EMA/473279/2012
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Kalydeco

ivacaftor

Procedure No.: EMEA/H/C/002494//0000

Note

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

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List of abbreviations

2-MeTHF	2-methyl tetrahydrofuran
AAG	α1 glycoprotein
AD	aldehyde dehydrogenase
AE	Adverse event
ALT	Alanine transaminase
ANCOVA	Analysis of covariance
AST	Aspartate transaminase
AUC_{0-24hr}	Area under the concentration versus time curve from time of dosing to 12 hours postdose
$AUC_{0-\infty}$	Area under the concentration versus time curve from time of dosing extrapolated to infinity
AV	Atrio-ventricular
BCS	Biopharmaceutics Classification System
BD	Bronchodilator
BDDCS	Biopharmaceutics Drug Disposition Classification System
BID	twice daily
cAMP	Cyclic adenosine monophosphate
CF	Cystic Fibrosis
CFQ-R	Cystic Fibrosis Questionnaire-Revised
CFTR	Cystic fibrosis transmembrane regulator [protein / gene]
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CL/F	Apparent clearance
C_{max}	Maximum observed concentration
C_{min}	Minimum observed concentration
CQA	Critical quality attribute
CRO	Contract Research Organisation
CSR	Clinical study report
CTD	Common Technical Document
CYP	Cytochrome P450
DDI	drug-drug interaction
DS	Design space
EC_x	concentration at which effect is at x% maximum
ECG	electrocardiogram
ELF	epithelial lining fluid
FA	Full analysis
FEV_1	forced expiratory volume in 1 second
GCP	Good clinical practice
GI	gastrointestinal
GLP	Good laboratory practice
GMP	Good manufacturing practice
HAS	human serum albumin?
HBE	Human Bronchial Epithelium
HDPE	High-density polyethylene
hERG	Human ether-a-go-go related gene
HGG	Human gamma globulin
HPMCAS	Hydroxypropyl methylcellulose acetate succinate, hypromellos acetate succinate
IC50	Half maximal inhibitory concentration
ICH	International Conference on Harmonisation
IGG	Immunoglobulin G
IPC	In-process control
K_i	inhibition constant
LC/MS/MS	liquid chromatography with tandem mass spectrometry
LLOQ	Lower limit of quantification
LOCF	last observation carried forward

LR	Linear Range
LS	least squares
M1	hydroxymethyl-ivacaftor
M6	ivacaftor carboxylate
MAO	Monoamine oxidase
MEK	Methyl ethyl ketone
MMRM	Mixed-Effects Model for Repeated Measures
MTD	maximum tolerated doses
NE	norethisterone
NOAEL	No observed adverse effect level
NOR	Normal operating range
NPD	Nasal potential difference
PAR	Proven acceptable range
PBT	Persistence, bioaccumulation and toxicity
PD	Pharmacodynamics
PE	Pulmonary exacerbation
PEC	Predicted environmental concentration
P-gp	P-glycoprotein
PK	Pharmacokinetics
PKA	Protein kinase A
PVP	Polyvinyl pyrrolidone (povidone)
PT	Preferred term
q12h	Every 12 hours
QbD	Quality by design
qd	Once a day
QoL	Quality of life
QTcF	QT interval corrected by Fridericia's formula
RMP	Risk Management Plan
SAE	Severe adverse event
SD	Standard deviation
SDD	spray-dried dispersion
SLS	Sodium lauryl sulphate
SmPC	Summary of the product characteristics
SOC	System organ class
SSC	special search category
SVPC	supraventricular premature complex
$T_{1/2}$	(elimination) half-life
T_{max}	time to maximum concentration
ULN	Upper limit of normal
URTI	Upper Respiratory Tract Infections
Vc/F	apparent volume of distribution of the central compartment
Vp/F	apparent volume of distribution of the peripheral compartment
VX-770	ivacaftor
Vz/F	apparent volume of distribution

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Vertex Pharmaceuticals (U.K.) Ltd. submitted on 27 October 2011 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Kalydeco, through the centralised procedure under Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 21 December 2010.

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 applicant applied for the following indication: the treatment of cystic fibrosis (CF) in patients age 6 years and older who have a gating mutation in the CFTR gene.

The legal basis for this application refers to:

Article 8(3) of Directive 2001/83/EC - complete and independent application.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and bibliographic literature supporting certain tests or studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/191/2011 on the agreement of a paediatric investigation plan (PIP).

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

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with the authorised orphan medicinal product Bronchitol (mannitol), EMEA/H/C001252.

New active Substance status

The applicant requested the active substance ivacaftor contained in the above medicinal product to be considered as a new active substance in itself.

Protocol assistance

The applicant received Protocol Assistance from the CHMP on 18 February 2010 and 16 December 2010. The Protocol Assistance pertained to quality, non-clinical and clinical aspects of the dossier.

Licensing status

A new application was filed in the following countries: United States of America.

The product was not licensed in any country at the time of submission of the application. During the assessment of the applicant, a marketing authorisation for ivacaftor has been granted in the United States of America.

1.2. Steps taken for the assessment of the product

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

Rapporteur: **Dr. Concepcion Prieto Yerro (ES)**	Co-Rapporteur: **Prof. János Borvendég (HU)**

- The application was received by the EMA on 27 October 2011.
- Accelerated Assessment procedure was agreed-upon by CHMP on 28 September 2011.
- The procedure started on 16 November 2011.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 10 February 2012. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 06 February 2012.
- During the meeting on 15 March 2012, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 15 March 2012.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 23 April 2012.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 10 May 2012.
- During the meeting on 21 - 24 May 2012, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Kalydeco on 24 May 2012.
- The CHMP adopted a report on non-similarity of Kalydeco with Bronchitol (mannitol) on 24 May 2012.

Following the CHMP positive opinion, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Kalydeco as an orphan medicinal product in the approved indication. The outcome of the COMP review can be found on the Agency's website ema.europa.eu/Find medicine/Rare disease designations.

2. Scientific discussion

2.1. Introduction

Problem statement

Cystic fibrosis 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. Although CF affects multiple organs, the leading cause of mortality is the progressive loss of lung function.

Cystic fibrosis is caused by a mutation in a gene that encodes the CFTR protein, which is expressed in many epithelial cells and blood cells. CFTR protein contains 2 ATP-hydrolysis domains (also termed nucleotide-binding domains) and 12 membrane-spanning alpha helixes. It has been established that CFTR conducts chloride across the cell membrane and is regulated by protein kinase A (PKA) in a cAMP-dependent fashion. The PKA sites within the protein serve as targets for phosphorylation. ATP hydrolysis is mediated by nucleotide-binding domains within the full-length ion channel (Rowe et al. 2005).

Although CFTR functions mainly as a chloride channel, it has many other regulatory roles, including inhibition of sodium transport through the epithelial sodium channel, regulation of the outwardly rectifying chloride channel, regulation of ATP channels, regulation of intracellular vesicle transport, acidification of intracellular organelles, and inhibition of endogenous calcium-activated chloride channels. CFTR is also involved in bicarbonate–chloride exchange. A deficiency in bicarbonate secretion leads to poor solubility and aggregation of luminal mucins (O'Suvillan et al. 2009).

CFTR mutations can be classified according to the mechanisms by which they disrupt CFTR function. Stop codon mutations (class I) result in a truncated nonfunctional CFTR, class II mutations consist of aberrantly folded CFTR protein that is degraded by the cell quality control system, while class III mutations lead to defective regulation of the CFTR protein and, consequently, the absence of CFTR function. These three classes usually lead to a classic CF phenotype with pancreatic insufficiency. CFTR mutations that lead to defective chloride conductance are grouped together in class IV. Class V mutations interfere with normal transcription, thereby reducing the amount of otherwise normal CFTR. These latter two classes are mostly associated with a milder expression of the disease (Proesmans M et al. 2008).

More than 1500 CFTR mutations have been identified, but the functional importance of only a small number is known. The most frequent is the class II mutation F508del, i.e. a 3 basepair (bp) deletion resulting in the deletion of a phenylalanine at position 508 (F508del) in the first of 2 cytoplasmic adenosine triphosphate (ATP) binding domains of CFTR which accounts for about two-thirds of mutated alleles in northern European and North American populations. Although CFTR mutation frequency varies from population to population, worldwide no other single mutation accounts for more than approximately 5% of CFTR mutations.

The primary defect caused by G551D CFTR, the prototypical and most common Class III (regulation or gating) mutation for which ivacaftor is intended, is a defect in CFTR channel opening. G551D is a missense mutation in the coding region for NBD1 (nucleotide binding domain 1) that results in the replacement of a glycine for an aspartic acid at position 551 of CFTR and in which CFTR reaches the apical cell membrane but does not respond appropriately to cAMP-mediated phosphorylation. Other CFTR gating mutations include G178R, S549N, S549R, G551S, G970R, G1244E, S1251N, S1255P, and G1349D.

The presence of suggestive clinical symptoms and signs combined with a sweat chloride concentration above 60 mmol/L and/or the presence of 2 clinically relevant CF-causing mutations is uniformly accepted as diagnostic for the classical form of the disease. However, patients with particular genotypes combining two CF-causing mutations may have a sweat chloride value in the intermediate range (30–60 mmol/L).

At present, there is no cure for CF. Current CF treatments target respiratory infections, inflammation, mucociliary clearance, and nutritional status but none of them targets the mechanism of CF rather than the downstream consequences of diminished CFTR function. An alternative therapeutic strategy to treat CF could be to increase CFTR function by gene therapy or drugs that either enhance the activity of mutant chloride channels present at the cell surface such as the G551D-CFTR protein (CFTR potentiators) or rescue the cell surface expression of mutant CFTR (CFTR correctors).

Even with the current treatments, the median age of survival of individuals born today with CF is predicted to be between 34.4 and 46.7 years (Stern 2008; Canadian CF PDR Report 2011; UK CF Registry 2011) while the actual median age at death is currently between 18.7 and 33.0 years (Stern 2008; CFF Patient Registry 2009; Colombo 2011).

It is acknowledged that patients with CF represent a high unmet medical need for effective therapies.

About the product

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 more than 10-fold over baseline.

Ivacaftor would be 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.

The initially applied for indication of ivacaftor was: "treatment of cystic fibrosis (CF) in patients age 6 years and older who have a gating mutation in the CFTR gene". During the assessment procedure the indication was restricted to "treatment of cystic fibrosis (CF) in patients age 6 years and older who have a *G551D* mutation in the *CFTR* gene". The restriction of the indication was based on the fact that the two pivotal studies included in the current application enrolled only patients who have a *G551D* mutation in at least one allele of the *CFTR* gene.

The proposed posology for adults and children age 6 years and older is 150 mg (film-coated tablets) taken orally every 12 hours (300 mg total daily dose) with fat-containing food.

Type of Application and aspects on development

The Marketing Authorisation Application for Kalydeco (ivacaftor) 150 mg film-coated tablets submitted by Vertex Pharmaceutical (U.K.) Limited is submitted in accordance with Article 6 of Regulation (EC) No 726/2004, as amended, and Article 8(3) of Directive 2001/83/EC, as amended.

EU Orphan Designation was granted on 08 July 2008 (EC Decision No. EU/3/08/556).

On 28 September 2011 the CHMP accepted the Applicant's request for accelerated assessment for the following reasons:

- Cystic fibrosis (CF) is an inherited disease with serious and chronically debilitating morbidities and high premature mortality, for which currently available therapies have an effect on the clinical consequences of the disease without addressing the underlying defect. Therefore, an unmet medical need for specific targeted therapies for CF patients, including sub-populations relevant for the specific target, exists;
- Ivacaftor is a selective potentiator of the CF transmembrane conductance regulator (CFTR) protein that acts by increasing the CFTR channel opening probability to enhance chloride transport. This mode of action potentially provides an innovative therapeutic approach by targeting the underlying

defect of CF (diminished CFTR function) rather than its downstream consequences hence offering added value to the current treatment armamentarium;

- The study package intended for submission is expected to provide a reasonable basis for the benefit risk assessment, the endpoints used in pivotal studies appear adequate and able to reflect a clinically meaningful effect;
- The preliminary review of the available data suggests that the effect on pulmonary function parameters might be of clinical interest. Furthermore, treatment with ivacaftor might potentially decrease the need for other medical therapies;
- Overall, the medicinal product is considered to be of major public health interest - in particular from the viewpoint of therapeutic innovation - for a clinical condition that constitutes an unmet medical need.

The development programme / compliance with CHMP guidance / scientific advice

Regulatory advice on the clinical development plan and the designs of Studies 102, 103, and 104 were sought from the regulatory authorities in the EU and US. Protocol Assistance has been provided by the CHMP on quality, non-clinical and clinical aspects of the development. In general the Applicant has complied with the advice provided at the Protocol assistance.

2.2. Quality aspects

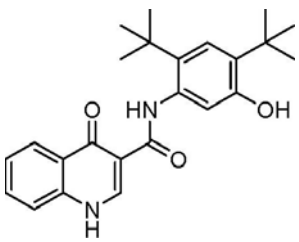
2.2.1. Introduction

Kalydeco contains the active substance ivacaftor. For other ingredients see the SmPC. The product is formulated as a light blue film-coated tablet, printed in black ink with "V 150" on one face, containing 150 mg of the active substance. The tablets are packaged in a thermoform blister (Aclar/foil) or a high-density polyethylene (HDPE) bottle with desiccant.

2.2.2. Active Substance

The chemical name of the active substance is N-(2,4-di-tert-butyl-5-hydroxyphenyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide.

The corresponding molecular formula is $C_{24}H_{28}N_2O_3$, molecular weight is 392.5 g/mol. The molecule is achiral.



Ivacaftor is a white to off-white crystalline solid. It is freely soluble in methylethyl ketone/water mixture, soluble in 2-methyl tetrahydrofuran and PEG 400, slightly soluble in methanol, acetone and ethanol and practically insoluble in water and buffers with pH 1.0 – 7.0.

The structure of ivacaftor drug substance was determined by elemental analysis and various spectrometric techniques, such as NMR (1H, 13C and two-dimensional NMR), FTIR, UV-Vis and high resolution mass spectrometry. The proof of structure is considered satisfactory.

The active substance shows polymorphism. Mixture of two major crystalline neat polymorphic forms (B and C) is obtained when manufactured by the commercial manufacturing process described. Form C is the most thermodynamically stable neat form. The polymorphic form is not of concern during the synthesis of the active substance, as the active substance is fully dissolved during manufacture of the finished product.

Manufacture

The starting materials used are considered appropriate as GMP starting materials. The synthetic routes for the starting materials have been described in detail and all potential related impurities or degradation products have been described and characterized. There are different suppliers for each starting material; however, the same synthetic route is applied by the different suppliers of the same starting material. Description of manufacturing process of the active substance including the in-process controls is adequate.

Quality by Design (QbD) approach has been used in product and process development of ivacaftor. For the active substance synthesis, a combination of multivariate analyses and range-finding studies was used to define a design space for each step. All parameters with a potential impact on critical quality attributes (CQAs) of the active substance were identified and thoroughly investigated. The Applicant has proposed a combination of proven acceptable ranges (PARs) and design spaces (DSs) for the manufacturing process of the active substance.

Design spaces have been developed at small laboratory scales (0.5-20 g) and the scale-up to production levels (100 kg) is wide (x 5000, x 10.000...). The applicant has submitted data and justifications to support the low risk of a scale effect. In addition 6 batches have been manufactured under the normal operating ranges (NORs), which is a defined area of the design space, where the process will normally operate during routine manufacture. Given the available development data on the establishment of the design space, the batch data provided and the submitted justifications on the effect of scale, there is enough reassurance to allow the approval of the proposed design space.

However there is still some uncertainty on the potential impact of excursions outside the NORs on the quality of the active substance. It is also uncertain whether the proposed control strategy will be capable of detecting potential unforeseen changes in the quality of the active substance and consequently on the safe and effective use of the finished product. For this reason it is important to confirm the validity of the Design Space every time there is an excursion outside the NORs and a verification protocol needs to be provided detailing the strategy (studies and controls) that will be used for this purpose.

The requirement for such verification protocol has been included as a condition of the Marketing Authorisation.

Specification

Control tests for the active substance include appearance, identification by FTIR spectrum, related substances and assay by HPLC, acetamide, sulphated ash, heavy metals and residual solvents.
A detailed study is presented on the potential, theoretical and observed organic impurities. Impurity limits in the specification are justified and found safe. The limit proposed for acetamide (hydrolysis by-product of the process solvent acetonitrile) in the active substance is established according to the Guideline on the Limits of Genotoxic Impurities.

The limits set for specification parameters are acceptable and in line with batch results, stability studies and CHMP guidelines. Analytical methods used are sufficiently described and fully validated in line with the CHMP requirements.

Results of analysis of eight production batches of the active substance were provided. Compliance with the specification was demonstrated.

Stability

The proposed retest period for ivacaftor drug substance is 30 months when stored in the intended container closure system. The retest period and storage conditions are supported by 18 months of primary stability data from three production-scale lots.

2.2.3. Finished Medicinal Product

Ivacaftor film-coated tablets consist of core tablet, film coat and printing ink.

The product contains both compendial and non-compendial excipients. Compendial excipients – microcrystalline cellulose (binder, diluent), lactose monohydrate (diluent), croscarmellose sodium (disintegrant), sodium lauryl sulphate (surfactant), colloidal silicon dioxide (flow agent), magnesium stearate (lubricant) and carnauba wax (polishing agent) - comply with the requirements of the European Pharmacopoeia (Ph.Eur.). The Ph.Eur. does not include a monograph for hypromellose acetate succinate (HPMCAS). HPMCAS used in the manufacture of ivacaftor SDD complies with the USP/NF monograph. Opadry II Blue (film coating mixture) and Opacode Black (printing ink) are non-compendial excipient mixtures wherein the individual components meet the appropriate requirements of the pharmacopoeias and/or international standards.

Pharmaceutical Development

The company identified the physico-chemical properties of the drug substance that are clinically relevant for the patient. These properties have been adequately analysed and are sufficiently controlled. Identification of the drug substance parameters that may impact the finished product critical quality attributes have been performed through systematic evaluation using risk assessment methodologies. Binary excipient compatibility studies were conducted.

Manufacturing process development of ivacaftor film-coated tablets was conducted under a Quality by Design approach. Six major stages were involved in the QbD strategy for the development of ivacaftor tablets – definition of the target product profile, identification of CQAs, initial assessment, criticality analysis, risk management and mitigation and defining process validation strategies.

Design spaces for each manufacturing step were defined. Criticality was assessed for each process parameter.

Statistical analysis was provided for all designs of experiments. The applicant has proposed a combination of design spaces and PARs for the spray-dried dispersion and the finished product.

The design spaces for the spray-dried dispersion and the finished product have been developed at commercial scale and have been found to be acceptable.

Adventitious agents

The only excipient of animal origin contained in the drug product is lactose monohydrate. It is manufactured in compliance with Guideline "Note for Guidance of Minimizing the Risk of Transmitting

Animal Spongiform Encephalopathy Agents by Human and Veterinary Products", current version. The BSE/TSE statement for lactose monohydrate is provided. Excipients of human origin are not used.

Manufacture of the product

Manufacture of the finished product consists of two stages – manufacture of spray dispersion and tabletting. The spray-dried dispersion (SDD) is manufactured using solvent based spray-drying followed by secondary drying to remove residual solvents. In the second stage, the amorphous SDD is blended with additional excipients, compressed into a core tablet, film-coated and printed to form the final drug product. Description of manufacturing process and process controls is provided.

Product specification

The product specification is adequate for this type of dosage form. The product is tested for appearance, identification by FTIR, assay and degradation products by HPLC, dissolution, uniformity of dosage units, physical form by XRPD, water content and microbiological purity.

The proposed test procedures and acceptance criteria follow the principles of the ICH Q6A guideline. All analytical methods are appropriately described. The analytical methods validation fulfils the requirements described in the ICH Q2 (R) guideline.

Batch analysis results of the SDD and tablets indicate satisfactory consistency and compliance with the proposed specification.

The quality profile of all reference materials has been correctly established.

Stability of the product

The studies are carried out in accordance with current ICH/CHMP guidelines. Validated stability-indicating methods are used to analyse the stability samples. Results of three primary stability batches, using commercial process and commercial-scale equipment, were provided. First full-scale commercial batches will also be monitored for stability, once manufactured.

All parameters remained within specification during the stability testing at all storage conditions. There is no trend in the data except for the water content, where a small increase can be seen. However, the water content also remains well below the acceptance criterion.

Stability studies support the shelf-life as defined in the SmPC.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

The active substance ivacaftor is a chemically synthesised compound, well characterised and manufactured under a Quality by Design approach. The substance is appropriately controlled by its specifications; only validated methods are used. Sufficient number of batches has been manufactured to demonstrate batch-to-batch consistency. The active substance is stable, as demonstrated by stability studies on production-scale lots.

A design space has been proposed for the manufacturing process of the active substance. The validity of the design space has been verified only at the normal operating ranges (NORs), which is a subset of the design space where the process is expected to run routinely. A stepwise approach to the verification is acceptable, depending on the commercial needs to move the operating ranges during the product lifecycle. When moving in non-verified areas of the design space, the potential scale up effect on the quality of the active substance should be evaluated according to a verification protocol. Such protocol defines the parameters that will be studied and the controls that will be used to identify

potential scale or equipment dependencies. These studies will be used to address the current uncertainty about the impact of excursions outside the NORs on the quality of the active substance and the adequacy of the approved control strategy to detect potential changes.

Based on the available data the proposed design space is approvable. However since an adequate verification protocol was not available at the time of the Opinion, the CHMP requested a condition in the MA for the submission of the verification protocol that will address the currently unknown impact of operating outside the NORs on the quality of the active substance and thus the safe and effective use of the product. This verification would validate the extension of the manufacturing of the active substance in operating settings broader than the NORs, to cover all areas of the design space.

The finished product is an immediate-release, film-coated tablet of 150 mg strength. Due to the active substance being insoluble in water, the active substance needs to be spray-dried with excipients to produce an amorphous form of the active substance, which only can be absorbed. Additional use of solubility enhancer ensures oral bioavailability. The spray-dried dispersion (SDD) is then compressed into tablets and film coated. Quality by Design approach is used at both the SDD and the finished product stages. The design spaces are generally acceptable, with the exception of scale-up for which the applicant needs to submit a verification protocol. The specifications are adequate; the product is tested by well described and validated analytical methods. Good stability is demonstrated in both types of container closure system.

The quality of the product is considered acceptable.

Quality Development

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

Taking into account the discussions in 2.2.4, the quality of the product is considered acceptable.

The CHMP has identified the following measures necessary to address the identified quality development issues:

The active substance quality is assured when manufactured under the normal operating ranges (NORs) of the design space, as defined in Module 3.2.S of the marketing authorisation dossier. In order to verify the validity of the design space at commercial scale a verification protocol should be submitted by December 2012.

2.2.6. Recommendation for future quality development

The applicant is recommended to revisit the criticality analysis and update the marketing authorisation dossier as appropriate.

2.3. Non-clinical aspects

2.3.1. Introduction

A comprehensive nonclinical development has been performed comprising of pharmacology, pharmacokinetic and toxicology studies.

The primary pharmacodynamic was investigated in *in vitro* studies. The safety pharmacological studies were carried out according to the Studies for Human Pharmaceuticals (July 2001) and the ICH S7B Guidance: Nonclinical Evaluation of the Potential for Delayed Ventricular Repolarisation (QT Interval Prolongation) by Human Pharmaceuticals (October 2005). The majority of studies in the safety

pharmacology program for ivacaftor, particularly all those considered pivotal to human safety assessment, were conducted in compliance with GLP regulations.

This application is supported by an extensive nonclinical pharmacokinetic development program. The pharmacokinetics of ivacaftor after oral administration have been investigated in various animal species including, mice, rats, rabbits, and dogs. Several formulations were studied as a result of ongoing pharmaceutical development.

Ivacaftor was thoroughly evaluated in acute toxicity, repeat-dose toxicity, genotoxicity, carcinogenicity, developmental and reproductive toxicity, local tolerance and skin antigenicity toxicity studies. The pivotal studies of this program were conducted in compliance with GLP regulations. The amorphous or spray-dried dispersion (SDD) forms of ivacaftor were used in all GLP studies as it proved to be optimal for oral administration of ivacaftor in all 4 animal species, since produced systemic exposures to ivacaftor that were high and sustained (or increasing) over the duration of the studies.

2.3.2. Pharmacology

Primary pharmacodynamic studies

It was showed *in vitro* that ivacaftor is a CFTR potentiator, since it increased the chloride transport and open probability of G551D-CFTR expressed in Fischer rat thyroid (FRT) cells, while it did not change the single channel conductance. The stimulation of cAMP-dependent protein kinase A (PKA) was required for ivacaftor to act, although ivacaftor did not act by stimulating the cAMP/PKA signalling pathway. Ivacaftor increased of the channel open probability of G551D-CFTR in excised membranes patches, suggesting that ivacaftor acts directly on G551D-CFTR.

In vivo pharmacodynamic studies were not performed due to lack of validated CF animal models. Therefore, an *in vitro* model comprising primary human bronchial epithelial (HBE) cells from CF patients was used. This model is considered adequate to test the pharmacological action of ivacaftor since CF HBE cells exhibit characteristics believed to be associated with the pathogenesis of CF in the lungs, including low chloride transport, excessive sodium transport, defective fluid regulation and decreased *cilia* beating. Ivacaftor potentiated chloride transport of G551D-CFTR protein, the most common CFTR gating mutation, in primary cultures of HBE cells isolated from the bronchi of a patient with CF carrying the G551D and F508del CFTR mutations (G551D/F508del-HBE). This increase was sufficient to restore the salt and fluid balance, prevent dehydration of the airway cell surface, and increase the ciliary beat frequency in these cells. Ivacaftor enhanced chloride transport in some, but not all, cultured HBE isolated from the bronchi of some F508del-homozygous patients with CF (processing mutation that is the most common CF-causing CFTR mutation), although the magnitude of the response to ivacaftor was less than that observed for cultured G551D/F508del-HBE cells.

The major circulating metabolite of ivacaftor, M1 (hydroxymethyl-ivacaftor, VRT-837018), was approximately 6-fold less potent than ivacaftor potentiating CFTR-mediated chloride transport in cultured G551D/F508del-HBE cells, thus was considered pharmacologically active. M6 metabolite (ivacaftor carboxylate, VRT-842917) was 50-fold less potent than ivacaftor in these cells and was not considered pharmacologically active.

Secondary pharmacodynamic studies

For ivacaftor, studies that may be classified as secondary pharmacodynamics studies have been performed and discussed under Safety Pharmacology. These studies showed that ivacaftor inhibited the competitive-binding of typical substrates or enzyme activities of only two targets with nanomolar potency of more than 140 enzymes and receptors tested in radioligand binding assays: the monoamine

transporter and serotonin 5-HT2C. However, tissue distribution studies in rats have shown that ivacaftor does not cross the blood-brain-barrier to an appreciable extent, therefore ivacaftor is unlikely to interact with these central nervous system targets in humans.

In electrophysiological studies, ivacaftor inhibited only CaV1.2 (IC50 = 1.3 μM) and KV1.5 (IC50 = 3.4 μM) with moderate potency and had little or no measurable activity (less than 50% inhibition at 10 μM) on the other sodium, calcium, and potassium channels tested, including hERG. The significance of these results in terms of human safety is unclear, since ivacaftor did not bind any of the 4 calcium channel targets or any of the 5 potassium channel targets in the receptor binding panel at <10 μM potency. Possible cardiac effects of ivacaftor are further discussed in safety pharmacology, toxicology and clinical sections.

No *in vitro* studies of inhibition of other receptors, enzymes and ion channels activities, including hERG, were conducted with the major metabolites of ivacaftor, M1 and M6. Since the synthesis of gram quantities of M1 and M6 is not technically feasible and as there was no evidence of meaningful, off-target effects resulting from interactions of these metabolites and ivacaftor (at therapeutic dosages) with other receptors, enzymes and ion channels activities, including hERG, the absence of such studies is justified.

Safety pharmacology programme

In a GLP study, ivacaftor showed a concentration-dependent inhibitory effect on hERG tail currents, producing a total inhibition of in hERG tail current of 34.6% at 8 μM.

Ivacaftor produced a dose-related, but transient increase in the arterial blood pressure parameters (systolic blood pressure, diastolic blood pressure, and mean arterial pressure) in dogs at single oral doses of up to 60 mg/kg. This effect was not considered adverse due to the small magnitude and brief nature of the response, thus the NOAEL for cardiovascular effects after oral single administration of ivacaftor to dogs was 60 mg/kg. ECG parameters were normal up to 60 mg/kg/day in the chronic 12-month study in dog. However, an increased incidence and severity of cardiomyopathy with coronary medial degeneration in the heart was observed at ≥100 mg/kg/day in the chronic 6-month study in rats, which was not completely recovered; instances of atrio-ventricular (AV) block at 60 mg/kg/day in the 3-month study in dog, which may be related to ivacaftor's demonstrated inhibition of the CaV1.2 (IC50 = 1.3 μM) channel; and increased incidence of supraventricular premature complex (SVPC) runs at ≥30 mg/kg/day in the chronic toxicity 12-month study. These effects were not considered adverse.

Ivacaftor did not produce adverse effects on central nervous and respiratory system in rats at single oral doses of up to 1000 mg/kg, however produced an inhibition of gastric emptying and gastrointestinal (GI) transit in male rats. The mechanism whereby decreased GI motility occurred at high doses in rats is unknown. In the repeated dose toxicity studies conducted in rats and dogs, there were no adverse effects on GI system at NOAELs, whose exposures were at least 9 (rats)- to 21 (dogs)-fold the expected exposures (steady-state $AUC_{0\text{-}24hr}$) at the human therapeutic dosage. However, dilated/cystic lymphatics in the small intestinal tract at dosages above the NOAEL in the 3-month study in rat, which was not completely recovered, as well as increases of abnormal stool (≥15 mg/kg/day) and vomiting (≥30 mg/kg/day) at dosages below the NOAEL in 12-month study in dog were observed.

There is increased incidence of nephropathy with tubular basophilia in the kidneys by ivacaftor at dosages ≥50 mg/kg/day in the chronic 6-month study in rats (not completely recovered), which was considered to involve rodent-specific mechanisms. The dosage of 50 mg/kg/day, considered the NOAEL in this study, had an exposure of least 9-fold times the expected exposure (steady-state $AUC_{0\text{-}24hr}$) at the human therapeutic dosage.

Pharmacodynamic drug interactions

No pharmacodynamic drug interactions studies were conducted, which is acceptable in the light of high CFTR selectivity of ivacaftor and the absence of other CF therapies targeting the CFTR protein.

2.3.3. Pharmacokinetics

Ivacaftor has been isolated in two physical forms, an amorphous form and a crystalline form. The absorption of ivacaftor in mouse, rats, rabbits and dogs is rapid, following oral administration of aqueous suspensions of the amorphous form, and bioavailability ranged from 30 to 100%. At the same time the crystalline form in suspension had a low oral bioavailability. The apparent permeability of ivacaftor in Caco-2 assay is high, which may have contributed to high oral bioavailability and suggest that human intestinal absorption will be high following oral administration. Ivacaftor and its metabolite M6 are not a substrate for efflux protein P-glycoprotein (P-gp), while its metabolite M1 may inhibit P-gp.

Systemic clearance following intravenous administration was lower than hepatic blood flow in mice, rats, dogs and monkeys and the intravenous elimination half-life of ivacaftor was shorter than that of oral administration, suggesting that exposure was limited by absorption.

Systemic exposure to ivacaftor tended to increase during repeated oral dosing at toxicological dose levels to mice, rats, rabbits and dogs, possibly due to accumulation of ivacaftor in plasma, and T_{max} increased with increasing dose levels, suggesting solubility limited absorption process. Therefore, a number of formulations studies were carried out in the preclinical phase to find an optimal formulation and dosage form. In these studies the bioavailability of ivacaftor in formulations studies ranged from 0.77 to 127% which shows a very profound effect of the formulation on the absorption.

