30 April 2020
EMA/297262/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Kalydeco

International non-proprietary name: ivacaftor

Procedure No. EMEA/H/C/002494/II/0082

Note

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

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List of abbreviations

AE	adverse event
AUC	area under the concentration versus time curve
BMI	body mass index
CF	cystic fibrosis
CFF	Cystic Fibrosis Foundation (US)
CFFPR	Cystic Fibrosis Foundation Patient Registry
CFQ-R	Cystic Fibrosis Questionnaire-Revised
CFTR	cystic fibrosis transmembrane conductance regulator gene
CFTR	cystic fibrosis transmembrane conductance regulator protein
CHMP	Committee for Medicinal Products for Human Use (EMA)
CI	confidence interval
Cmin	minimum observed concentration
CT	computed tomography
EMA	European Medicines Agency
EU	European Union
F508del or *F508del- CFTR*	*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 (US)
FEV1	forced expiratory volume in 1 second
G551D or *G551DCFTR*	*CFTR* missense gene mutation that results in the replacement of a glycine residue at position 551 of CFTR with an aspartic acid residue
IA1	first interim analysis (year 1)
ICH	International Council for Harmonization
IVA	ivacaftor
LS	least squares
MMRM	mixed-effects model for repeated measures
n	size of subsample
N	total sample size (e.g., number of subjects treated)
P	probability
P aeruginosa	*Pseudomonas aeruginosa*
PASS	post-authorization safety study
PD	pharmacodynamic, pharmacodynamics
PEx	pulmonary exacerbation(s)
PK	pharmacokinetic, pharmacokinetics
popPK	population PK
ppFEV1	percent predicted forced expiratory volume in 1 second
q12h	every 12 hours
R117H or *R117H-CFTR*	*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
SD	standard deviation
SE	standard error
SwCl	sweat chloride

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 21 October 2019 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 new population for Kalydeco 150 mg tablets to extend the use to patients with cystic fibrosis (CF) aged 6 years and older and weighing 25 kg or more who have an *R117H* mutation in the *CFTR* gene and for Kalydeco granules 75 mg and 50 mg, to add patients with CF aged 12 months and older and weighing 7 kg to less than 25 kg who have an *R117H* mutation in the *CFTR* gene. This is based on a clinical trial and literature data, and post-marketing experience with Kalydeco. As a consequence, sections 4.1, 4.2, 4.4 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. The RMP version 8.5 has also been submitted.

Information relating to orphan designation

Kalydeco, was designated as an orphan medicinal product (EU/3/08/556) on 08 July 2008 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 appointed by the CHMP was:

Rapporteur: Maria Concepcion Prieto Yerro

Timetable	Actual dates
Submission date	21 October 2019
Start of procedure:	2 November 2019
CHMP Rapporteur Assessment Report	13 January 2020
PRAC Rapporteur Assessment Report	7 January 2020
PRAC Outcome	16 January 2020
CHMP members comments	20 January 2020
Request for supplementary information (RSI)	30 January 2020
Submission:	28 February 2020
Re-start of procedure:	02 Mars 2020
CHMP Rapporteur Assessment Report	15 April 2020
PRAC Rapporteur Assessment Report	3 April 2020
PRAC Outcome	17 April 2020
CHMP members comments	22 April 2020
Updated CHMP Rapporteur Assessment Report	27 April 2020
Opinion	30 April 2020

2. Scientific discussion

2.1. Introduction

Cystic Fibrosis (CF) is an autosomal recessive, progressive, and life-threatening genetic disease caused by mutations in the CF Transmembrane Conductance Regulator (*CFTR*) gene that result in deficient CFTR protein function.

The *R117H-CFTR* mutation is a missense mutation that results in the replacement of an arginine residue at position 117 of CFTR with a histidine residue. Although generally characterized as a Class IV conductance mutation, *R117H-CFTR* is known to exhibit a defect in channel gating which has been documented in published studies *(Sheppard et al., 1993, Van Goor F et al, 2014)* supporting the use of ivacaftor for the treatment of patients with CF who have the *R117H* mutation.

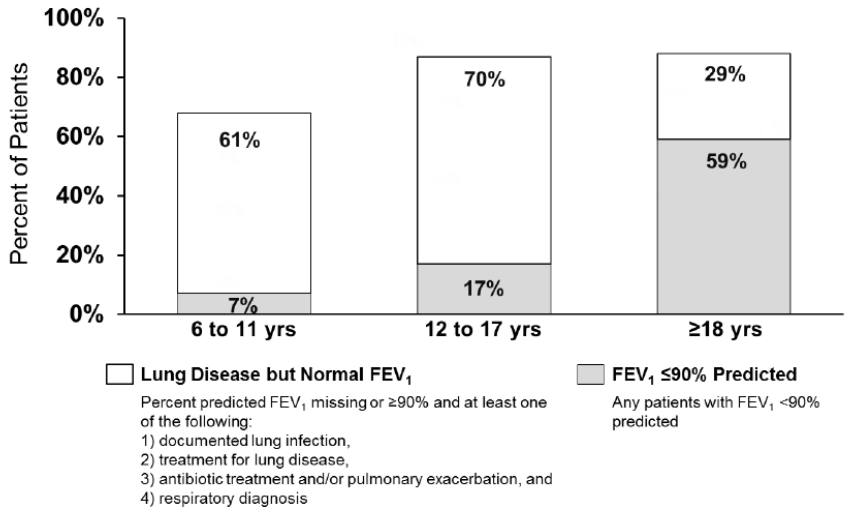
R117H is a *CFTR* variant of varying clinical consequences (clinical and functional translation of CFTR, CFTR2), i.e. by itself, *R117H* does not act as a CF-causing variant but under certain circumstances (and as always, when another CF-causing variant is present *in-trans*) *R117H* can cause disease. Whether or not *R117H* can cause disease is based on another region of the *CFTR* gene which is a polythymidine (Poly-T) repeat polymorphism located in *CFTR* Intron 8 (IVS8) or poly-T tract. The poly-T tract is present in every copy of the *CFTR* gene and occurs in one of three forms: 5T, 7T, or 9T. Depending on which poly-T form is present in the same copy of the *CFTR* gene (i.e. *in-cis*) with *R117H*, differing outcomes may occur. The combination of *R117H/5T* with a second CF-causing mutation such

as *F508del* is expected to result in CF while the combination of *R117H/7T* is unlikely to act as a disease-causing variant (particularly for females) but may result in male infertility. However, a person with this combination of variants and this form of the poly-T tract may have borderline or elevated sweat chloride and mild clinical symptoms of CF. *R117H/9T* is highly unlikely to act as a disease-causing variant; the vast majority of individuals with this combination will not have CF. Nevertheless, there may be other genetic and environmental factors which may also play a role on the phenotypic expression of the disease in individual patients.

R117H can be a CF disease-causing *CFTR* mutation that is associated with residual CFTR function. The prevalence of the *R117H-CFTR* mutation among individuals with CF is estimated to be 1.0% in Europe and 5.5% in the UK *(2017 ECFS Patient Registry Annual Data Report, UK Cystic Fibrosis Registry: 2017 Annual Data Report)*. While on a population basis, patients with residual function CFTR mutations have relatively higher rates of pancreatic sufficiency, and a later age of onset of disease manifestations than patients homozygous for the *F508del* mutation (the most common *CFTR* mutation), *R117H* patients may have a classical CF disease. Median life expectancy of patients with residual function, including patients with the *R117H-CFTR* mutation, is only 50 years, and the median age at death is 38 years in the US and 32 years in the UK *(Hoo ZH et al, 2014; McKone et al, 2014)*. These patients may develop all the co-morbidities associated with CF including bronchiectasis and recurrent lung infections, rhinosinusitis, CF-related diabetes, infertility, and pancreatic insufficiency.

Data from the US Cystic Fibrosis Foundation Patient Registry (CFFPR) show evidence of lung disease and decreased percent predicted FEV1 (ppFEV1) in patients 6 to 11 years of age, and a progressive loss of lung function with age (see Figure 1 below). In the 12- to 17-year-old subgroup, 17% of patients have ppFEV1 ≤90%, and this increases to 59% of patients ≥18 years of age which highlights the rationale for earlier intervention.

Figure 1 Prevalence of lung disease with normal ppFEV1 and reduced ppFEV1 in different age groups of patients in the US with the *R117H-CFTR* mutation



Source: CFF Registry; 2011 dataset[19]
FEV_1: forced expiratory volume in 1 second; $ppFEV_1$: percent predicted forced expiratory volume in 1 second; yrs: years

The delayed but progressive nature of CF in patients with the *R117H-CFTR* mutation was also documented by Wagener et al. (2018), using data from the US CFFPR. In this study, the rates of lung function decline in children 6 to 12 years of age and 13 to 17 years of age were slower (but present) in *R117H* patients compared to homozygous *F508del* patients, but the rates in adults (18 to 24 years of age and ≥25 years of age) were not significantly different. These data suggest that while disease progression is slower in children with *R117H*, by the time patients are 18 years of age, progression of

lung disease is comparable to *F508del* homozygous patients. Thus, patients with the *R117H-CFTR* mutation are likely to benefit from treatment before reaching 18 years of age. In addition, although residual function mutations are usually associated with exocrine pancreatic sufficiency, these mutations demonstrate a high propensity for ductal blockage and inflammation, resulting in pancreatitis. Over time, these episodes of recurrent pancreatitis develop defective acinar pancreatic secretion and a decline in pancreatic exocrine function, with 20% becoming pancreatic insufficient (*Johns JD and Rowe SM, 2019*).

Newborn screening allows individuals with the *R117H-CFTR* mutation to be identified early in life, often before the onset of advanced gastrointestinal or pulmonary manifestations. This provides the opportunity for early intervention, ideally before major irreversible organ damage has occurred. While most paediatric patients with the *R117H-CFTR* mutation may not have overt clinical manifestations of disease, they are at risk for lung damage and airway inflammation. Lung function decline is delayed but not decreased in patients with CF and the *R117H* gene mutation.

In the EU there are at present no approved CFTR modulators for the treatment of paediatric patients with CF who have an *R117H* mutation. However, Kalydeco is currently approved for adult patients with R117H mutation since September 2015. In this application the MAH is seeking an indication as follows:

Kalydeco tablets: treatment of adults, adolescents, and children aged 6 years and older and weighing 25 kg or more with cystic fibrosis (CF) who have an *R117H* mutation in the *CFTR* gene.

Kalydeco granules: treatment of patients with CF aged 6 months and older and weighing 5 kg to less than 25 kg who have an *R117H* mutation in the *CFTR* gene.

Of note, during the procedure, the applicant proposed to extend the initial request for Kalydeco granules from 12 months to 6 months.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP. However, an updated Environmental Risk Assessment (ERA) has been provided following the assessment of Kalydeco EMEA/H/C/002494/X/0075/G. The updated ERA submitted as part of this application summarised the degradation half-lives for unchanged VX-770 and Metabolite M2 in soil calculated according to the recommendations of EMA/CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

An environmental risk assessment of VX-770 (ivacaftor) in Kalydeco (Monotherapy) was submitted in Module 1.6 in the Marketing Authorisation Application for Kalydeco. This assessment was based on a single product at a maximum daily dose of 300 mg.

Kalydeco is now indicated in tablet form at a daily dose of 300 mg for the treatment of CF in patients aged 6 years and older who have a *G551D* mutation or other gating mutations in the *CFTR* gene. Kalydeco is also indicated in granule form at a daily dose of 150 mg for the treatment of CF in patients aged 2 years and older who have mutations in the *CFTR* gene including *G551D*. In addition, Kalydeco is indicated in tablet form at a daily dose of 300 mg for the treatment of CF in patients aged 18 years and older who have a *R117H* mutation.

VX-770 is also marketed as Orkambi in combination with VX-809 for the treatment of CF in patients who have been genotyped homozygous for the *F508del* mutation. The maximum daily dosage is 500 mg, administered orally.

VX-770 is also to be marketed in combination with VX-661 (Symkevi) and in combination with VX-445 and VX-661 for the treatment of CF in patients who have been genotyped for total *F508del* mutations. The maximum daily dosage of VX-770 is 300 mg, administered orally.

The applicant provided an ERA for Kalydeco as prescribed alone or in combination with other drugs, that can be summarised as follows:

Summary of main studies results:

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 IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**Value**	**Unit**	**Remarks**
Algae, Growth Inhibition *(Pseudokirchnerilla subcapita)*	OECD 201	NOEC	54.7	µg/L	Growth rate
Daphnia sp. Reproduction Test	OECD 211	NOEC	3.1	µg/L	
Fish, Early Life Stage Toxicity *(Pimephales promelas)*	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 (*Chironomus riparius*)	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. As requested, the ERA for Kalydeco has been updated and data have been provided in this application. Based on available data, the risk of ivacaftor to the environment, as previously assessed, remains low. Appropriate recommendations are already included in the product information in order to minimize any potential risks to the environment.

2.2.3. Conclusion on the non-clinical aspects

The updated data submitted in this application did not warrant any change to the product information. No new non-clinical issues are identified which could preclude the granting of the extension of indication for Kalydeco.

2.3. Clinical aspects

2.3.1. Introduction

In the EU Kalydeco as monotherapy is approved for patients with CF who have certain gating (class III) mutations in the *CFTR* gene as well as for patients with an *R117H-CFTR* mutation. For the latter, only adult subjects are covered by the indication. The subject of this application is an extension of the indication of Kalydeco tablets and granules for the treatment of patients with CF aged 6 months and older who have an *R117H* mutation in the *CFTR* gene.

The proposed recommended dose of ivacaftor (IVA) for *R117H-CFTR* patients is identical to the dose approved in children and adolescents with pre-specified gating (class III) *CFTR* mutations, i.e. 25 mg dose for patients weighing between 5 to < 7 kg, 50 mg dose for patients weighing between 7 to <14 kg, 75 mg dose for patients weighing between 14 to <25 kg, and 150 mg dose for patients weighing ≥25 kg.

The following clinical data were submitted to support this application:

- Study VX11-770-110 (study 110): a phase 3, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of ivacaftor in subjects aged 6 years of age and older with cystic fibrosis who have the *R117H-CFTR* mutation.

  Of note, this study has been previously assessed in variation application EMEA/H/C/002494/II/27 and led to the granting of an indication for adult patients with an *R117H-CFTR* mutation based on a pre-specified subgroup analysis by age. However, the request for an indication in adolescents (n=2) and children (aged 6 and older, n=17) was rejected by CHMP at that time. Further information can be found in the published EPAR for EMEA/H/C/002494/II/27.

- Study VX12-770-112 (study 112): a phase 3, two-arm, open-label, rollover study to evaluate the safety of long-term ivacaftor treatment in subjects 6 years of age and older with cystic fibrosis and a non-*G551D CFTR* mutation and who had previously been enrolled in study 110, study 111 or study 113.

  Interim data (until week 12) of study 112 were assessed in EMEA/H/C/002494/II/27, while the final study report was submitted later on and assessed in EMEA/H/C/002494/II/0054.

- Interim analysis 2 (IA2) of Study VX15-770-122 (study 122): a study in the Cystic Fibrosis Foundation Patient Registry (CFFPR) of patients (including patients below 18 years of age) with CF who have the *R117H-CFTR* mutation to confirm the long-term safety and effectiveness of Kalydeco where data captured in the CFFPR from an interventional cohort (Kalydeco cohort; no subjects enrolled) and a non-interventional cohort (Kalydeco cohort). Study 122 also included an historical cohort. Study 122 was requested as a post-marketing commitment by FDA at the time of approval of Kalydeco for children aged 6 years and older (and subsequently to younger age groups) who have the *R117H* mutation in the *CFTR* gene.

  The results of study 122 represent the only new clinical data submitted as part of this application and were not previously assessed.

GCP

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

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

- Tabular overview of clinical studies

Module/Study	Population	Study Title
Clinical Studies		
Module 5.3.5.1/VX11-770-110	CF subjects	A phase 3, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of ivacaftor in subjects with cystic fibrosis who have the *R117H-CFTR* mutation.
Module 5.3.5.2/VX12-770-112	CF subjects	A phase 3, two-arm, rollover study to evaluate the safety of long-term ivacaftor treatment in subjects 6 years of age and older with cystic fibrosis and a non-*G551D CFTR* mutation
Postmarketing Commitment Study		
Module 5.3.6/VX15-770-122	CF subjects	A study in US cystic fibrosis patients with the *R117H-CFTR* mutation to confirm the long-term safety and effectiveness of kalydeco, including patients <18 years of age, combining data captured in the cystic fibrosis foundation patient registry from an interventional cohort and a non-interventional cohort

CF: cystic fibrosis; IVA: ivacaftor

2.3.2. Pharmacokinetics

The MAH proposed to expand the approved therapeutic indication to include patients with the *R117H-CFTR* mutation who are 6 months to <18 years of age, using the film coated tablet (150 mg) and granule (75 mg, 50 mg and 25 mg) formulations. Discussion on dose recommendation is detailed below.

2.3.2.1. PopPK analysis

Methodology for patients aged 6 years and older

In procedure EMEA/H/C/002494/II/27, a popPK analysis was conducted via nonlinear mixed effects modelling using the previously developed popPK model for IVA. This model was updated with data from study 110 (Table 1).

Consistent with the previous model, IVA PK was described by a 2-compartment model with zero-order delivery to the absorption compartment and subsequent first-order absorption. The typical estimates (90% CI) of PK model parameters for the reference subject (70 kg, male, 18 years, CF subject, non-R117H mutation) were 18.2 (16.9, 19.3) L/h for CL/F, 246 (196, 254) L for apparent (oral) central volume of distribution (Vc/F), 150 (48.1, 362) L for apparent (oral) peripheral volume of distribution (Vp/F), 3.09 (1.98, 14.0) L/h for apparent (oral) intercompartmental clearance (Q/F), 2.96 (2.88, 3.17) hours for zero-order dose duration (D1) and 0.721 (0.530, 0.765) h-1 for first-order absorption rate (ka). The typical CL/F estimate is similar to that reported in the prior popPKmodel.

Allometric relationships using body weight were incorporated in the base model for all structural parameters to describe the effect of body weight on IVA PK.

Results

Body weight was the most important predictor of IVA disposition, with a change in IVA CL/F of 39% and 131% for the typical 20 kg and 100 kg subject, respectively, when compared to the reference subject (70 kg). Gender and patient status (healthy volunteer versus CF patient) did not account for variability in IVA PK in a clinically meaningful manner. Age was also not a clinically important covariate after accounting for body weight.

IVA CL/F was reduced 21% for subjects with the *R117H-CFTR* mutation relative to the non-*R117H* CF population (including other mutations that cause gating defects and *F508del* homozygotes), with an estimate of 14.3 (12.7, 16.0) L/h. However, this difference in the CL/F estimate should be interpreted with caution since all the data for *R117H* subjects came from a single study; therefore, factors such as study design and inherent inter-study variability may contribute to the difference in CL/F. This difference was not considered to be clinically relevant. IVA exposure (AUC and Cmin) in subjects in Study 110 was consistent with exposures observed in previous clinical studies in other CF populations (Table 1).

Table 1 Predicted IVA exposure at a dose of 150 mg q12h in CF subjects with *R117H-CFTR* mutation versus studies in CF subjects with other mutations

			$C_{min,ss}$ (ng/mL)		AUC_{ss} (ng·h/mL)	
Study/Phase	CF Population	N	Median (min, max)	Mean (SD)	Median (min, max)	Mean (SD)
102/Phase 3	12 years and older *G551D-CFTR*	82	658 (130, 1960)	714 (326)	10100 (3230, 26100)	10700 (4150)
103/Phase 3	6 to 11 years *G551D-CFTR*	26	1050 (367, 3020)	1190 (631)	15700 (6920, 39200)	18400 (8430)
104/Phase 2	12 years and older *F508del-CFTR*	112	482 (138, 1560)	545 (279)	7800 (3400, 21700)	8550 (3580)
110/Phase 3	6 years and older *R117H-CFTR*	34	740 (283, 2240)	810 (342)	11400 (5400, 29500)	12100 (4660)
111/Phase 3	6 years and older non-*G551D-CFTR*	38	814 (303, 2640)	891 (488)	12200 (5190, 38000)	13500 (7080)

Sources: Report J178/Table 7 and Table 9
CF: cystic fibrosis; max: maximum value; min: minimum value; N: total sample size; q12h: every 12 hours

Ivacaftor exposure in subjects 6 years to 11 years of age at the dose of 150 mg q12h is higher than ivacaftor exposure in subjects 18 years of age and older; however, this level of exposure was demonstrated to be safe and efficacious in this age group in clinical studies and has been addressed by the use of weight cut-offs in the labelling for Kalydeco. For children in this age range weighing 25 kg or more, the recommended dose is 150 mg twice daily while for those weighing ≥14 kg to less than 25 kg less the dose is 75 mg twice daily. The predicted systemic exposures are reflected in section 5.2 of the SmPC of Kalydeco.

Methodology for patients under 6 years of age

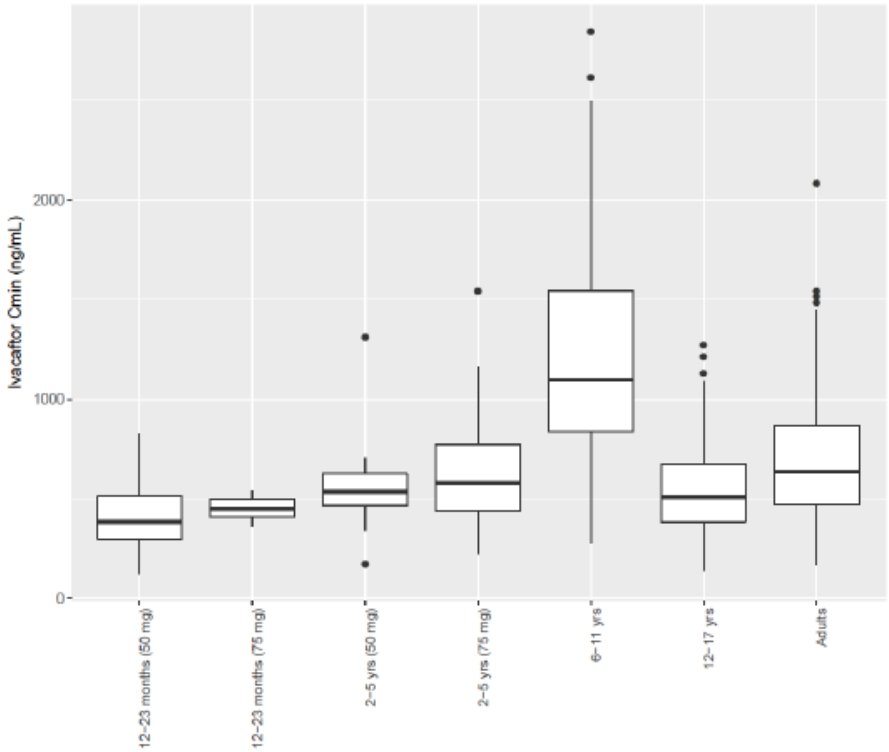
To support this extension of indication under 6 years of age and support dosing recommendations in this age group, key PK data provided in previous ivacaftor submissions from subjects 2 years through 5 years of age (Study 108) and 12 months to <24 months of age (Study 124) have been summarized by the MAH.

A PopPK analysis was conducted across different age groups of patients 12 months of age and older.

Results

Results from the popPK model showed that in subjects 12 months to <24 months of age administered either 50 mg (7 kg to <14 kg) or 75 mg (14 kg to <25 kg) IVA granules in Study 124, the exposures were generally consistent across the age group. The IVA exposure (Cmin and AUC) in subjects 12 months to <24 months of age was similar to that observed in the 2 years through 5 years of age group administered 50 mg (<14 kg) or 75 mg (≥14 kg) IVA granules in Study 108, and in subjects 12 years of age and older in the pivotal Phase 3 Studies 102 and 103. A summary of exposure across age range are shown in Figure 1-1 and Figure 1-2.

Figure 1-1 Predicted IVA Cmin distribution in CF subjects by age group

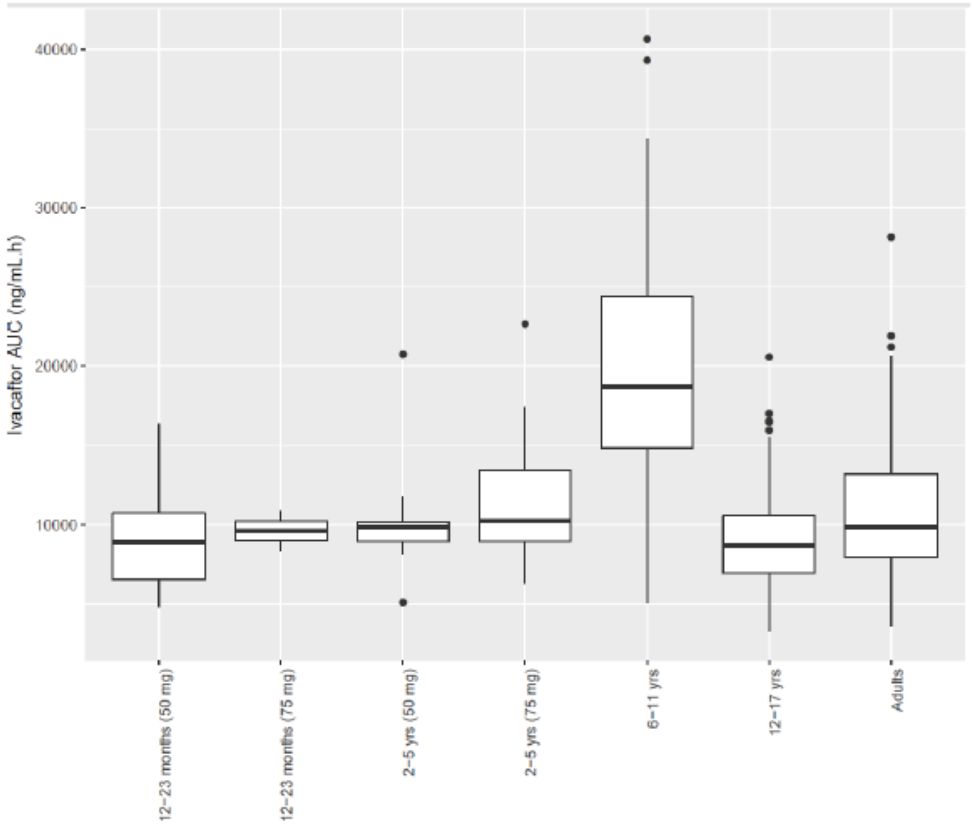


Source: Report N364/Figure 36

CF: cystic fibrosis; IQR: interquartile range; IVA: ivacaftor

Note: Black lines in the center of the box are medians, boxes are the IQR, whiskers are 1.5*IQR, and circles are outliers.

Figure 1-2 Predicted IVA AUC distribution in subjects with CF by age group



Source: Report N364/Figure 37
CF: cystic fibrosis; IQR: interquartile range; IVA: ivacaftor
Note: Black lines in the center of the box are medians, boxes are the IQR, whiskers are 1.5*IQR and circles are outliers.

For patients below 6 years of age, predicted IVA exposures in subjects 12 months to <6 years of age from previous submissions (Studies 124 and 108) were demonstrated to be similar to that observed in subjects 12 years of age and older in the Phase 3 pivotal studies (Studies 102 and 103). The PK results from Studies 124 and 108 confirm the appropriateness of the 50 mg dose for subjects weighing between 7 kg to <14 kg and the 75 mg dose for subjects weighing between 14 kg to <25 kg in the 12 months to <6 years of age group and thus, would be anticipated to be applicable for the *R117H* population in that genotype has not been identified as a relevant covariate influencing ivacaftor pharmacokinetics.

Exposure parameters (Cmin and AUC) for IVA in CF subjects, as determined from the popPK model, are compared across age groups in Table 2.

Table 2: Predicted IVA Exposure in CF Subjects by Age

Age Group	N	$C_{min,ss}$ (ng/mL) Median (min, max)	$C_{min,ss}$ (ng/mL) Mean (SD)	AUC_{ss} (ng·h/mL) Median (min, max)	AUC_{ss} (ng·h/mL) Mean (SD)
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 through 5 years (50 mg)	9	536 (170, 1310)	577 (317)	9840 (5120, 20800)	10500 (4260)
2 through 5 years (75 mg)	26	580 (225, 1540)	629 (296)	10200 (6260, 22700)	11300 (3820)
6 through 11 years[a] (150 mg)	40	1100 (275, 2840)	1240 (594)	18700 (5060, 40600)	20000 (8330)
12 through 17 years (150 mg)	78	508 (141, 1270)	564 (242)	8670 (3280, 20600)	9240 (3420)
18 years and older (150 mg)	190	634 (167, 2080)	701 (317)	9840 (3580, 28200)	10700 (4100)

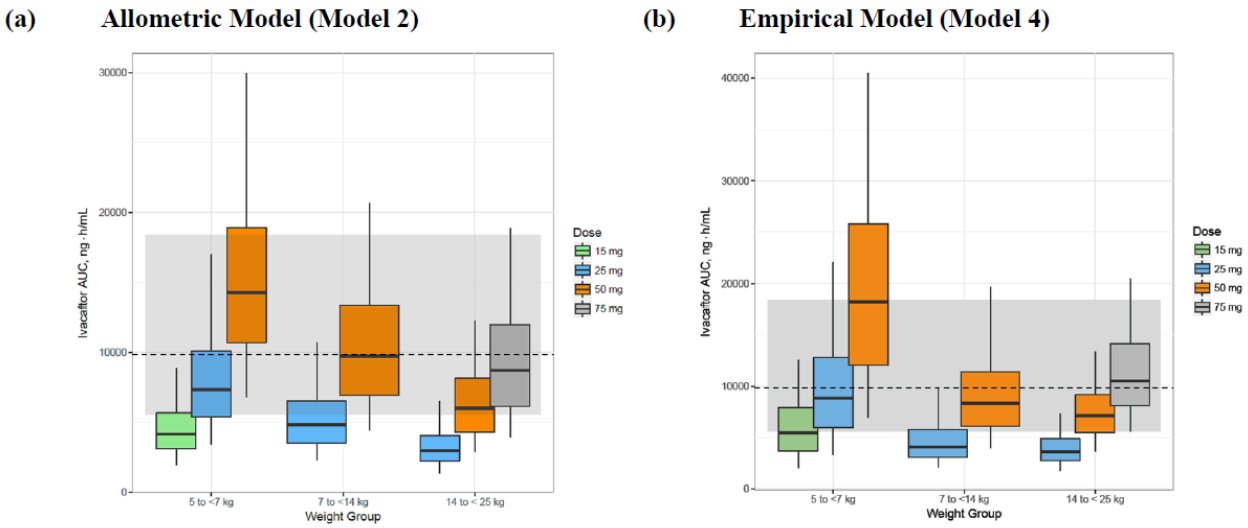
Sources: Report N364/Table 8 and Table 9

CF: cystic fibrosis; IVA: ivacaftor; max: maximum value; min: minimum value

[a] In Report K260/Table 8 and Table 9, $C_{min,ss}$ and AUC_{ss} were simulated for subjects 6 to 11 years of age based on weight. In subjects weighing ≥14 kg to <25 kg the mean (SD) for a 75 mg q12h dose 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 dose was 958 (546) ng/mL for $C_{min,ss}$ and 15300 (7340) ng·h/mL for AUC_{ss}.

In procedure EMEA/H/C/002492/X/75, population PK analysis was also conducted across different age groups of patients 6 months of age and older to support dosing recommendations for infants aged 6 to less than 12 months. This analysis led to the conclusion that age was not a covariate influencing ivacaftor pharmacokinetics but the number of children treated with the ivacaftor lower dose (25 mg) was very limited. Therefore, the MAH was requested to update the pop PK model with available pharmacokinetic (PK) data from a younger (than 6 months) and lower (than 5 kg) weight cohort treated in Study 124 (PK data from Part A, Cohort 3; subjects 3 to <6 months of age; N = 6). Results from several models were provided, including a refit model which incorporated only allometric scaling (Model 2), as well as additional models incorporating maturation and/or an empirical weight relationship on apparent oral clearance (e.g., Model 4). Figure 2 shows predicted IVA $AUC_{0\text{-}12hr}$ at steady-state for different dosing regimens for the paediatric population aged months to less than 12 months of age.

Figure 2 Simulation of IVA AUC0 - 12hr at steady-state for the different dosing regimens for the paediatric population 6 to <12 months of age



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

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

For infants aged 6 to less than 12 months of age and weighing at least 5 kg to less than 7 kg dosed with ivacaftor 25 mg twice daily, predicted $C_{min, ss}$ and $AUC_{tau,ss}$ are 336 ng/ml and 5410 ng*h/mL respectively.

2.3.3. Pharmacodynamics

Mechanism of action

Ivacaftor is a potentiator of the CFTR protein, i.e. in vitro ivacaftor increases CFTR channel gating to enhance chloride transport in specified mutations with reduced channel-open probability compared to normal CFTR. Ivacaftor also potentiated the channel-open probability of *R117H-CFTR*, which has both low channel-open probability (gating) and reduced channel current amplitude (conductance). The mechanism of action of ivacaftor has not been completely elucidated and further studies are needed to identify the site of ivacaftor binding on CFTR.

Primary and secondary pharmacology

A summary of the data previously assessed for study 110 is provided below.

The mean absolute change from baseline in sweat chloride through week 24 (MMRM analysis) was -26.28 mmol/L for the ivacaftor group and -2.31 mmol/L for the placebo group. The treatment difference for ivacaftor versus placebo was -23.97 mmol/L (95% CI: -28.01, -19.93). In the ivacaftor

group, 85.3% (29 out of the 34 subjects in the Full Analysis Set) had a reduction ≥ 10 mmol/l and 76.5% (26/34) had a reduction ≥ 15 mmol/l.

In the subgroup of patients ≥ 18 years of age, the mean absolute change from baseline was -25.90 mmol/L for the ivacaftor group and -4.03 mmol/L for the placebo group. The treatment difference for ivacaftor versus placebo was -21.87 mmol/L (95% CI: -26.46, -17.28). In subjects <12 years of age, the mean absolute change from baseline in sweat chloride through week 24 was -26.59 mmol/L for the ivacaftor group and 1.04 mmol/L for the placebo group. The treatment difference for ivacaftor versus placebo was -27.63 mmol/L (95% CI: -37.16, -18.10).

Only two adolescent subjects were randomised in study 110, one to ivacaftor and the other to placebo. The subject on ivacaftor showed a -17.25 mmol/L absolute change from baseline in sweat chloride which was slightly below the mean value seen in subjects ≥18 years of age in the ivacaftor group (-25.90 mmol/L) and in children 6 to less than 12 years old (-26.59 mmol/L).

No new clinical data have been submitted in this application regarding secondary pharmacology, which is considered acceptable.

2.3.4. Discussion on clinical pharmacology

PK - children aged 6 years and older

Dosing recommendations were supported by an updated pop-PK report which included data from study 110 previously submitted in the variation application extending the indication of Kalydeco in adult patients with *R117H* mutation (refer to EMEA/H/C/002494/II/27). The base model incorporated weight as an allometric function for all structural parameters. Sex, age and patient status did not explain in a clinically meaningful way the variability in ivacaftor PK. Ivacaftor CL/F was reduced by 21% in patients with the *R117H* mutation compared to CF subjects with a gating mutation. Ivacaftor Cmin and AUC values in study 110 overlapped with the values observed in previous studies with other mutations.

Similarly, PK data from children aged 6 to 11 years in study 110 showed the same trend as that seen in studies 103 and 111, i.e. exposure at the dose of 150 mg twice daily was higher in children than in adults.

An ivacaftor dose of 150 mg q12h achieved a mean Cmin,ss of 1240 ng/mL in paediatric patients from 6 to 11 years of age while the same dose resulted in a mean Cmin,ss of 701 ng/mL in adult subjects. Mean AUC was 20,000 ng/mL.h for 6 to 11 years old, compared to 10,700 g/mL.h for adults.

However, this level of exposure was demonstrated to be safe and efficacious in this age group in clinical studies with patients with other type of mutations. Further, this has been addressed by the use of weight cut-off for the posology in the product information for Kalydeco for children aged 6 to less than 12 years old.

PK - children under 6 years of age

Following responses to the request from CHMP during the procedure, the MAH proposed to further extend the *R117H* mutation indication to include patients with the *R117H-CFTR* mutation who are 6 months to <18 years of age, using the film coated tablet (150 mg) and granule (75 mg, 50 mg, and 25 mg) formulations.

The proposed recommended dose of ivacaftor (IVA) for *R117H-CFTR* patients is identical to the dose for the other approved genotypes in the same weight group, i.e. 25 mg dose for patients weighing between 5 to < 7 kg, 50 mg dose for patients weighing between 7 to <14 kg, 75 mg dose for patients weighing between 14 to <25 kg, and 150 mg dose for patients weighing ≥25 kg.

For children under the age of 6 years, dosing recommendations are based on PK data from study 108 (children aged 2 to less than 6 years with CF who have a [pre-specified] gating [class III] mutation in the *CFTR* gene [refer to EMEA/H/C/002494/X/34]) and on an interim analysis of study 124 in children down to 6 months of age (refer to EMEA/H/C/002494/II/0069 and EMEA/H/C/002492/X/75).

Results from the popPK model showed that in subjects 6 months to <24 months of age administered either 25 mg (5 kg to < 7 kg), 50 mg (7 kg to <14 kg) or 75 mg (14 kg to <25 kg) IVA granules in study 124, the exposures were generally consistent across the age groups.

Dose regimens and associated PK data have been established for children with CF ≥6 months of age with CF who have at least a predefined gating (class III) mutations in the *CFTR* gene. Predicted IVA exposures in subjects 6 months through 5 years of age from Studies 124 and 108 were similar to those observed in the Phase 3 pivotal studies in subjects 12 years of age and older. The PK results from Studies 124 and 108 confirmed the appropriateness of the 25 mg dose for subjects weighing between 5 to < 7 kg, the 50 mg dose for subjects weighing between 7 to <14 kg and the 75 mg dose for subjects weighing between 14 to <25 kg in the 6 months through 5 years of age group.

The most prevalent genotype in studies 108 and 124 was *G551D*/*F508del*. Taking into consideration that genotype was not identified as a relevant covariate explaining variability of IVA PK and the safety profile was overall similar and acceptable across age groups and genotypes, CHMP considered that the approved posology for children aged 6 months (weighing at least 5 kg) and older with CF who have a (pre-specified) gating (class III) mutation in the *CFTR* gene is applicable to children of the same age and body weight with CF who have an *R117H-CFTR* mutation.

Pharmacodynamics

In study 110, in the 6 to 11 years of age group, a pharmacodynamic effect on CFTR function was shown with a -26.59 mmol/L reduction in sweat chloride in the ivacaftor group. The improvement (reduction) observed in sweat chloride was similar in magnitude across all age groups in study 110.

While this is understood as a confirmation of activity at the cellular level, at the time of assessment of variation EMEA/H/C/002494/II/27, it was not considered sufficient to conclude on the efficacy of ivacaftor for paediatric subjects under 12 years of age (i.e. as a surrogate for clinical improvement). Since then additional data have been generated across different *CFTR* mutations and genotypes which show that the effects of CFTR modulators on sweat chloride generally parallel the clinical benefits observed in the patient population for which their use is intended (*Muhlebach MS et al, 2016*) e.g. the highest reduction in sweat chloride with ivacaftor has been observed in subjects with gating (class III) mutations where the highest clinical benefit was also achieved.

Given that intermediate effects are observed with ivacaftor in CF patients with the *R117H* mutation, moderate clinical improvements could very likely be expected in this patient population taking into account that individual changes in sweat chloride have not correlated directly with FEV1 improvements (*Fidler MC et al, 2017*).

Overall, exposure in the 6 to 11 years of age group in Study 110 is within the range of adult exposures, and a PD effect on CFTR function was shown. While a lack of FEV1 response was observed in *R117H* subjects 6 to 11 years of age in study 110, the PK findings seemed to indicate that this was not due to inadequate dosing or drug exposure, but rather to small sample size and large variability, as well as difficulty in showing IVA's effect in younger subjects with well-preserved lung function.

2.3.5. Conclusions on clinical pharmacology

The pharmacokinetics of IVA is well understood and is consistent across genotypes and among age ranges down to the age of 6 months. Based on the PK data presented by the MAH, the CHMP considered that the proposed recommended posology of ivacaftor for CF paediatric patients with *R117H-CFTR* mutation was sufficiently justified. Dosing recommendations are therefore as follows:

- 25 mg twice daily for patients weighing between 5 to < 7 kg
- 50 mg twice daily for patients weighing between 7 kg to <14 kg
- 75 mg twice daily for patients weighing between 14 kg to <25 kg
- 150 mg twice daily for patients weighing ≥25 kg

The above treatment recommendations are identical to the recommendations already approved for patients with class III gating mutations.

The CHMP also considered that from a pharmacodynamic point of view, treatment with ivacaftor of patients carrying a *R117H* mutation is justified as the predominant *in vitro* defect of the mutated *R117H-CFTR* protein is a defect in channel gating, although *R117H* is usually classified as a class IV, i.e. conductance mutation. Further, the magnitude of sweat chloride reduction after treatment with ivacaftor was similar in children and adults.

2.4. Clinical efficacy

2.4.1. Dose response study

No dose-response studies have been performed. Dosing recommendations are based on a population PK model analysis of the similarity of ivacaftor systemic exposure between paediatric and adult patients. The popPK analysis was based on studies which enrolled mainly patients with some pre-specified gating (class III) mutations i.e. children below 6 years of age in study 108 (2 to less than 6 years of age) and in study 124 (children below 2 years of age). Detailed information is provided in the pharmacology section. This approach was considered acceptable by CHMP as in population PK analysis genotype was not identified as a significant covariate explaining variability in ivacaftor pharmacokinetics. Therefore, dosing recommendations for children with these gating mutations are considered applicable to children with an *R117H-CFTR* mutation.

