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SCIENCE MEDICINES HEALTH

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EMA/530990/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Kalydeco

International non-proprietary name: ivacaftor

Procedure No. EMEA/H/C/002494/II/0086

Note

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



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List of abbreviations

ADR	adverse drug reaction
AE	adverse event
ALT	alanine transaminase
AST	aspartate transaminase
AUC	area under the concentration versus time curve
AUC _{ss}	AUC at steady-state
BID	twice per day (q12h)
BMI	body mass index
CF	cystic fibrosis
CFQ-R	Cystic Fibrosis Questionnaire Revised
CFTR	cystic fibrosis transmembrane conductance regulator gene
CHMP	Committee for Medicinal Products for Human Use
CL	clearance
CL/F	apparent clearance
C _{min}	minimum observed concentration
C _{min,ss}	C _{min} at steady-state
CYP	cytochrome P450
D1	zero-order dose duration
ECG	electrocardiogram
EU	European Union
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
FDA	Food and Drug Administration
FE 1	fecal elastase 1
G551D	CFTR missense gene mutation that results in the replacement of a glycine residue at position 551 of CFTR with an aspartic acid residue
h	hour
IA3R	Interim Analysis 3 Report
IPFT	infant pulmonary function test
IQR	interquartile range
IRT	immunoreactive trypsin and/or trypsinogen
IVA	ivacaftor

ka	first-order absorption rate
LCI	lung clearance index
LFT	liver function test
max	maximum value
min	minimum value
n	size of subsample
N	total sample size
na	not analyzed due to low incidence of events
ND	not determined
OE	ophthalmologic examination(s)
P	probability
PD	pharmacodynamic, pharmacodynamics
PDCO	European Medicines Agency Pediatric Committee
PEx	pulmonary exacerbation
PIP	pediatric investigation plan
PK	pharmacokinetic, pharmacokinetics
popPK	population PK
ppFEV1	percent predicted forced expiratory volume in 1 second
PT	Preferred Term
PWR	pediatric written request
Q/F	apparent (oral) intercompartmental clearance
q12h	every 12 hours
qd	daily
QTcF	QT interval corrected by Fridericia's formula
R117H	CFTR missense gene mutation that results in the replacement of an arginine residue at position 117 of CFTR with a histidine residue
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
sNDA	supplemental New Drug Application (US)
UK	United Kingdom
ULN	upper limit of normal
US	United States

V_c/F	apparent (oral) central volume of distribution
V_p	volume of distribution of the peripheral compartment
V_p/F	apparent (oral) peripheral volume of distribution

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Vertex Pharmaceuticals (Ireland) Limited submitted to the European Medicines Agency on 8 April 2020 an application for a variation.

The following variation was requested:

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

Extension of indication to include treatment of infants aged at least 4 months, toddlers and children weighing 5 kg to less than 25 kg with cystic fibrosis 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* for Kalydeco 25 mg granules. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 8.9 of the RMP has also been submitted.

The variation requested amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information relating to orphan designation

Kalydeco, was designated as an orphan medicinal product EU/3/08/556 on 25 July 2012 Kalydeco was designated as an orphan medicinal product in the following indication: Treatment of cystic fibrosis.

Information on paediatric requirements

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

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

Information relating to orphan market exclusivity

Similarity

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

Protocol assistance

The MAH did not seek Protocol Assistance at the CHMP.

1.2. Steps taken for the assessment of the product

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

Rapporteur: N/A Co-Rapporteur: Melinda Sobor

Timetable	Actual dates
Submission date	8 April 2020
Start of procedure:	25 April 2020
CHMP Co-Rapporteur Assessment Report	1 July 2020
PRAC Rapporteur Assessment Report	25 June 2020
PRAC Outcome	9 July 2020
CHMP members comments	13 July 2020
Updated CHMP Rapporteur Assessment Report	17 July 2020
Request for supplementary information (RSI)	23 July 2020
MAH's responses submitted to the CHMP on:	18 August 2020
PRAC Rapporteur Assessment Report	24 August 2020
PRAC members comments	26 August 2020
CHMP Rapporteur Assessment Report	1 September 2020
CHMP members comments	7 September 2020
Updated CHMP Rapporteur Assessment Report	10 September 2020
Opinion	17 September 2020

2. Scientific discussion

2.1. Introduction

This application is for an extension of indication of Kalydeco to include treatment of CF in children aged 4 to less than 6 months who have an *R117H* mutation or one of the currently approved gating mutations in the *CFTR* gene for Kalydeco 25 mg granules. To support this application, results of the third interim analysis of study 124 were submitted. The first and second interim analysis reports were submitted and assessed in variations II/69 (for the extension of indication to children aged 12 to less than 24 months) and X/75/G (for the extension of indication to children aged 6 to less than 12 months). Study 124 is included in the IVA paediatric investigation plan (PIP) in the EU. The PDCO agreed that the open-label roll-over study 126 would be captured in the Kalydeco Risk Management Plan (RMP). The MAH received scientific advice from the CHMP on the development plan in patients < 6 years of age.

The underlying cause of cystic fibrosis (CF), a loss of CFTR function that arises from a mutation in the gene encoding the CF transmembrane conductance regulator (CFTR) protein, has adverse effects that can be observed in newborns and continue to progress through adulthood. The CFTR protein is an epithelial chloride channel that aids in regulating salt and water absorption and secretion in various tissues. This function is defective in patients with CF due to a loss of cell surface expression and/or function of CFTR protein. The failure of mutated CFTR protein to regulate chloride transport results in the multisystem pathology associated with CF.

Since the introduction and continued advances of newborn and antenatal screening, many patients with CF are identified through a positive screening test and subsequently diagnosed within the first year of life. Approximately 63% of patients with CF in the EU and 75% of patients with CF in the UK are diagnosed by 1 year of age. In the US, more than 80% of patients with CF are diagnosed by 2 years of age. CF affects the paediatric population, as approximately half of the total CF patient population in the US, EU, and Australia and approximately 40% in Canada are less than 18 years of age.

Even before the widespread adoption of newborn screening, the majority of patients with CF were diagnosed in infancy or early childhood due to manifestations of the disease. In patients with severe genotypes (with gating mutations such as *G551D*), pancreatic destruction leading to pancreatic exocrine insufficiency begins in utero, and lung involvement, manifested by pulmonary inflammation and infection, begins shortly after birth. Loss of lung function is the major cause of morbidity and mortality in patients with CF. Infants with CF as young as 1 month show the presence of lung disease. High-resolution computed tomography studies of infants with CF who were diagnosed by newborn screening but considered clinically healthy showed that structural lung damage is common even very early in disease progression. In a cohort of 81 well-treated patients with CF in Australia, by the age of 3 years, 10% had *Pseudomonas aeruginosa* infection, and 84% had evidence of bronchiectasis. This is consistent with results of inflammatory marker studies that found that airway inflammation begins in infancy. Airway inflammation signals the beginning of the destructive cycles of chronic inflammation, infection, and irreversible lung damage that are characteristic of CF lung disease.

Exocrine pancreatic insufficiency and poor nutritional status are among the most significant clinical manifestations of CF in infants. These factors often lead to poor growth with subsequent growth delay, poorer cognitive development, and are associated with other clinical comorbidities such as decreased lung function and decreased survival. Malnourishment is associated with worsening lung function in children with CF 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.

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.

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

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, apart from the Environmental Risk Assessment data, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

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) was provided in Module 1.6.1 in procedure EMEA/H/C/002494/II/0082 which is resumed in the following table.

The prevalence data were for the total patient population, irrespective of age. Thus, the applied extension of indication in the 4 to 6 months age group is not considered to have an increase in environmental exposure to ivacaftor.

Substance (INN/Invented Name): VX-770							
CAS-number: 873054-44-5							
PBT screening			Result		Conclusion		
Bioaccumulation potential -log Kow			➤ 4.75 at pH 7		Potential PBT YES		
PBT-assessment							
Parameter		Result relevant for conclusion		Conclusion			
Persistence		DT ₅₀		DT _{50, system} = 1233/261 d (sandy silt loam sediment / sand sediment). DT ₅₀ soil = 166 to 316 days Soil DT ₅₀ values corrected to 12°C Conclusion: vP			
Bioaccumulation		BCF		<2000 Not B			
Toxicity		NOEC (aquatic)					
PBT-statement							
Phase I							
Calculation		Value		Unit	Remarks		
PEC _{surfacewater} Refined		0.026		0.081 µg/L	>0.01 threshold Yes		
Other concerns (e.g. chemical class)				None			
Phase II Physical-chemical properties and fate							
Study type		Test protocol		Results	Remarks		
Adsorption-Desorption		OECD 106		K _{oc} =11800 (sewage sludge) K _{oc} = 10800 (sewage sludge) K _{oc} = 3710 (sandy loam) K _{oc} = 1970 (sandy clay loam) K _{oc} = 5900 (clay loam)	Terrestrial studies triggered		
Ready Biodegradability Test		OECD 301		Not conducted	Considered not ready biodegradable		
Aerobic Transformation in Aquatic Sediment systems		OECD 308		DT ₅₀ water = 4.4 and 1.7 days DT ₅₀ sediment = 581 and 123 days % shifting to sediment (99 days) =78 % and 50.3% (VX-770); 96.3 % and 96.5% (total radioactivity)	No decline rate in the sediment phase could be calculated.		
Phase IIIa Effect studies							
Study type		Test protocol		Endpoint	Value	Unit	Remarks
Algae, Growth Inhibition (<i>Pseudokirchnerilla subcapita</i>)		OECD 201		NOEC	54.7	µg/L	Growth rate
<i>Daphnia</i> sp. Reproduction Test		OECD 211		NOEC	3.1	µg/L	
Fish, Early Life Stage Toxicity (<i>Pimephales promelas</i>)		OECD 210		NOEC	29	µg/L	
Activated Sludge, Respiration Test		OECD 209		NOEC	1 x 10 ⁶	µg/L	

Phase IIb Studies					
Study type	Test protocol	Endpoint	Value	Units	Remarks
Bioaccumulation	OECD 305	BCF	<2000		Not B
Aerobic Transformation in Soil (Four soils)	OECD 307	DT ₅₀ 166 to 316 days (DFOP model)			Combined VX-770 and M2 at 12°C
Soil Micro-organisms: Nitrogen Transformation Test	OECD 216	Effect			Not possible to estimate. It could be anticipated no effect at 100 x PECsoil
Terrestrial Plants, Growth (Six species)	OECD 208	NOEC	1000	mg/kg dw	Cabbage, carrot, lettuce, tomato, oat, and onion
Earthworm, Acute Toxicity Test	OECD 207	NOEC	1000	mg/kg dw	
Collembola, Reproduction Test	OECD 232	NOEC	1000	mg/kg dw	
Sediment dwelling organism (<i>Chironomus riparius</i>)	OECD 218	NOEC	7463	mg/kg dw	Corrected for 10% organic carbon

mg/kg dw = mg/kg dry weight of soil/sediment

2.2.2. Discussion on non-clinical aspects

No new non-clinical data have been submitted in the application, apart from the studies of updated ERA which was recently assessed in variation II/82 (extension of indication). This is accepted by CHMP.

2.2.3. Conclusion on the non-clinical aspects

The data submitted in the non-clinical part of the dossier are acceptable for this type of application. The updated data submitted in this application do not lead to a significant increase in environmental exposure further to the use of ivacaftor. Considering the above data, ivacaftor is not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

The third interim analysis of Cohorts 3 and 7 data from study 124 are submitted to support this application including patients from 3 months to less than 6 months. Of note, interim analysis report 1 and 2 were submitted and assessed in variations II/69 (Extension of Indication, children age 12 to less than 24 months) and X/75G (extension, children aged 6 to less than 12 months), respectively.

There is potential for patients with CF <6 months of age to benefit from IVA treatment based on evidence of unmet medical need and data showing a favourable benefit risk profile in older patient cohorts:

- Evidence of efficacy in subjects ≥6 years of age with a *G551D* mutation (Studies 102, 103, and 105) or a non-*G551D* mutation (Studies 111 and 112);
- Comparable PK and effects on sweat chloride (measure of *CFTR* function) in subjects 6 to <24 months of age with a *CFTR* gating mutation (Study 124 Cohorts 5 and 6); subjects 2 through 5 years of age with a *CFTR* gating mutation (Study 108); and subjects ≥6 years of age;
- The well-characterized safety profile in subjects ≥6 months of age;

- Evidence of complications of CF starting very early in life, including impaired pancreatic exocrine function, lung inflammation and poor weight gain; and
- Evidence supporting the benefits of early therapeutic intervention.

In the less than 6-month-old population, the rationale for IVA treatment is supported by the importance of slowing disease progression and the prevention of the negative consequences of CF such as compromised lung and pancreatic function and impaired nutritional status. It is expected that the primary benefit of IVA treatment in these younger CF subjects would derive from the potential to reduce the progression of disease before sustaining irreversible damage.

GCP

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

The applicant 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	<p>Part A:</p> <ul style="list-style-type: none"> • To evaluate the safety and PK of IVA treatment <p>Part B:</p> <ul style="list-style-type: none"> • To evaluate the safety, PK, PD, efficacy, and acceptability/ palatability of IVA treatment 	Nonrandomized, open-label, multiple-dose	IVA 25-, 50-, or 75-mg granules; 25, 50, or 75 mg q12h; PO	<p>Part A:</p> <p>Cohort 1: 7 subjects; Cohort 2: 6 subjects Cohort 3: 6 subjects</p> <p>Part B:</p> <p>Cohort 5: 19 subjects; Cohort 6: 11 subjects Cohort 7: 6 subjects</p> <p>Male and female subjects <24 months of age and have a <i>CFTR</i> gating mutation or <i>R117H</i> mutation (where approved for patients 2 to 5 years of age)</p>	<p>Part A:</p> <p>Days 1 through 3, and morning dose on Day 4</p> <p>Part B: 24 weeks</p>	<p>Ongoing; Cohorts 1 and 5; subjects 12 to <24 months of age are complete; Interim Analysis Report (IAR). Cohorts 2 and 6; subjects 6 to <12 months of age are complete; Interim Analysis 2 Report (IA2R). Cohort 3, subjects 3 to <6 months of age; and Cohort 7, subjects 4 to <6 months of age are complete; Interim Analysis 3 Report (IA3R).</p>

2.3.2. Pharmacokinetics

The pharmacokinetics (PK) of ivacaftor in the target age group of patients from 4 to <6 months of age was investigated in Study 124 which is an ongoing, two-part, open-label study, with part A assessing safety and PK and part B (24 weeks) assessing safety, PK, PD, and efficacy.

For Part A/Cohort 3, subjects who were 3 to less than 6 months of age and weighed ≥ 5 kg at Day 1 (IVA treatment initiation) and had an *R117H* mutation or *CFTR* gating mutation on at least 1 allele were eligible for enrolment. Because one 3-month-old subject (25-mg IVA q12h [every 12 hours]) had an AUC value above the 95th percentile of that observed in the adult population, Part B/Cohort 7 was limited to

subjects 4 to less than 6 months of age and weighing ≥ 5 kg at Day 1, with an *R117H* or *CFTR* gating mutation on at least 1 allele.

Dose: IVA was supplied as granules packaged in a foil-laminated sachet/packet and was administered orally q12h at the doses summarized in Table 1 after mixing with approximately 1 teaspoon (5 mL) of appropriate liquid or soft food and administered with an age-appropriate fat-containing meal or snack.

Table 1 Study 124 IVA Doses

Weight of Subjects	Part A/Cohort 3	Part B/Cohort 7	
	3 to <6 months of age	4 to <6 months of age ^a	≥ 6 months of age ^b
5 to <7 kg	25 mg	25 mg	25 mg
7 to <14 kg	50 mg	25 mg	50 mg
14 to <25 kg	75 mg	25 mg	75 mg

IVA: ivacaftor; q12h: every 12 hours

Note: All IVA doses were administered q12h.

^a Based on PK results in Part A/Cohort 3 (Section 2.1), all subjects in this age range in Part B/Cohort 7 received 25 mg IVA q12h regardless of weight.

^b After reaching 6 months of age in Part B/Cohort 7, the dose for each subject was adjusted at each study visit based on body weight, if necessary.

Sampling: The PK sampling schedule was as follows:

Part A	Day 4: pre-dose, between 2 and 4 hours, between 6 and 8 hours, and between 24 and 60 hours after dosing
Part B	Week 2: pre-dose, between 2 and 4 hours, and between 6 and 8 hours after the morning dose
	Week 8: pre-dose, 1 hour, and 4 hours after the morning dose
	Week 24: pre-dose and between 2 and 4 hours after the morning dose

Study population: From Study 124, PK data was available for Part A/Cohort 3 and Part B/Cohort 7. Study 124 data was added to a subset of the prior ivacaftor POP-PK data set that was previously constructed.

Methods: Nonlinear-mixed effect modelling was performed using NONMEM to construct a popPK model of IVA. In this analysis, the objective was to explore different IVA apparent oral clearance (CL/F) relationships to account for maturation as requested by CHMP.

A formal covariate search was not conducted. Instead, the effect of weight on CL/F was considered by either fixing the CL/F allometric exponent to 0.75, or implementing an empirical function to account for the effect of weight on CL/F.

Only the weight and age effects described above were tested as covariates affecting CL/F. Covariates were evaluated based on the improvement of the diagnostic plots, biological plausibility, and meaningful changes in the objective function. The suitability of all models was checked using standard goodness of fit plots and visual predictive checks.

Using select IVA population PK models, IVA exposures of area under the concentration-time curve for a dosing interval at steady state (AUC_{ss} or AUC_{0-12h}) were simulated for ages of 4 to <6 months at pre-specified weight groups of 5 to <7 kg and 7 to <14 kg. Steady state exposures were simulated for IVA doses of 15 mg q12h, 25 mg q12h, and 50 mg q12h. These results were compared to the adult reference range (i.e., the 5th and 95th percentiles of adult exposures). Body weights for the 4 to <6-month-old age group were randomly sampled from the World Health Organization growth charts (https://www.cdc.gov/growthcharts/who_charts.htm). At least 1000 subjects were sampled for each pre-

specified weight group. These simulations provide an appropriate comparison of the central tendency in AUC0-12h between these groups.

For the selected updated IVA popPK models, steady-state IVA AUC0-12h and Cmin values for Cohort7 from Study 124 were also calculated from empirical Bayes estimates and summarized (arithmetic mean and standard deviation). This cohort included subjects 4 to <6 months of age.

Exposure results:

Mean plasma concentrations of IVA, M1-IVA, and M6-IVA in Part A/Cohort 3 (Table 2) were consistent with plasma concentrations in subjects 6 months to <6 years of age and ≥ 12 years of age. These results supported continuing to dose this age group in Part B/Cohort 7 with the modifications described above.

Mean plasma concentrations of IVA, M1-IVA, and M6-IVA after 24 weeks of dosing IVA 25 mg q12h in Part B/Cohort 7 are presented in Table 2. The mean IVA, M1-IVA, and M6-IVA plasma concentrations in subjects 4 to <6 months of age in Part B/Cohort 7 were consistent with plasma concentrations previously observed in subjects 6 months to <6 years of age and ≥ 12 years of age.

Table 2 Study 124: Summary of Plasma Concentration by Nominal Time Point for IVA, M1-IVA, and M6-IVA in Subjects in Part A/Cohort 3 (3 to <6 Months) and Part B/Cohort 7 (4 to <6 Months) Administered 25 or 50 mg IVA q12h

Visit	Nominal Time (h)	N	Mean (SD) (ng/mL)		
			IVA	M1-IVA	M6-IVA
Part A/Cohort 3, IVA 25 (n = 3) or 50 mg (n = 3)					
	0	6	839 (845)	2050 (1490)	3220 (2110)
	2 to 4	6	999 (570)	1850 (1020)	2600 (1720)
	6 to 8	6	1310 (1000)	2690 (1920)	3250 (2210)
	24 to 60	5 ^a	106 (45.8)	403 (172)	1100 (863)
Part B/Cohort 7, IVA 25 mg ^b (N = 6)					
Week 2	0	6	426 (387)	1200 (906)	2530 (3400)
	2 to 4	6	880 (1340)	1760 (2450)	2710 (4240)
	6 to 8	4	1250 (1480)	2680 (2570)	3830 (4650)
Week 8 ^c	0	6	421 (270)	1430 (890)	2150 (1420)
	1	5	417 (131)	1240 (476)	2080 (1170)
	4	5	1090 (358)	2380 (440)	2280 (1010)
Week 24	0	6	310 (324)	1130 (737)	1890 (794)
	2 to 4	6	758 (534)	1580 (757)	1560 (637)

Source: Study 124 IA3R/Table 11-1 and Table 11-2

IVA: ivacaftor; n: size of subsample; N: total sample size; q12h: every 12 hours

Note: Subjects are shown in dose group according to their Day 1 dose.

^a One subject was excluded from analysis at 24 to 60 hours because of a dosing error (Study 124 IA3R/Table 11-1).

^b All 6 subjects went on to receive 50 mg IVA q12h after reaching 6 months of age and 7 kg.

^c One subject received 25 mg IVA at the Week 8 Visit, but should have received 50 mg IVA. This subject was excluded from the postdose descriptive statistics summary at Week 8 (Study 124 IA3R/Table 11-2).

Structural population PK model:

A popPK model that describes IVA disposition was used to evaluate the PK data from Study 124 including data from both Part A/Cohort 3 and Part B/Cohort 7 which used a sparse PK sampling approach. Based on the PK results of Part A/Cohort 3, Part B/Cohort 7 was limited to subjects 4 to less than 6 months of age. The objectives of the popPK analysis were to characterize the PK of IVA in subjects with CF 3 months

through 18 years of age and to compare exposures of subjects 4 to <6 months of age (the age group for which approval is being sought) to those previously obtained in adults.

PK data from Study 124 (both Part A/Cohort 3 and Part B/Cohort 7) were integrated with an existing dataset of Phase 3 studies conducted in subjects with CF, including paediatric subjects ≥ 6 months through 18 years of age.

IVA PK was described by a 2-compartment model with zero-order delivery to the absorption compartment and subsequent first-order absorption. The model incorporates both weight and age as predictors of apparent oral clearance (CL/F). 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 estimates of PK model parameters for the reference subject are provided in the popPK report. The medians of the individual parameter estimates for IVA in CF subjects from Part B/Cohort 7 (ages 4 to <6 months of age) were 4.33 L/h for CL/F, 9.13 L for apparent central volume (Vc/F), 9.60 L for apparent peripheral volume (Vp/F), 2.40 L/h for inter-compartmental clearance (Q/F), 2.79 h for zero-order dose duration (D1), and 0.191 h⁻¹ for the first-order absorption rate (ka). Most parameters were estimated precisely. In prior popPK analyses, body weight and age were the most significant predictors of IVA disposition; other covariates (race, gender, and patient status [CF versus healthy subject]) did not explain a significant portion of the inter-subject variability. For the current paediatric analysis, body weight and age were incorporated into the model to describe their effects on IVA disposition.

Table 3: Model Run Log

Table 2: IVA model run log

Run	Description	OFV	delta OFV
100	Base model, no covariates	23835	0
101	Allometric model without maturation	23652	-183
102	Estimated allometric without maturation	23647	-188
103	Empirical weight effect model without maturation	23652	-183
104	Empirical weight effect model with maturation [Selected Final Model]	23626	-209
105	Empirical weight effect model with maturation, remove IOV	23915	80
106	Allometric model with fast maturation	23654	-181
107	Allometric model with slow maturation	23756	-79

Source code: ./scriptFinal/ReportRunLog.R
Source tex: ./delivFinal/table/runlog.tex

*All delta OFV are referenced to the base model (Run 100).

From Table 4, the empirical model with maturation (Model 104) and the allometric model without maturation (Model 101) provide the most parsimonious descriptions of the data. Further investigation was performed to explore the fit of these models to the data (See tables and figures below).

