26 June 2014
EMA/CHMP/360053/2014 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/0009

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

AE	adverse event
ALT	alanine transaminase
ANCOVA	analysis of covariance
AST	aspartate transaminase
ATP	adenosine triphosphate
AUC	area under the concentration versus time curve
AUC0-tlast	AUC from time 0 to the time of last measurable concentration
BMI	body mass index
CDC	Centers for Disease Control (US)
CF	cystic fibrosis
CFQ-R	Cystic Fibrosis Questionnaire-Revised
CFTR	cystic fibrosis transmembrane conductance regulator gene
CFTR	cystic fibrosis transmembrane conductance regulator protein
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CL/F	apparent clearance
Cmax	maximum observed concentration
CSR	clinical study report
DMC	Data Monitoring Committee
DMPK	drug metabolism and pharmacokinetics
E_0	baseline (in population pharmacokinetic/pharmacodynamic model)
EC_{50}	drug concentration required to reach 50% of maximal effect
EC_{90}	drug concentration required to reach 90% of maximal effect
ECG	electrocardiogram
EMA	European Medicines Agency
E_{max}	maximum effect
EU	European Union
FDA	Food and Drug Administration
FEV1	forced expiratory volume in 1 second
G1244E	*CFTR* missense gene mutation that results in the replacement of a glycine residue at position 1244 of CFTR with a glutamic acid residue
G1349D	*CFTR* missense gene mutation that results in the replacement of a glycine residue at position 1349 of CFTR with an aspartic acid residue
G178R	*CFTR* missense gene mutation that results in the replacement of a glycine residue at position 178 of CFTR with an arginine residue
G551D	*CFTR* missense gene mutation that results in the replacement of a glycine residue at position 551 of CFTR with an aspartic acid residue
G551D	CFTR protein with a replacement of a glycine residue at position 551 with an aspartic acid residue
G551S	*CFTR* missense gene mutation that results in the replacement of a glycine residue at position 551 of CFTR with a serine residue
G970R	*CFTR* missense gene mutation that results in the replacement of a glycine residue at position 970 of CFTR with an arginine residue
GGT	gamma-glutamyl transpeptidase
IC_{50}	median effective concentration
IWRS	interactive web response system
Ki	inhibition constant
Km	substrate concentration for half-maximal activity
LFT	liver function test
LMM	linear mixed-effects model
LOCF	last observation carried forward
LS	least squares
LSLD	last subject last dose
M1	hydroxymethyl-ivacaftor, metabolite of ivacaftor
M6	ivacaftor carboxylate, metabolite of ivacaftor
MCID	minimal clinically important difference
MedDRA	Medical Dictionary for Regulatory Activities
MIC	minimal inhibitory concentration
MMRM	mixed-effects model for repeated measures

na	not analysed
NOS	not otherwise specified
OATP	organic anion transporter peptide
P aeruginosa	*Pseudomonas aeruginosa*
PD	pharmacodynamic, pharmacodynamics
PDCO	Paediatric Committee (EU)
PERT	pancreatic enzyme replacement therapy
PK	pharmacokinetic, pharmacokinetics
PKA	protein kinase A
PPFEV1	percent predicted forced expiratory volume in 1 second
PT	preferred term; prothrombin time
q12h	every 12 hours
QC	quality control
QCUB	quality control unblinded biostatistician
QNS	quantity not sufficient for analysis
RMP	Risk Management Plan
S	substrate
S aureus	*Staphylococcus aureus*
S1251N	*CFTR* missense gene mutation that results in the replacement of a serine residue at position 1251 of CFTR with an asparagine residue
S1255P	*CFTR* missense gene mutation that results in the replacement of a serine residue at position 1255 of CFTR with a proline residue
S549N	*CFTR* missense gene mutation that results in the replacement of a serine residue at position 549 of CFTR with an asparagine residue
S549R	*CFTR* missense gene mutation that results in the replacement of a serine residue at position 549 of CFTR with an arginine residue
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SEM	standard error of the mean
SET	study execution team
SmPC	Summary of Product Characteristics
SOC	system organ class
UB	unblinded biostatistician
UK	United Kingdom
ULN	upper limit of normal
US	United States
Vertex	Vertex Pharmaceuticals

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Vertex Pharmaceuticals (U.K.) Ltd. submitted to the European Medicines Agency on 9 October 2013 an application for a variation including an extension of indication.

This application concerns the following medicinal product:

Medicinal product:	**International non-proprietary name:**	**Presentations:**
Kalydeco	IVACAFTOR	See Annex A

The following variation was requested:

Variation(s) requested		**Type**
C.1.6 a	Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

Update of sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC to extend the indication of Kalydeco in the treatment of cystic fibrosis to patients aged 6 years and older who have a gating (class III) mutation in the *CFTR* gene other than *G551D*. Consequential changes to sections 1 and 4 of the PL.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet.

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-C2-000335-PIP01-08-M07 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP (P/0300/2012) was not yet completed.

The PDCO issued an opinion on compliance for the PIP (P/0300/2012).

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 applicant did submit a critical report addressing the possible similarity with the authorised orphan medicinal product Bronchitol (mannitol), EMEA/H/C001252.

Scientific advice

The applicant received Scientific Advice from the CHMP on 20 October 2011. The Scientific Advice pertained to quality, non-clinical and clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Concepcion Prieto Yerro Co-Rapporteur: Melinda Sobor

Submission date:	9 October 2013
Start of procedure:	25 October 2013
Co-Rapporteur's preliminary assessment report circulated on:	16 December 2013
PRAC Rapporteur assessment report circulated on:	27 December 2013
PRAC Rapporteur updated assessment report circulated on:	30 December 2013
Rapporteur's preliminary assessment report circulated on:	7 January 2014
PRAC RMP advice and assessment overview adopted by PRAC	9 January 2014
Joint Rapporteur's updated assessment report circulated on:	20 January 2014
Request for supplementary information and extension of timetable adopted by the CHMP on:	23 January 2014
MAH's responses submitted to the CHMP on:	21 February 2014
PRAC Rapporteur's preliminary assessment report circulated on:	26 March 2014
PRAC Rapporteur's updated assessment report circulated on:	2 April 2014
Joint Rapporteur's updated assessment report on the MAH's responses circulated on:	11 April 2014
PRAC RMP advice and assessment overview adopted by PRAC:	10 April 2014
2nd Request for supplementary information and extension of timetable adopted by the CHMP on:	25 April 2014
MAH's responses submitted to the CHMP on:	23 May 2014
PRAC Rapporteur assessment report circulated on:	2 June 2014
PRAC RMP advice and assessment overview adopted by PRAC:	12 June 2014
Joint Rapporteur's assessment report on the MAH's responses circulated on:	13 June 2014
CHMP opinion:	26 June 2014

2. Scientific discussion

2.1. Introduction

Cystic fibrosis (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 CF Transmembrane Conductance Regulator (*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 is a 1480–amino acid ATP-binding cassette transporter protein that contains two membrane-spanning domains (MSD1 and MSD2) that form the chloride channel pore, two nucleotide-binding domains (NBD1 and NBD2) that bind and hydrolyse ATP to open and close the channel pore (channel gating), and a regulatory domain with several protein kinase A phosphorylation sites. Formation of the *CFTR* channel requires the coordinated folding and assembly of the individual membrane and cytoplasmic domains. Each MSD is composed of six transmembrane segments (TM1–6 and TM7–12) that are associated with long α-helical cytosolic extensions known as coupling helices, which are connected by intracellular loops (ICLs). Contact formation between the ICLs and NBDs is critical for the proper assembly and Cl− channel function of *CFTR*.

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[2].

More than 1500 *CFTR* mutations have been identified, but the functional importance is known only for a small number. 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. Gating mutations result in a *CFTR* protein with a primary defect of low channel open probability compared to normal *CFTR*. Gating refers to the amount of time in which the *CFTR* channel is open and can transport chloride. Ten *CFTR* mutations that lead to a *CFTR* gating functional defect have been identified: *G551D, G178R, G551S, S549N, S549R, G970R, G1244E, S1251N, S1255P,* and *G1349D*[3].

Gating mutations are present in about 5% of the CF patient population worldwide and in the EU. Approximately 4% of patients have the *G551D* mutation (approximately 1083 patients in the EU and 2374 worldwide), and the remaining 1% has other gating mutations (205 subjects in the EU and 370 worldwide; see table below).

[2] Van Goor F, Yu H, Burton B, Hoffman BJ. Effect of ivacaftor on CFTR forms with missense mutations associated with defects in protein processing or function. J Cyst Fibros. 2014;13(1):29-36.
[3] Yu H, Burton B, Huang C-J, Worley J, Cao D, Johnson J Jr, et al. Ivacaftor potentiation of multiple CFTR channels with gating mutations. J Cyst Fibros. 2012;11:237-45.

Table 1. Prevalence of the *G551D-CFTR* and Other *CFTR* Gating Mutations in Patients with Cystic Fibrosis

Geographic Region	Total Number of Patients With CF	Number of Patients With *G551D* Mutation	Number of Patients With Other Gating Mutations[a]
European Community			
Austria[b]	1392	17	2
Belgium	1065[37]	4[38]	33[38,39,40,41]
Bulgaria	170[2]	0	3[38]
Cyprus	26[42]	n/a	n/a
Czech Republic	570[37]	47[43]	0
Denmark	471[c]	2[44]	0
Estonia	40[42]	n/a	n/a
Finland	64[42]	n/a	n/a
France	6000[45]	120[43]	60[43,46]
Germany	5300[d]	159[47]	14[47,48]
Greece	555[2]	4[38]	0
Hungary	410[2]	0	0
Ireland	1500[49]	180[50]	0
Italy	4556[e]	7[27]	48[f,27]
Latvia	30[42]	n/a	n/a
Lithuania	47[42]	n/a	n/a
Luxembourg	40[42]	n/a	n/a
Malta	23[42]	n/a	n/a
Netherlands	1140[g]	2[38]	21[40]
Poland	1150[h]	11[40]	0
Portugal	285[2]	0	1[38]
Romania	238[2]	0	0
Slovakia	340[2]	0	0
Slovenia	66[42]	n/a	n/a
Spain	2200[37]	16[38]	3[38]
Sweden	575[51]	0	0
United Kingdom	8284[37]	514[38,43]	20[38,43]
North America			
United States[3]	24019	1032	140[i]
Canada[4]	4200	126[j,43]	25[k,52]
Australia[5]	2986	133	n/a
TOTAL	**67742**	**2374**	**370**
Percentage of total	not applicable	3.5%	0.55%

CF: cystic fibrosis; *CFTR*: cystic fibrosis transmembrane conductance regulator gene; n/a: not available.

[a] Other *CFTR* gating mutations include G178R, S549N, S549R, G551S, G970R, G1244E, S1251N, S1255P, and G1349D.

[b] Total prevalent CF cases in Austria: Vertex data on file.

[c] Total prevalent CF cases in Denmark = Diagnosed cases[53] / Diagnosis rate of 0.95

[d] Total prevalent CF cases in Germany = Diagnosed cases[53] / Diagnosis rate of 0.95

[e] Total prevalent CF cases in Italy = Diagnosed cases[54] / Estimated diagnosis rate of 0.90

[f] References used to add a nominal figure for other gating mutation in Italy: G551S,[55] G970R.[56]

[g] Total prevalent CF cases in the Netherlands = Diagnosed cases[53] / Diagnosis rate[57]

[h] Total prevalent CF cases in Poland = Diagnosed cases[58] / Estimated diagnosis rate of 0.95

[i] Other gating mutations for the US were derived from CF Foundation Patient Registry Data for 2010.

[j] Total prevalent CF cases in Canada = Diagnosed cases[59] / Diagnosis rate[60]

[k] References used to add a nominal figure for other gating mutation in Canada: G178R,[61,62] G970R,[63] R352Q,[64] S945L.[63]

The *G551D* mutation is the most common gating mutation worldwide. While reports of individual cases and small cohorts of patients show variable phenotypes in patients carrying the *G551D* mutation the 3 largest genotype-phenotype association studies that evaluate patients from different geographical regions have classified the *G551D* mutation as being associated with a severe phenotype with rates of lung disease progression and mortality that are similar to other severe phenotypes. There are few published reports on the clinical features of patients with other non-*G551D* gating mutations; however an analysis of the US CF Foundation Patient Registry data revealed that the rates of lung disease progression in patients with these mutations are similar to that of patients with the *G551D* mutation.

Ivacaftor, also referred to as VX-770, is an orally bioavailable small molecule that claims to provide a new therapeutic approach to the treatment of CF by targeting the pathophysiology of cystic fibrosis – the dysfunctional *CFTR* protein. Ivacaftor represents a proposed new class of drugs, *CFTR* modulators, which restore the function of the *CFTR* protein. Ivacaftor is a type of *CFTR* modulator known as a *CFTR* potentiator. Ivacaftor acts on the *CFTR* protein to increase the channel open probability (or gating) to enhance chloride transport. Ivacaftor was found to be highly selective for *CFTR* in vitro, as determined

by its lack of ability to interact with, or modulate the activities of, a broad panel of receptors and enzymes. In vitro, ivacaftor increased the channel activity of *G551D-CFTR* protein expressed in recombinant cell and primary human bronchial epithelial cell cultures. In vitro results showed that ivacaftor increased chloride transport also in other *CFTR* gating mutations.

Ivacaftor is the first *CFTR* modulator to show an improvement in *CFTR* function and clinical benefit in subjects with CF who have a gating mutation in the *CFTR* gene. Kalydeco was authorised in the EU on 23 July 2012 for the treatment of cystic fibrosis (CF) in patients age 6 years and older who have a *G551D* mutation in the *CFTR* gene. The initially proposed extension to the indication is for the treatment of CF in patients age 6 years and older who have a *G551D* or other gating (or Class III, also referred as non-*G551D* gating mutation) in the *CFTR* gene.

2.2. Non-clinical aspects

The Applicant submitted results of an in vitro study (study CBDM304464 "Evaluation of the Substrate and Inhibitor Potential of VX-770, VRT-842917, and VRT-837018 of Organic Anion Transporting Polypeptide 1B1 and 1B3") that is described in the clinical section as it may have clinical relevance. No other new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

The MAH stated that the environmental assessment of ivacaftor submitted in the initial MAA is still applicable to the current submission, since the patient population considered in calculations of the initial assessment included all CF patients in the EU aged 6 years and over, so individuals with Gating mutations, which are included in the claimed indication, represent a small sub-set of the all CF patients. Therefore, the PECsw value for ivacaftor of 0.009 µg/L as derived from the initial assessment remains a conservative estimate, even if the extension of the indication is granted.

2.2.2. Discussion on non-clinical aspects

The study to investigate the substrate and inhibitor potential of ivacaftor and its metabolites M1 and M6 for OATP1B1 and OATP1B3 transporters in HEK cells is evaluated in the clinical part of this assessment report. Absence of other new non-clinical studies is accepted in the light of non-clinical data provided in the initial application and post-authorisation.

Regarding the environmental assessment of ivacaftor, the MAH pointed that the environmental assessment of ivacaftor submitted in the initial MAA is still applicable to the current submission, since the patient population considered in calculations of the initial assessment included all CF patients in the EU aged 6 years and over, so individuals with Gating mutations, which are included in the claimed indication, represent a small sub-set of the all CF patients. This justification for the lack of an update ERA assessment is adequate. Therefore, the PECsw value for ivacaftor is 0.009 µg/L as derived from the initial assessment.

2.2.3. Conclusion on the non-clinical aspects

Please refer to clinical section for discussion on in vitro study CBDM304464. Absence of any other new non-clinical data is considered acceptable by the CHMP.

Considering the available data, ivacaftor is not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

The pivotal study for the proposed extension to the indication of Kalydeco is study VX12-770-111 (study 111), a phase 3, two-part, randomized, double-blind, placebo-controlled, crossover study with an open-label period to evaluate the efficacy and safety of ivacaftor in subjects with cystic fibrosis who have a non-*G551D-CFTR* gating mutation. Only the results of the crossover part of the study (Part 1) are discussed in this report.

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.

2.3.2. Pharmacokinetics

No new pharmacokinetic data are discussed in the documentation provided in support of this extension of the indication with the exception of a population PK/PD model based on the prior model for ivacaftor and incorporating data from Part 1 of study 111 (Report J106). In addition, an update on the analytical methods is presented as well as a final report (dated September 17, 2013) of an in vitro study entitled "Evaluation of the Substrate and Inhibitor Potential of VX-770, VRT-842917, and VRT-837018 of Organic Anion Transporting Polypeptide 1B1 and 1B3" that is addressed in this section of the report.

Analytical methods

The Applicant has submitted the final bioanalytical study report J094 in which the calibration curve and quality control data met the pre-specified acceptance criteria for all batches of samples analysed.

An analytical method was developed and validated for the determination of ivacaftor, M1, and, M6 in K3EDTA or K2EDTA human plasma using d4-VX-770, d4-VRT-837018 (d4-M1) or d4-VRT-842917 (d4-M6) for ivacaftor, M1 and M6 ISTDs, respectively. The method was validated over the range of 2.00 to 2000 ng/mL (slightly lower for M1 after adjustment) for all analytes using LC-MS/MS. This method is described in Standard Analytical Method VX-770-008 and was validated in study VX-770-DMPK-VAL-033 (report number E053) and in several addenda.

The performance of this assay was carried out in line with international bioanalytical guidelines (Food and Drug Administration Bioanalytical Method Validation, 2001). The pre-study validations of the analytical methods are satisfactory. In-study validation was conducted for the individual studies, and validation data are submitted and included in the respective bioanalytical study summaries. The calibration curve and quality control data met the pre-specified acceptance criteria for all batches of samples analysed and are described in the bioanalytical report in Report IJ094. The QCs used are representative of the calibration range. Dilution samples were not necessary. No Incurred sample reanalysis (ISR) was performed as the ISR was performed in previous studies. For all analytes, the maximum storage period between collection and analysis was no longer that the current validated storage period at -80 ºC. All samples were analysed within the demonstrated long-term stability period. Chromatograms of calibrators, QCs, and subject samples (and corresponding sample sequences) from at least 20% of the subject samples analysed were included.

The MAH stated that in study 111 there were approximately 50% lower M1 metabolite exposure compared to studies in the original MAA submission. The apparent difference in M1 exposure has been attributed to the implementation of a new M1 reference standard lot. The purity of an older M1 reference standard used for analysis of samples in the original submission (Lot H04966-106) has been found to be significantly lower than originally measured, resulting in an overestimation of M1 concentrations in the studies supporting the original submission. How to deal with this issue is currently being discussed and is not in the scope of the current procedure as the lower purity of the old reference standard lot does not affect study 111. In this study, the lot REF-10-011 (P10525-015) has been used and the residue of ignition (ROI) has been taken into account for purity calculation. No correction due to the purity correct assay value is needed.

Interaction with Organic Anion Transporting Polypeptide 1B1 and 1B3

Considering that hepatic metabolism and elimination in the faeces are the predominant routes of elimination for ivacaftor and its metabolites, involvement of QATP1B1 and 1B3 uptake transporters should have been investigated. Within the current submission the MAH submitted the final report (dated September 17, 2013) of an in vitro study entitled "Evaluation of the Substrate and Inhibitor Potential of VX-770, VRT-842917, and VRT-837018 of Organic Anion Transporting Polypeptide 1B1 and 1B3", that is discussed in this section as even though it is an in vitro study it addresses potential interactions that may have clinical relevance.

The uptake transporter substrate and inhibition potential of ivacaftor (VX-770), VRT-837018 (M1), and VRT-842917 (M6) was evaluated in a cellular uptake assay. HEK cells transfected with human OATP1B1 and OATP1B3 were run in parallel with vector control (non-transfected) cells according to the Guideline on drug interactions. The IC_{50} values for OATP1B1 and OATP1B3 inhibition by M1 were 12.1 µM and 39.8 µM and for M6 were 23.9 µM and 86.5 µM, respectively.

It was concluded that ivacaftor and its metabolite M1 are not substrates of OATP1B1 or OATP1B3, whereas the metabolite M6 is a substrate for both OATP1B1 and OATP1B3. In addition, ivacaftor is not an inhibitor of OATP1B1 or OATP1B3 since the inhibition did not exceed 50%, whereas M1 and M6 showed greater than 50% inhibition towards OATP1B1 and OATP1B3.

The MAH was further requested to discuss the potential clinical relevance of the *in vitro* results of ivacaftor, M1 and M6 given that according to the Guideline on Investigations of Drug Interactions (EMA/CHMP/EWP/125211/2010) potential inhibition of hepatic uptake transporters should be based on comparison with a 25-fold unbound hepatic inlet concentration. For the unbound C_{max} or $I_{in,\ max}$ values for M1 and M6 were 0.0713 µM and 0.0578 µM, respectively. The multiplication by a factor of 25 will lead to unbound C_{max} or $I_{in,\ max}$ values of 1.78 µM and 1.45 µM. Since the 25-fold unbound hepatic inlet concentrations for both the M1 and M6 metabolites are much lower than IC_{50} values, clinically relevant interactions are not expected between ivacaftor or its metabolites and OATP1B1 and OATP1B3 substrates.

2.3.3. Pharmacodynamics

As for pharmacokinetics, no new pharmacodynamic data has been submitted in support of the indication extension with the exception of a population pharmacokinetic/pharmacodynamic (PK/PD) analysis including data from study 111, Part 1. The objectives of this PK/PD analysis are mainly descriptive. Available pharmacodynamic data (mainly from the initial MAA submission) supporting the use of ivacaftor in class III gating mutations other than *G551D* is presented and discussed below.

Primary pharmacodynamics

Ivacaftor has been shown in cell-based assays to increase *CFTR* channel gating and enhance chloride transport. However, the exact mechanism leading ivacaftor to prolong the gating activity of some mutant *CFTR* forms has not been completely elucidated. Taking into account that in recently published papers the mechanism of action of ivacaftor is further investigated the MAH was requested to provide an update of the mechanism of action of ivacaftor that focuses on *CFTR* gating mutations. If ivacaftor was shown to interact with the mechanisms involved in channel gating this would have provided further reassurance that all gating mutations are indeed suitable for treatment with ivacaftor from a mechanistic point of view.

The in vitro pharmacological activity of ivacaftor on multiple mutant CFTR forms has been characterized in electrophysiological and immunoblot studies using recombinant cell lines, such as Fischer rat thyroid (FRT) cells, or cultured CF HBE cells isolated from donor bronchi obtained from patients with CF. Each FRT cell line was engineered to express a single human mutant CFTR form. The use of recombinant cells to profile the activity of ivacaftor against multiple mutant CFTR forms was necessary as cultured CF human bronchial epithelia (HBE) cells were available only for a limited number of *CFTR* mutations. When available, cultured HBE provided a physiologically relevant cell system to monitor the pharmacological action of ivacaftor, as cultured CF HBE exhibit several defects in airway epithelial cell function that are believed to contribute to the development of CF lung disease, including low chloride transport, excessive sodium transport, defective fluid regulation, and decreased cilia beating.

Experimentally, CFTR-mediated chloride transport was measured in Ussing chamber studies as a change in the short circuit current (ISC) following addition of a cyclic adenosine monophosphate (cAMP) agonist, such as forskolin. To directly measure the channel open probability and conductance of a single CFTR channel at the cell surface, single-channel patch clamp techniques were used. The quantity of CFTR at the cell surface was assessed in immunoblot studies to measure the steady-state levels of extensively glycosylated, mature CFTR (170 - 180 kDa band), which is indicative of CFTR exit from the endoplasmic reticulum, passage through the Golgi complex, and subsequent delivery to the cell surface.

The selection of the missense *CFTR* mutations to be tested in the in vitro experiments performed was based on the presence of 10 or more alleles in the North American and European CF patient population or on a known molecular defect of interest. In addition to *G551D*, several other CF-causing *CFTR* mutations have been shown to produce a CFTR protein for which the predominant defect is a low channel open probability compared to normal CFTR. These include, *G178R*, *G551S*, *G970R*, *G1244E*, *S1255P*, and *G1349D*. Like *G551D-CFTR*, FRT cells expressing *G178R-*, *G551S-*, *G970R-*, *G1244E-*, *S1255P-*, and *G1349D-CFTR* had a low (< 10% of normal) level of baseline chloride transport in Ussing chamber studies. In addition to the previously described *CFTR* gating mutations, it is stated that the predominant defect associated with the *S549N*, *S549R*, and *S1251N CFTR* gene mutations is also a low channel open probability.

According to the MAH, CF-causing *CFTR* gating mutations as a group shared the following common functional and clinical characteristics:

- Residual or normal amounts of CFTR at the cell surface;
- Minimal baseline levels of CFTR chloride transport (<10% normal) in vitro;
- A large fold (>10-fold) increase over baseline chloride transport in response to ivacaftor in vitro.

Based on genotype-phenotype studies correlating in vivo CFTR function with the severity of CF, an increase in CFTR-mediated chloride transport by ≥10% of normal CFTR chloride transport was used as an in vitro threshold to distinguish between levels of CFTR function that may be associated with less severe CF.

The table below shows the in vitro effect of ivacaftor on chloride transport in Fischer rat thyroid (FRT) cells engineered to express the selected *CFTR* gating mutations.

Table 2. In vitro effects of ivacaftor on *CFTR*-gating mutations

Mutation	Sweat Cl^- (mmol/L) [b]	CFTR-mediated chloride transport [a]				
		Baseline (% normal)		With Ivacaftor (% normal)		Fold Increase over baseline [c]
		Mean	SEM	Mean	SEM	
CF-Causing *CFTR* gating mutations						
G551D	108	1.0	0.5	55.3 *	6.3	55.3
G178R	103	2.9	0.5	87.2 *	8.2	30.1
S549N	109	1.6	0.4	95.7 *	6.5	59.8
S549R	104	0.02	0.0	21.0 *	6.1	1050.0
G551S	85	9.7	0.7	157.6 *	8.2	16.2
G970R	101	1.6	0.6	48.8 *	9.8	30.5
G1244E	95	0.3	0.1	38.9 *	2.2	129.7
S1251N	92	3.9	0.7	98.2 *	8.6	25.2
S1255P	88	0.8	0.3	58.5 *	12.9	73.1
G1349D	107	1.7	0.5	79.3 *	4.1	46.7

[a] All data shown are the mean ± SEM (n = 3 – 6 replicate experiments); $P < 0.05$ vs. forskolin alone (paired t-test).
[b] Mean sweat chloride levels measured in patients with CF carrying the mutation.
[c] level of in vitro chloride transport with ivacaftor divided by the in vitro baseline level.
Source: Report G205

In vitro, ivacaftor stimulated chloride transport in cells expressing the *G551S-CFTR* mutant protein with a fold increase over baseline of 16.2 (the lowest fold change) while in cells expressing the *G1244E-CFTR* mutant the highest fold increase was achieved (i.e. 129.7). The difference between the two extreme values was 8-fold. Similar data with estimated EC_{50} values have been published[4]. Please note that for mutation *S549R* the fold increase over baseline value quoted in table above is 1050.0 while in the study by Yu et al the value quoted is >20 which represents a more conservative approach.

The MAH was requested to discuss if there exists a possible relationship between the observed obtained in vivo results (e.g. ΔFEV1 >5% improvement of baseline, decrease in CL, maximal CL concentration sweat etc.) and the in vitro restoration of the CTFR/chloride transport toward normal with ivacaftor. The analysis of the raw data does not show any apparent trend regardless of how the in vitro data of chloride transport is expressed, i.e. percent of normal or fold change over baseline. Table below show the data provided by the MAH in response to the above issue.

[4] Yu H et al. Ivacaftor potentiation of multiple *CFTR* channels with gating mutations. Journal of Cystic Fibrosis 2012; 11(3):237-45

Table 3. Relationship between the observed in-vivo results and the in vitro restoration of the CTFR/chloride transport

Non-*G551D* gating mutation (no. of patients)	Baseline (% normal)	In vitro chloride transport as % normal with ivacaftor	In vitro fold change over baseline in chloride transport with ivacaftor	Mean (SD) absolute change in sweat chloride (Week 8)	Mean (SD) absolute change in PPFEV1 (week 8)
G178R (n=5)	2.9	87.2	30.1	-52.5 (13.5)	8.4 (7.9)
S549N (n=6)	1.6	95.7	59.8	-74.3 (15.4)	11.3 (9.8)
S549R (n=4)*	0.00	21.0	>20.0	-60.7 (8.8)	5.2 (7.4)
G551S (n=1)	9.7	157.6	16.2	-68.0	3.1
G970R (n=4)	1.0	48.8	30.5	-6.3 (6.6)	2.6 (2.7)
G1244E (n=5)	0.3	38.9	129.7	-55.1 (18.1)	8.4 (8.7)
S1251N (n=8)	3.9	98.2	25.2	-54.4 (23.4)	8.7 (13.0)
S1255P (n=2)	0.8	58.5	73.1	-77.8 (6.0)	3.1 (6.5)
G1349D (n=2)	1.7	79.3	46.7	-80.3 (1.8)	19.7 (23.6)

*n=3 available for the analysis of absolute change in sweat chloride

A linear regression model was also applied to determine whether the absolute or relative change in either PPFEV1 or sweat chloride could be predicted by the absolute change in (in vitro) chloride transport after treatment with ivacaftor where the absolute change in chloride transport corresponds to the absolute difference before and after treatment with ivacaftor (both in % normal). The MAH justify the use of % normal (rather than the fold change) due to the fact that baseline values are usually only a few percent of normal for almost all mutations and therefore it was felt that fold change was not the most reliable and robust measure to express the effect of ivacaftor on chloride transport. This type of analysis did not show any significant linear correlation between the in vitro chloride transport and sweat chloride or PPFEV1 in vivo. The MAH states that the possibility that a relationship exists cannot be disproven by this limited data set. This is agreed, i.e. the lack of statistical significance does not mean that it does not exist. In addition, only linear relationship has been addressed. The MAH is encouraged to further explore an understanding of the relationships between in vitro and in vivo data.

Literature[5] shows that the gating mutations above considered cause protein alterations in the ATP binding pockets formed by the two NBDs required for normal CFTR channel gating (*G551S*, *G1244E*, *S1255P*, *G1349D S549N*, *S549R*, and *S1251N*) while the *G178R* and *G970R CFTR* mutations alter the intracellular cytoplasmic loops that are believed to link the ATP-driven conformational changes in the NBDs to the opening of the CFTR channel pore formed by the membrane spanning domains.

Cystic fibrosis transmembrane conductance regulator (*CFTR*) mutations may cause CF or be associated with *CFTR*-related disorders but they also may have no clinical consequences or have unknown or

[5] Yu H, Burton B, Huang C-J, Worley J, Cao D, Johnson J Jr, et al. Ivacaftor potentiation of multiple CFTR channels with gating mutations. J Cyst Fibros. 2012;11:237-45.

uncertain clinical relevance. All of the non-*G551D* gating mutations above considered are missense mutations for which the clinical role is difficult to anticipate[6].

A search has been performed in the Clinical and Functional Translation of *CFTR* (*CFTR*2) website (www.*CFTR*2.org) on the non-*G551D* gating mutations characterised in vitro by the MAH as well as on the mutations identified in the second allele of the *CFTR* of patients enrolled in study 111. *CFTR*2 is a project that assembled clinical data and accompanying *CFTR* variants from individuals with cystic fibrosis enrolled in national registries and large clinical centres from 24 countries. By focusing on variants present in individuals with a diagnosis of cystic fibrosis ascertained by expert clinicians, the project used a 'phenotype-driven' approach to data collection[7].

The non-*G551D* gating mutations that have been characterised by the MAH are all missense mutations for which the CFTR2 website states that they "would cause CF", i.e. they can cause CF when combined with another CF-causing mutation although the level of evidence does not seem to be the same for all of them, e.g. *G551S* is associated with borderline normal sweat electrolyte levels while for *G178R* and *S549N CFTR*2 it is stated that "The research published is insufficient to clearly determine whether or not the mutation is disease-causing".

It has to be noted that only two of the mutations identified in the second allele of the *CFTR* in patients enrolled in study 111 are missense mutations (*L1077P* and *N1303K*). They are also said to cause CF when combined with another CF-causing mutation. The remaining are nonsense (*Y913X, G542X, Q1313X, R1158X*), insertion/deletion (*F508del, 2183AA->G*, *2896insAG*) and splice (*621+1G->T, 2789+5G->A*) mutations that are known to significantly disrupt *CFTR* protein production and result in little or no functional *CFTR* protein in the cell.

