EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

24 September 2015
EMA/670896/2020 Corr.1[1]
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Kalydeco

International non-proprietary name: IVACAFTOR

Procedure No. EMEA/H/C/002494/II/0027

Note

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

[1] Subject and site IDs redacted

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List of abbreviations

ANCOVA	analysis of covariance
BMI	body mass index
CCS	Complete Case Set
CDC	Centers for Disease Control and Prevention
CF	cystic fibrosis
CFF	Cystic Fibrosis Foundation
CFQ-R	Cystic Fibrosis Questionnaire-Revised
CFTR	CF transmembrane conductance regulator gene
CFTR	CF transmembrane conductance regulator protein
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
DIOS	distal ileal obstruction syndrome
DMC	data monitoring committee
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
FEF25-75%	forced midexpiratory flow rate
FRT	Fisher rat thyroid
FESS	functional endoscopic sinus surgery
FEV1	forced expiratory volume in one second
FVC	forced vital capacity
G551D or *G551D-CFTR*	*CFTR* missense gene mutation that results in the replacement of a glycine residue at position 551 of *CFTR* with an aspartic acid residue
G551D or G551D-*CFTR*	*CFTR* protein with a replacement of a glycine residue at position 551 with an aspartic acid residue
HBE	human bronchial epithelia
IRT	Immunoreactive trypsin
IV	Intravenous
MCID	minimal clinically important difference
MMRM	mixed-effects model for repeated measures
MSSA	methicillin-sensitive Staphylococcus aureus
NOS	not otherwise specified
PCR	polymerase chain reaction
PD	pharmacodynamics
PK	pharmacokinetic
PPS	Per Protocol Set
PRO	patient-reported-outcome
q12h	every 12 hours
R117C or	

R117C-CFTR	a missense mutation that results in the replacement of an arginine residue at position 117 of *CFTR* with a cysteine residue
R117H or R117H-CFTR	a missense mutation that results in the replacement of an arginine residue at position 117 of CFTR with a histidine residue
R117H or R117H-CFTR	CFTR protein with the replacement of an arginine residue normally found at position 117 of the wild-type protein with a histidine residue

R117H-5T	*CFTR* allele with both an *R117H* mutation and a *5T* poly-T variant
R117H-7T	*CFTR* allele with both an *R117H* mutation and a *7T* poly-T variant
R117H-9T	*CFTR* allele with both an *R117H* mutation and a *9T* poly-T variant
SAP	Statistical Analysis Plan
SAE	severe adverse event
SEM	standard error of the mean
ULN	upper limit of normal

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Vertex Pharmaceuticals (Europe) Ltd. submitted to the European Medicines Agency on 11 July 2014 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 the treatment of of patients with cystic fibrosis (CF) aged 18 years and older who have an *R117H* mutation in the *CFTR* gene. Consequently, changes were proposed to sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC and to the Package Leaflet.

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

Kalydeco was designated as an orphan medicinal product EU/3/08/556 on 08 July 2008. Kalydeco was designated as an orphan medicinal product in the following indication: treatment of cystic fibrosis.

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

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision EMEA-000335-PIP01-08-M09 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP (P/0060/2014) was not yet completed.

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 applicant did not seek Protocol Assistance at the CHMP.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Concepcion Prieto Yerro Co-Rapporteur: Melinda Sobor

Timetable	Actual dates
Submission date	11 July 2014
Start of procedure:	25 July 2014
CHMP Rapporteur Assessment Report	8 October 2014
CHMP Co-Rapporteur Assessment Report	18 September 2014
PRAC Rapporteur Assessment Report	23 September 2014
Committees comments on PRAC Rapp Advice	29 September 2014
PRAC Rapporteur Updated Assessment Report	2 October 2014
PRAC Meeting, adoption of PRAC Assessment Overview and Advice	9 October 2014
CHMP comments	13 October 2014
CHMP Rapporteur Revised Assessment Report	20 October 2014
1st Request for supplementary information (RSI)	23 October 2014
CHMP Rapporteurs joint response Assessment Report	9 February 2015
PRAC Rapporteur response Assessment Report	9 February 2015
PRAC Rapporteur Updated response Assessment Report	13 February 2015
PRAC Meeting, adoption of PRAC Assessment Overview and Advice	12 February 2015
CHMP comments	16 February 2015
2nd Request for supplementary information (RSI)	26 February 2015
CHMP Rapporteurs joint response Assessment Report	11 June 2015
PRAC Rapporteur response Assessment Report	1 June 2015
PRAC Meeting, adoption of PRAC Assessment Overview and Advice	11 June 2015
CHMP comments	18 June 2015
3rd Request for supplementary information (RSI)	25 June 2015
CHMP Rapporteurs joint response Assessment Report	25 August 2015
PRAC Rapporteur response Assessment Report	24 August 2015
PRAC Rapporteur Updated Assessment Report	28 August 2015
PRAC Meeting, adoption of PRAC Assessment Overview and Advice	10 September 2015
CHMP comments	16 September 2015
CHMP Opinion	24 September 2015
The CHMP adopted a report on similarity of Kalydeco with Bronchitol (mannitol)	24 September 2015

2. Scientific discussion

2.1. Introduction

This assessment report concerns the requested extension of indication for Kalydeco (ivacaftor) to include cystic fibrosis (CF) patients aged 18 years and older who have an *R117H* mutation in the CF Transmembrane Conductance Regulator (*CFTR)* gene. CF is an autosomal recessive genetic condition with an incidence of approximately 1:3500 in most European and North American countries and 1:5000 to 1:20,000 in Latin America, the Middle East, and South Africa. Progressive obstructive lung disease causes over 90% of deaths in patients with CF. Mutations in the gene coding for the *CFTR* result in an absent or dysfunctional protein at the surface of certain epithelia. Although CF affects multiple organs, the leading cause of mortality is the progressive loss of lung function. *CFTR* normally transports chloride to regulate salt, fluid, and pH balance in multiple organs. In people with CF, the loss of chloride transport due to defects in the *CFTR* protein results in the accumulation of thick, sticky mucus in the bronchi of the lungs, loss of exocrine pancreatic function, impaired intestinal absorption, reproductive dysfunction and elevated sweat chloride concentration (Van Goor et al, 2014).

More than 1500 *CFTR* mutations have been identified, but only the functional importance of a small number is known. Evaluation of the molecular defect in the *CFTR* protein caused by *CFTR* mutations has shown that the loss of chloride transport can be due to a reduction in the quantity and/or function of *CFTR* channels at the cell surface. As for other ion channels, gating of the *CFTR* channel is measured by open probability, and conductance of the *CFTR* channel is measured by current amplitude. The *CFTR* form that has lower open probability than normal *CFTR* has a gating defect, and the *CFTR* form that has lower current amplitude than normal *CFTR* has a conductance defect.

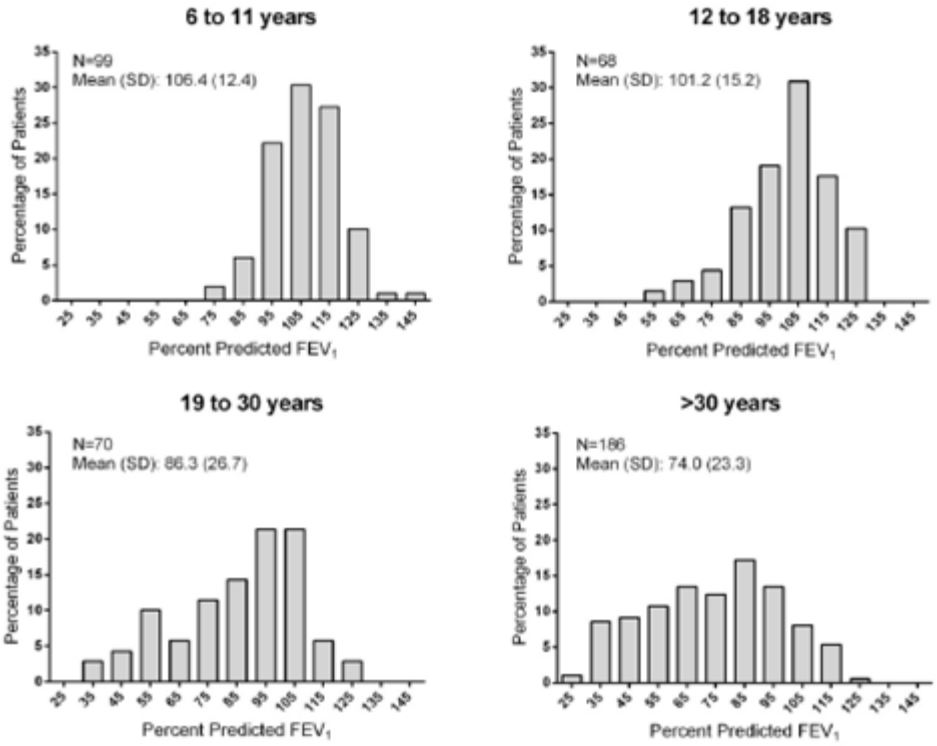
Some *CFTR* mutations cause more than 1 type of functional defect or reduce both the quantity and function of *CFTR*. Regardless of the type of defect caused by the *CFTR* mutation, CF disease severity generally correlates with the severity of the loss of chloride transport. A complete or near complete loss of *CFTR*-mediated chloride transport – referred to as "minimal function" of *CFTR*– results in severe CF. A more moderate loss of *CFTR*-mediated chloride transport – referred to as "residual chloride transport" or "residual function" – results in less severe CF.

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. It is associated with residual chloride transport and a CF phenotype characterized by exocrine pancreatic sufficiency. 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) and in studies conducted by the MAH. This finding supports, from a pharmacodynamic point of view, the use of ivacaftor, a *CFTR* potentiator that increases channel gating and, consequently, improves chloride transport, for the treatment of patients with cystic fibrosis and the *R117H* mutation in an allele of the *CFTR*. The clinical and functional analysis of the *R117H* mutation shows that it has variable expression or penetrance, i.e., it may result in a variable phenotype ranging from normal to cystic fibrosis. This phenotypic variability has been mainly attributed to the presence of a polypyrimidine (poly-T tract) variant located in another region of the *CFTR* gene in *cis* with *R117H* (Thauvin-Robinet C. et al, 2009).

The *R117H-CFTR* mutation is present in approximately 2 to 3% of patients with CF. In Europe, North America, and Australia, approximately 1,600 people with CF aged 6 years and older have at least 1 copy of an *R117H-CFTR* mutation. In the EU, approximately 744 people have the *R117H-CFTR* mutation, of whom approximately 360 people have the *R117H-CFTR* mutation and are 18 years of age or older.

Although the disease expression is relatively heterogeneous, the *R117H-CFTR* mutation may be associated with reduced lung function, gradually progressive obstructive lung disease, recurrent sinusitis and bronchitis, and increasing frequency of hospitalizations over the course of the lifespan due to pulmonary disease. As illustrated in figure below, which plots the distributions of percent predicted FEV1 in individuals with an *R117H-CFTR* mutation by age cohorts in the US Cystic Fibrosis Foundation (CFF) Registry, there is an evident progression in lung function decline with age. Among CF patients with an *R117H-CFTR* mutation who are 19 to 30 years of age, 34% of patients have a percent predicted FEV1 <80%, and that number increases to 55% for patients aged more than 30 years.

Percent Predicted FEV_1 by Age Cohorts for CF Patients With an *R117H-CFTR* Mutation



Source: CFF Registry Data, 2011; data on file at Vertex.

Although the *R117H-CFTR* mutation may result in CF disease, the severity of CF per age group is generally less than that caused by the *G551D-CFTR* mutation or other *CFTR* mutations associated with a severe phenotype. Historically, due to the milder presentation of disease, many individuals with an *R117H-CFTR* mutation were not diagnosed with CF until the late childhood or adult years, when the disease had progressed and symptoms became much more evident. This has recently changed because of advances in newborn screening for *CFTR* mutations. More individuals with an *R117H-CFTR* mutation are now identified earlier in life, often without advanced pulmonary or gastrointestinal manifestations, since the symptoms of CF progress with patient's age. Available data about life expectancy in CF patients with a less severe CF phenotype, such as those with the *R117H-CFTR*, also have a markedly reduced median life expectancy of just 50 years with the median age of death being 38 years in the US and 32 years in the UK. In contrast, the life expectancy for non-Hispanic white males in the US is 76 years, and for males in Europe is 72 years. Due to the small number of CF patients with an *R117H-CFTR* mutation who have contributed data to searchable registries and the likelihood that many subjects with mild CF are not genotyped at their time of death it is difficult to estimate the impact of the *R117H-CFTR* mutation on life expectancy. Based on a simple numerical comparison, *CFTR* mutations associated with a less severe phenotype appear to result in a disease process that is approximately 10 years slower than for CF

patients who have mutations associated with severe disease (approximate median age of death of 26 years for severe CF and 38 years for less severe CF). Thus, while the *R117H* mutation is in the less severe spectrum of CF, it is associated with severe disease when compared to a normal population. The MAH conclude that there is therefore a clear and substantial unmet need in this population.

2.2. Non-clinical aspects

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

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

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

The main study in support of this application was:

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

2.3.2. Pharmacokinetics

No major new pharmacokinetic data is discussed in the documentation provided in support of this extension of the indication with the exception of a Population pharmacokinetic (PK) study (Report J178) and exploratory PK/pharmacodynamic (PK/PD) analyses for study 110. In addition, analytical methods for the determination of ivacaftor, M1-ivacaftor, and M6-ivacaftor in human plasma are also provided.

A method for the determination of ivacaftor, M1-ivacaftor, and M6-ivacaftor in human plasma containing K2EDTA by HPLC-MS/MS over the calibration range of 2.00 to 2000 ng/mL for ivacaftor and M1-ivacaftor and range of 10.0 to 10000 ng/mL for M6-ivacaftor was developed and validated at Covance. The pre-study validations of the analytical methods are satisfactory. The method demonstrated acceptable selectivity and the presence of haemolysed red blood cells and natural high lipid content in human plasma did not affect the quantitation of ivacaftor, M1-ivacaftor, and M6-ivacaftor in this method. All calibration standards utilized within the regression had back-calculated values that were within the acceptance criteria. For QCs, all intra- and inter-assay precision and accuracy values were within the acceptance criteria. The data confirm that the presence of the co-administered drugs and selected concomitant medications (loratadine, triamcinolone, cetirizine dihydrochloride, DL-alpha tocopherol- vitamin E, ergocalciferol- vitamin D2, and ipratropium bromide monohydrate) does not affect the quantification of ivacaftor, M1-ivacaftor, and M6-ivacaftor. There was no evidence of carryover and the matrix factor was not considered to impact assay performance in either plasma or CF plasma.

In general, the in-study validation shows acceptable calibration standards and QCs as the precision and accuracy for all the three analytes met the acceptance criteria for all analytical runs. A total of 359 study samples were analysed in a total of nine analytical runs (no analytical runs failed) between November 20th, 2013 and November 25th, 2013 at Covance Laboratories Inc. (Covance) 3301 Kinsman Boulevard Madison, Wisconsin 53704 USA. A total of five study samples were re-assayed for ivacaftor with acceptable results (~1% of total number of samples analysed), 27 study samples were re-assayed for M1-ivacaftor with acceptable results (~8% of total number of samples analysed) and of six study samples were re-assayed for M6-ivacaftor with acceptable results (~2% of total number of samples analyzed).

The reasons for re-assay and the reported results were submitted and were considered acceptable. Incurred Sample Reproducibility was acceptable for all three analytes. For all analytes, the maximum storage period between collection and analysis was no longer that the current validated storage period at -60 ºC to – 80 ºC.

2.3.3. Pharmacodynamics

The *R117H* mutation is a missense mutation that results in the replacement of an arginine residue at position 117 of *CFTR* with a histidine residue. It affects the extracellular loop of the first of two membrane spanning domains that form the pore of the *CFTR* chloride ion channel. The *R117H* mutation is associated with residual chloride transport and a CF phenotype characterised by exocrine pancreatic sufficiency. Updated information on the mechanism of action of ivacaftor based on two recently published papers (Jih, K-Y, Hwang, T-C., 2013; Eckford, P.D.W, Li, C., Ramjeesingh, M., Bear, C.E., 2012) has been provided showing that ivacaftor increases the frequency of the ATP-independent channel gating mode, but the mechanism has not been completely elucidated.

Although *R117H* is usually considered as a class IV conductance mutation, the in vitro experiments performed in Fisher Rat Thyroid (FRT) cells expressing the aberrant *R117H-CFTR* protein show that the main molecular defect is a decrease in channel gating with a minor decrease in channel conductance compared to normal *CFTR* channels. This finding supports, from a pharmacodynamic point of view, the use of ivacaftor, a *CFTR* potentiator that increases channel gating and, consequently, improves chloride transport for the treatment of patients with CF and the *R117H* mutation in an allele of the *CFTR*. It should be noticed, however, that the in vitro responses seen in these experiments do not necessarily correspond to in vivo pharmacodynamic response (e.g. sweat chloride) or clinical benefit.

The clinical and functional analysis of the *R117H* mutation shows that it has variable expression or penetrance, i.e. it may result in a variable phenotype ranging from normal to cystic fibrosis. This phenotypic variability has been partially attributed to the presence of a polypyrimidine (poly-T tract) variant located in another region of the *CFTR* gene in *cis* with *R117H*. 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 with *R117H* (i.e. *in cis*) differing outcomes may occur. The *R117H* mutation in *cis* with the *5T* variant typically results in more severe CF than the *R117H* mutation in cis with the *7T* variant. Although many individuals with the *R117H* mutation associated to the poly-T variant *7T* will not have cystic fibrosis lung disease some cases of severe disease have been reported in patients carrying a severe CF mutation (Thauvin-Robinet, C. et al, 2009). The *9T* variant is highly unlikely to cause disease. The difference in clinical consequence is likely due to the lower amount of *CFTR* protein synthesized in people with the *5T* variant compared to those with the *7T* variant, as well as other factors such as modifier genes, environmental factors, and other complex *CFTR* alleles. Examples of complex *CFTR* alleles in addition to *5T* and *7T* include the number of TG repeats in intron 8 along with the 5T mutation (e.g., *TG11-5T*, *TG12-5T*, *TG13-5T*) as well as missense mutations, such as *M470V*, *R668C*, *G576A*, *D443Y*, *R74W*, and *D1270N*. In conclusion, *R117H* by itself does not act as a CF-causing mutation. However, under certain circumstances, and, as always, when another CF-causing mutation is present, *R117H* can cause disease. In order to correctly interpret data from the *R117H* mutation in *trans* with an additional *CFTR* mutation it is necessary to know the phase of the mutations. The phase refers to the specific combination of mutations that are present together in the same copy of the *CFTR* gene. For instance, a patient may have the following mutations: *R117H/G551D* and *5T/7T*. Determining the phase means determining which poly-T variant (*5T*, *7T*, *9T*) is in the same copy of the *CFTR* gene as *R117H* and which is in the same copy as *G551D*. For some patients, testing of their parents is necessary to determine the phase of the mutations. This information is relevant for the subgroup analysis by poly-T variant that was performed in study 110. The results of study 110 were analysed by the presence of the poly-T variant (*5T* or *7T*) in *cis* with the *R117H* mutation. However, this information was not available for all patients enrolled in the study for various reasons. As a consequence, some assumptions were made for

patients with the following genotypes: *R117H/F508del* and *R117H/R117H*. What is lacking is the complete genotype of all patients, i.e. including not only the mutations of the *CFTR* in *trans* but also the poly-T variants in *cis* for both alleles, i.e. the phase of the mutations. This is addressed in the section on clinical efficacy. Because of the phenotypic variability of the *R117H-CFTR* mutation, diagnosis of CF should be mainly based on clinical criteria alone. Patients with this mutation and a mutation that is known to cause CF should undergo periodic assessment as the clinical manifestations of the disease may appear later in life. Regarding the *CFTR* mutation in the second allele, the majority of patients (76.8%) enrolled in study 110 had the *F508del* mutation on the second allele, a processing mutation that results in minimal amounts of *CFTR* reaching the surface. Ivacaftor treatment did not result in clinical benefit in subjects homozygous for the *F508del-CFTR* mutation although limited in vitro response in chloride transport was seen, showing that this mutation has some defective channel gating. Each of the other second alleles was present in no more than 2 subjects.

