22 February 2024
EMA/110324/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment Report

Kalydeco

International non-proprietary name: ivacaftor

Procedure No. EMEA/H/C/002494/X/0115/G

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000

Administrative information

Name of the medicinal product:	Kalydeco
MAH:	Vertex Pharmaceuticals (Ireland) Limited Unit 49 Northwood Court Block F2 Santry Dublin 9 IRELAND
Active substance:	Ivacaftor
International Non-proprietary Name/Common Name:	ivacaftor
Pharmaco-therapeutic group (ATC Code):	other respiratory system products, other respiratory system products (R07AX02)
Therapeutic indication(s):	Kalydeco tablets are indicated: - As monotherapy for the treatment of adults, adolescents, and children aged 6 years and older and weighing 25 kg or more with cystic fibrosis (CF) who have an R117H CFTR mutation or one of the following gating (class III) mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N or S549R (see sections 4.4 and 5.1). - In a combination regimen with tezacaftor/ivacaftor tablets for the treatment of adults, adolescents, and children aged 6 years and older with cystic fibrosis (CF) 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. - In a combination regimen with ivacaftor/tezacaftor/elexacaftor tablets for the treatment of adults, adolescents, and children

	aged 6 years and older with cystic fibrosis (CF) who have at least one F508del mutation in the CFTR gene (see section 5.1). Kalydeco granules are indicated: - As monotherapy for the treatment of infants aged at least 1 month, toddlers and children weighing 3 kg to less than 25 kg with cystic fibrosis (CF) who have an R117H CFTR mutation or 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). - In a combination regimen with ivacaftor/tezacaftor/elexacaftor for the treatment of cystic fibrosis (CF) in paediatric patients aged 2 to less than 6 years who have at least one F508del mutation in the CFTR gene (see section 5.1).
Pharmaceutical form(s):	Film-coated tablet; Granules
Strength(s):	13.4 mg, 25 mg, 50 mg, 59.5 mg, 75 mg and 150 mg
Route(s) of administration:	Oral use
Packaging:	blister (aclar/PVC/alu); card, blister (aclar/alu), blister (aclar/alu); card, bottle (HDPE), sachet (BOPET/ PE/Foil/PE) and sachet (BOPET/PE/Foil/PE)
Package size(s):	28 tablets, 28 sachets, 56 tablets and 56 sachets

Table of contents

List of abbreviations

Abbreviation	Term
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
ALP	Alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration versus time curve
AUC0-∞	AUC from the time of dosing extrapolated to infinity
BA	bioavailability
BID	twice a day
BMI	body mass index
BOPET	Biaxially Oriented Polyethylene Terephthalate
BP	blood pressure
CF	cystic fibrosis
CFFPR	CF Foundation Patient Registry
CFQ-R	Cystic Fibrosis Questionnaire-Revised
CFTR	CF transmembrane conductance regulator gene
CI	confidence interval
CK	creatine kinase
CL	clearance
CL/F	apparent clearance
Cmax	maximum observed concentration
CQAs	Critical Quality Attributes
DDI	drug-drug interaction
DSL	design space limits
ECFSPR	European Cystic Fibrosis Society Patient Registry
ECG	electrocardiogram
ELX	elexacaftor
ERA	environmental risk assessment
EU	European Union
F/F	homozygous for F508del
F/MF	heterozygous for F508del and a CFTR minimal function mutation
F508del	CFTR gene mutation with an in-frame deletion of a phenylalanine codon corresponding to position 508 of the wild-type protein
FAS	Full Analysis Set
FDC	fixed-dose combination
FE-1	faecal elastase-1
FRT	Fisher Rat Thyroid
GGT	gamma-glutamyltransferase
HPLC	High performance liquid chromatography
HPMCAS	hypromellose acetate succinate
IA	interim analysis
ICH	International Council for Harmonization
IPD	important protocol deviation
IR	Infrared
IRT	immunoreactive trypsinogen
IVA	ivacaftor
ka	absorption rate constant
$LCI_{2.5}$	number of lung turnovers required to reduce the end tidal inert gas concentration to 1/40th of its starting value
LFT	Liver Function Test
LS	least squares
LUM	lumacaftor
MBW	multiple-breath washout
MF	minimal function

MMRM	mixed-effects model for repeated measures
n	size of subsample
NORs	Normal Operating Ranges
P	probability
PBPK	physiologically-based pharmacokinetic
PD	pharmacodynamic
PE	physical examination
PE	Polyethylene
PEx	pulmonary exacerbation
Ph. Eur.	European Pharmacopoeia
PK	pharmacokinetic
popPK	population PK
ppFEV1	percent predicted forced expiratory volume in 1 second
PT	preferred term
q12h	every 12 hours
qAM	once every morning
QbD	Quality by design
qd	once daily
Q/F	apparent (oral) intercompartmental clearance
qPM	once every evening
RF	residual function
RH	Relative Humidity
RSE	relative standard error
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SDD	spray dried dispersion
SE	standard error
SIMCYP	PBPK software
SLS	sodium lauryl sulfate
SmPC	Summary of Product Characteristics
SwCl	sweat chloride
TAMC	Total Aerobic Microbial Count
TEAE	treatment-emergent adverse event
TEZ	tezacaftor
TSE	Transmissible Spongiform Encephalopathy
TYMC	Total Combined Yeasts/Moulds Count
ULN	upper limit of normal
US	United States
UV	Ultraviolet
Vc/F	apparent (oral) central volume of distribution
VPC	Visual predictive checks
Vp/F	apparent (oral) peripheral volume of distribution
XR(P)D	X-Ray (Powder) Diffraction

DEFINITION OF TERMS

Adverse Events

For the purpose of the safety analyses described herein, treatment-emergent adverse events (TEAEs) were defined as adverse events (AEs) that worsened (either in severity or seriousness) or that were newly developed at or after the first dose date of the study drug through the end of the Treatment-emergent Period.

Unless otherwise specified, all TEAEs will be referred to as AEs in the text and tables.

1. Background information on the procedure

1.1. Submission of the dossier

Vertex Pharmaceuticals (Ireland) Limited submitted on 20 December 2022 a group of variation(s) consisting of an extension of the marketing authorisation and the following variation(s):

Variation(s) requested		**Type**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II
B.II.b.2.a	B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place	IA
A.5.b	A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release)	IA

Extension application to introduce a new strength (13.4 mg of ivacaftor granules in sachet), grouped with a type II variation (C.I.6.a) in order to extend the indication of the granule presentations to include children with cystic fibrosis aged 1 to less than 4 months of age and weighing 3 kg or more who have an R117H CFTR mutation or one of the approved 9 gating (class III) mutations based on interim results from study VX15-770-124 (study 124); this is a phase 3, 2-part, open-label study to evaluate the safety, pharmacokinetics, and pharmacodynamics of ivacaftor (IVA) in subjects with CF who are less than 24 months of age at treatment initiation and have a CFTR gating mutation. As a consequence, sections 1, 2, 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2, 6.3 and 8 of the SmPC of the granules presentations and sections 4.2, 4.8, 5.1 and 5.2 of the SmPC of the tablets presentations are updated. The Labelling for the 13.4mg granule presentation and the Package Leaflet of the granules and tablets presentations are updated in accordance. Version 15.2 of the RMP has also been submitted. In addition, the MAH took the opportunity to introduce minor editorial changes to the PI.

Type IA A.5.b - To change the name of the site responsible for quality control testing and processing operations of the medicinal product for the granule presentations from "Mayne Pharma Inc.", 1240 Sugg Parkway, Greenville, North Carolina, 27834-9006, United States to "Catalent Greenville, Inc."; the address remains unchanged.

Type IA B.II.b.2.a - To add PPD Development LP, 8551 Research Way, Suite 90, Middleton, WI 53562-4664, United Stated as an alternative site responsible for batch control and quality control testing for all the presentations of the finished product.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

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

1.3. Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decisions P/0163/2020 on the agreement of a paediatric investigation plan (PIP) .

At the time of submission of the application, the PIP P/0163/2020 was completed.

The PDCO issued an opinion on compliance for the PIP P/0163/2020.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

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

1.5. Scientific advice

The MAH did not seek Scientific advice at the CHMP.

1.6. Steps taken for the assessment of the product

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

Rapporteur: Maria Concepcion Prieto Yerro Co-Rapporteur: Beata Maria Jakline Ullrich

The Rapporteur appointed by the PRAC was:

PRAC Rapporteur: Monica Martinez Redondo

The application was received by the EMA on	20 December 2022
The procedure started on	26 January 2023
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	10 May 2023
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	19 May 2023
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	09 May 2023
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	12 May 2023
The CHMP agreed on the consolidated List of Questions to be sent to the MAH during the meeting on	25 May 2023
The MAH submitted the responses to the CHMP consolidated List of Questions on	04 August 2023
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	27 September 2023
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	N/A

The CHMP agreed on a list of outstanding issues to be sent to the MAH on	12 October 2023
The MAH submitted the responses to the CHMP List of Outstanding Issues on	14 November 2023
The CHMP Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	06 December 2023
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	N/A
The CHMP agreed on a 2nd list of outstanding issues to be sent to the MAH on	14 December 2023
The MAH submitted the responses to the 2nd CHMP List of Outstanding Issues on	24 January 2024
The CHMP Rapporteurs circulated the Joint Assessment Report on the responses to the 2nd List of Outstanding Issues to all CHMP and PRAC members on	09 February 2024
The outstanding issues were addressed by the MAH during an oral explanation before the CHMP during the meeting on	N/A
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	22 February 2024
The CHMP adopted a report on similarity of Kalydeco with TOBI Podhaler, Symkevi, and Kaftrio on (see Appendix on similarity)	22 February 2024

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 cure. CF is caused by mutations in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene that result in an absent or deficient function of the CFTR protein at the cell surface. The CFTR protein is an epithelial chloride channel responsible for regulating salt and water absorption and secretion. The failure to regulate chloride transport results in the multisystem pathology associated with CF.

In people with CF, loss of chloride transport due to defects in the CFTR protein results 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.

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

The CF phenotype differs considerably among patients, even among patients with the same genotype. The genotype primarily determines the degree of pancreatic exocrine dysfunction, sweat chloride concentration and malformation of the male reproductive tract. However, factors independent of the *CFTR* genotype are responsible for variation in lung disease, the primary cause of morbidity and mortality in CF. In lung disease, environmental factors, socio-economic factors and also the presence of modifier genes play an important role. Lung disease is the primary cause of morbidity and mortality in people with CF. Exocrine pancreatic dysfunction and structural lung disease in CF are evident in infancy. Pancreatic insufficiency and poor nutritional status are the most significant clinical manifestations of CF in infants.

2.1.2. Epidemiology and screening tools

The 2020 Annual Report of the European Cystic Fibrosis Society Patient Registry (ECFSPR)[1] shows that there were 52,246 patients registered in 39 countries (including patients from non-EU countries). The incidence and prevalence of CF vary between racial groups; CF is considerably more common in the Caucasian populations of North America and Europe than in Asian and African populations. Despite advances in treatment, the current median age of death in a patient with CF was approximately 32 years in 2020[1], and the predicted median age of survival in the UK is approximately 45.1 years[2]

The most common disease-causing mutation in the *CFTR* gene is *F508del*: approximately 85.8% of individuals in the US and 82.4% of individuals in Europe have at least one *F508del* allele. The *F508del* mutation causes severe defects in processing and trafficking that result in little-to-no F508del-CFTR protein at the epithelial cell surface.

2.1.3. Aetiology and pathogenesis

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, responsible for aiding in the regulation of 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.

CFTR mutations can be classified according to the mechanisms by which they disrupt CFTR function,

• Class I or Stop codon mutations: production of a truncated non-functional CFTR that lead to defective protein production

• Class II mutations: production of aberrantly folded CFTR protein (degraded by the cell quality control system) that lead to defective protein processing

• Class III mutations: lead to defective regulation of the CFTR protein

• Class IV mutations: lead to defective chloride conduction

• Class V mutations: interfere with normal transcription, thereby reducing the amount of otherwise normal CFTR protein

Class I, II and III usually lead to a classic (severe) CF phenotype with pancreatic insufficiency.

Class IV and V are mostly associated with a milder expression of the disease.

[11] ECFSPR Annual Report 2020, Orenti A, Zolin A, Jung A, van Rens J *et al*, 2022
[22] National Guideline Alliance (UK). Cystic Fibrosis: Diagnosis and management. London: National Institute for Health and Care Excellence (NICE); 2017 Oct 25. (NICE Guideline, No. 78.) Available from: https://www.ncbi.nlm.nih.gov/books/NBK464183/

The most prevalent mutation is an in-frame deletion in the *CFTR* gene resulting in a loss of phenylalanine at position 508 in the CFTR protein (*F508del-CFTR*), which is considered a Class II mutation: it prevents most of the CFTR protein from reaching the cell surface, resulting in little-to-no chloride transport. The decrease in the amount of F508del-CFTR at the cell surface is due to a defect in the processing and trafficking of the F508del-CFTR protein. The very small amount of F508del-CFTR protein that reaches the cell surface also has defective channel gating and a decreased stability at the cell surface. Patients who are homozygous with *F508del-CFTR* defects have little or no CFTR protein at the cell surface and hence suffer from a severe form of CF disease.

More than 2000 mutations in the *CFTR* gene have been identified. Most of the mutations are not associated with CF disease or are very rare. Currently, the CFTR2 database (an online resource that provides clinical and nonclinical data about CF-associated *CFTR* mutations) contains information on 804 of these identified mutations, with sufficient evidence to define 719 mutations as disease-causing.

CF-causing mutations can also be divided into 2 groups based on the extent of loss of chloride transport caused by the mutation. In general, a complete or near-complete loss of CFTR chloride is referred to as "minimal function" of CFTR (class I, II and III). A residual CFTR-mediated chloride transport is referred to as "residual function" of CFTR (class IV and V).

2.1.4. Clinical presentation, diagnosis and stage/prognosis

Exocrine pancreatic insufficiency and poor nutritional status are among the most significant clinical manifestations of CF in infants with severe genotypes. These factors often lead to poor growth with subsequent growth delay, poorer cognitive development, and are associated with other clinical comorbidities such as decreased lung function and decreased survival. Malnourishment is associated with worsening lung function and is an independent predictor of mortality in this population. In one study, fat malabsorption was present in 79% of infants tested at 6 months and 92% of infants by 12 months of age. Additionally, increased energy expenditure and appetite suppression due to lung disease contribute to poor somatic growth and poor nutritional status in young patients with CF.

Progressive loss of lung function is the leading cause of mortality. The clinical manifestations are those of progressive airway obstruction and bronchiectasis, with periods of worsening pulmonary symptoms associated with a decline in pulmonary function and increased bacterial density in airway secretions (pulmonary exacerbations). Obstruction of airways with thick mucus, establishment of a chronic bacterial infection in the airways, and damaging inflammatory responses are all thought to play a role in causing irreversible structural changes in the lungs, leading to respiratory failure.

Since the introduction and continued advances of newborn and antenatal screening, many patients with CF are identified through a positive screening test and subsequently diagnosed within the first year of life. Approximately 65% of patients in the ECFSPR 2020 Annual Report are diagnosed by 1 year of age, with a median (min., max.) age at diagnosis of 0.30 (0.00, 82.57) years. 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. Therefore, it is expected that the early initiation of treatment with CFTR modulators targeting the functional defects of the mutated CFTR protein could postpone or even prevent the onset of clinical manifestations of cystic fibrosis such as lung disease and impaired exocrine pancreatic function.

CF is diagnosed when both of the following criteria are met:

- Clinical symptoms consistent with CF in at least one organ system (CLASSIC), or positive newborn screening or genetic testing for siblings of patients with CF

  AND

- Evidence of CFTR dysfunction (any of the following):

  - Elevated sweat chloride ≥60 mmol/L (CLASSIC)
  - Presence of two disease-causing mutations in *CFTR*, one from each parental allele
  - Abnormal nasal potential difference

Around 2% of patients lack one or more of the "CLASSIC" features. They may have milder clinical symptoms and/or normal to intermediate sweat chloride results. These patients can still be diagnosed with CF if they meet genetic or functional criteria. In very young children, the usual manifestations of the disease may be absent or not that prominent.

2.1.5. Management

Existing treatments for CF can be broadly classified into 2 groups: (1) therapies that manage the symptoms, complications, and comorbidities of the disease (e.g., antibiotics, mucolytics, pancreatic enzyme replacement therapy) and (2) CFTR modulators (i.e., correctors and potentiators) which target the underlying cause of the disease. Concomitant administrations of these two groups are recommended to maintain and improve lung function, reduce the risk of infections and exacerbations, and improve quality of life.

(1) CF therapies currently available, including nutritional supplements, antibiotics, and mucolytics, target the downstream consequences and symptoms of the disease. These therapies are predominantly generic medicines authorized at a national level, apart from agents for the management of chronic pulmonary infections due to *Pseudomonas aeruginosa*.

(2) CFTR modulators are small molecules that target specific defects in the CFTR protein caused by mutations in the *CFTR* gene. Correctors (tezacaftor, lumacaftor and elexacaftor) facilitate the cellular processing and trafficking of *CFTR* to increase the quantity of *CFTR* at the cell surface. Potentiators (ivacaftor) increase the channel open probability (channel gating activity) of the *CFTR* protein delivered to the cell surface to enhance chloride transport. A combination of a corrector and a potentiator should result in sufficient levels of *CFTR* at the surface, which is then enhanced for its gating function. Kalydeco (ivacaftor, IVA), Orkambi (lumacaftor/ivacaftor, LUM/IVA), Symkevi (tezacaftor/ivacaftor, TEZ/IVA) and Kaftrio (ivacaftor/tezacaftor/elexacaftor, IVA/TEZ/ELX) are CFTR modulators approved for CF patients with specific mutations.

2.2. About the product

In the EU, Kalydeco granules are indicated as monotherapy for the treatment of infants aged at least 4 months, toddlers and children weighing 5 kg to less than 25 kg with cystic fibrosis (CF) who have an *R117H CFTR* mutation or 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 line extension procedure intends to support an extension of indication for Kalydeco granules as monotherapy to infants aged 1 month and weighing at least 3 kg. A new strength (13.4 mg) is also proposed to be added.

The MAH initially applied for the following dosing recommendations in section 4.2 of the SmPC:

- 13.4 mg BID for children aged 1 to less than 3 months weighing at least 3 kg
- 25 mg BID for children aged ≥ 3 to less than 4 months weighing at least 3 kg

The dose should be taken with fat-containing food. Examples of meals or snacks that contain fat are those prepared with butter or oils or those containing eggs, cheeses, nuts, whole milk, or meats.

2.3. Type of Application and aspects on development

The MAH did not request scientific advice.

2.4. Quality aspects

2.4.1. Introduction

The scope of the line extension is to introduce a new strength presented as granules in sachet containing 13.4 mg of ivacaftor as active substance. This is to be added to the existing Kalydeco 25 mg, 50 mg, 59.5 mg and 75 mg granules in sachet, and Kalydeco 75 mg and 150 mg film-coated tablets.

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

The product is available in Biaxially Oriented Polyethylene Terephthalate/Polyethylene/Foil/ Polyethylene (BOPET/PE/Foil/PE) sachet as described in section 6.5 of the SmPC.

In addition to the introduction of Kalydeco 13.4 mg granules in sachet, the MAH has applied for two type IA variations: one to change the name of the site responsible for manufacture and release and stability testing of all granules presentations; and another to add an alternative site responsible release and stability testing for all the presentations of the finished product.

2.4.2. Active Substance

The ivacaftor active substance is provided as an amorphous spray dried dispersion (SDD) intermediate in all Kalydeco dosage forms and strengths. No new information on the ivacaftor active substance or the ivacaftor SDD intermediate has been provided in this line extension application.

2.4.3. Finished Medicinal Product

2.4.3.1. Description of the product and pharmaceutical development

The new strength introduced with this line extension application is Kalydeco 13.4 mg immediate release granules in sachet for oral administration. The 13.4 mg ivacaftor granules differ from the approved Kalydeco granules strengths of 25 mg, 50 mg, 59.5 mg and 75 mg, only with respect to the amount of granules that are filled into the sachets.

The granules have a diameter of 2.0 mm, a target thickness of 2.1 mm and a target weight of 6.87 mg. Individual ivacaftor granules do not exceed the maximum bead size of 2.4 mm. Each granule contains a target of 1.92 mg of ivacaftor. The granules are filled by count into the primary container closure (sachet) to achieve the targeted strength.

The new strength is introduced to support the use of Kalydeco for the treatment of infants aged at least 1 month, toddlers and children weighing 3 kg to less than 25 kg with cystic fibrosis (CF).

As indicated above, ivacaftor active substance used to produce ivacaftor granules is provided as an amorphous spray dried dispersion (SDD) intermediate.

The active substance and SDD used in the ivacaftor granules 13.4 mg, 25 mg, 50 mg, 59.5 mg and 75 mg and the ivacaftor 150 mg tablets are identical.

Excipients are listed specifying their common name, the quantity present, their function and a reference to a relevant standard. The excipients are the same as those used for the already authorised granule strengths. 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.

Most of the pharmaceutical development relevant for Kalydeco 13.4 mg granules was performed for Kalydeco 150 mg film-coated tablets, Kalydeco 25 mg, 50 mg, 59.5 mg and 75 mg granules.

The dissolution medium and the dissolution conditions are the same for all Kalydeco granule strengths. The dissolution profiles and rates are shown to be independent of the granule strength.

As previously shown for the 50 mg, 59.5 mg and 75 mg strengths, the dissolution method is able to discriminate against granule formulations, with respect to the studied changes in granules material/granule attributes and process parameters. The same dissolution method has been approved for the currently approved Kalydeco granule strengths.

Product and manufacturing process development were conducted under a Quality by Design (QbD) paradigm which ensures that the desired product performance in terms of quality, safety, and efficacy is achieved. The critical quality attributes (CQAs) are: appearance, identification, assay, degradation products, uniformity of dosage units, physical form, dissolution, water content and microbial limits. These are the same as for authorised granules strengths and are considered adequate and the justification sufficient.

The primary packaging is Biaxially Oriented Polyethylene Terephthalate/Polyethylene/Foil/Polyethylene (BOPET/PE/Foil/PE) sachet. The material complies with Commission Regulation (EU) No 10/2011. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

2.4.3.2. Manufacture of the product and process controls

The manufacturing process of Kalydeco 13.4 mg granules is identical to the manufacturing process of Kalydeco 25 mg 50 mg, 59.5 mg and 75 mg granules, with the exception of the filling step (the number of granules per sachet is different in each strength).

A flow chart and a narrative description of the manufacturing process have been provided.

Briefly, the manufacturing of ivacaftor SDD consists of 3 steps: mixture preparation, spray drying and secondary drying. The ivacaftor granules are manufactured by direct compression, using three main steps: blending, compression and filling into sachets. The process is considered to be a standard manufacturing process.

Critical process parameters, design space limits (DSL) and normal operating ranges (NORs) have been defined.

Design spaces have been proposed for all steps of the manufacturing process of Kalydeco granules (same for all strengths), except filling. 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.

2.4.3.3. Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: appearance (visual inspection), identification (IR), assay (HPLC), degradation products (HPLC), uniformity of dosage units (Ph. Eur.), dissolution (Ph. Eur.), physical form (XRPD), water content (Karl Fischer), microbial limits (TAYMC, TYMC, *E.coli*) (Ph. Eur.).

The specification for Kalydeco 13.4 mg granules is the same as for the authorised Kalydeco 25 mg, 50 mg, 59.5 mg and 75 mg granules. The specification is considered acceptable.

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. 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. Batch analysis data from representative batches including three commercial scale batches of active substance and SDD from each manufacturer using a validated ICP-MS method was provided, demonstrating that each relevant elemental impurity was not detected above 30% of the respective PDE. Based on the risk assessment and the presented batch data it can be concluded that it is not necessary to include any elemental impurity controls. The information on the control of elemental impurities is satisfactory.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided, it is accepted that the risk of nitrosamine impurities in the active substance or the related finished product is low, and the product will consistently meet the nitrosamine impurities requirement. Therefore, no specific control measures on nitrosamines are deemed necessary.

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

No information on reference standards has been provided. This is acceptable since the same standards used for the active substance is used for the ivacaftor granules.

Batch analysis results are provided for one 13.4 mg granules commercial scale batch and multiple commercial batches of the authorized granules strengths. Process validation protocols for the validation of Kalydeco 13.4 mg granules at both of the proposed manufacturing sites have been provided and process validation will be completed at both sites prior to commercial distribution of Kalydeco 13.4 mg granules. The data presented confirm the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

2.4.3.4. Stability of the product

Stability data from three primary stability batches of Kalydeco 5.7 mg (not proposed for marketing) stored for up to 24 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. This was accompanied with stability data from six primary stability batches of 25 mg granules (authorized) and three primary stability batches of 100 mg granules (not proposed for marketing) stored for 48 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH).

The batches are representative to those proposed for marketing and were packed in the primary packaging proposed for marketing.

A bracketing design is proposed. This is acceptable.

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

All batches met commercial specifications at all time points at 25 °C/ 60% RH and 6 months at 40 °C/ 75% RH.

In addition to the primary stability data provided, several commercial validation and annual commitment lots of 25 mg, 50 mg, and 75 mg granules strengths demonstrate stability up to 48 months. Statistical analysis of the stability data to demonstrate that the 48 month shelf-life of higher strength granules is applicable to the 13.4 mg strength was also conducted. For each CQA analysed – dissolution, water content, and assay – no statistically significant impact of dose strength on the CQA's stability was observed.

As indicated above, the 13.4 mg ivacaftor granules strength differs from the approved Kalydeco granules strengths of 25, 50, 59.5 and 75 mg strengths, only with respect to the number of granules that are filled into the sachets. All strengths (including the 13.4 mg ivacaftor granules) are packaged from bulk granules of the same composition, manufacturing process, and packaging configuration. Therefore, the stability conclusions from the 25 mg and 100 mg granules, along with the 5.7 mg granules, support a 4 year shelf-life for all granules strengths.

The post-approval stability protocol and the stability commitment are considered acceptable.

Photostability testing was performed on one batch of ivacaftor granules after direct exposure of the granules to 1 x ICH visible and 3.7 x ICH UV light according to ICH Q1B (option 2). The results show that the granules are not sensitive to light.

As reported for the authorised granule strengths, an in-use stability study in food was also conducted in support of the SmPC instructions to administer the granules with mixed with 5 mL of age-appropriate soft food or liquid that is at or below room temperature. Samples were tested for assay, degradation products, dissolution, and physical form. 25 mg and 100 mg strength sachets were stored through 48 months at 30 °C/7 5% RH and then mixed with foods (applesauce, infant formula, non fat-yogurt, carrot puree and water) and tested after 1-hour contact time at room temperature. All results met the acceptance criteria for the attributes evaluated.