The identification of gating mutations as proposed by the MAH relies on in vitro work that may be not available for all the potential mutations as almost 2,000 variants have been reported in the *CFTR* coding and flanking sequences but only the functional importance of a small number is known. The MAH was initially proposing an indication for all gating mutations but the mutations that have been characterised *in vitro* and assessed in study 111 represent only a number of the possible gating mutations. Given the variable clinical consequences of missense mutations, the heterogeneity of the disease and the doubts raised on whether all of the non-*G551D* mutations above considered are disease-causing the MAH was requested to further address this issue. The MAH was also encouraged to develop an approach to keep treatment with ivacaftor only in those patients who really benefit from it, i.e. to develop a response-guided therapy. In response to CHMP Major Objection the MAH provided an extensive response and restricted the proposed indication, i.e. it was proposed to list the individual non-*G551D* gating mutations that have been studied in study 111.

Regarding whether all the non-*G551D* gating mutations are cystic fibrosis-causing, two mutations were in particular questioned, i.e. *G178R* and *S549N*.

The analysis of the *CFTR*2 data shows that there are 48 patients carrying the *G178R* mutation. Their average sweat chloride is 103 mmol/L, their PPFEV1 ranges from 28% to 107% (depending on age), 63% are pancreatic insufficient and 66% are colonised by *P aeruginosa*. Six patients with this *CFTR* mutation were enrolled in study 111. Their baseline sweat chloride ranged from 90.5 to 121.5 mmol/L and their PPFEV1 between 42.9% and 118.7%. The subgroup analysis by non-*G551D* gating mutation showed that at week 8 of study 111 the mean (SD) absolute change in PPFEV1 was -2.4 (4.9) and 8.4 (7.9) for the placebo (n=6)- and ivacaftor- (n=5) treated patients, respectively. Similarly, the mean

[6] Castellani C et al. Consensus on the use and interpretation of cystic fibrosis mutation analysis in clinical practice. Journal of Cystic Fibrosis 7 (2008) 179–196.
[7] Sosnay PR et al. Defining the disease liability of variants in the cystic fibrosis transmembrane conductance regulator gene. Nat Genet. 2013 Oct;45(10):1160-7.

(SD) absolute change from baseline in sweat chloride was -5.42 (8.5) and -52.50 (13.5) mmol/L, respectively. Overall, it is believed that patients with the *G178R-CFTR* mutation can benefit from ivacaftor.

As for *S549N*, the analysis of the *CFTR*2 data shows that there are 83 patients carrying this mutation. Their average sweat chloride is 99 mmol/L, their PPFEV1 ranges from 35% to 117% (depending on age), 90% are pancreatic insufficient and 52% are colonised by *P aeruginosa*. Six patients with this *CFTR* mutation were enrolled in study 111. Their baseline sweat chloride ranged from 89.0 to 118.0 mmol/L, i.e., in the range of pathological values, although 89 mmol/L corresponds to the upper limit of residual *CFTR* function (from 40 to 89 mmol/L), and their PPFEV1 between 77.9% to 102.9%. The subgroup analysis by non-*G551D* gating mutation showed that at week 8 the mean (SD) absolute change in PPFEV1 was -8.9 (9.9) and 11.3 (9.8) for the placebo (n=6)- and ivacaftor (n=6)-treated patients, respectively. At week 8 the mean (SD) absolute change from baseline in sweat chloride was -7.6 (10.8) and -74.3 (15.4) mmol/L, respectively. Overall, it is believed that patients with the S459N-*CFTR* mutation can benefit from ivacaftor.

In addition, the MAH acknowledged that two of the mutations considered are in the range of residual *CFTR* function, i.e. *G551S* and *S1251N*.

Regarding *G551S-CFTR* mutation, there are data from 8 patients carrying this mutation in *CFTR*2. Their average sweat chloride is 63 mmol/L, their PPFEV1 ranges from 65% to 91% for patients above 20 years old, 57% are pancreatic insufficient and 43% are colonised by *P aeruginosa*. The literature review of CFTR2 includes a reference to a paper describing three *delta-F508/G551S* compound heterozygous siblings with a mild CF phenotype, characterized by mild chronic pulmonary disease, pancreatic sufficiency and increased sweat chloride levels[8]. Overall, the available data suggest that patients with this genotype seem to have a mild disease phenotype. Two subjects were enrolled in study 111 with this mutation but only the results of one of them are available for analysis at week 8 in the placebo and ivacaftor groups. For both of them the second *CFTR* mutation was *F508del*. Their baseline sweat chloride ranged from 75.5 to 86.5 mmol/L. The mutation seems to be disease-causing but the evidence of efficacy of ivacaftor is weak in that only two patients were enrolled in study 111 and just one analysed. The only strong proof of activity of ivacaftor is found in the mean absolute change in sweat chloride of -68 mmol/L in the ivacaftor-treated patient versus -11.50 mmol/L in the placebo-treated patient. The analysis of the remaining endpoints assessed, i.e. PPFEV1, BMI and CFQ-R respiratory domain shows very modest improvements except in the CFQ-R respiratory domain. However, the limitation imposed by the single patient assessed precludes drawing firm conclusions.

As for *S1251N*, the analysis of CFTR2 shows that there are 69 patients with the same genotype (*S1251N/F508del*) as the one of patients enrolled in study 111. Their average sweat chloride is 91 mmol/L, the PPFEV1 for those older than 20 years old ranges from 34% to 91%, 87% are pancreatic insufficient and 54% are colonised by *P aeruginosa*. When considering all patients with the *S1251N-CFTR* mutation in CFTR2 data are available for 85 patients with an average sweat chloride of 89 mmol/L, a PPFEV1 ranging between 35% to 95%, 83% of them are pancreatic insufficient and 55% are colonised by *P aeruginosa*. Eight patients with this non-*G551D* gating mutation were enrolled in study 111. Their baseline sweat chloride ranged from 79.5 to 97.5 mmo/L (excluding the single patient with a normal sweat chloride value at baseline). The analysis by non-*G551D* gating mutation supports the efficacy of ivacaftor in this mutation. Lung disease in the patient with a normal baseline sweat chloride of 12 mmol/L can be mainly attributed to concomitant comorbidity, i.e. hyperimmunoglobulin E syndrome.

[8] Orozco et al. Mild cystic fibrosis disease in three Mexican delta-F508/G551S compound heterozygous siblings. Clin Genet. 1995 Feb;47(2):96-8.

The information currently included in SmPC section 5.1 regarding the mechanism of action is rather unspecific, therefore an update of this section of the SmPC is proposed. This is supported by the CHMP but the proposal of the MAH, reflecting the artificial conditions in which the *in vitro* experiments were performed, was felt to convey information that was not useful for physicians. As a consequence, this subsection has been only slightly amended to reflect the current lack of demonstration of relationship between *in vitro* and *in vivo* data.

Antibacterial activity

Ivacaftor has a quionoline ring in its molecule and has been shown to have direct antibacterial activity against Gram-positive bacteria[9]. The MAH was requested to discuss whether the effect of ivacaftor may be mediated by its antibacterial activity.

Ivacaftor has antibacterial activity against gram-positive microorganisms, particularly *S aureus* which is one of the main pathogens colonising the lungs of patients with cystic fibrosis, specially the youngest ones. It is somehow reassuring that no effect has been shown (in vitro) against *P aeruginosa*.

Data from the GOAL (G551D, observational) study[10], a prospective, multi-centre observational study in CF subjects with the *G551D-CFTR* mutation, conducted by the Cystic Fibrosis Foundation in the United States, showed that patients treated with ivacaftor had reduced *P aeruginosa* infections. The reduction in *P aeruginosa* infection suggests a positive effect from ivacaftor. However, according to the MAH this effect is judged to be independent of any direct antibacterial activity since ivacaftor was not shown to impact gram negative bacteria. The data from the GOAL study are reassuring.

Although the MAH does not believe that the effect of ivacaftor is mediated by its (*in vitro*) antibacterial activity this cannot be completely excluded with the data provided.

2.3.4. PK/PD modelling

A population pharmacokinetic/pharmacodynamic model has been developed to describe ivacaftor plasma concentrations and the effects observed on percent predicted forced expiratory volume in one second (PPFEV1) and on sweat chloride that includes data from different studies in healthy volunteers and patients with cystic fibrosis and a gating mutation in one allele of the *CFTR* gene. This model builds up on the prior model, i.e. data from Part 1 of study 111 have been added to update the model and its objectives are mainly descriptive in terms of ivacaftor pharmacokinetics and pharmacodynamics.

Ivacaftor PK was described by a 2-compartment model with zero-order delivery to the absorption compartment and subsequent first-order absorption. Body weight was the most important predictor of ivacaftor disposition while gender, patient status (CF versus non-CF subject), age, and formulation did not account for variability in ivacaftor PK in a clinically meaningful manner after accounting for weight. Ivacaftor CL/F was 39% and 131% of the reference value of 18.8 L/h for the typical 20 kg and 100 kg subject, respectively, when compared to the reference subject (70 kg).

A pop PK model has been developed for ivacaftor but not for metabolites M1 and M6 since lower M1 concentrations were observed in Study 111 when compared to previous studies. This difference prompted the MAH to search for the cause of this difference and was attributed to the actual content of the reference Lot H04966-106 being only 36% of the stated value. This reference standard was used in

[9] Leah Reznikov. Antibacterial Properties of the *CFTR* Potentiator Ivacaftor. Abstract 276, The 27th North American Cystic Fibrosis Conference, 2013
[10] Rowe SM, Heltshe SL, Gonska T, Donaldson S, Borowitz D, Gelfong D, et al. Results of the G551D observational study: the effect of ivacaftor in G551D patients following FDA approval [abstract]. 27th Annual Meeting of the North American Cystic Fibrosis Conference, 17-19 October 2013, Salt Lake City, Utah; Abstract 206.

some of the previous studies and due to this error, M1 concentrations were overestimated. It is unclear whether only Lot H04966-106 was the only one where actual and nominal contents differed several fold or other lots are also involved. Currently the misreporting of M1 concentrations is not a major concern given that the true M1 concentrations are lower than the reported ones. However, the overall clinical implications of this finding as well as possible changes needed in the Product Information of Kalydeco should be addressed outside the scope of the current procedure.

M1 has not been incorporated into the population-PK model but the MAH indicate that the population-PK model will be updated with accurate M1 values from all available studies to allow modelling of the metabolites to proceed for the ongoing study in subjects with CF who have a gating mutation age 2 to 5 years. Updating the model as proposed is endorsed. Current model-based simulations and predictions should be viewed with caution. Overall, this issue is considered not to have a major impact on the current application, but in a separate procedure the MAH is expected to address the bioanalytical issue of M1 and the changes needed in the SmPC to accurately reflect the available data.

For the covariate model the approach taken has been to predefine covariate-parameter relationships based on exploratory graphics, scientific interest and mechanistic plausibility of prior knowledge rather than using a stepwise hypothesis testing. According to the Modelling and Simulation Plan of analysis the following covariates were pre-defined to be included: sex, weight, age, drug formulation, genotype (*G551D* gating mutation vs. non-*G551D* gating mutations), creatinine clearance and race. Since the majority of subjects were Caucasian with little representation in other race categories, race was not finally considered as a descriptor in the covariate model. This is acceptable. However, creatinine clearance and, most importantly, genotype have not been incorporated into the model. Creatinine clearance was inadvertently included in the Modelling and Simulation Plan for study 111. Given the small contribution of renal mechanisms to ivacaftor clearance and the fact that most of the included participants had creatinine clearance values >80 mL/min it is considered that there is no need to test creatinine clearance as a covariate. This is acceptable. Genotype was also included as a possible covariate in the Modelling and Simulation Plan. However, it was not incorporated for evaluation in the population-PK model. Rather, the individual estimates of ivacaftor CL/F were used to calculate the mean CL/F in *G551DCFTR* vs. non- *G551D-CFTR* gating mutations (19.2 L/hr vs. 15.4 L/hr, respectively) and to conclude that there does not seem to be differences between both groups. As already stated, the current model should not be used to support dosing recommendations and model-based simulations should be viewed with caution.

The pop PK/PD report state that PK parameter values for ivacaftor were similar in CF subjects in study 111 compared to previous studies. There seems to be a lack of consistency when deciding the final covariates to be kept into the model, i.e. the final model includes some covariates in spite of the fact that they are expected not to have any impact into the model. Additional inconsistencies already highlighted at the time of MAA is that being body weight one of the main factors explaining variability in ivacaftor clearance dosing recommendations for Kalydeco are based on age rather than on body weight. In the case of children aged 6 years to less than 12 years the updated model again predicts that systemic exposure in these children is higher than in adults. Therefore, the same measures that have been adopted in the Risk Management Plan for children with a *G551D* mutation should be applied to children with a non-*G551D-CFTR* gating mutation.

Pharmacokinetic–pharmacodynamic models were constructed to describe the concentration–response relationships for PPFEV1 and sweat chloride. Instead of using FEV1 (L) as a PD endpoint, the current model uses PPFEV1. The prior PD model was used as a starting point for the PPFEV1 analysis. The typical estimates (90% CI) of PD model parameters for the reference covariate effects (male, 18 years) were 73.9 (69.3, 76.9) for E_0, 0.124 (0.104, 0.147) for E_{max}, and 74.2 ng/mL (37.1, 147) for

EC_{50}. The E_{max} estimate of 0.124 (0.104, 0.147) translates to an absolute increase in PPFEV1 of 9.16% (7.69%, 10.9%) from the population mean baseline of 73.9%. Age was the most important predictor for PPFEV1 at baseline, but instead of using age as a continuous variable it has been categorised into less than 18 years old and equal or older than 18 years old on grounds that PPFEV1 would be different in children below 18 years of age versus adult patients. The MAH stated that since the decline in PPFEV1 from 6 to 17 years was followed by a more rapid decline after 18 years of age, and the decline in the random effect for baseline PPFEV1 changed between 16 and 20 years of age, two separate relationships including both a continuous and a categorical (<18 years or ≥18 years) variable were incorporated into the PK/PD model to describe age effects on baseline PPFEV1. This selection was considered to be consistent with standard clinical age categorization. However, no mathematical data have been provided or clinical reasoning discussed to support the decision. The issue can be considered solved but the model should not be used to support dosing recommendations and model-based simulations should be viewed with caution. The MAH was asked using the pop-PK/PD model parameter estimates to predict the PPFEV1 improvements by different age groups such as 6, 8, 10, 12, 14, 16, 18, 20, 30 years and with different baseline PPFEV1 values such as 50%, 60%, 70%, 75% 80%, 85% and 90%. The requested predictions were provided. However, given the lack of robustness of the model they should be viewed with caution.

The sweat chloride base model was identical to the prior model, consisting of an E_{max} model with estimated baseline, and an effect compartment. The typical estimates (90% CI) of PD model parameters for the reference covariate effects (male, 18 years) were 102 mM (100,103) for E_0, -51.4 mM (-56.2, -46.2) for E_{max}, 92.9 ng/mL (57.3, 143) for EC_{50}, and 0.0213 h^{-1} (0.0157, 0.0266) for K_{E0}. Females had an 18% increase in sweat chloride E_{max} when compared to males, translating to an E_{max} value of -60.1 (-64.0, -56.5) mM for females.

The pop PK/PD modelling report states that for both PPFEV1 and sweat chloride, model runs were performed where a separate E_{max} or EC_{50} value was estimated for study 111 subjects (non-*G551D* gating mutation) and that these estimates were comparable to those obtained from *G551D* subjects. The information provided about intermediate models supports the lack of differences regardless of the underlying type of mutation, i.e. *G551D* or non-*G551D* gating mutations; however, it is not conclusive due to the limited sample size and range of exposure in study 111.

The stated objectives of the present model were not intended to give support to dose selection, something that certainly seems difficult with the model developed that shows differences in potency of the drug. In this regard, EC_{90} (90%CI) values for PPFEV1 and sweat chloride values from the current analysis are 668 ng/mL (334, 1323) and 836 ng/mL (516,1287), respectively while EC_{90} values from the prior analysis for FEV1 (L) and sweat chloride were 423 ng/mL (45.3, 865) and 900 ng/mL (766, 1008). The EC_{90} value for PPFEV1 is higher in the current analysis relative to that of the prior model for FEV1. The MAH has explained that such differences may be due to (i) inherent differences in the endpoints: FEV1 is an absolute measure, with a fixed upper limit dictated by lung size and baseline lung defect volume, but PPFEV1 has no upper limit and is based on a comparison to a population average for gender, age, and height; (ii) and difficulties to properly estimate it in the model due to the limited data in the lower exposure range. This answer further reinforces the limitations of the current pop PK-PD model.

The MAH has recognised that a precise PK threshold has not been identified as being predictive of clinical response in patients (e.g. $C_{min} > EC_{90}$). The MAH proposed to remove information on EC_{50} and EC_{90} from the SmPC. MAH's proposal to delete the information on pharmacokinetic/ pharmacodynamic relationship in section 5.2 of the SmPC is agreed.

Overall, the MAH's responses in relation to the pop PK-PD model make it clear that a better characterisation of ivacaftor PK in patients (including rich sampling) is highly desirable and that the PK/PD model lacks robustness in that:

- M1 concentrations cannot be incorporated into the model for the time being.
- The covariate modelling approach is questionable.
- The EC_{90} values estimated by the model are imprecise and not useful for physicians or for supporting the dose selection.
- Median C_{min} which was previously considered the target PK parameter for efficacy is no longer considered as such due to differences in drug potency seen when the model was updated with data from study 111.

No dose-response studies have been performed given the rarity of patients who have non-*G551D CFTR* gating mutations. The MAH considers that similar *in vitro* potency of ivacaftor towards non-*G551D* gating mutations relative to *G551D* and the efficacy and safety results obtained in studies 102 and 103 supported evaluation of 150 mg q12h in study 111. In addition, it is postulated that ivacaftor PK is similar in healthy subjects and patients with CF, and therefore differences in PK are not anticipated between patients with other gating mutations relative to patients with the *G551D* mutation.

In section 5.2 of the SmPC most pharmacokinetic data correspond to healthy volunteers. The MAH was asked to provide tabular quantitative information of the following PK parameters C_{max}, C_{min}, AUC, t1/2, Cl and V calculated by non-compartmental methods in healthy volunteers, and sorted by study (studies 102 and 103 in patients with a *G551D* mutation versus study 111) and by age group (6 to less than 12 years old, 12 to less than 18 years old and 18 years old and older). The MAH has provided the requested data (see table below). The PK parameters were calculated by means of non-compartmental analysis. Since studies 102, 103 and 111 did not include extensive sampling, $t_{1/2}$ and $V_{z/F}$ could not be calculated, and C_{trough} instead of C_{min} is reported. Moreover, C_{max} is an approximate value due to the limited sample points during the absorption phase in the above mentioned studies.

Table 4. Mean (SD) Steady-State Ivacaftor PK Parameters in CF Subjects and Healthy Subjects following VX_770 150 mg q12h

Population	*G551D*			Non-*G551D*			Healthy Subjects		
Study	102		103	111			016	011	010
Age group (years)	≥18	12 to <18	6 to <12	≥18	12 to <18	6 to <12		≥18	
N	16[a]	62[b]	26	19[c]	11	8	20[d]	24	21[d]
C_{max} (ng/mL)	1040 (566)	1310 (666)	2030 (1030)	1450 (720)	1370 (741)	2350 (1500)	1095 (267)	987 (335)	1158 (485)
AUC_{0-12} (ng·h/mL)	9000 (5850)	11700 (6680)	17400 (10900)	11700 (5150)	12400 (6790)	21900 (14100)	8586 (2857)	8650 (3300)	9544 (4603)
C_{trough} (ng/mL)	582 (472)	775 (565)	1040 (874)	962 (587)	853 (542)	1400 (934)	582 (227)	667 (275)	642 (342)
$t_{1/2}$ (h)	NR	NR	NR	NR	NR	NR	7.84 (2.54)	NR	14.7 (3.68)
CL_{ss}/F (L/h)	28.3 (25.6)	17.6 (11.9)	12.4 (7.63)	15.6 (7.27)	16.4 (9.27)	10.3 (8.01)	19.1 (5.62)	NR	22.1 (21.1)
V_z/F (L)	NR	NR	NR	NR	NR	NR	205 (59.6)	NR	353 (122)

NR: Not Reported
Note: PK sampling in Studies 102 and 103 was conducted at Week 24 and includes predose, 1.5, 3, 4, and 6 hour postdose samples; PK sampling for Study 111 was conducted at Week 2 or Week 14 and includes predose, 1, 2, 3, 4, and 6-8 hour postdose samples. The predose sample was recycled and used for C_{12} for the estimation of AUC_{0-12}.
[a] N = 17 for C_{max}; [b] N = 63 for C_{max}; [c] N = 15 for AUC and CL; [d] N = 19 for AUC, $t_{1/2}$, CL/F and V_z; [e] N=15 for $t_{1/2}$ and V_z.

According to the MAH the above PK parameters indicate similar levels of exposure in *G551D* and non-*G551D* adult CF subjects relative to healthy adult subjects. Exposure is also similar in adolescents and children with a *G551D-CFTR* mutation relative to those with a non-*G551D* gating mutation. This is agreed. However, it should also be pointed out that ivacaftor systemic exposure in children 6 to 12 year old with either a *G551D*- or non-*G551D-CFTR* gating mutation is approximately 2-fold higher than in adults. This makes it desirable that further dosing recommendations (in particular for children below

5 years old) are aimed at targeting adult exposures taking into account that C_{min} is no longer the target PK parameter for efficacy.

Based on the results discussed above the information in SmPC section 5.2 has been updated with a general statement. Detailed quantitative data are to be included when the bioanalytical issue of M1 overestimation in prior studies is resolved.

2.3.5. Discussion on clinical pharmacology

Only limited pharmacokinetic or pharmacodynamic data have been provided with this submission.

Analytical methods used for the measurement of ivacaftor and metabolites M1 and M6 in plasma

As requested the MAH has submitted the final bioanalytical study report J094 in which the calibration curve and quality control data met the pre-specified acceptance criteria for all batches of samples analysed. Lower concentrations of M1 were detected in study 111 as compared to previous studies. The apparent difference in M1 exposure has been attributed to the implementation of a new M1 reference standard lot. The composition of an older M1 reference standard lot used for analysis of samples in the original submission has been found to be significantly lower than originally measured, resulting in an overestimation of M1 concentrations in the studies supporting the original submission. The overall clinical implications of this finding as well as possible changes needed in the Product Information of Kalydeco should be addressed outside the scope of the current procedure, but currently do not warrant an immediate regulatory action. The MAH has confirmed that the PK/PD model will be updated with data from studies where M1 has been accurately determined. This is endorsed. However, it has to be noted that whether the ratio ivacaftor:M1 is similar across healthy volunteers and patients with cystic fibrosis is still questionable. This is expected to be addressed in the planned separate procedure mentioned above.

Population PK-PD modelling

A population pharmacokinetic/pharmacodynamic model has been developed to describe ivacaftor plasma concentrations and the effects observed on percent predicted forced expiratory volume in one second (PPFEV1) and on sweat chloride that includes data from different studies in healthy volunteers and patients with cystic fibrosis and a gating mutation in one allele of the *CFTR* gene. This model builds up on the prior model, i.e. data from Part 1 of study 111 have been added to update the model and its objectives are mainly descriptive in terms of ivacaftor pharmacokinetics and pharmacodynamics. The current model lacks robustness and should not be used to support dosing recommendations and model-based simulations should be viewed with caution. Indeed, the model was not intended to support dose selection for study 111 and its objectives are descriptive.

Ivacaftor PK parameters calculated by non-compartmental analysis show that the systemic exposure to ivacaftor is similar in *G551D* and non-*G551D* adult CF patients relative to healthy adult subjects. Exposure is also similar in adolescents and children regardless of whether the *CFTR* mutation is *G551D* or non-*G551D* gating mutation. However, in patients with *G551D*- and non-*G551D*-*CFTR* gating mutations, the exposure to ivacaftor is almost 2-fold higher in children 6-12 years old relative to that seen in adults. This information is reflected in section 5.2 of the SmPC for the time being as a general statement.

Interactions with Organic Anion Transporting Polypeptide 1B1 and 1B3

Metabolite M6 has been shown in vitro to be a substrate for the transporters OATP1B1 and OATP1B3. In addition, metabolites M1 and M6 have been shown in vitro to be inhibitors of both transporters OATP1B1 and OATP1B3. Conclusions about potential clinical relevant DDIs should be based on comparison with a 25-fold unbound hepatic inlet concentration according to the Guideline on Investigations of Drug Interactions (EMA/CHMP/EWP/125211/2010).

The IC_{50} values for OATP1B1 and OATP1B3 inhibition by M1 were 12.1 µM and 39.8 µM and for M6 were 23.9 µM and 86.5 µM, respectively (use IC_{50} instead Ki was found acceptable as for competitive inhibition if Km >> S, the IC_{50} values are expected to be approximately Ki). New calculations for the unbound C_{max} or $I_{in,\ max}$ resulted in values of 0.0713 µM and 0.0578 µM, respectively. The multiplication by a factor of 25 leads to unbound C_{max} or $I_{in,\ max}$ values of 1.78 µM and 1.45 µM. Since the 25-fold unbound hepatic inlet concentrations for both the M1 and M6 metabolites are much lower than IC_{50} values, clinically relevant interactions are not expected between ivacaftor or its metabolites and OATP1B1 and OATP1B3 substrates.

In vitro data on the effect of ivacaftor in non-G551D gating mutations

In vitro data on the effect of ivacaftor in non-*G551D* gating mutations that are the subject of the present submission initially were not re-discussed by the MAH. The MAH was requested to provide a comprehensive review of the mechanism of action of ivacaftor in *CFTR* gating mutations that also includes a discussion on its antibacterial properties and the role that this property may have in treatment outcomes in patients. Information in section 5.1 on ivacaftor mechanism of action was proposed to be updated according to currently available data, but for the reasons discussed above it has amended only slightly to indicate the lack of demonstration of a relationship between *in vitro* and *in vivo* data.

Regarding the antibacterial properties of ivacaftor it has been shown that *in vitro* ivacaftor has antibacterial activity against gram-positive microorganisms, particularly *S aureus* which is one of the main pathogens colonising the lungs of patients with cystic fibrosis, specially the youngest ones. It is somehow reassuring that no effect has been shown (*in vitro*) against *P aeruginosa*. The data from the GOAL study are also reassuring. Although the MAH do not believe that the effect of ivacaftor is mediated by its (*in vitro*) antibacterial activity this cannot be completely excluded with the data provided.

Information obtained from the *CFTR*2 website suggests that the evidence supporting that all of the non-*G551D* gating mutations assessed in study 111 are disease-causing is inconsistent. However, based on the reanalysis of this information and the subgroup analysis by non-*G551D* gating mutation it is concluded that there is no reason to exclude any of the non-*G551D* gating mutations based on these arguments. Nevertheless, whether ivacaftor is equally beneficial in all gating mutations has been questioned based on the *in vitro* and *in vivo* results presented. The main consequence is that the initially proposed unrestricted indication covering all non-*G551D* gating mutations could not be accepted, which was reflected in a Major Objection pertaining to clinical efficacy. In response to the CHMP objection the MAH proposed to restrict the indication to those mutations that have been investigated in study 111. Whether all the *CFTR*-mutations studied in this trial can be included in the indication is addressed in the section on clinical efficacy.

2.3.6. Conclusions on clinical pharmacology

The current PK/PD model lacks robustness and should not be used to support dosing recommendations while model-based simulations should be viewed with caution.

Non-compartmental analysis shows that ivacaftor pharmacokinetics is similar in patients with cystic fibrosis and healthy volunteers and also similar regardless of whether the underlying mutation is a *G551D* or a non-*G551D* gating mutation. However, in patients with *G551D*- and non-*G551D-CFTR* gating mutations, the exposure to ivacaftor is almost 2-fold higher in children 6-12 years old relative to that seen in adults.

Metabolite M6 has been shown in vitro to be a substrate for the transporters OATP1B1 and OATP1B3. In addition, metabolites M1 and M6 have been shown in vitro to be inhibitors of both transporters OATP1B1 and OATP1B3. However, since the 25-fold unbound hepatic inlet concentrations for both the M1 and M6 metabolites are much lower than IC_{50} values, clinically relevant interactions are not expected between ivacaftor or its metabolites and OATP1B1 and OATP1B3 substrates.

The clinical implications and possible changes in the Product Information of Kalydeco related to the finding that M1 concentrations were overestimated in prior studies of ivacaftor need to be addressed outside the current procedure as in study 111 the analysis for M1 is acceptable.

An *in vitro* antibacterial activity of ivacaftor against Gram positive microorganisms has been observed, and contribution of this activity to the mechanism of action cannot be completely excluded based on the data available.

Doubts were raised regarding whether all of the gating mutations characterised in vitro are cystic fibrosis-causing. In particular, *G178R*- and *S549N-CFTR* mutations have been questioned as being disease-causing. As for *G551S-CFTR* mutation the average sweat chloride of patients carrying this mutation in *CFTR*2 is 63 mmol/L (a borderline value). However, based on responses provided by the MAH, it is agreed that all non-*G551D* mutations assessed in study 111 can be considered as disease-causing although the available evidence supporting this is variable and stronger for some mutations than for others. The proposed indication was, however, amended from an unrestricted one to a more specific one where the individual mutations are listed (please see further discussion in the section on clinical efficacy).

2.4. Clinical efficacy

2.4.1. Dose response studies

No dose-response studies have been performed given the rarity of patients who have non-*G551D-CFTR* gating mutations. The MAH considered that similar *in vitro* potency of ivacaftor towards non-*G551D* gating mutations relative to *G551D* and the efficacy and safety results obtained in studies 102 and 103 supported evaluation of 150 mg q12h in study 111. In addition, it is argued that ivacaftor PK is similar in healthy subjects and patients with CF, and therefore differences in PK are not anticipated between patients with other gating mutations relative to patients with the *G551D* mutation.

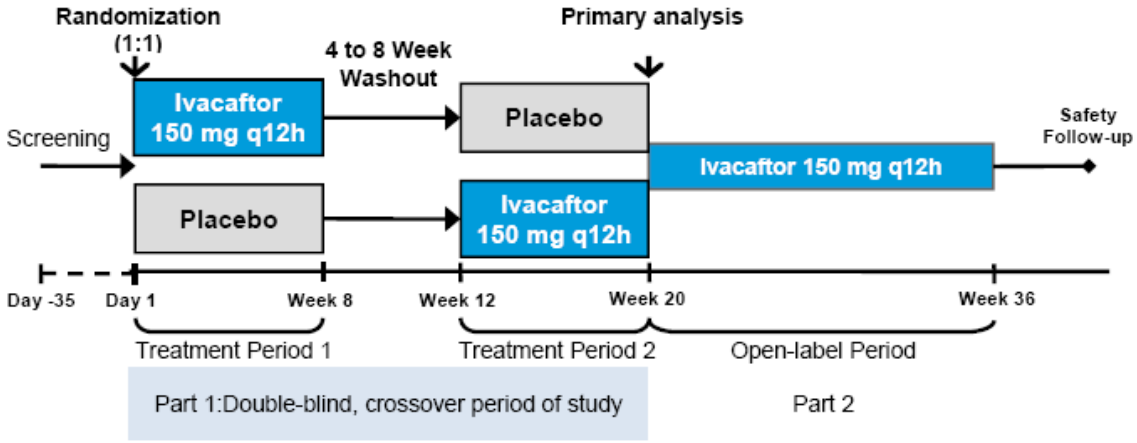
As previously discussed, the systemic exposure to ivacaftor is similar in *G551D* and non-*G551D* adult CF patients relative to healthy adult subjects. Exposure is also similar in adolescents and children regardless of whether the *CFTR* mutation is *G551D* or non-*G551D* gating mutation. However, in patients with *G551D*- and non-*G551D-CFTR* gating mutations, the exposure to ivacaftor is almost 2-fold higher in children 6-12 years old relative to that seen in adult patients. This information is included in section 5.2 of the SmPC.

2.4.2. Main study

Study 111

The pivotal study for the proposed extension to the indication of Kalydeco is study VX12-770-111 (study 111), a phase 3, two-part, randomized, double-blind, placebo-controlled, crossover study with an open-label period to evaluate the efficacy and safety of ivacaftor in subjects with cystic fibrosis who have a non-*G551D-CFTR* gating mutation. The crossover period was immediately followed by a 16-week open-label period to provide efficacy and safety results for a total of 24 weeks. This submission is based on the double-blind crossover period data (Treatment Period 1 through Treatment Period 2) assessing the primary efficacy endpoint. A schematic of the study design is provided in the figure below.

