are eligible to enrol in an uncontrolled extension study (Study 126) which will provide 96 weeks of ivacaftor treatment. Children under 2 years of age with confirmed cystic fibrosis disease who are clinically stable are being enrolled. Key exclusion criteria are the presence of abnormal liver function at screening or any prior history of clinically relevant elevated (>2 × upper limit of normal [ULN]) serum aspartate transaminase (AST), serum alanine transaminase (ALT), or bilirubin) and lung colonization with organisms associated with a more rapid decline in pulmonary status.

3.2. Favourable effects

A consistent effect in sweat chloride has been observed in all pivotal trials of ivacaftor in older subjects with class III gating mutations. This is also the case of infants in cohort 6 of study 124 in which treatment with ivacaftor resulted in a rapid reduction at Week 2 that was sustained to Week 24 as shown by a mean (SD) absolute change from baseline of -58.6 mmol/L (16.5) (n = 6) providing support for extrapolation of efficacy from older subjects. At Week 24, 3 subjects had a sweat chloride value <35 mmol/L, including 1 subject who had a sweat chloride value <30 mmol/L which is the diagnostic cut-off for normal sweat chloride. Mean (SD) absolute change from baseline at Week 24 in weight-for-age z-score, length-for-age Z-score, and weight-for-length-for-age Z-score were 0.36 (0.54), 0.27 (1.34), and 0.26 (1.30), respectively.

Markers of pancreatic exocrine function such as faecal elastase-1 (FE-1) and the immunoreactive trypsin and/or trypsinogen (IRT) also showed a pattern of change with treatment that suggests that indeed ivacaftor is able to improve pancreatic exocrine function. In seven infants with both baseline and Week 24 values who were pancreatic insufficient at baseline (defined as FE-1 < 200 µg/g), the mean (SD) absolute change was 203.1 µg/g (147.3). For the remaining parameters measured such IRT, total amylase, lipase, and faecal calprotectin, the changes in levels while on ivacaftor treatment seem consistent with that seen in FE-1.

Available data in the literature confirm the findings of the pivotal studies of ivacaftor, particularly in subjects older than the ones enrolled in study 124. The PASS study requested at the time of MA of Kalydeco in which long-term safety and effectiveness measures were assessed showed that in the UK and US registries where this study was conducted, ivacaftor-treated patients had a lower prevalence of CF-related complications and select microorganisms and had better preserved lung function.

3.3. Uncertainties and limitations about favourable effects

The dose finding in these young infants is based on targeting the adult dose that has been shown to be efficacious in the pivotal studies in older paediatric subjects and in adult subjects. This is acceptable, however the initial population PK model selected to support dosing recommendations for children below 12 months of age did not take into account any influence of CYP3A4 maturation on ivacaftor clearance.

Given that only one child in Part A/Cohort 2 had been dosed with 25 mg BID, the MAH was requested to update the model with PK data of younger children (below 6 months of age and/or below 5 kg of body weight) and to further discuss the potential influence of CYP3A4 maturation on ivacaftor clearance. This was done and additional models were developed and discussed. Of these, an empirical model with maturation function is the one that best describes the observed PK data in infants aged 6 to less than 12 months of age. The simulations based on Model 2 (fixed exponent allometric scaling, no maturation) and Model 4 (empirical with maturation effect) would lead to the same dosing recommendations as currently proposed.

The level of evidence of an interim analysis in two cohorts of an open-label study is limited by the lack of a control arm, the size of the cohort 6 (n=11), the duration of treatment and the uncertainty on whether the improvements observed are maintained. The lack of a control group raises uncertainty regarding the accuracy of the effect of ivacaftor in the target population as there may be many confounders, particularly in what refers to the anthropometric parameters that cannot be accounted for. Furthermore, additional information was requested that added to the uncertainties about the reliability of the results on anthropometric parameters. The proposal for the SmPC is to pool the results of the anthropometric parameters of children aged 12 to less than 24 months and of those from 6 to less than 12 months. This is acceptable but at the time of submission of the final results of Study 124 individual data of all subjects enrolled in Part B of this study may lead to an amendment of the SmPC amended as applicable. As for the markers of pancreatic exocrine function such as IRT or markers of intestinal inflammation such as faecal calprotectin, the lack of a control group and/or of normative data makes it difficult to interpret the data from a quantitative point of view and consequently these data are not reflected in the SmPC.