Based on available stability data, the proposed shelf-life of 4 years for all granule strengths as stated in the SmPC (section 6.3) are acceptable.

2.4.3.5. 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.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

Kalydeco 13.4 mg granules in sachet is a line extension of approved Kalydeco 25 mg, 50 mg, 59.5 mg and 75 mg granules in sachet. The new 13.4 mg ivacaftor granules differ from the approved Kalydeco granules strengths, only with respect to the amount of granules that are filled into the sachets. Therefore, manufacturing and stability conclusions for the 13.4 mg ivacaftor granules are bracketed by the approved Kalydeco granules strengths. Information on development, manufacture and control of the finished product has been presented in a satisfactory manner. The applicant 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.

The change in the name of the site responsible for manufacture and release and stability testing of all granules presentations and the addition of the alternative site responsible release and stability testing for all the presentations of the finished product are also introduced within this procedure.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

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

2.4.6. Recommendations for future quality development

n/a

2.5. Non-clinical aspects

2.5.1. Introduction

The MAH provided information related to environmental risk assessment (ERA) for ivacaftor. No additional non-clinical data (pharmacology, pharmacokinetics or toxicology) have been submitted in this application, which was considered acceptable by the CHMP.

2.5.2. Ecotoxicity/environmental risk assessment

The MAH conducted an environmental risk assessment (ERA) for ivacaftor in accordance with Article 8(3) (ca) and (g) of Directive 2001/83/EC. An updated ivacaftor ERA, 'VX-770: Kalydeco Monotherapy and in Combination with VX-809 or VX-661 or VX-445 and VX-661 Environmental Phase I and Phase II Risk Assessment Report, Amendment 01', dated 11 September 2019 was approved as part of the Type II extension of the indication variation, EMEA/H/C/002494/II/0082.

This submission encompasses a proposed extension of the indication for Kalydeco (ivacaftor) granules 13.4 mg for the treatment of children aged 1 to less than 4 months of age with cystic fibrosis (CF) who have at least one F508del mutation in the CFTR gene (see section 5.1). The calculations performed for the initial environmental risk assessment accounted for the entire population of CF patients (irrespective of age). This was done because it poses a worst-case scenario as far as environmental exposure. Therefore, the MAH states that there will be no increase in environmental exposure to ivacaftor (VX-770) from the administration to this new age group.

2.5.3. Discussion on non-clinical aspects

No pharmacodynamics, pharmacokinetics and toxicology studies have been submitted for this application which was considered acceptable by the CHMP.

According to the current *Guideline on the environmental risk assessment of medicinal products for human use* (EMA/CHMP/SWP/4447/00 corr 2[1*]), an update of the evaluation of the environmental impact should be made if there is an increase in the environmental exposure. In the current procedure, the MAH intention is to extend the cystic fibrosis indication from children aged 1 to less than 4 months of age, therefore, an updated ERA or an adequate justification for the absence of specific study data should be submitted. A justification of the absence of significant increase of the environmental exposure, demonstrated by suitable information, can be accepted as a justification for the absence of a complete ERA, according to the guideline EMA/CHMP/SWP/44609/2010 Rev. 1.

Ivacaftor is already used in existing marketed products and no significant increase in environmental exposure is anticipated, since calculations for Predicted Environmental Concentration and risk characterization ratios were based on the worst case scenarios: i.e. if the entire population of CF patients of the EU received ivacaftor and were already covering the proposed new indication.

Ivacaftor is not a PBT substance, considering the above data, ivacaftor is not expected to pose a risk to the environment.

Based on the environmental risk assessment, no adverse environmental effects are anticipated as a consequence of the use of ivacaftor for the treatment of cystic fibrosis as indicated in the SmPC.

2.5.4. Conclusion on the non-clinical aspects

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

Regarding the environmental risk assessment, no additional exposure is anticipated resulting from the extension of the indication for Kalydeco (ivacaftor) granules 13.4 mg for the treatment of children aged 1 to less than 4 months of age. Based on the current environmental risk assessment, no adverse environmental effects are anticipated as a consequence of the extension of indication in toddlers from 1 month of age .

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

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

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

- **Tabular overview of clinical studies**

Type of Study	Study Identifier/ Location	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of 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 5.3.5.1	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 Part A/B: • To evaluate the safety, PK, PD, and efficacy of IVA treatment	Nonrandomized, open-label, multiple-dose	IVA 5.7-, 25-, 50-, or 75-mg granules; 5.7, 11.4, 17.1, 22.8, 25, 50, or 75 mg q12h; PO	Part A: Cohort 1: 7 subjects; Cohort 2: 6 subjects Cohort 3: 6 subjects Part B: Cohort 5: 19 subjects; Cohort 6: 11 subjects Cohort 7: 6 subjects Part A/B: Cohort 8: 7 subjects Male and female subjects <24 months of age and have a *CFTR* gating mutation or *R117H* mutation or IVA-responsive *CFTR* mutation (Cohort 8 only)	Part A: Days 1 through 3, and morning dose on Day 4 Part B: 24 weeks Part A/B: 24 weeks	Ongoing; Cohorts 1 and 5; subjects 12 to <24 months of age are complete; Interim Analysis (IA) Report. Cohorts 2 and 6; subjects 6 to <12 months of age are complete; IA2 Report. Cohort 3, subjects 3 to <6 months of age; Cohort 7, subjects 4 to <6 months of age are complete; IA3 Report. Cohort 8, subjects 1 to <4 months of age, is complete; IA4 Report.

2.6.2. Clinical pharmacology

The current submission proposes to extend the approved indication of Kalydeco to include paediatric patients 1 to <4 months of age and weighing ≥3 kg, using the 25-mg ivacaftor granule dose, and a new 13.4-mg ivacaftor granule dose.

This submission is based on the analysis of Part A/B Cohort 8 (subjects 1 to <4 months of age) of Study VX-15-770-124 (Study 124), which is an open-label study in children <24 months of age.

On Days 1 through the morning dose of Day 15, subjects in Part A/B Cohort 8 received an initial low dose of ivacaftor (5.7 or 11.4 mg, q12h) based on their age and weight at Day 1. At Day 4, each subject provided PK samples to assess exposure and, if appropriate, the dose was adjusted at Day 15 (evening) to 5.7, 11.4, 17.1, 22.8, or 25 mg q12h to better match the adult median exposure. Subjects remained on this dose until the study visit after reaching 4 months of age and 5 kg, at which point subjects received the approved dose of 25 mg q12h. Table 1 shows how children in Cohort 8 were actually dosed with ivacaftor.

Table 1. Initial and Adjusted Doses for Subjects in Cohort 8

	Age at Day 1 (months)	Weight at Day 1 (kg)	Initial Dose (mg) q12h	Adjusted Dose (mg) q12h	Dose Adjusted at Day 15 (Y/N)
[a]	1	3.6	5.7	17.1	Y
	1	4.2	5.7	5.7	N
	1	4.3	5.7	11.4	Y
	2	5.0	11.4	17.1	Y
	2	6.1	11.4	22.8	Y
	3	5.3	11.4	22.8	Y
	3	6.0	11.4	25.0	Y

Source: Adapted from Report R269/Table 6-3

N: No; q12h: every 12 hours; SUBJID: subject identification number; Y: Yes

Note: Y/N designation indicates whether the dose was adjusted at Day 15.

[a] Subject discontinued study drug treatment on Study Day 63.

2.6.2.1. Pharmacokinetics

Bioavailability and food effect

The comparative bioavailability and food effect of granules 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 13.4 mg strength as the only difference between the already marketed granules relies on the strength.

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 condition 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.

Metabolism

The pharmacokinetics of ivacaftor metabolites M1 and M6 was part of the primary objectives of study 124. Plasma concentrations by time point have been described for the target paediatric age group, but not discussed. To that end, plots of the observed M1-IVA and M6-IVA plasma concentrations over time in subjects aged <24 months were provided and the levels compared to those of subjects ≥12 years of age and subjects 6 to <12 years of age. The M1-IVA plasma concentration median values from children 1 to <24 months of age are slightly below the median values of the subjects ≥12 years of age and are approximately half the value of the median of subjects 6 to <12 years of age over time. On the other hand, the M6-IVA plasma concentration median values from children 1 to <24 months of age are approximately 2-fold the value of the median values of subjects ≥12 years of age and are less than half the value of the median of

subjects 6 to <12 years of age over time. However, the limited number of subjects in each age cohort under 24 months of age included in the analysis and sparse PK sampling hampers a proper exposure comparison.

Pharmacokinetics in target population

Physiologically-based pharmacokinetic (PBPK) model (Report P138)

The objective of this modelling and simulation study was to develop a PBPK model for ivacaftor (IVA) that can be used for simulations to assist in dose selection for special populations, such as paediatric subjects less than 4 months of age.

The base PBPK model was constructed in SIMCYP using a combination of in vitro, preclinical, and clinical data.

Model verification

One internal and six external verification simulations were performed to demonstrate that the developed PBPK model accurately predicts PK exposures. In healthy volunteers, the model reasonably captures IVA PK data from multiple dosing in healthy volunteers for Study VX12-770-016. These data serve as an internal verification as they were used to construct the PBPK model.

Observed drug-drug interaction (DDI) AUC and Cmax ratios are presented in Table 2 and Table 3. All predicted to observed ratios were less than 2-fold and within the newly proposed Guest criterion, which qualifies the compound file for these scenarios.

Table 2. Summary of the Predicted vs. Observed AUC and Cmax of Multi-day Studies

	Observed	Mean (SD)	Predicted	Mean (SD)	Predicted/Observed Ratio of Mean
150 mg q12h	AUCt (ng*h/mL)	12300 (4480)	AUCt	10700 (5300)	0.85
	C_{max} (ng/mL)	1490 (475)	Cmax	1120 (468)	0.75
250 mg q12h	AUCt (ng*h/mL)	20700 (13000)	AUCt	18500 (9240)	0.89
	C_{max} (ng*h/mL)	2290 (1420)	Cmax	1930 (812)	0.84

Source for observed data: Table 11-8 & 11-25 of CSR VX10-809-006 (12). AUCt is the AUC over the dosing interval (12h). SD is the standard deviation.

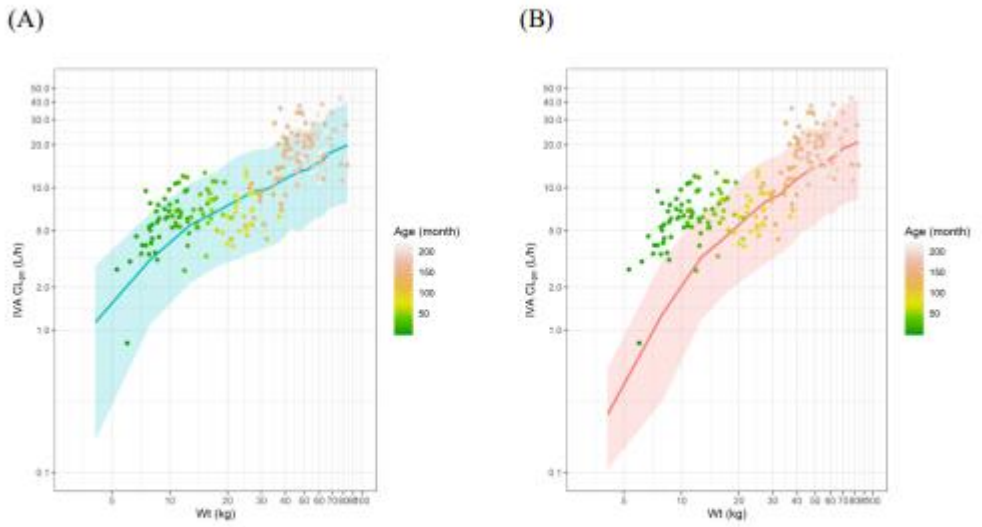
Table 3. Summary of the Predicted vs. Observed AUC and Cmax Ratios of DDI Studies

Study	IVA	Perpetrator	Observed (GLSM ratio)		Predicted (Geometric mean of ratio)		Pred./Obs. Ratio	Guest criterion
VX08-770-006	150 mg SD	Ketoconazole 400 mg QD	AUCRatio	8.45[a]	AUCRatio	9.03	1.07	4.42 – 16.15
			CmaxRatio	2.65[a]	CmaxRatio	2.18	0.82	1.54 – 4.55
VX09-770-009	150 mg SD	Rifampicin 600 mg QD	AUCRatio	0.114[b]	AUCRatio	0.126	1.11	0.06 – 0.22
			CmaxRatio	0.2[b]	CmaxRatio	0.29	1.45	0.11 – 0.37
VX09-770-010	150 mg q12h	Fluconazole 400/200 mg QD	AUCRatio	2.95[c]	AUCRatio	3.27	1.11	1.69 – 5.15
			CmaxRatio	2.47[c]	CmaxRatio	2.85	1.15	1.46 – 4.19
VX14-661-006	50 mg QD	Itraconazole 200 mg q12h/QD	AUCRatio	15.6[d]	AUCRatio	13	0.83	7.99 – 30.45
			CmaxRatio	8.6[d]	CmaxRatio	7.88	0.92	4.50 – 16.45

Note: a. Table 11-2 CSR (5); b. Table 2-3 CSR (6);c. Table 2-4CSR (7); d. Table 11-5 CSR (4); GLSM: Geometric least squares mean

For paediatric scenarios, simulations were performed using the PBPK model with either default SIMCYP ontogeny or updated Upreti ontogeny. The ontogeny equations proposed by Upreti resulted in predicted clearance values that were better aligned with those from CF subjects (derived from the popPK model) than those predicted by the default SIMCYP ontogeny – see Figure 1. Robust prediction of IVA clearance by the Upreti ontogeny supports the use of the developed IVA PBPK model for prediction of exposures in the paediatric population.

Figure 1. Observed and Simulated Oral Clearance of IVA in Paediatric CF Subjects for (A) Upreti ontogeny and (B) Default SIMCYP ontogeny

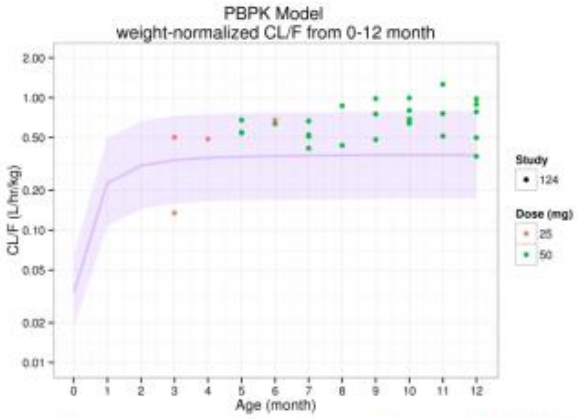


Notes: Solid line is the median oral clearance predicted by the PBPK model. Shaded area indicates 90% prediction interval for the population predicted by the PBPK model. Color dots indicate observed oral clearance derived from the popPK model.

Model application

The qualified models were utilised to simulate apparent oral clearance (CL/F) for paediatric CF subjects 0 to 12 months of age. Figure 2 presents the weight-normalized CL/F values versus age plot. The model predicts a sharp decrease in clearance for paediatric subjects <1 month of age, suggesting that CYP3A maturation effects will have the largest impact on IVA exposures for these subjects.

Figure 2. Simulation of Weight-Normalized CL/F of IVA q12h for the 0-12 Month Population



Notes: Solid line is the median oral clearance predicted by the PBPK model. Shaded area indicates 90% prediction interval for the population predicted by the PBPK model. Color dots indicate observed oral clearance derived from the popPK model.

Population PK model in subjects 1 to less than 4 months (Report R269)

This analysis is a continuation of the analysis presented in Report Q005, which included data from paediatric subjects 3 months through 18 years of age, including data from Cohorts 1 through 7 from Study 124 (subjects 3 to <24 months of age). The current analysis includes the final data from Study 124 Cohort 8 (subjects 1 to <4 months of age).

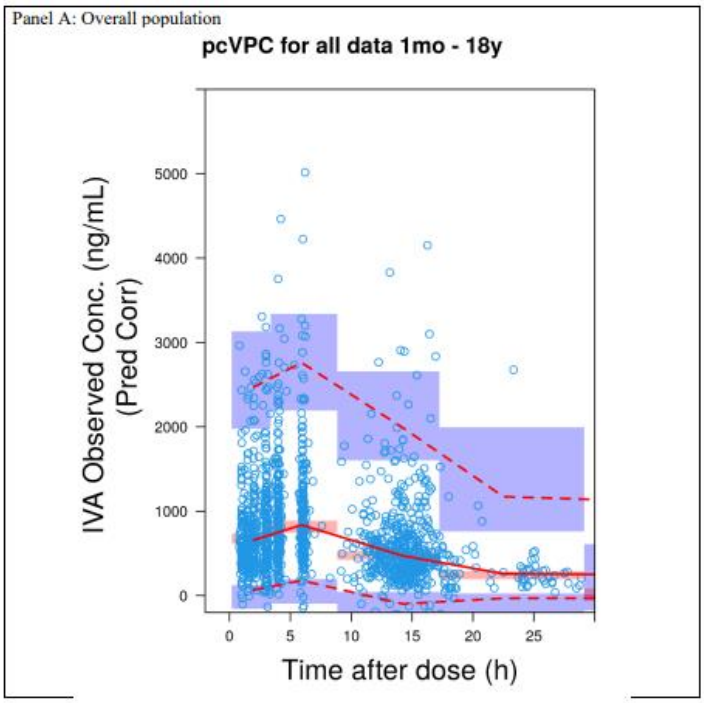
The PK dataset included 2,023 IVA plasma concentration measurements from 227 CF subjects 1 month through 18 years of age. The median weight was 26.8 kg (range: 3.6 kg to 84 kg). From Study 124 Cohort 8, 74 ivacaftor plasma concentration measurements were included from 7 subjects 1 to < 4 months of age. The median age and weight in Cohort 8 were 2 months (range: 1 to 3 months) and 5 kg (range: 3.6 to 6.1 kg), respectively.

Ivacaftor PK was described by a 2-compartment model with zero-order delivery to the absorption compartment and subsequent first-order absorption. The model incorporated age (by using an estimated maturation effect) and weight effects as predictors of CL/F. Other covariates (race, gender, genotype, and patient status [CF versus healthy subject]) were previously shown not to have a clinically significant impact on IVA disposition (Report J178 and Report K199). Allometric relationships using body weight with fixed exponents were incorporated for volume and intercompartmental clearance parameters to describe other effects of body size on IVA PK.

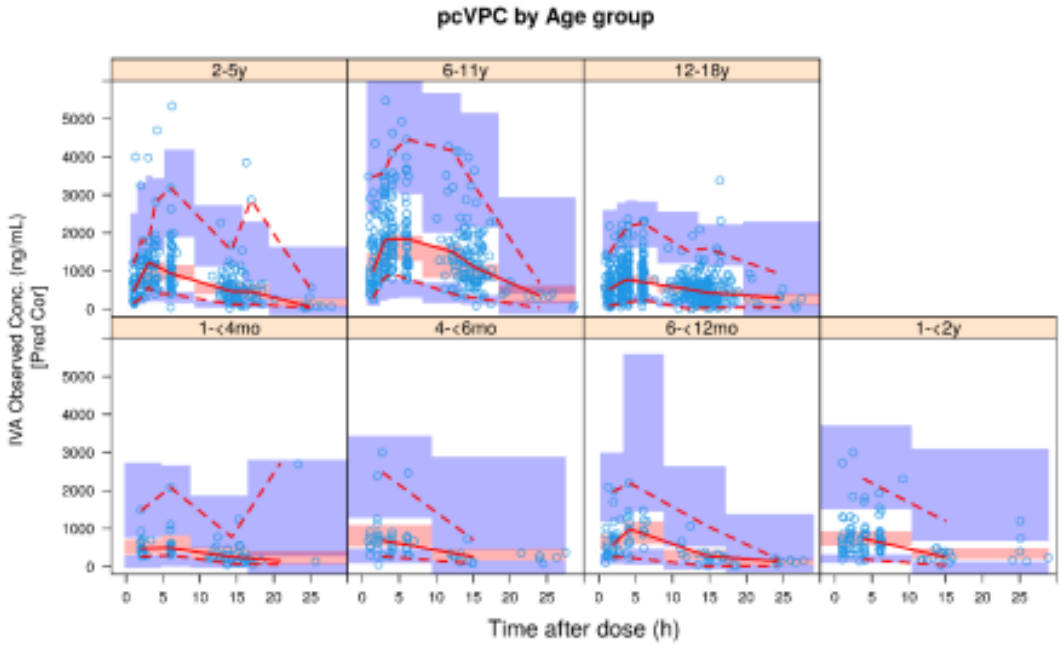
The medians of the individual parameter estimates for IVA in CF subjects 1 to <4 months of age were 1.94 L/h for CL/F, 6.12 L for apparent central volume (Vc/F), 7.40 L for apparent peripheral volume (Vp/F), 2.03 L/h for inter-compartmental clearance (Q/F), 2.55 h for zero-order dose duration (D1), and 0.191 h-1 for the first-order absorption rate (ka). Most parameters were estimated precisely. Apparent oral clearance (CL/F) was estimated at 7.1 L/h (relative standard error [RSE] = 6.30%) for a reference weight of 70 kg.

Visual predictive checks (VPCs) of the final ivacaftor popPK model were performed to verify that the model adequately predicted both the central tendency and the variability of the observed data at steady state. The VPCs were based on 500 simulated replicates of the model analysis dataset. Figure 3 shows the pcVPCs for the overall population (Panel A) as well as stratified by age (Panel B) and weight (Panel C).

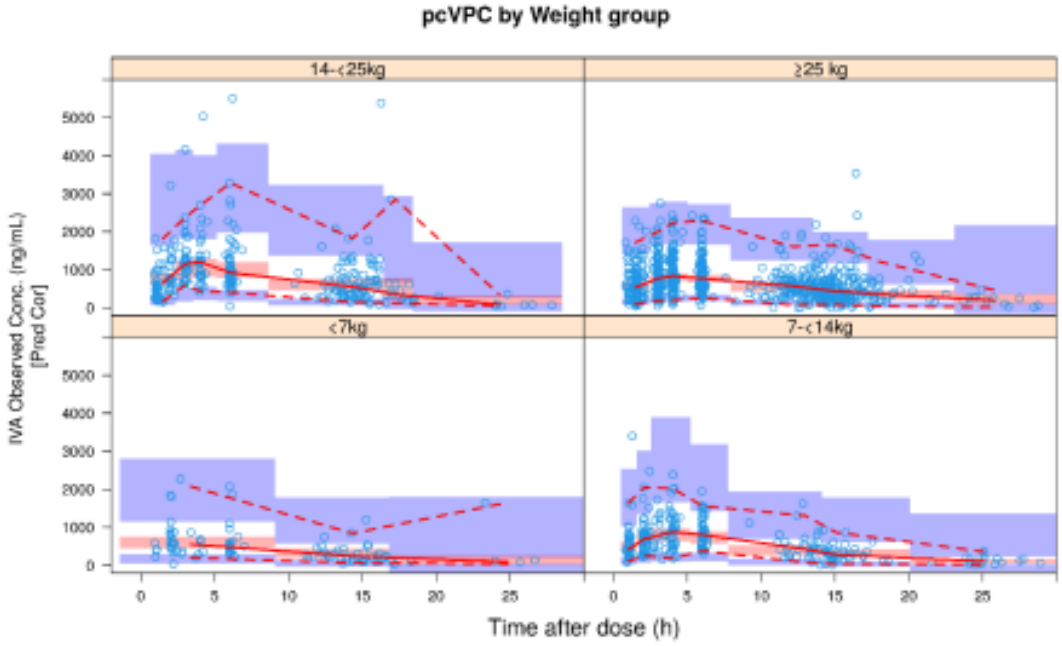
Figure 3. Prediction Corrected Visual Predictive Checks (pcVPCs) of the IVA Final Population PK Model



Panel B: Stratified by Age



Panel C: Stratified by Weight



Notes: visual predictive check of all data at steady-state. The units of the y-axis are ng/mL. The median and the 2.5th and 97.5th percentiles of the observed data are indicated with the solid red curve and the dashed red curves respectively. 95% CI of predictions are displayed as shaded areas in red (median) and blue (2.5th and 97.5th percentiles). Open blue circles represent the observed data. VPC are generated from 500 simulated replicate datasets.