The systemic exposure to ivacaftor's major metabolites was higher for M1 than for M6 for all 3 species investigated (mice, rats and dogs), with $AUC_{0\text{-}24hr}$ ratios of M1: ivacaftor ranging from 5 to 24% in mice, 6 to 34% in rats and 7 to 25% in dogs versus $AUC_{0\text{-}24hr}$ ratios of M6: ivacaftor ranging from 1 to 7% in mice, 1 to 20% in rats and 2 to 10% in dogs. Both M1 and M6 demonstrated dose-limitations to achieving high exposures by intravenous administration in rats, since they are practically insoluble in an aqueous vehicle suitable for repeat-dose studies, and had moderate to high clearance.

Ivacaftor was rapidly distributed across all tissues in rats, with detectable amounts noted in all tissues at 1 hour postdose. Tissues in the gastrointestinal tract showed highest ivacaftor exposure, followed by organs of eliminations (liver, kidney), organs of gland systems (adrenal, lymph nodes, pancreas, thyroid, thymus) and lungs. Lowest exposures were noted in the brain, eyes and testes. Ivacaftor was not bound to melanin containing tissues. Placental transfer of ivacaftor in rats and rabbits was minimal and the exposures to ivacaftor in foetuses were low. Ivacaftor accumulated in the milk of lactating rats.

Ivacaftor protein binding was high in mouse, rat, dog and human plasma and to isolated human plasma protein components. The active metabolite of ivacaftor M1 and M6 were also highly bound but to a somewhat lesser extent. In spite of this high protein binding, the ratio of ivacaftor levels to plasma was 3.8 and 0.939 for the lung and trachea, respectively. Thus, ivacaftor distributes more readily to the lung, trachea and lung epithelial lining fluid than to the plasma when administered orally to male rats. Furthermore the ratio of the concentration of ivacaftor in the epithelial lining fluid (ELF) to that in the plasma is 8.13, indicating substantial distribution of the compound to the lung and its excretion to the ELF. The mechanism of this presumably excretion process remains unclear, but in the absence of specific toxicity findings this is acceptable. The concentration of ivacaftor was relatively high in adrenal glands and lymphoid nodes were higher than plasma. This selective tissue accumulation might be

related to the high lipophilicity of ivacaftor. In the absence or any related toxicity findings the relatively higher lymphoid and adrenal concentrations are considered acceptable.

Extensive metabolism was observed in both rats and humans following oral administration of 14C-labelled ivacaftor. Using LC/MS and LC/MS/MS techniques, 11 metabolites were characterized/ identified from bile, urine, plasma and faecal samples. Ivacaftor was primarily metabolized to M1 and M6 by oxidation, M5 by glucuronidation, M1 sulfate by sulfation and to M8 metabolite by oxidation. M6 metabolite then further conjugated to glucuronic acid and decarboxylated to form M7 metabolite or undergoes ring closure to form furanone metabolite of ivacaftor, designated as M405. M8 metabolite also was further conjugated to glucuronic acid. A direct conjugation of ivacaftor led to M3 metabolite formation, which was observed in plasma and urine samples.

The metabolic profile of ivacaftor in both animals and humans are qualitatively similar. M1 and M6 were major circulating metabolites in all species studied, and systemic exposures to M1 in rats were high enough at the ivacaftor NOAEL to provide adequate toxicology coverage for human exposures at the intended therapeutic dose level. Faecal elimination is the predominant route of excretion in rat and humans.

In hepatocytes, metabolism of ivacaftor was observed in all species with the following trend monkey > rat > human > dog. Using S9 fractions and microsomes, marked species difference had been observed in the conversion rate between primates and rodents metabolic conversions rates. Indeed the relative concentration of M1 to ivacaftor is much higher in humans than was seen in animal studies.

Human cytochrome P450 (CYP) 3A4 and CYP3A5 are the predominant isozymes involved in the metabolism of ivacaftor and human metabolism was qualitatively similar to rats and dogs. *In vitro* inhibition studies suggest that ivacaftor and M1 may have pharmacokinetic interactions with other drugs that are CYP2C8, CYP2C9, CYP3A or P-gp substrates. These potential interactions are described in the SmPC.

Ivacaftor and M1 produced mild decreases in bufuralol 1'-hydroxylase activities upon preincubation with NADPH. The decreases in bufuralol 1'-hydroxylase activities may be attributed to the biotransformation of ivacaftor or M1 to more potent CYP2D6 inhibitors. Mechanism based inactivation of CYP2D6 by ivacaftor or M1 could not have been excluded.

2.3.4. Toxicology

Single dose toxicity

In the single dose toxicity studies, at the maximum tolerated doses (MTD = 2000 mg/kg in mice and 500 mg/kg in rats) the safety margins relative to the intended human therapeutic dose (150 mg every 12 hours), were 27 times in mice and 13 times in rats based on the surface-area extrapolation. Ivacaftor demonstrated a low potential for acute toxicity. In both species the histopathological findings in the forestomach are of questionable relevance to humans lacking this anatomical feature.

Repeat dose toxicity

In repeat dose toxicity studies in rats, hepatotoxicity was observed at high dosages ≥200 mg/kg/day in the GLP 3-month study and at ≥100 mg/kg/day in the GLP 6-month study. This effect was also observed in mice at ≥600 mg/kg/day in a 3-month study. The hepatic accumulation of ivacaftor, measured in the rat 3-month study, is believed to be a rodent-specific phenomenon of xenobiotic overload at high daily doses. This hypothesis is supported by the lack of hepatotoxicity in dogs, despite high daily doses and exposures to circulating ivacaftor which were similar to the high exposures achieved in mice and rats at hepatotoxic dosages. In addition, an increased incidence and severity of

cardiomyopathy with coronary medial degeneration was observed in the heart at ≥100 mg/kg/day and of nephropathy with tubular basophilia in the kidneys at dosages ≥50 mg/kg/day in the chronic 6-month study. Both effects were not completely recovered, although probably also involve rodent-specific mechanisms.

In dogs, occasional instances of atrio-ventricular block were observed at 60 mg/kg/day in the 3-month study, which is a well documented background finding in this species, but may be related to ivacaftor's demonstrated inhibition of the CaV1.2 (IC50 = 1.3 μM) channel, as well as a slight increase in the incidence of supraventricular premature complex (SVPC) runs in only 3 out of 40 dogs at dosages ≥30 mg/kg/day in the 12-month chronic toxicity study. The SVPC runs (multiple events within a single ECG recording) were not considered adverse since they were reversible, not accompanied by morphological changes in the heart or changes in health status, and are believed to be produced by mechanisms related to canine-specific control of heart rates and therefore do not translate to morbidity or mortality, in either dogs or humans.

In the chronic toxicity studies, ivacaftor exposures at the NOAEL in rats (50 mg/kg/day) and dogs (60 mg/kg/day), were at least 9- to 21-fold the expected exposure (steady-state $AUC_{0\text{-}24hr}$) at the human therapeutic dosage, derived from population-PK model estimates of $AUC_{0\text{-}24hr}$ in patients with CF (ages 6 to adult) in the phase 3 studies.

Genotoxicity

Ivacaftor has been shown to be non-mutagenic and non-clastogenic in the ICH standard battery of genotoxicity tests. Since M1 and M6 are produced in vitro in animal liver preparations, it is highly likely that these ivacaftor metabolites are also non-mutagenic and non-clastogenic in vitro. In addition, mice also produce both metabolites, so the mice used in the mammalian micronucleus assay would have been exposed to substantial amounts of these circulating metabolites at the highest ivacaftor dose tested (2000 mg/kg).

Carcinogenicity

It was concluded that ivacaftor was not carcinogenic in lifetime dosing (2 years) studies in mice at 200 mg/kg/day (4 to 7X the human exposure) and rats at 50 mg/kg/day (17 to 31X the human exposure). In addition, no pre-neoplastic lesions were seen in the mouse 3-month carcinogenicity dose range-finding study, the rat sub-chronic (3-month) and chronic (6-month) toxicity studies, or the dog sub-chronic (3-month) and chronic (12-month) studies, suggesting a low potential for ivacaftor-induced tumour promotion.

Reproduction Toxicity

Ivacaftor did not cause reproductive system toxicity in male and female rats at 200 and 100 mg/kg/day, respectively. Dosages above 100 mg/kg/day in females were associated to 54% reduction in overall fertility index and number of pregnancies, significant reductions in the average number of corpora lutea and implantation sites with subsequent reductions in the average litter size and the average number of viable embryos per litter. In males treated at 200 mg/kg/day, weight decreases of the seminal vesicles were observed.

Ivacaftor was not teratogenic dosed orally to pregnant rats and rabbits during the organogenesis stage of foetal development at 100 and more than 100 mg/kg/day (the highest dosage tested), respectively. The exposure of both doses is approximately 12X the exposure in human at the therapeutical dose. In rats, dosages above 100 mg/kg/day produced reductions of foetal body weight and increases in the following variations in skeletal development: cervical ribs, incompletely ossified ribs, wavy ribs and

sternal irregularities. These variations are commonly observed in the presence of maternally toxic doses, so they were not considered teratogenic.

Ivacaftor did not cause developmental defects (learning and memory, reproductive capacity, mating and fertility) in the offspring of pregnant rats dosed orally from pregnancy through parturition and weaning at 100 mg/kg/day. Higher dosages than this, were associated with reductions of survival and lactation indices (92 and 98%, respectively) and of pup body weight.

Toxicokinetic data

Toxicokinetic assessments were included in nearly all GLP studies and demonstrated that ivacaftor exposures after oral administration in the toxicology formulation were high and sustained throughout the dosing durations in all species studied.

Systemic exposures to M1 at the ivacaftor NOAEL in rats were greater than 1X in male rats, 0.6X in females and 0.3X in dog of either sex, while for M6 were 0.5X in male rats, 0.2X in female rats and <0.1X in dogs of either sex. Additional studies to characterize the toxicity of M1 and M6 were not feasible due to the extreme difficulty in synthesizing the quantities required, combined with the fact that they have physicochemical and pharmacokinetic limitations to achieving higher exposures by direct intravenous or oral administration routes than those already achieved in the rat after oral ivacaftor administration.

Local Tolerance

Ivacaftor has been shown to have no skin irritation, eye irritation or skin sensitization potential after topical administration. Ivacaftor is believed to have low potential for drug-induced cataract formation, photoirritation/photosensitization, or photocarcinogenicity after oral administration, based on clean ophthalmology exams in repeat-dose studies, absence of genotoxicity in the ICH standard battery, and no potential for carcinogenicity detected after 2 years of oral administration in rodents, combined with the fact that ivacaftor does not accumulate substantially in skin or eyes after oral administration, does not have a significant absorbance peak in the 290 to 700 nm wavelength range and does not undergo photodegradation.

Other toxicity studies

Dependence studies have not been conducted for ivacaftor, since tissue distribution studies in rats have shown that ivacaftor does not cross the blood-brain-barrier to any appreciable extent. In addition, ivacaftor had no effects on central nervous system function in standard safety pharmacology studies in rats, in repeat-dose toxicity studies in mice, rats, and dogs, or on behaviour and learning in developing pups in the prenatal and postnatal development study.

In a skin antigenicity study (murine local lymph node assay) ivacaftor did not show the potential to induce skin sensitization (delayed contact hypersensitivity).

All known and potential impurities in ivacaftor drug substance and drug product were qualified in the repeat-dose animal toxicity studies described above, in additional genotoxicity assays conducted for specific substances of concern (all 8 substances tested which included starting materials and potential process impurities were negative), or based on published toxicity studies. Specified impurities in the ivacaftor SDD/drug product, which are not controlled to ICH classification limits, include only the residual solvents as well as the US Pharmacopoeia/National Formulary compendial excipient, HPMC-AS. Qualification of the limits for residual solvents was based on literature evaluations of the toxicological characteristics of these compounds. Qualification of HPMC-AS is based on levels of this compendial

excipient in the chronic toxicity studies described, as well as on published pharmacology, general toxicity, and reproductive toxicity studies.

The Applicant notified during the procedure that findings of opacity of nucleus portion of lenses (cataracts) were observed in rats dosed at a high dose group (50 mg/kg/day) from postnatal day 7 through 35 from the juvenile toxicology study (VX-770-TX-025), which was ongoing at the time. The findings did not seem to be reversible. Preliminary histopathology results show that cataract formation in juvenile rats was not associated with structural damage (lenticular degeneration) to lens tissues.

2.3.5. Ecotoxicity/environmental risk assessment

The main results are summarised in the following table.

Substance (INN/Invented Name): ivacaftor			
CAS-number (if available):			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD Method 117	Partition coefficient (Log Pow) pH4; 3.5 pH7; 3.5 pH10; <1.0	No potential PBT
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
$PEC_{surfacewater}$, default or refined (e.g. prevalence, literature)	PECsw = 0.009 (CF patients in EU from 6 years of age) PECsw = 0.00036 (CF patients with G551D mutation) PECsw = 0.0016 (CF patients with other mutation)	µg/L	<0.01 threshold N

Ivacaftor $PEC_{surfacewater}$ value is below the action limit of 0.01 µg/L and it is not a PBT substance as log K_{ow} does not exceed 4.5.

2.3.6. Discussion on non-clinical aspects

Ivacaftor increased *in vitro* the chloride transport of multiple mutant CFTR forms associated with a variety of protein defects and disease severity.

The increase of chloride transport by ivacaftor was most pronounced in cells expressing CFTR gating mutations when compared to other types of CFTR mutations. This group included, G551D, G178R, S549N, S549R, G551S, G970R, G1244E, S1251N, S1255P and G1349D. The fold increase in chloride transport for all 10 studied gating mutation proteins was greater than 10.

Ivacaftor also potentiated chloride transport, of cells carrying CFTR mutations that are associated with residual CFTR function, although to a lesser extent than that observed for CFTR gating mutations, including CFTR conductance mutations (R117H, D110H, R117C, R347H and R352Q), mild CFTR processing mutations (E56K, P67L, L206W, A455E, D579G, S945L, R1070W and F1074L) and CFTR mutations with uncharacterized defects in the CFTR protein (D110E, D1152H, S1235R and D1270N). Finally, ivacaftor showed minimal effects in vitro on mutant CFTR forms that were associated with minimal chloride transport, including severe CFTR conductance mutations (R334W, T338I, R347P and L927P), severe CFTR processing mutations (F508del, A46D, G85E, E92K, S492F, I507del, V520F,

A559T, R560T, R560S, A561E, H1054D, G1061R, L1065P, L1065P, R1066C, R1066H, R1066M, L1077P, H1085R, M1101K and N1303K) and CFTR synthesis mutations (G542X, W1282X, 2184InsA and 2789+5G->A).

Studies that may be classified as secondary pharmacodynamics studies have been performed and discussed under Safety Pharmacology. In view of ivacaftor CFTR target selectivity, the CFTR dependence of the disease, lack of adequate animal disease model and low incidence of observed side effects in animal and clinical studies, it is scientifically justified not to perform additional studies on secondary pharmacodynamics. Similar reasons justify the absence of pharmacodynamic drug interactions studies in the application (i.e. high CFTR selectivity, absence of other CF therapies targeting the CFTR receptor).

Although the C_{max} for ivacaftor (5.0 µM) at the therapeutic dosage is comparable to the hERG IC15 (5.5 µM) value for ivacaftor, it was concluded that this value is not indicative of a risk for ivacaftor-induced QT prolongation at the therapeutic dose in patients with CF, since there is no evidence of ivacaftor-induced QT prolongation in these patients, as well as at supratherapeutic dose of 450 mg q12h (Cmax = 13.9 µM) after 5 days of dosing in the thorough QT study, and in a dog telemetry study at single doses as high as 60 mg/kg, or in ECG measurements from repeat-dose studies of up to 1 year duration at the 60 mg/kg/day dose level (36.2 µM to 47.6 µM).

Safety pharmacology studies did not reveal any concerns regarding renal system, central nervous and respiratory system. Decreased GI motility occurred at high doses in rats. While the mechanism of this is unknown, the safety margin between NOEL 9 (rats) to 21 (dogs) fold the expected exposure (steady-state $AUC_{0\text{-}24hr}$) at the human therapeutic dosage is regarded sufficient.

Rats and dogs are adequate for repeat dose toxicological studies since their metabolic profile are qualitatively similar to the humans. M1 and M6 were major circulating metabolites in all species studied.

The chronic toxicity studies in dog involved animals of young ages at the initiation of dosing (dogs as young as 3.5 months), so the indication from 6 years was sufficiently addressed by the Applicant.

The lens opacities observed in the juvenile rat toxicity study were located in the nucleus portion of the lens, which is the oldest portion of the lens. Therefore the initiating event in the development of cataracts is believed to have occurred during early lens development. Structural damage to lens tissues was not observed and these findings are believed not to be pharmacodynamically related to ivacaftor's mechanism of action, since ivacaftor is not active against rat CFTR. The Applicant has suggested that the finding of cataracts might be related to factors specific to the development of the eyes in newborn rats, in which, unlike in humans, hyaloid vessels persist until after birth by which time the retinal vessels have reached nearly to the periphery of the eye. In humans athrophy of hyaloid vessels is complete by the beginning of the third trimester of pregnancy and following complete involution of the vascular capsule during the second trimester *in utero* the human lens remains avascular and receives nutrition from the aqueous humor. Human eye development is recognised to be more complete at time of birth as compared to rats, therefore the risk of developing of cataracts is not expected in young children (children less than 6 years of age) and is believed to be not relevant for children aged 6 years and older. In support of this, there are examples in the literature of other substances that produce cataracts to rats dosed early in development but no to older rats, and there is no cataractogenic potential for ivacaftor detected in older rats or dogs from the chronic toxicity studies, neither in dosing pups via mother's milk from birth through Day 21 post-partum from in the developmental and reproductive toxicity study (Seg. III). In addition, there are no reports of cataracts in the clinical trial participants. Therefore the CHMP concludes that these findings are unlikely to be relevant for use in children above 6 years of age, but as the involved mechanism of these findings is

unclear, and in order to confirm non-relevance of findings, the following measures have been included in the risk management plan:

- The applicant should submit the final clinical study report of the rat juvenile toxicity study (VX-770-TX-025), including histopathology results
- The applicant should attempt to retrieve the head sections of the foetuses retained in alcohol from the rat embryo-foetal study and perform histological examination of the eyes and provide results

Ivacaftor predicted environmental concentration (PEC) surfacewater value was found to be below the action limit of 0.01 µg/L and was not found to be a persistence, bioaccumulation and toxicity (PBT) substance as log Kow does not exceed 4.5.

2.3.7. Conclusion on the non-clinical aspects

The pharmacologic, pharmacokinetic, and toxicological characteristics of ivacaftor were well characterized. No major findings were found in the non clinical studies. The information from juvenile toxicity study in rats about lens opacities has been adequately addressed in the risk management plan and additional data will be generated. The proposed SmPC appropriately reflects the relevant non-clinical findings.

2.4. Clinical aspects

2.4.1. Introduction

Ivacaftor is a new active substance with a novel mechanism of action and has been studied accordingly in several phase I studies aimed at assessing the PK, PD and safety properties and possible interactions. Several phase 2 and 3 studies have been included in the dossier, of which the pivotal phase 3 studies (studies 102 and 103) have studied use of ivacaftor in CF patients with G551D mutation in at least one allele at the posology proposed for clinical use (150 mg q12h).

The clinical development has followed guidance on the development of medicinal products for cystic fibrosis. The Applicant has received protocol assistance from the CHMP on the clinical development for ivacaftor.

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.

- Tabular overview of clinical studies

Study ID	Design	Study Posology	Study population	Duration	Type of study or Primary Endpoint
VX06-770-002	Phase 1, randomised, open-label, 3-period crossover, single-dose	150 mg	18 healthy male subjects	3 doses	Bioavailability study
VX08-770-007	Phase 1, randomised, open-label, crossover, single dose	150 mg	36 healthy male subjects	3 doses	Bioavailability study

VX10-770-012	Phase 1, randomised, crossover, open-label, single dose	150 mg	20 healthy male subjects	4 doses	Bioavailability study
VX05-770-001	Phase 1, randomised, double-blinded, placebo controlled, dose escalation single- and multiple dose	Parts A, B, C and D: VX-770 single dose 25 to 800 mg or placebo Part E: VX-770 125 and 250 mg q12h or placebo	Part A: 18 (healthy male) Part B: 9 (healthy female) Part C: 10 (healthy male) Part D: 6 (with pancreatic insufficient CF) Part E: 20 (healthy male)	Part A: 3 or 4 doses Part B: 3 doses Parts C and D: 2 doses Part E: 14 days	Safety and PK study
VX06-770-003	Phase 1, non-randomised, open-label, single dose	133 mg (^{14}C-ivacaftor)	7 healthy male subjects	1 dose	Absorption, distribution, metabolism and excretion study
VX10-770-013	Phase 1, non-randomised, open-label, single dose	150 mg	Group A: 12 (with moderate hepatic impairment) Group B: 12 (healthy)	1 dose	Safety and PK study
VX08-770-005	Phase 1, randomised, double-blinded, placebo-controlled, corssover, multiple dose	VX-770 150 mg or placebo q12h and NE 500 µg + EE 35 µg qd	34 healthy female subjects	2 x 28 days (including 21 days NE + EE)	Drug-drug interaction study
VX08-770-006	Phase 1, non-randomised, open-label, crossover, single dose	VX-770 150 mg single dose, ketoconazole 400 mg qd	24 healthy male subjects	1 dose; 10 days + 1 dose	Drug-drug interaction study
VX09-770-009	Phase 1, non-randomised, open-label, crossover, single dose	VX-770 150 mg single dose, rifampin 600 mg qd	24 healthy male subjects	1 dose; 10 days + 1 dose	Drug-drug interaction study
VX09-770-010	Phase 1, non-randomised, open-label, crossover, multiple dose	VX-770 150 mg q12h, midazolam 2 mg single dose, rosiglitazone 4 mg single dose, fluconazole 400 mg loading dose + 200 mg qd	24 healthy male subjects	10 days + 9 days (including single dosing)	Drug-drug interaction study

VX10-770-011	Phase 1, non-randomised, open-label, crossover, multiple dose	VX-770 150 mg q12h, desipramine 50 mg single dose	24 healthy male subjects	1 dose + 9 days (including second single dose)	Drug-drug interaction study
VX09-770-008	Phase 1, randomised, double-blind, placebo and active controlled, multiple dose	VX770 150 to 450 mg q12h or placebo; moxifloxacin 400 mg single dose	Part A: 8 healthy male subjects Part B: 72 healthy male and female subjects	Part A: dose escalation over 9 days Part B: 4 x 5 days	QTc
VX06-770-101	Phase 2[a], randomised, placebo-controlled, double-blinded, crossover, multiple-dose	25 mg, 75 mg, 150 mg, or 250 mg q12h	39 subjects with CF who have G551D mutation in the CFTR gene	Part 1: 2 x 14 days; Part 2: 28 days	PK, PD, Efficacy and Safety study
VX08-770-102	Phase 3, randomised, double-blind, placebo-controlled, parallel-group multicenter, multiple dose	150 mg q12h	161 subjects with CF who have G551D mutation in the CFTR gene	48 weeks (24 treatment + 24 weeks extension)	Absolute change from baseline in percent predicted FEV_1 through week 24 (%)
VX08-770-103	Phase 3, multicenter study. Part A was single-dose, open-label, to confirm the dose for Part B. Part B was randomised, double-blind	Part A: VX-770 100-mg Part B: VX-770 150-mg or placebo q12h	Part A: 12 Part B: 26 (VX-770) + 26 (placebo) subjects aged 6 to 11 years with the G551D-CFTR mutation in at least 1 allele	Part A: single dose Part B: 48 weeks (24 weeks treatment + 24 weeks extension)	Part B: absolute change in percent predicted FEV1 from baseline through Week 24
VX08-770-104 (Part B ongoing)	Phase 2, randomised, double-blind, placebo-controlled, parallel-group study (Part A) with an open-label extension (Part B)	Part A: 150 mg VX-770 or placebo q12h Part B: open-label 150 mg VX-770 q12h	Part A: 112 (VX-770) + 28 (placebo) subjects with CF who are homozygous for F508del-CFTR mutation	Part A: 16 weeks Part B: 96 weeks	Adjusted mean absolute change from baseline through Week 16 in percent predicted FEV1
VX08-770-105 (ongoing)	Phase 3, non-randomised, open-label, rollover study	VX-770 150-mg q12h	192 subjects with CF who have G551D mutation in the CFTR gene (enrolment ongoing)	96 weeks or until VX-770 marketed	Safety as determined by adverse events, clinical laboratory values, standard digital ECGs, vital signs, and physical examinations

VX10-770-106 (ongoing)	Phase 2, randomised, placebo-controlled, double-blinded, crossover, multiple-dose	VX-770 150-mg q12h or placebo	17 subjects with CF who have G551D mutation in the CFTR gene (enrolment ongoing)	28 days + 28 days	Safety and efficacy assessment
VX10-770-107 (ongoing)	Phase 2, single-centre, single-blind, placebo-controlled study of orally administered VX-770 in subjects with CF	VX-770 150-mg q12h or placebo	8 subjects with CF who have G551D mutation in the CFTR gene (enrolment ongoing)	14 days (placebo) + 28 days (VX-770) + 14 days (placebo)	Safety and efficacy assessment

The Applicant conducted also 3 other phase 1 studies (two palatability studies and one interaction study with another compound in development), which are not listed in the table above.

2.4.2. Pharmacokinetics

Analytical Methods

Ivacaftor (VX-770) and its two major metabolites, M1 (hydroxymethyl-ivacaftor; also known as VRT-837018 during clinical development) and M6 (ivacaftor carboxylate, also known as VRT-842917 during clinical development), were determined in human plasma and human urine. For human samples, the analytical method was validated in K_3EDTA or K_2EDTA human plasma over the range of 2.00 to 2000 ng/mL and in human urine over the range 2.00 to 2000 ng/mL by LC-MS/MS.

Transfer and cross validation of a method for the determination of VX-770, M1, and M6 in human plasma and urine was performed and successfully validated.

The linearity was demonstrated over the calibration range. The assay method was sufficiently selective for endogenous substances and met the requirements for precision and accuracy at each level for ivacaftor. The stock solution stability and long term stability in plasma samples were established.

In drug-drug interaction clinical studies, the interacting drug was also quantified in plasma using validated assays.

PK studies

The PK of ivacaftor has been extensively studied in 14 clinical studies. Two main PK studies evaluated the pharmacokinetics of Ivacaftor in healthy subjects and patients with cystic fibrosis:

- Phase 1 study VX05-770-001 in male and female healthy volunteers and in Subjects with Cystic Fibrosis with a 5-part (A-E), 7-panel double-blind, placebo-controlled, dose escalation, and randomized design. The ivacaftor was studied as single ascending oral doses of up to 800 mg and in repeated doses of up to 250 mg q12h.
- Phase 1 Mass Balance study VX05-770-003 to investigate the Absorption, Metabolism and Excretion of ^{14C}-ivacaftor following single oral administration to healthy male volunteers. This was an open-label, non-randomized, single dose, mass balance study in 6 healthy male subjects, to characterize the PK, route and extent of elimination and to identify the major metabolites of ivacaftor.

Apart from these 2 key PK studies, other studies also providing PK information of ivacaftor are studies 002, 007 and 012 (comparative BA of different ivacaftor formulations and interaction with food); 013

(moderate hepatic impairment); 005, 006, 009, 010 and 011 (DDI); 008 (TQT study); 101, 102, 103 and 104 (multiple dose in phase II-III studies in patients of different age strata and CF mutations).

In addition, a pop-PK modelling had been developed that included data from studies 002, 007, 010, 101, 102, 103 and 104.

Absorption

Due to the low solubility of ivacaftor in water (<0.05 µg/mL) no intravenous formulation has been developed. Therefore, the absolute bioavailability of ivacaftor in humans has not been determined.

Ivacaftor is orally available. Maximum concentrations of ivacaftor were reached within 2-3 hours after oral administration. C_{max} increased up to doses of 375 mg, after which it seemed to plateau.

Bioequivalence

A number of solid formulations have been assessed during early stages of clinical development of ivacaftor. Solid formulations (tablets) appear to be less bioavailable than the oral solution, though when administered in the fed state, the overall exposure increases to levels observed with the oral solution. Since the whole phase II-III clinical program has been conducted using the intended final formulation (film-coated tablets), the relevance of the results of these studies is minor.

Food interaction

There is a clear effect of concomitant food intake on the speed and magnitude of absorption of ivacaftor. In healthy volunteers high fat breakfast increased C_{max} and AUC of 150 mg tablet formulation by an order of magnitude around 2.5 and delayed T_{max} from 3 to 5 hours. A consistent effect was observed in patients with CF and pancreatic insufficiency in whom ivacaftor 275 mg oral solution was given. In this later case a standard CF meal (which contains up to 200% of the fat content of a standard meal) was compared with a fasted state. The impact of food on the PK of ivacaftor may have implications in clinical practice. Clinical studies were conducted advising patients to take ivacaftor with food containing fat. The recommendation given in the product information is consistent. However, since different fat content might result in relevantly different exposure to ivacaftor, upon a request from the CHMP, more detailed information on fat containing meals has been included in the SmPC.

Distribution

Ivacaftor and its metabolites M1 and M6 were highly bound to proteins in mouse, rat, dog, and human plasma, with >98% binding in all species. Protein binding percentages for ivacaftor, M1, and M6 were independent of concentration, indicating that no saturation of binding was evident up to 10 µM for ivacaftor and M6, and 20 µM for M1. Ivacaftor protein binding to human plasma components, HSA, AAG and HGG was greater than 97%, suggesting that ivacaftor was highly bound to most of the proteins of human plasma. M1 and M6 were highly (>90%) bound to HSA with moderate (30 to 90%) to low (0 to 30%) binding to AAG and HGG. The high degree of binding of ivacaftor, M1, or M6 through range of HSA concentrations (25 to 65 mg/mL) suggests that age or disease related variation in HSA concentrations are not likely to have a considerable impact on the clinical PK of ivacaftor, M1, and M6.

The potential for protein binding interactions between ivacaftor, M1, and M6 and warfarin was also evaluated in human plasma. Results indicated that protein binding of 3H-warfarin was high (99%) and unaltered in the presence of ivacaftor, M1 and M6. Similarly, the protein binding percentages of ivacaftor, M1 or M6 were not affected by the presence of warfarin. Therefore no plasma protein binding-related drug-drug interactions are expected.

Ivacaftor has a large apparent volume of distribution (Vz/F) suggesting penetration of ivacaftor into tissues. In study 001, where doses ranging from 25 mg to 800 mg of ivacaftor in oral solution where tested, Vz/F moved within the range of 250-350 L. In the population PK model, the population mean (95% confidence interval [CI]) estimate for Vz/F of ivacaftor as a tablet formulation (18-year-old, 70 Kg-male subject with CF) was 186 (170; 200) L for Vc/F (Vz/F of the central compartment) and 118 (77.2; 187) L for Vp/F (Vz/F of the peripheral compartment). The volume of distribution is much smaller for the biologically active M1 metabolite. The population PK estimates are 2.72 (Vc/F) and 18.1L (Vp/F). The Applicant stated that the high Vz/F of ivacaftor is a sign of good penetration of ivacaftor into tissues. However, the CHMP is of an opinion that the difference between Vd-s of ivacaftor and M1 could reflect the difference between their protein binding.

After oral administration of ivacaftor 150 mg every 12 hours for 7 days to healthy subjects in a fed state, the mean (±SD) for apparent volume of distribution of ivacaftor was 353 (122) L.

Elimination

Elimination in the faeces was the predominant route of elimination for ivacaftor and its metabolites, with a minimal renal excretion.

Following a single oral dose in fed state, the apparent terminal half-life was approximately 12 hours. The population PK model estimated that for an 18 years-old, 70-kg, male subject with CF, the mean estimate (95% CI) for the apparent clearance (CL/F) was 19.0 (17.5, 20.5) L/h.

Ivacaftor is extensively metabolized in humans. The major metabolic pathway involves oxidation of ivacaftor to M1 and M6. In vitro and clinical studies indicate that ivacaftor and M1 are primarily metabolised by CYP3A. In a mass balance study with radiolabelled ivacaftor, the metabolites accounted for approximately 65% of total dose excreted (M1-22%, M6-43%). M1 has approximately 1/6 the potency of ivacaftor and is considered pharmacologically active; M6 has less than 1/50 the potency of ivacaftor as is not considered pharmacologically active. Ivacaftor is mainly metabolised through CYP3A4, with some contribution probably from CY3A5. CYP3A4 distribution in the population is unimodal. Although CYP3A5 is bimodal, its limited contribution and the possibility to compensate lower metabolic rate trough an escape via CYP3A4 route makes a relevant influence of genetic polymorphism on the elimination of ivacaftor and its metabolites unlikely.