Lung function correlates with mortality in CF patients. There are no firm data to support lung function improvement (as spirometry cannot be performed at this age and LCI could be measured in a single infant in this study) or a slower rate of decline of lung function when starting treatment as early as of 6 months. This can be, however, hypothesised based on already existing long-term data in older subjects, but needs further confirmation. While long term data would be highly desirable to establish a definitive beneficial effect of ivacaftor on lung function and microbiological endpoints and to confirm positive results on nutrition in very young children, this cannot be addressed in the frame of a registration clinical trial, particularly if there is evidence of clinical benefit in older subjects.

Regarding extrapolation of efficacy the main uncertainty refers to the heterogeneity of target organs and the progression of the disease over time which lead to clinical manifestations that vary according to age and require efficacy endpoints tailored to the age of the population considered.

3.4. Unfavourable effects

Ivacaftor is generally considered safe and well tolerated in older patients. Adverse drug reactions identified from previously completed studies include nasopharyngitis, upper respiratory tract infection, headache, nasal congestion, oropharyngeal pain, rash, abdominal pain, and diarrhoea. Most of these ADRs are mild to moderate in severity and do not lead usually to treatment discontinuation.

Other adverse reactions include elevated transaminases and cataracts (lens opacities). These risks are properly managed through product labelling, including recommendations of close monitoring of unexplained elevations in transaminase levels until resolution. Baseline and follow-up ophthalmological examinations are recommended in paediatric patients treated with ivacaftor.

Safety results in subjects 6 to less than 12 months of age in Study 124 were generally consistent with those in older subjects, with no new safety concerns identified. The most common AEs were cough, pyrexia, vomiting and upper respiratory tract infection. Three serious adverse events were reported, i.e., viral rash, cough, and viral respiratory tract infection but they were not considered to be related to the

study drug. Transaminase (ALT) elevation (>3 x to ≤5 x ULN) was seen in a single subject who was kept on ivacaftor treatment. Four events of rash were reported. There was no need to change the dose in three of the cases but in one case treatment had to be discontinued and could be resumed later on.

3.5. Uncertainties and limitations about unfavourable effects

The safety database in the target paediatric population is limited in terms of size and drug exposure: only safety data from 11 children between 6 and 12 months of age from study 124 are available treated for 24 weeks with ivacaftor 50 mg BID. This precludes to properly characterising safety from a quantitative point of view as only the most frequent adverse reactions could be detected. Furthermore, CYP3A4 maturation may occur at a different pace in subjects of the same age. In addition to that, there are a number of CYP3A4 variants for which the rates of non-expressors in the population may be relatively high. This adds further uncertainty to the conclusions that could be reached based on the present data, particularly when the proposed dosing recommendations for infants with moderate hepatic impairment or receiving concomitant administration of moderate or strong CYP3A4 inhibitors are considered. No safety data are available in these two populations given that prior or concomitant use with moderate or strong CYP3A4 inhibitors was an exclusion criterion as it was the presence of abnormal liver function at screening or any prior history of clinically relevant elevation (> 2 x ULN) in ALT, AST or bilirubin. Non-specific biochemical abnormalities in liver function tests (ALT, AST, and gamma-glutamyltranspeptidase) are very common during the first years of life in children with CF. Most of these elevations tend to be of limited magnitude in the absence of intercurrent illnesses. The above criterion leads to the (apparently unnecessary) exclusion of children who may benefit from treatment on the basis of safety concerns in spite of the fact that these are very common in clinical practice.

At the present time and even taking into account the current acceptance of the proposed posology for infants aged 6 to less than 12 months, some concerns remain regarding the use of ivacaftor at the proposed doses in subjects with moderate hepatic impairment or receiving concomitant administration of moderate or strong CYP3A4 inhibitors. Therefore the MAH, as requested, included a cautionary sentence in section 4.4 of the SmPC to highlight that there are no safety data in children aged 6 to less than 12 months of age in these two situations.