Figure 1. Schematic of Phase 3 Study Design of Ivacaftor in Subjects with a Non-*G551D* Gating Mutation



q12h: every 12 hours
Notes: Schematic shown represents the full Study 111. This submission is based on the Part 1, double-blind, crossover period data (Treatment Period 1 through Treatment Period 2).
Treatment Sequence 1 is ivacaftor → placebo. Treatment Sequence 2 is placebo → ivacaftor.

Based on the time frame of response in studies 102 and 103 of CF patients with a *G551D-CFTR* mutation, the 8-week duration of the placebo-controlled treatment periods was expected to be sufficient to demonstrate a treatment effect and pattern of response in CF patients with a gating mutation other than *G551D*. The 16-week Open-label Period in Part 2 will allow for the assessment of ivacaftor effect over a 24-week period.

Methods

Study participants

Patients with CF, age 6 years and older, who have a non-*G551D-CFTR* gating mutation were enrolled provided that they met all the inclusion criteria and none of the exclusion criteria as follows (only key criteria shown):

Key inclusion criteria

1. Male or female patients aged 6 years and older with confirmed diagnosis of CF, defined as:

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

AND

- chronic sinopulmonary disease

2. Must have had at least 1 allele of the following *CFTR* gating mutations: *G178R, S549N, S549R, G551S, G970R, G1244E, S1251N, S1255P, G1349D.*
3. FEV1 ≥40% predicted normal for age, sex, and height (Hankinson or Wang equations at screening. 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.

Key exclusion criteria

1. *G551D-CFTR* mutation in at least 1 allele
2. An acute upper or lower respiratory infection, pulmonary exacerbation, or changes in therapy (including antibiotics) for pulmonary disease within 4 weeks before Day 1 (first dose of study drug)
3. Abnormal liver function, at screening, defined as ≥3 × upper limit of normal (ULN), of any 3 or more of the following: serum aspartate transaminase (AST), serum alanine transaminase (ALT), gamma-glutamyl transpeptidase (GGT), serum alkaline phosphatase, and total bilirubin.
4. Abnormal renal function at screening, defined as glomerular filtration rate (GFR) ≤30 mL/min/1.73 m^2 (calculated by the MDRD [Modification of Diet in Renal Disease] Study Equation) for subjects >18 years of age; ≤45 mL/min/1.73 m^2 (calculated by the Counahan-Barratt equation) for subjects age 6 to 17 years (inclusive).
5. History of solid organ or haematological transplantation
6. Colonization with organisms associated with a more rapid decline in pulmonary status (e.g., *Burkholderia cenocepacia*, *Burkholderia dolosa*, and *Mycobacterium abscessus*) at screening.
7. Use of inhaled hypertonic saline treatment. (Subjects who had stopped inhaled hypertonic saline treatment were eligible to participate, but they must have undergone a washout period of 4 weeks before Day 1 [first dose of study drug])
8. Use of any inhibitors or inducers of cytochrome P450 (CYP) 3A, including consumption of certain herbal medications (e.g., St. John's Wort) and grapefruit/grapefruit juice. Subjects must have stopped consuming these items from 14 days before Day 1 (first dose of study drug).
9. Evidence of cataract or lens opacity at screening.

Treatments

In Part 1, subjects were randomized to receive 150 mg of ivacaftor or placebo every 12 hours (q12h) during Treatment Periods 1 and 2 (8 weeks each). In Part 2, which was ongoing at the time of submission, all subjects were to receive 150 mg of ivacaftor every 12 hours for additional 16 weeks.

Study drugs were to be taken with fat-containing food such as a standard "CF" high-fat, high-calorie meal or snack.

Objectives

Primary objective of the study was to evaluate the efficacy of ivacaftor in subjects with CF who have a non-*G551D-CFTR* gating mutation.

Secondary Objectives were:

- To evaluate the safety of ivacaftor in subjects with CF who have a non-*G551D-CFTR* gating mutation
- To evaluate the durability of efficacy of ivacaftor in subjects with CF who have a non-*G551D-CFTR* gating mutation.

Tertiary Objectives were to characterize the plasma PK of ivacaftor and metabolites, hydroxymethyl-ivacaftor (M1) and ivacaftor carboxylate (M6) at steady state in subjects with CF who have a non-*G551D-CFTR* gating mutation.

Outcomes/endpoints

Endpoints in Part 1 of the study

Primary Endpoint was absolute change from baseline in percent predicted forced expiratory volume in 1 second (PPFEV1) through Week 8 in each period of Part 1.

Secondary Endpoints were:

- Change from baseline in BMI at 8 weeks of treatment
- Change from baseline in sweat chloride through 8 weeks of treatment
- Change from baseline in the respiratory domain of the Cystic Fibrosis Questionnaire-Revised (CFQ-R) through 8 weeks of treatment
- Safety, as determined by adverse events, clinical laboratory values (serum chemistry and haematology, and coagulation), ophthalmologic examinations, electrocardiograms (ECGs), and vital signs.

Tertiary Endpoints were:

- PK parameter estimates of ivacaftor and metabolites, M1 and M6, derived from plasma concentration-time data
- Pulmonary exacerbations
- Change from baseline in non-respiratory domains of the CFQ-R through 8 weeks of treatment
- Change from baseline in weight
- Change from baseline in height
- CF-related complications (pancreatitis or DIOS)
- Change from baseline in inflammatory mediators
- Change from baseline in qualitative microbiological cultures.

Endpoints in Part 2 of the study

Primary Endpoint was absolute change from baseline in percent predicted forced expiratory volume in 1 second (PPFEV1) through 24 weeks of treatment.

Secondary Endpoints were:

- Change from baseline in BMI at 24 weeks of treatment
- Change from baseline in sweat chloride through 24 weeks of treatment
- Change from baseline in the respiratory domain of the CFQ-R through 24 weeks of treatment
- Safety, as determined by adverse events, clinical laboratory values (serum chemistry, haematology, and coagulation), ophthalmologic examinations, ECGs, and vital signs.

Tertiary Endpoints were:

- PK parameter estimates of ivacaftor and metabolites, M1 and M6, derived from plasma concentration-time data
- Pulmonary exacerbations
- Change from baseline in non-respiratory domains of the CFQ-R through 24 weeks of treatment
- Change from baseline in weight
- Change from baseline in height
- CF-related complications (pancreatitis or DIOS)
- Change from baseline in inflammatory mediators
- Change from baseline in qualitative microbiological cultures.

Sweat chloride values were analysed at a central laboratory. It has been clarified that collection of sweat followed a standardized procedure and that study 111 site personnel were trained and qualified on this procedure by approved trainers. Collection of sweat samples were performed using a collection device, the Macroduct Model 3700 Sweat Collection System. The analytic measurement range for the sweat chloride assay was 10 to 160 mM/L. If samples fell outside that range, the result was reported as <10 mM/L or >160 mM/L, as appropriate.

Sample size

A minimum of 20 subjects up to a maximum of approximately 40 subjects were planned. A sample size of 20 subjects was expected to provide sufficient power for the mean change from baseline in PPFEV1. Table below presents the estimated study power for detecting different treatment effect sizes between ivacaftor and placebo in the change in PPFEV1, assuming 20 (minimum possible enrolment) or 40 (maximum possible enrolment) subjects. An SD of 8% and within-subject SD of 5% were assumed in the calculation. Enrolment of approximately 40 subjects allowed for a larger number of subjects with each of the non-*G551D-CFTR* gating mutations to be included.

Table 5. Power Estimates Under Possible Scenarios of Treatment Effect

Absolute Change in Percent Predicted FEV_1	Power of N = 20	Power of N = 40
3.0%	0.437	0.744
3.5%	0.556	0.863
4.0%	0.670	0.937
4.5%	0.770	0.975
5.0%	0.851	0.992
5.5%	0.910	0.998
6.0%	0.949	>.999
6.5%	0.974	>.999
7.0%	0.987	>.999
7.5%	0.994	>.999
8.0%	0.998	>.999
8.5%	>.999	>.999

Notes: Treatment effect = absolute change from baseline in percent predicted FEV1 for ivacaftor minus absolute change from baseline in percent predicted FEV1 for placebo. Power estimates were based on paired t-test with $\alpha = 0.05$. An SD of 8% and within-subject SD of 5% were assumed in the calculation.

Randomisation

Subjects were randomized 1:1 to receive 1 of 2 Treatment Sequences during the Treatment Periods:

- Treatment Sequence 1: ivacaftor in Treatment Period 1 → washout period → ivacaftor-matched placebo in Treatment Period 2
- Treatment Sequence 2: ivacaftor-matched placebo in Treatment Period 1 → washout period → ivacaftor in Treatment Period 2.

In addition, patients were stratified for age (6 to 11 years, 12 to 17 years, and ≥18 years) and FEV1 severity (<70%, ≥70% to ≤90%, and >90%).

The randomization codes were generated by Vertex or a designated vendor. To protect the study blind and maintain the scientific integrity of the study data, 3 biostatisticians were involved in the randomization process: a study biostatistician who was blinded to the actual treatment code, an unblinded biostatistician not associated with the study, and an unblinded quality check (QC) biostatistician. The study biostatistician created the randomization specification and dummy randomization codes, which were reviewed and approved by the unblinded biostatistician. After approval of the dummy codes, the unblinded biostatistician generated the final randomization list. The QC unblinded biostatistician reviewed and approved the final randomization list.

Blinding (masking)

This was a double-blind study. The subjects and all site personnel, including the investigator and the study monitor, were to remain blinded to treatment assignments until database lock. The MAH's study team remained blinded to treatment assignments until all subjects completed Part 1 of the study, and with the exception of the following:

- Any site personnel for whom this information was important to ensure the safety of the subject, in the event of a life-threatening medical emergency
- Any site personnel for whom this information was important to ensure the safety of the subject and their foetus in the event of a pregnancy

- Vertex Global Patient Safety (GPS) and Regulatory Affairs personnel, to satisfy SAE processing regulations
- Unblinded biostatisticians preparing the final (production) randomization list who were not part of the study team
- IVRS/IWRS vendor
- A single member of Drug Metabolism and Pharmacokinetics (DMPK) Sample Management
- Vertex Clinical Supply Chain
- DMC
- Vendor preparing the unblinded interim analysis and analyses for the DMC.

Sweat chloride laboratory personnel, and the designees (who were not members of the study team) reviewing the sweat chloride data on an ongoing basis, were unblinded to the sweat chloride results but remained blinded to treatment assignment.

A single member of Vertex DMPK Sample Management, independent from the study team, was unblinded, having access to the IVRS/IWRS, for the purpose of assembling samples intended for bioanalysis. PK samples collected from placebo-dosed subjects were not analysed in this study. All other MAH's DMPK laboratory personnel and MAH's Quality Compliance Management personnel were blinded to the treatment assignment. A clinical pharmacologist not involved in the conduct of the study may have reviewed the bioanalytical results on an ongoing basis but remained blinded to the subjects' identities (i.e., unique subject number and treatment assignment) in the clinical database.

Subjects and their parent/caregiver should not have been informed of their study-related spirometry results during the Treatment Periods and the Open-label Period.

Statistical methods

The primary analysis of study 111 was based on data from Part 1.

The following analysis sets were defined:

- The Full Analysis Set (FAS) – all randomized subjects who received at least 1 dose of study medicine. All analyses of background data and efficacy data were based on the FAS.
- The Per Protocol Set (PPS) – all FAS subjects without major protocol violations (i.e., subjects who had not been determined to have violated protocol requirements). Major protocol violations were defined as violations that may have had a substantial impact on efficacy assessment. The criteria used for excluding subjects from the PPS were determined before the database lock and were documented. The PPS analyses were only performed for primary and selected secondary endpoints to provide supportive evidence for efficacy.
- The Complete Case Set (CCS) – all subjects in the FAS who completed both Treatment Periods in Part 1. The analyses of primary and selected secondary endpoints were based on the CCS, in addition to the FAS.
- The Safety Set – all subjects who received at least 1 dose of study medicine (i.e., ivacaftor or placebo).

The primary analysis for the primary efficacy variable (absolute change in PPFEV1) was based on a mixed effects models for repeated measures (MMRM). The model included the absolute change from

the baseline in each Treatment Period as the dependent variable, with sequence, treatment, period, and visit within period as fixed effects, study baseline PPFEV1 and age as covariates, and subject nested within sequence as the random effect. In the model, visit was treated as a class variable. Compound symmetry covariance matrix was assumed for the repeated measurements on the same subject within each period. This model assumed equal variances of the repeated measures and equal covariances between each pairs of measures within each subject. Denominator degrees of freedom for the F-test for fixed effects were estimated using the Kenward-Roger approximation. With a mixed-effects model as the primary analysis model based on maximum likelihood estimation and assuming that data are missing at random conditional on fixed and random effects, no imputation of missing data were done.

The main effect of treatment obtained from the model was interpreted as the average treatment effect (effect of ivacaftor) across all post-baseline visits within the treatment period. The estimated mean treatment effect, a 95% confidence interval (CI), and a 2-sided P value were provided.

Sensitivity analyses including first-order autoregressive covariance in an otherwise identical model to the primary analysis, Wilcoxon signed ranksum, and analyses of covariance (ANCOVAs) were implemented for primary variable.

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

- LOCF-based MMRM analysis
- Worst-case based MMRM analysis
- Dropout reason-based imputation MMRM analysis:

The primary analysis was repeated based on the PPS and CCS. No sensitivity analysis was performed based on the PPS and CCS.

A carryover effect was not expected since the Washout Period occurred between Treatment Period 1 and Treatment Period 2. However, to provide a back-up analysis in the case when there was a strong carryover effect, analysis based on MMRM using data from Treatment Period 1 only was conducted. The model included absolute change from baseline in PPFEV1 as the dependent variable, treatment (ivacaftor versus placebo) and visit (Weeks 2, 4, and 8) as fixed effects, subject as a random effect, with adjustment for the continuous baseline value of age and PPFEV1. In the model, visit was treated as a class variable and a compound symmetry covariance matrix was assumed to model the within-subject variability. This analysis was based on the FAS.

In addition, change from baseline in PPFEV1 at Week 8 was categorized by the following rules: ≥5% or <5%, ≥7.5% or <7.5%, ≥10% or <10% and summarized as categorical variables.

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

The following subgroups were used:

- Age Group at Baseline (6 to 11 [inclusive], 12 to 17 [inclusive], and ≥18 years)

- PPFEV1 Severity at Baseline (<70%, 70% to 90% [inclusive], and >90% of the predicted value)
- Geographic Region (North America and Europe)
- Sex (Female and Male)
- *Pseudomonas aeruginosa* (*P aeruginosa*) infection status at Baseline (Yes and No)

All subgroup summaries were provided only for the FAS.

For Part 1, the safety analysis was based on the set of data associated with the period from signing of informed consent through the end of the Treatment Period 2. Summaries were by treatment received. The overall safety profile of ivacaftor versus placebo was assessed in terms of incidence of treatment-emergent adverse event (TEAEs), clinical laboratory values (haematology, serum chemistry, urinalysis, and coagulation studies), ECGs, vital signs. Safety variables were analysed based on the Safety Set. Only descriptive analysis of safety was performed (i.e., no formal between-treatment statistical testing was performed).

To control the overall type I error rate at 0.05, the primary endpoint and key secondary endpoints were tested in sequence as follows:

- Test 1: The primary efficacy endpoint was tested at significance level $\alpha = 0.05$.
- Test 2: If a statistically significant result was obtained from Test 1, the change from baseline in BMI through Week 8, and change from baseline in sweat chloride through Week 8 were tested using Hochberg's step-up procedure at significance level $\alpha = 0.05$.
- Test 3: If a statistically significant result was obtained from Test 2, change from baseline in CFQ-R respiratory domain score through Week 8 was tested.

Results

Participant flow

Forty-two (42) patients were screened and 39 randomised. See the flow of patients in table below.

Table 6. Participant flow in study 111

	Sequence 1 (I-P)	Sequence 2 (P-I)	Total
Randomisation	**20**	**19**	**39**
Period 1	20 (I)	19 (P)	39
Washout	-2 (P)	-1 (I)	-3 (2P&1I)
Period 2	18 (P)	18 (I)	36
Complete Case Analysis	**18**	**18**	**36**
Treatments per population			
FAS			
I	20 (P1)	18 (P2)	38
P	18 (P2)	19 (P1)	37
Complete Case Analysis			
I	18 (P1)	18 (P2)	36
P	18 (P2)	18 (P1)	36

I: Ivacaftor; P: Placebo; FAS: Full Analysis Set; P1: Period 1; P2: Period 2

Three subjects discontinued the study before Treatment Period 2; their genotypes were *G551S/DELF508, G178R/DELF508* and *G970R/2789+5G>A*. Therefore, a total of 38 subjects who received ivacaftor treatment and 37 subjects who received placebo were evaluated for efficacy.

One patient per treatment sequence discontinued the intervention for "Other reasons", e.g. due to the need to extend the Washout Period ("washout extended due to antibiotic usage" and "per sponsor, did not qualify to continue"). An additional patient was lost to follow-up.

Recruitment

Study Part 1 was initiated on 11 July 2012 (date first eligible subject signed informed consent form) and study Part 1completion was on 31 May 2013 (date last subject completed the last visit in Part 1).

Subjects were randomized at 8 study sites in the US, 3 in France and one in Belgium. The number of patients randomised was 22, 8 and 9 respectively.

Conduct of the study

The study protocol was amended 4 times by the time of the data cut for the Part 1 clinical study report. The final protocol (Version 5.0) is dated 05 December 2012.

Protocol Amendment 1

Version 2.0 of Protocol VX12-770-111, dated 17 February 2012, was the first amendment of the protocol (replacing Version 1.0, dated 07 February 2012) and was finalized before study initiation on 11 February 2012.

The main change implemented with this amendment related to the inclusion criterion for PPFEV1 that was changed from "40% to 90% inclusive for subjects age 12 years or older" and "40% to 105% inclusive for subjects age 6 to 11 years" to "FEV1 ≥40% predicted normal for age, sex, and height (Hankinson or Wang equations) at screening." This was changed because the original PPFEV1 range was included in error. This was also clarified in the randomization strata.

Protocol Amendment 2

Version 3.0 of Protocol VX12-770-111, dated 21 March 2012, was the second amendment of the protocol. The principal changes included the following but are not limited to them:

- Due to recent preliminary finding of a dose-related increase in cataracts in juvenile rats identified in a nonclinical study conducted to support clinical studies in patients with cystic fibrosis younger than 2 years of age, an additional screening assessment of a comprehensive ophthalmologic examination was added for all subjects.
- Clarification about cycling antibiotic therapy was added.
- The blinding process for the bioanalysis samples was updated.
- Clarification about collection of blood samples for the optional pharmacogenomic analysis was provided.

Protocol Amendment 3

Version 4.0 of Protocol VX12-770-111, dated 07 September 2012, was the third amendment of the protocol. The principal changes included the following but are not limited to them:

- Subjects who complete the Open-label Period and the Follow-up Visit and who choose not to enrol in the open-label treatment arm of Study VX12-770-112 (Study 112) were to be offered enrolment in the observational arm of Study 112.

- It was clarified that subjects who prematurely discontinue treatment and have received study drug for more than 4 weeks will be offered enrolment in the observational arm of Study 112.
- Ophthalmologic examinations were added as a safety endpoint for safety monitoring.
- Based on feedback from the Cystic Fibrosis Foundation Therapeutics Development Network and in order to reduce the number of assessments, the sweat chloride test at screening was made optional for subjects who have sweat chloride values documented in their medical records or if it is not needed to establish eligibility.
- The collection of qualitative microbiology culture samples at the Follow-up Visit was changed for subjects who prematurely discontinue treatment; if a sample was collected at the Early Termination Visit, the sample at the Follow-up Visit did not need to be collected.
- An assessment of a comprehensive ophthalmologic examination was added at the Week 36 Visit for subjects who are aged 6 to 11 years (inclusive) at the time of the Day 1 Visit.
- Unblinding of treatment assignments was changed specifying that the MAH's study team will remain blinded until all subjects have completed Part 1 of the study.
- Handling of sweat samples by a central laboratory was clarified to align with current central laboratory practices.

Protocol Amendment 4

Version 5.0 of Protocol VX12-770-111, dated 05 December 2012, was the fourth amendment of the protocol. The principal change implemented with this amendment was related to the following:

- It was corrected that the collection of sweat chloride at screening is required for subjects only if the value is not available in the subject's medical records and the value is needed for the diagnosis of CF to fulfill inclusion criterion 1. Collection of sweat chloride at screening is not required, but is optional, for those subjects who have sweat chloride values documented in their medical records and it is not needed to establish eligibility.

Changes to Planned Analyses

The Statistical Analysis Plan (SAP) was finalized before database lock and unblinding for this study and provides the final planned statistical analyses for Part 1. Difference from the last approved clinical study protocol (Version 5.0) included the following:

- Change covariance matrix from "unstructured covariance matrix" to "compound symmetry covariance matrix" for all MMRM models. This modification was made to ensure model convergence.

Difference from the last approved statistical analysis plan (dated 13 June 2013) included the following:

- Removed the baseline of analysed variables from model covariates for all LMM models. This modification was made to align the statistical methodology with desired clinical interpretability.
- Removed 'period' from the negative binomial regression model for count variables. This modification was made to ensure model convergence.
- Before Part 1 data lock, analysis of the responder category <5 mmol/L or ≥5 mmol/L to evaluate a lower range of sweat chloride response was added, and the responder category <15 mmol/L or ≥15 mmol/L was removed since any sweat chloride value that fell within this range would have

been reflected in the pre-specified responder categories <10 mmol/L or ≥10 mmol/L and <20 mmol/L or ≥20 mmol/L.

Baseline data

The majority of subjects in both Treatment Sequences were White (75.0% in Treatment Sequence 1 and 73.7% in Treatment Sequence 2) and of non-Hispanic or Latino ethnicity (75.0% in Treatment Sequence 1 and 68.4% in Treatment Sequence 2).

The mean age was 23.8 years (range: 6 to 57) in Treatment Sequence 1 and 21.7 years (range: 6 to 47) in Treatment Sequence 2; there were 19 subjects overall in the <18 years subgroup and 20 subjects overall in the ≥18 years subgroup. Mean baseline sweat chloride values (overall 97.54 mmol/L) and mean PPFEV1 at baseline (overall 78.3806%) were similar between the 2 Treatment Sequences.

Baseline data for the FAS are provided in the table below.

Table 7. Demographic and Baseline Characteristics, Part 1, Full Analysis Set

Variable	Treatment Sequence 1[a] N = 20	Treatment Sequence 2[b] N = 19	Overall N = 39
Sex, n (%)			
Male	13 (65.0)	9 (47.4)	22 (56.4)
Female	7 (35.0)	10 (52.6)	17 (43.6)
Race, n (%)			
White	15 (75.0)	14 (73.7)	29 (74.4)
Black or African American	1 (5.0)	1 (5.3)	2 (5.1)
Asian	0	0	0
American Indian or Alaska Native	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Other	0	0	0
Not Collected Per Local Regulations	4 (20.0)	4 (21.1)	8 (20.5)
Ethnicity, n (%)			
Hispanic or Latino	1 (5.0)	2 (10.5)	3 (7.7)
Not Hispanic or Latino	15 (75.0)	13 (68.4)	28 (71.8)
Not Collected Per Local Regulations	4 (20.0)	4 (21.1)	8 (20.5)

Variable	Treatment Sequence 1[a] N = 20	Treatment Sequence 2[b] N = 19	Overall N = 39
Geographic Region, n (%)			
North America	11 (55.0)	11 (57.9)	22 (56.4)
Europe	9 (45.0)	8 (42.1)	17 (43.6)
Genotype, n (%)			
S1251N/DELF508	4 (20.0)	4 (21.1)	8 (20.5)
G1244E /DELF508	0	3 (15.8)	3 (7.7)
G970R/DELF508	2 (10.0)	1 (5.3)	3 (7.7)
S549N/DELF508	1 (5.0)	2 (10.5)	3 (7.7)
G178R/DELF508	1 (5.0)	1 (5.3)	2 (5.1)
G551S/DELF508	1 (5.0)	1 (5.3)	2 (5.1)
S549R/DELF508	1 (5.0)	1 (5.3)	2 (5.1)
G178R/L1077P	1 (5.0)	1 (5.3)	2 (5.1)
S549N/N1303K	1 (5.0)	1 (5.3)	2 (5.1)
G1349D /2183 AA>G	1 (5.0)	0	1 (2.6)
G1349D/DELF508	0	1 (5.3)	1 (2.6)
G1244E/G1244E	0	1 (5.3)	1 (2.6)
G1244E/Y913X	1 (5.0)	0	1 (2.6)
G178R/2896INSAG	0	1 (5.3)	1 (2.6)
G178R/621+1G>T	1 (5.0)	0	1 (2.6)
S549N/G542X	1 (5.0)	0	1 (2.6)
G970R/2789+5G>A	1 (5.0)	0	1 (2.6)
S1255P/Q1313X	2 (10.0)	0	2 (5.1)
S549R/R1158X	0	1 (5.3)	1 (2.6)
S549R/SER945LEU	1 (5.0)	0	1 (2.6)
Genotype by Gating Mutation, n (%)			
S1251N	4 (20.0)	4 (21.1)	8 (20.5)
G178R	3 (15.0)	3 (15.8)	6 (15.4)
S549N	3 (15.0)	3 (15.8)	6 (15.4)
G1244E	1 (5.0)	4 (21.1)	5 (12.8)
S549R	2 (10.0)	2 (10.5)	4 (10.3)
G970R	3 (15.0)	1 (5.3)	4 (10.3)
G551S	1 (5.0)	1 (5.3)	2 (5.1)
S1255P	2 (10.0)	0	2 (5.1)
G1349D	1 (5.0)	1 (5.3)	2 (5.1)
Age (years)			
N	20	19	39
Mean	23.8	21.7	22.8
SD	13.25	12.92	12.96

Variable	Treatment Sequence 1[a] N = 20	Treatment Sequence 2[b] N = 19	Overall N = 39
Median	24.0	15.0	23.0
Minimum	6	6	6
Maximum	57	47	57
Age Group (years), n (%)			
6 to 11	3 (15.0)	5 (26.3)	8 (20.5)
12 to 17	6 (30.0)	5 (26.3)	11 (28.2)
≥18	11 (55.0)	9 (47.4)	20 (51.3)
Percent Predicted FEV_1			
n	20	19	39
Mean	77.7414	79.0535	78.3806
SD	21.57322	20.89595	20.97554
Median	80.3835	85.5985	84.4533
Minimum	42.900	42.968	42.900
Maximum	118.715	104.070	118.715
Percent Predicted FEV_1, n (%)			
<70%	7 (35.0)	6 (31.6)	13 (33.3)
≥70% to ≤90%	6 (30.0)	6 (31.6)	12 (30.8)
>90%	7 (35.0)	7 (36.8)	14 (35.9)
Height (cm)			
n	20	19	39
Mean	161.30	153.84	157.67
SD	19.644	20.908	20.354
Median	168.0	158.0	166.0
Minimum	106.0	114.0	106.0
Maximum	177.0	181.0	181.0
Weight (kg)			
n	20	19	39
Mean	59.80	55.01	57.46
SD	18.663	25.762	22.235
Median	62.0	54.0	59.0
Minimum	20.0	22.0	20.0
Maximum	88.0	126.0	126.0

Variable	Treatment Sequence 1[a] N = 20	Treatment Sequence 2[b] N = 19	Overall N = 39
BMI (kg/m²)			
n	20	19	39
Mean	22.26	21.99	22.13
SD	4.122	5.879	4.989
Median	21.70	20.34	21.34
Minimum	15.5	14.5	14.5
Maximum	31.2	38.5	38.5
Height-for-age z-score (points)			
n	9	10	19
Mean	-0.0956	-0.7988	-0.4657
SD	1.15808	0.84016	1.03882
Median	0.1180	-0.8845	-0.2800
Minimum	-2.488	-2.555	-2.555
Maximum	1.281	0.378	1.281
Weight-for-age z-score (points)			
n	9	10	19
Mean	0.3788	-0.1818	0.0837
SD	1.18287	1.02501	1.10900
Median	0.5280	-0.3740	0.2390
Minimum	-1.966	-1.457	-1.966
Maximum	2.286	1.480	2.286
BMI-for-age z-score (points)			
n	9	10	19
Mean	0.5031	0.2294	0.3591
SD	1.15906	1.09093	1.10084
Median	0.3690	0.1650	0.2590
Minimum	-1.593	-1.462	-1.593
Maximum	2.264	1.647	2.264
Sweat Chloride (mmol/L)			
n	20	19	39
Mean	94.58	100.66	97.54
SD	22.738	12.755	18.576
Median	101.75	104.50	102.00
Minimum	12.0[c]	75.5	12.0
Maximum	118.0	121.5	121.5

Variable	Treatment Sequence 1[a] N = 20	Treatment Sequence 2[b] N = 19	Overall N = 39

Source: Table 14.1.2.1

Notes: All results displayed are baseline results. Baseline was defined as the most recent measurement before intake of the first dose of study drug. Weight-for-age z-score and BMI-for-age z-score were calculated by using NCHS growth charts. Z-score was defined as missing if the subject's age was over 240 months old at the time of assessment.

[a] Treatment Sequence 1: ivacaftor in Treatment Period 1→Washout→placebo in Treatment Period 2.

[b] Treatment Sequence 2: placebo in Treatment Period 1→Washout→ivacaftor in Treatment Period 2.

[c] The minimum sweat chloride value in Treatment Sequence 1 was attributed to Subject [redacted] (see Listing 16.2.6.2). The subject's sweat chloride values were queried during review and confirmed by ICON Incorporated.

Medical history

The table below summarizes medical history consistent with a diagnosis of CF with an incidence of at least 15% in any treatment sequence group.

Table 8. Medical History Consistent with a Diagnosis of CF with an Incidence of at Least 15% of Subjects in Any Treatment Sequence, Part 1, Full Analysis Set

Condition	Treatment Sequence 1[a] N = 20 n (%)	Treatment Sequence 2[b] N = 19 n (%)	Overall N = 39 n (%)
Cystic Fibrosis Lung Disease	19 (95.0)	19 (100.0)	38 (97.4)
Pancreatic Insufficiency	14 (70.0)	17 (89.5)	31 (79.5)
Chronic Sinusitis	8 (40.0)	9 (47.4)	17 (43.6)
Asthma	6 (30.0)	9 (47.4)	15 (38.5)
Clubbing	8 (40.0)	6 (31.6)	14 (35.9)
Gastroesophageal Reflux Disease (GERD)	6 (30.0)	6 (31.6)	12 (30.8)
Nasal Polyps	4 (20.0)	8 (42.1)	12 (30.8)
Hepatic Enzyme Increased	6 (30.0)	4 (21.1)	10 (25.6)
Nasal Polypectomy	4 (20.0)	5 (26.3)	9 (23.1)
Constipation	5 (25.0)	2 (10.5)	7 (17.9)
Bacterial Disease Carrier	4 (20.0)	2 (10.5)	6 (15.4)
Depression	4 (20.0)	2 (10.5)	6 (15.4)
Vitamin D Deficiency	3 (15.0)	3 (15.8)	6 (15.4)
Pneumonia	1 (5.0)	3 (15.8)	4 (10.3)
Haemoptysis	3 (15.0)	1 (5.3)	4 (10.3)
Bronchopulmonary aspergillosis allergic	0	3 (15.8)	3 (7.7)

Condition	Treatment Sequence 1[a] N = 20 n (%)	Treatment Sequence 2[b] N = 19 n (%)	Overall N = 39 n (%)
Pancreatitis	0	3 (15.8)	3 (7.7)
Rectal Prolapse	0	3 (15.8)	3 (7.7)

Source: Table 14.1.4.1
Note: Percentages were calculated relative to the number of subjects in the full analysis set.
[a] Treatment Sequence 1: ivacaftor in Treatment Period 1→Washout→placebo in Treatment Period 2.
[b] Treatment Sequence 2: placebo in Treatment Period 1→Washout→ivacaftor in Treatment Period 2.