The involvement of non-CYP enzymes is not fully clear. The biologically active M1 is metabolized possibly further by aldehyde dehydrogenae (AO) and maybe by MAO. Data from inhibition studies in monkey and human liver fractions suggested a role of aldehyde oxidase and MAO isozymes in the conversion of M1 but it is poorly characterized.

In the mass balance study 003, total mean recovery of radioactivity was 94.6% of the administered dose over 19 days, with recovery in the faeces accounting for almost 90%. Most of the administered radioactivity (86.1%) was recovered in the first 168 hours postdose. Plasma radioactivity declined to low levels, with only M1-14C-ivacaftor detected in the 48-hour sample. Total recovery in individual subjects ranged from 84.3% to 99.0%. Only small amounts of unchanged parent drug, 2.5% of the dose, were excreted in faeces, suggesting that ivacaftor is metabolized extensively and excreted in faeces. Only 6.6% of the total radioactivity was excreted in urine. M6 and M1 accounted for 1.15 and 0.27% of the total administered radioactivity.

Dose proportionality and time dependencies

Since only one dose and strength of ivacaftor is recommended, dose proportionality is regarded not to be a major issue, but is of interest for the overall pharmacokinetic assessment of the substance. As

discussed above, increase in exposure at doses of ivacaftor higher than 375 mg is less than proportional, reaching in fact a plateau in both C_{max} and AUC.

Median accumulation rate of ivacaftor ranges from 2.2 to 2.9 in studies assessing multiple doses up to 150 mg/12h for 5 – 28 days. Accumulation rate was similar in healthy volunteers and in patients with CF. Ivacaftor exposure does not appear to be affected by circadian rhythm.

Special populations

PK of ivacaftor in patients with CF does not appear to differ essentially from that observed in healthy subjects. Pharmacokinetic parameters in males and females are comparable.

The pharmacokinetics of ivacaftor in children above 12 years is consistent with that observed in adults. However, specific pharmacokinetic assessment in CF subjects 6 to 11 years of age indicates that they have faster elimination than adults with a shorter apparent half-life, although some of the terminal slopes were estimated using only 2 time points and some included the C_{max} value, which may affect the precision of the estimates of $AUC_{0-\infty}$, CL/F, and $t_{1/2}$. Overall exposure as compared to equivalent doses in adults was similar in the non-compartmental analysis. Subjects aged 6 to 11 years had approximately 52% and 8% higher mean and median C_{min} for ivacaftor and approximately 2-fold higher mean and median AUC, but the total body clearance was lower in children (10L/h) than in adults (18.9L/h) while the relative clearance per kilogram as adjusted by body weight was larger at 20 kg (0.5 L/h/kg) than at 70 kg (0.27 L/h/kg). This is consistent with the faster elimination (larger relative clearance when adjusted for body weight) but smaller systematic clearance when not adjusted for body weight in subjects 6 to 11 years of age. These observations are also consistent with the predicted and observed higher AUC in children relative to adults at the 150 mg q12h dose (see below).

The 150 mg q12h dose regimen resulted in median and mean (SD) VX-770 C_{min} of 752 and 1180 (854) ng/mL in children aged 6 to 11 years, 492 and 556 (356) ng/mL for adolescents (12 to 17 years) and 690 and 774 (468) ng/mL for the adult subjects. Considering that the predicted EC_{90} for FEV_1 in CF subjects with a G551D-CFTR mutation is 423 ng/mL, it appears that the younger group may be overdosed. The CHMP therefore requested the Applicant to predict with a validated PK/PD model FEV_1 and sweat chloride concentrations for the age group of 6-11 years with the following doses: 50, 75, 100, 125 and 150 mg. Based on the population PK/PD model developed by the Applicant higher FEV_1 responses were predicted for higher doses - the median simulated FEV1 (90% predictive intervals) at Week 24 were 1.94 (1.07, 3.26) for the 150 mg dose, 1.94 (1.07, 3.25) for the 125 mg dose, 1.94 (1.07, 3.23) for the 100 mg dose, 1.93 (1.07, 3.22) for the 75 mg dose, and 1.91 (1.07, 3.18) for the 50 mg dose. The analysis also predicted that 70.8 % of the subjects would reach practically the maximum FEV_1 response with 2 x 100 mg dose and this response rate increased to 85.5% with 2 x 150 mg dose. Similarly, half-dose (75 mg) would be adequate for about 52% of the target population.

No PK data in ethnicities other than Caucasians has been provided, which is deemed acceptable as CF is predominantly found in Caucasians.

Considering the marginal renal contribution to the elimination of ivacaftor, the absence of a specific study in patients with renal impairment is accepted by the CHMP. No dose adjustment is therefore proposed for patients with mild to moderate renal impairment, which is reflected in the SmPC. The SmPC states in any case that caution should be exercised when administering ivacaftor to patients with severe renal impairment or end-stage renal disease.

A specific study was conducted to evaluate the effect of moderate hepatic impairment (Child-Pugh-B, clinical scores 7 to 9 points) on ivacaftor PK. Results showed similar C_{max} but approximately 2-fold increase in $AUC_{0-\infty}$ in hepatically impaired subjects compared to healthy subjects. The mean apparent terminal half-life of ivacaftor was increased and the CL/F of ivacaftor was decreased in subjects with

moderate hepatic impairment, both by approximately 2-fold of that in healthy subjects. The mean apparent terminal half-life of metabolites (M1 and M6) with moderate hepatic impairment was prolonged to approximately 1.6-fold of that in healthy subjects. Simulations for predicting steady-state exposure of ivacaftor showed that a dose of 150 mg q12h in subjects with Child-Pugh B would result in approximately 2-fold higher steady-state AUC, C_{max} and C_{min} values than those in healthy subjects Therefore a dose of 150 mg once daily is recommended for patients with CF who have moderate hepatic impairment. There is no clinical experience with the use of ivacaftor in patients with severe hepatic impairment.

Pharmacokinetic interaction studies

In vitro data

Ivacaftor was found to be metabolized by recombinant CYP3A4 and CYP3A5, and human metabolism was qualitatively similar to rats and dogs. In addition in vitro studies showed that ivacaftor has a potential for drug interactions through inhibition of CYP2C8, CYP2C9 and CYP3A.

K_i values for ivacaftor inhibition were 3.4 μM for the CYP2C8 pathway and 30 μM for the CYP2C9 pathway. Based on these results it is accepted that no interaction with CYP2C9 is expected and not conducting a DDI study with ivacaftor and a CYP2CP substrate is acceptable. However, since warfarin is metabolized by CYP2C9 and has a narrow therapeutic index, the SmPC states that concomitant use of ivacaftor may increase the concentration of warfarin, and monitoring of the international normalized ratio is recommended.

A study was carried out to evaluate the inhibition potential of ivacaftor, M1, and M6 on P-glycoprotein (P-gp) efflux activities in Caco-2 cell-based assay (ivacaftor-DMPK-DM-041). The results indicated that ivacaftor and M6 are not substrates for P-gp transporters, while metabolite M1 is a substrate for P-gp. However, *in vitro* studies of interactions of ivacaftor with digoxin (sensitive P-gp probe substrate), indicated that ivacaftor and M1 (but not M6) inhibit P-gp. This may increase the concentrations of sensitive P-gp substrates. Therefore it is recommended that in case concomitant use of ivacaftor with digoxin is indicated, digoxin should be monitored to obtain the desired clinical effect. It has been requested to further investigate this interaction post-authorisation.

In vivo data

In vivo evaluation of DDI was reasonably well characterised. The potential DDIs between ivacaftor and inhibitors, inducers, or substrates of CYP3A, and substrates of CYP2C8 and CYP2D6 was evaluated in studies in healthy subjects. These studies were conducted with: ketoconazole, fluconazole, rifampin (CYP3A inhibition and induction of ivacaftor metabolism), an oral contraceptive combination, midazolam (CYP3A), desipramine (CYP2D6) and rosiglitazone (CYP2C8).

Ketoconazole had a significant effect on the pharmacokinetics of ivacaftor by increasing ivacaftor systemic exposure. Based on DDI studies (also with fluconazole and rifampin), it can be concluded that CYP3A is the most relevant isoenzyme for metabolism of ivacaftor. Drug interactions are expected to occur with co-administration of CYP3A4 inhibitors and inducers.

The applicant initially suggested that ivacaftor should not be co-administered with ketoconazole or any strong inhibitor of CYP3A. However, in the light of unmet medical need in the target population and the fact that it is polymedicated (concomitant administration of potent CYP3A inhibitors might be medically indicated) the CHMP requested to consider alternative dosing approaches (reduced doses or prolonged intervals). Simulation with ivacaftor dosed at 150 mg q 72h in combination with ketoconazole showed C_{max}, C_{min} and AUC $_{0\text{-}72h}$ changes (90%CI) of 1.9 (1.5, 2.4), 0.95 (0.7, 1.3) and 1.4 (1.1, 1.8)-fold

relative to ivacaftor 150 mg q12h alone. Simulations with an ivacaftor twice-per-week schedule showed C_{max}, C_0 and $AUC_{0\text{-}tau}$ changes (90% CI) of 1.7 (1.4, 2.2), 0.6 (0.4, 0.9), and 1.3 (1.0, 1.6)-fold during the first part of the week (tau=72 hours) and 1.9 (1.5, 2.3), 0.9 (0.6, 1.2), and 1.2 (0.9, 1.5)-fold during the second part of the week (tau=96 hours) relative to ivacaftor 150 mg q12h alone. The 2 simulations of 150 mg q72h and 150 mg twice-per-week are generally comparable with the exception of the lower minimal concentration on 1 day of each week in the twice-per-week regimen. Therefore the CHMP concluded that, when co-dosing with a strong CYP3A inhibitor that is medically indicated, ivacaftor should be administered at 150 mg twice-per-week. This has been reflected in the SmPC.

Simulation with ivacaftor 150 mg once daily in combination with a moderate inhibitor (fluconazole) resulted in changes (90% CI) in ivacaftor steady-state AUC0-24h and Cmax of 1.5 (1.2, 1.9)-fold and C_{min} of 1.3 (1.0, 1.7)-fold when compared to ivacaftor 150 mg q12h administered alone. Therefore, when co-dosing with a moderate CYP3A inhibitor, ivacaftor should be administered at a dose of 150 mg once daily. This has been reflected in the SmPC.

Co-administration of ivacaftor at steady-state increased midazolam exposure, suggesting that ivacaftor is a mild CYP3A inhibitor (1.25 to 2 fold increase in AUC; <50% inhibition of oral CL). This interaction is reflected in the SmPC.

The Applicant proposes general caution and monitoring statements in the ivacaftor SmPC as well as specific recommendations about digoxin, cyclosporine and tacrolimus. A drug-drug interaction study with digoxin to further assess the inhibitory potential of ivacaftor on P-gp has been requested.

Co-administration of ivacaftor at steady state did not affect the exposure of rosiglitazone (CYP2C8 substrate), indicating that ivacaftor is not a CYP2C8 inhibitor.

Co-administration of ivacaftor at steady-state with desipramine did not affect its exposure or exposure to its metabolite, indicating that ivacaftor is not a CYP2D6 inhibitor.

Based on *in vitro* data aldehyde dehydrogenase (AO) and MAO may have a role in the metabolism of M1 (see discussion under Elimination).

Pharmacokinetics using human biomaterials

Results from in vitro studies using human biomaterials have been discussed in the respective parts of the PK section.

2.4.3. Pharmacodynamics

Mechanism of action

The effects of ivacaftor on CFTR-mediated Cl^- secretion *in vitro* were assessed in both recombinant cell lines (recombinant Fisher rat thyroid (FRT) cells expressing either human wild-type, G551D, or F508del CFTR) and primary cultures of human bronchial epithelia (HBE) isolated from the bronchi of CF and non-CF donor lungs.

Ivacaftor increased the channel activity of CFTR protein located at the cell surface through increased gating activity, resulting in increased chloride transport. For ivacaftor to act, the CFTR channel must first be activated by cAMP-dependent protein kinase A (PKA). However, the exact mechanism of action of ivacaftor, i.e. the molecular basis underlying the observed increased gating activity of the mutant G551D-CFTR channel is not known. *In vitro* no response to forskolin and ivacaftor addition was observed in FRT cells that did not express CFTR. In addition, ivacaftor increased chloride transport only after stimulation of cAMP-dependent PKA and acted by increasing the channel open probability of the

G551D-CFTR protein located at the cell surface. The ability of ivacaftor to increase the channel open probability of G551D-CFTR in excised membrane patches that are removed from the cytosolic signalling pathways suggested that ivacaftor acts directly on G551D-CFTR to increase its gating activity.

In vitro, several mutations have been studied and shown to respond to ivacaftor by increasing chloride transport (see table below). This was the case of several gating mutations (other than G551D) for which clinical data is not available.

Table 4 In vitro effects of ivacaftor on CFTR-gating mutations

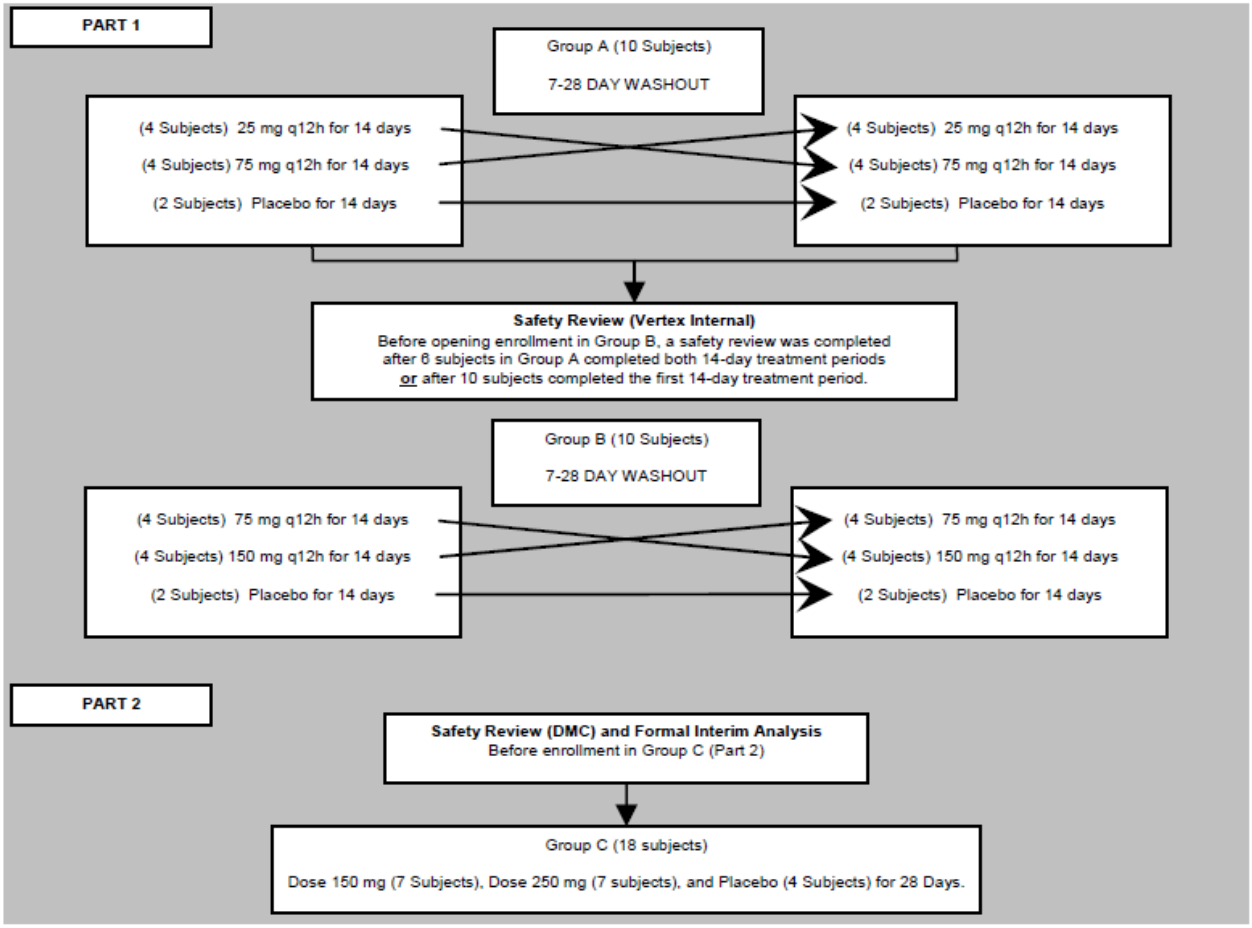
Mutation	Sweat Cl^- (mmol/L) [b]	CFTR-mediated chloride transport [a]				
		Baseline (% normal)		With Ivacaftor (% normal)		Fold Increase over baseline [c]
		Mean	SEM	Mean	SEM	
CF-Causing CFTR gating mutations						
G551D	108	1.0	0.5	55.3 [a]	6.3	55.3
G178R	103	2.9	0.5	87.2 [a]	8.2	30.1
S549N	109	1.6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

Primary pharmacology

Study 101 was a 2-part, randomised, double-blind, placebo-controlled, crossover, multiple-dose study where approximately 40 adult subjects with cystic fibrosis (CF) who have the G551D mutation in at least 1 allele of the CFTR gene were treated with 25 to 150 mg of ivacaftor q12h for 14 days (part 1) and 150 or 250 mg q12h for 28 days (part 2).

Figure 1 Schematic Description of the Design of Study 101



Adult patients with the G551D mutation in one allele of the CFTR gene were enrolled in study 101. The majority (32/39) of patients enrolled in study 101 had F508del-CFTR in the second allele. The analysis of the baseline characteristics of the disease and use of concomitant medications showed that 33 out of 39 (84.6%) were pancreatic insufficient as demonstrated by levels of immunoreactive trypsinogen (IRT) below 5 ng/ml. Pancreatic insufficiency was described in the medical history for 35 out of 39 patients (almost 90%) and approximately 37 patients were receiving pancreatic enzyme replacement therapy. It is concluded that most patients in study 101 were pancreatic insufficient.

At baseline in part 1 of the study patients receiving VX-770 25 mg/75 mg and 75 mg/150 mg had a higher median percent predicted FEV_1 (66% and 63%, respectively) than the overall median (56%) and subjects receiving 150 mg/75 mg VX-770 had a lower median percent predicted FEV_1 (49%). Patients on placebo had a median percent predicted FEV_1 of 57.3%. In part 2, the 150-mg VX-770 group had a slightly lower median percent predicted FEV_1 (65.1%) and median NPD (1.88 mV) than the other 2 groups (the NPD value refers to the zero chloride plus isoproterenol response data). In part 2, the mean sweat chloride was 95.50 mmol/L for the 19 patients participating in the trial (93.75 mmol/L on placebo, 100.13 on ivacaftor 150 mg BID and 95.50 on ivacaftor 250 mg BID).

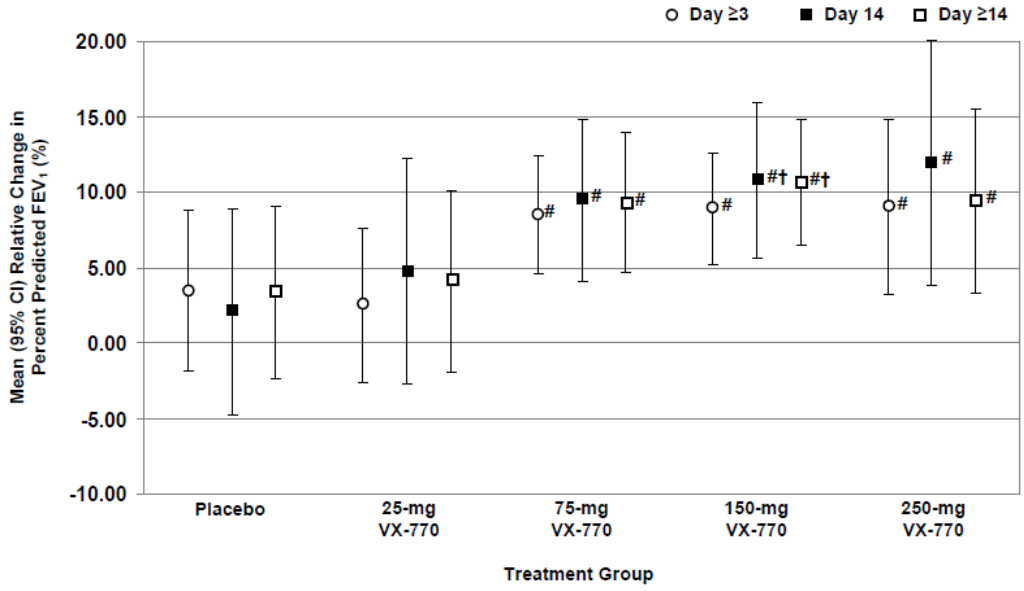
In part 1 and 2 combined 28 patients were described as having "lung infection pseudomonal" while 4 additional patients had "Pseudomonas infection". Apparently, twenty-two out of 39 patients (54%) were receiving tobramycin while colistin was being administered to 2 patients. The issue of pseudomonal infections is further discussed for the two pivotal trials.

In study 101 the effects of different doses of ivacaftor on FEV_1, nasal potential differences (NPD), sweat chloride and the Cystic Fibrosis Questionnaire-Revised (CFQ-R) were assessed.

The combined results of part 1 and part 2 of study 101 are discussed below (except when they are specific of one part, e.g. CFQ-R in part 2) as they cover the full range of ivacaftor doses tested.

The mean relative change from baseline in percent predicted FEV_1% for Day≥3, Day14, and Day ≥14 is represented in Figure below.

Figure 2 Combined Part 1 and Part 2: Mean (95% CI) Relative Change from Baseline in Percent Predicted FEV1 for Day ≥3, Day 14, and Day ≥14, Part 1 and Part 2 Combined, FA Set

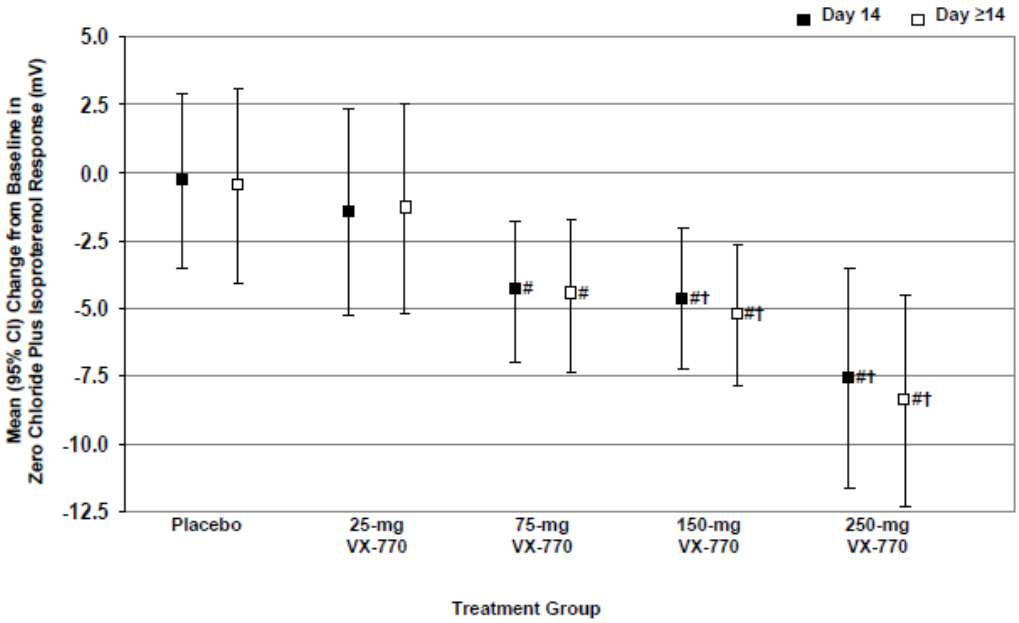


\# $P<0.05$ least square mean change from baseline, obtained from the linear mixed model with baseline, period, and dose group as fixed effects, subject as random effect, and change from baseline as the dependent variable.

† $P<0.05$ for treatment difference between change from baseline for VX-770 group versus placebo, obtained using linear mixed model.

Regarding Nasal Potential Difference (NPD), figure below show the mean (95% CI) change from baseline in zero chloride plus isoprotenereol response for Day 14 and Day≥14.

Figure 3 Combined Part 1 and Part 2: Mean (95% CI) Change from Baseline in NPD (Zero Chloride Plus Isoproterenol Response) for Day 14, and Day ≥14, FA Set

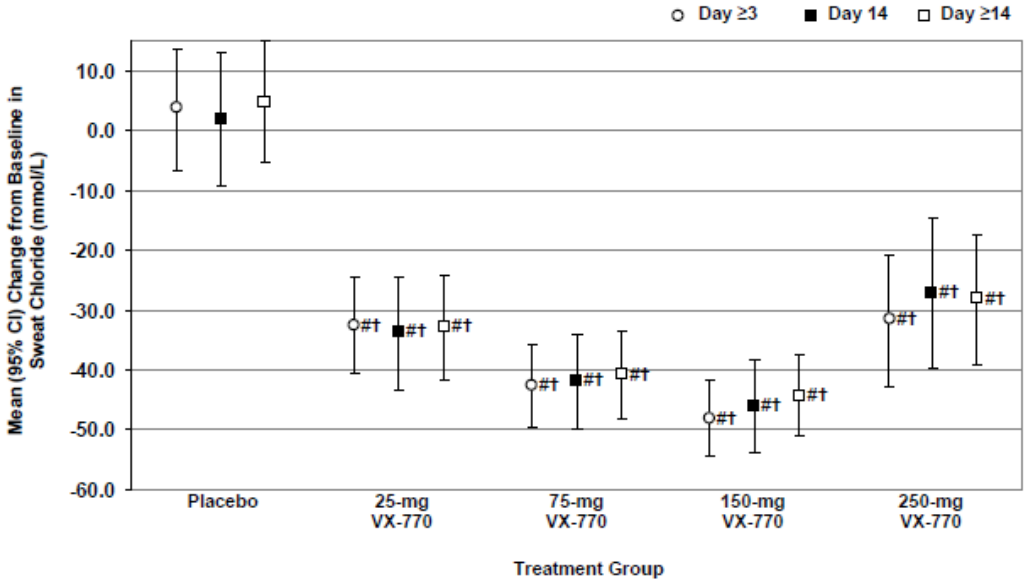


# $P<0.05$ least square mean change from baseline, obtained from the linear mixed model with baseline, period, and dose group as fixed effects, subject as random effect, and change from baseline as the dependent variable.

† $P<0.05$ for treatment difference between change from baseline for VX-770 group versus placebo, obtained using linear mixed model.

As for the sweat chloride test figure below show the mean (95% CI) change from baseline in maximum sweat chloride for Day ≥3, Day 14, and Day ≥14

Figure 4 Combined Part 1 and Part C: Mean (95% CI) Change from Baseline in Maximum Sweat Chloride for Day ≥3, Day 14, and Day ≥14, FA Set



# $P<0.05$ least square mean change from baseline, obtained from the linear mixed model with baseline, period, and dose group as fixed effects, subject as random effect, and change from baseline as the dependent variable.

† $P<0.05$ for treatment difference between change from baseline for VX-770 group versus placebo, obtained using linear mixed model.

In Part 2 of study 101, subjects were asked to complete the CFQ-R, which evaluated 9 quality of life domains including respiratory symptoms, digestive symptoms, emotion and health perception. The

median (min, max; P-value) change from baseline in CFQ-R (respiratory domain) was +5.56 points (+0.00, +16.67; P = 0.063) on Day 14 and +8.33 points (+0.00, +16.67; P= 0.063) on Day 28 for subjects in the 150-mg group and +5.56 points (-11.11, +11.11; P = 0.156) on Day 14 and +11.11 points (-5.56, +33.33; P = 0.078) on Day 28 for subjects in the 250-mg group. In contrast, subjects in the placebo group showed a median (minimum, maximum) increase of +2.78 points (-5.56, +11.11; P = 0.750) on Day 14 and +2.78 points (-5.56, +11.11; P = 0.750) on Day 28.

Results from exploratory analyses of inflammatory biomarkers for C-reactive protein (blood), neutrophil count (expectorated sputum) and total IGG (blood) were provided for Part 2 of study 101. The difference in the change from baseline at Day 28 in C-reactive protein and total IgG levels in the VX-770 groups versus the placebo group was not statistically significant. Due to the small number of subjects providing samples, it was not possible to evaluate the effect of VX-770 on neutrophil count in sputum.

A number of subgroup analyses were conducted (by immunoreactive trypsinogen in Part 1 and Part 2; and by baseline FEV_1 severity, genotype, tobramycin use, bronchodilator use, azithromycin use, and inhaled sodium chloride use in Part 2 only). Due to the few patients included the results of these subgroups are of limited value and showed in some cases inconsistent results.

PK/PD modelling has been developed to further elucidate the relationship between drug plasma levels and the effect on the 3 key variables.

Regarding FEV_1 (the most clinically relevant measured variable) the PK/PD model predicted higher FEV_1 responses at higher doses. The median maximum response derived from 1000 simulated paediatric patients with covariate values sampled from study 103 were 1.94 (1.07, 3.26) for the150-mg dose, 1.94 (1.07, 3.25) for the 125-mg dose, 1.94 (1.07, 3.23) for the 100-mg dose, 1.93 (1.07, 3.22) for the 75-mg dose, and 1.91 (1.07, 3.18) for the 50-mg dose. The analysis also predicted that the 70.8% of the subjects would reach practically the maximum FEV_1 response with 2 x 100 mg dose and this response rate increased to 85.5% with 2 x 150 mg dose. Similarly, half-dose (75 mg) was found to be adequate for about 52% of the target population. The results from the sweat chloride would support the use of 150mg dose bid.

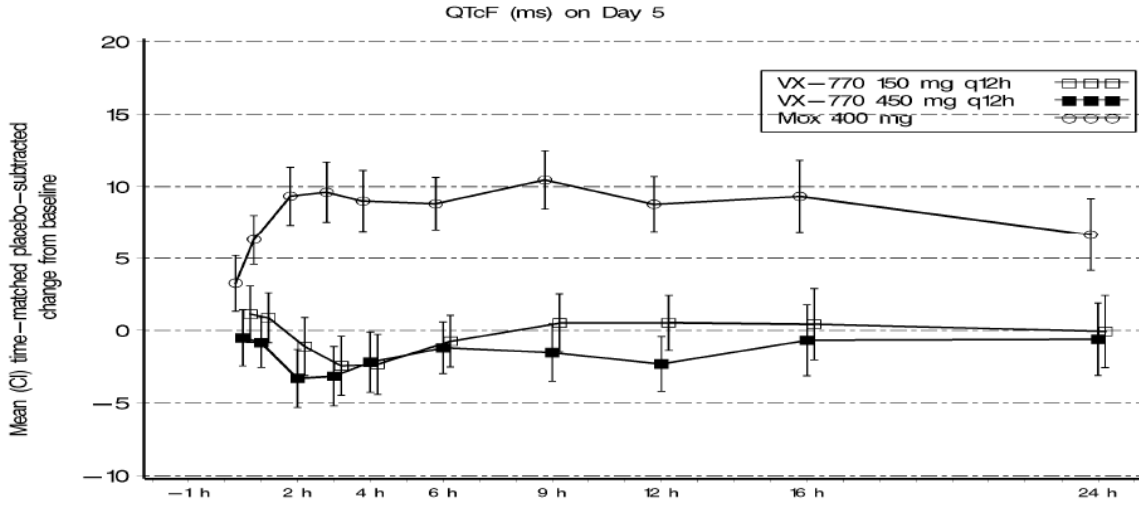
The observed FEV_1 and sweat chloride values appeared to be unrelated, however, simulations from the population PK/PD models yielded a FEV_1 and sweat chloride correlation, but the 90% predictive interval included the value of zero, which indicated that a correlation between FEV and sweat chloride measures has not yet been proven.