2.4.2. Main study

2.4.2.1. Study VX11-770-110

This study has previously been assessed in variation (EMEA/H/C/002494/II/27).

Title of Study

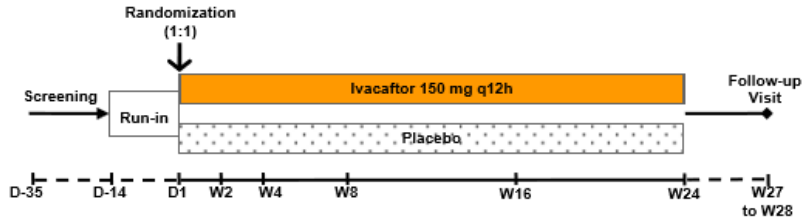
Study VX11-770-110: A Phase 3, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of ivacaftor in subjects with cystic fibrosis who have the *R117H-CFTR* mutation.

Methods

Study participants

The pivotal study for the proposed extension to the indication of Kalydeco is study VX11-770-110 (study 110).

Figure 3. Schematic of Study Design VX11-770-110



Source: VX11-770-110 CSR/Figure 9-1
D: Day; IVA: ivacaftor; q12h: every 12 hours; W: Week
Note: Since the study was terminated early by the sponsor, IVA was administered for periods of up to 24 weeks.

The study included a Screening Period (Day -35 to Day -15 relative to the first dose of study drug), a Run-In Period (Day -14 to Day -1 relative to the first dose of study drug), a Treatment Period (Day 1 [first dose of study drug] through Week 24), and a Follow-up period 3 to 4 weeks after the last week of study drug. Study visits during the Treatment Period occurred on Day 1, Weeks 2, 4, 8, 16, and 24. Patients were offered after the Follow-up period to be enrolled in study 112.

Patients with CF, age 6 years and older, who have a *R117H-CFTR* mutation were enrolled provided that they met all the inclusion criteria and none of the exclusion criteria as follows (only key criteria shown):

Key inclusion criteria

1. Male or female patients aged 6 years (on the date of signed ICF, and where appropriate data of assent) and older with confirmed diagnosis of CF, defined as:

    - a sweat chloride value ≥60 mmol/L by quantitative pilocarpine iontophoresis OR 2 CF-causing mutations (all as documented in the subject's medical record)

    AND

    - chronic sinopulmonary disease

2. Must have had at least 1 allele of the *R117H-CFTR* mutation

3. FEV1 predicted normal for age, sex, and height (Hankinson or Wang equations) at screening:

    - 40% to 90% inclusive for subjects aged 12 years or older
    - 40% to 105% inclusive for subjects aged 6 to 11 years

All subjects enrolled in this study would have had the *R117H-5T* or *R117H-7T* alleles because the study entry criteria required that subjects have CF, as evidenced by sinopulmonary disease and a sweat chloride ≥60 mmol/L or 2 CF-causing mutations. *CFTR* genotyping provided the subjects' poly-T variant genotype, but it did not specify which *CFTR* allele each variant was located on (i.e. the phase of the mutation) because that requires a different sequencing assay (allele-specific long-range PCR).

Therefore, allele-specific long-range PCR was conducted using an optional DNA sample (Sample A) from the subjects who consented to that sample.

For subjects who either had DNA samples that could not be analysed or did not consent to the optional DNA samples, the poly-T variant for the *R117H* allele was derived if the subject had either a *R117H/F508del* or *R117H/R117H* genotype. All subjects who had the *R117H/F508del* genotype had one 9T variant; it was assumed that the 9T was on the *F508del* allele, and therefore the other variant (5T or 7T) was on the *R117H* allele. This assumption was considered valid because: (1) if a subject had *R117H-9T* they would have had a very mild disease phenotype (e.g., sweat chloride <60 mmol/L) and would not have qualified for entry into the study, and (2) a survey of the scientific literature indicates that the *F508del* allele has always been reported with the 9T variant except in some Lebanese Maronites (*Desgeorges M et al, 1997*), North Iranian individual (*Tabaripour R et al, 2012*) and 1 Hispanic individual (*Dharajiya N et al, 2013*). For subjects who did not have either a *R117H/F508del* or *R117H/R117H* genotype, the 5T/7T status for the *R117H* allele could not be derived.

Key exclusion criteria

1. *CFTR* gene mutation leading to CFTR channel with gating defect (i.e. any 1 of the following mutations: *G551D*, *G178R*, *G551S*, *S549N*, *S549R*, *G970R*, *G1244E*, *S1251N*, *S1255P*, or *G1349D*)
2. An acute upper or lower respiratory infection, pulmonary exacerbation, or changes in therapy (including antibiotics) for pulmonary disease within 4 weeks before Day 1 (first dose of study drug).
3. Abnormal liver function, at screening, defined as ≥3 × upper limit of normal (ULN), of any 3 or more of the following: serum aspartate transaminase (AST), serum alanine transaminase (ALT), gamma-glutamyl transpeptidase (GGT), serum alkaline phosphatise (ALP), total bilirubin.
4. History of solid organ or hematological transplantation.
5. Colonization with organisms associated with a more rapid decline in pulmonary status (e.g. *Burkholderia cenocepacia*, *Burkholderia dolosa*, and *Mycobacterium abscessus*) at screening.
6. Current or prior (within 14 days before study Day 1) use of any inhibitors or inducers of cytochrome P450 (CYP) 3A, including consumption of certain herbal medications (e.g., St. John's Wort) and grapefruit/grapefruit juice.
7. Evidence of cataract or lens opacity at Screening.

Treatments

Study drug (ivacaftor 150 mg or ivacaftor-matched placebo) was administered every 12 hours with fat-containing food such as a standard "CF" high-fat, high-calorie meal or snack for up to 24 weeks. Subjects should remain on stable CF medication regimens from 4 weeks before study Day 1 through the Follow-up Visit.

Objectives

Primary objective: to evaluate the efficacy of ivacaftor in subjects with CF who have a *R117H-CFTR* mutation.

Secondary Objective: to evaluate the safety of ivacaftor in subjects with CF who have a *R117H-CFTR* mutation.

Tertiary Objective: to characterize the plasma PK of ivacaftor and metabolites, hydroxymethyl-ivacaftor (M1) and ivacaftor carboxylate (M6), at steady state in subjects with CF who have the *R117H-CFTR* mutation.

Outcomes/endpoints

Primary Endpoint: absolute change from baseline in percent predicted forced expiratory volume in 1 second (FEV1) through Week 24.

Secondary Endpoints:

- Rate of change from baseline in body mass index (BMI) at Week 24.
- Absolute change from baseline in sweat chloride concentration through Week 24.
- Change from baseline in the respiratory domain score of the Cystic Fibrosis Questionnaire-Revised (CFQ-R) through Week 24.
- Time-to-first pulmonary exacerbation.
- Safety, as determined by adverse events, clinical laboratory values (serum chemistry, hematology, and coagulation), electrocardiogram (ECG), ophthalmologic examinations, and vital signs.

A number of tertiary endpoints were also assessed such as pulmonary exacerbations, change from baseline in immunoreactive trypsinogen (IRT), change from baseline in faecal elastase-1 etc.

Sample size

Enrolment was planned for a minimum of 40 and a maximum of approximately 80 subjects in total who have the *R117H-CFTR* mutation on at least 1 allele. Table 3 presents the estimated study power for detecting different treatment effect sizes between the ivacaftor and placebo groups in the absolute change in percent predicted FEV1 from baseline through the Week 24 Visit, assuming 40, 60, or 80 randomized subjects. Subjects were randomized in 1:1 ratio. The treatment effect sizes and standard deviation are based on the results of Study 102 and Study 103, and a review of the clinical CF literature.

Table 3 Power estimates (%) under possible scenarios of treatment effect and number of randomized and evaluable subjects

Absolute Change in Percent Predicted FEV_1	Total Number of Randomized and Evaluable Subjects		
	40	60	80
3.5%	27.1	38.5	48.9
4.0%	33.8	47.8	59.8
4.5%	41.1	57.2	70.0
5.0%	48.7	66.3	78.8
5.5%	56.3	74.5	85.9
6.0%	63.7	81.5	91.2
6.5%	70.7	87.2	94.8
7.0%	76.9	91.5	97.2
7.5%	82.4	94.6	98.5
8.0%	86.9	96.8	99.3

Notes: Treatment effect = absolute change from baseline in percent predicted FEV_1 for ivacaftor minus absolute change from baseline in percent predicted FEV_1 for placebo. Power estimates are based on 2-sided t-test with $\alpha = 0.0448$, assuming a common standard deviation of 8%.

An interim analysis (IA) for safety and efficacy was carried out after 40 subjects completed the Week 8 Visit. The IA data were reviewed by the Data Monitoring Committee (DMC). Vertex clinical study personnel remained blinded to IA results. In order to control the overall type I error rate, a Bonferroni-type adjustment was applied. This reflected an allocated significance of 0.0052 for the IA. The significance level for the final analysis was set at 0.0448 as enrolment was not stopped after the IA.

Based upon the existing power calculations for the study and after exceeding the minimum number of subjects defined in the study protocol, the study was terminated early by the sponsor and recruitment was halted after 70 subjects were randomized. Subjects completed all protocol-defined study visits prior to the closure of the study including the Follow-up Visit. Subjects who did not have their Week 24 Visit were considered to have completed their assigned treatment duration and were offered enrolment in the open-label treatment arm of Study 112; subjects who chose not to enrol in the open-label treatment arm were offered enrolment in the observational arm of Study 112. All available data was included in the final analyses regardless of whether subjects completed 24 weeks of study drug treatment or not.

Randomisation

Subjects were randomized in a 1:1 ratio, stratifying for age (≥18 years, 12 to 17 years [inclusive], and 6 to 11 years [inclusive]) and percent predicted FEV1 severity (<70%, ≥70% to ≤90% [inclusive], and >90%) to receive either 150-mg ivacaftor or ivacaftor-matching placebo q12h (in addition to their usual prescribed CF therapy).

Blinding (masking)

Ivacaftor-matched placebo was administered to subjects in the control group.

The subjects, all site personnel including the investigator, the study monitor, and the Vertex study team remained blinded to treatment assignments until database lock and study unblinding, with the exception of any site personnel for whom this information was important to ensure the safety of the subject and their fetus in case of pregnancy or in case of a life-threatening medical emergency; Vertex staff to satisfy SAE processing regulations; unblinded biostatisticians; IWRS vendor; a member of DMPK sample management, Vertex clinical supply chain; DMC; etc.

Sweat chloride laboratory personnel were unblinded to the sweat chloride results but remained blinded to treatment assignment.

A single member of Vertex DMPK Sample Management, independent from the study team, was unblinded for the purpose of assembling samples intended for bioanalysis.

Subjects and their parent/caregiver should not have been informed of their study-related spirometry results during the Treatment Period (through Week 24).

Statistical methods

The statistical analysis plan (SAP), Final Version 2.0, dated 15 November 2013 is for the Final Analysis of Study VX11-770-110 (Study 110) data and is based on the approved clinical study protocol (CSP), dated 11 June 2013, Version 4.0 and the approved electronic case report form (eCRF), dated 19 March 2013, Version 6.0.

Analysis sets

The following analysis sets were defined:

- Full Analysis Set (FAS): The FAS will include all randomized subjects who received at least 1 dose of study drug (i.e., ivacaftor or placebo). Subjects will be analysed according to the study drug to which they were assigned. All analyses of background data and efficacy data will be performed using the FAS.
- Complete Case Set (CCS): The CCS will include all FAS subjects who had the opportunity to complete the full 24-week treatment period. The CCS will only be performed for primary and key secondary endpoints to assess the impact of early termination of the study which resulted in a small number of subjects being unable to complete 24 weeks of assessment.
- Per Protocol Set (PPS): The PPS will include all FAS subjects without major protocol violations (i.e., subjects who have not been determined to have violated protocol requirements). Major protocol violations are defined as violations that may have a substantial impact on efficacy assessment. The criteria to be used for excluding subjects from the PPS will be determined before the database lock and will be documented. The PPS analyses will only be performed for the primary endpoint to provide supportive evidence for efficacy.
- Safety Set: The Safety Set will include all subjects who received at least 1 dose of study drug (i.e., ivacaftor or placebo). Subjects will be analysed according to the study drug they actually received. All summaries of safety will be based on the Safety Set.

Statistical analysis of the primary efficacy variable

The primary analysis for the primary efficacy variable was based on a mixed-effects model for repeated measures (MMRM). The model included absolute change from baseline in percent predicted FEV1 as the dependent variable, treatment (ivacaftor versus placebo), visit (Week 2, Week 4, Week 8, Week 16, and Week 24), and treatment by visit interaction as fixed effects, and subject as a random effect, with adjustment for the continuous baseline values of age and percent predicted FEV1. In the model, visit was treated as a class variable and a compound symmetry covariance matrix was assumed to model the within-subject variability. Denominator degrees of freedom for the F-test for fixed effects was estimated using the Kenward-Roger approximation. With a mixed-effects model as the primary analysis model based on maximum likelihood estimation and assuming that conditional on fixed and random effects, data were assumed missing at random and no imputation of missing data was done.

The main effect of treatment obtained from the model was interpreted as the average treatment effect (effect of ivacaftor) across all post-baseline visits. This was a weighted average of the treatment effect across all post-baseline visits under the no treatment by visit interaction model. The estimated mean treatment effect, a 95% confidence interval (CI), and a 2-sided P value was provided. The consistency of treatment effect over different visits was evaluated using the above model. If there was evidence of a qualitative treatment by visit interaction, a descriptive summary of the treatment difference for each visit was used to identify the nature of the interaction.

Sensitivity analyses of the primary variable

The following sensitivity analyses of the primary variable were performed to assess the robustness of the primary analysis:

- Nonparametric analysis: Stratified Wilcoxon rank-sum test (Van Elteren test) on the mean change from baseline in percent predicted FEV1, stratified by baseline values of age group (≥18 years of age, 12 to 17 years [inclusive], 6 to 11 years [inclusive]) and FEV1 severity (<70%, 70% to 90% [inclusive], >90% of the predicted value). If the number of subjects in a stratum was less than 5 subjects per treatment group, the stratum was collapsed with others to create meaningful

comparison categories. The mean change in percent predicted FEV1 was the mean change from baseline across all post-baseline visits for each subject.

With a mixed-effects model as the primary analysis model, no imputation of missing data was done. However, the following sensitivity analyses were conducted to assess the impact of missing efficacy evaluations on the treatment effect estimated through MMRM:

- Pattern mixture model (PMM): Assessment of the effect of missing patterns on treatment effect, and an overall treatment effect were obtained from the PMM, if there was more than 10% missing data in either treatment group.
- Dropout reason-based multiple imputation: For subjects who terminated from treatment prior to the end of the analysis period for any of the following reasons: adverse event, noncompliance with study procedures, death, physician decision, or required prohibited medication, missing measurements were imputed using a multiple imputation method. Complete data were analyzed using ANCOVA and MI ANALYZE; multiple-imputation was performed to remedy loss of variance information.

  The imputation distribution for the missing change in percent predicted FEV1 from baseline at Week 24 was a normal distribution.

  All randomized subjects were classified as Completer, Dropout Category 1, or Dropout Category 2, based on the following rules:

  - Completer: Subjects completed 24 weeks treatment duration
  - Dropout Category 1: Subjects discontinued treatment due to adverse events, noncompliance with study requirements, death, physician decision, or requires prohibited medication.
  - Dropout Category 2: Subjects discontinued treatment due to all other reasons, including study termination.

If any of the sensitivity analyses used to assess the impact of missing efficacy evaluations yielded a result that was inconsistent with the result of the primary analysis, the nature of the discrepancy was to be examined and discussed in the clinical study report.

Subgroup analyses of the primary variable

Due to small sample size, subgroup analyses were primarily descriptive in nature and consisted of summary statistics. These subgroup analyses were used to examine the consistency of treatment effect across subgroups. If an adequate sample size (i.e., ≥5 subjects in both treatment groups) was available in any of the subgroups described below, a model-based analysis similar to that described for the primary analysis was conducted within the subgroup. Minimally, summary statistics were provided by treatment group at each visit. The FAS was used for all subgroup summaries/analyses.

The following subgroups were used:

- Age Group at Baseline (≥18 years, 12 to 17 years [inclusive], and 6 to 11 years [inclusive])
- Percent Predicted FEV1 severity at Baseline (<70%, 70% to 90% [inclusive], and >90% of the predicted value)
- Geographic Region (North America and Europe)
- Sex (Female and Male)
- *Pseudomonas aeruginosa* (*P aeruginosa*) infection status at baseline (Yes and No)

- *R117H* poly-T variant (*5T, 7T, 9T*).

Ad hoc analyses

Following database lock, ad hoc analyses were carried out to gain a better understanding of the main study results. These analyses were primarily focused on understanding any potential differences in results due to subject age, baseline percent predicted FEV1, and *R117H* allele poly-T variant. Additional summary statistics were also carried out based on subject age, baseline percent predicted FEV1, and genotype characteristics.

Interim analysis

An interim analysis (IA) for safety and efficacy was carried out after 40 subjects had completed the Week 8 visit. In order to control the overall type I error rate, a Bonferroni-type adjustment was applied. This reflected an allocated significance of 0.0052 for the IA. The significance level for the final analysis (week 24) will be set at 0.0448 as enrolment was not stopped after the IA.

The IA was conducted by a CRO independent of the sponsor; the CRO communicated directly with the DMC, as described in DMC Charter. Following review of the IA data and after applying the pre-specified rules, the DMC recommended to Vertex Pharmaceuticals, Inc. to continue with enrolment.

Results

Participant flow

Table 4 Subject Disposition

Subject Disposition

Disposition Category	Placebo n (%)	Ivacaftor n (%)	Overall n (%)
All Screened Subjects	NA	NA	108
All Randomized Subjects	36	34	70
Safety Set	35	34	69
Full Analysis Set (FAS)	35	34	69
Complete Case Set (CCS)	31	30	61
Per Protocol Set (PPS)	33	30	63
Never Dosed[a]	NA	NA	39
Last Scheduled Visit Completed:			
Day 1	0	0	0
Week 2	1 (2.9)	2 (5.9)	3 (4.3)
Week 4	1 (2.9)	0	1 (1.4)
Week 8	1 (2.9)	2 (5.9)	3 (4.3)
Week 16	1 (2.9)	2 (5.9)	3 (4.3)
Week 24	31 (88.6)	28 (82.4)	59 (85.5)
Completed Full Assigned Duration of Dosing	35 (100)	32 (94.1)	67 (97.1)
Failed to Complete Full Assigned Duration of Dosing	0	2 (5.9)	2 (2.9)
Reason for Discontinuation			
Adverse Event	0	0	0
Refused Further Dosing (Not Due to AE)	0	0	0
Lost to Follow-up	0	0	0
Death	0	0	0
Did Not Meet Eligibility Criteria	0	0	0
Non-Compliance with Study Drug	0	0	0
Other Non-Compliance	0	1 (2.9)[b]	1 (1.4)
Physician Decision	0	0	0
Required Prohibited Medication	0	0	0
Pregnancy (Self or Partner)	0	1 (2.9)	1 (1.4)
Study Terminated by Sponsor	0	0	0
Other	0	0	0

NA: not applicable; AE: adverse event
Notes: Percentages are calculated relative to the number of subjects in the FAS. FAS is defined as all randomized subjects who received at least 1 dose of study drug. Safety Set is defined as all subjects who received at least 1 dose of study drug. CCS is defined as all FAS subjects who had the opportunity to complete the full 24 week treatment period. PPS is defined as all FAS subjects without major protocol violations that could affect efficacy data.

[a] The 39 subjects counted as "never dosed" were screen failures. In addition, 1 subject (Subject [redacted] was randomized to the placebo group but not dosed (reason: PI decision due to high percent predicted FEV_1 value [115.318%] on Day 1).

[b] Subject [redacted] was discontinued from the study due to non-compliance in completing the required ophthalmologic examination at Screening.

One hundred and eight patients were screened out of whom 70 patients were randomised to ivacaftor (n=34) or to placebo (n=36). Thirty-eight screened patients were not randomized and hence not dosed. One subject was randomized to placebo but was not dosed.

Four subjects in the ivacaftor group and 2 subjects in the placebo group were excluded from the PPS due to major protocol violations.

Four subjects in the ivacaftor group and 4 subjects in the placebo group were excluded from the CCS because they did not complete the full 24-week treatment period.

A total of 67 subjects (32 in the ivacaftor group and 35 in the placebo group) completed their full assigned duration of dosing. Two subjects in the ivacaftor group discontinued treatment prematurely: 1 because of noncompliance with the ophthalmologic examination and 1 because of pregnancy. Of the

67 subjects who completed the assigned duration of dosing, 59 subjects (28 in the ivacaftor group and 31 subjects in the placebo group) completed the full 24-week Treatment Period. The remaining 8 subjects did not complete 24 weeks of treatment because the study was terminated early by the sponsor. For these 8 subjects, the last Treatment Period study visit was: Week 2 for 2 subjects, Week 4 for 1 subject, Week 8 for 3 subjects, and Week 16 for 2 subjects. These subjects were considered to have completed their assigned treatment duration.

Recruitment

Study initiation was 03 July 2012 (date first eligible subject signed informed consent form) and study completion was 25 October 2013 (date last subject completed the last visit).

Subjects were randomized at 27 study sites in North America (25) and Europe (2 centres in the UK where 15 patients were randomised).

Conduct of the study

The clinical study protocol was amended 4 times, 1 of which was a country-specific amendment for the UK, by the time of the data cut for this clinical study report (CSR). The final protocol (Version 4.0) is dated 11 June 2013.

The main amendments were related to the clarification of the statistical analysis that was to be performed for the interim analysis and the control of the type I error. Also, amendments had to be implemented to deal with the analysis of patients who had not had their Week 24 Visit completed in the event of early study termination. These patients were to be considered to have completed their assigned treatment duration. In addition, clarifications were provided regarding concomitant medication, e.g. cycling antibiotic therapy. The exclusion of hypertonic saline use as part of the concomitant medication was removed.

Baseline data

All subjects in both treatment groups were white, and the majority of subjects in both treatment groups were of non-Hispanic or Latino ethnicity (placebo: 100%; ivacaftor: 97.1%). The mean age was 32.7 years (range: 6 to 68 years) for the placebo group and 29.2 years (range: 6 to 55 years) for the ivacaftor group. There were 19 subjects overall in the <18 years subgroup (2 of whom were 12 to 17 years of age) and 50 subjects overall in the ≥18 years subgroup.

Baseline percent predicted FEV1 and BMI were slightly higher in the ivacaftor group than in the placebo group, and baseline sweat chloride and *P aeruginosa* infection rate were slightly lower for the ivacaftor group than the placebo group. In data from subjects for whom the *R117H* allele poly-T variant was confirmed or derived, the *R117H-5T* variant was more prevalent in the placebo group (placebo: 27 of 34 subjects; ivacaftor: 21 of 33 subjects).

The mean sweat chloride value of about 70 mmol/L for the FAS is consistent with the residual function phenotype generally associated with the *R117H-CFTR* mutation.

Selected baseline data are shown in Table 5 by age group.

Table 5 Selected baseline demographic and disease characteristics, study 110 by age group (excluding adolescents, n=2), Full Analysis Set

	≥ 18 years		6-11 years	
Variable	Placebo (n=26)	Ivacaftor (n=24)	Placebo (n=8)	Ivacaftor (n=9)
Age (years) Mean (SD) [range]	 40.6 (12.56) [18-68]	 37.5 (12.06) [18-55]	 9.0 (1.60) [6-11]	 8.8 (1.92) [6-11]
Sex, n (%) Male Female	 10 (38.5) 16 (61.5)	 11 (45.8) 13 (54.2)	 5 (62.5) 3 (37.5)	 4 (44.4) 5 (55.6)
ppFEV1 (pp) Mean (SD) [range]	 62.21 (14.41) [37.39-85.84]	 67.03 (15.37) [32.54-92.62]	 93.98 (8.36) [79.96-102.85]	 97.49 (8.61) [84.08-105.50]
ppFEV1 Severity, n (%) <70% ≥70% to ≤90% >90%	 15 (57.7) 11 (42.3) –	 13 (54.2) 10 (41.7) 1 (4.2)	 – 2 (25.0) 6 (75.0)	 – 3 (33.3) 6 (66.7)
Sweat Chloride (mmol/l), Mean (SD) [range]	 73.01 (17.32) [35.50-102.25]	 69.34 (24.10) [23.25-120.00]	 74.66 (28.61) [22.50-108.75]	 64.16 (22.59) [33.00-100.50]
Body weight (kg) Mean (SD) [range]	 71.74 (22.52) [42.0, 148.3]	 77.90 (16.73) [56.0, 111.0]	 34.03 (9.10) [22.0, 51.0]	 32.86 (13.33) [19.0, 64.0]
Weight-for-age z-score[a] (points) Mean (SD) [range]	 –	 –	 0.31 (0.68) [-0.67, 1.46]	 -0.02 (0.96) [-1.24, 1.81]
BMI (kg/m2) Mean (SD) [range]	 24.95 (5.71) [17.04-37.83]	 26.89 (5.23) [21.50-42.87]	 17.10 (2.48) [13.64-21.50]	 17.65 (3.30) [14.37-24.69]
BMI-for-age z-score[a] (points) Mean (SD) [range]	 –	 –	 0.01 (0.95) [-1.74, 1.31]	 0.19 (0.89) [-0.78, 1,58]
Faecal Elastase-1, n (%) <200 µg/g ≥200 µg/g Missing	 5 (19.2) 20 (76.9) 1 (3.8)	 2 (8.3) 22 (91.7) –	 – 7 (87.5) 1 (12.5)	 – 9 (100.0) –
CFTR Genotype, n (%)				
R117H/F508del	19 (73.1)	19 (79.2)	6 (75.0)	8 (88.9)
R117H/3659DELC	1 (3.8)	--		
R117H/621+1G>T	--	1 (4.2)		
R117H/DELTA I507	--	1 (4.2)		
R117H/E60X	1 (3.8)	--		
R117H/G103X	1 (3.8)	--		
R117H/G542X	--	1 (4.2)		
R117H/R117H	--	1 (4.2)	1 (12.5)	--
R117H/R553X	1 (3.8)	--		
R117H/R560T	--	1 (4.2)		
R117H/S341P	1 (3.8)	--		
R117H/UNKNOWN	1 (3.8)	--		
R117H/W1282X	1 (3.8)	--		
R117H/2184INSA			1 (12.5)	--
R117H/S489X			--	1 (11.1)
CFTR Poly-T Variant[b], n				

5T on *R117H* allele				
5T/5T	--	--	--	--
5T/7T	4	1	1	--
5T/9T	17	16	4	4
7T on *R117H* allele				
7T/5T	1	--	--	--
7T/7T	1	1	1	1
7T/9T	2	5	2	4
P aeruginosa Infection Status, n (%) Yes No	 18 (69.2) 8 (30.8)	 14 (58.3) 10 (41.7)	 1 (12.5) 7 (87.5)	 1 (11.1) 8 (88.9)

[a] Weight-for-age z-score and BMI-for-age z-score are calculated by using National Center for Health Statistics (NCHS) growth charts. Z-scores are defined as missing if the subject is over 240 months old at the time of assessment.
[b] The poly-T variant for the R117H allele was derived for subjects where this information was missing and the subject had either R117H/F508DEL or R117H/R117H

Only 2 subjects 12 to 17 years of age enrolled in the study; 1 subject randomized to ivacaftor and 1 subject randomized to placebo.

Subject 10-033-02 was a 13-year-old female with CFTR genotype *R117H-7T/F508DEL-9T*. At baseline, the subject had a percent predicted FEV1 of 87.6%, a sweat chloride value of 44.3 mmol/L, a BMI of 28.04 kg/m^2, and a CFQ-R respiratory domain score of 100.0 points. The subject was discontinued from the study 16 days after the first dose of ivacaftor due to non-compliance in completing the required ophthalmologic examination at Screening.

Subject 10-014-02 was a 17-year-old female with CFTR genotype *R117H-5T/W1282X-7T*, who completed the full 24 weeks of treatment (randomized to placebo). At baseline, the subject had a percent predicted FEV1 of 88.7%, a sweat chloride value of 74.8 mmol/L, a BMI of 21.86 kg/m2, and a CFQ-R respiratory domain score of 77.8 points.

Medical history

Table 6 summarizes medical history consistent with a diagnosis of CF with an incidence of at least 15% in any treatment group.

Table 6 Medical history consistent with a diagnosis of CF with an incidence of at least 15% of subjects in any treatment group, Full Analysis Set

Condition	Placebo N = 35 n (%)	Ivacaftor N = 34 n (%)	Overall N = 69 n (%)
Cystic fibrosis lung disease	35 (100.0)	34 (100.0)	69 (100.0)
Gastroesophageal reflux disease	16 (45.7)	11 (32.4)	27 (39.1)
Chronic sinusitis	11 (31.4)	14 (41.2)	25 (36.2)
Drug hypersensitivity	12 (34.3)	6 (17.6)	18 (26.1)
Asthma	5 (14.3)	12 (35.3)	17 (24.6)
Constipation	9 (25.7)	7 (20.6)	16 (23.2)
Pancreatic insufficiency	10 (28.6)	3 (8.8)	13 (18.8)
Nasal polyps	7 (20.0)	5 (14.7)	12 (17.4)
Osteopenia	7 (20.0)	4 (11.8)	11 (15.9)
Sinusitis	6 (17.1)	3 (8.8)	9 (13.0)
Seasonal allergy	7 (20.0)	2 (5.9)	9 (13.0)
Anxiety	6 (17.1)	2 (5.9)	8 (11.6)

Source: Table 14.1.4.1.
Notes: Percentages were calculated relative to the number of subjects in the FAS. Medical history events were coded from MedDRA, Version 15.1.

Concomitant medication

Table 7 summarizes concomitant medications received by at least 15% of subjects while receiving placebo or ivacaftor. The most commonly reported concomitant medications were indicated for management of CF complications. The use of concomitant medications received by at least 15% of subjects while receiving placebo or ivacaftor was similar with the exceptions of paracetamol (placebo: 37.1%; ivacaftor: 11.8%) and pancreatin (placebo: 20.0%; ivacaftor: 2.9%).

Table 7 Concomitant medications received by at least 15% of subjects in any treatment group; Full Analysis Set

WHO Drug Dictionary Classification	Placebo N = 35 n (%)	Ivacaftor N = 34 n (%)	Overall N = 69 n (%)
Subjects with Any Concomitant Medication	**35 (100.0)**	**34 (100.0)**	**69 (100.0)**
Salbutamol	28 (80.0)	22 (64.7)	50 (72.5)
Dornase Alfa	23 (65.7)	21 (61.8)	44 (63.8)
Azithromycin	18 (51.4)	14 (41.2)	32 (46.4)
Multivitamins, Combinations	10 (28.6)	13 (38.2)	23 (33.3)
Fluticasone Propionate	10 (28.6)	9 (26.5)	19 (27.5)
Paracetamol	13 (37.1)	4 (11.8)	17 (24.6)
Tobramycin	9 (25.7)	7 (20.6)	16 (23.2)
Colecalciferol	7 (20.0)	7 (20.6)	14 (20.3)
Ibuprofen	5 (14.3)	9 (26.5)	14 (20.3)
Seretide	7 (20.0)	7 (20.6)	14 (20.3)
Omeprazole	9 (25.7)	4 (11.8)	13 (18.8)
Cetirizine Hydrochloride	9 (25.7)	3 (8.8)	12 (17.4)
Ciprofloxacin	5 (14.3)	7 (20.6)	12 (17.4)
Aztreonam Lysine	6 (17.1)	4 (11.8)	10 (14.5)
Budesonide w/Formoterol Fumarate	6 (17.1)	4 (11.8)	10 (14.5)
Colistin	6 (17.1)	1 (2.9)	7 (10.1)

Doxycycline	6 (17.1)	2 (5.9)	8 (11.6)
Levofloxacin	6 (17.1)	2 (5.9)	8 (11.6)
Pancreatin	7 (20.0)	1 (2.9)	8 (11.6)

Source: Table 14.1.5.2.
Notes: Preferred Terms (PT) are sorted in descending order of frequency in the Overall column. A subject with multiple concomitant medications within Anatomical Therapeutic Chemical (ATC) level or PT is counted only once within the ATC level or PT. Concomitant medications were coded from the WHO Drug Dictionary Enhanced, March 2012.

Numbers analysed

All efficacy and exploratory analyses were conducted using the FAS, which included 69 subjects who were randomized and received at least 1 dose of study drug (35 on placebo and 34 on ivacaftor).

Sixty-seven (35 in the placebo group and 32 in the ivacaftor group) completed their full assigned duration of dosing. Two subjects in the ivacaftor group discontinued treatment prematurely: 1 because of noncompliance with the ophthalmologic examination and 1 because of pregnancy. Of the 67 subjects who completed the assigned duration of dosing, 59 subjects (28 in the ivacaftor group and 31 subjects in the placebo group) completed the full 24-week Treatment Period. The remaining 8 subjects did not complete 24 weeks of treatment because the study was terminated early by the sponsor. For these 8 subjects, the last Treatment Period study visit was: Week 2 for 2 subjects, Week 4 for 1 subject, Week 8 for 3 subjects, and Week 16 for 2 subjects. Out of the 8 patients who did not complete 24 weeks of treatment 3 were children and 5 adult patients. Their genotype was *R117H/F508del* (n=7) and *R117H/R117H* (n=1). Their poly-T status was 5T/9T (n=6), 7T/7T (n=1) and 7T/9T.

The CCS comprises 61 patients (31 on placebo and 30 on ivacaftor) and the PPS includes 63 (33 subjects in the placebo group and 30 subjects in the ivacaftor group). Six patients were excluded from the PPS for major protocol violations.

Limited analyses of efficacy were conducted using the PPS and CCS. Both pre-planned and ad hoc FAS subgroup analyses were performed for primary and secondary endpoints. Tables and figures generated as a result of ad hoc analyses are indicated by an "ad" at the end of the table number.

Outcomes and estimation

Absolute change from baseline in percent predicted FEV1 through Week 24 (primary efficacy variable)

Table 8 shows the results of the absolute change from baseline in percent predicted FEV1 (ppFEV1).

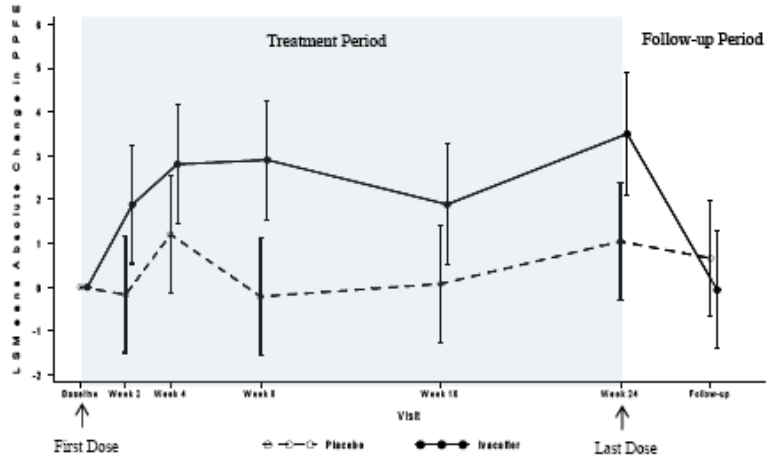
Table 8 Absolute change from baseline in percent predicted FEV1 by MMRM, Full Analysis Set

Visit or Time Period	Treatment Group	Sample Statistics		Absolute Change From Baseline[a]		Treatment Effect (Ivacaftor vs Placebo)	
		n	Mean	N	LS Mean	Difference (95% CI)	*P* value
Baseline	Placebo	35	70.2315	--	--	--	--
	Ivacaftor	34	75.6968	--	--		
Overall Post-baseline	Placebo	35	71.1264	35	0.4611	2.1114 (-1.1305, 5.3532)	0.1979
	Ivacaftor	34	78.0432	34	2.5724		

Source: Table 14.2.1.2.1.
Note: Sample statistics are unadjusted results. Difference is ivacaftor – placebo. A positive difference favors ivacaftor.
[a] Estimates were obtained from MMRM with absolute change from baseline as the dependent variable; with treatment group, categorical visit (Weeks 2, 4, 8, 16, and 24) and treatment by visit interaction as fixed effects; with subject as a random effect; and with adjustment for the continuous baseline value of age and percent predicted FEV_1 using compound symmetry covariance matrix.

The mean absolute change from baseline in ppFEV1 through Week 24 by MMRM for the FAS was greater for the ivacaftor group (2.57 percentage points) than the placebo group (0.46 percentage points). The estimated treatment difference for ivacaftor versus placebo was 2.11 percentage points (95% CI: -1.13, 5.35, P=0.1979). The absolute change from baseline in ppFEV1 including the Follow-up Visit is provided in Figure 4 which shows that the change seen in ppFEV1 for the ivacaftor group during the treatment period reversed in the Follow-up Period when the subjects were no longer receiving ivacaftor.

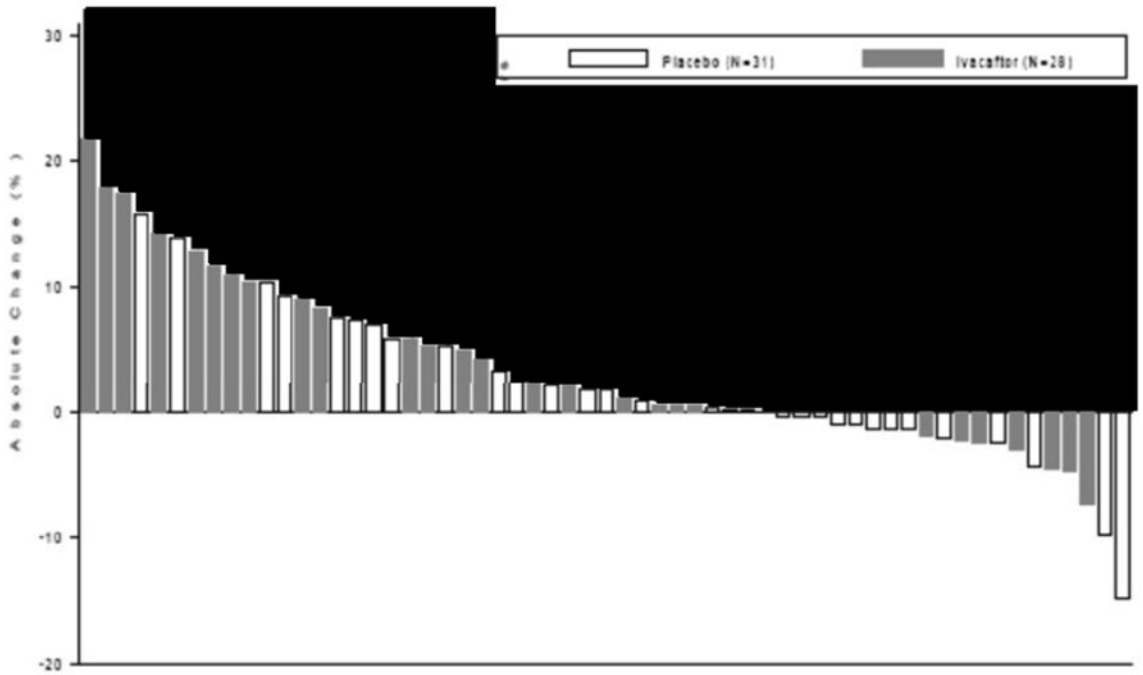
Figure 4 Modelled absolute change from baseline in percent predicted FEV1 by treatment up to Follow-up Visit, Full Analysis Set



Source: Figure 14.2.1.3.

The absolute change from baseline in ppFEV1 at Week 24 for individual subjects is presented Figure 5.

Figure 5 Waterfall plot of absolute change from baseline in percent predicted FEV1 by treatment, Full Analysis Set



Source: Figure 14.2.1.4.1.
Note: Subjects who did not reach the Week 24 Visit are not included in this figure.

Out of the 28 subjects in the ivacaftor group who completed 24 weeks of treatment, 20 had an improvement in ppFEV1 after 24 weeks of treatment, 1 had no change, and 7 had a decline in ppFEV1. Six of the 7 subjects in the ivacaftor group who had a decline in ppFEV1 were children 6 to 11 years old.

A responder analysis was conducted by categorizing the absolute change from baseline in ppFEV1 through Week 24 as ≥3.5% or <3.5%, ≥5% or <5%, ≥7.5% or <7.5%, ≥10% or <10%. Results are presented in Table 9 and show that the number of responders favours ivacaftor at all thresholds, with approximately twice as many responders in the ivacaftor group as the placebo group.

Table 9 Responder analysis of absolute change through week 24 in percent predicted FEV1, Full Analysis Set

Category	Placebo N = 35 n (%)	Ivacaftor N = 34 n (%)	*P* value
≥3.5%	8 (22.9)	13 (38.2)	0.1975
<3.5%	27 (77.1)	21 (61.8)	
≥5%	7 (20.0)	13 (38.2)	0.1165
<5%	28 (80.0)	21 (61.8)	
≥7.5%	4 (11.4)	8 (23.5)	0.2182
<7.5%	31 (88.6)	26 (76.5)	
≥10%	2 (5.7)	5 (14.7)	0.2595
<10%	33 (94.3)	29 (85.3)	

Sources: Table 14.2.1.1.7 and Table 14.2.1.1.7.1ad through Table 14.2.1.1.7.4ad.
Note: Absolute change through Week 24 is the average change from baseline over 24 weeks for percent predicted FEV_1.

Absolute change from baseline in sweat chloride through Week 24 (secondary efficacy variable)

The mean absolute change from baseline in sweat chloride through Week 24 by MMRM for the FAS is presented in Table 10.