Table 4: Parameter Estimates and Precisions for Model 104 (Empirical Model With Maturation)**Table 3:** Population PK parameter estimates from the empirical model with maturation (Run 104)

Description	Parameter	Estimate	%RSE	Variability
apparent initial clearance	$CL_i/F \sim \theta_1$	7.05 L/hr	7.74	
apparent central volume	$V_c/F \sim \theta_2$	94.9 L	22.6	
apparent peripheral volume	$V_p/F \sim \theta_3$	98.1 L	34.6	
apparent intercompartmental clearance	$Q/F \sim \theta_4$	13.7 L/hr	32.4	
first order absorption rate	$k_a \sim \theta_5$	0.191 hr ⁻¹	22	
zero order absorption time	$D1 \sim \theta_6$	2.79 hr	2.63	
maximum apparent clearance for weight range	$CL_{max}/F \sim \theta_7$	12.0 L/hr	11.9	
Hill coefficient for body weight scaling	$hcw \sim \theta_8$	12.0	63.2	
body weight to achieve half maximum clearance	$WT_{50} \sim \theta_9$	35.8 kg	4.09	
weight effect on V_c/F	$\sim \theta_{10}$	1.00 Fixed		
weight effect on V_p/F	$\sim \theta_{11}$	1.00 Fixed		
weight effect on Q/F	$\sim \theta_{12}$	0.750 Fixed		
Hill coefficient for maturation	$hcm \sim \theta_{13}$	5.74	54.5	
time to reach half mature clearance	$TM_{50} \sim \theta_{14}$	58.2 weeks	8.25	
Interindividual variance of CL_i/F	$IIV_{CL_i/F} \sim \Omega_{1,1}$	0.167	12.4	%CV = 42.6
Interindividual covariance of CL_i/F and V_c/F	$IIV_{CL_i/F-V_c/F} \sim \Omega_{2,1}$	0.0149	219	CORR = 0.0561
Interindividual variance of V_c/F	$IIV_{V_c/F} \sim \Omega_{2,2}$	0.425	38	%CV = 72.8
Interindividual covariance of CL_i/F and $D1$	$IIV_{CL_i/F-D1} \sim \Omega_{3,1}$	0.0579	28.6	CORR = 0.341
Interindividual covariance of V_c/F and $D1$	$IIV_{V_c/F-D1} \sim \Omega_{3,2}$	0.0953	44.7	CORR = 0.352
Interindividual variance of $D1$	$IIV_{D1} \sim \Omega_{3,3}$	0.173	14	%CV = 43.5
Interoccasion variance of $F1$	$IOV_{F1} \sim \Omega_{4,4}$	0.207	16.3	%CV = 48.0
proportional residual error	$err_{prop} \sim \Sigma_{1,1}$	0.0461	14.4	%CV = 21.5
additive residual error	$err_{add} \sim \Sigma_{2,2}$	4620	22.4	SD = 68.0 ng/mL

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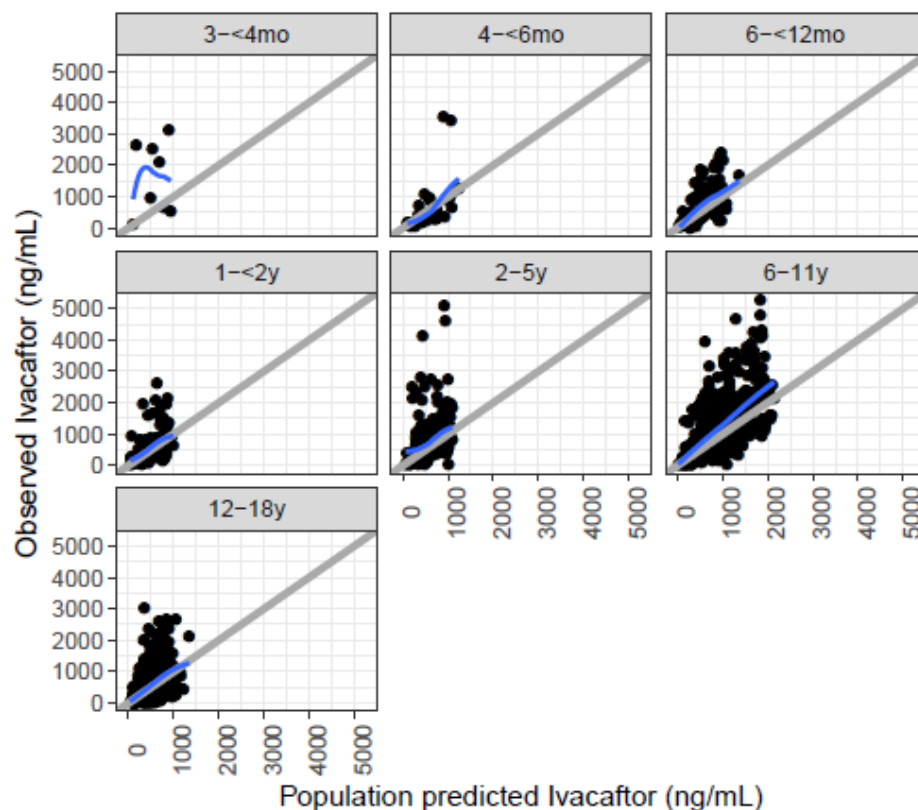
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Figure 1: Selected Diagnostics for Model 104 (Empirical with Maturation) Indicate Reasonable Fit for All Subjects

(a)

Figure 3: Observed vs. population predicted IVA concentration: stratified by age, empirical model with maturation (Run 104)

Observed concentrations are plotted vs. population predictions. Values are indicated by black circles with a loess smooth trend line (solid blue) through the data. The line of identity (solid gray) is included as a reference.



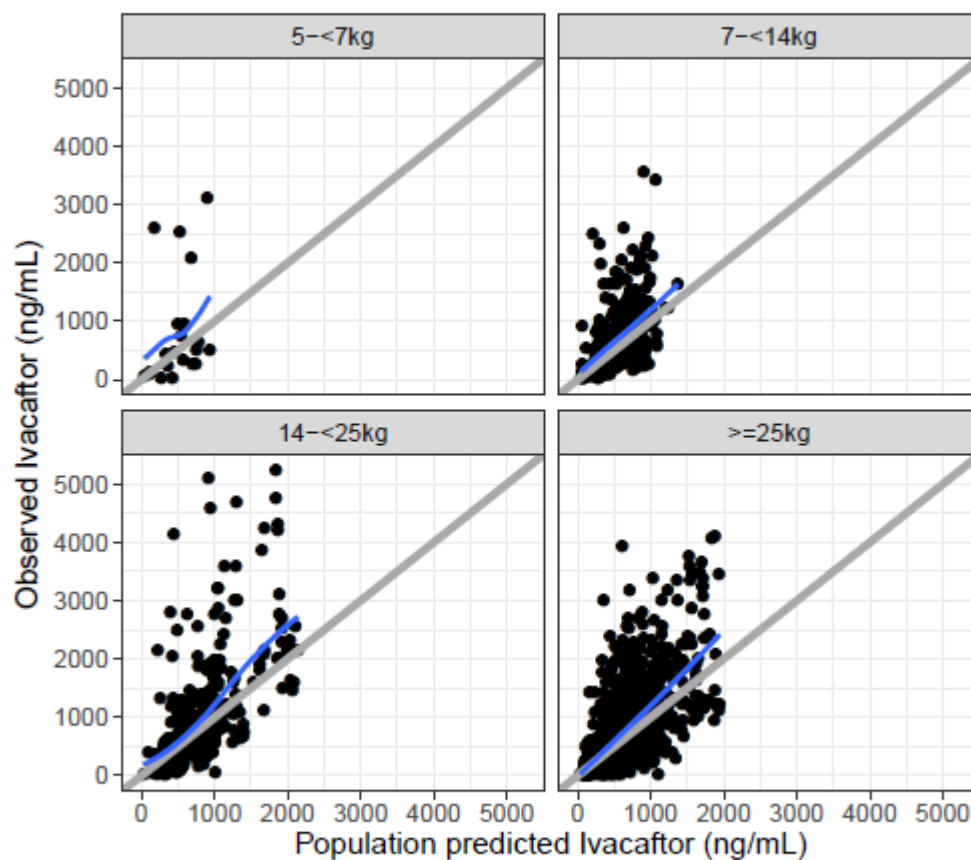
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(b)

Figure 4: Observed vs. population predicted IVA concentration: stratified by weight, empirical model with maturation (Run 104)

Observed concentrations are plotted vs. population predictions. Values are indicated by black circles with a loess smooth trend line (solid blue) through the data. The line of identity (solid gray) is included as a reference.



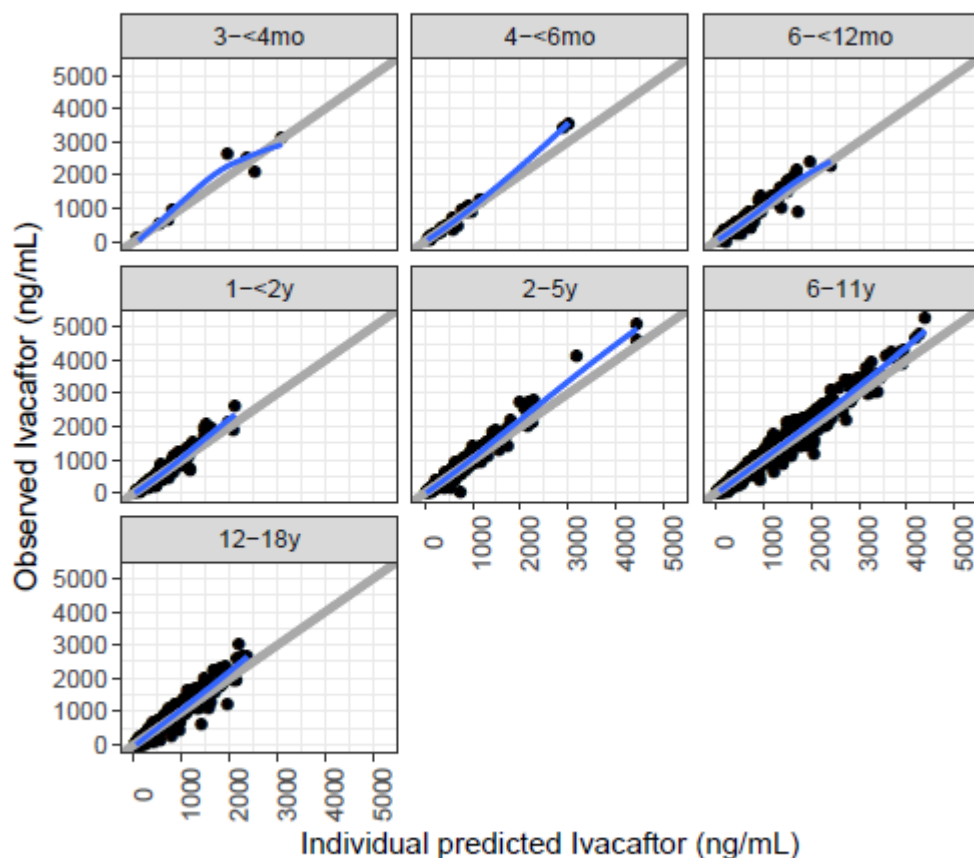
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Source graphic: ./delivFinal/figure/diagPlots_finWT_dv_pred.pdf

(c)

Figure 6: Observed vs. individual predicted IVA concentration: stratified by age, empirical model with maturation (Run 104)

Observed concentrations are plotted vs. individual predictions. Values are indicated by black circles with a loess smooth trend line (solid blue) through the data. The line of identity (solid gray) is included as a reference.



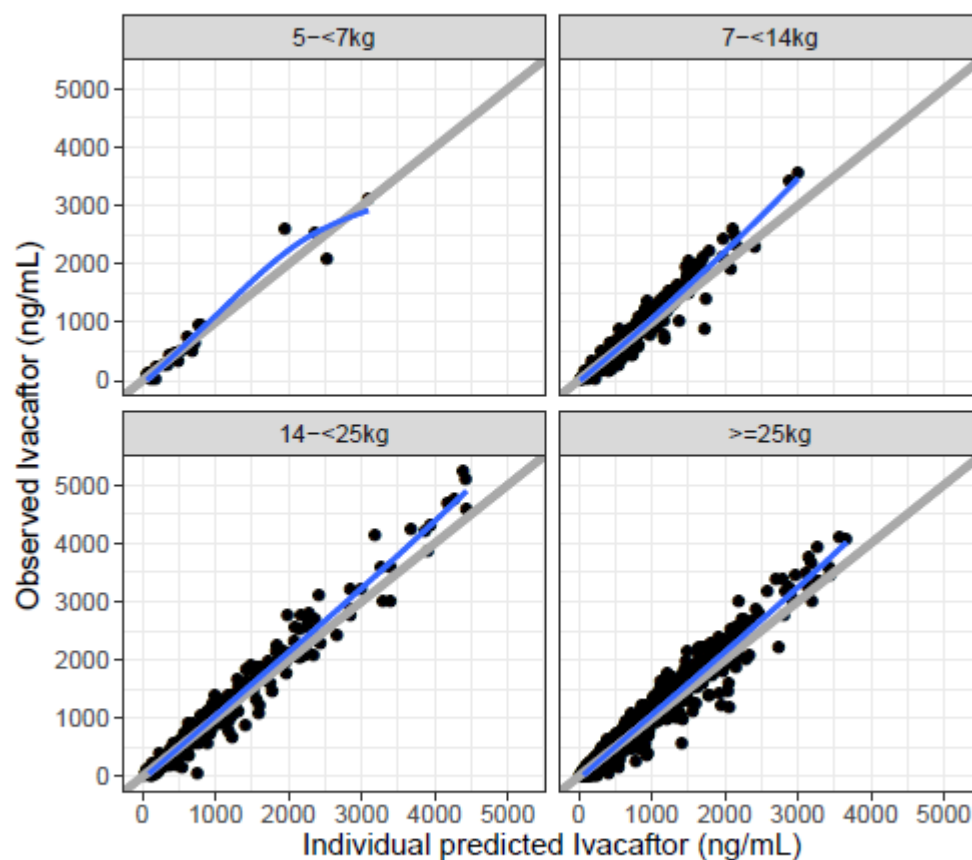
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(d)

Figure 7: Observed vs. individual predicted IVA concentration: stratified by weight, empirical model with maturation (Run 104)

Observed concentrations are plotted vs. individual predictions. Values are indicated by black circles with a loess smooth trend line (solid blue) through the data. The line of identity (solid gray) is included as a reference.



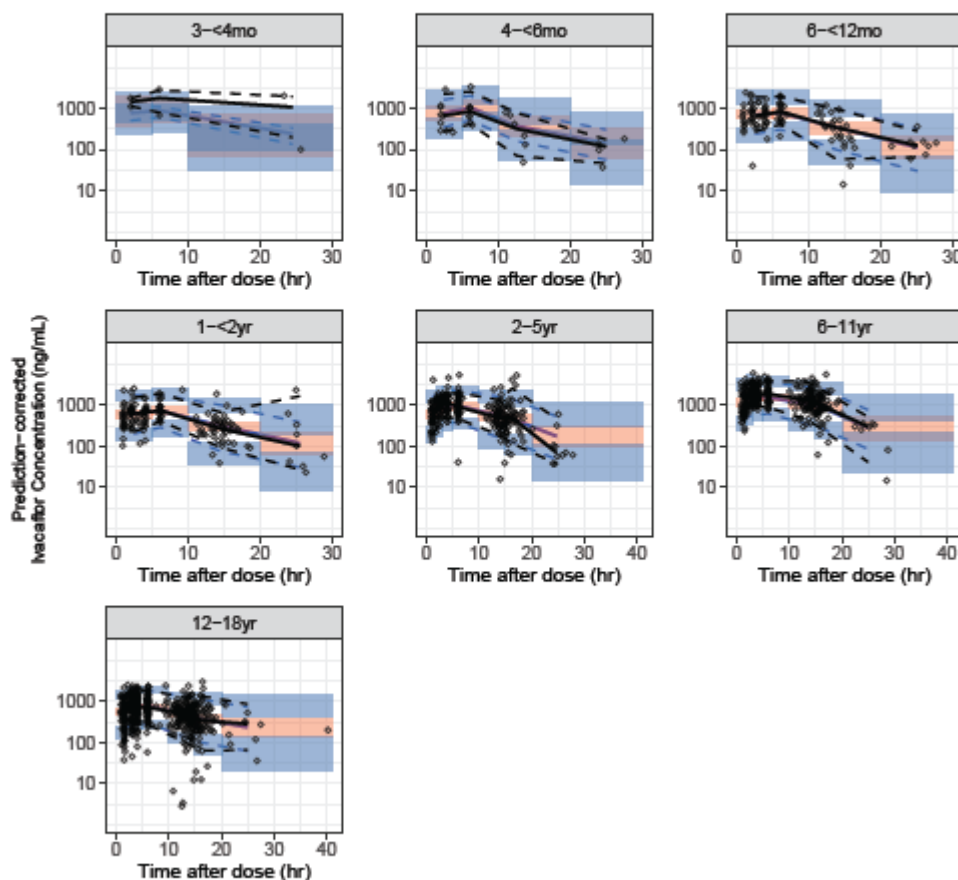
Source code: diagPlots.R

Source graphic: /delivFinal/figure/diagPlots_finWT_dv_ipred.pdf

(e)

Figure 32: Prediction-corrected VPC: stratified by age, empirical model with maturation (Run 104)

Observed concentrations at steady state are plotted (black circles) vs. time after dose with the 5th (black dashed line), 50th (black solid line), and 95th percentiles (black dashed line) of the observed data. The red shaded area represents the 90% prediction bands of the 50th percentile of the simulated data (blue solid line). The blue shaded area represents the 90% prediction bands of the 5th and 95th percentiles of the simulated data (blue dash lines). Data are presented on the y-axis in log scale.



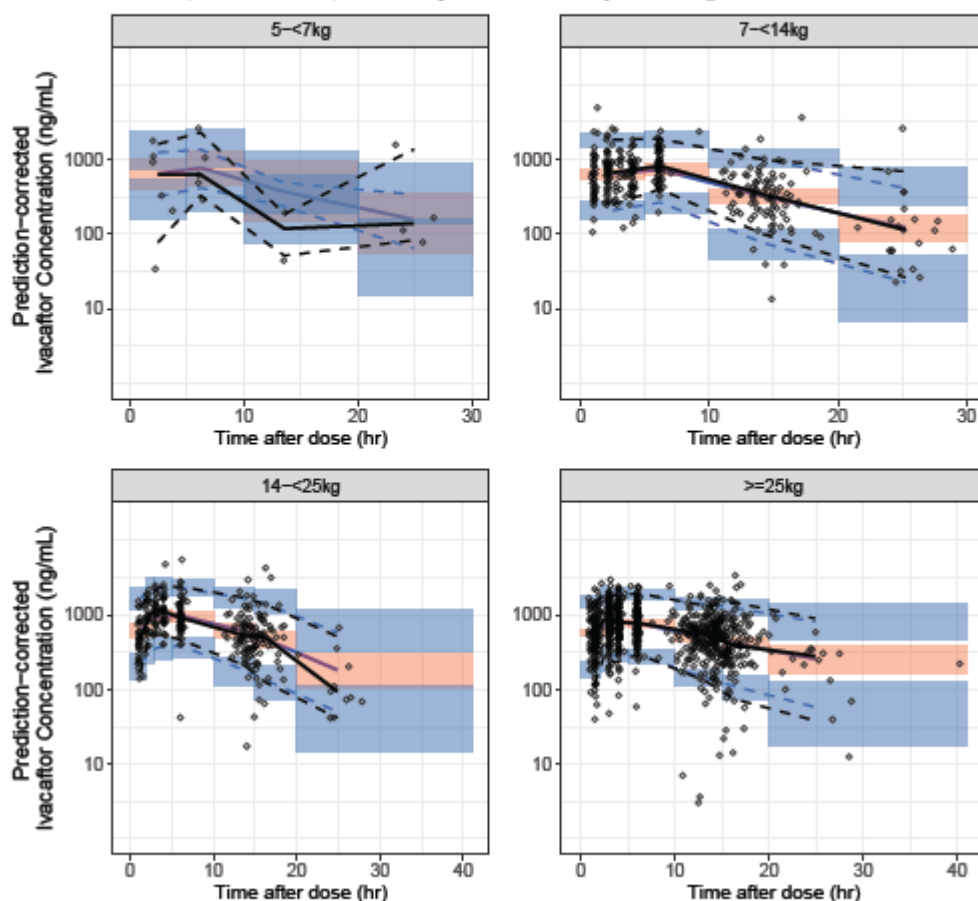
Source code: PKpredcheck.R

Source graphic: JdelivFinalFigure/PKpredcheck_Emax_pcvpc_age.pdf

(f)

Figure 33: Prediction-corrected VPC: stratified by weight, empirical model with maturation (Run 104)

Observed concentrations at steady state are plotted (black circles) vs. time after dose with the 5th (black dashed line), 50th (black solid line), and 95th percentiles (black dashed line) of the observed data. The red shaded area represents the 90% prediction bands of the 50th percentile of the simulated data (blue solid line). The blue shaded area represents the 90% prediction bands of the 5th and 95th percentiles of the simulated data (blue dash lines). Data are presented on the y-axis in log scale.



Source code: PKpredcheck.R

Source graphic: JdelivFinalfigure/PKpredcheck_Emax_pcvpc_wt.pdf

Table 5: Parameter Estimates and Precisions for Model 101 (Allometric Model Without Maturation)

Table A1: Population PK parameter estimates from the allometric model without maturation (Run 101)

Description	Parameter	Estimate	%RSE	Variability
apparent clearance	$CL/F \sim \theta_1$	22.0 L/hr	3.54	
apparent central volume	$V_c/F \sim \theta_2$	85.5 L	23.6	
apparent peripheral volume	$V_p/F \sim \theta_3$	76.3 L	51.1	
apparent intercompartmental clearance	$Q/F \sim \theta_4$	11.8 L/hr	43.3	
first order absorption rate	$k_a \sim \theta_5$	0.174 hr ⁻¹	23.4	
zero order absorption time	$D1 \sim \theta_6$	2.77 hr	2.78	
weight effect on CL/F	$\sim \theta_7$	0.750 <i>Fixed</i>		
weight effect on Vc/F	$\sim \theta_8$	1.00 <i>Fixed</i>		
weight effect on Vp/F	$\sim \theta_9$	1.00 <i>Fixed</i>		
weight effect on Q/F	$\sim \theta_{10}$	0.750 <i>Fixed</i>		
interindividual variance of CL/F	$IV_{CL/F} \sim \Omega_{1,1}$	0.200	12	%CV = 47.1
interindividual covariance of CL/F and Vc/F	$IV_{CL/F-V_c/F} \sim \Omega_{2,1}$	0.0190	190	CORR = 0.0622
interindividual variance of Vc/F	$IV_{V_c/F} \sim \Omega_{2,2}$	0.466	38	%CV = 77.0
interindividual covariance of CL/F and D1	$IV_{CL/F-D1} \sim \Omega_{3,1}$	0.0778	23.1	CORR = 0.426
interindividual covariance of Vc/F and D1	$IV_{V_c/F-D1} \sim \Omega_{3,2}$	0.0936	50.7	CORR = 0.336
interindividual variance of D1	$IV_{D1} \sim \Omega_{3,3}$	0.166	14.8	%CV = 42.5
interoccasion variance of F1	$IOV_{F1} \sim \Omega_{4,4}$	0.214	16.1	%CV = 48.8
proportional residual error	$err_{prop} \sim \Sigma_{1,1}$	0.0447	14	%CV = 21.1
additive residual error	$err_{add} \sim \Sigma_{2,2}$	4560	21.7	SD = 67.5 ng/mL

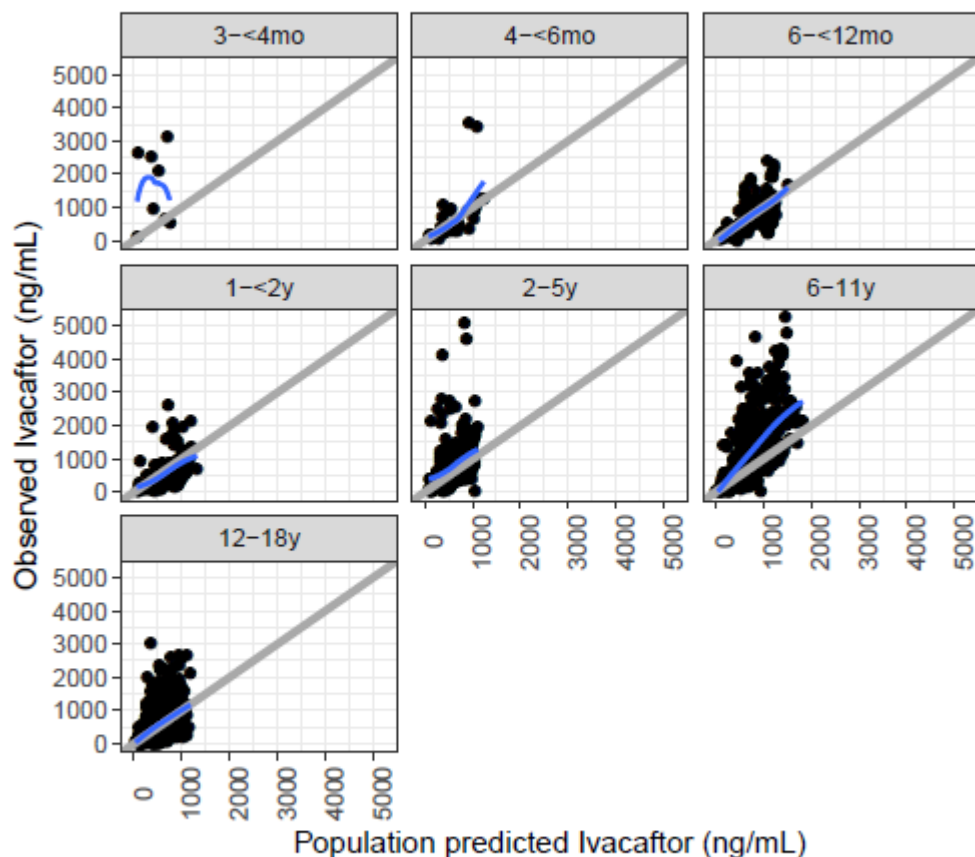
Source code: ./scriptFinal/ReportParamTables.R
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Figure 2: Selected Diagnostics for Model 101 (Allometric Model Without Maturation)

(a)

Figure A2: Observed vs. population predicted IVA concentration: stratified by age, allometric model without maturation (Run 101)

Observed concentrations are plotted vs. population predictions. Values are indicated by black circles with a loess smooth trend line (solid blue) through the data. The line of identity (solid gray) is included as a reference.



