24 September 2015
EMA/733450/2015 Corr.1[1]
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Kalydeco

International non-proprietary name: ivacaftor

Procedure No. EMEA/H/C/002494/X/0034/G

Note

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

[1] Subject and site IDs redacted

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Table of contents

1. Background information on the procedure

1.1. Submission of the dossier

The Marketing Authorisation Holder, Vertex Pharmaceuticals (Europe) Ltd., ("MAH") submitted to the European Medicines Agency (EMA) on 10 October 2014 an application for a grouping of variations in accordance with Article 7(2) of Regulation (EC) No 1234/2008 consisting of an extension of the marketing authorisation and a Type II C.I.4. variation for Kalydeco.

The MAH applied for an extension of the marketing authorisation consisting in the addition of a new pharmaceutical form with two strengths (50 mg and 75 mg) to support an extension of the target population covered by the authorised therapeutic indication of Kalydeco to treat cystic fibrosis (CF) patients aged 2 to less than 6 years old, grouped with a variation to align the Summary of Product Characteristics and Patient Information leaflet currently approved for Kalydeco 150 mg with the new submitted data.

The MAH applied for the following indication for 50 mg and 75 mg granules in sachet:

- *Kalydeco granules are indicated for the treatment of children with cystic fibrosis (CF) aged 2 years and older and weighing less than 25 kg who have one of the following gating (class III) mutations in the CFTR gene: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, or S549R (see sections 4.4 and 5.1)*.

For the approved 150 mg film-coated tablets, the applicant requested the following variation:

- Update of sections 4.2, 4.4, 4.5, 4.8 and 5.2 of the Summary of Product Characteristics to provide clarity and relevant updates in line with the proposed extension application. The requested variation proposed consequential amendments to the Package Leaflet.

Kalydeco, was designated as an orphan medicinal product EU/3/08/556 on 8 July 2008 for the following therapeutic indication: Treatment of cystic fibrosis.

The legal basis for this application refers to:

Article 19 of Commission Regulation (EC) No 1234/2008 and Annex I (point 2 c and d) thereof – Extension of marketing authorisation

Article 10 of Commission Regulation (EC) No 1234/2008 – "Prior Approval" procedure for major variation of type II

Article 7(2) of Commission Regulation (EC) No 1234/2008 - Grouping of variations

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on MAH's own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0060/2014 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0060/2014 was not yet completed 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(3) of Commission Regulation (EC) No 847/2000, the MAH did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

MAH's request(s) for consideration

Additional Data/Market exclusivity

The MAH requested consideration of one year data/market exclusivity in regards of its application for a new indication in accordance with Article 14(11) of Regulation (EC) No 726/2004, read in conjunction with Commission "*Guidance on elements required to support the significant benefit in comparison with existing therapies of a new therapeutic indication in order to benefit from an extended (11 years) marketing protection period*".

Scientific Advice

The MAH received Scientific Advice from the CHMP on 20 October 2011. Scientific Advice pertained to clinical aspects of the dossier.

Licensing status

A new application was filed in the following countries: 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: Concepcion Prieto Yerro Co-Rapporteur: Melinda Sobor

- The application was received by the EMA on 10 October 2014.
- The procedure started on 29 October 2014.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 23 January 2015. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 16 January 2015.
- PRAC RMP Advice and assessment overview as endorsed by PRAC on 12 February 2015
- During the meeting on 26 February 2015, the CHMP agreed on the consolidated List of Questions to be sent to the MAH. The final consolidated List of Questions was sent to the MAH on 2 March 2015.
- The MAH submitted the responses to the CHMP consolidated List of Questions on 19 March 2015.
- The following GMP inspection was requested by the CHMP and its outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product:

– A GMP inspection at a finished product manufacturing site in the United States of America between 23rd February 2015 and 27th of February 2015

- The Rapporteurs circulated the Joint Assessment Report on the MAH's responses to the List of Questions to all CHMP members on 30 April 2015.

- The Rapporteurs circulated the updated Joint Assessment Report on the MAH's responses to the List of Questions to all CHMP members on 5 May 2015.
- PRAC Rapporteur's Risk Management Plan (RMP) Assessment Report as endorsed by PRAC on 7 May 2015
- During the CHMP meeting on 21 May 2015, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the MAH.
- The MAH submitted the responses to the CHMP List of Outstanding Issues on 22 June 2015.
- PRAC Rapporteur's Risk Management Plan (RMP) Assessment Report as endorsed by PRAC on 9 July 2015
- The Rapporteurs circulated the updated Joint Assessment Report on the MAH's responses to the List of Questions to all CHMP members on 15 July 2015
- During the CHMP meeting on 23 July 2015, the CHMP agreed on a 2nd list of outstanding issues to be addressed in writing and/or in an oral explanation by the MAH.
- The MAH submitted the responses to the CHMP List of Outstanding Issues on 24 August 2015.
- PRAC Rapporteur's Risk Management Plan (RMP) Assessment Report as endorsed by PRAC on 10 September 2015
- The Rapporteurs circulated the updated Joint Assessment Report on the MAH's responses to the List of Questions to all CHMP members on 11 September 2015
- During the meeting on 24 September 2015, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for the group of variations.
- The CHMP adopted a report on similarity of Kalydeco with Bronchitol on 24 September 2015
- Furthermore, on 24 September 2015, the CHMP adopted a report on the significant clinical benefit brought by the extension of the target population covered by the approved therapeutic indication for Kalydeco in comparison with existing therapies

2. Scientific discussion

2.1. Introduction

Cystic fibrosis (CF) is an autosomal recessive disease with serious, chronically debilitating morbidities and high premature mortality and at present, there is no cure. CF affects approximately 70,000 individuals worldwide. The incidence and prevalence of CF varies between racial groups. Based on the size of the population, CF qualifies as an orphan disease.