Concomitant medication

The table below summarizes concomitant medications received by at least 15% of subjects while receiving placebo or ivacaftor. The most commonly reported concomitant medications were indicated for management of CF complications. The use of concomitant medications received by at least 15% of subjects while receiving placebo or ivacaftor was similar with the exception of levofloxacin (16.2% of subjects while receiving placebo and 2.6% of subjects while receiving ivacaftor).

Table 9. Concomitant Medications Received by At Least 15% of Subjects in Any Treatment Sequence, Part 1, Full Analysis Set

WHO Drug Dictionary Classification	Placebo N = 37 n (%)	Ivacaftor N = 38 n (%)
Subjects with Any Concomitant Medication	**37 (100)**	**38 (100)**
Dornase Alfa	30 (81.1)	30 (78.9)
Pancreatin	24 (64.9)	24 (63.2)
Azithromycin	19 (51.4)	20 (52.6)
Salbutamol	16 (43.2)	17 (44.7)
Seretide	13 (35.1)	12 (31.6)
Vitamins NOS w/Zinc	12 (32.4)	12 (31.6)
Colecalciferol	11 (29.7)	11 (28.9)
Sodium Chloride	10 (27.0)	9 (23.7)
Bactrim	10 (27.0)	10 (26.3)
Ibuprofen	9 (24.3)	11 (28.9)
Macrogol	9 (24.3)	10 (26.3)
Tocopheryl Acetate	9 (24.3)	9 (23.7)
Tobramycin	9 (24.3)	8 (21.1)
Colistimethate Sodium	9 (24.3)	7 (18.4)
Paracetamol	8 (21.6)	11 (28.9)
Fluticasone Propionate	8 (21.6)	8 (21.1)
Levosalbutamol Hydrochloride	8 (21.6)	7 (18.4)
Omeprazole	7 (18.9)	7 (18.4)
Vitamin D NOS	7 (18.9)	6 (15.8)
Amoxi-Clavulanico	6 (16.2)	7 (18.4)
Multivitamins With Minerals/90003801/	6 (16.2)	6 (15.8)
Influenza Vaccine	6 (16.2)	5 (13.2)
Levofloxacin	6 (16.2)	1 (2.6)

Source: Table 14.1.5.2
NOS: not otherwise specified.
Notes: A subject with multiple concomitant medications within a PT was counted only once within a PT.
Concomitant medications were coded from the WHO Drug Dictionary Enhanced, March 2012.

Numbers analysed

Table below shows the number of patients analysed per study population.

Table 1. Subject Disposition, Part 1

Disposition Category	Treatment Sequence 1[a] n (%)	Treatment Sequence 2[b] n (%)	Overall n (%)
All Screened Subjects			42
All Randomized Subjects	20	19	39
Safety Set	20	19	39
Full Analysis Set (FAS)	20	19	39
Per Protocol Set (PPS)	11	15	26
Complete Case Set (CCS)	18	18	36
Never Dosed	0	0	3

A total of 39 subjects were included in the Full Analysis Set (FAS) and the Safety Set: 20 subjects in Treatment Sequence 1 (ivacaftor in Treatment Period 1 → Washout → placebo in Treatment Period 2) and 19 subjects in Treatment Sequence 2 (placebo in Treatment Period 1 → Washout → ivacaftor in Treatment Period 2). Three subjects discontinued the study before Treatment Period 2 (2 subjects in Treatment Sequence 1 and 1 subject in Treatment Sequence 2); therefore, a total of 38 subjects who received ivacaftor treatment and 37 subjects who received placebo were evaluated for efficacy.

Seven subjects in Treatment Sequence 1 and 3 subjects in Treatment Sequence 2 were excluded from the PPS due to major protocol violations. Of these, 8 subjects were excluded from the PPS for prohibited medications (i.e., ciprofloxacin, erythromycin ethylsuccinate, fluconazole, hypertonic saline, pentobarbital, prednisolone, Prozac); 1 subject was excluded because of the timing of his inhaled antibiotic use (TOBI) relative to study drug dosing on Day 1 (i.e., the subject was randomized at the end of an "on" cycle instead of an "off" cycle; and 1 subject (in Treatment Sequence 2) was excluded for study drug compliance <80% in Treatment Period 1. Three additional subjects were excluded from the PPS because they discontinued before Treatment Period 2 (2 subjects in Treatment Sequence 1; 1 subject in Treatment Sequence 2). These three subjects were also excluded from the CCS because they discontinued before Treatment Period 2.

A total of 18 subjects in each Treatment Sequence completed the full assigned duration of dosing.

Outcomes and estimation

Change from baseline in PPFEV1

Primary efficacy variable was absolute change from baseline in PPFEV1 through Week 8 in each Treatment Period of Part 1. The table below shows the results of the absolute change from baseline in PPFEV1.

Table 10. Absolute Change From Baseline in PPFEV1 by MMRM, Part 1, Full Analysis Set

Visit or Time Period	Treatment Group	Sample Statistics		Absolute Change From Baseline[a]		Treatment Effect (Ivacaftor vs Placebo)	
		n	Mean	n	LS Mean	Difference (95% CI)	*P* value
Baseline	Placebo	37	79.3361	--	--	--	--
	Ivacaftor	38	76.3659	--	--		
Overall Post-baseline	Placebo	37	76.0380	37	-3.1912	10.6780 (7.2559, 14.1000)	<0.0001
	Ivacaftor	38	83.7058	38	7.4868		

Source: Table 14.2.1.2.1

Note: Sample statistics are unadjusted results.

[a] Estimates were obtained from MMRM, with absolute change from baseline as the dependent variable; with treatment, sequence, period, and visit within period (Week 2, Week 4, and Week 8) as fixed effects; with subject nested within sequence as a random effect; and with adjustment for the continuous baseline values of age and percent predicted FEV_1, using a compound symmetry covariance matrix.

The mean absolute change from baseline in PPFEV1 through Week 8 by MMRM was greater during ivacaftor treatment (7.4868%) than during placebo treatment (-3.1912%). The estimated treatment difference (95% CI) for ivacaftor versus placebo was 10.6780% (7.2559, 14.1000). To assess potential carryover effects, treatment sequence and treatment period were included in the MMRM analysis of the primary efficacy endpoint. No significant effects of treatment sequence or treatment period were observed for the primary efficacy endpoint, suggesting no carryover effect.

The consistency of treatment effect over study visits for the absolute change from baseline in PPFEV1 by MMRM is presented in the table below. Statistically significant treatment differences (P <0.0001) were observed by Week 2 (first post-baseline time point assessed; 8.3142% [95% CI: 4.5109, 12.1175]) and were sustained through Week 8 (13.7554% [95% CI: 9.9414, 17.5694].

Table 11. Absolute Change From Baseline in PPFEV1 by MMRM, Consistency of Treatment Effect Over Visits, Part 1, Full Analysis Set

Visit or Time Period	Treatment Group	Sample Statistics		Absolute Change From Baseline[a]		Treatment Effect (Ivacaftor vs Placebo)	
		n	Mean	n	LS Mean	Difference (95% CI)	*P* value[b]
Baseline	Placebo	37	79.3361	--	--	--	--
	Ivacaftor	38	76.3659	--	--		
Week 2	Placebo	37	77.8637	37	-1.4209	8.3142 (4.5109, 12.1175)	<0.0001
	Ivacaftor	38	83.5950	38	6.8933		
Week 4	Placebo	37	76.7878	37	-2.2903	9.9908 (6.1874, 13.7941)	<0.0001
	Ivacaftor	38	83.9181	38	7.7005		
Week 8	Placebo	37	73.4624	37	-5.8472	13.7554 (9.9414, 17.5694)	<0.0001
	Ivacaftor	37	83.6015	37	7.9082		

Source: Table 14.2.1.2.2

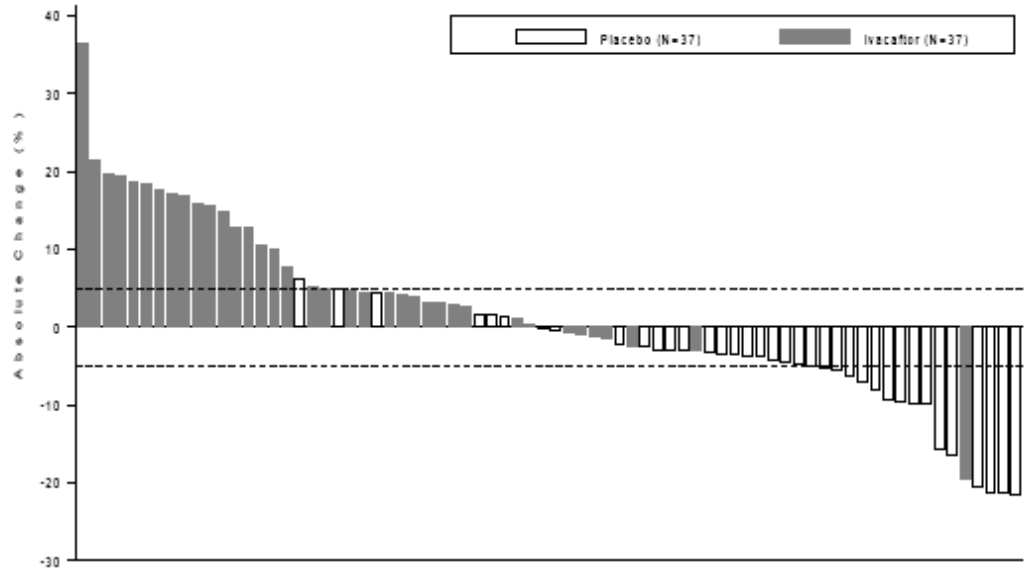
Note: Sample statistics are unadjusted results.

[a] Estimates were obtained from MMRM, with absolute change from period baseline as the dependent variable; with treatment, sequence, period, visit within period (Week 2, Week 4, and Week 8), and treatment by visit interaction as fixed effects; with subject nested within sequence as a random effect; and with adjustment for the continuous baseline values of age and percent predicted FEV_1, using a compound symmetry covariance matrix.

[b] *P* value for Overall Post-Baseline was from the main treatment effect; *P* values at individual visits were from linear contrasts between the 2 treatments at the given visit.

To evaluate individual subject response to ivacaftor and placebo, a waterfall plot showing the absolute change from baseline in PPFEV1 at Week 8 by treatment is presented in the figure below.

Figure 2. Waterfall Plot of Absolute Change From Baseline in PPFEV1 at Week 8 by Treatment, Part 1, Full Analysis Set



Source: Figure 14.2.6.1.1
Note: The horizontal (dashed) reference line at 5% and -5% refers to the lowest responder criteria level.

The pattern of response suggests a clear distinction in treatment effect between ivacaftor and placebo. One subject had -19.573% decrease from baseline in PPFEV1 at Week 8 of ivacaftor treatment but this was attributed to an adverse event of infective pulmonary exacerbation that was not related to ivacaftor.

The results of sensitivity analyses performed to assess the robustness of the primary analysis are shown in the table below.

Table 12. Absolute Change From Baseline in PPFEV1, Sensitivity Analysis, Part 1, Full Analysis Set

Sensitivity Analysis	Treatment Group	Absolute Change From Baseline		Treatment Effect (Ivacaftor vs Placebo)	
		n	LS Mean	Difference (95% CI)	*P* value
MMRM with First Order Autoregressive Covariance[a]	Placebo	37	-3.2546	10.8600 (7.5966, 14.1234)	<0.0001
	Ivacaftor	38	7.6054		
MMRM with Last Observation Carried Forward[b]	Placebo	37	-3.2027	10.6696 (7.2421, 14.0972)	<0.0001
	Ivacaftor	38	7.4669		
MMRM with Worst Case Imputation[b]	Placebo	37	-3.2027	10.6696 (7.2421, 14.0972)	<0.0001
	Ivacaftor	38	7.4669		
MMRM with Dropout Reason-based Imputation[b]	Placebo	37	-3.2027	10.6696 (7.2421, 14.0972)	<0.0001
	Ivacaftor	38	7.4669		
ANCOVA[c]	Placebo	37	-5.7900	13.8452 (9.8943, 17.7961)	<0.0001
	Ivacaftor	37	8.0551		
Wilcoxon[d]	Placebo	36	-4.2675	--	<0.0001
	Ivacaftor	36	5.0955		

Source: Table 14.2.1.2.3

[a] Estimates were obtained from MMRM, with absolute change from baseline as the dependent variable; with treatment, sequence, period, and visit within period (Week 2, Week 4, and Week 8) as fixed effects; with subject nested within sequence as a random effect, adjusted for the continuous baseline values of age and percent predicted FEV_1, using an AR(1) covariance matrix.

[b] Identical MMRM model described in Footnote a was used, except using compound symmetry covariance matrix. Missing data were imputed with Last Observation Carried Forward, Worst Case Imputation, and Dropout Reason-based methods as indicated. Multiple imputation was applied to remedy loss of variance information.

[c] ANCOVA was based on the absolute change from baseline at Week 8 in each Treatment Period.

[d] Wilcoxon Rank-Sum Test was based on the absolute change from baseline at Week 8, with medians displayed in the LS Mean column.

A supportive analysis based on MMRM using data only from Treatment Period 1 was conducted to explore if any carryover effect between Treatment Period 1 and Treatment Period 2 was evident. Results from the analysis are presented in the table below.

Table 13. Absolute Change From Baseline in PPFEV1 by MMRM, Treatment Period 1, Part 1, Full Analysis Set

Visit or Time Period	Treatment Group	Sample Statistics		Absolute Change From Baseline[a]		Treatment Effect (Ivacaftor vs Placebo)	
		n	Mean	n	LS Mean	Difference (95% CI)	*P* value
Baseline	Placebo	19	79.0533	--	--	--	--
	Ivacaftor	20	77.7414	--	--		
Overall Post-baseline	Placebo	19	76.6564	19	-2.1638	8.2330 (2.5012, 13.9648)	0.0061
	Ivacaftor	20	83.6186	20	6.0692		

Source: Table 14.2.1.2.7

Notes: Sample statistics are unadjusted results. Only data from crossover Treatment Period 1 are used.

[a] Estimates were obtained from MMRM, with absolute change from baseline as the dependent variable, with treatment and visit (Week 2, Week 4, and Week 8) as fixed effects, with subject nested within sequence as a random effect, and with adjustment for the continuous baseline values of age and percent predicted FEV_1, using a compound symmetry covariance matrix.

To provide additional supportive information, a responder analysis was conducted by categorizing the absolute change from baseline in PPFEV1 at Week 8 as ≥5% or <5%, ≥7.5% or <7.5%, ≥10% or <10%. Results are presented in the table below and show that only a single subject on placebo had a ≥5% response compared to almost half the ivacaftor subjects. Over 40% of ivacaftor subjects responded by ≥10% after 8 weeks of treatment.

Table 14. Responder Analysis of Absolute Change at Week 8 in PPFEV1 Part 1, Full Analysis Set

Category	Placebo N = 37 n (%)	Ivacaftor N = 38 n (%)
≥5%	1 (2.7)	18 (47.4)
<5%	36 (97.3)	19 (50.0)
Total	**37 (100.0)**	**37 (97.4)[a]**
≥7.5%	--	17 (44.7)
<7.5%	37 (100.0)	20 (52.6)
Total	**37 (100.0)**	**37 (97.4)[a]**
≥10%	--	16 (42.1)
<10%	37 (100.0)	21 (55.3)
Total	**37 (100.0)**	**37 (97.4)[a]**

Source: Table 14.2.1.1.7

Notes: Period baseline was defined as the most recent non-missing measurement collected prior to initial administration of study drug in each Treatment Period, with additional requirement for the Treatment Period 2 baseline that it needed to be from an assessment after 14 days in the Washout Period. If the Treatment Period 2 baseline was missing, the Treatment Period 1 baseline was used.

[a] Subject [redacted] was randomized to Treatment Sequence 1 but discontinued from the study after completing the Week 4 Visit and subsequently did not complete Treatment Period 1; subject was lost to follow-up (see Listing 16.2.1).

Both the responder analysis of changes in PPFEV1 and the waterfall plot show that there were a number of patients who improved on placebo as well as some who deteriorated on ivacaftor. As a consequence, and upon request of the CHMP, the MAH provided the individual narratives of these patients. The narratives of seven patients were discussed. Two of these patients with genotypes *S1251N/F508del* and *S549N/G542X* had the maximum decreases during ivacaftor treatment, i.e. -19.57 at week 8 and -6.97 at week 4, respectively. While it was stated that patient *S1251N/F508del* experienced a pulmonary exacerbation during ivacaftor treatment, the narrative of the patient with the genotype *S549N/G542X* did not offer any reasonable explanation for the observed decrease in FEV1 at week 4 but the patient experienced a much more pronounced decline in FEV1 during placebo-treatment (-21.55). The remaining patients with genotypes *S549R/F508del*, *G178R/L1077P*, *G1244E/F508del*, *S1255P/Q1313X* and *G970R/F508del* had more limited decreases in lung function that ranged from -3.53 to -0.78.

Change from baseline in BMI

The mean absolute change from baseline in BMI at Week 8 (rate of change difference) by LMM is shown in the table below.

Table 15. Absolute Change From Baseline in BMI (kg/m2) by LMM, Part 1, Full Analysis Set

Visit or Time Period	Treatment Group	Sample Statistics		Rate of Change in Treatment Period[a]		Treatment Effect (Ivacaftor vs Placebo)	
		n	Mean	n	LS Mean	Difference (95% CI)	*P* value[b]
Baseline	Placebo	37	22.527	--	--	--	--
	Ivacaftor	38	22.241	--	--		
Week 8	Placebo	37	22.570	37	0.0163	0.6624 (0.3366, 0.9881)	<0.0001
	Ivacaftor	37	23.101	38	0.6787		

Source: Table 14.2.4.2.5

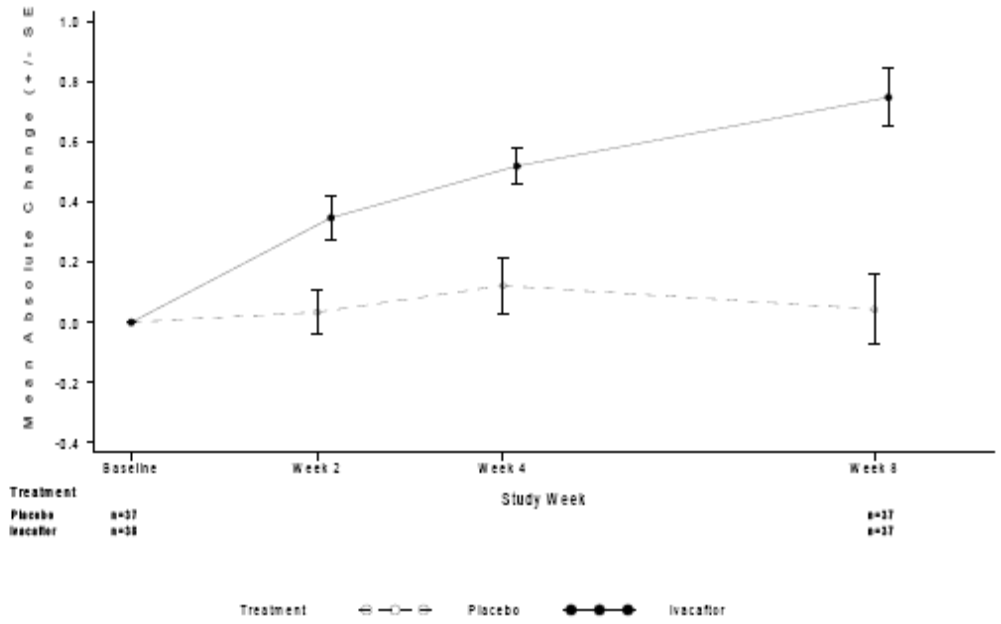
Note: Sample statistics are unadjusted results.

[a] Estimated change from baseline per 56 days was obtained from a linear mixed model, with BMI as the dependent variable; with treatment, sequence, and period as fixed effects; and with intercept, visit (days on study, including all visits through Week 8 in each period), and treatment by visit interaction as random effects, with adjustment for baseline percent predicted FEV_1 and age.

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

Mean (standard error, SE) changes from baseline in BMI at study visits across the Treatment Periods are presented in the figure below. Increases from baseline in BMI during treatment with ivacaftor were observed at Week 2 (first post-baseline time point assessed) and continued through Week 8.

Figure 3. Mean Absolute Change From Baseline in BMI (kg/m2) by Treatment, Part 1, Full Analysis Set



Source: Figure 14.2.4.1

BMI-for-age z-scores were calculated using the CDC growth chart for the 19 subjects who were 20 years of age or younger. The mean absolute change from baseline in BMI-for-age z-score at Week 8 by LMM was greater during treatment with ivacaftor (0.2437 points) than during placebo treatment (-0.0392 points) (see table below).

Table 16. Absolute Change From Baseline in BMI-for-Age Z-Score by LMM, Part 1, Full Analysis Set

Visit or Time Period	Treatment Group	Sample Statistics		Rate of Change in Treatment Period[a]		Treatment Effect (Ivacaftor vs Placebo)	
		n	Mean	n	LS Mean	Difference (95% CI)	*P* value[b]
Baseline	Placebo	17	0.4914	--	--	--	--
	Ivacaftor	19	0.3151	--	--		
Week 8	Placebo	17	0.4915	17	-0.0392	0.2830 (0.1167, 0.4492)	0.0010
	Ivacaftor	18	0.6246	19	0.2437		

Source: Table 14.2.4.2.6

Notes: Sample statistics are unadjusted results. BMI-for-age z-scores were calculated using National Center for Health Statistics (NCHS) growth charts. Analysis was conducted only when the number of subjects with results in each treatment group ≥5 and the model converged.

[a] Estimated change from baseline per 56 days was obtained from a linear mixed model, with BMI-for-age z-score as the dependent variable; with treatment, sequence, and period as fixed effects and with intercept, visit (days on study, including all visits through Week 8 in each period), and treatment by visit interaction as random effects, with adjustment for baseline percent predicted FEV_1 and age.

[b] *P* value for the treatment effect is from the slope of BMI-for-age z-score versus time (days).

Change from baseline in sweat chloride

The mean absolute change from baseline in sweat chloride (mmol/L) through Week 8 by MMRM is shown in the table below.

Table 17. Absolute Change From Baseline in Sweat Chloride (mmol/L) by MMRM, Part 1, Full Analysis Set

Visit or Time Period	Treatment Group	Sample Statistics		Absolute Change From Baseline[a]		Treatment Effect (Ivacaftor vs Placebo)	
		n	Mean	n	LS Mean	Difference (95% CI)	*P* value
Baseline	Placebo	37	94.2297	--	--	--	--
	Ivacaftor	38	93.3684	--	--		
Overall Post-baseline	Placebo	37	91.3551	37	-3.1134	-49.1667 (-56.9527, -41.3807)	<0.0001
	Ivacaftor	37	40.6165	37	-52.2801		

Source: Table 14.2.2.2.1

Note: Sample statistics are unadjusted results.

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

Statistically significant treatment differences were detected by Week 2 (first post-baseline time point assessed; -45.7161 mmol/L [95% CI: -53.9486, -37.4836]) and were sustained through Week 8 (-49.6331 mmol/L [95% CI: -57.7951, -41.4711]) (see table below).

Table 18. Absolute Change From Baseline in Sweat Chloride (mmol/L) by MMRM, Consistency of Treatment Effect Over Visits, Part 1, Full Analysis Set

Visit or Time Period	Treatment Group	Sample Statistics		Absolute Change From Baseline[a]		Treatment Effect (Ivacaftor vs Placebo)	
		n	Mean	n	LS Mean	Difference (95% CI)	*P* value[b]
Baseline	Placebo	37	94.2297	--	--	--	--
	Ivacaftor	38	93.3684	--	--		
Week 2	Placebo	35	92.1714	35	-2.4864	-45.7161 (-53.9486, -37.4836)	<0.0001
	Ivacaftor	33	44.5000	33	-48.2025		
Week 4	Placebo	36	93.6111	36	-0.8764	-52.0888 (-60.2920, -43.8856)	<0.0001
	Ivacaftor	34	40.1912	34	-52.9652		
Week 8	Placebo	36	88.3056	36	-5.9533	-49.6331 (-57.7951, -41.4711)	<0.0001
	Ivacaftor	36	37.4583	36	-55.5863		

Source: Table 14.2.2.2.2

Note: Sample statistics are unadjusted results.

[a] Estimates were obtained from MMRM, with absolute change from period baseline as the dependent variable; with sequence, period, treatment, visit within period (Week 2, Week 4, and Week 8), and treatment by visit interaction as fixed effects with subject nested within sequence as a random effect; and with adjustment for the continuous baseline values of age and percent predicted FEV_1, using a compound symmetry covariance matrix.

[b] *P* value for Overall Post-Baseline is from the main treatment effect; *P* values at individual visits are from linear contrasts between the 2 treatments at the given visit.

A responder analysis was conducted by categorizing absolute change from baseline in sweat chloride values at Week 8 as ≥5 mmol/L or <5 mmol/L decrease, ≥10 mmol/L or <10 mmol/L decrease, and ≥20 mmol/L or <20 mmol/L decrease. Results of this analysis are presented in the table below and show that the majority of subjects treated with ivacaftor who had ≥5 mmol/L decrease at Week 8 also had ≥20 mmol/L decrease at Week 8.

Table 19. Responder Analysis of Absolute Change at Week 8 of Sweat Chloride (mmol/L), Part 1, Full Analysis Set

Category	Placebo (N = 37) n (%)	Ivacaftor (N = 38) n (%)
≥5 mmol/L decrease	18 (48.6)	33 (86.8)
<5 mmol/L decrease	18 (48.6)	3 (7.9)
Total	**36 (97.3)**	**36 (94.7)[a]**
≥10 mmol/L decrease	11 (29.7)	32 (84.2)
<10 mmol/L decrease	25 (67.6)	4 (10.5)
Total	**36 (97.3)**	**36 (94.7)[a]**
≥20 mmol/L decrease	3 (8.1)	31 (81.6)
<20 mmol/L decrease	33 (89.2)	5 (13.2)
Total	**36 (97.3)**	**36 (94.7)[a]**

Source: Table 14.2.2.1.8

Notes: Period baseline was defined as the most recent non-missing measurement collected prior to initial administration of study drug in each Treatment Period, with additional requirement for the Treatment Period 2 baseline that it needed to be from an assessment after 14 days in the Washout Period. If the Treatment Period 2 baseline was missing, the Treatment Period 1 baseline was used.

[a] Subject [redacted] was randomized to Treatment Sequence 1 but discontinued from the study after completing the Week 4 Visit and subsequently did not complete Treatment Period 1; subject was lost to follow-up (see Listing 16.2.1).

The responder analysis of changes in sweat chloride at week 8 showed that three subjects had a >20 mmol decrease in sweat chloride while on placebo and three subjects had <5 mmol decrease in sweat chloride while receiving ivacaftor. Upon request of the CHMP the MAH provided the individual narratives of these patients as well as waterfall plots of changes in sweat chloride at weeks 2, 4 and 8.

The narratives provided for patients who had the smallest decreases in sweat chloride values while on treatment with ivacaftor showed that all of them carried the *G970R-CFTR* mutation. The analysis at week 8 of the mean absolute change in sweat chloride showed that in 3 out of the 4 patients enrolled in study 111 the reduction was below 5 mmol/L and between 5 and 20 mmol/L for the remaining patient. Similarly, the mean (SD) absolute change in percent predicted FEV1 at week 8 was 0.4 (3.7) and 2.6 (2.7) for placebo- and ivacaftor-treated patients. These results are comparatively inferior to those achieved by patients with other non-*G551D* gating mutations.

The analysis of patients with a decrease in sweat chloride above 20 mmol/L while on placebo (i.e., higher than anticipated in the absence of an active treatment) did not suggest any specific pattern in terms of genotype. Narratives were provided for three patients with the following genotypes: *G1349D/2183AA>G*, *S549R/F508del* and *S549N/N1303K*. All three of them had pancreatic insufficiency.

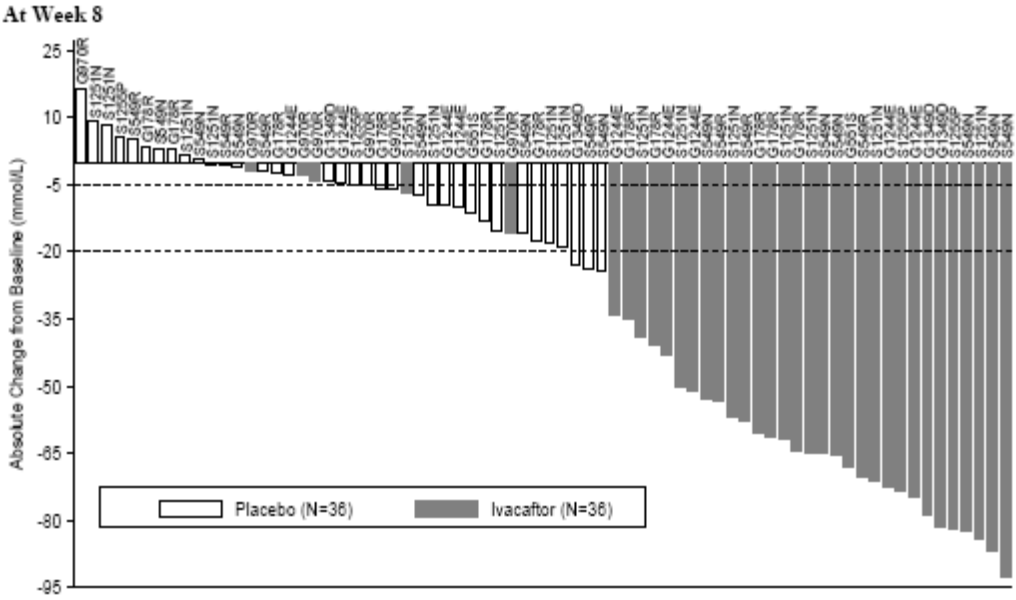
The patient with the genotype *S549N/N1303K* had at Day 1 (start of ivacaftor dosing) a sweat chloride of 118 mmol/L that after 8 weeks of treatment decreased to 31 mmol/L. At Week 12 (start of placebo dosing) his sweat chloride has increased to 105.5 mmol/L and decreased after 8 weeks of placebo treatment to 93.5 mmol/L.

For the patient with the genotype *S549R/F508del* the amount of sweat chloride was not sufficient for analysis in most of the study visits where this measurement was performed. At baseline his sweat chloride was 105 mmol/L and 80 mmol/L during the run-in. The first day of ivacaftor-treatment the value was 103.5 mmol/L and after 8 weeks of placebo treatment it was 79.5 mmol/L. The lack of quantifiable sweat chloride amounts in most of the study visits precludes a clear interpretation of the data.

Patient with the genotype *G1349D/2183AA>G* had while on ivacaftor a decrease in sweat chloride from 102 to 20.5 mmol/L. At week 12 (at the time of starting placebo treatment) his sweat chloride value had returned to the run in value prior study initiation. After 8 weeks of placebo treatment his sweat chloride dropped from 97 to 79 mmol/L.

The waterfall plots provided of change in sweat chloride at weeks 2, 4, and 8 showed that the majority of the patients had a clear reduction in sweat chloride during ivacaftor treatment, i.e. almost all mutations consistently displayed a decrease in sweat chloride well above 20 mmol/L with ivacaftor. The only exceptions were *G970R* patients and single examples for *S1251N* subjects (see figure below).

Figure 4. Individual CFTR genotypes: waterfall plots for absolute change from baseline in sweat chloride, full analysis set



Source: Figure Adhoc 2014.013.3
Note: The horizontal reference lines at -5 mmol/L and -20 mmol/L identify subjects who were treated with ivacaftor who had a <5 mmol/L decrease in sweat chloride and subjects who were treated with placebo who had a >20 mmol/L decrease in sweat chloride.

Change from baseline in CFQ-R Respiratory Domain Score

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

Results of the mean absolute change from baseline in the respiratory domain score of the CFQ-R through Week 8 by MMRM and by questionnaire version are shown in the table below.