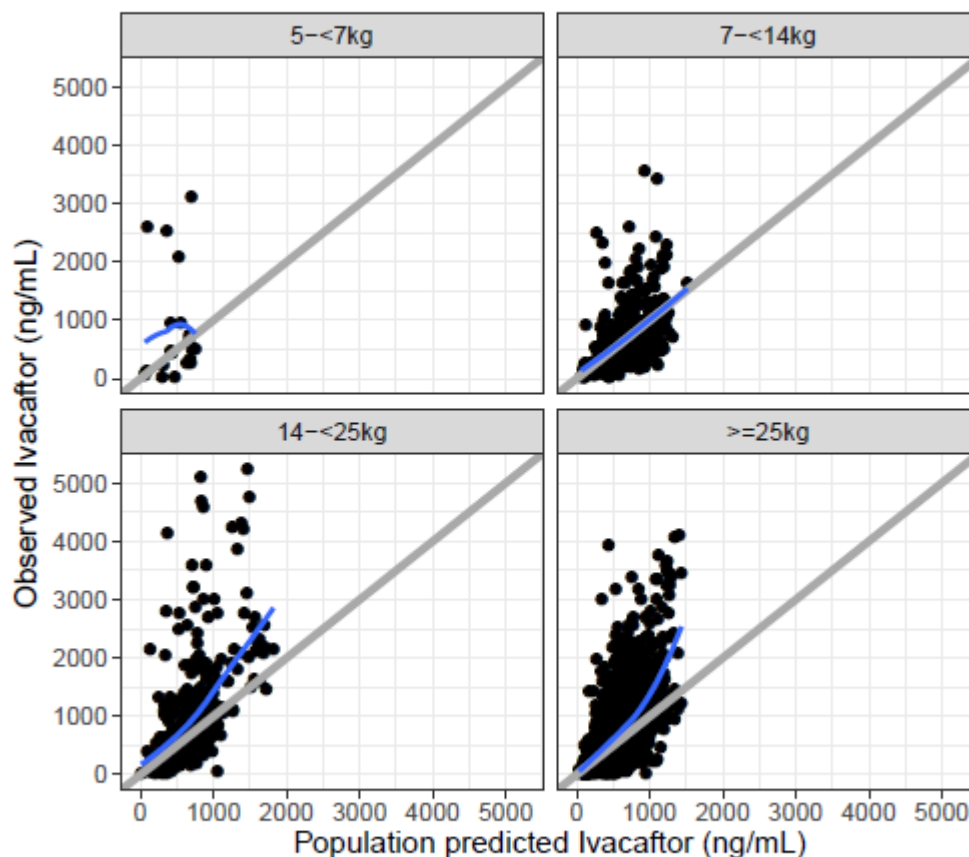
Source code: diagPlots.R

Source graphic: ./delivFinal/figure/diagPlots_alloAGE_dv_pred.pdf

(b)

Figure A3: Observed vs. population predicted IVA concentration: stratified by weight, allometric model without maturation (Run 101)

Observed concentrations are plotted vs. population predictions. Values are indicated by black circles with a loess smooth trend line (solid blue) through the data. The line of identity (solid gray) is included as a reference.



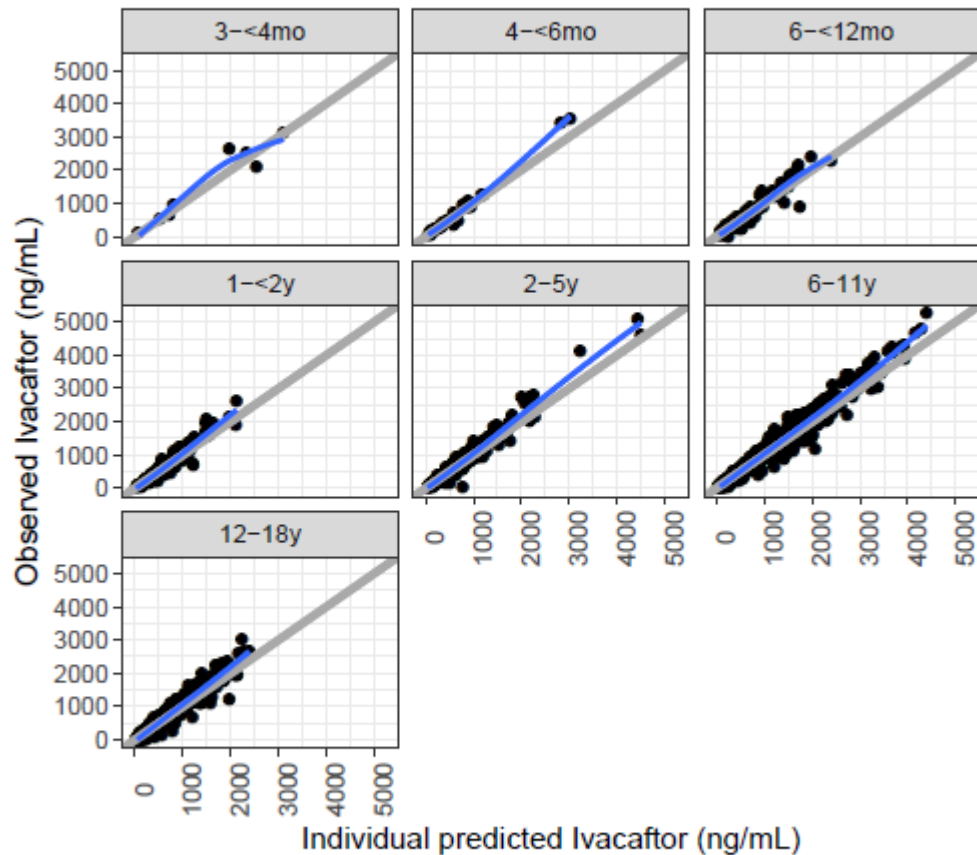
Source code: diagPlots.R

Source graphic: ./delivFinal/figure/diagPlots_alloWT_dv_pred.pdf

(c)

Figure A5: Observed vs. individual predicted IVA concentration: stratified by age, allometric model without maturation (Run 101)

Observed concentrations are plotted vs. individual predictions. Values are indicated by black circles with a loess smooth trend line (solid blue) through the data. The line of identity (solid gray) is included as a reference.



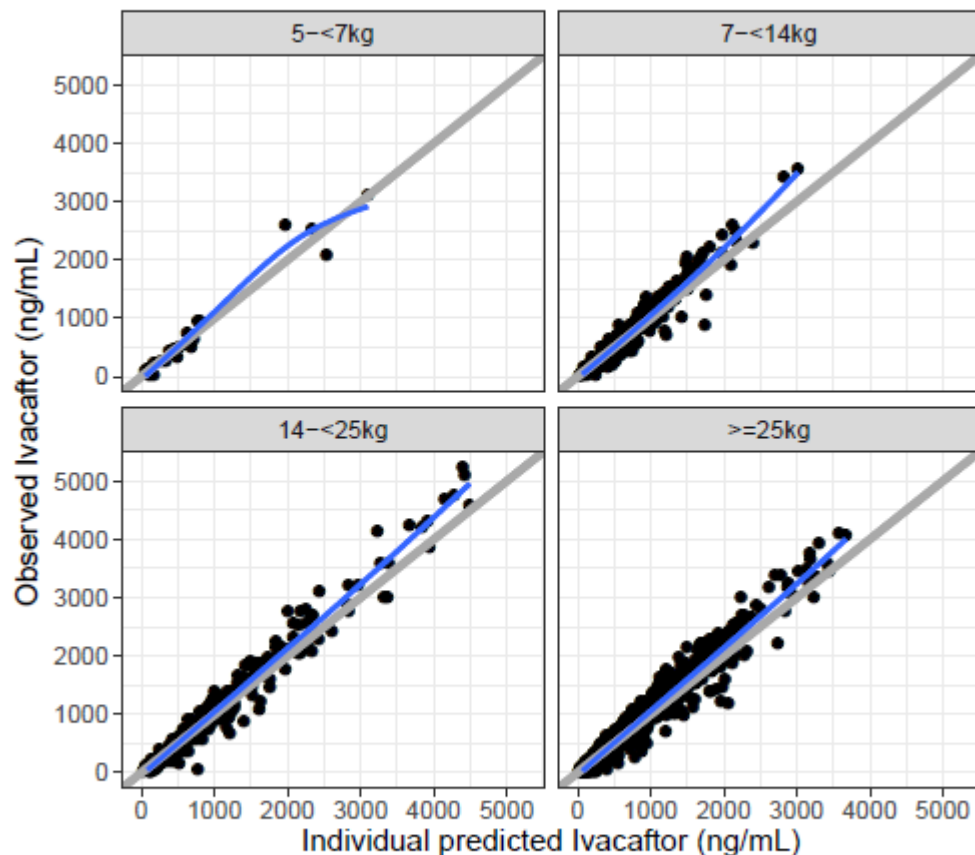
Source code: diagPlots.R

Source graphic: ./delivFinal/figure/diagPlots_alloAGE_dv_ipred.pdf

(d)

Figure A6: Observed vs. individual predicted IVA concentration: stratified by weight, allometric model without maturation (Run 101)

Observed concentrations are plotted vs. individual predictions. Values are indicated by black circles with a loess smooth trend line (solid blue) through the data. The line of identity (solid gray) is included as a reference.



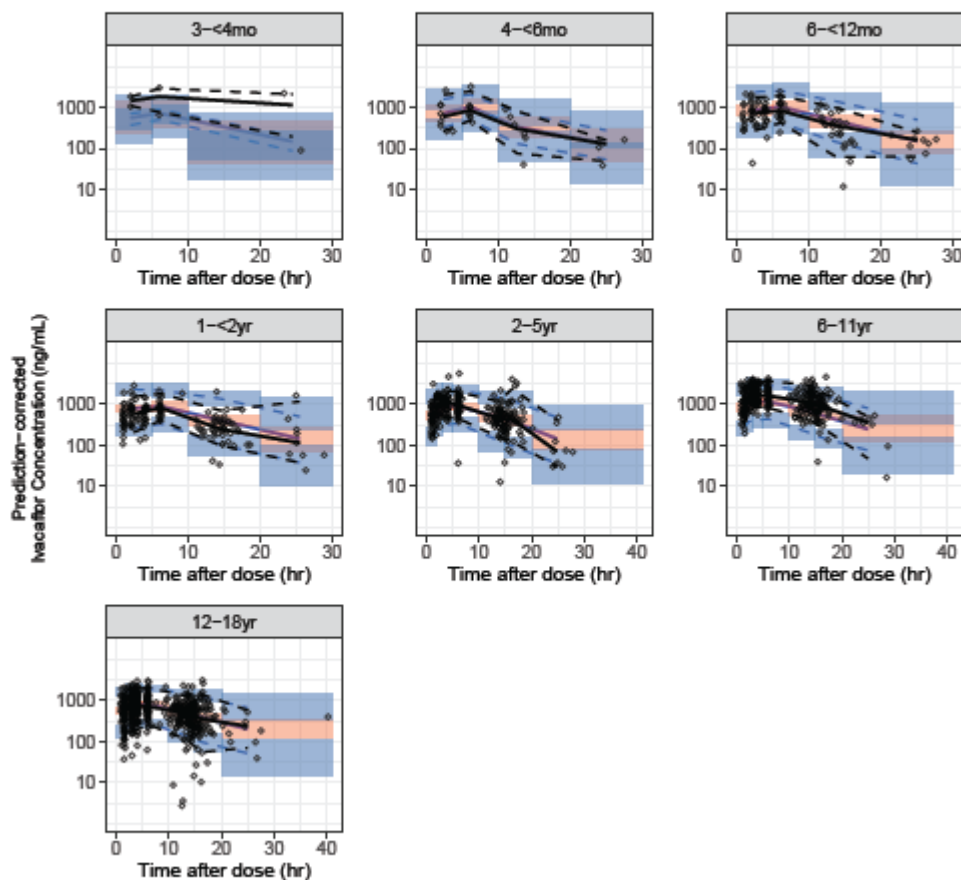
Source code: diagPlots.R

Source graphic: /delivFinal/figure/diagPlots_alloWT_dv_ipred.pdf

(e)

Figure A31: Prediction-corrected VPC: stratified by age, allometric model without maturation (Run 101)

Observed concentrations at steady state are plotted (black circles) vs. time after dose with the 5th (black dashed line), 50th (black solid line), and 95th percentiles (black dashed line) of the observed data. The red shaded area represents the 90% prediction bands of the 50th percentile of the simulated data (blue solid line). The blue shaded area represents the 90% prediction bands of the 5th and 95th percentiles of the simulated data (blue dash lines). Data are presented on the y-axis in log scale.



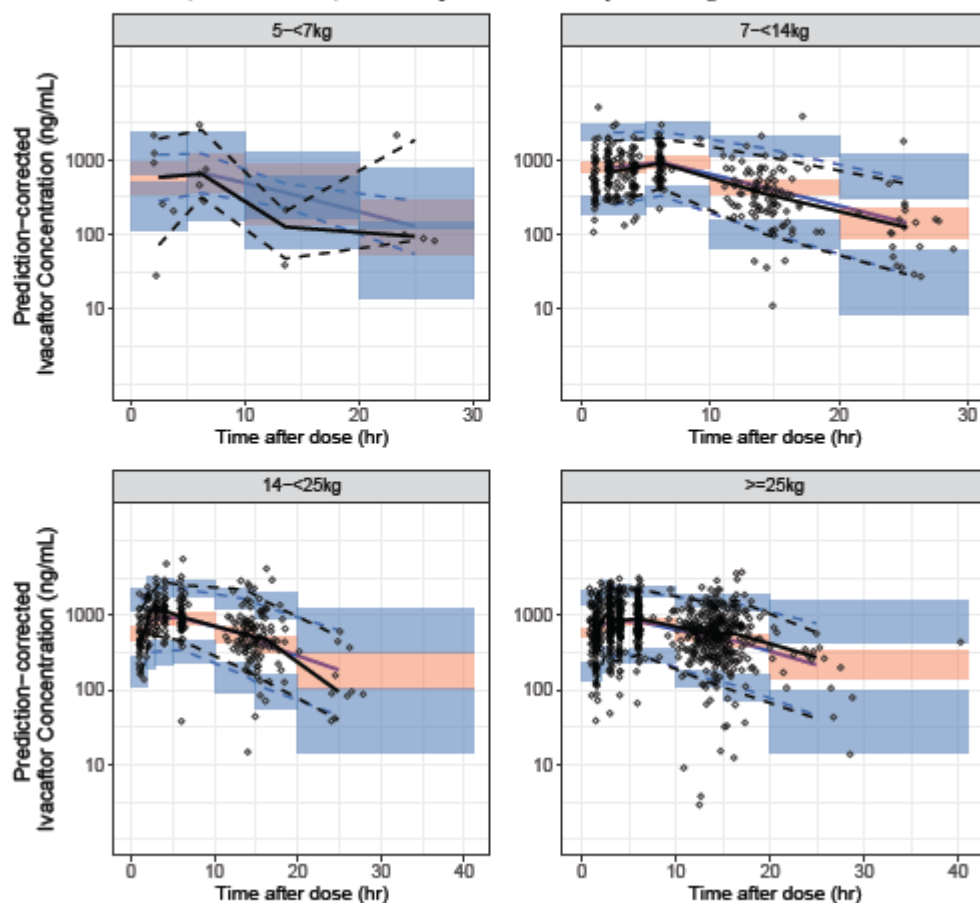
Source code: PKpredcheck.R

Source graphic: ./delivFinal/figure/PKpredcheck_Alo_pcvpc_age.pdf

(f)

Figure A32: Prediction-corrected VPC: stratified by weight, allometric model without maturation (Run 101)

Observed concentrations at steady state are plotted (black circles) vs. time after dose with the 5th (black dashed line), 50th (black solid line), and 95th percentiles (black dashed line) of the observed data. The red shaded area represents the 90% prediction bands of the 50th percentile of the simulated data (blue solid line). The blue shaded area represents the 90% prediction bands of the 5th and 95th percentiles of the simulated data (blue dash lines). Data are presented on the y-axis in log scale.



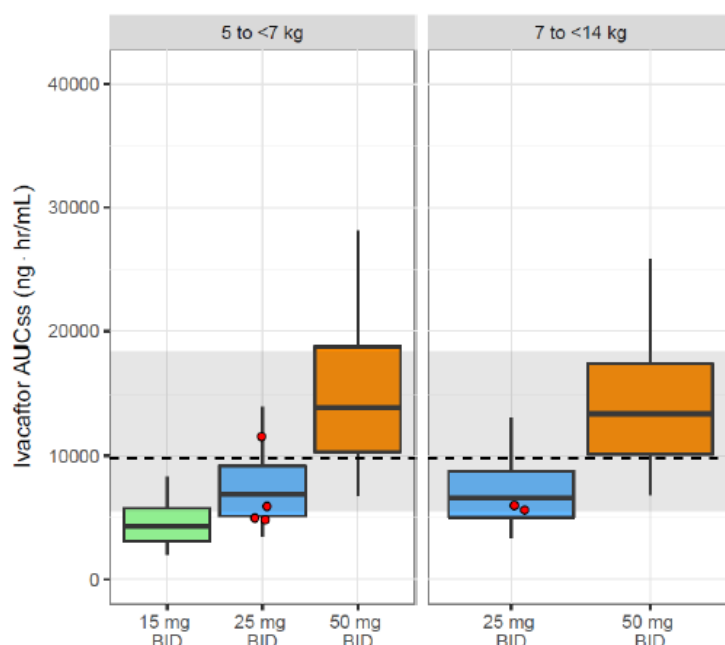
Source code: PKpredcheck.R
Source graphic: JdelivFinalfigure/PKpredcheck_Allo_pcvpc_wt.pdf

IVA exposures:

In Part A/Cohort 3 (subjects 3 to <6 months of age), mean plasma concentrations of IVA, M1-IVA, and M6-IVA were consistent with plasma concentrations in subjects 6 months to <6 years of age and ≥ 12 years of age. Similarly, in Part B/Cohort 7 (subjects 4 to <6 months of age), mean plasma concentrations of IVA, M1-IVA, and M6-IVA were consistent with plasma concentrations in subjects 6 months to <6 years of age and ≥ 12 years of age.

Results from the selected final popPK model (104, empirical model with maturation) show that in subjects 4 to <6 months of age administered 25 mg q12h IVA granules in Study 124, IVA AUC exposure was similar to that observed in adults administered IVA 150 mg tablets q12h as shown in Figure 3. The majority of the AUC exposures are predicted to be in the adult exposure range, albeit at the lower end of this range. These exposures are deemed appropriate given that IVA is a sensitive CYP3A substrate and there is a potential for higher IVA exposures due to the variability in CYP3A maturation in this age group.

Figure 3: Predicted IVA AUC Distribution in Subjects 4 to <6 Months With CF



Source: [Report Q005/Figure 39](#)

BID: twice per day (q12h); CF: cystic fibrosis; IQR: interquartile range; IVA: ivacaftor; q12h: every 12 hours

Notes: Boxplots are simulated subjects 4 to <6 months of age, where black lines in the center of the box are medians, boxes are the IQR, and whiskers are the 5th to 95th percentile region. Red circles are exposures from subjects in Part B/Cohort 7. The shaded area represents the adult 5th to 95th percentile region with the median exposure shown as a dashed line.

Exposure parameters for IVA in subjects with CF, as determined from the popPK model, are compared across age groups in Table 6. The AUC exposure levels of IVA in subjects 4 to <6 months of age in Study 124 are similar with those previously shown to be safe and efficacious in Phase 3 studies in subjects with CF 6 months to <6 years of age and ≥12 years of age (Studies 102, 108, and 124). These exposure data for IVA and metabolites confirm the appropriateness of the doses evaluated in Study 124 for the treatment of CF patients 4 to <6 months of age.

Table 6: IVA Exposure in Subjects with CF by Age

Age Group	N	C _{min,ss} (ng/mL)		AUC _{ss} (ng·h/mL)	
		Median (min, max)	Mean (SD)	Median (min, max)	Mean (SD)
4 to <6 months (25 mg) ^a	6	300 (232, 733)	371 (183)	5770 (4830, 11500)	6480 (2520)
6 to <12 months (25 mg) ^b	1	336	336	5410	5410
6 to <12 months (50 mg)	16	365 (172, 987)	508 (252)	7600 (3600, 16200)	9140 (4200)
12 to <24 months (50 mg)	19	383 (124, 829)	440 (212)	8900 (4830, 16400)	9050 (3050)
12 to <24 months (75 mg)	2	451 (363, 540)	451 (125)	9600 (8330, 10900)	9600 (1800)
2 to 5 years (50 mg)	9	536 (170, 1310)	577 (317)	9840 (5120, 20800)	10500 (4260)
2 to 5 years (75 mg)	26	580 (225, 1540)	629 (296)	10200 (6260, 22700)	11300 (3820)
6 to 11 years ^c	40	1100 (275, 2840)	1240 (594)	18700 (5060, 40600)	20000 (8330)
12 to 17 years	78	508 (141, 1270)	564 (242)	8670 (3280, 20600)	9240 (3420)
Adults	190	634 (167, 2080)	701 (317)	9840 (3580, 28200)	10700 (4100)

Sources: Report Q005/Table 6 (ages 4 to <6 months); Report P268/Table 5 (ages 6 to <12 months); and Report N364/Tables 8 and 9 (all other age groups)

CF: cystic fibrosis; IVA: ivacaftor; N: total sample size; q12h: every 12 hours

^a For the 4 to <6 month age group, only subjects from Study 124 Part B/Cohort 7 were included.

^b Values are based on data from a single subject; the SD is not reported.

^c In Report K260/Tables 8 and 9, C_{min,ss} and AUC_{ss} were simulated for ages 6 through 11 years based on weight. In subjects weighing ≥14 to <25 kg, the mean (SD) for a 75 mg q12h dosage was 641 (329) ng/mL for C_{min,ss} and 10760 (4470) ng·h/mL for AUC_{ss}. In subjects weighing ≥25 kg, the mean (SD) for a 150 mg q12h dosage was 958 (546) ng/mL for C_{min,ss} and 15300 (7340) ng·h/mL for AUC_{ss}.

2.3.3. Pharmacodynamics

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

2.3.4. Discussion on clinical pharmacology

The pharmacokinetics (PK) of ivacaftor in the target age group of patients from 3 months of age until 6 months was investigated in Study 124. In Part A/Cohort 3 (subjects 3 to <6 months of age), mean plasma concentrations of IVA, M1-IVA, and M6-IVA were consistent with plasma concentrations in subjects 6 months to <6 years of age and ≥12 years of age. Similarly, in Part B/Cohort 7 (subjects 4 to <6 months of age), mean plasma concentrations of IVA, M1-IVA, and M6-IVA were consistent with plasma concentrations in subjects 6 months to <6 years of age and ≥12 years of age.

The Clinical Pharmacology of ivacaftor in paediatric patients from 3 to 6 months of age has been characterized using a previous population PK model developed in older paediatric and adult patients. The popPK model has been updated to account for the allometric and maturation effects observed in CL. Two

alternatives were finally selected and assessed with the experimental observations of IVA. The popPK model including simultaneously an empirical function to describe the maturation effect based on body weight and allometric effects provided a better description of the data. This approach was accepted by CHMP.

The MAH provided the experimental and predicted IVA AUC values after 50 mg q12h from Part A model-predicted IVA AUC values in paediatric patients receiving 50 mg q12h are slightly over-predicted compared to the very few experimental AUC observations (only available in paediatric patients from 7 to <14 kg). This result suggests that the dosing recommendation proposed in paediatric patients from 3 to 6 months of age from 7 to <14 kg (50 mg q12h) is adequate since the experimental IVA AUC values lay within the 5th and 95th percentile region of the adult exposure.

Upon CHMP's request, the MAH provided confirmation that C_{min} observations available in paediatric patients from 4 to <6 months of age from 5 to <14 kg of weight were adequately captured by model predictions.

Results from the popPK model show that in subjects 4 to <6 months of age administered 25 mg q12h IVA granules in Study 124, IVA AUC exposure was similar to that observed in adults administered IVA 150 mg tablets q12h. The majority of the AUC exposures are predicted to be in the adult exposure range, albeit at the lower end of this range. These exposures are deemed appropriate given that IVA is a sensitive CYP3A substrate and there is a potential for higher IVA exposures due to the variability in CYP3A maturation in this age group. Thus, the suggested dose recommendation for this age group is supported by the popPK data.

2.3.5. Conclusions on clinical pharmacology

The recommended dose of IVA granules for patients 4 to <6 months is 25 mg for patients weighing >5kg, administered q12h with fat-containing food. The proposed dosing recommendation is agreed by the CHMP.

2.4. Clinical efficacy

The efficacy presented for this extension of indication is based on an interim analysis from study 124 reporting data from subjects 3 to <6 months of age (Part A/Cohort 3) and subjects 4 to <6 months of age (Part B/Cohort 7).

Study 124 is an ongoing, phase 3, 2-part, open-label study in subjects <24 months with 1 of the following mutations on at least 1 *CFTR* allele: *G551D*, *G178R*, *S549N*, *S549R*, *G551S*, *G1244E*, *S1251N*, *S1255P*, or *G1349D*. Subjects with an *R117H* mutation were eligible to enrol in regions where IVA was granted marketing authorization for use in patients 2 through 5 years of age with an *R117H* mutation. Part A had a 5-day treatment period to assess safety and pharmacokinetics (PK) in advance of Part B, and Part B had a 24-week treatment period to assess safety, PK, pharmacodynamics (PD), efficacy, and acceptability/palatability.