Table 10 Absolute change from baseline in Sweat Chloride (mmol/L) by MMRM, Full Analysis Set

Visit or Time Period	Treatment Group	Sample Statistics		Absolute Change From Baseline[a]		Treatment Effect (Ivacaftor vs Placebo)	
		N	Mean	N	LS Mean	Difference (95% CI)	*P* value
Baseline	Placebo	35	73.4357	--	--	--	--
	Ivacaftor	32	67.2578	--	--		
Overall Post-baseline	Placebo	35	71.2500	35	-2.3078	-23.9693 (-28.0094, -19.9293)	<0.0001
	Ivacaftor	32	42.5620	32	-26.2771		

Source: Table 14.2.2.2.1.

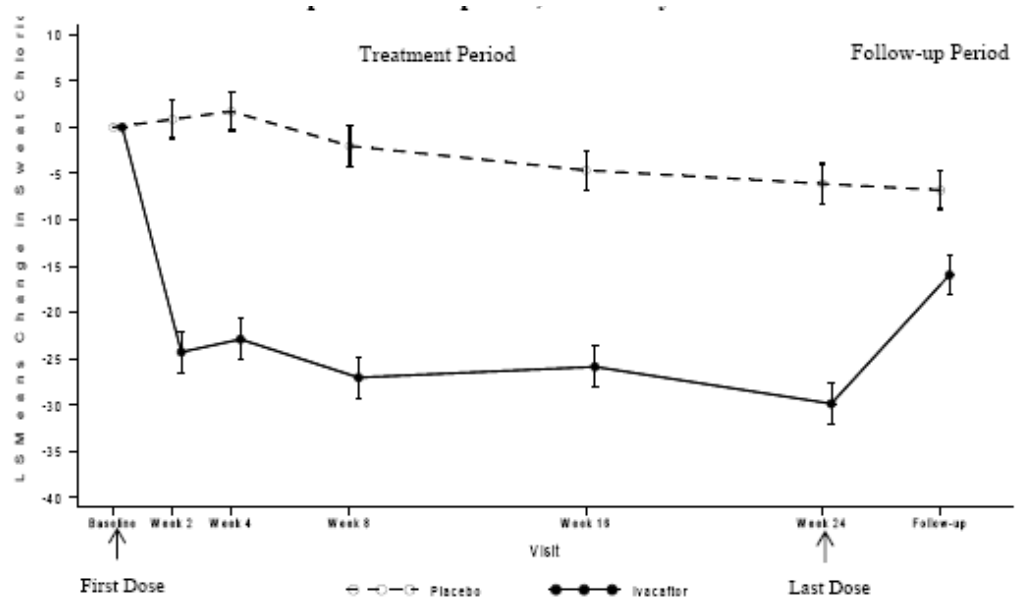
Note: Sample statistics are unadjusted results. Difference is Ivacaftor – Placebo. A negative difference favors Ivacaftor.

[a] Estimates were obtained from MMRM with absolute change from baseline as the dependent variable; with treatment group, categorical visit (Weeks 2, 4, 8, 16, and 24), and treatment by visit interaction as fixed effects; with subject as a random effect; and with adjustment for the continuous baseline value of age, percent predicted FEV_1, and sweat chloride, using a compound symmetry covariance matrix.

The mean absolute change from baseline was -26.28 mmol/L for the ivacaftor group and -2.31 mmol/L for the placebo group. The treatment difference for ivacaftor versus placebo was -23.97 mmol/L (95% CI: -28.01, -19.93, p<0.0001), which favoured ivacaftor.

The absolute change from baseline in sweat chloride including the Follow-up Visit is provided in Figure 6.

Figure 6 Mean absolute change from baseline in Sweat Chloride (mmol/L) by treatment up to Follow-up Visit, Full Analysis Set



Source: Figure 14.2.2.2.

A responder analysis was conducted by categorizing absolute change from baseline in sweat chloride through Week 24 as ≥5 or <5 mmol/L decrease, ≥10 or <10 mmol/L decrease, ≥15 or <15 mmol/L decrease, and ≥20 or <20 mmol/L decrease (see Table 11).

Table 11 Responder analysis of absolute change through week 24 of Sweat Chloride (mmol/L), full Analysis Set

Category	Placebo (N = 35) n (%)	Ivacaftor (N = 34) n (%)
≥5 mmol/L decrease	13 (37.1)	31 (91.2)
<5 mmol/L decrease	22 (62.9)	1 (2.9)
≥10 mmol/L decrease	9 (25.7)	29 (85.3)
<10 mmol/L decrease	26 (74.3)	3 (8.8)
≥15 mmol/L decrease	1 (2.9)	21 (61.8)
<15 mmol/L decrease	34 (97.1)	11 (32.4)
≥20 mmol/L decrease	---	9 (26.5)
<20 mmol/L decrease	35 (100.0)	23 (67.6)

Source: VX11-770-110 CSR/ Table 14.2.2.1.8
Note: Absolute change through Week 24 is the average change from baseline over 24 weeks for sweat chloride.

The majority of subjects in the ivacaftor group who had ≥5 mmol/L decrease in sweat chloride at Week 24 also had ≥15 mmol/L decrease at Week 24. Only 1 subject (2.9%) in the placebo group achieved a ≥15 mmol/L decrease in sweat chloride compared to 21 subjects (61.8%) in the ivacaftor group.

Absolute change from baseline in BMI (secondary efficacy variable)

The absolute of change from baseline in BMI at Week 24 by LMM is shown in Table 12.

Table 12 Rate of change from baseline in BMI (kg/m2) by LMM, Full Analysis Set

Visit or Time Period	Treatment Group	Sample Statistics		Rate of Change in Treatment Period[a]		Treatment Effect (Ivacaftor vs Placebo)	
		n	Mean	n	LS Mean	Difference (95% CI)	*P* value[b]
Baseline	Placebo	35	23.066	--	--	--	--
	Ivacaftor	34	24.480	--	--		
Week 24	Placebo	31	23.735	35	0.2284	0.2626 (-1.5698, 2.0950)	0.7780
	Ivacaftor	28	24.542	34	0.4910		

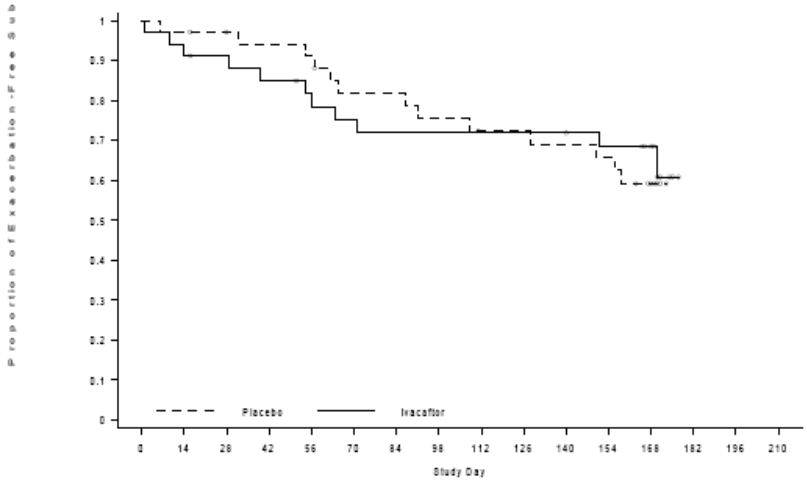
Source: Table 14.2.4.2.5.
Note: Sample statistics are unadjusted results.
[a] Estimated change from baseline per 168 days was obtained from a linear mixed model, with BMI as the dependent variable; with treatment as a fixed effect; with intercept and visit (days on study, including all visits through Week 24) as random effects; and with adjustment for baseline percent predicted FEV_1, age, and visit by treatment interaction included as covariates in the model.
[b] *P* value for the treatment effect is from the slope of BMI (kg/m^2) versus time (days).

BMI-for-age z-scores were calculated using the CDC growth chart for the 22 subjects who were 20 years of age or younger. The rate of change from baseline in BMI-for-age z-score at Week 24 by LMM was greater for the ivacaftor group (0.13 points) than the placebo group (0.03 points). However, the treatment difference of 0.10 points (95% CI: -0.57, 0.77) was not statistically significant (*P* = 0.7692).

Time-to-First Pulmonary Exacerbation (secondary efficacy variable)

Figure 7 presents the survival curves by treatment group for time-to-first pulmonary exacerbation. The calculated hazard ratio of 0.928 favoured ivacaftor but was not statistically significant (P = 0.8556).

Figure 7 Time-to-First pulmonary exacerbation, Full Analysis Set



Source: Figure 14.2.5.1.1.
Note: The open circles on the plot denote censored subjects.

The number of events and model-based estimates of event rates of pulmonary exacerbations through Week 24 (tertiary efficacy variables) are summarized in Table 13. The event rate of pulmonary exacerbations was similar, but numerically favoured ivacaftor (ivacaftor: 0.249; placebo: 0.295); the rate ratio was 0.843 (95% CI: 0.409, 1.737, p value = 0.6432). Rates for subcategories of pulmonary exacerbations (i.e., requiring hospitalization and requiring IV antibiotics) were not calculated due to low event incidence, however, the number of events requiring hospitalization or IV antibiotics was notably lower for the ivacaftor group.

Table 13 Number of pulmonary exacerbations, Full Analysis Set

Event Type	Statistics	Placebo N = 35	Ivacaftor N = 34	Rate Ratio (95% CI)	*P* value[a]
	Total Number of Days on Study	5485	5182	--	--
All Pulmonary Exacerbations[b]	Number of Subjects with Events	13	11	--	--
	Number of Events (Event Rate)	17 (0.295)	13 (0.249)	0.843 (0.409, 1.737)	0.6432
Requiring Hospitalization	Number of Subjects with Events	6	2	--	--
	Number of Events	7	2	--	0.2595
Requiring IV antibiotic therapy	Number of Subjects with Events	6	2	--	--
	Number of Events	8	2	--	0.2595

Source: Table 14.2.5.1.
Notes: Estimates were obtained from negative binomial regression with the number of events as the dependent variable, treatment as a fixed effects, and adjustment for baseline percent predicted FEV_1 and age, with log (time on study) as an offset. Negative binomial regression was conducted only when the number of subjects with events in each treatment group was ≥5 and the models converged.

[a] When estimates are presented, *P* values are from the treatment effect in negative binomial regression; otherwise, *P* values are from Fisher's Exact test.

[b] Pulmonary exacerbation includes events that met the protocol definition of pulmonary exacerbations (i.e., treatment with new or changed antibiotic therapy for ≥4 sinopulmonary signs/symptoms).

Change from Baseline in CFQ-R Respiratory Domain Score (secondary efficacy variable)

Four versions of the questionnaire were used: 3 in which the subject was interviewed or information was self-reported (Children Ages 6 to 11 Years, Children Ages 12 to 13 Years, and Adolescents and Adults) and 1 in which the subject's parent or caregiver was the respondent (Parent/Caregiver). Pooled questionnaire analyses were defined as all questionnaire versions except for the Parent/Caregiver version.

The mean absolute change from baseline in the pooled CFQ-R respiratory domain score through Week 24 by MMRM is presented in Table 14.

Table 14 Absolute change from baseline in pooled CFQ-R respiratory domain score by MMRM, Full Analysis Set

Visit or Time Period	Treatment Group	Sample Statistics[a]		Absolute Change From Baseline		Treatment Effect (Ivacaftor vs Placebo)	
		n	Mean	n	LS Mean	Difference (95% CI)	*P* value
Baseline	Placebo	34	66.4216	--	--	--	--
	Ivacaftor	33	75.2693	--	--		
Overall Post-baseline	Placebo	34	67.5347	34	-0.8289	8.3874 (2.1658,14.6090)	0.0091
	Ivacaftor	33	80.7946	33	7.5585		

Source: Table 14.2.3.2.1.

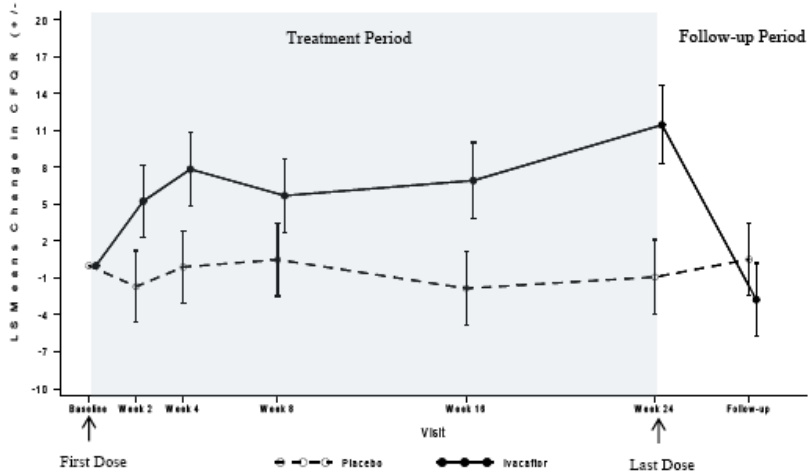
Notes: Pooled is defined as all questionnaire versions except for the parent/caregiver version. The Children Ages 6 to 11 Years (interviewer format) CFQ-R instrument response option cards may not have been used. Difference is ivacaftor – placebo. A positive difference favors ivacaftor.

[a] Estimates were obtained from MMRM with absolute change from baseline as the dependent variable; with treatment group, categorical visit (Weeks 2, 4, 8, 16, and 24), and treatment by visit interaction as fixed effects; with subject as a random effect; and with adjustment for the continuous baseline value of age, percent predicted FEV_1, and CFQ-R respiratory domain score, using compound symmetry covariance matrix.

The mean absolute change from baseline in the pooled CFQ-R respiratory domain score was greater for the ivacaftor group (7.56 points) than the placebo group (-0.83 points). The treatment difference for ivacaftor versus placebo was 8.39 points (95% CI: 2.17, 14.61; p value = 0.0091), which is approximately double the defined minimal clinically important difference (MCID) of 4 points.

As shown in Figure 8, the change seen in the CFQ-R respiratory domain score for the ivacaftor group during the Treatment Period reversed in the Follow-up Period when subjects were no longer on ivacaftor.

Figure 8 Mean absolute change from baseline in pooled CFQ-R respiratory domain score by Treatment Follow-up Visit, Full Analysis Set



Source: Figure 14.2.3.2.

The PPS and CCS analyses were performed for the primary and secondary endpoints to provide supportive evidence for efficacy through Week 24. The results of the CCS analyses are presented in Table 15 and were consistent with the results of the FAS analysis in that no statistically significant differences were seen between treatment groups regarding the absolute change from baseline in ppFEV1.

Table 15 Efficacy Results: Complete Case Set

Visit or Time Period	Placebo n	Placebo LS Mean	Ivacaftor n	Ivacaftor LS Mean	Difference vs Placebo (95% CI)	*P* value
Absolute Change From Baseline in Percent Predicted FEV_1 by MMRM (Primary Endpoint)[a,b]						
Overall Post-baseline	31	1.0760	30	3.7594	2.6834 (-0.4069, 5.7736)	0.0875
Rate of Change From Baseline in BMI (kg/m^2) by LMM[b,c,d]						
Overall Post-baseline	31	0.2314	30	0.3966	0.1652 (-1.7346, 2.0650)	0.8641
Absolute Change From Baseline in Sweat Chloride (mmol/L) by MMRM[a,e]						
Overall Post-baseline	31	-2.4413	28	-27.0264	-24.5851 (-28.8717, -20.2985)	<0.0001
Absolute Change From Baseline in Pooled CFQ-R Respiratory Domain Score by MMRM[a,b,f]						
Overall Post-baseline	30	-1.6064	29	9.1124	10.7188 (4.3599, 17.0777)	0.0014
Relative Change From Baseline in in Percent Predicted FEV_1 by MMRM[a,b]						
Overall Post-baseline	31	0.7355	30	6.6634	5.9279 (0.8396, 11.0162)	0.0232

Sources: Table 14.2.1.2.5, Table 14.2.4.2.9, Table 14.2.2.2.4, Table 14.2.3.2.4, and Table 14.2.1.3.2.3ad.
Notes: CCS is defined as all FAS subjects who had the opportunity to complete the full 24-week Treatment Period. Sample statistics are unadjusted results.

[a] Estimates were obtained from MMRM with absolute or relative change from baseline as the dependent variable; with treatment group, categorical visit (Weeks 2, 4, 8, 16, and 24), and treatment by visit interaction as fixed effects; with subject as a random effect; and with adjustment for the continuous baseline value of age, percent predicted FEV_1, and the corresponding baseline value of the analyzed variable, using a compound symmetry covariance matrix.

[b] Difference is ivacaftor - placebo. A positive difference favors ivacaftor.

[c] Estimated change from baseline per 168 days was obtained from a linear mixed model with dependent variable weight and treatment as a fixed effect. Adjustment for baseline percent predicted FEV_1, age and visit by treatment interaction were included as covariates in the model. Intercept, visit (days on study, including all visits through Week 24) were included as random effects.

[d] *P* value for the treatment effect is from the slope of BMI (kg/m^2) versus time (days).

[e] Difference is ivacaftor - placebo. A negative difference favors ivacaftor.

[f] Pooled was defined as all questionnaire versions except for the Parent/Caregiver version. The Children Ages 6 to 11 (interviewer format) CFQ-R instrument response option cards may not have been used.

Tertiary endpoints

Change from baseline in non-respiratory domains of the CFQ-R

The treatment differences favoured ivacaftor in the pooled analysis for the CFQ-R non-respiratory domains (treatment difference [95% CI]): physical (6.7224 [-1.0433, 14.4881]), emotion (5.4440 [1.7232, 9.1649]), social (7.1716 [2.1042, 12.2390]), eating (4.6528 [0.1939, 9.1117]), and digestion (2.5616 [-1.7858, 6.9089]).

Change from baseline in Weight

Rate of change from baseline in weight through Week 24 was slightly greater for the ivacaftor group (1.8490 kg) than the placebo group (0.9214 kg). The mean treatment difference was 0.9275 kg (95% CI: -5.9659, 7.8210).

For subjects 20 years of age or younger, weight-for-age z-scores were calculated using the CDC growth chart. The mean rate of change from baseline for weight-for-age z-score through Week 24 was slightly greater for the ivacaftor group (0.1829 points) than the placebo group (-0.0256 points). The mean treatment difference was 0.2085 points (95% CI: -0.4505, 0.8675).

Change from baseline in Height

The mean absolute change from baseline in height through Week 24 was slightly lower for the ivacaftor group (0.3699 cm) than the placebo group (1.7551 cm). The treatment difference was -1.3851 cm (95% CI: -10.8213, 8.0510).

For subjects 20 years of age or younger, height-for-age z-scores were calculated using the CDC growth chart. The treatment difference between groups was 0.0794 cm (95% CI: -0.4803, 0.6391).

CF-Related Complications

No analysis of CF-related complications was performed because no episodes of pancreatitis or DIOS occurred during the study.

Ancillary analyses

The following pre-planned subgroups analyses were included in the SAP for the primary and secondary efficacy variables:

- Age Group at Baseline (6 to 11years [inclusive], 12 to 17 years [inclusive], and ≥ 18 years);
- Percent Predicted FEV1 Severity at Baseline (<70%, 70% to 90% [inclusive], and >90% of the predicted value);
- Geographic Region (US and EU);
- Sex (Female and Male);
- *Pseudomonas infection* status at baseline (yes or no);
- Poly T status (5T, 7T, 9T). This subgroup analysis was only to take place if Poly T status relating to *R117H* allele can be obtained.

In Study 110, following database lock, ad hoc analyses (e.g., by poly-T variant within each age category) were also carried out in the age subgroups ≥18 years old and 6 to 11 years old. These analyses were primarily focused on understanding any potential differences in results due to subject age, baseline percent predicted FEV1, and *R117H* allele poly-T variant.

In this report only treatment differences for ivacaftor versus placebo by age group for the primary and secondary endpoints as well as by poly-T variant are shown. Other subgroup analyses have been addressed in EMEA/H/C/2494/II/027.

Subjects ≥ 18 years old (26 on placebo; 24 on ivacaftor)

Results of subgroup analyses limited to subjects aged ≥ 18 years are presented in Table 16.

Table 16 Efficacy endpoint results, Full Analysis Set, Subjects ≥18 years of age

Analysis	Treatment Group	N	LS Mean	Treatment Difference (Ivacaftor vs Placebo)	*P* value
Primary Endpoint					
Percent Predicted FEV_1 (percentage points): Absolute Change from Baseline	Placebo	26	-0.4567	4.9647 (1.1497,8.7796)	0.0119
	Ivacaftor	24	4.5080		
Additional FEV_1 Endpoint					
Percent Predicted FEV_1 (percentage points): Relative Change from Baseline	Placebo	26	-1.4581	9.1339 (2.4649, 15.8029)	0.0083
	Ivacaftor	24	7.6758		
Secondary Endpoints					
Sweat Chloride (mmol/L): Absolute Change from Baseline	Placebo	26	-4.0263	-21.8685 (-26.4556, -17.2814)	<0.0001
	Ivacaftor	23	-25.8948		
BMI (kg/m^2): Rate of Change from Baseline	Placebo	26	0.2186	0.3064 (-1.9009, 2.5136)	0.7845
	Ivacaftor	24	0.5250		
Pooled CFQ R Respiratory Domain Score (points)[a]: Absolute Change from Baseline	Placebo	26	-0.4596	12.6369 (5.0208, 20.2530)	0.0017
	Ivacaftor	24	12.1773		

Sources: Tables 14.2.1.2.4, Table 14.2.1.3.2.4ad, Table 14.2.2.2.3, Table 14.2.4.2.7, and Table 14.2.3.2.3.
NA: not applicable.
[a] Pooled is defined as all questionnaire versions except for the Parent/Caregiver version.

The mean absolute change from baseline in ppFEV1 through Week 24 by MMRM for subjects ≥18 years of age was greater for the ivacaftor group (4.51 percentage points) than the placebo group (-0.46 percentage points). The treatment difference for ivacaftor versus placebo was 4.96 percentage points (95% CI: 1.15, 8.78; p value = 0.0119).

In a responder analysis (see Table 17) of the mean absolute change from baseline in ppFEV1 through Week 24, a higher number of patients in the ivacaftor group (n=24) than in the placebo group (n=26) experienced a change in ppFEV1 ≥3.5% (54.2% vs. 19.2%), ≥5% (54.2% vs. 15.4%), and ≥7.5% (33.3% vs. 3.8%).

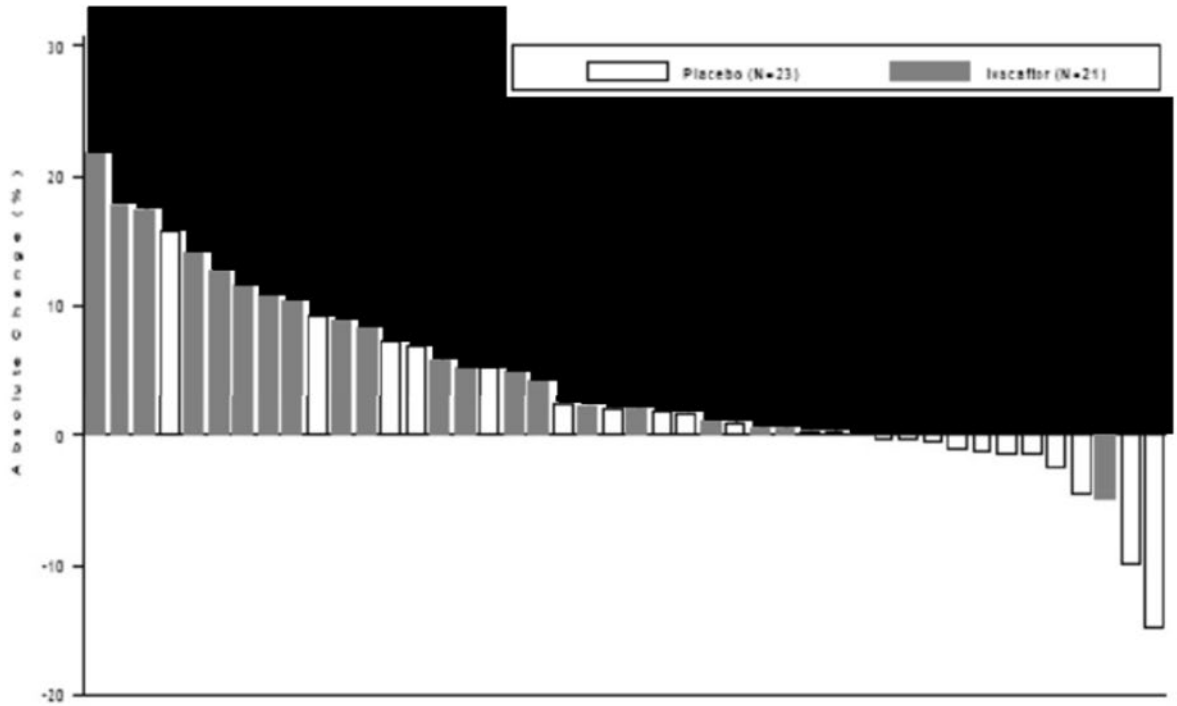
Table 17 Responder analysis of absolute change through week 24 in percent predicted FEV1; Full Analysis Set, Subjects ≥ 18 years of age

Category	Placebo N = 26 n (%)	Ivacaftor N = 24 n (%)	*P* value
≥3.5%	5 (19.2)	13 (54.2)	0.0176
<3.5%	21 (80.8)	11 (45.8)	
≥5%	4 (15.4)	13 (54.2)	0.0066
<5%	22 (84.6)	11 (45.8)	
≥7.5%	1 (3.8)	8 (33.3)	0.0094
<7.5%	25 (96.2)	16 (66.7)	
≥10%	1 (3.8)	5 (20.8)	0.0925
<10%	25 (96.2)	19 (79.2)	

Sources: Table 14.2.1.1.7.1ad through Table 14.2.1.1.7.4ad.
Notes: Absolute change through Week 24 is the average change from baseline over 24 weeks for percent predicted FEV_1. *P* value is from Fishers Exact Test.

Individual subject responses for the absolute change from baseline in percent predicted FEV1 at Week 24 for subjects ≥18 years of age who completed 24 weeks of treatment are shown in a waterfall plot (see Figure 9).

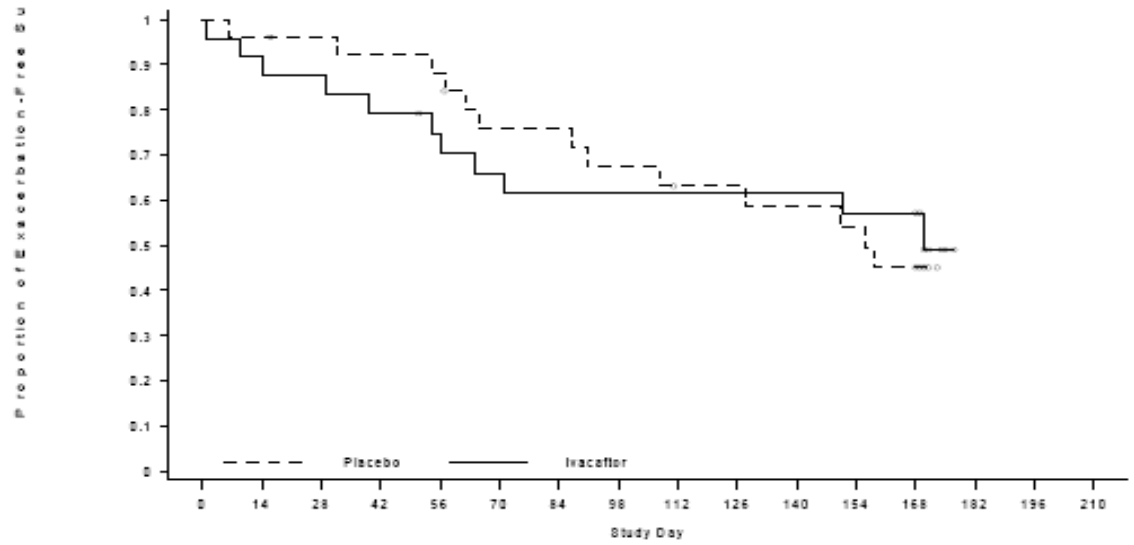
Figure 9 Waterfall plot of absolute change from baseline at week 24 in percent predicted FEV1 by treatment; Full Analysis Set, Subjects ≥ 18 years of age



Source: Figure 14.2.1.4.2ad.
Note: Subjects who did not reach the Week 24 Visit are not included in this figure.

Figure 10 presents the survival curves by treatment group for time-to-first pulmonary exacerbation for subjects ≥18 years of age. The pattern of the survival curve is consistent with the FAS time-to-first pulmonary exacerbation survival curve.

Figure 10 Time-to-First Pulmonary Exacerbation; Full Analysis Set, Subjects ≥ 18 Years of Age



Source: Figure 14.2.5.1.2.
Note: The open circles on the plot denote censored subjects.

Results of the analyses for other efficacy variables are presented in Table 18 (see below).

Table 11-32 Absolute Change From Baseline Through Week 24 in Percent Predicted FEV_1 by MMRM: Presented by Percent Predicted FEV_1 at Baseline, Sex, Geographic Region, and *P aeruginosa* Infection Status at Baseline, Subjects ≥18 Years of Age, Full Analysis Set

			Absolute Change From Baseline[a]		Treatment Effect (Ivacaftor vs Placebo)	
Subgroup	Subgroup Category	Treatment Group	n	LS Mean	Difference (95% CI)	*P* value
Percent Predicted FEV_1 at Baseline	<70%	Placebo	15	0.4484	4.0126 (-2.0920, 10.1171)	0.1878
		Ivacaftor	13	4.4609		
	≥70% to ≤90%	Placebo	11	-1.3463	6.4370 (1.8173, 11.0567)	0.0090
		Ivacaftor	10	5.0907		
	>90%	Placebo	0	--	--	--
		Ivacaftor	1	--		
Sex	Male	Placebo	10	0.9135	2.1001 (-4.4149, 8.6152)	0.5043
		Ivacaftor	11	3.0136		
	Female	Placebo	16	-1.2026	6.9625 (1.5593, 12.3657)	0.0136
		Ivacaftor	13	5.7599		
Geographic Region	North America	Placebo	21	-0.5740	4.8108 (-0.0707, 9.6922)	0.0532
		Ivacaftor	16	4.2368		
	Europe	Placebo	5	0.4532	4.5108 (-3.6710, 12.6926)	0.2438
		Ivacaftor	8	4.9640		
P aeruginosa Infection Status at Baseline	Yes	Placebo	18	-0.5470	4.3181 (-1.2470, 9.8832)	0.1231
		Ivacaftor	14	3.7711		
	No	Placebo	8	-0.1709	5.7348 (0.2702, 11.1994)	0.0410
		Ivacaftor	10	5.5639		

Source: Table 14.2.1.2.4.2ad.

Notes: Sample statistics are unadjusted results. Analysis conducted only when the number of subjects with results in each treatment group ≥5. Difference is ivacaftor – placebo. A positive difference favors Ivacaftor.

[a] Estimates were obtained from MMRM with absolute change from baseline as the dependent variable; with treatment group, categorical visit (Weeks 2, 4, 8, 16, and 24), and treatment by visit interaction as fixed effects; and with adjustment for the continuous baseline value of age and percent predicted FEV_1 using compound symmetry covariance matrix. For the subgroup percent predicted FEV_1 severity, no adjustment was made for baseline percent predicted FEV_1.

Ad-hoc subgroup analyses were also performed for poly-T variant within each age category and should be interpreted with caution as this was not a pre-planned analysis and as it is an assessment of a subgrouping of a subgroup.

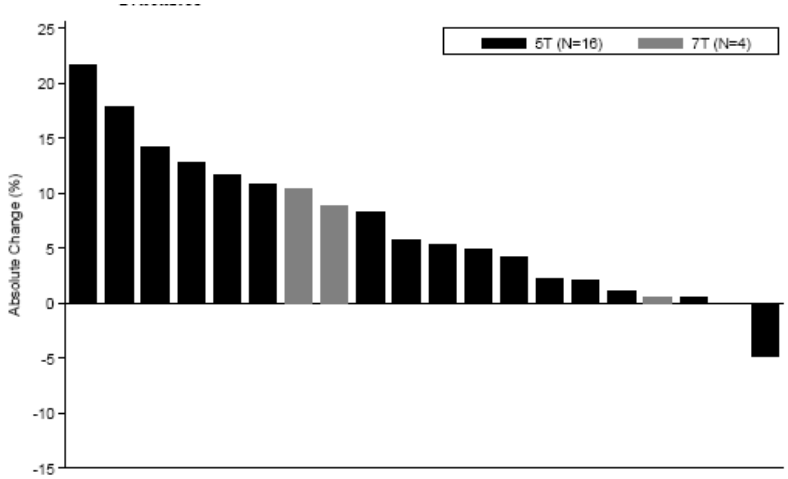
In the Full Analysis Set of study 110, the LS mean absolute change from baseline in ppFEV1 in subjects above 18 years of age with the confirmed 5T variant was 0.73 percentage points in the placebo group and 6.02 percentage points in the ivacaftor group. The treatment difference was 5.29 percentage points (95% CI: 1.27, 9.32). In the group of subjects with the confirmed 7T variant, the treatment difference was 0.20 (95% CI: -8.14, 8.54). In the confirmed plus derived dataset of subjects with the *R117H-5T*, the treatment difference between groups was 3.20 percentage points (95% CI: -0.48, 6.87) in favour of ivacaftor while for subjects with the 7T variant, the treatment difference was -1.46 percentage points (95% CI: -8.69, 5.76).

The analysis restricted to subjects ≥ 18 years by poly-T variant (confirmed plus derived dataset) shows a larger absolute change from baseline in the ivacaftor group both in subjects with the *R117H-7T* variant (ivacaftor: 4.98 pp; placebo: 0.75 pp) and in those with the *R117H-5T* variant (ivacaftor:

7.42 pp; placebo: 0.78 pp). The response was larger in subjects with the *R117H-5T* variant than in subjects with the *R117H-7T* variant. In subjects with the *5T* variant, the estimated (by MMRM) treatment difference for ivacaftor versus placebo at week 24 was 6.87 pp (95% CI: 2.19, 11.56).

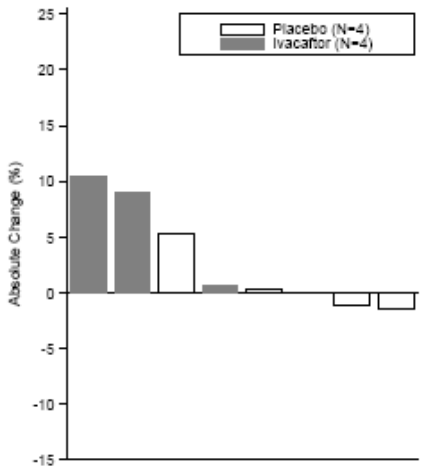
An MMRM analysis was conducted on the 10 subjects ≥18 years of age with *R117H-7T* which show a treatment difference at week 24 of -0.25 (95% CI: -14.16, 13.66). A waterfall plot analysis of individual subject responses at Week 24 suggests that some *R117H-7T* subjects did respond to ivacaftor treatment (see figures below).

Figure 11 Waterfall Plot of Absolute Change from Baseline at Week 24 in Percent Predicted FEV1 for Subjects ≥ 18 years of Age Receiving IVacaftor



Source: Module 5.3.5.1 R117H Addendum/Figure Adhoc 2014.003.4.3

Figure 12 Waterfall Plot of Absolute Change from Baseline at Week 24 in Percent Predicted FEV1 for Subjects ≥ 18 years of Age With *R117H-7T*



Source: Module 5.3.5.1 R117H Addendum/Figure Adhoc 2014.003.4.2

Regarding sweat chloride, for patients with the *5T* variant, the mean (SD) absolute change at week 24 was -8.2 mmol/l (2.8) in the placebo group and -33.9 mmol/L (3.0) in the ivacaftor group. The estimated (by MMRM) treatment difference between groups was -25.64 mmol/l (95% CI: -33.86, -17.42). For patients with a *7T* variant, the mean (SD) absolute change at week 24 was -11.7 mmol/l (11.9) and -19.3 mmol/l (6.9) in the placebo and ivacaftor groups, respectively.

As for the respiratory domain score of the CFQ-R (pooled), for patients with the *5T* variant, the mean (SE) absolute change at week 24 was -2.48 points (4.0) in the placebo group and 16.99 points (4.28) in the ivacaftor group. The estimated (by MMRM) treatment difference between groups was 19.47 points (95% CI: 7.66, 31.27). For patients with a *7T* variant, the mean (SD) absolute change at week 24 was -5.56 points (10.14) and 11.11 points (19.77) in the placebo and ivacaftor groups respectively.

Adolescents

Only 2 subjects 12 to 17 years of age (inclusive) enrolled in the study, 1 subject randomized to ivacaftor and 1 subject randomized to placebo. No inferential statistical analysis was performed for this subgroup because the number of subjects with results in each treatment group was <5.

One subject was a 13-year-old female with CFTR genotype *R117H-7T/F508DEL-9T*. At baseline, the subject had a percent predicted FEV1 of 87.633%, a sweat chloride value of 44.25 mmol/L, a BMI of 28.04 kg/m2, and a CFQ-R respiratory domain score of 100 points. The subject was discontinued from the study 16 days after the first dose of ivacaftor due to non-compliance in completing the required ophthalmologic examination at Screening. The only Treatment Period visit that the subject had was the Week 2 Visit, at which there was no substantial change in percent predicted FEV1 (baseline 87.633%; Week 2: 88.232%), but the subject's sweat chloride showed a -17.25 mmol/L absolute change from baseline.

The other subject was a 17-year-old female with CFTR genotype *R117H-5T/W1282X-7T*, who completed the full 24 weeks of treatment. At baseline, the subject had a percent predicted FEV1 of 88.668%, a sweat chloride value of 74.75 mmol/L, a BMI of 21.86 kg/m2, and a CFQ-R respiratory domain score of 77.778 points. At the Week 24 Visit, the subject had a 7.534 percentage points absolute change in percent predicted FEV1 from baseline and a corresponding increase in CFQ-R respiratory domain score to 94.444 points. The subject’s sweat chloride value at the Week 24 Visit was slightly higher than at baseline.

Children aged 6 to 11 years old (inclusive)

Table 19 presents the mean absolute change from baseline in ppFEV1 through Week 24 by MMRM for subjects 6 to 11 years of age. The mean absolute change (increase) in the placebo group was substantial, i.e. from 93.98 pp at baseline to 98.43 pp overall post-baseline, while the ivacaftor group had a slight decline in mean ppFEV1 from 97.49 pp at baseline to 96.25 pp overall post-baseline. The mean treatment difference estimated by MMRM for the absolute change from baseline was -6.33 percentage points (95% CI: -11.96, -0.71; p value = 0.0301) favouring the placebo group.

Table 19 Absolute Change From Baseline in Percent Predicted FEV1 by MMRM; Full Analysis Set, Subjects 6 to 11 Years of Age (Inclusive)

Visit or Time Period	Treatment Group	Sample Statistics		Absolute Change From Baseline[a]		Treatment Effect (Ivacaftor vs Placebo)	
		n	Mean	n	LS Mean	Difference (95% CI)	*P* value
Baseline	Placebo	8	93.9806	--	--	--	--
	Ivacaftor	9	97.4854	--	--		
Overall Post-baseline	Placebo	8	98.4296	8	3.5101	-6.3334 (-11.9602, -0.7066)	0.0301
	Ivacaftor	9	96.2475	9	-2.8233		

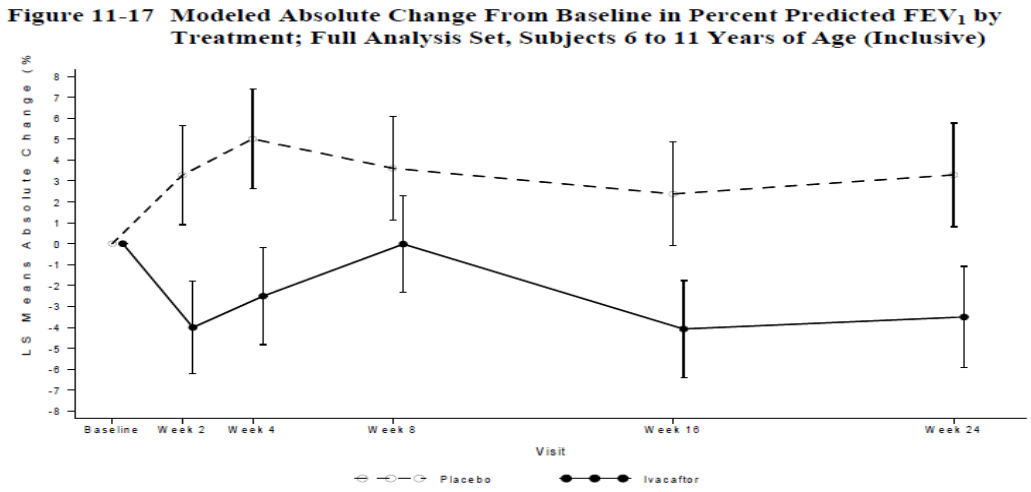
Sources: Table 14.2.1.2.4, and Table 14.2.1.2.2.1ad.

Notes: Sample statistics are unadjusted results. Difference is ivacaftor – placebo. A positive difference favors ivacaftor.

[a] Estimates were obtained from MMRM with absolute change from baseline as the dependent variable; with treatment group, categorical visit (Weeks 2, 4, 8, 16, and 24) and treatment by visit interaction as fixed effects; with subject as a random effect; and with adjustment for the continuous baseline value of percent predicted FEV_1 using compound symmetry covariance matrix.

The consistency of treatment effect over study visits for the absolute change from baseline in ppFEV1 by MMRM for subjects 6 to 11 years of age (inclusive) is presented in Figure 13. The mean ppFEV1 was >93% for both treatment groups at all time points. While the mean ppFEV1 for the placebo group at baseline was 93.98 pp, the mean during the treatment period ranged from 97.36 (Week 2) to 99.10 pp (Week 8). The mean ppFEV1 for the ivacaftor group at baseline was 97.49 pp and ranged from 93.46 pp (Week 2) to 99.01 pp (Week 8) during the treatment period.