CF is caused by mutations in the *CFTR* gene that result in absent or deficient function of the *CFTR* protein at the cell surface. The *CFTR* protein is an epithelial chloride channel responsible for aiding in the regulation of salt and water absorption and secretion, and is located in the apical membrane of epithelial cells in multiple organs, including lungs, pancreas, intestinal tract, biliary tract, sweat glands, and vas deferens. The failure to regulate chloride transport in these organs results in the multisystem pathology associated with CF. In the lungs, the dysfunction in the *CFTR* protein leads to obstruction of airways with thick mucus, establishment of chronic bacterial infection, 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 premature death. The diagnosis of CF is suggested by the presence of one or more characteristic clinical features, a history of CF in a sibling, or a positive newborn screening test result, and is confirmed by laboratory evidence of abnormal *CFTR* protein function or by genotyping analysis (Farrell PM et al, 2008). In children with CF, pancreatic insufficiency (O'Sullivan BP et al, 2013) and poor nutritional status (Farrell PM et al, 2001) are the most significant clinical manifestations of the disease. Malnourishment is associated with worsening lung function and is also an independent predictor of mortality (Sharma R et al, 2001). Presence of lung disease (Ramsey KA, Ranganathan S, 2014) and liver disease (Leeuwen L et al, 2014) has also been shown. Structural lung damage is common very early in disease progression (Mott LS et al, 2012); e.g. bronchiectasis, air-trapping. Airway infection in the CF lung also varies with age. The majority of children less than 6 years old are colonized with *Staphylococcus aureus* or *Haemophilus influenza*e, and approximately 40% of them colonized with *P aeruginosa*. Approximately 29% of infants with *P aeruginosa* infection develop nonmucoid infection in the first 6 months of life (Li Z et al, 2005).

Traditional pulmonary function tests, such as spirometry parameters, are not sufficiently sensitive to detect early manifestations of lung disease and for assessing drug effects in young children with CF. In addition, change in percent predict FEV1, recommended primary endpoint, is not feasible in children from birth through 5 years of age because FEV1 involves spirometry, which can only be performed in children 6 years of age and older. Two methods to evaluate pulmonary function in children 0 (birth) through 5 years of age have been developed: infant pulmonary functioning tests (iPFTs) (for use in children less than 2 years of age) and preschool PFTs (for use in children 3 through 5 years of age).

The MAH stated that early therapeutic intervention is beneficial to young children with CF and that improved measures of growth, nutrition, and lung disease through early intervention in diagnosed newborns have been demonstrated. As a consequence, introduction of treatments that are aimed at correcting the function of the defective *CFTR* protein at a young age might postpone or even prevent the onset of clinical manifestation of CF. While there seems to be clear evidence that earlier intervention improves growth and nutritional status, data seem to be scant regarding lung disease although the introduction of more sensitive methods to detect early manifestations of lung disease in young children with CF may further clarify this issue in the future.

Kalydeco (ivacaftor) may be expected to be effective in patients with virtually no irreversibly fixed lung abnormalities by correcting the function of the defective *CFTR* protein in cystic fibrosis airways. Ivacaftor is a potentiator of the *CFTR* protein, i.e. in vitro, ivacaftor increased the channel activity of G551D-*CFTR* protein and some other non-G551D *CFTR* proteins with gating defects expressed in recombinant cell and primary human bronchial epithelial cell cultures. The in vitro responses seen in single channel patch clamp experiments using membrane patches from rodent cells expressing mutant *CFTR* forms do not necessarily correspond to in vivo pharmacodynamic response or clinical benefit. The exact mechanism leading ivacaftor to potentiate the gating activity of normal and some mutant *CFTR* forms in this system has not been completely elucidated.

In the EU, Kalydeco is currently authorised for the treatment of CF in patients age 6 years and older who have one of the following mutations in the *CFTR* gene: *G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N,* or *S549R*. Kalydeco was granted a centralised marketing authorisation by the European Commission on 23 July 2013.

The current application for grouping of variations refers to a change to existing marketing authorisation leading to an extension to the Kalydeco Marketing Authorisation to include a new pharmaceutical form covering 2 strengths (50 mg and 75 mg unit doses) to support an extension of the target population covered by the currently authorised therapeutic indication to enable administration of Kalydeco to patients aged 2 to less than 6 years of age and weighing less than 25 kg who have one of the following gating (class III) mutations in the *CFTR* gene: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, or S549R.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as granules in sachet containing 50 mg and 75 mg of ivacaftor as active substance. This new pharmaceutical form is being introduced to enable administration of Kalydeco to patients aged 2 to less than 6 years old.

Other ingredients are: colloidal silicon dioxide, croscarmellose sodium, hypromellose acetate succinate, lactose monohydrate, magnesium stearate, mannitol, sucralose, sodium lauryl sulfate.

The product is packaged in a biaxially oriented polyethylene terephthalate/polyethylene/foil/polyethylene (BOPET/PE/Foil/PE) sachet.

2.2.2. Active Substance

The active substance and its spray-dried dispersion (SDD) used in ivacaftor 50 mg and 75 mg granules, are identical to those used in the already approved Kalydeco 150 mg tablets. Therefore, no information on the active substance and the SDD has been submitted within this line extension.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

The quality target product profile (QTPP) was to obtain a bioavailable, safe and efficacious, palatable, immediate release formulation for oral administration of ivacaftor to children aged 2 to less than 6 years old, which could be mixed with food, and with a 24-month shelf life at room temperature.

Ivacaftor has low aqueous solubility. A granule dosage form was pursued for ease of administration. Palatability of the product was assessed through human sensory studies and confirmed in the pivotal study.

All excipients used in ivacaftor granules are also used in Kalydeco 150 mg tablet with exception of mannitol and sucralose. Physical and chemical compatibility studies of ivacaftor SDD with mannitol and sucralose were conducted and confirmed the compatibility of the active substance with these excipients.

Briefly, the excipients in ivacaftor granules are HPMCAS (stabilizer), SLS (wetting agent), lactose monohydrate (filler), mannitol (filler), sucralose (sweetener), croscarmellose sodium (disintegrant), colloidal silicon dioxide (glidant) and magnesium stearate (lubricant). All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards.

As in the original MAA dossier for Kalydeco 150 mg tablets, product and manufacturing process development were conducted under a Quality by Design (QbD) paradigm.

The CQAs for the ivacaftor granules are: appearance, identification, assay, physical form, degradation products, water content, dissolution, content uniformity and microbial attributes.

Once the granule critical quality attributes (CQAs) were identified, an initial risk assessment was performed on the granules to determine which materials and process steps could potentially impact the CQAs. This risk assessment together with prior knowledge was used to design multivariate experiments to evaluate main effects and interactions. Data from these studies were used to determine criticality and establish the design spaces for blending and compression that ensure all CQAs are within acceptable limits. The control strategy includes control of input material attributes, critical process parameters, in-process controls, and product specifications.

The formulation used during clinical studies is the same as the one used for marketing. A bioequivalence study was performed showing bioequivalence between the clinical formulation and the proposed commercial formulations.

An in-vitro dissolution method was developed for testing ivacaftor granules. The discriminatory power of the dissolution method has been demonstrated.

The primary packaging is a biaxially oriented Polyethylene Terephthalate/Polyethylene/Foil/Polyethylene (BOPET/PE/Foil/PE) sachet. The material complies with Ph.Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of four main steps: preparation of ivacaftor spray-dried dispersion (SDD) -which comprise mixture preparation, spray drying and secondary drying-, blending, compression, and filling.