Table 20. Absolute Change From Baseline in CFQ-R Respiratory Domain Score by MMRM, Part 1, Full Analysis Set

Questionnaire Version	Visit or Time Period	Treatment Group	Sample Statistics n	Sample Statistics Mean	Absolute Change From Baseline[a] n	Absolute Change From Baseline[a] LS Mean	Treatment Effect (Ivacaftor vs Placebo) Difference (95% CI)	Treatment Effect (Ivacaftor vs Placebo) *P* value
Children Ages 6 to 11 Years	Baseline	Placebo	8	78.1250	--	--	--	--
		Ivacaftor	8	70.8333	--	--		
	Overall Post-baseline	Placebo	8	83.3333	8	5.6308	11.3391 (-4.9020, 27.5802)	0.1472
		Ivacaftor	8	87.8473	8	16.9699		
Children Ages 12 to 13 Years	Baseline	Placebo	2	75.0000	--	--	--	--
		Ivacaftor	3	77.7777	--	--		
	Overall Post-baseline	Placebo	2	73.6110	2	--	--	--
		Ivacaftor	3	67.7083	3	--		
Adolescents and Adults	Baseline	Placebo	27	73.4568	--	--	--	--
		Ivacaftor	27	69.7531	--	--		
	Overall Post-baseline	Placebo	27	70.0960	27	-2.6581	11.3360 (5.4081, 17.2639)	0.0004
		Ivacaftor	27	79.2181	27	8.6779		
Parents and Caregivers	Baseline	Placebo	10	73.3334	--	--	--	--
		Ivacaftor	11	71.8182	--	--		
	Overall Post-baseline	Placebo	10	78.4814	10	4.8973	7.2743 (-1.0717, 15.6203)	0.0800
		Ivacaftor	11	84.4096	11	12.1715		
Pooled[b]	Baseline	Placebo	37	74.5496	--	--	--	--
		Ivacaftor	38	70.6141	--	--		
	Overall Post-baseline	Placebo	37	73.1481	37	-0.6720	9.6105 (4.4874, 14.7336)	0.0004
		Ivacaftor	38	80.2360	38	8.9385		

Source: Table 14.2.3.2.1

Notes: Sample statistics are unadjusted results. Analysis was conducted only when the number of subject with results in each treatment group ≥5.

[a] Estimates were obtained from MMRM, with absolute change from baseline as the dependent variable; with treatment, sequence, period, and visit within period (Week 2, Week 4, and Week 8) as fixed effects with subject nested within sequence as a random effect; and with adjustment for the continuous baseline values of age, percent predicted FEV_1, and CFQ-R respiratory domain score using a compound symmetry covariance matrix.

[b] Pooled was defined as all questionnaire versions except for the Parents and Caregivers version.

The Children of Ages 12 to 13 Years version was not analysed with MMRM due to sample size constraints.

A responder analysis was conducted by categorizing the absolute change from baseline in the pooled CFQ-R respiratory domain score through Week 8 as either ≥4 points or <4 points (which is considered the minimal clinically important difference). During treatment with ivacaftor, the majority of subjects (73.7%) had a ≥4 point increase from baseline in the CFQ-R respiratory domain score at Week 8; during treatment with placebo, the majority of subjects (70.3%) had <4 point increase from baseline.

Tertiary Efficacy Variables

Pulmonary exacerbations

The number of events and model-based estimates of event rates of pulmonary exacerbations through Part 1 (Week 20) are summarized in table below.

Table 21. Number of Pulmonary Exacerbations, Part 1, Full Analysis Set

Event Type	Statistics	Placebo N = 37	Ivacaftor N = 38	Rate Ratio[b] (95% CI)	*P* value[c]
	Total Number of Days on Study	2941	3001	--	--
All Pulmonary Exacerbations[a]	**Number of Subjects with Events**	8	9	--	--
	Number of Events	10	10	0.807	0.5687
	(Event Rate)	(0.197)	(0.159)	(0.386, 1.688)	
Requiring Hospitalization	Number of Subjects with Events	5	2	--	--
	Number of Events	5	2	--	0.4531
	(Event Rate)	(--)	(--)	(--)	
Requiring IV antibiotic therapy	Number of Subjects with Events	5	3	--	--
	Number of Events	5	3	--	0.7266
	(Event Rate)	(--)	(--)	(--)	

Source: Table 14.2.5.1

Notes: Estimates were obtained from negative binomial regression with the number of events as the dependent variable, treatment and sequence as fixed effects, and adjustment for baseline percent predicted FEV_1 and age, with log (time on treatment period) as an offset.

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

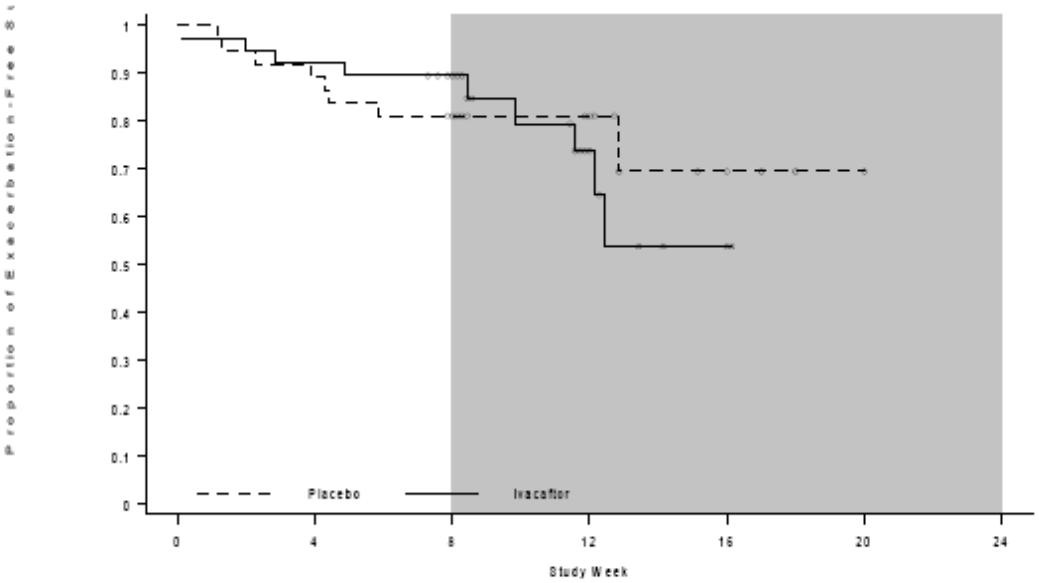
[b] Event rate and rate ratios were calculated when the number of subjects with events in each treatment group ≥5.

[c] *P* values are from the treatment effect using negative binomial regression when the number of subjects with events in each treatment group ≥5 and the model converged; otherwise, when the number of subjects with events is <5, *P* values are from the McNemar test.

The mean (SD) duration of pulmonary exacerbations was lower during treatment with ivacaftor (2.92 [6.027] days) compared with placebo (4.43 [9.487] days), but this difference was not statistically significant (P = 0.2166).

Figure below presents the survival curves by treatment group for time-to-first pulmonary exacerbation in Part 1. Subjects received ivacaftor or placebo during the first 8 weeks of the curve; subsequent time points represent the Washout Period when subjects did not receive study drug. The Washout Period duration may have extended beyond 4 to 8 weeks for some subjects due to acute illness.

Figure 5. Time-to-First Pulmonary Exacerbations, Part 1, Full Analysis Set



Source: Figure 14.2.5.1

Notes: The open circles on the plot denote censored subjects. The shaded region from Week 8 to Week 24 represents the Washout Period when subjects did not receive study drug; the Washout Period may have been extended beyond 4 to 8 weeks for some subjects due to acute illness. The non-shaded region represents the time subjects were actively treated with study drug (i.e., Treatment Period 1 and Treatment Period 2). The analysis included Treatment Period 1 and Treatment Period 2 (i.e., active treatment with study drug) and the Washout Period when subjects did not receive study drug from Week 8 to Week 12. Events that started (or increased in severity) during the Washout Period were attributed to the treatment received in Treatment Period 1.

Change from baseline in weight

Change from baseline in weight through 8 weeks of treatment by LMM is summarized in table below.

Table 22. Absolute Change From Baseline in Weight (kg) by LMM, Part 1, Full Analysis Set

Visit or Time Period	Treatment Group	Sample Statistics		Change From Baseline[a]		Treatment Effect (Ivacaftor vs Placebo)	
		n	Mean	n	LS Mean	Difference (95% CI)	*P* value[b]
Baseline	Placebo	37	58.59	--	--	--	--
	Ivacaftor	38	57.93	--	--		
Week 8	Placebo	37	59.00	37	0.3425	1.6674 (0.7098, 2.6250)	0.0007
	Ivacaftor	37	60.31	38	2.0099		

Source: Table 14.2.4.2.3

Note: Sample statistics are unadjusted results.

[a] Estimated change from baseline per 56 days was obtained from a linear mixed model, with weight as the dependent variable; with treatment, sequence, and period as fixed effects; and with intercept, visit (days on study, including all visits through Week 8 in each period), and treatment by visit interaction as random effects, with adjustment for baseline percent predicted FEV_1 and age.

[b] *P* value for the treatment effect is from the slope of weight (kg) versus time (days).

Positive mean (SE) absolute changes from baseline in weight occurred by Week 2 and increased during the 8-week Treatment Period.

The mean change from baseline for weight-for-age z-score through Week 8 is presented in table below for patients 20 years of age or younger (CDC growth chart).

Table 23. Absolute Change From Baseline in Weight-for-Age Z-Score by LMM, Part 1. Full Analysis Set

Visit or Time Period	Treatment Group	Sample Statistics		Change From Baseline[a]		Treatment Effect (Ivacaftor vs Placebo)	
		n	Mean	n	LS Mean	Difference (95% CI)	*P* value[b]
Baseline	Placebo	17	0.1470	--	--	--	--
	Ivacaftor	19	0.0652	--	--		
Week 8	Placebo	17	0.1464	17	-0.0397	0.2569 (0.1248, 0.3890)	0.0002
	Ivacaftor	18	0.2993	19	0.2172		

Source: Table 14.2.4.2.4

Notes: Sample statistics are unadjusted results. Weight-for-age z-scores were calculated using NCHS growth charts.

[a] Estimated change from baseline per 56 days was obtained from a linear mixed model, with weight-for-age z-score as the dependent variable; with treatment, sequence, and period as fixed effects; and with intercept, visit (days on study, including all visits through Week 8 in each period), and treatment by visit interaction as random effects, with adjustment for baseline percent predicted FEV_1 and age.

[b] *P* value for the treatment effect is from the slope of weight-for-age z-score versus time (days).

Change from baseline in height

Change from baseline in height through Week 8 by LMM is summarized in the table below.

Table 24. Absolute Change From Baseline in Height (cm) by LMM, Part 1, Full Analysis Set

Visit or Time Period	Treatment Group	Sample Statistics		Change From Baseline[a]		Treatment Effect (Ivacaftor vs Placebo)	
		n	Mean	n	LS Mean	Difference (95% CI)	*P*-value[b]
Baseline	Placebo	26	152.2	--	--	--	--
	Ivacaftor	30	155.4	--	--		
Week 8	Placebo	17	145.3	26	0.5877	0.1832 (-0.3807, 0.7471)	0.5207
	Ivacaftor	18	146.6	30	0.7709		

Source: Table 14.2.4.2.1

Note: Sample statistics are unadjusted results.

[a] Estimated change from baseline per 56 days was obtained from a linear mixed model, with height as the dependent variable; with treatment, sequence, and period as fixed effects; and with intercept, visit (days on study, including all visits through Week 8 in each period), and treatment by visit interaction as random effects, with adjustment for baseline percent predicted FEV_1 and age.

[b] *P* value for the treatment effect is from the slope of height (cm) versus time (days).

Change from baseline in height through Week 8 was slightly greater during ivacaftor treatment (0.7709 cm) than during placebo treatment (0.5877 cm), but the treatment difference (95% CI) of 0.1832 cm (-0.3807, 0.7471) was not statistically significant (P = 0.5207). The lack of statistical significance may be attributed, in the MAH's opinion, to the short duration of study drug treatment (i.e., 8 weeks) and that the majority of subjects were adults (i.e., ≥18 years of age).

For subjects 20 years of age or younger, height-for-age z-scores were calculated using the CDC growth chart. Change from baseline in height through 8 weeks of treatment is summarized by treatment group in the table below. The treatment difference (95% CI) of 0.0209 cm (-0.0607, 0.1024) was not statistically significant (P = 0.6130).

Table 25. Absolute Change From Baseline in Height-for-Age Z- score by LMM, part 1, Full Analysis Set

Visit or Time Period	Treatment Group	Sample Statistics		Change From Baseline[a]		Treatment Effect (Ivacaftor vs Placebo)	
		n	Mean	n	LS Mean	Difference (95% CI)	*P* value[b]
Baseline	Placebo	17	-0.5857	--	--	--	--
	Ivacaftor	19	-0.4392	--	--		
Week 8	Placebo	17	-0.5751	17	-0.0011	0.0209 (-0.0607, 0.1024)	0.6130
	Ivacaftor	18	-0.5048	19	0.0197		

Source: Table 14.2.4.2.2

Notes: Sample statistics are unadjusted results. Height-for-age z-scores were calculated using NCHS growth charts.

[a] Estimated change from baseline per 56 days was obtained from a linear mixed model, with height-for-age z-score as the dependent variable; with treatment, sequence, and period as fixed effects; and with intercept, visit (days on study, including all visits through Week 8 in each period), and treatment by visit interaction as random effects, with adjustment for baseline percent predicted FEV_1 and age.

[b] *P* value for the treatment effect is from the slope of height-for-age z-score versus time (days).

Change from baseline in inflammatory mediators (blood samples)

The mean concentrations and mean log-transformed concentrations of inflammatory mediators (leukocytes, CRP, IgG, and IL-8) are presented in the table below.

Table 26. Absolute Change From Baseline in Inflammatory Mediator and Log-Transformed Inflammatory Mediator Concentrations by MMRM, Part 1, Full Analysis Set

Visit or Time Period	Treatment Group	Sample Statistic		Absolute Change From Baseline[a]		Treatment Effect (Ivacaftor vs Placebo)	
		n	Mean	n	LS Mean	Difference (95% CI)	*P* value[b]
Leukocytes (10^9/L)							
Period Baseline	Placebo	37	8.0311	--	--	--	--
	Ivacaftor	38	9.0958	--	--		
Overall Postbaseline	Placebo	37	7.9290	37	-0.4599	-0.8530 (-1.7202,0.0142)	0.0537
	Ivacaftor	38	7.4223	38	-1.3130		
Leukocytes 10^9/L), Log-Transformed Data							
Period Baseline	Placebo	37	0.9301	--	--	--	--
	Ivacaftor	38	0.9789	--	--		
Overall Postbaseline	Placebo	37	0.9312	37	-0.0142	-0.0392 (-0.0764,-0.0019)	0.0398
	Ivacaftor	38	0.9092	38	-0.0534		
C-reactive Protein (nmol/L)							
Period Baseline	Placebo	37	53.2894	--	--	--	--
	Ivacaftor	37	67.8019	--	--		
Overall Postbaseline	Placebo	37	62.2060	37	2.2423	-21.3978 (-50.2791,7.4836)	0.1432
	Ivacaftor	38	42.6539	37	-19.1555		
C-reactive Protein (nmol/L), Log-Transformed Data							
Period Baseline	Placebo	37	1.2884	--	--	--	--
	Ivacaftor	37	1.4430	--	--		
Overall Postbaseline	Placebo	37	1.3891	37	0.0442	-0.2655 (-0.4472,-0.0838)	0.0050
	Ivacaftor	38	1.1678	37	-0.2213		
Immunoglobulin G (g/L)							
Period Baseline	Placebo	36	12.3992	--	--	--	--
	Ivacaftor	38	13.1074	--	--		
Overall Postbaseline	Placebo	37	12.7320	36	0.1579	-0.6728 (-1.2127,-0.1329)	0.0157
	Ivacaftor	38	12.4164	38	-0.5149		
Immunoglobulin G (g/L), Log-Transformed Data							

Visit or Time Period	Treatment Group	Sample Statistic n	Sample Statistic Mean	Absolute Change From Baseline[a] n	Absolute Change From Baseline[a] LS Mean	Treatment Effect (Ivacaftor vs Placebo) Difference (95% CI)	Treatment Effect (Ivacaftor vs Placebo) *P* value[b]
Period Baseline	Placebo	36	1.1034	--	--	--	--
	Ivacaftor	38	1.1296	--	--		
Overall Postbaseline	Placebo	37	1.1145	36	0.0051	-0.0214 (-0.0383,-0.0045)	0.0143
	Ivacaftor	38	1.1077	38	-0.0162		
Interleukin-8 (pg/mL)							
Period Baseline	Placebo	37	13.1486	--	--	--	--
	Ivacaftor	37	14.3514	--	--		
Overall Postbaseline	Placebo	37	15.0225	37	--	--	--
	Ivacaftor	38	11.2864	37	--		
Interleukin-8 (pg/mL), Log-Transformed Data							
Period Baseline	Placebo	37	1.0871	--	--	--	--
	Ivacaftor	37	1.1327	--	--		
Overall Postbaseline	Placebo	37	1.0832	37	-0.0191	-0.0613 (-0.1169,-0.0056)	0.0316
	Ivacaftor	38	1.0373	37	-0.0803		

Sources: Table 14.2.6.2 and Table 14.2.6.3

Notes: Sample statistics are unadjusted results. Analysis conducted only when the number of subjects with results in each treatment group ≥5 and the model converged.

[a] Estimates were obtained from MMRM, with absolute change from baseline (or in log-transformed inflammatory mediators, as applicable) as the dependent variable; with treatment, sequence, period, and visit within period (Week 2, Week 4, and Week 8) as fixed effects with subject nested within sequence as random effect; and with adjustment for the continuous baseline values of age, percent predicted FEV_1, and inflammatory mediators (or log- transformed inflammatory mediators, as applicable), using a compound symmetry covariance matrix.

[b] *P* value is the from the main treatment effect.

Change from baseline in qualitative microbiological cultures

Shift from period baseline in qualitative microbiology cultures from throat swabs and sputum samples is presented by treatment in the table below for 8 common or important microbiological organisms that affect patients with CF: *Achromobacter xylosoxidans*, *Burkholderia cenocepacia*, *Haemophilus influenzae*, *P aeruginosa* (small colony variant), *P aeruginosa* (mucoid), *P aeruginosa* (non-mucoid), *Staphylococcus aureus*, and *Stenotrophomonas maltophilia*.

In general, shifts to higher or lower amounts of each microbe were sporadic and did not show any patterns across the treatment groups; however, this analysis is limited by the small number of subjects and a high incidence of unknown results for sputum samples.

Additional efficacy variables

Relative change from baseline in PPFEV1

The mean relative change from baseline in PPFEV1 through Week 8 was greater during ivacaftor treatment (10.7549%) than during placebo treatment (-3.4147%); the treatment difference (95% CI) of 14.1696% (9.8953, 18.4439) was statistically significant (P <0.0001).

Statistically significant treatment differences in relative change from baseline in PPFEV1 were detected by Week 2 (first post-baseline time point assessed; 11.2346% [95% CI: 6.3175, 16.1517]; P <0.0001) and increased through Week 8, with the largest treatment difference observed at Week 8 (17.7334% [95% CI: 12.8020, 22.6649]; P <0.0001).

Change from baseline in additional spirometry endpoints (FEV1 (L), FVC, FEF25%-75%, FEV1/FVC, Percent Predicted FVC, Percent Predicted FEF25%-75%, and PPFEV1/FVC)

The mean changes from baseline through Week 8 was greater in the ivacaftor group than in the placebo group for all parameters analysed; these differences were statistically significant (P <0.01).

Ancillary analyses

Subgroup analyses were performed for primary and secondary endpoints. Comparisons were made between treatment groups within subgroup categories as follows for both the primary and secondary endpoints:

- Age Group at Baseline (6 to 11 years [inclusive], 12 to 17 years [inclusive], and ≥18 years)
- PPFEV1 Severity at Baseline (<70%, 70% to 90% [inclusive], and >90% predicted)
- Geographic Region (North America and Europe)
- Sex (Female and Male)
- *P aeruginosa* Infection Status at Baseline (Yes and No)

The following subgroup comparison was made between treatment groups only for the secondary endpoints:

- Change From Baseline in PPFEV1 at Week 8 During Ivacaftor Treatment (≥5% and <5%)

The tables below show these results.

Table 27. Subgroup Analyses of Primary and Secondary Endpoints by Age Group at Baseline, Percent FEV1 at Baseline, and Geographic Region, Part 1

Treatment Difference Versus Placebo (95% CI) *P* Value							
Subject Age (years)			Baseline Percent Predicted FEV_1			Geographic Region	
6 to 11	12 to 17	≥18	<70%	≥70% to ≤90%	>90%	N. America	Europe
Absolute Change From Baseline in Percent Predicted FEV_1 (%)[a]							
N = 8:8	N = 9:11	N = 20:19	N = 13:13	N = 11:11	N = 13:14	N = 21:21	N = 16:17
5.1788 (-4.5696, 14.9272) 0.2531	9.1454 (3.4067, 14.8840) 0.0052	8.6598 (4.7096, 12.6101) 0.0001	7.9698 (3.5024, 12.4373) 0.0015	9.0362 (4.0151, 14.0573) 0.0019	9.8877 (3.2127, 16.5627 0.0067	6.1305 (2.9258, 9.3352) 0.0006	11.7607 (5.6163, 17.9052) 0.0009
Absolute Change From Baseline in BMI (kg/m^2)[b,c]							
N = 8:8	N = 9:11	N = 20:19	N = 13:13	N = 11:11	N = 13:14	N = 21:21	N = 16:17
0.9153 (0.2568, 1.5738) 0.0075	0.6339 (0.0124, 1.2554) 0.0457	0.5783 (0.1603, 0.9963) 0.0071	0.7533 (0.2611, 1.2456) 0.0032	0.4250 (-0.1458, 0.9958) 0.1417	0.7694 (0.2173, 1.3216) 0.0069	0.6391 (0.2044, 1.0739) 0.0043	0.6950 (0.2222, 1.1677) 0.0044
Absolute Change From Baseline in BMI-for-Age Z-score[b,c,d]							
N = 8:8	N = 9:11	N = 0:0	N = 2:2	N = 6:7	N = 9:10	N = 9:10	N = 8:9
0.3227 (0.0614, 0.5839) 0.0166	0.2505 (0.0446, 0.4564) 0.0181	NA	NA	0.1778 (-0.1753, 0.5310) 0.3137	0.3553 (0.1855, 0.5250) 0.0001	0.2807 (0.0334, 0.5281) 0.0269	0.2918 (0.0690, 0.5145) 0.0114
Absolute Change From Baseline in Sweat Chloride (mmol/L)[a,e]							
N = 8:8	N = 9:11	N = 20:19	N = 13:13	N = 11:11	N = 13:13	N = 21:20	N = 16:17
NA	-51.1909 (-66.7448,-35.6371) <0.0001	-45.1011 (-55.2262,-34.9760) <0.0001	-37.9323 (-55.7777,-20.0869) 0.0006	-60.2924 (-77.2211,-43.3637) <0.0001	-51.3602 (-59.0944,-43.6260) <0.0001	-54.7133 (-62.4992,-46.9274) <0.0001	-42.7760 (-59.1852,-26.3669) <0.0001
Absolute Change From Baseline in CFQ-R Respiratory Domain Score (points): Pooled Analysis[a,f]							
N = 8:8	N = 9:11	N = 20:19	N = 13:13	N = 11:11	N = 13:14	N = 21:21	N = 16:17
11.2925 (-4.2536, 26.8386) 0.1350	8.0980 (-4.4151, 20.6111) 0.1801	10.5969 (3.5680, 17.6257) 0.0045	11.1053 (3.0203, 19.1903) 0.0099	11.5497 (2.4271, 20.6723) 0.0170	8.3024 (-3.3333, 19.9381) 0.1507	8.4521 (0.3715, 16.5328) 0.0409	9.7827 (3.6864, 15.8790) 0.0033

Sources: Table 14.2.1.2.4, Table 14.2.2.2.3, Table 14.2.3.2.3, Table 14.2.4.2.7, and Table 14.2.4.2.8
Notes: Number of subjects (N) is presented as placebo: ivacaftor. Analysis conducted only when the number of subjects with results in each treatment group was ≥5.

[a] Estimates were obtained from MMRM, with absolute change from baseline as the dependent variable; with treatment, sequence, period, and visit within period (Week 2, Week 4, and Week 8) as fixed effects; with subject nested within sequence as a random effect; and with adjustment for the continuous baseline values of age and percent predicted FEV_1 and corresponding baseline value of the analyzed variable, using a compound symmetry covariance matrix. For the subgroups of percent predicted FEV_1 severity and age, no adjustment was made for baseline percent predicted FEV_1 and age, respectively

[b] Estimated change from baseline per 56 days was obtained from linear mixed models conducted by subgroup, with BMI or BMI-for-age z-score as the dependent variable; with treatment, sequence, and period as fixed effects; and with intercept, visit (days on study through Week 8), and treatment by visit interaction as random effects, adjusted for baseline percent predicted FEV_1 and age. For the subgroups Percent Predicted FEV_1 Severity and Age, models include no adjustment for baseline Percent Predicted FEV_1 and age, respectively.

[c] *P* value for the treatment effect is from the slope of BMI (kg/m^2) or BMI-for-age z-score versus time (days).

[d] BMI-for-age z-score is calculated using NCHS growth charts.

[e] Analysis conducted only when the number of subjects with results in each treatment group ≥5 and the model converged.

[f] Pooled is defined as all questionnaire versions except for the Parent/Caregiver version.

Table 28. Subgroup Analysis of Primary and Secondary Endpoints by Subject Sex, *P Aeruginosa* Infection Status at Baseline, and >5% and ≤5% Change From Baseline in PPFEV1 At Week 8 During Ivacaftor Treatment, Part 1

Treatment Difference Versus Placebo (95% CI) *P* Value					
Subject Sex		*P aeruginosa* Infection Status at Baseline		Change From Baseline in Percent Predicted FEV_1 at Week 8 of Ivacaftor Treatment	
Male	Female	Yes	No	<5%	≥5%
Absolute Change From Baseline in Percent Predicted FEV_1 (%)[a]					
N = 22:22	N = 15:16	N = 20:19	N = 17:19	NA	NA
8.7833 (3.3648, 14.2017) 0.0027	8.0494 (4.4461, 1.6528) 0.0001	7.4846 (3.1328, 11.8365) 0.0018	8.0704 (3.6263, 12.5146) 0.0010	NA	NA
Absolute Change From Baseline in BMI (kg/m^2)[b]					
N = 22:22	N = 15:16	N = 20:19	N = 17:19	N = 19:20	N = 18:18
0.6896 (0.2531, 1.1260) 0.0022	0.6169 (0.1386, 1.0951) 0.0121	0.8918 (0.4238, 1.3598) 0.0003	0.4248 (0.0393, 0.8102) 0.0311	0.6027 (0.2056, 0.9998) 0.0033	0.7318 (0.2101, 1.2534) 0.0064
Absolute Change From Baseline in BMI-for-Age Z-score[b,c]					
N = 11:11	N = 6:8	N = 5:5	N = 12:14	N = 8:10	N = 9:9
0.2948 (0.0894, 0.5003) 0.0056	0.2659 (-0.0162, 0.5481) 0.0639	0.5855 (0.2563, 0.9147) 0.0011	0.1580 (-0.0207, 0.3366) 0.0822	0.2367 (0.0102, 0.4631) 0.0409	0.3238 (0.0933,0.5543) 0.0068
Absolute Change From Baseline in Sweat Chloride (mmol/L)[a,d]					
N = 22:21	N = 15:16	N = 20:18	N = 17:19	N = 19:19	N = 18:18
-45.4918 (-57.7603, -33.2233) <0.0001	-54.1873 (-64.2248, -44.1497) <0.0001	-47.6322 (-57.4974, -37.7669) <0.0001	-52.4854 (-64.5158, -40.4549) <0.0001	-46.3512 (-59.7663, -32.9360) <0.0001	-52.8373 (-60.5540,-45.1205) <0.0001
Absolute Change From Baseline in CFQ-R Respiratory Domain Score (points): Pooled Analysis[a,e]					
N = 22:22	N = 15:16	N = 20:19	N = 17:19	N = 19:20	N = 18:18
10.7640 (2.7952, 18.7329) 0.0099	7.0890 (-0.1194, 14.2974) 0.0536	13.6021 (6.7099, 20.4943) 0.0004	4.2778 (-3.3627, 11.9183) 0.2598	4.0411 (-2.4474, 10.5296) 0.2107	16.3948 (8.1546, 24.6351) 0.0004

Sources: Table 14.2.1.2.4, Table 14.2.2.2.3, Table 14.2.3.2.3, Table 14.2.4.2.7, and Table 14.2.4.2.8
Notes: Number of subjects (N) is presented as placebo: ivacaftor. Analysis conducted only when the number of subjects with results in each treatment group was ≥5.

[a] Estimates were obtained from MMRM, with absolute change from baseline as the dependent variable; with treatment, sequence, period, and visit within period (Week 2, Week 4, and Week 8) as fixed effects; with subject nested within sequence as a random effect; and with adjustment for the continuous baseline values of age and percent predicted FEV_1 and corresponding baseline value of the analyzed variable, using a compound symmetry covariance matrix. For the subgroups of percent predicted FEV_1 severity and age, no adjustment was made for baseline percent predicted FEV_1 and age, respectively.

[b] Estimated change from baseline per 56 days was obtained from linear mixed models conducted by subgroup, with BMI or BMI-for-age z-score as the dependent variable; with treatment, sequence, and period as fixed effects; and with intercept, visit (days on study through Week 8), and treatment by visit interaction as random effects, adjusted for baseline percent predicted FEV_1 and age. For the subgroups Percent Predicted FEV_1 Severity and Age, models include no adjustment for baseline Percent Predicted FEV_1 and age, respectively.

[c] *P* value for the treatment effect is from the slope of BMI (kg/m^2) or BMI-for-age z-score versus time (days).

[d] Analysis conducted only when the number of subjects with results in each treatment group ≥5 and the model converged.

[e] Pooled is defined as all self-reporting questionnaire versions, except for the Parent/Caregiver version.

Efficacy results by non-G551D gating mutation

Upon CHMP request the MAH conducted subgroup analysis by the non-*G551D* gating mutation. The following table displays in vitro (fold change over baseline in chloride transport) and clinical (mean [SD] absolute change at week 8 in sweat chloride and in PPFEV1) in the ivacaftor group in study 111 by non-*G551D* gating mutation.

Table 29. In vitro (fold change over baseline in chloride transport) and in vivo (absolute change in sweat chloride and in PPFEV1) of ivacaftor treatment by non-*G551D* gating mutation

Non-*G551D* gating mutation (number of patients available for analysis in the ivacaftor group at week 8)	In vitro fold change over baseline in chloride transport	Mean (SD) absolute change in sweat chloride (Week 8)	Mean (SD) absolute change in PPFEV1 (Week 8)
G178R (n=5)	30.1	-52.5 (13.5)	8.4 (7.9)
S549N (n=6)	59.8	-74.3 (15.4)	11.3 (9.8)
S549R (n=4)*	>20.0	-60.7 (8.8)	5.2 (7.4)
G551S (n=1)	16.2	-68.0	3.1
G970R (n=4)	30.5	-6.3 (6.6)	2.6 (2.7)
G1244E (n=5)	129.7	-55.1 (18.1)	8.4 (8.7)
S1251N (n=8)	25.2	-54.4 (23.4)	8.7 (13.0)
S1255P (n=2)	73.1	-77.8 (6.0)	3.1 (6.5)
G1349D (n=2)	46.7	-80.3 (1.8)	19.7 (23.6)

*n=3 available for the analysis of absolute change in sweat chloride

Predictability of the effect of ivacaftor

To give further support to the results obtained in study 111 after 8 weeks of treatment with ivacaftor, predictability of efficacy results through week 24 based on results through week 8 has been assessed by the MAH in two ways. First by providing a correlation between the Week 8 and Week 24 value for absolute change in PPFEV1 for the ivacaftor group that was 0.67884 (P <0.0001) in study 102 and 0.86614 (P <0.0001) in study 103, supporting in the MAH's opinion the utility of the Week 8 values in predicting the Week 24 treatment effect. And second, by performing a post-hoc analysis on the persistence of FEV1 response for subjects in the ivacaftor treatment group based on the value observed at Week 8. This analysis found that 60 (72%) of 83 subjects in study 102 maintained the same status of improvement at Week 24: 52 who had a ≥5 percentage-point improvement at both time points and 8 who had a ≥0 to <5 percentage-point improvement at both time points. In Study 103, 19 (73%) of 26 subjects maintained the same Week 8 status of improvement at Week 24: 16 who had a ≥5 percentage-point improvement at both time points and 3 who had ≤0 percentage-point improvement at both time points. Secondary efficacy variables in study 102 and 103 have also been analysed in this regard.