Figure 13 Modelled Absolute Change From Baseline in Percent Predicted FEV1 by Treatment: Full Analysis Set, Subjects 6 to 11 Years of Age (Inclusive)

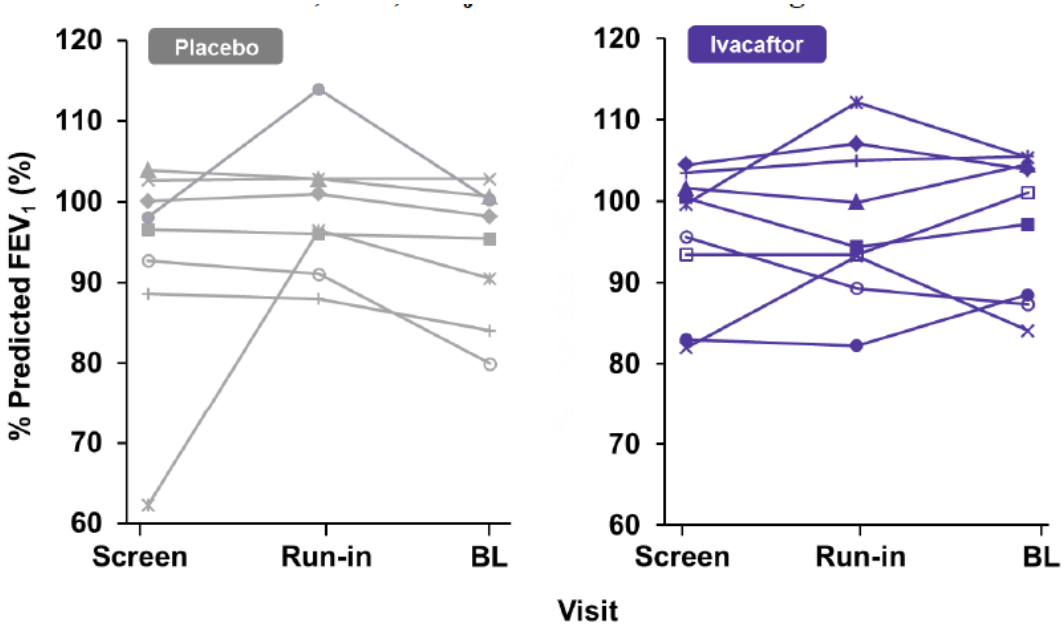


Source: Figure 14.2.1.7ad.

In view of the large placebo response and to further understand the treatment difference seen between the ivacaftor and placebo groups in subjects 6 to 11 years of age, the treatment effect over study visits for the absolute change from the Screening Visit in ppFEV1 was analysed to assess if any pre-treatment trends may have influenced the outcomes (see Figure 14). Comparison of the Screening and Day 1 (i.e. Baseline) values shows that in the placebo group, many subjects had a decrease in ppFEV1 between Screening and Baseline, and a number of ivacaftor subjects had an increase in ppFEV1 between Screening and Baseline. In the analysis of change from Screening value, there were no statistically significant (P value of <0.05) treatment difference in the absolute change in ppFEV1 at

any time point, including Overall Post-baseline. The MAH is of the opinion that the placebo group changes between the Screening Visit and Day 1 contributed to the observed treatment difference in the primary endpoint in subjects 6 to 11 years of age.

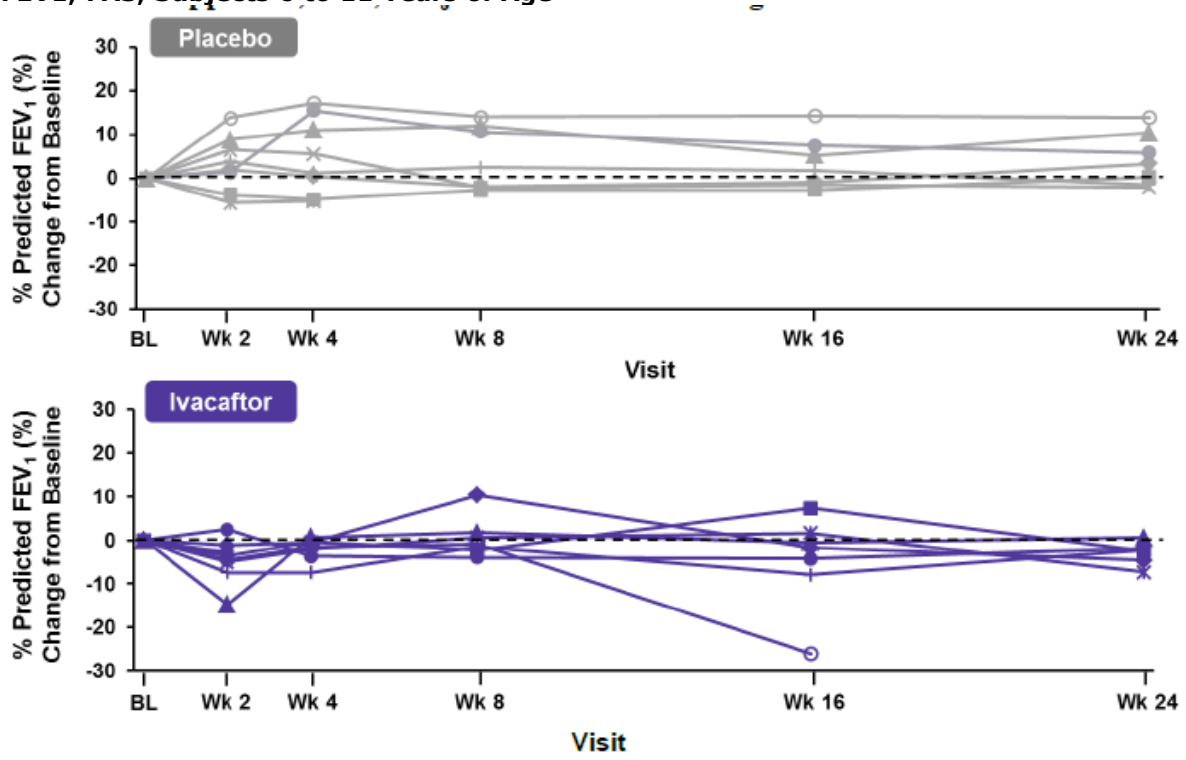
Figure 14 Study 110: Individual Subject Results for ppFEV1 at Screening, Run-in, and Baseline; FAS, Subjects 6 to 11 Years of Age



Source: Kalydeco Rapporteur/Co-rapporteur Pre-submission Meeting Briefing Package Type II Variation for New Indication/ Figure 4-3
BL: baseline; FAS: Full Analysis Set; $ppFEV_1$: percent predicted forced expiratory volume in 1 second

To evaluate individual subject response to ivacaftor and placebo, spaghetti plots (see Figure 15) were generated for the individual ppFEV1 of subjects in the placebo and ivacaftor groups.

Figure 15 Study 110: Individual Subject Results for Absolute Change From Baseline in ppFEV1; FAS, Subjects 6 to 11 Years of Age



Source: Kalydeco Rapporteur/Co-rapporteur Pre-submission Meeting Briefing Package Type II Variation for New Indication/ Figure 4-2
BL: baseline; FAS: Full Analysis Set; ppFEV$_1$: percent predicted forced expiratory volume in 1 second; Wk: week

In the ivacaftor group, one subject had a serious decline in ppFEV1 at Week 16 (26 percentage points) that coincided with an SAE of pulmonary exacerbation; this subject remained on ivacaftor and had another substantial decline in FEV1 during the follow-up period (47 percentage points). The subject enrolled in the IVA arm of Study 112, and his FEV1 returned to baseline during IVA treatment in Study 112. The next worse response in the 6- to 11-year-old subgroup in Study 110 was a subject who had a baseline ppFEV1 value of 105.5 pp and an average ppFEV1 value of 100.2 pp post-dose, ending at a ppFEV1 value of 103.2 pp at Week 24. Aside from these 2 subjects, all other 6- to 11-year-old subjects had less than a 5-percentage point relative change (comparing post-dose average to baseline), and 3 subjects had average ppFEV1 values >100% during the 24-week treatment period.

The LS mean absolute change from baseline in sweat chloride was -26.59 mmol/L for the ivacaftor group and 1.04 mmol/L for the placebo group. The treatment difference for ivacaftor versus placebo was -27.63 mmol/L (95% CI: -37.16, -18.10). This treatment difference favoured ivacaftor and was very similar to that of subjects ≥18 years of age (-21.87 mmol/L [95% CI: -26.46, -17.28]).

Treatment differences were detected by Week 2 (first post-baseline time point assessed; -28.01 mmol/L (95% CI: -40.29, -15.73) and were sustained through Week 24 (-26.35 mmol/L [95% CI: -39.88, -12.83]. These treatment differences favoured ivacaftor and were very similar to those for subjects ≥18 years of age.

No protocol-defined pulmonary exacerbations occurred in subjects 6 to 11 years of age (inclusive) during the treatment period.

The mean absolute change from baseline in BMI-for-age z-score (calculated using the CDC growth chart for subjects who were 20 years of age or younger) at Week 24 by LMM was greater in the

ivacaftor group (0.13 points) than in the placebo group (0.08 points). The mean treatment difference between groups was 0.05 points (95% CI: -0.69, 0.80). The mean treatment difference of the absolute change from baseline in BMI at Week 24 in children aged 6 to 11 years was -0.18 kg/m2 (95% CI: -2.38, 2.01).

Two versions of the CFQ-R questionnaire were used to collect data on subjects 6 to 11 years of age (inclusive) 1 in which the subject was interviewed (Children Ages 6 to 11 Years version) and 1 in which the subject's parent or caregiver was the respondent (Parent/Caregiver version). Only data collected from the Children Ages 6 to 11 Years questionnaire were used in efficacy analyses.

The mean absolute change from baseline in the CFQ-R respiratory domain score through Week 24 by MMRM for subjects 6 to 11 years of age was -1.56 points in the placebo group and -7.69 points in the ivacaftor group. The treatment difference for ivacaftor versus placebo was -6.13 points (95% CI: -15.68, 3.41), in favour of placebo.

Little variation was seen in the CFQ-R respiratory domain scores for the placebo group during the Treatment Period, while the ivacaftor group experienced a substantial decrease in the mean CFQ-R respiratory domain scores at Week 2 and Week 16. For Weeks 4, 8, and 24, there were no clinically meaningful difference between the ivacaftor and placebo groups. The MAH is therefore of the opinion that caution is warranted in interpretation of the overall post-baseline differences.

The following subjects in the ivacaftor group had substantial decreases in the CFQ-R respiratory domain score at the indicated week(s): one subject at Week 2 and Week 16, one subject at Week 2, one subject at Week 2 and Week 16, one subject at Week 2 and Week 16, and one Subject at Week 16. All individual substantial decreases in the CFQ-R respiratory domain score occurred at Week 2 and Week 16. Some of these subjects with notable changes in CFQ-R also had notable variability in FEV1. Complete efficacy and safety narratives for these subjects, and all subjects <18 years of age, have been provided.

Table 20 shows summary statistics by poly-T status for the youngest age group.

Table 20 Summary statistics of absolute change from baseline at week 24 in efficacy variables by poly-T status (Confirmed+Derived dataset), FAS population (children aged 6 to 11 years)

Poly-T status	Percent Predicted FEV1 (%)			Sweat chloride (mmol/L)			Respiratory Domain CFQ-R (pooled)		
	Baseline Mean (SD)	Week 24 Mean (SD)	Absolute change Mean (SD)	Period baseline Mean (SD)	Week 24 Mean (SD)	Absolute change Mean (SD)	Baseline Mean (SD)	Week 24 Mean (SD)	Absolute change Mean (SD)
R117H-5T - placebo (n=5)	97.19 (7.54) (n=5)	100.39 (10.76) (n=5)	3.20 (5.18) (n=5)	92.70 (12.49) (n=5)	89.50 (15.50) (n=5)	-3.20 (25.54) (n=5)	91.67 (5.89) (n=5)	93.33 (7.0) (n=5)	1.67 (9.13) (n=5)
- ivacaftor (n=4)	94.49 (10.39) (n=4)	100.62 (3.71) (n=2)	-2.62 (0.57) (n=2)	81.00 (14.18) (n=4)	52.00 (1.41) (n=2)	-33.25 (20.15) (n=2)	91.67 (8.33) (n=3)	83.33 (n=1)	0.00
R117H-7T -placebo (n=3)	88.63 (7.91) (n=3)	94.76 (1.27) (n=2)	7.06 (9.69) (n=2)	44.58 (19.56) (n=3)	49.25 (2.47) (n=2)	-6.38 (8.31) (n=2)	91.67 (11.79) (n=2)	83.33 (n=1)	0.00
- ivacaftor (n=5)	99.88 (7.15) (n=5)	96.72 (6.81) (n=5)	-3.16 (2.97) (n=5)	47.31 (15.28) (n=4)	25.88 (8.17) (n=4)	-21.44 (13.49) (n=4)	93.33 (7.0) (n=5)	91.67 (10.21) (n=5)	-1.67 (9.13) (n=5)

Overall, no evidence of a spirometry and of a CFQ-R respiratory domain response to ivacaftor therapy was seen in subjects from this age group with either of the *R117H* poly-T variants. The MAH is of the view that this decrease in ppFEV1 in the IVA group may be partially explained by a subject with a pulmonary exacerbation and by the changes between the Screening Visit and baseline (Day 1).

Summary statistics revealed clear and consistent sweat chloride responses for both *R117H* poly-T variant subgroups which began at Week 2 and were sustained through Week 24.

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 21. Summary of Efficacy for trial VX-11-770-110

<table>
<tr><td colspan="4">A Phase 3, Randomized, Double-blind, Placebo-Controlled, Parallel Group Study to Evaluate the Efficacy and Safety of Ivacaftor in Subjects With Cystic Fibrosis Who Have the R117H-CFTR Mutation.</td></tr>
<tr><td>Study identifier</td><td colspan="3">Protocol VX11-770-110</td></tr>
<tr><td rowspan="2">Design</td><td colspan="3">Randomized, double-blind, placebo-controlled, parallel-group, multicenter study.</td></tr>
<tr><td colspan="2">Duration of main phase:
Duration of Run-in phase:
Duration of Extension phase:</td><td>24 weeks
Day -14 to Day -1 relative to the first dose of study drug
Patients enrolled in study 110 were offered enrolment in an extension study, study 112.</td></tr>
<tr><td>Hypothesis</td><td colspan="3">Superiority (not explicitly formulated)</td></tr>
<tr><td rowspan="2">Treatments groups</td><td colspan="2">Ivacaftor group</td><td>Ivacaftor 150 mg every 12 hours for 24 weeks with fat-containing food</td></tr>
<tr><td colspan="2">Placebo group</td><td>Ivacaftor-matched placebo every 12 hours for 24 weeks with fat-containing food</td></tr>
<tr><td rowspan="5">Endpoints and definitions</td><td>Primary endpoint</td><td>PPFEV1, 24 weeks</td><td>Absolute change from baseline in ppFEV1 through Week 24 (%)</td></tr>
<tr><td>Secondary endpoint</td><td>BMI, 24 weeks</td><td>Rate of change from baseline in BMI at Week 24 (kg/m^2)</td></tr>
<tr><td>Secondary endpoint</td><td>Sweat chloride, 24 weeks</td><td>Absolute change from baseline in sweat chloride through Week 24 (mmol/L)</td></tr>
<tr><td>Secondary endpoint</td><td>Respiratory domain score of the pooled CFQ-R, 24 weeks</td><td>Absolute change from baseline in the respiratory domain score of the pooled CFQ-R through Week 24 (Pooled questionnaire analyses were defined as all questionnaire versions except for the Parents and Caregivers version)</td></tr>
<tr><td>Secondary endpoint</td><td>Pulmonary exacerbations</td><td>Time-to- First Pulmonary Exacerbation</td></tr>
<tr><td>Database lock
Study completion (date last subject completed the last visit)</td><td colspan="3">25 October 2013</td></tr>
<tr><td colspan="4"><u>Results and Analysis</u></td></tr>
</table>

A Phase 3, Randomized, Double-blind, Placebo-Controlled, Parallel Group Study to Evaluate the Efficacy and Safety of Ivacaftor in Subjects With Cystic Fibrosis Who Have the *R117H-CFTR* Mutation.			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Full analysis set: all randomized patients who received at least 1 dose of study drug (i.e., ivacaftor or placebo). Patients were analyzed according to the study drug to which they were assigned at/through Week 24. Eight patients did not complete 24 weeks of treatment because the study was terminated early by the sponsor. For these 8 subjects, the last Treatment Period study visit was: Week 2 for 2 subjects, Week 4 for 1 subject, Week 8 for 3 subjects, and Week 16 for 2 subjects. Out of the 8 patients who did not complete 24 weeks of treatment 3 were children and 5 adult patients.		
Descriptive statistics and estimate variability	Treatment group	Ivacaftor	Placebo
	Number of subject	34	35
	LS mean ppFEV1 (change from baseline through week 24)	2.5724	0.4611
	Standard error (SE)	1.1532	1.1313
	LS mean BMI (change from baseline at week24)	0.4910	0.2284
	Standard error	0.6653	0.6504
	*LS mean sweat chloride (change from baseline through week 24) Standard error	-26.2771 1.4584	-2.3078 1.3716
	**LS mean Respiratory domain pooled CFQ-R (change from baseline through week 24) Standard error	7.5585 2.2073	-0.8289 2.1569
	Proportion of event-free patients	0.683	0.575
	95% CI	0.489, 0.817	0.380, 0.729
Effect estimate per comparison	Primary endpoint	Ivacaftor vs. Placebo	
		ppFEV1, MMRM	2.1114
		95% CI	-1.1305, 5.3532
		P-value	0.1979

A Phase 3, Randomized, Double-blind, Placebo-Controlled, Parallel Group Study to Evaluate the Efficacy and Safety of Ivacaftor in Subjects With Cystic Fibrosis Who Have the *R117H-CFTR* Mutation.			
	Secondary endpoint		
		BMI, LMM	0.2626
		95% CI	-1.5698, 2.0950
		P-value	0.7780
	Secondary endpoint		
		Sweat chloride, MMRM	-23.9693
		95% CI	-28.0094, -19.9293
		P-value	<0.0001
	Secondary endpoint		
		Respiratory domain, pooled CFQ-R, MMRM	8.3874
		95% CI	2.1658, 14.6090
		P-value	0.0091
	Secondary endpoint		
		Time-to-First Pulmonary Exacerbation	0.928 (hazard ratio)
		P-value	0.8556
Notes	*Sweat chloride: n= 32 on ivacaftor ** Respiratory domain pooled CFQ-R: n= 33 on ivacaftor, n=34 on placebo		
Analysis description	A number of tertiary endpoints, additional spirometry variables, subgroup analyses and post-hoc analyses have also been performed.		

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

No pre-specified efficacy analyses have been performed across trials. However, baseline data and disease characteristics of patients enrolled in study 110 have been compared to those of patients enrolled in studies 102 (adult and adolescent patients with a *G551D* mutation), 103 (patients aged 6 to 11 years with a *G551D* mutation) and study 111 (patients aged 6 years and older with a non-*G551D-CFTR* gating mutation). It is concluded that consistently with the milder phenotype associated to the *R117H-CFTR* mutation patients in study 110 had lower mean sweat chloride concentrations (approximately 70 mmol/L) than subjects from studies 102, 103, and 111 (approximately 100 mmol/L). The recruited *R117H* subjects had well preserved BMIs (mean: 23.76 kg/m2) and a higher proportion were pancreatic sufficient (as assessed by a low rate of pancreatic enzyme replacement therapy use [pancreatin: 11.6%; pancrelipase: 5.8%] and a high rate of faecal elastase-1 ≥200 µg/g [87.0%]) compared to the subject populations of studies 102 and 103.

Regarding ppFEV1 study 110 patients who were 6 to 11 years of age had a baseline mean ppFEV1 approximately 10 percentage points higher than study 103 patients and a categorical distribution favouring higher baseline ppFEV1 values. The high preservation of lung function in Study 110 subjects 6 to 11 years of age is not unexpected given the known clinical progression of CF in patients with an *R117H-CFTR* mutation; that is, patients with an *R117H-CFTR* mutation have less advanced disease in childhood and adolescence than patients of the same age with more severe genotypes.

The results of these studies have been discussed to provide further supportive information for the efficacy shown in study 110. In studies 102, 103, and 111 (Part 1) analysis of the primary endpoint (absolute change in ppFEV1) performed in patients with other mutations than *R117H* showed a substantial treatment effect in favour of ivacaftor that was statistically significant. Treatment differences in mean absolute change from baseline through week 24 in ppFEV1 were in all cases above

10.0 percentage points. In particular, in study 103 the treatment difference was 12.5 percentage points.

Although in Study 110, subjects 6 to 11 years of age (inclusive) showed a comparable sweat chloride response to those ≥18 years of age, the younger age group did not show any other meaningful clinical response to ivacaftor treatment. In this age group, the ppFEV1 treatment difference favoured placebo. Therefore, the extension of indication was refused during procedure EMEA/H/C/002494/II/27.

Clinical studies in special populations

The results of studies 110 and 112 have been discussed elsewhere in this report; both studies included paediatric population.

Narratives have been provided for two patients ≥65 years old enrolled in study 110. Both of them were randomised to placebo. One of them experienced adverse events of cough, sputum increased and pyrexia that are reported as not related and of moderate severity. They were considered as non-serious adverse events in study 112. A moderate increase in ppFEV1 was seen for both patients after twelve and two weeks of treatment with ivacaftor in study 112. Regarding sweat chloride, no change was seen in one of these patients while for the other a decrease of 30 mmol/l was seen at week 2 of study 112.

The overall median age in study 110 was 32 years while it was 23 years in study 111 (non-*G551D* gating mutations) and 24 years in study 102 (*G551D-CFTR* mutation). The maximum age reported in these studies is 68, 57 and 53 years respectively. The MAH was requested to provide the number of patients ≥55 years old treated with ivacaftor in studies 110, 111 and 102 and the corresponding roll-over studies. A total of 10 patients ≥55 years of age were treated with ivacaftor, of which 5 subjects turned 55 during ivacaftor treatment. In addition, 4 subjects from study 113 were ≥55 years of age during either study 113 (a pilot study testing the effect of ivacaftor on lung function in subjects with CF and residual CFTR function) or the rollover study 112.

Overall, CHMP considered that the number of patients treated with ivacaftor who are at least 55 years old is still limited.

Supportive studies

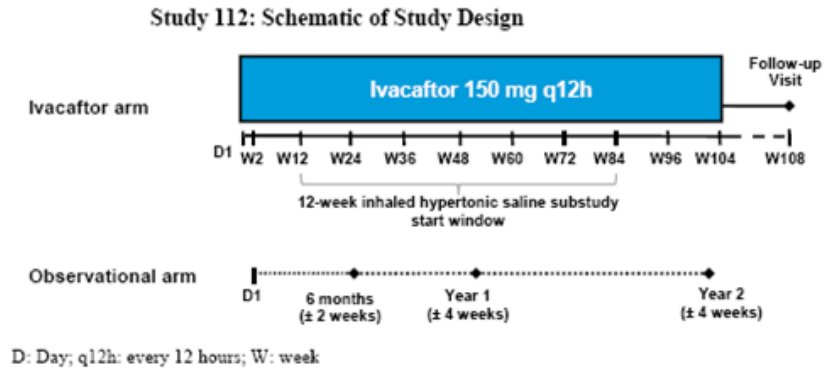
Study VX12-770-112: Phase 3, multicentre, 2-arm, open-label, rollover study of orally administered ivacaftor in subjects with CF who were 6 years of age and older, had a non-G551D-CFTR mutation, and who had previously been enrolled in Study VX11-770-110 (Study 110), Study VX12-770-111 (Study 111), or Study VX12-770-113 (Study 113).

Methods

Study 112 was an open-label study designed to evaluate the long-term safety, efficacy, and pharmacokinetic of ivacaftor in subjects from Study 110 (subjects with an *R117H-CFTR* mutation), study 111 (subjects with a non-*G551D-CFTR* gating mutation that causes a severe gating defect) and study 113 (subjects who have phenotypic or molecular evidence of residual *CFTR* function). The final report of study 112 was assessed within procedure EMEA/H/C/002494/II/0054 in 2017.

A schematic of the study 112 design is provided in **Figure 16**.

Figure 16 Schematic of Study Design



At the time of the initial application of the extension of the indication to subjects with CF aged 6 years and older with an *R117H-CFTR* mutation (EMEA/H/C/002494/II/27), results from interim analysis (through Week 12 Visit) of data from patients who were previously enrolled in study 110 was provided. Patients from study 111 and study 113 who enrolled in study 112 were not included in this interim analysis. Although in study 110 subjects 6 to 11 years of age did not show any meaningful clinical response to ivacaftor treatment except for sweat chloride response, they were enrolled in study 112. Consequently, this interim analysis provides additional information.

Baseline was defined as the most recent measurement before intake of the first dose of study drug in Study 112. This measurement was generally taken at the Day 1 Visit for Study 112, which was also the Follow-up Visit of Study 110, and which occurred 3 to 4 weeks after the last dose of study drug in Study 110. For study 110 patients who enrolled in the ivacaftor arm of study 112, the Safety Follow-up Visit for study 110 was used as the Baseline Visit for study 112.

In the following, patients from the ivacaftor group in study 110 are referred to as patients in the ivacaftor/ivacaftor group (i.e. patients who received ivacaftor in study 110 and in study 112), and patients from the placebo group in study 110 will be referred to as patients in the placebo/ivacaftor group (i.e. patients who received placebo in study 110 and ivacaftor in study 112).

Of the 69 patients enrolled in study 110, 65 enrolled in the ivacaftor arm of study 112, 2 enrolled in an observational arm of study 112 and 2 did not enrol in study 112 due to early discontinuation of treatment in study 110. The Full Analysis Set (FAS) for this interim analysis includes 65 patients: 30 patients in the ivacaftor/ivacaftor group and 35 patients in the placebo/ivacaftor group. Out of these, 64 patients completed at least 12 weeks of treatment in Study 112. A patient in the ivacaftor/ivacaftor group discontinued between Week 2 and 12 and three other patients (1 placebo/ivacaftor and 2 ivacaftor/ivacaftor) discontinued after Week 12.

Fifteen patients 6 to 11 years of age at the start of study 110 enrolled in study 112 (placebo/ivacaftor: 8 patients; ivacaftor/ivacaftor: 7 subjects). Their overall baseline mean ppFEV1 was 92.1% (97.5% in the placebo/ivacaftor group and 85.8% in the ivacaftor/ivacaftor group). Percent predicted FEV1 baseline in the ivacaftor/ivacaftor group was lower than that of study 110 (97.5%). This difference was likely due to a patient who suffered a large decrease in ppFEV1 during study 110 due to a pulmonary exacerbation. This subject remained on ivacaftor throughout the pulmonary exacerbation and his FEV1 returned to baseline during study 112. In study 112, the baseline sweat chloride concentration was 62.8 mmol/L in the placebo/ivacaftor group and 60.4 mmol/L in the ivacaftor/ivacaftor group.

Summary statistics were the pre-planned analysis for the overall population, patients aged ≥18 years, and patients aged 6 to 11 years. Following database lock additional analyses were conducted to evaluate the absolute change from baseline to Week 12 in ppFEV1 using a one-sample t-test.

Outcomes

Interim analysis through the Week 12 Visit of study 112 results previously described in variation (EMEA/H/C/002494/II/27)

Full Analysis Set, all patients (n=65)

Summary statistics show that the mean (SD) absolute change in ppFEV1 from baseline at week 12 in the placebo/ivacaftor group was 5.00 percentage points (7.67) and 6.04 percentage points (10.42) in the ivacaftor/ivacaftor group (n=27 from the initial number of 30 at baseline). For the overall population, the mean (SD) change from baseline in ppFEV1 at week 12 was 5.45 percentage points (8.91).

Full Analysis Set, Patients ≥18 Years of Age (n=49)

Summary statistics show that the mean (SD) absolute change in ppFEV1 from baseline at week 12 in the placebo/ivacaftor group was 5.47 (7.89) percentage points and 4.73 (6.39) percentage points in the ivacaftor/ivacaftor group (n=20 from the initial number of 23 at baseline). The mean (SD) overall absolute change in ppFEV1 from baseline to Week 12 in study 112 was 5.15 percentage points (7.21)

Full Analysis Set, Patients 12 to 17 Years of Age

Only 1 patient in this age group was enrolled in the placebo/ivacaftor group, a 17-year-old White female with *R117H-5T/W1282X-7T*. At study 110 baseline his ppFEV1 and sweat chloride were 88.67% and 74.75 mmol/l. At study 112 baseline, these figures were as follows: 96.477% and 82 mmol/l, i.e. she had experienced an increase of 7.5% and 7.3 mmol/l in ppFEV1 and sweat chloride respectively. At study 112 week 12 his ppFEV1 was 100.59 (above the baseline of study 110 and study 112). At week 2 his sweat chloride was 44.5 mmol/l, i.e. a large reduction was observed with respect to baseline values of studies 110 and 112.

Full Analysis Set, Patients 6 to 11 Years of Age (n=15)

The mean (SD) absolute change in ppFEV1 from baseline at week 12 in the placebo/ivacaftor group was 3.58 (7.76) percentage points and 9.78 (17.87) percentage points in the ivacaftor/ivacaftor group. There was a slight decrease in ppFEV1 in the placebo/ivacaftor group at week 2 in study 112. Although the decrease is numerically very small, similar phenomenon was observed by the analysis of the youngest subgroup in study 110 that was attributed to unlucky pre-treatment trends in study 110. No further issues were raised given the limited magnitude of the drop. The mean (SD) overall absolute change in percent predicted FEV1 from baseline to Week 12 in study 112 was 6.47 percentage points (13.31).

Overall, the results seen in study 112 in terms of change from baseline at week 12 in ppFEV1 in the placebo/ivacaftor group improve the results seen in study 110 in patients receiving ivacaftor (for which the mean absolute change from baseline was 2.57 as compared to 5.00 percentage points in the placebo/ivacaftor group of study 112, FAS population, all patients). This seems also to be the case of patients in the age group ≥18 years old and particularly in those aged 6 to 11 years old. With a single exception (patients aged 18 years and older) the change (increase) at week 12 in ppFEV1 is higher in the ivacaftor/ivacaftor group than in the placebo/ivacaftor group. The results of the post-hoc statistical analyses performed show treatment differences between groups in ppFEV1 that are (nominally) statistically significant except for patients in the 6 to 11-year-old group. This was attributed by the MAH to a single patient in the ivacaftor/ivacaftor group who had an increase of 49.72 percentage points at week 12 following resolution of a pulmonary exacerbation.

Final study report of study 112: Results previously submitted in variation (EMEA/H/C/002494/II/0054)

In study 110, 17 children were enrolled (8 patients on placebo; 9 on ivacaftor). The mean absolute change (increase) in the placebo group in ppFEV1 was substantial, i.e. from 93.98 pp at baseline to 98.43 pp overall post-baseline, while the ivacaftor group had a slight decline in mean pp FEV1 from 97.49 pp at baseline to 96.25 pp overall post-baseline. The mean treatment difference for the absolute change from baseline was -6.33 percentage points (95% CI: -11.96, -0.71) favouring the placebo group.

Thirteen children rolled over from study 110 into study 112. Their mean (SD) baseline ppFEV1 was 90.7 (18.8) percentage points.

At study 112 week 104, children from study 110 (n=4) experienced a mean (SD) absolute change in ppFEV1 of 8.2 percentage points (23.8) which is in contrast with the value observed in study 110. However, at all study 112 visits the range of values of absolute change in ppFEV1 includes a negative minimum value (ranging from -3.1 to -10.9). At earlier points in time where the number of children with available data was higher (e.g., n=10 at week 48), the mean (SD) absolute change in ppFEV1 from study 112 baseline was 4.2 percentage points (8.1).

Similarly, a response in the respiratory domain of CFQ-R was observed at almost all time points in study 112. At baseline, mean (SD) respiratory domain score was 82.1 (20.4) points. Changes from baseline in the 6 to 11 years of age subgroup remained above the MCID at all but 1 time point (i.e., at Week 36) and ranged from 3.2 to 10.1 points.

For the two adolescents who rolled over into study 112 from study 110, at week 84 (last visit at which data were available), the mean (SD) change from baseline in ppFEV1 was 5.8 (4.8) percentage points. At the earlier termination visit (i.e., as soon as possible after the last ivacaftor dose), this value was 2.6 (6.4) percentage points.

Study VX15-770-122: A study in US cystic fibrosis patients with the *R117H-CFTR* mutation to confirm the long-term safety and effectiveness of Kalydeco, including patients <18 years of age, combining data captured in the Cystic Fibrosis Foundation Patient Registry from an interventional cohort and a non-interventional cohort

The MAH was requested by FDA to conduct an open-label, single-arm study as a post-marketing requirement to evaluate the long-term safety of Kalydeco in CF paediatric patients following approval of Kalydeco for CF aged 6 years and older who have the *R117H* mutation in the *CFTR* gene. Study VX15-770-122 (study 122) was designed as an observational, phase 4 study using data collected via the Cystic Fibrosis Foundation Patient Registry (CFFPR).

The schedule of reporting of data from this study is detailed below:

Table 22 Schedule for Interim Analyses and Report Submission Dates

Study Report	Scope	Submission Date
Interim Analysis 1	Historical Cohort analyses and analysis of baseline characteristics of the Non-interventional Cohort (all patients who initiated therapy by the end of 2016; i.e., the Kalydeco Cohort).	31 December 2017
Interim Analysis 2	Disease progression in the Non-interventional Cohort (Kalydeco Cohort) prior to treatment initiation and at least 2 years after treatment initiation (follow-up through the end of 2018).	31 December 2019
Final Analysis	Disease progression in the Non-interventional Cohort (Kalydeco Cohort) prior to treatment initiation and at least 3 years after treatment initiation (follow-up through the end of 2019).	31 December 2020

Notes: An Interventional Cohort was planned per protocol but did not recruit any subjects because all patients had access to Kalydeco. In addition, the number of patients in the Non-interventional Cohort was sufficient to address the study assessments.

In this application, interim analysis 1 (IA1) was submitted and interim analysis 2 (IA2) was provided upon request from CHMP during the procedure. Outcome measures summarised in this assessment report are those of the IA2, unless stated otherwise.

Methods

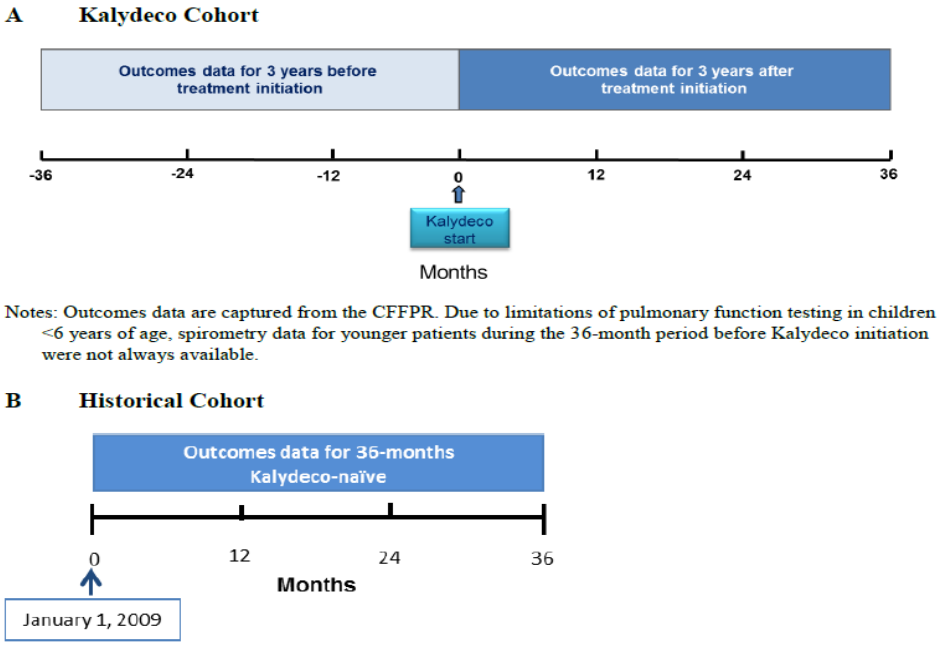
Study 122 is an ongoing Phase 4, non-interventional, observational study to confirm the long-term effectiveness and safety of Kalydeco in CF patients who have the *R117H* mutation. The study leverages existing data collected via the CFFPR. Observational cohorts of patients receiving Kalydeco and historical patients who were never treated with Kalydeco were established in the registry as described below.

A Non-Interventional Kalydeco Cohort (hereafter referred to as "Kalydeco Cohort") is comprised of paediatric (<18 years of age) and adult *R117H* patients who were included in the CFFPR and had a record of Kalydeco treatment initiation from 01 January 2015 through 31 December 2016. Analyses of data for 36 months before and 36 months after the initiation of Kalydeco treatment will permit a within-group comparison of outcome measures of effectiveness and safety before and after treatment.

A Historical Cohort is comprised of longitudinal data from an earlier time period (i.e. 2009 through 2011) for paediatric (<18 years of age) and adult patients with the *R117H* mutation who had never been exposed to Kalydeco and will provide additional context.

A schematic of the study design for Non-Interventional Cohort is provided in Figure 17.

Figure 17 Study VX15-770-122 Design



Notes: Outcomes data are captured from the CFFPR. Due to limitations of pulmonary function testing in children <6 years of age, spirometry data for younger patients during the 36-month period before Kalydeco initiation were not always available.

Study participants

The inclusion criteria for each study cohort are summarized in Table 23.

Table 23 Study Cohort Inclusion Criteria

Cohort	Inclusion Criteria
Kalydeco Cohort	• Male or female with confirmed diagnosis of CF (as defined in the protocol) • Must have at least 1 allele of the *R117H* mutation • Enrolled in the US CFFPR (as demonstrated by signing of the CFF Informed Consent/Assent Form) • With a record of Kalydeco treatment initiation from 01 January 2015 through 31 December 2016
Historical Cohort[a]	• Patients with CF in the CFFPR as of 01 January 2009 • Must have at least 1 allele of the *R117H* mutation • Patients with no evidence of any prior Kalydeco exposure

[a] Appendix 1 provides a detailed explanation about the attempted matching process for the final data set used in this interim analysis (IA). Patients in the Historical Cohort were not matched to those in the Kalydeco Cohort. Instead, data from all eligible, Kalydeco-naïve patients with at least 1 copy of the *R117H* mutation in the CFFPR were included in the Historical Cohort.

Each patient in the Kalydeco cohort was attempted to be matched with at least 1 corresponding patient from the Historical cohort but the specified matching algorithm did not successfully achieve balance in ppFEV1 in the adult populations. Therefore, patients in the Historical cohort were not matched to those in the Kalydeco cohort.

In the final study protocol, an Interventional Cohort was planned as part of the post-marketing requirement to ensure adequate paediatric enrolment (i.e., a minimum of 50 patients ≥8 to <18 years of age with evaluable data on key endpoints). However, as it became clear that this target had been achieved in the Non-Interventional Cohort, the Interventional Cohort was closed and no patients were enrolled.

Objectives

Primary Objective: confirm the long-term safety and effectiveness of Kalydeco in US CF patients with the *R117H-CFTR* mutation who are <18 years of age.

Secondary Objective: describe the long-term safety and effectiveness of Kalydeco in CF patients with the *R117H-CFTR* mutation overall and in patients ≥18 years of age.

Outcomes/endpoints

The outcomes captured in the CFFPR and assessed as study endpoints include:

- Lung function measurements (ppFEV1 and ppFVC) using the Global Lung Initiative (GLI) standards.
- Pulmonary exacerbations (PEx) (which, by definition, include the use of intravenous antibiotics at home or in the hospital), use of intravenous antibiotics.
- Nutritional parameters (weight, body mass index [BMI], and associated z-scores).
- Deaths or transplantation.
- Hospitalizations.
- Selected CF complications (symptomatic sinus disease, pulmonary complications, CF-related diabetes [CFRD], distal intestinal obstruction syndrome [DIOS], hepatobiliary complications, and pancreatitis).
- Selected pulmonary microorganisms (e.g., *Pseudomonas aeruginosa* [*P aeruginosa*], *Staphylococcus aureus* [*S aureus*]).

Study Size

No prespecified sample size calculation was made. The sample size was dependent on the use of Kalydeco in the real-world setting. The study intent was to evaluate a minimum of 50 patients who were ≥8 to <18 years of age, had at least 2 years of acceptable spirometry data in the CFFPR, and had attended at least 2 of the CFF quarterly recommended scheduled CF clinic visits per year. The minimum number of adult patients in the Kalydeco cohort was intended to be 100. There was no maximum number for either paediatric or adult patient groups, although, if the above criteria were met, further enrolment would be targeted to stop on 31 December 2016.

Statistical methods

Two Statistical Analyses Plans (SAP) were submitted, i.e., for the IA1 (version 1.0 of 20 FEB 2017) and for the IA2 and final analysis (version 1.0 of 20 February 2019). The final analysis is due by 31 December 2020. Data below correspond to the SAP of IA2 in which modifications from the IA1 SAP were made to accommodate the data available.

The mixed-effects model for repeated measures (MMRM) analysis and linear mixed effects (LME) analyses of spirometry endpoints and the LME analyses of nutritional parameters described in the study protocol as potential analyses to be performed if warranted by the data were not performed for none of the interim analyses and there is no plan to perform this kind of analyses in the final report.

For the purpose of analysis of the outcome measures, two periods were defined for this study based on timing relative to the start of Kalydeco treatment (defined as the index date):

- Period 1 (pre-treatment) is defined as the 36-month period before the index date.

- Period 2 (post-treatment) is defined as the index date through the end of the study, i.e. through the 36 months after the index date. For IA2, this was limited to the first 24 months of post-treatment data for all Kalydeco Cohort patients, and up to 36 months of post-treatment outcomes data for patients who initiated Kalydeco in 2015.