Of the 793 patients with cystic fibrosis carrying a *R117H* mutation in *CFTR*2, 590 had *F508del* in the second allele. Their average sweat chloride is 60 mEq/L, their percent predicted FEV1 is in the range of 72-113% in patients below 10 years old (n=36); for those between 10-20 years old (n=75) their percent predicted FEV1 ranges between 67-121% and between 29-113% for patients above 20 years of age (n= 213). Twenty-four percent are pancreatic-insufficient and 25% are infected by *P aeruginosa*. Regarding other *CFTR* mutations in the second allele of patients enrolled in study 110, stop codon (nonsense) mutations such as *E60X*, *G103X*, *G542X*, *R553X*, *S489X*, and *W1282X* are expected to significantly disrupt *CFTR* protein production and result in little or no functional *CFTR* protein in the cell. As a consequence, it was expected that patients in study 110 with a stop codon mutation had sweat chloride values above the threshold of 60 mmol/l. This is the case with the exception of a single patient randomised to placebo who had as a second *CFTR* mutation *R553X-7T* and a baseline sweat chloride of 52.25 mmol/l. With the exception of *G103X* all other stop codon mutation are described in *CFTR*2. Patients carrying these mutations in the *CFTR*2 database have sweat chloride values well above 60 mEq/L. No information has been found for *G103X* in *CFTR*2. *G103X* is described in a single patient in *CFTR*1. The patient in study 110 with the genotype *R117H-5T*/*G103X-7T* was randomised to placebo, his baseline percent predicted FEV1 was 63.50% and his baseline sweat chloride 82 mmol/l. Average sweat chloride of patients included in *CFTR*2 who carry one of the below mutations found in the second allele of the *CFTR* gen of patients enrolled in study 110 are as follows:

- *2184InsA:* this is an insertion/deletion mutation that it is considered a CF-causing mutation. The average sweat chloride of patients with CF carrying this mutation (n=132) in the *CFTR*2 database is 98 mEq/L.
- *3659DELC:* this is an insertion/deletion mutation that is considered a CF-causing mutation. The average sweat chloride of patients with CF carrying this mutation (n=247) in the *CFTR*2 database is 101 mEq/L.
- *621+1G->T:* This is an splice mutation that is considered a CF-causing mutation. The average sweat chloride of patients with CF carrying this mutation (n=793) in the *CFTR*2 database is 102 mEq/L.
- *DELTA I507*: This is an insertion/deletion mutation that that is considered a CF-causing mutation. The average sweat chloride of patients with CF carrying this mutation (n=306) in the *CFTR*2 database is 97 mEq/L.
- *R560T*: This is a missense mutation that that is considered a CF-causing mutation. The average sweat chloride of patients with CF carrying this mutation (n=196) in the *CFTR*2 database is 101 mEq/L.
- *S341P*: This is a missense mutation that that is considered a CF-causing mutation. The average sweat chloride of patients with CF carrying this mutation (n=7) in the *CFTR*2 database is 98 mEq/L. This

mutation has been shown in vitro to cause a severe conductance defect that is not responsive to ivacaftor in vitro (Van Goor F, Yu H, Buron B, Hoffman BJ.; 2014).

For an additional patient the *CFTR* mutation in the second allele was unknown. Two patients were homozygous for *R117H*.

2.3.4. PK/PD modelling

The MAH provided an updated Pop-PK model for ivacaftor based on the prior model by adding data from study 110. In addition, revised plasma concentration datasets for studies 007 (single dose, cross-over, relative bioavailability/food study), study 101 (phase 2a dose escalation in CF patients with the *G551D* mutation), study 102 (phase 3 study in CF patients aged 12 years and older with the *G551D* mutation), and 104 (phase 2 study in CF patients homozygous for F508del-*CFTR* mutation) replaced previous datasets for this analysis, while data from study 002 (single dose, cross-over, relative bioavailability/food study) were not incorporated into the model due to the reported issues with the bioanalytical assay. The model does not incorporate metabolites M1 and M6. Thirty-four ivacaftor-treated patients with the *R117H-CFTR* mutation contributed to the analysis with 321 ivacaftor concentrations. The original model was refined, starting from the base model, and the covariate modelling approach followed was similar to the one performed for the prior model, i.e., parameter estimation was emphasized in front of the stepwise hypothesis testing. Formulation was removed from the model as a potential covariate. The reason was that formulation was not a significant covariate in the previous model, consistent with the similar relative bioavailability for the 50% DL-SDD and 80% DL-SDD formulations. 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. The estimated values for CL/F (90%CI) was 14.3 (12.7, 16.0) L/h for patients with *R117H* mutation vs. 18.2 (16.9, 19.3) L/h for patients with non-*R117H* mutation. This change is claimed not to be clinically significant.

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/hr 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) h for zero-order dose duration (D1) and 0.721 (0.530, 0.765) h-1 for first-order absorption rate (ka). Summary statistics for ivacaftor Cmin and AUC in study 110 show overlap with the values observed in previous studies. Similarly, when data from children aged 6 to 11 years in study 110 are added the same tendency remains, i.e. exposure in them is higher than in adults. An ivacaftor dose of 150 mg q12 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 683 ng/mL for adults. Mean AUC was 19,300 ng/mL.h for 6 to 11 year olds, compared to 10,300 g/mL.h for adults.

For comparison purposes with previous studies, the MAH was asked to provide non-compartmental PK analysis of study 110 sorted out by age subgroup. The non-compartmental PK analysis shows that there is a considerable overlapping in PK parameters between studies. Oral clearance per age group in study 110 is similar to that of patients with *G551D* and non-*G551D* gating mutations with the only exception being the clearance observed in the adolescent group of study 102 which seems abnormally higher.

No attempt has been made to include PD endpoints in the modelling exercise as the graphical inspection of potential relationships between PK parameters and PD endpoints such as change in percent predicted FEV1 did not give any insight in this direction.

2.3.5. Discussion on clinical pharmacology

The newly provided data refer to the analytical methods that have been used in study 110 in order to determine ivacaftor, M1 and M6 concentrations in human plasma. In addition, updated pop-PK analysis

including data from study 110 was discussed. The pop PK analysis estimates that patients with a *R117H* mutation have a small reduction in clearance. A non-compartmental analysis of study 110 PK data by age group shows that there is a considerable overlapping in the PK parameters between this study and prior studies of ivacaftor. As in the prior studies exposure in children aged 6 to less than 12 years old is higher in relation to that seen in adult patients.

The in vitro experiments performed by the MAH (and also published data) confirm that the main molecular defect of the aberrant *R117H-CFTR* protein is a defect in channel gating rather than a defect in conductance (also present). This justifies, from a pharmacodynamic point of view, treatment with ivacaftor of patients carrying this mutation.

The clinical and functional analysis of the *R117H* mutation shows that it has variable expression or penetrance, i.e. it may result in a variable phenotype ranging from normal to CF. This phenotypic variability has been mostly attributed to the presence of a polypyrimidine (poly-T tract) variant located in another region of the *CFTR* gene in *cis* with *R117H* (Thauvin-Robinet, C. et al, 2009). Depending on which poly-T form is present in the same copy of the *CFTR* gene with *R117H* (i.e. *in cis*) various outcomes may occur. The *R117H* mutation in *cis* with the *5T* variant typically results in more severe CF than the *R117H* mutation in *cis* with the *7T* variant. Although many individuals with the *R117H* mutation associated to the poly-T variant *7T* will not have CF lung disease some cases of disease with early symptoms have been reported in patients carrying a severe CF mutation (Thauvin-Robinet, C. et al, 2009). The *9T* variant is highly unlikely to cause disease. Those subjects who have the mutation known to cause CF should undergo periodic assessment as the clinical manifestations of the disease may appear later in life.

It can be concluded that by itself, *R117H* does not act as a CF-causing mutation. However, under certain circumstances, and, as always, when another CF-causing mutation is present, *R117H* can cause disease. In general, the mutations present in the second allele of the *CFTR* (i.e. in *trans*) of patients enrolled in study 110 are all considered disease-causing mutations in *CFTR*2. No information has been found in *CFTR*2 for *G103X* which seems to be a nonsense mutation, i.e. also a severe *CFTR* mutation. This mutation is described in a single patient in *CFTR*1. In study 110, patient with the genotype *R117H-5T*/*G103X-7T* was randomised to placebo and his baseline percent predicted FEV1 was 63.50%, his baseline sweat chloride 82 mmol/l.

2.3.6. Conclusions on clinical pharmacology

The pop-PK analysis indicates that parameter estimates seen in patients with the *R117H-CFTR* mutation are similar to those of patients with *CFTR* mutations such as *G551D*, non-*G551D* gating mutations and patients homozygous for *F508del-CFTR* mutation with the exception of a reduction in clearance, for which no physiological explanation is evident but is attributed to variability. A non-compartmental PK analysis of study 110 shows that there is a considerable overlapping in PK parameters between studies. Oral clearance per age group in study 110 is similar to that of patients with *G551D* and non-*G551D* gating mutations. As in the prior studies, exposure in children aged 6 to less than 12 years old is higher than in adult patients.

From a pharmacodynamic point of view, treatment with ivacaftor of patients carrying a *R117H* mutation is justified because the predominant in vitro defect of the aberrant *R117H-CFTR* protein is a defect in channel gating, although *R117H* is usually classified as a class IV, i.e. conductance mutation. However, given its phenotypic variability and the usually milder course of the disease with symptoms and signs appearing sometimes later in life, treatment with ivacaftor should be considered for patients with a disease phenotype compatible with cystic fibrosis.

2.4. Clinical efficacy

2.4.1. Dose response study

No dose-response studies have been performed. Patients in studies 110 and 112 (open label extension) were treated with ivacaftor 150 mg q12h based on the in vitro potency of ivacaftor towards the *R117H* mutation relative to other mutations that cause gating defects as well as tolerability, pharmacokinetic data, and the responses observed in studies 102 and 103, supporting the initial MAA submission of Kalydeco. A population PK model was subsequently developed based on the prior model for ivacaftor and incorporating data from study 110 showing, as previously mentioned, that parameter estimates seen in patients with the *R117H-CFTR* mutation are similar to those of patients with other *CFTR* mutations studied in the ivacaftor clinical programme.

2.4.2. Main study

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 110 was a Phase 3, randomized, double-blind, placebo-controlled, parallel-group multicenter study to evaluate the efficacy and safety of ivacaftor in patients with CF aged 6 years and older who have a *R117H-CFTR* mutation. As shown in figure below, the study included a Screening Period (Day -35 to Day -15), 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] to 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 a confirmed diagnosis of CF (defined as a sweat chloride value ⩾60 mmol/L [by quantitative pilocarpine iontophoresis] OR 2 CF-causing mutations AND chronic sinopulmonary disease), aged 6 years and older, were required to have at least 1 allele of the *R117H-CFTR* mutation. Patients were excluded if they had a *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*). In addition, patients must have had percent predicted FEV1 of 40% to 90% inclusive for subjects aged 12 years and older or 40% to 105% inclusive for subjects aged 6 to 11 years (inclusive) based on the Hankinson or Wang equations. The Hankinson standard was used for male subjects 18 years and older and female subjects 16 years and older. The Wang standard was used for male subjects aged 6 to 17 years and for female subjects aged 6 to 15 years.

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 in addition to patients' usual prescribed CF therapy. An amendment of the study protocol allowed patients to receive hypertonic saline in an attempt to improve enrolment.

The primary objective was to evaluate the efficacy of ivacaftor in patients CF who have the *R117H-CFTR* mutation using as the main efficacy variable the absolute change in percent predicted FEV1 from baseline through week 24. Secondary endpoints were absolute change from baseline in BMI at week 24, absolute change from baseline in sweat chloride through week 24, change from baseline in the respiratory domain of the Cystic Fibrosis Questionnaire-Revised (CFQ-R) through week 24 and time to first pulmonary exacerbation. Safety was a secondary objective. There were also a number of exploratory (tertiary)

endpoints.

Enrolment was planned for a 40-80 subjects. An unblinded interim analysis for safety and efficacy was performed by the Data Monitoring Committee (DMC) after 40 patients had completed Week 8 Visit and, based on the results and rules pre-specified in the Statistical Analysis Plan (SAP), the DMC did not recommend any changes. Enrolment was kept open until the study was terminated early by the sponsor and recruitment was halted after 70 subjects were randomized, based upon the power calculations and after exceeding the minimum number of subjects defined in the protocol. Subjects who did not have their Week 24 Visit by the time of study termination were considered to have completed their assigned treatment duration and were offered enrolment study 112. All available data were included in the final analyses regardless of whether subjects completed 24 weeks of study drug treatment.

Study 110 was planned to be analysed with approximately 80 subjects but recruitment was halted after 70 subjects were randomised. The MAH was requested to provide a detailed justification for not proceeding to 80 patients based on power calculations and the arguments used to stop the trial recruitment. The MAH's response states that based on feasibility, enrolment in study 110 was planned for a minimum of 40 and a maximum of approximately 80 subjects. The study enrolled at the high end of the planned range (70 subjects). The MAH estimate that 50 adult patients is equivalent to approximately 18% of all the adult EU patients with an *R117H* allele, and approximately 40% to 60% of those eligible for a study requiring FEV1 less than 90 percent predicted. One of the scenarios for sample size estimation discussed by the MAH is that with 80 patients and assuming a treatment effect of 5% in absolute change from baseline in percent predicted FEV1 and a standard deviation (SD) of 8%, the study would have been powered at 80%. As a consequence, with 70 patients (8 of whom were not allowed to complete the full course of treatment), it seems that the study was underpowered. This may be justified by the limited number of patients available. According with the MAH there are about 1600 patients in Europe, Australia and the United States with a *R117H* allele and cystic fibrosis. The actual sample size of study 110 represents about 5% of them. The fact that 38 patients were screened but considered not eligible mainly due to the requirements on percent predicted FEV1 at baseline seems to reinforce the MAH's view that the number of patients available meeting all the inclusion and exclusion criteria is limited.

Patients were randomized in a 1:1 ratio, stratifying for age and percent predicted FEV1 at screening to receive either 150-mg ivacaftor or ivacaftor-matching placebo q12h, in addition to their usual prescribed CF therapy. Only two adolescent patients were enrolled which could be attributed to the fact that the specific inclusion criterion related to the baseline percent predicted FEV1 stipulated that patients aged 12 years and older should have a percent predicted FEV equal or below 90%, which apparently is not the case for most adolescent patients with an *R117H* mutation.

The MAH stated that the SAP was finalised 5 days before the database lock and the unblinding of data, which guarantees the independence of the SAP to the current data. The primary analysis for the primary efficacy variable (absolute change from baseline in percent predicted FEV1 through Week 24) was based on a mixed-effects model for repeated measures (MMRM) in the Full Analysis Set (FAS) that includes all randomized subjects who received at least 1 dose of study drug. Data were assumed missing at random and no imputation of missing data was done for the primary analysis. The MAH was requested to clarify the assumption that missing data occurred indeed at random. According to the MAH, there was very little missing data in study 110, with only 2 subjects withdrawing from treatment during the study. These 2 subjects withdrew due to a pregnancy and non-compliance with the study protocol. There were additional 8 subjects who were not allowed to complete the full 24 weeks of treatment due to the sponsor's decision to stop the study early. All of them were considered as missing at random (MAR). While the argumentation for considering some of the cases as MAR is not fully supported, it is acknowledged that the amount of missing data is limited and that the sensitivity analyses showed that results are consistent with the underlying assumptions. Given the small amount of missing data (with at least some of them likely to be MAR), the consistency of the treatment effect estimates results from the different approaches,

it is considered that the selection of the estimate would be unlikely to impact study conclusions. In relation to the covariance matrix used in the MMRM analysis, it has been clarified that the compound symmetry covariance matrix was used because it was found to be suitable for analyses of spirometry data in previous studies of ivacaftor. Alternative covariance matrices have been used and all results were found to be consistent with that of the primary analysis. The consistency of treatment effect over different visits was evaluated using the primary MMRM with treatment by visit interaction added to the model. To assess the robustness of the primary analysis, sensitivity analyses including pattern mixture model, dropout reason-based multiple imputation (using ANCOVA), and stratified Wilcoxon rank-sum test were implemented. Regarding the Wilcoxon rank-sum test it has been clarified that no imputation of missing data was done for the primary analysis. Two patterns were modelled; the completer and early termination patterns. This is considered acceptable taking into account the small amount of missing data. A responder analysis was also conducted by categorizing the absolute change from baseline in percent predicted FEV1 at Week 24 as ⩾3.5% or <3.5, ⩾5% or <5%, ⩾7.5% or <7.5%, and ⩾10% or <10%. The analysis for rate of change from baseline in BMI (secondary efficacy variable) was based on a linear mixed effects model (LMM). The primary analyses for change from baseline in sweat chloride value and change from baseline in the CFQ-R respiratory domain score were similar to that of the primary efficacy endpoint, i.e. MMRM. Time to first pulmonary exacerbation was analyzed using Cox regression; additionally, Kaplan-Meier methods were used to produce graphical presentations of the survival curves by treatment and to estimate cumulative survival rates by treatment.

Subgroup analyses of the primary and secondary endpoints were performed in the same manner as the primary analysis for the following subgroups: age at baseline (⩾18 years and 6 to 11 years [inclusive]); percent predicted FEV1 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); and *R117H* allele poly-T variant (*5T, 7T, or 9T*). A subgroup analysis for subjects aged 12 to 17 years (inclusive) was not conducted because there were only 2 subjects in that age group.