The 50 mg and 75 mg strengths are prepared from the same bulk granule batches, the only difference is the fill amount per sachet .

The manufacture of a SDD is a non-standard method of manufacture. Since this step of the manufacturing process is common to the approved Kalydeco 150 mg tablets, the MAH had extensive experience and provided validation data at commercial scale.

Design spaces have been proposed for the following steps of the manufacturing process of the medicinal product: spray drying, secondary drying, blending and compression. The robustness of the process was verified during validation at commercial scale. The available development data, the proposed control strategy and batch analysis data from commercial scale batches fully support the proposed design spaces.

Major steps of the manufacturing process have been validated by a number of studies. It has been demonstrated that the manufacturing process is capable of producing the finished product of

intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: appearance, identification (IR), assay (HPLC), degradation products (HPLC), uniformity of dosage units (Ph. Eur.), dissolution, physical form (XRPD), water content (Karl Fischer) and microbial limits (Ph. Eur.)

Batch analysis results were provided for two pilot scale batches of 50 mg granules and three pilot scale batches of 75 mg granules confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification. Additional batch analysis data on three pilot scale batches of ivacaftor granules 25 mg and 100 mg strengths used during the stability studies, but not proposed for marketing, were also presented.

The finished product is released on the market based on the above release specifications, through traditional final product release testing.

Stability of the product

The MAH applied a bracketing design for the stability testing of the drug product.

Stability data on three pilot scale batches of ivacaftor granules 25 mg and 100 mg stored under long term conditions for twelve months at 25 ºC / 60% RH and for up to six months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were provided. These strengths are not proposed for marketing, but since the different strengths (25, 50, 75 and 100 mg) are only differentiated by the amount of granules filled into the sachet, the stability results from the extremes are considered representative to those from the strengths proposed for marketing. Samples were tested for appearance, water content, assay, degradation products, dissolution and physical form.

Supportive six-month stability data from two pilot scale batches of 50 mg granules and one pilot scale batch of 75 mg granules stored under long term (25 ºC / 60% RH) and accelerated (40 ºC / 75% RH) conditions were also provided. Samples were tested for appearance, water content, assay, degradation products, dissolution, physical form and microbial limits.

The analytical procedures used are stability indicating.

All results met the acceptance criteria for the attributes evaluated at all test points under all storage conditions.

In addition, an in-use stability of ivacaftor granules in food was conducted as part of the stability program. Batches of 25 mg and 100 mg ivacaftor granules were mixed with food (e.g. applesauce, yogurt, puréed vegetable, water) and tested after 1-hour contact time at room temperature. Chemical and physical stability of granules mixed with food was evaluated by testing assay and degradation products, dissolution, and physical form. All results met the acceptance criteria for the attributes evaluated. Therefore, the in-use stability results support the administration of ivacaftor granules in food.

Based on available stability data, a shelf-life of two years and storage below 30 °C stated in the SmPC are acceptable.

Adventitious agents

It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on

Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the 50 mg and 75 mg granules developed to enable administration of ivacaftor to pediatric population has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

The MAH has applied QbD principles in the development of the finished product and their manufacturing process. Design spaces have been proposed for several steps in the manufacture of the finished product. The design spaces have been adequately verified.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendation(s) for future quality development

n/a

2.3. Non-clinical aspects

The pharmacological, pharmacokinetic and toxicological characteristics of ivacaftor have been previously described. Based on the nonclinical safety evaluation, ivacaftor was considered to be safe for chronic use in juvenile and adult patients for the treatment of CF. This line extension does not contain new non-clinical studies. The current submission proposes to expand the approved indications to paediatric patients from 2 to 5 years. The age group from 2 to 11 years defined as children but the relevant CHMP guideline (Guideline On Guideline On The Role Of Pharmacokinetics In The Development Of Medicinal Products In The Paediatric Population, EMEA/CHMP/EWP/147013/2004) emphasizes that the children group is not homogenous and children aged 2-4 years is "probably the least predictable within this group." The MAH justified that absorption/distribution/metabolism/elimination (ADME) processes have no role in fate of ivacaftor in the human body. There is no pharmacokinetic result which would suggest that ADME of ivacaftor would be significantly altered in the 2-6 age group compared to older children or adults.

The lens opacities (cataracts) observed in the previously submitted and evaluated juvenile rat toxicity study (VX-770-TX-025) were considered ivacaftor-related. No cataractogenic potential for ivacaftor was detected in previous chronic toxicity studies using rats as young as 7 weeks old at the start of dosing and dogs as young as 3.75 months old at the start of dosing. In the former peri-postnatal toxicity study in rats, there were no eye opacities in the offspring however it is known that ivacaftor concentration in rat milk exceeds that is in maternal plasma. The cataract observations in very young rats are not likely to be applicable to humans aged 2 through 5 years because human eye development is significantly more advanced prior to birth than in the rat. Thus, this finding is considered to have little relevance to infants and children. No concerns regarding hepatotoxicity were raised in toxicology studies. In a juvenile rat toxicity study (VX-770-TX-025) there was no ivacaftor-related difference in liver weights of males and females in the 10, 25, and 50 mg/kg/day groups at the PND 35 or 63 necropsies; neither did ivacaftor cause macroscopic or

microscopic findings of the liver at the PND 35 and 63 necropsies. There were no ivacaftor-related alterations in serum chemistry parameters. In a 12-months toxicity study in dogs (VX-770-TX-011) beagle dogs no ivacaftor-related adverse effects were observed on body weight, food consumption, hematology, coagulation parameters, or in the ophthalmology, urinalysis or organ weights. There were no ivacaftor-related macroscopic or microscopic findings in the tissues and organs of any dog examined, no differences in liver weights and no macroscopic or microscopic effects on the liver.