Secondary pharmacology

A dedicated QTc study (Study 008) was designed and conducted in line with ICHE14 recommendations. Study sensitivity is considered proven as the 4 (i.e. at predefined time points: 2, 3, 4, and 6 hours post-dose on Day 5) lower limits of the 2-sided 97.5% CI of baseline-adjusted and placebo-corrected QTcF for moxifloxacin exceeds 5 msec. The upper 90% two-sided CI limits for the highest mean change in QTcF interval were 3.1 at 0.5 hours postdose for 150-mg and 1.9 at 24 hours postdose for 450-mg (see figure below). The 95% two-sided confidence intervals for the two ivacaftor doses have been provided upon CHMP request. The upper limit of the 95% 2-sided CIs for the highest mean time-matched change from baseline in QTcF under treatment minus the time-matched change from baseline during placebo use was below 10 msec for both doses (150 mg and 450 mg).

At approximately ivacaftor T_{max} none of the upper limits of the 90% 2-sided CI for the two doses of 150 mg and 450 mg exceeded the threshold of 10 msec.

Figure 5 Adjusted Mean and 90% CI of Time-Matched Placebo-Subtracted Change From Baseline in QTcF Interval on Day 5- Part B, Complete Case Analysis Set



No relationship between concentrations of VX770, M1 or M6 and the time-matched, placebo-substracted differences of QTcF were found.

2.4.4. Discussion on clinical pharmacology

The pharmacokinetic documentation for ivacaftor is extensive and contains 14 different studies, 2 of them (001 and 003) being pivotal for the PK characterisation of the drug.

The validation of the methods for determination of ivacaftor, M1 and M6 are adequate and the in-study validation of the bioanalitycal methods is sufficient.

Due to its low solubility the absolute oral bioavailability of ivacaftor has not been determined. It is orally bioavailable, and according to the high metabolism rate, it is acknowledged that it is likely to be highly permeable. It was found that food intake increases the availability of ivacaftor and delay t_{max}. The content in fat of the meal appears to be a major determinant of exposure.

M1 (active) and M6 are the main metabolites of ivacaftor and both are a result of oxidative processes where CYP3A is involved. More than 90 % of ivacaftor is excreted in the faeces, mainly metabolised.

The exposure to ivacaftor and its metabolites at doses above 375 mg are not proportional, but ivacaftor is only recommended at 150 mg BID dosing (OD in moderate hepatic failure).

No intrinsic factor other than weight appears to play a major role in the PK of ivacaftor. However, data on the PK in children below 12 years not consistent and the role that weight might have played in these findings is unclear.

In vitro and in vivo studies indicate that CYP3A is the main isoenzyme involved in the metabolism of ivacaftor, and therefore is a clear target for drug-drug interactions. In addition, ivacaftor and M1 inhibit P-gp. This may increase the concentrations of sensitive P-gp substrates. A phase I study in healthy volunteers to examine the effects of ivacaftor on the pharmacokinetics of digoxin has been included as a measure in the risk management plan in order to fully investigate this interaction.

PK of ivacaftor in patients with CF does not appear to differ essentially from that observed in healthy subjects. In CF subjects 6 to 11 years of age there appears to be a faster elimination than in adults with a shorter apparent half-life.

A higher exposure in children aged 6 – 11 years with the proposed dose has been predicted in PK analyses. In children aged 6 to 11 years the 150 mg q12h dose regimen resulted in median and mean

(SD) VX-770 C_{min} of 752 and 1180 (854) ng/mL, which was above the predicted EC_{90} for FEV_1 in CF subjects with a G551D-CFTR mutation of 423 ng/mL. Data from PK/PD modelling suggest that children may potentially benefit from a dosing according to their body weight in order to avoid higher exposure relative to older children and adults. However, based on the available data no particular safety concern has been identified with the fixed dose of 150 mg q12h in this population, and the efficacy has been demonstrated, hence the proposed dosing is considered acceptable. Nevertheless, the applicant should explore an alternative dosing regime for children from 6 to 11 years old that mimics closer the exposure in older children and adults. Appropriate measures have been defined in the Risk Management Plan.

Considering the marginal renal contribution to the elimination of ivacaftor, the absence of a specific study in patients with renal impairment is accepted by the CHMP. No dose adjustment is therefore proposed for patients with mild to moderate renal impairment, which is reflected in the SmPC. The SmPC states that caution should be exercised when administering ivacaftor to patients with severe renal impairment or end-stage renal disease.

A dose of 150 mg once daily is recommended for patients with CF who have moderate hepatic impairment. There is no clinical experience with the use of ivacaftor in patients with severe hepatic impairment. Therefore, the use of ivacaftor in these patients is not recommended unless the benefits outweigh the risks. In such case, the starting dose should be 150 mg every other day and the dosing intervals should be modified according to clinical response and tolerability.

Based on the *in vitro* studies performed ivacaftor has been qualified as a CF transmembrane conductance regulator (CFTR) potentiator, i.e. a compound that enhances the activity of mutant chloride channels present at the cell surface increasing the flow of ions through them. *In vitro*, several mutations have been studied and shown to respond to ivacaftor by increasing chloride transport. This is the case not only of the most prevalent gating mutation G551D but also of other gating mutations for which clinical data is not available. Until further clinical data exploring ivacaftor in other gating mutations can be provided, the indication should be restricted to patients with a G551D mutation.

Study 101 assessed how the mechanism of action hypothesised based on *in vitro* investigations translates in the clinical setting and was also the main basis for dose selection for phase 3 clinical development. The effect of different doses of ivacaftor on FEV_1, nasal potential differences (NPD), sweat chloride and the Cystic Fibrosis Questionnaire-Revised (CFQ-R) were assessed. While FEV_1 is the recommended primary clinical endpoint in efficacy studies for cystic fibrosis as the rate of decline in FEV_1 has been demonstrated to correlate with survival and to be the strongest clinical predictor of mortality, Nasal Potential Difference (NPD) and sweat chloride remain biomarkers of the disease that are useful for testing activity of compounds aiming to restore CFTR function (CFTR activity). At the same time it is recognised that these parameters do not necessarily translate into clinical benefit, e.g. structural airway damage in the lung may not be reversible even if full CFTR activity is restored.

Nasal PD examines different aspects of transepithelial ion transport by the nasal epithelium. In CF, this ion transport profile is abnormal and the nasal PD measurement distinguishes CF and non-CF. The line delineating CF from non-CF generally runs around a basal PD of −30 mV and a Cl− free/isoprenaline response of −5 to −10 mV, though many classical CF subjects will have basal values of −50 mV, and combined Cl− responses of 0 mV, whereas non-CF subjects will have values of −20 mV for basal PD and −30 mV for the combined Cl− responses (De Boeck K. et al, 2011). The transepithelial NPD under conditions of zero chloride concentration perfusion solution in the presence of isoproterenol was the primary PD assessment in study 101.

The sweat chloride test (quantitative pilocarpine iontophoresis) is the most commonly used diagnostic tool for CF. A sweat chloride concentration of at least 60 mmol/L is considered indicative of CF, whereas a sweat chloride concentration less than 40 mmol/L is considered normal. Genotype–

phenotype correlations for disease severity are associated with alterations in sweat chloride. Normal adults without CFTR mutations generally have mean sweat chloride of approximately 20 mmol/L although there can be wide variability. Patients with two severe mutations have the most severe sweat chloride abnormalities, averaging greater than 100 mmol/L.

In summary, study 101 shows that ivacaftor is able to increase the activity of mutant CRFT harbouring the most frequent class III mutation G551D (as shown by PND and sweat chloride) and also that this is associated with clinical benefit for patients (based on FEV_1 improvement and CFQ-R). No biomarkers related to the gastrointestinal manifestations of the disease (e.g. exocrine pancreatic insufficiency) have been collected. As most patients enrolled in this trial were pancreatic insufficient and received pancreatic enzyme replacement therapy, it is recognised that this would have been difficult.

Overall, doses ranging from 75 to 250 mg show an effect than can be distinguished from placebo in the 3 key fields of parameters studied (spirometry, NPD and sweat chloride). Among them, the intermediate one (150 mg) has been selected for further development. In the light of the rarity of condition and the limited number of patients studied, it is acknowledged that expecting more solid conclusions would have been unrealistic. Therefore the choice of the dose in general is accepted, even though no clear dose-response curve can be identified.

PK/PD modelling was developed to further elucidate the relationship between drug plasma levels and the effect on the 3 key variables. It predicted higher FEV_1 responses at higher doses, and the results from the sweat chloride would support the use of 150mg dose bid, however, this measure has a smaller relevance in clinical practice.

There are two possible explanations for the controversy between the observed responses and the responses predicted by the structural model regarding relationship of FEV_1 and sweat chloride outcomes. First, FEV_1 measurements are associated with a high degree of variability. This variability is also true for the sweat chloride measurements, although to a lesser extent. Second, in the population PK/PD model, many of the data points lie well into the flat part of the exposure/response range, occurring at or near maximal response. Given these maximal responses and the observed variability for FEV_1 and sweat chloride, it is not surprising that individual changes in FEV_1 do not correlate with individual changes in sweat chloride. These results highlight that due to design problems the PK/PD model cannot be validated and cannot be refuted. Therefore PK/PD model-based predictions, particularly extrapolations, should be considered as hypothesis-generating rather than hypothesis-confirming predictions.

In the QTc study the upper 90% two-sided CI limits did not exceed 10 msec, indicating that VX 770 does not have a clinically significant effect on the QTcF interval at the therapeutic and supratherapeutic dose levels. At approximately T_{max} of ivacaftor none of the upper limits of the 90% 2-sided CI for the two doses of 150 mg and 450 mg exceeded the threshold of 10 msec. Similarly the categorical analysis does not suggest that ivacaftor is associated to a significant risk to increase the QT interval. Overall, it is concluded that ivacaftor does not have a clinically significant effect on the QTcF interval at the therapeutic and supratherapeutic dose levels.

2.4.5. Conclusions on clinical pharmacology

Pharmacokinetic and pharmacodynamic properties of ivacaftor have been sufficiently characterised. It was noted that in children aged 6 to 11 years an analysis of PK data shows a higher exposure as compared to older children and adults. Based on the available clinical efficacy and safety data, the currently proposed dosing is deemed acceptable. Nevertheless, attempts should be made in order to refine the dosing regimen in order to match the PK profile in this subpopulation ; the Risk management Plan addresses this. PK of ivacaftor are affected by hepatic impairment and use of CYP3A inhibitors;

the modified dosing regimens addresses this point adequately. The dose recommendation for patients with renal impairment as stated in the SmPC are appropriate, also considering the marginal renal contribution to the elimination of ivacaftor.

Ivacaftor has shown effect on defective CFTR protein in case of several types of mutations, however, supportive clinical data is available only in patients with G551D mutation in at least one allele.

2.5. Clinical efficacy

2.5.1. Dose response studies

Dose response has been assessed in Study 101, which is also a PD study. Please refer to Clinical Pharmacology: Primary Pharmacology for discussion on the choice of dose for the pivotal phase 3 studies.

2.5.2. Main studies

Two pivotal trials (studies 102 and 103) and one extension study (study 105) to assess the effect of ivacaftor on patients with CF have been provided. The pivotal trials were randomized, double-blind, placebo-controlled and parallel-group multicenter studies.

Study VX08-770-102

Methods

This was a Phase 3, randomized, double-blind, placebo-controlled, parallel-group multicenter study.

The study included a Screening Period (Day -35 to Day -15), a Run-In Period (Day -14 to Day -1), a Treatment Period (Day 1 to Week 24), and an Extension Period (Week 25 to Week 48).

Study Participants

This study recruited CF patients of both sexes aged 12 years and older with predicted FEV_1 between 40% and 90% of predicted normal for age, gender, and height (Knudson standards) at screening and bearing G551D-CFTR mutation in at least 1 allele. Diagnosis of CF was defined as (1) a sweat chloride value ≥ 60 mmol/L or 2 CF causing mutations (all as documented in the subject's medical record) and (2) chronic sinopulmonary disease or gastrointestinal/ nutritional abnormalities.

Subjects with clinically significant abnormalities in haematology, serum chemistry, coagulation, and urinalysis results at screening or history of illnesses or conditions that could confound the results of the study or pose an additional risk were excluded from participation in the study. Exclusion criteria also included acute upper or lower respiratory infection, pulmonary exacerbation, or changes in therapy (including antibiotics) for pulmonary disease during last 4 weeks and colonization with organisms associated with a more rapid decline in pulmonary status, e.g., B. cenocepacia, B. dolosa, and M. abscessus. Patients receiving inhaled hypertonic saline treatment and those who concomitantly used any inhibitors or inducers of CYP3A4 were also excluded.

Females of child-bearing potential had to have a negative serum pregnancy test at screening and all subjects of child-bearing potential and who were sexually active had to meet contraception requirements.

Treatments

The participants received either ivacaftor 150 mg or placebo q12h for 48 weeks (24 weeks in the Treatment Period and 24 weeks in the Extension Period). The subjects were recommended to take study drug 30 minutes after the start of a standard CF high-fat, high calorie meal or snack.

It was recommended that subjects remain on stable medication regimens for their CF (including high-dose ibuprofen, dornase alfa, inhaled antibiotics). Use of short-acting and long-acting bronchodilators and any other prior and concomitant medications was documented.

Objectives

The objective of the study was to evaluate the efficacy and safety of VX-770 after 24 and 48 weeks of treatment in subjects with CF and a G551D-CFTR mutation. In addition the study was aimed at evaluating PK of VX-770 and its metabolites M1 and M6 after multiple oral doses of VX-770.

Outcomes/endpoints

The primary efficacy endpoint for the pivotal trials was the absolute change from baseline in percent predicted FEV_1 through 24 weeks of treatment.

The main secondary endpoints were the absolute change from baseline in CFQ-R; absolute change from baseline in sweat chloride; time to first pulmonary exacerbation; absolute change from baseline in weight and absolute change from baseline in percent predicted FEV_1 through Week 48.

Sample size

A minimum of 80 subjects were planned to be randomized to either VX-770 or placebo. This calculation was aimed at having at least 80% power to detect an expected treatment effect of 4.5% in absolute change from baseline in percent predicted FEV_1.

Randomisation

Subjects were randomized in a 1:1 ratio to groups of VX-770 and placebo, stratifying for age (<18 vs. ≥18 years of age) and FEV_1 (<70% vs. ≥70% predicted) at screening.

Blinding (masking)

The subjects, study site personnel, study monitors and the study team of the sponsor were blinded for treatment allocation. Most of them were blinded also for sweat chloride, bioanalysis and spirometry results. Emergency unblinding procedures were defined.

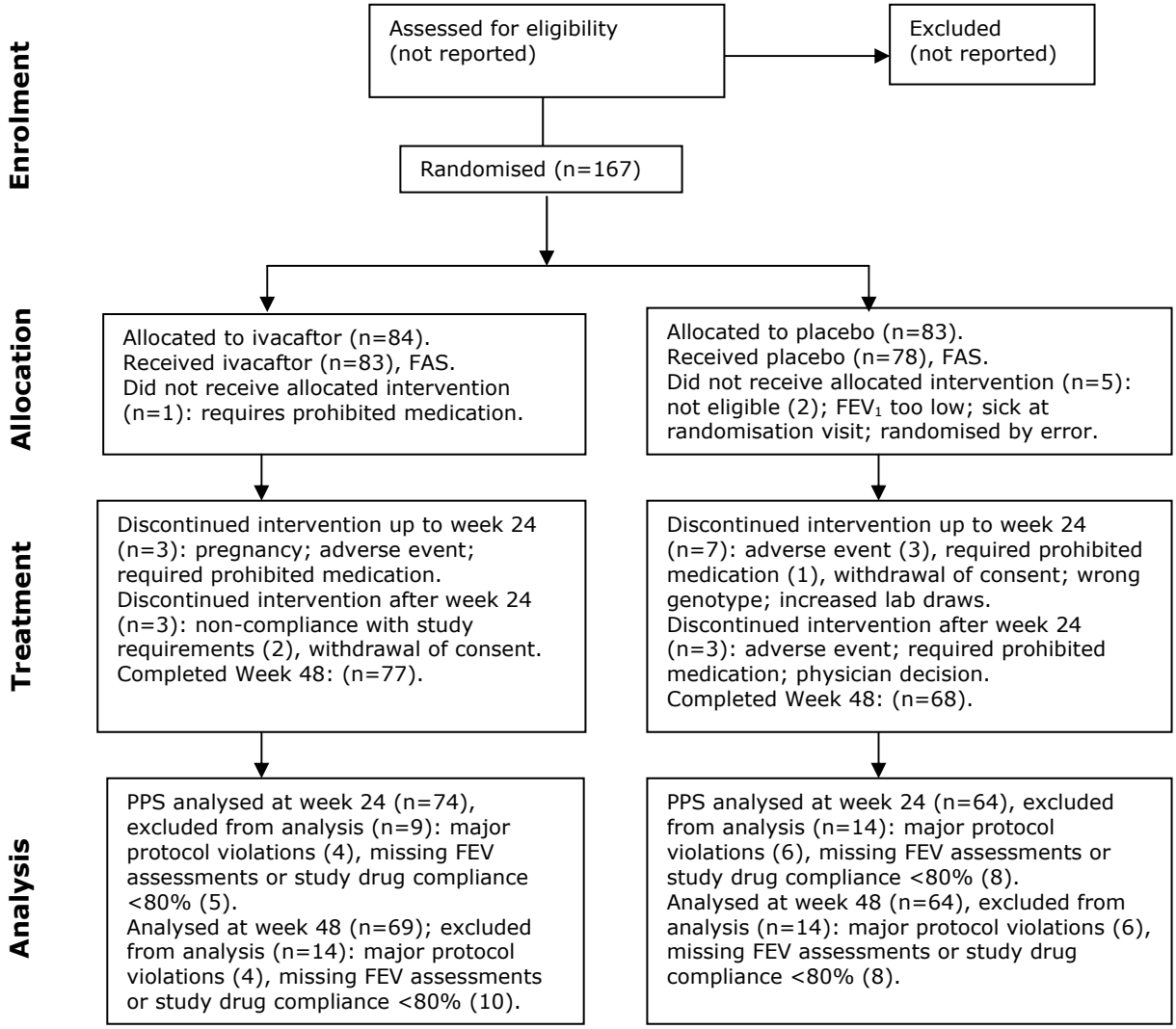
Statistical methods

The analysis for the primary endpoint was based on a Mixed-Effects Model for Repeated Measures (MMRM). No imputation on missing data was done for the primary analysis. In addition to the primary analysis based on FAS, a supportive analysis based on the PPS was conducted. To assess the robustness of the primary analysis, analyses were conducted using different variance-covariance matrices in MMRM, nonparametric analysis, and analysis of covariance (ANCOVA) with missing data imputed using 3 methods: the last observation carried forward (LOCF), worst-case, and dropout reason-based. Subgroup analyses of the primary endpoint were performed in the same manner as the primary analysis for the following subgroups: age (<18 and ≥18 years), percent predicted FEV_1 severity at baseline (<70% and ≥ 70% predicted), sex (female and male), and geographic region

(North America, Europe, and Australia). Sensitivity and subgroup analyses were only performed based on the FAS.

Results

Participant flow



Recruitment

Subjects were randomized at 65 study sites in the North America, Europe, and Australia. First subject signed informed consent on 10 June 2009 and last subject completed the last Week 48 Visit on 11 January 2011.

Conduct of the study

The study protocol was amended 4 times. Changes were numerous and related to the addition of the extension period up to week 48 (including additional endpoints at week 48), adjustments to inclusion and exclusion criteria and subject discontinuation rules, additional investigations and other changes.

The majority of protocol deviations were related to completion of study assessments, subject visits that were out of the protocol-specified visit window, study drug administration, PK blood collection, minor, nonreportable completion errors of the ICF form, and use of prohibited medications.

Baseline data

Baseline characteristics were in general quite balanced en both treatment groups. In study 102 mean predicted FEV_1 at baseline was 64% (range: 31.6% to 98.2%) and mean age was 26 years (range: 12 to 53 years). 77.1% of patients on ivacaftor and 74.3% of patients on placebo had F508del-CFTR as the second allele. Pancreatic insufficiency was reported in 89.2% of ivacaftor-treated patients and 96.2% of those on placebo.

Table 5 Demographics and Baseline Characteristics in study 102, Full Analysis Set

Variable	Placebo N = 78	VX-770 N = 83	Overall N = 161
Sex, n (%)			
Male	38 (48.7)	39 (47.0)	77 (47.8)
Female	40 (51.3)	44 (53.0)	84 (52.2)
Race, n (%)			
White	77 (98.7)	81 (97.6)	158 (98.1)
Black or African American	0	0	0
Not Allowed to Ask Per Local Regulations	1 (1.3)	2 (2.4)	3 (1.9)
Age (years)			
n	78	83	161
Mean	24.7	26.2	25.5
SD	9.21	9.85	9.54
Median	23.0	25.0	24.0
Minimum	12	12	12
Maximum	53	53	53
Geographic Region, n (%)			
North America	50 (64.1)	50 (60.2)	100 (62.1)
Europe	19 (24.4)	23 (27.7)	42 (26.1)
Australia	9 (11.5)	10 (12.0)	19 (11.8)
Percent Predicted FEV_1			
n	78	83	161
Mean	63.6688	63.4622	63.5623
SD	16.83001	16.14409	16.42858
Median	67.1890	66.1400	66.7020
Minimum	31.570	37.289	31.570
Maximum	97.130	98.229	98.229

Weight (kg)			
n	78	83	161
Mean	61.21	61.70	61.47
SD	13.926	14.257	14.056
Median	58.65	58.80	58.80
Minimum	31.9	30.2	30.2
Maximum	109.9	107.2	109.9
Sweat Chloride (mmol/L)			
n	74	78	152
Mean	100.13	100.35	100.24
SD	10.626	9.999	10.275
Median	100.25	100.50	100.50
Minimum	58.0	74.5	58.0
Maximum	121.5	128.0	128.0

The mean weight-for-age z-scores (points) at baseline were -0.5747 and -0.4645 in the placebo and ivacaftor groups, respectively which is indicative that this group of patients are, overall, well nourished. These figures for mean BMI-for-age z-scores (points) were -0.5605 and -0.4681.

More patients on placebo than on ivacaftor were receiving prior medication targeting pulmonary function, i.e. prior medications that were used with at least a 5 percentage point higher frequency in the placebo group than in the ivacaftor group were dornase alfa (73.1% versus 65.1%), salbutamol (53.8% versus 42.2%), tobramycin (44.9% versus 33.7%), and Seretide (41.0% versus 27.7%).

Numbers analysed

A total of 167 subjects were randomized, of which 84 subjects were randomized to VX-770 and 83 subjects were randomized to placebo treatment. Full Analysis set consisted of subjects who received at least 1 dose of the study drug – 83 subjects in the VX-770 group and 78 subjects in the placebo group.

The Per Protocol Set at Week 24 included 138 subjects (74 subjects in the VX-770 group and 64 subjects in the placebo group), and at Week 48 133 subjects (69 subjects in the VX-770 group and 64 subjects in the placebo group). This set was defined as all subjects without major protocol violations having at least 80% overall study drug compliance and having completed at least 80% of the analysis period as well as having necessary predefined FEV_1 measurements available.

Outcomes and estimation

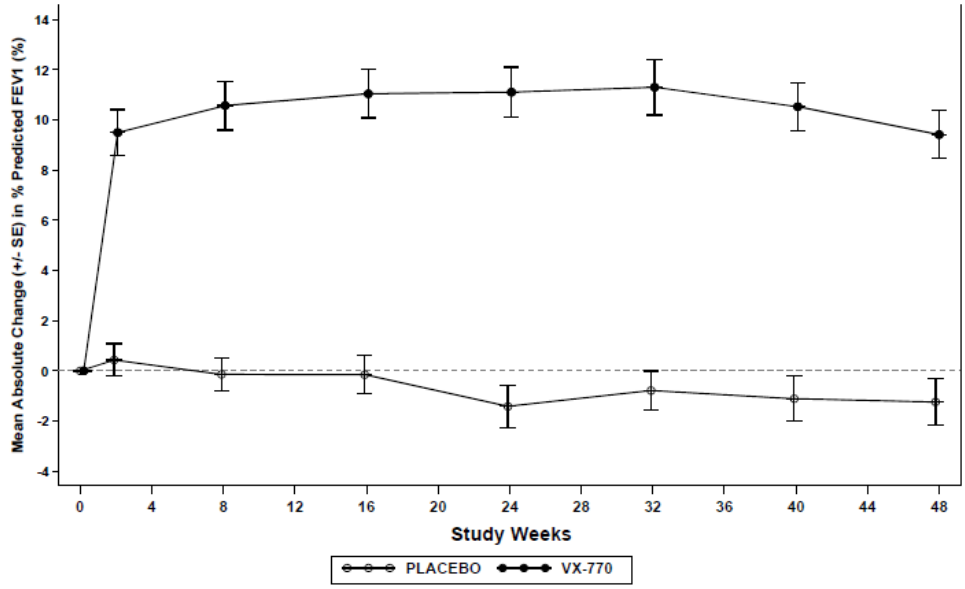
Table 6 Results for Primary and Selected Secondary Efficacy Endpoints in Study 102, Full Analysis Set

Endpoint	Treatment Difference[a] (95% CI)	*P* value
Absolute Change from Baseline in Percent Predicted FEV_1 (percentage points)		
Through Week 24 (Primary Endpoint)	10.6 (8.6, 12.6)	<0.0001
Through Week 48	10.5 (8.5, 12.5)	<0.0001
Change from Baseline in CFQ-R Respiratory Domain Score (points)[b]		
Through Week 24 (Key Secondary Endpoint)	8.1 (4.7, 11.4)	<0.0001
Through Week 48	8.6 (5.3, 11.9)	<0.0001
Change from Baseline in Sweat Chloride (mmol/L)		
Through Week 24 (Key Secondary Endpoint)	-47.9 (-51.3, -44.5)	<0.0001
Through Week 48	-48.1 (-51.5, -44.7)	<0.0001
Time to First Pulmonary Exacerbation		
Through Week 24	0.40 (0.23, 0.71)[c]	0.0016
Through Week 48 (Key Secondary Endpoint)	0.46 (0.28, 0.73)[c]	0.0012
Change from Baseline in Weight (kg)		
At Week 24	2.8 (1.8, 3.7)	<0.0001
At Week 48 (Key Secondary Endpoint)	2.7 (1.3, 4.1)	0.0001

[a] Treatment difference is ivacaftor to placebo (least squares [LS] mean absolute change)
[b] Data pooled from CFQ-R versions for adolescents/adults and for 12 to 13 years of age
[c] Hazard ratio (CI)

Regarding the primary endpoint, the adjusted mean absolute change from baseline through Week 24 in percent predicted FEV_1 (the primary efficacy endpoint) was greater in the ivacaftor group (10.39%) than the placebo group (-0.18%) in study 102 with a difference in favour to ivacaftor of 10.58% (95% CI: 8.57, 12.59). Similar effect size was observed at week 48 with a difference between ivacaftor and placebo of 10.50% (8.50, 12.50) and 9.99% (4.52, 15.47) for studies 102 and 103, respectively.

Figure 6 Mean Absolute Change From Baseline in Percent Predicted FEV1 by Treatment in Study 102, Full Analysis Set



A positive effect was also seen for other secondary and tertiary endpoints, like CFTR function measured as change in sweat chloride concentrations, time to first pulmonary exacerbation, change in body weight and quality of life.

Figure 7 Mean Absolute Change From Baseline in Sweat Chloride by Treatment, Full Analysis Set

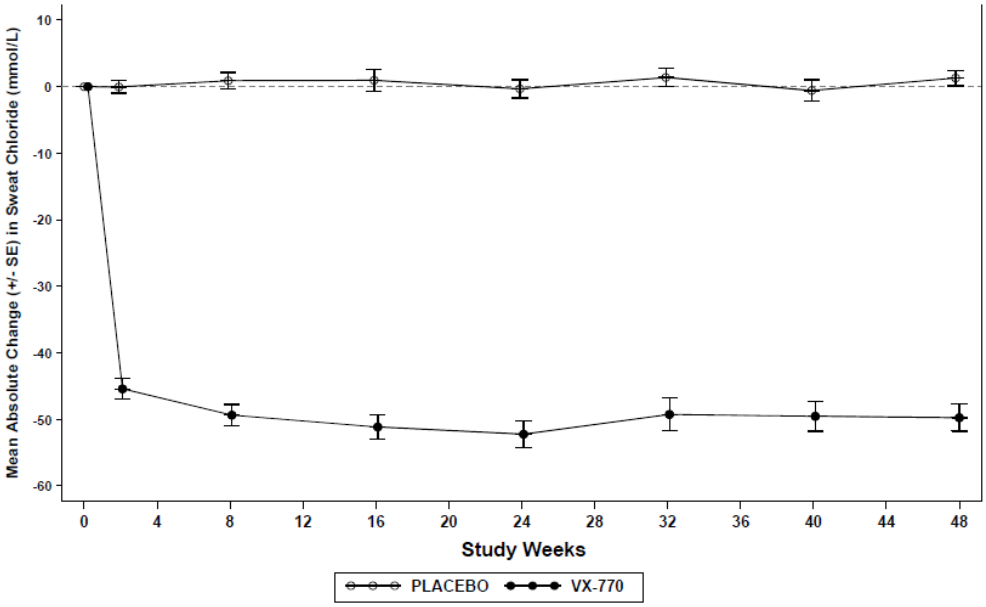


Figure 8 Time to First Pulmonary Exacerbation, Censored at Week 48

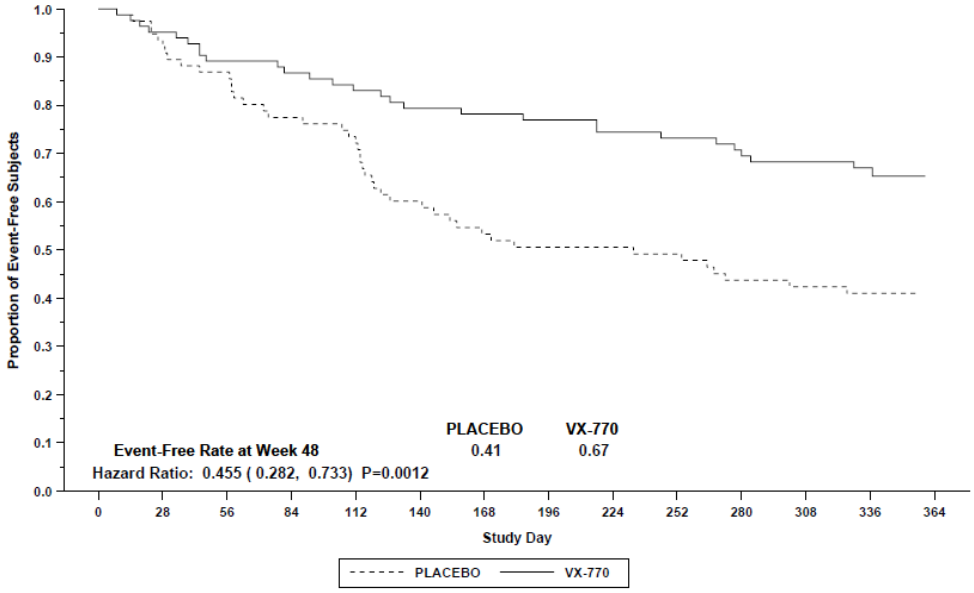
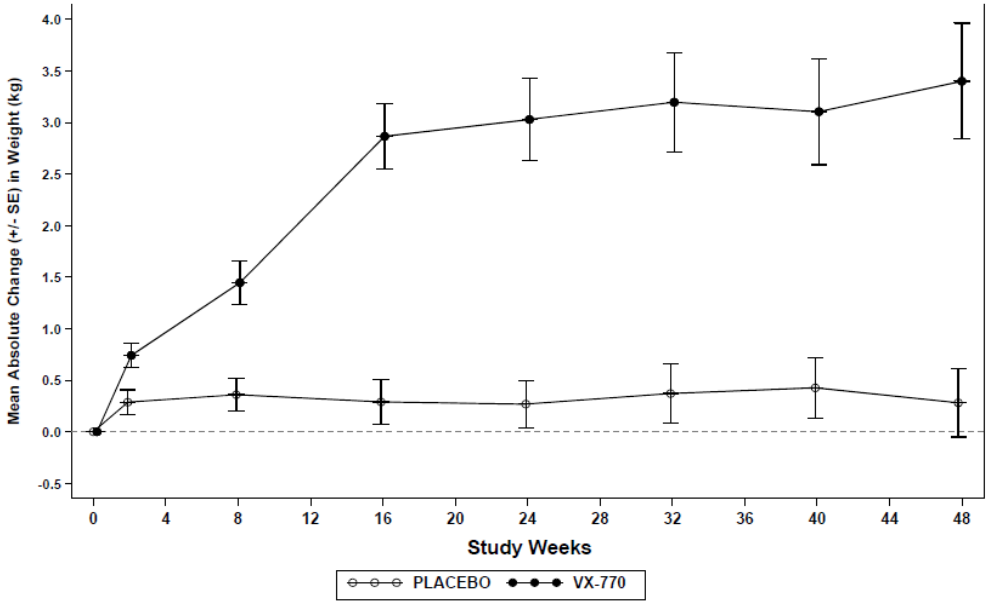
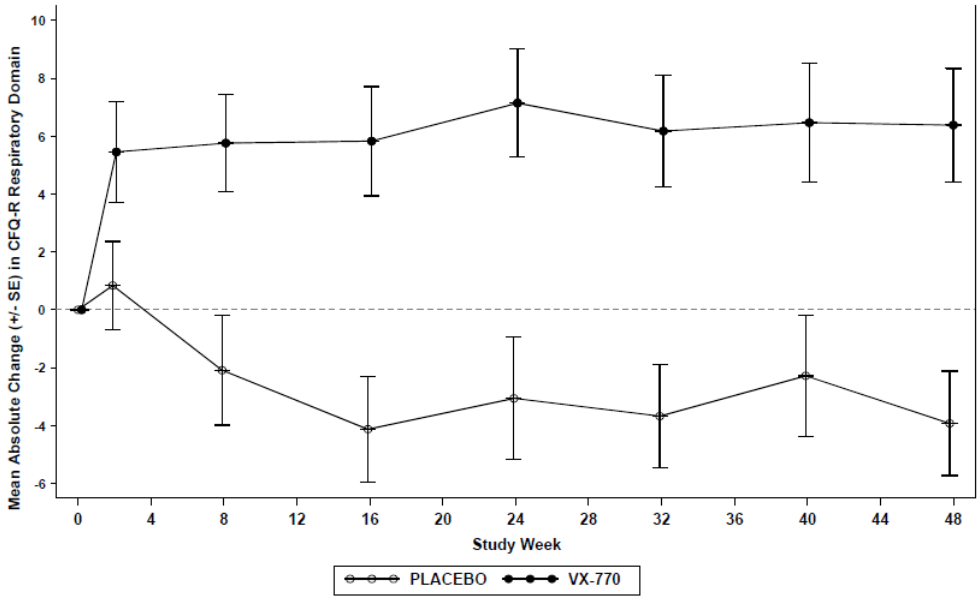


Figure 9 Mean Absolute Change From Baseline in Weight by Treatment, Full Analysis Set



The mean change from baseline at Week 48 for weight-for-age z-score was 0.2998 points in the ivacaftor group vs -0.0307 points in the placebo group. The estimated treatment difference for ivacaftor versus placebo was 0.3305 points (95% CI: 0.0399, 0.6210). The mean change from baseline at Week 24 for weight-for-age z-score was 0.3062 points in the ivacaftor vs. -0.0129 points in the placebo group. The estimated treatment difference for ivacaftor versus placebo was 0.3192 points (95% CI: 0.1462, 0.4921). The mean change from baseline at Week 48 for BMI-for-age z-score was greater in the ivacaftor group (0.2491 points) than in the placebo group (-0.0765 points). The estimated treatment difference for ivacaftor versus placebo was 0.3256 points (95% CI: 0.0015, 0.6497). The mean change from baseline at Week 24 for BMI-for-age z-score was greater in the ivacaftor group (0.2989 points) than in the placebo group (-0.0441 points). The estimated treatment difference for ivacaftor versus placebo was 0.3431 points (95% CI: 0.1419, 0.5443).