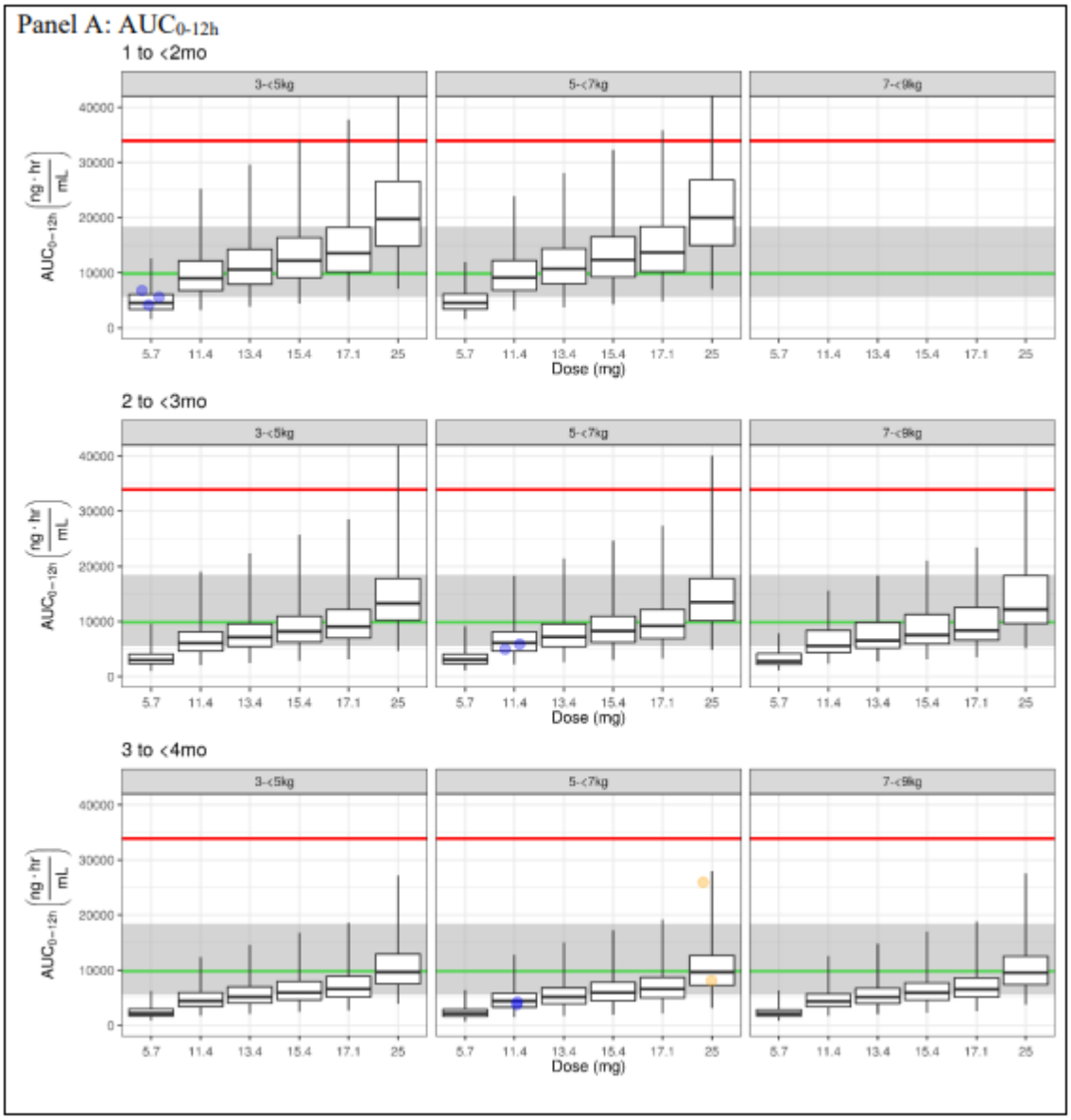
Considering the popPK model-based simulations, the initially proposed dosing recommendations for children aged 1 month to less than 4 months were as follows:

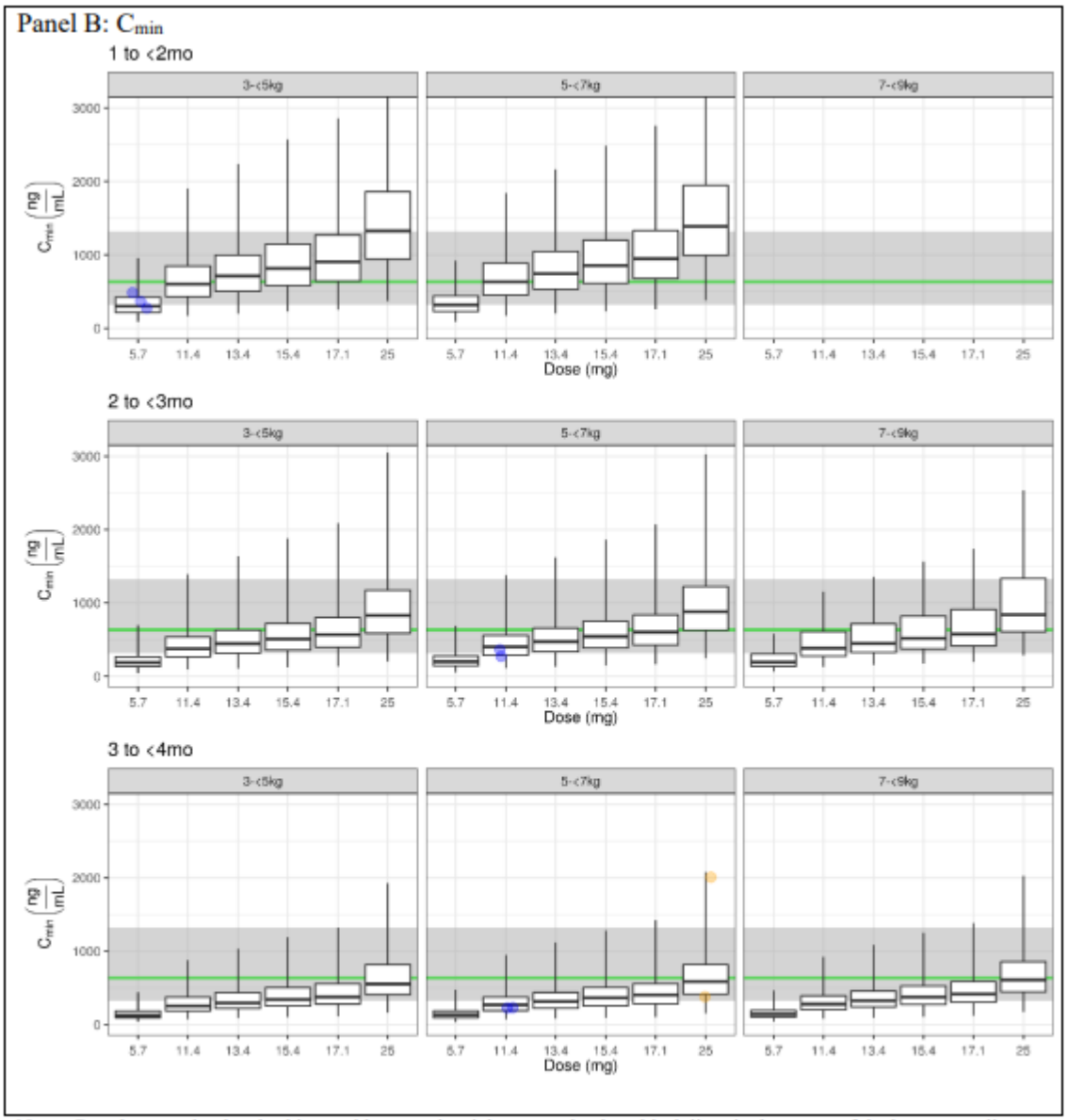
- Ivacaftor 13.4 mg q12h for patients 1 to <3 months of age and weighing ≥3 kg

- Ivacaftor 25 mg q12h for patients 3 to <4 months of age and weighing ≥3 kg

Dosing is recommended for patients 3 to <4 months of age weighing ≥3 to <5 kg even though they were not enrolled in Cohort 8. Ivacaftor PK for this group was predicted to be similar to that shown to be safe and efficacious in adults, as well as to that of 3 to <4-month subjects weighing ≥5 kg; see Figure 4.

Figure 4. IVA Predicted Exposures by Age and Weight Group for Multiple Doses





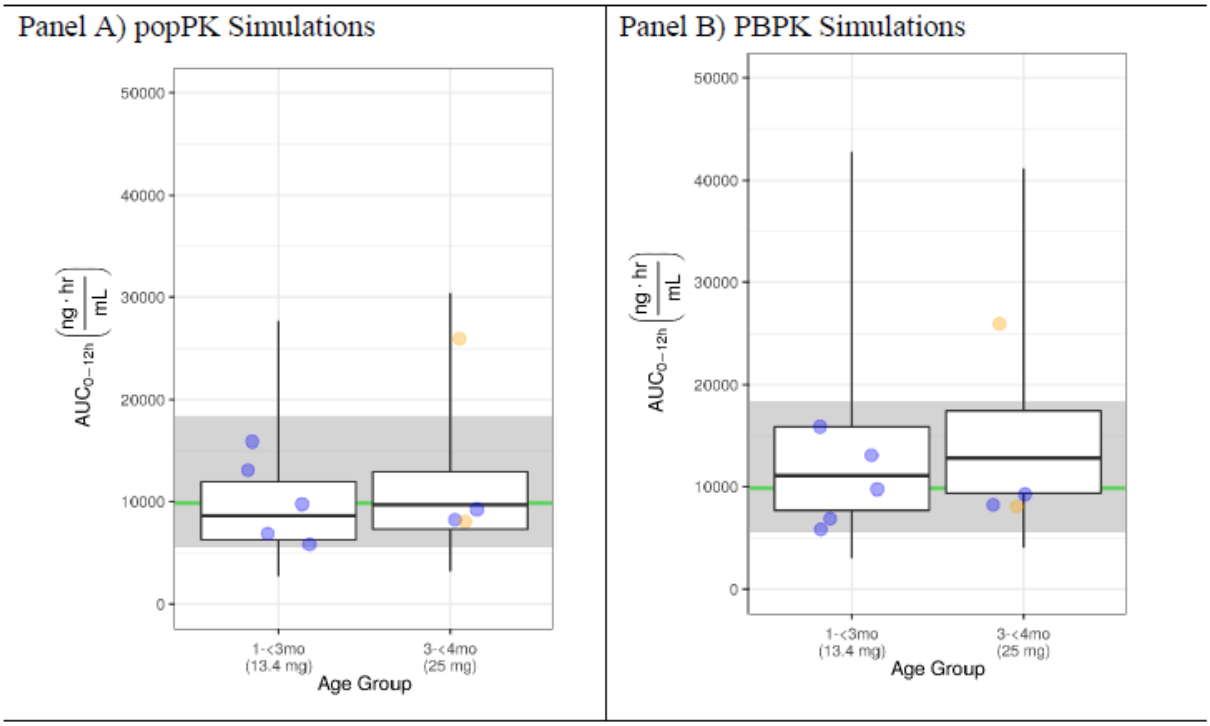
Notes: Boxplots are simulated subjects with age and weight as noted, where black lines in the center of the box are medians, boxes are the IQR, and whiskers are the 0.5th to 99.5th percentile region. Circles represent the predicted exposures of subjects enrolled in Part A/B Cohort 8 (blue) and in Part A Cohort 3 (orange) receiving their initial study dose. Gray area represents the adult 5th to 95th percentile region of IVA exposures with the median exposure shown as a green line.

The lower body weight of 3 kg has been selected given that there are 3-month-old subjects who are expected to weigh between 3 to <5 kg based on simulations from the WHO growth charts, while subjects 4 months of age and older are not expected to weigh <5 kg. Similarly, dosing is recommended for patients 1 to <3 months of age weighing ≥3 kg, noting that based on simulations from the WHO growth charts, the minimum expected weight for 1-month-old subjects is 3 kg. In addition, data from the US CF Foundation (CFF) Patient Registry indicates that it is not expected that patients 1 month of age will weigh <3 kg. Together these results support a lower weight bound of 3 kg for both, subjects 3 to <4 and 1 to <3 months of age.

Upon CHMP request, stochastic simulations were conducted using both the PBPK and the popPK approaches to compare the predicted exposures (see Figure 5). The PBPK model incorporates physiologically-based relationships for how weight and age (via maturation effects) impact PK. This model overpredicts PK

exposures for children 1 to <6 months of age and therefore provides a conservative reference range for this age group. The popPK model incorporates empirical age and weight relationships on CL/F to describe the PK and even though it appears to adequately capture the observed PK data and variability, the limited experimental data gathered and the lack of mechanistic description of maturation and allometric relationships may result in inaccurate predictions for children with demographics not studied, such as infants with very low weights. Overall, then, the results from the popPK model are considered less informative for children below 6 months of age.

Figure 5. Simulated Exposures for the Proposed Dosing Regimen



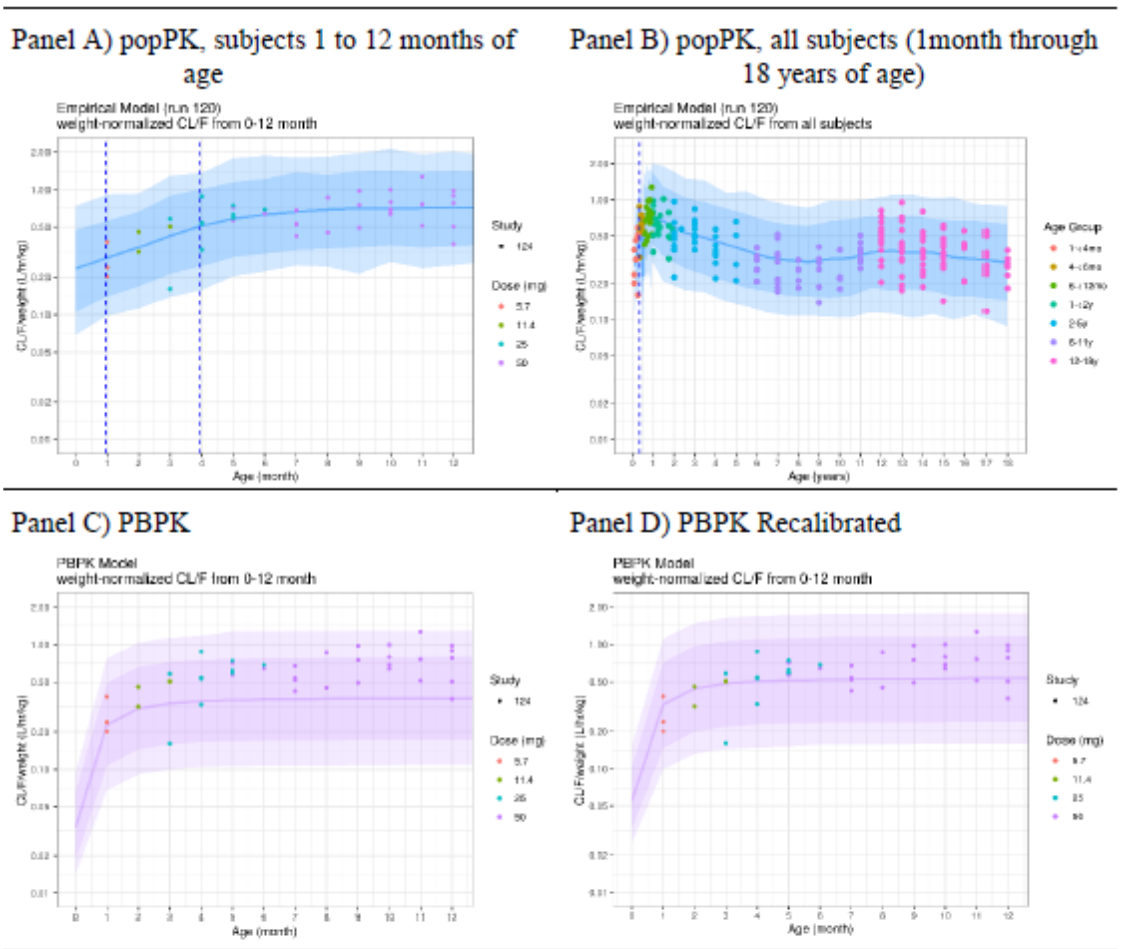
Source Panel A: updated from Report R269/Figure 6-18; Panel B: data on file
AUC_{0-12h}: area under the concentration versus time curve from 0 to 12 hours; IQR: interquartile range; IVA: ivacaftor; mo: months; PBPK: physiologically-based pharmacokinetic; popPK: population pharmacokinetic
Notes: Boxplots are simulated subjects 1 to <4 months of age, where black lines in the center of the box are medians, boxes are the IQR, and whiskers are the 0.5^{th} to 99.5^{th} percentile region. Circles represent the individual predicted exposures of subjects enrolled in Study 124 Cohort 8 (blue) and in Part A Cohort 3 (orange) receiving the proposed dosing regimen. Gray area represents the adult 5^{th} to 95^{th} percentile region of IVA AUC_{0-12h} exposures with the median exposure shown as a green line.

In view of the fact that 1) a 3-month old child in Cohort 3 (3 to less than 6 months) dosed with 25 mg q12h exhibited the highest ivacaftor plasma concentration (i.e., 3110 ng/ml at Day 4, 6 hours post-dose); 2) a 1-month-old subject had to be discontinued from the study due to transaminase elevations which did not return to baseline levels after treatment interruption; and 3) an additional 1-month-old subject could not adjust the initial dose of 5.7 mg until the subject was 5.7 months old, the CHMP asked the MAH to establish the dosage regimens in children between 1 and 4 months with a more conservative adult range of reference thereby reducing the possibility of placing these children at exposure levels higher than those observed in adults dosed with 150 mg q12h. To that end, the MAH recalibrated the PBPK model to predict the observed AUC0-12

(Figure 6, Panel C) and weight-normalized CL/F (Figure 7, Panel D), which resulted in model predictions that better aligned with the observed data for the 1 to <4 month age group.

The dose selection strategy was conducted by evaluating different q12h regimens in paediatric patients from 1 to 6 months of age and 3 kg body weight (Figure 8).

Figure 6. Weight-normalized CL/F by Age for the PopPK and PBPK Models

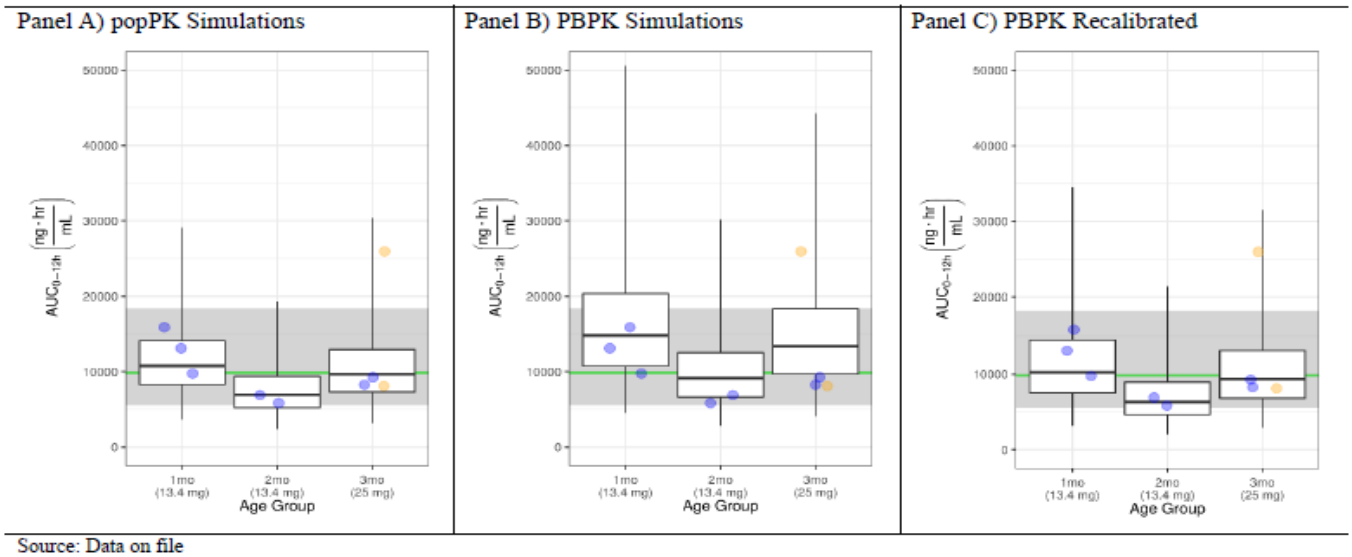


Source: Panels A and B: Report R269/Figure 6-11; Panels C and D: Data on file

CL/F: apparent oral clearance; mo: months; PBPK: physiologically-based pharmacokinetic; popPK: population pharmacokinetics; y: years

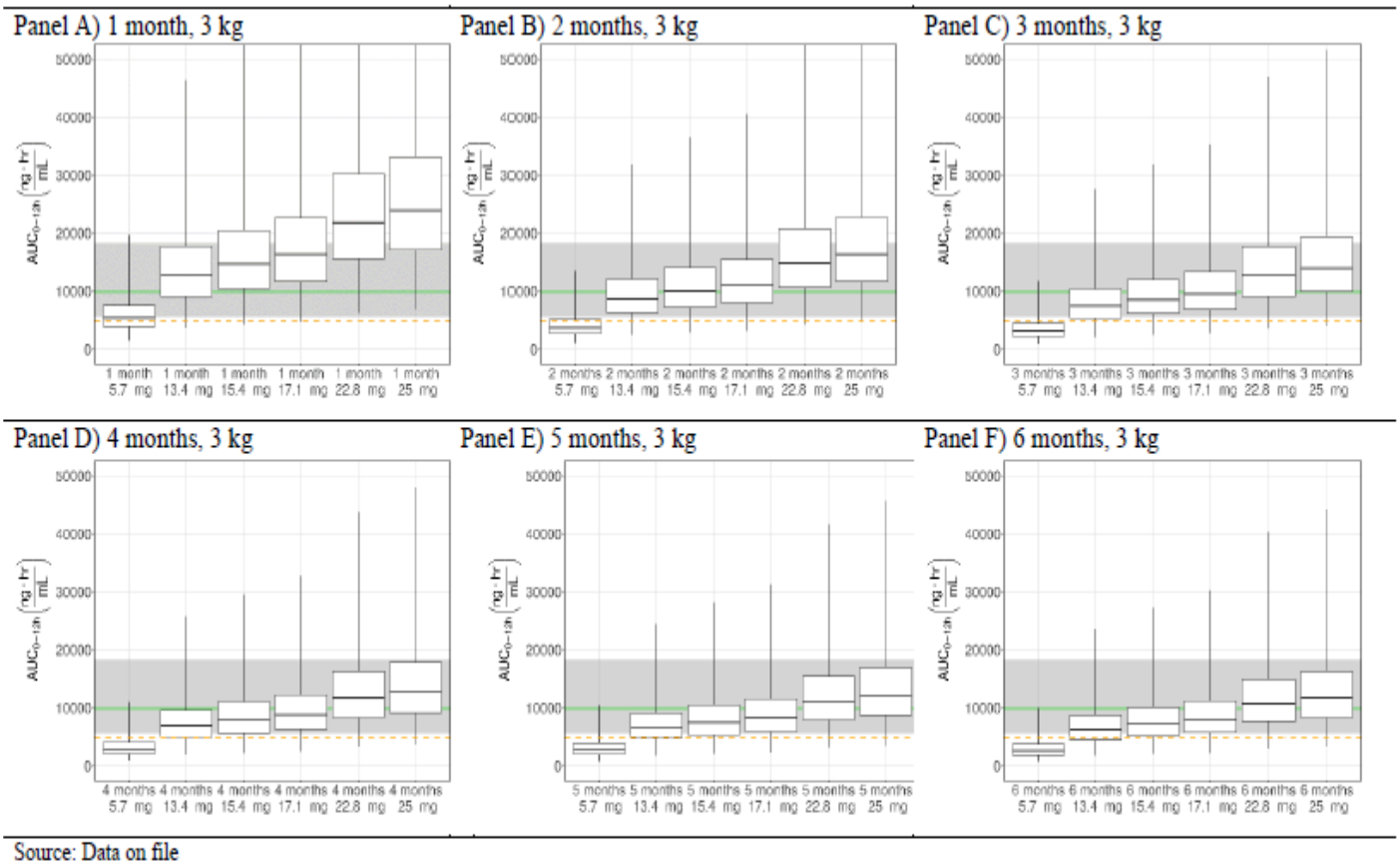
Notes: Blue and purple dark and light shaded area represent the 90% and 99% prediction intervals simulated from the final popPK (blue) and PBPK (purple) models. Continuous lines represent the median of the prediction interval. Blue vertical dashed lines denote the age interval of the population of interest (1 to <4 months of age). Points are the weight-normalized CL/F values derived from empirical Bayes estimates for individual subjects in the data set.

Figure 7. Simulated Exposures for the Originally Proposed Dosing Regimen – Children of Representative Weights for Age



Source: Data on file
IQR: interquartile range; IVA: ivacaftor; mo: months; PBPK: physiologically-based pharmacokinetics; popPK: population pharmacokinetics
Notes: Boxplots are simulated subjects 1 to <4 months of age, where black lines in the center of the box are medians, boxes are the IQR, and whiskers are the 0.5th to 99.5th percentile region. Circles represent the individual predicted exposures of subjects enrolled in Study 124 Cohort 8 (blue) and in Part A Cohort 3 (orange) receiving the proposed dosing regimen. Gray area represents the adult 5th to 95th percentile region of IVA $AUC_{0\text{-}12h}$ exposures with the median exposure shown as a green line.

Figure 8. AUC0-12h Exposures Simulated From the Recalibrated PBPK Model for the Requested q12h Dosing Regimens for Children 1 to 6 Months of Age Weighing 3 kg



Source: Data on file

IQR: interquartile range; IVA: ivacaftor; PBPK: physiologically-based pharmacokinetics; q12h: every 12 hours

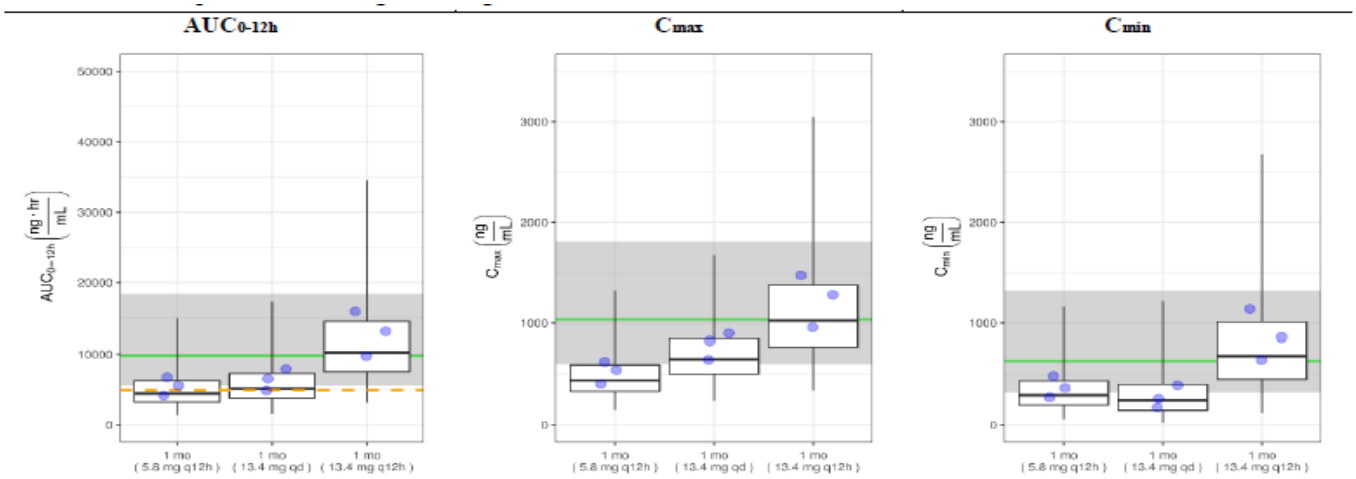
Notes: Boxplots are 1000 simulated subjects 1, 2, 3, 4, 5, and 6 months of age weighing 3 kg receiving the dose noted in the x-axes, where black lines in the center of the box are medians, boxes are the IQR, and whiskers are the 0.5th to 99.5th percentile region. Gray area represents the adult 5th to 95th percentile region of IVA $AUC_{0\text{-}12h}$ exposures receiving 150 mg q12h dosing regimen with the median exposure shown as a green line. Dashed orange line is the median exposure based on simulated exposures from adult subjects receiving IVA 75 mg q12h. All approved IVA granule strengths are prepared from granules with a target IVA content of 1.92 mg per granule.