Given the underlying pathophysiology of CF and as outlined in the ICH guideline E11 (Clinical Investigation of Medicinal Products in the Paediatric Population), efficacy data in subjects 4 to <6 months of age can also be extrapolated from data from older populations of subjects as suggested below:

- Results from placebo-controlled Phase 3 studies in subjects with CF ≥6 years of age who had the *G551D* mutation (Studies 102 and 103) or a non-*G551D* gating mutation (Study 111) showed that IVA is effective in the treatment of subjects with CF, 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, respiratory symptoms, and weight gain.

- In addition, the safety, PK, PD and efficacy of IVA treatment in subjects 2 through 5 years of age with a gating mutation was evaluated in open-label Study 108. Results of Study 108 demonstrated the safety and PK of IVA treatment in subjects 2 through 5 years of age. Furthermore, results from Study 108 demonstrated that IVA improved *CFTR* function in subjects 2 through 5 years of age, with corresponding positive effects on pancreatic function, and nutritional status.

2.4.1. Dose response study

No formal dose-response study has been performed, however, selection of doses for Part A and Part B in Study 124 was supported by PopPK simulation data.

Based on the dosing regimen confirmed in part A/Cohort 3, patients received 25 mg ivacaftor every 12 hours in Part B/Cohort 7. Initially, Cohort 7 was planned to include children aged 0-6 months. In part A, one subject who received 25 mg q12h ivacaftor had an AUC value above the 95th percentile of that observed in the adult population, suggesting that IVA exposures may be impacted by maturation at this age. To ensure IVA exposure did not exceed the targeted adult range (95th percentile), Part B/Cohort 7 was limited to subjects 4 to <6 months of age, weighing ≥ 5 kg.

2.4.2. Main study

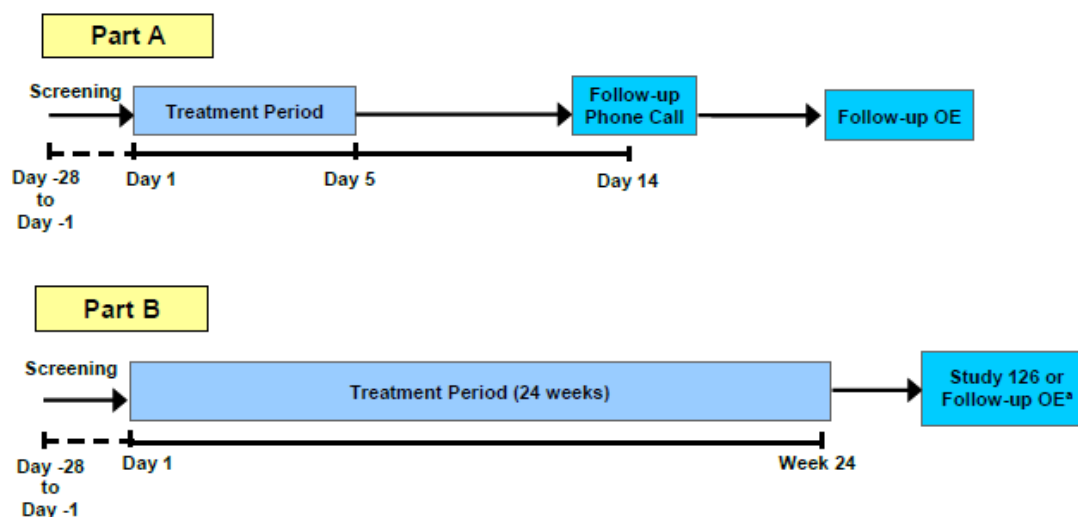
Title of Study

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

Methods

Study 124 is an ongoing Phase 3, 2-part, open-label study of orally administered IVA in subjects with CF who were <24 months of age at treatment initiation (Day 1) and have a *CFTR* gating mutation or *R117H* (currently in the US only) on at least 1 allele. This present analysis of data from study 124 corresponds to the Interim Analysis 3 Report in the cohort of patients from 3 to less than 6 months of age. Part A was designed to evaluate the safety and PK of multiple-dose administration of IVA over 4 days of dosing, and to confirm (or adjust if necessary) the doses for Part B. Part B was designed to evaluate the safety, PK, PD, and efficacy of IVA in subjects over 24 weeks.

Figure 4: Study 124 Design



Source: Study 124 IA3R/Figure 9-1

OE: ophthalmologic examination

Note: Each cohort in Parts A and B includes at least 5 subjects. Subjects who completed 24 weeks of treatment in Part B had the option of enrolling in an open-label extension study (Study 126).

^a The Follow-up OE was not required for subjects who enrolled in the treatment arm of Study 126.

The study is ongoing as younger subjects are being enrolled in subsequent descending age cohorts of the study following PK and safety assessments for each age cohort, as follows:

- Cohort 1: subjects aged 12 to <24 months
- Cohort 2: subjects aged 6 to <12 months
- Cohort 3: subjects aged 3 to <6 months
- Cohort 4: subjects aged 0 to <3 months

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

- Cohort 5: subjects aged 12 to <24 months
- Cohort 6: subjects aged 6 to <12 months
- Cohort 7: subjects aged 4 to <6 months

Subjects 3 to <6 months of age were enrolled in Part A/Cohort 3. To ensure IVA exposure was not above the adult 95th percentile, the Part B/Cohort 7 dose and age range were selected such that Part B/Cohort 7 was limited to subjects 4 to <6 months of age weighing ≥ 5 kg.

Cohorts 3 and cohort 7 are the subject of this application and assessed thereafter.

Study participants

Key inclusion criteria

- Male or female with confirmed diagnosis of CF, defined as a sweat chloride value ≥ 60 mmol/L by quantitative pilocarpine iontophoresis OR 2 CF-causing mutations.
- Must have had 1 of the following 9 *CFTR* mutations on at least 1 allele: *G551D*, *G178R*, *S549N*, *S549R*, *G551S*, *G1244E*, *S1251N*, *S1255P*, or *G1349D*. Subjects who had an *R117H-CFTR*

mutation were eligible in regions where IVA is approved for use in subjects 2 through 5 years of age with an *R117H-CFTR* mutation.

- Aged 0 to <24 months at Day 1; subjects who completed Part A who were ≥ 24 months of age on Day 1 in Part B were not eligible to enrol in Part B.
- For Cohorts 4 and 7 only, gestational age ≥ 38 weeks.
- Weight at screening within the weight limits as defined for the study drug dose levels.

Key exclusion criteria

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

Treatments

IVA granules were administered orally every 12 hours (q12h) at the doses presented in Table 7 (Study 124 IVA Doses) after mixing with approximately 1 teaspoon (5 mL) of appropriate liquid or soft food and administered with an age-appropriate fat-containing meal or snack.

Table 7: Study 124 IVA Doses

Weight of Subjects	Part A/Cohort 3	Part B/Cohort 7	
	3 to <6 months of age	4 to <6 months of age ^a	≥ 6 months of age ^b
5 to <7 kg	25 mg	25 mg	25 mg
7 to <14 kg	50 mg	25 mg	50 mg
14 to <25 kg	75 mg	25 mg	75 mg

IVA: ivacaftor; PK: pharmacokinetic; q12h: every 12 hours

Note: All IVA doses were administered q12h

^a Based on PK results in Part A/Cohort 3 (Module 2.7.2/Section 2.1), all subjects in this age range in Part B/Cohort 7 received 25 mg IVA q12h regardless of weight.

^b After reaching 6 months of age in Part B, the dose for each subject was adjusted at each study visit based on body weight, if necessary.

In Part A, IVA was administered for 4 days to obtain steady-state concentrations of IVA.

In Part B, IVA was administered for 24 weeks. This treatment duration was consistent with analyses of Phase 3 studies of IVA in subjects ≥ 2 years of age (Studies 102, 103, and 108).

Prior and concomitant medications: Subjects were encouraged to remain on their prescribed CF therapies during Study 124. Selected concurrent medications, such as moderate and strong CYP3A inhibitors or inducers, were prohibited if the potential existed for untoward drug-drug interactions.

Objectives

Part A

Primary

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

Part B

Primary

- To evaluate the safety of IVA

Secondary

- To evaluate the PK of IVA and metabolites M1-IVA and M6-IVA
- To evaluate the pharmacodynamics (PD) of IVA

Tertiary

- To evaluate the efficacy of IVA
- To evaluate the acceptability/palatability of IVA granules

Outcomes/endpoints

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

PK endpoints: refer to PK section of this report.

Primary safety endpoints: AEs, clinical laboratory values (haematology and serum chemistry), OEs, standard 12-lead ECGs, vital signs

Pharmacodynamic endpoint: sweat chloride test

Tertiary efficacy endpoints: Absolute change from baseline for weight, length, weight-for-length, weight-for-age z-score, length-for-age z-score, weight-for-length-for-age z-score, lung clearance index (LCI)/multiple breath washout (MBW) at qualified study sites, infant pulmonary function tests (IPFT) including forced expiratory volume in 0.5 seconds, forced mid-expiratory flow rate, forced vital capacity, and functional residual capacity at qualified study sites, marker of pancreatic function (FE-1), markers of pancreatic inflammation/injury (IRT, lipase, and amylase; lipase and amylase levels were collected as part of safety assessments), markers of intestinal inflammation (faecal calprotectin), qualitative microbiology cultures; pulmonary exacerbations (PEx), CF-related hospitalizations, and acceptability/palatability of IVA granules.

Sample size

A minimum of 5 subjects were planned to enrol in each of the cohorts for Parts A and B. In this interim analysis, the Full Analysis Set (FAS) and Safety Set included:

- Part A/Cohort 3: 6 subjects who enrolled in Cohort 1 and received at least 1 dose of IVA
- Part B/Cohort 7: 6 subjects who enrolled in Cohort 5 and received at least 1 dose of IVA

Randomisation

Not applicable, as this was a single-treatment-arm study.

Blinding (masking)

This was an open-label study.

Statistical methods

Study 124 is still ongoing study. The sample size was based on the availability of the subject population and PK analysis considerations, and not on any statistical consideration. Therefore, the study is not powered to detect a significant treatment effect. Continuous variables and categorical variables were summarized by standard descriptive statistics. The CHMP considered that the applied descriptive methods were adequate for the limited study goals set in protocol.

Results

Participant flow

PART A: A total of 6 subjects were enrolled and included in the Safety Set. All 6 subjects completed 4 days of treatment.

PART B: A total of 6 subjects were enrolled and included in the Safety Set. All subjects completed the 24 weeks of treatment. No subjects prematurely discontinued study drug treatment

Recruitment

Subjects from Cohort 3 were enrolled at 6 sites in the UK, and the US. Subjects from Cohort 7 were enrolled at 6 sites in the UK and the US.

Conduct of the study

Protocol amendments

The original protocol was amended once but did not have a major impact on the conduct of the study.

A dose justification memo (05 November 2018) provided an update to the cohort age and dose for subjects in Part B/Cohort 7 such that enrolment would be limited to subjects 4 to <6 months of age, weighing ≥ 5 kg.

Protocol deviations

There was 1 protocol deviation that was identified as an important protocol deviation (IPD). Due to pharmacist oversight at the Week 8 Visit, one subject was incorrectly dispensed 25 mg IVA instead of 50 mg IVA. The subject should have received 50 mg IVA at this visit because the subject had reached 6 months of age and weighed >7 kg. The subject was correctly dispensed the correct dose (50 mg IVA) approximately 1 week later. No safety concerns were identified.

The data cut for this interim analysis occurred on 13 January 2020.

Baseline data

PART A/Cohort 3

Demographics: The mean age of the 3 subjects in the 25-mg group was 3.3 months (range: 3 to 4 months) at Day 1. In the 50-mg group, the mean age of the 3 subjects was 5.0 months (range: 5 to 5 months). All 6 subjects were White and not of Hispanic or Latino ethnicity. All subjects had the G551D mutation. The most prevalent genotype was G551D/F508del (5 of 6 subjects).

Baseline characteristics: In general, as expected from the weight-based dosing, weight, length, weight-for-length, and body mass index (BMI) values were greater in the subjects in the 50-mg group than in the subjects in the 25-mg group, see table 8 below.

Table 8: Baseline Characteristics, Safety Set, Part A/Cohort 3

Characteristic	IVA 25 mg N = 3	IVA 50 mg N = 3	Total N = 6
Weight (kg)			
n	3	3	6
Mean (SD)	5.8 (0.5)	7.8 (0.5)	6.8 (1.2)
Median	6.0	8.1	6.7
Min, max	5.3, 6.2	7.2, 8.1	5.3, 8.1
Length (cm)			
n	3	3	6
Mean (SD)	61.7 (3.8)	67.2 (0.9)	64.4 (3.9)
Median	60.0	67.2	66.2
Min, max	59.0, 66.0	66.3, 68.1	59.0, 68.1
Weight-for-length (percentile)			
n	3	3	6
Mean (SD)	30.7 (33.1)	53.3 (25.2)	42.0 (29.1)
Median	26.1	56.6	41.6
Min, max	0, 66	27, 77	0, 77
BMI (kg/m²)			
n	3	3	6
Mean (SD)	15.41 (1.73)	17.26 (0.80)	16.33 (1.58)
Median	15.23	17.47	16.80
Min, max	13.77, 17.22	16.38, 17.94	13.77, 17.94

Source: [Table 14.1.3.1.a3](#)

BMI: body mass index; IVA: ivacaftor; n: size of subsample; N: total sample size

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 in Part A.

Prior and concomitant medications: In general, concomitant medication use was typical of a CF population. The most commonly reported concomitant medications were vitamins (100.0%), medications related to pancreatic enzyme replacement therapy (83.3%), and salbutamol (50.0%). Flucloxacillin, paracetamol, and ranitidine were each taken by 33.3% of subjects.

PART B /Cohort 7

Demographics: The mean weight at baseline was 6.9 kg (range: 5.9 to 7.9 kg). The mean age at baseline was 4.5 months (range: 4 to 5 months). All subjects were White and of non-Hispanic or Latino ethnicity. Five subjects had a *G551D* mutation, and 1 subject had an *R117H* mutation. The most prevalent genotype was *G551D/F508del* (4 of 6 subjects).

Baseline characteristics: weight, length, weight-for-length, and BMI values were within the normal range, but below the median of the reference population, for this age group, see table 9 below.

Table 9: Baseline Characteristics, Safety Set, Part B/Cohort 7

Characteristic	IvA 25 mg N = 6
Weight (kg)	
n	6
Mean (SD)	6.9 (0.7)
Median	6.9
Min, max	5.9, 7.9
Length (cm)	
n	6
Mean (SD)	65.2 (3.4)
Median	64.1
Min, max	61.2, 70.0
Weight-for-length (percentile)	
n	6
Mean (SD)	30.7 (28.7)
Median	25.4
Min, max	4, 81
BMI (kg/m²)	
n	6
Mean (SD)	16.19 (1.17)
Median	16.25
Min, max	14.87, 18.16
Weight-for-age z-score	
n	6
Mean (SD)	-0.65 (0.98)
Median	-0.77
Min, max	-1.92, 0.98
Length-for-age z-score	
n	6
Mean (SD)	-0.12 (1.71)
Median	-0.54
Min, max	-1.99, 2.79
Weight-for-length-for-age z-score	
n	6
Mean (SD)	-0.66 (0.97)
Median	-0.67
Min, max	-1.72, 0.88

Source: [Table 14.1.3.1.b7](#)

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

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

Medical history: 6 (100.0%) subjects had microbiological (oropharyngeal) assessments at baseline. Two of the 6 subjects had positive baseline Hemophilus influenzae cultures and 2 different subjects had positive baseline methicillin-susceptible Staphylococcus aureus cultures.

Table 10: Medical History That Occurred in At Least 2 Subjects, Safety Set, Part B/Cohort 7

Condition (Preferred Term)	IVA 25 mg N = 6 n (%)
CF lung ^a	3 (50.0)
Pancreatic failure	3 (50.0)

Source: Table 14.1.4.b7

CF: cystic fibrosis; IVA: ivacaftor; n: size of subsample; N: total sample size; PT: Preferred Term

Notes: A subject with multiple events within a PT was counted only once within the PT. Medical history events were coded with MedDRA Version 22.1.

^a CF lung indicates clinical manifestation of CF lung disease. Age of onset of CF lung disease varies.

Prior and concomitant medication: In general, concomitant medication use was typical of a CF population. The most commonly reported concomitant medications were vitamins (100.0%), medications related to pancreatic enzyme replacement therapy (83.3%), and sodium chloride (66.7%). Amoxicillin, flucloxacillin, and salbutamol were each taken by 33.3% of subjects.

Outcomes and estimation

Sweat chloride (Secondary efficacy pharmacodynamic endpoint):

The absolute changes from baseline were calculated at each time point for those subjects in Part B/Cohort 7 that had both a baseline value and a value at that time point. Two subjects had a missing baseline sample because of insufficient sweat sample volume or test not performed. For these subjects, historical sweat chloride values were used for baseline. Five subjects did not have a Week 2 sweat chloride measurement (1 not collected, 4 sweat sample volumes were insufficient). Three subjects did not have sweat chloride measurements at Week 24: for 1 subject, measurements were not collected, and for 2 subjects, sweat sample volumes were insufficient.

The mean (SD) sweat chloride level at baseline was 97.4 (16.4) mmol/L. Mean absolute sweat chloride levels decreased (improved) by Week 2 to near carrier levels, and this improvement was durable during the 24-week treatment period (Figure 11-1). The mean (SD) absolute change from baseline in sweat chloride was -34.0 (SD not applicable [NA]) mmol/L (n = 1) at Week 2, -65.6 (12.0) mmol/L (n = 5) at Week 12, and -50.0 (17.3) mmol/L (n = 3) at Week 24. Mean absolute changes from baseline in sweat chloride concentration are summarized in Table 11 and Figure 5.

The absolute changes from baseline in sweat chloride are summarised in Table 11 and Figure 5 below.

Table 11: Absolute Change From Baseline in Sweat Chloride (mmol/L) at Each Visit, FAS, Part B/Cohort 7

Visit	Statistic	IVA 25 mg N = 6	
		Sweat Chloride (mmol/L)	Absolute Change From Baseline at Visit (mmol/L)
Baseline	n	6	NA
	Mean (SD)	97.4 (16.4)	NA
	Median	101.0	NA
	Min, max	75.0, 119.5	NA
Week 2	n	1	1
	Mean (SD)	41.0 (–)	-34.0 (–)
	Median	41.0	-34.0
	Min, max	41.0, 41.0	-34.0, -34.0
Week 12	n	5	5
	Mean (SD)	36.3 (6.3)	-65.6 (12.0)
	Median	34.0	-66.0
	Min, max	31.0, 46.5	-81.5, -51.0
Week 24	n	3	3
	Mean (SD)	37.7 (2.9)	-50.0 (17.3)
	Median	36.0	-41.0
	Min, max	36.0, 41.0	-70.0, -39.0

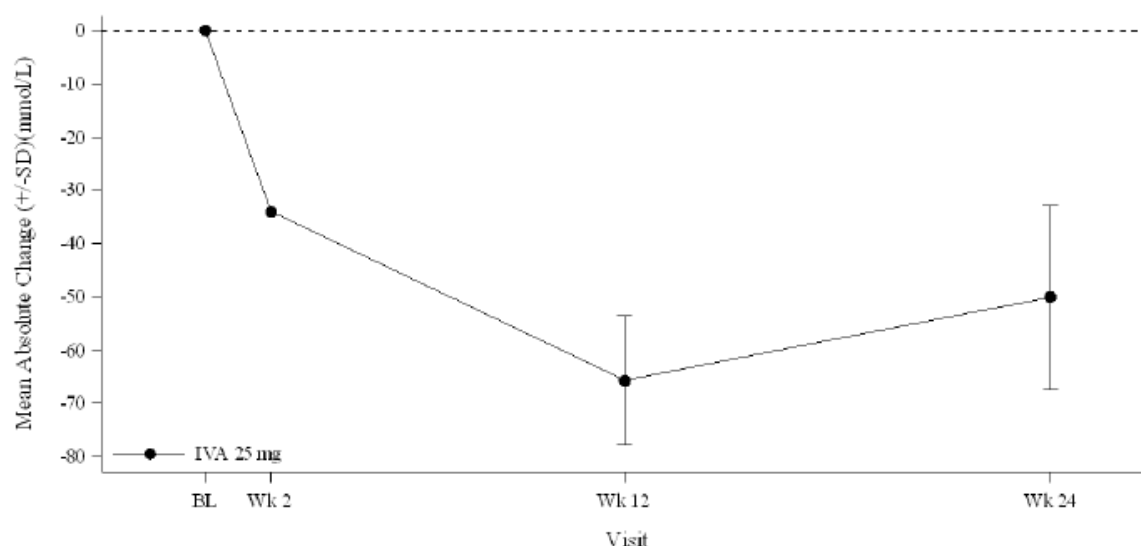
Source: Table 14.2.1.1.b7

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

Notes: Baseline was defined as the most recent measurement before the first dose of study drug in Part B.

Subjects shown in dose group according to their Day 1 dose in Part B.

Figure 5: Mean absolute change from baseline in Sweat Chloride by Visit, FAS, Part B/Cohort 7



Source: Figure 14.2.1.1.b7

BL: baseline; FAS: Full Analysis Set; IVA: ivacaftor; n: size of subsample; Wk: week

Note: n for each visit was as follows: BL: n = 6; Wk 2: n = 1; Wk 12: n = 5; Wk 24: n = 3

To evaluate individual subject response to IVA, a waterfall plot showing the absolute change from baseline in sweat chloride at Week 12 (for subjects with baseline and Week 12 results) and Week 24 (for subjects with baseline and Week 24 results) is presented in Figure 6 and Figure 7, respectively.

Figure 6 **Study 124 Part B/Cohort 7: Waterfall Plot of Mean Absolute Change From Baseline at Week 12 in Sweat Chloride (mmol/L)**

Mean Absolute Change (mmol/L)

Source: [Study 124 IA3R/Figure 11-2](#)

IVA: ivacaftor

Note: Only subjects who had both baseline and Week 12 sweat chloride values are included in this figure. All of these subjects had a *G551D* mutation.

Figure 7 Study 124 Part B/Cohort 7: Waterfall Plot of Mean Absolute Change From Baseline at Week 24 in Sweat Chloride (mmol/L)

Mean Absolute Change (mmol/L)

Source: Study 124 IA3R/[Figure 11-3](#)

IVA: ivacaftor

Note: Only subjects who had both baseline and Week 24 sweat chloride values are included in this figure. The bar on the farthest left represents the subject with an *R117H/F508del* genotype. The other 2 bars represent subjects who had a *G551D/F508del* genotype.

Sweat chloride concentration decreased in all of these subjects at both visits: changes ranged from -81.5 to -51.0 mmol/L at Week 12 and -70.0 to -39.0 at Week 24.

Nutritional status (Tertiary efficacy endpoint):

For each nutritional parameter evaluated, mean values were normal at baseline, but below the median of the reference population, and increased during the 24 weeks of IVA treatment. Mean absolute changes from baseline at Week 24 demonstrated increases in weight, length, and weight-for-length and their corresponding z-scores. Results for each nutritional parameter are summarized below.

Weight and Weight-for-age Z-score

The absolute change from baseline in weight-for-age-Z-score is presented in table 12 below.

Table 12: Absolute Change From Baseline in Weight-for-age Z-score, FAS, Part B/Cohort 7

Visit	Statistic	IVA 25 mg N = 6	
		Weight-for-age Z-score	Absolute Change From Baseline at Visit
Baseline	n	6	NA
	Mean (SD)	-0.65 (0.98)	NA
	Median	-0.77	NA
	Min, max	-1.92, 0.98	NA
Week 2	n	6	6
	Mean (SD)	-0.55 (0.99)	0.09 (0.23)
	Median	-0.76	0.02
	Min, max	-1.46, 1.27	-0.13, 0.46
Week 12	n	6	6
	Mean (SD)	-0.05 (0.90)	0.60 (0.45)
	Median	-0.36	0.64
	Min, max	-0.65, 1.70	0.11, 1.28
Week 24	n	6	6
	Mean (SD)	0.18 (0.97)	0.82 (0.54)
	Median	-0.11	0.97
	Min, max	-0.65, 2.04	0.09, 1.53

Source: Table 14.2.2.1.b7

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

WHO: World Health Organization

Notes: Baseline was defined as the most recent measurement before the first dose of study drug in Part B.

Z-scores were calculated using WHO Child Growth Standards for children 0 to 24 months of age. Subjects shown in dose group according to their Day 1 dose in Part B.

Length and Length-for-age Z-score

The absolute change from baseline in length-for-age-Z-score is presented in table 13 below.

Table 13: Absolute Changes From Baseline in Length-for-age Z-scores, FAS, Part B/Cohort 7

Visit	Statistic	IVA 25 mg N = 6	
		Length-for-age Z-score	Absolute Change From Baseline at Visit
Baseline	n	6	NA
	Mean (SD)	-0.12 (1.71)	NA
	Median	-0.54	NA
	Min, max	-1.99, 2.79	NA
Week 2	n	6	6
	Mean (SD)	0.22 (1.28)	0.34 (0.88)
	Median	0.14	-0.06
	Min, max	-1.24, 2.30	-0.49, 1.71
Week 12	n	6	6
	Mean (SD)	0.13 (1.61)	0.25 (0.45)
	Median	-0.26	0.21
	Min, max	-1.77, 2.98	-0.37, 0.92
Week 24	n	6	6
	Mean (SD)	0.44 (1.59)	0.56 (0.86)
	Median	-0.11	0.88
	Min, max	-0.87, 3.58	-0.88, 1.40

Source: Table 14.2.2.1.b7

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

WHO: World Health Organization

Notes: Baseline was defined as the most recent measurement before the first dose of study drug in Part B.