Figure 10 Mean Absolute Change From Baseline in Pooled CFQ-R Respiratory Domain Score by Treatment, Full Analysis Set



Ancillary analyses

Subgroup analyses for Study 102 show statistically significant results in favour of ivacaftor for all subgroups analysed. The absolute change from baseline in percent predicted FEV_1 at week 24 was slightly higher in adolescents (11.9%) than in adults (9.9%) while the absolute change from baseline in weight at week 48 was higher among patients with a FEV_1(%) of less than 70% than in those with a FEV_1(%) of 70% or higher (3.40 kg vs. 1.75kg).

Results of performed sensitivity analyses were found to be consistent with the results of the primary analyses.

Study 103 (part B)

Methods

This was a phase 3, two-part, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the pharmacokinetics, efficacy, and safety of ivacaftor in subjects aged 6 to 11 years with cystic fibrosis and the G551D mutation in at least 1 allele.

It had two parts (A and B). Part B is discussed in this section. Part B included a Screening Period (Days -35 to -15), a Run-in Period (Days -14 to -1), a Treatment Period (Day 1 to Week 24), and an Extension Period (Week 25 to Week 48).

Study Participants

Study 103 recruited subjects aged 6 to less than 12 years with 40 to 105% of FEV_1 of predicted normal for age, gender, and height (Knudson standards) and weight ≥15 kg at screening. Other inclusion criteria, as well as exclusion were in general similar to those in study 102.

Treatments

VX-770 150-mg tablet or placebo was to be administered orally in the fed state (30 minutes after the start of a standard "CF" high-fat, high calorie meal or snack) q12h for 48 weeks (24 weeks in the Treatment Period and 24 weeks in the Extension Period).

Objectives

For Part B the primary objective was to evaluate the efficacy of orally-administered ivacaftor after 24 weeks of treatment in children who have CF and the G551D CFTR mutation on at least 1 allele.

Outcomes/endpoints

The primary efficacy endpoint was the absolute change from baseline in percent predicted FEV_1 through 24 weeks of treatment.

The main secondary endpoints were the absolute change from baseline in CFQ-R; absolute change from baseline in sweat chloride; time to first pulmonary exacerbation; absolute change from baseline in weight and absolute change from baseline in percent predicted FEV_1 through Week 48.

Sample size

Enrolment was planned for a minimum of 30 subjects, with a minimum of 20 subjects having a Day -14 FEV1 of ≤90% of the predicted value. Sample size was declared to be based on the availability of the subject population and not on any statistical consideration. It was estimated by the Applicant that

30 subjects represented approximately 35% of eligible subjects with CF with mild or moderate lung disease in North America, Europe, and Australasia, aged 6 to 11 years who have the G551D mutation on at least 1 allele.

Therefore, the study was not designed to be powered to detect a significant treatment effect.

Randomisation

Subjects were randomized in a 1:1 ratio within FEV_1 severity strata (<70%, 70% to 90% [inclusive], and >90% predicted).

Blinding (masking)

The subjects, study site personnel, study monitors and the study team of the sponsor were blinded for treatment allocation. Most of them were blinded also for sweat chloride and bioanalysis results. Emergency unblinding procedures were defined.

A database lock and subsequent analysis were conducted based on the data from the first 24 weeks of treatment, while the double-blinded extension period from Week 25 through Week 48 remained ongoing. Sponsor's personnel who became unblinded to the treatment assignment to analyze and report the Week 24 data were replaced during the extension period from the time of unblinding until the lock of the Week 48 database.

Statistical methods

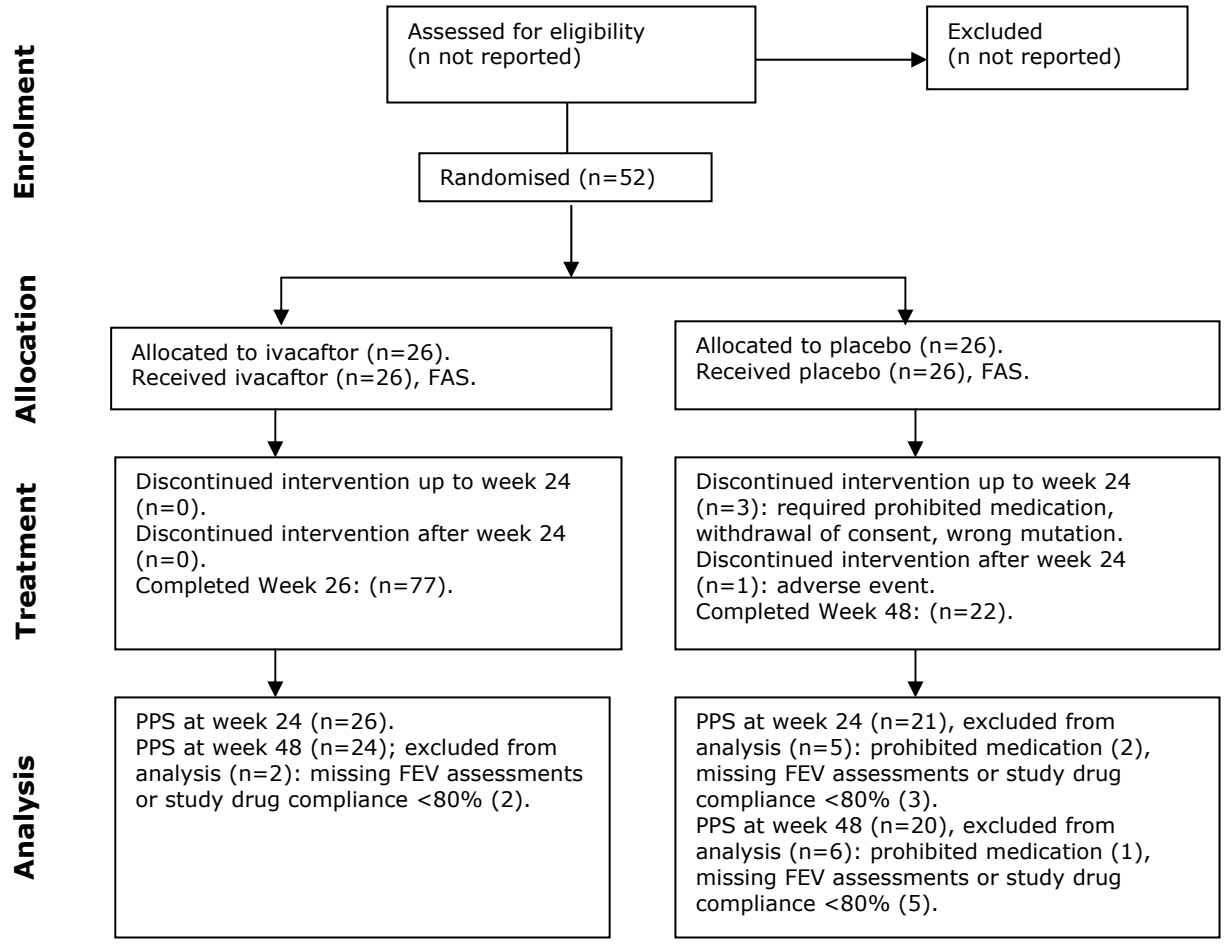
The primary analysis for the primary efficacy variable was based on an MMRM and was conducted in Full Analysis Set. No imputation of missing data was done, but sensitivity analyses were conducted to assess the impact of missing efficacy evaluations.

Subgroup analyses primarily consisted of summary statistics and covered subgroups of percent predicted FEV_1 severity at baseline, geographic regions and sexes.

Several sensitivity analyses were performed to assess the robustness of the primary analysis and secondary endpoints.

Results

Participant flow



Recruitment

Subjects were randomized at 24 study sites in the North America, Europe, and Australia. First informed consent for part B was signed on 12 March 2010 and last subject completed the last Week 48 Visit on 28 April 2011.

Conduct of the study

The study protocol was amended 6 times. Changes were numerous and related to the addition of the extension period up to week 48 (including additional endpoints at week 48), increase of the dose from 100 mg to 150 mg in Part B (based on preliminary results from Part A), increase of the upper limit of eligible FEV_1 to 105% predicted value, other adjustments to inclusion and exclusion criteria, subject discontinuation rules, additional investigations, updates to secondary endpoints, changes to statistical analysis (mostly sensitivity and subgroup analysis) and other changes.

The majority of protocol deviations were related to completion of study assessments, subject visits that were out of the protocol specified visit window, study drug administration, PK blood collection, minor nonreportable completion errors of the ICF, and prohibited medications. One subject was found not to have the G551D-CFTR mutation, for one other subject the study site accidentally triggered an emergency unblinding.

Baseline data

Baseline characteristics were in general quite balanced in both treatment groups. In study 103 mean predicted FEV_1 at baseline was 84% (range: 44.0% to 133.8%) and mean age was 9 years (range: 6 to 12 years). Eighty-five percent of patients on ivacaftor and 77% of patients on placebo had F508del-CFTR as the second allele. Pancreatic insufficiency was reported in 96.2% of ivacaftor-treated patients and 96.2% of those on placebo.

Table 7 Demographics and Baseline Characteristics in study 103, Full Analysis Set

Variable	Placebo N = 26	VX-770 N = 26	Overall N = 52
Sex, n (%)			
Male	16 (61.5)	9 (34.6)	25 (48.1)
Female	10 (38.5)	17 (65.4)	27 (51.9)
Race, n (%)			
White	23 (88.5)	22 (84.6)	45 (86.5)
Other	1 (3.8)	2 (7.7)	3 (5.8)
Not allowed to ask per local regulations	2 (7.7)	2 (7.7)	4 (7.7)
Age (years)			
n	26	26	52
Mean (SD)	8.9 (1.86)	8.9 (2.00)	8.9 (1.91)
Median	8.5	9.0	9.0
Min;max	6;12	6;12	6;12
Height (cm)			
n	26	26	52
Mean (SD)	132.59 (12.195)	134.92 (14.378)	133.75 (13.252)
Median	131.40	133.05	132.00
Min;max	110.5;155.8	115.0;168.6	110.5;168.6
Weight (kg)			
n	26	26	52
Mean (SD)	30.04 (7.159)	31.81 (9.949)	30.93 (8.628)
Median	29.70	28.15	28.60
Min;max	17.8;46.3	18.8;62.6	17.8;62.6

Geographic region, n (%)			
North America	15 (57.7)	12 (46.2)	27 (51.9)
Europe	5 (19.2)	6 (23.1)	11 (21.2)
Australia	6 (23.1)	8 (30.8)	14 (26.9)
% predicted FEV_1			
N	26	26	52
Mean (SD)	83.7407 (20.36540)	84.7272 (15.82624)	84.2339 (18.06477)
Median	85.3500	85.2140	85.2140
Min;max	44.016;116.272	52.404;133.791	44.016;133.791
Sweat chloride (mmol/L)			
n	24	24	48
Mean (SD)	104.79 (8.872)	104.31 (14.541)	104.55 (11.919)
Median	105.00	104.75	105.00
Min;max	92.0;121.0	54.0;128.0	54.0;128.0

The mean baseline weight-for-age z-scores were -0.1574 (n=26) and -0.0175 (n=26) in the placebo and ivacaftor groups, respectively. For mean BMI-for-age z-scores these figures were 0.0808 (n=26) and 0.0877 (n=26).

The proportion of subjects receiving the most commonly used prior medications that target pulmonary effects was similar in the placebo and ivacaftor groups, except for dornase alfa (84.6% in the placebo group and 69.2% in the ivacaftor group) and Seretide (19.2% in the placebo group and 11.5% in the ivacaftor group).

Numbers analysed

A total of 52 subjects were randomized: 26 subjects were randomized to VX-770 and 26 subjects were randomized to placebo treatment. All of these subjects received at least 1 dose of study drug and were included in the Full Analysis Set.

Outcomes and estimation

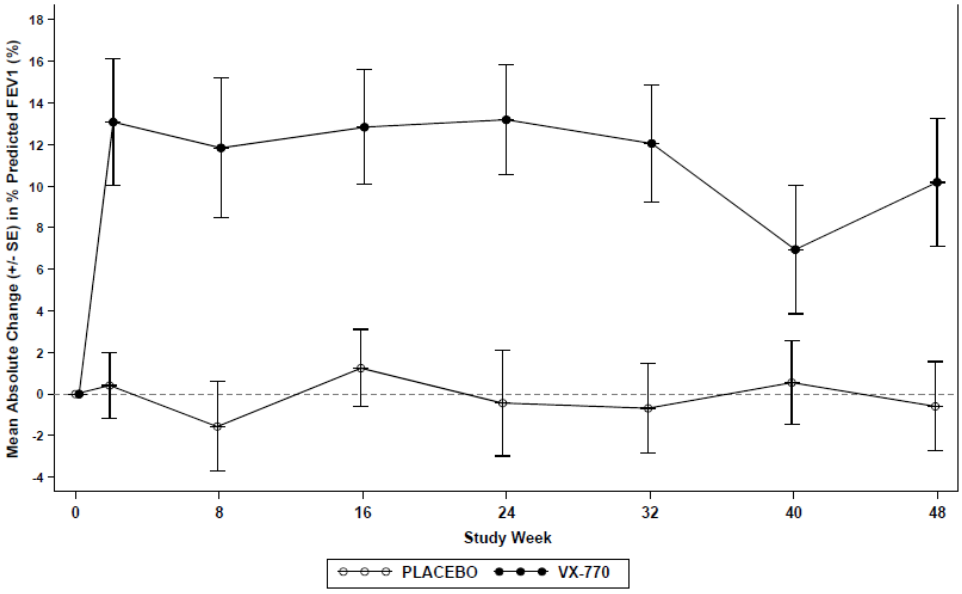
Table 8 Results for primary and selected secondary efficacy endpoints in study 103, Full Analysis Set

Endpoint	Treatment Difference[a] (95% CI)	*P* value
Absolute Change from Baseline in Percent Predicted FEV_1 (percentage points)		
Through Week 24 (Primary Endpoint)	12.5 (6.6, 18.3)	<0.0001
Through Week 48	10.0 (4.5, 15.5)	0.0006
Change from Baseline in CFQ-R (Children Ages 6 to 11) Respiratory Domain Score (points)		
Through Week 24 (Key Secondary Endpoint)	6.1 (-1.4, 13.5)	0.1092
Through Week 48	5.1 (-1.6, 11.8)	0.1354
Change from Baseline in Sweat Chloride (mmol/L)		
Through Week 24 (Key Secondary Endpoint)	-54.3 (-61.8, -46.8)	<0.0001
Through Week 48	-53.5 (-60.9, -46.0)	<0.0001
Change from Baseline in Weight (kg)		
At Week 24 (Key Secondary Endpoint)	1.9 (0.9, 2.9)	0.0004
At Week 48	2.8 (1.3, 4.2)	0.0002

[a] Treatment difference is ivacaftor to placebo (LS mean absolute change)

In study 103, the mean absolute change was also greater in the ivacaftor group (12.58%) than the placebo group (0.13%) with an estimated treatment difference for ivacaftor versus placebo of 12.45% (95% CI: 6.56, 18.34). Similar effect size was observed at week 48 with a difference between ivacaftor and placebo of 10.50% (8.50, 12.50) and 9.99% (4.52, 15.47) for studies 102 and 103, respectively.

Figure 11 Mean Absolute Change From Baseline in Percent Predicted FEV1 by Treatment in study 103, Full Analysis Set



A positive effect was also seen for other secondary and tertiary endpoints, like CFTR function measured as change in sweat chloride concentrations, change in body weight and quality of life.

Figure 12 Mean Absolute Change From Baseline in Sweat Chloride by Treatment, Full Analysis Set

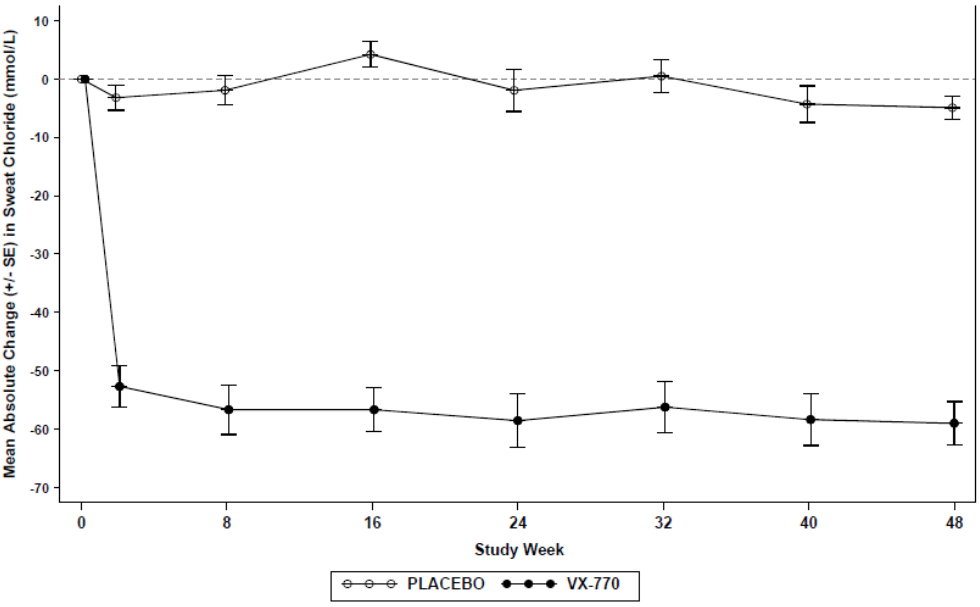
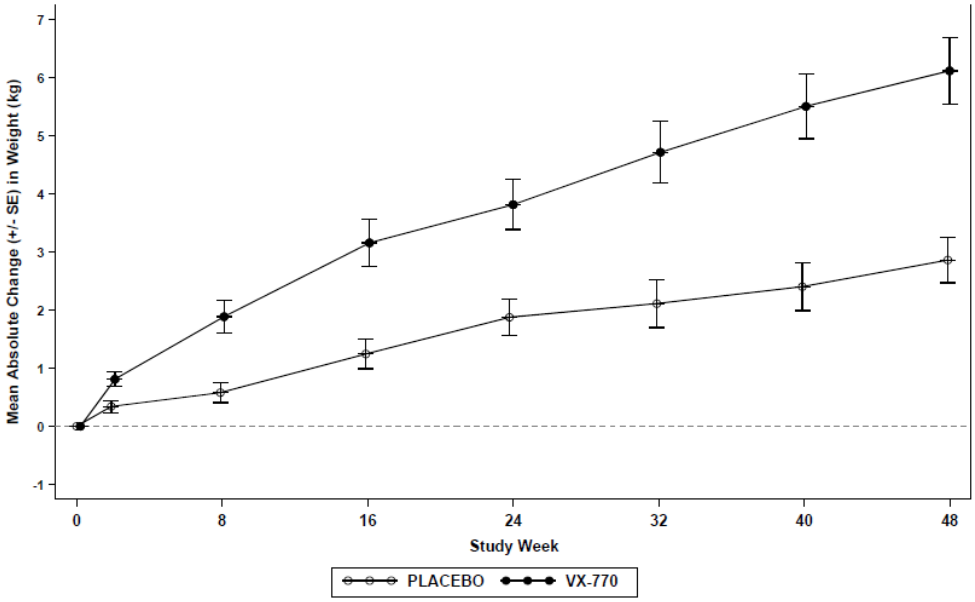
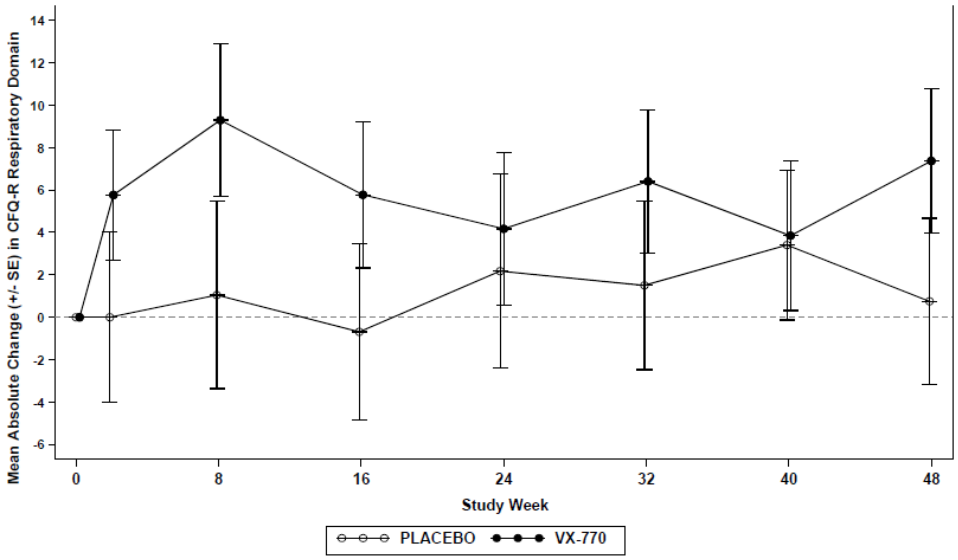


Figure 13 Mean Absolute Change From Baseline in Weight by Treatment, Full Analysis Set



The estimated treatment difference for weight-for-age z-score for VX-770 versus placebo at Week 24 was 0.2730 points (95% CI: 0.1508, 0.3951). The estimated treatment difference for VX-770 versus placebo at Week 48 was 0.3873 points (95% CI: 0.2406, 0.5340). The mean change from baseline at Week 24 for BMI-for-age z-score was greater in the VX-770 group (0.3046 points) than the placebo group (-0.0330 points). The estimated treatment difference for VX-770 versus placebo was 0.3376 points (95% CI: 0.1607, 0.5144). The mean change from baseline at Week 48 for the BMI-for-age z-score was greater in the VX-770 group (0.2788 points) than the placebo group (-0.1755 points). The estimated treatment difference for VX-770 versus placebo was 0.4543 points (95% CI: 0.2575, 0.6511).

Figure 14 Mean Absolute Change From Baseline in CFQ-R Respiratory Domain Score, Full Analysis Set (Questionnaire Version: Children Ages 6 to 11 Years)



Ancillary analyses

Subgroup analyses in study 103 show that treatment effect was less in children with baseline FEV_1(%) above 90% when compared with those having a FEV_1(%) of ≥70% to ≤ 90% (absolute change from

baseline in percent predicted FEV_1 at week 24 was 9.3% and 6.9%, respectively). As for the absolute change from baseline in weight at week 24 these figures were 2.59 and 1.29 kg. A firm conclusion cannot be drawn due to the low numbers analysed (11 on placebo and 10 on ivacaftor).

Subgroup analysis for FEV_1% <70% shows that the mean (SD) absolute change in FEV_1% predicted in the placebo group was 3.1087 (9.02458) versus 21.9313 (14.20915) in the ivacaftor group.

Results of performed sensitivity analyses were found to be consistent with the results of the primary analyses.

Summary of main studies

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

Table 7. Summary of Efficacy for trial VX08-770-102

Title: A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of VX-770 in Subjects with Cystic Fibrosis and the G551D Mutation			
Study identifier	VX08-770-102 Eudra CT number: 2008-007416-15		
Design	Phase 3, randomized, double-blind, placebo-controlled, parallel-group multicenter study of orally administered VX-770 in subjects with CF who have the G551D-CFTR mutation in at least 1 allele.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		24 weeks 14 days 24 weeks (Week 25 to Week 48)
Hypothesis	Superiority		
Treatments groups	VX-770		150 mg VX-770 every 12 hours (84 subjects randomized)
	Placebo		Placebo every 12 hours (83 subjects randomized)
Endpoints and definitions	Primary endpoint	FEV_1 24 weeks	absolute change from baseline in percent predicted FEV_1 through week 24 (%)
	Secondary endpoint	FEV_1 48 weeks	absolute change from baseline in percent predicted FEV_1 through week 48 (%)
	Secondary endpoint	CFQ-R score	absolute change from baseline in pooled respiratory CFQ-R score through Week 24 (pooled data from adolescents/adults and 12 to 13 year-old versions)
	Secondary endpoint	Sweat chloride	absolute change from baseline in sweat chloride through Week 24 (mmol/L)
	Secondary endpoint	Time to exacerbation	time to first pulmonary exacerbation through Week 48
	Secondary endpoint	Weight	absolute change from baseline in body weight at Week 48 (kg)

Database lock	Database lock on 05 February 2011, last subject completed the last week 48 visit on 11 January 2011		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Modified Intent to treat ('Full analysis set'): all randomized subjects who received at least 1 dose of study drug		
Descriptive statistics and estimate variability	Treatment group	VX-770	Placebo
	Number of subjects	83	78
	FEV_1 24 weeks, LS mean	10.3947	-0.1846
	variability statistic	Not reported	Not reported
	FEV_1 48 weeks, LS mean	10.1260	-0.3715
	variability statistic	Not reported	Not reported
	CFQ-R score, LS mean	5.97*	-2.10*
	variability statistic	Not reported	Not reported
	Sweat chloride, LS mean	-48.70*	-0.77*
	variability statistic	Not reported	Not reported
	Time to exacerbation, exacerbation-free rate, %	67*	41*
	variability statistic	Not reported	Not reported
	Weight, LS mean	3.11	0.40
	variability statistic	Not reported	Not reported
Effect estimate per comparison	Comparison groups	VX-770 vs. Placebo	
	Primary endpoint	FEV_1 24 weeks	10.5793
		95% CI	(8.5666, 12.5920)
		P-value	<0.0001
	Secondary endpoint	FEV_1 48 weeks	10.4975
		95% CI	(8.4985, 12.4966)
		P-value	<0.0001
	Secondary endpoint	CFQ-R score*	8.08
		95% CI	(4.73, 11.42)
		P-value	<0.0001
	Secondary endpoint	Sweat chloride*	-47.93
		95% CI	(-51.34, -44.52)
		P-value	<0.0001
	Secondary endpoint	Time to exacerbation* (hazard ratio)	0.455
		95% CI	(0.282, 0.733)
		P-value	0.0012
	Secondary endpoint	Weight	2.71
		95% CI	(1.33, 4.09)
		P-value	0.0001

Notes	* Data from less subjects than the modified ITT has been used for calculation of results for CFR-Q score (80 VX-770, 71 placebo), Sweat chloride (78 VX-770, 74 placebo). Number of subjects in calculation of time to exacerbation endpoint not declared in the study report.

Table 8. Summary of Efficacy for trial VX08-770-103 (part B)

Title: A Phase 3, 2-Part, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Pharmacokinetics, Efficacy, and Safety of VX-770 in Subjects Aged 6 to 11 Years with Cystic Fibrosis and the G551D Mutation			
Study identifier	VX08-770-103 Eudra CT number: 2008-007479-26		
Design	Phase 3, 2-part, randomized, double-blind, placebo-controlled, parallel-group, multicenter study of orally-administered VX-770 in subjects aged 6 to 11 years with the G551D-CFTR mutation on at least 1 allele. Part A was designed to evaluate a single dose of VX-770 and was used to confirm the dose for Part B. Part B was designed to evaluate dosing of VX-770 administered every 12 hours for up to 48 weeks. Results of part B are reflected in this table.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		24 weeks 14 days 24 weeks (Week 25 to Week 48)
Hypothesis	Superiority		
Treatments groups	VX-770		150 mg VX-770 every 12 hours (26 subjects randomized)
	Placebo		Placebo every 12 hours (26 subjects randomized)
Endpoints and definitions	Primary endpoint	FEV_1 24 weeks	absolute change from baseline in percent predicted FEV_1 through week 24
	Secondary endpoint	FEV_1 48 weeks	absolute change from baseline in percent predicted FEV_1 through week 48
	Secondary endpoint	CFQ-R score	adjusted mean absolute change from baseline through Week 24 for the CFQ-R (child) respiratory domain score
	Secondary endpoint	Sweat chloride	absolute change from baseline in sweat chloride through Week 24 (mmol/L)
	Secondary endpoint	Weight	absolute change from baseline in body weight at Week 24
Database lock	Database lock for 48 week data 24 May 2011, last subject completed the last Week 48 Visit (part B) on 28 April 2011		
<u>Results and Analysis</u>			
Analysis description	**Primary Analysis**		

Analysis population and time point description	Modified Intent to treat ('Full analysis set'): all randomized subjects who received at least 1 dose of study drug		
Descriptive statistics and estimate variability	Treatment group	VX-770	Placebo
	Number of subjects	26	26
	FEV_1 24 weeks, LS mean	12.5787	0.1275*
	variability statistic	Not reported	Not reported
	FEV_1 48 weeks	10.6691	0.6761*
	variability statistic	Not reported	Not reported
	CFQ-R score	6.31	0.25*
	variability statistic	Not reported	Not reported
	Sweat chloride, LS mean	-55.53*	-1.21*
	variability statistic	Not reported	Not reported
	Weight, LS mean	3.69	1.79
	variability statistic	Not reported	Not reported
Effect estimate per comparison	Comparison groups	VX-770 vs. Placebo	
	Primary endpoint	FEV_1 24 weeks*	12.4511
		95% CI	(6.5627, 18.3395)
		P-value	<0.0001
	Secondary endpoint	FEV_1 48 weeks*	9.9930
		95% CI	(4.5214, 15.4645)
		P-value	0.0006
	Secondary endpoint	CFQ-R score*	6.06
		95% CI	(-1.41, 13.53)
		P-value	0.1092
	Secondary endpoint	Sweat chloride*	-54.32
		95% CI	(-61.83, -46.82)
		P-value	<0.0001
	Secondary endpoint	Weight	1.90
		95% CI	(0.86, 2.94)
		P-value	0.0004
Notes	* Data from less subjects than the modified ITT has been used for calculation of results for FEV_1 24 weeks (26 VX-770, 25 placebo), FEV_1 48 weeks (26 VX-770, 25 placebo), CFQ-R score (26 VX-770, 23 placebo), Sweat chloride (23 VX-770, 23 placebo).		