The tertiary efficacy variables included pulmonary exacerbations, change from baseline in non-respiratory domains of the CFQ-R through 24 weeks of treatment, rate of change from baseline in weight, rate of change from baseline in height, CF-related complications, change from baseline in inflammatory mediators, change from baseline in qualitative microbiology cultures, change from baseline in immunoreactive trypsinogen (IRT), and change from baseline in faecal elastase-1. The primary analysis for tertiary efficacy variables was performed for the FAS only.

Following database lock, post-hoc analyses were carried out. These analyses were primarily focused on exploring any potential differences in results due to age, baseline percent predicted FEV1, and *R117H* allele poly-T variant. Additional summary statistics were also carried out based on age, baseline percent predicted FEV1, and genotype characteristics.

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) was 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 recommendation was to continue with enrolment. While the Bonferroni- type adjustment to control the overall type I error has not been justified and it is not usually applied for conducting interim analysis, the alpha levels are agreeable. The plan to handle multiplicity as stated in the SAP is endorsed. Thus, the level of significance is set at 4.48% two-sided level.

Results

Participant flow

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.

The above table shows patient disposition in study 110. One hundred and eight patients were screened, out of whom 70 patients were randomised to ivacaftor (n=36) or to placebo (n=34). 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 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.

Recruitment

Study 110 was initiated on 03 July 2012 and completed on 25 October 2013 in 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. 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

Selected baseline data are provided in tables below for all subjects and by age subgroups in the Full Analysis Set.

Selected baseline demographic and disease characteristics data, study 110, Full Analysis Set, all patients

	FAS	
Variable	Placebo (n=35)	Ivacaftor (n=34)
Age (years), mean (SD) [range]	32.7 (17.43) [6-68]	29.2 (16.57) [6-55]
Sex, n (%) Male Female	 15 (42.9) 20 (57.1)	 15 (44.1) 19 (55.9)
ppFEV1 (mean %) [range]	70.23 [37.39-102.85]	75.70 [32.54-105.50]
ppFEV1 Severity, n (mean %) <70% ⩾70% to ⩽90% >90%	 15 (42.9) 14 (40.0) 6 (17.1)	 13 (38.2) 14 (41.2) 7 (20.6)
BMI (kg/m2), mean [range]	13.64 [13.64-37.83]	24.48 [14.37-42.87]
Sweat Chloride (mmol/L), mean [range]	73.44 [22.50-108.75]	67.26 [23.25-120.00]
CFTR Genotype, n (%)		
R117H/F508del	25 (71.4)	28 (82.4)
R117H/3659DELC	1 (2.9)	--
R117H/621+1G>T	--	1 (2.9)
R117H/DELTA I507	--	1 (2.9)
R117H/E60X	1 (2.9)	--
R117H/G103X	1 (2.9)	--
R117H/G542X	--	1 (2.9)
R117H/R117H	1 (2.9)	1 (2.9)
R117H/R553X	1 (2.9)	--
R117H/R560T	--	1 (2.9)
R117H/S341P	1 (2.9)	--
R117H/UNKNOWN	1 (2.9)	--
R117H/W1282X	2 (5.7)	--
R117H/2184INSA	1 (2.9)	--

R117H/S489X	--	1 (2.9)
CFTR Poly-T Variant[a], n		
5T on *R117H* allele		
5T/5T	--	--
5T/7T	6	1
5T/9T	21	20
7T on *R117H* allele		
7T/5T	1	--
7T/7T	2	2
7T/9T	4	10
P aeruginosa Infection Status, n (%) Yes No	 19 (54.3) 16 (45.7)	 15 (44.1) 19 (55.9)

[a] *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*

Selected demographic and disease characteristics data, study 110 by age subgroup (excluding adolescents), 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) [18-65]	 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 (mean %) [range]	62.21 [37.39-85.84]	67.03 [35.54-92.62]	93.98 [79.96-102.85]	97.49 [84.08-105.50]
ppFEV1 Severity, n (mean %) <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)
BMI (kg/m2), mean [range]	24.95 [17.04-37.83]	26.89 [37.83-42.87]	17.10 [13.64-21.50]	17.65 [14.37-24.69]
Sweat Chloride (mmol/L), mean [range]	73.01 [35.50-102.25]	69.34 [23.25-120.00]	74.66 [22.50-108.75]	64.16 [33.00-100.50]
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[a], 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	18 (69.2)	14 (58.3)	1 (12.5)	1 (11.1)
No	8 (30.8)	10 (41.7)	7 (87.5)	8 (88.9)

[a] 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

Numbers analysed

The below table shows the number of patients analysed per study population.

Disposition Category	Placebo n (%)	Ivacaftor n (%)	Overall n (%)
All Randomized Subjects	36	34	70
Full Analysis Set (FAS)	35	34	69
Completed Full Assigned Duration of Dosing	35 (100)	32 (94.1)	67 (97.1)
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)
Failed to Complete Full Assigned Duration of Dosing	0	2 (5.9)	2 (2.9)
Reason for Discontinuation			
Other Non-Compliance	0	1 (2.9)[a]	1 (1.4)
Pregnancy (Self or Partner)	0	1 (2.9)	1 (1.4)

Notes: Percentages were calculated relative to the number of subjects in the FAS. FAS was defined as all randomized subjects who received at least 1 dose of study drug. Safety Set was defined as all subjects who received at least 1 dose of study drug. CCS was defined as all FAS subjects who had the opportunity to complete the full 24-week treatment period. PPS was defined as all FAS subjects without major protocol violations that could have affected efficacy data.

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

A total of 70 patients were randomized (36 to placebo and 34 to ivacaftor) and 69 of them were dosed (a patient randomised to placebo was never dosed). Therefore, 69 patients were included in the full analysis set (FAS), i.e., 35 in the placebo group and 34 in the ivacaftor group. The Per Protocol Set (PPS) includes 63 patients, i.e. 33 patients on placebo and 30 on ivacaftor. Six patients were excluded from the PPS for major protocol violations.

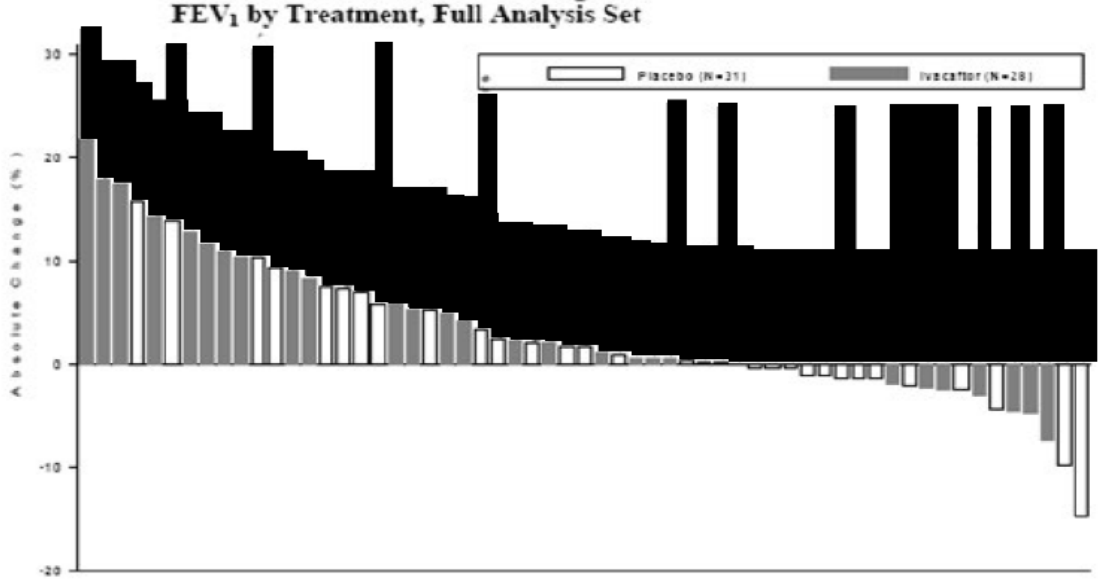
Outcomes and estimation

The primary efficacy variable of study 110 was the absolute change from baseline in percent predicted FEV1 through week 24, which is the recommended primary clinical endpoint in efficacy studies for CF given that lung function in cystic fibrosis CF declines with age and is a significant predictor of mortality.

The mean absolute change from baseline in percent predicted FEV1 through Week 24 by MMRM for the FAS was 2.57 percentage points in the ivacaftor group versus 0.46 percentage points in the placebo group. The estimated treatment difference (95%CI) for ivacaftor versus placebo was 2.11% (-1.13, 5.35). This difference was not statistically significant. The MAH stated that this result, even if not statistically significant, favours ivacaftor. However, the lack of statistical significance and the 95%CI indicate that either an improvement or impairment are possible. In contrast, the analysis of the mean absolute change in percent predicted FEV1 by mixed model from Week 24 through the Follow-up Visit (a treatment-free period after the last dose of ivacaftor or placebo) in study 110 showed a treatment difference (95%CI) of ivacaftor versus placebo of -2.32 (-4.28, -0.36). Results of the sensitivity analyses of the primary efficacy variable were consistent with the results of the primary analysis, i.e. no statistical significant differences between both groups of treatment were seen. Similarly, analysis of the primary variable in the PPS and CCS were consistent with the results of the analysis in the FAS.

The absolute change from baseline in percent predicted FEV1 at Week 24 for individual subjects is presented in figure below.

Waterfall Plot of Absolute Change From Baseline in Percent Predicted FEV_1 by Treatment, Full Analysis Set



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

Of the 28 patients in the ivacaftor group who completed 24 weeks of treatment, 20 had an improvement in percent predicted FEV1 after 24 weeks of treatment, 1 had no change in percent predicted FEV1, and 7 had a decline in percent predicted FEV1. Six of the 7 patients in the ivacaftor group who had a decline in percent predicted FEV1 were children 6 to 11 years old.

Table below shows the results of a responder analysis conducted by categorizing the absolute change from baseline in percent predicted FEV1 through Week 24 as ≥ 3.5% or <3.5%, ≥ 5% or <5%, ≥ 7.5% or <7.5%, ≥ 10% or <10%.

Responder Analysis of Absolute Change Through Week 24 in Percent Predicted FEV_1, 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)	

Note: Absolute change through Week 24 is the average change from baseline over 24 weeks for percent predicted FEV_1.

Narratives were requested for those patients on ivacaftor who had an increase from baseline in percent predicted <5% as well as for patients on placebo whose percent predicted FEV1 increased ≥5%. A total of 16 patients in the ivacaftor group had an absolute change in percent predicted FEV1 <5% at Week 24 (11 females and 5 males). Of these, 7 (43.75%) had a decline in percent predicted FEV1 that ranged between -7.3 (an 11-year-old female patient with *R117H-7T/F508del-9T*) to -2.0 (a 9-year-old female with *R117H-7T/F508del-9T*). Five patients were females and 2 male patients. Six of these were children (i.e. under the age of 12 years) and the *poly-T* variant was *7T* in four cases. Two patients with a stop codon mutation in the second *CFTR* allele had a decreased of -4.7 (an 8-year-old male patient with

R117H-7T/S489X-7T) and almost no change from baseline (0.6) in the case of a 22-year-old female patient with *R117H-5T/G542X-9T*.

Overall, the above results show that children and patients with the *7T* variant tend to respond worse to ivacaftor, although the MAH suggest that age confounds the results from the *R117H-7T* subgroup. While the analysis of the absolute change in percent predicted FEV1 for all patients by sex shows that female patients have a better response to ivacaftor, among patients in the ivacaftor group who experienced a decreased from baseline in percent predicted FEV1 5 were female patients versus 2 male patients.

Sweat chloride

The mean absolute change from baseline in sweat chloride through Week 24 was -26.3 mmol/L for the ivacaftor group and -2.3 mmol/L for the placebo group. The treatment difference (95%CI) for ivacaftor versus placebo was -24.0 mmol/L (-28.0, -19.9). Table below shows the results of a responder analysis that 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.

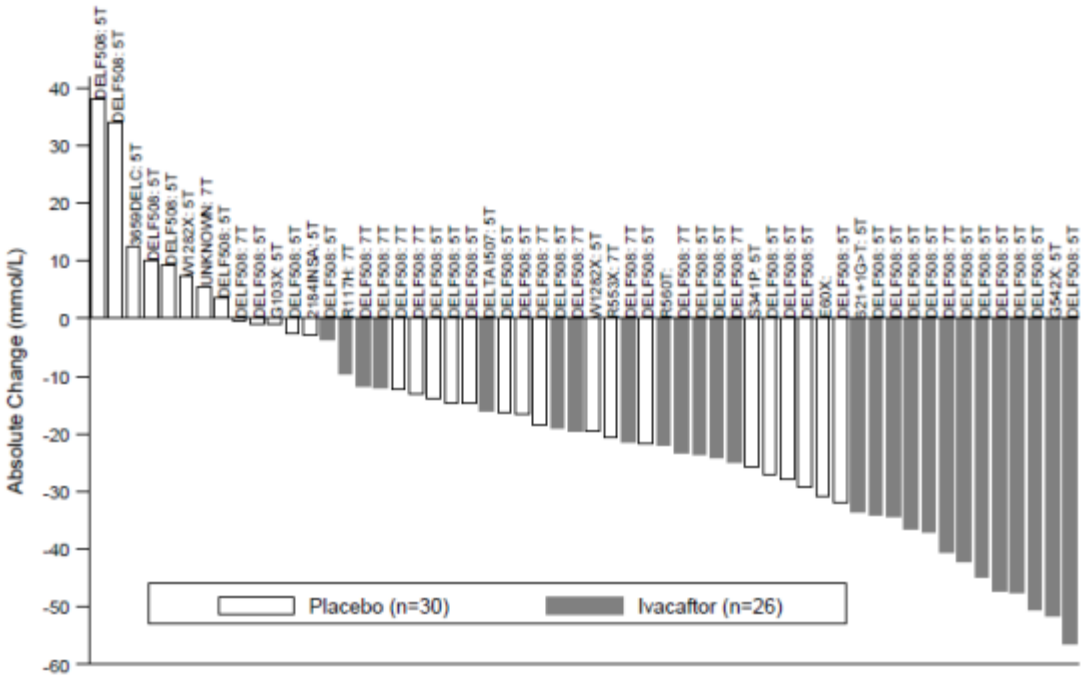
Responder Analysis of Absolute Change Through Week 24 of Sweat Chloride (mmol/L), Full Analysis Set

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	3 (8.6)	26 (76.5)
<15 mmol/L decrease	32 (91.4)	6 (17.6)
≥20 mmol/L decrease	1 (2.9)	21 (61.8)
<20 mmol/L decrease	34 (97.1)	11 (32.4)

Absolute change through week 24 is the average change from baseline over 24 weeks for sweat chloride

Narratives were requested for ivacaftor-treated patients who had less than 10 mmol/L of decrease from baseline in sweat chloride and for placebo patients with a decrease equal to or above 10 mmol/L. In addition, waterfall plots of changes from baseline in sweat chloride at week 2 and at week 24 (see figure below) were provided with the individual genotypes identified.

Study 110: Waterfall Plot of Absolute Change from Baseline in Sweat Chloride Concentration by Treatment, Genotype on the Second Allele, and Derived *R117H* Poly-T at the Week 24 Visit



Note: Labels on the bars give the subject's second *CFTR* allele followed by the poly-T tract on the *R117H* allele.

Only two patients on ivacaftor experienced a decrease in sweat chloride below 10 mmol/L. One of them was a 54-year-old male who was homozygous for *R117H-7T* and an 18-year-old female with *R117H-5T/F508del-9T*. Both of them had sweat chloride values at baseline below 60 mmol/l (i.e. 43 and 45.8 mmol/l) and they experienced a mild decrease in sweat chloride at week 24 of -3.75 and -9.5 mmol/l, respectively. The number of patients on placebo who had a decrease in sweat chloride >10 mmol/L at week 24 was 17, most of them with the *5T* variant (12 patients). The decrease ranged between -32 mmol/L and -12.25 mmol/L. This includes three patients with a stop codon mutation in the second *CFTR* allele. While variability in the measure of sweat chloride may explain some of these changes, it is difficult to explain the highest decreases. Data at week 2 of study 112 shows that almost all of these patients had a decrease in sweat chloride when they were switched to ivacaftor but the magnitude of the change was, in general, limited. The change in sweat chloride at week 24 is based on 30 patients on placebo and 26 on ivacaftor out of the 35 and 34 in the overall FAS population of study 110. It is assumed that 8 patients (4 in each group) are those who were not allowed to complete 24 weeks of treatment. Two additional patients withdrew due to a pregnancy and non-compliance with the study protocol. Therefore, sweat chloride values are not available for 3 additional patients.

Body Mass Index (BMI)

The mean absolute change from baseline in BMI at Week 24 by LMM in the FAS was 0.49 kg/m2 in the ivacaftor group versus 0.23 kg/m2 in the placebo group. The treatment difference (95%CI) was 0.26 kg/m2 (-1.57, 2.10). The mean change from baseline in BMI-for-age z-score (CDC growth chart for the 22 patients who were 20 years of age or younger) at Week 24 by LMM was 0.13 points in the ivacaftor group versus 0.03 points in the placebo group. The treatment difference (95% CI) was 0.10 points (-0.57, 0.77). The result is not surprising since the body weight in these patients was normal (some patients were even overweight or obese) and the majority of subject were pancreatic sufficient. However,

it would be informative to look at individual changes from baseline in body weight/BMI in underweight or pancreatic insufficient patients. Hence, the MAH was requested to perform an additional analysis in such patients. The MAH did not provide the requested data; only individual baseline characteristics and summary statistics were presented. Two and 8 patients were underweight at baseline in the ivacaftor and placebo groups, respectively. This rate is in line with the imbalance in the rate of pancreatic insufficient patients in the ivacaftor and placebo groups. Both underweight ivacaftor patients were <11 years old and carried *R117H-5T* variant. One of the underweight ivacaftor-treated patients had weight data only until week 2 visit, and this patient had a weight gain of 1 kg from baseline by week 2. The other patient had a weight gain of 1 kg (increase in weight-for-age z-score of 0.35) and a BMI increase of 0.710 (z-score: 0.4390) by week 24. According to the data provided there was at least one patient in the placebo group who had weight gain of 2 kg (BMI increase: 0.94 kg/m2). All pancreatic insufficient patients (at baseline, based on fecal-elastase-1 values) were older than 40 years, their genotype was *R117H-5T/ F508DEL-9T*. Two of them received ivacaftor, 5 received placebo. All pancreatic insufficient patients were well-nourished or even obese. One patient in ivacaftor put on weight by 1.3 kg (BMI increased by 0.49 kg/m2) and the other one 2 kg (BMI increased by 0.59 kg/m2) during the 24 week period. There were only 3 patients in the placebo group who had weight and BMI values at week 24, the values varies between high boundaries, one of them lost weight by 4 kg and other put on weight by 3 kg during 24 weeks. Nutritional status has been improved in the two ivacaftor-patients, but it cannot be clearly concluded that this favourable effect is different from placebo.

Overall, based on the currently available data, a conclusion cannot be drawn on whether ivacaftor may improve nutritional status in underweight or pancreatic insufficient patients.