Z-scores were calculated using WHO Child Growth Standards for children 0 to 24 months of age. Subjects shown in dose group according to their Day 1 dose in Part B.

Weight-for-length and Weight-for-length-for-age Z-score

The absolute change from baseline in weight-for-length-for-age-Z-score is presented in table 14 below.

Table 14: Absolute Changes From Baseline in Weight-for-length-for-age Z-score, FAS, Part B/Cohort 7

Visit	Statistic	IVA 25 mg N = 6	
		Weight-for-length-for-age Z-score	Absolute Change From Baseline at Visit
Baseline	n	6	NA
	Mean (SD)	-0.66 (0.97)	NA
	Median	-0.67	NA
	Min, max	-1.72, 0.88	NA
Week 2	n	6	6
	Mean (SD)	-0.84 (0.88)	-0.17 (1.01)
	Median	-0.57	0.04
	Min, max	-2.17, 0.00	-1.63, 0.84
Week 12	n	6	6
	Mean (SD)	-0.03 (0.51)	0.63 (0.59)
	Median	-0.04	0.72
	Min, max	-0.69, 0.62	-0.26, 1.20
Week 24	n	6	6
	Mean (SD)	0.02 (0.53)	0.68 (1.12)
	Median	-0.04	0.67
	Min, max	-0.73, 0.72	-1.13, 2.07

Source: Table 14.2.2.1.b7

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

WHO: World Health Organization

Notes: Baseline was defined as the most recent measurement before the first dose of study drug in Part B.

Z-scores were calculated using WHO Child Growth Standards for children 0 to 24 months of age. Subjects shown in dose group according to their Day 1 dose in Part B.

Qualitative Microbiology Cultures

There were no identifiable trends in qualitative microbiology oropharyngeal culture outcomes. All 6 subjects had paired samples for evaluation of *Burkholderia*, *Hemophilus influenzae* (*H. influenzae*), methicillin-susceptible *Staphylococcus aureus* (*S. aureus*; methicillin-susceptible *Staphylococcus aureus* [MSSA]), methicillin-resistant *S. aureus* (MRSA), and *Pseudomonas aeruginosa* (*P. aeruginosa*; mucoid, non-mucoid, and small colony variant) at baseline and Week 24.

- Two subjects had positive *H. influenzae* cultures at baseline, and negative cultures at Week 24. A different subject had a negative culture at baseline, and a positive culture at Week 24.
- Two subjects had positive MSSA cultures at baseline; 1 of these subjects had a positive culture at Week 24. Two additional subjects who had negative MSSA cultures at baseline had positive cultures at Week 24.

No cases of MRSA, *P. aeruginosa*, or *Burkholderia* were observed over the treatment period.

Pulmonary Exacerbations

Two definitions were used for the analyses of PEx because there is no consensus definition for PEx in younger paediatric patients.

Number of Pulmonary Exacerbations

- Definition 1: 2 (33.3%) subjects had a total of 2 PEx events (event rate/year = 0.73).
- Definition 2: 1 (16.7%) subject had a total of 1 PEx event (event rate/year = 0.37).

Duration of Pulmonary Exacerbations

- Definition 1: normalized mean (SD) duration was 9.4 (14.8) days.

- Definition 2: normalized mean (SD) duration was 5.4 (13.2) days.

Time-to-first Pulmonary Exacerbation

- Definition 1: The event-free probability was 0.667 (95% CI: 0.195, 0.904) at Week 24. Seventy-five percent of subjects were event-free for 11.4 weeks; median and 25th percentile were not estimated.
- Definition 2: The event-free probability was 0.833 (95% CI: (0.273, 0.975) at Week 24, and therefore median, 25th, and 75th percentiles for event-free time were not estimated.

No obvious trends could be discerned from the patterns of the Kaplan-Meier curves of PEx.

CF-related Hospitalizations

One subject had 1 CF-related hospitalization (event rate/year = 0.37). This subject was hospitalized for viral aetiology. The normalized mean (SD) duration of CF-related hospitalizations was 0.7 (1.8) days.

Measures of Pancreatic Function and Inflammation

Faecal elastase (FE-1)

An increase in the mean FE-1 was observed by Week 2 and sustained through Week 24, suggesting improvement in pancreatic exocrine function with IVA treatment. The mean FE-1 at Week 24 (398.3 µg/g) was increased compared to baseline (184.0 µg/g). The mean (SD) absolute change from baseline was 86.5 (75.5) µg/g (n = 4) at Week 2 and 181.0 (122.9) µg/g (n = 4) at Week 24.

Table 15: Absolute Changes From Baseline in Fecal Elastase-1 (µg/g), FAS, Part B/Cohort 7

Visit	Statistic	IVA 25 mg N = 6	
		FE-1 (µg/g)	Absolute Change From Baseline at Visit (µg/g)
Baseline	n	5	NA
	Mean (SD)	184.0 (190.8)	NA
	Median	85.0	NA
	Min, max	51, 500	NA
Week 2	n	5	4
	Mean (SD)	253.2 (192.4)	86.5 (75.5)
	Median	135.0	60.0
	Min, max	88, 500	32, 194
Week 12	n	6	5
	Mean (SD)	357.8 (149.0)	145.4 (96.3)
	Median	372.0	137.0
	Min, max	181, 500	0, 245
Week 24	n	4	4
	Mean (SD)	398.3 (117.5)	181.0 (122.9)
	Median	400.5	226.0
	Min, max	292, 500	0, 272

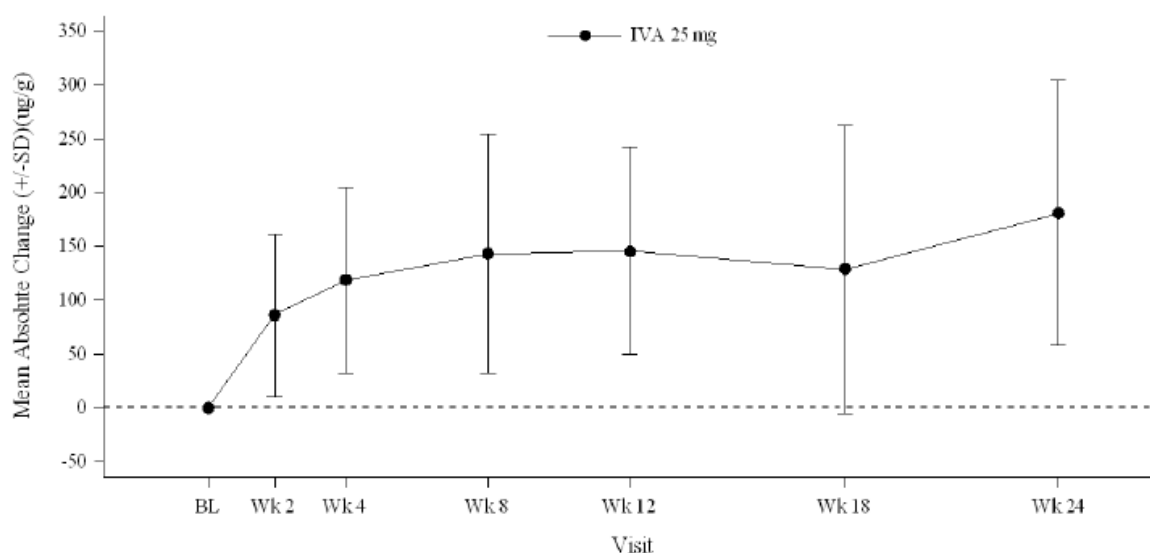
Source: Table 14.2.2.7.1.b7

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

Note: Baseline was defined as the most recent measurement before the first dose of study drug in Part B.

Reported values of <15 µg/g were replaced by 7.5 µg/g. Reported values of >500 µg/g were replaced by 500 µg/g. Subjects shown in dose group according to their Day 1 dose in Part B.

Figure 8: Mean absolute change from Baseline in Fecal Elastase-1, FAS, Part B/Cohort 7



Source: [Figure 14.2.2.7.5.b7](#)

BL: baseline; FAS: Full Analysis Set; IVA: ivacaftor; Wk: week

Subjects with CF who have FE-1 levels $\leq 200 \mu\text{g/g}$ are considered pancreatic insufficient.

Four subjects had FE-1 values at baseline and at Week 24; one subject did not have an FE-1 value at baseline or Week 24 and one subject did not have an FE-1 value at Week 24:

- Three subjects were pancreatic insufficient (FE-1 values $\leq 200 \mu\text{g/g}$) at baseline.
 - Two of the 3 subjects with FE-1 values $\leq 200 \mu\text{g/g}$ at baseline had FE-1 values $> 200 \mu\text{g/g}$ at Week 24 (values $> 200 \mu\text{g/g}$ are indicative of pancreatic sufficiency).
 - One subject did not have a Week 24 FE-1 value but had an FE-1 value $> 200 \mu\text{g/g}$ at Week 12 (the last visit at which FE-1 was determined for this subject).
- Two subjects had FE-1 values $> 200 \mu\text{g/g}$ at baseline. FE-1 values in these 2 subjects remained $> 200 \mu\text{g/g}$ throughout the 24 weeks of treatment.
- The subject with a missing baseline and Week 24 FE-1 value had FE-1 values $> 200 \mu\text{g/g}$ at all other study visits.

Table 16: Absolute Fecal Elastase-1 Shift-from-baseline by Visit, FAS, Part B/Cohort 7

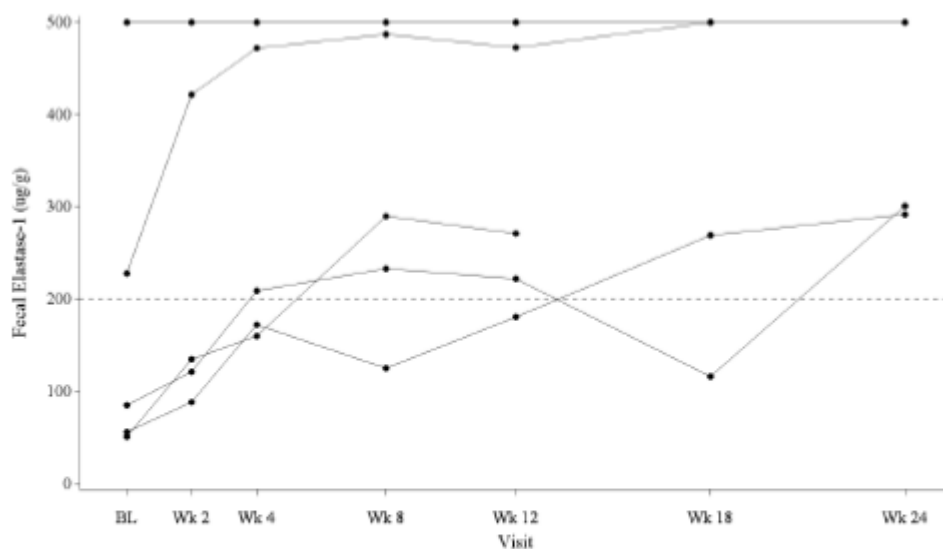
Visit	Treatment	Baseline Result (µg/g)	Post-baseline Result (µg/g)				Total n (%)
			<50 n (%)	≥50 and ≤200 n (%)	>200 n (%)	Unknown n (%)	
Week 12	IVA 25 mg (N = 6)	<50	0	0	0	0	0
		≥50 and ≤200	0	1 (16.7)	2 (33.3)	0	3 (50.0)
		>200	0	0	2 (33.3)	0	2 (33.3)
		Unknown	0	0	1 (16.7)	0	1 (16.7)
		Total	0	1 (16.7)	5 (83.3)	0	6 (100.0)
Week 24	IVA 25 mg (N = 6)	<50	0	0	0	0	0
		≥50 and ≤200	0	0	2 (33.3)	1 (16.7)	3 (50.0)
		>200	0	0	2 (33.3)	0	2 (33.3)
		Unknown	0	0	0	1 (16.7)	1 (16.7)
		Total	0	0	4 (66.7)	2 (33.3)	6 (100.0)

Source: [Table 14.2.2.7.2.b7](#)

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

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

To evaluate individual subject response to IVA, individual FE-1 values over time are presented in Figure 9. FE-1 values increased over 24 weeks of IVA treatment in the majority of subjects.

Figure 9: Individual Fecal Elastase-1 Over Time, FAS, Part B/Cohort 7

Source: [Figure 14.2.2.7.3.b7](#)

BL: baseline; FAS: Full Analysis Set; Wk: week

Note: The line at 500 µg/g reflects 2 subjects with overlapping fecal elastase-1 values.

Mean FE-1 data by visit are presented in [Figure 14.2.2.7.4.b7](#). FE-1 data are presented by subject in [Listing 16.2.6.9.b7](#).

IRT

The mean IRT level decreased over the 24-week treatment period, suggesting improvement in pancreatic inflammation/injury with IVA treatment. The mean (SD) absolute change from baseline at Week 24 in IRT was -593.8 (402.5) ng/mL (n = 4). The absolute changes from baseline were only calculated at each time point for those subjects who had a baseline value.

Table 17: Absolute Changes From Baseline in IRT (ng/mL), FAS, Part B/Cohort 7

Visit	Statistic	IVA 25 mg N = 6	
		IRT (ng/mL)	Absolute Change From Baseline at Visit (ng/mL)
Baseline	n	5	NA
	Mean (SD)	1200.0 (0.0)	NA
	Median	1200.0	NA
	Min, max	1200.0, 1200.0	NA
Week 2	n	5	4
	Mean (SD)	1142.1 (129.4)	-72.3 (144.7)
	Median	1200.0	0.0
	Min, max	910.7, 1200.0	-289.3, 0.0
Week 12	n	5	4
	Mean (SD)	1011.9 (175.2)	-154.4 (182.6)
	Median	939.3	-130.4
	Min, max	843.0, 1200.0	-357.0, 0.0
Week 24	n	5	4
	Mean (SD)	724.9 (438.2)	-593.8 (402.5)
	Median	506.9	-754.9
	Min, max	334.5, 1200.0	-865.5, 0.0

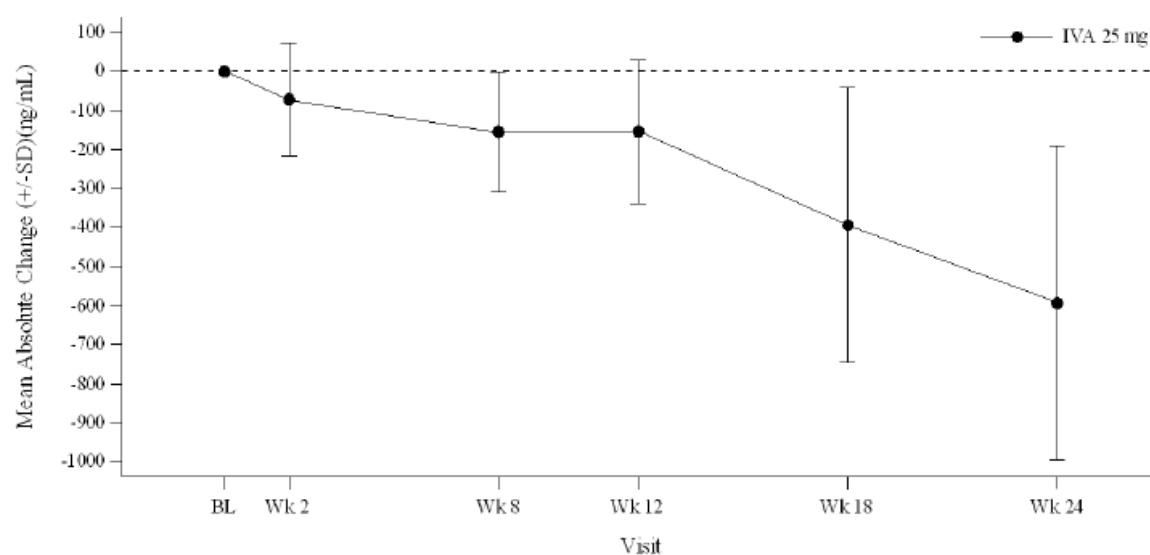
Source: Table 14.2.2.9.b7

FAS: Full Analysis Set; IRT: immunoreactive trypsin and/or trypsinogen; IVA: ivacaftor; n: size of subsample;

N: total sample size; NA: not applicable

Notes: Baseline was defined as the most recent measurement before the first dose of study drug in Part B.

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. Subjects shown in dose group according to their Day 1 dose in Part B.

Figure 10: Mean absolute change from Baseline in IRT, FAS, Part B/Cohort 7

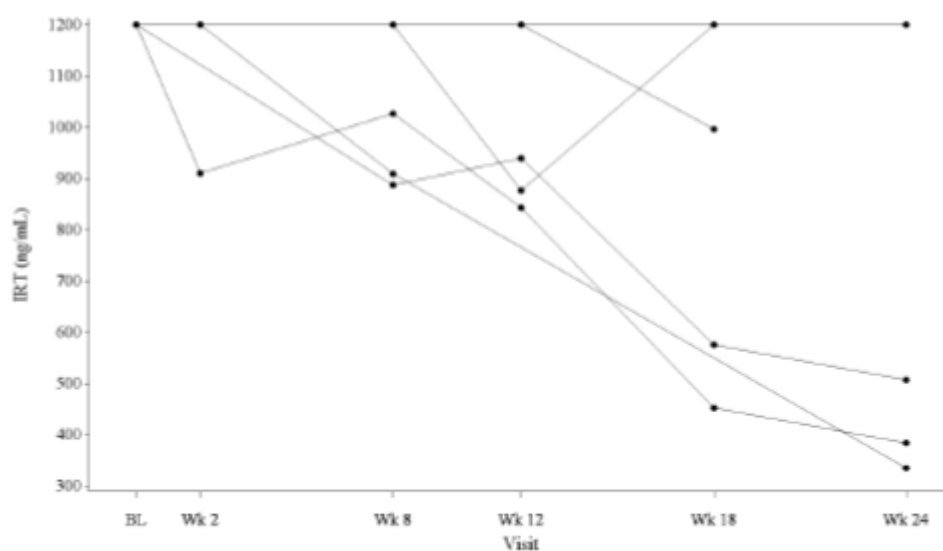
Source: Figure 14.2.2.9.3.b7

BL: baseline; FAS: Full Analysis Set; IRT: immunoreactive trypsin and/or trypsinogen; IVA: ivacaftor;

Wk: week

To evaluate individual subject response to IVA, individual IRT values over time are presented in Figure 11. A reduction in IRT from baseline was sustained through Week 24 for most of the subjects.

Figure 11: Individual IRT Over Time, FAS, Part B/Cohort 7



Source: [Figure 14.2.2.9.1.b7](#)

BL: baseline; FAS: Full Analysis Set; IRT: immunoreactive trypsin and/or trypsinogen; Wk: week

Mean IRT data by visit are presented in [Figure 14.2.2.9.2.b7](#). IRT data are presented by subject in [Listing 16.2.6.10.b7](#).

Lipase and amylase

Lipase and amylase levels were collected as part of safety assessments. The results are included in the efficacy assessments because they are useful indicators of pancreatic inflammation/injury. Lipase values were elevated at baseline and rapidly decreased during IVA treatment in both Parts A and B. Amylase levels were elevated at baseline and generally stable throughout the 24 weeks of treatment.

In Part A/Cohort 3, 6 of 6 subjects had lipase and amylase results at both baseline and Day 5. For these subjects, there was a reduction in the mean lipase value at Day 5; the mean amylase value was stable.

In Part B/Cohort 7, there was a mean decrease in lipase levels observed by Week 2 that was sustained through Week 24, suggesting reduced pancreatic inflammation/injury with IVA treatment. Mean amylase levels were generally stable throughout the 24 weeks of treatment.

Part A/Cohort 3:

- Mean (SD) absolute change from baseline in lipase level at Day 5 was -139.83 (76.71) U/L (n = 6).
- Mean (SD) absolute change from baseline in amylase level at Day 5 was -1.2 (11.0) U/L (n = 6).

Part B/Cohort 7:

- Mean (SD) absolute change from baseline in lipase level at Week 24 was -258.67 (158.41) U/L (n = 6).
- Mean (SD) absolute change from baseline in amylase level at Week 24 was -10.3 (37.2) U/L (n = 6).

Markers of Intestinal Inflammation (faecal calprotectin)

Mean faecal calprotectin levels decreased over the 24 weeks of treatment. The mean (SD) absolute change from baseline at Week 24 in faecal calprotectin was -150.40 (324.43) $\mu\text{g/g}$, suggesting improvement in intestinal inflammation. The normal range of reference for faecal calprotectin is 15.6 to 162.9 $\mu\text{g/g}$, however the range in CF infants has been reported to be much larger.

Table 18: Absolute Changes From Baseline in Fecal Calprotectin ($\mu\text{g/g}$), FAS, Part B/Cohort 7

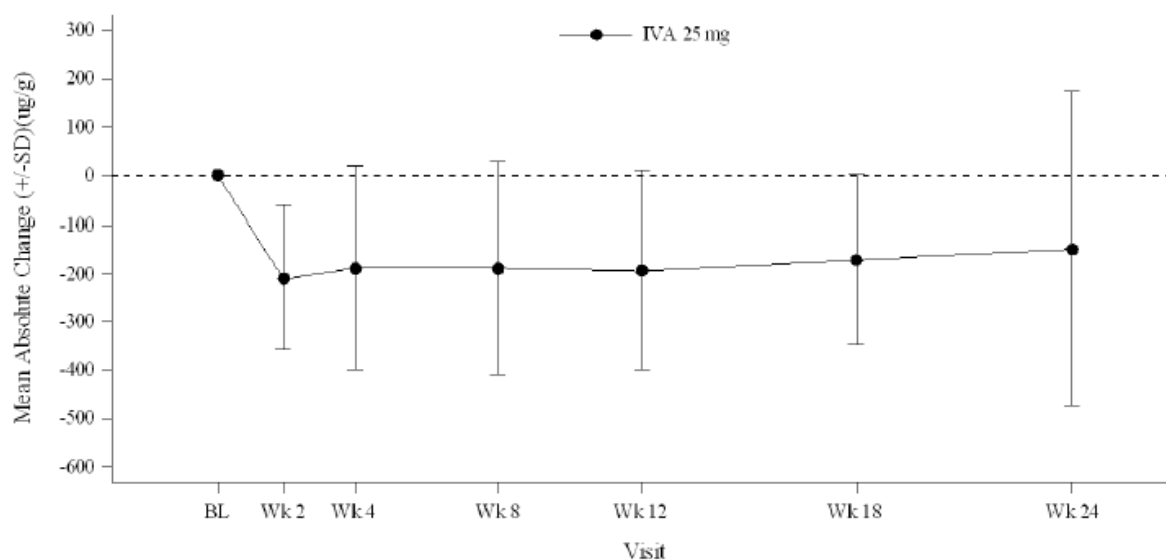
Visit	Statistic	IVA 25 mg N = 6	
		Fecal Calprotectin ($\mu\text{g/g}$)	Absolute Change From Baseline at Visit ($\mu\text{g/g}$)
Baseline	n	5	NA
	Mean (SD)	241.60 (203.12)	NA
	Median	220.60	NA
	Min, max	78.2, 581.5	NA
Week 2	n	5	4
	Mean (SD)	68.10 (63.62)	-210.25 (146.99)
	Median	47.40	-196.85
	Min, max	15.9, 179.0	-402.5, -44.8
Week 12	n	6	5
	Mean (SD)	40.53 (19.54)	-194.52 (203.21)
	Median	42.00	-172.20
	Min, max	7.8, 63.3	-535.2, -36.9
Week 24	n	4	4
	Mean (SD)	96.45 (152.90)	-150.40 (324.43)
	Median	26.90	-156.05
	Min, max	7.8, 324.2	-535.5, 246.0

Source: Table 14.2.2.8.b7

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

Notes: Baseline was defined as the most recent measurement before the first dose of study drug in Part B.

Reported values of $<15.6 \mu\text{g/g}$ were replaced by $7.8 \mu\text{g/g}$. Reported values of $>2000 \mu\text{g/g}$ are replaced by $2000 \mu\text{g/g}$. Subjects shown in dose group according to their Day 1 dose in Part B.

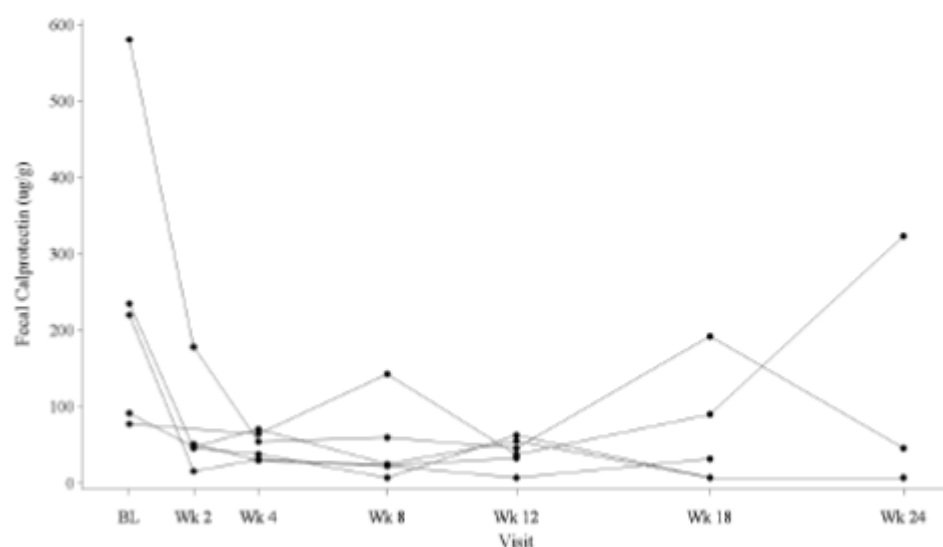
Figure 12: Mean Absolute Change from baseline in fecal calprotectin, FAS, Part B/Cohort 7

Source: Figure 14.2.2.8.3.b7

BL: baseline; FAS: Full Analysis Set; IVA: ivacaftor; Wk: week

To evaluate individual subject response to IVA, individual fecal calprotectin values over time are presented in Figure 13.