Ecotoxicity/environmental risk assessment

In terms of the environmental aspects, the extension of the current indication of Kalydeco results in a larger patient exposure and hence, calculations provided in the original environmental phase I assessment have been revised. The refined Fpen used for PECsurfacewater (PECsw) calculation is the prevalence of non-F508del homozygous CF patients of all ages in the EU, which is calculated using the prevalence data of CF in the EU according to the Orphanet Report Series 2014 and the prevalence data of F508del homozygote CF patients reported in the European CF Society Patient Registry. The refined Fpen is equal to 0.0000693 (= 0.000126 x 0.55). The prevalence data of all CF patients in EU has been taken as the 'worst-case' and this is considered adequate. Regarding the provided prevalence data of F508del homozygote CF patients in EU, the MAH justified using the average value of several member states instead of the highest value reported taking in account the high variability of this value from country to country, and that this average value is subtracted from the overall CF population, which is also an average value and the worst case value. This justification is considered acceptable. The maximum daily dose used for PECsw calculation is equal to the maximum daily dose averaged proportionally over age groups above and below 5 years, which is obtained multiplying the adult daily dose of 300 mg with the sum of fraction of adult daily doses for patients <5 years of age and for all patients >5 years of age. For this calculation, 150 and 300 mg are considered as the maximum daily dose for all patients <5 years of age and for all patients >5 years of age, respectively, as well as the proportion of CF patients <5 years of 12% according to Mehta et al 2010. The sum of fraction of adult daily doses for patients <5 years of age and for all patients >5 years of age is equal to 0.94, and the DOSEai is equal to 282 mg/day. This approximation is considered acceptable. Using WASTEWinhab and DILUTION default values, as well as the maximum daily dose and the refined Fpen values calculated above, the calculated PECsw is equal to 0.00977 µg/L. Since the ivacaftor PECsw is below the action limit of 0.01 µg/L, no phase II environmental fate and effect analysis is required. Therefore ivacaftor is not expected to pose a risk to the environment when used in the extended indication.

The nonclinical profile of ivacaftor was considered to be sufficiently characterised.

2.3.1. Discussion on non-clinical aspects

The pharmacologic, pharmacokinetic and toxicological characteristics of ivacaftor have been previously described. Based on the nonclinical safety evaluation, ivacaftor was considered to be safe for chronic use in juvenile and adult patients. No new non-clinical studies were sudmitted. The rat juvenile toxicity study, in which the cataract findings were determined, was designed and conducted to assess the potential for additional risk of ivacaftor treatment in patients with CF who are <2 years of age. Other than the eye opacity finding, the results did not indicate any specific target organ for toxicity, suggesting that ivacaftor would be well tolerated in patients from 2 through 5 years of age. No concerns regarding other organ toxicities were raised in toxicology studies. The use of ivacaftor in the proposed larger population does not lead to a significant increase of the current environmental exposure and ivacaftor is not expected to pose a risk to the environment.

2.3.2. Conclusion on the non-clinical aspects

Based on the non-clinical discussions provided by the MAH, the CHMP considered the non-clinical profile of ivacaftor sufficiently characterised and no additional measures or investigations are necessary.

2.4. Clinical aspects

2.4.1. Introduction

The clinical development programme was designed to support the proposed to extension of the approved indications in CF patients 6 years of age and older to include paediatric patients 2 through 5 years of age. The proposed formulation for the treatment of 2-5 year olds includes 50-mg and 75-mg strength ivacaftor granules and the proposed doses are 50 mg every 12 hours for patients weighing <14 kg and 75 mg q12h for patients weighing ⩾14 kg to <25 kg . A 2-part, open-label, phase 3 study to evaluate the safety, pharmacokinetics, and pharmacodynamics of ivacaftor in subjects with CF 2-5 year of age who have a *CFTR* mutation that causes a *CFTR* gating defect. The results of this study are the key for this submission.

GCP

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

- Tabular overview of clinical studies

Studies supporting the major milestones in the overall ivacaftor clinical development program are described below.

Clinical Study Milestones in Ivacaftor Clinical Development Program

	Population	Milestone
VX05-770-001	Healthy subjects and subjects with CF	Phase 1 first-in-human study providing safety and PK data
VX06-770-101	Subjects with CF	Phase 2 proof-of-concept and dose-finding study to establish effect of ivacaftor on CFTR channel activity (nasal potential difference and sweat chloride concentration) and on clinical endpoints (FEV_1) in subjects 18 years of age and older with CF and the *G551D* mutation in the *CFTR* gene
VX08-770-102	Subjects with CF	Phase 3 registration study to establish the efficacy and safety of ivacaftor in subjects 12 years of age and older with CF and the *G551D* mutation in the *CFTR* gene
VX08-770-103	Subjects with CF	Phase 3 registration study to establish the efficacy and safety of ivacaftor in subjects 6 to 11 years of age (inclusive) with CF and the *G551D* mutation in the *CFTR* gene
VX08-770-104	Subjects with CF	Phase 2 study to determine the safety and efficacy of ivacaftor in subjects 12 years of age and older with CF and homozygous for the *F508del* mutation in the *CFTR* gene (population representing the majority of patients with CF)
VX08-770-105	Subjects with CF	Phase 3, open-label, rollover study to evaluate the long-term safety and efficacy of ivacaftor in subjects 6 years of age and older with CF and the *G551D* mutation in the *CFTR* gene
VX11-770-108	Subjects with CF	A Phase 3 registration to evaluate the safety, pharmacokinetics, and pharmacodynamics of ivacaftor in subjects with CF 2 through 5 years of age and have a *CFTR* gating mutation
VX11-770-109	Subjects with CF	A Phase 3, 2-arm, roll-over study to evaluate the long-term safety and pharmacodynamics of ivacaftor treatment in pediatric subjects with cystic fibrosis and a *CFTR* gating mutation
VX11-770-110	Subjects with CF	Phase 3 registration study to evaluate the efficacy and safety of ivacaftor in subjects 6 years of age and older with CF and the *R117H* mutation in the *CFTR* gene
VX12-770-111	Subjects with CF	Phase 3 registration study to evaluate the efficacy and safety of ivacaftor in subjects 6 years of age and older with CF and a non-*G551D CFTR* gating mutation
VX12-770-112	Subjects with CF	Phase 3, 2-arm, rollover study to evaluate the safety of long-term ivacaftor treatment in subjects 6 years of age and older with cystic fibrosis and a non-*G551D CFTR* mutation

2.4.2. Pharmacokinetics

Analytical Methods

The analytical validation methods were assessed previously. Narratives on performance characteristics of assay validation, QC are provided as they were necessary to confirm that minor changes in the method did not affect the validity of the method. Sample analysis were performed at two analytical sites in study VX12-770-108, hence, a formal cross-validation was conducted between the DMPK and Covance Laboratories. The results of the cross-validation experiment

showed that data were comparable between the two laboratories and it was, therefore, determined to be acceptable to combine for plasma concentration data generated at two different laboratories. All samples were analysed within the demonstrated long-term stability period. In-study validation was conducted for the individual studies. The reasons for the reanalysis of samples are acceptable for all studies. Incurred Samples Re-assay (ISR) was evaluated by additional analyses on a selection of samples plasma for all analytes. The results demonstrated reproducibility as of the incurred sample repeats met the acceptance criteria (± 20%). The ISR was not performed for study VX12-770-108 Part A, but it was performed in Part B.