Respiratory domain of the CFQ-R

The mean absolute change from baseline in the pooled CFQ-R respiratory domain score through Week 24 was greater in the ivacaftor group (7.6 points) than in the placebo group (-0.8 points). The estimated treatment difference (95%CI) was 8.4 points (2.17, 14.61).

Pulmonary exacerbations

All protocol defined pulmonary exacerbations occurred in patients ≥18 years of age. In the placebo group (n=35) 13 patients had 17 pulmonary exacerbations (event rate: 0.30) while in the ivacaftor group (n=34) 11 patients had 13 events (event rate: 0.25). The rate ratio (95%CI) was 0.84 (0.41, 1.73). The number of patients with pulmonary exacerbations requiring hospitalisation or IV therapy was 6 on placebo and 2 on ivacaftor. The proportion of event-free patients was 0.69 in the ivacaftor group versus 0.58 in the placebo group. The calculated hazard ratio of 0.93 was not statistically significant. The survival curve shows that there seems to be a different temporal pattern with more pulmonary exacerbations in the ivacaftor group at the beginning of the study (e.g. Days 0-15: 3 events; Days 16-56: 4 events) than in the placebo group (1 and 2 events, respectively). Whether this is related to the effect that has been described for some ivacaftor-treated patients, especially at the beginning of treatment, related to the increase in pulmonary secretions is not known.

In summary, study 110 did not meet the primary objective, which was to show that treatment with ivacaftor for 24 weeks was superior to placebo as the treatment difference in the absolute change from baseline in percent predicted FEV1 was not statistically significant. As for the secondary variables, changes in sweat chloride and in the respiratory domain of the CFQ-R show larger changes in the ivacaftor group. The sweat chloride is considered a marker of the *CFTR* activity. The results of study 110 in terms of sweat chloride are reassuring when the *in vitro* pharmacodynamic data is considered but so far no correlation with the change in percent predicted FEV1 could have been shown.

Table below summarizes the tertiary efficacy endpoint results for the FAS (with the exception of number and count of pulmonary exacerbations that have been shown above). No analysis of CF-related complications was performed because no episodes of pancreatitis or DIOS occurred during the study.

Tertiary Efficacy Endpoint Results, Full Analysis Set

Endpoint and Result	*P* Value
Rate of Change from Baseline in Height Through Week 24	
Ivacaftor group: 0.3699 cm; placebo group: 1.7551 cm Treatment difference: -1.3851cm (95% CI: -10.8213, 8.0510)	$P = 0.7709$
Change from Baseline in Log-Transformed Inflammatory Mediator Concentrations	
Treatment difference (95% CI)	
Leukocytes (109/L), Log Transformed Data: -0.0363 (-0.0650, -0.0076)	$P = 0.0140$
C-reactive Protein (nmol/L), Log Transformed Data: -0.1331 (-0.2633, -0.0028)	$P = 0.0455$
Immunoglobulin G (g/L), Log Transformed Data: -0.0197 (-0.0353, -0.0041)	$P = 0.0142$
Interleukin-8 (pg/mL), Log Transformed Data: -0.1013 (-0.1513, -0.0513)	$P = 0.0001$
Shift from Baseline in Qualitative Microbiology Cultures	
Shifts were sporadic and did not show any patterns across treatments; however, this analysis was limited by the small number of subjects and a high incidence of unknown results for sputum samples.	Not done
Change from Baseline in IRT Through Week 24	
Ivacaftor group: -9.2588 ng/mL; placebo group: 3.9988 ng/mL Treatment difference: -13.2576 ng/mL (95% CI: -27.5323, 1.0171)	$P = 0.0679$
Change from Baseline in Fecal Elastase-1 Through Week 24	
Ivacaftor group: 0.1587 µg/g; placebo group: -15.2619 µg/g. Treatment difference: 15.4206 µg/g (95% CI: -29.4148, 60.2560)	$P = 0.4922$

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, 12 to 17 years, and ≥ 18 years);
- Percent Predicted FEV1 Severity at Baseline (<70%, 70% to 90%, >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).

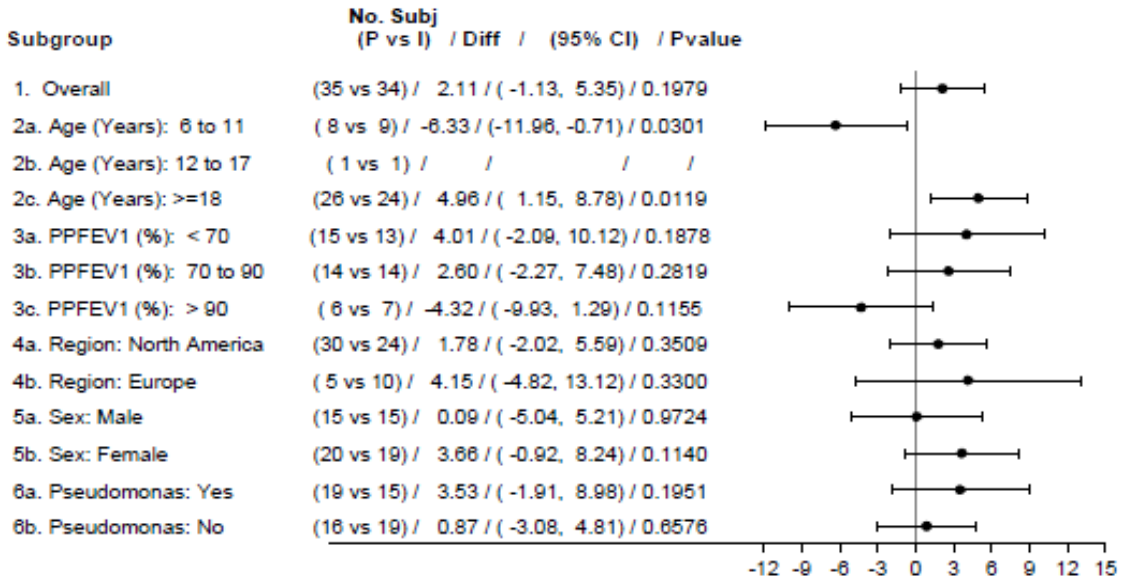
Only subgroup analyses by age at baseline, by poly-T variant and by baseline percent predicted are detailed. For the remaining subgroups above mentioned the results of the analyses performed on the absolute change from baseline in percent predicted FEV1 are as follows: Female patients had a larger treatment difference (95%CI) than male patients, i.e. females: 3.66 percentage points (-0.92, 8.24); males: 0.09 percentage points (-5.04, 5.21). This difference is not explained by imbalances in age or *R117H* poly-T variant between the male and female patients, i.e. it remains basically unexplained. Among patients in the ivacaftor group who experienced a decreased from baseline in percent predicted FEV1, 5 were female patients versus 2 male patients. The treatment differences (95%CI) were larger in Europe than in North America; i.e. North America: 1.78 percentage points (-2.02, 5.59); Europe: 4.15 percentage points (-4.82, 13.12). Patients with *P aeruginosa* infection at baseline had a larger treatment difference than subjects without *P aeruginosa* infection at baseline, i.e., infected: 3.53 percentage points (-1.91, 8.98); not infected: 0.87 percentage points (-3.08, 4.81). Sweat chloride response was consistent across all subgroups and for all of them treatment differences favoured the ivacaftor group. The analysis

of the change from baseline in percent predicted FEV1 by baseline percent predicted FEV1 (<70%; ≥70%-≤90%; >90%) showed the following results:

- subgroup of <70%: the mean (SE) absolute change in percent predicted FEV1 was 0.45 percentage points (2.03) in the placebo group (n=15) and 4.46 percentage points (2.16) in the ivacaftor group (n=13). The treatment difference (95%CI) between groups was 4.01 percentage points (-2.09, 10.12).
- subgroup ≥70%-≤90%: the mean (SE) absolute change in percent predicted FEV1 was 0.21 percentage points (1.63) in the placebo group (n=14) and 2.81 percentage points (1.70) in the ivacaftor group (n=14). The treatment difference (95%CI) between groups was 2.60 percentage points (-2.27, 7.48).
- subgroup >90%: the mean (SE) absolute change in percent predicted FEV1 was 2.22 percentage points (1.82) in the placebo group (n=6) and -2.11 percentage points (1.64) in the ivacaftor group (n=7). The treatment difference (95%CI) between groups was -4.32 percentage points (-9.93, 1.29).

Larger absolute changes in percent predicted FEV1 were seen for the ivacaftor group across the above subgroups of baseline percent predicted FEV1, with the exception of the baseline percent predicted FEV1 >90% subgroup. The figure below summarises these results.

Study110: Treatment Difference in Mean Absolute Change from Baseline in Percent Predicted FEV1 Trough Week 24 by Subgroups, Full Analysis Set (all patients)

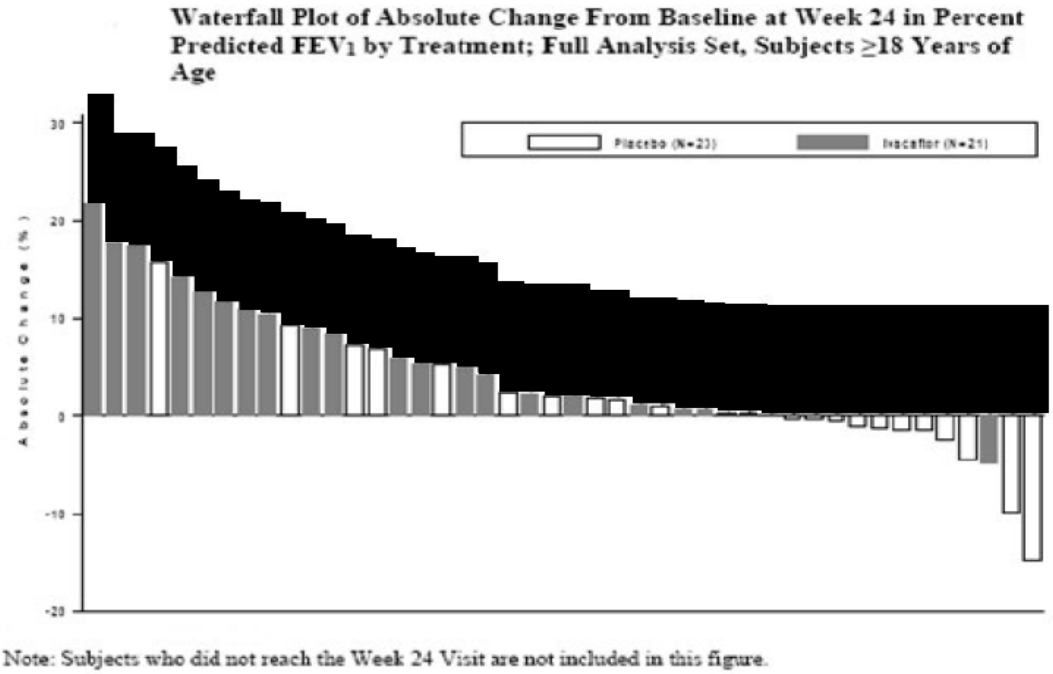


Patients ≥ 18 Years of Age (26 patients on placebo; 24 on ivacaftor): The mean absolute change from baseline in percent predicted FEV1 through Week 24 by MMRM for patients ≥ 18 years of age was greater for the ivacaftor group (4.51 percentage points) than for the placebo group (-0.46 percentage points). The treatment difference (95%CI) for ivacaftor versus placebo was 4.97 percentage points (1.15, 8.78). Based on the fact that a statistically significant and clinically relevant difference favouring ivacaftor versus placebo was observed in the age group of patients aged 18 years and older, the MAH sought an indication limited to adult patients. This, in the opinion of the MAH, was scientifically sound because it was already anticipated that children and adolescents could show different efficacy profiles in response to ivacaftor treatment primarily because of the differences in the manifestation of disease at different ages. Specifically, CF patients with the *R117H-CFTR* mutation have less advanced disease in childhood and adolescence compared to older patients. Therefore, a pre-planned subgroup analysis by patient age was

included in the SAP for the primary and secondary endpoints (although these pre-planned subgroup analyses were not intended for regulatory claims).

Consistently with an effect of ivacaftor is the fact that during the (treatment-free) Follow-up Period of Study 110, a greater decline in percent predicted FEV1 occurred in the ivacaftor group (-3.15%) than in the placebo group (-1.13%). A responder analyses for the mean absolute change from baseline in percent predicted FEV1 through Week 24 shows that 13 (54.2%) ivacaftor-treated patients experienced an increase in percent predicted FEV1 of ≥ 5% versus 4 (15.4%) placebo-treated patients.

Individual patient 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 the below waterfall plot.



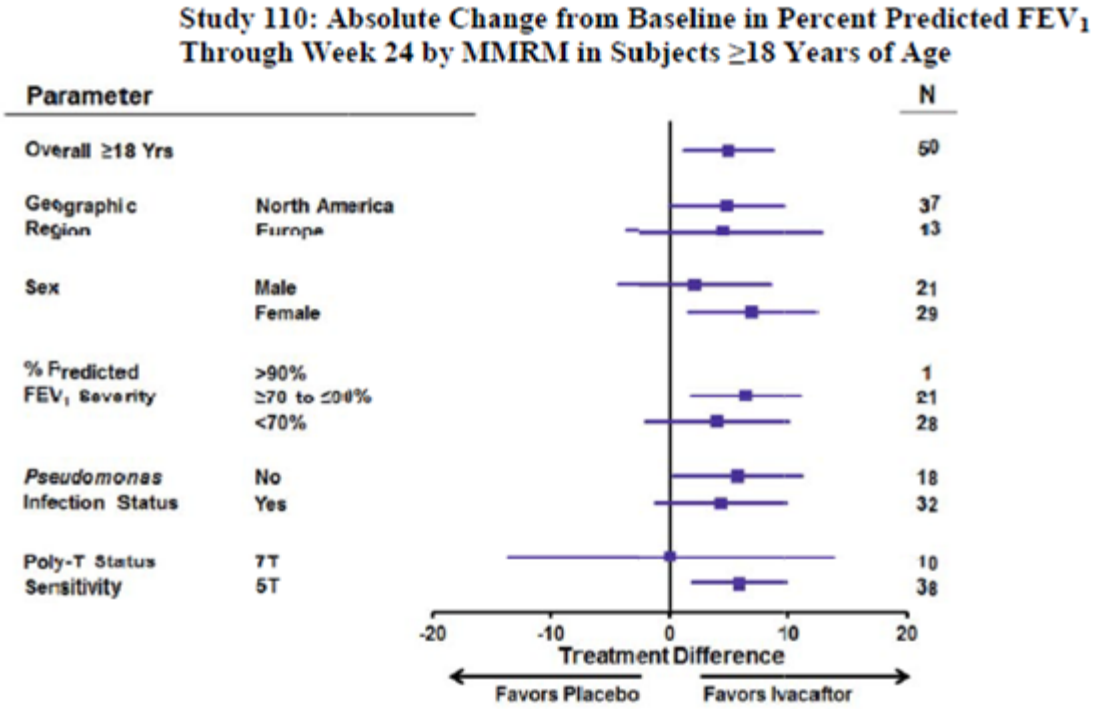
Note: Subjects who did not reach the Week 24 Visit are not included in this figure.

Of the 21 ivacaftor-treated patients with 24 week data, 19 had an increase in percent predicted FEV1 and 1 had no change in percent predicted FEV1. Only an ivacaftor-treated patient had a decline in percent predicted FEV1 at Week 24. This patient's percent predicted FEV1 values were low throughout the study: 42.3 percentage points on Day 1; 41.91 percentage points at Week 2; 44.66 percentage points at Week 4; 40.88 percentage points at Week 8; 40.88 percentage points at Week 16, and 37.44 percentage points at Week 24. This patient did not have a pulmonary exacerbation or other respiratory adverse events reported around the time of the Week 24 visit.

Regarding the secondary variables, the mean change from baseline in sweat chloride in the placebo group was -4.0 mmol/L and -25.9 mmol/L in the ivacaftor group (n=23). The treatment difference (95%CI) between groups was -21.9 mmol/L (-26.5,-17.3). Larger mean changes were also observed for the mean change in BMI (placebo: 0.22 kg/m2; ivacaftor: 0.53 kg/m2) and in the pooled respiratory domain of the CFQ-R (placebo: -0.46; ivacaftor: 12.18). Protocol-defined pulmonary exacerbations occurred only in patients in this age group and, consequently, the results described for the overall population apply.

As a consequence of the difference observed in this age group in the change in percent predicted FEV1, post-hoc analyses (following database lock) were also carried out in this age group and in the 6 to 11 year-old group. These analyses were primarily focused on exploring 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.

Results of these subgroup analyses limited to the subjects ≥ 18 years old are presented in figure below for the primary efficacy variable.



In the above subgroup analyses limited to patients ≥ 18 years old, the following trends were observed: Patients in the ivacaftor group with a baseline percent predicted FEV1 of ≥ 70% to ≤ 90% showed a larger mean change from baseline in percent predicted FEV1 (5.09 percentage points) than patients in the placebo group (-1.35 percentage points). Similar results were observed in patients with a baseline percent predicted FEV1 of <70% (4.46 and 0.45 percentage points respectively). When the geographical region is considered, the mean absolute change in percent predicted FEV1 was similar between the 2 subgroups (Europe: 4.51 percentage points; North America: 4.81 percentage points). Treatment differences for change from baseline in sweat chloride (Europe: -22.6 mmol/L; North America: -22.9 mmol/L) were similar for both geographic regions. When *P aeruginosa* infection status at baseline is considered, a larger treatment difference in the absolute change in percent predicted FEV1 was seen for the patients not infected with *P aeruginosa* than those infected (infected: 4.32 percentage points; not infected: 5.73 percentage points). The treatment differences for absolute change from baseline in sweat chloride (infected: -23.0 mmol/L; not infected: -24.4 mmol/L) were similar for both subgroups.

Patients aged 12 to 17 years (a patient in each group): No statistical analysis was conducted because only 2 patients were enrolled.

First patient was a 13-year-old female with *CFTR* genotype *R117H-7T/F508DEL-9T*. At baseline, this patient had a percent predicted FEV1 of 87.63, 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 patient 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 87.63; Week 2: 88.23), but the patient's sweat chloride showed a -17.25 mmol/L absolute change from baseline.

Second patient, randomised to placebo, was a 17-year-old female with a *CFTR* genotype *R117H-5T/W1282X-7T*, who completed the full 24 weeks of treatment. At baseline, the subject had a percent predicted FEV1 of 88.67 percentage points, a sweat chloride value of 74.75 mmol/L, a BMI of 21.86 kg/m2, and a CFQ-R respiratory domain score of 77.78 points. At the Week 24 Visit, the patient had a 7.53 percentage points absolute change in percent predicted FEV1 from baseline and a corresponding increase in CFQ-R respiratory domain score to 94.44 points. The subject's sweat chloride value at the Week 24 Visit was slightly higher than at baseline.