Additional safety data are being generated in the ongoing open-label study 126 for 96 weeks. At the time of the cut-off data (09 April 2019), 63 children had been enrolled in Study 126. Twenty-eight out of these 63 children rolled over from Study 124. Most of them were 12 to < 24 months of age (n=24) and 4 were ≥ 24 months. The MAH confirmed that no new safety concerns had been identified so far and this is reassuring. The final CSR of study 126 will be completed in 2022. Final data from study 126 are to be submitted as soon as available in order to further fully assess if the safety profile of Kalydeco in this young population.

3.6. Effects Table

Effects Table for Kalydeco granules for the treatment of children with cystic fibrosis (CF) aged 6◦months and older and weighing 5◦kg to less than 25◦kg who have one of the following gating (class III) mutations in the *CFTR* gene: *G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N* or *S549R* (data cut-off for Cohort 2 and 6: 19 October 2018).

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
Sweat chloride	Absolute changes from	mmol/L, mean	-58.6 (16.5)	none	Uncontrolled study, indirect	Study 124, Cohort 6

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
	baseline at Week 24 (n=6)	(SD) median (min, max)	-62.3 (-73.5, -31.0)		comparison, consistency with previous results/ Robust and clinically relevant change, secondary endpoint.	
Weight-for-age z-score	Absolute changes from baseline at Week 24 (n=11)	unit mean (SD) median (min, max)	0.36 (0.54) 0.45 (-0.29, 1.63)	none	Tertiary endpoint, uncontrolled data, difficult to interpret due to potential confounder factors and to some anomalous results at individual level / Mean improvement (but some subjects overweight).	Study 124, Cohort 6
Length-for-age z-score	Absolute change from baseline at Week 24 (n=11)	unit, mean (SD) median (min, max)	0.27 (1.34) 0.25 (-1.81, 3.38)	none	Tertiary endpoint, uncontrolled data, difficult to interpret due to potential confounder factors and to some anomalous results at individual level / Mean improvement	Study 124, Cohort 6
Weight-for-length-for-age Z-score	Absolute changes from baseline at Week 24 (n=11)	unit, mean (SD) median (min, max)	0.26 (1.30) 0.35 (-2.04, 2.22)	none	Tertiary endpoint, uncontrolled data, difficult to interpret due to potential confounder factors and to some anomalous results at individual level / Mean improvement	Study 124, Cohort 6

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Faecal elastase-1 (FE-1)	Absolute change from baseline at Week 24 (only for subjects with pancreatic exocrine insufficiency at baseline, n=7)	(µg/g), mean (SD) median (min, max)	203.1 (147.3) 236 (0, 424)	none	Uncontrolled data, not known how this translates in quality of life, need for exogenous pancreatic enzymes and if it is maintained over time / Relevant mean increase from baseline in infants with well-established exocrine pancreatic insufficiency (EPI).	Study 124, Cohort 6
Immunoreactive trypsin and/or trypsinogen (IRT)	Absolute change from baseline at Week 24	(ng/mL) mean (SD)	-450.6 (376.7) (n=6)	none	Uncontrolled data, difficult to interpret (assay used, normative data) / Mean improvement in infants with EPI, in line with the increase in FE-1.	Study 124, Cohort 6
Lipase	Absolute change from baseline at Week 24	(U/L), mean (SD)	-90.50 (75.04) (n=10)	none	Uncontrolled data/lack of normative data Mean improvement (decrease) in infants with EPI, in line with the trends observed in FE-1 and IRT.	Study 124, Cohort 6
Total amylase	Absolute change from baseline at Week 24	(U/L), mean (SD)	-7.8 (31.1) (n=10)	none	Uncontrolled data, total amylase (instead of pancreatic isoamylase), lack of normative data/ Average improvement (decrease).	Study 124, Cohort 6
Faecal calprotectin	Absolute change from baseline at Week 24	(µg/g), mean (SD)	-44.21 (146.9) (n=7)	none	Uncontrolled data, range of the assay used developed for subjects with inflammatory bowel disease/ Mean	Study 124, Cohort 6