Bioavailability studies

Study VX12-770-012 (Study 012)

This study was assessed previously and the results showed that administration of the prototype granule formulation with a high-fat meal resulted in an increase in exposure of ivacaftor with a 3.4-fold increase in AUC0-∞ (90% CI: 2.90, 4.00) and a 3.3-fold increase in Cmax (90% CI: 2.68, 4.09). A comparable food effect was observed for the tablet formulation, which had a 3.0-fold increase in AUC0-∞ (90% CI: 2.56, 3.48) and a 3.9-fold increase in Cmax (90% CI: 3.12, 4.86). In the fed state, the prototype granule formulation had lower exposures than the tablet formulation with AUC0-∞ being 32% lower (GLSMR: 0.685, 90% CI: 0.588, 0.797); and Cmax being 41% lower (GLSMR: 0.588, 90% CI: 0.475, 0.727). In the fasted state, the prototype granule formulation had lower exposures than the tablet formulation with AUC0-∞ being 39% lower (GLSMR: 0.610, 90% CI: 0.518, 0.717) and Cmax being 34% lower (GLSMR: 0.658, 90% CI: 0.528, 0.818).

Study VX12-770-015 (Study 015)

This was a Phase 1, randomized, open-label, 4-sequence, 4-period, cross-over study using a Williams' design (see the table below) with a washout of at least 7 days. This study was designed to investigate the relative BA of 150-mg ivacaftor as granule formulation versus the film-coated ivacaftor tablet formulation in the fed state, the effect of food on the BA of 150-mg ivacaftor as granule formulation, and the dose proportionality of the ivacaftor granule formulation between 50 and 150 mg in the fed state. A total of 20 subjects (all male) were randomized and received at least 1 dose of ivacaftor in the study. Nineteen (95.0%) subjects completed the study and 1 (5.0%) subject discontinued the study for non-AE reasons.

PK parameters, summarized by treatment, are presented in the table below. The ivacaftor PK parameters obtained with T1F were similar to those obtained with RF. The median tmax and mean t1/2 were comparable between T1F and RF.

Parameter	RF (N = 20)	T1 (N = 20)	T1F (N = 20)	T2F (N = 19)
$AUC_{0-\infty}$ (ng•h/mL)	8530 (2520)	3010 (1200) [a]	8150 (2630)	2530 (814)
$AUC_{0-tlast}$ (ng•h/mL)	8310 (2380)	2720 (1160)	7970 (2520)	2440 (778)
C_{max} (ng/mL)	617 (165)	176 (117)	568 (161)	159 (39.0)
$t_{1/2}$ (h)	12.2 (2.91)	19.8 (7.61) [a]	11.9 (2.33)	11.8 (2.41)
t_{max} (h) [b]	5.00 (3.00, 12.00)	3.00 (2.00, 5.00)	6.00 (3.00, 12.0)	5.00 (4.00, 12.0)

$AUC_{0-\infty}$: area under the concentration versus. time curve from the time of dosing extrapolated to infinity; $AUC_{0-tlast}$: AUC from the time of dosing to the time of last measurable concentration; C_{max}: maximum observed concentration; N: number of subjects; SD: Standard deviation; $t_{1/2}$: half-life; t_{max}: time of the maximum concentration.

Notes: RF = reference formulation (150-mg film-coated tablet) administered in the fed state; T1F = 150-mg minitablet dose administered in the fed state; T1 = 150-mg minitablet dose administered in the fasted state; T2F = 50-mg minitablet dose administered in the fed state

[a] n = 19, λ_z and its related parameters such as $AUC_{0-\infty}$ and $t_{1/2}$ values could not be estimated for Subject [redacted] due to insufficient data at the terminal phase.

[b] Median (minimum, maximum) for t_{max}.

The relative BA was only evaluated in the fed condition since the granule formulation should be administered in the fed condition in the clinical setting as a result of the significant food effect observed on the food interaction study (study 012) for both, tablet and prototype granules formulations. In addition, ivacaftor should be taken with fat-containing food, as advised by the SmPC.

Based on these analyses, the granule formulation is considered comparable to the film-coated tablet formulation under fed conditions, although the 90% CI for Cmax is slightly outside of the conventional 90% CI (0.750, 1.12).

As it is expected the granule formulation administered with food significantly increased ivacaftor exposure (AUC: approx. 3-fold and Cmax approx. 3.7-fold) and resulted in longer median tmax and shorter mean t1/2. A comparable food effect was observed for the tablet formulation, which had a 3.0-fold increase in AUC0-∞ and a 3.9-fold increase in Cmax. As the magnitude of food effect for the final granule formulation is similar to that of the 150-mg tablet when administered with a high-fat meal relative to fasted conditions, the proposed dosage and administration directions for Kalydeco granules indicate that they are to be administered with fat-containing food, the same as Kalydeco 150-mg tablets.

For the granule formulation in the fed state the increase in ivacaftor exposure from 50 mg to 150 mg was dose proportional for AUC close to 1 and 90% CI within (0.80, 1.25). Lack of dose-proportionality was observed for Cmax in the dose-normalized relative bioavailability analysis and the power model analysis. However, this deviation is not considered clinically relevant because the mean deviation is only a 15%. The intra-subject variability was obtained from the linear mixed effects model analysis on T1F and T2F. The intra-subject variability obtained from this analysis was 15%, 15%, and 24% for ivacaftor $AUC_{0-\infty}$, $AUC_{0-tlast}$, and C_{max} respectively, when the granule formulation was administered in the fed state. The inter-subject variability was 32% for AUC0-∞.