These simulations demonstrated that a large proportion of paediatric patients from 2 to <4 months of age and 3 kg receiving 13.4 mg q12h would be within the conservative adult range selected. Therefore, the adequacy of the proposed dosing regimen is endorsed.

For children 1 to <2 months of age, two alternative dosing regimens were evaluated (5.8 mg q12h or 13.4 mg once daily). Simulations for these dosing regimens for children 1 to <2 months of age are presented in Figure 9 (children with representative weights for that age range) and Figure 10 (children weighing exactly 3 kg). Optimal exposure levels were predicted with the 5.8 mg q12h, since larger proportion of paediatric patients with 1 month of age and 3 kg of body weight would be within the conservative adult range. Alternatively, the 13.4 mg once daily regimen is predicted to result in similar AUC and Cmin levels, while slightly higher Cmax levels are expected with the 13.4 mg once daily regimen versus 5.8 mg twice daily. However, the proportion of paediatric patients between 1 to <2 months of age and 3 kg of body weight with Cmax levels above the more conservative reference adult range of exposure is expected to be less than 25%. Furthermore, as age and/or body weight increases, the Cmax levels are expected to decrease, so the proportion of paediatric patients above the reference conservative adult range is expected to be less than

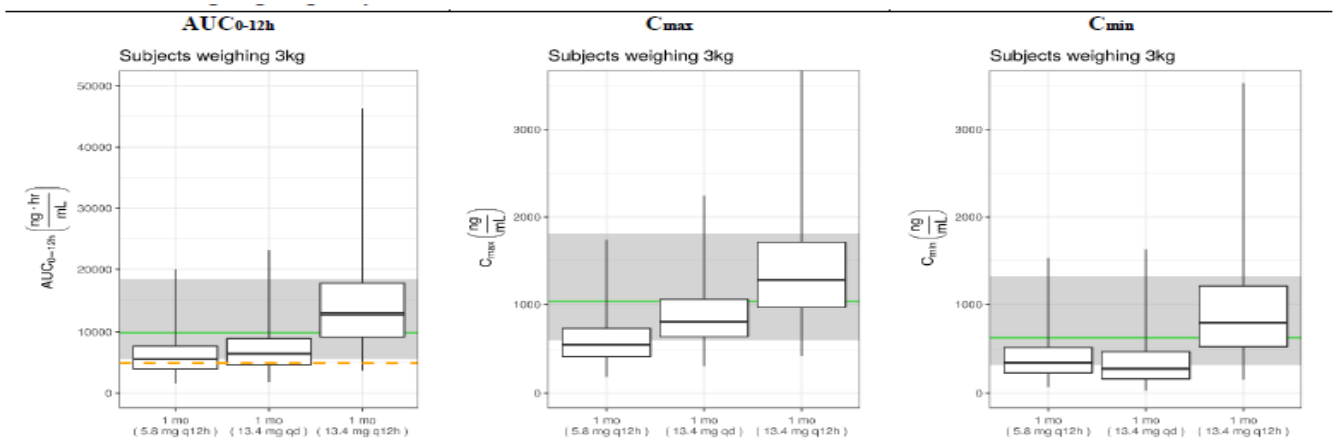
25% in the clinical practice. Therefore, from an efficacy perspective, no relevant difference between 5.8 q12h and 13.4 mg qd are expected based on the similar predicted AUC and Cmin levels and, from a safety perspective, the selection of 13.4 mg qd is unlikely to result in clinically relevant concerns. Therefore, the selection of 13.4 mg qd regimen for 1-month to less than 2 months paediatric patients is accepted.

Figure 9. Simulated Exposures for the Alternative Dosing Regimens for Children 1 to <2 Months of Age – Children of Representative Weights for Age



Source: Data on file
IQR: interquartile range; IVA: ivacaftor; mo: months; q12h: every 12 hours; qd: once daily
Notes: Boxplots are simulated subjects 1 to <2 months of age, where black lines in the center of the box are medians, boxes are the IQR, and whiskers are the 0.5th to 99.5th percentile region. Circles represent the individual predicted exposures of subjects 1 to <2 months of age enrolled in Study 124 Cohort 8 (blue) receiving the proposed dosing regimen. Gray area represents the adult 5th to 95th percentile region of IVA $AUC_{0\text{-}12h}$ exposures with the median exposure shown as a green line. Dashed orange line is the median exposure based on simulated exposures from adult subjects receiving IVA 75 mg q12h. All approved IVA granule strengths are prepared from granules with a target IVA content of 1.92 mg per granule; the 5.8-mg packet strength contains 3 granules.

Figure 10. Simulated Exposures for the Alternative Dosing Regimens for Children 1 to <2 Months of Age – Children Weighing 3 kg Only



Source: Data on file
IQR: interquartile range; IVA: ivacaftor; mo: months; q12h: every 12 hours; qd: once daily
Notes: Boxplots are simulated subjects 1 to <2 months of age, where black lines in the center of the box are medians, boxes are the IQR, and whiskers are the 0.5th to 99.5th percentile region. Gray area represents the adult 5th to 95th percentile region of IVA $AUC_{0\text{-}12h}$ exposures with the median exposure shown as a green line. Dashed orange line is the median exposure based on simulated exposures from adult subjects receiving IVA 75 mg q12h. All approved IVA granule strengths are prepared from granules with a target IVA content of 1.92 mg per granule; the 5.8-mg packet strength contains 3 granules.

In conclusion, based on the recalibrated PBPK model-based simulations, the proposed dosing regimens are as follows:

- Ivacaftor 13.4 mg once daily (qd) for patients 1 month to <2 months of age and weighing ≥3 kg
- Ivacaftor 13.4 mg q12h for patients 2 to <4 months of age and weighing ≥3 kg

Children under 1 month of age (excluded from the indication)

No children under 1 month of age were enrolled in study 124. However, pancreatic exocrine insufficiency is established very soon after birth. Upon CHMP request, the MAH provided an estimation of the number of infants under 1 month of age who would qualify for treatment with ivacaftor and concluded that the unmet need with respect to population size was very low as the estimated number was 2 to 4 infants of the 20 total infants born each year in Europe. In addition, the MAH argued that the definitive diagnosis and genotyping to support intervention with ivacaftor through newborn screening programs typically takes approximately 4 weeks.

The argument, however, which seems more definitive is the difficulty to predict the systemic exposure due to immature CYP metabolism, particularly in the absence of any experimental PK data in children less than 1 month of age. In spite of that, model-based simulations for AUC0-12h assuming different scenarios in terms of clearance were provided. Deterministic simulations from the final popPK and physiologically-based PK (PBPK) models were provided for different dosing regimens for infants <1 month of age which predicted relevant differences in the exposure (AUC0-12h and Cmin) of these children between both models. Although model predictions should be considered with caution as there is not enough evidence to definitively support one modelling strategy over the other, it could be more conservative to rely on model predictions from the PBPK model than on the popPK model for this particular age range. According to the results provided for exposure every 12 hours for 1 month, a greater probability of reaching concentrations similar to those observed in adult patients is observed with the 5.8 mg every other day (qod) for 0 to <2 weeks followed by 5.8 mg q12h from 2 weeks to less than 4 weeks for both AUC0-12h and Cmin. However, based on the uncertainties previously mentioned in older paediatric patients (1-6 months), the proposal of the MAH not to extend the indication to children under 1 month of age was accepted.

Children aged 4 to less than 12 months weighing ≥ 3 kg to less than 7 kg (not concerned by the present procedure)

No dosing recommendations are specified in Table 1, section 4.2 of the SmPC of Kalydeco granules for children aged 4 months to less than 6 months or for children aged 6 months to less than 12 months weighing less than 5 kg. To address this issue, popPK model-based simulations of AUC0-12h for children in this age range weighing 3-<5, and 5-<7 kg receiving 13.4, 25 and 50 mg q12h dosing regimens were provided which supported a dosing regimen of 25 mg q12h for children weighing at least 3 kg. However, it seems prudent to keep the weight limit at 5 kg in view of the request to establish the paediatric dosing regimens of very young children with a more conservative target, and also considering that the expected number of children ≥6 months of age weighing less than 5 kg is very limited. With respect to the group of 4 months to less than 6 months, the simulations based on the recalibrated PBPK model (Figure 8) show that the optimal exposure in paediatric patients from 4 to less than 6 months weighing 3 to 5 kg is achieved with 13.4 mg q12h and therefore it seems also prudent to keep the lower body weight at 5 kg. In addition, the WHO weight-for-age growth charts show that 3 kg is well below the third percentile for the age of 4 months. Therefore, it is proposed that for children aged 4 months to less than 6 months and for those between 6 and less than 12 months, the lower age limit remains at 5 kg as currently authorised.

Pharmacokinetics in special populations

Of the covariates tested in the popPK study only body weight (with fixed allometric relationships) and age as a marker of maturation were considered as covariates for the analysis.

The evaluation of the PK in this age group suggests that there is an age-dependent effect on CL/F that is consistent with the potential contribution of CYP3A4 maturation in this age range. The impact of hepatic impairment in combination with the maturation of the CYP3A4 enzymes involved in ivacaftor metabolism for this age group is uncertain. Therefore, treatment with ivacaftor is not recommended in patients 1 to <4 months of age with any level of hepatic impairment.

Pharmacokinetics interactions studies

Patients 1 to <4 months of age may receive therapeutic agents that include strong and moderate CYP3A inhibitors during the course of their treatment with ivacaftor. The evaluation of PK data in this age group suggests that there is an age-dependent effect on CL/F that is consistent with the potential contribution of CYP3A4 maturation. The impact of CYP3A inhibitors in combination with the maturation of CYP3A4 enzymes involved in ivacaftor metabolism for this age group is uncertain. Therefore, treatment with ivacaftor is not recommended in patients 1 to <4 months of age who are taking concomitant strong or moderate CYP3A inhibitors. Based on the PBPK model this recommendation was extended to all children under 6 months of age.

2.6.2.2. Pharmacodynamics

No new data have been provided regarding the mechanism of action and primary/secondary pharmacology. This is considered acceptable. 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.

2.6.3. Discussion on clinical pharmacology

The current submission proposes to extend the approved indication of ivacaftor as monotherapy in the treatment of CF to include paediatric patients from 1 to less than 4 months of age and weighing ≥3 kg. A new strength of 13.4 mg granules is proposed for authorisation (line extension) to support the proposed dosing recommendations.

Two studies were performed to investigate the relative bioavailability and the influence of food on ivacaftor granules versus the tablet formulation, i.e., study 012 and study 015 respectively that have been assessed in prior procedures. The comparative bioavailability as well as the food effect have been investigated with the 150 mg dose (2x75 mg). The conclusions regarding bioavailability and food effect can be extrapolated to the 13.4 mg strength based on the fact that the granules are identical and the difference relies on the number of granules in the sachet. 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 extension of the indication is based on the fourth interim analysis (IA) of Study VX-15-770-124 (Study 124) reporting data from subjects 1 to <4 months of age who completed Part A/Part B Cohort 8 (through 24 weeks of ivacaftor treatment). In the original study protocol, Cohort 7 was to enrol children from birth to less than 6 months. However, in part A (Cohort 3), a 3-month-old subject who received 25 mg q12h ivacaftor had an AUC which fell above the 95th percentile of the adult population. To ensure ivacaftor exposure did not exceed the targeted adult range (95th), Part B/Cohort 7 was limited to subjects 4 to <6 months of age,

weighing ≥ 5 kg (refer to procedure EMEA/H/002494/II/0086, Extension of indication to include treatment of infants aged at least 4 months, toddlers and children weighing 5 kg to less than 25 kg). Study 124 design was therefore amended and Cohort 8 (the cohort concerned by the present procedure) included only children under 4 months of age. This cohort is now quoted as Part A/B Cohort 8 because Parts A and B were carried out sequentially (i.e., without a gap between study parts) in each individual subject, rather than performing a cohort analysis of Part A before starting Part B.

This is the reason why children enrolled in Cohort 8 were given an initial low dose of ivacaftor which was adjusted individually at Day 15 based on Day 4 PK assessments. In spite of that, two fixed doses regimens were initially proposed, i.e.,

- 13.4 mg BID for children aged 1 to less than 3 months weighing at least 3 kg
- 25 mg BID for children aged ≥ 3 months to less than 4 months weighing at least 3 kg

which were based on simulations from the popPK model (as described in Report R269). A previously developed population PK model in subjects 6 to <12 months of age including an empirical ontogeny function on CL together with standard allometric exponents on disposition parameters has been used to characterize the ivacaftor time-course in subjects 1 to <4 months of age from Cohort 8 in study 124. This modelling strategy is overall endorsed. In addition, a PBPK model was also developed that could be used for simulations to assist in dose selection for paediatric subjects less than 4 months of age.

The pharmacokinetics of ivacaftor metabolites M1 and M6 was part of the primary objective of Study 124. In a prior procedure (EMEA/H/C/002494/X/0034/G, extension of the indication to children aged 2 to less than 6 years) the attempts to develop an integrated population PK model for metabolites M1 and M6 were not successful and subsequent models described only ivacaftor disposition. This is also the case of the model described in Report R269 (Population PK model in subjects 1 to less than 4 months).

Population PK model evaluation based on stratified VPC suggested a moderate prediction capacity in the target population (1-<4 m) although very scarce experimental evidence was available (2 bins were considered), which may explain the width of the prediction intervals for each percentile. Once the population PK model had been updated, dose selection was based on simulated ivacaftor (AUC0-12h and Cmin) exposures for different dosing regimens in virtual subjects 1 to <4 months of age with demographics sampled from the WHO growth charts.

Given the scarce experimental data available from children enrolled in Cohort 8, as well as some concerns related to the available data in children under 6 months of age, the MAH was requested to compare the predicted exposure with the PBPK model vs the population PK model using the proposed dosing regimens. Stochastic simulations were conducted using both approaches to compare the predicted exposures. The PBPK model overpredicts PK exposures for children 1 to <6 months of age and therefore provides a conservative reference range for this age group. The popPK model incorporates empirical age and weight relationships on CL/F to describe the PK and even though it appears to adequately capture the observed PK data and variability, the limited experimental data and the lack of mechanistic description of maturation and allometric relationships may result in inaccurate predictions for children with demographics not studied, such as infants with very low weights. The correlation between the observed and the predicted ivacaftor plasma concentrations of children in Cohort 8 dosed with 22.8 mg or with 25 mg q12h showed that a systematic under-prediction of concentrations levels above 600 ng/mL is detected. Overall, the results from the popPK model were considered less informative for children below 6 months of age.

As a consequence, the CHMP asked the MAH to establish the dosage regimens in children between 1 and 4 months targeting a more conservative adult reference range thereby reducing the possibility of placing these

children at exposure levels higher than those observed in adults dosed with 150 mg q12h. The MAH has conducted the requested model-based simulations using a recalibrated version of the PBPK model, which optimised the apparent clearance normalised by body weight for patients below 12 months of age. The updated CL/F/weight better characterises individual CL/F across the different age cohorts. Overall, the recalibrated PBPK model is considered appropriate for dose selection in paediatric patients below 6 months of age.

The recalibrated PBPK model-based simulations demonstrated that a large proportion of paediatric patients from 2 to <4 months of age and weighing 3 kg receiving 13.4 mg q12h would be within the conservative adult range selected (which ranged from the median exposure after 75 mg to the median exposure after 150 mg twice daily). For 1-month and 3 kg paediatric patients, model-based simulations were conducted with 5.8 mg q12h and 13.4 mg qd. Optimal exposure levels were predicted with the 5.8 mg q12h, since a larger proportion of paediatric patients aged 1 month and weighing 3 kg would be within the conservative adult range. Alternatively, the 13.4 mg qd provides very similar AUC and Cmin levels, but slightly higher Cmax levels compared to the 5.8 mg q12h. However, the predicted proportion of paediatric patients outside the conservative adult range is not considered relevant. Furthermore, lower exposure is expected in 1-month paediatric patients as body weight increases. Therefore, the selection of 13.4 mg qd regimen for 1-month paediatric patients is accepted.

In conclusion, the currently proposed dosing recommendations are as follows:

- Ivacaftor 13.4 mg once daily (qd) for children 1 to less than 2 months of age and weighing ≥3 kg
- Ivacaftor 13.4 mg twice daily (q12h) for children 2 to less than 4 months of age and weighing ≥3 kg

In the group of children from 4 months to less than 12 months of age, dosing recommendations were absent for those weighing ≥ 3 kg to less than 5 kg. The MAH proposal was to dose these children also with 25 mg q12h based on popPK simulations. Considering the need to target a more conservative adult range of systemic exposure for the paediatric dosing regimens for young children, it was decided to keep the lower limit of body weight for the age groups of 4 months to less than 6 months and of 6 months to less than 12 months at 5 kg as currently authorised (instead of lowering it at 3 kg), keeping the 25 mg q12h dosing recommendations for which there are post-marketing experience.

No dose recommendations are proposed for children under 1 month of age given the uncertainty about model predictions in the presence of rapid changes in maturation and in the absence of any PK data as children under 1 month of age were not enrolled in the study. The number of children under 1 month of age who would benefit from the treatment with ivacaftor is, according to the estimation provided by the MAH, very limited. This was accepted by the CHMP.

A recommendation was made by the MAH not to use ivacaftor for children aged from 1 month to less than 4 months with any degree of hepatic impairment as well as for children who receive concomitant treatment with moderate or strong CYP3A inhibitors. In both cases, the rationale is the unpredictability in terms of systemic exposure of any dosing recommendations given the changes in CYP3A maturation on a background of liver disease or drug-drug interactions. This was acknowledged by the CHMP and based on the PBPK model the recommendation to not use ivacaftor was extended to all children under 6 months of age. This is now reflected in sections 4.2, 4.4 and 4.5 of the SmPC of Kalydeco granules.

2.6.4. Conclusions on clinical pharmacology

The pharmacokinetics of ivacaftor in paediatric patients from 1 to <4 months of age have been characterised using a previous population PK model developed in older paediatric and adult patients that has been updated

to account for the allometric and maturation effects observed in CL. A physiologically based pharmacokinetic (PBPK) model has also been developed to support the dose selection strategy.

While the popPK appeared to adequately describe the observed PK data and the variability, the limited experimental data in children enrolled in Cohort 8 as well as some of the observed data in this young age group, triggered a request to the MAH to establish the dosage regimens in children between 1 and 4 months with a more conservative adult reference range of systemic exposure. In response, model-based simulations using a recalibrated version of the PBPK model were performed, which optimised the apparent clearance normalised by body weight for patients below 12 months of age.

Based on the above, the currently proposed dosing recommendations are as follows:

- Ivacaftor 13.4 mg once daily for children 1 to less than 2 months of age and weighing ≥3 kg
- Ivacaftor 13.4 mg twice daily for children 2 to less than 4 months of age and weighing ≥3 kg

2.6.5. Clinical efficacy

2.6.5.1. Dose response study

No dedicated dose response study has been performed but a model-based approach for establishing the optimal dosing regimen of ivacaftor in subjects 1 to <4 months of age for the treatment of cystic fibrosis was developed. (see section 2.6.2 Clinical pharmacology).

2.6.5.2. Main study

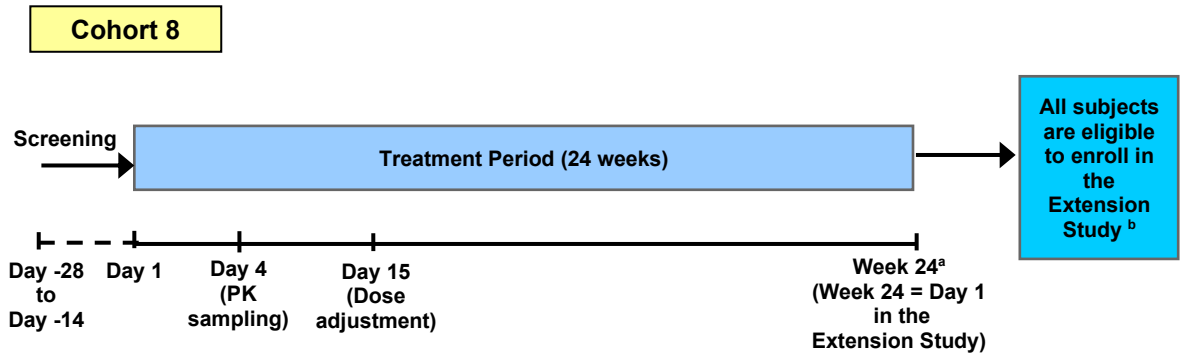
***VX15-770-124:* A Phase 3, 2-Part, Open-label Study Evaluating the Safety, Pharmacokinetics, and Pharmacodynamics of Ivacaftor in Subjects With Cystic Fibrosis Who Are Less Than 24 Months of Age at Treatment Initiation and Have an Ivacaftor-responsive CFTR Mutation**

Methods

The present extension of the indication is based on the fourth interim analysis (IA) of Study VX-15-770-124 (study 124) reporting data from subjects 1 to <4 months of age who completed Part A/Part B Cohort 8 (through 24 weeks of ivacaftor treatment). Part A/B Cohort 8 was completed; all data collected, as of the data cut date of 25 July 2022, were included in this IA report (Version 1.0 16 September 2022). Upon request, the final clinical study report Version 1.0, Date 10 March 2023 was also provided.

Study 124 is a Phase 3, 2-part, open-label study in subjects <24 months of age. For Cohort 8 (Part A/B), subjects aged 1 to less than 4 months at Day 1 (ivacaftor treatment initiation) and who had a *CFTR* gating mutation on at least 1 allele were eligible to enrol. Subjects with an *R117H* mutation were eligible to enrol in regions where ivacaftor was granted marketing authorization for use in subjects with this mutation. Subjects eligible for Part A/B Cohort 8 may also have other ivacaftor-responsive mutations.

Figure 11. Study 124 Cohort 8 Design



OE: ophthalmologic examination; PK: pharmacokinetics

[a] A Follow-up OE occurred approximately 12 weeks after last dose of study drug unless the subject enrolled in the Extension Study.

[b] All subjects who completed 24 weeks of study drug treatment were eligible to enroll in the open-label treatment arm of the Extension Study. All other subjects were eligible to enroll in the observational arm of the Extension Study. Subjects who prematurely discontinued were required to have a Follow-up OE approximately 12 weeks after last dose of study drug.

- **Study Participants**

A total of 7 infants aged 1 month to less than 4 months weighing ⩾3 kg were enrolled in Cohort 8 at 4 sites in the US and Ireland.

Children were required to have a confirmed diagnosis of cystic fibrosis defined as a sweat chloride value ⩾60 mmol/L by quantitative pilocarpine iontophoresis OR 2 CF-causing mutations. They 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. Those with an R117H-CFTR mutation were eligible in regions where ivacaftor was approved for use in this mutation and they should have the 5T variant or a sweat chloride value ⩾60 mmol/L. Children with other ivacaftor-responsive mutations were also eligible for Part A/B Cohort 8.

Children with an acute upper or lower respiratory infection, or pulmonary exacerbation, or with recent changes in therapy (including antibiotics) for pulmonary disease were excluded. 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) was also an exclusion criterion.

- **Treatments**

On Days 1 through the morning dose of Day 15, subjects in Part A/B Cohort 8 received an initial low dose of IVA (5.7 or 11.4 mg, q12h) based on their age and weight at Day 1, see Table 1.

At Day 4, each subject provided PK samples to assess exposure and, if appropriate, the dose was adjusted at Day 15 (evening) to 5.7, 11.4, 17.1, 22.8, or 25 mg q12h to better match the adult median exposure. Subjects remained on this dose until the study visit after reaching 4 months of age and 5 kg, at which point subjects received the approved dose of 25 mg q12h.

Each dose of granules was mixed with approximately 1 teaspoon (5 mL) of appropriate liquid or soft food and administered orally q12h with an age-appropriate fat-containing meal or snack.

- **Objectives**

  Primary objectives were to evaluate the safety of ivacaftor and the pharmacokinetics of ivacaftor and metabolites M1 and M6. Secondary objective was to evaluate the pharmacodynamics (PD) of ivacaftor. Tertiary objectives included efficacy endpoints.

- **Outcomes/endpoints**

  According to the above objectives, safety (trough 24 weeks of treatment) and PK assessments were considered primary endpoints.

  Sweat chloride test (measured as absolute change from baseline) was considered as a secondary endpoint, while other variables were considered exploratory. These include (but are not limited to) growth parameters and markers of pancreatic function and inflammation such as faecal elastase-1 and immunoreactive trypsin and/or trypsinogen.

- **Sample size**

  Sample size of study 124 was based on the availability of the subject population and PK analysis considerations. In this interim analysis, the Full Analysis Set (FAS) included all subjects who enrolled in Part B or Part A/B Cohort 8 and received at least 1 dose of IVA. The Safety Set included all subjects who enrolled in Part A, combined Part B and Part A/B Cohort 8 and received at least 1 dose of IVA.

- **Randomisation and Blinding (masking)**

  Not applicable, as this is a single-arm study.

- **Statistical methods**

  Descriptive analysis of safety was performed; raw values, changes from baseline, threshold analyses, and clinical abnormalities were summarized, where applicable.

  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 R269).

  Sweat chloride results (including changes from baseline) were analysed as a continuous variable using descriptive summary statistics and presented by visit.

  Results

- **Participant flow**

  A total of 7 subjects were enrolled in Part A/B cohort 8. Six subjects (85.7%) completed the 24 weeks of treatment; one subject (14.3%) discontinued treatment with ivacaftor prematurely due to an adverse event. Four subjects (57.1%) rolled over into the extension Study 126.

  There was 1 protocol deviation that was identified as important protocol deviation (IPD). One child had an IPD of a dose administration error in which two 25-mg sachets were administered instead of the expected one 25-mg sachet for the evening dose. There were no identified safety concerns related to this IPD.

- **Recruitment**

  Study Initiation: 27 January 2021 (date first eligible subject in Cohort 8 signed the informed consent form for Part A/B)

End of Interim Analysis: 28 June 2022 (date last subject in Cohort 8 completed the last study visit in Part A/B)

- **Conduct of the study**

  The original protocol was amended 4 times. The current protocol is version 4.0 (01 April 2021). The date of the report of the interim analysis 4 is 16 September 2022.