Predictive potential of the sweat chloride test

The MAH was requested to discuss the predictive potential of the sweat chloride test in identifying which patients would benefit from continuation of the therapy. This has been accomplished by the MAH as follows. First, an analysis of data from ivacaftor treated patients in study 111 has been performed aimed at determining the correlation of (change in) sweat chloride values with changes in FEV1, BMI and the respiratory domain of CFQ-R at week 8. No correlation was found as shown by Pearson's correlations of -.0931, -.0473 and -.0877 respectively indicating that there is no linear relationship between the variables studied. Other analyses using changes in PPFEV1 did not show any correlation

either. The MAH also discussed 3 papers where this concept has been investigated. Two of them[11] [12] conclude that there is no correlation between the reduction in sweat chloride seen with ivacaftor in phase 3 studies in patients with a *G551D-CFTR* mutation and improvement in lung function (measured as FEV1). Third paper[13] reached the same conclusion using a different patient population. The paper by Seliger et al (2013) investigated additionally the use of sweat chloride changes at day 15 as a predictive marker of response (i.e. an increase in FEV1 ≥ 5%) to ivacaftor at week 16 using data from phase 3 studies in patients with a *G551D-CFTR* mutation. Two thresholds (sweat chloride concentration ≤ 80 mmol/L, and a raw change in sweat chloride ≥ 20 mmol/L) were used to calculate Positive Predictive Value (86.3%), sensitivity (73.9%), Negative Predictive Value (65.5%), and specificity (80.9%) for an improvement in FEV1 of ≥5% from baseline at week 16. The Negative Predictive Value of both thresholds combined is 65.5%, i.e. if the combined threshold is not reached the probability that the improvement in lung function can be achieved is still high, discouraging (in the opinion of the authors) the use of sweat chloride as a tool to identify ivacaftor non-responsive patients. Of note is that the improvement in FEV1 of equal or above 5% is based on FEV (L) rather than on PPFEV1.

Summary of main study

The following table summarise the efficacy results from the main study 111 supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 30. Summary of Efficacy for trial VX12-770-111

A Phase 3, Two-part, Randomized, Double-blind, Placebo-controlled, Crossover Study With an Open-label Period to Evaluate the Efficacy and Safety of Ivacaftor in Subjects With Cystic Fibrosis Who Have a Non-*G551D-CFTR* Gating Mutation			
Study identifier	Protocol VX12-770-111		
Design	Randomized, double-blind, placebo-controlled, two-part study (Part 1: 8-week crossover part with a 4 to 8 week wash-out followed by Part 2: 16-week open-label period).		
	Duration of main phase:		Two treatment periods of 8-week duration each separated by a 4 to 8-week washout period, i.e. 20- to 24-week crossover study.
	Duration of Run-in phase:		Day -14 (±2 days) relative to first dose of study drug in Treatment Period 1
	Duration of Extension phase:		16 weeks (up to a total length of treatment with ivacaftor of 24 weeks)
Hypothesis	Superiority (not explicitly formulated)		
Treatments groups	Treatment Sequence 1 (each sequence has two Treatment Periods)		Ivacaftor 150 mg every 12 hours in Treatment Period 1 (8 weeks) → washout → placebo of ivacaftor in Treatment Period 2 (8 weeks), 20 randomised patients
	Treatment Sequence 2 (each sequence has two Treatment Periods)		Placebo of ivacaftor in Treatment Period 1 → washout → ivacaftor 150 mg every 12 hours in Treatment Period 2, 19 randomised patients
	Primary endpoint	PPFEV1, 8 weeks	Absolute change from baseline in PPFEV1 through Week 8 (%)

[11] Durmowicz AG, Witzmann KA, Rosebraugh CJ, Chowdhury BA. Change in sweat chloride as a clinical endpoint in cystic fibrosis clinical trials: the ivacaftor experience. Chest. 2013;143(1):14-8.
[12] Seliger VI, Rodman D, Van Goor F, Schmelz A, Mueller P. The predictive potential of the sweat chloride test in cystic fibrosis patients with the *G551D* mutation. J Cyst Fibros. 2013;12(6):706-13.
[13] Barry PJ, Jones AM, Webb AK, Horsley AR. Sweat chloride is not a useful marker of clinical response to ivacaftor. Thorax. 2013; Nov 20. doi: 10.1136/thoraxjnl-2013-204532 [Epub ahead of print].

Endpoints and definitions	Secondary endpoint	BMI, 8 weeks	Absolute change from baseline in BMI at 8 weeks of treatment (kg/m^2)
	Secondary endpoint	Sweat chloride, 8 weeks	Absolute change from baseline in sweat chloride through 8 weeks of treatment (mmol/L)
	Secondary endpoint	Respiratory domain score of the pooled CFQ-R, 8 weeks	Absolute change from baseline in the respiratory domain score of the pooled CFQ-R through Week 8 (Pooled questionnaire analyses were defined as all questionnaire versions except for the Parents and Caregivers version)
Database lock	25 June 2013 (Part 1)		

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 medicine (i.e., ivacaftor or placebo). Patients were analysed according to the study medicine to which they were assigned at/through week 8 of treatment.		
Descriptive statistics and estimate variability	Treatment group	Ivacaftor	Placebo
	Number of subjects	37	37
	FEV_1 8 weeks, LS Mean	7.4868	-3.1912
	Standard error	1.2292	1.2459
	BMI 8 weeks, LS mean	0.6787	0.0163
	Standard error	0.4948	0.4954
	*Sweat chloride 8 weeks, LS mean	-52.2801	-3.1134
	Standard error	2.7210	2.7172
	Respiratory domain pooled CFQ-R 8 weeks, LS mean	8.9385	-0.6720
	Standard error	1.8178	1.8475
Effect estimate per comparison	Primary endpoint	Ivacaftor vs. Placebo	
		PPFEV1, MMRM	10.6780
		95% CI	7.2559, 14.1000
		P-value	<0.0001
	Secondary endpoint	Ivacaftor vs. Placebo	
		BMI, LMM	0.6624
		95% CI	0.3366, 0.9881
		P-value	<0.0001
	Secondary endpoint	Ivacaftor vs. Placebo	
		Sweat chloride, MMRM	-49.1667
		95% CI	-56.9527, -41.3807
		P-value	<0.0001

	Secondary endpoint	Ivacaftor vs. Placebo	
		Respiratory domain, pooled CFQ-R, MMRM	9.6105
		95% CI	4.4874, 14.7336
		P-value	0.0004
Notes	*Sweat chloride: n=36		
Analysis description	A number of tertiary endpoints (including pulmonary exacerbations), additional spirometry variables and subgroup analyses have also been performed.		

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

Study VX12-770-111 (study 111) was a phase 3, two-part, randomized, double-blind, placebo-controlled, crossover study with an open-label period to evaluate the efficacy and safety of ivacaftor in subjects with cystic fibrosis who have a non-*G551D-CFTR* gating mutation. The crossover period (Part 1) was immediately followed by a (currently) finished 16-week open-label period (Part 2) to provide efficacy and safety results for a total of 24 weeks of treatment with ivacaftor. This submission is based on the double-blind crossover period data (Part 1).

In Part 1 of the study patients were randomized 1:1 to receive 1 of 2 Treatment Sequences during 8-week Treatment Periods. The washout period lasted for 4 to 8 weeks. Based on the time frame of response in studies 102 and 103, the 8-week duration of the Treatment Periods was expected to be sufficient to demonstrate a treatment effect and pattern of response in CF patients with a *CFTR* gating mutation other than *G551D*. This study was the subject of a CHMP Follow-Up Protocol Assistance where the short term duration was endorsed provided that results were consistent with those of prior studies in patients with a *G551D-CFTR* mutation.

Part 2 of study 111 has finished and the final CSR is expected to be available by June 2014. It should be provided as soon as it is available. Submission of results of this study is foreseen in the RMP.

Patients with a confirmed diagnosis of CF (defined as chronic sinopulmonary disease AND a sweat chloride value ≥60 mmol/L or 2 CF-causing mutations), aged 6 years and older, with at least 1 allele of the following *CFTR* gating mutations *G178R*, *S549N*, *S549R*, *G551S*, *G970R*, *G1244E*, *S1251N*, *S1255P*, and *G1349D* were enrolled. In addition, patients must have had ≥40% predicted FEV1 based on the Hankinson (male subjects 18 years and older and female subjects 16 years and older) or Wang (male subjects aged 6 to 17 years and for female subjects aged 6 to 15 years) equations. Patients having a *G551D* mutant *CFTR* allele were excluded as its presence was expected to hamper the interpretation of the study results.

A minimum of 20 subjects and a maximum of approximately 40 subjects were planned to be enrolled but no criterion was given upfront to determine the final sample size. Therefore, the MAH was requested to provide justification for the Standard Deviation (SD) used to estimate the study sample size. The MAH have clarified that the standard deviation of 8% corresponds to the mean of the SD of the ivacaftor and placebo groups at week 8 in studies 102 and 103. This is acceptable.

Forty-two patients were screened and 39 randomised in a 1:1 ratio to Treatment Sequence 1 (ivacaftor 150 mg every 12 hours → washout period → placebo) or Treatment Sequence 2 (placebo → washout

period → ivacaftor 150 mg every 12 hours). In addition, patients were stratified for age (6 to 11 years, 12 to 17 years, and ≥18 years) and FEV1 severity (<70%, ≥70% to ≤90%, and >90%).

Three screened patients were not randomised and three randomised patients discontinued Part 1 of study 111. As not all of the patients enrolled received study drug treatment in Treatment Period 2, the numbers per treatment were lower than the total number of subjects enrolled in the study. Thirty-eight (38) patients who received ivacaftor and 37 patients who received placebo were evaluable for efficacy analysis.

The majority of patients in both Treatment Sequences were White (75.0% in Treatment Sequence 1 and 73.7% in Treatment Sequence 2) and of non-Hispanic or Latino ethnicity. The mean age was 23.8 years (range: 6 to 57) in Treatment Sequence 1 and 21.7 years (range: 6 to 47) in Treatment Sequence 2; there were 19 patients overall in the <18 years subgroup and 20 patients overall in the 18 years subgroup. Patients were enrolled in North America (22 [56.4%] subjects) and the EU (17 [43.6%] subjects).

Mean baseline sweat chloride value (overall 97.54 mmol/L) and mean PPFEV1 at baseline (overall 78.39%) were similar between the two Treatment Sequences. However, in Treatment Sequence 1 the minimum sweat chloride value was 12 mmol/l, i.e. completely within the normal range. This patient was a 57-year-old White female with *CFTR* genotype *S1251N*/*F508del*. At Day 1 (start of study drug dosing), she had a PPFEV1 value of 43.27% and a sweat chloride value of 12 mmol/L. After 8 weeks of ivacaftor treatment her PPFEV1 was 53.91% and her sweat chloride 5 mmol/L. The low baseline sweat chloride value and the presence of a hyperimmunoglobulin E syndrome that courses (among others) with sinus and lung (staphylococcal) infections of repetition that lead to chronic cystic lung disease as one of the later features of the disease question whether the lung phenotype of this patient indicates cystic fibrosis. However, the subgroup analysis by non-*G551D* gating mutation supports the efficacy of ivacaftor in patients with the *S1251N*-*CFTR* mutation and an exploratory analysis excluding this patient showed consistency with those of the analysis including this patient.

Maximum PPFEV1 was 118.7%. Distribution per PPFEV1 category was as follows: 7 patients (35%) in Treatment Sequence 1 and 6 (31.6%) in Treatment Sequence 2 had a baseline PPFEV1 of less than 70%. In the category from ≥70% to ≤90% these figures were 6 (30%) and 6 (31.6) respectively. Last, the number and percentage of patients with a PPFEV1 higher than 90% was 7 (35%) and 7 (36.8%) in Treatment Sequences 1 and 2, respectively.

The study intended to enrol a minimum of 2 patients per non-*G551D* mutation. The most frequent *CFTR* genotype was *S1251N*/*F508del* with 4 patients per Treatment Sequence, i.e. a total of 8 patients. Most subjects had the class II *F508del* mutation on the second *CFTR* allele (24 out of the 39 subjects).

Although the MAH concluded that the demography of subjects was generally balanced between the two treatment sequences there seems to be an uneven distribution of some factors between treatment sequences.

Mean body weight (Kg) was 59.8 Kg in Treatment Sequence 1 as compared to 55.1 in Treatment Sequence 2. However, the maximum body weight quoted in Treatment Sequence 2 is 126 kg. This body weight corresponds to a 39-year-old White male patient whose *CFTR* genotype was *F508del*/*G1349D*. At Day 1 (start of placebo dosing), he had a PPFEV1 value of 84.5%, a sweat chloride value of 104.5 mmol/L, and a BMI of 38.5 kg/m2. After 8 weeks of ivacaftor treatment his BMI was 40.0 kg/m2, his PPFEV1 was 85.0% and his sweat chloride value was 15 mmol/L. Concomitant medications as well as his medical history support the diagnosis of cystic fibrosis with pancreatic insufficiency. The MAH states that obesity is increasingly seen among patients with cystic fibrosis and

refer to literature[14] where the prevalence of overweight/obesity in a cross-sectional study of 68 patients with cystic fibrosis at a single centre in Greece was reported as 13.2% (9/68) using the 2005 Cystic Fibrosis Foundation criteria. The authors conclude that certain degree of obesity (i.e. below 23 kg/m2) in CF appears to exert a rather positive effect on lung function contrary to what is known about its role in non-CF populations. Overweight/obese patients in this study had pancreatic sufficiency (89.9%), mutations other than *F508del* (66.7%) and no traits of the metabolic syndrome. This does not seem to be the case of the obese patient enrolled in study 111 as he had pancreatic insufficiency and carried an *F508del-CFTR* mutation. There seems to be two additional patients with a BMI above 30 kg/m2 with a genotype that involves the *CFTR* mutations *G1244E* and *S549N*. There are also a number of patients in study 111 with a BMI above 25 kg/m2.

Genotype by gating mutation was evenly distributed except for *G1244E-CFTR* mutation (one patient in Treatment Sequence 1 and 4 patients in Treatment Sequence 2).

CFTR mutations may cause CF or be associated with *CFTR*-related disorders but they also may have no clinical consequences or have unknown or uncertain clinical relevance[15]. All of the non-*G551D* gating mutations discussed are missense mutations for which the clinical role is difficult to assess. Therefore, it seems important to ensure that patients enrolled in study 111 had a clinical phenotype that is consistent with the clinical picture of CF as requested per inclusion criteria. The diagnostic criteria used in study 111 are in line with consensus recommendations. However, 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 mutations present are disease-causing. This is particularly the case of missense mutations such as the non-*G551D* gating mutations considered in this procedure. 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 or borderline values.

The data provided show that 14 (70%) patients in Treatment Sequence 1 and 17 (89.5%) in Treatment Sequence 2 were pancreatic insufficient while 19 (95%) and 19 (100%) had CF lung disease.

The number of patients receiving pancreatic enzyme replacement therapy was 26, below the number of 31 who had pancreatic insufficiency. Overall, 65% (13) of patients and 36.8% (7) of patients in Treatment Sequences 1 and 2 respectively received or were receiving inhaled antibiotics. The number of bacterial carriers per Treatment Sequence was 4 (20.0%) and 2 (10.5%) respectively. On the other hand, the subgroup analysis by *P aeruginosa* infection status at baseline shows that the percentage of patients on placebo and ivacaftor who were positive for this variable was 54.1% (20 patients) and 47.4% (19), respectively. Nine patients on placebo (24.3%) and 8 on ivacaftor (21.1%) were receiving tobramycin while these figures for colistimethate sodium were 24.3% (9 patients) and 18.4% (7 patients), respectively.

Overall, there seems to be some mismatch between the number of patients with the above conditions and the numbers receiving medications intended for these conditions, e.g. there seems to be discrepancies between the numbers of patients who were positive at baseline for *P aeruginosa* infection and the number of patients who received inhaled antibiotics. It would have been desirable that the

[14] Panagopoulou P, Maria F, Nikolaou A, Nousia-Arvanitakis S. Prevalence of malnutrition and obesity among cystic fibrosis patients. Pediatr Int. 2013. doi: 10.1111/ped.12214 [Epub ahead of print].
[15] Castellani C et al. Consensus on the use and interpretation of cystic fibrosis mutation analysis in clinical practice. Journal of Cystic Fibrosis 7 (2008) 179–196.

patient population had been better characterised in terms of *P aeruginosa* lung infection/colonisation and in terms of patients receiving inhaled antibiotics for this reason.

The primary efficacy variable of study 111 was the absolute change from baseline in PPFEV1 through 8 weeks of treatment which 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. The primary efficacy analysis was based on a Mixed Effects Model for Repeated Measures (MMRM) in the Full Analysis Set. Sensitivity analyses to assess the robustness of the primary analysis were also performed.

Overall, the methods of the study 111 are considered acceptable and this study is deemed suitable to investigate efficacy in the particular CF genotypes.

Efficacy data and additional analyses

The mean absolute change from baseline in PPFEV1 through Week 8 by MMRM was greater during ivacaftor treatment (7.4868%) than during placebo treatment (-3.1912%). The estimated treatment difference (95%CI) for ivacaftor versus placebo was 10.6780% (7.2559, 14.1000). Statistically significant treatment differences were observed by Week 2 (first post-baseline time point assessed; 8.3142% [95% CI: 4.5109, 12.1175]) and were sustained through Week 8 (13.7554% [95% CI: 9.9414, 17.5694]. Sensitivity analyses supported the results of the main analysis.

The responder analysis of changes in PPFEV1 as well as the waterfall plot provided showed, however, that there were a number of patients whose FEV1 deteriorated while on ivacaftor. As a consequence, the MAH was asked to provide the individual narratives of these patients. The narratives of seven patients were discussed. Two of these patients with genotypes *S1251N/F508del* and *S549N/G542X* had the maximum decreases during ivacaftor treatment, i.e. -19.57 at week 8 and -6.97 at week 4, respectively. While it was stated that patient *S1251N/F508del* experienced a pulmonary exacerbation during ivacaftor treatment, the narrative of the patient with the genotype *S549N/G542X* did not offer any reasonable explanation for the observed decrease in FEV1 at week 4, nevertheless, the patient experienced a much more pronounced decline in FEV1 during placebo-treatment (-21.55).The remaining patients with genotypes *S549R/F508del*, *G178R/L1077P*, *G1244E/F508del*, *S1255P/Q1313X* and *G970R/F508del* had more limited decreases in lung function that ranged from -3.53 to -0.78.

Patients in the placebo group showed a decline in PPFEV1 that seems relatively rapid and consistent, but that has not been observed in the placebo arm of studies 102 and 103. In case this trend had continued during the 4-8 weeks washout period, the baseline PPFEV1 values of these patients in Sequence 2 would have been significantly lower than those of patients who were treated with ivacaftor in Sequence 1. As a consequence, the MAH was requested to address a possible inconsistency across studies in this regard and to provide the baseline characteristics and efficacy data separately for Sequence 1 and Sequence 2 (for both groups of patients, i.e. placebo-treated and ivacaftor-treated). It has been shown that outcomes at week 8 in studies 102 and 103 are similar to those observed in study 111. This is the case not only for the point estimates of the difference between treatments but also for the 95% confidence intervals that show a high degree of overlap. However, the absolute change from baseline trough week 8 in the placebo group differs between study 111 and studies 102 and 103 as shown by a mean change of -0.2 and -1.7 in studies 102 and 103 respectively and -5.85 in study 111. This relatively rapid and consistent decrease in FEV1 in study 111 could not be fully explained by the MAH. It is argued that likely the small numbers and the inherent variability in the disease may partially explain this issue. The response also shows that variability (assessed based on standard deviations) was systematically lower in the placebo group of the three studies than in the ivacaftor group.

Regarding the placebo group, the statistical MMRM model included sequence, treatment, period, and visit within period as fixed effects, study baseline value and age as covariates, and subject nested within sequence as the random effect. Therefore and taking into account the effects included in that model, it would be the sequence effect, confounded with a carry-over effect in a 2x2 design, which might be considered as a potential source of concern in the analysis but not the period effect. In principle, despite the lack of statistical significance of the sequence effect, that term might be still considered as a source of concern in case of relevant clinical magnitude. However, given the relatively small sample size and the observed magnitudes this is not the case. In summary, with the current data there is no evidence of a statistically or clinically relevant carry-over effects which could impair the interpretation of the study results.

Subgroup analyses of the main efficacy variable should be viewed with caution due to the small numbers but it is noticed that patients enrolled in the USA showed a lower mean absolute change from baseline in PPFEV1 of 6.1% as compared to that of patients enrolled in Europe (11.8%). No full explanation for the observed numerical difference in response seen between the two regions was provided, but this difference, in the opinion of the MAH, lacks clinical relevance given the overlap in the 95%CI intervals of the difference between treatments in the two regions. This can be accepted but it cannot be excluded that the patient population enrolled in these two regions could differ in some characteristics (e.g. the 4 patients with the *G970R-CFTR* mutation have been all enrolled in Europe) or that there could be differences in the standard of care that may help to explain this observation. As the overall results of the trial should be considered, no additional issues are raised in this regard.

Children aged 6 to less than 12 years showed a smaller change in PPFEV1 (5.2%) as compared to adolescents (9.2%) and adults (8.7%). The small number of children (overall n=8) and often the poor reproducibility of pulmonary function in them likely influenced the change in PPFEV1 seen in this population.

The presence of *P aeruginosa* infection at baseline (20 patients on placebo and 19 patients on ivacaftor) had little impact on the change in PPFEV1 (7.5% vs. 8.1% for those not having *P aeruginosa* infection at baseline).

Subgroup analysis by the non-*G551D* gating mutation was not initially performed. The MAH rationale that "… a reliable analysis of efficacy and safety results by genotype was not feasible because each mutation was only represented by a small number of patients" is acknowledged. However, given the potential heterogeneity of the patient population it was considered that an analysis by non-*G551D* gating mutation considering also the mutation in the second allele should have been provided and discussed as this could facilitate a more detailed evaluation on the consistency of efficacy across genotypes. As a consequence, these subgroup analyses were performed and discussed by the MAH. Efficacy results were presented and summarised at different points in time for the endpoints studied and for every non-*G551D* mutation. Results (confined to the changes in sweat chloride and PPFEV1) are shown for patients treated with ivacaftor in Table 29 of this report.

As stated in the section on clinical pharmacology the analysis of the relationship between *in vitro* (either as fold change over baseline in chloride transport or as percent of normal with ivacaftor) and *in vivo* data (absolute change from baseline at week 8 of ivacaftor treatment in any of the primary or secondary variables assessed in study 111) did not show a correlation or trend.

Summary statistics for absolute change in BMI by treatment arms and type of non-*G551D* mutation showed that the smallest increase in BMI was observed in patients with the *G551S*- and *G970R-CFTR* mutations. The smallest decrease in sweat chloride values during ivacaftor treatment was also seen in patients with the *G970R-CFTR* mutation compared to subjects with other *CFTR* mutations. This was

also the case of the respiratory domain of the CFQ-R, i.e. the smallest change in this parameter was observed in patients with the *G970R* mutation. The results by non-*G551D* gating mutation are included in Section 5.1 of the SmPC.

The overall conclusion is that patients carrying non-*G551D* gating mutations constitute a heterogeneous population. As part of the response to the CHMP Major Objection the MAH proposed to detail the individual *CFTR* gating mutations in section 4.1 of the SmPC (instead of the initial unrestricted indication proposed for all non-*G551D* gating mutations). However, for listing all mutations studied in trial 111 there are some signals which cannot be ignored, such as the consistent lower efficacy of ivacaftor in patients carrying a *G970R-CFTR* mutation.

Given this heterogeneity and as far as the rationale behind the lack of response to ivacaftor for specific mutations is unclear changes in sweat chloride and PPFEV1 by non-*G551D* gating mutation (including *G970R*) are being included in section 5.1 of the SmPC.

Analysis by the mutation affecting the second allele of the *CFTR* gene has been performed but not discussed by the MAH on grounds that about 75% of the study 111 patients had a second allele genotype that could be considered unresponsive to ivacaftor (i.e. *F508del-CFTR* and stop codon mutations) and, consequently, it is unlikely that the second allele had any substantial effect on the overall efficacy outcomes in this study. The results provided indicate that patients with a stop codon mutation are the ones who have the greatest reduction in sweat chloride with ivacaftor (-74.75 mmol/L) while at the same time experienced the smallest change in PPFEV1 (1.73). The stop codon mutations concerned are Y913X, G542X, or Q1313X. An additional stop codon mutation (R1158X) was mistakenly included in a different category for the analysis. The MAH stated that this does not impact the interpretation of the data for either grouping category.

Secondary endpoints were change from baseline in BMI at 8 weeks of treatment, change from baseline in sweat chloride through 8 weeks of treatment, change from baseline in the respiratory domain of the CFQ-R through 8 weeks of treatment and safety. As it can be seen for most efficacy variables the change from baseline is calculated through 8 weeks of treatment while for BMI it is estimated at week 8 suggesting that the expected change in BMI may be achieved later.

The mean absolute change from baseline in BMI at Week 8 (rate of change difference) by LMM was greater during ivacaftor treatment (0.6787 kg/m^2) than during placebo treatment (0.0163 kg/m^2). The treatment difference (95%CI) was 0.6624 kg/m^2 (0.3366, 0.9881). The mean absolute change from baseline in BMI-for-age z-score (CDC growth chart for the 19 subjects who were 20 years of age or younger) at Week 8 by LMM was greater during treatment with ivacaftor (0.2437 points) than during placebo treatment (-0.0392 points). The treatment difference (95%CI) was 0.2830 points (0.1167, 0.4492). Change from baseline in weight through Week 8 (tertiary endpoint) was greater during ivacaftor treatment (2.0099 kg) than during placebo treatment (0.3425 kg). The treatment difference (95% CI) was 1.6674 kg (0.7098, 2.6250).

The change from baseline in BMI was relatively rapid and the highest (0.9) in patients of 6-11 years of age. The MAH was requested to comment the possible role of water retention. The MAH response focused on showing that there is no signal that suggests problematic fluid retention in ivacaftor-treated patients. However, assessment of the nutritional status requires (in addition to weight or BMI) measurements of body composition, anthropometric and other measurements that have not been collected in the ivacaftor trials so far.

It can be suggested that the beneficial effect of ivacaftor on the nutritional status i.e. clinically meaningful increase in body weight is an indirect proof of the better absorption of lipids and proteins. In study 111, 63-65% of patients were treated with pancreatic enzymes for their insufficient enzyme

secretion. In order to refine evaluation of the effect of ivacaftor on the exocrine pancreatic function the MAH was requested to provide an analysis on BMI-z-scores by baseline use of pancreatic enzymes. The MAH's data and analyses showed that ivacaftor therapy should be optimized with exogenous pancreatic enzyme therapy in the majority of CF patients. An indirect proof that ivacaftor may improve the impaired exocrine pancreatic function (pancreatic bicarbonate secretion) has been provided[16].

The mean absolute change from baseline in sweat chloride (mmol/L) through Week 8 was greater during ivacaftor treatment (-52.2801 mmol/L) than during placebo treatment (-3.1134 mmol/L). The estimated treatment difference (95%CI) for ivacaftor versus placebo was -49.1667 mmol/L (-56.9527, -41.3807). Statistically significant treatment differences were detected by Week 2 (first post-baseline time point assessed).

The responder analysis of absolute change at Week 8 in sweat chloride shows that three subjects had a >20 mmol decrease in sweat chloride on placebo while similarly three subjects had <5 mmol decrease in sweat chloride while receiving ivacaftor. The waterfall plots provided of change in sweat chloride at weeks 2, 4, and 8 show that the majority of the patients had a clear reduction in sweat chloride during ivacaftor treatment, i.e. almost all mutations consistently displayed a decrease in sweat chloride well above 20 mmol/L with ivacaftor (see Figure 4).

Patients who had the smallest decreases in sweat chloride values while on treatment with ivacaftor all carried the *G970R-CFTR* mutation. The analysis at week 8 of the mean absolute change in sweat chloride shows that in 3 out of the 4 patients enrolled in study 111 the reduction was below 5 mmol/L and between 5 and 20 mmol/L for the remaining patient. Similarly, the mean (SD) absolute change in PPFEV1 at week 8 was 0.4 (3.7) and 2.6 (2.7) for placebo- and ivacaftor-treated patients. These results are comparatively inferior to those achieved by patients with other non-*G551D* gating mutations and, therefore, patients with a *G970R-CFTR* gating mutation should be excluded from the proposed indication given these consistent findings.

There were three patients with a decrease in sweat chloride above 20 mmol/L while on placebo. All of them had pancreatic insufficiency and their genotype (*G1349D/2183AA>G, S549R/F508del* and *S549N/N1303K*) did not suggested a specific pattern. The MAH has not provided any suitable explanation for this finding (methodological or otherwise). In spite of that, for all the mutations to be included in the indication there are patients substantially reducing their sweat chloride with ivacaftor even in relation to the placebo patients above mentioned. Given the small numbers it is considered that this evidence is sufficient.

The mean absolute change from baseline in the pooled (excluding the Parents and Caregivers version) CFQ-R respiratory domain score through Week 8 by MMRM was greater during ivacaftor treatment (8.9385 points) than during placebo treatment (-0.6720 points). The estimated treatment difference (95%CI) for ivacaftor versus placebo was 9.6105 points (4.4874, 14.7336) and exceeds the defined minimal clinically important difference (MCID) of 4 points. Subgroup analysis by age show that the change in CFQ-R respiratory domain score was not statistically significant in subjects aged 6-11 years and also in subjects who had ≥70% of PPFEV1 baseline values. CFQ-R is a relatively insensitive instrument, particularly in children and adolescents and therefore the lack of significant effect in these populations is not surprising.

A number of tertiary endpoints have been also assessed in study 111. Overall, their results are consistent with the analysis of the main and secondary endpoints although for some of them

[16] Gelfond D, Borowitz D, Frederick C, Uluer A, Sicilian L, Konstan M, et al. Impact of ivacaftor therapy on the intestinal pH profile in CF subjects with G551D mutation [abstract]. 27th Annual Meeting of the North American Cystic Fibrosis Conference, 17-19 October 2013, Salt Lake City, Utah; Abstract 540.

statistically significant differences versus placebo were not shown (e.g. pulmonary exacerbations event rate) but trends are not unfavourable for ivacaftor.

A tertiary endpoint assessed was change from baseline in qualitative microbiological cultures but the analysis was limited by the small number of subjects and a high incidence of unknown results for sputum samples. This is unfortunate as ivacaftor has a quionoline ring in its molecule and has been shown to have direct antibacterial activity against Gram-positive bacteria[17].

In conclusion, statistically significant differences in favour of ivacaftor 150 g every 12 hours versus placebo were seen in the primary and secondary endpoints of study 111. Results of the primary endpoint are not only statistically significant but also clinically relevant. However, the narratives provided for patients with unexpected results in sweat chloride while on treatment with ivacaftor or placebo and the analysis by specific non-*G551D* gating mutation show that the patient population is likely very heterogeneous and consequently a broader indication for patients with any non *G551D-CFTR* gating mutation cannot be accepted. The MAH's latest proposed indication is limited to the specific mutations that have been studied in study 111 and excluding the *G970R* mutation in which efficacy could not be demonstrated. This is endorsed.

Based on information provided on predictability of efficacy results in other studies through week 24 based on results through week 8, there seems to be a good agreement between results at week 8 and week 24. However, this is based on post-hoc analyses and as such conclusions should be drawn with caution.

The MAH stated that in their view the mutation-by-mutation approach to implementing personalized medicine for CF is not optimal as there will continue to be rare mutations discovered, including severe gating mutations, which can be functionally characterized but would have no practical pathway for being included in the label. This is acknowledged. However, as far as the rationale behind the lack of response to ivacaftor of specific mutations/patients is unclear it is not possible to ignore the consistent effect seen in patients with the *G970R-CFTR* mutation treated with ivacaftor. If a response-guided therapy were available (see below) this would be less of a concern as patients could be assessed individually. Overall, the MAH is encouraged to further pursue the characterisation of the mechanism of action of ivacaftor as well as the identification of individual factors that may be predictive of response to it.