Population pharmacokinetics modelling

Due to the sparse PK sampling schedule used in study 108, a population PK model that describes ivacaftor disposition was utilized for evaluation of PK in children 2-5 years of age. For the model development data in children 2-5 years old were combined with data from healthy adult volunteers and patients 6 years of age and older with CF. In summary, ivacaftor PK was described by a two-compartment model with zero-order delivery to the absorption compartment and subsequent first-order absorption. The typical estimates (95% CI) of final PK model parameters for the reference covariate effects (70 kg, male, 18 years, white race, and CF patient) were 16.4 (15.5, 17.4) L/hr for apparent (oral) clearance (CL/F), 165 (150, 181) L for apparent (oral) central volume of distribution (Vc/F), 81.7 (59.7, 99.0) L for apparent (oral) peripheral volume of distribution (Vp/F), 12.1 (9.24, 14.2) L/h for apparent (oral) intercompartmental clearance (Q/F), 3.09 (2.94, 3.21) h,

for zero-order dose duration (D1) and 0.483 (0.402, 0.557) h^{-1} for first-order absorption rate (ka). Structural parameters were dependent on body weight. The relationship was described using an allometric model. Ivacaftor CL/F was 39% and 131% of the reference value of 16.4 L/h for the typical 20 kg and 100 kg subject, respectively, when compared to the reference subject (70 kg). Small differences in CL/F were observed with other covariates (age, females, non-white race, healthy subject); however, no reduction in the unexplained random variability was achieved in the final model which suggests that age, sex, patient status, and non-white race did not contribute to variability in ivacaftor PK in a meaningful manner. Median (min-max) AUCss and Cmin,ss predicted by the model for children 2 to 5 years old weighing less than 14 kg receiving 50 mg are 9840 ng/ml.h (5120-20800) and 536 ng/ml (170-1310), respectively. For children 2 to 5 years old weighing at least 14 kg receiving 75 mg these are 10200 ng/ml.h (6260-22700) and 580 ng/ml (225-1540) respectively. Both median and mean predicted values are in the range of those predicted for the approved dose of ivacaftor (i.e. 150 mg BID) in adolescents (8670 ng/mL.h and 508 ng/mL) and adults (9840 ng/mL.h and 634 ng/mL). Conversely, the values of these parameters predicted for children 2 to 5 years old are almost half of the value predicted for children 6-11 years old after the approved dose of 150 mg (18700 ng/mL.h and 1100 ng/mL).

2.4.3. Pharmacodynamics

For this application, no new data were provided on pharmacodynamics. This is considered acceptable.

2.4.4. Discussion on clinical pharmacology

The PK study VX12-770-015 showed that the ivacaftor PK parameters obtained with T1F (2 x 75 mg granule) were similar to those obtained with RF (150 mg tablet) with comparable tmax and t1/2 in the fed conditions. Hence, the granule formulation is considered comparable to the film-coated tablet formulation under fed conditions. As expected, the granule formulation administered with food showed a significantly higher ivacaftor exposure and a longer median tmax and shorter mean t1/2. The magnitude of food effect for the final granule formulation is similar to that of the 150-mg tablet when administered with a high-fat meal relative to fasted conditions. The proposed dosage and administration for Kalydeco granules is thus similar with that of Kalydeco 150-mg tablets.

The approach used to determine the PK of ivacaftor in young children enrolled in study 108 (population PK analysis) is appropriate considering the sparse sampling schedule with the purpose of minimising the number of blood extractions needed. Based on the final selected model, the PK parameters of ivacaftor in children aged 2 through 5 years with CF and a *CFTR* gating mutation do not significantly differ from those in older children, adolescents or adults once body weight is considered. Clearance tends to be smaller in children than in adults. However, the exposure to ivacaftor - in terms of model-predicted AUC and Cmin - is similar to that predicted in adolescents (12-17 years old) and adults. Section 5.2 of the SmPC quotes the relevant PK parameters as estimated via pop-PK modelling based on the observed concentrations.

2.4.5. Conclusions on clinical pharmacology

The final ivacaftor granule formulation was determined to have similar bioavailability as the 150-mg commercial tablet and showed a significantly higher ivacaftor exposure under fed conditions. This effect was comparable with that observed with the tablet formulation. Ivacaftor exposure increased approximately proportional to dose from 50 mg to 150 mg when administered as the granule formulation, although for Cmax, there is a small, but clinically insignificant higher deviation. As the magnitude of food effect for the final granule formulation is similar to that of the

150-mg tablet when administered with a high-fat meal relative to fasted conditions, the proposed dosage and administration directions for Kalydeco granules indicate that they are to be administered with fat-containing food, the same as Kalydeco 150-mg tablets. No dedicated dose-finding study was performed. Dose finding for children aged 2-5 years was based on modelling and simulation and based on the obtained results, the dosing regimen as currently recommended in the SmPC is considered acceptable. The posology in section 4.2 of the SmPC of Kalydeco granules is weight-based for children aged 2 years and older and weighing less than 25 kg.

No new data have been provided regarding pharmacodynamics. This is acceptable as this extension of the indication refers to *CFTR* gating mutations.

The CHMP considers the pharmacological profile of Kalydeco to be sufficiently characterised and there are no additional measures related to pharmacology.

2.5. Clinical efficacy

2.5.1. Dose response study

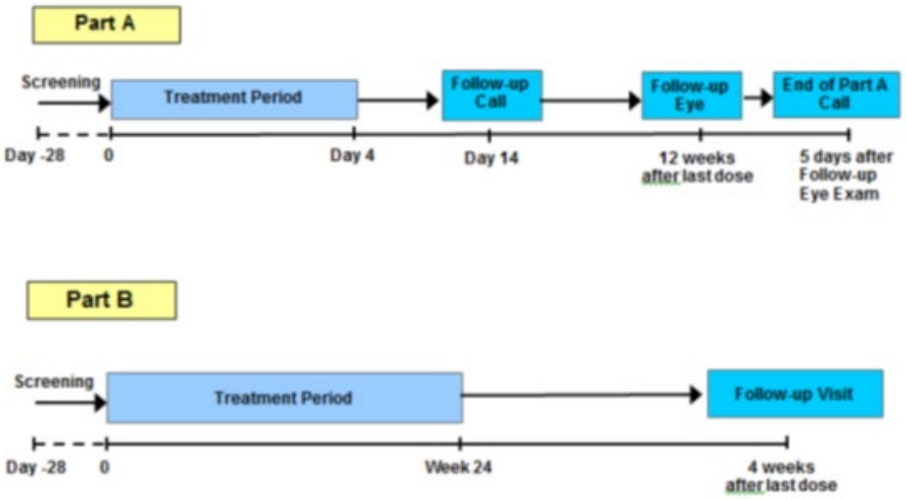
No dedicated dose-finding studies have been performed. Study 108 was a 2-part study. The main objective of Part A was to evaluate the PK of multiple-dose (4-day period) administration of ivacaftor in subjects 2 through 5 years of age and to confirm (or adjust if necessary) the doses for Part B. No dose adjustment was deemed necessary and consequently in Part B the same posology was administered. The doses administered in study 108 Part A were chosen based on similar *in vitro* potency of ivacaftor toward mutations that cause gating defects and the efficacy and safety results of dosing with 150-mg ivacaftor q12h in subjects 6 years of age and older in Studies 102 and 103. Population PK analyses were conducted by incorporating the effect of weight on ivacaftor PK using an allometric model. For dose selection in subjects 2 through 5 years of age, simulations were performed to target exposure parameters minimum observed concentration (Cmin) and area under the concentration versus time curve (AUC) similar to that observed in adults; and a median Cmin of at least 423 ng/mL concentration that results in 90% of the maximum effect (EC90) and an AUC not exceeding the AUC observed in subjects 6 to 11 years of age. PK results from Part A were incorporated into the population PK model to confirm the appropriateness of the doses for further evaluation in Part B.