For patients for whom the precise start of Kalydeco dosing was not known, the visit at which the first use of Kalydeco was indicated was considered the index date.

For the purposes of change from baseline analyses of lung function and nutritional parameters, baseline was defined as the last encounter visit up to 31 days before the date of first initiation of Kalydeco. For patients for whom the precise start of Kalydeco dosing was not known, baseline was defined as the last encounter before the visit at which the use of Kalydeco was indicated for the first time.

Baseline demographic and clinical characteristics included age, age at diagnosis, sex, race, weight, weight-for-age z-score, height, height-for-age z-score, BMI, BMI-for-age z-score, pulmonary function (ppFEV1 as both a continuous and categorical variable [<70, ≥70 to ≤90, and >90]), ppFVC and poly-T status (as captured in the registry). These characteristics are summarized separately for each age group within the Kalydeco Cohort as of the index date. Baseline demographic and clinical characteristics for the Historical Cohort are summarized by age group as of 01 January 2009.

Exposure data are summarized separately for each age group. Exposure to Kalydeco (duration of treatment in months) is summarized by means of descriptive summary statistics and also categorically (<6 months, ≥6 to <12 months, ≥12 months to <24 months, and ≥24 months to <36 months). Changes in exposure after Kalydeco initiation (treatment discontinuation, death, or loss to follow-up) are also summarized as number (%) of patients. Treatment discontinuations are defined as having no record of Kalydeco use recorded at a later date and before the end of the study.

Visit frequency is described by the proportions of patients in each age group having <2, ≥2 to <4, and ≥4 clinic visits per year, as well as the mean annual number of visits as recorded in the registry.

Lung function data are summarized using descriptive statistics for the observed values at the index date and for each 12-month interval in the pre- and post-treatment periods. Where more than one value was available in any given 12-month interval, the average of the values was used. Analysis Comparing Post-Treatment Data with Historical Cohort Data: ppFEV1 observed data for the ≥6 to <18 Years of Age analysis set, and the corresponding subset from the Historical Cohort, will be summarized and compared using descriptive statistics. Plots will be provided as appropriate to aid in the interpretation of data.

All summary statistics and descriptive statistics provided for the ppFEV1 endpoint are repeated for ppFVC. No inferential statistics will be provided for ppFVC.

The number and percentage of patients with PEx and PEx requiring hospitalization are summarized for each 12-month interval in the pre- and post-treatment periods. Percentages of patients with PEx and PEx requiring hospitalization are compared between the 12-month interval in the period immediately preceding the start of Kalydeco treatment and the 12-month intervals after treatment initiation using a McNemar's test. A Wilcoxon Signed-Rank test for paired data was used to compare the number of PEx and PEx requiring hospitalization between the 12-month interval in the period immediately preceding the start of Kalydeco treatment and the first 12-month intervals after treatment initiation.

Analyses of hospitalizations and CF disease-related hospitalizations are carried out in a similar way to analyses of PEx.

Descriptive statistics on observed values of weight, weight-for-age z-scores, height, height-for-age z-scores, BMI, and BMI-for-age z-scores at the index date and for each 12-month interval in the pre- and post-treatment periods are provided. For IA2, not all subjects have reached the final 12-month interval; data for all available subjects in that interval are presented. Changes from baseline at each 12-month interval are also summarized descriptively. Z-scores are calculated using the CDC growth charts which are designed for use only in subjects aged 2 to 20 years of age. Further details are described in the SAP.

Deaths and transplantations are summarized for relevant analysis sets and by cohort. This analysis was only presented for the Kalydeco Cohort but not for the Historical Cohort.

The prevalence of the selected complications is presented for each 12-month interval in the pre- and post-treatment periods.

The number and percentage of patients with a culture positive for bacteria, including positive for *P aeruginosa*, and patients with cultures positive for bacteria other than *P. aeruginosa* are summarized for each 12-month interval in the pre- and post-treatment periods for those patients who had a microbiology culture result.

The evaluation of safety is a co-primary objective of study 122. Certain effectiveness analyses, including absolute change in ppFEV1 and PEx, will also be used to support the overall safety objective of the study. In accordance with its observational nature, no additional safety reporting is applicable for the Kalydeco Cohort.

The following ad hoc analyses were performed as part of IA1. Both analyses were applicable only to the Kalydeco Cohort (and not to the Historical Cohort).

- Visit frequency was assessed in the year before Kalydeco treatment initiation.
- Data on the following parameters were assessed in the subset of patients who had data available in all time intervals: ppFEV1, PEx (overall and those requiring hospitalization), weight, weight-for-age z-score, BMI, BMI-for-age z-score, hospitalizations, prevalence of selected complications, and positive microbiology culture results.

Analysis Sets

The following analysis sets were defined within the overall Kalydeco Cohort by age at the time of Kalydeco initiation:

- All Patients Set (will comprise all patients who received at least 1 dose of Kalydeco)
- ≥18 Years of Age (named the Adult Analysis Set in the protocol)
- ≥6 to <18 Years of Age (named the Primary Full Analysis Set in the protocol, and focus of the primary analyses to fulfil the primary objective of this study)
- ≥2 to <6 Years of Age

Similar analyses sets were defined within the Historical Cohort by age as of 01 January 2009.

Results

In this report outcome measures from the Interim Analysis 2 (IA2) are presented unless otherwise specified. These include:

- Analysis of baseline and post-treatment period up to 2 years for Kalydeco Cohort (follow-up through the end of 2018).
- Supplemental analysis of Historical Cohort not previously reported in IA1, i.e., analyses of ppFVC, height, and height-for-age z-score.

In the IA1 report data were presented on the following:

- baseline demographic and clinical characteristics of the Kalydeco Cohort;
- evaluations of up to 36 months of pre-treatment outcomes data and up to 12 months of post-treatment safety and effectiveness data in the Kalydeco Cohort.
- evaluations of up to 36 months of outcomes data in the Historical Cohort to provide additional context for future analyses.

Participants flow

Kalydeco cohort

There were 368 *R117H* patients with a record of Kalydeco initiation between 01 January 2015 and 31 December 2016.

The table below present patients included per age category as of December 2016, December 2017 and December 2018. (Table 24).

Table 24 Kalydeco Cohort

Kalydeco Cohort (a)	N
All Patients as of December 31, 2016	368
2-<6 years	65
6–<18 years	107
18+ years	196
All Patients as of December 31, 2017	270
2-<6 years	58
6–<18 years	87
18+ years	125
All Patients as of December 31, 2018	235
2-<6 years	53
6–<18 years	83
18+ years	99

Baseline data

Paediatric subjects

Table 25 summarizes key baseline demographic and clinical characteristics of paediatric Kalydeco Cohort patients by age subgroup as provided in the IA1. The exact number of paediatric subjects does not exactly coincide with that of IA2 (i.e., 107 paediatric patients aged ≥ 6 to less than 18 years of age and 65 patients ≥ 2 to less than 6 years) in which no baseline data were discussed with a few exceptions.

Table 25 Demographic and Clinical Characteristics of Paediatric Patients at Kalydeco Initiation (Interim Analysis 1)

Characteristic	Patients ≥6 to <18 Years of Age (N = 109)	Patients ≥2 to <6 Years of Age (N = 64)
Sex, n (%)		
Male	55 (50.5)	43 (67.2)
Female	54 (49.5)	21 (32.8)
Age at index (years)		
Mean (SD)	11.1 (3.4)	3.9 (1.1)
Age at CF diagnosis (years)		
Mean (SD)	2.9 (4.0)	0.4 (0.9)
Race, n (%)		
White Non-Hispanic	106 (97.2)	62 (96.9)
Other	3 (2.8)	2 (3.1)
Poly-T status, n (%)		
5T	16 (14.7)	13 (20.3)
7T	16 (14.7)	19 (29.7)
9T	2 (1.8)	1 (1.6)
Not 5T	1 (0.9)	4 (6.3)
Unknown	74 (67.9)	27 (42.2)
Weight-for-age z-score		
n	104	62
Mean (SD)	0.4 (1.0)	0.4 (1.0)
BMI-for-age z-score		
n	103	62
Mean (SD)	0.5 (1.0)	0.5 (1.0)
ppFEV$_1$[a]		
n	97	--
Mean (SD)	99.3 (13.7)	--
ppFEV$_1$ severity, n (%)		
Missing[b]	12 (11.0)	64 (100)
<70%	2 (1.8)	--
70% to 90%	17 (15.6)	--
>90%	78 (71.6)	--

Sources: Table 2.0 and Table 2.1

Note: Demographic and clinical characteristics were summarized at the index date. If the index date was not known, data from the last encounter visit up to 31 days before Kalydeco use were used.

[a] GLI equations[20] were used to determine ppFEV$_1$.

[b] ppFEV$_1$ values were not available for patients <6 years of age.

Mean BMI-for-age z-score in patients ≥6 to <18 years of age (0.5) and patients ≥2 to <6 years of age (0.5) were considered normal, which is not unexpected for this residual function CF patient population. Similarly, ppFEV1 in patients ≥6 to <18 years of age was well preserved at baseline (mean [SD] = 99.3 [13.7]). Most patients had unknown poly-T status, precluding any subgroup analyses being conducted by this characteristic.

Table 26 summarise ivacaftor exposure data in paediatric patients of the Kalydeco cohort. Among paediatric patients ≥6 to <18 years of age, the mean (SD) duration of Kalydeco exposure was 27.30 (9.95) months; the majority (77.6%) had at least 24 months of exposure; 17.8% had a record of Kalydeco discontinuation. In the 12 months immediately preceding Kalydeco treatment initiation, patients ≥6 to <18 years of age had an average of 3.7 visits per year and 49.5% of patients had ≥4 visits per year; in the second year after Kalydeco initiation, 36 patients (41.4%) had ≥2 to <4 visits and 48 (55.2%) had ≥ 4 visits per year.

Similarly, among paediatric patients ≥2 to <6 years of age, the majority (83%) had at least 24 months of Kalydeco exposure with only 8 (12.3%) patients having a record of treatment discontinuation. In the 12 months immediately preceding treatment initiation, patients ≥2 to <6 years of age had an average of 4.0 visits per year and 60.9% of patients had ≥4 visits per year; in the second year after Kalydeco initiation, 25 patients (43.9%) had ≥2 to <4 visits and 32 (56.1%) had ≥ 4 visits per year.

Patients in the Kalydeco Cohort were followed from their first record of Kalydeco treatment in the CFFPR until they discontinue Kalydeco treatment (i.e. no record of Kalydeco use in the registry), die, or are lost to follow-up, whichever occurs first. Among paediatric patients aged ≥6 to less than 18 years, 17.8% had a record of treatment discontinuation, a patient had a record of therapy with other CFTR modulator, and 4 were lost to follow-up. These figures for children aged ≥2 to less than 6 years were 12.3%, 1.5%, 4.6%. In addition, a patient in this age group died.

Table 26 Exposure to Kalydeco Among Paediatric Patients (Interim Analysis 2)

Exposure Summary	Patients ≥6 to <18 Years of Age (N = 107)	Patients ≥2 to <6 Years of Age (N = 65)
Exposure duration, months[a]		
Mean (SD)	27.30 (9.95)	28.49 (13.18)
Exposure duration, n (%)		
<6 months	12 (11.2)	6 (9.2)
≥6 to <12 months	8 (7.5)	1 (1.5)
≥12 to <24 months	4 (3.7)	4 (6.2)
≥24 to <36 months	72 (67.3)	48 (73.8)
36 months	11 (10.3)	6 (9.2)
Change in exposure record following initiation, n (%)		
Treatment discontinuation record in the registry[b]	19 (17.8)	8 (12.3)
Record of other modulator therapy	1 (0.9)	1 (1.5)
Patient lost to follow-up[c]	4 (3.7)	3 (4.6)
Patient died	0	1 (1.5)

Source: Study 122 IA2 CFF Tables/Table 1.1
n: size of subsample; N: total sample size
[a] Exposure duration as of 31 December 2018.
[b] Treatment discontinuations were defined as having no record of Kalydeco use at last encounter in the registry.
[c] Lost to follow-up included patients who had no record of data in the registry for 1 year or more as of 31 December 2018.

Adult subjects

Key baseline demographic and clinical characteristics of adult Kalydeco Cohort patients and the overall Kalydeco-treated population as provided in the IA1 are summarised in table below.

Table 27 Demographic and Clinical Characteristics of Adult Patients and Overall Population at Kalydeco Initiation

Characteristic	Patients ≥18 Years of Age (N = 196)	All Patients (N = 369)
Sex, n (%)		
Male	83 (42.3)	181 (49.1)
Female	113 (57.7)	188 (50.9)
Age at index (years)		
Mean (SD)	42.9 (14.2)	26.8 (20.3)
Age at CF diagnosis (years)		
Mean (SD)	25.3 (19.5)	14.4 (18.5)
Race, n (%)		
White Non-Hispanic	190 (96.9)	358 (97.0)
Other	6 (3.1)	11 (3.0)
Poly-T status, n (%)		
5T	23 (11.7)	52 (14.1)
7T	11 (5.6)	46 (12.5)
9T	1 (0.5)	4 (1.1)
Not 5T	2 (1.0)	7 (1.9)
Unknown	159 (81.1)	260 (70.5)
Weight (kg)		
n	187	353
Mean (SD)	76.5 (19.6)	56.3 (29.0)
BMI (kg/m^2)		
n	183	348
Mean (SD)	26.5 (5.9)	22.7 (6.4)
ppFEV$_1$[a]		
n	181	278
Mean (SD)	70.8 (24.6)	80.7 (25.3)
ppFEV$_1$ severity, n (%)		
Missing	15 (7.7)	91 (24.7)
<70	87 (44.4)	89 (24.1)
70 to 90	47 (24.0)	64 (17.3)
>90	47 (24.0)	125 (33.9)

Sources: Table 2.0 and Table 2.1

Note: Demographic and clinical characteristics were summarized at the index date. If the index date was not known, data from the last encounter visit up to 31 days before Kalydeco use were used.

[a] GLI equations[20] were used to determine ppFEV$_1$.

Among adult patients in the Kalydeco Cohort, mean BMI (kg/m^2) at baseline was 26.5 kg/m^2, slightly above the World Health Organization's (WHO) threshold of 25 kg/m^2 for normal weight. In the overall Kalydeco Cohort, mean BMI (kg/m^2) at baseline was 22.7 kg/m^2, which was well within the WHO normal weight range; this is not unexpected for this patient population with residual CFTR function.

At baseline, the mean (SD) ppFEV1 in adults was 70.8 (24.6) percentage points, which was lower than the baseline ppFEV1 observed in paediatric patients and consistent with the progressive nature of CF disease. Lung function in the overall Kalydeco Cohort with non-missing values at baseline was similar to that observed for adults, with a mean (SD) ppFEV1 of 80.7 (25.3) pp.

The mean (SD) duration of Kalydeco exposure in adult patients was 20.25 (11.79) months. The majority (52%) of adult patients had at least 24 months of Kalydeco exposure. Among adult patients, there were 24.5% (48 patients) with a record of ivacaftor discontinuation in the registry, 2.6% (5 patients) had a record of other modulator therapy, 22.4% (44 patients) were lost to follow-up, and 1.0% (2 patients) die.

In the 12 months immediately before Kalydeco treatment initiation, adult patients had an average of 3.3 visits per year with 35.3% having 4 or more visits per year; in the second year after Kalydeco initiation, 50 patients (40.7%) had ≥2 to <4 visits and 53 (43.1%) had ≥ 4 visits per year.

Historical cohort

At the start of data collection in January 1, 2009 there were 509 (as compared to 518 reported in the Interim Analysis 1) Kalydeco-naïve patients with an *R117H* mutation in the (unmatched) Historical Cohort, including 282 adult and 227 paediatric patients, of whom 128 were ≥6 to <18 years of age.

Table 28 summarizes key demographic and clinical characteristics of the unmatched Historical Cohort patients overall and by age subgroup as provided in the Interim Analysis 1 (note the slight difference in the number of patients).

Table 28 Historical Cohort: Demographic and Clinical Characteristics in 2009 (Interim Analysis 1)

Characteristic	Patients ≥2 to <6 Years of Age (N = 97)	Patients ≥6 to <18 Years of Age (N = 134)	Patients ≥18 Years of Age (N = 287)	All Historical Patients (N = 518)
Sex, n (%)				
Male	53 (54.6)	70 (52.2)	138 (48.1)	261 (50.4)
Female	44 (45.4)	64 (47.8)	149 (51.9)	257 (49.6)
Age at year start (years)				
Mean (SD)	3.8 (1.2)	10.9 (3.5)	37.7 (13.3)	24.4 (18.0)
Age at CF diagnosis (years)				
Mean (SD)	0.6 (1.1)	3.9 (4.3)	23.4 (17.4)	14.1 (16.8)
Race, n (%)				
White Non-Hispanic	93 (95.9)	131 (97.8)	274 (95.5)	498 (96.1)
Other	4 (4.1)	3 (2.2)	13 (4.5)	20 (3.9)
Poly-T status, n (%)				
5T	7 (7.2)	6 (4.5)	19 (6.6)	32 (6.2)
7T	15 (15.5)	14 (10.4)	9 (3.1)	38 (7.3)
9T	1 (1.0)	2 (1.5)	2 (0.7)	5 (1.0)
Not 5T	0	2 (1.5)	1 (0.3)	3 (0.6)
Unknown	74 (76.3)	110 (82.1)	256 (89.2)	440 (84.9)
Weight-for-age z-score				
n	93	126	--	--
Mean (SD)	0.5 (0.9)	0.5 (1.1)	--	--
BMI-for-age z-score				
N	93	125	--	--
Mean (SD)	0.1 (1.0)	0.5 (1.0)	--	--
Weight (kg)				
n	93	126	249	468
Mean (SD)	17.4 (3.9)	43.5 (20.8)	74.7 (17.7)	55.0 (28.5)
BMI (kg/m^2)				
n	93	125	249	467
Mean (SD)	16.1 (1.5)	19.9 (5.2)	25.5 (5.7)	22.1 (6.3)
ppFEV$_1$[a]				
n	--	120	239	359
Mean (SD)	--	96.2 (12.5)	74.2 (23.8)	81.5 (23.1)
ppFEV$_1$ severity, n (%)				
Missing[b]	97 (100)	14 (10.4)	48 (16.7)	159 (30.7)
<70	--	3 (2.2)	102 (35.5)	105 (20.3)
70 to 90	--	32 (23.9%)	69 (24.0)	101 (19.5)
>90	--	85 (63.4)	68 (23.7)	153 (29.5)

Sources: Table 14.1, Table 14.3

Note: Demographic and clinical characteristics were summarized at the index date. If the index date was not known, data from the last encounter visit up to 31 days before Kalydeco use were used.

[a] GLI equations[20] were used to determine ppFEV$_1$.

[b] ppFEV$_1$ values were not available for patients <6 years of age.

At the beginning of follow-up (i.e., 2009) for paediatric Historical Cohort patients, mean BMI-for-age z-scores in patients ≥6 to <18 and ≥2 to <6 years of age were within 0.5 SD of the referent CDC population, indicating normal BMI in these patients. Lung function was well preserved at the beginning of follow-up among patients ≥6 to <18 years; the mean (SD) ppFEV1 was 96.2 (12.5) percentage points.

The mean BMI in both adults and in the overall Historical Cohort population were normal. Mean ppFEV1 was 74.2% in adults and 82.7% in the overall population.

In the Paediatric Historical Cohort patients ≥6 to <18 years of age had a mean (SD) of 3.4 (2.1) clinic visits per year; only 34.3% of patients in this age group had the recommended ≥4 clinic visits per year. Similarly, Historical Cohort patients ≥2 to <6 years of age had a mean (SD) of 3.5 (2.0) visits per year, and only 36.1% of patients in this younger age group had an average of ≥4 visits per year. Adult patients in the Historical Cohort had a mean (SD) of 3.3 (2.3) clinic visits per year with only 25.8% having the recommended number of yearly visits (i.e., quarterly). In the overall population, patients had a mean (SD) of 3.4 (2.2) visits per year, and only 29.9% had the recommended number of yearly clinic visits.

Table 29 shows the demographic and disease characteristics of paediatric patients in the Kalydeco cohort at the index date (i.e., at the time of treatment initiation) and Table 30 shows data in the matched Historical cohort at the beginning of the follow-up period in January 2009. The matched historical cohort consisted of patients with CF, with at least 1 allele of the *R117H-CFTR* mutation, in the CFF Patient Registry as of 01 January 2009, with no evidence of any prior Kalydeco exposure, matched to Kalydeco Cohort patients on age, gender, and lung function.

Table 29 Demographic and Disease Characteristics of Paediatric Subjects in the Kalydeco cohort at Index (treatment initiation)

Kalydeco Cohort		
	≥6 - <18 (N = 109)	≥2 - <6 (N =64)
Demographic Characteristics		
Sex, n (%)		
Male	55 (50.5)	43 (67.2)
Female	54 (49.5)	21 (32.8)
Age at Index		
N	109	64
Mean (SD)	11.1 (3.4)	3.9 (1.1)
Median	10	4
Min, Max	6.0,17.9	2.0, 5.9
Age at CF diagnosis		
N	109	64
Mean (SD)	2.9 (4.0)	0.4 (0.9)
Median	1	0
Min, Max	-0.4, 16.8	0.0, 3.6
Race, n (%)		
White Non-Hispanic	106 (97.2)	62 (96.9)
Other	3 (2.8)	2 (3.1)
Poly-T Status, n (%)		
5T	16 (14.7)	13 (20.3)
7T	16 (14.7)	19 (29.7)
9T	2 (1.8)	1 (1.6)
Not 5T	1 (0.9)	4 (6.3)
Unknown	74 (67.9)	27 (42.2)
Clinical Characteristics		

Kalydeco Cohort		
Weight (kg)		
N	104	62
Mean (SD)	43.3 (18.4)	17.3 (3.6)
Median	39	17
Min, Max	18.6, 100.9	11.2, 26.6
Weight-for-age z-score		
N	104	62
Mean (SD)	0.4 (1.0)	0.4 (1.0)
Median	0	0
Min, Max	-1.4, 3.1	-1.7, 3.8
BMI (kg/m2)		
N	103	62
Mean (SD)	19.8 (4.4)	16.5 (1.6)
Median	19	16
Min, Max	14.3, 34.9	13.9, 22.9
BMI-for-age z-score		
N	103	62
Mean (SD)	0.5 (1.0)	0.5 (1.0)
Median	0	0
Min, Max	-1.9, 2.6	-1.9, 3.8
ppFEV1		
N	97	
Mean (SD)	99.3 (13.7)	
Median	98	
Min, Max	68.0, 142.4	
ppFEV1 severity, n (%)		
Missing	12 (11.0)	64 (100)
<70%	2 (1.8)	
70% to 90%	17 (15.6)	
>90%	78 (71.6)	

Table 30 Demographic and Disease Characteristics of Paediatric Subjects in the Matched Historical Cohort at Start of Data Collection on 01 January 2009

Matched Historical Cohort		
	≥6 - <18 (N=113)	≥2 - <6 (N=101)
Demographic Characteristics		
Sex, n (%)		
Male	56 (49.6)	63 (62.4)
Female	57 (50.4)	38 (37.6)
Age at Index		
N	113	101
Mean (SD)	10.8 (3.5)	3.4 (1.4)
Median	10	3
Min, Max	6.1, 17.9	1.1, 6.0
Age at CF diagnosis		
N	113	101
Mean (SD)	3.8 (4.2)	0.5 (0.9)
Median	2	0
Min, Max	-0.4, 14.9	-0.4, 4.0
Race, n (%)		
White Non-Hispanic	110 (97.3)	96 (95.0)
Other	3 (2.7)	5 (5.0)
Poly-T Status, n (%)		
5T	6 (5.3)	10 (9.9)
7T	12 (10.6)	19 (18.8)
9T	1 (0.9)	0

Not 5T	0	0
Unknown	94 (83.2)	72 (71.3)
Clinical Characteristics		
Weight (kg)		
N	112	101
Mean (SD)	43.3 (20.8)	16.7 (4.1)
Median	37	16
Min, Max	17.6, 131.8	9.5, 38.8
Weight-for-age z-score		
N	112	84
Mean (SD)	0.5 (1.1)	0.5 (0.9)
Median	0	1
Min, Max	-1.7, 3.2	-2.1, 3.3
BMI (kg/m2)		
N	112	101
Mean (SD)	19.8 (5.1)	16.2 (1.5)
Median	19	16
Min, Max	13.1, 41.9	12.8, 21.4
BMI-for-age z-score		
N	112	84
Mean (SD)	0.5 (1.0)	0.2 (1.0)
Median	0	0
Min, Max	-2.0, 2.8	-3.0, 2.5
ppFEV1		
N	110	
Mean (SD)	97.0 (11.2)	
Median	97	
Min, Max	70.7, 126.0	
ppFEV1 severity, n (%)		
Missing	3 (2.7)	101 (100)
<70%	0	
70% to 90%	31 (27.4)	
>90%	79 (69.9)	

Outcomes and estimation

- **Lung function**

Percent predicted FEV1 and ppFVC data are not available for patients ≥2 to <6 years of age because spirometry is not widely performed on patients before the age of 6 years.

Kalydeco cohort

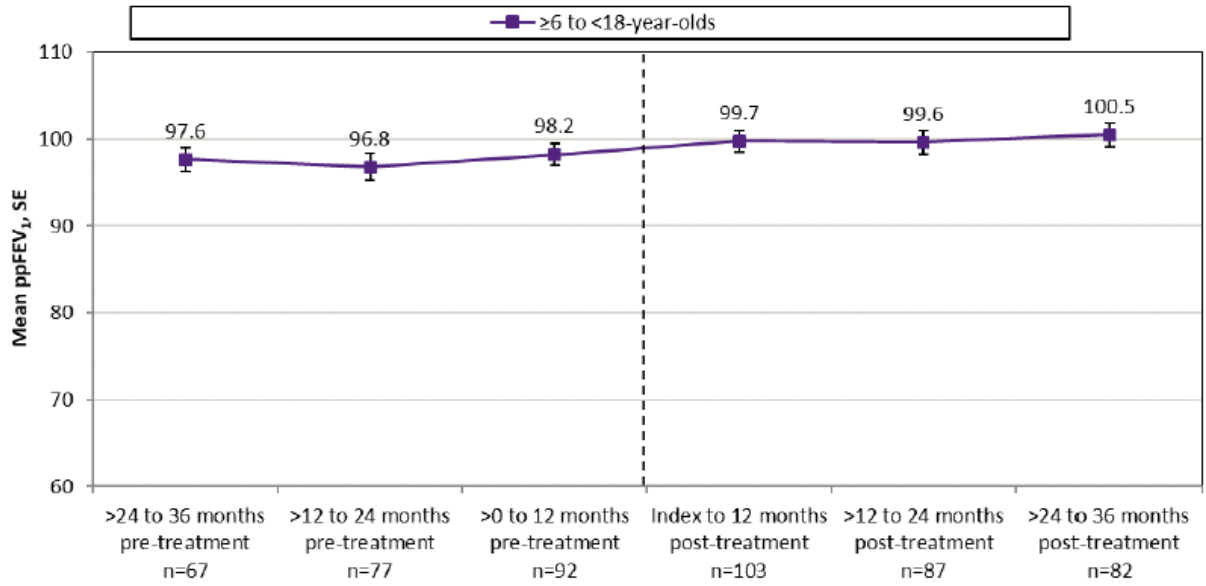
- ppFEV1 results

Patients ≥6 to <18 years:

Figure 18 summarizes ppFEV1 over time in Kalydeco-treated paediatric patients ≥6 to <18 years of age. Among patients ≥6 to <18 years of age, 92 (out of the 107 in the cohort) had non-missing ppFEV1 data available in the year preceding treatment with Kalydeco. In the second-year post-treatment, ppFEV1 values were available for 87 children.

In the 36 months before Kalydeco initiation, ppFEV1 was relatively stable with a mean of 98.2 percentage points in the 12 months immediately before treatment initiation. In the 36 months following Kalydeco treatment initiation, mean ppFEV1 increased slightly and remained above the pre-treatment baseline.

Figure 18 Kalydeco Cohort Patients ≥6 to <18 Years of Age: Change in ppFEV1 Over Time, 36 Months Before and 36 Months After Kalydeco Treatment Initiation (Interim Analysis 2)



Source: Study 122 IA2 CFF Tables/Table 4.0
n: size of subsample; $ppFEV_1$: percent predicted forced expiratory volume in 1 second
Note: The dotted line indicates the initiation of Kalydeco treatment.

Mean ppFEV1 (percentage points) numerically increased from pre-treatment baseline during the first 12 months of Kalydeco treatment (mean [SD]:1.1 [7.2]; this increase was maintained in the second (mean [SD]: 0.5 [9.1]), and third (mean [SD]: 1.0 [9.1]) 12-month intervals after treatment initiation, among patients who had available data in the respective intervals.

Adult patients:

In adult subjects (n=196), in the 36 months before Kalydeco treatment initiation, ppFEV1 was relatively stable with a mean (SD) of 69.2 (23.7) percentage points in the 12 months immediately before treatment initiation (n=170). Following Kalydeco treatment, ppFEV1 slightly increased to 71.9 (23.5) in the first year post-treatment (n=188), to 72.2 (23.2) pp in the second year (n=120), and to 71.3 (23.5) percentage points in the third year post-treatment initiation (n=95). The mean (SD) absolute change from the index date to the >12 to 24-month interval post treatment initiation was 2.3 (9.7) percentage points based on data from 109 adult subjects.

Ad-hoc analysis with non-missing ppFEV1 data in paediatric patients aged ≥ 6 years to less than 18 years:

Within the IA1 (05 December 2017), the MAH presented the results of an ad-hoc analysis which was confined to subjects in the Kalydeco cohort with non-missing ppFEV1 data in all three pre-treatment intervals and first year post-treatment interval. Among the 71 (out of 109) paediatric patients aged ≥ 6 years to less than 18 years, the mean (SD) ppFEV1 was 97.0 (12.1) pp in the year preceding treatment initiation. In the 12 months after treatment initiation, the mean ppFEV1 increased to 99.6 (12.6) pp. Among the 110 (out of 196) adult subjects with non-missing data, mean (SD) ppFEV1 in the year preceding treatment with Kalydeco was 66.7 (24.4) pp which increased to 68.1 (23.8) pp in the year following treatment initiation.

- ppFVC results

Patients ≥6 to <18 years:

In terms of percent predicted Forced Vital Capacity (ppFVC), in patients ≥6 to <18 years of age with data available in the 12-month interval preceding treatment initiation (92 out of the 107) the mean (SD) ppFVC was 101.7 (11.9) pp. In the second-year post-treatment this value was 102.3 (12.7) (n=87). The mean (SD) absolute change from the index date value (102.57 pp, n=91) to the first 12-month interval post-treatment was 0.96 (5.7) pp. The change from the index date to the second 12-month interval post-treatment (n=80) was 0.01 (7.1) pp. For the 75 patients with data available, the change from the index date to the third 12-month interval post-treatment was 1.01 (9.10) pp.

Adult patients:

In the group of adult subjects, the mean (SD) absolute change in ppFVC from the value at the index date (82.14 [19.83], n=149 out of the 196 in this age group) to the first (n=149), second (n=109) and third (n=86) year post-treatment was 1.2 (7.9), 1.8 (9.5), and 1.3 (10.6) pp respectively.

Historical cohort

- ppFEV1 results

Patients ≥6 to <18 years:

In the Unmatched Historical cohort, among the 120 (out of the 134 in this age group in IA1) patients aged ≥6 to <18 years, mean (SD) ppFEV1 was 95.7 (12.4) pp in the first year of follow-up. During the last year of follow-up (2011), mean (SD) ppFEV1 was 95.4 (12.9) pp (n=105). In adult patients, these figures were 73.3 (24.1) and 72.0 (23.9) pp in these two periods of time based on a number of patients of 246 and 201 respectively out of the 287 in the adult group.

- ppFVC results

Patients ≥6 to <18 years:

Regarding ppFVC, in patients ≥6 to <18 years of age the mean (SD) ppFVC was 101.1 (12.7) pp at the beginning of the follow-up in 2009 (n=118 out of the 128 in this age group). At the end of the follow-up in 2011 (n=102/128), the mean (SD) pp FVC was 99.4 (11.8) pp. In the adult group these values were 83.1 (20.1) pp based on data from 242 patients out of the 282 in this age group and 81.7 (19.5) pp at the end of the follow-up period in 2011 (n=191/282).

Within IA1, the MAH provided descriptive statistics for the observed values of ppFEV1 in each 12-month interval of follow-up for the Matched Historical cohort. Among 110 (out of 113) patients aged ≥6 to <18 years with available data, mean (SD) ppFEV1 was 96.5 (11.2) pp in the first year of follow-up. During the last year of follow-up (2011), mean (SD) ppFEV1 was 96.2 (11.4) pp (n=93). In adult patients, these figures were 75.2 (23.8) and 75.2 (23.3) pp in these two periods of time based on a number of patients of 180 and 134 respectively out of the 187 in the adult group.

Table 31 summarises descriptive statistics for ppFEV1 in paediatric patients of the Kalydeco Cohort, ppFEV1 values shown in the first two rows correspond to those of the Interim Analysis 2 and, highlighted in red, data corresponding to subjects with non-missing data pre-treatment and during the first 12-month interval post-treatment (ad-hoc analysis of Interim Analysis 1). Table 32 summarises data for the Matched Historical Control, obtained from the Interim Analysis 1.

Table 31 Descriptive Statistics for ppFEV1 in paediatric patients aged ≥6 to less than 18 years in the Kalydeco cohort (IA1 data presented in red and IA2 results in black)

Kalydeco Cohort	
	≥6 - <18 y.o. (N=107 / 109) Primary Full Analysis Set
ppFEV1 Index Value	
N	91 / 71
Mean (SD)	99.0 (12.9) / 97.0 (12.1)
Median	98.0 / 96
Min, Max	68.5, 142.2 / 73.9, 142.1
ppFEV1 in interval > 0 to 12 months post-treatment	
N	103 / 71
Mean (SD)	99.7 (12.5) / 99.6 (12.6)
Median	100.3 / 99
Min, Max	71.4, 141.3 / 72.2, 141.0
ppFEV1 in interval >12 to 24 months post-treatment	
N	87
Mean (SD)	99.6 (12.5)
Median	99.6
Min, Max	71.1, 134.6
Absolute change from index date to 12 months post-treatment initiation	
N	91
Mean (SD)	1.13 (7.22)
Median	1.10
Min, Max	-24.7, 23.8
Absolute change from index date to >12 to 24 months post treatment Initiation	
N	80
Mean (SD)	0.48 (9.06)
Median	0.7
Min, Max	-26.9, 22.1
Absolute Change from Index Date to >24 to 36 Months Post Treatment Initiation	
N	75
Mean (SD)	1.01 (9.10)
Median	1.01
Min, Max	-18.0, 21.4

Table 32 Descriptive Statistics for ppFEV1 in paediatric patients aged ≥6 to less than 18 years in the Matched Historical cohort from IA1.

	Matched Historical Cohort
	≥6 - <18 y.o. (N=113)
January 1, 2009 to December 31, 2009	
N	110
Mean (SD)	96.5 (11.2)
Median	97
Min, Max	67.5, 126.0
January 1, 2010 to December 31, 2010	
N	102
Mean (SD)	96.6 (12.1)
Median	97
Min, Max	57.2, 134.0
January 1, 2011 to December 31, 2011	
N	93
Mean (SD)	96.2 (11.4)
Median	97
Min, Max	61.0, 120.9

- **Pulmonary Exacerbations and Hospitalizations**

Pulmonary exacerbations (PEx) are defined as intravenous (IV) antibiotic use at home or in the hospital; PEx requiring hospitalization represent a subset of PEx as above defined.

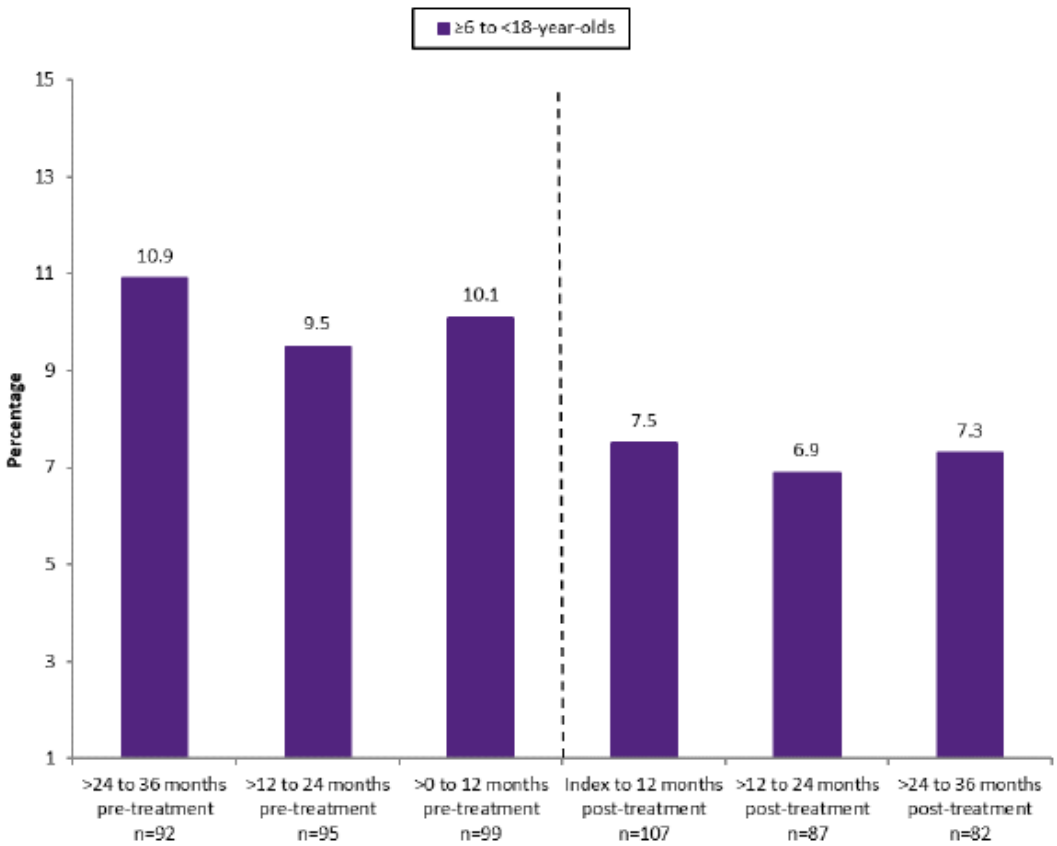
Kalydeco cohort

Patients ≥6 to <18 years:

In the 36 months before Kalydeco treatment initiation, the annual proportion of patients ≥6 to <18 years of age experiencing at least 1 PEx was relatively stable (Figure 19).

In each of the 12-month intervals after Kalydeco treatment initiation, the proportion of patients with at least 1 PEx was numerically lower than in the period before treatment initiation. Statistical comparisons between the proportion of patients with at least 1 PEx in the 12-month interval immediately preceding treatment initiation and each 12-month post-treatment interval are presented in Table 33; these comparisons are based on the subgroups of patients with non-missing data in both intervals of interest.

Figure 19 Kalydeco Cohort Patients ≥6 to <18 Years of Age: Proportion of Patients with ≥1 PEx by 12-month Interval During the 36 Months Before and 36 Months After Treatment Initiation (Analysis Interim 2)



Source: Study 122 IA2 CFF Tables/Table 5.0
n: size of subsample; PEx: pulmonary exacerbation
Note: The dotted line indicates the initiation of Kalydeco treatment.

Table 33 Kalydeco Cohort Patients ≥6 to <18 Years of Age: Statistical Comparisons of the Proportion of Patients With ≥1 PEx or Hospitalization in the 12 Months Before Kalydeco Treatment Initiation and Each 12-month Post-treatment Interval (Analysis interim 2)

	PEx	Hospitalizations
Number of patients with non-missing data in the 12 months before treatment and first 12-month post-treatment intervals	99	99
Number of patients with ≥1 event in 12 months before treatment, n (%)	10 (10.1)	16 (16.2)
Number of patients with ≥1 event in first 12 months after treatment, n (%)	8 (8.1)	13 (13.1)
P value	0.59	0.44
Number of patients with non-missing data in the 12 months before treatment and second 12-month post-treatment intervals	82	82
Number of patients with ≥1 event in 12 months before treatment, n (%)	8 (9.8)	14 (17.1)
Number of patients with ≥1 event in second 12 months after treatment, n (%)	6 (7.3)	8 (9.8)
P value	0.56	0.13
Number of patients with non-missing data in the 12 months before treatment and third 12-month post-treatment intervals	78	78
Number of patients with ≥1 event in 12 months before treatment, n (%)	7 (9.0)	13 (16.7)
Number of patients with ≥1 event in third 12 months after treatment, n (%)	6 (7.7)	8 (10.3)

Source: Study 122 IA2 CFF Tables/Table 5.1 and Table 13.1
n: size of subsample; PEx: pulmonary exacerbation
Note: Statistical testing was not performed for the third 12-month post-treatment interval, as not all patients had accrued the full 36 months of follow-up as of 31 December 2018.