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
					improvement (decrease) in infants with EPI, in line with the trends observed in FE-1 and IRT.	
Unfavourable Effects						
AEs	Subjects with any AEs	n (%)	10 (90.9)	none	Uncontrolled data, low sample size, indirect comparison to previous study results suggest comparable safety profile	Study 124, Cohort 6
AEs	Total number of AEs	n	69	none	Uncontrolled data, low sample size, indirect comparison to previous study results suggest comparable safety	Study 124, Cohort 6
Related AEs	Subjects with related AEs	n (%)	2 (18.2)	none	Uncontrolled data, low sample size, indirect comparison to previous study results suggest comparable safety	Study 124, Cohort 6
SAEs	Subjects with SAEs	n (%)	3 (27.3)	none	Uncontrolled data, low sample size, indirect comparison to previous study results suggest comparable safety	Study 124, Cohort 6

Benefit-risk assessment and discussion

3.6.1. Importance of favourable and unfavourable effects

Studies performed in children diagnosed following newborn screening suggest that early intervention is associated to improved outcomes. Therefore, there is an expectation that early treatment in life, particularly with the CFTR modulators that target the functional defect of the mutant CFTR protein, may translate in slowing disease progression. However, a clear demonstration of efficacy in these very young children is hampered by the absence of endpoints that are sufficiently sensitive to detect changes in response to treatment. Lung disease is the primary cause of morbidity and mortality in cystic fibrosis. However, in very young children with preserved lung function conventional tests (such as spirometry) are

not sufficiently sensitive. Alternative tests such as the Lung Clearance Index (LCI) or imaging techniques (e.g., CT scan) would be required to detect the initial changes in lung function or the structural changes present in the lung since birth. Each of these present their own problems such as the potential need for sedation, the requirement for specific equipment and training (LCI) or the risk of radiation (CT scan). Pulmonary exacerbations, a clinical relevant endpoint in older subjects with cystic fibrosis, is not of help either to assess response to treatment as very young children (usually) experience a limited number of these events. In addition, showing that disease progression is halted requires a prolonged period of follow-up that cannot be performed pre-authorisation, particularly when data are available supporting the beneficial effect of ivacaftor in older subjects.

Given that in very young children the most prominent features of the disease are those of the gastrointestinal tract, demonstration of a favourable effect on nutritional status and pancreatic function would support the benefit of treatment. Interim results from Study 124 demonstrated that ivacaftor improves CFTR function in infants aged 6 to less than 12 months who have a mutation that causes CFTR gating defects, with a clear positive effect on sweat chloride. This seems also to be the case for markers of exocrine pancreatic function (particularly faecal elastase-1). Consistent trends with that seen in faecal elastase-1 have been observed in other biomarkers of gastrointestinal function and inflammation although for some of them age-related variations have been described which would require an age matched control group for a correct interpretation. Anthropometric parameters are also important as a reflection of the nutritional status but they are difficult to interpret if no additional data are provided (e.g. haematological markers of nutritional status, body composition, daily intake and appetite etc.). These data are included in section 5.1 of the SmPC. Final results of Study 124 along with individual data are awaited for all children enrolled in Part B of the study.

No new AEs were identified in Cohorts 2 or 6 of study 124 and the safety profile was consistent with that known for older patients with class III gating mutation for whom data on long term are available. However, the safety database in the target paediatric population is limited in terms of size and drug exposure, i.e., only safety data from 17 children between 6 and 12 months of age from study 124 are available and only 11 out of them were treated for approximately 24 weeks with ivacaftor 50 mg BID. This precludes to properly characterising the safety profile from a quantitative point of view as only frequent adverse reactions could be detected.

Furthermore, CYP3A4 maturation may occur at a different pace in subjects of the same age. In addition to that, there are a number of CYP3A4 variants for which the rates of non-expressors in the general population are relatively high. This adds further uncertainty to the conclusions that could be reached based on the present safety data, particularly when the proposed dosing recommendations for infants with moderate hepatic impairment or receiving concomitant administration of moderate or strong CYP3A4 inhibitors are considered.

There are no safety data available in these two populations as prior or concomitant use with strong CYP3A4 inhibitors was an exclusion criterion as it was the presence of abnormal liver function at screening or any prior history of clinically relevant elevation (> 2 x ULN) in ALT, AST or bilirubin. At the present time and even taking into account the current acceptance of the proposed posology for infants aged 6 to less than 12 months, some concerns remain regarding the use of ivacaftor at the proposed doses in subjects with moderate hepatic impairment or receiving concomitant administration of moderate or strong CYP3A4 inhibitors. To raise this uncertainty to the prescriber the MAH, as requested, included a cautionary sentence in section 4.4 of the SmPC to highlight that there are no safety data in children aged 6 to less than 12 months of age in these two situations.