2.5.2. Main study

The application for the extension of the indication of Kalydeco to children aged 2 to 5 years is based on a single study as follows:

Protocol VX11-770-108 (study 108): A Phase 3, 2-Part, Open-Label Study to Evaluate the Safety, Pharmacokinetics, and Pharmacodynamics of Ivacaftor in Subjects With Cystic Fibrosis Who Are 2 Through 5 Years of Age and Have a CFTR Gating Mutation.

This was a Phase 3, open-label, 2-part study as depicted in figure below:



Study 108 was designed to assess safety, PK, and PD of ivacaftor treatment (50-mg for subjects <14 kg; or 75-mg for subjects ≥14 kg; q12h) in subjects 2 through 5 years of age who have a *CFTR* gating mutation in at least 1 allele. Part A was designed to evaluate the safety and PK of multiple-dose (4-day period) administration of ivacaftor in subjects 2 through 5 years of age and to confirm (or adjust if necessary) the doses for Part B. Part B was designed to evaluate the safety, PK, PD, and efficacy of ivacaftor in subjects 2 through 5 years of age after 24 weeks of treatment.

Methods

Study Participants

Key inclusion criteria

- Male or female with confirmed diagnosis of CF, defined as a sweat chloride value ≥60 mmol/L by quantitative pilocarpine iontophoresis OR 2 CF-causing mutations (all as documented in the subject's medical record).
- Must have had one of the following *CFTR* gating mutation in at least 1 allele: *G551D, G178R S549N, S549R G551S, G970R, G1244E, S1251N, S1255P, G1349D.*
- Aged 2 through 5 years at screening and Day 1 (in Part A and for subjects who participated in Part A or in Part B for subjects who participated in only Part B); subjects who completed Part A who are older than 5 years of age at screening or Day 1 in Part B were eligible to enrol in Part B.
- Weight ≥8 kg at screening and Day 1.

Key exclusion criteria

- An acute upper or lower respiratory infection, or pulmonary exacerbation, or changes in therapy (including antibiotics) for pulmonary disease within 4 weeks before Day 1
- Abnormal liver function, at screening, defined as ≥3 × upper limit of normal (ULN) range, of any 3 or more of the following: serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma-glutamyl transpeptidase (GGT), or total bilirubin.
- History of solid organ or hematological transplantation.
- Colonization with organisms associated with a more rapid decline in pulmonary status (e.g., *Burkholderia cenocepacia*, *Burkholderia dolosa*, and *Mycobacterium abcessus*) at screening.
- Use of any moderate or strong inducers or inhibitors of cytochrome P450 (CYP) 3A within 2 weeks before Day 1
- Abnormal renal function at screening, defined as creatinine clearance <75 mL/min/1.73 m2 using the Counahan-Barratt equation
- Presence of a lens opacity or cataract identified at the screening ophthalmologic examination or inability to undergo an adequate slit-lamp examination

Treatments

In Parts A and B of Study 108, subjects weighing <14 kg on Day 1 were administered 50-mg ivacaftor every 12 hours (q12h) and subjects weighing ≥14 kg on Day 1 were administered 75-mg ivacaftor q12h. The doses in Part B were confirmed before the start of Part B based on the preliminary analysis of PK data from Part A, along with safety and tolerability data from Part A. No dose adjustments were made in Part B of this study as a consequence of weight change. Each dose of ivacaftor granules was mixed with approximately 1 teaspoon (5 mL) of applesauce, pureed carrots, nonfat yogurt, or water and administered orally with fat-containing food, such as a standard "CF" high-calorie, high-fat meal or snack. Subjects in Study 108 continued to receive their usual, prescribed CF therapy in addition to ivacaftor. The use of hypertonic saline was allowed.

Objectives

Part A

Primary objectives:

- To evaluate the safety of ivacaftor treatment in subjects with CF who are 2 through 5 years of age and have a *CFTR* gating mutation
- To evaluate the PK of ivacaftor and metabolites hydroxymethyl-ivacaftor (M1) and ivacaftor carboxylate (M6) in subjects with CF who are 2 through 5 years of age and have a *CFTR* gating mutation
- Exploratory: To evaluate the palatability of ivacaftor granules in subjects with CF who are 2 through 5 years of age and have a *CFTR* gating mutation.

Part B

Primary objective:

- To evaluate the safety of ivacaftor treatment in subjects with CF who are 2 through 5 years of age and have a *CFTR* gating mutation

Secondary objectives:

- To evaluate the PK of ivacaftor and metabolites M1 and M6 in subjects with CF who are 2 through 5 years of age and have a *CFTR* gating mutation
- To evaluate the PD of ivacaftor treatment in subjects with CF who are 2 through 5 years of age and have a *CFTR* gating mutation

Tertiary objectives:

- To evaluate the efficacy of ivacaftor in subjects with CF who are 2 through 5 years of age and have a *CFTR* gating mutation
- To evaluate the palatability of ivacaftor granules in subjects with CF who are 2 through 5 years of age and have a *CFTR* gating mutation

Outcomes/endpoints

Part A

Primary endpoints:

- Safety, as determined by adverse events, clinical laboratory values (serum chemistry, hematology, and coagulation studies), standard 12-lead electrocardiograms (ECGs), vital signs, and ophthalmologic examinations
- PK parameter estimation of ivacaftor and metabolites M1 and M6 after 4 days of ivacaftor treatment

Part B

Primary endpoint:

- Safety, as determined by adverse events, clinical laboratory values (serum chemistry, hematology, and coagulation studies), ECGs, vital signs, and ophthalmologic examinations.

Secondary Endpoints:

- PK parameter estimation of ivacaftor and metabolites M1 and M6

- Absolute change from baseline in sweat chloride through 24 weeks of ivacaftor treatment: sweat chloride was collected in Part B at baseline and 4 post-baseline time points (Weeks 2, 8, 16, and 24). Sweat chloride results (including changes from baseline) were analyzed as a continuous variable using descriptive summary statistics and presented by scheduled visit and treatment (each dose level and overall). The mean absolute change from baseline in sweat chloride was also displayed in a waterfall plot by scheduled visit and treatment. Change from baseline in sweat chloride was categorized by the following rules: <5 mmol or ≥5 mmol, <10 mmol or ≥10 mmol, <15 mmol or ≥15 mmol, <20 mmol or ≥20 mmol.