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

Upon request from the CHMP the Applicant provided analyses of absolute change in height, height-for-age Z score, height-for-age ratio and weight/height ratio for patients less than 20 years of age (23 placebo-treated patients and 24 ivacaftor-treated patients in study 102; all patients in study 103). The question was intended to provide further insight on whether ivacaftor improves the nutritional status of children with cystic fibrosis given that a classic distinction between acute malnutrition ("wasting" or low weight for height) and chronic malnutrition ("stunting" or low height for age) is widely adopted. In children, failure to gain weight precedes linear growth deceleration: thus the weight/height ratio (% weight for age/% height for age according to the CDC table) is lessened. With chronic malnutrition,

linear growth decelerates and the weight/height ratio returns to normal, but the child is still stunted (decreased height for age).

The results show that the treatment difference between groups at week 48 in mean change in height (cm) (95% CI) was 0.10 (-1.57, 1.77) in study 102 and 0.99 (0.07, 1.92) in study 103. These figures for height-for-age Z scores were 0.06 (-0.10, 0.21) and 0.12 (-0.004, 0.24).

Two logistic regression models were used to estimate the height-for-age ratio and the weight/height ratio. In these analyses height-for-age ratio and weight/height ratio cut-offs of (less than) 90% and (less than) 95% respectively were identified as appropriate categories of response. Results are presented as odds ratio, i.e. the ratio of odds of height-for age-ratio <95% (or <90% for weight/ideal body weight ratio) in the ivacaftor group versus the placebo group. Few patients where identified below the specified cut-offs (indicative of acute and chronic malnutrition, respectively) and the results of the analyses presented should be viewed with caution.

In study 102 at week 24 and 48 the respective odds ratio (95% CI) for height-for-age ratio were 0.759 (0.004, 144.7) and 0.063 (0,43.671). In study 103 the odds ration could not be estimated at week 24 while at week 48 the estimate was not meaningful due to huge 95% Confidence Interval.

Regarding weight/height ratio the odds ratio (95% CI) were 0.415 (0.039, 4.383) at week 48 in study 102. The odds ratio could not be estimated at week 24. In study 103, the odds ratio at week 24 was 0.044 (0.001, 3.275) and 0.095 (0.001, 7.879) at week 48.

Upon request from the CHMP the Applicant also performed analysis of the primary endpoint in both pivotal clinical studies by the functional class of the second allele of CFTR gene, and by presence or absence of events of URTI and bacteria in sputum during the study.

Table 9 Absolute Change From Baseline to Week 24 in Percent Predicted FEV_1, by Second CFTR Allele Class

	Study 102				Study 103			
Second *CFTR* Allele	**Placebo**		**Ivacaftor**		**Placebo**		**Ivacaftor**	
Class	**N**	**Mean (SD)**	**N**	**Mean (SD)**	**N**	**Mean (SD)**	**N**	**Mean (SD)**
Class I	11	0.3 (4.40)	10	11.9 (11.85)	3	-0.2 (3.52)	1	6.2 (NA)
Class II	60	-0.6 (4.92)	70	10.2 (6.70)	20	-0.4 (8.54)	23	14.4 (13.62)
Class III	1	-0.2 (NA)	0	NA	0	NA	2	-3.1 (12.37)
Class IV	2	-0.7 (5.32)	2	2.4 (2.35)	1	6.9 (NA)	0	NA
Class V	1	0.3 (NA)	0	NA	0	NA	0	NA
Unknown	1	7.6 (NA)	1	30.5 (NA)	0	NA	0	NA

Table 10 Subgroup Analysis of Absolute Change From Baseline in Percent Predicted FEV_1 by Presence or Absence of URTI

	Study 102		Study 103	
	Placebo	**Ivacaftor**	**Placebo**	**Ivacaftor**
Week 24				
n With URTI	12	19	2	6
Mean Absolute Change in Percent Predicted FEV_1	-1.9	13.8	7.2	19.8
n Without URTI	64	64	22	20
Mean Absolute Change in Percent Predicted FEV_1	-0.01	9.5	-0.7	10.6
Week 48				
n With URTI	12	19	2	6
Mean Absolute Change in Percent Predicted FEV_1	-2.7	13.5	13.3	26.9
n Without URTI	64	64	22	20
Mean Absolute Change in Percent Predicted FEV_1	-0.2	9.4	-0.8	9.2

Table 11 Subgroup Analysis of Absolute Change From Baseline in Percent Predicted FEV_1 by Presence or Absence of Bacteria in Sputum

	Study 102		Study 103	
	Placebo	Ivacaftor	Placebo	Ivacaftor
Week 24				
n With Bacteria in Sputum	1	6	3	2
Mean Absolute Change in Percent Predicted FEV_1	-8.6	12.9	1.3	32.6
n Without Bacteria in Sputum	75	77	23	24
Mean Absolute Change in Percent Predicted FEV_1	-0.2	10.3	-0.2	11.1
Week 48				
n With Bacteria in Sputum	1	6	3	2
Mean Absolute Change in Percent Predicted FEV_1	-6.0	12.4	-0.1	27.5
n Without Bacteria in Sputum	75	77	21	24
Mean Absolute Change in Percent Predicted FEV_1	-0.5	10.1	0.03	10.1

Clinical studies in special populations

Children have been included in all phase III studies. No other studies in special populations have been conducted, which is acceptable in the light of rarity of the condition.

Supportive studies

Extension study (Study 105)

All subjects who completed treatment in studies 102 or 103 were eligible for study 105 whose objective was to obtain further information on the safety and efficacy of long-term ivacaftor treatment (approximately 96 weeks). During this rollover study, all subjects received 150-mg ivacaftor every 12 hours. The percent predicted FEV_1 range at the beginning of study 105 was 29.1% to 110.4%. The use of inhaled hypertonic saline was permitted (it was not permitted in the pivotal studies). This study is currently ongoing. Interim analyses have been pre-specified in this study. Latest results have been submitted with responses to the List of Questions.

A total of 192 subjects were enrolled in study 105: 144 subjects from Study 102, and 48 subjects from study 103. Of the 144 subjects enrolled from study 102, 67 subjects received placebo and 77 subjects received ivacaftor in study 102. Of the 48 subjects enrolled from study 103, 22 subjects received placebo and 26 subjects received ivacaftor in study 103. Overall, 7 patients discontinued treatment in study 105.

For patients treated with ivacaftor in the pivotal studies 102 and 103 the maximum length of exposure in study 105 is 96 weeks (study 102) and 72 weeks (study 103). For placebo-treated patients, maximum length of exposure in study 105 is 48 weeks (study 102) and 24 weeks (study 103).

In ivacaftor-treated patients in study 102 improvement in percent predicted FEV_1 was maintained after additional 24 and 48 weeks of treatment with ivacaftor in study 105, i.e. the mean absolute change in percent predicted FEV_1 (SD) was 10.3 (9.31) and 9.5 (10.13), respectively. Similar results were seen in previously placebo-treated patients as these figures were 10.0 (9.52) and 8.0 (8.14) at weeks 24 and 48, respectively. Ivacaftor-treated patients in study 103 showed a mean absolute change from baseline in percent predicted FEV_1 (SD) of 10.1 (14.18) at week 24 in study 105 while in previously placebo-treated patients this figure was 7.5 (10.90).

Initial weight gain is kept after the additional 24 and 48 weeks of treatment with ivacaftor in study 105. In ivacaftor-treated patients in study 102 the mean (SD) change from baseline is 3.6 (5.82) kg at week 24 and 3.9 (6.32) kg at week 48. In placebo-treated patients the mean (SD) absolute change in

weight was 2.9 (3.56) kg at week 24 and 3.5 (4.42) kg at week 48. The change was especially apparent in study 103 (as expected given that only children aged 6 to 11 years were included), i.e. 8.5 (3.79) kg in ivacaftor-treated patients and 6.5 (3.47) kg in placebo-treated patients.

Regarding pulmonary exacerbations, among ivacaftor-treated patients in study 102 more subjects had pulmonary exacerbations and the duration of pulmonary exacerbations was longer during the first 48 weeks of study 105 (38 subjects had 64 events; mean [SD] duration: 19.8 [38.70] days) than during the 48-week treatment period in study 102 (25 subjects had 41 events; mean [SD] duration: 11.6 [23.54] days). Pulmonary exacerbation was not a secondary endpoint in study 103. In study 105 (after an additional 48 weeks of treatment in ivacaftor-treated patients in study 103) the mean (SD) number of subjects with events was 3 out of 26, the number of events was 4 and the mean (SD) duration 3.7 (12.76). No placebo-treated patients in study 103 reported a pulmonary exacerbation after 24 weeks of treatment with ivacaftor in study 105.

While the improvement in CFQ-R respiratory domain scores after an additional 24 week treatment with ivacaftor in study 105 was similar to the one previously observed in ivacaftor-treated patients in studies 102 (8.0 and 7.2 for patients previously treated with placebo and ivacaftor, respectively) and 103 (9.8 and 9.0 for patients previously treated with placebo and ivacaftor), the change after an additional 48 week treatment with ivacaftor was almost half of the one previously observed (4.5 and 4.8 for patients previously treated with placebo and ivacaftor in study 102, respectively).

Study 104

Study 104 (Part A) was a 16-week, 4:1 randomised, double-blind, placebo-controlled, parallel-group Phase 2 study of ivacaftor (150 mg every 12 hours) in 140 patients with CF age 12 years and older who were homozygous for the F508del mutation in the CFTR gene and who had FEV_1 ≥40% predicted.

The mean absolute change from baseline through Week 16 in percent predicted FEV_1 (primary efficacy endpoint) was 1.5 percentage points in the ivacaftor group and -0.2 percentage points in the placebo group. The estimated treatment difference for ivacaftor versus placebo was 1.7 percentage points (95% CI: -0.6, 4.1); this difference was not statistically significant (p=0.15).

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

Overall design of the pivotal studies 102 and 103 is deemed acceptable and in line with the applicable regulatory guidelines and the protocol assistance provided by the CHMP.

A considerable number of amendments were implemented in both trials. The majority of the amendments for Study 102 and Study 103 did not affect the main endpoints (primary endpoints and key secondary endpoints) and there is no evidence that the number and extent of amendments would compromise the study results.

Only patients with a G551D CFTR mutation were included in studies 101, 102 and 103, therefore in the presence of clinical data only for patients with this particular mutation in at least one allele, the proposed indication has been restricted (initially applied for indication included all gating mutations). Tests for CFTR genotyping are available in Europe, where it is performed using a variety of CE-marked commercial assays.

The primary efficacy endpoint for the pivotal trials was the absolute change from baseline in percent predicted FEV_1 through 24 weeks of treatment. This is an accepted endpoint to measure the effect of a medicinal product in CF population. Rate of decline in FEV_1 has been demonstrated to correlate with

survival and to be the strongest clinical predictor of mortality, with a more marked effect in patients with pancreatic-insufficient disease. Therefore, the primary endpoint selected for both trials and its timing (24 weeks) is considered appropriate.

Spirometry was performed according to the American Thoracic Society Guidelines. While in study 101 the Hankinson standards have been used this is not the case in the two pivotal trials where the Knudson equations were specified. In order to investigate to what extent this fact might affect the interpretation of results, upon request from the CHMP an analysis of the mean absolute change from baseline in percent predicted FEV_1% using the Knudson reference equations was performed and showed that results do not essentially differ from those using the Hankinson standards.

In study 103 inclusion of children with FEV_1 in the range of 90% to 105% predicted was permitted to adjust for the overestimation of percent predicted FEV_1 that occurs in children 6 to 11 years of age with the use of Knudson prediction equations. The Applicant has confirmed that this wide range of FEV_1 was intended to optimize the number of patients eligible for study participation without expanding the patient population to include patients with normal lung function and presumably limited potential for treatment response, however, the subgroup analysis by baseline percent predicted FEV_1 ≥90% in study 103 shows that avoiding limited potential for treatment response in this subgroup might not been achieved.

Another important aspect that required clarification was the number of patients in which spirometry was performed pre-bronchodilation or post-bronchodilation. It has been clarified that changes from baseline in percent predicted FEV_1 were calculated and used in the main analysis only when the baseline and the post-baseline assessments were done at the same time relative to bronchodilator (BD) use (i.e., "paired," both pre-BD or both post-BD). A post-hoc analysis of study 101 of mean changes from baseline in FEV_1 % predicted measured pre-BD and post-BD showed consistent results in both groups of patients (pre- and post-BD use). Overall, the use of BD before spirometry is likely to influence lung function parameters. In spite of this it is believed that the positive findings consistently seen for the remaining endpoints in the pivotal studies and the size of the effect in terms of predicted FEV_1% supersede the likely confounding effect of the use of bronchodilators.

Nasal Potential Difference (NPD) and sweat chloride are regarded as biomarkers of the disease that are useful for testing activity of compounds targeted at restore CFTR function (CFTR activity) which does not necessarily translates into clinical benefit, i.e. while structural airway damage in the lung may not be reversible even if full CFTR activity is restored this is not the case of the sweat gland which is not damaged by disease pathogenesis.

Efficacy data and additional analyses

Regarding the primary endpoint, the adjusted mean absolute change from baseline through Week 24 in percent predicted FEV_1 (the primary efficacy endpoint) was greater in the ivacaftor group (10.39%) than the placebo group (-0.18%) in study 102 with a difference in favour to ivacaftor of 10.58% (95% CI: 8.57, 12.59). In study 103, the mean absolute change was also greater in the ivacaftor group (12.58%) than the placebo group (0.13%) with an estimated treatment difference for ivacaftor versus placebo of 12.45% (95% CI: 6.56, 18.34). Similar effect size was observed at week 48 with a difference between ivacaftor and placebo of 10.50% (8.50, 12.50) and 9.99% (4.52, 15.47) for studies 102 and 103, respectively.

The magnitude of the effect on the primary endpoint in both pivotal studies is considered as meaningful in a population for whom a rate of decline in FEV_1 of around 1% per year can be observed even when patients are treated with the standard of care. The relevance of this finding is apparent, as reductions in FEV_1 are also associated to increased morbidity and mortality rates.

In relation to Study 103, there seems to be some imbalance between the placebo and ivacaftor groups regarding the baseline FEV_1 percent predicted while in study 102 the number of patients receiving concomitant medications, in particular tobramycin and other antibiotics was higher in the placebo group. While it is quite likely patients on placebo were not exactly comparable at baseline (i.e. they suffered from a more advanced pulmonary disease) to patients in the ivacaftor group, the fact that a treatment effect in favour of ivacaftor is consistently seen across several subgroup analyses is reassuring. Nevertheless, the imbalances between treatment groups are described in the SmPC as they are relevant for interpretation of results.

In study 102 the results of different subgroup analyses consistently show the improvement of ivacaftor-treated patients vs. those on placebo. In study 103 results are not so clear cut but overall, the low number of patients makes it difficult to draw firm conclusions.

It should be noticed that the effect of ivacaftor has only been shown in patients with mild to moderate lung disease (percent predicted FEV_1 between 40 and 105% at baseline). Results from a limited number of patients with percent predicted FEV_1 <40% have been discussed showing that the results are consistent with those seen in the overall population. In spite of this, the limited number of patients analysed (4 patients treated with ivacaftor during 96 weeks and 8 patients treated during 48 weeks) preclude drawing any sound conclusions. Uncertainties about the effect in advanced stages of CF (since patients with FEV_1 <40% were excluded from studies) are reflected in the SmPC and use of ivacaftor in this population has to be addressed in the RMP.

There is evidence suggesting that the rate of decline of FEV_1 per year differs between patients aged 6 and older with 1 allele of the G551D mutation and 1 allele of a mutation known to be associated with a severe phenotype and those with a second allele of a known "mild" mutation (e.g., R117H). While the first group of patients have a similar decline in percent predicted FEV_1 per year as patients homozygous for the ΔF508 CFTR mutation, the latter have a smaller decline. In study 102 the mean (SD) absolute change from baseline in percent predicted FEV_1 for ivacaftor-treated patients with a class II mutation was 14.4 (13.62) vs. -0.4 (8.54) in placebo-treated patients. In those with a class I mutation in the second allele these figures were 11.9 (11.85) and 0.3 (4.40), respectively. In study 103 the figures were -0.2 (3.52) and 6.2 (not applicable due to n=1). However, the number of patients in studies with class III, IV or V mutations in the second allele does not exceed 9. Therefore it is not possible to conclude that there is sufficient data to substantiate that efficacy of ivacaftor would be independent of the mutation present in the second allele of CFTR gene.

While FEV_1 is the recommended primary clinical endpoint in efficacy studies for cystic fibrosis sweat chloride remain as biomarker of the disease that is useful for testing activity of compounds targeted at restore CFTR function (CFTR activity) which does not necessarily translates into clinical benefit. Nevertheless, the effect on sweat chloride concentration would be consistent with the activity of ivacaftor as a potentiator of the CFTR protein. In study 102 the mean absolute change from baseline to week 24 in sweat chloride values was greater in ivacaftor than in placebo group (-48.7 mmol/L and -0.77 mmol/L) with a difference between the two groups in this value was -47.93mmol/L. The mean levels of sweat chloride through week 24 (50.76 mmol/L) and through week 48 (50.76 mmol/L) in the ivacaftor group was much lower than the sweat chloride values in placebo group through week 24 and week 48 (100.85 mmol/L and 100.67 mmol/L respectively).

Significant reduction in sweat chloride concentration could also be observed in patients participating in study 103 due to the treatment with ivacaftor. The treatment difference of -54.3 mmol/L from baseline through week 24 and -53.5 mmol/L from baseline through week 48 could be observed. The mean change in sweat chloride concentration was -55.5mmol/L in the ivacaftor group vs -1.2 mmol/L in placebo group from baseline through week 24 and -56mmol/L in ivacaftor group vs -2.6mmol/L in placebo group through week 48.

Data on changes in sweat chloride are supportive of the efficacy of ivacaftor.

Weight is a relevant clinical endpoint to be assessed in CF population. Patients with CF do not gain weight due to many factors such as malabsorption or increased caloric needs due to chronic lung disease. In addition, it is known that poor weight gain predicts clinical lung disease, i.e. that progressive lung disease leads to poor weight gain. Weight is also indirectly related to exocrine pancreatic function. In both trials, treatment with ivacaftor resulted in a significant weight gain at week 48. In study 102 the mean change from baseline was 3.11 kg in the ivacaftor group and 0.40 kg in the placebo group with a difference of 2.71 kg (95%CI: 1.33, 4.09). In study 103 the treatment difference at week 48 was 2.77 kg (95% CI: 1.31, 4.23).

The positive effect of ivacaftor on weight gain also suggests that this product may have a potential for improving exocrine pancreatic function. In the clinical studies (102, 103) biomarkers of exocrine pancreatic function have not been studied. The lack of the data for a comprehensive view on height, body composition etc. as well as regarding any nutritional intervention in these patients limits the conclusions that can be done about the influence of ivacaftor on weight gain.

Like weight, length gain is also important for children. In the additional analysis of absolute change in height, height-for-age Z score, height-for-age ratio and weight/height ratio for patients less than 20 years of age difference between ivacaftor and placebo reached statistical significance. Therefore, concluding that ivacaftor has a systemic (particularly gastrointestinal) effect in this population of almost all pancreatic insufficient patients receiving pancreatic enzyme replacement therapy, fat soluble vitamins and quite likely also nutritional counselling is not possible on the basis of available data. The only anthropometric measure for which a positive finding has been shown is weight-for-age Z scores. Mean absolute change in weight provide very limited information if sex and age are not taken into account. Furthermore, weight gain can occur not only due to an increase in lean body mass and this has not been addressed in the clinical development of ivacaftor. However, the effect of ivacaftor on pulmonary function is sufficiently relevant and supersedes any other consideration, especially since a deleterious effect of ivacaftor on body weight has not been seen.

Pulmonary exacerbations (PE) cause important morbidity and mortality and have a relevant impact on quality of life of patients with CF. As PEs may lead to a permanent decline in lung function their control is one of the main objectives of the treatment of CF. Given that there is not a universally accepted definition of PE a comparison of the results among different studies is very difficult. The definition of PE used in trials 102 and 103 is acceptable from the clinical point of view. Ivacaftor treatment resulted in a statistically significant reduction in the rates of pulmonary exacerbations through week 48 (76.3% in the ivacaftor group and 57.4% in placebo) in study 102. However, given the low number of children in study 103 and the low number of pulmonary exacerbations occurred no statistical analyses were made in that study. The decreased rate of pulmonary exacerbations claimed with ivacaftor is expected to translate mainly in a decrease versus placebo in the use of systemic antibiotics. Antibiotics usually used for pulmonary exacerbations were used by 14.1% and 10.3% of patients on placebo respectively. In the ivacaftor group these figures were 4.8% and 7.2%, respectively, which supports efficacy.

The interim results from study 105 in terms of pulmonary exacerbations are unexpected and not consistent with the results observed for the other endpoints, where consistent positive effect was observed. In light of the limited number of patient no conclusion on a long-term effect on pulmonary exacerbations can be drawn. The applicant should provide yearly updates on study 105 as well as the final study results once available. Furthermore, a long-term observational study should be performed addressing amongst others exacerbation rates.

An increased incidence of Upper Respiratory Tract Infections (URTI) events was seen in patients treated with ivacaftor as compared to those on placebo. In patients treated with ivacaftor more bacteria were isolated in sputum, while patients colonised with bacteria associated with an increased

decline in lung function (e.g., *Burkholderia cenocepacia*, *Burkholderia dolosa*, and *Mycobacterium abcessus*) were excluded from the study. The applicant provided the percentage of patients with at least a *P. aeruginosa* isolate in the 12 months prior to the screening visit, the percentage of patients receiving inhaled antibiotics, and a subgroup analysis of the main variable (percent predicted FEV_1) by presence/absence of *P. aeruginosa*. As expected the number of patients in whom *P. aeruginosa* was isolated is higher in study 102 than in study 103. However, the information provided does not permit to distinguish between patients with early lung colonisation/infection and those in the chronic phase. Most often, initial infection with *P. aeruginosa* is with non-mucoid strains, but with time phenotype changes with the emergence of mucoid strains. The mucoid strains have been associated with the chronic evolution of the lung disease with an unfavorable prognosis for survival.

The subgroup analysis by presence/absence of *P. aeruginosa* shows that in study 102 in patients with *P. aeruginosa* isolated during the previous 12 months treatment difference in the mean absolute change in FEV1% predicted was 11.3%. In those without *P. aeruginosa* the treatment difference was 6.9%. In study 103 these figures were as follows: 7.3% and 18.7%. With the single exception of patients with *P. aeruginosa* in study 103 the results quoted were statistically significant and favoured ivacaftor. These results should be viewed with caution. In addition, in study 102 the results are somehow unexpected in that the treatment difference in FEV_1 is higher in patients with *P. aeruginosa* than in those without it.

While the change from baseline in percent predicted FEV_1 is considerably lesser in placebo-treated patients with URTI (or with bacteria in sputum) as expected the opposite occurs in ivacaftor-treated patients where this change is higher precisely in patients with URTI (or with bacteria in sputum). If this phenomenon is an AE connected with the ivacaftor treatment, its consequences can be evaluated only with the results of a long term study. Otherwise the cause of the increase incidence in ivacaftor treated patients is unknown at present. These issues are addressed through a long term study with endpoints generating data on the consequences of treatment with ivacaftor on microbiological and clinical related issues such as periodic sputum/oropharyngeal cultures, colony density (patients with chronic infection) and pulmonary exacerbations.

Quality of life was measured using the Cystic Fibrosis Questionnaire-Revised (CFQ-R, a validated disease-specific instrument that measures health-related quality of life for people with CF 14 years of age and older). There is a validated version of the CFQ-R available for school-aged children (ages 6 to 11, and ages 12 and 13) with CF and their parents. The adjusted mean absolute change from baseline through week 24 for the respiratory domain score in the pooled adolescents/adults and 12 to 13 year-old versions of CFQ-R was 5.97 points for ivacaftor group and -2.10 points for placebo group through week 24. The estimated treatment difference ivacaftor-placebo was 8.08 points (95% CI: 4.73, 11.42). Results of the analysis of the CFQ-R respiratory domain scores through Week 24 for adolescents and adults CFQ-R version were similar. Some improvement could also be observed in this secondary endpoint of absolute change from baseline in CFQ-R (child) respiratory domain score through week 24 in study 103 in subjects aged 6 – 11 years with CF. However the difference was not statistically significant.

Finally it should be mentioned that the treatment with ivacaftor caused a slight reduction in inflammatory mediators and also of other markers of inflammation i.e. neutrophils, platelets and leukocytes. In patients aged 12 or older small improvement in the EQ-5D score and oxygen saturation could also be observed through week 24 and week 48.

Maintenance of the effect is an important issue in a chronic condition that requires to be treated for life. Long-term data beyond 48 weeks are currently limited. While current data show convincing efficacy, a longer term follow-up is necessary. To address the need for long-term data, the Applicant is

requested to provide the final data of study 105 when available and set-up a long term observational study.

2.5.4. Conclusions on the clinical efficacy

CF lung disease is the primary cause of morbidity and mortality in CF. In the lungs, the dysfunctional CFTR protein leads to obstruction of airways with thick mucus, establishment of chronic bacterial infection in the airways, and damaging inflammatory responses that are all thought to play a role in causing irreversible structural changes. Patients with CF typically experience a progressive loss of lung function ultimately resulting in respiratory failure and death.

Results from studies 102 and 103 show consistent and positive effects of ivacaftor on most variables studied. Especially relevant is the effect on FEV_1, on weight and on pulmonary exacerbations and related events due to their implication in morbidity and mortality of CF patients. Statistically significant results for study 103 appear reassuring considering that the studies were not powered to find statistical differences. Results of sensitivity analyses performed for the primary endpoint are consistently robust, supporting the results of the primary endpoint analysis.

Treatment with ivacaftor treatment has shown to improve pulmonary function (measured as the absolute change from baseline in percent predicted FEV_1 through 24 weeks of treatment) resulting in a clinically significant change in CF patients aged 6 years and older with a G511D-CFTR mutation. The magnitude of this effect (of around 10% from baseline) from the clinical perspective is notable and relevant as poor FEV_1 is known to be associated to an increase in morbidity and mortality.

Ivacaftor has also shown a positive effect on other relevant clinical endpoints like body weight and pulmonary exacerbations and related events. This effect on weight gain also suggests that ivacaftor may have a potential for improving exocrine pancreatic function.

Pulmonary exacerbations are major cause of morbidity and may significantly affect quality of life of these patients. Ivacaftor treatment resulted in a significant reduction in the rates of pulmonary exacerbations and the mean duration of exacerbations in the pivotal study 102. It is noted that interim data from the ongoing long-term study appear to suggest an increased incidence of pulmonary exacerbations with time, whilst at the same time other relevant endpoints in this study show a positive effects seen. The long-term benefits of ivacaftor should be studied further.

Ivacaftor was practically ineffective in patients homozygous for the F508del-CFTR mutation. The indication for ivacaftor has been restricted to patients with a G551D-CFTR mutation, since that is the only mutation in which clinical efficacy has been shown.

As the limited number of patients studied prevents to draw sound conclusions regarding the impact of ivacaftor on infections caused by *P. aeruginosa*, long term effects of ivacaftor should be studied also on microbiological endpoints.

The CHMP considers the following measures necessary to address issues related to efficacy:

- The applicant should submit the final clinical study report of the ongoing study VX08-770-105 which evaluates the long-term safety and efficacy in patients with cystic fibrosis
- The applicant should conduct a 5-year long-term observational study with ivacaftor in patients with cystic fibrosis, including also microbiological and clinical endpoints (e.g. exacerbations), according to a protocol agreed with the CHMP.

2.6. Clinical safety

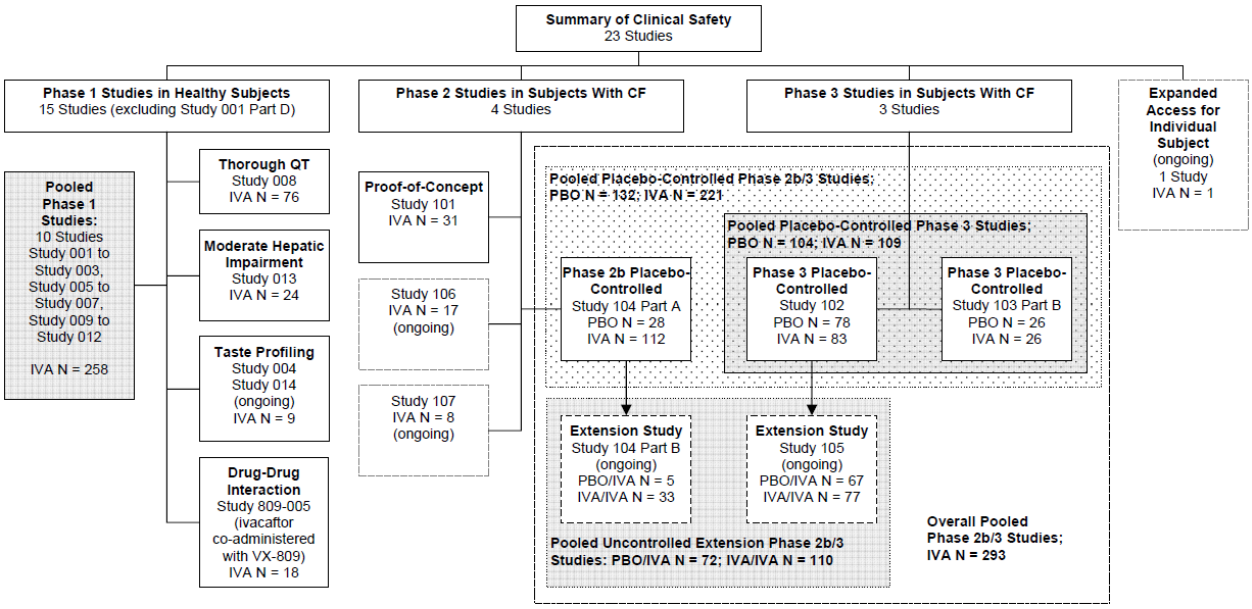
Patient exposure

The safety database contained a total of 700 subjects who received at least one dose of ivacaftor in 23 studies as of 01 July 2011. The majority of studies were pooled to provide the safety analysis of ivacaftor. Phase 1 pooling studies included 258 subjects and phase 2b/3 pooling studies included 293 patients. Six additional studies were not pooled and included in total 162 subjects.