Figure 13: Individual Fecal Calprotectin Over time, FAS, Part B/Cohort 7



Source: Figure 14.2.2.8.1.b7

BL: baseline; FAS: Full Analysis Set; Wk: week

Palatability

A palatability assessment was performed at the Day 1 Visit. The administered doses of IVA were palatable; all subjects fully consumed the dose. The majority of subjects (5 [83.4%]) liked the food with study drug (either very much or a little).

Summary of main study

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

Table 19. Summary of Efficacy for trial Study VX15-770-124 (This report is for Cohort 3 (Part A), subjects 3 to <6 months of age and Cohort 7 (Part B), subjects 4 to <6 months of age.

Title: A Phase 3, 2-Part, Open-label Study to Evaluate the Safety, Pharmacokinetics, and Pharmacodynamics of Ivacaftor in Subjects With Cystic Fibrosis Who Are Less Than 24 Months of Age at Treatment Initiation and Have a CFTR Gating Mutation		
Study identifier	VX15-770-124	
Design	phase 3, two-part, open-label	
	Duration of main phase:	treatment period in Part A: Day 1-Day5, follow-up phone call at Day 14, follow-up for ocular examination 8 weeks \pm 14 days after last dose treatment period in Part B: Day 1-week24, rollover to Study 126 OR follow-up 4 weeks after last dose and follow-up for ocular examination 24 weeks after last dose
	Duration of Run-in phase:	N/A
	Duration of Extension phase:	from Part B at week 24 visit to Study 126
Hypothesis	N/A	

Treatments groups	Part A: Ivacaftor 25 mg q12h for children from 3 to <6 months old and weighing 5 to less than 7 kg on Day 1 Ivacaftor 50 mg q12h for children from 3 to <6 months old and weighing 7 to less than 14 kg on Day 1 Part B: 4 to <6 months of age and weighing ≥5 kg at Day 1, and dosed with 25 mg q12h regardless of weight until reaching 6 months of age		PART A: ivacaftor 25 mg, N=3, ivacaftor 50 mg N=3, duration: 4 days PART B: ivacaftor 25 mg, N=6, duration: 24 weeks	
Endpoints and definitions	Primary endpoints	Part B Safety		
	Secondary endpoints	Part B: PK: Sweat chloride:	PK parameter estimates of ivacaftor and metabolites M1 and M6. Absolute change from baseline in sweat chloride concentration at week 24 (mmol/L)	
	Part B Selected Tertiary endpoints: 1. measures of nutritional status 2.measures of pancreatic function	1.weight, length, weight-for-length, weight-for-age, length-for-age, and weight-for-length-for-age z-scores 2.fecal elastase-1 and IRT	absolute change from baseline at week 24	
Database lock	ongoing			
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 subjects	6		
	abs. change from BL in sweat chloride mean (SD), mmol/L	-50.0 (17.3) N=3		

	Absolute Changes From Baseline in Weight-for-age Z-score mean (SD)	0.82 (0.54) N=6		
	Absolute Changes From Baseline in Length-for-age Z-score (unit), mean (SD)	0.56 (0.86) N=6		
	Absolute Changes From Baseline in Weight-for-length-for-age Z-score mean (SD)	0.68 (1.12) N=6		
	Change From Baseline in Fecal Elastase-1 (µg/g), mean (SD)	181.0 (122.9) N=4		
	Change From Baseline in IRT (ng/mL), mean (SD) (Cisbio assay)	-593.8 (402.5) N=4		
Notes	the study is currently ongoing, End of Interim Analysis: 11 December 2019 (date last subject in Cohort 7 completed Part B Week 24 Visit)			

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

The results from the Phase 3, placebo-controlled studies in subjects with the *G551D* gating mutation ≥6 years of age (Studies 102 and 103) and subjects with a non-*G551D* gating mutation (Study 111) are summarized in the Table 20 below (model-based treatment differences). In all 3 studies, IVA was highly effective across 24 weeks of treatment as evidenced by improvement in *CFTR* function and substantial improvements in clinically important outcomes, including ppFEV₁, respiratory symptoms, and nutritional status.

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), and subjects with a gating mutation 6 to <12 months of age (Study 124, Cohort 6), are shown in Table 21. Results from these previous studies provide context for the efficacy results of subjects 4 to <6 months of age in Part B/Cohort 7 of Study 124. In both placebo-controlled and open-label studies, treatment with IVA led to improvement in *CFTR* function.

Table 20: IVA Treatment Effects in Placebo-Controlled Phase 3 Studies in Subjects 6 Years and Older (Studies 102, 103, and 111)

		Study 102 <i>G551D</i> Subjects ≥12 Years		Study 103 <i>G551D</i> Subjects 6 to 11 Years		Study 111 Non- <i>G551D</i> Gating Mutation Subjects ≥6 Years		
Analysis	Time Point	Treatment Difference ^a	<i>P</i> value	Treatment Difference ^a	<i>P</i> value	Time Point	Treatment Difference ^a	<i>P</i> value
Lung function								

Table 20: IVA Treatment Effects in Placebo-Controlled Phase 3 Studies in Subjects 6 Years and Older (Studies 102, 103, and 111)

Analysis	Time Point	Study 102 <i>G551D</i> Subjects ≥12 Years		Study 103 <i>G551D</i> Subjects 6 to 11 Years		Study 111 Non- <i>G551D</i> Gating Mutation Subjects ≥6 Years		
		Treatment Difference ^a	<i>P</i> value	Treatment Difference ^a	<i>P</i> value	Time Point	Treatment Difference ^a	<i>P</i> value
Absolute change from baseline in ppFEV ₁	Through Week 24	10.6 percentage points	<0.0001	12.5 percentage points	<0.0001			
	Through Week 48	10.5 percentage points	<0.0001	10.0 percentage points	0.0006	Through Week 8	10.7 percentage points	<0.0001
Other pulmonary outcomes								
Relative risk of pulmonary exacerbation (hazard ratio)	Through Week 24	0.40	0.0016	na ^b	na ^b			
	Through Week 48	0.46	0.0012	na ^b	na ^b	Through Week 8	0.81 ^c	0.5687
Absolute change from baseline in CFQ-R respiratory domain score ^d	Through Week 24	8.1 points	<0.0001	6.1 points	0.1092			
	Through Week 48	8.6 points	<0.0001	5.1 points	0.1354	Through Week 8	9.6 points	0.0004
Nutritional status								
Absolute change from baseline in body weight	At Week 24	2.8 kg	<0.0001	1.9 kg	0.0004			
	At Week 48	2.7 kg	<0.0001	2.8 kg	0.0002	At Week 8	1.7 kg	0.0007
Absolute change from baseline in BMI-for-age z-score ^e	At Week 24	0.34 points	0.0010	0.34 points	0.0002			
	At Week 48	0.33 points	0.0490	0.45 points	<0.0001	At Week 8	0.28 points	0.0010
CFTR function								
Absolute change from baseline in sweat chloride	Through Week 24	-47.9 mmol/L	<0.0001	-54.3 mmol/L	<0.0001			
	Through Week 48	-48.1 mmol/L	<0.0001	-53.5 mmol/L	<0.0001	Through Week 8	-49.2 mmol/L	<0.0001

Source: [Module 2.7.3 R117H Addendum/Table 16](#)

BMI: body mass index; CF: cystic fibrosis; CFQ-R: Cystic Fibrosis Questionnaire-Revised; IVA: ivacaftor; na: not analyzed due to low incidence of events; *P*: probability; ppFEV₁: percent predicted forced expiratory volume in 1 second

^a Treatment difference (model-based) = effect of IVA – effect of placebo.

^b Due to the small sample size and low incidence of clinical events observed during Study 103, the analysis of clinical events did not support inferential conclusions regarding the risk, frequency, or duration of CF-related clinical events (including pulmonary exacerbations).

^c For Study 111, the event rate ratio (estimated by negative binomial regression) is presented.

^d Pooled adults/adolescent and 12- to 13-year-old CFQ-R versions in Studies 102 and 111; child version in Study 103.

^e BMI-for-age z-scores were only determined for subjects age ≤20 years in Studies 102 and 111.

Table 21: Mean Absolute Change From Baseline (SD) for Selected Efficacy Endpoints After 24 Weeks of IVA Treatment in Subjects 6 Months of Age and Older (Studies 102, 103, 111, and 108, and Study 124, Cohorts 5 and 6)

Analysis	Study 102 <i>G551D</i> Subjects ≥12 Years	Study 103 <i>G551D</i> Subjects 6 to 11 Years	Study 111 Non- <i>G551D</i> Gating Mutation Subjects ≥6 Years	Study 108 Gating Mutation Subjects 2 to 5 Years	Study 124 Cohort 5 Gating Mutation Subjects 12 to <24 Months	Study 124 Cohort 6 Gating Mutation Subjects 6 to <12 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)
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)
Weight-for-age z-score	0.36 (0.309)	0.30 (0.255)	0.41 (0.193)	0.20 (0.251)	0.15 (0.42)	0.36 (0.54)
BMI (kg/m ²)	0.93 (1.145)	1.11 (0.920)	1.26 (0.759)	0.32 (0.538)	ND	ND
BMI-for-age z-score	0.36 (0.324)	0.33 (0.364)	0.42 (0.276)	0.37 (0.424)	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)
Stature-for-age z-score ^a	ND	ND	0.12 (0.13)	-0.01 (0.33)	0.28 (0.60)	0.27 (1.34)
Weight-for-length (percentile)	ND	ND	ND	ND	1.5 (17.1)	2.8 (38.3)
Weight-for-length-for-age z-score	ND	ND	ND	ND	0.07 (0.65)	0.26 (1.30)
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
Pancreatic function						
FE-1 (μg/g)	ND	ND	ND	99.8 (138.35)	164.7 (151.9)	159.3 (154.4)
IRT (ng/mL)	ND	ND	ND	-20.70 (23.991) ^c	-647.1 (339.3) ^c	-406.2 (363.3) ^c

Sources: [Module 2.5 Pediatric Addendum/Tables 8, 9, 19, and 20](#), and [Study 102/Table 14.3.7](#), [Study 103/Table 14.3.7](#), [Study 111/Table 14.2.4.1.1ole](#), [Study 108/Table 14.2.2.7b](#), and [Study 124/Tables 14.2.1.1.b5, 14.2.2.1.b5, 14.2.2.7.1.b5, 14.2.2.9.b5, 14.2.1.1.b6, 14.2.2.1.b6, 14.2.2.7.1.b6, and 14.2.2.9.b6](#)

BMI: body mass index; FE-1: fecal elastase-1; IRT: immunoreactive trypsin and/or trypsinogen; IVA: ivacaftor; ND: not determined; ppFEV₁: 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 patient population could provide baseline and post-treatment spirometry values, and the results showed considerable variability.

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

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

Study 124 is an ongoing, open-label, 2-part phase 3 study to assess safety, PK, PD, efficacy and acceptability/palatability of ivacaftor patients <24 months of age, who have a gating type *CFTR* mutation in at least one allele. This submission is based on:

- Interim analysis of Cohorts 3 and 7 data from study 124 in patients from 3 months to less than 6 months of age.
- Efficacy and safety results of study 108 (children aged 2-5 years),
- previous evidence from well-controlled studies in CF subjects aged 6 years or older with gating mutations,

This approach is considered appropriate to support an extension of indication. Lack of randomisation limits conclusion, however, extrapolation of efficacy from adults, adolescents and children of other age groups is accepted as the pathophysiology of the underlying disease and the mechanism of action of ivacaftor is the same.

No formal dose-response study was conducted, selection of doses for Part A/Cohort3 and Part B/Cohort7 was supported by simulation exercise using previously developed popPK modelling. With proposed dose the same AUC values were targeted as that in adults and children aged >6 months. Subjects 3 to <6 months of age were enrolled in Part A/Cohort 3. To ensure ivacaftor exposure was not above the adult 95th percentile, the Part B/Cohort 7 dose and age range were selected such that Part B/Cohort 7 was limited to subjects 4 to <6 months of age. In Part A, subjects received ivacaftor q12h based on body weight: 25 mg q12h, 5 to <7 kg or 50 mg q12h 7 to <14 kg. In Part B, all subjects 4 to <6 months of age received ivacaftor 25 mg q12h regardless of weight.

The inclusion and exclusion criteria in study 124 were appropriate and mostly in line with previous studies conducted with ivacaftor in children. Diagnosis of CF was based on abnormal sweat test OR presence of two CF-causing mutations. Inclusion criteria did not include clinical features of CF lung disease, this was acknowledged by CHMP. Lung and other organ damage are evident at this very young age, these children usually do not present lung disease manifestations, the leading clinical signs or symptoms are related to GI tract manifestations rather (i.e. malnutrition).

Subjects were encouraged to remain on their prescribed CF therapies during Study 124. Selected concurrent medications, such as moderate and strong CYP3A inhibitors or inducers, were prohibited if the potential existed for untoward drug-drug interactions.

Safety and PK were evaluated in Part A (4 days of ivacaftor treatment, assessed over 5 days to obtain steady-state concentrations). Safety, PK, PD, efficacy (tertiary parameters: nutritional parameters, biomarkers for pancreatic and intestinal inflammation, pulmonary exacerbation and hospitalisation due to CF), and acceptability/palatability were evaluated in Part B (24 weeks of ivacaftor treatment). Infant pulmonary function test (IPFT) and lung clearance index (LCI)/ multiple breath washout (MBW) assessments were not conducted in any of the 4- to <6-month-old subjects in Cohort 7.

The efficacy evaluation was a tertiary objective in this study (Part B, Cohort 7). Efficacy was assessed by using nutritional parameters, biomarkers for pancreatic and intestinal inflammation, pulmonary exacerbation, and hospitalisation due to CF. Lung function by spirometry cannot be measured in this age group and if it could it was not informative for disease. To measure ventilation inhomogeneity, usually lung clearance index (LCI) measure is encouraged in young children. This is a multiple breath washout

parameter detected by inert gas inhalation. LCI is an encouraged parameter to test small children's ventilation; however, the test requires specific centres.

Study protocol amendments to the original study protocol were made but overall are not considered to have a major impact on the conduct of the study. Study protocol and SAP (last version 2.3) amendments were performed before data cut for the third interim analysis. According to a dose justification memo, enrolment into Part B/Cohort 7 was limited to children 4 to <6 months of age. This was acknowledged by CHMP.

Efficacy data and additional analyses

In this third interim analysis from study 124, the Full Analysis Set and Safety Set included 6 subjects who enrolled in Cohort 3 (Part A), and 6 subjects who enrolled in Cohort 7 (Part B). Six subjects received 25 mg ivacaftor q12h at Day 1; all subjects completed the study. Six subjects received an increased dose of 50 mg IVA q12h during the study after reaching 6 months of age and 7 kg. Study population of Cohorts 3 and 7 reflected well the targeted population.

In cohort 7, Part B of study 124, the mean weight at baseline was 6.9 kg (range: 5.9 to 7.9 kg). The mean age at baseline was 4.5 months (range: 4 to 5 months). Five subjects had a G551D mutation, and 1 subject had an R117H mutation. The most prevalent genotype was G551D/F508del (4 of 6 subjects).

The most commonly reported concomitant medications were vitamins (100%), medications related to pancreatic enzyme replacement therapy (83.3%), and sodium chloride (66.7%). Amoxicillin, flucloxacillin, and salbutamol were each taken by 33.3% of subjects.

In part B, the mean (SD) sweat chloride value at baseline was 97.4 (16.4) mmol/L. Nutritional parameters (weight, length, weight-for-age z-score, length-for-age z-scores, weight-for-length-for-age z-scores, and weight-for-length percentiles) were normal at baseline, but below the median of the reference population. Some children /child must have been undernourished at baseline, as minimum values suggest. 3 out of 6 children had pancreatic failure, 3 children had CF lung disease. In this cohort, only one patient had week 2 sweat chloride measure, but, in this single patient, reduction of CI was substantial at week 2. At week 12, there were five patients and at week 24, there were 3 patients who had sweat chloride measures. The mean (SD) absolute change from baseline in sweat chloride was -34.0 (mmol/L (n = 1) at week 2, -65.6 (12.0) mmol/L (n = 5) at week 12, and -50.0 (17.3) mmol/L (n = 3) at week 24. These data are comparable to that previously observed with ivacaftor treatment in other children and adolescents.

Mean nutritional parameters were normal at baseline, but below the median of the reference population, and increased during the 24 weeks of ivacaftor treatment. Mean absolute changes from baseline were: weight, +2.5 kg; length, +9.3 cm, weight-for-length percentile, +20.0%; normalized mean changes were: weight-for-age z-score, +0.82; length-for-age z-score, +0.56; and weight-for-length-for-age z-score, +0.68. Study subjects were between 4 and 5 months of age at baseline. All 6 patients had both baseline and week 24 data available. Weight-for-length percentile improvement of +20% suggest an overall improvement in nutrition. Upon CHMP's request, the MAH compared the change from baseline through week 24 in weight, length and respective z-scores of study subjects to historical values in those who were not treated with ivacaftor and had the same mutation in CFTR gene and were at the same age. Nutritional parameters of six patients from study 124, Cohort 7 and 19 subjects' data from US Cystic Fibrosis Foundation Patient Registry were presented for comparative reasons. Due to very small numbers and non-matched comparison, data should be compared with caution and interpretation has limitations. Data from treated and untreated patients show similar patterns. Mean change from baseline in weight, length and respective z-scores are similar in magnitude. Additional nutritional data and narratives provided for subjects with weight-for-length-for-age z-scores slightly below -1 SD at screening. All of

them had week 24 weight-for-length-for-age z-score increased to within 1 SD, one of them had above 0. No serious AEs occurred in any of these subjects. Non-serious AEs occurred in these subjects were moderate or mild in severity, not related to study drug and resolved without treatment (URTI, vomiting diarrhea, rhinorrhea) or with treatment (otitis media or cough/antibiotic).

No cases of MRSA, *P. aeruginosa*, or *Burkholderia* were observed over the treatment period. In this study, 2 definitions of PEx were used for analyses because there is no consensus definition for PEx in younger paediatric subjects. Definition 1: 2 (33.3%) subjects had a total of 2 PEx events (event rate/year = 0.73). Definition 2: 1 (16.7%) subject had a total of 1 PEx event (event rate/year = 0.37). There were no identifiable trends in qualitative microbiology oropharyngeal culture outcomes, however, any firm trend for PEx or microbiology was not expected due to the very limited sample size and short period; and to the characteristics of this patient population (generally low rate of events).

Mean increases in Faecal Elastase-1 (FE-1) were observed by week 2 and sustained through Week 24. The mean (SD) absolute change from baseline in FE-1 at week 24 was 181.0 (122.9) $\mu\text{g/g}$ ($n = 4$), suggesting improvement in pancreatic function with ivacaftor treatment. 3 subjects were pancreatic insufficient (FE-1 values $\leq 200 \mu\text{g/g}$) at baseline. These 3 subjects had FE-1 values $>200 \mu\text{g/g}$ at week 24 ($n = 2$) or at the last available FE-1 assessment, week 12 ($n = 1$). The remaining 3 subjects were pancreatic sufficient (FE-1 values $>200 \mu\text{g/g}$). 5/6 patients received pancreatic enzyme replacement. Pancreatic enzyme replacement therapy was continued throughout the study in subjects who were pancreatic insufficient at baseline and had FE-1 levels above 200 $\mu\text{g/g}$.

Immunoreactive trypsin and/or trypsinogen (IRT) is a marker for pancreatic duct obstruction and elevated in neonates with CF. As CF disease progresses and pancreatic tissue becomes more fibrotic, IRT levels decline. In Cohort 7, 1/6 patient had stable high (1200 ng/ml) IRT values through week 24 of observation, 1/6 had slight decrease in IRT and in 3/6 subjects IRT levels decreased continuously and substantially through week 24. Absolute mean change (SD) from baseline in IRT at week 24 was -593.8 (402.5) ng/mL ($n = 4$). This decrease was comparable that seen in previous age groups of children in study 124. As discussed in previous assessments of Kalydeco (II/69 and X/75) the assay used in children aged 2 to less than 6 years of age (study 108) to measure IRT is not the same as the one used in study 124 as the values cannot be directly compared. IRT levels are expected to decline with age, but the rapid and steep decline after starting ivacaftor in this limited number of subjects who were pancreatic insufficient at baseline strongly suggests a treatment effect and, supports the hypothesis that early intervention with ivacaftor can improve pancreatic function in young children. As IRT levels decrease with age, in the lack of control group definite interpretation of IRT data is not possible (to what extent it can be attributed to ivacaftor). However, this issue cannot be further pursued due to very low number of patients with week 24 result (4 patients) and since the IRT decrease in 3/6 subject along with results on FE-1, lipase, amylase and nutritional parameters, may support assumption of beneficial effect of ivacaftor on pancreatic manifestation of CF.

Lipase has been reported to be increased at birth in patients with CF and to decline over the first years of life, and the decline has been linked to the development of pancreatic insufficiency. Regarding normal range (LLN and ULN), limits are assay dependent. The MAH specified 1-17 U/L or 6-44 and 4-29 or 4-23 U/L for amylase and lipase, respectively. It seems that all 6 patients had week 24 data for both lipase and amylase. The mean lipase level was elevated at baseline and a mean decrease in lipase was observed by week 2 and sustained through week 24, suggesting reduced pancreatic inflammation/injury with ivacaftor treatment. The mean amylase level was elevated at baseline and generally stable throughout the 24 weeks of treatment. In Part B, absolute mean change from baseline in lipase level at Week 24 was -258.67 (158.41) U/L ($n = 6$). Absolute mean change from baseline in amylase level at Week 24 was -10.3 (37.2) U/L ($n = 6$). Similar findings were seen for lipase and amylase levels after 4 days of ivacaftor treatment, assessed across 5 days in Part A. In previous assessment it was concluded that values below the normal range for amylase and lipase appear to correlate with pancreatic insufficiency

and normal or above normal values with preservation of exocrine pancreatic function. In this study there were extremely low number of patients in each group, and similar patterns could be observed in both pancreatic insufficient and subjects with normal function, furthermore, lipase values decrease with time over the first years of life without ivacaftor treatment, as well. Amylase levels and changes were variable, and it is therefore agreed with the MAH that interpretation of data is strongly limited by a low contribution of pancreatic versus salivary to total amylase levels and variable kinetics of both fractions in this age group. Thus, no clear conclusion can be drawn on the impact of ivacaftor treatment on pancreatic function based on lipase and amylase measures merely, however, it seems reassuring that indeed, lipase values decreased to above-normal values in both patient groups through week 24.

Mean faecal calprotectin (FC) levels decreased (improved) over 24 weeks of treatment. The mean (SD) absolute change from baseline at Week 24 was -150.40 (324.43) µg/g (n = 4). The MAH states that the normal range of reference for faecal calprotectin is 15.6 to 162.9 µg/g, however the range in CF infants has been reported to be much larger. According to individual faecal calprotectin data, 3 subjects might have had elevated FC level (based on 162.9 µg/g threshold, however, the reference range for this specific age group is not exactly known). It can be clearly seen at individual level that elevated FC levels decreased rapidly in the patients with elevated FC at baseline and levels fluctuates later on but generally remained lower than baseline at week 4,8,12 and 18. The MAH clarified previously (in procedure X/75), that faecal calprotectin (FC) is an inflammatory marker that it is not CF-specific which is known to be elevated in patients with CF, particularly in pancreatic insufficient (PI) patients (Garg M et al 2017). FC levels are usually low in infants with cystic fibrosis during the first year of life and increase afterwards until the age of four years remaining stable after than point. As a consequence of distinctive age-related variations in the values, careful interpretation of levels of FC is required in children under four years of age. Upon request by CHMP, the MAH confirmed that three out of 6 patients had elevated FC at baseline, following initiation of ivacaftor treatment all of 3 subjects had normal FC (at week 24 or at week12-in one case it was the last measurement). Although data are very scarce, this can be considered reassuring as it may suggest decreased intestinal inflammation in these individuals after initiation of ivacaftor. Of note, one subject who had normal FC value at BL, had elevated FC level at week 24. The MAH did not comment it further. This was not further pursued by CHMP.

Palatability assessments indicated that IVA doses were palatable. All subjects in Part B accepted and fully consumed the first dose of study drug.

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

2.4.4. Conclusions on the clinical efficacy

The third interim analysis of study 124 provides PK, safety, PD (sweat chloride) and some efficacy data (tertiary endpoints) of the treatment with ivacaftor in infants aged 4 to less than 6 months with at least a pre-specified gating mutation in an allele of the *CFTR* gene.