- **Baseline data**

  In Part A/B Cohort 8, seven infants were enrolled (4 females and 3 males). At Day 1, three subjects were 1 to <2 months of age, two subjects were 2 to <3 months of age, and two subjects were 3 to <4 months of age. The mean age (SD) at baseline was 1.9 months (0.90). The mean age at CF diagnosis was 0.4 months and the mean gestational age at delivery was 38.1 weeks. The 3 subjects (one male and 2 females) in the 5.7 mg group were 1 month of age and weighed 3.6, 4.2, and 4.3 kg. In the 11.4 mg group, two subjects (one male and one female) were 2 months of age and weighed 6.1 kg and 5.0 kg respectively; and two subjects (one male and one female) were 3 months of age and weighed 6 kg and 5.3 kg respectively. Median (min, max) weight-for-age, length-for-age, and weight-for length z-scores were -1.32 (-1.93, 0.70), -1.06 (-1.57, 2.15), and -0.92 (-1.70, 0.41). All 7 subjects were White and of non-Hispanic or Latino ethnicity.

  Four subjects had the *G551D* mutation, and the three remaining subjects had mutations responsive to ivacaftor (*R117H*, *R117C*, and *S945L*). The most prevalent genotype was *G551D/F508del* (2 out of the of 7 subjects). Mean (SD) sweat chloride (n=7) at baseline was 73.8 mmol/L (19.1).

  Some selected baseline demographic and disease characteristics are summarised in the following two tables (Table 4 and Table 5).

Table 4. Subject Demographics, Safety Set, Part A/B, Cohort 8, 1 to <4 Months

Characteristic	Cohort 8[a] IVA 5.7 or 11.4 mg N = 7
Sex, n (%)	
Male	3 (42.9)
Female	4 (57.1)
Age at Screening (Months)	
n	7
Mean (SD)	1.3 (0.49)
Median	1.0
Min, max	1, 2
Age at baseline/Day 1 (Months)	
n	7
Mean (SD)	1.9 (0.90)
Median	2.0
Min, max	1, 3

Characteristic	Cohort 8[a] IVA 5.7 or 11.4 mg N = 7
Ethnicity, n (%)	
Not Hispanic or Latino	7 (100.0)
Race, n (%)	
White	7 (100.0)
Geographical region, n (%)	
North America	3 (42.9)
Europe	4 (57.1)
Genotype, n (%)	
G551D/F508del	2 (28.6)
R117H/F508del	1 (14.3)
G551D/R1066H[b]	1 (14.3)
G551D/R117H	1 (14.3)
S945L/N1303K	1 (14.3)
R117C/W1282X	1 (14.3)

Source: Table 14.1.2.ab8
IVA: ivacaftor; n: size of subsample; N: total sample size; PI: pancreatic insufficient; q12h: every 12 hours; RF: residual function
Notes: Percentages were calculated relative to the number of subjects in the Safety Set. Mutation type by pancreatic insufficiency for IVA-responsive mutations[1]: Severe: *G551D* (90% PI); RF–intermediate: *R1066H* and *S945L* (30%, 40% PI); RF–mild: *R117H* and *R117C* (23, 24% PI)
[a] Subjects received an initial low dose of IVA (5.7 or 11.4 mg, q12h) based on their age and weight at Day 1. At Day 4, each subject's exposure was evaluated, and if appropriate, the dose was adjusted at Day 15 to 5.7, 11.4, 17.1, 22.8, or 25 mg q12h to better match the adult median exposure. Subjects received this dose until the study visit after reaching 4 months of age and 5 kg, at which point the approved age- and weight-based dosing was initiated (Section 9.4.1). Subjects shown in dose group according to their Day 1 dose.
[b] *R1066H* corresponds to *3197G>A*.

Table 5. Baseline Characteristics, Safety Set, Part A/B, Cohort 8, 1 to <4 Months

Characteristic	Cohort 8[a] IVA 5.7 or 11.4 mg N = 7
Weight (kg)	
n	7
Mean (SD)	4.9 (0.9)
Median	5.0
Min, max	3.6, 6.1
Length (cm)	
n	7
Mean (SD)	57.8 (4.1)
Median	56.0
Min, max	52.5, 63.4
BMI (kg/m^2)	
n	7
Mean (SD)	14.62 (1.04)
Median	14.93
Min, max	13.06, 15.94

Source: Table 14.1.3.1.ab8
BMI: body mass index; IVA: ivacaftor; n: size of subsample; N: total sample size; q12h: every 12 hours; 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. Subjects shown in dose group according to their Day 1 dose.
[a] Subjects received an initial low dose of IVA (5.7 or 11.4 mg, q12h) based on their age and weight at Day 1. At Day 4, each subject's exposure was evaluated, and if appropriate, the dose was adjusted at Day 15 to 5.7, 11.4, 17.1, 22.8, or 25 mg q12h to better match the adult median exposure. Subjects received this dose until the study visit after reaching 4 months of age and 5 kg, at which point the approved age- and weight-based dosing was initiated (Section 9.4.1).

Medical history

The only medical history condition that occurred in at least 2 subjects was pancreatic failure (3 [42.9%] subjects).

Prior and concomitant medication

The most commonly reported concomitant medications were vitamins (100.0%), sodium chloride (71.4%), flucloxacillin (57.1%), pancreatin (42.9%), and salbutamol (28.6%).

- **Numbers analysed**

A total of 7 subjects were enrolled and included in the Safety Set. As previously mentioned, a child discontinued study drug treatment at Week 9, but did not discontinue the study until Week 24. Data for this subject were included in the efficacy analyses.

- **Outcomes and estimation**

Sweat chloride

The absolute changes from baseline were calculated at each time point for those subjects in Part A/B Cohort 8 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, a historical sweat chloride value was used for baseline. Three subjects did not have a Day 15 sweat chloride measurement (sample volumes were

insufficient). Six subjects did not have sweat chloride measurements at Week 24: 1 subject discontinued the study at Week 24, and sample volumes were insufficient for 5 subjects.

Mean absolute changes from baseline in sweat chloride concentration are summarized in Table 6.

Table 6. Absolute Change from Baseline in Sweat Chloride (mmol/L) at each visit, FAS, Part A/ B Cohort 8, 1 to <4 months

		Cohort 8 IVA 5.7 or 11.4 mg[a] N = 7	
Visit	Statistic	Sweat Chloride (mmol/L)	Absolute Change From Baseline at Visit (mmol/L)
Baseline	n	7	NA
	Mean (SD)	73.8 (19.1)	NA
	Median	69.0	NA
	Min, max	49.0, 103.0	NA
Day 15	n	4	4
	Mean (SD)	29.8 (8.7)	-50.6 (24.2)
	Median	32.8	-58.0
	Min, max	17.0, 36.5	-71.0, -15.5
Week 4	n	5	5
	Mean (SD)	30.3 (6.2)	-46.0 (24.8)
	Median	32.0	-55.0
	Min, max	19.5, 35.0	-72.0, -14.0
Week 8	n	5	5
	Mean (SD)	33.8 (11.8)	-42.5 (22.9)
	Median	39.0	-56.0
	Min, max	14.5, 44.0	-60.0, -8.5
Week 12[b]	n	5	5
	Mean (SD)	43.4 (17.9)	-32.9 (33.8)
	Median	43.0	-56.0
	Min, max	18.0, 67.5	-60.0, 7.5
Week 18[b]	n	4	4
	Mean (SD)	35.4 (21.6)	-47.8 (37.0)
	Median	29.0	-60.8
	Min, max	17.0, 66.5	-76.0, 6.5
Week 24	n	1	1
	Mean (SD)	51.5 (--)	2.5 (--)
	Median	51.5	2.5
	Min, max	51.5, 51.5	2.5, 2.5

Source: Table 14.2.1.1.ab8

FAS: Full Analysis Set; IVA: ivacaftor; n: size of subsample; N: total sample size; NA: not applicable; q12h: every 12 hours

Notes: Baseline was defined as the most recent measurement before the first dose of study drug in Part A/B Cohort 8. Subjects shown in dose group according to their Day 1 dose in Part A/B Cohort 8.

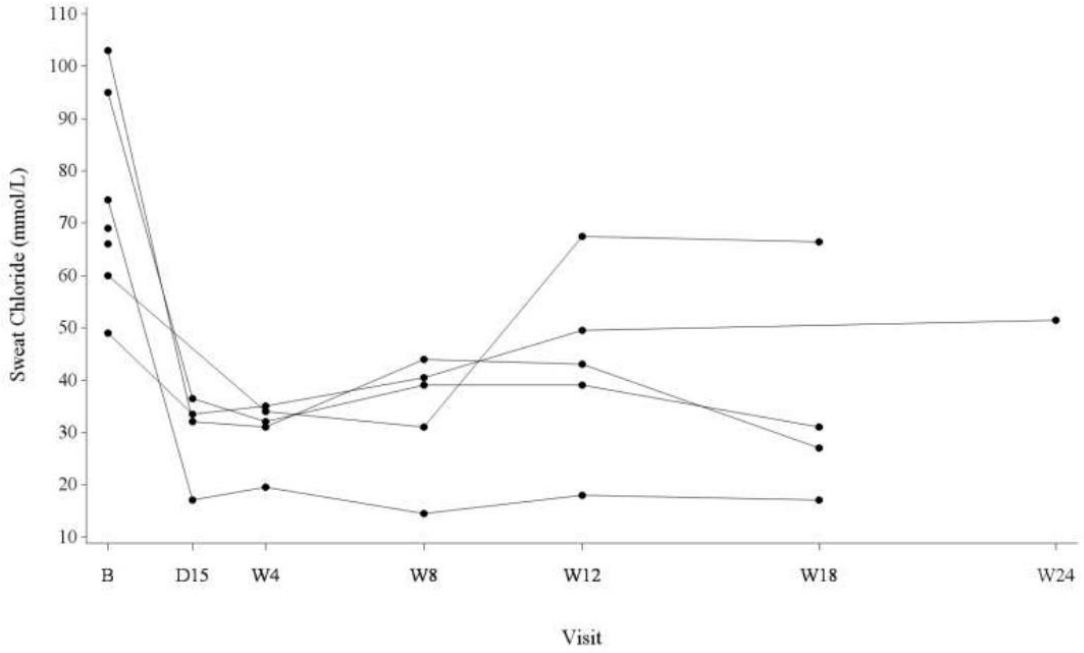
[a] Subjects received an initial low dose of IVA (5.7 or 11.4 mg, q12h) based on their age and weight at Day 1. At Day 4, each subject's exposure was evaluated, and if appropriate, the dose was adjusted at Day 15 to 5.7, 11.4, 17.1, 22.8, or 25 mg q12h to better match the adult median exposure. Subjects received this dose until the study visit after reaching 4 months of age and 5 kg, at which point the approved age- and weight-based dosing was initiated (Section 9.4.1).

[b] One subject discontinued study drug treatment at Week 9, but did not discontinue the study until Week 24. Data for this subject were included in the efficacy analyses (Listing 16.2.1.2.ab8).

Due to the large number of missing samples at Week 24, an ad hoc analysis of the average change from baseline in sweat chloride through Week 24 was performed for all post-baseline visits; the mean (SD) average change from baseline through Week 24 was -40.3 (29.2) mmol/L (n=5).

To evaluate individual subject response to IVA, a spaghetti plot showing sweat chloride values at each visit is presented in the Figure 12 below.

Figure 12. Spaghetti Plot of Sweat Chloride over Time, Full Analysis Set, Part A/B, Cohort 8, 1 to <4 Months



Absolute change from baseline in Sweat Chloride from Cohorts 5 through 8 including subjects 1 to <24 months is presented in the table below:

Table 7. Summary of Average Sweat Chloride and Change from Baseline with CI at Week 24 for Subjects Aged 1 to Less Than 24 Months Full Analysis Set, Parts B & A/B, 1 to < 24 Months

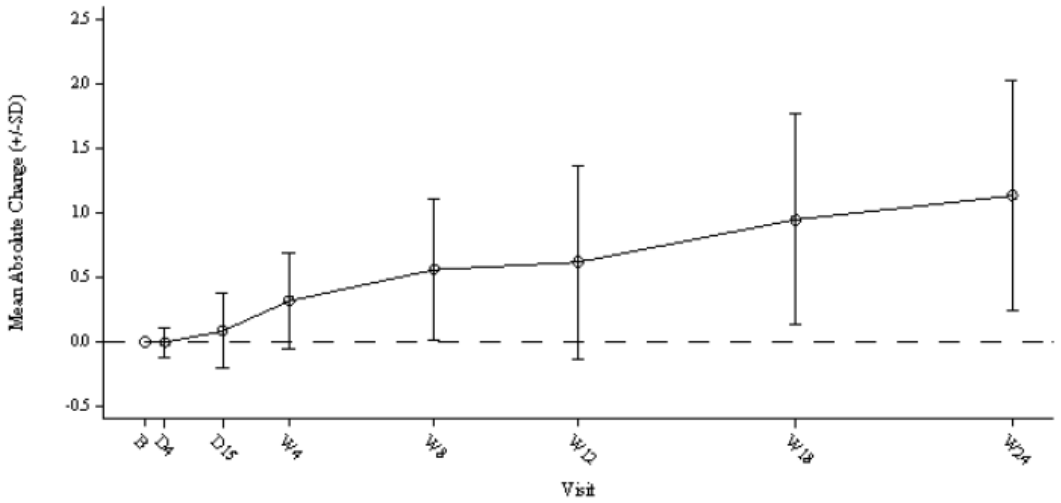
Visit	Statistic	Total N = 43
Baseline	n	41
	Mean (SD)	96.9 (17.1)
	SE	2.7
	Median	102.0
	Min, Max	49.0, 120.5
Week 24	n	24
	Mean (SD)	37.3 (13.3)
	SE	2.7
	Median	36.0
	Min, Max	14.5, 80.5
Change from Baseline at Week 24	n	23
	Mean (SD)	-62.0 (22.2)
	SE	4.6
	Median	-64.0
	Min, Max	-97.5, 2.5
	95% CI	(-71.6, -52.4)

Growth parameters

For each parameter evaluated, mean values were normal at baseline, but below the median of the reference population (WHO Growth Standards for Infants and Children 0 to 2 Years of Age).

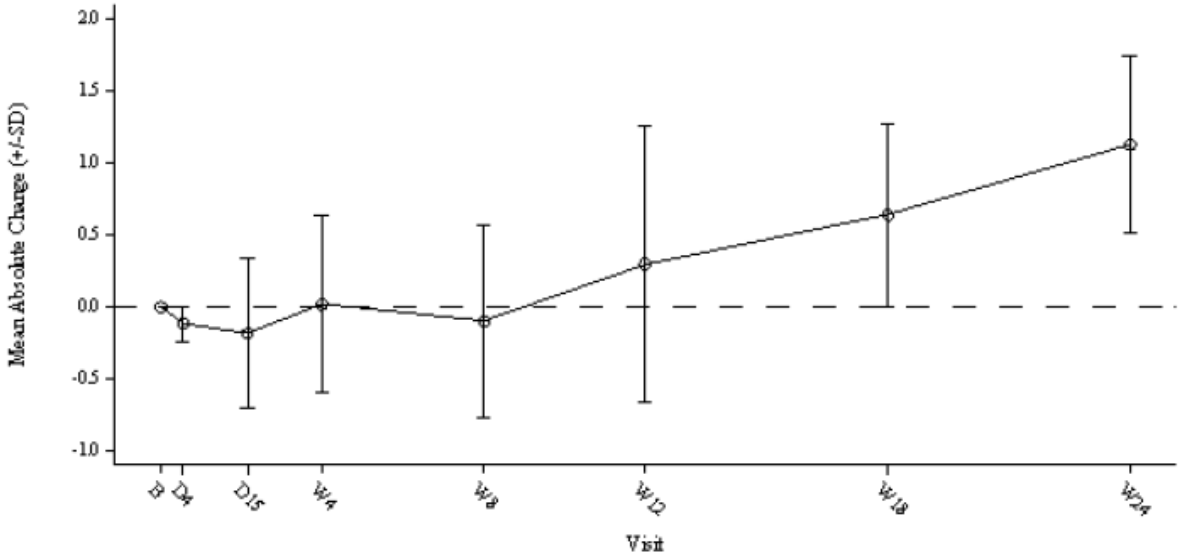
The median (min, max) absolute change from baseline (n=7) at week 24 in the weight-for-age z-score was 1.01 (0.14, 2.66) (n=6). These figures for length-for-age z-score and weight-for length z-score were as follows: 1.15 (0.18, 2.06) and 0.48 (-0.61, 2.18) respectively. The mean absolute changes from baseline in the z-scores of these growth parameters are shown in the following three figures (Figure 13, Figure 14, Figure 15).

Figure 13. Mean Absolute Change From Baseline in Weight-for-age Z-scores, FAS, Part A/B, Cohort 8, 1 to <4 Months



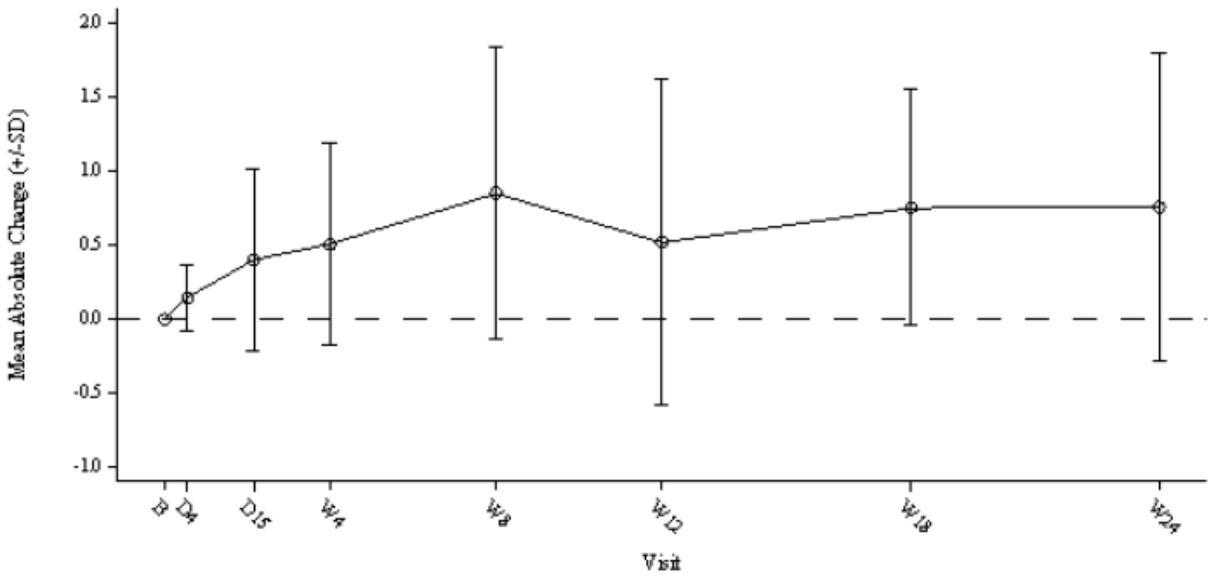
Source: Figure 14.2.2.1.4.ab8
B: baseline; D: day; FAS: Full Analysis Set; IVA: ivacaftor; W: week
Note: One subject discontinued study drug treatment at Week 9, but did not discontinue the study until Week 24. Data for this subject were included in the efficacy analyses (Listing 16.2.6.2.ab8).

Figure 14. Mean Absolute Change From Baseline in Length-for-age Z-scores, FAS, Part A/B Cohort 8, 1 to <4 Months



Source: Figure 14.2.2.1.5.ab8
B: baseline; D: day; FAS: Full Analysis Set; IVA: ivacaftor; W: week
Note: One subject discontinued study drug treatment at Week 9, but did not discontinue the study until Week 24. Data for this subject were included in the efficacy analyses (Listing 16.2.6.2.ab8).

Figure 15. Mean Absolute Changes From Baseline in Weight-for-length Z-scores, FAS, Part A/B Cohort 8, 1 to <4 Months



Source: Figure 14.2.2.1.6.ab8
B: baseline; D: day; FAS: Full Analysis Set; IVA: ivacaftor; W: week
Note: One subject discontinued study drug treatment at Week 9, but did not discontinue the study until Week 24. Data for this subject were included in the efficacy analyses (Listing 16.2.6.2.ab8).

Baseline and absolute change from baseline in growth parameters from Cohorts 5 through 8 including subjects 1 to <24 months are presented in the table below:

Table 8. Baseline and absolute change from baseline in Nutritional/Growth parameters at week 24, FAS, Parts B and A/B. cohorts 5 through 8, subjects 1 to <24 months of age

Parameter Statistic	Total N = 43 Baseline	Total N = 43 Absolute Change From Baseline at Week 24
Weight (kg)		
n	43	41
Mean (SD)	8.7 (2.3)	2.0 (1.0)
Median	8.7	1.8
Min, max	3.6, 12.4	0.5, 4.9
Length (cm)		
n	43	40
Mean (SD)	71.5 (8.2)	8.1 (3.3)
Median	73.6	7.4
Min, max	52.5, 84.2	3.0, 16.1
Weight-for-length Z-score		
n	43	40
Mean (SD)	0.07 (1.02)	0.32 (0.99)
Median	0.14	0.32
Min, max	-1.72, 2.16	-2.04, 2.22
Length-for-age Z-score		
n	43	40
Mean (SD)	-0.03 (1.11)	0.44 (0.92)
Median	-0.03	0.52
Min, max	-1.99, 2.79	-1.81, 3.38
Weight-for-age Z-score		
n	43	41
Mean (SD)	0.00 (0.94)	0.45 (0.64)
Median	0.07	0.30
Min, max	-1.93, 1.79	-0.54, 2.66
Weight-for-length (percentile)		
n	43	40
Mean (SD)	52.1 (31.0)	7.7 (30.2)
Median	55.7	7.0
Min, max	4, 98	-69, 67

Source: Table 14.2.2.1.bfinal

FAS: Full Analysis Set; max: maximum value; min: minimum value; n: size of subsample; N: total sample size

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

Markers of pancreatic function and inflammation

Faecal Elastase-1 (FE-1)

The mean absolute changes from baseline in FE-1 are shown in Table 9.

Table 9. Absolute Change From Baseline in Faecal Elastase-1 (µg/g), FAS, Part A/B, Cohort 8, 1 to <4 Months

Visit	Statistic	Cohort 8 IVA 5.7 or 11.4 mg[a] N = 7 FE-1 (µg/g)	Absolute Change From Baseline at Visit (µg/g)
Baseline	n	6	NA
	Mean (SD)	344.8 (197.5)	NA
	Median	424.5	NA
	Min, max	31.0, 500.0	NA
Day 15	n	7	6
	Mean (SD)	420.9 (169.1)	62.8 (93.2)
	Median	500.0	8.0
	Min, max	47.0, 500.0	0.0, 210.0
Week 12[b]	n	7	6
	Mean (SD)	446.7 (120.4)	93.0 (131.2)
	Median	500.0	72.5
	Min, max	176.0, 500.0	-42.0, 304.0
Week 24	n	5	5
	Mean (SD)	417.2 (185.1)	103.4 (131.4)
	Median	500.0	55.0
	Min, max	86.0, 500.0	0.0, 311.0

Source: Table 14.2.2.5.1.ab8

FAS: Full Analysis Set; FE-1: fecal elastase-1; IVA: ivacaftor; n: size of subsample; N: total sample size; NA: not applicable; q12h: every 12 hours

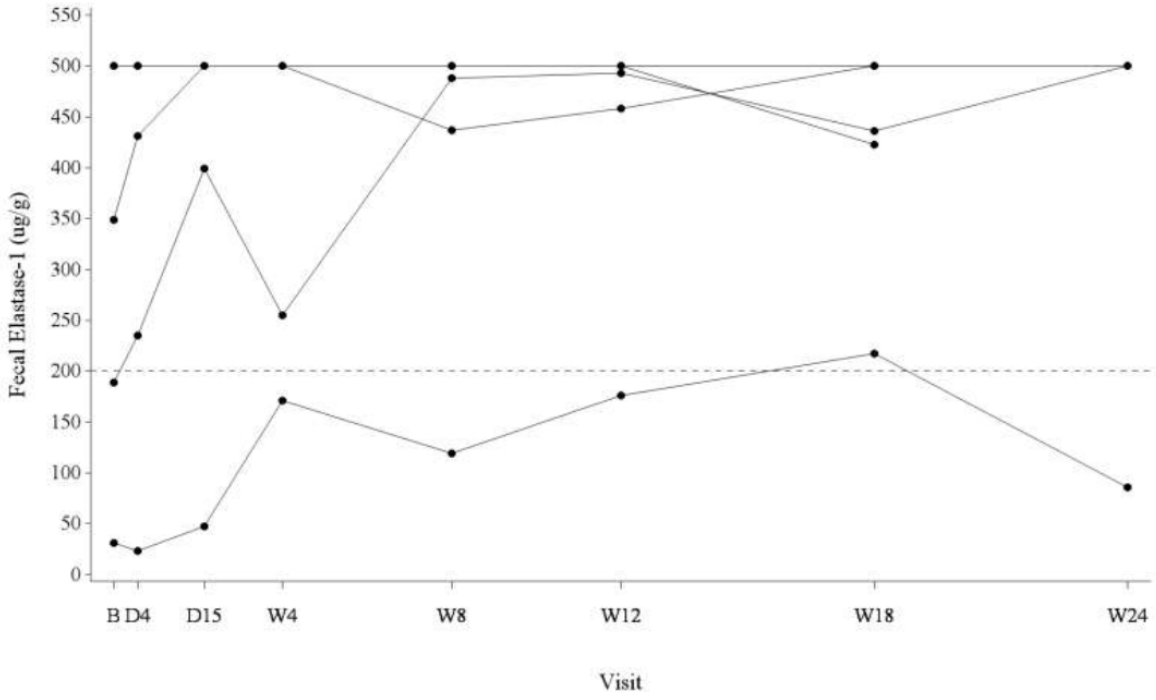
Notes: Baseline was defined as the most recent measurement before the first dose of study drug in Part A/B Cohort 8. Reported values of <15 µg/g were replaced by 7.5 µg/g. Reported values of >500 µg/g were replaced by 500 µg/g. Subjects shown in dose group according to their Day 1 dose in Part A/B Cohort 8.

[a] Subjects received an initial low dose of IVA (5.7 or 11.4 mg, q12h) based on their age and weight at Day 1. At Day 4, each subject's exposure was evaluated, and if appropriate, the dose was adjusted at Day 15 to 5.7, 11.4, 17.1, 22.8, or 25 mg q12h to better match the adult median exposure. Subjects received this dose until the study visit after reaching 4 months of age and 5 kg, at which point the approved age- and weight-based dosing was initiated (Section 9.4.1).