Within the IA1, in the subset of patients with non-missing data both in the 12 months pre- and post-treatment initiation (n=101 out of the 109 patients in this age group), there was a numeric decrease in the proportion of patients who had at least 1 PEx in the 12 months after treatment initiation (7.9%, n=8 patients) compared to the 12 months immediately preceding treatment initiation (9.9%, n=10). An ad-hoc analysis restricted to patients with non-missing visits in all three pre-treatment intervals and first post-treatment interval (n=93 out of 109 patients in this age group) showed that in the 12 months immediately before treatment initiation the proportion of patients who had at least a PEx was 8.6% (n=8 patients who experienced 9 events). In the first year after treatment initiation the proportion was the same, i.e. 8.6%, i.e., no reduction was observed. Given that hospitalisation may occur due not only to PEx, the proportion of patients with at least an event of hospitalisation was higher in all periods of time than the proportion of patients with at least an event of PEx. In the year preceding treatment initiation, 16.2% (16/99) patients had at least an event of hospitalisation. This proportion was reduced to 13.1% (n=14 patients) in the first-year post-treatment. Similarly, there was a reduction of hospitalisation during the second-year post-treatment (from 17.1% to 9.8%, based on data available from 82 patients). The ad-hoc analysis provided with the IA1 for PEx requiring hospitalisation (n=93) showed exactly the same results as in the case of PEx (i.e., 8.6% patients had at least an event of this type in the year pre-treatment and in the year post-treatment). The results of the IA2 limited to hospitalisation due to PEx show similar results, i.e., all events of PEx in the age group ≥ 6 to less than 18 years old appear to require hospitalisation.

Patients ≥2 to <6 years:

Among patients ≥2 to <6 years, the proportion of patients with ≥1 PEx in the year immediately before treatment was 10.8% (7 out of the 65 paediatric patients with non-missing data in the time intervals

of interest who experienced 10 events). In the first and second-year post-treatment, this proportion was 4.6% (3 out of the 65 patients who experienced 5 events) and 8.6% (5 out of the 58 paediatric patients with non-missing data who experienced 7 events) respectively. An ad-hoc analysis (provided with the Interim Analysis 1) restricted to patients with non-missing visits in all three pre-treatment intervals and first post-treatment interval (n=52) shows that in the 12 months immediately before treatment initiation the proportion of patients who had at least a PEx was 13.5% (7 patients who experienced 10 PEx). In the first year after treatment initiation the proportion was 5.8% (3 patients who experienced 5 events).

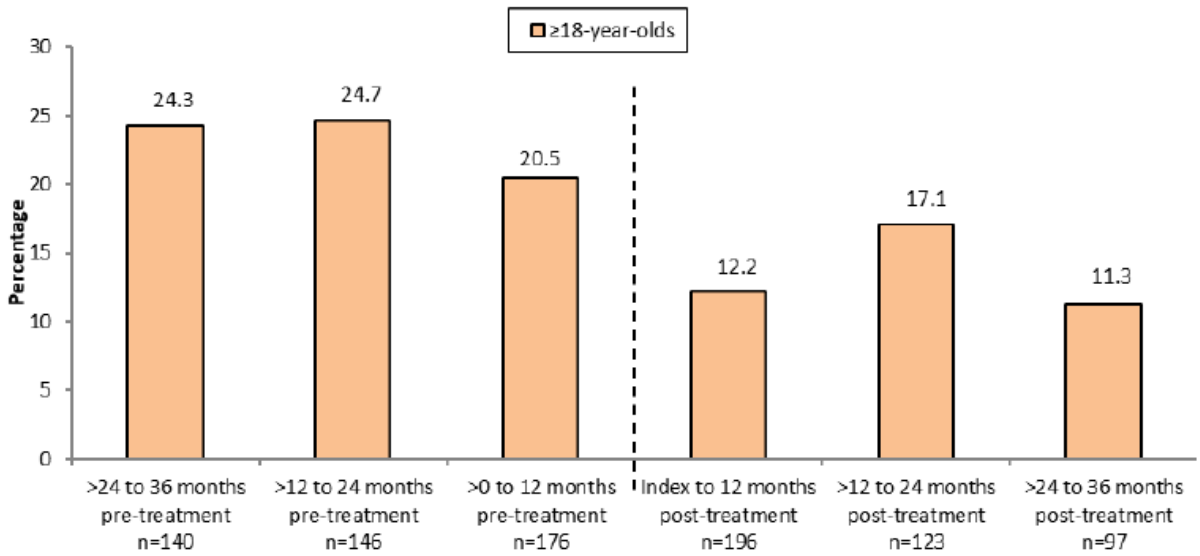
As for hospitalisations, in the year preceding treatment initiation, 15.4% (10 out of the 65 patients with non-missing data who experienced 13 events) had at least an event of hospitalisation. This proportion was reduced to 10.8% (7 patients who experienced 9 events of this type) in the first-year post-treatment. In the second-year post-treatment, 8.6% (5 out of the 58 patients with non-missing data who experienced 7 events) had at least an event of hospitalisation. The ad-hoc analysis provided with the IA1 for PEx requiring hospitalisation (n=52) showed that in the year preceding treatment, the proportion of patients with at least an event of this type was 13.5% (7 patients who experienced 10 events), while in the first year post-treatment initiation this figure was 5.8% (3 patients who experienced 5 events). The results of the IA2 on PEx leading to hospitalisation show similar results, i.e., all events of PEx in the age group ≥2 to less than 6 years old appear to require hospitalisation.

Adults:

In the 36 months before Kalydeco treatment initiation, the annual proportion of adult patients experiencing at least 1 PEx was relatively stable (see Figure 20).

In each 12-month interval after Kalydeco treatment initiation, the proportion of adult patients with at least 1 PEx was numerically lower than in the period before treatment initiation.

Figure 20 Kalydeco Cohort Adult Patients: Proportion of Patients With ≥1 PEx by 12-month Interval During the 36 Months Before and 36 Months After Treatment Initiation



Source: Study 122 IA2 CFF Tables/Table 5.0
n: size of subsample; PEx: pulmonary exacerbation
Note: The dotted line indicates the initiation of Kalydeco treatment.

Among adult patients treated with Kalydeco, there was a numeric decrease in the proportion of patients experiencing at least an event of PEx in the 12 months after treatment was initiated (12.2%,

n=24 subjects out of the 196 with non-missing data) as compared to the 12 months immediately before treatment began (20.5%, n=36 subjects out of the 176 with non-missing data). During the second-year post-treatment initiation, the proportion of adult patients with at least an event of PEx was 17.1% (n=21 subjects out of the 123 with non-missing data). A similar pattern was observed for PEx requiring hospitalizations although in adults not all of these events required hospitalisation.

Regarding hospitalisations of any cause, there was a numeric decrease in the proportion of patients experiencing at least an event of hospitalisation in the 12 months after treatment was initiated (13.8%, n=27 patients out of the 196 with non-missing data) as compared to the 12 months immediately before treatment began (23.3%, n=41 subjects out of the 176 with non-missing data). During the second-year post-treatment initiation, the proportion of adult patients with at least an event of hospitalisation was 18.7% (n=23 subjects out of the 123 with non-missing data). Most events of hospitalisation in adult subjects are due to PEx.

Historical cohort

Unmatched Historical cohort:

At the beginning of the follow up in January 2009 (N=518), the proportion of Unmatched Historical cohort patients who experienced at least an event of PEx was 7.8% (n=10 out of the 129 patients with non-missing data), 20.6% (n=52/252), and 3.2% (n=3/94) in the oldest paediatric group (N=134), adult group (N=282), and the youngest age group (N=97) which corresponds to a total number of events of 11, 89, and 3 respectively. The mean (SD) number of PEx was 0.09 (0.31), 0.35 (0.87), and 0.03 (0.18) respectively. At the end of the follow-up period, in December 2011, these figures were 11.0% (n=12), 19.9% (n=41), and 4.1% (n=3) which corresponds to a total number of events of 15, 52, and 3 respectively. The mean (SD) number of PEx was 0.14 (0.44) 0.25 (0.60) 0.04 (0.20) respectively although based on a reduced number of subjects (due to missing data). After 3 years of follow-up, the percentage of adult subjects who experienced at least a PEx slightly decreased from 20.6% to 19.9% while for the other two groups these figures were from 7.8% to 11.0% (≥ 6 to less than 18 year-old group) and from 3.2% to 4.1% (≥2 to less than 6 year-old group).

Matched Historical cohort:

At the beginning of the follow-up in January 2009, the proportion of Matched Historical cohort patients who experienced at least a PEx was 8 (7.1%), 35 (19.4%), and 3 (3.0%) in the oldest paediatric group, adult group, and the youngest age group respectively which corresponds to a total number of events of 8, 59, and 3. The mean (SD) number of PEx was 0.07 (0.26), 0.32 (0.85), and 0.03 (0.26) respectively. At the end of the follow-up period, in December 2011, these figures were 0.11 (0.34), 0.21 (0.57), and 0.04 (0.19) although based on a reduced number of subjects (due to missing data). After 3 years of follow-up, the percentage of adult subjects who experienced at least a PEx decreased from 19.4% to 16.9% while for the other two groups these figures were from 7.1% to 9.6% (≥ 6 to less than 18 year-old group) and from 3.0% to 3.7% (≥2 to less than 6 year-old group). Descriptive statistics for Unmatched Historical cohort:

Descriptive statistics for number of PEx requiring hospitalization are only provided for the unmatched Historical cohort (IA1 report) for 475 patients out of the 518 in the cohort distributed as follows in the first period of the follow-up (2009): 129 in the oldest paediatric group, 252 adults, and 94 in the youngest group. The mean (SD) number of these events was 0.08 (0.30), 0.29 (0.78), and 0.03 (0.18) respectively which corresponds to 9 (7.0%), 44 (17.5%), and 3 (3.2%) patients having at least one of these events with a total number of events of 10, 73, and 3. In 2011, the number of subjects with available data was 389 (109, 206, and 74 patients respectively). The mean (SD) number of events was 0.14 (0.44), 0.17 (0.40), and 0.04 (0.20) with 12 (11.0%), 33 (16.0%), and 3 (4.1%) patients having at least one of the event of interest. The number of events was 15, 35, and 3

respectively. The results after 3 years of follow-up are somehow unexpected for the adult group in which the percentage of patients with PEx leading to hospitalisation decreased from 17.5% (73 events) in 2009 to 16.0% (33 events) in 2011.

Regarding hospitalisation of any cause, the number and percentage of subjects in the Unmatched Historical cohort who had at least an event of this type at the beginning of the follow-up period in 2009 was 16 (12.4%), 61 (24.2%), and 5 (5.3%) which corresponds to a total number of events of 22, 103, and 5 in the oldest paediatric group (n=129 with non-missing data), adult group (n=252), and the youngest age group (n=94) respectively. After three years of follow-up (2011), these figures were 14 (12.8%), 51 (24.8%), and 8 (10.8%) which correspond to a total number of events of 27, 63, and 8 in each of these age groups albeit based on a reduced number of subjects (i.e., 109, 206, and 74 subjects respectively) due to missing data.

Overall, as in the Kalydeco cohort, most PEx in the two paediatric age groups required hospitalisation and most hospitalisations were due to PEx.

Table 34 summarises descriptive statistics for number of subjects who experienced at least an event of PEx and of PEX requiring hospitalisation for the Kalydeco cohort and Table 35 for the matched historical Cohort. For patients in the Kalydeco cohort, results are based on the IA2. For the Historical Control data were obtained from the IA1.

Table 34 Descriptive Statistics for Number of Pulmonary Exacerbations (PEx) and Pulmonary Exacerbations Requiring Hospitalisation

	Kalydeco Cohort	
	≥6 - <18 (N=107) Primary Full Analysis Set	≥2 - <6 (N=65)
Pulmonary exacerbations		
Patients with non-missing data in >0-12month pre- and index to 12month post-treatment, n		
	99	65
Patients who had at least one PEx, n (%)		
>0-12 months pre-treatment	10 (10.1)	7 (10.8)
Index to 12 months post-treatment	8 (8.1)	3 (4.6)
p-value (12-month pre- vs. 12-month post-treatment initiation)	0.593	0.1025
Patients with non-missing data in >0-12month pre- and >12 to 24 month post treatment, n		
	82	58
Patients who had at least one PEx, n (%)		
>0-12 months pre-treatment	8 (9.8)	7 (12.1)
>12 to 24 months post-treatment	6 (7.3)	5 (8.6)
p-value (12-month pre- vs. >12 to 24 month post-treatment initiation)	0.5637	0.4795
Patients with non-missing data in >0-12 month pre- and >24 to 36 month post treatment, n		
	78	51
Patients who had at least one PEx, n (%)		
>0-12 months pre-treatment	7 (9.0)	5 (9.8)
>24 to 36 months post-treatment	6 (7.7)	5 (9.8)
Pulmonary exacerbations Requiring Hospitalization		

Patients with non-missing data in >0-12 month pre-and index to 12 month post-treatment, n		
	99	65
Patients who had at least one event, n (%)		
>0-12 months pre-treatment	10 (10.1)	7 (10.8)
Index to 12 months post-treatment	8 (8.1)	3 (4.6)
p-value (12-month pre- vs. 12-month post-treatment initiation)	0.593	0.1025
Patients with non-missing data in >0-12 month pre- and >12 to 24 month post treatment, n		
	82	58
Patients who had at least one event, n (%)		
>0-12 months pre-treatment	8 (9.8)	7 (12.1)
>12 to 24 months post-treatment	6 (7.3)	5 (8.6)
p-value (12-month pre- vs. >12 to 24 month post-treatment initiation)	0.5637	0.4795
Patients with non-missing data in >0-12 month pre- and >24 to 36 month post treatment, n		
	78	51
Patients who had at least one event, n (%)		
>0-12 months pre-treatment	7 (9.0)	5 (9.8)
>24 to 36 months post-treatment	6 (7.7)	5 (9.8)

Table 35 Descriptive Statistics for Number of Pulmonary Exacerbations (PEx) and Pulmonary Exacerbations Requiring Hospitalisation

	Matched Historical Cohort	
	≥6 - <18 (N=113)	≥2 - <6 (N=101)
Pulmonary exacerbations		
	January 1, 2009 to December 31, 2009	
n	94	82
Patients who had at least one PEx, n (%)	9 (9.6)	3 (3.7)
	January 1, 2010 to December 31, 2010	
n	119	83
Patients who had at least one PEx, n (%)	8 (6.7)	2 (2.4)
	January 1, 2011 to December 31, 2011	
n	109	74
Patients who had at least one PEx, n (%)	12 (11.0)	3 (4.1)
Pulmonary exacerbations Requiring Hospitalization		
	January 1, 2009 to December 31, 2009	
n	129	94
Patients who had at least one event, n (%)	9 (7.0)	3 (3.2)
	January 1, 2010 to December 31, 2010	

n	119	83
Patients who had at least one event, n (%)	8 (6.7)	2 (2.4)
	January 1, 2011 to December 31, 2011	
n	109	74
Patients who had at least one event, n (%)	12 (11.0)	3 (4.1)

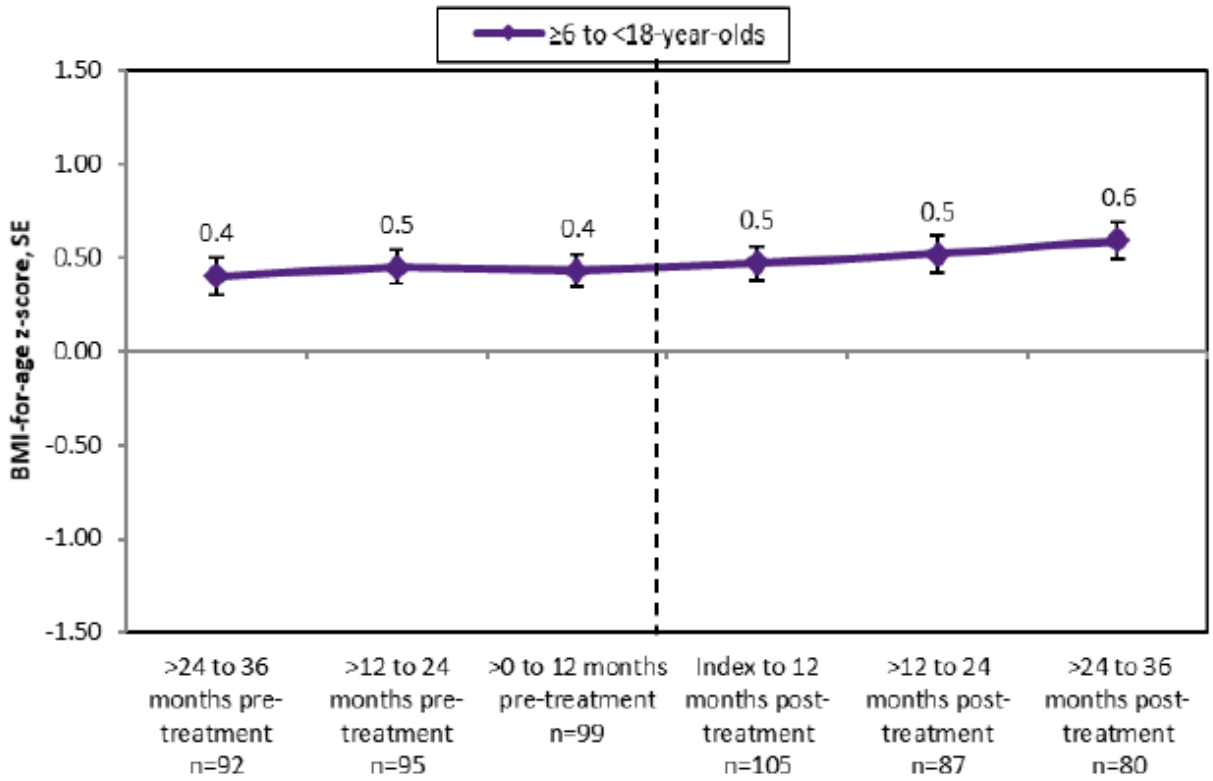
- **Nutritional Parameters**

Kalydeco cohort

Patients ≥6 to <18 years:

During the 36 months before Kalydeco treatment initiation, body mass index (BMI)-for-age z-scores in patients ≥6 to <18 years of age (N=107) were in the normal range and stable (Figure 21). In the 36 months following treatment initiation, mean (SD) BMI-for-age z-scores remained stable in the normal range as shown by a mean (SD) absolute change from the index date to the first (n=94): -0.02 (0.41); second (n=81): -0.03 (0.47); third (n=74): 0.00 (0.57) 12-month intervals after treatment initiation.

Figure 21 Kalydeco Cohort Patients ≥6 to <18 Years of Age: Change in BMI-for-age z-score Over Time During the 36 Months Before and 36 Months After Treatment Initiation



Source: IA2 CFF Tables/Table 11.0

Regarding weight-for-age z-scores, in the 12-month interval immediately preceding treatment initiation, the mean (SD) weight-for-age z-score was 0.32 (0.92) (n=99) in children aged 6 to less than 18 years. In the 36 months following treatment initiation, the mean (SD) absolute change from the value at the index date (0.42 [1.00], n=94) to the first 12-month interval (n=94) was 0.02 (0.26); it was 0.04 (0.37) during the second interval (n=81) and 0.06 (0.51) during the third one (n=75)

(Table 36). These figures for height-for-age z-score were 0.06 (1.01) at the index date (n=94), 0.03 (0.15) during the first 12-month interval (n=94) after treatment initiation, 0.05 (0.26) during the second interval (n=81), and 0.06 (0.36) during the third one (n=74).

Patients ≥2 to less than 6 years:

Among children aged ≥2 to less than 6 years, the mean (SD) BMI-for-age z-score in the year immediately preceding treatment initiation (n=61) was 0.45 (1.05). In the 36 months following treatment initiation, the mean (SD) absolute change from the value at the index date (0.46 [1.05], n=60) to the first 12-month interval (n=60) was 0.11 (0.46); it was 0.07 (0.56) during the second interval (n=55) and 0.05 (0.68) during the third one (n=49).

The absolute change in mean weight-for-age z-score from the index date (0.39 [1.00), n=60) to the first 12-month interval (n=60) was 0.07 (0.30); it was 0.11 (0.45) during the second interval (n=55) and 0.10 (0.57) during the third one (n=49). These figures for height-for-age z-score were 0.19 (0.98) at the index date (n=60), -0.01 (0.33) during the first 12-month interval (n=60) after treatment initiation, 0.07 (0.39) during the second interval (n=55), and 0.04 (0.50) during the third one (n=49).

Among the 196 adult subjects in the Kalydeco cohort, 151 patients have data available on BMI at the index date and the first-year post-treatment initiation. The mean (SD) absolute change in BMI from the value at the index date (26.3 kg/m^2 [5.9]) to the first-year post-treatment initiation was 0.3 kg/m^2 (1.19). During the second (n=111) and third (n=86) year, the mean (SD) absolute change in BMI was 0.65 kg/m^2 (1.80) and 1.01 kg/m^2 (2.09) respectively. The mean (SD) weight at index date was 75.9 kg (19.6) with a range from 44.6 to 161.5 kg. The mean (SD) absolute change from the value at the index date to the first 12-month interval following treatment initiation (n=157) was 0.9 kg (3.5). During the second (n=117) and third year (n=92), the mean (SD) absolute change was 1.7 kg (5.8) and 2.4 kg (6.6).

Historical cohort

Patients ≥6 to less than 18 years old and ≥2 to less than 6 years old:

During the initial year of follow-up (2009), the number of patients ≥6 to less than 18 years old and ≥2 to less than 6 years old with data available for weight-for-age z-score was 127 and 93 respectively. This number decreased (i.e., 106 and 72 respectively) at the end of the follow-up in 2011. The number of adult patients with available data on body weight and BMI decreased from 249 to 207.

Mean (SD) BMI-for-age z-score was in the initial period 0.4 (1.0) and 0.2 (1.0) while in the final period of follow-up they were 0.4 (1.0) and 0.2 (0.9) (Table 37). The mean (SD) weight-for-age z-score was in the first period of follow-up 0.3 (1.2) and 0.1 (0.9) for the oldest and the youngest paediatric groups, respectively. At the end of the follow-up these values were 0.4 (1.2) in the oldest group and 0.1 (0.9) in the youngest one (Table 37). Mean (SD) height-for-age z-scores at the beginning of the follow-up period in 2009 was -0.12 (1.20) in children aged ≥ 6 to less than 18 years (n=124) and -0.12 (0.93) in children aged ≥2 to less than 6 years (n=95). At the end of the follow-up period in 2011, these figures were -0.01 (1.04) and -0.09 (0.95), respectively based on 103 and 78 patients with non-missing data for this parameter. Overall, the mean values of the anthropometric parameters were within 0.5 SD of the CDC referent population and stable during the 3 years of follow-up.

Adults:

As for adults, mean (SD) body weight in the initial period was 74.6 kg (17.7) which increased to 75.1 kg (18.5) at the end of the follow-up. Mean (SD) BMI was 25.4 kg/m2 (5.6) and 25.7 kg/m2 (5.6) in these two periods which are in the upper range of what is considered normal weight according to the

WHO threshold. As for the Kalydeco cohort, maximum and minimum values indicate that the Historical cohort included underweight and overweigh/obese patients.

Table 36 and Table 37 show the data of BMI-for-age z-score and weight-for-age z-score and for paediatric patients in both cohorts.

Table 36 Descriptive Statistics for BMI-for-age z-score and Weight-for-age z-score Absolute Change from Index in Each 12-month Interval Post-Treatment Initiation (Kalydeco Cohort)

Kalydeco Cohort		
	≥6 - <18 (N=107) Primary Full Analysis Set	≥2 - <6 (N=65)
BMI-for-age z-score Absolute Change from Index in Each 12-month Interval Post-Treatment Initiation		
Index		
N	94	60
Mean (SD)	0.52 (1.02)	0.46 (1.05)
Median	0.43	0.44
Min, Max	-1.9, 2.7	-1.9, 3.8
Absolute Change from Index Date to 12 Months Post Treatment Initiation		
N	96	60
Mean (SD)	-0.02 (0.41)	0.11 (0.46)
Median	0.02	0.05
Min, Max	-2.2, 0.8	-1.0, 1.8
Absolute Change from Index Date to >12 to 24 Months Post Treatment Initiation		
N	81	55
Mean (SD)	-0.03 (0.47)	0.07 (0.56)
Median	-0.05	0.05
Min, Max	-2.0, 1.1	-1.1, 1.8
Absolute Change from Index Date to >24 to 36 Months Post Treatment Initiation		
N	74	49
Mean (SD)	0.00 (0.57)	0.05 (0.68)
Median	0.04	-0.02
Min, Max	-2.0, 1.2	-1.1, 2.1
Weight-for-age z-score Absolute Change from Index in Each 12-month Interval Post-Treatment Initiation		
Index		
N	94	60
Mean (SD)	0.42 (1.0)	0.39 (1.0)
Median	0.48	0.38
Min, Max	-1.4, 3.1	-1.7, 3.8
Absolute Change from Index Date to 12 Months Post Treatment Initiation		
N	94	60
Mean (SD)	0.02 (0.26)	0.07 (0.30)
Median	0.03	0.05
Min, Max	-1.3, 0.6	-0.7, 1.0
Absolute Change from Index Date to >12 to 24 Months Post Treatment Initiation		
N	81	55
Mean (SD)	0.04 (0.37)	0.11 (0.45)
Median	0.02	0.09
Min, Max	-1.0, 1.0	-1.1, 1.2
Absolute Change from Index Date to >24 to 36 Months Post Treatment Initiation		
N	75	49
Mean (SD)	0.06 (0.51)	0.10 (0.57)
Median	0.13	0.08
Min, Max	-1.5, 1.2	-1.1, 1.2

Table 37 Descriptive Statistics for BMI-for-age z-score and Weight-for-age z-score Absolute Change from Index in Each 12-month Interval Post-Treatment Initiation (Unmatched Historical Cohort)

	Unmatched Historical Cohort	
	≥6 - <18 (N=134)	≥2 - <6 (N=97)
BMI-for-age z-score Absolute Change from Index in Each 12-month Interval Post-Treatment Initiation		
	January 1, 2009 to December 31, 2009	
N	126	93
Mean (SD)	0.4 (1.0)	0.2 (1.0)
Median	0	0
Min, Max	-2.0, 3.1	-2.6, 2.7
	January 1, 2010 to December 31, 2011	
N	114	81
Mean (SD)	0.4 (1.0)	0.2 (1.0)
Median	0	0
Min, Max	-2.0, 2.9	-2.7, 3.0
	January 1, 2011 to December 31, 2011	
N	106	72
Mean (SD)	0.4 (1.0)	0.2 (0.9)
Median	0	0
Min, Max	-1.4, 3.1	-2.5, 2.8
Weight-for-age z-score Absolute Change from Index in Each 12-month Interval Post-Treatment Initiation		
	January 1, 2009 to December 31, 2009	
N	127	93
Mean (SD)	0.3 (1.2)	0.1 (0.9)
Median	0	0
Min, Max	-3.0, 3.5	-2.6, 3.0
	January 1, 2010 to December 31, 2010	
N	114	82
Mean (SD)	0.3 (1.1)	0.1 (0.9)
Median	0	0
Min, Max	-2.4, 3.1	-2.8, 2.5
	January 1, 2011 to December 31, 2011	
N	106	72
Mean (SD)	0.4 (1.2)	0.1 (0.9)
Median	0	0
Min, Max	-2.4, 3.3	-1.7, 2.3

- **Deaths and Transplantations**

In the Kalydeco cohort, as of 31 December 2018, there were no organ transplants among all paediatric patients <18 years of age. In 2018, there was 1 death among patients ≥2 to <6 years of age. There were 2 deaths in the adult population and 1 adult patient received an organ (kidney) transplant as reported in the first interim analysis (IA1).

- **Chronic CF Complications**

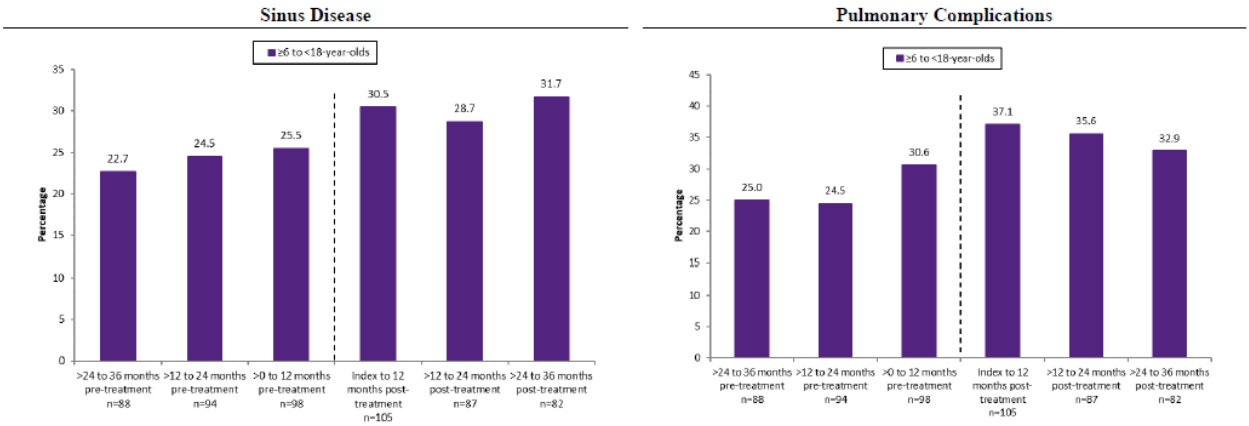
Six selected complications of cystic fibrosis were analysed, i.e., (symptomatic) sinus disease, pulmonary complications (allergic bronchopulmonary aspergillosis, asthma, haemoptysis, and

pneumothorax); cystic fibrosis-related diabetes (CFRD); distal intestinal obstruction syndrome (DIOS), hepatobiliary complications; and pancreatitis. For the composite outcome measure of hepatobiliary complications, events of gall stones, liver disease (cirrhosis), hepatic steatosis, liver disease (other), acute hepatitis and acute liver failure are included as defined by registry data collection. Analyses by individual entities were not prespecified in the approved study protocol and are therefore not provided.

Kalydeco cohort

The proportion of patients ≥6 to <18 years of age with sinus disease or pulmonary complications showed a slightly upward trend over time during the 36 months before Kalydeco initiation. While the proportion of patients with sinus disease or pulmonary complications continued to increase during the first 12 months after treatment initiation (Figure 22), the prevalence remained stable in the second and third 12-month intervals after treatment initiation.

Figure 22 Kalydeco Cohort Patients ≥6 to <18 Years of Age: Changes in Sinus Disease and Pulmonary Complications Over Time During the 36 Months Before and 36 Months After Treatment Initiation



Source: IA CFF Tables/Table 14.0

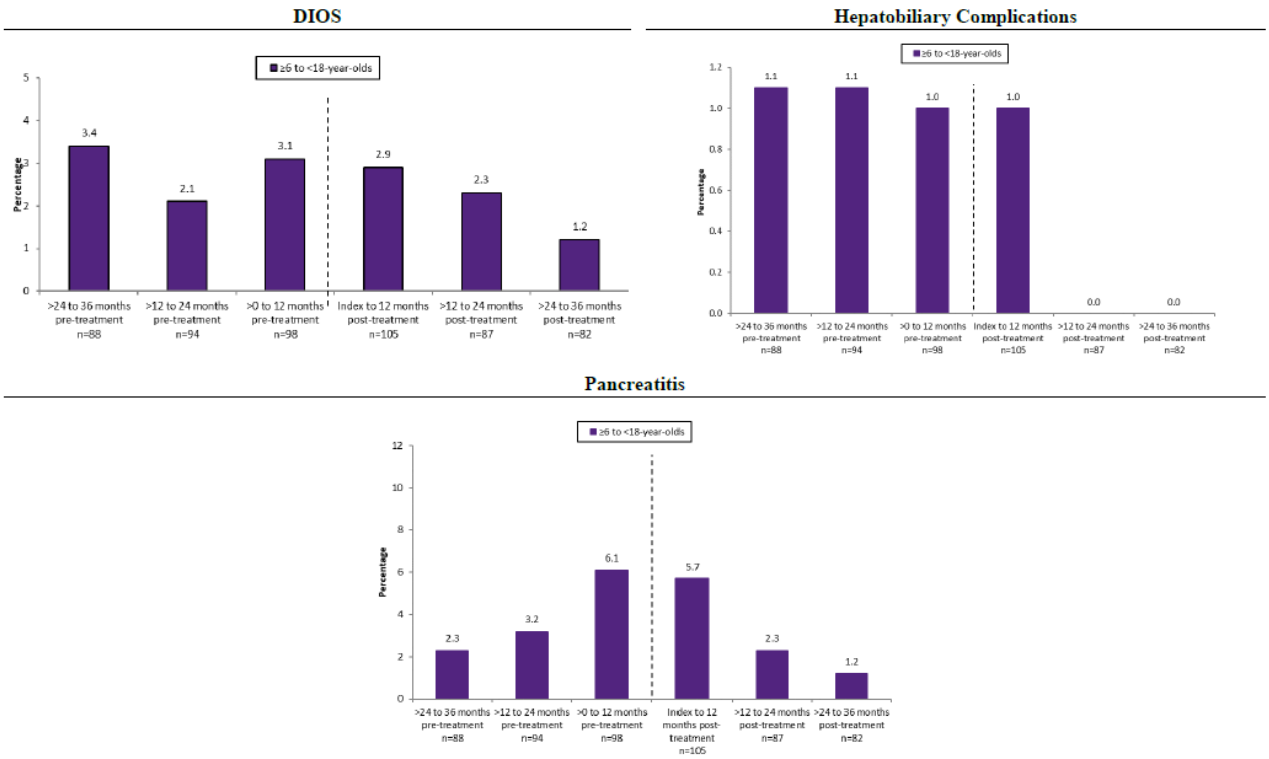
In subjects with non-missing encounter data, 12 months before treatment initiation the percentage of paediatric patients with sinus disease in the age group ≥6 to less than 18 years old, adults, and children ≥ 2 to less than 6 years old was 25.5%, 49.1%, and 9.7% respectively (see Table 38 further below). Twelve months after treatment initiation, these figures were 30.5%, 55.2%, and 10.8% respectively. During the second 12-month interval, the percentage of patients with sinus diseases was as follows: 28.7%, 61%, and 10.5% (see Table 38 further below).

Regarding pulmonary complications, 12 months before treatment initiation the percentage of paediatric patients aged 6 to less than 18 years old, adults, and children aged to 2 to less than 6 years was 30.6%, 43.3%, and 9.7% which increased to 37.1%, 44.3%, and 12.3% during the first 12 months after treatment initiation respectively. In the second 12-month interval after treatment initiation these figures were 35.6%, 47.2%, and 12.3% respectively (Table 38).

Regarding the remaining chronic complications assessed, in general, prevalence of these complications was low (<7%) in paediatric patients. In patients ≥6 to <18 years old, prevalence of DIOS was generally stable in the 36 months before Kalydeco initiation and decreased in each 12-month interval following treatment initiation. The prevalence of pancreatitis increased in each 12-month interval before Kalydeco initiation; in the 36 months following treatment initiation, prevalence decreased in each 12-month interval (Figure 23). There were no hepatobiliary complications reported in the second and third 12-month intervals after treatment initiation. As expected for *R117H* patients, rates of CFRD

were 0% at every pre- and post-treatment interval. Trends in other chronic complications showed no discernible patterns.

Figure 23 Kalydeco Cohort Patients ≥6 to <18 Years of Age: DIOS, Hepatobiliary Complications, and Pancreatitis, Over Time During the 36 Months Before and 36 Months After Treatment Initiation



Source: IA2 CFF Tables/Table 14.0
DIOS: distal intestinal obstruction syndrome

Historical cohort

During the initial year of follow-up (2009), the number of patients ≥6 to less than 18 years old and ≥2 to less than 6 years old with data available on sinus disease was 129 and 93 respectively. This number decreased at the end of the follow-up in 2011 (i.e., 108 and 72 respectively). The number of adult patients with available data on this complication decreased from 252 to 210.

The percentage of paediatric subjects with sinus disease in the first period of follow-up was 14.7% and 9.7% in the oldest and the youngest paediatric groups respectively. At the end of the follow-up, these values were 14.8% and 18.1% respectively. As for adults, the percentage of subjects with this complication was 33.3% in the initial period which increased to 44.8% after 3 years of follow-up.

Regarding pulmonary complications, the percentage of paediatric subjects with such complications in the first period of follow-up (2009) was 14.7% (≥6 to less than 18 years old) and 5.4% (≥2 to less than 6 years old). At the end of the follow-up, these values were 20.4% and 22.2%, respectively. As for adults, these figures were 25.4% and 31.9% in each period respectively.

There were no discernible trends in other chronic complications including DIOS, hepatobiliary complications, pancreatitis, and CFRD in any age group.

Table 38 and Table 39 shows the prevalence of disease complications in paediatric patients of both cohorts. For the Kalydeco cohort data from the interim analysis 2 are provided while for the Historical Cohort data correspond to the Interim Analysis 1.

Table 38 Prevalence of Selected Complications

Kalydeco Cohort		
	≥6 - <18 (N=107)	≥2 - <6 (N=65)
>0 to 12 months pre-treatment		
Number of patients with non-missing encounter data	98	62
Sinus disease, n (%)	25 (25.5)	6 (9.7)
Pulmonary complications, n (%)	30 (30.6)	6 (9.7)
DIOS, n (%)	3 (3.1)	2 (3.2%)
Hepatobiliary complications, n (%)	1 (1.0)	0
Pancreatitis	6 (6.1)	0
Number of patients with non-missing annualized data	97	63
CF related diabetes (CFRD), n (%)	0	0
Index to 12 months post-treatment		
Number of patients with non-missing encounter data	105	65
Sinus disease, n (%)	32 (30.5)	7 (10.8)
Pulmonary complications, n (%)	39 (37.1)	8 (12.3)
DIOS, n (%)	3 (2.9)	2 (3.1)
Hepatobiliary complications, n (%)	1 (1.0)	0
Pancreatitis, n (%)	6 (5.7)	1 (1.5)
Number of patients with non-missing annualized data	107	65
CF related diabetes (CFRD), n (%)	0	0
>12 to 24 months post-treatment		
Number of patients with non-missing encounter data	87	57
Sinus disease, n (%)	25 (28.7)	6 (10.5)
Pulmonary complications, n (%)	31 (35.6)	7 (12.3)
Distal intestinal obstruction syndrome, n (%)	2 (2.3)	1 (1.8)
Hepatobiliary complications, n (%)	0	0
Pancreatitis, n (%)	2 (2.3)	0
Number of patients with non-missing annualized data	93	59
CF related diabetes (CFRD), n (%)	0	0
>24 to 36 months post-treatment		
Number of patients with non-missing encounter data	82	51
Sinus disease, n (%)	26 (31.7)	5 (9.8)
Pulmonary complications, n (%)	27 (32.9)	7 (13.7)
Distal intestinal obstruction syndrome, n (%)	1 (1.2)	0
Hepatobiliary complications, n (%)	0	0
Pancreatitis, n (%)	1 (1.2)	0
Number of patients with non-missing annualized data	85	56
CF related diabetes (CFRD), n (%)	0	0

Table 39 Prevalence of Selected Complications

	Unmatched Historical Cohort	
	≥6 - <18 (N=134)	≥2 - <6 (N=97)
January 1, 2009 to December 31, 2009		
Number of patients with non-missing encounter data	129	93
Sinus disease, n (%)	19 (14.7)	9 (9.7)
Pulmonary complications, n (%)	19 (14.7)	5 (5.4)
DIOS, n (%)	2 (1.6)	1 (1.1)
Hepatobiliary complications, n (%)	1 (0.8)	0
Pancreatitis	5 (3.9)	0
Number of patients with non-missing annualized data	134	97
CF related diabetes (CFRD), n (%)	1 (0.7)	0
January 1, 2010 to December 31, 2010		
Number of patients with non-missing encounter data	115	82
Sinus disease, n (%)	15 (13.0)	12 (14.6)
Pulmonary complications, n (%)	25 (21.7)	9 (11.0)
DIOS, n (%)	2 (1.7)	1 (1.2)
Hepatobiliary complications, n (%)	1 (0.9)	1 (1.2)
Pancreatitis, n (%)	8 (7.0)	0
Number of patients with non-missing annualized data	125	86
CF related diabetes (CFRD), n (%)	1 (0.8)	0
January 1, 2011 to December 31, 2011		
Number of patients with non-missing encounter data	108	72
Sinus disease, n (%)	16 (14.8)	13 (18.1)
Pulmonary complications, n (%)	22 (20.4)	16 (22.2)
Distal intestinal obstruction syndrome, n (%)	1 (0.9)	1 (1.4)
Hepatobiliary complications, n (%)	0	0
Pancreatitis, n (%)	8 (7.4)	0
Number of patients with non-missing annualized data	115	77
CF related diabetes (CFRD), n (%)	1 (0.9)	0

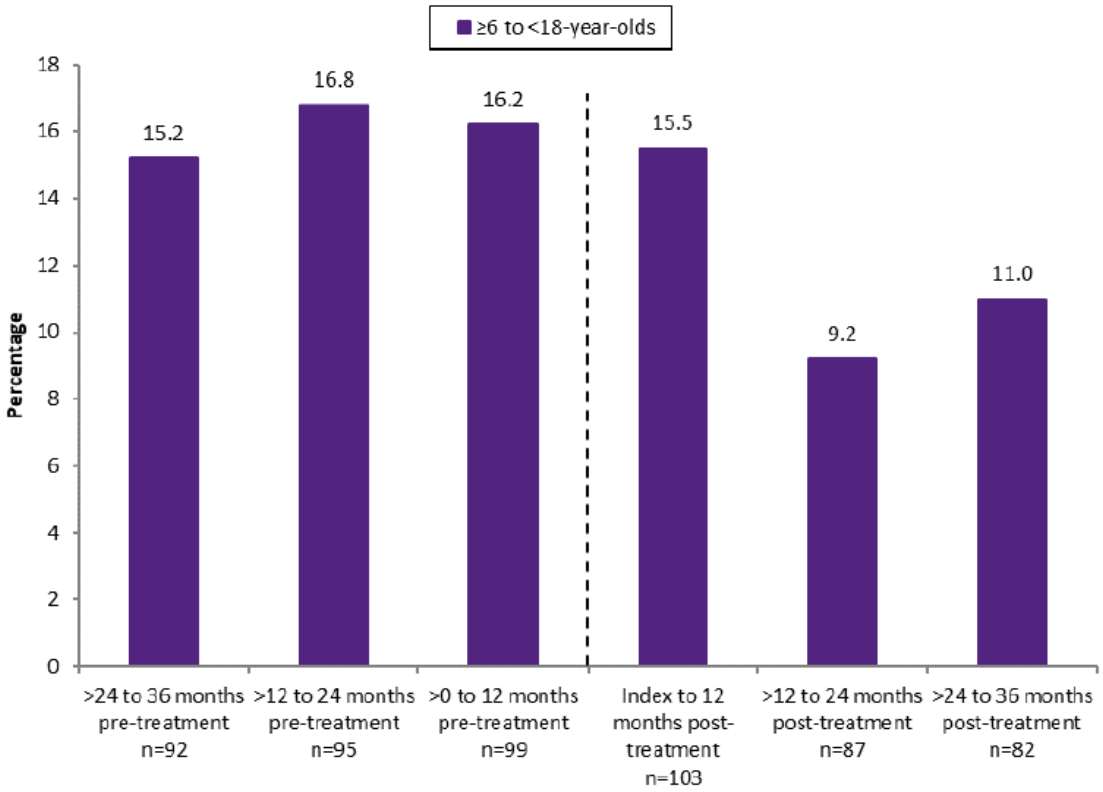
- **Pulmonary Microorganisms**

The prevalence of *P aeruginosa* and other pulmonary microorganisms including methicillin-sensitive *S aureus*, methicillin-resistant *S aureus* (MRSA), *H influenzae*, *S maltophilia*, *A xylosoxidans*, *B cepacia complex*, *A fumigatus*, and nontuberculous mycobacteria were examined.