Study 124 is an uncontrolled study and low sample size of PART B/Cohort 7 limits interpretation of the results. However, the robust decrease in sweat chloride comparable to that seen in previous studies /previous interim results in older subjects provide support for extrapolation of efficacy from placebo-controlled Phase 3 studies in subjects ≥6 years of age and support the use of ivacaftor in children with CF 4 to <6 months of age with indicated *CFTR* mutations. Beneficial effect of ivacaftor in this age group may be further supported by limited data on nutritional parameters and markers of exocrine pancreas function/GI inflammation.

Based on results on the dosing regimen used in part A/Cohort 3, patients received 25 mg ivacaftor every 12 hours in Part B/Cohort 7. Initially, Cohort 7 was planned to include children aged 0-6 months.

In part A, one subject who received 25 mg q12h ivacaftor had an AUC value above the 95th percentile of that observed in the adult population, suggesting that IVA exposures may be impacted by maturation at this age. Therefore, in order to ensure that IVA exposure did not exceed the targeted adult range (95th percentile), Part B/Cohort 7 was limited to subjects 4 to <6 months of age, weighing ≥ 5 kg. Therefore, this justifies the indication from 4 months of age (see below).

Overall, it is considered that from a clinical point, sufficient safety data has been provided to support the new indication from the age of 4 months as follows:

Kalydeco granules are indicated 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).

2.5. Clinical safety

Introduction

This extension of indication is based on the 3rd interim analysis of Study 124, an ongoing Phase 3, open-label study of orally administered IVA in subjects with CF who were <24 months of age at treatment initiation (Day 1) and have a *CFTR* gating mutation or *R117H* (in the US only at the time of 3rd interim analysis) on at least 1 allele. This study consisted of two parts: in Part A, PK and safety was evaluated over 5 days (4 days of ivacaftor treatment) in four age cohorts. In part B, based on the dosing regimen confirmed in part A, safety, PK, PD, efficacy and acceptability/palatability of ivacaftor granules were investigated over 24 weeks.

This submission includes data from subjects 3 to <6 months of age (Part A/Cohort 3) and subjects 4 to <6 months of age (Part B/Cohort 7) at Day 1 (ivacaftor treatment initiation).

Primary objective of both parts of Study 124 was the evaluation of the safety of IVA in the above-mentioned age cohorts (i.e. Cohort 3 in Part A and Cohort 7 in Part B).

Adverse Events (AEs), clinical laboratory values (haematology and serum chemistry), ophthalmological and physical examinations, standard 12-lead ECGs and vital signs were defined as primary safety endpoints.

Patient exposure

In Part A/Cohort 3, 3 subjects received 25 mg IVA, and 3 subjects received 50 mg IVA. All 6 subjects completed the 5-day treatment period (4 days of IVA treatment).

In Part B/Cohort 7, all 6 subjects received 25 mg IVA on Day 1, and all 6 completed the study. All 6 received an increased dose of 50 mg IVA after reaching 6 months of age and 7 kg. The mean (SD) exposure to study drug was 23.8 (0.56) weeks (range: 23 to 24 weeks).

Six subjects were enrolled and included in the Safety Set of **Part A/Cohort 3**. All 6 subjects completed Part A. No subjects continued into *Part B/Cohort 7* because all subjects aged out before enrolment of Part B/Cohort 7 began. One subject enrolled in *Part B/Cohort 6* (subjects 6 to <12 months of age) and 4 subjects enrolled directly into the *Extension Study 126*.

In **Part B/Cohort 7**, six subjects were enrolled and included in the Safety Set. No subject prematurely discontinued study drug treatment. After the completion of Study 124 Part B/Cohort 7, all 6 subjects from Cohort 7 was enrolled into *Study 126* and therefore did not have a Follow-up Visit, per protocol.

Adverse events

Part A/Cohort 3

Three (50.0%) of the 6 subjects had AEs: 1 (33.3%) subject in the 25-mg group and 2 (66.7%) subjects in the 50-mg group. No AE occurred in more than a single subject. AEs are presented by SOC and PT in Table 5.5.2.

All but one AEs were mild or moderate of severity. The only severe AE was a thrombocytopenia AE, it was considered as a SAE as well and is described in detail in the Serious adverse event section of Clinical Safety part of this AR.

None of the AEs were considered to be related to study drug by the investigator (related AEs include related and possibly related AEs).

Table 22: Adverse Events by System Organ Class and Preferred Term, Safety Set, Part A/Cohort 3

System Organ Class Preferred Term	IVA 25 mg N = 3 n (%)	IVA 50 mg N = 3 n (%)	Total N = 6 n (%)
Subjects with any AEs	1 (33.3)	2 (66.7)	3 (50.0)
Blood and lymphatic system disorders	1 (33.3)	0	1 (16.7)
Thrombocytopenia	1 (33.3)	0	1 (16.7)
Gastrointestinal disorders	0	1 (33.3)	1 (16.7)
Teething	0	1 (33.3)	1 (16.7)
Infections and infestations	0	1 (33.3)	1 (16.7)
Infective PEx of CF	0	1 (33.3)	1 (16.7)
Upper respiratory tract infection	0	1 (33.3)	1 (16.7)
Respiratory, thoracic and mediastinal disorders	0	1 (33.3)	1 (16.7)
Wheezing	0	1 (33.3)	1 (16.7)
Skin and subcutaneous tissue disorders	0	1 (33.3)	1 (16.7)
Eczema	0	1 (33.3)	1 (16.7)
Vascular disorders	0	1 (33.3)	1 (16.7)
Flushing	0	1 (33.3)	1 (16.7)

AE: adverse event; CF: cystic fibrosis; IVA: ivacaftor; n: size of subsample; N: total sample size; PEx: pulmonary exacerbation; PT: Preferred Term; SOC: System Organ Class

Notes: A subject with multiple events within a category (Any, SOC, or PT) was counted only once in that category. Table is sorted in descending order of Total column by SOC, and by PT within each SOC. Subjects shown in dose group according to their Day 1 dose in Part A. Events were coded with MedDRA Version 22.1.

Part B/Cohort 7

All 6 patients experienced an AE; there were 19 AEs and 1 SAE in total. All but one AEs were mild or moderate in severity. The only severe AE was a bronchiolitis AE, it was considered as a SAE as well and is described in detail in the Serious adverse event section below. All AEs, including the SAE of bronchiolitis, were considered unlikely related or not related to study drug.

Table 23: Overview of Adverse Events

Category	IVA 25 mg N = 6
Number of AEs, n	19
Number of SAEs, n	1
Number of non-serious AEs, n	18
Subjects with any AEs, n (%)	6 (100.0)
Subjects with related AEs, n (%)	0
Subjects with AEs leading to treatment discontinuation, n (%)	0
Subjects with AEs leading to treatment interruption, n (%)	0
Subjects with SAEs, n (%)	1 (16.7%)
Subjects with AEs leading to death, n (%)	0

AE: adverse event; IVA: ivacaftor; 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 22.1.

Table 24: Adverse events by SOCs and PTs, Study 124 Part B/Cohort 7, Safety Set

System Organ Class Preferred Term	IVA 25 mg N = 6 n (%)
Subjects with Any TEAEs	6 (100.0)
Infections and infestations	4 (66.7)
Upper respiratory tract infection	2 (33.3)
Bronchiolitis	1 (16.7)
Otitis media	1 (16.7)
Respiratory, thoracic and mediastinal disorders	4 (66.7)
Cough	3 (50.0)
Rhinorrhoea	1 (16.7)
General disorders and administration site conditions	2 (33.3)
Pyrexia	2 (33.3)
Gastrointestinal disorders	1 (16.7)
Constipation	1 (16.7)
Diarrhoea	1 (16.7)
Vomiting	1 (16.7)
Skin and subcutaneous tissue disorders	1 (16.7)
Dry skin	1 (16.7)

MedDRA version 22.1.

TEAE: Treatment-emergent adverse event.

A subject with multiple events within a category (Any, System Organ Class (SOC), or Preferred Term (PT)) is counted only once in that category. Table is sorted in descending order by SOC, and by PT within each SOC. Subjects shown in dose group according to their Day 1 dose in Part B.

The SOC with the greatest incidence of AEs were 1) infections and infestations and 2) respiratory, thoracic, and mediastinal disorders (Table 24).

Most AEs were common manifestations of CF for patients in this age group. The most commonly occurring AEs (occurring in 2 or more subjects) included cough, pyrexia, and upper respiratory tract infection. The incidence of AEs by SOC and PT is presented in Table 24.

Serious adverse event/deaths/other significant events

Part A Cohort 3

There were no deaths in Part A Cohort 3 of Study 124.

A subject with a *CFTR* mutation had 1 SAE of thrombocytopenia. The SAE of thrombocytopenia was considered resolved (platelet count of 310 K/mm³).

The subject continued into the Extension Study, Study 126, and platelet levels were in the normal range for the 84 weeks of IVA treatment to date.

The SAE of thrombocytopenia was considered by the investigator to be severe in intensity and not related to study drug. Omeprazole was considered the suspect etiology.

Part B Cohort 7

There were no deaths in Study 124 Part B Cohort 7.

A subject with a *CFTR* mutation had a SAE of bronchiolitis, which was considered by the investigator to be unlikely related to study drug. The SAE of bronchiolitis was considered resolved.

The SAE of bronchiolitis was considered by the investigator to be severe in intensity and unlikely related to study drug. Acquired viral infection was considered as the alternative suspected etiology.

Laboratory findings

Part A Cohort 3

Liver Function Test Results

There were no LFT elevations considered to be AEs. The mean absolute changes from baseline to Day 5 were not clinically significant for either dose group.

There were no elevations in ALT, AST, or total bilirubin $>2 \times$ ULN. For ALT, maximum on-study elevation of ALT was found between 1xULN and 2xULN for 4 of 6 patients, while the remaining two patients experienced less than 1xULN maximal ALT elevation. For AST, all but one patient had maximum on-study elevation of less than 1xULN, the remaining one patient experienced a maximum AST elevation between 1xULN and 2xULN. Maximum on-treatment value of total bilirubin was below 1xULN for all patients in Part A Cohort 3.

Lipase and Amylase Results

Lipase levels showed a decline after the start of IVA treatment in Part A/Cohort 3. The overall mean (SD) lipase level was 245.17 (125.52) U/L (normal range: 4 to 29 U/L [<6 months]; 4 to 23 U/L [6 months to <1 year]) at baseline and decreased to 105.33 (54.54) U/L at Day 5. The mean (SD) absolute change from baseline at Day 5 was -139.83 (76.71) U/L.

Serum amylase levels were generally stable during the 4 days of IVA treatment, assessed across 5 days in Part A/Cohort 3. The overall mean (SD) amylase level was 52.8 (25.4) U/L at baseline (normal range: 1 to 17 U/L [<6 months]; 6 to 44 U/L [6 months to <1 year]) and was 51.7 (29.6) U/L at Day 5.

Of note, Lipase and serum amylase levels were assessed as safety (clinical chemistry) parameters, however it is discussed in the Clinical efficacy part of this AR.

Other Clinical Chemistry Parameters

The mean changes from baseline in clinical chemistry parameters (excluding lipase, which trended downwards) were small and not considered clinically significant. There were no clinical chemistry values considered by the investigator to be AEs.

Haematology

For all parameters, the mean changes from baseline were small and not considered clinically significant. One subject had thrombocytopenia at Day 5; this event was considered to be an SAE (see part Deaths/Serious AEs of Clinical Safety section of this AR). There were no other haematology values considered by the investigator to be AEs.

Part B Cohort 7

Liver Function Test Results

Fluctuations from baseline in mean LFT measurements throughout the 24-week treatment period were not considered clinically significant. All subjects had maximum on-treatment ALT, AST, and bilirubin $\leq 1 \times$ (upper limit of normal) ULN.

Lipase and Amylase

Mean (SD) lipase at baseline was elevated at 308.83 (168.28) U/L (normal range: 4 to 29 U/L [<6 months]; 4 to 23 U/L [6 months to 1 year]). The mean (SD) lipase level decreased to 50.17 (32.98) U/L at Week 24.

Mean (SD) serum amylase at baseline was elevated at 69.2 (30.3) U/L (normal range: 1 to 17 U/L [<6 months]; 6 to 44 U/L [6 months to 1 year]). The mean (SD) amylase level was 58.8 (27.4) U/L at Week 24.

Other Clinical Chemistry Parameters

For all clinical chemistry parameters (excluding lipase and amylase, which trended downwards), the mean changes from baseline were small, and no apparent trends were observed. No subjects had any laboratory related AEs.

Haematology

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

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

Part A Cohort 3

Vital Signs and Physical Examinations

According to the MAH, no clinically significant changes from baseline were observed for BP, pulse rate, oxygen saturation, temperature, or respiratory rate.

Table 25: Summary of Vital Signs Results and Change from Baseline at Each Visit Safety Set Part A, Cohort 3, 3-<6 Months

Parameter Name (Units): Systolic Blood Pressure (mmHg)				
Visit	Statistic	IVA 25 mg N = 3	IVA 50 mg N = 3	Total N = 6
Baseline	n	3	3	6
	Mean (SD)	100.7 (24.8)	100.3 (7.6)	100.5 (16.4)
	SE	14.3	4.4	6.7
	Median	114.0	97.0	103.0
	Min, Max	72, 116	95, 109	72, 116
Day 5	n	2	3	5
	Mean (SD)	88.0 (21.2)	87.3 (11.9)	87.6 (13.6)
	SE	15.0	6.9	6.1
	Median	88.0	82.0	82.0
	Min, Max	73, 103	79, 101	73, 103
Change from Baseline at Day 5	n	2	3	5
	Mean (SD)	-5.0 (8.5)	-13.0 (18.1)	-9.8 (14.2)
	SE	6.0	10.4	6.3
	Median	-5.0	-15.0	-11.0
	Min, Max	-11, 1	-30, 6	-30, 6
Parameter Name (Units): Diastolic Blood Pressure (mmHg)				
Visit	Statistic	IVA 25 mg N = 3	IVA 50 mg N = 3	Total N = 6
Baseline	n	3	3	6
	Mean (SD)	63.3 (13.3)	57.3 (9.1)	60.3 (10.7)
	SE	7.7	5.2	4.4
	Median	70.0	61.0	62.5
	Min, Max	48, 72	47, 64	47, 72
Day 5	n	2	3	5
	Mean (SD)	55.0 (5.7)	47.7 (14.5)	50.6 (11.4)
	SE	4.0	8.4	5.1
	Median	55.0	48.0	51.0
	Min, Max	51, 59	33, 62	33, 62
Change from Baseline at Day 5	n	2	3	5
	Mean (SD)	-5.0 (22.6)	-9.7 (18.5)	-7.8 (17.5)
	SE	16.0	10.7	7.8
	Median	-5.0	1.0	1.0
	Min, Max	-21, 11	-31, 1	-31, 11

While the magnitude of changes in vital signs pulse rate, oxygen saturation, temperature, or respiratory rate can be taken as minor, changes in systolic and diastolic blood pressure are noted. Median systolic BP for the Cohort 3 IVA 25 mg group decreased from 114.0 mmHg to 88.0 mmHg during the 5 days of the study and decreased from 97 mmHg to 82 mmHg for the Cohort 3 50 mg IVA group. Median diastolic BP decreased from 62.5 mmHg to 51 mmHg for the whole Cohort 3 population. Although minimum and maximum values for systolic blood pressure were in normal range at baseline and remained largely in it at day 5, the minimum of decrease in systolic blood pressure was -30 mmHg in the 50 mg ivacaftor group, while -11 mmHg in the 25 mg ivacaftor group. Similarly, for diastolic blood pressure: a -31 mmHg the minimum of change was seen in the 50 mg ivacaftor group and -21 mmHg in the 25 mg ivacaftor group. Decreased BP values in Study 124 Part A/Cohort 3, were also within the normal range of the investigated age group and most likely originate from the known high variability of BP measurements in infants.

Length, weight, weight-for-length, and BMI data for each subject are presented and discussed in Clinical efficacy part of this AR.

Electrocardiograms

No clinically important trends were identified in changes in ECG findings. No subject had a clinically significant abnormal ECG finding during the treatment.

Maximum QTcF intervals were below 450 ms for all patients in Cohort 3 during Part A of Study 124.

Ophthalmologic Examination

There were no treatment-emergent cataracts (lens opacities) identified.

Part B Cohort 7

Vital Signs and Physical Examinations

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 BP.

There were some variations in the mean BP levels over the course of the study, these were considered as small one by the MAH. Abnormal physical examination results were captured as AEs.

Length, weight, weight-for-length, and BMI data for each subject are presented and discussed in Clinical efficacy part of this AR.

Table 26: Summary of Vital Signs Results and Change from Baseline at BL ant Week 24, Safety Set, Part B, Cohort 7, 4-<6 Months - Systolic Blood Pressure (mmHg)

Visit	Statistic	IVA 25 mg N = 6
Baseline	n	6
	Mean (SD)	89.7 (11.3)
	SE	4.6
	Median	91.0
	Min, Max	72, 105
Week 24	n	6
	Mean (SD)	100.8 (6.0)
	SE	2.5
	Median	101.5
	Min, Max	94, 107
Change from Baseline at Week 24	n	6
	Mean (SD)	11.2 (8.7)
	SE	3.5
	Median	9.5
	Min, Max	2, 22

Table 27: Summary of Vital Signs Results and Change from Baseline at BL ant Week 24, Safety Set, Part B, Cohort 7, 4-<6 Months - Diastolic Blood Pressure (mmHg)

Visit	Statistic	IVA 25 mg N = 6
Baseline	n	6
	Mean (SD)	52.8 (6.3)
	SE	2.6
	Median	52.5
	Min, Max	45, 63

Week 24	n	6
	Mean (SD)	63.0 (13.9)
	SE	5.7
	Median	65.5
	Min, Max	37, 76
Change from Baseline at Week 24	n	6
	Mean (SD)	10.2 (14.8)
	SE	6.1
	Median	13.5
	Min, Max	-16, 28

Median systolic BP was 91 mmHg at baseline (BL), minimum and maximum BL systolic BP values were 72 mmHg and 105 mmHg, respectively. At Week 24, median systolic BP was 101.5 mmHg, minimum and maximum systolic BP values were 94 mmHg and 107 mmHg, respectively. During the 24 Week of Study 124 Part B Cohort 7, as high as 130 mmHg systolic blood pressure value was measured as well. Systolic blood pressure values above ULN for infants 0 to 12 months of age (normal SBP range 65 to 106 mmHg) were measured at almost all visits, but in different patients and not consequently in the same patient.

Five patients had one or more systolic BP measures during the 24 weeks of Study 124, Part B Cohort 7 which seem to be higher than the upper level of normal range of systolic BP for infants. All patients had diastolic BP values higher than the upper level of normal range of diastolic BP for infants.

There was high variability in BP measurements in Study 124 due to difficulties in obtaining accurate BP measurements in infants 4 to <6 months of age.

There was one subject in Cohort 7, who had systolic BP (SBP) of 130 mm Hg. The subject's BP values at all other study visits, from screening through Week 24, were within the normal range, or very close to the upper limit of normal (ULN) (for infants 0 to 12 months, normal range SBP: 65 to 106 mm Hg; diastolic BP [DBP]: 45 to 66 mm Hg). This BP excursion might have been caused by the variability of BP measurements in infants.

Minimal value of oxygen saturation was 96% through Week 24 of Study 124 Part B Cohort 7 and there was no patient with consequently lower saturation.

Electrocardiograms

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

Ophthalmologic Examination

No treatment-emergent cataracts (lens opacities) were identified during the 24-week treatment period. All subjects had both the screening and the Week 24 OE.

Safety related to drug-drug interactions and other interactions

Extrinsic Factors

A reduction in the IVA dose is recommended for patients ≥ 6 months of age during co-administration with strong or moderate **CYP3A inhibitors**.

It is expected that patients 4 to <6 months of age may receive therapeutic agents that include strong and moderate CYP3A inhibitors during the course of their treatment with IVA. Due to variability in maturation of CYP enzymes involved in IVA metabolism, treatment with IVA is not recommended in patients 4 to <6 months of age who are taking concomitant strong or moderate CYP3A inhibitors, unless the benefits

outweigh the risks. In such cases, a reduction in the IVA dose is recommended. The recommended IVA dose for patients 4 to <6 months of age and weighing ≥ 5 kg is 25 mg twice weekly or less frequently during concomitant dosing with strong or moderate CYP3A inhibitors. Dosing intervals should be modified according to the clinical response and tolerability.

Intrinsic Factors

Based on the results of Study 124 and Phase 1 Study 013 in adult subjects with moderate hepatic impairment, a reduction in the IVA dose is recommended in patients ≥ 6 months of age with moderate hepatic impairment.

Although moderate hepatic impairment is rare in children <6 months of age with CF, such a level of liver disease may occur.

Due to variability in maturation of CYP enzymes involved in IVA metabolism, treatment with IVA is not recommended in patients 4 to <6 months of age with hepatic impairment, unless the benefits outweigh the risks. In such cases, a reduction in the IVA dose is recommended. The recommended IVA dose for patients 4 to <6 months of age and weighing ≥ 5 kg with hepatic impairment is one 25-mg sachet/packet of granules once daily (qd) or less frequently. Dosing intervals should be modified according to the clinical response and tolerability.

Discontinuation due to adverse events

There were no AEs that led to permanent treatment discontinuation or treatment interruption in Part A Cohort 3 as well as in Part B Cohort 7.

Post marketing experience

IVA is approved in Australia, Brazil, Canada, EU, Israel, Liechtenstein, New Zealand, Switzerland, and the US. Cumulatively, 6,962 patients (representing 20,054.6 person-years) received at least one dose of IVA during the period from the Development International Birth Date of IVA (31 January 2012) to 23 January 2020. No new safety concerns have been identified based on ongoing post-marketing surveillance data; data have been consistent with those from clinical studies and the established safety profile of IVA.

2.5.1. Discussion on clinical safety

The safety database in the target paediatric population is limited in terms of size and drug exposure. Only safety data from 12 children between 4 to 6 months of age from study 124 are available and only 6 of them received 25 mg q12h for approximately 24 weeks. This precludes CHMP from fully characterising the safety profile from a quantitative point of view as only frequent adverse reactions could be detected. However, based on the available data coming from the interim analysis 3 of study 124, ivacaftor seems well tolerated with reported AEs that are consistent with those observed in older children.

In part A/Cohort 3

There was one serious adverse event (SAE) of thrombocytopenia noted at Day 5. The investigator assessed the SAE as not related to study drug and considered omeprazole as the suspected aetiology. Thrombocytopenia is a rare but known adverse drug reaction of omeprazole. Thus, the aetiology of the thrombocytopenia as an omeprazole-induced one seems to be possible. The assignment of this SAE as not related to IVA treatment is thus accepted by CHMP, and also underlined by the fact that the re-initiation of IVA therapy in Study 126 did not caused a new onset of thrombocytopenia in this patient during the 84 week spent by this patient to date in the ongoing Study 126.

There were no deaths, treatment interruptions, or treatment discontinuations.

There were no notable adverse trends in clinical laboratory or ECG parameters.

While the magnitude of changes in vital signs pulse rate, oxygen saturation, temperature, or respiratory rate is considered to be minor, changes in systolic and diastolic blood pressure are noted. Median systolic BP for the IVA 25 mg group decreased from 114.0 mmHg to 88.0 mmHg during the 5 days of the study, For the Cohort 3 50 mg IVA group decreased from 97 mmHg to 82 mmHg. Median diastolic BP decreased from 62.5 mmHg to 51 mmHg for the whole Cohort 3 population. Although minimum and maximum values for systolic blood pressure were in normal range at baseline and remained largely in it at day 5, the minimum of decrease in systolic blood pressure was -30 mmHg in the 50 mg ivacaftor group, while -11 mmHg in the 25 mg ivacaftor group. Similarly, for diastolic blood pressure: a -31 mmHg the minimum of change was seen in the 50 mg ivacaftor group and -21 mmHg in the 25 mg ivacaftor group. Decreased BP values in Study 124 Part A/Cohort 3, were also within the normal range of the investigated age group and most likely originate from the known high variability of BP measurements in infants.

Part B/Cohort 7

Most AEs were common manifestations of CF for patients in this age group. The most common AEs (occurring in 2 or more subjects) included cough, pyrexia, and upper respiratory tract infection.

All AEs were mild or moderate in severity except for one event of bronchiolitis, assessed as severe. The event of bronchiolitis was also an SAE; there were no other SAEs. All AEs, including the SAE of bronchiolitis, were considered unlikely related or not related to study drug.

There were no deaths, treatment interruptions, or treatment discontinuations.

No subject had elevated alanine transaminase (ALT), aspartate transaminase (AST) or total bilirubin during the 24 weeks of treatment.

No treatment-emergent cataracts (lens opacities) were observed.

There were no notable adverse trends in clinical laboratory or ECG parameters.

Rise of systolic and diastolic BP was observed from BL through Week 24 in Part B Cohort 7. Moreover, some systolic BP results in 5/6 patients exceeded the upper limit of normal systolic BP range in infants. All patients had higher than normal diastolic BP measures as well. However this could be explained by the high variability in BP measurements in Study 124 due to difficulties (including poor compliance) in obtaining accurate BP measurements in infants 4 to <6 months of age.

In Study 126, there were no pre-planned interim analyses performed until now. Upon CHMP's request, the MAH presented baseline demography, disease characteristics and available safety data on the last data cut dated on 10 March 2020. According to these data, majority of patients in Study 126 are White, non-Hispanic/Latino and carry mutations G551D/F508del. Safety findings were generally consistent with those observed in Study 124 Part A Cohort 3 and Part B/Cohort 7.