The MAH was asked to elaborate and discuss a rule of decision that may help physicians to decide whether to keep or to interrupt treatment with ivacaftor based on these results, e.g. similarly to what has been done by Van Goor et al[18] for the predictive potential of the sweat chloride test in cystic fibrosis patients with the *G551D* mutation. However, as explained by the MAH a suitable response-guided therapy cannot be identified. Therefore, the indication for ivacaftor in patients with cystic fibrosis carrying a non-*G551D-CFTR* mutation should be based on the identification of those individual mutations for which a benefit is seen in a clinical study. As a consequence, the individual mutations have been listed in section 4.1 of the SmPC excluding, as previously discussed, the *G970R-CFTR* mutation. Data for this mutation are still included in section 5.1 of the SmPC.

2.4.4. Conclusions on the clinical efficacy

Statistically significant differences in the primary and secondary endpoints have been attained favouring ivacaftor over placebo in study 111 where patients aged 6 years and older with cystic fibrosis

[17] Leah Reznikov. Antibacterial Properties of the *CFTR* Potentiator Ivacaftor. Abstract 276, The 27th North American Cystic Fibrosis Conference, 2013
[18] Van Goor F. et al. The predictive potential of the sweat chloride test in cystic fibrosis patients with the G551D mutation. Journal of Cystic Fibrosis 12 (2013) 706–713.

and a non-*G551D* gating mutation in an allele of the *CFTR* gene were enrolled. Overall, these patients seem to have a mild to moderate disease phenotype. Consistency has been observed between the primary and secondary endpoints in study 111. This seems also to be the case across studies, i.e. with studies 102 and 103 in patients with a *G551D* mutation. In spite of the above results concerns were raised regarding the potential heterogeneity of gating mutations and the patient population enrolled in study 111, as well as on whether all of the non-*G551D* gating mutations assessed in this study were disease-causing. The narratives provided for patients with unexpected results in changes in sweat chloride while on treatment with ivacaftor or placebo and the analysis by specific non-*G551* gating mutation show that the patient population is indeed heterogeneous and consequently a broader indication for patients with any non *G551D-CFTR* gating mutation could not be accepted. As a consequence, the MAH proposed to limit the indication to the specific mutations that were assessed in study 111, excluding patients carrying the *G970R* gating mutation as for this mutation efficacy could not be demonstrated.

The discussion of a possible response guided therapy (i.e. a rule to identify patients who benefit from treatment with ivacaftor) was requested, however, a suitable response-guided therapy could not be identified.

2.5. Clinical safety

Introduction

The MAH provided in the current submission short-term safety data from patients with CF aged 6 years and older and a non-*G551D* gating mutation in an allele of the *CFTR* gene exposed to ivacaftor and/or placebo in Part 1 (20 to 24 week crossover study) of study 111.

Patient exposure

A total of 38 subjects who received ivacaftor treatment and 37 subjects who received placebo were evaluated for safety. Table below provides summary statistics for the mean duration of ivacaftor and placebo treatment.

Table 31. Study Drug Exposure, part 1, Safety Set

Exposure Summary	Statistic/ Category	Placebo (N = 37)	Ivacaftor (N = 38)
Exposure to Study Drug (Days)	Mean (SD)	56.4 (2.14)	54.7 (6.56)
	Median (Min, Max)	56.0 (52, 62)	56.0 (23, 60)
Exposure Classification (Weeks)	0 to <2	0	0
	2 to <4	0	1 (2.6)
	4 to <8	10 (27.0)	11 (28.9)
	≥8	27 (73.0)	26 (68.4)

Source: Table 14.1.8
Note: Exposure to Study Drug (days) was defined as the last known dose date – the first dose date within each Treatment Period + 1.

The mean treatment duration (SD) was similar for both ivacaftor (54.7 [6.56] days) and placebo (56.4 [2.14] days). The maximum study drug exposure was 60 days for ivacaftor and 62 days for placebo. Most subjects received at least 8 weeks of treatment; all but 1 subject received at least 4 weeks of treatment.

Subject disposition and the reasons provided by the investigator for the premature discontinuation of study drug in the non-pooled Phase 3 study (Study 111) are provided in the table below. In Part 1 of Study 111, 1 subject was lost to follow-up and 2 subjects discontinued for "other" reasons ("washout extended due to antibiotic usage" and "per sponsor, did not qualify to continue").

Table 32. Subject Disposition and Reasons for Discontinuation: Non-Pooled Phase 3 Study 111

	Placebo-Controlled Crossover Study 111, Part 1[a]		
	Ivacaftor→ Placebo[b] n (%)	Placebo→ Ivacaftor[c] n (%)	Overall n (%)
Safety Set	20 (100)	19 (100)	39 (100)
Full Analysis Set	20 (100)	19 (100)	39 (100)
Completed treatment	18 (90.0)	18 (94.7)	36 (92.3)
Discontinued treatment	2 (10.0)	1 (5.3)	3 (7.7)
Reason for discontinuation			
Adverse event	0	0	0
Lost to follow-up	1 (5.0)	0	1 (2.6)
Noncompliance with study requirements	0	0	0
Death	0	0	0
Physician decision	0	0	0
Pregnancy	0	0	0
Required prohibited medication	0	0	0
Study termination by sponsor	0	0	0
Withdrawal of consent	0	0	0
Other[d]	1 (5.0)	1 (5.3)	2 (5.1)

Source: Module 5.3.5.1/VX12-770-111/Table 10-1

[a] Percentages were calculated relative to the number of subjects in the Full Analysis Set (FAS). The FAS was defined as all 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.

[b] Treatment Sequence 1: ivacaftor in Treatment Period 1→Washout→placebo in Treatment Period 2.

[c] Treatment Sequence 2: placebo in Treatment Period 1→Washout→ivacaftor in Treatment Period 2.

[d] Other reasons subjects discontinued treatment were due to the need to extend the Washout Period ("washout extended due to antibiotic usage" and "per sponsor, did not qualify to continue").

Adverse events

In this crossover study, adverse events were attributed to the study drug (ivacaftor or placebo) the subject received during the treatment period in which the event occurred. Adverse events that started (or increased in severity) during the Washout Period between Treatment Period 1 and Treatment Period 2 were attributed to the treatment received in Treatment Period 1. Adverse event summary tables include TEAEs only. The incidence of adverse events is provided for Study 111 in the table below.

Table 33. Summary of Adverse Events Incidence: Phase 3 Crossover study 111

Category	Placebo (N = 37) n (%)	Ivacaftor (N = 38) n (%)
Subjects With Any Adverse Events	**31 (83.8)**	**28 (73.7)**
Subjects With Related Adverse Events	3 (8.1)	8 (21.1)
Subjects With Adverse Events Leading to Death	0	0
Subjects With SAEs	7 (18.9)	4 (10.5)
Subjects With Related SAEs	1 (2.7)	1 (2.6)
Subjects With Adverse Events Leading to Study Drug Interruption[a]	1 (2.7)	0
Subjects With Related Adverse Events Leading to Study Drug Interruption	0	0
Subjects With Adverse Events Leading to Study Drug Withdrawal	0	0

Source: Module 5.3.5.1/VX12-770-111/Table 12-2.
Note: Related includes related and possibly related to study drug categories.
[a] The number of subjects who had an adverse event that led to interruption of treatment with placebo does not include 3 subjects who had an interruption of study drug coincident with adverse events (Subject [redacted] [missing 18 doses], Subject [redacted] [missing 9 doses], and Subject [redacted] [missing 1 dose]). The investigator reported the interruptions as "missing doses" (Module 5.3.5.1/ VX12-770-111/Listing 16.2.5.2.1.3) and not as study drug interruptions for adverse events; therefore, these interruptions are not captured in the adverse events database or reflected in summary Module 5.3.5.1/ VX12-770-111/Table 14.3.1.1 and Module 5.3.5.1/VX12-770-111/ Listing 16.2.7.1.

The proportion of subjects with adverse events during ivacaftor treatment was 73.7% while the proportion of subjects with adverse events in the placebo group was 83.8%. The incidence of subjects with adverse events considered by the investigator to be related to the study drug was higher during ivacaftor (21.1%) than during placebo treatment (8.1%).

The adverse events with an incidence of at least 3% of subjects during either treatment are presented by SOC and PT in table below.

Table 34. Adverse Events Occurring in At Least 3% of Subjects During Either treatment by System Organ Class and Preferred Term, Part 1, Safety Set

System Organ Class Preferred Term	Placebo (N = 37) n (%)	Ivacaftor (N = 38) n (%)
Subjects With Any Adverse Events	**31 (83.8)**	**28 (73.7)**
Infections and Infestations	**17 (45.9)**	**15 (39.5)**
Infective Pulmonary Exacerbation of CF	11 (29.7)	9 (23.7)
Rhinitis	2 (5.4)	3 (7.9)
Influenza	2 (5.4)	2 (5.3)
Sinusitis	2 (5.4)	1 (2.6)
Upper Respiratory Tract Infection	2 (5.4)	1 (2.6)
Respiratory, Thoracic and Mediastinal disorders	**16 (43.2)**	**11 (28.9)**
Cough	7 (18.9)	5 (13.2)
Sputum Increased	3 (8.1)	3 (7.9)
Haemoptysis	2 (5.4)	1 (2.6)
Oropharyngeal Pain	4 (10.8)	1 (2.6)
Rales	3 (8.1)	1 (2.6)
Rhinorrhoea	2 (5.4)	1 (2.6)

System Organ Class Preferred Term	Placebo (N = 37) n (%)	Ivacaftor (N = 38) n (%)
Productive Cough	2 (5.4)	0
Respiratory Tract Congestion	2 (5.4)	0
Sinus Congestion	2 (5.4)	0
General disorders and Administration Site Conditions	**2 (5.4)**	**9 (23.7)**
Pyrexia	1 (2.7)	3 (7.9)
Fatigue	0	2 (5.3)
Gastrointestinal Disorders	**12 (32.4)**	**6 (15.8)**
Constipation	0	2 (5.3)
Abdominal Pain	4 (10.8)	1 (2.6)
Nausea	3 (8.1)	1 (2.6)
Flatulence	2 (5.4)	0
Gastrooesophageal Reflux Disease	2 (5.4)	0
Nervous System Disorders	**6 (16.2)**	**5 (13.2)**
Headache	5 (13.5)	3 (7.9)
Investigations	**2 (5.4)**	**4 (10.5)**
Musculoskeletal and Connective Tissue Disorders	**1 (2.7)**	**4 (10.5)**
Arthralgia	0	2 (5.3)
Skin and subcutaneous tissue disorders	**5 (13.5)**	**4 (10.5)**
Rash	2 (5.4)	1 (2.6)

Source: Table 14.3.1.2.1

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.

The SOC with the highest incidence of adverse events during both treatments was infections and infestations (39.5% during ivacaftor and 45.9% during placebo treatment). Other classes with an incidence of at least 10% during ivacaftor treatment and a higher incidence than during placebo treatment were as follows:

- General disorders and administration site conditions (23.7% during ivacaftor treatment and 5.4% during placebo)
- Investigations (10.5% during ivacaftor treatment and 5.4% during placebo)
- Musculoskeletal and connective tissue disorders (10.5% during ivacaftor treatment and 2.7% during placebo)

By PT, the adverse events with the highest incidence during both treatments were infective pulmonary exacerbation of CF and cough. The incidence of both events was lower during ivacaftor than placebo treatment:

- Infective pulmonary exacerbation of CF (23.7% of subjects during ivacaftor treatment and 29.7% of subjects during placebo)
- Cough (13.2% of subjects during ivacaftor treatment and 18.9% of subjects during placebo)

Adverse events for which the incidence was at least 5% higher with ivacaftor than placebo treatment were as follows:

- Fatigue (5.3% [2 subjects] ivacaftor treatment and 0 subjects during placebo treatment)
- Constipation (5.3% [2 subjects] during ivacaftor treatment and 0 subjects during placebo treatment)

- Arthralgia (5.3% [2 subjects] during ivacaftor treatment and 0 subjects during placebo treatment)
- Pyrexia (7.9% [3 subjects] during ivacaftor treatment and 2.7% [1 subject] during placebo treatment)

The majority of adverse events during both treatments were considered by the investigator to be not related or unlikely related to the study drug (not related: 28.9% during ivacaftor and 40.5% during placebo treatment; unlikely related: 23.7% during ivacaftor and 35.1% during placebo treatment). The proportion of subjects who had adverse events considered by the investigator to be possibly related to the study drug was higher during ivacaftor (21.1% [8 subjects]) than during placebo treatment (8.1% [3 subjects]).

The incidence of all adverse events considered related or possibly related to the study drug by SOC and PT is presented in table below.

Table 35. Related or Possibly Related Adverse Events by System Organ Class and Preferred Term by Treatment, Part 1, Safety Set

System Organ Class Preferred Term	Placebo (N = 37) n (%)	Ivacaftor (N = 38) n (%)
Subjects With Any Related Adverse Events	**3 (8.1)**	**8 (21.1)**
Respiratory, Thoracic and Mediastinal Disorders	**1 (2.7)**	**3 (7.9)**
Sputum Increased	0	2 (5.3)
Dysphonia	0	1 (2.6)
Haemoptysis	0	1 (2.6)
Paranasal Cyst	1 (2.7)	0
Investigations	**0**	**2 (5.3)**
Alanine Aminotransferase Increased	0	1 (2.6)
Blood Creatinine Increased	0	1 (2.6)
Gamma-Glutamyl Transferase Increased	0	1 (2.6)
Blood and Lymphatic System Disorders	**0**	**1 (2.6)**
Anaemia	0	1 (2.6)
Gastrointestinal Disorders	**0**	**1 (2.6)**
Distal Ileal Obstruction Syndrome	0	1 (2.6)
Nervous System Disorders	**0**	**1 (2.6)**
Dysgeusia	0	1 (2.6)
Reproductive System and Breast Disorders	**0**	**1 (2.6)**
Metrorrhagia	0	1 (2.6)
Skin and Subcutaneous Tissue Disorders	**2 (5.4)**	**0**
Rash	1 (2.7)	0
Urticaria	1 (2.7)	0

Source: Table 14.3.1.4

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

During both treatments, the majority of subjects had adverse events that were mild or moderate in severity. Compared with placebo, ivacaftor was associated with a lower incidence of moderate and severe events (moderate: 18.4% during ivacaftor treatment versus 35.1% during placebo treatment; severe: 10.5% during ivacaftor treatment versus 21.6% during placebo treatment). There were no life-threatening adverse events in this study.

The severe adverse events that occurred during the study are presented by SOC and PT in table below.

Table 36. Severe Adverse Events by Treatment: Safety Set

System Organ Class Preferred Term	Placebo (N = 37) n (%)	Ivacaftor (N = 38) n (%)
Subjects With Any Severe Adverse Events	**8 (21.6)**	**4 (10.5)**
Infections and Infestations	**3 (8.1)**	**2 (5.3)**
Infective Pulmonary Exacerbation of CF	2 (5.4)	2 (5.3)
Tonsillitis	1 (2.7)	0
Respiratory, Thoracic and Mediastinal Disorders	**2 (5.4)**	**0**
Paranasal Cyst	1 (2.7)	0
Pneumothorax	1 (2.7)	0
Gastrointestinal Disorders	**3 (8.1)**	**1 (2.6)**
Distal Ileal Obstruction Syndrome	1 (2.7)	1 (2.6)
Appendiceal Mucocoele	1 (2.7)	0
Distal Intestinal Obstruction Syndrome	1 (2.7)	0
Intussusception	1 (2.7)	0
Nervous System Disorders	**0**	**1 (2.6)**
Headache	0	1 (2.6)
Investigations	**1 (2.7)**	**0**
Hepatic Enzyme Increased	1 (2.7)	0
Musculoskeletal and Connective Tissue Disorders	**0**	1 (2.6)
Intervertebral Disc Protrusion	0	1 (2.6)

Source: Table 14.3.1.5

Notes: SOC and PT within SOC are sorted in descending order of frequency in the ivacaftor column. PT n (%) = n/N × 100. A subject with multiple events within a SOC or within a PT is counted only once within a SOC or PT, respectively. A subject with multiple severities for the same AE is counted only under the AE with the maximum severity. Adverse events were coded from MedDRA, Version 15.1.

Subgroup Analyses of Adverse Events

Adverse events were summarized for subgroups based on age at baseline (6 to 11 years [inclusive], 12 to 17 years [inclusive], and ≥18 years at baseline), sex (female and male), PPFEV1 at baseline (<70%, ≥70% to ≤90%, and >90% predicted), and geographic region (North America and Europe).

Age subset

Table below provides the adverse events with an incidence of at least 15% by age group.

Table 37. Adverse Events Occurring in At Least 15% of Subjects During Either Treatments by Preferred Term and Age Subgroups, Part 1, Safety Set

System Organ Class Preferred Term	Placebo Age 6 to 11 Years (Inclusive) (N = 8) n (%)	Placebo Age 12 to 17 Years (Inclusive) (N = 9) n (%)	Placebo Age ≥18 Years (N = 20) n (%)	Ivacaftor Age 6 to 11 Years (Inclusive) (N = 8) n (%)	Ivacaftor Age 12 to 17 Years (Inclusive) (N = 11) n (%)	Ivacaftor Age ≥18 Years (N = 19) n (%)
Subjects With Any Adverse Events	**8 (100.0)**	**8 (88.9)**	**15 (75.0)**	**7 (87.5)**	**10 (90.9)**	**11 (57.9)**
Subjects With Any SAEs	**3 (37.5)**	**1 (11.1)**	**3 (15.0)**	**1 (12.5)**	**0**	**3 (15.8)**
Infections and Infestations	**6 (75.0)**	**3 (33.3)**	**8 (40.0)**	**4 (50.0)**	**6 (54.5)**	**5 (26.3)**
Infective Pulmonary Exacerbation of CF	3 (37.5)	3 (33.3)	5 (25.0)	2 (25.0)	4 (36.4)	3 (15.8)
General Disorders and Administration Site Conditions	**0**	**1 (11.1)**	**1 (5.0)**	**1 (12.5)**	**5 (45.5)**	**3 (15.8)**
Pyrexia	0	1 (11.1)	0	1 (12.5)	2 (18.2)	0
Respiratory, Thoracic and Mediastinal disorders	**4 (50.0)**	**4 (44.4)**	**8 (40.0)**	**0**	**4 (36.4)**	**7 (36.8)**
Cough	1 (12.5)	2 (22.2)	4 (20.0)	0	1 (9.1)	4 (21.1)
Sputum Increased	0	1 (11.1)	2 (10.0)	0	2 (18.2)	1 (5.3)
Rhinorrhoea	0	2 (22.2)	0	0	1 (9.1)	0
Oropharyngeal Pain	0	2 (22.2)	2 (10.0)	0	0	1 (5.3)
Nervous System Disorders	**1 (12.5)**	**2 (22.2)**	**3 (15.0)**	**0**	**2 (18.2)**	**3 (15.8)**
Headache	1 (12.5)	2 (22.2)	2 (10.0)	0	2 (18.2)	1 (5.3)

Sources: Table 14.3.1.2.2, Listing 16.2.7.1, and Listing 16.2.4.1.1

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.

Sex

Table below provides the subgroup analysis of adverse events with an incidence of at least 15% by sex.

Table 38. Adverse Events Occurring in At Least 15% of Subjects During Either Treatment by Preferred Term and Sex Subgroups, Part 1, Safety Set

System Organ Class Preferred Term	Placebo Male (N = 22) n (%)	Placebo Female N = 15 n (%)	Ivacaftor Male (N = 22) n (%)	Ivacaftor Female N = 16 n (%)
Subjects With Any Adverse Events	**18 (81.8)**	**13 (86.7)**	**16 (72.7)**	**12 (75.0)**
Infections and Infestations	**9 (40.9)**	**8 (53.3)**	**8 (36.4)**	**7 (43.8)**
Infective Pulmonary Exacerbation of CF	4 (18.2)	7 (46.7)	6 (27.3)	3 (18.8)
Rhinitis	2 (9.1)	0	0	3 (18.8)
Respiratory, Thoracic and Mediastinal Disorders	**10 (45.5)**	**6 (40.0)**	**6 (27.3)**	**5 (31.3)**
Cough	3 (13.6)	4 (26.7)	2 (9.1)	3 (18.8)
Rales	0	3 (20.0)	0	1 (6.3)
Gastrointestinal Disorders	**7 (31.8)**	**5 (33.3)**	**3 (13.6)**	**3 (18.8)**
Nausea	0	3 (20.0)	0	1 (6.3)
Nervous system Disorders	**5 (22.7)**	**1 (6.7)**	**3 (13.6)**	**2 (12.5)**
Headache	4 (18.2)	1 (6.7)	2 (9.1)	1 (6.3)

Source: Table 14.3.1.2.2

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

Baseline PPFEV1

Table below provides the baseline PPFEV1 value subgroup analysis results for adverse events with an incidence of at least 15%.

Table 39. Adverse Events Occurring in At Least 15% of Subjects During Either Treatment by Preferred Term and Baseline FEV1 Predicted Value Subgroups, Part 1, Safety Set

	Placebo			Ivacaftor		
	Percent Predicted FEV_1 Severity			Percent Predicted FEV_1 Severity		
System Organ Class Preferred Term	<70% N = 13 n (%)	≥70% to ≤90% N = 11 n (%)	>90% N = 13 n (%)	<70% N = 13 n (%)	≥70% to ≤90% N = 11 n (%)	>90% N = 14 n (%)
Subjects With Any Adverse Events	**11 (84.6)**	**9 (81.8)**	**11 (84.6)**	**7 (53.8)**	**8 (72.7)**	**13 (92.9)**
Infections and Infestations	**9 (69.2)**	**3 (27.3)**	**5 (38.5)**	**4 (30.8)**	**3 (27.3)**	**8 (57.1)**
Infective Pulmonary Exacerbation of CF	6 (46.2)	2 (18.2)	3 (23.1)	4 (30.8)	2 (18.2)	3 (21.4)
Rhinitis	2 (15.4)	0	0	0	1 (9.1)	2 (14.3)
Respiratory, Thoracic and Mediastinal Disorders	**7 (53.8)**	**6 (54.5)**	**3 (23.1)**	**3 (23.1)**	**3 (27.3)**	**5 (35.7)**
Cough	2 (15.4)	4 (36.4)	1 (7.7)	2 (15.4)	0	3 (21.4)
Haemoptysis	2 (15.4)	0	0	0	1 (9.1)	0
Rales	2 (15.4)	0	1 (7.7)	1 (7.7)	0	0
Oropharyngeal Pain	1 (7.7)	3 (27.3)	0	1 (7.7)	0	**0**
Productive cough	2 (15.4)	0	0	0	0	0
General Disorders and Administration Site Conditions	**1 (7.7)**	**0**	**1 (7.7)**	**2 (15.4)**	**4 (36.4)**	**3 (21.4)**
Pyrexia	0	0	1 (7.7)	0	2 (18.2)	1 (7.1)
Gastrointestinal Disorders	**3 (23.1)**	**4 (36.4)**	**5 (38.5)**	**0**	**3 (27.3)**	**3 (21.4)**
Constipation	0	0	0	0	2 (18.2)	0
Abdominal Pain	1 (7.7)	1 (9.1)	2 (15.4)	0	0	1 (7.1)
Nausea	0	0	3 (23.1)	0	0	1 (7.1)
Nervous System Disorders	**0**	**2 (18.2)**	**4 (30.8)**	**2 (15.4)**	**1 (9.1)**	**2 (14.3)**
Headache	0	1 (9.1)	4 (30.8)	0	1 (9.1)	2 (14.3)
Skin and Subcutaneous Tissue Disorders	**0**	**4 (36.4)**	**1(7.7)**	**3 (23.1)**	**0**	**1(7.1)**
Rash	0	2 (18.2)	0	1 (7.7)	0	0

Source: Table 14.3.1.2.2

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

Geographic Region

Table below provides the subgroup analysis by geographic region.

Table 40. Adverse Events Occurring in At Least 15% of Subjects During Either Treatment by Preferred term and Geographic Region Subgroups, Part 1, safety Set

	Placebo		Ivacaftor	
	North America	Europe	North America	Europe
System Organ Class Preferred Term	N = 21 n (%)	N = 16 n (%)	N = 21 n (%)	N = 17 n (%)
Subjects With Any Adverse Events	**16 (76.2)**	**15 (93.8)**	**15 (71.4)**	**13 (76.5)**
Infections and Infestations	**11 (52.4)**	**6 (37.5)**	**7 (33.3)**	**8 (47.1)**
Infective Pulmonary Exacerbation of CF	9 (42.9)	2 (12.5)	4 (19.0)	5 (29.4)
Rhinitis	0	2 (12.5)	0	3 (17.6)
Respiratory, Thoracic and Mediastinal Disorders	**10 (47.6)**	**6 (37.5)**	**6 (28.6)**	**5 (29.4)**
Cough	6 (28.6)	1 (6.3)	3 (14.3)	2 (11.8)
Oropharyngeal Pain	4 (19.0)	0	1 (4.8)	0
Gastrointestinal Disorders	**4 (19.0)**	**8 (50.0)**	**0**	**6 (35.3)**
Abdominal Pain	1 (4.8)	3 (18.8)	0	1 (5.9)
Nausea	0	3 (18.8)	0	1 (5.9)
Nervous System Disorders	**2 (9.5)**	**4 (25.0)**	**1 (4.8)**	**4 (23.5)**
Headache	1 (4.8)	4 (25.0)	0	3 (17.6)

Source: Table 14.3.1.2.2

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

Serious adverse events, deaths, other significant events

There were no deaths in this study.

The proportion of subjects with at least 1 serious adverse event (SAE) during ivacaftor treatment was 10.5% as compared to 18.9% of patients in the placebo group. The incidence of SAEs considered by the investigator to be related to the study drug was similar during the 2 treatments: 2.6% during ivacaftor and 2.7% during placebo treatment. During each treatment, 1 subject had a SAE considered possibly related to study drug (paranasal cyst during placebo treatment and DIOS during ivacaftor treatment). Table below presents the incidence of SAEs by SOC and PT.

Table 41. Serious Adverse Events by System Organ Class and Preferred Term; Safety Set

System Organ Class Preferred Term	Placebo (N = 37) n (%)	Ivacaftor (N = 38) n (%)
Subjects With Any Serious Adverse Events	**7 (18.9)**	**4 (10.5)**
Infections and Infestations	**6 (16.2)**	**2 (5.3)**
Infective Pulmonary Exacerbation of CF	6 (16.2)	2 (5.3)
Gastrointestinal Disorders	**1 (2.7)**	**1 (2.6)**
Distal Ileal Obstruction Syndrome	0	1 (2.6)
Appendiceal Mucocoele	1 (2.7)	0
Intussusception	1 (2.7)	0
Musculoskeletal and Connective Tissue Disorders	**0**	**1 (2.6)**
Intervertebral Disc Protrusion	0	1 (2.6)
Respiratory, Thoracic and Mediastinal Disorders	**2 (5.4)**	**0**
Paranasal Cyst	1 (2.7)	0
Pneumothorax	1 (2.7)	0

Source: Table 14.3.2.1

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

Laboratory findings

Clinical laboratory evaluations were conducted at baseline and at 2, 4, and 8 weeks following the first dose of each treatment.

Liver Function Tests

Mean absolute changes from baseline for LFT parameters are presented in table below.

Table 42. Liver Function Test Parameter Absolute Changes From Baseline at Week 8, Part 1, Safety Set

	Placebo N = 37				Ivacaftor N = 38			
Parameter	n	Mean Change (SD)	Median Change	Min/Max	n	Mean Change (SD)	Median Change	Min/Max
Alanine Transaminase (U/L)	37	−1.3 (12.71)	1.0	−44/16	36	4.6 (12.78)	2.0	−15/50
Alkaline Phosphatase (U/L)	37	0.3 (21.21)	1.0	−55/70	35	−4.2 (19.09)	−7.0	−47/44
Aspartate Transaminase (U/L)	37	0.08 (9.754)	0.0	−35/28.0	35	3.26 (8.318)	2.00	−8.0/28.0
Gamma-glutamyl Transferase (U/L)	37	−2.30 (5.806)	−1.00	−22.0/10.0	36	1.64 (9.430)	1.00	−20.0/37.0
Total Bilirubin (µmol/L)	37	−0.3 (2.65)	0.0	−7/4	36	1.3 (3.95)	0.0	−3/19

Source: Table 14.3.4.3

Notes: Period baseline was defined as the most recent non-missing measurement collected before the initial administration of study drug in each Treatment Period, with the additional requirement for the Treatment Period 2 baseline that it needed to be from an assessment after 14 days in the Washout Period. If the Treatment Period 2 baseline was missing, the Treatment Period 1 baseline was used.

Most subjects had maximum on-treatment ALT, AST, and total bilirubin results ≤2 × ULN (94.7%, 100.0%, and 100.0%, respectively, on ivacaftor treatment and 91.9%, 97.3%, and 100.0%, respectively, on placebo treatment). No differences >5% were noted between the placebo and ivacaftor treatments for any category (≤2 × ULN, >2 × to ≤3 × ULN, >3 × to ≤5 × ULN, >5 × to ≤8 × ULN, and >8 × ULN).

During ivacaftor treatment, no subjects had a maximum ALT or AST value that was >5 × ULN. Two (5.3%) subjects had at least 1 maximum ALT value >3 x ULN to ≤5 x ULN. During placebo treatment, 1 subject (2.7%) had ALT >2 x ULN to ≤3 x ULN, 1 subject (2.7%) had ALT >3 x ULN to ≤5 x ULN, and 1 subject (2.7%) had a maximum on-treatment ALT and AST values >8 × ULN. No subjects had a maximum total bilirubin value >2 × ULN during either treatment.

One subject had normal ALT (24 U/L) and AST (33 U/L) values at baseline and received placebo during Treatment Period 1. At Week 2 (Day 15 after the first dose of placebo), the subject's ALT and AST values were found to be elevated: ALT of 558 U/L (>8 × ULN) and AST of 955 U/L (>8 × ULN). An adverse event of increased hepatic enzymes occurred, and study drug was interrupted. Results of laboratory assessments obtained at the local laboratory within 2 days (Study Day 17) of the initial elevation showed that ALT was 288 U/L (>3 x ULN to ≤5 x ULN) and AST was 63 U/L (≤2 x ULN). At the next assessment on Study Day 22, ALT had further declined to 114 U/L, and AST was 90 U/L. By Week 4, ALT was 69 U/L (>2 × ULN), and by Week 8, it had further decreased to 34 U/L (≤2 × ULN). AST values returned to ≤2 × ULN by Week 8 (48 U/L). Study drug was resumed on Day 28, and the subject continued in the study with no further LFT increases. Bilirubin values were not elevated at any time during this placebo treatment.

None of the subjects had elevations of LFTs that met the criteria for Hy's Law.

Other clinical chemistry parameters (creatinine, total protein, and albumin)

The mean values for all parameters fluctuated during each treatment but remained within normal limits at all time points. The slight changes in each parameter were generally consistent for both treatments, and no notable trends were observed over time. Overall, shifts to low or high values were infrequent throughout the study, and the incidence of shifts was similar for both treatments.

Adverse events associated with abnormal chemistry values occurred infrequently, and none resulted in the discontinuation of study drug. Adverse events of ALT increased, blood creatinine increased, CRP increased, and GGT increased were each reported by 1 subject (2.6%) during ivacaftor treatment; hypoglycaemia and hepatic enzyme increased were each reported by 1 subject (2.7%) during placebo treatment.

Haematology

Mean concentrations for all parameters remained relatively stable and within normal limits through Week 8. The slight changes from baseline in most parameters were similar for both treatments. During ivacaftor treatment, mean values for haemoglobin, neutrophils, platelets, and leukocytes demonstrated a trend toward decreases from baseline up to Week 4 and remained relatively stable thereafter. The magnitude of the mean change for these same parameters was smaller during placebo treatment. The incidence of shifts to low or high values was generally similar during both treatments.

Adverse events associated with abnormal haematology values were infrequent, and none resulted in the discontinuation of study drug. Adverse events associated with abnormal haematology values included neutrophil count increased, WBC count increased, and anaemia, each reported by 1 subject (2.6%) during ivacaftor treatment.