Kalydeco cohort

In paediatric patients ≥6 to <18 years of age, the prevalence of *P aeruginosa* was constant during the 36 months before Kalydeco initiation (Figure 24). In each of the 12-month intervals following treatment initiation, prevalence of *P aeruginosa* was numerically lower than in the 12 months before treatment initiation.

Figure 24 Kalydeco Cohort Patients ≥6 to <18 Years of Age: Changes in *P aeruginosa* Prevalence Over Time During the 36 Months Before and 36 Months After Treatment Initiation



Source: Study 122 IA2 CFF Tables/Table 15.0
n: size of subsample
Note: The dotted line indicates the initiation of Kalydeco treatment.

In patients ≥6 to <18 years of age, prevalence of methicillin-sensitive *S aureus*, MRSA, and *H influenzae* were relatively stable in the 36 months before Kalydeco initiation. In the 36 months following initiation of Kalydeco, prevalence of methicillin-sensitive *S aureus* and MRSA had slight numeric increases while the prevalence of *H influenzae* decreased in the third 12-month interval after treatment initiation. No discernible patterns were observed for prevalence of other pulmonary microorganisms in paediatric patients ≥6 to <18 years of age, nor in patients ≥2 to <6 years of age (see Table 40).

In the first 12 months of Kalydeco treatment, the prevalence of *P aeruginosa* among adult patients declined from 43.9% in the 12 months before treatment initiation to 39.7%. This decline was

maintained during the second 12-month interval after treatment initiation (40.4%). In the third 12-month interval after treatment initiation, prevalence of *P aeruginosa* had a slight increase to 44.3%; it is noted that not all adult patients have completed the full 36 months of follow-up after treatment initiation.

The prevalence of other pulmonary microorganisms was also assessed (Table 40). Among the adult population, there was a slight decline in the prevalence of methicillin-sensitive *S aureus* during the 36 months after treatment initiation. There were no discernible patterns observed in the prevalence of other microorganisms in the adult population.

Historical cohort

During the initial year of follow-up (2009), the number of patients ≥6 to less than 18 years old and ≥2 to less than 6 years old with bacterial culture available was 125 and 90 respectively. This number decreased at the end of the follow-up in 2011 (i.e., 104 and 72 respectively). The number of adult patients with available data decreased from 228 to 188.

The prevalence of *P aeruginosa* in the paediatric group in the first period of follow-up was 12.8% and 2.2% in the oldest and in the youngest paediatric groups respectively. At the end of the follow-up, these values were 12.5% and 6.9% in these two groups. As for adults, these figures were 39.9% in the initial period which increased to 45.2% after 3 years of follow-up.

The prevalence of MSSA at the beginning period of follow-up in 2009 was 52.8% (≥6 to less than 18 years old), 45.6% (≥2 to less than 6 years old), and 37.3% (adults). At the end of follow-up, three years later, these values were as follows: 56.7%, 52.8%, and 38.8%.

As in the Kalydeco cohort, *B cepacia complex* was isolated in very few patients.

Table 40 and Table 41 show the prevalence of selected organisms in paediatric patients in both cohorts. For the Kalydeco cohort data from the Interim Analysis 2 are provided. For the Historical cohort data correspond to those of the Interim Analysis 1.

Table 40 Positive Result of a Microbiology Culture

	Kalydeco Cohort	
	≥6 - <18 (N=107)	≥2 - <6 (N=65)
>0 to 12 months pre-treatment		
Patients with bacterial culture available	99	63
Pseudomonas aeruginosa, n (%)	16 (16.2)	10 (15.9)
Methicillin-sensitive S *aureus*, n (%)	58 (58.6)	32 (50.8)
Methicillin-resistant *S aureus*, n (%)	16 (16.2)	7 (11.1)
*Haemophilus influenza*e, n (%)	28 (28.3)	20 (31.7)
Index to 12 months post-treatment		
Patients with bacterial culture available	103	65
Pseudomonas aeruginosa, n (%)	16 (15.5)	2 (3.1)

Methicillin-sensitive *S aureus*, n (%)	58 (56.3)	38 (58.5)
Methicillin-resistant *S.aureus*, n (%)	17 (16.5)	6 (9.2)
*Haemophilus influenza*e, n (%)	28 (27.2)	18 (27.7)
>12 to 24 months post-treatment		
Patients with bacterial culture available	87	58
Pseudomonas aeruginosa, n (%)	8 (9.2)	2 (3.4)
Methicillin-sensitive *S aureus*, n (%)	55 (63.2)	31 (53.4)
Methicillin-resistant *S aureus*, n (%)	12 (13.8)	5 (8.6)
*Haemophilus influenza*e, n (%)	22 (25.3)	16 (27.6)
>24 to 36 months post-treatment		
Patients with bacterial culture available	82	51
Pseudomonas aeruginosa, n (%)	9 (11.0)	0
Methicillin-sensitive *S aureus*, n (%)	52 (63.4)	30 (58.8)
Methicillin-resistant *S aureus*, n (%)	15 (18.3)	7 (13.7)
*Haemophilus influenza*e, n (%)	11 (13.4)	7 (13.7)

Table 41 Positive Result of a Microbiology Culture

	Unmatched Historical Cohort	
	≥6 - <18 (N=134)	≥2 - <6 (N=97)
January 1, 2009 to December 31, 2009		
Patients with bacterial culture available	125	90
Pseudomonas aeruginosa, n (%)	16 (12.8)	2 (2.2)
Methicillin-sensitive S *aureus*, n (%)	66 (52.8)	41 (45.6)
Methicillin-resistant *S aureus*, n (%)	22 (17.6)	7 (7.8)
*Haemophilus influenza*e, n (%)	21 (16.8)	27 (30.0)
January 1, 2010 to December 31, 2010		

Patients with bacterial culture available	113	82
Pseudomonas aeruginosa, n (%)	14 (12.4)	3 (3.7)
Methicillin-sensitive *S aureus*, n (%)	59 (52.2)	38 (46.3)
Methicillin-resistant *S.aureus*, n (%)	19 (16.8)	3 (3.7)
*Haemophilus influenza*e, n (%)	25 (22.1)	25 (30.5)
January 1, 2011 to December 31, 2011		
Patients with bacterial culture available	104	72
Pseudomonas aeruginosa, n (%)	13 (12.5)	5 (6.9)
Methicillin-sensitive *S aureus*, n (%)	59 (56.7)	38 (52.8)
Methicillin-resistant *S aureus*, n (%)	13 (12.5)	2 (2.8)
*Haemophilus influenza*e, n (%)	19 (18.3)	17 (23.6)

2.4.3. Discussion on clinical efficacy

This extension of indication for Kalydeco for the treatment of paediatric patients with CF who have the ***R117H-CFTR*** mutation is now from the age of 6 months, instead of 12 months as initially proposed by the MAH. This was considered to be acceptable by CHMP given that Kalydeco granules (25 mg twice daily) are approved for children aged 6 months and weighing 5 kg with CF who have a pre-specified gating (class III) mutation in the *CFTR* gene (refer to procedure EMEA/H/C/002492/X/75). This is also further discussed in the clinical pharmacology part of this report.

The main study in this application is **study 110**, a phase 3, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of ivacaftor in patients with CF aged 6 years and older who have an *R117H-CFTR* mutation. Supportive studies to this application are **study 112**, an open label extension study in which patients from study 110 were offered to roll over for an additional period of 104 weeks, and **study 122** which is an ongoing, non-interventional study being conducted in subjects with CF who have the *R117H* mutation aged 2 years and older, adolescents, and adults.

Study 110

This study was initially submitted in variation procedure EMEA/H/C/002494/II/0027, the ppFEV1 results in the small number of subjects 6 to 11 years of age (N = 17) favoured the placebo over

ivacaftor. With the exception of the sweat chloride response, which was comparable to that seen in patients ≥18 years of age, no other meaningful clinical responses to ivacaftor treatment were seen in children. The indication was therefore restricted to adults with CF and an *R117H-CFTR* mutation. With this application, the MAH reiterated the factors that could have affected the FEV1 results. The MAH considered that an increase in ppFEV1 in the placebo group combined with a modest decrease in ppFEV1 in the ivacaftor group could explain the observed results with ppFEV1 through week 24. Further, relevant mean reduction in sweat chloride levels was seen in all age subgroups in the ivacaftor arm, including 6 to 11 years of age (-26.59 mmol/L) in comparison with 1.04 mmol/L for the placebo group. Further, mean sweat chloride reduction was detected by Week 2 (first post-baseline time point assessed; -25.22 mmol/L) and were sustained through Week 24. The magnitude of the mean reduction was very similar to that of subjects ≥18 years of age in the ivacaftor arm. Treatment differences at all time points where sweat chloride levels were determined favoured ivacaftor. Little variation was seen in the CFQ-R respiratory domain scores for the placebo group during the treatment period, while the ivacaftor group experienced a substantial decrease in the mean CFQ-R respiratory domain scores at Week 2 and Week 16. For Weeks 4, 8, and 24, the mean differences versus placebo were smaller and ranged between -3.8 to 3.4 points.

A correlation between sweat chloride and ppFEV1 was also explored. Overall, the data demonstrate that changes in sweat chloride are not predictive of changes in pulmonary function at the individual subject level which is not unexpected given that while the sweat glands, and sweat chloride concentrations, of CF patients show little change throughout life, the lungs and other organs are progressively damaged with age. However, when the data were evaluated together at a population-level, the data do support that a positive relationship is observed i.e. populations who show improvements in sweat chloride would be expected to show improvements in pulmonary function when evaluated in totality as a population.

Further, subjects enrolled in study 110 were required to have at least an allele of *R117H-CFTR* mutation and CF defined as either a sweat chloride value ≥60 mmol/L OR 2 CF-causing mutations AND chronic sinopulmonary disease. An assumption was made that all subjects would have had the *R117H-5T* or *R117H-7T* alleles based on the study entry criteria but for a number of subjects an assumption needed to be made as the poly-T status and the phase of it was unknown. Within the request for supplementary information, the MAH was requested to clarify in which EU countries the *R117H* mutation was included in panels for genetic analysis and whether the poly-T status was determined. The MAH clarified that in most countries for which data have been provided the mutation was included in the panels and the poly-T status was determined. As the claimed indication clearly states that patients should have CF disease and the *R1117H* mutation, the CHMP concluded that there was no need to include a warning in the SmPC of Kalydeco indicating that patients with *R117H* mutation should have the poly-T status determined as this should be part of the diagnostic algorithm of cystic fibrosis, in particular in young children who may be asymptomatic or minimally symptomatic after newborn screening. Therefore, the below warning included in section 4.4. of the SmPC has been removed:

'Whenever possible the phase of the poly-T variant identified with the R117H mutation should be determined as this may be informative in considering treatment of patients with an R117H mutation (see section 4.2).'

However, the below statement included in section 4.2 of the SmPC is maintained

"The phase of the poly T variant identified with the R117H mutation should be determined in accordance with local clinical recommendations."

Based on non-published data, the MAH estimated that there may be approximately 1000 subjects with

CF and the *R117H* mutation in the EU of whom ~52% are adults.

Study 112

Results from an interim analysis (through the Week 12 visit) of data from patients who were previously enrolled in study 110 was provided in variation procedure EMEA/H/C/002494/II/27. The final study results were provided in variation procedure EMEA/H/C/002494/II/0054. Patients from study 111 and study 113 who also rolled over into study 112 were not included in this interim analysis.

Out of the 17 children from study 110, 13 rolled over to study 112. Their mean (SE) ppFEV1 was 90.7 (5.2) percentage points at study 112 baseline. At study 112 week 104, only 4 children had data available on ppFEV1. At earlier points in time when the number of children with available data was higher (e.g., n=10 at week 48), the mean (SE) absolute change in ppFEV1 from study 112 baseline was 4.0 percentage points (2.5). These results were in contrast with the value observed in study 110. Similarly, a response in the respiratory domain of CFQ-R was observed at almost all time points in study 112. At baseline, mean (SE) respiratory domain score was 82.1 (5.6) points. Changes from baseline in the 6 to 11 years of age subgroup remained above the MCID at all but 1 time point (i.e., at Week 36) and ranged from 3.2 to 10.3.

Only a small number of adolescents were enrolled in study 110 and rolled over into study 112. No issues of concern were identified in either study 110 or study 112 but overall definitive conclusions on efficacy could not be reached based on the small number of paediatric patients.

Overall, the CHMP considered that the results of the randomised, double-blind study 110 could not be ignored and that results from study 112 could not supersede them. However, it was acknowledged that certain factors in study 110 could have played a role in the lack of response to ivacaftor because subjects 6 to 11 years of age had higher baseline ppFEV1 and were more likely to have an *R117H-7T* allele; and data from study 112 were reassuring in that the seemingly deteriorating effect in ppFVE1 seen in study 110 was not kept in this age group at a longer duration of exposure.

Extrapolation of efficacy from adult subjects to children (*R117H* mutation)

Extrapolation of ivacaftor efficacy from adult subjects to children was considered. The MAH was of the view that extrapolation of ivacaftor efficacy from subjects ≥18 years of age to younger subjects is appropriate and in accordance with ICH E11 guideline based on the following:

- Adequate systemic exposure is achieved in children/adolescents, i.e., in the range of adult systemic exposure;
- Adequate safety data in children and adolescents as assessed in study 110, 112 and in other studies of ivacaftor in children and adolescents with gating (class III) mutations;
- Evidence that the same disease process exists in both adults and children;
- The fact that the ivacaftor mechanism of action and the sweat chloride/CFTR response to ivacaftor is similar across age groups.

The CHMP acknowledged that the basic difference between adults and paediatric subjects (and particularly the youngest ones) refers to disease manifestations which are usually more advanced in older ages. Similarly, in classical CF, the predominant manifestation of the disease at young ages is at the level of the gastrointestinal tract in the form of exocrine pancreatic insufficiency while in older subjects the main cause of morbidity is lung disease. Other complications of CF also show a temporal

pattern and are more frequent in the paediatric age.

Study 122

The MAH initially submitted the first interim analysis (IA1) of this study which was due by 31 December 2017. Upon request, the second interim analysis (IA2) which was scheduled in December 2019 was provided with the responses to the Request for Supplementary Information. This analysis covers full 24 months of post-treatment outcome measures for all Kalydeco cohort patients, and up to 36 months of post-treatment outcomes data for some of them. The final analysis is due in December 2020, and this study is included in the EU RMP as a category 3 study.

Statistical methods

There were a number of differences between the analyses performed in IA1 and analyses described in the Statistical Analysis Plan. The most relevant are described below:

As specified in the protocol, patients in the Historical Cohort were planned to be matched on age, sex, and lung function to patients in the Kalydeco Cohort. However, due to the differences in demographic and clinical characteristics of the 2 cohorts, effective matching was not achieved. Therefore, all patients enrolled in the CFFPR as of 01 January 2009 with an *R117H* mutation and without any record of previous exposure to CFTR modulators were included in the Historical Cohort. The SAP of IA2/final analysis indicates that there is no plan to perform further analysis on the matched Historical cohort.

Both the final study 122 protocol and the SAP of the Interim Analysis 1 indicate that mixed-effects model for repeated measures (MMRM) and linear mixed effects (LME) analyses of spirometry endpoints and the LME analyses of nutritional parameters were described as potential analyses to be performed if warranted by the data. Model-based analyses as described in the protocol were not performed in the IA2 report and will not be performed in the final analysis.

Baseline data

Key baseline demographic and clinical characteristics of paediatric Kalydeco Cohort patients by age subgroup were provided in the IA1. Although the exact number of paediatric subjects does not coincide (i.e., 107 paediatric patients aged ≥ 6 to less than 18 years of age and 65 patients ≥ 2 to less than 6 years in IA2) the slight difference is not expected to have an important impact on the baseline characteristics of the Kalydeco cohort. This is endorsed by CHMP considering that baseline demographic and disease characteristics will be provided in the final study report and re-discussed based on the final number of patients.

Study participants

To fulfil the objectives of the study two cohorts of patients were established in the registry; a non-interventional Kalydeco cohort (referred to as 'Kalydeco cohort') and a historical cohort.

Each patient in the Kalydeco cohort was attempted to be matched with at least one corresponding patient from the Historical cohort but the specified matching algorithm did not successfully achieve balance in ppFEV1 in the adult populations. Therefore, patients in the Historical cohort were not matched to those in the Kalydeco cohort which limits the accuracy of the conclusions that can be reached by comparing these two cohorts.

Nevertheless, results in terms of ppFEV1 and PEx are presented for the Historical cohort matched to Kalydeco cohort patients on age, gender, and lung function in the IA1 analysis. As the main interest of the present study is the paediatric population, the MAH was requested by CHMP to provide and discuss comparative results between both cohorts for all outcome measures using the matched historical cohort. The MAH did not provide such comparison justifying that as per SAP IA2 no analyses are

planned on the matched historical cohort but only on the full, unmatched cohort. Data from the matched Historical cohort are presented within the IA1 analysis.

Clarification has been also provided that even though model-based analyses of spirometry endpoints and nutritional parameters were described in the study protocol as potential analyses to be performed, these have been not been performed and will not be performed in the final analysis. As study 122 has been included in the Risk Management Plan (Category 3) this issue and the one mentioned above will be further reviewed at the time of assessment of the final analysis of study 122.

Results

- ***Baseline data***

Kalydeco cohort

Overall, the baseline data of the Kalydeco cohort are consistent with what is known about patients with the *R117H* mutation in terms of delayed diagnosis (mean age diagnosis in the adult cohort was 25.3 years vs. 4 months in the youngest children identified via newborn screening), as well as nutritional status and lung function.

Most patients had unknown poly-T status, precluding any subgroup analyses being conducted by this characteristic which is unfortunate but likely due to local recommendations on the genetic testing on the poly-T variant as suggested by the MAH in response to the CHMP question in this respect.

In the all patients set of the Kalydeco cohort, 75 (20.4%) subjects (including 48 adults, 19 paediatric subjects in the oldest age group and 8 in the youngest one) have a record of Kalydeco treatment discontinuation which is not due to patients' death or lost to follow-up. Compared to paediatric patients, adult patients had higher percentages of Kalydeco treatment discontinuation (24.5%) and loss to follow-up (22.4%).

Historical cohort

Mean (SD) ppFEV1 was 76.2 (23.5) in adults and 97.0 percentage points (pp) (11.2) in the paediatric group aged ≥6 years and older. Thirty-seven percent (36.9%) of adult subjects have ppFEV1 <70% while 27.4% of paediatric patients had PPFEV1 between 70 to 90 percentage points. Similar values were observed in the age groups of the Kalydeco cohort (99.3 [13.7] in paediatric patients aged ≥6 years and older and 70.8 [24.6] in the adult group). Higher variability is observed in the adult group in both cohorts.

Nutritional status for the paediatric population was normal for both the Historical cohort and the Kalydeco cohort while the mean BMI for adult population was higher and exceeded the WHO threshold of normal weight (25 kg/m2).

As for the Kalydeco cohort, very few patients in the Historical cohort had their poly-T variant identified.

Overall, the frequency of visits to the clinic in the year before treatment initiation was higher in the Kalydeco cohort than in the unmatched Historical cohort with less patients in the latter having the recommended number of yearly visits (i.e., quarterly). In children ≥6 to <18 years of age, 34.3% of patients in the Historical cohort had the recommended ≥ 4 clinic visits per year compared to 49.5% of patients in the same age group in the Kalydeco cohort. For the youngest children, these figures were 36.1% versus 60.9% respectively while in adults the percentage of subjects in the Historical cohort having ≥ 4 visits was 25.8% versus 35.3% in the Kalydeco cohort. Once treatment with ivacaftor was initiated in the Kalydeco cohort, the percentage of patients with ≥ 4 visits to the clinic increased. This is particularly evident during the first-year post-treatment in the paediatric population. Later, this

percentage tends to decrease or stabilise in all age groups.

Further, in study 122, the age group from 6 to less than 18 years of age is presented together for both cohorts. However, compared to children, adolescents are at a higher risk of lung function decline. The MAH was requested to provide demographic and disease characteristics at baseline for children aged 6 to less than 12 years and for adolescents in specific subsets of both cohorts (i.e., patients in the Kalydeco cohort with non-missing pre-treatment/index and post-treatment initiation data; and for the Historical cohort matched to patients in the Kalydeco cohort). This was not provided by the MAH based on the fact that the existing analyses of the 3 age subgroups predefined by the study protocol and SAP are sufficient to address the research question. In addition, the MAH considered that analysing subgroups of a subgroup post hoc would not be expected to be informative due to sample size limitations. This issue will be further assessed and discussed when the final analysis of study 122 (listed as a category 3 study in the RMP) will be submitted for review.

Outcomes and estimation

The main goal of the Historical cohort is to give some context to the results observed in the Kalydeco cohort and to gather some temporal trends in the data. However, a systematic discussion comparing the same endpoints in both cohorts was lacking in both reports of the IA1 and IA2. The tables of study 122 included in this report for changes in the outcome measures over time for both cohorts and from the matched Historical cohort when available, were therefore built during the assessment based on information available to CHMP and should be viewed with caution as they correspond to interim analyses of the data and due to the number of missing data over time.

1. Lung function

Kalydeco cohort

Better trends in ppFEV1 are observed in the subset of paediatric patients with non-missing data in the three pre-treatment intervals and in the first-year post-treatment initiation. The analysis restricted to paediatric subjects with non-missing data as above mentioned (n=71) shows an increase in mean ppFEV1 from 97 in the year preceding treatment initiation to 99.6 percentage points in the first year post-treatment, while in the Interim Analysis 2 the mean absolute change in ppFEV1 slightly increased after treatment initiation with a mean absolute change from the index date that ranged between 0.48 to 1.13 percentage points during the three years post-treatment initiation. Of note, ppFEV1 data are not available for patients ≥2 to <6 years of age because spirometry is not widely performed on patients before the age of 6 years.

Regarding the adult cohort the analysis restricted to subjects with non-missing data (n=110) shows a modest increase of the mean ppFEV1 from 66.7 pp in the year preceding treatment initiation to 68.1 (23.8) pp in the year following treatment initiation. In the adult group, the mean absolute change in ppFEV1 ranged between 1.28 (first year post-treatment initiation) to 2.32 (second year) (Interim Analysis 2).

The MAH was requested to provide not only the mean absolute change in ppFEV1 from the index value to the first-12 month after treatment initiation, but also the absolute values to calculate this change. Even though absolute changes were provided for subjects with observed ppFEV1 data based on which descriptive statistics were provided, the absolute ppFEV1 values which allow the calculation of the mean absolute change were lacking as this requires non-missing data prior and after treatment initiation. In the absence of further clarification, the CHMP considered that this issue remains unsolved and will be further discussed and assessed when the final analysis will be submitted for review.

Historical cohort

Regarding the Unmatched Historical cohort, at the beginning of the follow-up, the mean (SD) ppFEV1 in paediatric patients aged 6 to less than 18 years (n=120 out of the 134 paediatric patients) was 95.7 (12.4) pp while in the adult group (n=246 out of 287 adult subjects) this value was 73.3 (24.1). At the end of the follow-up period, these figures were 95.4 (12.9) and 72.0 (23.9) pp respectively based on data available from 105 paediatric and 201 adult patients.

As for the Matched Historical Control, at the beginning of the follow-up, the mean (SD) ppFEV1 (pp) in paediatric patients aged 6 years and older (n=110) was 96.5 pp (11.2) while in the adult group (n=180) this value was 75.2 pp (23.8). At the end of the follow-up period, these figures were 96.2 pp (11.4) and 75.2 pp (23.3) based on data from 93 and 134 subjects respectively. The percent of missing data with respect to the number of subjects who had ppFEV1 values collected at the beginning of the follow-up period is 15.5% and 25.5% respectively. As far as it can be concluded due to subjects with missing data, it seems that ppFEV1 remained stable in both paediatric and adult patients over the time of follow-up.

The comparison of both cohorts in terms of ppFEV1 shows that in the Matched Historical cohort at the end of the follow-up period the mean ppFEV1 was 96.2 pp in paediatric patients aged 6 years and older versus 99.6 pp in the Kalydeco cohort the first year after treatment initiation (n=71 subjects with non-missing data in the three periods pre-treatment and the first year post-treatment, IA1). In the second-year post-treatment initiation mean ppFEV1 was 99.6 pp (n=87 out of the 107 paediatric patients with data available, IA2). These figures for adult subjects were 75.2 pp (n=134 out of the 187 adult subjects in the Matched Historical cohort) versus 68.1 pp in the first-year after treatment initiation (n= 110 out of the 196 adult subjects with data available at the above indicated time intervals, IA1) and 72.2 in the second-year post-treatment initiation (n=120 out of the 196 adult subjects with data available, IA2).

2. Pulmonary exacerbations and pulmonary exacerbations requiring hospitalisation

According to the report of IA1, pulmonary exacerbations (PEx) and use of IV antibiotics were the endpoints to be collected and analysed while the endpoint discussed was "pulmonary exacerbations and hospitalizations". Reasons for hospitalization recorded by the registry could include not only PEx, but also pulmonary complication, gastrointestinal complication, transplant related, sinus infection, nontransplant surgery, and other. The MAH was requested to address hospitalisations due to PEx and due to other reasons independently. It was clarified that separate analyses for hospitalizations outside the context of PEx were not available because these were not prespecified in the approved study protocol. Nevertheless, data on PEx requiring hospitalisation and hospitalisations due to PEx and other causes are provided. In addition, it was clarified that PEx is defined as intravenous (IV) antibiotic use at home or in the hospital.

Statistical comparisons of the percentage of patients with PEx between the 12-month interval immediately preceding the start of Kalydeco treatment and the first and second 12-month intervals after treatment initiation using the McNemar's test did not show any statistically significant difference between periods in any of the sets of patients analysed except in the overall population (P =0.02) during the first year post-treatment initiation, a result that is driven by the reduction seen in adult subjects. Furthermore, no statistically significant differences were seen in the number of exacerbations in the paediatric groups which is not unexpected. However, in adult patients, a statistically significant difference (P = 0.005) was seen during the first-year post-treatment.

In the 12 months preceding treatment initiation with Kalydeco, the percentage of subjects aged 6 to less than 18 years old who had at least an event of PEx was 10.9%. This figure for the youngest children was 11.5%. At the end of the follow-up of the matched Historical control the percentages in these two groups were 9.6% and 3.7%. The number of subjects in the Kalydeco cohort who had at

least one PEx prior treatment initiation with Kalydeco was systematically higher than that of the Historical cohort which is somehow a striking finding as historical cohorts usually show worse outcomes than more recent cohorts as standard of care improves over time. After treatment initiation, percentages were 6.9% and 8.6% during the second-year post-treatment initiation in the oldest and the youngest age groups respectively which in the case of the latter is still above the value seen in the Historical Cohort; this will be further addressed below.

3. Nutritional Parameters

Kalydeco cohort

Data show that patients with the *R117H-CFTR* mutation tend to have, as a group, normal growth which may be related to the fact that many of them are usually pancreatic sufficient and present with preserved lung function. Treatment with Kalydeco in paediatric patients was not associated with meaningful changes with respect to the period pre-treatment which is not unexpected taking into account the normal range of the mean anthropometric parameters at the index date and during the pre-treatment period.

CF has usually been associated with malnutrition. However, due to early diagnosis, nutritional supplements, and increased prevalence of obesity in the general population, overweight, and obesity in the CF patient population is also of concern. In the Kalydeco cohort there were both malnourished and overweight/obese subjects as shown by the range of values of the growth parameters analysed. Weight-for-age z-score in children aged ≥ 6 to less than 18 years ranged in the year immediately before treatment initiation between -1.7 to 2.4. During the second-year post-treatment these figures were -1.4 and 3.0. In the youngest children in the Kalydeco cohort, two years after treatment initiation weight-for-age z-score ranged from -1.1 to 3.9. While according to WHO definitions no paediatric patients were underweight as the minimum value was above -2SD of the population of reference (but closed to it), the maximum value is indicative that some paediatric patients may be overweight/obese. This is confirmed by the maximum value of BMI-for-age z-score in the two paediatric age groups which exceeds the cut-off of + 2SD (indicative of overweight) and of + 3SD (indicative of obesity). The latter is particularly the case of the youngest children.

In the case of adult patients, the mean BMI values at the year immediately preceding treatment with Kalydeco and during the second year post-treatment were 25.44 kg/m2 and 26.67 kg/m2 which are above the cut-off of 25 that defines overweight according to the WHO definition. The minimum values of BMI also indicate that some subjects were malnourished as shown by minimum BMI values.

The MAH was requested to provide a separate analysis confined to malnourished and overweight/obese paediatric subjects using the appropriate WHO definitions. Nevertheless, the MAH clarified that such analysis was not possible due to the absence of patients meeting the WHO definition of malnourished and the lack of sufficient numbers of overweight/obese patients (<5 expected). This is acceptable by CHMP.

Unmatched Historical cohort

During the initial year of follow-up, the number of patients ≥6 to less than 18 years old and ≥2 to less than 6 years old with data available for weight-for-age was 127 and 93 respectively. This number decreased (i.e., 106 and 72 respectively) at the end of the follow-up. The number of adult patients with available data on body weight and BMI decreased from 249 to 207.

The mean (SD) weight-for-age z-score in the first period of follow-up was 0.3 (1.2) and 0.1 (0.9) for the oldest and the youngest paediatric groups respectively. At the end of the follow-up these values were 0.4 (1.2) in the oldest paediatric cohort and 0.1 (0.9) in the youngest one. Mean (SD) BMI-for-age z-score was in the initial period 0.4 (1.0) and 0.2 (1.0) while in the final period of follow-up they

were 0.4 (1.0) and 0.2 (0.9). Therefore, values of these parameters were within 0.5 SD of the CDC referent population and stable during the 3 years of follow-up.

As for adults, mean (SD) body weight in the initial period was 74.6 kg (17.7) which increased to 75.1 kg (18.5) at the end of the follow-up. Mean (SD) BMI was 25.4 kg/m2 (5.6) and 25.7 kg/m2 (5.6) in these two periods which are in the upper range of what is considered normal weight according to the WHO threshold. As for the Kalydeco cohort, maximum and minimum values indicate that the Historical cohort included underweight and overweigh/obese patients.

4. Deaths and Transplantations

In the Kalydeco cohort, as of 31 December 2018, there were no organ transplants among all paediatric patients <18 years of age. In 2018, there was 1 death among patients ≥2 to <6 years of age. There were 2 deaths in the adult population and 1 adult patient received an organ (kidney) transplant as reported in the first interim analysis (IA1).

No data were provided for the Historical cohort on deaths and transplantation during the follow-up period. Upon request by CHMP, the MAH clarified that these data will be provided with the final study report.

5. Chronic CF Complications

Analyses by individual entities within each of the CF complications analysed have not been performed as they were not prespecified in the study protocol and SAP. In addition, due to sample size limitations and low incidence and prevalence of some of these events in the paediatric population they may not be sufficiently informative.

An increase in the percentage of subjects with sinus disease and pulmonary complications in the three age groups was observed in the first 12 months following treatment initiation with ivacaftor which was attributed by the MAH to the chronic, progressive nature of CF. Indeed, patients with classical CF disease have a high incidence of (chronic) rhinosinusitis. While progression of the disease over time is in line with the observed upward trend of these two complications during the 36 months before treatment initiation, some of the very common adverse events described for ivacaftor overlap with the classical symptoms of rhinosinusitis such as rhinorrhoea, nasal obstruction, mouth breathing, and headache. Therefore, it cannot be ruled out that treatment with ivacaftor may have also contributed to the increased incidence of these complications. Nevertheless, the records of treatment discontinuation during the first 12-month interval post-treatment for the overall population of this cohort were small (i.e., 9.5%) which suggests that these complications could be managed. During the second and third 12-month intervals of treatment, these complications tend to stabilise in paediatric patients while among adult patients their prevalence continued to increase. As for all other outcome measures, additional comparative data between two specific subsets of subjects in the Kalydeco and the matched Historical cohort was requested to gather further information. This has not been provided by the MAH but the data submitted with the Interim Analysis 2 partially address the concern caused by the increased prevalence of these complications in paediatric patients after treatment initiation with ivacaftor.

Trends in other chronic complications including DIOS, hepatobiliary complications, and CFRD showed no discernible patterns in either adults or paediatric patients. Mild to moderate liver enzyme elevations are not uncommon among young children with CF. Treatment with ivacaftor has been associated with liver enzymes increases, in particular transaminases, which is slightly more frequent in young children than in older patients. The present data do not suggest that treatment initiation with Kalydeco is associated with an increase in hepatobiliary complications. The SmPC of Kalydeco includes recommendations to monitor liver function tests.

Data on pancreatitis show a progressive decrease over time in the three age groups of the Kalydeco cohort that seems particularly relevant in the oldest paediatric group and in adult subjects and consistent with literature data on the manifestation and evolution of the CF disease.

6. Pulmonary Microorganisms

The results in terms of pulmonary microorganisms should be interpreted with caution and in light of the changing microbiology of the lung with age. Initially the main colonising bacteria is the Gram-positive *Staphylococcus aureus*, which affects around 50% of patients during infancy. However, its incidence declines later in life and infections with the Gram-negative *Pseudomonas aeruginosa* become more prominent. Other microorganisms also known to infect the CF airways include *H. influenzae*, methicillin-resistant *S. aureus* (MRSA) and *S. maltophilia* which can be routinely and appropriately treated while *Burkholderia (ceno)cepacia* are harder to detect and treat. Infections with B*. (ceno)cepacia* have a low incidence but are associated with a high mortality.

The number of subjects in the Kalydeco cohort with bacterial culture available in the 12-month interval preceding treatment initiation was 99 (≥6 to less than 18 years old), 164 (adults), and 63 (≥2 to less than 6 years old). In the oldest paediatric group, the prevalence of *P aeruginosa* was 16.2% in the 12-month interval preceding treatment initiation and decreased to 15.5%, 9.2%, and 11.0% in the three 12-month intervals following treatment initiation with Kalydeco. In the youngest children, these figures were 15.9% (pre-treatment) and 3.1%, 3.4%, and 0% post-treatment. As expected the highest prevalence is seen in adult subjects, i.e., 43.9% in pre-treatment and 39.7%, 40.4%, and 44.3% in each of three 12-month intervals post-treatment. Overall, the prevalence of *P aeruginosa* numerically decreased during the post-treatment period except for the third 12-motnh interval for which data are not completed.

An ad-hoc analysis performed at the time of the Interim Analysis 1 in a subset of subjects who have data available in all three time intervals pre-treatment and during the first 12 months post-treatment, showed that the number of subjects with available data (i.e., bacterial culture) as indicated was 92 (≥6 to less than 18 years old), 113 (adults), and 50 (≥2 to less than 6 years old). In the oldest paediatric group, the prevalence of *P aeruginosa* was 15.2% in the period from >24 to 36 months pre-treatment and decreased to 13.0% in the first 12-month interval after treatment initiation with Kalydeco. In the youngest children, these figures were 6.0% and 2.0% in these two periods. As expected the highest prevalence is seen in adult subjects, i.e., 50.4% in the first period and 46.0% after treatment initiation with Kalydeco.

The prevalence of methicillin-susceptible *S aureus* (MSSA), a more relevant pathogen for children as many of them with classical CF are chronically colonised by this organism, was 58.6% in the 12-month interval preceding treatment initiation and 56.3%, 63.2%, and 63.4% in the three 12-month intervals following treatment initiation with Kalydeco. In the youngest children, these figures were 15.9% (pre-treatment), and 58.5%, 53.4%, and 58.8% in each of the three 12-month intervals post-treatment. In adult subjects, the prevalence of MSSA was 39.6% (pre-treatment), and 43.6%, 35.1%, and 31.8% post-treatment. The prevalence of methicillin-resistant *S aureus* (MRSA) in the three age groups during the 36 months pre-treatment and after treatment initiation remained below 20%. While in adult patients, after treatment with ivacaftor, the overall prevalence of *P aeruginosa* decreased, this was not the case of *S. aureus* in paediatric patients.

The prevalence of *P aeruginosa* in the 12-month interval prior treatment initiation with Kalydeco seems abnormally high in the youngest paediatric group (15.9%) when compared to the prevalence of the Historical cohort at the beginning of the follow-up period in that cohort (2.2%). Over time, prevalence of *P aeruginosa* tended to increase in the Historical cohort (6.9% at the end of the follow-up period) and to decrease in the Kalydeco cohort (3.4% during the second 12-month interval post-treatment

initiation) for this group of patients. The prevalence of *P aeruginosa* in adult subjects in the Kalydeco cohort pre-and post-treatment as well as that of the Historical cohort are higher than reported for patients with this mutation in CFTR2 (i.e., 27% among 1,819 patients with this mutation in the database distributed as follows: 156 children below 10 years of age, 287 between 10 to 20 years and 661 older than 20 years of age). In the overall population of the Kalydeco and Historical cohorts these percentages are 21.6% (second 12-month interval post-treatment) and 28.3% (at the end of the follow-up period in 2011) which are more similar to the percentage in CFTR2.

In summary, in study 122, treatment with Kalydeco seems to be associated with a limited increase in ppFEV1 and a reduction in PEx that are more relevant for the adult population. Very limited changes are seen in terms of body weight and BMI which is not unexpected given the preserved nutritional status of subjects in the Kalydeco cohort as shown by mean values within the normal range or, even, values exceeding normal weight as overweight/obesity is an increasing concern in patients with CF which may also have a deleterious effect on lung function. Among the 3 age groups in the Kalydeco Cohort, the proportion of patients with sinus disease and pulmonary complications showed an upward trend over time during the 36 months before Kalydeco initiation. During the first 12 months after treatment initiation, the proportion of patients with sinus disease and pulmonary complications continued to numerically increase and later during the second and third 12-month intervals post-treatment, these complications tend to stabilise in paediatric patients while the opposite trend is observed among adult patients. The overall increase observed in the Kalydeco cohort seems to be attributed to disease progression. However, it cannot be completely ruled out that ivacaftor has a role as some of its common adverse effects overlap with the classical symptoms of sinus disease. In terms of pulmonary microorganisms, the prevalence of *P aeruginosa* declined during the first 12 months of treatment as compared to the 12-month interval immediately preceding the index. This was not the case of *S aureus* in paediatric patients.

The above results should be viewed with caution given that missing data may introduce misclassification of exposure and outcomes data in observational studies. The US CFFPR, however, has robust systems in place to minimize missing data in its database. In addition, in observational studies with non-randomised treatment assignments, confounding by indication may be of concern as indeed patients treated with Kalydeco may be systematically different and have different risk factors for adverse outcomes than patients who are not treated. This is limited by the within-group comparison of outcomes in patients for 36 months before and 36 months after initiation of Kalydeco. Finally, precise treatment start dates and event occurrence dates may not be available. Consequently, the person-time data may be unavailable and the temporal relationship between exposure and outcome challenging to establish.

Further, use of a historical cohort from an earlier time period may be biased by the different standards of care that were applied from 2009 through 2011, as well as by differences in the population of CF patients over time. In this respect, it is noted that for the outcome measures of PEx, sinus disease, pulmonary complications and prevalence of *P aeruginosa*, patients in the Kalydeco cohort in the pre-treatment period showed, in general, worse outcomes (i.e., higher frequency) than those of the Historical cohort at the beginning of the follow-up period (and for some of them even at the end of the 3-year follow-up). Considering that historical cohorts usually show worse outcomes than more recent ones as standard of care improves over time, further clarifications were requested. Possible explanations from the MAH include the following, i.e., 1) changes in the standard of care of CF patients over time as well as changes in registry data collection practices over time; 2) the lower frequency of visits in the historical period which may explain also the lower recorded frequency of select outcome measures compared to the pre-treatment period in the Kalydeco Cohort; and 3) channelling bias or confounding by indication, where sicker patients would be more likely to initiate Kalydeco therapy. It is agreed that all, but particularly the channelling bias, appear likely factors that

may contribute to the above findings.

Overall discussion on efficacy

Kalydeco has now been approved down to children aged 6 months and weighing at least 5 kg with CF who have certain gating (class III) mutations in the *CFTR* gene based on single arm pharmacokinetic and safety studies (with efficacy variables collected as secondary/exploratory endpoints). Extrapolation of efficacy from adults to the paediatric population has been accepted based on similar systemic exposure as in adults or older paediatric patients at the selected doses, the mechanism of action of ivacaftor which acts similarly in adults and paediatric patients, a similar response in sweat chloride and on the pathogenesis of the disease that is expected to be comparable between paediatric and adult populations, although there may be significant age-dependency for the presence of certain symptoms and signs of the disease or showing a different pattern of organ damage.