Patients 6 to 11 years of age (8 patients on placebo; 9 on ivacaftor): Table below summarizes the primary endpoint, the secondary endpoints, and the relative change from baseline in percent predicted FEV1 results for FAS patients 6 to 11 years of age (both inclusive). No protocol-defined pulmonary exacerbations occurred in children 6 to 11 years of age (inclusive) during the treatment period.

Study 110: Efficacy Endpoint Results, Full Analysis Set, Subjects 6 to 11 Years of Age

Analysis	N (Placebo; Ivacaftor)	Treatment Difference (Ivacaftor vs Placebo)	*P* value
Primary Endpoint			
Percent Predicted FEV_1: Absolute Change from Baseline	(8; 9)	-6.3334 percentage points (-11.9602, -0.7066)	0.0301
Additional FEV_1 Endpoint			
Percent Predicted FEV_1: Relative Change from Baseline	(8; 9)	-6.7675% (-13.1990, -0.3360)	0.0405
Secondary Endpoints			
Sweat Chloride: Absolute Change from Baseline	(8; 8)	-27.6322 mmol/L (-37.1640, -18.1005)	<0.0001
BMI: Rate of Change from Baseline	(8; 9)	-0.1813 kg/m^2 (-2.3763, 2.0136)	0.8693
BMI-for-age z-scores: Rate of Change from Baseline	(8; 9)	0.0520 points (-0.6927, 0.7966)	0.8894
Pooled CFQ-R Respiratory Domain Score[a]: Absolute Change from Baseline	(7; 8)	-6.1327 points (-15.6774, 3.4121)	0.1856

vs: versus

[a] 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.

Absolute change from baseline in percent predicted FEV1 was 3.51 and -2.82% percentage points in the placebo and ivacaftor groups, respectively with the upper limit of the 95% confidence interval of the treatment difference between ivacaftor and placebo below zero. This is not consistent with the results observed for this age group in studies 103 (*G551D-CFTR* mutation) and 111 (non-*G551D-CFTR* gating mutations) where the difference between placebo and ivacaftor in the absolute change in percent predicted FEV1 favoured ivacaftor and was above 10 percentage points. The MAH suggest that this appears to be a spurious result driven by an unusual placebo response and generally no or minimal change in FEV1 in subjects in the ivacaftor group. The placebo group had an improvement in mean percent predicted FEV1, from 93.98% at baseline to 98.43% overall post-baseline, while the ivacaftor group had a slight decline in mean percent predicted FEV1 from 97.49% at baseline to 96.25% overall post-baseline. To further explore this issue a comparison of the change from baseline in percent predicted FEV1 values was performed that showed that in the placebo group 4 patients had a decrease in percent

predicted FEV1 between Screening and Baseline, and 6 ivacaftor patients had an increase in percent predicted FEV1 between Screening and Baseline. This could have contributed to the observed treatment difference in the primary endpoint in subjects 6 to 11 years of age. The run-in period in study 110 was used to stabilise patients before dosing them. Those patients whose clinical status was not stable during this period were excluded from the study but it would appear that there were a number of patients whose FEV1 increased or decreased during this period. The MAH was requested to discuss how exclusion criteria were applied at screening and baseline in study 110, particularly in the youngest age group. Patients were required to be clinically stable during screening; however, FEV1 measurement is associated with a degree of inherent variability and can vary between visits, even in subjects who are clinically stable. In this respect, the American Thoracic Society/European Respiratory Society criteria for spirometry set an upper limit of 150 mL for variance between pulmonary function tests at the same visit/time (or 100 mL if the FVC is $\leq$ 1.0 L). It is accepted that variation in percent predicted FEV1 can be seen even in stable patients. However, it is still unclear why some subjects had a decrease in percent predicted FEV1 between screening and baseline in the placebo group. Moreover, the fluctuation in spirometry parameters seems very high and does not seem to be related either to the study drug or to changes in clinical status. Further clarification was requested for four patients who showed substantial changes in spirometry parameters that could not be explained either by the study drug or by changes in clinical status. No appropriate explanation for the high observed variability in FEV1 could be given other than the expected high variability in spirometry in young children in general.

Subgroup analyses by *R117H* poly-T variant (*5T* or *7T*): The *CFTR* poly-T tract is present in every copy of the *CFTR* gene and occurs as 1 of 3 variants (*5T*, *7T*, or *9T*). *R117H-5T* results in a more severe disease phenotype than *R117H-7T*, while *R117H-9T* is highly unlikely to cause disease. CF genotyping was performed on all subjects at screening. Although this analysis provided the subjects' poly-T variant genotype, it did not specify the phase of the mutations, i.e. which *CFTR* allele each variant was located on, since different sequencing assay would have to be used. 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 were considered to have 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, 1 North Iranian individual, and 1 Hispanic individual. 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.

In the FAS population, the number of patients with confirmed *R117H-5T* was 24 in the placebo group and 14 on the ivacaftor group. These figures for the *R117H-7T* poly-T variant were 5 and 11, respectively. The poly-T variant *5T* (which usually confers an increased risk of disease severity) was more frequent in patients randomised to placebo. The poly-T variant that predominates in patients with a second mutation other than *F508del* is *7T*. The confirmed plus derived dataset includes the following number of patients: 27 patients on placebo and 21 on ivacaftor with the *5T* variant while for the *7T* variant the numbers are 7 and 12 respectively. Eight of these 19 patients were children. The largest difference is seen in the number of patients in the ivacaftor group for whom a *5T* variant has been derived, i.e. 7 patients. The analysis by poly-T status *5T* or *7T* in the confirmed plus derived dataset is based on some assumptions for 15 patients for whom the poly-T status could not be identified. The assumption related to the poly-T variant *9T* in *cis* with the *F508del* mutation is acceptable. However, it is unclear how assignment of the poly-T status in *cis* with *R117H* was done for these patients with no confirmed variant. Overall, there were 19 patients with sweat chloride below 60 mmol/l (10 on ivacaftor and 9 on placebo). Out of these, 15 (7 on

placebo and 8 on ivacaftor) had sweat chloride values below 60 mmol/l and a confirmed poly-T status. In 10 of them the confirmed variant is *7T* and in the remaining 5 it is *5T*. Therefore, the assumption that if a subject had *R117H-9T* they would have had a very mild disease phenotype (e.g., sweat chloride <60 mmol/L) does not seem completely justified. The analysis by poly-T status in the confirmed plus derived dataset should be viewed with caution. The analysis performed in the confirmed data set of the FAS shows that the mean (SD) absolute change in percent predicted FEV1 in patients with the *5T* variant was 0.73 percentage points (1.20) in the placebo group and 6.02 percentage points (1.57) in the ivacaftor group. The treatment difference for ivacaftor versus placebo was 5.3 percentage points [95% CI 1.3, 9.3]. For the *7T* variant the results were as follows: placebo: -0.92 percentage points (3.09); ivacaftor: -0.72 percentage points (2.10). The treatment difference for ivacaftor versus placebo was 0.2 percentage points (95% CI -8.1, 8.5).

In the confirmed plus derived dataset, the mean (SD) baseline percent predicted FEV1 for patients with a *5T* variant was 68.30 (18.84) in the placebo group and 70.48 (17.40) in the ivacaftor group. At Week 24 these figures were as follows: 71.16 (23.10) and 74.50 (17.23) respectively. The mean (SD) absolute change from baseline at week 24 was 1.57 (6.45) and 6.30 (7.33) in the placebo and ivacaftor groups, respectively. The estimated (by MMRM) treatment difference (95%CI) between groups was 3.19 (-0.48, 6.87). At week 24 percent predicted FEV1 was only available for 24 and 18 patients in the placebo and ivacaftor groups respectively. As for patient with the *7T* variant (confirmed plus derived), the mean (SD) baseline percent predicted FEV1 was 81.05 (9.01) in the placebo group and 84.85 (20.48) in the ivacaftor group. At Week 24 these figures were as follows: 82.32 (10.08) and 87.94 (19.24) respectively. The mean (SD) absolute change from baseline at week 24 was 2.85 (5.93) and 0.45 (5.82) in the placebo and ivacaftor groups respectively. The estimated (by MMRM) treatment difference (95%CI) between groups was -1.46 (-8.69, 5.77). At week 24 percent predicted FEV1 was only available for 6 and 9 patients in the placebo and the ivacaftor groups respectively.

Regarding sweat chloride the results of the absolute mean change from baseline favour the ivacaftor group in patients with a *5T* or a *7T* variant. For patients with the *5T* variant, the mean (SD) absolute change at week 24 was -6.6 mmol/l (19.2) in the placebo group and -35.4 mmol/L (14.3) in the ivacaftor group. The estimated (by MMRM) treatment difference (95%CI) between groups was −25.1 (-30.1, -20.0). For patients with a *7T* variant, the mean (SD) absolute change at week 24 was −9.9 mmol/l (10.3) and −20.4 mmol/l (10.0) for the placebo and the ivacaftor groups respectively. The estimated (by MMRM) treatment difference (95%CI) between groups was −20.6 (-28.1, -13.1).

Table below shows these results by poly-T status for the adult group.

Absolute change from baseline at week 24 in efficacy endpoints by poly-T status (Confirmed+Derived version), FAS population (patients ⩾18 years old)

Poly-T status	Percent Predicted FEV1 (%)			Sweat chloride (mmol/L)		
	Period baseline Mean	**Week 24** Mean	**Absolute change Mean (SD)**	**Period baseline** Mean	**Week 24** Mean	**Absolute change Mean (SD)**
R117H-5T						
- placebo (n=21)	60.46	61.65 (n=18)	0.27 (1.59)	75.96	70.35 (n=17)	-8.43 (17.97)
- ivacaftor (n=17)	64.8324	71.23 (n=16)	7.15 (1.72)	81.03 (n=16 at baseline)	45.83 (n=15)	-35.67 (14.30)
R117H-7T						
-placebo (n=4)	75.3545	76.10	0.75 (3.10)	55.94	44.25	-11.69 (11.91
-ivacaftor (n=6)	71.8512	76.96 (n=4)	4.98 (5.45)	39.30	24.50 (n=4)	-19.31 (6.93)

A waterfall plot analysis of individual subject responses at Week 24 suggests that some *R117H*-7T subjects may respond to ivacaftor treatment (see figure below).

Study 110: Waterfall Plot of Absolute Change from Baseline at Week 24 in Percent Predicted FEV_1 for Subjects ≥18 Years of Age With *R117H-7T*

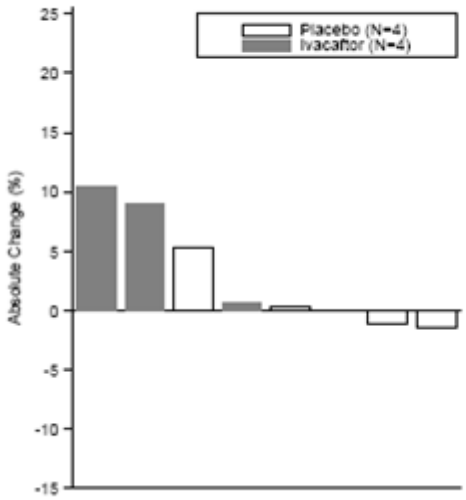


Table below shows the results by poly-T status confined to children.

Absolute change from baseline at week 24 in efficacy variables by poly-T status (Confirmed+Derived version), FAS population (children aged 6 to 11 years)

Poly-T status	Percent Predicted FEV1 (%)			Sweat chloride (mmol/L)		
	Period baseline Mean	**Week 24** Mean	**Absolute change** Mean (SD)	**Period baseline**	**Week 24**	**Absolute change** Mean (SD)
R117H-5T - placebo (n=5) - ivacaftor (n=4)	97.19 94.49	100.39 100.62 (n=2)	3.20 (5.18261) -2.66 (0.56851)	92.70 81.00	89.50 52.00 (n=2)	-3.20 (25.54) -33.25 (20.1525)
R117H-7T -placebo (n=3) -ivacaftor (n=5)	88.63 99.88	94.76 96.72	7.06 (9.69) -3.16 (2.97)	44.58 47.31	49.25 25.88	-6.38 (8.31) -21.44 (13.49)

It has been considered whether *R117H-7T* patients should be excluded from the indication as this variant leads to normal splicing and is rarely associated with disease manifestations and these are usually mild. However, severe lung disease has been also described in these patients and consequently their inclusion in the indication is supported but a cautionary warning is included in section 4.4 of the SmPC with a cross-reference to section 5.1 indicating the limitations of the effect seen in ivacaftor in patients with a 7T variant. The results by the poly-T variant *7T* previously shown may be confounded by age given that out of the 19 patients (confirmed plus derived dataset) in study 110 with an *R117H-7T* allele, 8 were children 6 to 11 years of age. Of the patients ≥18 years of age with an *R117H-7T* allele, 4 were in the placebo group and 6 were in the ivacaftor group. Although these numbers are small, no clear FEV1 response was evident in the subgroup of subjects ≥ 18 years of age with an *R117H-7T* allele either. This issue should be

taken into account by prescribing physicians. If treatment with ivacaftor is being considered for patients with an *R117H* mutation the phase of the poly-T variant should be identified whenever possible, as described in the SmPC.

Subgroup analyses by the second *CFTR* mutation: The majority of subjects (76.8%) had the F508del mutation on the second allele. Although ivacaftor can potentiate *F508del-CFTR*, the processing defect caused by *F508de*l results in minimal amounts of *CFTR* reaching the surface, and ivacaftor treatment did not result in clinical benefit in subjects homozygous for the *F508del-CFTR* mutation. Each of the other second alleles was present in no more than 2 subjects. The non-*F508del* second alleles are known to produce either no or truncated *CFTR* protein (*2184InsA, 3659DelC*, *621+1G>T*, *E60X*, *G103X, G542X*, *R553X*, *S489X*, and *W1282X*) to cause severe processing defects (*F508Del*, *R560T*, and *DelI507*), or to cause a severe conductance defect that is not responsive to ivacaftor in vitro (*S341P*). One ivacaftor-treated patient with the genotype *R117H-7T*/*R553X-7T* had, however, a baseline sweat chloride below of 52.3 mmol/l. Table below shows summary statistics of the mean (SD) absolute change from baseline at Week 24 in percent predicted FEV1 for patients in the FAS population.

Mean (SD) change from baseline at Week 24 in percent predicted FEV1 by second *CFTR* mutation

	Percent Predicted FEV1 Mean (SD)		
	FAS		
2nd *CFTR* mutation	Period baseline	Week 24	Absolute change
F508del			
- placebo (n=25)	68.98 (19.51)	72.98* (22.14)	2.51 (6.67)
- ivacaftor (n=28)	76.35 (19.80)	80.10* (19.22)	4.90 (7.65)
Stop codon			
- placebo (n=5)	64.73 (20.22)	63.84 (25.16)	-0.90 (6.15)
- ivacaftor (n=2)	83.53 (28.79)	81.49 (25.11)	-2.04 (3.68)
Other			
- placebo (n=5)	82.01 (11.68)	80.79 (13.92)	0.8993 (1.81566)
- ivacaftor (n=4)	67.21 (11.68)	74.99 (16.27)	7.78 (7.85)

**22 patients on placebo/22 patients on ivacaftor*

The data above presented suggest that patients with a stop codon mutation responded worse to ivacaftor than patients with the *F508del* mutation as shown by an absolute change from baseline at week 24 of -2.04 versus 4.9 percentage points. In the FAS population the number of patients with the *F508del* mutation is 25 (71.4%) on placebo and 28 (82.4%) on ivacaftor. In age group ≥18 years of age, 19 patients in each group (73.1% on placebo, 79.2% on ivacaftor) had this mutation in the second allele of the *CFTR*.

Summary statistics by age subgroup were provided for the mean change from baseline in percent predicted FEV1 and sweat chloride for patients with a second *CFTR* mutation as follows: *F508del*, stop

codon mutations and "other" mutations in the second allele. Only two patients (a child and an adult) were in both the stop codon and ivacaftor groups while five patients (an adolescent and four adults) were in both the stop codon and placebo groups. Due to the limited data, a firm conclusions on whether patients with a second stop codon mutation respond worse to ivacaftor cannot be made. The mean change from baseline in percent predicted FEV1 was -4.65 (child) and 0.56 (adult) percentage points in the two ivacaftor-treated patients. In terms of the mean change in sweat chloride, data at week 24 are not available for the child while the adult patient showed a decrease of 51.5 mmol/L from baseline. In patients aged 18 years and older, an analysis is presented by the second *CFTR* allele (i.e. *F508del*; Other) that shows the following: nineteen patients in each group had *F508del* as the second *CFTR* mutation in this age group; seven patients on placebo and 5 on ivacaftor had other mutations. The treatment difference (95%CI) for those with the *F508del* was 4.41 percentage points (-0.36, 9.18). The treatment difference (95%CI) for patients with other mutations was 6.85 (0.5414, 13.1500) percentage points.

Summary of main study

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

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="3">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>
</table>

Database lock Study completion (date last subject completed the last visit)	20 November 2013		
Results and Analysis			
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.		
Descriptive statistics and estimate variability	Treatment group	Ivacaftor	Placebo
	Number of subject	34	35
	PPFEV1, 24 weeks, LS Mean	2.5724	0.4611
	Standard error	1.1532	1.1313
	BMI, 24 weeks, LS mean	0.4910	0.2284
	Standard error	0.6653	0.6504
	*Sweat chloride, 24 weeks, LS mean Standard error	-26.2771 1.4584	-2.3078 1.3716
	**Respiratory domain pooled CFQ-R, 24 weeks, LS mean 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
	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 analyses were performed across trials. However, baseline data and disease characteristics of patients enrolled in study 110 were 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 with 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 high proportion with pancreatic sufficiency. Regarding percent predicted study 110 patients who were 6 to 11 years of age had a baseline mean percent predicted FEV1 approximately 10 percentage points higher than study 103 patients and a categorical distribution favouring higher baseline percent predicted FEV1 values. Similarly, the results of these studies have been discussed to give context for the efficacy claim of study 110. In studies 102, 103, and 111 (Part 1) analysis of the primary endpoint (absolute change in percent predicted FEV1) 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 percent predicted FEV1 were in all cases above 10.0 percentage points. In particular, in study 103 the treatment difference was 12.5 percentage points. The relevance of data from the previous studies of ivacaftor to support its efficacy in the age subgroup of patients aged 18 years and older with a *R117H* mutation is questionable. Precisely because the latter patient population is usually less severe better results would have been expected. On the other hand it is acknowledged that there may be less room for showing improvement. However, there are factors (such as the poly-T variant, the usually milder phenotype etc. in the case of the *R117H-CFTR* mutation) that make comparisons across these populations complex.