Table 16 Number of Subjects Exposed to ivacaftor, Any Dose and Duration

Study Type (Population)	Subjects Exposed to Ivacaftor
Pooled Studies	
Pooled Phase 1 (10 studies in healthy subjects: Studies 001 [excluding Part D] through 003, 005 through 007, 009 through 012)	258
Pooled Phase 2b/3 studies (Studies 102, 103 Part B, 104, and 105 in subjects with CF)	293
Non-Pooled Studies	
Non-pooled Phase 1 (Study 008 in healthy subjects)	76
Non-pooled Phase1 (Study 809-005 in healthy subjects)	18
Non-pooled Phase 1 (Study 013 in 12 hepatic impaired subjects and 12 healthy subjects)	24[a]
Non-pooled Phase 1 (Study 001, Part D in subjects with CF)	4
Non-pooled Phase 2a (Study 101 in subjects with CF)	31[b]
Non-pooled Phase 3 (Study 103 Part A in subjects with CF)	9[c]
Total Exposure: Subjects With CF	**324[b,c, d]**
Total Exposure: Healthy Subjects	**364[a]**
Total Exposure: All Subjects	**700[e]**

Figure 15 Overview of Studies and Poolings in the safety database of ivacaftor



The phase 1 pooling included 258 adult healthy subjects and the median treatment duration was 3 days (range: 1 to 14).

The majority of safety data came from 293 patients exposed to ivacaftor in placebo-controlled phase 2b/3 studies. The proportion by sex in this pooling was similar (male: 48.5% and female 51.5%) and the majority of subjects were white (97.3%) and aged 18 years or older (64.2%). In this pooling, only

109 patients had the G551D mutation in the CFTR gene (for whom ivacaftor is applied for). There were only 23 patients with age from 6 to 11 years-old (study 103 part B) who received ivacaftor in these studies.

All phase 2b/3 studies used the same dose of ivacaftor: 150 mg q12h. Studies 102 and 103 part B had 48-week treatment duration in subjects with G551D-CFTR mutation. Study 104 Part A had 16-week treatment duration in subjects with G508del-CFTR mutation. Study 105, an extension study of Studies 102 and 103 part B, will provide data on durability of ivacaftor treatment for up to 144 weeks (48 weeks in Study 102 or Study 103 plus up to 96 weeks in Study 105), but is currently ongoing. Study 104 Part B, an extension study of 104 part A, provided a total duration of 40 weeks of ivacaftor treatment (16 weeks in Study 104 Part A and 24 weeks in Study 104 Part B).

In this pooling, only 109 patients who received ivacaftor had the G551D mutation in the CFTR gene. There were only 23 patients with age from 6 to 11 years-old (study 103 part B) who received ivacaftor. Safety data from these 6 to 11 years-old subjects seems not to be different to older than 12 years old.

Baseline disease characteristics showed that subjects in ivacaftor group had better predicted FEV_1 values than in placebo group: the median values were 74.5 and 69.1 respectively. Additionally, there were less patients with severe and very severe obstructive component (<40% and ≥40 to <70% predicted FEV_1) and more mild and normal values on the predictive FEV_1 (≥70 to ≤90% and >90%) in the ivacaftor group as compared to placebo group.

Adverse events

Table 12 Adverse events in pooled Phase 2b/3 studies

	Placebo-controlled Studies (102, 103 Part B, 104 Part A)		**Uncontrolled Extension Studies (104 Part B and 105)**		**Overall Phase 2b/ 3 Studies**
Subjects With:	**Placebo (N = 132) n = %**	**Ivacaftor (N = 221) n = %**	**Placebo/ Ivacaftor (N = 72) n = %**	**Ivacaftor/ Ivacaftor (N = 110) n = %**	**All Ivacaftor (N = 293) n = %**
At least 1AE	128 (97.0)	204 (92.3)	54 (75.0)	91 (82.7)	263 (89.8)
At least 1 related AE	45 (34.1)	74 (33.5)	15 (20.8)	16 (14.5)	98 (33.4)
At least 1 AE leading to death	0	0	0	0	0
At least 1 SAE	46 (34.8)	39 (17.6)	5 (6.9)	21 (19.1)	55 (18.8)
At least 1 related SAE	5 (3.8)	9 (4.1)	1 (1.4)	0	10 (3.4)
At least 1 AE leading to study drug interruption	10 (7.6)	16 (7.2)	4 (5.6)	6 (5.5)	25 (8.5)
At least 1 related AE leading to study drug interruption	3 (2.3)	5 (2.3)	1 (1.4)	2 (1.8)	8 (2.7)
At least 1 AE leading to study drug discontinuation	7 (5.3)	4 (1.8)	1 (1.4)	1 (0.9)	6 (2.0)
At least 1 related AE leading to study drug discontinuation	5 (3.8)	4 (1.8)	0	1 (0.9)	5 (1.7)

Note: Related includes related and possibly related to study drug categories. A subject may appear in multiple categories.

Adverse events occurring in at least 3% of subjects are summarised in the tables below for pooled phase 1 studies and pooled phase 2b/3 studies.

Table 13 Adverse Events Occurring in At Least 3% of Subjects in Any Treatment Group by System Organ Class and Preferred Term: Pooled Phase 1 Studies, Safety Set

System Organ Class Preferred Term	Placebo N = 33 n (%)	Ivacaftor Alone N = 228 n (%)	Ivacaftor With a Co-administered Drug N = 122 n (%)	Any Ivacaftor N = 258 n (%)
Subjects with any adverse event	**27 (81.8)**	**109 (47.8)**	**54 (44.3)**	**149 (57.8)**
General disorders and administration site conditions	**27 (81.8)**	**58 (25.4)**	**6 (4.9)**	**64 (24.8)**
Product quality issue[a]	27 (81.8)	56 (24.6)	0	56 (21.7)
Pyrexia	0	0	4 (3.3)	4 (1.6)
Nervous system disorders	**3 (9.1)**	**38 (16.7)**	**25 (20.5)**	**61 (23.6)**
Headache	3 (9.1)	28 (12.3)	20 (16.4)	46 (17.8)
Dizziness	0	9 (3.9)	4 (3.3)	13 (5.0)
Hypoaesthesia	1 (3.0)	0	0	0
Gastrointestinal disorders	**3 (9.1)**	**31 (13.6)**	**23 (18.9)**	**53 (20.5)**
Diarrhea	2 (6.1)	12 (5.3)	6 (4.9)	18 (7.0)
Nausea	0	6 (2.6)	10 (8.2)	16 (6.2)
Abdominal pain upper	0	7 (3.1)	0	7 (2.7)
Vomiting	0	2 (0.9)	4 (3.3)	6 (2.3)
Retching	1 (3.0)	0	0	0
Respiratory, thoracic, and mediastinal disorders	**1 (3.0)**	**25 (11.0)**	**17 (13.9)**	**40 (15.5)**
Cough	0	6 (2.6)	10 (8.2)	16 (6.2)
Oropharyngeal pain	1 (3.0)	8 (3.5)	3 (2.5)	11 (4.3)
Rhinorrhoea	0	1 (0.4)	4 (3.3)	5 (1.9)
Infections and infestations	**0**	**6 (2.6)**	**18 (14.8)**	**23 (8.9)**
Nasopharyngitis	0	0	7 (5.7)	7 (2.7)
Musculoskeletal and connective tissue disorders	2 (6.1)	4 (1.8)	7 (5.7)	11 (4.3)
Back pain	1 (3.0)	1 (0.4)	1 (0.8)	2 (0.8)
Arthralgia	1 (3.0)	0	0	0
Psychiatric disorders	1 (3.0)	4 (1.8)	2 (1.6)	6 (2.3)
Depressed mood	1 (3.0)	1 (0.4)	0	1 (0.4)
Reproductive system and breast disorders	0	1 (0.4)	4 (3.3)	5 (1.9)
Dysmenorrhoea	0	1 (0.4)	4 (3.3)	5 (1.9)
Renal and urinary disorders	1 (3.0)	2 (0.9)	2 (1.6)	4 (1.6)
Pollakiuria	1 (3.0)	1 (0.4)	0	1 (0.4)

Source: Module 5.3.5.3/VX-770 ISS/Table 1.3.2
Note: A subject with multiple events within a system organ class or within a preferred term is only counted once. Percentages are based on the number of subjects in the Safety Set. This table is sorted in descending frequency of the "Any Ivacaftor" column by SOC and preferred term within each SOC. SOC and preferred term were coded using MedDRA, Version 12.0.

[a] Product quality issue (i.e., bad taste) was an adverse event that occurred in subjects who were administered the initial ivacaftor formulation (polyethylene glycol solution).

Table 14 Adverse Events With an Incidence of At Least 3% in Any Treatment Group by Preferred Term: Pooled Phase 2b/3 Studies, Safety Set (initially submitted studies)

	Placebo-Controlled Studies (102, 103 Part B, 104 Part A)		Uncontrolled Extension Studies (104 Part B and 105)		Overall Phase 2b/3 Studies
Preferred Term	Placebo (N = 132) n (%)	Ivacaftor (N = 221) n (%)	Placebo/ Ivacaftor (N = 72) n (%)	Ivacaftor/ Ivacaftor (N = 110) n (%)	All Ivacaftor (N = 293) n (%)
Cough	55 (41.7)	74 (33.5)	7 (9.7)	17 (15.5)	94 (32.1)
Cystic fibrosis lung	68 (51.5)	65 (29.4)	14 (19.4)	36 (32.7)	100 (34.1)
Headache	19 (14.4)	37 (16.7)	3 (4.2)	5 (4.5)	44 (15.0)
Upper respiratory tract infection	16 (12.1)	35 (15.8)	5 (6.9)	10 (9.1)	46 (15.7)
Nasal congestion	17 (12.9)	35 (15.8)	3 (4.2)	3 (2.7)	41 (14.0)
Oropharyngeal pain	22 (16.7)	34 (15.4)	2 (2.8)	3 (2.7)	38 (13.0)
Pyrexia	18 (13.6)	25 (11.3)	3 (4.2)	2 (1.8)	29 (9.9)
Productive cough	17 (12.9)	23 (10.4)	3 (4.2)	7 (6.4)	29 (9.9)
Nausea	12 (9.1)	23 (10.4)	0	8 (7.3)	28 (9.6)
Rash	7 (5.3)	23 (10.4)	0	3 (2.7)	25 (8.5)
Abdominal pain	14 (10.6)	21 (9.5)	7 (9.7)	4 (3.6)	31 (10.6)
Diarrhoea	12 (9.1)	20 (9.0)	2 (2.8)	4 (3.6)	26 (8.9)
Nasopharyngitis	12 (9.1)	20 (9.0)	2 (2.8)	2 (1.8)	24 (8.2)
Abdominal pain upper	13 (9.8)	17 (7.7)	1 (1.4)	4 (3.6)	22 (7.5)
Fatigue	12 (9.1)	17 (7.7)	1 (1.4)	4 (3.6)	20 (6.8)
Sinusitis	11 (8.3)	16 (7.2)	2 (2.8)	6 (5.5)	21 (7.2)
Vomiting	17 (12.9)	15 (6.8)	2 (2.8)	2 (1.8)	18 (6.1)
Rales	12 (9.1)	14 (6.3)	4 (5.6)	3 (2.7)	18 (6.1)
Haemoptysis	18 (13.6)	13 (5.9)	4 (5.6)	6 (5.5)	20 (6.8)
Rhinitis	4 (3.0)	13 (5.9)	1 (1.4)	1 (0.9)	15 (5.1)
Dizziness	3 (2.3)	12 (5.4)	2 (2.8)	1 (0.9)	15 (5.1)
Arthralgia	6 (4.5)	11 (5.0)	1 (1.4)	7 (6.4)	18 (6.1)
Rhinorrhoea	12 (9.1)	11 (5.0)	1 (1.4)	0	12 (4.1)
Wheezing	7 (5.3)	11 (5.0)	1 (1.4)	0	12 (4.1)
Bacteria sputum identified	5 (3.8)	11 (5.0)	0	0	11 (3.8)
Sinus congestion	5 (3.8)	10 (4.5)	3 (4.2)	4 (3.6)	17 (5.8)
Blood glucose increased	4 (3.0)	10 (4.5)	2 (2.8)	3 (2.7)	13 (4.4)
C-reactive protein increased	4 (3.0)	10 (4.5)	3 (4.2)	0	13 (4.4)
Respiratory tract congestion	9 (6.8)	9 (4.1)	0	4 (3.6)	13 (4.4)
Aspartate aminotransferase increased	6 (4.5)	9 (4.1)	1 (1.4)	4 (3.6)	12 (4.1)
Musculoskeletal chest pain	5 (3.8)	8 (3.6)	1 (1.4)	2 (1.8)	11 (3.8)

Alanine aminotransferase increased	10 (7.6)	8 (3.6)	0	2 (1.8)	9 (3.1)
Pain in extremity	5 (3.8)	8 (3.6)	0	1 (0.9)	9 (3.1)
Sinus headache	4 (3.0)	8 (3.6)	0	0	8 (2.7)
Back pain	6 (4.5)	7 (3.2)	0	4 (3.6)	11 (3.8)
Dyspnoea	5 (3.8)	7 (3.2)	0	2 (1.8)	9 (3.1)
Hypoglycaemia	4 (3.0)	7 (3.2)	1 (1.4)	1 (0.9)	8 (2.7)
Lymphadenopathy	4 (3.0)	7 (3.2)	1 (1.4)	0	8 (2.7)
Pharyngeal erythema	1 (0.8)	7 (3.2)	0	1 (0.9)	8 (2.7)
Prothrombin time prolonged	2 (1.5)	7 (3.2)	0	1 (0.9)	8 (2.7)
Myalgia	3 (2.3)	6 (2.7)	0	4 (3.6)	10 (3.4)
Pleuritic pain	3 (2.3)	6 (2.7)	1 (1.4)	3 (2.7)	9 (3.1)
Pruritus	3 (2.3)	6 (2.7)	1 (1.4)	2 (1.8)	9 (3.1)
Pulmonary function test decreased	17 (12.9)	6 (2.7)	0	3 (2.7)	9 (3.1)
Hepatic enzyme increased	4 (3.0)	6 (2.7)	0	2 (1.8)	8 (2.7)
Constipation	8 (6.1)	4 (1.8)	2 (2.8)	3 (2.7)	9 (3.1)
Dysphonia	4 (3.0)	4 (1.8)	1 (1.4)	1 (0.9)	6 (2.0)
Weight decreased	4 (3.0)	4 (1.8)	2 (2.8)	0	6 (2.0)
Respiration abnormal	4 (3.0)	4 (1.8)	0	1 (0.9)	5 (1.7)
Paranasal sinus hypersecretion	6 (4.5)	4 (1.8)	0	0	4 (1.4)
Glucose urine present	1 (0.8)	4 (1.8)	1 (1.4)	4 (3.6)	8 (2.7)
Gamma-glutamyl transferase increased	5 (3.8)	3 (1.4)	1 (1.4)	2 (1.8)	5 (1.7)
Ear infection	4 (3.0)	3 (1.4)	0	1 (0.9)	4 (1.4)
Influenza	4 (3.0)	3 (1.4)	1 (1.4)	0	4 (1.4)
Breath sounds abnormal	6 (4.5)	3 (1.4)	0	0	3 (1.0)
White blood cell count increased	4 (3.0)	2 (0.9)	0	1 (0.9)	3 (1.0)
Joint sprain	4 (3.0)	2 (0.9)	0	0	2 (0.7)
Viral infection	5 (3.8)	2 (0.9)	0	0	2 (0.7)
Laryngitis	4 (3.0)	1 (0.5)	0	0	1 (0.3)

Note: A subject with multiple events within a preferred term is counted only once within the preferred term. Preferred terms are sorted in descending order of frequency in the ivacaftor column (placebo-controlled studies). Preferred terms are coded using MedDRA, Version 12.0.

In phase 2b/3 trials there was no relevant difference between placebo and ivacaftor groups in the incidence of AEs. Cough and Cystic fibrosis lung (preferred term for pulmonary exacerbation) were reported more frequently in placebo group. However, URTI, headache, and skin disorders were reported more frequently in Ivacaftor group.

The AEs by SOCs did not show important differences on cardiovascular disorders, gastrointestinal disorders, renal and urinary system, musculoskeletal disorders, metabolism disorders, psychiatric disorders, blood and lymphatic system, immune system and neoplasm disorders.

Nervous system disorders: according to data submitted by the applicant around 9% of patients who received Ivacaftor had dizziness and 24% had headache; these data shows clear difference in incidence with greater incidence in Ivacaftor group (around 8% for both AEs).

Table 15 Incidence of Adverse Events With At Least 3% Difference Between the Ivacaftor and Placebo Groups by Preferred Term: Pooled Placebo-Controlled Phase 2b/3 and Phase 3 Studies, Safety Set

	Pooled Placebo-Controlled Phase 2b/3 Studies			Pooled Placebo-Controlled Phase 3 Studies		
Preferred Term	Placebo (N = 132) n (%)	Ivacaftor (N = 221) n (%)	Difference in Incidence	Placebo (N = 104) n (%)	Ivacaftor (N = 109) n (%)	Difference in Incidence
Dizziness	3 (2.3)	12 (5.4)	3.1	1 (1.0)	10 (9.2)	8.2
Headache	19(14.4)	37 (16.7)	2.3	17 (16.3)	26 (23.9)	7.6

In the pooled placebo-controlled Phase 2b/3 studies, the overall incidence of URTI SSC events was similar between the ivacaftor and the placebo groups. The incidences were 59.1% and 58.4% respectively. In Phase 3 studies these incidences were 65.4% and 74.3% for patients who received placebo and ivacaftor respectively. Therefore the incidence of any UTRI was around 9% more frequent in the Ivacaftor group. Regarding the severity of these URTI, 39.4% in the ivacaftor group and 44.2% in the placebo group were considered mild and 33.9% in the ivacaftor group were considered moderate against 19.2% in the placebo group. The incidence of any URTI events were very common in patients treated with Ivacaftor 81 out of 109 (74.3%) and 37 out of 109 (33.9%).

While in the pooled placebo-controlled Phase 2b/3 studies, the overall incidence of URTI SSC events was similar between the ivacaftor and the placebo groups, in Phase 3 studies the incidence was higher (phase 3 studies included patients in which Ivacaftor shown efficacy and it is the target population). These increased frequencies are reflected in section 4.8 of the SmPC.

Incidence of ear and labyrinth disorders was slightly higher in the ivacaftor group than in the placebo group in Phase 3 studies (102, 103 part B Studies) 4.8% against 9.2%.

Table 16 Incidence of Ear and Labyrinth Events by System Organ Class and Preferred Term: Pooled Phase 2b/3 Studies, Safety Set

	Placebo-Controlled Phase 2b/3 Studies (102, 103 Part B, 104 Part A)		Placebo-Controlled Phase 3 Studies (102, 103 Part B)	
System Organ Class Preferred Term	Placebo (N = 132) n (%)	Ivacaftor (N = 221) n (%)	Placebo (N = 104) n (%)	Ivacaftor (N = 109) n (%)
Infections and infestations	**70 (53.0)**	**105 (47.5)**	**61 (58.7)**	**67 (61.5)**
Otitis media	1 (0.8)	5 (2.3)	1 (1.0)	4 (3.7)
Ear infection	4 (3.0)	3 (1.4)	3 (2.9)	2 (1.8)
Otitis externa	0	1 (0.5)	0	1 (0.9)
Labyrinthitis	0	1 (0.5)	0	1 (0.9)
Ear and labyrinth disorders	**5 (3.8)**	**11 (5.0)**	**5 (4.8)**	**10 (9.2)**
Ear discomfort	0	4 (1.8)	0	4 (3.7)
Ear pain	2 (1.5)	4 (1.8)	2 (1.9)	4 (3.7)
Tinnitus	0	3 (1.4)	0	2 (1.8)
Tympanic membrane hyperaemia	0	2 (0.9)	0	2 (1.8)
Deafness	1 (0.8)	1 (0.5)	1 (1.0)	1 (0.9)
Ear congestion	0	1 (0.5)	0	1 (0.9)
Vestibular disorder	0	1 (0.5)	0	1 (0.9)
Ear pruritus	1 (0.8)	0	1 (1.0)	0
Middle ear effusion	1 (0.8)	0	1 (1.0)	0

The incidence of breast and nipple disorders (6 cases: around 3%) was more frequent in Ivacaftor than in Placebo Group (no cases 0%). These 6 cases were reported as breast inflammation, breast mass,

breast tenderness, nipple disorder, nipple, pain and gynecomastia. Four out of them were possibly related to ivacaftor and 2 out of them were severe (1 gynecomastia and 1 nipple disorder).

Rash was a very common adverse event in the pooled placebo-controlled Phase 2b/3 studies, with a higher incidence in the ivacaftor group (at least 5%), 10.4% in the ivacaftor group (23 of 221 subjects) and 5.3% in the placebo group (7 of 132 subjects). When other types of "rashes" are considered, the incidence of "Rash SSC events" was also higher in the ivacaftor group than in the placebo group: 14.5% (32 out of 221) in the ivacaftor group and 11.4% (15 of 132) in the placebo group. The majority of these rashes were mild or moderate in severity.

Serious adverse event/deaths/other significant events

Table 17 Incidence of SAEs in At Least 2 Subjects in Any Treatment Group by System Organ Class and Preferred Term: Pooled Phase 2b/3 Studies, Safety Set

	Placebo-Controlled Studies (102, 103 Part B, 104 Part A)		Uncontrolled Extension Studies (104 Part B and 105)		Overall Phase 2b/3 Studies
System Organ Class Preferred Term	Placebo (N = 132) n (%)	Ivacaftor (N = 221) n (%)	Placebo/ Ivacaftor (N = 72) n (%)	Ivacaftor/ Ivacaftor (N = 110) n (%)	All Ivacaftor (N = 293) n (%)
Subjects with Any SAE	**46 (34.8)**	**39 (17.6)**	**5 (6.9)**	**21 (19.1)**	**55 (18.8)**
Congenital, familial and genetic disorders	**35 (26.5)**	**23 (10.4)**	**2 (2.8)**	**17 (15.5)**	**36 (12.3)**
Cystic fibrosis lung	35 (26.5)	23 (10.4)	2 (2.8)	17 (15.5)	36 (12.3)
Respiratory, thoracic, and mediastinal disorders	**7 (5.3)**	**7 (3.2)**	**1 (1.4)**	**2 (1.8)**	**10 (3.4)**
Haemoptysis	4 (3.0)	2 (0.9)	1 (1.4)	2 (1.8)	5 (1.7)
Gastrointestinal disorders	**3 (2.3)**	**4 (1.8)**	**1 (1.4)**	**0**	**5 (1.7)**
Abdominal pain	0	2 (0.9)	0	0	2 (0.7)
Infections and infestations	**4 (3.0)**	**4 (1.8)**	**0**	**3 (2.7)**	**7 (2.4)**
Pneumonia	0	1 (0.5)	0	1 (0.9)	2 (0.7)
Investigations	**1 (0.8)**	**3 (1.4)**	**0**	**0**	**3 (1.0)**
Hepatic enzyme increased	0	2 (0.9)	0	0	2 (0.7)
Metabolism and nutrition disorders	**0**	**2 (0.9)**	**0**	**0**	**2 (0.7)**
Hypoglycaemia	0	2 (0.9)	0	0	2 (0.7)

Note: A subject with multiple events within a system organ class (SOC) is counted only once in the SOC. A subject with multiple events within a Preferred Term (PT) is counted only once in the PT. This table is sorted in descending frequency of the ivacaftor column in the placebo-controlled studies for SOC and PT within each SOC. SOC and PT are coded using MedDRA, Version 12.0. A subject who participated in 104 Part A and 104 Part B is counted once in the overall column. A subject who participated in Studies 102 and 105 is counted once in the overall column

No deaths were reported during the conduct of the clinical program.

In phase 2b/3 studies the incidence of SAEs was lower in the ivacaftor group (17.6%) than in the placebo group (34.8%). Thirty five SAEs (26.5%) were reported as "cystic fibrotic lung" in patients who received placebo and 23 SAEs (10.4%) in patients who receive ivacaftor.

Laboratory findings

The descriptive statistics and incidence in categorical shifts from baseline for the majority of the clinical laboratory parameters (serum chemistry, haematology, and coagulation studies) assessed in the pooled placebo-controlled Phase 2b/3 studies showed minor differences between the ivacaftor and placebo groups that were not considered to be clinically meaningful.

Liver-related parameters have been presented in more detail because there were reports of adverse events related to this parameter which led to study drug discontinuation.

Table 18 Comparison of the Incidence of Maximum On-Treatment Transaminase Values: Placebo-Controlled Phase 2b/3 Studies

Incidence of Maximum On-Treatment Transaminase Values Post-Baseline[a]										
	<2 × ULN n (%)		≥2 × ULN to <3 × ULN n (%)		≥3 × ULN to <5 × ULN n (%)		≥5 × ULN to <8 × ULN n (%)		≥8 × ULN n (%)	
Parameter	Placebo N = 131	Ivacaftor N = 221	Placebo N = 131	Ivacaftor N = 221	Placebo N = 131	Ivacaftor N = 221	Placebo N = 131	Ivacaftor N = 221	Placebo N = 131	Ivacaftor N = 221
ALT	115 (87.8)	191 (86.4)	8 (6.1)	18 (8.1)	5 (3.8)	8 (3.6)	1 (0.8)	2 (0.9)	2 (1.5)	2 (0.9)
AST	119 (90.8)	203 (91.9)	7 (5.3)	11 (5.0)	3 (2.3)	2 (0.9)	1 (0.8)	1 (0.5)	1 (0.8)	4 (1.8)
ALT or AST[b]	109 (83.2)	185 (83.7)	11 (8.4)	22 (10.0)	8 (6.1)	8 (3.6)	1 (0.8)	2 (0.9)	2 (1.5)	4 (1.8)
Cumulative Incidence of Maximum On-Treatment Transaminase Values Post-Baseline[c]										
	<2 × ULN n (%)		≥2 × ULN n (%)		≥3 × ULN n (%)		≥5 × ULN n (%)		≥8 × ULN n (%)	
Parameter	Placebo N = 131	Ivacaftor N = 221	Placebo N = 131	Ivacaftor N = 221	Placebo N = 131	Ivacaftor N = 221	Placebo N = 131	Ivacaftor N = 221	Placebo N = 131	Ivacaftor N = 221
ALT	115 (87.8)	191 (86.4)	16 (12.2)	30 (13.6)	8 (6.1)	12 (5.4)	3 (2.3)	4 (1.8)	2 (1.5)	2 (0.9)
AST	119 (90.8)	203 (91.9)	12 (9.2)	18 (8.1)	5 (3.8)	7 (3.2)	2 (1.5)	5 (2.3)	1 (0.8)	4 (1.8)
ALT or AST[b]	109 (83.2)	185 (83.7)	22 (16.7)	36 (16.3)	11 (8.4)	14 (6.3)	3 (2.3)	6 (2.7)	2 (1.5)	4 (1.8)

Note: One subject who received placebo had a baseline measurement and no maximum on-treatment value.

[a] Each subject is counted only once.

[b] This row provides data such that each subject is tabulated once, according to the level of their maximum on-treatment transaminase (ALT or AST) value, except for the <2 × ULN column which includes subjects in whom both maximum on-treatment ALT and AST were <2 × ULN.

[c] Cumulative incidence provides data such that each subject is tabulated in every category, within and above which, their maximum on-treatment transaminase (ALT, AST) applies. For instance, a subject with ALT > 8 × ULN would be tabulated in all 4 categories from ≥2 × ULN to <3 × ULN through ≥8 × ULN.

Table 19 Incidence of Liver-Related Adverse Events by Preferred Term: Pooled Phase 2b/3 Studies, Safety Set

	Placebo-Controlled Studies (102, 103 Part B, 104 Part A)		Uncontrolled Extension Studies (104 Part B and 105)		Overall Phase 2b/3 Studies
System Organ Class Preferred Term	Placebo (N = 132) n (%)	Ivacaftor (N = 221) n (%)	Placebo/ Ivacaftor (N = 72) n (%)	Ivacaftor/ Ivacaftor (N = 110) n (%)	All Ivacaftor (N = 293) n (%)
Aspartate aminotransferase increased	6 (4.5)	9 (4.1)	1 (1.4)	4 (3.6)	12 (4.1)
Alanine aminotransferase increased	10 (7.6)	8 (3.6)	0	2 (1.8)	9 (3.1)
Hepatic enzyme increased	4 (3.0)	6 (2.7)	0	2 (1.8)	8 (2.7)
Liver palpable subcostal	1 (0.8)	1 (0.5)	0	0	1 (0.3)
Liver function test abnormal	2 (1.5)	0	0	0	0
Transaminase increased	1 (0.8)	0	0	0	0
Total Incidence of Liver-Related Events[a]	**16 (12.1)**	**16 (7.2)**	**1 (1.4)**	**6 (5.5)**	**21 (7.2)**

Notes: A subject with multiple events within a Preferred Term (PT) is counted only once in the PT. Table is sorted in descending frequency of the placebo-controlled ivacaftor column. PT is coded using MedDRA, Version 12.0. A subject who participated in 104 Part A and 104 Part B is counted once in the overall column. A subject who participated in 102 and 105 is counted once in the overall column.

Safety in special populations

There is no data in patients older than 53 years-old and younger than 6 years-old. Additionally, there were only 23 patients with age from 6 to 11 years-old who received ivacaftor in these studies. Safety data of these subjects seems not to differ from subjects older than 12 years.

The overall incidence of subjects with AE was similar in the two age groups(<18 years and ≥18 years at baseline); however some AE-s like cough, headache, nasal congestion, URTI oropharyngeal pain had at least 10 % higher incidence in the <18 year subgroup than ≥18 years subgroup. (See table 12-6)

Table 20 Adverse Events Occurring in At Least 15% of Subjects in the VX-770 Group, by Preferred Term and Age Subgroups, Week 48, Safety Set, Study 102

	< 18 Years		≥ 18 Years	
Preferred Term[a]	**Placebo N = 17 n (%)**	**VX-770 N = 19 n (%)**	**Placebo N = 61 n (%)**	**VX-770 N = 64 n (%)**
Cystic Fibrosis Lung[b]	13 (76.5)	8 (42.1)	37 (60.7)	26 (40.6)
Cough	13 (76.5)	8 (42.1)	20 (32.8)	19 (29.7)
Headache	7 (41.2)	7 (36.8)	6 (9.8)	12 (18.8)
Upper Respiratory Tract Infection	0	6 (31.6)	12 (19.7)	13 (20.3)
Oropharyngeal Pain	7 (41.2)	6 (31.6)	8 (13.1)	11 (17.2)
Nasal Congestion	2 (11.8)	1 (5.3)	10 (16.4)	16 (25.0)
Abdominal Pain	3 (17.6)	3 (15.8)	7 (11.5)	10 (15.6)
Nausea	2 (11.8)	7 (36.8)	7 (11.5)	6 (9.4)

[a] A subject with multiple events within a preferred term was counted only once within the preferred term.
[b] CF exacerbations were coded as "cystic fibrosis lung."

Ivacaftor has not been studied in subjects with moderate or severe renal impairment.

According to the results of Study 013 subjects with moderate hepatic impairment had similar ivacaftor Cmax, but approximately 2-fold increase in ivacaftor $AUC_{0-\infty}$, compared with healthy subjects matched for demographics. Results showed that incidence of adverse events were higher in subjects with moderate hepatic impairment. Studies have not been conducted in patient with severe hepatic impairment. (Child-Pugh C). Patients with CF and hepatic impairment were excluded from Phase IIb/III studies of ivacaftor; therefore no safety data in this population are available.

There were no important differences in the incidence of AEs between placebo and ivacaftor populations at 16 weeks when they were compared by SOCs and between genotype mutations.

Safety related to drug-drug interactions and other interactions

Please refer to discussion regarding Pharmacokinetic interactions. No additional safety information regarding interactions has been identified in the pooled safety database.