[b] One subject discontinued study drug treatment at Week 9, but did not discontinue the study until Week 24. Data for this subject were included in the efficacy analyses (Listing 16.2.6.7.ab8).

Individual FE-1 values over time are presented in the Figure 16.

Figure 16. Spaghetti Plot of Faecal Elastase-1 Over Time, Full Analysis Set Part A/B, Cohort 8, 1 to 4 Months



Subjects with CF who have FE-1 levels ≤200 µg/g are considered pancreatic insufficient (Borowitz D, Baker SS, Duffy L et al., 2004). Two subjects were pancreatic insufficient (FE-1 values ≤200 µg/g) at baseline. One of these 2 subjects had an FE-1 value >200 µg/g at the Week 18 visit (FE-1 for this subject was ≤200 µg/g at all other visits), and the other subject had FE-1 values >200 µg/g from Day 4 through Week 24. The other 5 subjects were pancreatic sufficient (FE-1 values >200 µg/g) at all study visits with non-missing samples.

Absolute change from baseline in FE-1 from Cohorts 5 through 8 including subjects 1 to <24 months is presented in the table below:

Table 10. Absolute changes from baseline in Faecal Elastase-1 (µg/g) at selected study visits, FAS, Parts B and A/B. cohorts 5 through 8, subjects 1 to <24 months of age

		Total N = 43	
Visit	**Statistic**	**FE-1 (µg/g)**	**Absolute Change From Baseline at Visit (µg/g)**
Baseline	n	40	NA
	Mean (SD)	191.2 (211.3)	NA
	Median	55.0	NA
	Min, max	7.5, 500.0	NA
Week 2/Day 15	n	38	35
	Mean (SD)	258.1 (208.2)	48.5 (90.1)
	Median	175.5	24.5
	Min, max	7.5, 500.0	-236.8, 215.5
Week 12	n	37	34
	Mean (SD)	322.8 (185.2)	127.1 (144.7)
	Median	362.0	117.8
	Min, max	7.5, 500.0	-140.3, 492.5
Week 24	n	33	33
	Mean (SD)	339.5 (158.4)	155.9 (142.0)
	Median	357.0	126.0
	Min, max	7.5, 500.0	-23.0, 423.5

Source: Table 14.2.2.7.1.bfinal

FAS: Full Analysis Set; FE-1: fecal elastase-1; max: maximum value; min: minimum value; 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 Parts B or A/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.

Immunoreactive trypsin and/or trypsinogen (IRT)

Mean absolute changes from baseline in IRT are shown in Table 11.

Table 11. Absolute Changes From Baseline in IRT (ng/mL), FAS, Part A/B, Cohort 8, 1 to <4 Months

		Cohort 8 IVA 5.7 or 11.4 mg[a] N = 7	
Visit	**Statistic**	**IRT (ng/mL)**	**Absolute Change From Baseline at Visit (ng/mL)**
Baseline	n	5	NA
	Mean (SD)	1094.9 (234.9)	NA
	Median	1200.0	NA
	Min, max	674.7, 1200.0	NA
Week 12[b]	n	5	3
	Mean (SD)	840.6 (495.7)	-152.3 (263.8)
	Median	1200.0	0.0
	Min, max	217.7, 1200.0	-457.0, 0.0
Week 24	n	5	4
	Mean (SD)	781.0 (440.7)	-392.5 (272.6)
	Median	765.3	-474.2
	Min, max	161.0, 1200.0	-621.5, 0.0

Source: Table 14.2.2.7.ab8

FAS: Full Analysis Set; IRT: immunoreactive trypsin and/or trypsinogen; IVA: ivacaftor; n: size of subsample; N: total sample size; NA: not applicable; q12h: every 12 hours

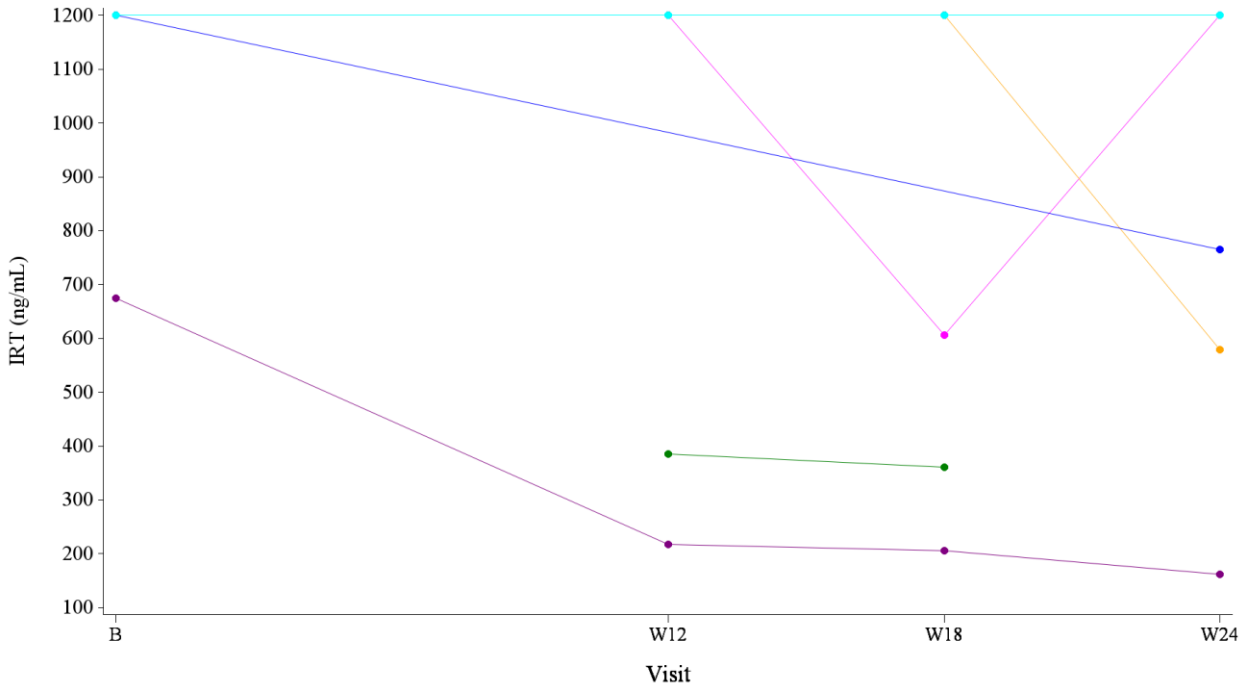
Notes: Baseline was defined as the most recent measurement before the first dose of study drug in Part A/B Cohort 8. Subjects shown in dose group according to their Day 1 dose. Reported values of <14 ng/mL were replaced by 7 ng/mL. Reported values of >1200 ng/mL were replaced by 1200 ng/mL because that is the maximum value measurable by the assay.

[a] Subjects received an initial low dose of IVA (5.7 or 11.4 mg, q12h) based on their age and weight at Day 1. At Day 4, each subject's exposure was evaluated, and if appropriate, the dose was adjusted at Day 15 to 5.7, 11.4, 17.1, 22.8, or 25 mg q12h to better match the adult median exposure. Subjects received this dose until the study visit after reaching 4 months of age and 5 kg, at which point the approved age- and weight-based dosing was initiated (Section 9.4.1).

[b] One subject discontinued study drug treatment at Week 9, but did not discontinue the study until Week 24. Data for this subject were included in the efficacy analyses (Listing 16.2.6.8.ab8).

Individual IRT values over time are presented in the Figure 17.

Figure 17. Spaghetti Plot of IRT Over Time, Full Analysis Set, Part A/B, Cohort 8, 1 to 4 Months



Faecal Calprotectin (FC)/marker of intestinal inflammation

Mean absolute changes from baseline in faecal calprotectin are shown in Table 12.

Table 12. Absolute Change From Baseline in Faecal Calprotectin (µg/g), FAS, Part A/B, Cohort 8, 1 to <4 Months

		Cohort 8 IVA 5.7 or 11.4 mg[a] N = 7	
Visit	**Statistic**	**Fecal Calprotectin (µg/g)**	**Absolute Change From Baseline at Visit (µg/g)**
Baseline	n	6	NA
	Mean (SD)	272.00 (249.64)	NA
	Median	148.50	NA
	Min, max	80.0, 632.0	NA

Visit	Statistic	Cohort 8 IVA 5.7 or 11.4 mg[a] N = 7 Fecal Calprotectin (µg/g)	Absolute Change From Baseline at Visit (µg/g)
Day 15	n	5	5
	Mean (SD)	162.00 (113.12)	-146.60 (219.06)
	Median	201.00	-37.00
	Min, max	45.0, 302.0	-416.0, 94.0
Week 12[b]	n	7	6
	Mean (SD)	236.00 (396.16)	-181.67 (183.23)
	Median	84.00	-95.50
	Min, max	13.0, 1110.0	-521.0, -57.0
Week 24	n	5	5
	Mean (SD)	46.00 (39.01)	-154.00 (162.57)
	Median	48.00	-75.00
	Min, max	5.0, 105.0	-435.0, -41.0

Source: Table 14.2.2.6.ab8

FAS: Full Analysis Set; IVA: ivacaftor; n: size of subsample; N: total sample size; NA: not applicable; q12h: every 12 hours

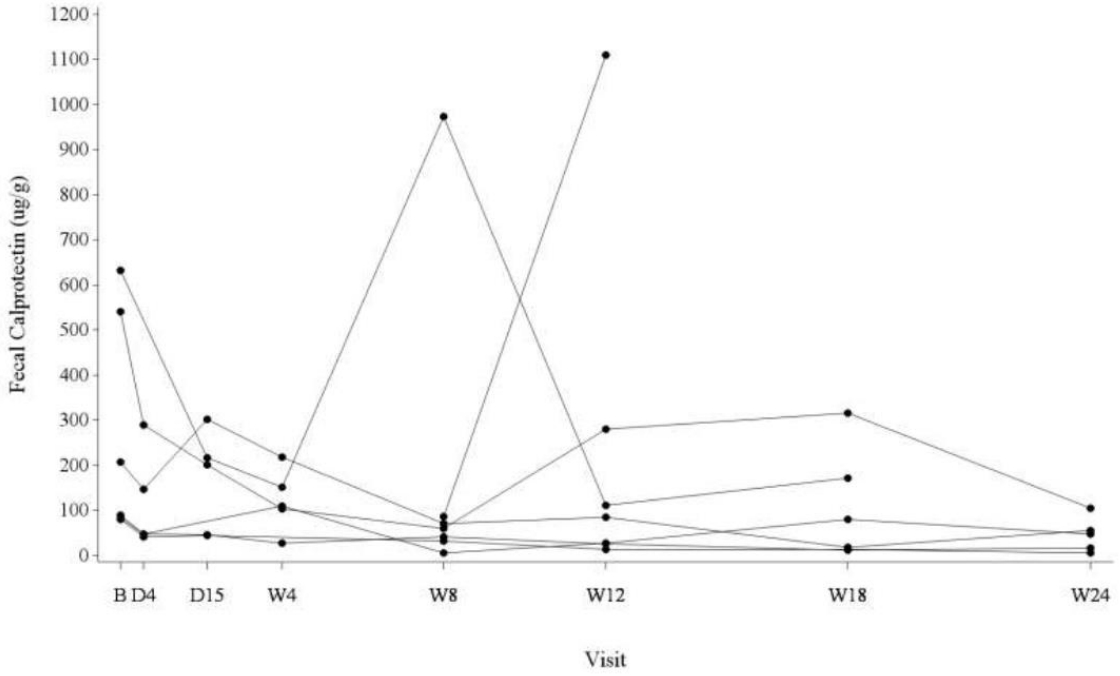
Notes: Baseline was defined as the most recent measurement before the first dose of study drug in Part A/B Cohort 8. Subjects shown in dose group according to their Day 1 dose. Reported values of <15.6 µg/g were replaced by 7.8 µg/g. Reported values of >2000 µg/g are replaced by 2000 µg/g. The normal range of reference for fecal calprotectin is 15.6 to 162.9 µg/g, however the range in CF infants has been reported to be much larger.[28, 29]

[a] Subjects received an initial low dose of IVA (5.7 or 11.4 mg, q12h) based on their age and weight at Day 1. At Day 4, each subject's exposure was evaluated, and if appropriate, the dose was adjusted at Day 15 to 5.7, 11.4, 17.1, 22.8, or 25 mg q12h to better match the adult median exposure. Subjects received this dose until the study visit after reaching 4 months of age and 5 kg, at which point the approved age- and weight-based dosing was initiated (Section 9.4.1).

[b] One subject discontinued study drug treatment at Week 9, but did not discontinue the study until Week 24. Data for this subject were included in the efficacy analyses (Listing 16.2.6.9.ab8).

Individual faecal calprotectin values over time are presented in Figure 18.

Figure 18. Spaghetti Plot of Faecal Calprotectin Over Time, Full Analysis Set, Part A/B, Cohort 8, 1 to 4 Months



Other exploratory endpoints

Other exploratory endpoints include qualitative microbiology (oropharyngeal) cultures, pulmonary exacerbations, CF-related hospitalisations, Lung Clearance Index, and acceptability and palatability of the formulation.

Multiple-breath washout (MBW) was included as an optional assessment for Cohorts 5, 6, and 7 (subjects 4 to <24 months of age). MBW assessment of lung clearance index (LCI) was not included as an assessment for Part A/B Cohort 8 (subjects 1 to <4 months of age).

Acceptability/palatability of IVA granules were assessed and established for Cohorts 5, 6, and 7 (subjects 4 to <24 months of age). Facial expressions are limited, highly variable, and difficult to interpret in subjects 1 to <4 months of age; therefore, acceptability/palatability was not included as an assessment for Part A/B Cohort 8.

- **Ancillary analyses**

  Not applicable.

- **Summary of main efficacy results**

  The following Table 13. Summary of Efficacy for the Interim Analysis 4 Report on Part A/B Cohort 8, infants aged 1 month to less than 4 months of age of Study VX15-770-124 summarises the efficacy results from the main study supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 13. Summary of Efficacy for the Interim Analysis 4 Report on Part A/B Cohort 8, infants aged 1 month to less than 4 months of age of Study VX15-770-124

Title: 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 an ivacaftor-responsive *CFTR* mutation		
Study identifier	Study VX15-770-124 (Study 124) Report S266 (Interim Analysis 4 Report), Version 1.0 (16 September 2022) EudraCT Number: 2015-001997-16	
Design	Phase 3, open-label, two-part,	
	Duration of main phase:	24-week treatment period For Cohort 8, Part A and B were carried out sequentially (i.e., without a gap between study parts) in each individual subject
	Duration of Run-in phase:	N/A
	Duration of Extension phase:	Open-label extension Study 126
Hypothesis	Descriptive statistics	

Treatments groups	Ivacaftor granules	Part A/B (Cohort 8, N=7): Day 1 up to Day 15 Dose: 5.7 mg BID (n=3), 11.4 mg BID (n=4) Day 15 (evening) adjusted dose: Ivacaftor 5.7 mg BID, n= 1 Ivacaftor 11.4 mg BID, n=1 Ivacaftor 17.1 mg BID, n=2 Ivacaftor 22.8 mg BID, n=2 Ivacaftor 25 mg BID, n=1 Subjects remained on this dose until the study visit after reaching 4 months of age and 5 kg, at which point subjects received the approved dose of 25 mg q12h.	
Endpoints and definitions	Primary endpoint	Safety and PK	
	Secondary endpoint	Sweat chloride	Absolute change from baseline at Week 18 (the last study visit with >1 subject with non-missing data)

	Tertiary endpoints - Growth parameters	- Weight, length, weight-for length and their respective z-scores.	Absolute change from baseline at Week 24
	- Markers of pancreatic exocrine function	- FE-1, IRT	Absolute change from baseline at Week 24
	- Markers of intestinal inflammation	- Faecal calprotectin	Absolute change from baseline at Week 24
Database lock	Part A/B Cohort 8 has completed; all data collected, as of the data cut date of 25 July 2022, are included in this Interim Analysis 4. Final Clinical Study Report Version and Date: 10 March 2023, Version 1.0		

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	7		
	Mean (SD) sweat chloride, mmol/L	-47.8 (37.0) (n = 4)		

	Median (Min, max) weight-for-age z-score, units	1.01 (0.14, 2.66) (n=6)		
	Median (Min, max) length-for-age z-score, units	1.15 (0.18, 2.06) (n=6)		
	Median (Min, max) weight-for-length z-score, units	0.48 (-0.61, 2.18) (n=6)		
	Median (Min, max) FE-1, µg/g	55.0 (0.0, 311.0) (n=5)		
	Median (Min, max) IRT, ng/ml	-474.2 (-621.5, 0.0) (n=4)		
	Median (Min, max) FC, µg/g	-75.00 (-435.0, -41.0) (n=5)		
Notes	An interim report (corresponding to the Interim Analysis 4) has been submitted to support the extension of the indication for ivacaftor as monotherapy down to children aged 1 month. The final CSR of the study (including the data for all children under 24 months of age) has also been provided.			
Analysis description	Results are summary statistics of changes from baseline at Week 24 for continuous variables based on the observed data (i.e. subjects with non-missing data). For sweat chloride an ad-hoc analysis of the average change from baseline through Week 24 was performed for all post-baseline visits (results not shown in this table).			

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

Results from placebo-controlled Phase 3 studies in subjects with CF ≥6 years of age showed that ivacaftor is effective in treating patients with CF who have either the *G551D CFTR* mutation (Studies 102 and 103) or at least 1 non *G551D* mutation that causes CFTR gating defects (Study 111), as evidenced by sustained improvements in CFTR channel function (measured by reduction in sweat chloride concentration) and corresponding substantial and durable improvements in lung function, pulmonary exacerbations (PEx), respiratory symptoms, and weight.

Open-label studies designed to evaluate safety, PK, PD, efficacy, and palatability in subjects with CF who have a gating or *R117H* mutation include Study 108 (gating) and Cohorts 5, 6, and 7 of Study 124 Part B (gating or *R117H*). Results in both studies demonstrated that IVA was generally safe and well tolerated, and

study drug exposures were similar to exposures in older subjects. Data from subjects 2 through 5 years of age (Study 108) and subjects 4 to <24 months of age (Study 124 Part B/Cohorts 5, 6, and 7) demonstrated that IVA improves CFTR function (measured by reduction in sweat chloride concentration), and provided supportive trends for other outcome measures.

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), subjects with a gating mutation 12 to <24 months of age (Study 124, Cohort 5), subjects with a gating mutation 6 to <12 months of age (Study 124, Cohort 6), and subjects with a gating mutation 4 to <6 months of age (Study 124, Cohort 7) are shown in Table 14. Mean Absolute Change From Baseline (SD) for Selected Efficacy Endpoints After 24 Weeks of IVA Treatment in Subjects 4 Months of Age and Older (Studies 102, 103, 111, and 108 and Study 124/Part B, Cohorts 5, 6, and 7).

Table 14. Mean Absolute Change From Baseline (SD) for Selected Efficacy Endpoints After 24 Weeks of IVA Treatment in Subjects 4 Months of Age and Older (Studies 102, 103, 111, and 108 and Study 124/Part B, Cohorts 5, 6, and 7)

					Study 124		
					Gating or *R117H* Mutation		
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 through 5 Years**	**Cohort 5 Subjects 12 to <24 Months**	**Cohort 6 Subjects 6 to <12 Months**	**Cohort 7 Subjects 4 to <6 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)	–58.6 (16.5)	-50.0 (17.3)
Nutritional status							
Weight (kg)	3.0 (3.60)	3.8 (2.18)	3.8 (1.90)	1.4 (0.56)	1.4 (0.6)	1.8 (0.7)	2.5 (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)	0.36 (0.54)	0.82 (0.54)
BMI (kg/m^2)	0.93 (1.145)	1.11 (0.920)	1.26 (0.759)	0.32 (0.538)	ND	ND	ND
BMI-for-age z-score (unit)	0.36 (0.324)	0.33 (0.364)	0.42 (0.276)	0.37 (0.424)	ND	ND	ND
Stature (cm)[a]	0.5 (1.21)	3.3 (1.11)	2.7 (1.34)	3.3 (1.17)	6.1 (1.6)	7.7 (3.5)	9.3 (2.1)
Stature-for-age z-score (unit)[a]	ND	ND	0.12 (0.13)	-0.01 (0.33)	0.28 (0.60)	0.27 (1.34)	0.56 (0.86)

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 through 5 Years	Study 124 Gating or *R117H* Mutation		
					Cohort 5 Subjects 12 to <24 Months	Cohort 6 Subjects 6 to <12 Months	Cohort 7 Subjects 4 to <6 Months
Weight-for-length (percentile)	ND	ND	ND	ND	1.5 (17.1)	2.8 (38.3)	20.0 (37.0)
Weight-for-length z-score (unit)	ND	ND	ND	ND	0.07 (0.65)	0.26 (1.30)	0.68 (1.12)
Lung function							
$ppFEV_1$ (percentage point)	11.1 (8.92)	13.2 (13.51)	13.5 (10.18)	1.8 (17.81) [b]	ND	ND	ND

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 through 5 Years	Study 124 Gating or *R117H* Mutation Cohort 5 Subjects 12 to <24 Months	Study 124 Gating or *R117H* Mutation Cohort 6 Subjects 6 to <12 Months	Study 124 Gating or *R117H* Mutation Cohort 7 Subjects 4 to <6 Months
Pancreatic function							
FE-1 (µg/g)	ND	ND	ND	99.8 (138.35)	164.7 (151.9)	159.3 (154.4)	181.0 (122.9)
IRT (ng/mL)	ND	ND	ND	-20.70 (23.991)[c]	-647.1 (339.3)[c]	-406.2 (363.3)[c]	-593.8 (402.5)[c]

Sources: Module 2.5 Pediatric Addendum/Tables 8, 9, 19, and 20; Study 102/Table 14.2; Study 103/Table 14.2; Study 111/Table 14.2.4.1.1ole; Study 108/Table 14.2.2.7b; Study 124 IA1/Tables 14.2.1.1.b5, 14.2.2.1.b5, 14.2.2.7.1.b5, and 14.2.2.9.b5; Study 124 IA2/Tables 14.2.1.1.b6, 14.2.2.1.b6, 14.2.2.7.1.b6, and 14.2.2.9.b6; and Study 124 IA3/Tables 14.2.1.1.b7, 14.2.2.1.b7, 14.2.2.7.1.b7, and 14.2.2.9.b7

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 at Week 24.

[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 subject 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.

2.6.6. Discussion on clinical efficacy

The current submission proposes to expand the approved indication of Kalydeco as monotherapy to include paediatric patients from 1 month to less than 4 months of age and weighing at least 3 kg.

The proposed indication for Kalydeco granules reads as follows:

"Kalydeco granules are indicated as monotherapy for the treatment of infants aged at least 1 month, toddlers and children weighing 3 kg to less than 25 kg with cystic fibrosis (CF) who have an R117H CFTR mutation or

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 currently proposed posology is as follows:

- 13.4 mg once daily for children aged 1 to less than 2 months weighing at least 3 kg
- 13.4 mg twice daily for children aged 2 months to less than 4 months weighing at least 3 kg

No formal dose-response studies were conducted. Dose selection in the paediatric target age range was driven by matching the adult systemic exposure that has been shown to be efficacious and safe in the pivotal studies in older paediatric and adult subjects. This approach has been discussed and accepted for the approval of ivacaftor for older children given the lack of age-specific issues related to the mechanism of action which targets the mutated CFTR protein. Concerns related to the scarcity of experimental data and to some of the available data generated in children under 6 months of age triggered a request to establish the paediatric dosing regimens for the youngest children targeting a lower adult range of reference of systemic exposure which led to the above dosing recommendations which are more conservative than what has been initially proposed by the MAH (see section 2.6.3 Discussion on clinical pharmacology).

Design and conduct of clinical study

The extension of the indication is based on the fourth interim analysis (IA) of Study VX-15-770-124 (Study 124) reporting data from subjects 1 to <4 months of age who completed Part A/Part B Cohort 8 (through 24 weeks of ivacaftor treatment). Part A/B Cohort 8 was completed; all data collected, as of the data cut date of 25 July 2022, were included in this IA report (Version 1.0 16 September 2022). The final clinical study report including data from all children under 24 months of age has also been provided (Version 1.0, 10 March 2023).

Study 124 is a phase 3, 2-part, open-label study in subjects <24 months of age. For Cohort 8 (Part A/B), subjects aged 1 to less than 4 months at Day 1 (ivacaftor treatment initiation) and who had a *CFTR* gating mutation on at least 1 allele were eligible to enrol. Subjects with an *R117H* mutation were eligible to enrol in regions where ivacaftor was granted marketing authorization for use in subjects with this mutation. Subjects eligible for Part A/B Cohort 8 could also have other ivacaftor-responsive mutations.

The inclusion and exclusion criteria were mostly in line with previous studies conducted with ivacaftor in children. Children with 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) were excluded. However, non-specific biochemical abnormalities in liver enzymes 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 exclusion may have led to the exclusion of children who may have benefited from treatment on grounds of safety (hepatotoxicity).

In Cohort 8, children received an initial low dose of ivacaftor (5.7 or 11.4 mg) every 12 hours (BID or q12h) based on their Day 1 age and weight up to the morning dose on Day 15. At Day 4, PK samples were taken to assess exposure. Based on that, the dose was adjusted (if appropriate) at Day 15 (evening) to 5.7, 11.4, 17.1, 22.8, or 25 mg BID to better match the adult median exposure. This dose was kept until the children reached 4 months of age and 5 kg, at which point they received the approved dose of 25 mg BID. Ivacaftor granules were mixed with approximately 1 teaspoon (5 mL) of appropriate liquid or soft food and administered orally BID with an age-appropriate fat-containing meal or snack.

Endpoints

The primary objectives of the study were to evaluate the safety of ivacaftor trough 24 weeks of treatment and the pharmacokinetics. Secondary objective was the sweat chloride test. Other PD and efficacy endpoints were considered as exploratory including growth parameters, lung clearance index (LCI), markers of pancreatic function such as faecal elastase-1 (FE-1) and immunoreactive trypsin and/or trypsinogen (IRT), and acceptability/palatability of ivacaftor granules.

Lung Clearance Index was not finally assessed in children enrolled in Cohort 8 (and basically in none of the children enrolled in the study) for various reasons (including that according to the MAH it remains unclear if multi-breath washout indices can detect structural lung disease in children with CF) and that the assessment adds an additional subject burden of sedation. The argument put forward regarding whether LCI may detect structural lung disease does not seem consistent with the fact that this measure is being assessed in paediatric studies with other CFTR modulators. In Study 124 only two subjects had MBW performed; 1 subject in Cohort 5 and 1 subject in Cohort 6. Therefore, with respect to this endpoint nothing can be concluded.