Clinical studies in special populations

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

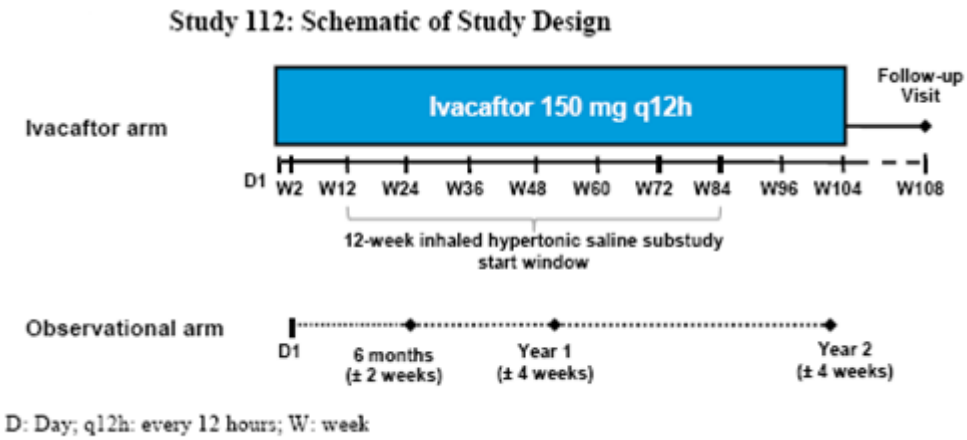
Two 68-year-old patients were enrolled in study 110. Both of them were randomised to placebo. One of them apparently experienced adverse events of cough, sputum increased and pyrexia that are reported as not related and of moderate severity. They were considered as non-serious AEs in study 112. A moderate increase in percent predicted FEV1 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. Narratives have been provided strictly for two patients ≥ 65 years old enrolled in study 110. However, 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. As a consequence, a more conservative approach would have been to consider at the very least to provide narratives for patients ≥ 60 years old. The MAH is 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 cystic fibrosis and residual *CFTR* function) or the rollover study 112. As a conclusion the number of patients treated with ivacaftor who are at least 55 years old is still limited.

Supportive study

Study 112 is an ongoing, open-label, rollover study of orally administered ivacaftor (150 mg q12h) 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 (patients with an *R117H-CFTR* mutation), study 111 (patients with a non-*G551D-CFTR* gating mutation), and study 113 (patients who have phenotypic or molecular evidence of residual *CFTR* function). Summarized in this report are results from a study 112 interim analysis, through the Week 12 Visit, of data from patients who were previously enrolled in study 110. Patients from study 111 and study 113 who enrolled in study 112 were not included in this interim analysis.

A schematic of the study 112 design is provided in figure below.



Because patients in study 110 underwent a 3 to 4-week washout during the study 110 Follow-up Period, data from study 112 can provide additional information about ivacaftor efficacy in subjects with a *R117H-CFTR* mutation, i.e. the purpose of the inclusion of this data in the present submission is to give support to the claim of efficacy of ivacaftor in patients aged 18 years and older. In addition, in spite of the fact that patients aged 6 to 11 years did not respond to ivacaftor in study 110 they were enrolled in study 112. Consequently, this study also provides helpful information for them. 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 FAS for this interim analysis includes 65 patients: 30 patients in the ivacaftor/ivacaftor group and 35 patients in the placebo/ivacaftor group. The 2 patients enrolled in the observational arm of study 112 were included in the Safety Set but not in the FAS. Of the 65 patients in the FAS, 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. Of these only one patient in the ivacaftor/ivacaftor group discontinued dosing due to an adverse event of pulmonary exacerbation. Of the 65 patients enrolled in the ivacaftor treatment arm of study 112, 49 were ≥ 18 years of age at the start of study 110, 15 were 6 to 11 years of age, and 1 was 12 to 17 years of age. Baseline mean percent predicted FEV1 was 71.0% in the placebo/ivacaftor group and 72.7% in the ivacaftor/ivacaftor group, which was comparable to the baseline FEV1 in Study 110 (placebo: 70.2%; ivacaftor: 75.7%; overall: 72.9%) because of the 3 to 4-week wash out at the end of study 110. In study 112, the mean baseline sweat chloride concentration was 65.4 mmol/L in the placebo/ivacaftor group and 55.3 mmol/L in the ivacaftor/ivacaftor group. Forty-nine FAS patients who were ≥ 18 years of age at the start of study 110 enrolled in the ivacaftor arm of study 112 (placebo/ivacaftor: 26 patients; ivacaftor/ivacaftor: 23 patients). Baseline mean percent predicted FEV1 was 61.9% in the placebo/ivacaftor group and 68.7% in the ivacaftor/ivacaftor group, which was again comparable to the baseline FEV1 in study 110 (placebo: 62.2%; ivacaftor: 67.0%). In study 112, the baseline sweat chloride concentration was 66.0 mmol/L in the placebo/ivacaftor group and 53.8 mmol/L in the ivacaftor/ivacaftor group. Fifteen FAS 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 percent predicted FEV1 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 percent predicted FEV1 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 percent predicted FEV1 using a one-sample t-test.

Outcomes

Full Analysis Set, all patients (n=65)

Summary statistics show that the mean (SD) absolute change in percent predicted FEV1 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). There is a discrepancybetween the initial number of patients in the ivacaftor/ivacaftor group (30) and those for whom spirometry data is available (27) at week 12 that has been addressed by the MAH. The reasons for the lack of data for these 3 patients have been clarified as requested. For the overall population, the mean (SD) change from baseline in percent predicted FEV1 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 percent predicted FEV1 from baseline at week 12 in the placebo/ivacaftor group was 5.47 (7.99) 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 MAH should clarify this discrepancy in the number of patients in the ivacaftor/ivacaftor group. The mean (SD) overall absolute change in percent predicted FEV1 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 percent predicted FEV1 and sweat chloride were 88.67 and 74.75 mmol/l. At study 112 baseline, these figures were as follows: 96.20 and 82 mmol/l, i.e. she had experienced an increase of 7.5 and 7.3 mmol/l in percent predicted FEV and sweat chloride respectively. At study 112 week 12 his percent predicted FEV1 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)

Summary statistics show that the mean (SD) absolute change in percent predicted FEV1 from baseline at week 12 in the placebo/ivacaftor group was 3.58 (7.76) percentage points and 9.78 (10.42) percentage points in the ivacaftor/ivacaftor group. There was a slight decrease in percent predicted FEV1 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. The MAH argues that a dip in percent predicted FEV1 in the placebo/ivacaftor group in 6-12 years old is not consistently seen across ivacaftor/ivacaftor or adult subgroups or previous studies with ivacaftor. In addition, no safety concern was raised. The argumentation, that if a drug-based mechanism was responsible for the dip at week 2, then the effect would be expected in both age groups is not completely understood, since the MAH explains the age restriction with different clinical effect of ivacaftor across age groups. No further issues are 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).

In conclusion, the results seen in study 112 in terms of change from baseline at week 12 in percent predicted FEV1 in the placebo/ivacaftor group improve the results seen in study 110 in patients receiving ivacaftor. This is seen in the age group ≥ 18 years old, particularly in those aged 6 to 11 years old. With a single exception, the increase at week 12 in percent predicted FEV1 is higher in the ivacaftor/ivacaftor group than in the placebo/ivacaftor group for all subjects and age groups. The results of the post-hoc statistical analyses performed show treatment differences between groups in percent predicted FEV1 that are statistically significant except for patients in the 6 to 11 year-old group. This is attributed 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.

However, results of study 112 require detailed discussion of the follow-up period of study 110 in which none of the patients received treatment. Summary statistics of the progression of percent predicted FEV1 and sweat chloride at week 24 and at the end of the follow-up period in study 110 for all patients in the FAS as well as for the age subgroups of 6 to 11 years old and ≥ 18 years old have been provided upon request. Tables below show this information and also baseline and week 12 data from study 112 for percent predicted FEV1 and sweat chloride.

PPFEV1 Mean (SD)	**Study 110**			**Study 112***	
	Baseline	Week 24	Follow-up	Baseline	Week 12
All patients (FAS) - placebo (35)	70.23 (18.94)	72.51 (21.65)	70.97 (21.45)	71.00 (21.47)	75.99 (21.08)
- ivacaftor (34)	75.70 (19.26)	79.47 (18.54)	75.54 (19.04)	72.69 (19.45)	79.17 (18.57)
Age group ≥18 years (FAS) - placebo (26)	62.22 (14.41)	64.49 (16.90)	61.81 (15.73)	61.85 (15.79)	67.32 (16.26)
- ivacaftor (24)	67.03 (15.34)	73.35 (17.19)	69.82 (16.24)	68.68 (17.15)	73.42 (17.64)
Age group 6 to					

11 years (FAS) - placebo (8)	93.98 (8.36)	98.78 (9.22)	97.54 (11.85)	97.53 (11.85)	101.11 (11.30)
- ivacaftor (9)	97.49 (8.61)	97.83 (6.07)	88.77 (20.00)	85.84 (22.07)	95.62 (9.13)

*Numbers in study 112 are as follows:

- All patients: 35 on placebo/ivacaftor; 30 on ivacaftor/ivacaftor
- ≥18 years old: 26 on placebo/ivacaftor; 23 on ivacaftor/ivacaftor
- 6 to 11 years old: 8 on placebo/ivacaftor; 7 on ivacaftor/ivacaftor

The above table shows that in the ivacaftor group baseline values of study 112 are systematically lower than values at follow-up of study 110. This leads to an increase in the change from baseline in percent predicted FEV1 at week 12 in the ivacaftor/ivacaftor group.

Regarding sweat chloride (see table below), the same applies, i.e. sweat chloride values at follow-up of study 110 and at study 112 baseline do not coincide with the highest differences seen in the ivacaftor group. The only exception corresponds to the analysis of all FAS patients in which the mean sweat chloride at follow-up of study 110 is higher than that at study 112 baseline. The decrease in the mean absolute change from baseline after 2 weeks of treatment with ivacaftor in study 112 was of similar magnitude in the placebo/ivacaftor and ivacaftor/ivacaftor groups and ranged from a minimum of 14.8 mmol/l (patients ≥ 18 years old) in the ivacaftor/ivacaftor group to a maximum of 25.4 mmol/l (age group from 6 to 11 years) also in the ivacaftor/ivacaftor group).

Sweat chloride **Mean (SD)**	**Study 110**			**Study 112***	
	Baseline	**Week 24**	**Follow-up**	**Baseline**	**Week 2**
All patients (FAS) - placebo (35)	73.4 (19.7)	68.3 (20.0)	65.7 (19.3)	65.4 (19.5)	44.8 (16.8)
- ivacaftor (32)	67.3 (23.5)	39.8 (14.6)	59.9 (18.8)	55.3 (18.1)	38.8 (14.9)
Age group ≥18 years (FAS) - placebo (26)	73.0 (17.3)	64.6 (18.4)	66.4 (17.6)	66.0 (17.8)	46.9 (16.1)
- ivacaftor (24)	69.3 (24.1)	41.3 (14.6)	51.3 (17.4)	53.8 (15.8)	40.0 (15.4)
Age group 6 to 11 years (FAS) - placebo (8)	74.7 (28.6)	78.0 (23.4)	62.8 (26.2)	62.8 (26.2)	38.1 (20.0)
- ivacaftor (9)	64.2 (22.6)	34.6 (15.0)	54.5 (24.4)	60.4 (25.7)	35.1 (13.8)

*Numbers in study 112 are as follows:

- All patients: 33 on placebo/ivacaftor; 26 on ivacaftor/ivacaftor
- ≥18 years old: 26 on placebo/ivacaftor; 23 on ivacaftor/ivacaftor
- 6 to 11 years old: 8 on placebo/ivacaftor; 7 on ivacaftor/ivacaftor

2.4.3. Discussion on clinical efficacy

This extension of the indication of Kalydeco to patients with cystic fibrosis with an *R117H-CFTR* mutation is based on a single, randomised, double-blind, placebo controlled study (study 110) of 24 weeks of duration. As such, and in line with regulatory guidance, this study is expected to provide a compelling evidence of efficacy in the concerned patient population. CF being a rare disease and the allele *R117H* not as frequent as other *CFTR* mutations such as *F508del* it is justified that a single study is conducted. In Europe, North America, and Australia, approximately 1,600 people with CF aged 6 years and older have at least 1 copy of an *R117H-CFTR* mutation according to the MAH. Study 110 enrolled 70 patients in North America and Europe and was terminated prematurely by the sponsor. The MAH justified this with

the limited number of available patients with an *R117H* allele and CF who would meet the inclusion and exclusion criteria, in particular the restrictions imposed by baseline percent predicted FEV1. This is reinforced by the fact that out of the 108 patients screened in study 110, 38 could not be randomized mainly due to the failure to meet the inclusion criterion related to percent predicted FEV1.

Of the three main pillars on which the diagnosis of cystic fibrosis is based the great are of uncertainty is related to the decision on whether the two mutations present are disease-causing. This is particularly the case of the *R117H* mutation that is described as a mutation of variable penetrance. Therefore, it would appear that requiring two disease-causing mutations AND a compatible clinical (lung disease) AND biochemical (i.e. sweat chloride values well in the range of the disease) phenotype (rather than two disease-causing mutations OR a sweat chloride ≥60 mmol/L) could have overcome issues related to patients/mutations having a normal sweat chloride value at baseline. As the diagnostic criteria of CF used in study 110 stipulated that chronic sinopulmonary should be presented no further issues were raised except for the charcaterisation of patients with sweat chloride below 60 mmol/L.

Additional concerns of the CHMP included differences in baseline of study population in terms of severity of the lung disease: *P aeruginosa* lung infection/colonisation at baseline (one of the main phenotypic features of CF lung disease) was present in 54.3% of patients on placebo and 44.1% of patients on ivacaftor. The mean baseline percent predicted FEV1 in the FAS population was 70.23% in the placebo group and 75.70% in the ivacaftor group. In the oldest age group these values are 62.21% and 67.03%. Pancreatic insufficiency was also more frequent in the placebo group (28.6% versus 8.8%). In the confirmed plus derived dataset the number of patients on placebo with the poly-T variant *5T* is 27 and 21 on ivacaftor. In the age group ≥ 18 years old these numbers are 21 and 17 respectively. The treatment difference in the mean absolute change from baseline in percent predicted FEV1 was not statistically significant. However, in a pre-planned subgroup analysis by age, a difference between treatment groups was seen, which favoured ivacaftor in the age group ≥ 18 years of age. Data from patients ≥18 years of age were considered independently based on the following:

- ivacaftor has been proven to be effective for other *CFTR* mutations based on its mechanism of increasing *CFTR* channel open probability,
- there is age-based heterogeneity in the Full Analysis Set of patients enrolled in study 110
- more patients ≥ 18 years of age were enrolled than the minimum enrolment target set for the entire study
- biological plausibility exists for a different treatment response in the age groups
- a consistency of treatment effect is observed across subgroups when limited to subjects ≥ 18 years of age, and
- the study 110 results were replicated in study 112

The MAH supplied plausible explanation for the differential results seen in adults and children with an *R117H* mutation. While there is no age dependency on the effect of ivacaftor at the level of the sweat gland, the lungs of CF patients are progressively damaged with age. Three types of additional analyses have been provided and discussed by the MAH: a forest plot analysis of absolute change in percent predicted FEV1 among the subgroups, including P values and the treatment by subgroup interaction as requested (refer to the description of the results of study 110), a regression analysis (conducted by FDA) and a data-driven tree procedure, labelled as "interaction trees". Unlike other subgroups, there is a clear separation of the point estimates for the age subgroups, and the confidence intervals are non-overlapping. Furthermore, the age is the most significant predictor of therapeutic effect. The regression analysis considered partitions by baseline FEV1 (<70% predicted, 70% to 90% predicted, and >90%) and by poly-T variant genotype (*5T* or *7T*). Both factors were correlated with age because subjects 6 to

11 years of age had higher baseline FEV1 and were more likely to have *R117H-7T* allele. In the 6 to 11 year-old group, only 8% of the patients have decreased FEV1 and 46% of the patients have no clinical symptoms at all. According to published data, the average age when mild form of CF is diagnosed is 11.8 years. It is noted that there are reports of serious clinical symptoms in younger children, but the Cystic Fibrosis Foundation registry data provided by the MAH show that clinical symptoms which require medical treatment are indeed more common over the age of 18 years. It is acknowledged, however, that numbers in the children group are limited and that the results in this group may be partially driven by the fact that a high number of children have well-preserved lung function and the *7T* variant.

In addition, patients with the *7T* allele are a cause for concern as they represent a separate subgroup. The average response is practically zero, hence some patients improved and some patients actually deteriorated. Given the extremely small sample size (ivacaftor n= 4, placebo n= 6) it is not possible for the CHMP to draw any firm conclusion. Treatment decisions should be made considering all factors in the clinical practise. An adequate warning has been included in section 4.4 of the SmPC with a cross-reference to section 5.1.

Overall, based on the above information, the CHMP concluded that an indication for adult patients with an *R117H-CFTR* mutation could be approvable.

In the context of a potential extrapolation from adults to children, the MAH was requested to discuss treatment with ivacaftor for patients with lung disease as shown by percent predicted FEV1 equal to or less than 90% given the results seen in the adult group of patients included in study 110. This has been rejected by the MAH on grounds that lung disease may exist even in the presence of a normal percent predicted FEV1 and also because the data set available in study 110 to support defining a percent predicted FEV1 cut-off for the *R117H* mutation is limited. No other proposals were discussed but it is recognised that there may be young patients with an *R117H* mutation for whom treatment with ivacaftor could be considered based on clinical findings. These are, for instance, not only percent predicted FEV1, but also its trajectory over time, as well as the frequency of exacerbations, hospitalizations, and pulmonary infections (such as *P. aeruginosa*), the period at which a patient is at greater risk of decline in lung function (e.g. adolescence) and the presence of additional risk factors such as the *5T* variant. This was acknowledged and therefore, the CHMP accepted that an indication based on a pre-specified percent predicted FEV cut-off was not reasonable.

The MAH was also requested to discuss the available evidence of benefit in treating adult and paediatric patients with an *R117H* mutation who have well preserved lung function. However, in study 110 almost all subjects with higher than 90% percent predicted FEV1 at baseline were children, due to the inclusion criteria. The efficacy data are therefore almost the same in the subgroup of patients with >90% percent predicted FEV1 baseline as in the subgroup of children: FEV1 and the respiratory domain of the CFQ-R data favoured placebo and even the individual results suggest that the true effect of ivacaftor seems zero in these subjects. In study 103 (children with a *G551D-CFTR* mutation), 52 children aged 6 to less than 12 years old were enrolled to receive placebo or ivacaftor 150 mg BID. Their mean baseline PPFEV1 was around 85% (as compared to 94.0 and 97.5 percentage points in the placebo group and ivacaftor groups of study 110 respectively). The mean absolute change in percent predicted FEV1 was greater in the ivacaftor group (12.58%) than in the placebo group (0.13%) with an estimated treatment difference for ivacaftor versus placebo of 12.45 percentage points (95% CI: 6.56, 18.34). In study 111 (patients with gating mutations other than *G551D*) the treatment difference was 9.8 percentage points (14 patients in the ivacaftor group and 13 in the placebo group). In contrast, a seemingly deteriorating effect was observed in children in study 110 and there are practically no data in adolescents. Beyond central values and statistical considerations even individual data suggest that the true effect of ivacaftor may be zero. Or rather more precisely, these effects –even if exist- are undetectable by parameters such as spirometry, CFQ-R rating scale or measurement of indirect nutritional parameters in such a relatively short duration. No new data can be generated for the moment. There is some evidence from case reports

that children with an *R117H-CFTR* mutation may be clinically ill but the benefit of ivacaftor has not been proven in this age group. Consequently, the indication remains restricted to adult patients.