Discontinuation due to adverse events

Table 21 Subject Disposition and Reasons for Discontinuation: Pooled Phase 2b/3 Studies, Safety Set

	Placebo-Controlled Studies (102, 103 Part B[a], 104 Part A)		Uncontrolled Extension Studies (104 Part B[b] and 105[c])		Overall Phase 2b/3 Studies[a,b,c,d]
	Placebo n (%)	Ivacaftor n (%)	Placebo/ Ivacaftor n (%)	Ivacaftor/ Ivacaftor n (%)	All Ivacaftor n (%)
Safety Set	**132**	**221**	**72**	**110**	**293**
Completed the pooled treatment arm	**116 (87.9)**	**207 (93.7)**	**0[d]**	**0[d]**	**71 (24.2)[d]**
Reason for discontinuation from the pooled treatment arm	**16 (12.1)**	**14 (6.3)**	**2 (2.8)**	**5 (4.5)**	**21 (7.2)**
Adverse event	7 (5.3)	4 (1.8)	1 (1.4)	1 (0.9)	6 (2.0)
Lost to follow-up	0	1 (0.5)	0	0	1 (0.3)
Noncompliance with study requirements	0	4 (1.8)	0	1 (0.9)	5 (1.7)
Death	0	0	0	0	0
Physician decision	1 (0.8)	0	0	0	0
Pregnancy	0	1 (0.5)	1 (1.4)	0	2 (0.7)
Requires prohibited medication	3 (2.3)	2 (0.9)	0	0	2 (0.7)
Study termination by sponsor	0	0	0	0	0
Withdrawal of consent	2 (1.5)	1 (0.5)	0	2 (1.8)	3 (1.0)
Other[e]	3 (2.3)	1 (0.5)	0	1 (0.9)	2 (0.7)

Note: Safety Set is defined as all subjects who received at least 1 dose of study drug in the pooled treatment arm. Percentages are based on the number of subjects in the Safety Set. The 'Overall' column represents subjects unique to ivacaftor treatment (received ivacaftor in a placebo-controlled study, or received placebo in a placebo-controlled study and then received ivacaftor in 1 of the uncontrolled extension studies).

[a] Study 103 Part B is the placebo-controlled, 48-week part of the study; treatment with study drug has been completed.

[b] Study 104 Part B is the open-label extension study that is ongoing. Data through 40 weeks (16 weeks from Part A and 24 weeks from Part B) of treatment with ivacaftor is included in the 'Overall' column. A subject who participated in Study 104 Parts A and B is counted once in the 'Overall' column.

[c] Study 105 is the open-label extension study; study is ongoing. Data through 12 weeks of treatment (Study 102 subjects only; Study 103 subjects have not completed treatment through Week 12 at the time of the safety data cut-off) is included in the 'Overall' column. A subject who participated in Studies 102 and 105 is counted once in the overall column.

[d] No subject completed the placebo/ivacaftor or ivacaftor/ivacaftor treatment arms as the studies (Studies 104 Part B and 105) are currently ongoing.

[e] Other reasons subjects discontinued treatment included incorrect genotype, discomfort with phlebotomy, no longer meeting eligibility criteria as pregnancy was desired, and at the request of the sponsor.

In pooled phase 2b/3 studies 4 (1.8%) subjects in the ivacaftor group discontinued for AEs: 1 subject for arthritis; 1 for myopathy; 1 for asthenia, fatigue, and headache; and 1 for hepatic enzyme increased. The incidence of drug interruption in these studies was similar between the ivacaftor (7.2%) and placebo (7.6%) groups.

Post marketing experience

Ivacaftor has not been authorised is any country at the time of submission of current application.

2.6.1. Discussion on clinical safety

The safety data base included a total of 700 subjects who received at least one dose of ivacaftor from 23 studies as of 01 July 2011. More than half of the subjects included during development program were healthy volunteers (364 out of 700 subjects). These subjects had a better health state than

patients with CF, therefore safety data coming from this healthy population could make the safety profile of ivacaftor appear better in the total safety database.

Due to the very limited patient number (n=23), there is only very limited safety data in children from 6 to 11 years-old. This fact is reflected in the SmPC and safety in this population is to be further addressed with additional pharmacovigilance activities as specified in the RMP.

The phase 1 studies that were pooled included in total 258 adult healthy subjects. The median treatment duration was 3 days (range: 1 to 14). With this short drug exposure in pooling 1; the AEs in the Ivacaftor group were more frequent than in the placebo group in nervous system, gastrointestinal, respiratory, infections and infestation disorders. The incidence of headache, dizziness and abdominal pain upper was higher (at least 3% higher) in the ivacaftor alone group than the placebo group. The incidence of nauseas vomiting, nasopharyngitis and dysmenorrhoea was also higher in the ivacaftor group.

The most important safety data come from 293 patients exposed to ivacaftor in pooled placebo-controlled phase 2b/3 studies. Studies 102 and 103 part B had 48-week treatment duration in subjects with G551D-CFTR mutation. Study 104 Part A had 16-week treatment duration in subjects with G508del-CFTR mutation. Study 105 is an extension study of Studies 102 and 103 part B and will provide data on durability of ivacaftor treatment for up to 144 weeks (48 weeks in Study 102 or Study 103 plus up to 96 weeks in Study 105). However, final results of this study are not yet available. Study 104 Part B, was an extension study of 104 part A; this provided a total duration of 40 weeks of ivacaftor for Study 104 Part B subjects (16 weeks of ivacaftor in Study 104 Part A and 24 weeks of ivacaftor in Study 104 Part B).

In this phase 2b/3 pooling, only 109 patients who received ivacaftor had the G551D mutation in the CFTR gene. The proportion by sex was balanced (male: 48.5% and female 51.5%) and the majority of subjects were White (97.3%).

Baseline disease characteristics showed that the predicted FEV_1 were not similar across the ivacaftor and placebo groups. The observed worse baseline condition in the placebo group could enhance the AEs rate observed on these patients.

In the pooled phase 2b/3 studies the global incidence of AEs showed that cough and cystic fibrosis lung (preferred term for pulmonary exacerbation) were reported more frequently in placebo group. However, headache, URTI and rash were reported more frequently in the Ivacaftor group. The AEs by SOCs didn't show important differences on cardiovascular disorders, gastrointestinal disorders, renal and urinary system, musculoskeletal disorders, metabolism disorders, psychiatric disorders, blood and lymphatic system, immune system and neoplasm disorders. Nonetheless, a higher incidence of headache, URTI and rash also were reported in the ivacaftor group. Additionally, dizziness, ear and labyrinth disorders and breast disorders were also seen more frequently in the ivacaftor group in phase 3 pooling studies. Therefore, the SmPC has been updated accordingly to reflect the frequency of these ADRs. Rash, headache and dizziness, ear and labyrinth disorders and breast and nipple disorders should be closely monitored in future PSURs.

Nearly all subjects in the ivacaftor (92.3%) and placebo (97.0%) groups in pooled phase 2b/3 studies had adverse events. The incidence of adverse events considered by the investigator to be related to the study drug (i.e., ivacaftor or placebo) was similar between the ivacaftor (33.5%) and placebo (34.1%) groups. The "related" SAEs were similar in both groups (3.8% in the placebo group and 4.1% in the Ivacaftor group); however, the incidence of SAEs (related or no related) was lower in the ivacaftor group (17.6%) than in the placebo group (34.8%). The majority of these SAEs were directly related to CF disease (clinical pulmonary exacerbation) and they were reported as "cystic fibrotic lung" (10% in the Ivacaftor group and 26% in placebo group). This lower incidence of SAEs observed in the

ivacaftor group could be related to ivacaftor action itself; however, this imbalance in SAEs could also be related to the baseline characteristic of patients included in these studies that seems not to be quite similar.

Overall, a similar proportion of subjects in the ivacaftor and placebo groups had maximum transaminase levels exceeding a range of thresholds including ≥2 ×, ≥3 ×, ≥5 ×, and ≥8 × ULN. The incidence of elevations of ALT or AST between ≥2 × to <3 × ULN and ≥3 × to <5 × ULN were similar. The incidence of ALT or AST increases was similar between the ivacaftor and placebo group across the different ranges: 6.3% (≥3 × ULN) in the ivacaftor group and 8.4% (≥3 × ULN) in the placebo group; 2.7% (≥5 × ULN) in the ivacaftor group and 2.3% (≥5 × ULN) in the placebo group; 1.8% (≥8 × ULN) in the ivacaftor group and 1.5% (≥8 × ULN) in the placebo group. The population with hepatic impairment was not included in main pivotal studies therefore no safety analysis on this population was conducted. The proportion of patients with "history" of liver enzyme elevation was similar in both groups (around 15%). In this subgroup of patients, a higher proportion of subjects in the Ivacaftor group had maximum on-treatment ALT or AST elevation compared to those in the placebo group. The effect of Ivacaftor on liver toxicity and /or hepatic enzyme elevation is unclear at this time; therefore, hepatotoxicity and hepatic enzyme elevation are to be monitored until this issue has been clarified. This has been accordingly included as important potential risk in the Risk Management Plan.

In the light of high unmet medical need in all CF patients, including patients with other mutations in the CFTR gene and younger children, a significant risk of off-label use can be expected. This potential risk has been included in the Risk Management Plan.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

Assessment of paediatric data on clinical safety

In general the safety profile in paediatric population is not expected to significantly differ from adult population, however, safety database in the age group from 6 to 11 years of age is very limited and safety profile in this population are addressed with additional pharmacovigilance activities in the RMP.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.6.2. Conclusions on the clinical safety

The treatment with ivacaftor appears to be well tolerated. Few subjects have discontinued treatment due to adverse events. The majority of adverse events associated with ivacaftor were mild to moderate in severity. There were no deaths in any ivacaftor studies. The number of subjects in some important subgroups of the target population (e.g. population from 6 to 11 years-old) is very limited, therefore safety in these subgroups is addressed with additional pharmacovigilance activities.

The most common adverse events in the ivacaftor group were cough, CF lung (pulmonary exacerbation), headache, dizziness, URTI, nasal congestion, oropharyngeal pain, nausea, and rash. More patients in ivacaftor reported bacteria isolated in sputum. The mechanism of nervous system disorders is not known. Ear and labyrinths disorder and breast disorders have been observed with ivacaftor.

The adverse events that are believed to have at least plausible causal relationship with the use of ivacaftor (adverse reactions) have been reflected in the SmPC. The most common adverse reactions are nasopharyngitis, upper respiratory tract infection, headache, nasal congestion, oropharyngeal pain, abdominal pain, diarrhoea and rash.

The CHMP considers the following measures necessary to address issues related to safety:

- The applicant should conduct a 5-year long-term observational study with ivacaftor in patients with cystic fibrosis, including also microbiological and clinical endpoints (e.g. exacerbations), according to a protocol agreed with the CHMP.
- The applicant should submit the final clinical study report of the ongoing study VX08-770-105 which evaluates the long-term safety and efficacy in patients with cystic fibrosis.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The applicant submitted a risk management plan, which included a risk minimisation

Table 22 Summary of the risk management plan

Safety issue	Agreed pharmacovigilance activities	Agreed risk minimisation activities
Important identified risks – none		
Important potential risks		
Effects on liver function tests	Ongoing surveillance through routine pharmacovigilance practices Study 105 - An Open-Label, Rollover Study to Evaluate the Long-Term Safety and Efficacy of VX-770 in Subjects With Cystic Fibrosis 2-Year Follow-up of subjects who prematurely discontinued from studies 102 (A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of VX-770 in Subjects with Cystic Fibrosis and the G551D Mutation), 103 (A Phase 3, 2-Part, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Pharmacokinetics, Efficacy and Safety of VX-770 in Subjects Aged 6 to 11 Years with Cystic Fibrosis and the G551D Mutation) and 104 (A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Safety and Efficacy of VX-770 in Subjects Aged 12 Years and Older with Cystic Fibrosis who are Homozygous for the F508del-CFTR Mutation)	The proposed SmPC (Section 4.4) includes transaminase monitoring and management. The proposed SmPC (Section 4.8) describes the elevated transaminase incidence and discontinuation rate in clinical studies.

Cataract	Ongoing surveillance through routine pharmacovigilance practices Full ophthalmologic examination added to subjects in Study 105 who initiated ivacaftor between 6 to 11 years of age Review of final data from rat juvenile toxicity study (Study VX-770-TX-025), including histopathology results Retrieval and histological examination of the head sections of the foetuses from the rat embryo-foetal study	Human relevance of this finding is under investigation. The initial assessment does not suggest an increased risk in children 6 years and older. Therefore, it is considered that it is unnecessary to recommend any meaningful post-authorisation risk minimisation activities.
Concomitant use of ivacaftor with potent CYP3A inhibitors or inducers	Ongoing surveillance through routine pharmacovigilance practices Study 105 2-Year Follow-up of subjects who prematurely discontinued from Studies 102, 103, and 104. Dose optimization exploration activity	Information in the proposed SmPC (Section 4.2) (Posology) The proposed SmPC (Section 4.4) Special warnings. The proposed SmPC (Section 4.5) describes the interactions.
Cardiac arrhythmias	Ongoing surveillance through routine pharmacovigilance practices Study 105 2-Year Follow-up of subjects who prematurely discontinued from Studies 102, 103, and 104.	The proposed activities are based on this being a theoretical risk from non-clinical findings. It has not been confirmed in humans. Statement in the proposed SmPC, Section 5.3 (Preclinical safety data)
Off label use in children less than 6 years old of age and in patients with other mutations (non-G551D CFTR gating mutations and non-class III mutations)	Ongoing surveillance through routine pharmacovigilance practices Long-term safety study: An Observational Study to Evaluate the Long-Term Safety of Ivacaftor in Patients With Cystic Fibrosis Study 110 Study 111	The proposed SmPC includes information in: Therapeutic indications (section 4.1) Posology and method of administration (section 4.2) Special warnings and precautions for Use (Section 4.4)
Important missing information		
Use in Pregnant and Lactating Women	Ongoing surveillance through routine pharmacovigilance practices Long-term Safety Study	The proposed SmPC, Section 4.6 describes the available information about safety in pregnant and lactating women.
Pulmonary exacerbations, and bacterial sputum colonization with long term ivacaftor treatment	Ongoing surveillance through routine pharmacovigilance practices Study 105 2-Year Follow-up of subjects who prematurely discontinued from Studies 102, 103, and 104. Long-term safety study	The proposed SmPC, Section 4.8, provides information regarding bacterial sputum colonization as adverse drug reaction.
Use in children between 6 to 11 years	Ongoing surveillance through routine pharmacovigilance practices	The proposed SmPC, Section 4.8 acknowledges the limited

old	Study 105 Study 110 Study 111 Study 112 (includes 2-yr follow-up of patients from study 110) 2-Year Follow-up of subjects who prematurely discontinued from study 103. Long-term safety study PK analysis to develop possible alternative dosing regimen to avoid higher exposure relative to older children and adults	knowledge about the safety profile of Kalydeco in children between 6 to 11 years old. The proposed SmPC, Section 5.2 includes detailed information on pharmacokinetics in the paediatric population.
Patients with FEV1 <40 %	Ongoing surveillance through routine pharmacovigilance practices Study 105 2-Year Follow-up of subjects who prematurely discontinued from Studies 102, 103, and 104. Long-term safety study	The proposed statement in SmPC, Section 4.4
Safety in patients with cardiac diseases	Ongoing surveillance through routine pharmacovigilance practices Long-term safety study	The proposed activities are based on theoretical risk from non-clinical findings. It has not been confirmed in humans. The statement in proposed SmPC, Section 5.3 (Preclinical safety data).
Long-term safety	Ongoing surveillance through routine pharmacovigilance practices Study 105 2-Year Follow-up of subjects who prematurely discontinued from Studies 102, 103, and 104. Long-term safety study Study 109 Study 112	The proposed warning in SmPC, Section 4.4. The proposed SmPC Section 5.1 describes the available clinical evidence, including the number and extent of exposure in clinical studies.
Clinical relevance of P-gp inhibition by ivacaftor	Ongoing surveillance through routine pharmacovigilance practices Digoxin DDI Study - An Open-Label Phase 1 Study in Healthy Adult Subjects to Examine the Effects of Ivacaftor (VX-770) on the Pharmacokinetics of Digoxin	The interaction is described in the SmPC Section 4.5.
Patients with moderate or severe hepatic impairment	Ongoing surveillance through routine pharmacovigilance practices Long-term safety study Dose optimization exploration activity	In the proposed SmPC Sections 4.2 and 4.4, description of posology and method of administration and precautions for use in these patients has been included, respectively. The proposed SmPC Section 5.2

		includes more details about the results available from clinical development programme

The CHMP, having considered the data submitted, was of the opinion that the below listed pharmacovigilance activities in addition to the use of routine pharmacovigilance are needed to investigate further some of the safety concerns:

Description	Due date
The applicant should conduct a 5-year long-term observational study with ivacaftor in patients with cystic fibrosis, including also microbiological and clinical endpoints (e.g. exacerbations), according to a protocol agreed with the CHMP. The applicant should submit yearly interim analyses and the final CSR	Interim reports: yearly Final CSR: December 2017
The applicant should submit the final clinical study report of the ongoing study VX08-770-105 which evaluates the long-term safety and efficacy in patients with cystic fibrosis. The applicant should also submit yearly interim reports within PSURs.	Interim reports: yearly Final CSR: December 2015
The applicant should submit the final clinical study report of the rat juvenile toxicity study (VX-770-TX-025), including histopathology results.	June 2012
The applicant should attempt to retrieve the head sections of the foetuses retained in alcohol from the rat embryo-foetal study and perform histological examination of the eyes and provide results	December 2012
The applicant should submit final CSR of a phase I study in healthy volunteers to examine the effects of ivacaftor on the pharmacokinetics of digoxin	December 2013
The applicant should submit the final clinical study report of Study 111: A Phase 3 Study to Evaluate the Efficacy and Safety of Ivacaftor in Subjects With Cystic Fibrosis Who Have a Non-G551D CFTR Gating Mutation	June 2015
The applicant should submit the final clinical study report of Study VX11-770-110: A Phase 3 Study to Evaluate the Efficacy and Safety of Ivacaftor in Subjects With Cystic Fibrosis who Have the R117H-CFTR Mutation	September 2014
The applicant should submit an analysis of PK data with proposal for potential additional strengths of ivacaftor to be developed for use in modified dosing regimens in 6 – 11 y.o. children with higher exposure to ivacaftor	December 2012
The applicant should submit an analysis of PK data (compartmental and pop PK analysis) including data from any completed study where children from 6 to 11 years old are enrolled (e.g. Study 110, Study 111) on a need to perform a dose finding study in children 6 – 11 y.o. in order to develop possible alternative dosing regimen to avoid higher exposure relative to older children and adults. Any safety data in this age range should be summarised.	September 2014
Following identification of possible alternative dosing regimen options in children aged 6-11 years old, the applicant should apply for registration of presentations of ivacaftor with reduced strengths suitable for modified dosing (according to previously submitted analyses of PK data)	June 2016

No additional risk minimisation activities were required beyond those included in the product information.

2.8. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

Benefits

Beneficial effects

Ivacaftor has shown in early clinical studies an effect clearly distinguishable from placebo in patients with CF and a *G551D-CFTR* mutation in terms of FEV_1, Nasal Potential Differences, sweat chloride and QoL. This has been further confirmed in two pivotal placebo-controlled, 48-week duration trials (studies 102 and 103) where the primary endpoint was the absolute change from baseline in percent predicted FEV_1. A roll-over study (study 105) is currently ongoing and will address the long-term effects of ivacaftor.

In the two pivotal studies treatment with ivacaftor resulted in a clinically significant improvement in FEV_1% through 24 weeks (timing of the primary efficacy variable) and 48 weeks that was around 10% in patients with CF aged 6 years and older with a G551D mutation in at least one allele of the CFTR gene and with FEV_1% predicted at baseline higher than 40%. FEV_1 is the recommended primary clinical endpoint in efficacy studies for cystic fibrosis targeting lung function as the rate of decline in FEV_1 has been demonstrated to correlate with survival and to be the strongest clinical predictor of mortality. Therefore, it is considered that the magnitude of the effect is notable and relevant from the clinical point of view in a population where a rate of decline in FEV_1% of around 1% per year is expected even when patients are being treated with the standard of care.

Ivacaftor has also shown to have an impact on clinical endpoints that are of particular interest in CF such as pulmonary exacerbations and related events (hospitalization etc). Pulmonary exacerbations are a major cause of morbidity and decreased quality of life for patients with CF. Recurrent pulmonary exacerbations are associated with long-term decline in lung function and shortened survival. That is why exacerbation prevention is an important goal of CF therapy. Ivacaftor treatment resulted in a significant reduction in the rate of pulmonary exacerbations in the pivotal studies. The mean duration of exacerbations was also shorter in patients treated with ivacaftor.

A statistically significant change in weight (around 2 kg) was observed in both trials. It is known that poor weight gain predicts clinical lung disease and progressive lung disease leads to poor weight gain. Moreover, a good nutritional status is associated with better FEV_1 and survival. Analysis of weight-for-age z scores in patients aged 20 years and younger confirms that weight gain occurred in ivacaftor-treated patients and to a lesser extent in placebo-treated patients after 24 and 48 weeks of treatment in the pivotal studies.

Efficacy results were consistent within studies and between both studies. Results of sensitivity analyses for the primary endpoint provided are consistently robust, supporting the results of the primary analysis.

Results from the second interim analysis of study 105 show that although the magnitude of the treatment effect in FEV_1% is slightly decreased in comparison to that seen at week 24 or 48 in the original studies, it is still clinically relevant.

Uncertainty in the knowledge about the beneficial effects

The positive effect of ivacaftor has only been shown in patients with a *G551D* mutation in at least one allele of the *CFTR* gene. Given that clinical data are not available in patients with any gating mutation other than G551D, while in patients homozygous for the (class II) *F508del* mutation treatment with ivacaftor did not result in a clinical relevant improvement the indication has been restricted to patients with a *G551D* mutation.

In addition, only patients with mild to moderate stages of the disease (with baseline FEV_1% between 40 and 105%) were included in these trials. Limited data in patients with baseline FEV_1% predicted <40% is available suggesting that patients may also benefit from treatment with ivacaftor. On the contrary, subgroup analysis by baseline FEV_1% >90% in study 103 suggest that the benefit of patients with more preserved lung function could be less pronounced. However, the available data are not conclusive due to the low number of patients analysed.

The finding in study 105 regarding the incidence of pulmonary exacerbations in patients treated with ivacaftor in the pivotal studies, an increase of bacteria isolated in sputum and an increased reporting of URTI in ivacaftor-treated patients are noted. Adequate pharmacovigilance measures have been identified in the Risk Management Plan. Furthermore, the long-term data from study 105 as well as the data from the 5-year observational study will be addressing this point.

Body weight gain can be interpreted as an indirect measure of improved exocrine pancreatic function. However, whether the weight gain seen with ivacaftor can be exclusively attributed to an increase in lean body mass remains unknown. Analyses of absolute change in height, height-for-age Z score and other anthropometric parameters in patients less than 20 years of age have not shown statistically significant differences between ivacaftor and placebo. Therefore, based on the available data no conclusion can be drawn whether ivacaftor improves the pancreatic exocrine function (without a direct assessment such as improved bile salt absorption).

Given the chronic nature of CF it is crucial to know whether the effect of ivacaftor is maintained over time. Available interim data from the ongoing study 105 suggest that the effect of ivacaftor on relevant endpoints remains stable at least up to 60 weeks. Results of a pre-planned second interim analysis of study 105 has been presented showing that at week 96 (ivacaftor-treated patients from study 102) and at week 72 (ivacaftor-treated patients from study 103) the effect in several endpoints is maintained although slightly decreased when compared with those attained in the initial 48 weeks of treatment. In particular, the incidence and duration of pulmonary exacerbations are higher in patients treated with ivacaftor during 96 weeks. In spite of this, the results provided of study 105 (with the single exception of pulmonary exacerbations) suggest that ivacaftor is of clinical benefit. Longer term follow-up is necessary and adequate measures have been identified with the long-term data from study 105 as well as the data from the 5-year observational study.

Risks

Unfavourable effects

Ivacaftor seems to be well tolerated. Cough, Cystic fibrosis lung (pulmonary exacerbation), nervous system disorders (as headache and dizziness), URTI, nasal congestion, oropharyngeal pain, and rash were the adverse events more commonly observed. Additionally, ear and labyrinth disorders (including otitis) and breast disorders were observed more frequent in Ivacaftor group than in placebo group. More patients in ivacaftor group reported bacteria isolated in sputum.

In the pivotal studies, four patients (1.8%) subjects in the ivacaftor group discontinued for AEs (1 subject for arthritis; 1 for myopathy; 1 for asthenia, fatigue, and headache; and 1 for hepatic enzyme

increased). The incidence of drug interruption was (8.5%) the majority of them ere due to CF lung (2.7%), hepatic enzyme increased (2%) and abdominal pain (0.7%).

In the light of high unmet medical need in CF patients outside the recommended indication for ivacaftor, it is expected that there could be a significant risk of off-label use in other mutations in the CFTR gene and possibly also younger age groups. This risk has been included in the Risk Management Plan.

Uncertainty in the knowledge about the unfavourable effects

There is no experience of use of ivacaftor in patients with severe hepatic impairment. In this case a careful individualised approach is recommended and ivacaftor should be administered only in those patients in whom their clinical circumstances allow to predict that the benefits will likely out-weight the risks. In that case a dosing of 150 mg of ivacaftor every other day is recommended, as stated in the SmPC.

Ivacaftor has a high potential for drug interaction when concomitantly administered with drugs inhibiting CYP3A. Strong inhibitors have shown to increase drug exposure by 8 times. PK simulations indicate that longer dose intervals (e.g. twice a week) may yield in comparable exposure to that observed with the standard daily administration in subjects not receiving concomitant inhibitors. This proposal is accepted, provided that these patients are closely monitored for efficacy and safety; the SmPC provides adequate guidance.

There are uncertainties associated to the long-term use of ivacaftor, especially in 6 to 11 years old children on whom there is limited data. Safety aspects of long-term use of ivacaftor in this and in general target population have to be further investigated. Adequate measures have been described in the Risk Management Plan.

Patients with moderate and severe renal impairment have not been studied. Nevertheless, this is not considered as important missing information given that the renal route of elimination is negligible for ivacaftor, with minimal excretion of ivacaftor and metabolites.

Patient with moderate and severe hepatic impairment have not been included in phase 2b/3 pooling studies. Cases of hepatotoxicity were observed in pre-clinical phase. Several cases of liver enzyme elevation have been reported with slightly higher incidence in the ivacaftor group, mainly in patients with history elevated liver enzyme. Also, there is no experience in patients with cardiovascular disease and in those undergoing organ transplantation. Monitoring liver function tests is recommended in the SmPC while use in patients with moderate or severe hepatic impairment is regarded as important missing information and has been addressed in the RMP.

Non-compartmental and compartmental analysis of PK data shows that systemic exposure in children is higher than in adults. In the light of the convincing efficacy data and the available safety data in this patient group, which is overall reassuring, the currently proposed dosing regime is deemed adequate. Nevertheless, a refinement of the dosing regimen in this patient population should be further explored, as identified in the Risk Management Plan.

Quality aspects

Considering that the design space for the active substance has been verified at commercial scale only within the normal operating ranges (NORs) and in the absence of an adequate verification protocol it is uncertain whether the currently approved control strategy is adequate to detect changes to the quality of the active substance resulting from operating outside the well-verified NORs. Although expected to

be low risk based on the available development data, it is also uncertain what the impact might be on the quality of the active substance and thus the safe and effective use of the product. This verification would ensure that the extension of the manufacturing of the active substance in operating settings broader than the NORs has no negative impact on the quality of the active substance.

In order to extend the manufacturing of the active substance in operating settings broader than the NORs, to cover all areas of the design space, the applicant should submit a verification protocol, as defined in Annex II of the Marketing Authorisation.

Benefit-risk balance

Importance of favourable and unfavourable effects

Cystic fibrosis (CF) lung disease is the primary cause of morbidity and mortality in CF. In the lungs, the dysfunctional CFTR protein leads to obstruction of airways with thick mucus, establishment of chronic bacterial infection in the airways, and damaging inflammatory responses that are all thought to play a role in causing irreversible structural changes. Patients with CF typically experience a progressive loss of lung function ultimately resulting in respiratory failure and death.

Ivacaftor has shown to have a clinically relevant effect on pulmonary function (measured as the absolute change from baseline in percent predicted FEV_1 through 24 weeks of treatment) in CF patients aged 6 years and older with a *G551D-CFTR* mutation. Consistent effects have also been observed in a relevant clinical variable such as pulmonary exacerbations and related events. Analysis of body weight change and weight-for-age z scores (the latter only in patients aged 20 years and younger) shows that ivacaftor-treated patients experienced higher body weight gain than placebo patients although it remains unknown if this is due to an increase of lean body mass. Results from study 105 confirm that (absolute) weight gain occurred in ivacaftor-treated patients and to a lesser extent in placebo-treated patients after 24 and 48 weeks of treatment in the pivotal studies. However, some uncertainties mainly related to the novel mode of action and the limited data on the long-term use of ivacaftor remain. Very limited data are available for patients with advanced stages of the disease (baseline FEV_1<40%) suggest that these patients may also benefit from treatment with ivacaftor. Information on the impact of ivacaftor on infections by *P. aeruginosa* is limited.

Ivacaftor seems to be well tolerated. The main uncertainties are related to the long-term use of ivacaftor mainly in children from 6 to 11 years old for which there is limited data. Overall, the safety database is limited which is not unexpected due to prevalence of the mutation considered. Several cases of liver enzyme elevation have been reported with slightly higher incidence in the ivacaftor group, mainly in patients with previous history of increased liver enzymes. Upper Respiratory Tract Infections (URTI), nervous system disorders as headache and dizziness), otitis, rash and breast AEs were numerically more frequent among ivacaftor-treated patients than in placebo.

Benefit-risk balance

The benefit risk balance of ivacaftor in the treatment of cystic fibrosis in patients age 6 years and older who have a G551D mutation in the CFTR gene is positive.

Discussion on the benefit-risk balance

Ivacaftor has convincingly shown clinically relevant efficacy in patients with CF and a G551D mutation in at least one allele of CFTR gene from age of 6 years onwards. The safety profile is acceptable. Also considering the high unmet medical need in this population, the benefits of ivacaftor clearly outweighs their risks.

The number of subjects studied in clinical trials reflects the target population being a subpopulation of an orphan condition, and had not prevented from reaching statistically significant results in clinical trials. The design and duration of studies is in line with regulatory requirements. Limited information is available on long-term safety and efficacy hence further data should be obtained on the safety and efficacy of ivacaftor in long term use. Adequate requirements have been identified including data from an ongoing long-term follow-up study as well as the initiation of a 5-year observational registry.

The benefits of use of ivacaftor in target population are clearly established and do outweigh the identified risks, therefore the benefit-risk balance is positive.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Kalydeco (ivacaftor) is not similar to Bronchitol (mannitol) within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. See appendix 1.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus decision that the risk-benefit balance of Kalydeco in the treatment of cystic fibrosis in patients age 6 years and older who have a G551D mutation in the CFTR gene is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the Marketing Authorisation

Risk Management System

The MAH must ensure that the system of pharmacovigilance, presented in Module 1.8.1 of the marketing authorisation, is in place and functioning before and whilst the product is on the market.

The MAH shall perform the pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in the RMP presented in Module 1.8.2 of the Marketing Authorisation and any subsequent updates of the RMP agreed by the Committee for Medicinal Products for Human Use (CHMP).

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted:

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- at the request of the EMA

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Not applicable.

Obligation to complete post-authorisation measures

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

Description	Due date
The applicant should conduct a 5-year long-term observational study with ivacaftor in patients with cystic fibrosis, including also microbiological and clinical endpoints (e.g. exacerbations), according to a protocol agreed with the CHMP. The applicant should submit yearly interim analyses and the final CSR by December 2017	December 2017
The applicant should submit the final clinical study report of the ongoing study VX08-770-105 which evaluates the long-term safety and efficacy in patients with cystic fibrosis by December 2015. The applicant should also submit yearly interim reports within PSURs.	December 2015
The applicant should submit the verification protocol for scale-up of the Design Space in case of any changes to the Normal Operating Ranges (NORs) in the manufacture of the active substance. The Applicant can only move into unverified areas of the approved design space after setting up an appropriate verification scheme, submitted as a variation to the marketing authorisation.	December 2012

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

New Active Substance Status

Based on the CHMP review of data on the quality, non-clinical and clinical properties of the active substance, the CHMP considers that ivacaftor is qualified as a new active substance.

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0039/2012 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.