No safety data from the long term extension study (study 126) have been presented in the current submission. Upon request the MAH updated this information. At the time of the cut-off data (09 April 2019), 63 children (including the novo patients) were enrolled in Study 126. Twenty-eight out of these 63

children rolled over from Study 124. Most of them, were 12 to < 24 months of age (n=24) and 4 were ≥ 24 months. The MAH confirmed that no new safety concerns had been identified at that time which is reassuring. The final CSR of study 126 will be completed in 2022.

3.6.2. Balance of benefits and risks

Cystic fibrosis represents an area of unmet medical need for specific targeted therapies. Study 124 is an uncontrolled study with safety and PK as primary endpoints. According to ICH E11 (Clinical Investigation of Medicinal Products in the Paediatric Population) "when a medicinal product is to be used in younger paediatric patients for the same indication(s) as those studied in older paediatric patients, the disease process is similar, and the outcome of therapy is likely to be comparable, extrapolation of efficacy from older to younger paediatric patients may be possible. In such cases, pharmacokinetic studies in the relevant age groups of paediatric patients likely to receive the medicinal product, together with safety studies, may be sufficient to provide adequate information for paediatric use." Based on the reduction of sweat chloride extrapolation of efficacy has been accepted. In this situation PK and safety data are the main elements supporting the adequacy of the data. In this particular case, the adequacy of dosing recommendations for children aged 6 to less than 12 months was initially questioned as the pop-PK models initially selected to support the dose regimen did not incorporate any maturation function. Further models were developed and it has been concluded that both weight and age (maturation) need to be taken into account but the influence of weight seems to be more relevant than that of the age in infants aged 6 to less than 12 months. Therefore, dosing recommendations as proposed by the MAH are considered acceptable. However, a concern exists regarding the proposed posology for children with moderate hepatic impairment or receiving concomitant treatment with moderate or strong CYP3A4 inhibitors. To address this concern the MAH, as requested, included a cautionary sentence in section 4.4 of the SmPC to highlight that there are no safety data in children below 12 months of age in these two situations. This was proposed taking into account that CYP3A4 maturation may occur at a different pace in subjects of the same age, the unknown effect of CYP3A4 polymorphisms, and the lack of safety data in these two situations given that they were exclusion criteria in Study 124.

The safety database provided is limited both in terms of size and length of exposure and this has an obvious impact on the characterisation of the safety profile of ivacaftor in these young children. However, it is reassuring that no new AEs had been identified in study 124 compared to what it is already known for older patients with class III gating mutations. The already agreed open label extension study 126 will provide additional safety data for 96 weeks.

At the time of the cut-off data (09 April 2019), 63 children had been enrolled in Study 126. Twenty-eight out of these 63 children rolled over from Study 124. Most of them were 12 to < 24 months of age (n=24) and 4 were ≥ 24 months. The MAH confirmed that at that time no new safety concerns had been identified which is reassuring. The final CSR of study 126 will be provided upon completion in 2022, as stated in the RMP.

3.6.3. Additional considerations on the benefit-risk balance

Not applicable.

3.7. Conclusions

The overall B/R of Kalydeco is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality and safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Kalydeco 25mg granules in sachet in the treatment of cystic fibrosis in children aged 6 to less than 12 months old is favourable in the following indication:

Kalydeco granules are indicated for the treatment of infants aged at least 6 months, toddlers and children weighing 5 kg to less than 25 kg with cystic fibrosis (CF) who have one of the following gating (class III) mutations in the CFTR gene: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N or S549R (see sections 4.4 and 5.1).

The RMP (version 8.3) is updated in accordance.
In addition, the MAH took the opportunity to implement minor updates in the Product Information.

Furthermore, the PI is brought in line with the latest QRD template version 10.1.

The CHMP therefore recommends the extension of the marketing authorisation for Kalydeco subject to the following conditions:

Conditions or restrictions regarding supply and use

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

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

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

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

Risk Management Plan (RMP)

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

An updated RMP should be submitted:

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