A stopping rule based on sweat chloride for patients with an *R117H-CFTR* mutation was also proposed for patients with an *R117H-CFTR* mutation and not for patients with gating mutations which (as a group) are believed to be at an increased risk for more progressive and aggressive lung disease. Furthermore, two published papers (Seliger V et al, 2013; Durmowicz A et al, 2013) were discussed at the time of assessment of the extension of the indication of Kalydeco to patients with *CFTR* gating mutations other than *G551D* that show that some patients may respond to ivacaftor in spite of the fact that their sweat chloride did not decrease at least 20 mmol/l from baseline. However, the studies by Selinger and Durmowitz are based on limited datasets (patients with *G551D-CFTR* mutation). The MAH was requested to perform a similar analysis of study 110 versus studies 102, 103 and 111. Scatter plots of absolute change from baseline in percent predicted FEV1 at week 24 (week 8 for study 111) sorted by type of mutation (*G551D* versus *R117H*) versus absolute change from baseline in sweat chloride at the earliest point in time at which it was measured in each of the studies considered were provided for the ivacaftor and placebo groups. The graphical inspection of the scatter plots provided show that almost all patients with a *G551D-CFTR* mutation who showed a decrease in sweat chloride of at least 20 mmol/l also showed an increase (improvement) in percent predicted FEV1 at week 24. More variability in response was seen in patients with non-*G551D* gating mutations and in patients with an *R117H-CFTR* mutation. However, no correlation was found for ivacaftor-treated patients with the exception of children with an *R117H-CFTR* mutation (n=5) for whom the correlation coefficient was -0.70. The inspection of the scatter plot of study 110 shows that sweat chloride values were not sufficiently discriminative at the level of individual patients in order to make a decision on whether a particular patient should stop treatment with ivacaftor when sweat chloride level has not decreased. This conclusion is based on the database provided that only includes patients with sweat chloride and FEV1 values available at the points in time above requested (i.e., first available value of sweat chloride and the one of percent predicted FEV1).

2.4.4. Conclusions on the clinical efficacy

The CHMP raised several questions during the assessment of the results of study VX11-770-110. However, after the assessment of the responses of the MAH, no issues pertaining to clinical efficacy were pending since the MAH adequately responded to all raised issues. The CHMP concluded that the benefit/risk ratio in the extended indication of Kalydeco is positive and the new indication is:

Kalydeco tablets are indicated for the treatment of patients with cystic fibrosis (CF) aged 6 years and older who have one of the following gating (class III) mutations in the CFTR gene: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N or S549R (see sections 4.4 and 5.1).

Kalydeco is also indicated for the treatment of patients with cystic fibrosis (CF) aged 18 years and older who have an R117H mutation in the CFTR gene (see sections 4.4 and 5.1).

A cautionary statement is included in section 4.4 in relation to patients with an *R117H*7T genotype and a cross-reference to section 5.1 was made where results by poly-T status are mentioned (including the limitations of such an analysis given the small numbers of patients with a confirmed 7T variant). The physicians are advised that less evidence of a positive effect of ivacaftor has been shown for patients with an *R117H-*7T mutation associated with less severe disease. 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.

2.4.5. Clinical safety

Introduction

The MAH provided 24-week safety data from patients with cystic fibrosis who have an *R117H* mutation in an allele of the *CFTR* gene exposed to ivacaftor and/or placebo in study 110. Week 12 interim data from the long-term (104 weeks) open-label study 112 are also submitted. This study 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). Only serious adverse events from patients from study 110 are addressed. Therefore, the main basis for the safety analysis is study 110.

Patient exposure

The safety set of study 110 includes 69 patients who have received at least 1 dose of ivacaftor or placebo in study 110. Out of these 69 patients, 45 received treatment (21 on ivacaftor, 24 on placebo) for a period equal or longer than 24 weeks. The number of patients who received at least 24 weeks of treatment is below the expected number of 59 (i.e. 8 patients who could not complete the 24-week course of treatment plus the two ivacaftor-treated patients who discontinued prematurely). This discrepancy is assumed to be due to patients who missed some of their doses. Of the 69 patients enrolled in study 110, 65 enrolled in the ivacaftor arm of study 112 and 2 enrolled in the observational arm of study 112. Two patients did not enrol in study 112 due to early discontinuation of treatment in study 110. All ongoing patients completed the Week 12 Visit in study 112, with the exception of 1 subject.

Adverse events

In study 110, the proportion of patients with adverse events during ivacaftor treatment was 94.1% (32/34) versus 100% (35/35) in the placebo group. The System Organ Class (SOC) with the highest incidence of adverse events during both treatments was infections and infestations (61.8% of ivacaftor-treated patients and 68.6% of placebo-treated patients). By Preferred Term, the AEs with the highest incidence in both treatment groups were infective pulmonary exacerbation of CF (38.2% [13 patients] in the ivacaftor group and 40.0% [14 patients] in the placebo group) and cough (29.4% [10 patients] in the ivacaftor group and 25.7% [9 pateints] in the placebo group). Sputum increased was reported by 5 (14.7%) ivacaftor-treated patients and 4 (11.4%) placebo-treated patients (see table below).

Study 110: Adverse Events Occurring in At Least 10% of Subjects in Either Treatment Group by System Organ Class and Preferred Term, Safety Set

System Organ Class Preferred Term	Placebo (N = 35) n (%)	Ivacaftor (N = 34) n (%)
Subjects with any AEs	**35 (100.0)**	**32 (94.1)**
Infections and infestations	**24 (68.6)**	**21 (61.8)**
Infective pulmonary exacerbation of CF	14 (40.0)	13 (38.2)
Upper respiratory tract infection	5 (14.3)	3 (8.8)
Sinusitis	5 (14.3)	2 (5.9)
Respiratory, thoracic, and mediastinal disorders	**19 (54.3)**	**18 (52.9)**
Cough	9 (25.7)	10 (29.4)
Sputum increased	4 (11.4)	5 (14.7)
Nasal congestion	2 (5.7)	5 (14.7)
Oropharyngeal pain	2 (5.7)	5 (14.7)
Wheezing	1 (2.9)	4 (11.8)
Haemoptysis	6 (17.1)	0
Gastrointestinal disorders	**13 (37.1)**	**13 (38.2)**
Diarrhoea	4 (11.4)	5 (14.7)
Abdominal pain	0	4 (11.8)
Vomiting	4 (11.4)	3 (8.8)
General disorders and administration site conditions	**11 (31.4)**	**7 (20.6)**
Pyrexia	6 (17.1)	2 (5.9)
Nervous system disorders	**9 (25.7)**	**6 (17.6)**
Headache	5 (14.3)	6 (17.6)
Musculoskeletal and connective tissue disorders	**8 (22.9)**	**2 (5.9)**
Arthralgia	4 (11.4)	0

Notes: SOC and PT within SOC were sorted in descending order of frequency in the ivacaftor column. A subject with multiple events within an SOC or within a PT was counted only once within an SOC or PT, respectively. Adverse events were coded from MedDRA, Version 15.1.

Taking into account the limited sample size it can be questioned that only those adverse events that occurred in at least 10% of patients treated with ivacaftor are summarised. In particular those adverse events that have been specifically requested to be followed in the PSURs such as hypersensitivity reactions, depression and suicide/self-injury, cataracts, haemoptysis and hyperbilirubinaemia are very unlikely to be captured with this approach. The MAH responded that the AEs of depression and suicide/self-injury, cataracts, and hyperbilirubinemia did not occur in either treatment group in study 110 while hypersensitivity and haemoptysis occurred only in placebo-treated patients; hence, no update to the SmPC was needed. The CHMP made the following observations after assessing the submitted data: while abdominal pain was reported for 4 patients in the ivacaftor group and none in the placebo group, there were also two additional preferred terms of "abdominal pain upper", "abdominal discomfort" making a total of 8 patients on ivacaftor with these related symptoms versus 2 on placebo. "Abdominal tenderness" is an additional related preferred term that was reported by a placebo-treated patient. Within the SOC of "Investigations", the number of Preferred Terms related to results of liver function tests include "alanine aminotransferase increased", "blood bilirubin increased", "hepatic enzyme increase" and "liver function test abnormal". While it is stated that no patients experienced hyperbilirubinemia in study 110, the AE data in children include a case of blood bilirubin increased (apparently below 2xULN). Overall, this does not change the conclusions about the safety of ivacaftor but is relevant information for the Product Information and, consequently, the MAH was requested to recalculate the frequency of these and other adverse events that seem to be split in different preferred terms. Consequently, an extensive revision of section 4.8 was performed by the MAH, also in line with the SmPC guideline. This is acceptable to the CHMP.

The incidence of patients with AEs considered by the investigator to be related or possibly related to the study drug was 8.8% (3 patients) in the ivacaftor group and 20.0% (7 patients) in the placebo group.

One (2.9%) patient in the ivacaftor group had an AE of increased C-reactive protein (CRP) that was considered by the investigator to be related to the study drug. Regarding the severity of the adverse events reported, compared with placebo, ivacaftor was associated with a higher incidence of mild events (50.0% during ivacaftor treatment versus 28.6% during placebo treatment) and a lower incidence of severe events (2.9% during ivacaftor treatment versus 14.3% during placebo treatment). There were no life-threatening adverse events in this study.

Serious adverse event/deaths/other significant events

There were no deaths in study 110. Four patients (11.8%) treated with ivacaftor and 6 patients (17.1%) treated with placebo reported serious adverse events (SAE). The most common SAE in both treatment groups was infective pulmonary exacerbation of CF: 3 patients (8.8%) in the ivacaftor group and 6 patients (17.1%) in the placebo group. SAEs of cellulitis and constipation each occurred in 1 (2.9%) patient in the ivacaftor group. None of the SAEs were considered related to the study drug. Patients from study 110 who rolled into study 112 reported a total of 12 SAEs. These SAEs were reported by 8 patients treated with ivacaftor (there were no SAEs in the observational arm). Of the 12 SAEs, 9 were infective pulmonary exacerbations of CF (one of them was considered possibly related to study drug), 1 was influenza, and two were angioedema and urticaria. There were no SAEs in the observational arm.

Laboratory findings

Results of all Liver Function Tests (LFT) at all-time points were not available for 6 patients in the placebo group and 7 patients in the ivacaftor group and hence, the absolute change from baseline to Week 24 in LFT could not be determined. The narratives of the 4 patients randomised to ivacaftor who did not complete 24 weeks of treatment show that in study 110 none of these patients had laboratory results in which alkaline phosphatise was >2 x upper limit of normal (ULN), ALT was >3 x ULN, AST was >3 x ULN, or total bilirubin was >2 x ULN. Out of the 13 patients with no LFT values at week 24, two additional patients discontinued the study and in the remaining 3 patients (one of them on ivacaftor) LFT measurements were not performed at week 24 for unexplained reasons. While the incidence of shifts from normal to high LFT values at Weeks 2, 4, 8, 16, and 24 was low (<15% across study visits), and there was no clear pattern for an increasing incidence of shifts over time in either treatment group for alkaline phosphatase, AST, total bilirubin, and gamma-glutamyl transferase (GGT), this is not the case for ALT for which 4 patients in the ivacaftor group (versus none in the placebo group) had a shift from normal at baseline to high at week 24. In the ivacaftor group, no patients had a maximum ALT or AST that was >5 × ULN. Two patients (5.9%) had at least 1 maximum ALT value >2 x ULN to ≤ 3 x ULN. One patient had at least 1 maximum ALT value >3 x ULN to ≤ 5 x ULN; this patient also had at least 1 maximum AST value >2 x ULN to ≤ 3 x ULN. Figures of liver function tests show that there is an overlap of values between both treatment groups for almost all liver function tests. However, the mean change in total bilirubin is systematically higher in the ivacaftor group with almost no overlapping between groups. The magnitude of the change is limited as shown by a maximum mean change of 5 micromol/L (i.e. 0.3 mg/dl). Hyperbilirubinemia is one of the lab abnormalities being followed in the PSURs. In study 110, no subjects had a maximum total bilirubin value >2 × ULN in either treatment group.

A considerable degree of overlapping exists in the mean change of other chemistry parameters that have been plotted over time (e.g., albumin, total protein and creatinine); however, in general, the magnitude of the changes is limited. Activated Partial Thromboplastin Time (sec), Prothrombin Time (sec) and Prothrombin Time INR (ratio) were the coagulation parameters determined. There is no hint that ivacaftor affects coagulation but the results of the analysis of these parameters in study 110 should be viewed with caution due to the fact that a considerable number of samples were affected by an insufficient sample.

With respect to ECG assessment, no subject had a QTc value greater than 500 msec. Two patients had maximum increases into the category of >450 to ≤ 480 msec in QT interval corrected by Bazett's

formula (QTcB) in the ivacaftor group. One patient (2.9%) in the placebo group and 4 patients (11.8%) in the ivacaftor group had maximum increases of >30 to ≤ 60 msec in QTcB. No patients in the placebo group and 2 patients (5.9%) in the ivacaftor group had maximum increases of >30 to ≤ 60 msec in QT interval corrected by Fridericia's formula (QTcF). No patient had a maximum on-treatment increase from baseline in QTc interval >60 msec. The CHMP did not raise a concern.

Safety in special populations

Analyses of the incidence of adverse events by subgroups in study 110 were discussed by the MAH only for those occurring in at least 15% of patients, something that makes their interpretation more difficult. A total of 17 patients aged 6 to 11 years (inclusive), 2 patients in the 12 to 17 years (inclusive), and 50 patients in the ≥ 18 year-old group were included in study 110. In the ≥ 18 year-old subgroup, 26 patients received treatment with placebo, and 24 patients received treatment with ivacaftor. Among patients aged 6 to 11 years, 8 patients received placebo and 9 patients received ivacaftor. Table below shows adverse event that occurred in at least 15% of patients sorted out by age group.

Study 110: Adverse Events Occurring in At Least 15% of Subjects in Either Treatment Group by System Organ Class, Preferred Term, and Age Subgroups, Safety Set

	Age ≥18 Years		Age 6 to 11 Years (Inclusive)	
System Organ Class Preferred Term	Placebo (N = 26) n (%)	Ivacaftor (N = 24) n (%)	Placebo (N = 8) n (%)	Ivacaftor (N = 9) n (%)
Respiratory, thoracic, and mediastinal disorders	**14 (53.8)**	**16 (66.7)**	**4 (50.0)**	**2 (22.2)**
Cough	7 (26.9)	9 (37.5)	1 (12.5)	1 (11.1)
Sputum increased	4 (15.4)	5 (20.8)	0	0
Haemoptysis	6 (23.1)	0	0	0
Nasal congestion	1 (3.8)	5 (20.8)	1 (12.5)	0
Oropharyngeal pain	0	4 (16.7)	2 (25.0)	1 (11.1)
Wheezing	1 (3.8)	4 (16.7)	0	0
Gastrointestinal disorders	**10 (38.5)**	**9 (37.5)**	**3 (37.5)**	**4 (44.4)**
Abdominal pain	0	2 (8.3)	0	2 (22.2)
Diarrhoea	3 (11.5)	4 (16.7)	1 (12.5)	1 (11.1)
Abdominal pain upper	0	1 (4.2)	2 (25.0)	1 (11.1)
General disorders and administration site conditions	**8 (30.8)**	**5 (20.8)**	**2 (25.0)**	**2 (22.2)**
Pyrexia	3 (11.5)	1 (4.2)	2 (25.0)	1 (11.1)
Nervous system disorders	**7 (26.9)**	**4 (16.7)**	**1 (12.5)**	**2 (22.2)**
Headache	3 (11.5)	4 (16.7)	1 (12.5)	2 (22.2)
Psychiatric disorders	**1 (3.8)**	**0**	**2 (25.0)**	**0**
Attention deficit/hyperactivity disorder	0	0	2 (25.0)	0

Notes: A subject with multiple events within an SOC or within a PT was counted only once within an SOC or PT, respectively. Adverse events were coded from MedDRA, Version 15.1.

More patients on placebo than on ivacaftor reported adverse events in the ≥ 18 year-old age group, i.e. 26 (100.0%) patients versus 23 (95.8%) respectively. Adverse events more commonly reported by ivacaftor-treated patients (as compared to placebo) were nasal congestion (20.8% on ivacaftor versus 3.8% on placebo), oropharyngeal pain (16.7% and 0% respectively), and wheezing (16.7% versus 3.8% respectively). In the 6 to 11 year-old group all patients in each treatment group reported at least an adverse event. Adverse events reported by children were oropharyngeal pain (25.0% on ivacaftor versus 11.1% on placebo, respectively), nasal congestion (12.5% versus 0% respectively), abdominal pain (22.2% versus 0%, respectively) and headache (22.2% versus 12.5% respectively). The incidence of infective pulmonary exacerbation of CF in the ≥ 18 years subgroup was 45.8% (11 patients, 14 events) in the ivacaftor group and 50.0% (13 patients, 23 events) in the placebo group. The incidence of cough was 37.5% (9 patients, 12 events) in the ivacaftor group and 26.9% (7 patients, 8 events) in the placebo group. None of the subjects in the ≥ 18 years or 6 to 11 years subgroups had haemoptysis.

Given that only those adverse events that occurred in at least 15% of patients are discussed, the MAH has been requested to provide in tabular format the number and percentage of all adverse events per treatment group sorted out by SOC and Preferred Term, which was performed by the MAH. Two patients (8.3%) in the ivacaftor group and 6 patients (23.1%) in the placebo group reported at least 1 SAE in the ≥ 18 years subgroup. The most common SAE in both treatment groups was infective pulmonary exacerbation of CF. One patient had a SAE of cellulitis in the ivacaftor group.

There was 1 pregnancy in study 110, where the patient received her last dose at study Week 16; no doses were missed. Based on the subject's history of premature rupture of membranes, she had a cervical cerclage procedure performed at 14 weeks and 2 days of gestation. She was admitted for cervical insufficiency at 15 weeks gestation and developed gestational diabetes mellitus at 25 weeks and 5 days. The subject delivered a healthy baby at 28 weeks gestation via caesarean section due to premature rupture of membranes. The investigator confirmed that cervical insufficiency and gestational diabetes were not AEs.