Acceptability and palatability of the granule formulation (considered an exploratory endpoint) was not tested either. The MAH justified the lack of palatability assessment on the basis that infants less than 4 months are less picky on taste issues than older children. Therefore, regarding palatability it is likely that the results in older children are of relevance for the youngest ones. However, swallowability in children aged 4 months and older is not necessarily representative for the less than 4 months age group. The MAH stated that there were no problems reported and no episodes of choking, however, these data should be viewed with some caution as this has not been actively and systematically asked and collected. The MAH clarified that the granules immediately disintegrate into fine particles within approximately one minute of mixing with liquid. This is reassuring. Still, the reason not to collect acceptability and palatability as assessed by the parents/caregivers was not well understood, but was not further pursued by the CHMP.

Statistics

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. 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. The difficulties to measure certain variables (e.g. sweat chloride) in these young children are acknowledged.

Efficacy data and additional analyses

A total of 7 subjects were enrolled in Part A/B cohort 8. Six subjects (85.7%) completed the 24 weeks of treatment. A single child discontinued treatment with ivacaftor prematurely (week 9) due to an adverse event of increased ALT, but was kept in the study and contributed to the efficacy analysis. In the end, the child was discontinued from the study upon decision of the physician.

Four subjects (57.1%) rolled over into the extension Study 126. Two children out of the six who completed the 24-week period of treatment in study 124 did not roll over to the extension study 126 as they initiated treatment with commercial drug (i.e. Kalydeco).

Out of the 7 infants enrolled, 4 were females and 3 males. At Day 1, three subjects were 1 to <2 months of age, two subjects were 2 to <3 months of age, and two subjects were 3 to <4 months of age. The mean age (SD) at baseline was 1.9 months (0.90). The mean age at CF diagnosis was 0.4 months and the mean gestational age at delivery was 38.1 weeks. The 3 subjects (one male and 2 females) in the 5.7 mg group

were 1 month of age and weighed 3.6, 4.2, and 4.3 kg. In the 11.4 mg group, two subjects (one male and one female) were 2 months of age and weighed 6.1 kg and 5.0 kg respectively; and two subjects (one male and one female) were 3 months of age and weighed 6 kg and 5.3 kg respectively. Median (min, max) weight-for-age, length-for age, and weight-for length z-scores were -1.32 (-1.93, 0.70), -1.06 (-1.57, 2.15), and -0.92 (-1.70, 0.41). All 7 subjects were White and of non-Hispanic or Latino ethnicity.

Four subjects had the G551D mutation, and the three remaining subjects had mutations responsive to ivacaftor (R117H, R117C, and S945L). The most prevalent genotype was G551D/F508del (2 out of the 7 subjects). The mean (SD) sweat chloride (n=7) level at baseline was 73.8 (19.1) mmol/L.

Three subjects (42.9%) were reported to have pancreatic failure and receive pancreatic enzyme replacement therapy. Two subjects had at baseline faecal elastase-1 values under 200 µg/g.

Given the small number of subjects in Cohort 8, a full set of baseline data for each of the subjects enrolled in the study was provided. For four of the 7 subjects enrolled in Cohort 8, the diagnosis of cystic fibrosis was made at the time of birth.

Outcomes and estimation

Baseline sweat chloride values ranged from a minimum of 49.0 to a maximum of 103.0 mmol/L indicative of the presence of children with *CFTR* mutations associated to sweat chloride values within the normal range (i.e. below 60 mmol/L).

The change from baseline at week 24 in sweat chloride was severely affected by the large number of missing samples which is not unexpected in these young children. From older patients, it is known that the effect of ivacaftor on sweat chloride is well established after 15 days of treatment. This is also the case in this cohort of very young children in which the mean (SD) change from baseline after 15 days of treatment with ivacaftor was -50.6 (24.2) mmol/L. The mean (SD) change at Week 18 (the latest visit with >1 subject with non-missing data) was -47.8 (37.0) mmol/L which is within the range of the decrease seen in older children and adult patients.

The additional analyses presented by the MAH (e.g., mean sweat chloride results excluding subjects with an *R117H* or other residual function mutation) were consistent with the effect seen at Day 15 and at week 18.

Increases in all mean absolute changes from baseline in z-scores of the growth parameters (weight-for-age, length-for-age, and weight-for length) have been observed after 24 weeks of treatment with ivacaftor. The baseline medical history of the children enrolled in Cohort 8 indicated that 3 of them suffered from pancreatic failure (although only 2 were considered pancreatic insufficient based on the FE-1 values at baseline) and were receiving exogenous pancreatic enzymes as well as liposoluble vitamins etc. Therefore, the improvement seen in these growth parameters is reassuring, but cannot be (solely) attributed to the treatment with ivacaftor given the multidisciplinary approach that children with cystic fibrosis usually receive. Considering also that this population (infants of 1-4 months of age) is normally a rapidly growing one, a comparison was requested of the change from baseline through week 24 in weight-, length-, and weight-for-length z-scores of study subjects to historical values of children of the same age and who have a gating mutation in at least one allele of the *CFTR* gene and who have not been treated with ivacaftor. This was not done because comparison to historical data for infants with gating mutations would be difficult to interpret, particularly given that 5 of the 7 subjects enrolled in Study 124 Cohort 8 had a residual function *CFTR* mutation. Even though the main manifestation of cystic fibrosis in these young children is usually seen at the level of the gastrointestinal tract in the form of pancreatic exocrine insufficiency, only two of the children enrolled in Cohort 8 were considered pancreatic insufficient. The issue was not further pursued by the CHMP.

The median (min, max) absolute change from baseline (n=7) at week 24 in the weight-for-age z-score was 1.01 (0.14, 2.66) (n=6). These figures for length-for-age z-score and weight-for length z-score were as follows: 1.15 (0.18, 2.06) and 0.48 (-0.61, 2.18) respectively. The median (min, max) absolute change in the weight-for-length percentile decreased however from 17.8 (4, 66) to 11.5 (-24, 67) reflecting the difficulties to interpret these results in isolation. Spaghetti plots of the individual values of weight-for-age, length-for-age, and weight-for length z-scores were provided showing in general positive trends under treatment with ivacaftor.

The median FE-1 (Min, max) at baseline (n=6) was 424.5 (31.0, 500.0) µg/g (compared to the mean value of 344.8 µg/g, indicative of a skewed distribution of values). The median (Min, max) absolute change at week 24 (n=5) was 55.0 (0.0, 311.0) µg/g. The mean (SD) absolute change from baseline to week 24 was 103.4 (131.4) µg/g. The use of the median values is a most conservative approach to analyse these data. Overall, from baseline to week 24, FE-1 values increased (improved).

Faecal elastase-1 values over the time for the two subjects with values ≤200 µg/g were provided. Their genotype was *N1303K/S945L* and *G551D/DELF508* with FE-1 values at baseline of 189.0 and 31.0 µg/g respectively. Overall, for both subjects the evolution of FE-1 values over time under treatment with ivacaftor was positive even though one of them remained pancreatic insufficient at week 24. The assay used to determine FE-1 was the Sche-Bo FE-1 assay (immunoassay) with the same limit of detection (LOD) and of quantification (LOQ), i.e., 15 µg/g, and an upper limit of quantification (ULOQ) of 500 µg/g.

Immunoreactive trypsin and/or trypsinogen (IRT) is elevated immediately after birth in neonates with cystic fibrosis 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 in patients with loss of exocrine tissue. In Cohort 8 of study 124, the mean IRT level (n=5) decreased over the 24-week treatment period, suggesting improvement in pancreatic inflammation/injury, although not all children experienced a decrease of IRT upon treatment. For the two children with faecal elastase-1 values ≤200 µg/g, the change from baseline at week 24 was -621.5 ng/ml (*N1303K/S945L*) and -434.7 ng/ml (*G551D/DELF508*). The assay used to determine serum IRT is the Cisbio assay. The LOD is 8 ng/mL, the LOQ is 14 ng/mL, and the ULOQ is 1200 ng/mL.

Mean faecal calprotectin levels decreased over the 24 weeks of treatment, which may be indicative of improvement in intestinal inflammation. The results in terms of the change from baseline are reassuring, but the evidence available did not allow to conclude that this can be attributed (solely) to the treatment with ivacaftor. Furthermore, the median (max, min) change from baseline at week 24 was -75.00 (-435.0, -41.0) µg/g which showed that not all children experienced a decrease of similar magnitude. The assay used is the Liason Fecal Calprotectin with a LOD and LOQ of 5 µg/g (for both), and an ULOQ of 8000 µg/g.

There were no identifiable trends in the exploratory endpoints of qualitative microbiology (oropharyngeal) cultures, pulmonary exacerbations, and CF-related hospitalisations which was somehow expected given the very young age of children enrolled in Cohort 8.

The final study report of study 124 (version 1.0, 10 March 2023) including a pooled analysis of all cohorts under 24 months of age has been provided as requested by the CHMP in order to include these data in section 5.1 of the SmPC. In study 124 in patients with CF aged 1 months to less than 24 months, the mean absolute change from baseline in sweat chloride was -62.0 mmol/L (95% CI -71.6, -52.4) at week 24. The table showing the effect of ivacaftor on growth parameters was also updated with pooled results for patients aged 1 month to less than 24 months.

2.6.7. Conclusions on the clinical efficacy

The fourth interim analysis of study 124 provides PK, safety, PD (sweat chloride) and some exploratory efficacy data of the treatment with ivacaftor as monotherapy in infants aged 1 month to less than 4 months who had a *CFTR* gating mutation on at least 1 allele or other ivacaftor-responsive mutations.

Study 124 is a single arm study in which a small number of subjects was enrolled in Part A/B Cohort 8 (n=7). Given the lack of age-specificities related to the mechanism of action of ivacaftor, the extrapolation of efficacy (and of safety to a certain extent) to these young children relies on the demonstration of similar systemic exposure of the selected paediatric doses with respect to that of adult and older paediatric patients, coupled with a similar effect in sweat chloride. This approach has been discussed and accepted for the approval of ivacaftor for older children and is considered acceptable for this younger patient population. Concerns related to the limited experimental data as well to some of the results observed in children under 4 months of age in Study 124 led to establish dosing recommendations for these young children more conservatively taking into account the influence of age on CYP3A maturation.

The CHMP concluded that the data available support the following indication :

Kalydeco granules are indicated as monotherapy for the treatment of infants aged at least 1 month, toddlers and children weighing 3 kg to less than 25 kg with cystic fibrosis (CF) who have an R117H-CFTR mutation or 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).

2.6.8. Clinical safety

2.6.8.1. Patient exposure

A total of 7 subjects were enrolled and included in de Safety Set. Six (85.7%) subjects completed the 24 weeks of treatment (see Table 1). Four subjects enrolled into the open-label Study 126.

The median (Min, max) treatment duration with ivacaftor was 24.0 (9, 25) weeks. Six subjects received at least 24 weeks of treatment, and 1 subject received 9 weeks of treatment due to study drug treatment discontinuation (due to an adverse event (AE) of ALT increased).

2.6.8.2. Adverse events

Four (57.1%) subjects had a total of 14 AEs. No subject had a related AE. There were no deaths, treatment-emergent serious adverse events (SAEs), or AEs leading to study drug interruption. One subject discontinued study drug treatment due to an AE of ALT increased. There were no AEs that led to the interruption of study drug (see Table 15 below). An overview of adverse events is shown in the Table 15 below.

Table 15. Overview of Adverse Events, Safety Set, Part A/B Cohort 8, 1 to <4 Months

Category	Cohort 8 IVA 5.7 or 11.4 mg[a] N = 7
Number of AEs, n	14
Number of SAEs, n	0
Number of non-serious AEs, n	14
Subjects with any AEs, n (%)	4 (57.1)
Subjects with related AEs, n (%)	0
Subjects with AEs leading to treatment discontinuation, n (%)	1 (14.3)
Subjects with AEs leading to treatment interruption, n (%)	0
Subjects with SAEs, n (%)	0
Subjects with AEs leading to death, n (%)	0

Source: Table 14.3.1.1.ab8

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

Notes: When summarizing number of events, a subject with multiple events within a category was counted multiple times in that category. When summarizing number and percentage of subjects, a subject with multiple events within a category was counted only once in that category. Related AEs included related, possibly related, and missing AEs. Events were coded with MedDRA Version 25.0. Subjects shown in dose group according to their Day 1 dose.

[a] Subjects received an initial low dose of IVA (5.7 or 11.4 mg, q12h) based on their age and weight at Day 1. At Day 4, each subject's exposure was evaluated, and if appropriate, the dose was adjusted at Day 15 to 5.7, 11.4, 17.1, 22.8, or 25 mg q12h to better match the adult median exposure. Subjects received this dose until the study visit after reaching 4 months of age and 5 kg, at which point the approved age- and weight-based dosing was initiated (Section 9.4.1).

At the CHMP request, the final study report of study 124 has been provided and the safety analysis of the age cohorts under 24 months of age in Part B and Part A/B (Cohorts 5 through 8) shows that after a median (min, max) exposure of 24 (2, 25) weeks with 79.1% (34/43) of the study population exposed for at least 24 weeks, the percentage of children with adverse events (AE) was 88.4% (38/43) with 20.9% (9/43) of children with related adverse events. Overall, the pooled analysis of safety does not raise concerns with respect to the safety analysis confined to each of the age cohorts enrolled in study 124.

Table 16. Overview of adverse events, safety set, Parts B and A/B, cohorts 5 through 8, subjects 1 to <24 months of age

Category	Total N = 43
Number of AEs, n	241
Number of SAEs, n	8
Number of non-serious AEs, n	233
Subjects with any AEs, n (%)	38 (88.4)
Subjects with related AEs, n (%)	9 (20.9)
Subjects with AEs leading to treatment discontinuation, n (%)	1 (2.3)
Subjects with AEs leading to treatment interruption, n (%)	3 (7.0)
Subjects with SAEs, n (%)	6 (14.0)
Subjects with related SAEs, n (%)	1 (2.3)
Subjects with AEs leading to death, n (%)	0

Source: Table 14.3.1.1.bfinal
AE: adverse event; n: size of subsample; N: total sample size; SAE: serious adverse event
Notes: When summarizing number of events, a subject with multiple events within a category was counted multiple times in that category. When summarizing number and percentage of subjects, a subject with multiple events within a category was counted only once in that category. Related AEs included related, possibly related, and missing AEs. Events were coded with MedDRA Version 25.1.

Incidence of adverse events

No individual AE occurred in more than 1 subject. Table 17 shows the incidence of AEs by PT.

Table 17. Adverse Events by Preferred Term, Safety Set, Part A/B, Cohort 8, 1 to <4 months

Preferred Term	Cohort 8 IVA 5.7 or 11.4 mg[a] N = 7 n (%)
Subjects with any AEs	4 (57.1)
Accidental overdose	1 (14.3)
ALT increased	1 (14.3)
Bronchiolitis	1 (14.3)
Constipation	1 (14.3)
Contusion	1 (14.3)
Diarrhoea	1 (14.3)
Enterovirus test positive	1 (14.3)
Faeces discoloured	1 (14.3)
Human rhinovirus test positive	1 (14.3)
Irritability	1 (14.3)
Nasal congestion	1 (14.3)

Preferred Term	Cohort 8 IVA 5.7 or 11.4 mg[a] N = 7 n (%)
Rhinorrhoea	1 (14.3)
Vomiting	1 (14.3)

Source: Table 14.3.1.3.ab8
AE: adverse event; ALT: alanine transaminase; IVA: ivacaftor; n: size of subsample; N: total sample size; PT: Preferred Term; q12h: every 12 hours
Notes: A subject with multiple events within a category (Any, or PT) was counted only once in that category. The table was sorted in descending order by PT. Events were coded with MedDRA Version 25.0. Subjects shown in dose group according to their Day 1 dose.
[a] Subjects received an initial low dose of IVA (5.7 or 11.4 mg, q12h) based on their age and weight at Day 1. At Day 4, each subject's exposure was evaluated, and if appropriate, the dose was adjusted at Day 15 to 5.7, 11.4, 17.1, 22.8, or 25 mg q12h to better match the adult median exposure. Subjects received this dose until the study visit after reaching 4 months of age and 5 kg, at which point the approved age- and weight-based dosing was initiated (Section 9.4.1).

Severity of Adverse Events

All AEs were considered mild in severity.

Relationship of Adverse Events

No AEs were considered possibly related or related to study drug.

In the final study report of study 124 including pooled results from Cohorts 5 through 8, the only related AEs occurring in 2 or more subjects were ALT increased (6 [14.0%] subjects), AST increased (5 [11.6%] subjects), and cough (3 [7.0%] subjects).

Adverse Events of Special Interest

No specific information has been provided by the MAH on this issue.

In section 4.8 of the SmPC, transaminase elevations are described as selected adverse reactions of ivacaftor as monotherapy and in combination regimens with other CFTR modulators.

2.6.8.3. Serious adverse event/deaths/other significant events

There were no deaths or treatment-emergent SAEs. As previously mentioned, one subject had an AE of ALT increased that led to treatment discontinuation. The AE of ALT increased was assessed by the investigator as unlikely related to study drug.

In the final study report including pooled results from Cohorts 5 through 8, there were no deaths and only an adverse event of constipation associated to distal intestinal obstruction syndrome was considered serious.

2.6.8.4. Laboratory findings

The following clinical laboratory data were assessed: haematology, chemistry, lipase and amylase, as well as subjects with abnormal laboratory measurements.

Liver Function Test (LFT)

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 Table 18. One subject had maximum ALT of >8 × ULN which led to treatment interruption. The 1-month-old patient had (after approximately 50 days of treatment with ivacaftor) an elevated ALT value, which peaked at >8 × ULN 7 days later. The patient also had a concomitant elevation of AST which peaked at >3 × ULN to ≤5 ULN. Ivacaftor was withdrawn (initially considered a study drug interruption), with the intention of study drug resumption after resolution of the event. Alkaline phosphatase (ALP) values were 1 to <2 × ULN at all study visits; all other LFT values, including gamma glutamyl transferase (GGT) and total bilirubin remained within the normal range throughout the study. Because the child was unable to achieve a stable return to baseline or <2 × ULN for ALT and AST off-treatment, ivacaftor was not resumed following the last dose (at the time of the first adverse event of ALT elevation) and the patient was discontinued from the study, per decision of the investigator and the subject's family.

One subject had a total bilirubin level of >2 to ≤3 × ULN with normal AST and ALT: total bilirubin was elevated >3 × ULN at baseline (during screening, classified as physiological neonatal jaundice) and decreased to normal on treatment. No subject had a transaminase elevation (ALT or AST >3 × ULN) concurrent with a bilirubin elevation >2 × ULN.

Table 18. Maximum On-treatment LFT Results, Part A/B, Cohort 8, 1 to <4 Months

Maximum On-treatment Result	Cohort 8 IVA 5.7 or 11.4 mg[a] N = 7 n (%)
ALT or AST	
≤1 × ULN	2/7 (28.6)
>1 to ≤2 × ULN	3/7 (42.9)
>2 to ≤3 × ULN	1/7 (14.3)
>8 × ULN	1/7 (14.3)
ALT (U/L)	
≤1 × ULN	2/7 (28.6)
>1 to ≤2 × ULN	3/7 (42.9)
>2 to ≤3 × ULN	1/7 (14.3)
>8 × ULN	1/7 (14.3)
AST (U/L)	
≤1 × ULN	6/7 (85.7)
>3 to ≤5 × ULN	1/7 (14.3)
Total Bilirubin (µmol/L)	
≤1 × ULN	6/7 (85.7)
>2 to ≤3 × ULN	1/7 (14.3)
ALT (or AST) >3 × ULN and Total Bilirubin >2 × ULN	0 (0.0)

Source: Table 14.3.4.3.1.ab8

ALT: alanine transaminase; AST: aspartate transaminase; IVA: ivacaftor; LFT: liver function test; n: size of subsample; N: total sample size; q12h: every 12 hours; ULN: upper limit of normal

Notes: The categorized result was the maximum of all post-baseline, on-treatment LFT assessments. Denominator is the number of subjects with at least 1 post-baseline assessment. One subject discontinued study drug treatment at Week 9, but did not discontinue the study until Week 24. Data for this subject were included in the safety analyses (Listing 16.2.8.1.2.ab8). Subjects shown in dose group according to their Day 1 dose.

[a] Subjects received an initial low dose of IVA (5.7 or 11.4 mg, q12h) based on their age and weight at Day 1. At Day 4, each subject's exposure was evaluated, and if appropriate, the dose was adjusted at Day 15 to 5.7, 11.4, 17.1, 22.8, or 25 mg q12h to better match the adult median exposure. Subjects received this dose until the study visit after reaching 4 months of age and 5 kg, at which point the approved age- and weight-based dosing was initiated (Section 9.4.1).

In the final study report including pooled results from Cohorts 5 through 8, The maximum on-treatment LFT results are presented in Table 19.

Table 19. Maximum On-treatment Liver Function Test Results, Parts B and A/B, Cohorts 5 Through 8, Subjects 1 to <24 Months of Age

Maximum On-treatment Result, n/N1 (%)	Total N = 43 n (%)
ALT	
≤1 × ULN	25/42 (59.5)
>1 × ULN to ≤2 × ULN	8/42 (19.0)
>2 × ULN to ≤3 × ULN	2/42 (4.8)
>3 × ULN to ≤5 × ULN	4/42 (9.5)
>5 × ULN to ≤8 × ULN	0
>8 × ULN	3/42 (7.1)
AST	
≤1 × ULN	32/42 (76.2)
>1 × ULN to ≤2 × ULN	6/42 (14.3)
>2 × ULN to ≤3 × ULN	2/42 (4.8)
>3 × ULN to ≤5 × ULN	2/42 (4.8)
ALT or AST	
≤1 × ULN	23/42 (54.8)
>1 × ULN to ≤2 × ULN	10/42 (23.8)
>2 × ULN to ≤3 × ULN	2/42 (4.8)
>3 × ULN to ≤5 × ULN	4/42 (9.5)
>5 × ULN to ≤8 × ULN	0
>8 × ULN	3/42 (7.1)
Total Bilirubin (µmol/L)	
≤1 × ULN	41/42 (97.6)
>2 × ULN to ≤3 × ULN	1/42 (2.4)
ALT (or AST) >3 × ULN and Total Bilirubin >2 × ULN	0

Maximum On-treatment Result, n/N1 (%)	Total N = 43 n (%)

Source: Table 14.3.4.3.1.bfinal

ALT: alanine transaminase; AST: aspartate transaminase; LFT: liver function test; n: size of subsample; N: total sample size; TE: treatment emergent; ULN: upper limit of normal

Notes: The categorized result was the maximum of all post-baseline, on-treatment LFT assessments. n/N1 (%): n is the number of subjects with a value meeting the parameter criteria category for the corresponding parameter during the treatment-emergent period. N1 is number of subjects with at least one non-missing measurement during the TE period. Percentage is n/N1.

Lipase and Amylase

There were no identifiable trends in amylase and lipase levels over 24 weeks of treatment. All subjects with elevations in lipase and/or amylase at baseline were asymptomatic.

Other Clinical Chemistry Parameters

For all clinical chemistry parameters, the mean changes from baseline were small, and no apparent trends were observed.

The only AE related to clinical chemistry was ALT increased.

Hematology

For all hematology parameters, the mean changes from baseline were small, and no apparent trends were observed. There were no AEs related to hematology parameters.

Electrocardiogram (ECG)

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 >60 msec. There were no ECG results that were considered by the investigator to be AEs.

Vital Signs, Physical Findings, and Other Observations Related to Safety

No clinically relevant trends or changes from baseline were observed over the 24-week treatment period for pulse rate, oxygen saturation, temperature, respiratory rate, or blood pressure (BP). Abnormal physical examination results were captured as AEs.

There were small variations in the mean BP levels over the course of the study.

Ophthalmologic Examination

No treatment-emergent cataracts (lens opacities) were identified during the 24-week treatment period.

2.6.8.5. Safety in special populations

Although hepatic impairment is rare in children less than 6 months of age with CF, such a level of liver disease may occur[3,4]. The evaluation of the PK in this age group suggests that there is an age-dependent effect on CL/F that is consistent with the potential contribution of CYP3A4 maturation in this age range. The impact of hepatic impairment in combination with the maturation of the CYP3A4 enzymes involved in ivacaftor metabolism for this age group is uncertain. Therefore, treatment with ivacaftor is not recommended in patients 1 to <6 months of age with any level of hepatic impairment.

2.6.8.6. Immunological events

One subject had a serious adverse event of pyrexia and vomiting which were related to a typical vaccine reaction. The event was reported as of mild severity and was considered solved.

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

Even though it cannot be excluded that patients 1 to <6 months of age may be in need of receiving therapeutic agents that include strong and moderate CYP3A inhibitors, the evaluation of PK data in this age group suggests that there is an age-dependent effect on CL/F that is consistent with the potential contribution of CYP3A4 maturation in this age range. The impact of CYP3A inhibitors in combination with the maturation of CYP3A enzymes involved in ivacaftor metabolism for this age group is uncertain. Therefore,

[3] Lamireau T, Monnereau S, Martin S, Marcotte J-E, Winnock M, Alvarez F. Epidemiology of liver disease in cystic fibrosis: a longitudinal study. J Hepatol. 2004;41(6):920-5.
[4] Bhardwaj S, Canlas K, Kahi C, Temkit M, Molleston J, Ober M, et al. Hepatobiliary abnormalities and disease in cystic fibrosis: epidemiology and outcomes through adulthood. J Clin Gastroenterol. 2009;43(9):858-64.

treatment with ivacaftor is not recommended in patients 1 to less than 6 months of age who are taking concomitant strong or moderate CYP3A inhibitors.

2.6.8.8. Discontinuation due to adverse events

Adverse Events that led to Discontinuation of Study Drug

One subject had an AE of ALT increased that led to treatment discontinuation at Week 9. This AE was assessed as unlikely related to study drug.

In the final study report including pooled results from Cohorts 5 through 8, in total three (7.0%) subjects interrupted study drug treatment due to at least 1 AE (1 subject due to an AE of rash, 1 subject due to AEs of ALT elevated, AST elevated, and GGT elevated, and 1 subject due to AEs of ALT elevated and AST elevated). One (2.3%) subject from Cohort 8 (see above) discontinued study drug treatment due to an AE of ALT elevated which was considered unlikely related to study drug.

Adverse Events that led to Interruption of Study Drug

There were no AEs that led to the interruption of study drug in Cohort 8.