Coagulation

Mean absolute changes from baseline in prothrombin time remained relatively stable throughout both treatments. Twenty subjects had at least 1 abnormal thromboplastin or prothrombin time value during the study; however, these abnormalities occurred with similar incidence during both treatments, and none of the subjects had adverse events related to abnormal coagulation parameters during either treatment.

ECG

There were no clinically important trends attributable to ivacaftor treatment identified in the standard digital ECGs. None of the patients had a QTc interval >450 msec during the ivacaftor or placebo treatment. Two patients (5.3%) had maximum increases of >30 to ≤60 msec in QTcF during the ivacaftor treatment. Increases in QTcB of >30 to ≤60 msec were observed in 3 patiens (8.1%) during the placebo treatment and 3 patients (7.9%) during the ivacaftor treatment. None of the patients had a QTcF or QTcB increase of >60 msec during either treatment. There were no adverse events associated with ECG abnormalities in study 111.

Adverse events of interest – increased airway secretions

Due to a report in literature[19] that "increased bronchial secretions may warrant increased physiotherapy and intravenous antibiotic treatment in these patients when ivacaftor is initiated" the MAH was asked to discuss increased airway secretions.

According to the MAH, the review of the available clinical data did not suggest that the first 8 weeks of ivacaftor treatment was associated with increased airway secretions or increased secretions that would lead to the need for clinical intervention, including additional intravenous antibiotic therapy in subjects with severe CF (<40% predicted FEV1). In placebo-controlled, Phase 3 studies, no increase in the incidence of events associated with increased airway secretions in ivacaftor-treated subjects (10.0%) compared with placebo (11.5%) was observed. Several other literature reports describe the clinical experience of compassionate use ivacaftor in patients with an FEV1 <40%, and do not include mention an increase in airway secretions. In preliminary data from the US expanded access programme, 4 out of 44 (9.1%) patients had increased secretions (comprising preferred terms of respiratory tract congestion and sputum increased) comparable to the rate observed in the first 8 weeks of treatment in the Phase 3 studies. Additionally, events with onset within 8 weeks of the start of ivacaftor treatment were all non-serious, mild in severity, and most resolved without treatment.

Safety in special populations

In Study 111, the incidence of adverse events was summarized for subgroups based on age at baseline (6 to 11 years [inclusive], 12 to 17 years [inclusive], and ≥18 years at baseline), sex (female and male), PPFEV1 severity at baseline (<70%, ≥70% to ≤90%, and >90% predicted), and geographic region (North America and Europe). While small sample sizes in the subgroups preclude definitive conclusions, subgroup analyses did not suggest any notable differences in safety based on age, sex, baseline FEV1 severity, or geographic region. A meaningful analysis of safety by genotype was not feasible because each mutation was only represented by a small number of subjects. Safety results of the subgroup analyses based on age, sex, baseline PPFEV1, and geographic region have been presented previously.

Discontinuation due to adverse events

No subjects had adverse events that led to study drug interruption during ivacaftor treatment. During placebo treatment, 1 subject (2.7%) had an adverse event of increased hepatic enzymes that led to study drug interruption. The event resolved and the subject resumed dosing and continued in the study following the interruption.

During placebo treatment, 3 other subjects had an interruption of study drug coincident with adverse events (Subject [missed 18 doses], Subject [missed 9 doses], and Subject [missed 1 dose]). However, the investigator reported the interruptions as "missing doses" and not as study drug interruptions for adverse events.

Post marketing experience

Ivacaftor is marketed in the US, European Union, Canada, and Australia. A cumulative and interval summary tabulation of serious and non-serious adverse reactions was provided in second Periodic Safety Update Report (24 January 2013 to 23 July 2013), which covered a total of 1789 patients and

[19] Hebestreit et al. Effects of ivacaftor on severely ill patients with cystic fibrosis carrying a *G551D* mutation. Journal of Cystic Fibrosis 12 (2013) 599-603

489018 person-days (286 patients 6 to 11 years of age) who received at least 1 dose of ivacaftor during the time period from the International Birth Date of ivacaftor (31 January 2012) to 23 July 2013. There has been no significant change in the potential or identified risks and no new potential or identified risks.

2.5.1. Discussion on clinical safety

Short-term safety data from patients with CF aged 6 years and older and a non-*G551D-CFTR* gating mutation exposed to ivacaftor and/or placebo in Part 1 of study 111 were provided.

The Safety Set includes 39 patients who were randomised to Treatment Sequence 1 (n=20) and Treatment Sequence 2 (n=19). Twenty-seven (73%) placebo-treated patients and 26 (68.4%) ivacaftor-treated patients received at least 8 weeks of treatment while the median length of therapy in 10 (27.0%) and 11 (28.9) patients respectively was from 4 to less than 8 weeks. All patients but 1 subject received at least 4 weeks of treatment.

The proportion of patients with adverse events during ivacaftor treatment was 73.7% (28/38) while the proportion of patients with adverse events in the placebo group was 83.8% (31/37). Twenty-eight ivacaftor-treated patients reported a total of 91 adverse events while 31 placebo-treated patients reported 109 adverse events.

The SOC with the highest incidence of adverse events during both treatments was Infections and Infestations (39.5% during ivacaftor and 45.9% during placebo treatment). Within this SOC infective pulmonary exacerbation of CF were reported by 9 (23.7%) patients during ivacaftor treatment and 11 (29.7%) patients during placebo. Sputum increased was reported by 3 (7.9%) ivacaftor-treated patients and 3 (8.1%) placebo-treated patients.

By Preferred Term the incidence of the following adverse events was higher in ivacaftor-treated patients than in placebo-treated patients: rhinitis was reported by 3 (7.9%) ivacaftor patients and 2 (5.4%) placebo patients; pyrexia was reported by 3 (7.9%) ivacaftor patients and 1 (2.7%) placebo patient; fatigue and constipation were reported by 2 (5.3%) ivacaftor patients each; in the SOC Investigations 4 (10.5%) ivacaftor patients reported some adverse event versus 2 (5.4%) placebo patients. The adverse events that belong to the SOC Investigations will be addressed later (see Liver Function Tests). Arthralgia was reported by 2 (5.3%) ivacaftor patients. However, the number of adverse events reported in the SOC Musculoskeletal and Connective Tissue Disorders is 4 in the ivacaftor group. The remaining adverse events reported were intervertebral disk protrusion (1 event), back pain (1 event) and torticollis (1 event). Pyrexia is described within the SOC General Disorders and Administration Site Conditions. The number of patients reporting adverse events in this SOC is 9 (23.7%) for ivacaftor and 2 (5.4%) for placebo. Other Preferred Terms used within this SOC are malaise and fatigue that have been reported only by ivacaftor-treated patients.

The incidence of patients with adverse events considered by the investigator to be related to the study drug (i.e. adverse reactions) was higher during ivacaftor (21.1% [8 patients]) than during placebo treatment (8.1%, [3 patients]). By Preferred Term sputum increased was reported by 2 (5.3%) ivacaftor-treated patients while none of the placebo patients reported this adverse reaction. Treatment-related investigations (increased ALT, increased blood creatinine, increased GGT) only occurred during ivacaftor treatment (5.3% [2 patients]) while treatment-related skin and subcutaneous tissue disorders only occurred during placebo treatment (5.4% [2 patients]). The incidence of adverse reactions in all other SOCs was 1 patient during ivacaftor treatment and the Preferred Terms include anaemia, dysgeusia, distal ileal obstructive syndrome and metrorrhagia. The

incidence of adverse events considered related or possibly related to study drug during placebo treatment was 1 patient (2.7%) each for paranasal cyst, rash, and urticaria.

Regarding the severity of the adverse events reported, compared with placebo, ivacaftor was associated with a lower incidence of moderate and severe events (moderate: 18.4% during ivacaftor treatment versus 35.1% during placebo treatment; severe: 10.5% during ivacaftor treatment versus 21.6% during placebo treatment). There were no life-threatening adverse events in study 111. There was a severe adverse event of headache in an ivacaftor-treated patient that apparently was not considered treatment related although headache is listed in section 4.8 of the Kalydeco SmPC as a very common adverse reaction.

There were no deaths in study 111. The number of patients with at least 1 serious adverse event (SAE) during ivacaftor treatment was 4 (10.5%) as compared to 7 (18.9%) patients in the placebo group. The most common SAE during both treatments was infective pulmonary exacerbation of CF (5.3% [2 patients] during ivacaftor treatment and 16.2% [6 patients] during placebo treatment). SAEs of DIOS and intervertebral disc protrusion were each reported for 1 patient during ivacaftor treatment; appendiceal mucocele, intussusception, paranasal cyst, and pneumothorax were each reported for 1 patient during placebo treatment. During each treatment, 1 patient had a SAE considered possibly related to study drug (paranasal cyst during placebo treatment and DIOS during ivacaftor treatment).

Interpretation of safety analysis by subgroups is hampered by the small number of patients and therefore it should be considered exploratory only.

A total of 8 patients aged 6 to 11 years (inclusive) received ivacaftor and placebo; among patients aged 12 to 17 years (inclusive), 9 patients received placebo and 11 patients received ivacaftor treatment. In the subgroup ≥18 years, 20 patients received placebo and 19 patients received ivacaftor treatment. The overall incidence of patients with adverse events was lower in the ≥18 years subgroup than in the other two age subgroups during both ivacaftor and placebo treatment.

During ivacaftor treatment, the incidence of infective pulmonary exacerbation of CF in the ≥18 years subgroup was 15.8% (3 patient, 4 events) compared to 25.0% (2 patients, 2 events) in the 6 to 11 years (inclusive) subgroup and 36.4% (4 patients, 4 events) in the 12 to 17 years (inclusive) subgroup. During placebo treatment, the incidence of infective pulmonary exacerbation of CF in the ≥18 years subgroup was 25.0% (5 patients, 7 events) compared to 37.5% (3 patients, 4 events) in the 6 to 11 years (inclusive) subgroup and 33.3% (3 patients, 3 events) in the 12 to 17 years (inclusive) subgroup. Adverse events more commonly reported by ivacaftor-treated patients (as compared to placebo) were as follows: Upper respiratory tract infection (2 events), pruritus (2 events), investigations (2 events), pyrexia (1 event) and arthralgia (1 event) in the 6 to 11 years (inclusive) age subset. For adolescents these adverse events were sputum increased (2 events), pyrexia (2 events), fatigue (1 event), malaise (1 event), arthralgia (1 event), back pain (1 event), torticollis (1 event) and headache (3 events). As previously stated headache is listed in section 4.8 of the Kalydeco SmPC as a very common adverse reaction. A serious adverse event occurred in one ivacaftor-treated child as compared to 3 placebo-patients.

A total of 16 female patients received ivacaftor while 15 received placebo. The overall incidence of adverse events was slightly lower for male patients than for female patients during both treatments (male: 72.7% [16 patients, 45 events] during ivacaftor treatment and 81.8% [18 patients, 64 events] during placebo; female: 75.0% [12 patients, 46 events] during ivacaftor treatment and 86.7% [13 patients, 45 events] during placebo). The incidence of serious adverse events was higher in the placebo group than in the ivacaftor group and higher in females than in males, i.e. placebo group: 26.7% (4/15) of females versus 13.6% (3/12) of males; ivacaftor group: 12.5% (2/16) versus 9.1%

(2/22), respectively. The absolute numbers are, however, too small. In both males and females pulmonary exacerbations were the most frequent serious adverse events.

A total of 13 patients with a baseline FEV1% predicted <70% received ivacaftor; in the categories of ≥70% to ≤90% and >90% this number was 11 and 14, respectively. These figures for patients receiving placebo were 13, 11 and 13, respectively. The overall incidence of patients with any adverse events was lower during ivacaftor than during placebo treatment in the FEV1 <70% and in the FEV1 ≥70% to ≤90% predicted subgroups: 53.8% (7 patients, 27 events) during ivacaftor treatment and 84.6% (11 patients, 43 events) during placebo treatment in the FEV1 <70% subgroup and 72.7% (8 patients, 24 events) during ivacaftor treatment and 81.8% (9 patients, 33 events) during placebo treatment in the FEV1 ≥70% to ≤90% predicted subgroup. In the FEV1 >90% predicted subgroup, the incidence of patients with adverse events was higher during ivacaftor treatment (92.9% [13 patients, 40 events]) than during placebo treatment (84.6% [11 patients, 33 events]). The incidence of infective pulmonary exacerbation of CF was lower during ivacaftor treatment (4 patients) than during placebo treatment (6 patients) in the <70% subgroup. The incidence was the same during both treatments in the ≥70% to ≤90% subgroup and similar during both treatments in the >90% subgroup.

Twenty-one patients from North America and 16 from Europe received placebo and 21 and 17 received ivacaftor, respectively. The overall incidence of subjects with adverse events during ivacaftor treatment was 71.4%, (15 patients, 46 events) in North America and 76.5% (13 patients, 45 events) in Europe. The overall incidence of infective pulmonary exacerbations of CF during ivacaftor treatment was 19.0% (4 patients, 5 events) in North America and 29.4% (5 patients, 5 events) in Europe. During placebo treatment, the overall incidence of patients with adverse events was 76.2% (16 patients, 68 events) in North America and 93.8% (15 patients, 41 events) in Europe; the incidence of infective pulmonary exacerbation of CF was 42.9% (9 patients, 11 events) in North America and 12.5% (2 patients, 3 events) in Europe.

The subgroup analysis by region suggests a different behaviour in the reporting system between the two regions. It is somehow difficult to understand the high number of adverse events reported in Europe by placebo patients as compared to North America (almost a 20% difference between the two regions). Similarly, the difference between the two regions regarding the percentage of infective pulmonary exacerbation of CF reported is surprising. The MAH was requested to discuss the differences. The MAH acknowledged that there is a numerical difference in reporting rates for the AE of infective pulmonary exacerbation of CF reported in EU by placebo patients as compared to North America. No consistent pattern could be found between regions when compared the ivacaftor and placebo treatment periods. The MAH stated that this may be a chance finding due to multiple comparisons in small numbers. This may be the case but as previously stated it cannot be completely excluded that the patient population enrolled in these two regions differs in some characteristics and/or that there are differences in the standard of care that may help to explain this observation. No further questions are raised as the overall results of the trial are considered.

For the above mentioned subgroups of patients the MAH was requested to provide also the incidence of serious adverse events. The only trend clearly seen was the higher incidence of pulmonary exacerbations considered as serious adverse events reported for placebo-treated patients from North America (28.6% [6/21]) versus that reported for patients from Europe (0 events [0/16]). Five of these pulmonary exacerbations met the protocol definition of pulmonary exacerbation. The incidence in the ivacaftor group was similar in both regions (a serious pulmonary exacerbation in each region). The interpretation of the MAH was again that this may represent a chance finding when making multiple comparisons in relatively small samples. This may be the case but it cannot be completely excluded that the patient population enrolled in these two regions differs in some characteristics and/or that

there are differences in the standard of care that may help to explain this observation. As in the previous case the overall results of the trial are to be considered.

Liver functions tests (LFT), haematology, chemistry and coagulation tests were collected at several study visits and analysed to describe changes in laboratory parameters over time and with treatment.

Regarding liver function tests, 2 ivacaftor-treated patients reported an adverse event of increased alanine aminotransferase and increased GGT each. Both were considered by the investigator to be related or possibly related to ivacaftor. The analysis of the maximum on-treatment liver function tests results show that most ivacaftor-treated patients had ALT, AST and total bilirubin ≤ 2 x Upper Limit (94.7%, 100.0%, and 100.0%, respectively, on ivacaftor treatment and 91.9%, 97.3%, and 100.0%, respectively, on placebo treatment). During ivacaftor treatment, two (5.3%) patients had at least 1 maximum ALT value >3 x ULN to ≤5 x ULN.

During placebo treatment, 1 patient (2.7%) had a maximum on-treatment ALT and AST values >8 × ULN. Study drug was interrupted at Week 2 and resumed on Day 28, and the patient continued in the study with no further LFT increases.

Plots of mean changes in liver function tests over time showed that with the exception of alkaline phosphatase all other LFT parameters suffered an increase that was in general higher in ivacaftor-treated patients than in placebo patients. The magnitude of the increases was, however, limited.

Changes in other chemistry parameters, haematology and coagulation were descriptively addressed by the MAH. The data provided (mean changes and shifts from normal to low and high values) do not suggest any specific pattern in the lab parameters discussed.

There were no clinically important trends attributable to ivacaftor treatment identified in the standard digital ECGs and no adverse events associated with ECG abnormalities in study 111.

No patients had adverse events that led to study drug interruption during ivacaftor treatment. During placebo treatment, 1 patient (2.7%) had an adverse event of increased hepatic enzymes that led to study drug interruption. As previously stated, the event resolved and the patient resumed dosing and continued in the study following the interruption.

In conclusion, the safety profile of ivacaftor in patients with non-*G551D* gating mutations included in study 111 was consistent with that observed in studies 102 and 103 in patients with a *G551D* mutation. However, it was noted that in the literature[20] describing the experience of the use of ivacaftor in 14 patients on a named patient program in Germany it has been reported that "increased bronchial secretions may warrant increased physiotherapy and intravenous antibiotic treatment in these patients when ivacaftor is initiated". The MAH was asked to discuss whether in the clinical trials so far conducted, i.e. not limited to study 111, similar observations have been made (i.e. in close relationship with the start of ivacaftor treatment). Sputum increased was one of the commonly seen adverse events in previous trials. Overall, the MAH provided a comprehensive overview of the adverse events of interest, but the analysis was limited to patients with FEV1 below 40%. The safety profile of ivacaftor includes respiratory symptoms and signs such as sinus congestion, rhinitis, sputum increased, rhinorrhoea etc., all of them compatible with an increased hydration of the sinopulmonary secretions. This issue should be addressed in the successive PSURs and the discussion should not be limited to patients with FEV1 less than 40%.

Further safety data will be gathered in the open label extension of study 111. The MAH also plans to rollover patients from study 111 to study 112 for an additional period of two years to generate long

[20] Hebestreit et al. Effects of ivacaftor on severely ill patients with cystic fibrosis carrying a *G551D* mutation. Journal of Cystic Fibrosis 12 (2013) 599-603

term safety data. This approach is endorsed. Submission of results of studies 111 and 112 is foreseen in the RMP.

2.5.2. Conclusions on clinical safety

In conclusion, the safety profile of ivacaftor in cystic fibrosis patients aged 6 years and older with non-*G551D-CFTR* gating mutations studied in Part 1 of trial 111 was consistent with that observed in studies 102 and 103 in patients with a *G551D* mutation. No new safety concerns emerge from the review of this safety data. There seems to be some differential effect between the two regions in the reporting of some adverse events, in particular pulmonary exacerbations that were more frequently reported by patients in the placebo group in North America. It is speculated that this may be the consequence of performing multiple comparisons in small numbers. This may well be the case but it cannot be completely ruled out that the patient population enrolled in the two regions differs in some characteristics and/or that there are differences in the standard of care that may help to explain this observation. The overall results of the trial should be considered and, therefore, no further issues are raised in this respect.

2.5.3. PSUR cycle

The PSUR cycle remains unchanged.

The annex II related to the PSUR refers to the EURD list which remains unchanged.

2.6. Risk management plan

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

> The PRAC considered that the risk management system version 2.7 is acceptable. In addition, minor revisions were recommended to be taken into account at the next RMP update. The PRAC endorsed PRAC Rapporteur assessment report is attached.

The CHMP endorsed the PRAC advice without changes. The MAH consolidated the changes in the RMP introduced in other procedures concluding at the same time (variations II/0013 and II/0015/G). The CHMP endorsed the consolidated Risk Management Plan version 2.8.

The endorsed Risk Management Plan had the following content:

Safety concerns

Table 43. Summary of Safety Concerns

Important identified risks	None
Important potential risks	• Effects on liver function tests • Cataract • Concomitant use of ivacaftor with strong CYP3A inhibitors or inducers • Cardiac arrhythmias • Off-label use in children less than 6 years of 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 6 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

Pharmacovigilance plans

Table 44. Ongoing and Planned Additional Pharmacovigilance Studies/Activities in the Pharmacovigilance Plan

Study/Activity Title and Study Type	**Objectives**	**Safety Concerns Addressed**	**Status (Planned, Started)**	**Date for Submission of Interim or Final Reports (Planned or Actual)**
Study VX08-770-105 (Interventional, 1)	To evaluate the long-term safety and efficacy of VX-770 in subjects with CF	• Effects on liver function tests • Concomitant use with strong CYP3A inhibitors or inducers • Cardiac arrhythmias • Pulmonary exacerbations and bacterial sputum colonization • Use in patients with FEV_1 <40% • Patients with cardiac disease • Long-term safety • Use in children between 6 to 11 years old	Started	Interim Report annually (with the PSUR) Final Report: December 2015
Study VX11-770-110 (Interventional, 3)	To evaluate the efficacy and safety of ivacaftor in subjects with CF who have the *R117H-CFTR* mutation	Use in children between 6 to 11 years old	Started	September 2014
Study VX12-770-111 (Interventional, 3)	To evaluate the efficacy and safety of ivacaftor in subjects with CF who have a non-*G551D CFTR* gating mutation	Use in children between 6 to 11 years old	Started	June 2015
Long-term Safety Study (Non-interventional, 1)	To evaluate the long-term safety of ivacaftor in patients with CF	• Cardiac arrhythmias • Off-label use in children less than 6 years of age and in patients without an approved *CFTR* mutation • Use in pregnancy and lactation • Pulmonary exacerbations and bacterial sputum colonization • Use in children between 6 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/Activity Title and Study Type	Objectives	Safety Concerns Addressed	Status (Planned, Started)	Date for Submission of Interim or Final Reports (Planned or Actual)
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 (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
(Nonclinical, 3)	An analysis of PK data, including data from Study 110 and Study 111 on a need to perform a dose finding study in children 6 to 11 years of age	Avoidance of potential overexposure in children	Planned	September 2014
(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 potential overexposure in children	Planned	June 2016

Risk minimisation measures

No new risk minimisation measures were introduced with this procedure. There are no additional risk minimisation activities in place for this product.

2.7. 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. Particularly, a new warning with regard to lack of clinically relevant improvement from treatment in patients with *G970R* mutation in the *CFTR* gene has been added to the product information.

The Package Leaflet has been updated accordingly.

3. Benefit-Risk Balance

Benefits

Beneficial effects

Ivacaftor 150 mg every 12 hours has been shown in a short-term, placebo-controlled cross-over study (Part 1 of study 111) to be statistically different from placebo in a number of efficacy variables including PPFEV1 in patients with cystic fibrosis with non-*G551D-CFTR* gating mutations included in this study. The primary endpoint was the mean absolute change from baseline in PPFEV1 which 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. The observed treatment difference (95%CI) between ivacaftor and placebo was 10.7 % (7.3, 14.1) and is not only statistically significant but also clinically relevant.

Positive outcomes were also observed for the secondary endpoints mean absolute change from baseline in BMI and mean absolute change in the respiratory domain of the CFQ-R. These results were also statistically significant and consistent with the primary endpoint. The effect of ivacaftor on *CFTR* function was also assessed by the mean absolute change in sweat chloride from baseline through 8 weeks, for which a statistically significant difference versus placebo was also observed.

In conclusion, consistency has been observed not only between the primary and secondary endpoints in Part 1 of study 111 but also across studies, i.e. studies 102 and 103 in patients with a *G551D* mutation, another gating mutation for which ivacaftor is already indicated.

Uncertainty in the knowledge about the beneficial effects

The efficacy of ivacaftor for patients with the studied non-*G551D-CFTR* gating mutations with mild to moderate lung disease has been shown in a limited number of patients (n=39) and for a short time. Therefore, efficacy data on the maintenance of the effect is lacking and is especially relevant given the chronic condition of the disease.

The initially claimed indication covered all gating mutations despite that only a limited number of them have been characterised *in vitro* and assessed *in vivo*, i.e. *G178R*, *S549N*, *S549R*, *G551S*, *G970R*, *G1244E*, *S1251N*, *S1255P*, *S1255P* and *G1349D*. All of them are missense mutations for which the clinical consequences are difficult to anticipate. Concerns were raised regarding whether all of the mutations considered were disease-causing and also regarding the heterogeneity of the patient population enrolled in study 111 and patients with gating mutations in general.

Narratives provided for patients with an unexpected small reduction in sweat chloride while on ivacaftor and analyses by specific non-*G551D* gating mutation showed that patients with a *G970R-CFTR* mutation consistently respond to ivacaftor with a limited reduction in sweat chloride when compared to patients with other non-*G551D* gating mutations. The analysis also showed that indeed patients with a non-*G551D* gating mutation constitute a heterogeneous population in terms of clinical response to ivacaftor. As a consequence and in spite of the fact that an indication limited to the specific mutations assessed in study 111 was proposed by the MAH, it was considered that the *G970R-CFTR* mutation should not be part of the indication. The MAH latest proposal for section 4.1 of the SmPC is in line with this.

The uncertainties about the exact mechanism of action (the interaction with *CFTR* protein) and lack of a demonstrated strong correlation between the *in vitro* and *in vivo* results for particular mutations at

present prevent considering potential *in vitro* data driven extrapolation of the demonstrated efficacy to other mutations.

No suitable response guided therapy has been identified by the MAH as all the analyses performed suggest that there is no correlation between sweat chloride levels and changes in FEV1 improvement. As the dataset is still limited the MAH is encouraged to further pursue an understanding of potential relationships.

Regarding the maintenance of the effect, the MAH performed a *post-hoc* analysis of the efficacy data of studies 102 and 103 (pivotal studies that assessed the efficacy and safety of ivacaftor for 48 weeks in patients with a *G551D* gating mutation) and have shown that the majority of patients who respond to ivacaftor at Week 8 keep this improvement at Week 24. This is also expected for patients with a non-*G551D* gating mutation. The 16-week open label extension of study 11 could help to address whether the effect of ivacaftor is kept up to 24 weeks of treatment (8 weeks in the cross-over portion of the trial plus 16 weeks in the open label extension). This open-label extension has finished and the final CSR of study 111 is expected in June 2014. It should be made available as soon as possible. Furthermore, patients will be rolled over to an extension study (study 112) for an additional 2-year period after the last dose of study drug in study 111. Submission of results for studies 111 and 112 is foreseen in the RMP.

Risks

Unfavourable effects

The safety profile of ivacaftor in cystic fibrosis patients aged 6 years and older with a non-*G551D-CFTR* gating mutation in Part 1 of study 111 was consistent with that observed in studies 102 and 103 in patients with a *G551D* mutation. No new safety concerns emerge from the review of the safety data.

The incidence of the following adverse events was higher in ivacaftor-treated patients than in placebo-treated patients: rhinitis (7.9%), pyrexia (7.9%); fatigue and constipation were reported by 2 (5.3%) ivacaftor patients each; in the SOC Investigations 4 (10.5%) ivacaftor patients reported some adverse event versus 2 (5.4%) placebo patients. Arthralgia was reported by 2 (5.3%) ivacaftor patients.

Sputum increased (considered treatment related) was reported by 2 (5.3%) ivacaftor-treated patients while none of the placebo patients reported this adverse reaction. Treatment-related investigations (increased ALT, increased blood creatinine, increased GGT) only occurred during ivacaftor treatment (5.3% [2 subjects]).

Uncertainty in the knowledge about the unfavourable effects

It is likely that the short-term duration of the trial limits the number of adverse events reported. Similarly, the low number of patients enrolled would make it difficult that the less frequent adverse reactions appear. Further safety data from the studies ongoing is expected to become available and will increase the safety database.

Benefit-Risk Balance

Importance of favourable and unfavourable effects

Cystic fibrosis (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 and

death. The rate of decline in FEV1 may be variable depending on several factors such as genotype and environmental factors. Correlation between the genotype and the lung disease phenotype is particularly weak. *CFTR* mutations may cause CF or be associated with *CFTR*-related disorders but they also may have no clinical consequences or have unknown or uncertain clinical relevance. All of the non-*G551D* gating mutations assessed in study 111 are missense mutations for which the clinical implications are difficult to assess. Narratives provided for patients with an unexpected small reduction in sweat chloride while on ivacaftor and analyses by specific non-*G551D* gating mutations show that patients with a *G970R-CFTR* mutation consistently respond to ivacaftor with a limited reduction in sweat chloride when compared to patients with other non-*G551D* gating mutations. As a consequence and in spite of the fact that an indication limited to the specific mutations assessed in study 111 was already proposed by the MAH, this was considered insufficient and the *G970R-CFTR* mutation was excluded from the proposed indication.

However, the MAH expressed their concern that this mutation-by-mutation approach (rather than grouping them) would preclude the inclusion of new mutations in the labelling given their rarity. This is acknowledged, however, it would not be acceptable to ignore the results of ivacaftor in patients carrying the *G970R* mutation. Overall, the MAH is encouraged to further pursue the characterisation of the mechanism of action of ivacaftor as well as the identification of individual factors that may be predictive of response to it.

The effect of ivacaftor in lung function (measured as FEV1% predicted) in a patient population with mild to moderate lung disease is clinically relevant in terms of the treatment effect observed. A smaller effect has been observed in children who are more likely to have a mild lung disease. This is not unexpected. Positive effects have been also observed on extrapulmonary outcomes such as BMI and quality of life. These effects are in line with what is already known for ivacaftor in patients with a *G551D-CFTR* mutation. The analysis by specific non-*G551D* mutation, however, showed that the magnitude of the response to ivacaftor varies among the different mutations likely reflecting the heterogeneity of this patient population.

Although CF is a chronic condition the long-term data are limited. Nevertheless, *post-hoc* analyses performed in studies 102 and 103 in patients with a *G551D* gating mutation suggest that the majority of patients who respond to ivacaftor at Week 8 keep this improvement at Week 24. This is also expected for patients with a non-*G551D* gating mutation but needs to be confirmed. Results from the extension phase (Part 2) of study 111 could help to confirm the effect of ivacaftor up to 24 weeks of treatment.

No new safety concerns have emerged from the review of the safety data of Part 1 of study 111. Overall, the safety profile is consistent with what is known for patients with a *G551D* gating mutation for whom data on the long term are available. There is no reason to believe that this would not be the case for patients with a non-*G551D* gating mutation but the open label extension of study 111 and the rollover study 112 will address this issue.

Discussion on the Benefit-Risk Balance

Cystic fibrosis represents an area of a high-unmet medical need for specific targeted therapies. In patients with cystic fibrosis lung function declines with age and is a significant predictor of mortality. Ivacaftor has been shown to improve lung function in patients with mild to moderate disease and the following gating mutations in the *CFTR* gene: *G551D, G1244E, G1349D, G178R, G551S, G970R, S1251N, S1255P, S549N,* or *S549R*. Gating mutations as a group do not have high prevalence (when compared with the prevalence of *F508del*) and, consequently, the number of subjects who can benefit from treatment with ivacaftor for the time being is limited.

Overall, the results of Part 1 of study 111 demonstrate that patients with the non-*G551D* gating mutations mentioned above can be expected to benefit from treatment with ivacaftor, and these benefits outweigh the risks identified in the safety profile of the product, which in this population does not considerably differ from the profile in patients with *G551D* mutation (for which ivacaftor is already authorised).

As previously discussed the therapeutic indication has been amended from an unrestricted indication to a more specific one to address the heterogeneity of the different mutations and the consistent findings that patients carrying the *G970R-CFTR* gating mutation respond less to ivacaftor. The MAH has agreed to that and the current proposal for section 4.1 of the SmPC is in line with this.

The overall benefit/risk balance of Kalydeco in treatment of CF patients from age of 6 with respective gating mutations in the *CFTR* gene (*G1244E*, *G1349D*, *G178R*, *G551S*, *S1251N*, *S1255P*, *S549N* and *S549R*) is considered positive.

In addition, the CHMP considered that the applicant should submit the following safety data the next PSUR: in future PSURs the MAH should analyse the events of increased respiratory secretions, not limiting the analysis to patients with FEV1 below 40% predicted.

4. Recommendations

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. See appendix 1.

Final 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(s) requested		**Type**
C.1.6 a	Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

Extension of Indication to include additional gating (class III) mutations in the *CFTR* gene: *G1244E*, *G1349D*, *G178R*, *G551S*, *S1251N*, *S1255P*, *S549N* and *S549R*.

As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC have been updated. Particularly, a new warning with regard to lack of clinically relevant improvement from treatment in patients with *G970R* mutation in the *CFTR* gene has been added to the product information. The Package Leaflet has been updated accordingly.

The requested variation proposed amendments to the SmPC and Package Leaflet.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0300/2012 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.