A total of 13 patients with a baseline percent predicted FEV1% <70% received ivacaftor; in the categories of ≥ 70% to ≤ 90% and >90% these numbers were 14 and 7, respectively. These figures for patients receiving placebo were 15, 14 and 6, respectively. The incidence of infective pulmonary exacerbation of CF was similar during both treatments for the three baseline FEV1% predicted categories. However, in the category of baseline percent predicted FEV1 <70% the incidence of pulmonary exacerbations was higher than in the other two categories, i.e. 8 (53.8%) patients on ivacaftor versus 5 (35.7%) in those with ≥ 70% to ≤ 90% and 1 (14.3%) in those with >90%. The incidence of adverse events in the SOC "Respiratory, thoracic, and mediastinal disorders" is higher in the ivacafor group than in the placebo group for patients with baseline percent predicted <70%. Six (42.6%) patients on ivacaftor and 5 (33.3%) on placebo reported cough. Nasal congestion was reported by 1 (6.7%) and 5 (38.5%) patients, respectively. Oropharyngeal pain was reported only by 4 (30.8%) ivacaftor-treated patients. Other adverse events reported by more ivacaftor-treated patients are wheezing (3 patients vs. 1), upper-airway cough syndrome (2 patients vs. none on placebo). No ivacaftor-treated patients reported haemoptysis during study 110. However, this adverse event was reported by 6 placebo-treated patients (5 of them in the category of percent predicted FEV1<70%).

The overall incidence of patients with adverse events during ivacaftor treatment was 95.8%, (23 patients, 119 events) in North America and 90.0% (9 patients, 37 events) in Europe. The overall incidence of infective pulmonary exacerbations of CF during ivacaftor treatment was 33.3% (8 patients) in North America and 50.0% (5 patients) in Europe. In placebo group, the overall incidence of patients with adverse events was 100.0% (30 patients, 173 events) in North America and 100.0% (5 patients, 31 events) in Europe; the incidence of infective pulmonary exacerbation of CF was 33.3% (10 patients, 13 events) in North America and 80.0% (4 patients, 11 events) in Europe. The higher incidence of infective pulmonary exacerbation of CF, cough, and haemoptysis in Europe in the placebo group was justified by the small number of patients in this subgroup and the fact that all 5 patients in the Europe placebo subgroup were ≥ 18 years of age. By comparison, the North America placebo subgroup included patients 6 to 11 years of age (8 patients), 12 to 17 years of age (1 patient), and ≥ 18 years of age (21 patients).

Discontinuation due to adverse events

No patients had adverse events that led to study drug interruption during ivacaftor treatment. During ivacaftor treatment, 2 patients missed doses of ivacaftor treatment (one case missed 8 doses, one case missed one dose) due to AEs of infective pulmonary exacerbation of CF. The events were considered by the investigator to be not related to the study drug. Two patients in the placebo group had AEs that led to study drug interruption. One patient had dehydration, gastroenteritis, and hypokalaemia that were considered by the investigator to be not related to the study drug. An additional patient had diarrhoea

and vomiting and missed 14 doses of placebo. The events resolved and were considered by the investigator to be possibly related to the study drug.

Post marketing experience
Adverse events of special interest that are being monitored in the PSURs are hypersensitivity reactions, depression and suicide/self-injury, haemoptysis and hyperbilirubinaemia. Due to the finding of a dose-related increase in cataracts in juvenile rats in a nonclinical study, an ophthalmologic examination was performed at screening for all subjects. A follow-up ophthalmologic examination was also carried out in subjects aged 6 to 11 years (inclusive) at Week 24. Minimal changes in visual acuity were observed in both treatment groups, and no clinically important trends attributable to ivacaftor treatment were detected. No subjects developed lens opacities during study 110. According to the MAH the non-congenital cases are confounded by the absence of a pre-treatment ophhalmological examination and a strong risk factor for development of cataract such as diabetes type I, corticosteroid use or familiar history of cataract. However, in one of the cases the patient underwent an eye examination prior to initiation of ivacaftor, without mention of cataracts and other of the patients underwent ophthalmological examination during treatment with ivacaftor without diagnostic of cataract but a follow–up ophthalmological examination several months after identified lens opacity. Therefore, a causal association to ivacaftor in these 2 cases could not be excluded. In addition, the progression of these lens abnormalities and the impact on vision in the long-term exposure is unknown. Given that lens opacities (cataracts) observed in the juvenile rat toxicity study were considered ivacaftor-related, there is a plausible causal relationship. This was already addressed by the PRAC and an adequate warning was included in the PI of Kalydeco tablets. Cataracts are being followed in the PSURs. At the time of assessment of the current procedure the MAH informed CHMP that a report of cataracts had been received in a paediatric patient older than 12 years old via PSUR.

2.4.6. Discussion on clinical safety

The MAH provided 24-week safety data from patients with cystic fibrosis who have an *R117H* mutation in an allele of the *CFTR* gene exposed to ivacaftor and/or placebo in study 110. The safety set of this study includes 69 patients who have received at least 1 dose of ivacaftor or placebo. Week 12 interim data from the long-term (104 weeks) open-label study 112 are also submitted. This study 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). Analysis of the occurrence of AEs and SEAs, 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. The CHMP requested some re-calculations of originally submitted analyses and these were provided by the MAH. The current Product Information of this medicinal product reflects the latest safety profile.

2.4.7. Conclusions on clinical safety

In conclusion, the CHMP was of the opinion that the safety profile of ivacaftor in patients with *R117H-CFTR* mutation in study 110 was consistent with the one already known for this medicinal product. Some concerns were raised in order to clarify or to provide further safety data related to liver toxicity and coagulation parameters among others, but they were not considered critical and have been adequately addressed by the MAH during this procedure; the SmPC reflects the most up-to-date safety profile of Kalydeco.

2.4.8. PSUR cycle

The PSUR cycle should follow the EURD list.

2.5. Risk management plan

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

The PRAC considered that the risk management plan version 4.6 is acceptable. An updated risk management plan consolidating the versions submitted for procedures EMEA/H/C/002494/X/0034G (version 4.8) and EMEA/H/C/002494/II/0027 (version 4.6) was submitted within version 4.9. In addition, minor revisions were recommended to be taken into account with the next RMP update. The PRAC endorsed PRAC Rapporteur assessment report is attached.

The CHMP endorsed the Risk Management Plan version 4.9 with the following content:

Safety concerns

Important identified risks	None
Important potential risks	• Hepatotoxicity • Cataract • Concomitant use of ivacaftor with strong CYP3A inhibitors or inducers • Cardiac arrhythmias • Off-label use in children and adolescents not of an approved age and in patients without an approved *CFTR* mutation
Missing information	• Use in pregnant and lactating women • Pulmonary exacerbations and bacterial sputum colonization with long-term ivacaftor treatment • Use in children between 2 to 11 years old • Patients with FEV_1 <40% • Safety in patients with cardiac diseases • Long-term safety • Clinical relevance of P-gp inhibition by ivacaftor • Patients with moderate or severe hepatic impairment

CFTR: cystic fibrosis transmembrane conductance regulator; CYP: cytochrome P450; FEV_1: forced expiratory volume in 1 second; P-gp: permeability glycoprotein

Pharmacovigilance plan

Study/Activity Type, Title, and Category (1-3)	Objectives	Safety Concerns Addressed	Status (Planned, Started)	Date for Submission of Interim or Final Reports (Planned or Actual)

Study/Activity Type, Title, and Category (1-3)	Objectives	Safety Concerns Addressed	Status (Planned, Started)	Date for Submission of Interim or Final Reports (Planned or Actual)
Long-term Safety Study (Non-interventional, 1)	To evaluate the long-term safety of ivacaftor in patients with CF	• Cardiac arrhythmias • Off-label use • Use in pregnancy and lactation • Pulmonary exacerbations and bacterial sputum colonization • Use in children between 2 to 11 years old • Use in patients with FEV_1 <40% • Patients with cardiac disease • Long-term safety • Patients with hepatic impairment	Started	Annual Reports: December 2013/2014/ 2015/2016 Final Report: December 2017
Study VX12-770-112 (Interventional, 3)	To evaluate the safety of long-term ivacaftor treatment in subjects 6 years of age and older with CF and a non-*G551D CFTR* mutation	• Use in children between 6 to 11 years old • Long-term safety	Started	June 2017
Study VX12-770-115 (Non-interventional, 3)	An Ocular Safety Study of Ivacaftor-Treated Pediatric Patients 11 Years of Age or Younger With Cystic Fibrosis	Cataract	Started	Interim Report annually (with the PSUR) Final Report: December 2016
Study VX11-770-109 (Interventional, 3)	To evaluate the long-term safety and pharmacodynamics of ivacaftor in pediatric subjects with CF and a *CFTR* gating mutation	• Hepatotoxicity • Cataracts • Cardiac arrhythmias • Use in children between 2 to 5 years old • Long-term safety	Started	Final Report: December 2016
(Nonclinical, 3)	Provisionally, apply for registration of presentation of ivacaftor with reduced strengths suitable for modified dosing (according to previously submitted analyses of PK data)	Avoidance of overexposure in children	Planned	June 2016
CYP3A: cytochrome P450 - enzyme subfamily 3A; FEV_1: forced expiratory volume in 1 second; PSUR: Periodic Safety Update Report.				

Risk minimisation measures

No changes to the additional risk minimisation measures are necessary.

2.6. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC have been updated and the Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to implement minor editorial changes in the annexes and to align the product information with the latest QRD template.

3. Benefit-Risk Balance

Benefits

Beneficial effects

Ivacaftor 150 mg administered every 12 hours for 24 weeks has been associated with an improvement in the absolute change in percent predicted FEV1 in a subgroup of patients aged 18 years and older with cystic fibrosis and an *R117H* mutation of the *CFTR* who were enrolled in a 24-week, randomised, double-blind, placebo-controlled 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 for ivacaftor versus placebo was 4.97 percentage points (95% CI: 1.15, 8.78). Percent predicted FEV1 is the recommended primary clinical endpoint in efficacy studies for CF given that lung function in CF declines with age and is a significant predictor of mortality. This improvement in FEV1 was accompanied by a decrease from baseline in sweat chloride (a marker of *CFTR* activity) and by an increase in the respiratory domain of the pooled Cystic Fibrosis Questionnaire-Revised (CFQ-R) that was above the minimal clinically important difference. Descriptive statistics show that the improvement in percent predicted FEV1 was observed in this age group in patients with baseline percent predicted FEV1 equal to or below 90% (a single adult patient was enrolled with percent predicted FEV1 >90%). Similarly, the results indicate that the presence of the poly-T variant *5T,* which is known to affect the phenotypic expression of patients carrying the *R117H* mutation, does not seem to impair the effect of ivacaftor on these patients.

In the overall population of study 110, the effect on sweat chloride in the ivacaftor arm was consistent across all age groups. The mean absolute change from baseline in sweat chloride through Week 24 was -26.3 mmol/L for the ivacaftor group and -2.3 mmol/L for the placebo group. The treatment difference (95%CI) for ivacaftor versus placebo was -24.0 mmol/L (-28.0, -19.9).

After the last dose of ivacaftor or placebo in study 110 patients were followed for 3 to 4 weeks before being enrolled in study 112, a roll-over, ongoing study intended to address the long-term safety and efficacy of ivacaftor in patients with a *R117H-CFTR* mutation (patients with non-*G551D* gating mutations are also being followed in this study). The data provided seem to show that, as a group, during the treatment-free follow-up period patients who were on ivacaftor lost their moderate gain in percent predicted FEV1 seen during the 24-treatment period of study 110. Similarly, the limited data provided for study 112 (12-week interim analysis) show that patients who were randomised to placebo in study 110 improved their FEV1 when they started to receive ivacaftor in study 112. This was also the case of patients who were initially randomised to ivacaftor and enrolled in study 112.

Uncertainty in the knowledge about the beneficial effects

Study 110 where ivacaftor 150 mg was administered every 12 hours for 24 weeks did not meet its objective, as treatment with ivacaftor was not shown to be statistically different from placebo in a number of efficacy variables including change in percent predicted FEV1, change in BMI and time to first pulmonary exacerbation. The mean absolute change from baseline in percent predicted FEV1 through Week 24 for the FAS (all patients) was 2.57 percentage points in the ivacaftor group versus 0.46 percentage points in the placebo group. The estimated treatment difference (95%CI) for ivacaftor versus placebo was 2.11 percentage points (-1.13, 5.35). In a pre-planned subgroup analysis by age, a difference between treatment groups favouring ivacaftor in the age group ≥ 18 years was observed. In the adult group, although larger mean changes were observed for the mean change in BMI for the ivacaftor group (placebo: 0.22 kg/m^2; ivacaftor: 0.53 kg/m^2), the 95% confidence interval of the treatment difference was (-1.90, 2.51). Similarly, it is not known whether ivacaftor may be efficacious in adult patients with a percent predicted FEV1 above 90% since only a single adult patient on ivacaftor was

available for the analysis while in children the effect seem favoured the placebo group. Hence, no amendments to the prescriber's information in this respect can be justified.

In essence, positive results from a subgroup analysis in the event of a failed primary endpoint in a pivotal trial are not sufficient for gaining regulatory approval unless there are exceptional circumstances. The draft guidance "EMA/CHMP/539146/2013, Guideline on the investigation of subgroups in confirmatory clinical trials", classifies the current situation as "Scenario 3": "The clinical data presented fail to establish statistically persuasive evidence but there is an interest in identifying a subgroup, where a relevant treatment effect is evident and there is compelling evidence of a favourable risk-benefit". This guidance defines the minimum requirements that should be met in order to justify "exceptional circumstances". Overall, it is accepted that the results in the adult group have biological plausibility and that further analyses performed support the notion of a positive effect of ivacaftor in this group when all other evidence is considered.

The effect of discontinuing prescribed therapies for CF while remaining on ivacaftor treatment has not been evaluated. During study 110, patients continued on their prescribed CF therapies. Thus, ivacaftor will remain recommended for use in addition to other prescribed therapies for CF.

Risks

Unfavourable effects

The safety profile of ivacaftor in patients with an *R117H-CFTR* mutation in study 110 was consistent with that observed in studies 102, 103 and 111 in patients with gating mutations and no new safety concerns emerge from the review of the safety data. The AEs with the highest incidence in both treatment groups were infective pulmonary exacerbation of CF and cough. The number of pulmonary exacerbations reported for safety purposes is usually higher than the number of protocol-defined pulmonary exacerbations analysed for efficacy that should meet stricter criteria. AEs for which the incidence was at least 5% higher with ivacaftor treatment than with placebo treatment included nasal congestion, oropharyngeal pain, abdominal pain, wheezing, upper airway cough syndrome, bacterial disease carrier and others. All of them were reported previously. In the ivacaftor group, no patients had a maximum ALT or AST value that was >5 × ULN. Two patients had at least 1 maximum ALT value >2 x ULN to $\leq$ 3 x ULN. Hyperbilirubinemia is one of the laboratory abnormalities being monitored in the PSURs. AEs associated with abnormal liver function tests (LFTs) occurred in 3 (8.6%) subjects in the placebo group and 1 (2.9%) subject in the ivacaftor group. Lens opacities, which are of concern in the paediatric population, were not reported in study 110. The risks are considered to be in line with previous findings, no other significant unfavourable effect could be observed in studies 110 and 112. Overall, the safety profile of ivacaftor was well characterised and remains within that observed with the use so far. Adverse drug reactions and potential risks are readily identified clinically or with routine laboratory monitoring, and are considered adequately managed with appropriate risk-management tools described in the SmPC and in the RMP.

Uncertainty in the knowledge about the unfavourable effects

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. The MAH is obliged to monitor and report a number of specific AE in the PSURs, which is reassuring. The SmPC reflects the most accurate safety information on ivacaftor and is hence considered acceptable to the CHMP. As discussed previously, the newly available data do not alter the overall safety profile of Kalydeco.

Benefit-Risk Balance

Importance of favourable and unfavourable effects

CF lung disease is the primary cause of morbidity and mortality in CF. Patients with CF typically experience a progressive loss of lung function, ultimately resulting in respiratory failure. The rate of FEV1 decline may vary depending on several factors, such as genotype and environmental factors. Correlation between the genotype and the lung disease phenotype is particularly weak. The *R117H-CFTR* mutation is considered to have variable penetrance, i.e. it may result in a variable phenotype ranging from normal to cystic fibrosis. This phenotypic variability has been mainly attributed to the presence of a polypyrimidine (poly-T tract) variant located in another region of the *CFTR* gene in *cis* with *R117H*.

Although study 110 did not achieve its objective, i.e. ivacaftor 150 mg every 12 hours for 24 weeks was not shown to be statistically different from placebo in a number of efficacy variables including change in percent predicted FEV1, a difference between treatment groups was seen that favours ivacaftor in the age group ≥ 18 years in a pre-planned subgroup analysis by age. As a consequence, the claimed indication was restricted to this age group; adults with CF who had an *R117H-CFTR* mutation.

While the *R117H* mutation may cause a disease that is in the less severe spectrum of CF, it may be associated with severe disease when compared to a normal population. Overall, it was accepted that the results seen in the adult group have biological plausibility and that the further analyses performed support the notion of a positive effect of ivacaftor in this age group when all other evidence is considered.

In summary, based on the above information, the CHMP concluded that an indication for adult patients with an *R117H-CFTR* mutation could be approvable and would bring benefit to the patient with this diagnosis.

Benefit-risk balance

Discussion on the Benefit-Risk Balance

Cystic fibrosis represents an area with a high-unmet medical need for specific targeted therapies. In patients with CF, lung function declines with age and is a significant predictor of mortality. Treatments that target the underlying chloride transport defect by restoring the function of the *CFTR* protein may decrease the morbidity and increase the lifespan of individuals with CF. In addition, the opportunity to intervene at an earlier stage in the progression of disease may further limit organ damage, reduce the morbidity, and prolong life. Although there is evidence of a pharmacodynamic response to ivacaftor in patients with an *R117H* mutation, no statistically significant improvement in percent predicted FEV1 was observed with ivacaftor in the overall study population in study 110. However, in the subgroup of patients aged 18 years and older an effect of ivacaftor cannot be excluded. In addition, further analyses have been performed that support the notion of a positive effect of ivacaftor in patients with clinical manifestations of CF, in particular with lung disease, who had an *R117H-CFTR* mutation. The main exception refers to patients with the *7T* variant. The apparent lack of efficacy of ivacaftor in this group of patients is addressed with appropriate warnings in the SmPC. The safety risks are considered to be in line with previous findings, no other significant unfavourable effect could be observed in studies 110 and 112. Based on the data and analyses provided in the frame of this procedure, the CHMP considered that the benefit-risk ration for ivacaftor remains positive and the indication can be broadened to patients with CF aged 18 years and older who have a *R117H* mutation in the *CFTR* gene.

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(s):

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, II, IIIA and IIIB

Extension of indication to include the treatment of cystic fibrosis in patients aged 18 years and older who have a *R117H* mutation in the *CFTR* gene. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC have been updated and the Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to implement minor editorial changes in the annexes and to align the product information with the latest QRD template. An updated RMP version 4.9 was agreed as part of this procedure.

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

Similarity with authorised orphan medicinal products

The CHMP is of the opinion that Kalydeco is not similar to Bronchitol (mannitol) within the meaning of Article 3 of Commission Regulation (EC) No. 847/200.