Most AEs were common manifestations of CF for patients in this age group. Related AEs occurred in 15.9% of patients. Severe AEs were experienced by 11% of patients. Serious AEs were occurred in 24.4% of patients, whereas 15.9% of patients had SAEs belonging to Infections and infestations SOC. Treatment discontinuation was carried out for 2 patients due to transaminase elevations. Most discontinuations were caused not by AEs but by possibility of switching the patient to other, commercially already available presentations of Kalydeco.

Comparison of these safety findings with those from Study 124 Part A/Cohort 3 and Part B/Cohort 7 should be handled with caution due to the short duration of Study 124 Part A/Cohort 3 and to the low number of patients in both Cohorts of Study 124. Overall, main safety findings in Study 124 Part

B/Cohort 7 and Study 126 seem to be rather similar: remarkable part of AEs and SAEs belonged to the Infections and infestations SOC and were the common manifestations/complications of CF. No subjects discontinued from Study 124 Part A/Cohort 3 and Part B/Cohort 7 and 2 patients discontinued due to AEs (transaminases increased) from Study 126 up to the last data cut (10 March 2020). Of note, liver enzyme elevations resolved upon discontinuation except from one subject for whom it is stated that AST elevation was not resolved. This issue will be further evaluated when the final CSR for study 126 will be submitted. Other reasons for discontinuation in Study 126 was due to switching of some patient from study product to commercially available Kalydeco presentations.

2.5.2. Conclusions on clinical safety

Overall, the small sample size, the lack of placebo control and the relative short duration of study 124 make it difficult to perform a comprehensive safety evaluation of ivacaftor in children with CF aged 4 to less than 6 months. However, the available data suggest that the safety profile in the target paediatric population is similar to that seen in older children.

IVA was generally safe and well tolerated in subjects with CF 3 to <6 months of age during the 4 days of IVA treatment assessed over 5 days in Part A/Cohort 3, and subjects 4 to <6 months of age during the 24 weeks of treatment in Part B/Cohort 7. Most AEs were common manifestations of CF for patients in this age group and mild or moderate in severity. There were no deaths, treatment interruptions, or treatment discontinuations due to AEs. There were no notable adverse trends in clinical laboratory or ECG parameters, and no treatment-emergent cataracts (lens opacities). Systolic and diastolic BP showed a remarkable decrease during the five days of Study 124 Part A Cohort 3. In Part B Cohort 7, however, rise of systolic and diastolic BP was observed from baseline through Week 24. Moreover, some systolic BP results in 5/6 patients exceeded the upper limit of normal systolic BP range in infants. All patients had higher than normal diastolic BP measures as well, no consistent trend for a suspected AE could be assessed.

The safety results of this study in subjects 3 to <6 months of age (Part A/Cohort 3) and 4 to <6 months of age (Part B/Cohort 7) were overall consistent with the safety results from subjects 6 months of age and older. There were no new safety concerns. Issues related to BP experienced in Study 124 Part A/Cohort 3 and Part B/Cohort 7 were caused most likely by the high variability of BP measurements due to difficulties of BP measurements in infants. Some available safety findings obtained from the ongoing Study 126 suggest similar safety profile in study 126 compared to that observed in study 124, however, final evaluation and conclusion will be performed once final complete CSR will be submitted. The product information will be updated as needed.

2.5.3. PSUR cycle

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.

2.6. Risk management plan

The MAH submitted/was requested to submit an updated RMP version with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 10.0 is acceptable.

The CHMP endorsed the Risk Management Plan version 10.0 with the following content:

Safety concerns

Important identified risks	<ul style="list-style-type: none"> • None
Important potential risks	<ul style="list-style-type: none"> • Hepatotoxicity • Cataract • Concomitant use of IVA with strong CYP3A inhibitors or inducers
Missing information	<ul style="list-style-type: none"> • Use in pregnant and lactating women • Indicated use in children aged less than 6 years

Pharmacovigilance plan

Study/Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 1 – Imposed mandatory additional PV activities which are Conditions of the MA (key to benefit risk)				
None				
Category 2 – Imposed mandatory additional PV activities which are Specific Obligations in the context of a conditional MA under exceptional circumstances (key to benefit risk)				
None				
Category 3 – Required additional PV activities (by the competent authority)				
Study 126 Ongoing	<u>IVA Arm</u> In subjects with CF who are <24 months of age at treatment initiation and have an approved IVA-responsive mutation: <ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • Hepatotoxicity • Cataract • Use in children aged 12 to <24 months old at initiation 	Final Report	March 2022
Study 122 Ongoing	<ul style="list-style-type: none"> • To confirm the long-term safety and effectiveness of Kalydeco (IVA) in US CF patients with the <i>R117H-CFTR</i> mutation <18 years of age • To describe the long-term 	<ul style="list-style-type: none"> • Indicated use in children aged <6 years (with the <i>R117H</i> mutation) 	Final Report	December 2020

	safety and effectiveness of Kalydeco in CF patients with the <i>R117H-CFTR</i> mutation overall and in patients ≥ 18 years of age			
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CF: cystic fibrosis; IVA: ivacaftor; PD: pharmacodynamics

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

Risk minimisation measures

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

Use in pregnant and lactating women	Routine risk minimisation measure: SmPC Section 4.6 where advice is given on to use Kalydeco during pregnancy only if clearly needed and during breastfeeding if the potential benefit outweighs the potential risks. PL Section 2 Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection Prescription only Pregnancy follow-up form Additional PV activities: None
Indicated use in children aged less than 6 years	Routine risk minimisation measure: SmPC Section 4.2 where the posology is described SmPC Sections 4.8 and 5.2 PL Section 2 Additional risk minimisation measures: No risk minimisation measures	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection Prescription only Additional PV activities: Study 126 Study 122

CYP: cytochrome P450, PL: Patient Leaflet; SmPC: Summary of Product Characteristics, Note: Study 126 addresses a subpopulation of the Missing Information of "Indicated use in children aged less than 6 years."

Conclusion

The CHMP and PRAC considered that the risk management plan version 10.0 is acceptable.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

2.7.1. User consultation

No justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH. However, the changes to the package leaflet are minimal and do not require user consultation with target patient groups.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

CF is an autosomal recessive disease with serious, chronically debilitating morbidities and high premature mortality. CF affects approximately 30,000 individuals in the US and 48,000 individuals in the EU. CF

greatly affects the paediatric population, as approximately half of the total population with CF is <18 years of age. Pancreatic destruction leading to pancreatic exocrine insufficiency begins in utero, and lung involvement, manifested by pulmonary inflammation and infection, begins shortly after birth. While the disease affects multiple organs, progressive loss of lung function is the leading cause of mortality. Despite progress in the treatment of CF with antibiotics and mucolytics, the predicted median age of survival for a person with CF is 44.4 years. Although the disease affects multiple organs, progressive loss of lung function is the leading cause of mortality.

Studies performed in children diagnosed following newborn screening suggest that early intervention is associated to improved outcomes. Therefore, there is an expectation that early treatment in life, particularly with the CFTR modulators that target the functional defect of the mutant CFTR protein, may translate in slowing disease progression.

3.1.2. Available therapies and unmet medical need

There is currently no cure available for CF. The goals of current CF therapies are to slow or reverse disease progression, manage symptoms and complications such as pancreatic insufficiency and respiratory infections, and improve quality of life. The majority of CF therapies currently available, including nutritional supplements, antibiotics, and mucolytics, target the downstream consequences and symptoms of the disease. *CFTR* modulators (i.e., correctors and potentiators) target the underlying cause of CF with the potential to alter the course of the disease. These *CFTR* modulators are not a cure for CF and must be taken chronically for the patient to maintain treatment benefits.

Kalydeco (ivacaftor), Orkambi (lumacaftor/ivacaftor), Symkevi (tezacaftor/ivacaftor) and Kaftrio (elexacaftor/tezacaftor/ivacaftor) are the *CFTR* modulators currently approved for CF patients.

Treatment with ivacaftor targets the underlying pathophysiology of CF and improves *CFTR* function, resulting in clinically relevant and statistically significant improvements in ppFEV1, Cystic Fibrosis Questionnaire-Revised respiratory domain, weight/BMI, and commensurate changes in sweat chloride for subjects ≥6 years of age.

At this time, there is no approved *CFTR* modulator therapy available for CF patients <6 months of age. An approval is sought for the treatment of infants aged at least 4 months, toddlers and children weighing 5 kg to less than 25 kg with CF who have an *R117H* mutation or one of the following gating (class III) mutations in the *CFTR* gene: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N or S549R.

3.1.3. Main clinical studies

This application is based on results provided for the ongoing open label Study 124 in patients aged <24 months. Interim (week 24) analysis was submitted in two cohorts (3 and 7) of this study from patients aged 3 months to less than 6 months. Results of 6 patients have been provided.

These data are supported with efficacy data from previous evaluated studies in older patients as follows:

- Studies 102, 103, and 111 performed in subjects with gating or R117H mutation in at least one allele of *CFTR* gene (≥6 years of age).
- Study 108 (uncontrolled open label study) in subjects 2 through 5 years of age.
- Studies 105, 112 and 109 (OL-long term studies) in subjects ≥6 years of age and in subjects 2 through 5 years of age, respectively (Study 109).
- Registry studies: Long-term Safety Study (US and UK CF registries).

The previously above studies support the current submission as data can be partially extrapolated

The lack of randomisation from open label studies limits conclusion, however, extrapolation of efficacy from adults, adolescents and children of other age groups is accepted as the pathophysiology of the underlying disease and the mechanism of action of ivacaftor is the same.

3.2. Favourable effects

Interim analysis of cohort A and B of study 124 demonstrated the ability of ivacaftor to increase *CFTR* function in subjects 4 to <6 months, as evidenced by substantial decreases in sweat chloride concentration in Study 124. The data are limited to 6 patients aged 4 months and less than 6 months. The mean (SD) absolute change from baseline in sweat chloride was -34.0 (mmol/L (n = 1) at week 2, -65.6 (12.0) mmol/L (n = 5) at week 12, and -50.0 (17.3) mmol/L (n = 3) at week 24. These data are comparable to that previously observed with ivacaftor treatment in other children and adolescents. This provides additional support for extrapolation of efficacy from the older population to the younger patients from 4 months of age. The mean nutritional parameters were normal at baseline, but below the median of the reference population, and increased during the 24 weeks of ivacaftor treatment. Mean absolute changes from baseline were: weight, +2.5 kg; length, +9.3 cm, weight-for-length percentile, +20.0%; normalized mean changes were: weight-for-age z-score, +0.82; length-for-age z-score, +0.56; and weight-for-length-for-age z-score, +0.68. Mean increases in Faecal Elastase-1 (FE-1) were observed by week 2 and sustained through Week 24. The mean (SD) absolute change from baseline in FE-1 at week 24 was 181.0 (122.9) $\mu\text{g/g}$ (n = 4), suggesting improvement in pancreatic function with ivacaftor treatment. Three subjects were pancreatic insufficient (FE-1 values $\leq 200 \mu\text{g/g}$) at baseline. These 3 subjects had FE-1 values $>200 \mu\text{g/g}$ at week 24 (n = 2) or at the last available FE-1 assessment, week 12 (n = 1). Absolute mean change (SD) from baseline in IRT at week 24 was -593.8 (402.5) ng/mL (n = 4). This decrease was comparable that seen in previous age groups of children in study 124.

Results from Study 108 previously evaluated demonstrated that ivacaftor improves *CFTR* function in subjects 2 through 5 years of age, resulting in positive effects on nutritional status and pancreatic function.

Sustained, long-term benefits of IVA treatment were demonstrated in clinical studies of ivacaftor in subjects ≥ 6 years of age (Studies 105 and 112) and in subjects 2 through 5 years of age (Study 109). Furthermore, in the Long-term Safety Study lower risks for death, organ transplantation, hospitalizations, PEx, and serious safety outcomes in IVA-treated patients relative to untreated comparators were observed up to 5 years of follow up.

Overall, based on the above data in young patients from 4 months of age supported by efficacy data in older patients, the CHMP considered that the clinical benefits of ivacaftor has been sufficiently demonstrated in children from 4 months to less than 6 months.

3.3. Uncertainties and limitations about favourable effects

Initially, Cohort 7 was planned to include children aged 0-6 months. In part A, one subject who received 25 mg q12h ivacaftor had an AUC value above the 95th percentile of that observed in the adult population, suggesting that IVA exposures may be impacted by maturation at this age. To ensure IVA exposure did not exceed the targeted adult range (95th percentile), Part B/Cohort 7 was limited to subjects 4 to <6 months of age, weighing ≥ 5 kg.

PK and efficacy data are provided in 6 patients aged 4 months to less than 6 months. The level of evidence of an interim analysis in two cohorts of an open-label study is limited. The benefit of ivacaftor treatment (on sweat chloride) may be further supported in this age range by positive effects on

pancreatic exocrine function and evidence of acutely reduced pancreatic inflammation/injury, as well as maintained generally normal (or even improve below normal) nutritional status, as measured by growth parameters. Results were generally encouraging and generally consistent with that observed in the 6-month-old through 5-year-old population.

The duration of study is rather short and there is uncertainty whether the improvement is maintained.

Through week 24, all growth parameter increased however, due to the lack of control group these results are difficult to interpret. The consistency observed in all parameters measured is nevertheless reassuring.

Regarding faecal calprotectin levels, results may be indicative of reduction of inflammation, however, elevated faecal calprotectin naturally declines from birth to its nadir at 4 years and therefore the interpretation of the above results is confounded by this issue in the absence of a control group. The very similar consideration applies for IRT levels. Based on FE-1 levels (with a cut-off at 200 µg/g), the MAH states that some children became pancreatic sufficient. However, all patients received pancreatic enzyme substitution at baseline (N=5) continued substitution therapy through week 24. Data beyond 24 weeks of treatment are needed to confirm that the results in FE-1, IRT etc. would be maintained.

The effect of discontinuing prescribed therapies for CF while remaining on ivacaftor treatment has not been evaluated. During Study 124, subjects continued on their prescribed CF therapies.

Lung function correlates with mortality in CF patients. Spirometry cannot be performed in these very young children; pulmonary function decrease cannot be seen at this age and LCI/IPFM was not measured in this age cohort. Results on pulmonary exacerbation and microbiological cultures did not show any consequent trend, however, this cannot be expected in a short-term study including patients that have generally low PEx and colonisation rates. Long-term data are needed in these young patients to establish a beneficial effect of ivacaftor on lung function and microbiological endpoints and to confirm positive results on nutrition in this age group.

Based on the mechanism of action of ivacaftor and clinical experience in older patients, tolerance is not expected to develop in patients with CF 4 to <6 months of age. However, the duration of study is rather short and there is uncertainty whether the improvement is maintained. Further data are expected to be provided when the final results for study 126 will be available in order to assess maintenance of effect over time.

3.4. Unfavourable effects

Safety results in subjects 4 to <6 months in Study 124 were generally consistent with those in older population, with no new safety concerns identified. In Part A/Cohort 3, there was one event of thrombocytopenia at Day 5, considered unrelated to study drug and for which a negative IVA re-challenge was observed in the Extension study 126. In part B/Cohort 7, the most common AEs (occurring in 2 or more subjects) included cough, pyrexia, and upper respiratory tract infection. Otitis media, constipation, diarrhoea and vomiting occurred as well. There was also one event of bronchiolitis considered not related to study drug.

BP changes observed during Part A in Cohort 3 and Part B in Cohort 7 as well as outlier BP values should be interpreted with caution because of the known difficulties in BP measure methodology as well as the low sample size. According to the MAH's, the BP issues were caused by the high variability of BP measurements in infants due to some difficulties (including poor compliance) of BP measurement in this age group. This can be endorsed by CHMP.

Overall the safety profile of ivacaftor has been well characterised since approval in older patients populations. Adverse drug reactions identified from previously completed studies include nasopharyngitis,

upper respiratory tract infection, headache, nasal congestion, oropharyngeal pain, rash, abdominal pain, and diarrhoea. Most of these ADRs are mild to moderate in severity and resolved with continued ivacaftor treatment. Other potential risk includes elevated transaminase, drug-drug interactions, and cataract (lens opacities). These risks are managed through product information, including recommendation of close monitoring of liver function including elevations in transaminase levels until resolution. Furthermore, dose adjustments are required when IVA is used concomitantly with moderate or strong CYP3A inhibitors. In addition, baseline and follow-up ophthalmological examinations are recommended in paediatric patients treated with IVA.

3.5. Uncertainties and limitations about unfavourable effects

The changes observe in BP during Part A in Cohort 3 and Part B in Cohort 7 should be interpreted with caution as BP measurement in infants can be challenging.

Overall, the low sample size, the uncontrolled design of the study and the short duration of Part B are limitations to the characterisation of the safety profile in patients from 4 months of age. All patients from Part B continued in Extension study 126. The interim safety findings obtained from Study 126 were generally comparable with those seen in Study 124 Part A/cohort 3 and Part B/Cohort 7. The safety of long-term ivacaftor treatment in subjects 4 to <6 months is being evaluated in the 96-week open-label extension Study 126, and final results of which are due in March 2022. This will allow characterisation of the safety profile in this young patient population

3.6. Effects Table

Table 28. Effects Table for Kalydeco granules for the treatment of children with cystic fibrosis (CF) aged 4 to <6 months and weighing 5 kg to less than 25 kg who have an *R117H* mutation or one of the following gating (class III) mutations in the CFTR gene: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N or S549R (data cut-off for Cohort 3 and 7: 11 December 2019).

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
sweat chloride	Absolute Changes From Baseline at week 24	(mmol/L), mean, SD	-50.0 (17.3)	none	robust and clinically relevant change, secondary endpoint, indirect comparison suggest consistency with previous results open-label, uncontrolled study, improvement,	Study 124, Cohort 7
weight-for-age z-score	Absolute Changes From Baseline in Weight-for-age Z-score at week 24	unit mean, SD	0.82 (0.54)	none	tertiary endpoint, uncontrolled data, indirect comparison is requested to register data	Study 124, Cohort 7
Length-for-age Z-score	Absolute Changes From Baseline in Length-for-age Z-score at week 24	unit, mean, SD	0.56 (0.86)	none	improvement tertiary endpoint, uncontrolled data, indirect comparison is requested to	Study 124, Cohort 7

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Weight-for-length-for-age Z-score	Absolute Changes From Baseline in Weight-for-length-for-age Z-score at week 24	unit, mean, SD	0.68 (1.12)	none	register data improvement but tertiary endpoint, uncontrolled data, indirect comparison is requested to register data	Study 124, Cohort 7
FE-1	absolute change From Baseline in Fecal Elastase-1	(µg/g), mean, SD	181.0 (122.9)	none	improvement uncontrolled data	Study 124, Cohort 7
IRT (Cisbio assay)	absolute change From Baseline in IRT	(ng/mL), mean, SD	-593.8 (402.5)	none	uncontrolled data	Study 124, Cohort 7
lipase	absolute change from baseline	(U/L)	-258.67 (158.41)	none	improvement uncontrolled data	Study 124, Cohort 7
amylase	absolute change from baseline	(U/L)	-10.3 (37.2)	none	generally stable levels during treatment uncontrolled data	Study 124, Cohort 7
Unfavourable Effects						
AEs		Subjects with any AEs, n (%) Part A Cohort 3: 3 (50%), Part B Cohort 7: 6 (100%)		none	uncontrolled data, low sample size, indirect comparison to previous study results suggest comparable safety	Study 124, Cohort 7
AEs	Part A Cohort 3: teething, PEx of CF, URTI, wheezing, eczema, flushing and thrombocytopenia, Part B Cohort 7: cough, pyrexia, and upper respiratory tract infection, otitis media, constipation, diarrhoea vomiting dry skin, rhinorrhoea.	total No. of AEs Part A Cohort 3: 7, Part B cohort 7: 19		none	uncontrolled data, low sample size, indirect comparison to previous study results suggest comparable safety	Study 124, Cohort 7
Related AEs	none	Subjects with related AEs, n (%) 0		none	uncontrolled data, low sample size, indirect comparison to previous study results suggest comparable safety	Study 124, Cohort 7
SAEs	Part A Cohort 3: Thrombocytopenia Grade: severe, not related to IVA	Subjects with SAEs, n (%) Part A cohort 3: 1,		none	uncontrolled data, low sample size, indirect comparison to previous study results suggest	Study 124, Cohort 7

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
	Part B Cohort 7: Bronchiolitis Grade: severe, not related to IVA	Part B Cohort 7: 1			comparable safety	

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

A clear demonstration of efficacy in these very young children (4 to less than 6 months) is hampered by the absence of endpoints that are sufficiently sensitive to detect changes in response to treatment. Lung disease is the primary cause of morbidity and mortality in cystic fibrosis. However, in very young children with preserved lung function conventional tests (such as spirometry) are not sufficiently sensitive. Alternative tests such as the Lung Clearance Index (LCI) or imaging techniques (e.g., CT scan) would be required to detect the initial changes in lung function or the structural changes present in the lung since birth. Each of these present their own problems such as the potential need for sedation, the requirement for specific equipment and training (LCI) or the risk of radiation (CT scan). Pulmonary exacerbations, a clinically relevant endpoint in older subjects with cystic fibrosis, is not of help either to assess response to treatment as very young children (usually) experience a limited number of these events. In addition, showing that disease progression is halted requires a prolonged period of follow-up that cannot be performed pre-authorisation, particularly when data are available supporting the beneficial effect of ivacaftor in older subjects.

Given that in very young children the most prominent features of the disease are those of the gastrointestinal tract, demonstration of a favourable effect on nutritional status and pancreatic function would be supportive as surrogate for the benefit of treatment. Interim results from Study 124 demonstrated that ivacaftor improves CFTR function in infants aged 4 to less than 6 months who have a mutation that causes CFTR gating defects in line with the ivacaftor indication, with a clear positive effect on sweat chloride. Final results of Study 124 along with individual data are not yet available for all children enrolled in Part B of the study and will provide further long-term efficacy and safety data in the paediatric CF population.

No new AEs were identified in Cohorts 3 or 7 of study 124 and the safety profile was consistent with that known for older patients with class III gating mutation for whom data on long term safety data are available.

Safety findings from study 126 that were provided by the MAH upon request form CHMP, were generally consistent with those observed in Study 124 Part A Cohort 3 and Part B/Cohort 7 which is reassuring. The final CSR of study 126 will be completed in 2022.

However, the safety database in the target paediatric population remains limited in terms of size and drug exposure, i.e., only safety data from 6 children between 4 and <6 months of age from study 124 are available and only 6 out of them were treated for approximately 24 weeks with ivacaftor 50 mg q12h. This precludes to properly characterising the safety profile in this very young population from a quantitative point of view as only frequent adverse reactions could be detected.

3.7.2. Balance of benefits and risks

Cystic fibrosis represents an area of unmet medical need for specific targeted therapies. Study 124 is an uncontrolled study with safety and PK as primary endpoints, the 3rd interim analysis results demonstrated that ivacaftor improves CFTR function in subjects aged 4 to <6 months who have a mutation that causes CFTR gating defects, with positive effects on sweat chloride. Results on nutritional status and pancreatic function that are very relevant in this age group and may be supportive for a positive benefit/risk. According to ICH E11 (Clinical Investigation of Medicinal Products in the Paediatric Population) “when a medicinal product is to be used in younger paediatric patients for the same indication(s) as those studied in older paediatric patients, the disease process is similar, and the outcome of therapy is likely to be comparable, extrapolation of efficacy from older to younger paediatric patients may be possible. In such cases, pharmacokinetic studies in the relevant age groups of paediatric patients likely to receive the medicinal product, together with safety studies, may be sufficient to provide adequate information for paediatric use.” Although the underlying defect in cystic fibrosis is the same across all ages, the heterogeneity of disease effects in target organs and the progression of the disease over time lead to clinical manifestations that vary according to age. The implementation of newborn screening programmes has shown that early interventions such as nutritional support, eradication of early lung colonisation/infection etc. are associated to improved health outcomes and quality of life. It can be assumed that drugs targeting the basic defect of the mutant CFTR protein cystic fibrosis such as CFTR modulators may have the potential to slow disease progression and earlier treatment would result in better outcomes.

The safety database provided is limited both in terms of size and length of exposure and this has an obvious impact on the characterisation of the safety profile of ivacaftor in these young children. However, it is reassuring that no new AEs had been identified in study 124 compared to what it is already known for older patients with class III gating mutations. Furthermore, safety data from study 126 were consistent with those from Study 124 Part A/Cohort 3 and Part B/Cohort 7, and the final study report will provide additional safety data for 96 weeks. The final CSR of study 126 will be provided upon completion in 2022, as stated in the RMP.

Based on the principles of paediatric extrapolation, the benefits of ivacaftor treatment can be extended to patients between 4 to <6 months of age and with all approved mutations.

3.7.3. Additional considerations on the benefit-risk balance

For subjects 2 through 5 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 cannot be feasible due to the small number of available children in this age group.

3.8. Conclusions

The overall B/R of Kalydeco is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and

therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include treatment of infants aged at least 4 months, toddlers and children weighing 5 kg to less than 25 kg with cystic fibrosis 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* for Kalydeco 25 mg granules. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. The RMP is updated accordingly (version 10.0).

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annexes I and IIIB and to the Risk Management Plan are recommended.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0353/2018 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

Similarity with authorised orphan medicinal products

The CHMP is of the opinion that Kalydeco is not similar to Bronchitol, TOBY Podhaler, Symkevi and Kaftrio within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. See appendix 1.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'Kalydeco-H-C-002494-II-Var.86'