Further, in studies in children under 6 years of age with specified *CFTR* gating mutations, faecal elastase-1 and immunoreactive trypsinogen which are markers of exocrine pancreatic insufficiency, were also assessed. Exocrine pancreatic insufficiency is usually established early in life and the greatest chance to assess whether ivacaftor is able to delay or reverse the progression of this CF complication is in the youngest children. The available results of study 108 (children aged 2 to less than 6 years of age) and of study 124 (children below 2 years of age, still ongoing in the age cohort below 6 months) showed that in some children faecal elastase-1 values reverse to normal or near normal levels. Despite normal or stable lung function as measured by FEV1, studies using high-resolution computed tomography (HRCT) have shown lung damage (such as airway wall thickening and bronchiectasis). HRCT studies in infants with CF who were diagnosed by newborn screening, but were considered clinically healthy, indicate that structural lung damage is common even very early in disease progression. In addition, there may be further systemic beneficial effects expected given that CFTR dysfunction affects multiple organs in CF patients. As life-expectancy in patients with CF increases, other complications, which are also important causes of morbi-mortality, such as CF-related diabetes (*Barrio R, 2015*) and CF-related liver disease (*Leeuwen L et al, 2014*) have emerged which may respond to treatment with CFTR modulators. The benefits of an early intervention have been shown in children diagnosed soon after birth, particularly in what refers to promote normal growth as early diagnosis allows nutritional intervention. Therefore, there is a reasonable expectation that by starting ivacaftor treatment early in life, disease progression can be slowed down or halted on the basis that CFTR modulators target the mutated CFTR protein rather than the downstream consequences of its defect. This is currently being explored in an ongoing registry-based post-authorisation efficacy study of ivacaftor in young children with certain class III gating mutations. Such study has been included in the RMP and final results will be provided as a post-approval commitment.

A major objection was raised to further discuss the rationale behind the proposed unrestricted indication, in particular for children under the age of 6 years (and even more under 2 years of age), as ivacaftor is expected to be administered lifelong in these children, who may be minimally symptomatic at the time of diagnosis and who may eventually not develop the classical form of disease. Additionally, the MAH was also requested to discuss possible markers allowing the identification of young CF patients at a higher risk of lung disease as well as the upward trend in sinus disease and pulmonary complications seen during the 12 months post Kalydeco treatment. In response, no markers which may permit the identification of young CF patients with the *R117H-CFTR* mutation who are at higher risk of lung disease (or other complication of CF) were discussed on grounds that CF disease is present since birth as shown (e.g.) by structural lung disease in high-resolution computed tomography. Regarding the upward trend of sinus disease and pulmonary complications that was observed in the Kalydeco cohort of study 122 during the first 12 months following treatment initiation

with ivacaftor, the additional data presented in the Interim Analysis 2 showed that in the paediatric age groups both complications tended to stabilise during the second and third 12-month interval post-treatment. This is acknowledged by CHMP.

According to current diagnostic consensus guidelines, the diagnosis of CF is confirmed if the subject harbours an *R117H-5T* mutation. For subjects with an *R117H-7T* mutation, the diagnosis of CF is confirmed in case sweat chloride is above 60 mmol/l or other evidence of CFTR dysfunction is present (e.g., nasal potential difference or intestinal current measurement). The diagnosis of CF is not confirmed in case of an *R117H-7T* mutation and sweat chloride below 60 mmol/l in the absence of advanced testing as above mentioned. In Europe, these babies are named CF screen positive inconclusive diagnosis (CFSPID), and a balance is trod between 'ignoring' their potential for developing problems and over-medicalising them. Currently most infants detected on newborn screening with an *R117H-7T* will not fulfil CF diagnostic criteria and will remain asymptomatic. Children with an *R117H-7T* mutation who does not fulfil the current, stringent diagnostic criteria for CF should not be treated with CFTR modulators unless their diagnosis evolves over time and/ or is influenced by the development of CF disease or a relevant family history, all of which would be grounds to reconsider the treatment with CFTR modulators. Given that sweat chloride concentrations may increase, particularly in the first few years of life, these can be monitored in those with intermediate levels initially.

Therefore, the key issue in the view of the CHMP is the confirmation of the diagnosis of cystic fibrosis in presence of the *R117H-CFTR* mutation. In asymptomatic young children this requires genetic analysis (including the poly-T status) and sweat chloride determination. Most subjects with the *R117H-7T* mutation will never developed cystic fibrosis but as there are cases reported, the CHMP considered that the indication should be kept broad (for patients with CF and *R117H* mutation) to allow treatment of the subjects if needed.

In summary the data provided in this application for patients less than 18 years are considered sufficient to approve the extension of indication of Kalydeco to paediatric patients with CF and the *R117H* mutation considering also extrapolation of efficacy from adult subjects with the *R117H-CFTR* mutation.

2.4.4. Conclusions on the clinical efficacy

The final clinical study report of study 112, submitted two years after the initial application, gives reasonable reassurance that the seemingly deteriorating effect of ivacaftor in lung function seen in study 110 in children aged 6 to 11 years old (inclusive) was not present, although the magnitude of the effect of ivacaftor in ppFEV1 was limited. A positive effect was also seen in the respiratory domain of the CFQ-R. Further, the magnitude of the decrease of sweat chloride in these paediatric patients was similar to the reduction seen in adult subjects. The trends in outcomes in paediatric patients observed in the interim analysis of Study 122 are consistent with the trends observed in adult patients with the *R117H-CFTR* mutation, and with the known benefit-risk profile of ivacaftor.

The CHMP considered that extrapolation of efficacy from adults with *R117H* mutation to children may be applied on the basis that adequate systemic exposure is achieved in children/adolescents, there are evidence that the same disease process exists in both adults and children; and the ivacaftor mechanism of action and the sweat chloride/CFTR response to ivacaftor is similar across age groups.

In light of the above, the CHMP concluded that the indication claimed, i.e., for the treatment of paediatric patients aged 6 months and older WITH cystic fibrosis AND who have an *R117H* mutation is therefore acceptable.

2.5. Clinical safety

Study 110 and Study 112

Comparative safety data have been generated in a small number of paediatric patients aged 6 years and older and in a single adolescent (n = 10) with CF and the *R117H* mutation who have been treated with ivacaftor in study 110 up to 24 weeks. Longer-term safety data up to 96 weeks of additional treatment are available from study 112. Both studies were assessed in prior procedures and therefore only a brief summary is provided below.

The safety set of study 110 included 69 patients (adults and paediatric subjects) who have received at least 1 dose of ivacaftor or placebo. Analysis of the occurrence of AEs and SAEs, including events of special interest, laboratory parameters, safety data in special populations, etc., did not reveal major inconsistencies with the already known profile of ivacaftor. It is likely that the limited number of patients enrolled in study 110 contributed to the difficulty to capture the AEs that occur less frequently.

Study 112 enrolled patients with CF who completed study 110, study 111 (patients with a non-*G551D-CFTR* mutation), and study 113 (patients who have phenotypic or molecular evidence of residual CFTR function). Study 110 contributed with 54% of the studied safety population.

Overall, results of the safety assessment indicated that ivacaftor was well tolerated for up to 96 weeks of additional treatment. The safety findings were also consistent with the known safety profile of ivacaftor. Although an increase in blood pressure without clinical relevance was identified, no changes in the Product Information were deemed necessary at this stage. Nevertheless, the MAH was requested to closely monitor this safety concern in future PSURs.

The number of children aged 6 to 11 years of age (inclusive) and adolescents with an *R117H* mutation is very small for a full characterisation of the safety profile of ivacaftor in children. However, given that the genotype has not been identified as relevant from the safety perspective, reassurance on the safety profile is obtained from paediatric patients with class III gating mutations. The ivacaftor safety database includes 61 patients between 6 to less than 12 years of age and 94 patients between 12 to less than 18 years of age.

Similarly, for children aged 2 years to less than 6 years who have the *R117H* mutation, the only source of data is study 122 (see below) but safety can be also extrapolated from children with class III gating mutations enrolled in study 108 (2 to less than 6 years old) which have been assessed in procedure EMEA/H/C/002494/X/34. The ivacaftor safety database includes 34 patients between 2 to less than 6 years of age.

Study 122

In this study children 2 to less than 6 years of age, ≥6 to less than 18 years of age, and adults all of them with the *R117H* mutation are being followed. Study 122 is the only source of data in children aged 2 to less than 6 years with this variant. Although one of the stated objectives of this study is to confirm the long-term safety of ivacaftor, no detailed discussion is provided on safety in the report of the interim analysis 2 but some of the outcome measures of the study (e.g., deaths, some selected disease complications etc.) are useful from a safety perspective. Given that study 122 is a non-interventional study based on the secondary use of data, reporting of suspected adverse reactions as individual case safety reports is not required. This is acknowledged.

Death

Three deaths have been reported in the Interim Analysis 2 in the Kalydeco cohort of this study, two adult patients and a child aged ≥2 to less than 6 years died.

Sinus disease and pulmonary complications

An increase in sinus disease and pulmonary complications was observed in all age groups before treatment initiation and during the first 12 months after treatment initiation in the Interim Analysis 1.

Sinus disease:

In subjects with non-missing encounter data, 12 months before treatment initiation the percentage of paediatric patients with sinus disease in the age group ≥6 to less than 18 years old, adults, and children ≥ 2 to less than 6 years old was 25.5%, 49.1%, and 9.7% respectively.

Twelve months after treatment initiation, these figures were 30.5%, 55.2%, and 10.8% respectively.

During the second 12-month interval, the percentage of patients with sinus diseases was as follows: 28.7%, 61%, and 10.5%.

Pulmonary complication:

Regarding pulmonary complications, 12 months before treatment initiation the percentage of paediatric patients ≥6 to less than 18 years old, adults, and children aged to 2 to less than 6 years was 30.6%, 43.3%, and 9.7% which increased to 37.1%, 44.3%, and 12.3% during the first 12 months after treatment initiation respectively. In the second 12-month interval after treatment initiation these figures were 35.6%, 47.2%, and 12.3% respectively.

Data from the Interim Analysis 2 suggest that in the paediatric population sinus disease and pulmonary complications tended to stabilise in the second 12-month interval following treatment. However, this was not the case for adult subjects where the numerical increase continued.

No safety data are available for children under 2 years of age who have the *R117H-CFTR* mutation. Safety, in this case, is extrapolated from children with class III gating mutations enrolled in study 124 below 2 years of age. The ivacaftor safety database includes 25 patients between 12 months to less than 24 months of age and 14 patients between 6 months to less than 12 months of age.

Post marketing experience

Since the initial IVA marketing approval in January 2012, more than 6500 patients have been treated with IVA, representing over 17,000 person-years of exposure. Post-marketing exposure in patients less than 18 years of age is estimated to be approximately 30% of overall post-marketing exposure. The safety data from post-marketing experiences were consistent with data from clinical studies, including the 5-year post-authorization safety study (PASS), and are also consistent between patients 18 years of age and older and patients less than 18 years of age.

2.5.1. Discussion on clinical safety

The overall safety database of paediatric patients is small, in particular for the youngest children but supported by post-marketing data. Safety risks from placebo-controlled studies (study 103 and study 110) and from single arm studies (study 108 and study 124) did not reveal significant unfavourable effects which were not known already.

With regards to study 122, although one of the stated objectives was to confirm the long-term safety of ivacaftor, no discussion could be found on safety in the interim analysis reports. While some of the outcome measures could be useful from a safety perspective (e.g., deaths, some selected disease complications etc.) when it comes to adverse events no data were provided. Upon request by CHMP,

the MAH clarified that as study 122 is based on the secondary use of data, reporting of suspected adverse reactions as individual case safety reports is not required. This was acknowledged by CHMP.

Increase in sinus disease and pulmonary complications were seen in the Kalydeco cohort of study 122. The MAH was of the view that those observations made over time and during the first year after treatment initiation with ivacaftor were consistent with the chronic and progressive nature of CF. Patients with classical CF disease have a high incidence of (chronic) rhinosinusitis. Nevertheless, some of the common adverse events described for ivacaftor overlap with the classical symptoms of rhinosinusitis such as rhinorrhoea, nasal obstruction, mouth breathing, and headache. Therefore, it cannot be ruled out that treatment with ivacaftor may also be contributing to the increased incidence of these complications. However, the records of treatment discontinuation in the registry for the overall population of this cohort were small (i.e., 9.5%) during the first year which suggests that these complications could be managed. Although, comparative data in specific datasets of subjects in the Kalydeco cohort and in the matched Historical cohort were requested to gather further information, this has not been done by the MAH. Nevertheless, the request is partially superseded by the results of the Interim Analysis 2 which show that sinus disease and pulmonary complications tended to stabilise during the second year of treatment in the paediatric population while this was not the case for adult patients. Indeed, for adult patients with poor lung function it has been described that increased bronchial secretions may warrant increased physiotherapy and intravenous antibiotic treatment when ivacaftor is initiated.

Further, mild to moderate liver enzyme elevations are not uncommon among children with cystic fibrosis. Treatment with ivacaftor has been associated with liver function enzymes increase, in particular transaminases, which is slightly more frequent in young children than in older subjects. Data from study 122 do not suggest that treatment initiation with Kalydeco is associated with an increase in hepatobiliary complications. Therefore, no update of the safety profile is necessary. Section 4.8 adequately described the safety profile in the population less than 18 years of age.

2.5.2. Conclusions on clinical safety

Overall, the safety profile of ivacaftor in patients with *R117H-CFTR* mutation in study 110 and study 112 was consistent with the already known safety profile for this medicinal product. The additional data presented in study 122 show that the increase seen in sinus disease and pulmonary complications during the first year of treatment tended to stabilise during the second 12-month interval in the paediatric patients.

The safety data are limited especially in very young patients, however given the current experience and indication in children above 6 months for other mutations, extrapolation of safety from these patients is acceptable and support approval in patients with cystic fibrosis and with *R117H* mutations above 6 months of age.

The SmPC adequately reflects the safety profile for the patient population above 6 months of age in patients with cystic fibrosis and with an *R117H* mutation.

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 8.7 with this application to include study 122 in the pharmacovigilance plan. In addition, other versions of the RMPs are currently under review in other ongoing procedures. A consolidated version of the RMP should be submitted at the finalisation of all those ongoing procedures.

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

The PRAC considered that the risk management plan version 8.7 is acceptable.

The CHMP endorsed the Risk Management Plan version 8.7 with the following content:

Safety concerns

Important identified risks	None
Important potential risks	• Hepatotoxicity • Cataract • Concomitant use of IVA with strong CYP3A inhibitors and inducers
Missing information	• 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: • 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>	• Hepatotoxicity • Cataract • Use in children aged 12 to <24 months old at initiation	Final Report	March 2022

Study/Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
	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			
Study 122 Ongoing	• To confirm the long-term safety and effectiveness of Kalydeco (IVA) in US CF patients with the *R117H-CFTR* mutation <18 years of age • To describe the long-term safety and effectiveness of Kalydeco in CF patients with the *R117H-CFTR* mutation overall and in patients ≥18 years of age	• Indicated use in children aged <6 years (with the *R117H* mutation)	Final Report	December 2020

CF: cystic fibrosis; IVA: ivacaftor; PD: pharmacodynamics
Note: Studies 126 and 122 address 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	**Routine risk minimisation measure:** SmPC Section 4.4 where advice is given on monitoring LFTs. SmPC Section 4.8 PL Section 4 **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection** Prescription only **Additional PV activities:** Study 126
Cataract	**Routine risk minimisation measure:** SmPC Section 4.4 where advice is given on recommended ophthalmological examinations SmPC Section 5.3 PL Section 2 **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection** Prescription only **Additional PV activities:** Study 126

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Concomitant use of IVA with strong CYP3A inhibitors or inducers	**Routine risk minimisation measure:** SmPC Section 4.2 where dose reductions are recommended when co-administered with a strong inhibitor of CYP3A. SmPC Section 4.4 PL Section 2 **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection** Prescription only **Additional PV activities:** None
Use in pregnant and lactating women	**Routine risk minimisation measure:** SmPC Section 4.6 where advice is given on to use Kalydeco during pregnancy only if clearly needed and during breastfeeding if the potential benefit outweighs the potential risks. PL Section 2 **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection** Prescription only Pregnancy follow-up form **Additional PV activities:** None
Indicated use in children aged less than 6 years	**Routine risk minimisation measure:** SmPC Section 4.2 where the posology is described SmPC Sections 4.8 and 5.2 PL Section 2 **Additional risk minimisation measures:** No risk minimisation measures	**Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection** Prescription only **Additional PV activities:** Study 126 Study 122

CYP: cytochrome P450, PL: Patient Leaflet; SmPC: Summary of Product Characteristics
Note: Studies 126 and 122 address a subpopulation of the Missing Information of "Indicated use in children aged less than 6 years."

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4 and 5.1 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 therefore it is considered that a user consultation with target patient groups is not needed.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Cystic fibrosis is an autosomal recessive monogenic disorder affecting approximately 70,000 individuals worldwide. It is caused by variants in the cystic fibrosis transmembrane conductance regulator (CFTR), a cAMP-regulated chloride and bicarbonate channel. CF manifests considerable allelic heterogeneity with over 2,000 CFTR variants identified to date and broad clinical variability, rendering the relationship between genotype and phenotype difficult to fully elucidate.

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

While severe *CFTR* genotypes are associated with early-onset pancreatic insufficiency and severe respiratory disease, genotypes with one or more residual *CFTR* function mutation, such as *R117H-CFTR*, can initially present with preserved respiratory and pancreatic functions.

The *R117H-CFTR* mutation is a missense mutation that results in the replacement of an arginine residue at position 117 of CFTR with a histidine residue. The prevalence of the *R117H-CFTR* mutation among individuals with CF is estimated to be 1.0% in Europe and 5.5% in the UK.

R117H is associated with varying clinical consequences and is influenced by the poly-T status of the *cis*-located intron 8 polythymidine tract. Poly-T tract is present in every copy of the *CFTR* gene and occurs in one of three forms: 5T, 7T, or 9T. Depending on which poly-T form is present, differing outcomes may occur. The combination of *R117H/5T* with a second CF-causing mutation such as *F508del* is expected to result in CF while the combination of *R117H/7T* is unlikely to act as a disease-causing variant (particularly for females) but may result in male infertility. However, a person with this combination of variants and this form of the poly-T tract may have borderline or elevated sweat chloride and mild clinical symptoms of CF. *R117H/9T* is highly unlikely to act as a disease-causing variant and will not lead to CF in the majority of cases. Nevertheless, there may be other genetic and environmental factors which may also play a role on the phenotypic expression of the disease in individual patients.

Kalydeco tablets are currently authorised for the treatment of adults aged 18 years and older with cystic fibrosis (CF) who have an *R117H* mutation in the *CFTR* gene while Kalydeco granules are not yet approved for patients with CF and an *R117H* mutation.

The aim of the present procedure is the extension of the indication of Kalydeco tablets to children aged 6 years and above and weighing 25 kg or more with CF who have an *R117H* mutation in the *CFTR* gene; and to extend the indication of Kalydeco granules to children aged at least 6 months and weighing 5 kg to less than 25 kg with CF who have an *R117H* mutation.

Dosing recommendations for patients aged 6 months and older:

- 25 mg twice daily for patients weighing between 5 to < 7 kg
- 50 mg twice daily for patients weighing between 7 kg to <14 kg
- 75 mg twice daily for patients weighing between 14 kg to <25 kg
- 150 mg twice daily for patients weighing ≥25 kg

3.1.2. Available therapies and unmet medical need

There is currently no fully effective cure for CF. The majority of CF therapies available including nutritional supplements, antibiotics, and mucolytics target the downstream consequences and symptoms of the disease. The CFTR modulators such as ivacaftor are small molecules that target the functional defect of the mutant CFTR protein. These CFTR modulators are not a cure for CF and must be taken chronically for the patient to maintain treatment benefits.

At present, there are no CFTR modulators approved for the treatment of paediatric subjects with cystic fibrosis and with the *R117H* mutation.

3.1.3. Main clinical studies

This application corresponds to an extension of the indication of Kalydeco tablets and granules for the treatment of patients with cystic fibrosis aged 6 months and older who have an *R117H* mutation in the *CFTR* gene. It is based on one main clinical study (study VX11-770-110) and two supportive clinical studies (study VX11-770-112 and study VX15-770-122).

Study VX11-770-110 (study 110) is a phase 3, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of ivacaftor in subjects aged 6 years of age and older with cystic fibrosis who have the *R117H-CFTR* mutation. This study was assessed in EMEA/H/C/002494/II/27 and led to the granting of an indication for adult patients with an *R117H-CFTR* mutation based on a pre-specified subgroup analysis by age. However, the request for adolescents (n=2) and children (aged 6 and older, n=17) was rejected.

Study VX12-770-112 (study 112) is an open-label, rollover study designed to evaluate the safety (primary endpoint) and efficacy of long-term (approximately 104 weeks) ivacaftor treatment. This study enrolled patients with CF who completed study 110, study 111 (patients with a non-*G551D-CFTR* gating mutation), and study 113 (patients who have phenotypic or molecular evidence of residual CFTR function). Interim data (until week 12) and the final study report of study 112 were assessed in EMEA/H/C/002494/II/27 and EMEA/H/C/002494/II/0054 respectively.

Study VX15-770-122 is a non-interventional registry-based study of ivacaftor in patients with the *R117H-CFTR* mutation, aimed at confirming the long-term effectiveness and safety of Kalydeco in both paediatric patients (≥2 to <18 years of age) and adults in the US (i.e., in the Cystic Fibrosis Foundation Patient Registry, CFFPR).

Of note, studies in children under 6 years of age with CF who have at least a pre-specified class III gating mutations are also relevant for this application because they provide the needed data to support extrapolation of PK and safety to CF children below that age with the *R117H* mutation.

3.2. Favourable effects

Study 110-patients with *R117H* mutation:

Adult patients

In study 110, the mean absolute change from baseline in percent predicted FEV1 through week 24 for patients ≥18 years of age was greater for the ivacaftor group (4.51 percentage points) than the placebo group (-0.46 percentage points). The treatment difference of ivacaftor versus placebo was 4.96 percentage points (95% CI: 1.15, 8.78). This improvement in ppFEV1 was accompanied by a decrease from baseline in sweat chloride (21.87 mmol/l) and by an increase in the respiratory domain of the pooled Cystic Fibrosis Questionnaire-Revised (CFQ-R) above the minimal clinically important difference (mean treatment difference was 12.64 points). The response was larger in subjects with the *R117H-5T* variant than in subjects with the *R117H-7T* variant with a treatment difference of ivacaftor vs. placebo at week 24 of 6.87 pp (95% CI: 2.19, 11.56) favouring ivacaftor.

Adolescents (n=2)

Only two adolescents were enrolled in study 110 and rolled over into study 112. In study 112, at week 84, the mean (SD) change from baseline in ppFEV1 was 5.8 (4.9) percentage points and decreased to 2.6 (6.4) at the earlier termination visit. No issues of concern were identified in either study 110 or study 112 but overall definitive conclusions on efficacy could not be reached based on the small number of paediatric patients.

Children from 6 to 11 years (n=17)

A relevant mean reduction in sweat chloride levels was seen in all age subgroups in the ivacaftor arm, including 6 to 11 years of age (-26.59 mmol/L) in comparison with 1.04 mmol/L for the placebo group. Further, mean sweat chloride reduction was detected by Week 2 (first post-baseline time point assessed; -25.22 mmol/L) and were sustained through Week 24. The magnitude of the mean reduction was very similar to that of subjects ≥18 years of age in the ivacaftor arm. Treatment differences at all time points where sweat chloride levels were determined favoured ivacaftor.

Study 112 (Follow up of study 110) - Children from 6 to 11 years (n = 10)

Thirteen children rolled over from study 110 into study 112. Their mean baseline ppFEV1 was 90.7 percentage points. Children from study 110 experienced a mean (SE) absolute change in ppFEV1 of 4.0 percentage points (2.5) and 8.6 percentage points (3.2) at week 48 (n=10) and week 96 (n=5) respectively. Results from study 112 in children were reassuring in that the seemingly deteriorating effect in ppFEV1 seen in study 110 was not seen in this age group at a longer duration of exposure. Similarly, a response in the respiratory domain of CFQ-R was observed at almost all time points in study 112. Changes from baseline in the 6 to 11 years of age subgroup remained above the MCID at almost all time points and ranged from 3.2 to 10.3 points.

Study 122 (Non interventional study) – Adults and paediatric patients aged 2 to less than 18 years:

In study 122 in the Kalydeco cohort for 'paediatric patients aged 6 to <18 years', the mean (SD) ppFEV1 increased from pre-treatment baseline during the first 12 months of Kalydeco treatment (1.1 [7.2]); this increase was maintained in the second (0.5 [9.1]) 12-month interval after treatment initiation among patients who had available data in the respective intervals. The percentage of patients with at least one pulmonary exacerbation was reduced from 10.1% (12-month pre-treatment) to 6.9% (24 months post-treatment). Similarly, the mean number of pulmonary exacerbations changed from 0.13 to 0.07 in these two periods. For 'children aged 2 years to less than 6 years', these figures were 10.8% and 0.15 pre-treatment and 8.6% and 0.12 post-treatment. The prevalence of pancreatitis decreased in paediatric patients aged ≥6 to less than 18 years (from 6.1% pre-treatment to 2.3% during the second 12-month interval post-treatment) and in adults (10.5% pre-treatment to 7.3% post-treatment).

Extrapolation of efficacy from adults to the paediatric population has been accepted based on 1) similar systemic exposure as in adults or older paediatric patients at the selected doses, 2) the mechanism of action of ivacaftor which acts similarly in adults and paediatric patients, 3) a similar response in sweat chloride and 4) on the pathogenesis of the disease although there may be significant age-dependency for the presence of certain symptoms and signs of the disease or showing a different pattern of organ damage.

Overall, the main clinical study in adults with *R117H* mutations and in particular the positive sweat chloride results along with the well-established PK for ivacaftor in the adolescents and children population support extrapolation of efficacy to younger patients <18 years of age with *R117H* mutation. Additionally, the post marketing experience in children with the *R117H-CFTR* mutation outside EU provide supportive data.

3.3. Uncertainties and limitations about favourable effects

The very low number of subjects involved in the main pivotal study (study 110) was a limitation especially in the younger age of the group. In study 110, 17 children (8 patients on placebo; 9 on ivacaftor) and 2 adolescents (one in each group) were enrolled.

In children aged 6 to 11 years (inclusive), the mean ppFEV1 was >93% for both treatment groups at all time points. While the mean ppFEV1 for the placebo group at baseline was 93.98 pp, the mean during the treatment period ranged from 97.36 (Week 2) to 99.10 pp (Week 8). The mean ppFEV1 for the ivacaftor group at baseline was 97.49 pp and ranged from 93.46 pp (Week 2) to 99.01 pp (Week 8) during the treatment period.

In these children, the mean treatment difference for the absolute change from baseline in ppFEV1 was -6.3 percentage points (95% CI: -11.96, -0.71) favouring the placebo group. With the exception of the sweat chloride response, no other meaningful clinical responses to ivacaftor treatment (i.e., anthropometric parameters, respiratory domain score of the CFQ-R questionnaire, and pulmonary exacerbations) were seen in children. In this age group, the ppFEV1 treatment difference favoured placebo, which the MAH interpreted as a spurious result driven by an unusual placebo response and generally no or minimal change in FEV1 in the ivacaftor group. In spite of that, the indication in the EU was restricted to adults with cystic fibrosis who have the *R117H-CFTR* mutation.

There are certain limitations with study 112, in particular the clinical design of such study (uncontrolled study) as well as the very small number of paediatric patients (n=15) who rolled over from study 110 and which was further decreased towards the end of the study as patients were transferred to commercial drug. Based on the inherent limitations of non-randomised studies, the results of study 112 should therefore be interpreted with caution.

Results for the age group from 6 to less than 18 years of age are presented together in study 122. However, compared to children, adolescents are at a higher risk of lung function decline. The lack of comparative matched cohort data provide limitation to the results. Indeed, demographic and disease characteristics at baseline for children (6 to 12 years of age) and for adolescents in specific subsets of cohorts was not satisfactorily addressed by the MAH despite the request by CHMP. Further, patients in the Historical cohort could not be matched to those in the Kalydeco cohort which limits the accuracy of the conclusions that can be reached by comparing these two cohorts.

In addition, for study 122, use of a historical cohort from an earlier time period may be biased by the different standards of care and by potential differences in the CF population over time. In this respect, for the outcome measures of PEx, sinus disease, pulmonary complications and prevalence of *P aeruginosa*, patients in the Kalydeco cohort in the pre-treatment period showed, in general, worse

outcomes (i.e., higher frequency) than those of the Historical cohort. Possible explanations of the unusual worse outcomes of the Kalydeco cohort in comparison to Historical cohort include 1) changes in the standard of care of CF patients over time as well as changes in registry data collection practices over time; 2) the lower frequency of visits in the historical period which may explain also the lower recorded frequency of select outcome measures compared to the pre-treatment period in the Kalydeco Cohort; and 3) channelling bias or confounding by indication, where sicker patients would be more likely to initiate Kalydeco therapy. The channelling bias, in particular, appears a likely factor that may contribute to the above finding.

Further, the impact of missing data which may introduce misclassification of exposure and outcomes data as well as the potential confounding by indication may be of concern as patients treated with Kalydeco may be systematically different and have different risk factors than patients who are not treated. Although more robust data have been presented with the request for supplementary information in the form of an additional interim analysis (IA2) covering until 24 months (and for a number of patients until 36) of follow-up under ivacaftor treatment the above concerns cannot be ignored. In addition, the prevalence of certain cystic fibrosis complications is lower in the paediatric population than in adults which may make it difficult to accurately capture them.

3.4. Unfavourable effects

The overall comparative safety database of paediatric patients with an *R117H* mutation is small and limited to children aged 6 years and older. Children below that age have not been enrolled in clinical studies. Due to the very limited safety data especially in very young patients, safety is extrapolated from patients with gating (class III) mutations enrolled in study 108 and study 124.

In study 110, the adverse events with the highest incidence in both treatment groups were infective pulmonary exacerbations of CF and cough. Treatment AEs with at least 5% higher incidence with ivacaftor compared to placebo included nasal congestion, oropharyngeal pain, abdominal pain, wheezing, upper airway cough syndrome, bacterial disease carrier, influenza-like illness, and abdominal discomfort. All of them have been reported in prior studies and are included in section 4.8 of the SmPC. Lens opacities, which are of concern in the paediatric population, were not reported in study 110.

Nevertheless, results of the safety assessment indicated that ivacaftor was well tolerated. Further, analysis of the occurrence of AEs and SAEs, including events of special interest, laboratory parameters, safety data in special populations, etc., did not reveal major differences with the known safety profile of ivacaftor.

In study 112, an increase in blood pressure without clinical relevance was identified. No changes to the PI were deemed necessary. This safety concern is currently monitored in the post-marketing setting as part of PSURs.

Treatment with ivacaftor has been associated with liver function enzymes increase, in particular transaminases, which is slightly more frequent in young children than in older subjects. Data from study 122 do not suggest that treatment initiation with Kalydeco is associated with an increase in hepatobiliary complications which is reassuring.

Three deaths (one in a young paediatric patient and two in adults) have been reported in the Kalydeco cohort of study 122.

In study 122 an observed increase in sinus disease and pulmonary complications in the Kalydeco cohort was observed consistent with the chronic and progressive nature of CF. Interim Analysis 2 results showed that sinus disease and pulmonary complications stabilised during the second year of

treatment in the paediatric population while this was not the case for adult patients. Trends in other chronic complications in paediatric patients including distal intestinal obstruction syndrome and hepatobiliary complications, showed no discernible patterns.

Patients with classical cystic fibrosis disease have a high incidence of chronic rhinosinusitis, therefore the increased frequency of sinus disease and pulmonary complications with ivacaftor (Kalydeco cohort) observed in the three age groups could be linked with the chronic, progressive nature of CF. Some of the common adverse events described for ivacaftor overlap with the classical symptoms of rhinosinusitis such as rhinorrhea, nasal obstruction, mouth breathing, and headache. The interim analysis (IA2) covering 24 months (36 months follow-up for some patients) showed that sinus disease and pulmonary complications tended to stabilise over time in the two paediatric age groups but not in adult patients. However, it cannot be ruled out that treatment with ivacaftor may also be contributing to the increased incidence of these complications. The MAH did not provide comparative data in specific datasets of subjects in the Kalydeco cohort and in the matched Historical cohort as requested by CHMP to allow firm conclusion.

Post-marketing exposure in patients less than 18 years of age represents approximately 30% of overall post-marketing exposure (about 17,000 person-years). The safety data from post-marketing experiences were consistent with data from clinical studies, including the 5-year post-authorization safety study (PASS), and are also consistent between patients 18 years of age and older and patients less than 18 years of age.

Overall, no update of the safety profile is necessary and section 4.8 adequately describes the safety profile in the paediatric population less than 18 years of age.

3.5. Uncertainties and limitations about unfavourable effects

The number of children aged 6 to 11 years of age and adolescents with an *R117H* mutation for which comparative (24 weeks) safety data are available from study 110 is very small (n=19) to allow an appropriate characterisation of the safety profile of ivacaftor. Longer-term safety data have been generated in study 112 only in 15 of these patients. Further, the only data available for children aged 2 to less 6 years of age who have the *R117H* mutation come from the observational study 122 which is a non-interventional study based on the secondary use of data and thus reporting of suspected adverse reactions as individual case safety reports is not required which limits the availability of safety data in paediatric patients with CF and an *R117H* mutation.

Further, study 122 is a registry-based observational study and therefore has inherent limitations such as the potential impact of missing data which may introduce misclassification of exposure and outcomes data as well as the potential confounding by indication which is also of concern as patients treated with Kalydeco may be systematically different and have different risk factors than patients who are not treated.

The higher frequency of pulmonary exacerbations, sinus disease, pulmonary complications and prevalence of *P aeruginosa*, at the beginning and even at the end of the 3-year follow-up period (for some patients) observed in the Kalydeco cohort compared to the Historical cohort would not be expected as historical cohorts usually show worse outcomes than more recent ones as standard of care improves over time. It is reassuring, however, that the records of treatment discontinuation during the first year post-treatment in study 122 for the overall population of the Kalydeco cohort were small (i.e., 9.5%) which suggests that these complications could be managed. Potential explanations for the observed numeric differences could be due to changes in the standard of care of CF patients as well as changes in registry data collection practices over time; lower frequency of visits in the historical period (leading to a lower recorded frequency of outcome measures) compared to the pre-treatment period

in the Kalydeco Cohort; and channelling bias or confounding by indication, where sicker patients would be more likely to initiate Kalydeco therapy. All of them, but particularly the channelling bias, appear likely factors that may contribute to the above finding.

No safety data are available for children under 2 years of age who have the *R117H-CFTR* mutation. Safety, in this case, is extrapolated from children with class III gating mutations enrolled in study 124 (below 2 years of age).

3.6. Effects Table

The only study which has not been previously assessed is study 122, a non-interventional registry-based study. As such, reporting of suspected adverse reactions as individual case safety reports is not required and therefore, no effects table could be provided.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

A consistent effect in sweat chloride has been observed in all age subgroups in the pivotal study 110.

A relevant mean reduction in sweat chloride levels was seen in all age subgroups in the ivacaftor arm, including 6 to 11 years of age (-26.59 mmol/L) in comparison with 1.04 mmol/L for the placebo group. Further, mean sweat chloride reduction was detected by Week 2 (first post-baseline time point assessed; -25.22 mmol/L) and were sustained through Week 24. The magnitude of the mean reduction was very similar to that of subjects ≥18 years of age in the ivacaftor arm. Treatment differences at all time points where sweat chloride levels were determined favoured ivacaftor.

The principles of extrapolation apply in what refers to the systemic exposure in children, observed to be within the range of adult systemic exposure to efficacy as well as on the similar reduction in sweat chloride observed in study 110 across all age groups in the ivacaftor arm.

Clinical efficacy data are provided in adult, adolescents, and children patients with *R117H* mutation from studies 110, 112 and 122. These data provide some support of clinical efficacy in children above 2 years of age. Results from study 112 in children aged 6 to less than 12 years (n=15) were reassuring in that the seemingly deteriorating effect in ppFEV1 seen in study 110 was not kept in this age group at a longer duration of exposure. As for study 122, the second interim analysis in paediatric patients less than 18 years old provides reassurance in terms also of ppFEV1 as well as pulmonary exacerbations.

From a safety perspective, the database of paediatric subjects enrolled in study 110 and study 112, is small but further reassurance on the safety profile across age groups is obtained from children of the same age with gating (class III) mutations as well as by post-marketing data. The limitation in terms of size is particularly evident for very young children as safety data is available for 25 patients between 12 months to less than 24 months of age and 14 patients between 6 to less than 12 months of age with class III gating mutations).

An increase in sinus disease and pulmonary complications was seen in all subjects in the Kalydeco cohort of study 122 during the first-year post-treatment initiation but tended to stabilise in the paediatric population over time which seems reassuring. Sinus disease and pulmonary complications will be further reviewed as part of the final study report for study 122 expected to be finalised by December 2020.

Overall, results of the safety assessment indicated that ivacaftor was well tolerated and consistent with the known safety profile of ivacaftor.

The safety data from post-marketing experiences were consistent with data from clinical studies, including the 5-year post-authorization safety study (PASS), and similar between adults and paediatric patients less than 18 years of age.

3.7.2. Balance of benefits and risks

This application is based on clinical PK, efficacy, and safety data in paediatric patients with an *R117H* mutation. The PK of ivacaftor is well understood and is consistent across genotypes and among age ranges down to 6 months of age based on completed studies.

Taking into consideration that genotype was not identified as a relevant covariate explaining variability of ivacaftor pharmacokinetics and the safety profile was overall similar and acceptable across age groups and genotypes, the approved posology for children aged 6 months (weighing at least 5 kg) and older with CF who have a (pre-specified) gating (class III) mutation in the *CFTR* gene is considered to be also applicable to children of the same age and body weight with CF who have an *R117H-CFTR* mutation.

Extrapolation of efficacy from adults has been the principle on which ivacaftor has been approved for children younger than 6 years of age with some pre-specified gating (class III mutations) based on single arm studies assessing the PK and safety of ivacaftor with efficacy endpoints collected as secondary endpoints. The same approach is proposed for children with the *R117H* mutation.

Interim data from the non-interventional registry-based study 122 provide further reassurance that the use of ivacaftor may be of benefit for paediatric patients in terms of lung function (ppFEV1), pulmonary exacerbations, *P. aeruginosa* lung colonisation, and pancreatitis to which patients with the *R117H* mutation may be prone to.

The results of the safety assessment indicated that ivacaftor was well tolerated and that the safety findings were consistent with the known safety profile of ivacaftor. Even though the paediatric safety database in paediatric patients with this *CFTR* variant is very limited (children aged 6 years and older and adolescents) or even non-existing (children under 6 years of age), safety data can be extrapolated from children of the same age range with gating mutations based on similar systemic exposure which is not expected to be influenced on the basis of a different genotype.

The safety data from post-marketing experiences were consistent with data from clinical studies, including the 5-year post-authorization safety study (PASS), and similar between adults and paediatric patients less than 18 years of age. Additional safety data in the younger population are expected to be generated by the ongoing open-label study 126 (a phase 3, 2-arm, open-label study to evaluate the safety and PD of long-term IVA treatment in subjects with CF who are less than 24 months of age at treatment initiation and have an approved IVA-responsive mutation). The final CSR of study 126 is expected to be completed by March 2022 to provide further data to characterise the safety profile of ivacaftor in these young children.

In patients with the *R117H* mutation, the diagnosis of CF may be particularly challenging but once the diagnosis is confirmed these children are followed and managed as classical CF. Given that the biochemical defect in the *CFTR* conductance channel is present from birth and although the disease can take many years to become manifested in full, there is evidence of respiratory and other organ involvement since birth even if there may not be overt disease manifestations that can be captured by the usual clinical endpoints. Therefore, the present extension of the indication of Kalydeco will allow

treatment initiation at a young age as this may modify the progress of the disease by correction, or at least by improvement of the biochemical defect.

The approval of Kalydeco for the treatment of paediatric patients down to 6 months of age with cystic fibrosis and who have the *R117H-CFTR* mutation will cover an existing unmet medical need.

In asymptomatic young children diagnosis of cystic fibrosis requires genetic analysis (including the poly-T status) and sweat chloride determination. Currently most infants detected on newborn screening with an *R117H-7T* will not fulfil CF diagnostic criteria and will remain asymptomatic. However, there are cases reported with the CF disease.

As a consequence, the CHMP considered that the indication should be kept broad to allow treatment to patients with an R117H-CFTR mutation who have cystic fibrosis without restricting the poly-T variant. Therefore, the previous precautionary statement in section 4.4 of the SmPC has been removed while information about the need to confirm the genotype (if not already available from the clinical records of patients) before starting treatment with ivacaftor as well as to determine the phase of the poly-T variant is kept in section 4.2.

In conclusion, the data support an extension of the indication in patients with CF who have an *R117H* mutation from 6 months of age.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

3.8. Conclusions

The overall B/R of Kalydeco for the treatment of paediatric patients down to 6 months of age and weighing 5 kg with cystic fibrosis and who have the *R117H-CFTR* mutation 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 cystic fibrosis in children aged 6 years and older and weighing 25 kg or more for Kalydeco 150 mg tablets and in children aged 6 months and older and weighing 5 kg to less than 25 kg for Kalydeco granules 25 mg, 50 mg and 75 mg who have an *R117H* mutation in the CFTR gene. As a consequence, sections 4.1, 4.2, 4.4 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. The RMP version 8.7 has also been submitted.

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

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 by consensus is of the opinion that Kalydeco is not similar to Bronchitol (mannitol), TOBI Podhaler (tobramycin inhalation powder) and Symkevi (tezacaftor/ivacaftor) within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. See appendix 1. CHMP AR on similarity dated 30 January 2020.

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.No 0082'