2.6.8.9. Post marketing experience

As of 17 July 2023, ivacaftor was commercially available for patients 1 to <4 months of age in the US only (approved 03 May 2023). As such, there were no post-marketing safety data in this age group available at that time and this may still be the case.

2.6.9. Discussion on clinical safety

The safety database in the target paediatric population is limited in terms of size and drug exposure since only safety data from 7 infants aged 1 month to less than 4 months from Study 124 Part A/B Cohort 8 who received ivacaftor granules for approximately 24 weeks are available.

Based on the available data, ivacaftor at the doses studied seems well tolerated with reported AEs that are consistent with those observed in older adult and paediatric patients. The additional data which were requested for all children who received the adjusted doses of 22.8 mg and 25 mg q12h (3 children) in this cohort have not added new information in this respect.

The AEs reported in 4 of the 7 subjects from Cohort 8 were the following: constipation, diarrhoea, faeces discoloured, vomiting, accidental overdose, contusion, nasal congestion, rhinorrhoea, bronchiolitis, alanine aminotransferase increased, enterovirus test positive, human rhinovirus test positive, and irritability. Some of these AEs are included as the most common adverse reactions experienced by children aged 6 years and older according to section 4.8 of the Kalydeco SmPC: nasal congestion, diarrhoea and transaminase elevations. All AEs were considered mild in severity and the incidence of each AE by preferred term was the same [1 (14.3%)]. None of the AE were considered related to study drug.

There was an AE that led to treatment discontinuation. A 1-month-old patient had (after approximately 50 days of treatment with ivacaftor) an elevated ALT value, which peaked at >8 × ULN 7 days later. The patient also had a concomitant elevation of AST which peaked at >3 × ULN to ≤5x ULN . Ivacaftor was withdrawn (initially considered a study drug interruption), with the intention of resuming it after resolution of the event. Because the child was unable to achieve a stable return to baseline or <2 × ULN for ALT and AST off-treatment, ivacaftor was not resumed following the last dose (at the time of the first adverse event of ALT elevation) and the patient was discontinued from the study. The event was considered mild and not related to ivacaftor even though transaminase elevations are included in section 4.8 of the SmPC. For that subject, PK

data during ivacaftor treatment and after treatment interruption have been provided which shown that ivacaftor plasma concentrations were below the limit of quantification at Week 12 and Week 18 (treatment with ivacaftor was interrupted between the Week 8 and Week 12 study visits). Even though the adverse event of transaminase increase was considered by the investigator to be mild in severity and unlikely related to study drug and alternative aetiologies were found for the event, the relationship with ivacaftor cannot be completely ruled out. This event is therefore described in section 4.8 of the SmPC of Kalydeco granules.

Even though no adverse events are reported which led to treatment interruption, this is understood to be due to the fact that the child above mentioned permanently discontinued the study.

No deaths or serious treatment-emergent adverse events were reported. A child reported a serious adverse event of pyrexia and vomiting consistent with a typical vaccine reaction which was considered as mild and solved.

There were no safety concerns in ECG parameters and ophthalmological examinations.

Final study report (Parts B and A/B, Cohorts 5 to 8)

The final study report of study 124 has been provided and the safety analysis of the age cohorts under 24 months of age in Part B and Part A/B (Cohorts 5 through 8) shows that after a median (min, max) exposure of 24 (2, 25) weeks with 79.1% (34/43) of the study population exposed for at least 24 weeks, the percentage of children with adverse events (AE) was 88.4% (38/43) with 20.9% (9/43) of children with related adverse events. The only related AEs occurring in 2 or more subjects were ALT increased (6 [14.0%] subjects), AST increased (5 [11.6%] subjects), and cough (3 [7.0%] subjects). There were no deaths and only an adverse event of constipation associated to distal intestinal obstruction syndrome was considered serious. Three (7.0%) subjects interrupted study drug treatment due to at least 1 AE (1 subject due to an AE of rash, 1 subject due to AEs of ALT elevated, AST elevated, and GGT elevated, and 1 subject due to AEs of ALT elevated and AST elevated). One (2.3%) subject discontinued study drug treatment due to an AE of ALT elevated which was considered unlikely related to study drug. Maximum ALT or AST >3, >5, and >8 × ULN occurred in 7 (16.7%), 3 (7.1%), and 3 (7.1%) subjects, respectively. No subject had ALT or AST >3 × ULN concurrent with total bilirubin >2 × ULN. Overall, the pooled analysis of safety does not raise concerns with respect to the safety analysis confined to each of the age cohorts enrolled in study 124. Based on these results the table describing the transaminase elevations in patients with ivacaftor as monotherapy in section 4.8 of the SmPC was updated. Transaminase (ALT or AST) elevations in infants under 24 months of age are presented in section 4.8 of the SmPC in two different age groups, i.e., from 12 to less than 24 months of age and from 1 month to less than 12 months of age given that most of these elevations occurred in the former.

Children under 1 month of age are excluded from the indication in section 4.1 of the SmPC given the uncertainty about model predictions in the presence of rapid changes in maturation and in the absence of any PK data as no children of that age were enrolled in the study. The recommendation not to use ivacaftor in children under 4 months of age with any degree of hepatic impairment and in children in need of treatment with strong or moderate CYP3A inhibitors has been extended to children under 6 months of age based on the uncertainty posed by CYP3A maturation on a background of hepatic impairment and drug-drug interactions. This is now reflected in section 4.2 and section 4.4 of the SmPC of Kalydeco granules.

No safety data beyond week 24 were provided for the target population even if an open-label extension study (Study 126) was ongoing. High-level safety data have been presented by the MAH. No unexpected adverse events have been identified through 96 weeks of treatment. In total, 86 subjects were enrolled in Study 126 which included 4 children from Study 124, Cohort 8. Seventeen (17) subjects were 12 to <24 months of age, 11 subjects were 6 to <12 months of age, and 6 subjects were 4 to <6 months of age at treatment initiation.

The remaining subjects initiated ivacaftor treatment in Study 126 (or participated only in Study 124 Part A), and were 4 to <24 months of age at treatment initiation. Presently, the majority of subjects are expected to have more than 72 weeks of ivacaftor exposure in Study 126, but none of the children enrolled in this study were under 4 months of age. This study is a category 3 study included in the RMP and final results will be submitted in March 2024.

As of July 2023, ivacaftor was commercially available for patients 1 to <4 months of age in the US only. Limited post-marketing data may be available.

2.6.10. Conclusions on the clinical safety

No new AEs were identified in children enrolled in Cohort 8 of Study 124 and the safety profile was overall consistent with that known for adult and older paediatric patients. The final study report of Study 124 has been requested and a safety analysis has been performed for the overall population under 2 years of age which does not raise concerns with respect to the safety analysis confined to each of the age cohorts enrolled in the study. High-level safety data discussed for the extension study 126 through 96 weeks of treatment is reassuring, but lacking for children under 4 months of age. Due to the very small sample size no definite conclusion can be drawn for the very young age group and the safety profile will be further characterised in the post approval setting.

2.7. Risk Management Plan

2.7.1. Safety concerns

Important identified risks	None
Important potential risks	• Hepatotoxicity • Cataract
Missing information	• Use in pregnant and lactating women • Indicated use in children aged less than 6 years

2.7.2. 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	IVA Arm	• Hepatotoxicity	Final Report	March 2024

Study/Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Ongoing	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	• Cataract • Indicated use in children aged <24 months old at initiation		

CF: cystic fibrosis; IVA: ivacaftor; MA: market authorisation; PD: pharmacodynamics; PV: pharmacovigilance

Note: Study 126 addresses a subpopulation of the Missing Information of "Indicated use in children aged less than 6 years."

2.7.3. Risk minimisation measures

Safety Concern	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 Prescription only **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection** None **Additional PV activities:** Study 126

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Cataract	**Routine risk minimisation measure:** SmPC Section 4.4 where advice is given on recommended ophthalmological examinations SmPC Section 5.3 PL Section 2 Prescription only **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection** None **Additional PV activities:** Study 126
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 Prescription only **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection** Pregnancy follow-up form **Additional PV activities:** None
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 Prescription only **Additional risk minimisation measures:** No risk minimisation measures	**Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection** None **Additional PV activities:** Study 126

: Patient Leaflet; SmPC: Summary of Product Characteristics

:e: Study 126 addresses a subpopulation of the Missing Information of "Indicated use in children aged less than 6 years."

2.7.4. Conclusion

The CHMP considered that the risk management plan version 15.5 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

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

2.8.2. Periodic Safety Update Reports submission requirements

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

2.9. Product information

As a consequence of this new indication, sections 1, 2, 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2, 6.5 and 8 of the SmPC of the granules presentations and sections 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC of the tablets presentations are updated. The Package Leaflet has been updated accordingly.

In addition, at the CHMP request, the MAH updated the study numbers in the SmPC with the real study numbers to facilitate the identification of the studies. Upon CHMP request, the description of selected adverse events for Kalydeco in combination with tezacaftor/ivacaftor and ivacaftor/tezacaftor/elexacaftor in section 4.8 was also updated to be in line with the SmPC of tezacaftor/ivacaftor and ivacaftor/tezacaftor/elexacaftor.

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: updates made to the package leaflets are minimal, and the structure and guidance for caregivers remains aligned to the principles agreed on in procedure EMEA/H/C/002494/X/0034/G (where readability testing was conducted for the Kalydeco 50 mg and 75 mg granules package leaflet).

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The indication applied for is:

"Kalydeco granules are indicated as monotherapy for the treatment of infants aged at least 1 month, toddlers and children weighing 3 kg to less than 25 kg with cystic fibrosis (CF) who have an *R117H CFTR* mutation or 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)."

Cystic Fibrosis (CF) is an autosomal recessive disease with serious, chronically debilitating morbidities and high premature mortality for which, at present, there is no cure. Cystic fibrosis is caused by mutations in the *CFTR* gene that result in the absence or deficient function of the CFTR protein at the cell surface, which is responsible for 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.

The aim of the therapy with ivacaftor is to improve CFTR channel function (gating) at the cell surface which is expected to translate in an improvement of the target organs affected by the disease, which may differ depending on the degree of tissue damage. The organ susceptibility to the increased sweat chloride levels

differs between different organs, but the implementation of newborn screening allowing early interventions has translated into better outcomes and survival. It can be then postulated that drugs targeting the basic defect of the mutant CFTR protein such as the CFTR modulators may have the potential to slow disease progression and earlier treatment would result in better outcomes.

3.1.2. Available therapies and unmet medical need

In the treatment of CF, CFTR modulators such as ivacaftor are currently important therapies as they hold the potential to modify disease progression by maintaining or improving the lung function, reducing the risk of exacerbations and improving quality of life.

A second type of therapy is symptomatic therapy, which targets specific disease symptoms, such as nutritional supplements, antibiotics, and mucolytics.

The CFTR modulators are not a cure for CF and must be taken chronically for the patient to maintain treatment benefits. At present, there is no approved CFTR modulator therapy available for infants with cystic fibrosis under 4 months of age. There is therefore an unmet medical need.

3.1.3. Main clinical study

The pharmacokinetics and safety of ivacaftor in children under 24 months of age have been assessed in Study VX-15-770-124 (study 124), a single-arm study. The present submission is based on the interim analysis 4 of Study 124 which includes all data from the seven infants from 1 month to less than 4 months of age who enrolled in Cohort 8 Part A/B (through 24 weeks of treatment).

The primary objectives of the study were to evaluate the safety of ivacaftor trough 24 weeks of treatment and the pharmacokinetics. A secondary objective was to assess efficacy based on the sweat chloride test. Other PD and efficacy endpoints were considered as exploratory including growth parameters, markers of pancreatic function such as faecal elastase-1 (FE-1) and immunoreactive trypsin and/or trypsinogen (IRT), and markers of gastrointestinal inflammation such as faecal calprotectin.

As stated above, Study 124 is a single arm study in which a small number of subjects was enrolled in Part A/B Cohort 8 (n=7). Given the lack of age-specificities related to the mechanism of action of ivacaftor, the extrapolation of efficacy (and safety to a certain extent) from older patients to the young children under 4 months of age relies on the demonstration of similar systemic exposure of the selected paediatric doses with respect to adult and older paediatric patients, coupled with a similar effect in sweat chloride.

3.2. Favourable effects

Treatment with ivacaftor for 15 days was associated to a mean (SD) absolute change from baseline in sweat chloride of -50.6 (24.2) mmol/L. The mean (SD) change at Week 18 (the latest visit with >1 subject with non-missing data) was -47.8 (37.0) mmol/L, which is within the range of the decrease seen in older children and adult patients.

Mean changes from baseline in growth parameters, faecal elastase-1 (FE-1), immunoreactive trypsin and/or trypsinogen (IRT), and faecal calprotectin overall improved, suggesting a potential to alleviate the gastrointestinal disease which is the most prominent clinical presentation of cystic fibrosis in very young children.

3.3. Uncertainties and limitations about favourable effects

The calculated within-group change in sweat chloride from baseline at week 24 was severely affected by the large number of missing samples, but the various analyses performed (including an ad hoc analysis of the average change from baseline through Week 24) were consistent and all showed similar degree of decrease.

As for growth parameters, faecal elastase-1, immunoreactive trypsin and/or trypsinogen (IRT), and faecal calprotectin, the magnitude of improvement was variable among the children enrolled in Cohort 8.

Data provided were very limited (7 infants), but considered acceptable in view of the rarity of the disease and the expected potential of CFTR modulators to modify the course of the disease. Additional characterisation of the efficacy will be provided in the post approval setting.

No formal dose-response studies were conducted, but selection of doses for the population targeted in the present procedure was supported by a popPK model-based approach, using the previous population PK model developed in subjects 6 to <12 months of age. Two dosing regimens were initially proposed (i.e., 13.4 mg q12h for children aged 1 to less than 3 months weighing at least 3 kg and 25 mg q12h for children aged ≥3 months to less than 4 months weighing at least 3 kg).

While the modelling approach for dose selection is endorsed, there seems to be some differences between the popPK-based simulations and the simulations performed with the PBPK model. The latter overpredicts PK exposures for children 1 to <6 months of age and therefore provides a more conservative reference range for this age group. Even though the popPK model appeared to adequately describe the observed PK data and the variability, the limited experimental data available from 7 subjects coupled with some concerns related to the data generated in these young children, triggered a request to the MAH to establish dosage regimens in children between 1 and 4 months with a more conservative adult reference range of systemic exposure. In response, simulations based on a recalibrated PBPK model were performed and new dosing recommendations proposed which are more conservative (i.e., lower) than the ones initially proposed. For children aged 1 month to less than 2 months and weighing ≥ 3 kg the recommended regimen is 13.4 mg once daily while for children aged 2 months to less than 4 months the proposal is 13.4 mg twice daily.

The once daily dosing regimen of 13.4 mg recommended for children aged 1 to less than 2 months has not been assessed in any children. This regimen is predicted to result in similar AUC0-12 as the dosing regimen of 5.8 mg q12h, but in higher Cmax levels as compared to a twice daily regimen. This high Cmax is not anticipated to raise safety concerns as the proportion of paediatric patients between 1 to <2 months of age and 3 kg of body weight with Cmax levels above the more conservative reference adult range of exposure is expected to be less than 25%. Furthermore, as age and/or body weight increases, the Cmax levels are expected to decrease, so the proportion of paediatric patients above the reference conservative adult range is expected to be less than 25% in clinical practice. From an efficacy perspective, no relevant difference between 5.8 mg q12h and 13.4 mg qd are expected based on the similar predicted AUC and overlapping (even slightly lower) Cmin levels.

The claimed indication excludes children under 1 month of age due to concerns about the uncertainty of model-based predictions given the influence of CYP3A maturation and in the absence of any PK data as children under 1 month of age were not enrolled in the study. On the other hand, the number of children under 1 month of age who would benefit from the treatment with ivacaftor is, according to the estimation provided by the MAH, limited as 4 weeks may be the time needed to confirm the diagnosis. Therefore, the recommendation for an indication from one month of age is considered acceptable.

A recommendation not to use ivacaftor as monotherapy in children under 6 months of age with any degree of hepatic impairment or in need of concomitant administration of moderate or strong CYP3A inhibitors is included in section 4.2 of the SmPC of Kalydeco granules. This is endorsed in view of the uncertainties to make predictions in a situation of rapid changes in CYP3A enzymes on top of hepatic impairment or co-administration of CYP3A inhibitors and the anticipated limited impact this may have in terms of the estimated size of the population affected.

3.4. Unfavourable effects

Safety results in subjects 1 to <4 months in study 124 (Part A/B, Cohort 8) were generally consistent with those in older population, with no new safety concerns identified.

The AEs reported in 4 of the 7 subjects included in Cohort 8 were the following: constipation, diarrhoea, faeces discoloured, vomiting, accidental overdose, contusion, nasal congestion, rhinorrhoea, bronchiolitis, alanine aminotransferase increased, enterovirus test positive, human rhinovirus test positive, and irritability. Some of these AEs (nasal congestion, diarrhoea and transaminase elevations) are included as the most common adverse reactions experienced by children aged 6 years and older.

All AEs were considered mild in severity and the incidence of each AE by preferred term was the same [1 (14.3%)]. One subject had a SAE (a typical vaccine reaction) that was reported as mild in severity and it was resolved.

One subject had elevation of ALT that led to premature treatment discontinuation at week 9. This subject had maximum ALT of >8 × ULN and maximum AST of >3 to ≤5 × ULN which was considered unrelated to treatment. Another subject had a total bilirubin level of >2 to ≤3 × ULN with normal AST and ALT: total bilirubin was elevated >3 × ULN at baseline (during screening, classified as physiological neonatal jaundice) and decreased to normal while on treatment.

There were no deaths in the study. There were no relevant safety findings in ECG parameters and ophthalmological examination.

3.5. Uncertainties and limitations about unfavourable effects

The safety profile observed is similar to that already known for ivacaftor in older populations but the very small sample size, the uncontrolled design of study 124 and its short duration are limitations to the characterisation of the safety profile for patients 1 to less than 4 months of age. The final study report of Study 124 has been provided and the pooled safety analysis of the age cohorts under 24 months of age in Part B and Part A/B (Cohorts 5 through 8) after a median (min, max) exposure of 24 (2, 25) weeks does not raise concerns with respect to the safety analysis confined to each of the age cohorts enrolled in Study 124.

Even though the event of transaminase increase reported for a 1-month old child who first interrupted treatment with ivacaftor and then was discontinued from the study, was considered not related to ivacaftor, the lack of relationship in the view of the CHMP cannot be completely ruled out. This case is described in section 4.8 of the SmPC.

No safety data beyond week 24 were discussed for the target population even though 4 children from Cohort 8 have been rolled over to the extension Study 126. High-level safety data from this study were presented. While no unexpected adverse events have been identified through 96 weeks of treatment, no children under 4 months of age were treated in this study. The majority of subjects are expected to have more than 72 weeks of ivacaftor exposure. The study is included in the RMP as a category 3 study, final results will be

submitted in March 2024. In view of the limited safety data available, the safety profile will be monitored in the post approval setting for further characterisation in the younger patient population.

3.6. Effects Table

Table 20. Effects Table for Kalydeco for the treatment of infant aged 1 month to 4 months with CF (data cut-off: 16 September 2022)

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
Sweat chloride	Absolute mean (SD) change from baseline at Week 18	mmol/l	-47.8 (37.0)	-	**Unc**: open-label, single-arm trial	Study VX15-770-124 (study 124) (Cohort 8)
Unfavourable Effects						
Elevated Transaminase Events	Event of increased alanine aminotransferase (ALT)	n (%)	1 (14.3)	-	**Unc**: Open-label, single arm study. This AE led to premature discontinuation of treatment at week 9	Study VX15-770-124 (study 124) (Cohort 8)

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Importance of favourable effects

From older patients, it is known that the effect of ivacaftor on sweat chloride is well established after 15 days of treatment. This is also the case in the very young children enrolled in Cohort 8 of Study 124 in which the mean (SD) change from baseline after 15 days of treatment with ivacaftor was -50.6 (24.2) mmol/L.

Strength of the evidence

In CF, sweat chloride is increased, and a decrease can be considered as an effect on the underlying pathology. Therefore, the observed reduction in sweat chloride is an important parameter for measuring the effect of a CFTR modulator. Observed reductions in sweat chloride concentrations were consistent with previous results in adult and older paediatric patients.

In very young children with cystic fibrosis, pancreatic insufficiency and poor nutritional status are the most significant clinical manifestations of the disease. Therefore, demonstration of a favourable effect on growth parameters and pancreatic function would be supportive as surrogate for the benefit of treatment. Mean changes from baseline in growth parameters, faecal elastase-1, immunoreactive trypsin and/or trypsinogen (IRT), and faecal calprotectin were overall supportive of treatment with ivacaftor.

Uncertainties

While the modelling approach for dose selection is endorsed, there seems to be some differences between the popPK-based simulations and the simulations performed with the PBPK model. Concerns were raised that the proposed dosing regimens based on popPK modelling may result in higher (than predicted) systemic exposures as compared to the adult range of reference. At the CHMP request, alternative dosing regimens were simulated for the age range of 1 month to less than 4 months based on a recalibrated PBPK model and targeting a more conservative reference range of systemic exposure in adults. This led to the proposal of lower dosing regimens for children aged 1 to less than 2 months (13.4 mg once daily) and for children aged 2 to less than 4 months of age (13.4 mg twice daily). The once daily dosing regimen of 13.4 mg is predicted to result in similar AUC0-12 and Cmin and higher Cmax as compared to 5.8 mg q12h.

As Study 124 is a single-arm study only within-group changes from baseline are available, which could be impacted by subjects with missing data in an extremely small age cohort.

Even though PD endpoints such as faecal elastase-1 showed an overall improvement after treatment with ivacaftor, the magnitude of the reported change was variable. Similarly, while the improvement in growth parameters is reassuring to a certain extent, this cannot be (solely) attributed to the treatment with ivacaftor given the multidisciplinary approach that children with cystic fibrosis usually receive.

The exclusion of children under 1 month of age from the indication in section 4.1 and the recommendation not to use ivacaftor as monotherapy in children under 6 months of age with any degree of hepatic impairment or in need to concomitant treatment with strong or moderate CYP3A inhibitors are not based on clinical data but rather on concerns related to the uncertainties of potential dosing regimens based on modelling and simulation due to the ongoing CYP3A maturation.

Safety

No new AEs were identified in Cohort 8 of Study 124 and the safety profile was overall consistent with that known for adult and older paediatric patients. The final report of the study has been provided and the safety analysis for the overall population under 2 years of age does not raise concerns with respect to the safety analysis confined to each of the age cohorts enrolled in Study 124. However, the very small number of treated children in this very young age range is, in itself, an important limitation.

Safety data beyond week 24 are being gathered in an open label study (Study 126) for 96 weeks. The high-level safety discussed by the MAH do not raise concerns, but no children under 4 months of age have been treated in this study.

3.7.2. Balance of benefits and risks

The proposed extension of the indication of ivacaftor as monotherapy to infants aged 1 month to less than 4 months weighing at least 3 kg is based on extrapolation of efficacy (and to a certain extent, also of safety) from adults and older paediatric patients in which efficacy and safety were shown (source population). To that end, the paediatric doses proposed should result in similar systemic exposure as in the source population, with acceptable safety, and a similar PD/efficacy effect.

The final selected dosing regimens were 13.4 mg qd for paediatric patients 1 to <2 months of age and $\geqslant$ 3 kg, and 13.4 mg q12h for paediatric patients 2 to <4 months of age and $\geqslant$ 3 kg, both providing similar exposure for each sub-group of paediatric patients with the reference conservative adult exposure range. In view of the limited efficacy and safety data available, the efficacy and safety profile will be monitored in the post approval setting for further characterisation in the younger patient population.

3.7.3. Additional considerations on the benefit-risk balance

For subjects 2 - 6 years of age a PAES is ongoing to address whether starting treatment at the age of two years may have an impact on disease progression. It was agreed by the CHMP that for children below 2 years of age a similar PAES could not be performed due to the small number of available children in this age group.

3.8. Conclusions

The overall benefit/risk balance of Kalydeco is positive.

4. Recommendations

Similarity with authorised orphan medicinal products

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

Outcome

Based on the CHMP review of data on quality and safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Kalydeco 13.4 mg granules is favourable in the following indication:

Kalydeco granules are indicated as monotherapy for the treatment of infants aged at least 1 month, toddlers and children weighing 3 kg to less than 25 kg with cystic fibrosis (CF) who have an *R117H-CFTR* mutation or 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 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 Marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being

received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

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

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

Description	**Due date**
Long-term effectiveness study to compare disease progression among children with CF who have a specified CFTR gating mutation and are aged 2 through 5 years at the time of Kalydeco treatment initiation versus disease progression among concurrent matched cohort of children with CF who have never received Kalydeco treatment.	Interim analysis 1: December 2017 Interim analysis 2: December 2019 Interim analysis 3: December 2021 Final report: December 2023

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0163/2020 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

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

Variations requested		**Type**	**Annexes affected**
A.5.b	A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release)	Type IA	None
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB
X.02.III	Annex I_2.(c) Change or addition of a new strength/potency	Line Extension	I, IIIA, IIIB and A
B.II.b.2.a	B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place	Type IA	None

Extension application to introduce a new strength (13.4 mg of ivacaftor granules in sachet), grouped with a type II variation (C.I.6.a) in order to extend the indication of the granules presentations to include children with cystic fibrosis aged 1 to less than 4 months and weighing 3 kg or more who have an R117H CFTR

mutation or one of the approved 9 gating (class III) mutations based on interim results from study VX15-770-124 (study 124); this is a phase 3, 2-part, open-label study to evaluate the safety, pharmacokinetics, and pharmacodynamics of ivacaftor (IVA) in subjects with CF who are less than 24 months of age at treatment initiation and have a CFTR gating mutation. As a consequence, sections 1, 2, 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2, 6.5 and 8 of the SmPC of the granules presentations and sections 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC of the tablets presentations are updated. The Labelling and the Package Leaflet are updated in accordance. Version 15.5 of the RMP has also been approved. In addition, the MAH took the opportunity to introduce minor editorial changes to the PI.

Type IA A.5.b - To change the name of the site responsible for quality control testing and processing operations of the medicinal product for the granule presentations from "Mayne Pharma Inc.", 1240 Sugg Parkway, Greenville, North Carolina, 27834-9006, United States to "Catalent Greenville, Inc."; the address remains unchanged.

Type IA B.II.b.2.a - To add PPD Development LP, 8551 Research Way, Suite 90, Middleton, WI 53562-4664, United Stated as an alternative site responsible for batch control and quality control testing for all the presentations of the finished product.