- Absolute change from baseline in weight at 24 weeks of ivacaftor treatment: weight (kg) was collected in Part B at baseline and 7 post-baseline time points (Weeks 2, 4, 8, 12, 16, 20, and 24). Weight must have been measured with shoes off and light clothing.

- Absolute change from baseline in stature at 24 weeks of ivacaftor treatment: stature (m) was collected in Part B at baseline and 7 post-baseline time points (Weeks 2, 4, 8, 12, 16, 20, and 24). At 2 years of age and older, if children could stand unassisted and follow directions, stature should have been measured as height; otherwise, stature was measured as length. Stature must have been measured with shoes off and light clothing.

- Absolute change from baseline in body mass index (BMI) at 24 weeks of ivacaftor treatment

Tertiary Endpoints

- Weight-for-age z-score/Stature-for-age z-score/BMI-for-age z-score: all 3 parameters were adjusted for sex and age and summarized as weight-for-age, stature-for-age, and BMI-for-age z-scores. Z-scores were calculated using the National Center for Health Statistics (NCHS) Growth Chart Equations for children and adolescents, 2 to 20 years of age.

- Qualitative microbiology cultures: if bacteria were found, the amount was recorded as light, moderate, or heavy growth.

- Pulmonary exacerbations: each instance of a new or changed antibiotic therapy administered for sinopulmonary signs and symptoms was assessed to determine if it met 1 of the 2 protocol definitions of pulmonary exacerbation provided in Section 9.5.5.1. All events, whether or not they met the definition of pulmonary exacerbation, were considered "antibiotic therapy for sinopulmonary signs/symptoms" (i.e., "sinopulmonary sign/symptom" events).

- Unplanned antibiotic therapy: this endpoint referred to all events of new or changed antibiotic therapy administered. The same set of variables described for pulmonary exacerbations was analyzed for unplanned antibiotic therapy. The definitions of count, duration, and time-to-first event were consistent with the definitions provided for the pulmonary exacerbation variables.

- Hospitalizations: the dates for hospitalizations and the reasons were collected. The definitions of count, duration, and time-to-first event were consistent with the definitions provided for the pulmonary exacerbation variables.

- Outpatient sick (i.e. non-study) visits: The date of each outpatient sick visit was collected. The definitions of count, duration, and time-to-first event were consistent with the definitions provided for the pulmonary exacerbation variables.

- Spirometry: spirometry assessments were performed in Part B at qualified study sites at the following study visits: Day -28 to Day-1, Day 1, Week 2, Week 8, Week 16 and week 24 for subjects 3 years of age or older who met the ATS/ERS acceptability criteria for preschool spirometry. The following parameters were determined as part of the spirometry assessment: FEV1 (L), Forced expiratory volume in 0.50 seconds (FEV0.5), Forced expiratory volume in 0.75 seconds (FEV0.75), Forced vital capacity (FVC), Forced mid-expiratory flow rate (FEF25%-75% [L/sec]), Forced expiratory time (FET).

- Fecal elastase-1

- Immunoreactive trypsinogen (IRT)

- Palatability of ivacaftor granules: all subjects had their acceptance of the dose administered and the volume consumed recorded. All subjects were also be observed by their facial expressions and any spontaneous comments in regards to likes or dislikes were noted. Palatability of ivacaftor granules was further assessed in subjects 4 years of age and older in the study using a visual analog scale that incorporates a 5-point facial hedonic scale. All interviews were conducted on a one-on-one basis in the clinic setting. Subjects were familiarized with the scale using hypothetical situations before taste testing was conducted. Immediately after receiving their first dose of ivacaftor, subjects 4 through 5 years of age were asked to rate their degree of liking using the visual analog scale.

Sample size

In Part A, enrolment was planned for a minimum of 8 subjects. For Part A, no formal sample size calculations were performed, but the sample size chosen was deemed adequate to meet the PK objectives of this study. The sample size of a minimum of 20 subjects in Part B was based on the availability of the subject population and not on any statistical consideration; therefore, the study was not powered to detect a significant treatment effect. The sample size of minimum of 20 subjects represented approximately 7% of the estimated number of patients with CF 2 through 5 years of age worldwide who have the *G551D* and non-*G551D-CFTR* gating mutations in at least 1 allele, based on data from the US Cystic Fibrosis Foundation Patient Registry and estimates of subjects worldwide.

Randomisation

Randomisation was not conducted as this was an uncontrolled study.

Blinding (masking)

Blinding was not conducted as this was an uncontrolled study.

Statistical methods

All analyses were presented for Part A and Part B separately. For Part A, a preliminary PK analysis took place after all samples have been collected and bioanalysis is complete. The available data were used to confirm dose for use in Part B. Part A safety analyses consisted primarily of individual subject data listings. Efficacy analysis was applicable to Part B only. In Part A and Part B, only descriptive analysis of safety (and when applicable, efficacy) parameters will be performed; point and interval estimates will be provided where useful.

The following subgroups were used: age group at baseline (2, 3, and 4 to 5 years of age), geographic region (North America and Europe), sex (female and male), and percent predicted FEV1 severity category at baseline (<70%, ≥70% to ≤90%, >90%, and not done). Medications used in the study were identified as prior, concomitant, or both, according to the rules given below.

Results

Participant flow

Part A: A total of 11 subjects were screened, of whom 9 subjects were enrolled and included in the Safety Set. Two subjects were screen-failures and did not enter the treatment period. All 9 subjects completed the 4-day treatment period.

Part B: A total of 37 patients were screened with 34 enrolled and included in the Safety Set, of whom 10 patients received ivacaftor 50 mg q 12 hours and 24 patients received 75 mg q 12hours. Eight of the 9 patients who participated in Part A were enrolled in Part B. A total of 33 patients completed the 24-week treatment period. One patient, in the ivacaftor 50 mg dose group, prematurely discontinued study drug treatment due to an adverse event of increased transaminases and did not complete the Follow-up Visit.

Recruitment

Part A study was initiated on 08 January 2013; part B on 28 June 2013. Study was completed on 18 March 2014. Subjects in Part A were included at 5 sites in North America. In Part B, subjects were included at 15 sites (11 sites in the US, 3 sites in the United Kingdom, and 1 site in Canada).

Conduct of the study

Final version of study protocol 108 is version 4.0 dated 08 May 2013. Four amendments were implemented in the initial version of the protocol. The date of the study report is 19 August 2014. The Statistical Analysis Plan (SAP) version 1.0 is dated 18 March 2014, i.e. at the time when last subject completed the last visit. There were no changes to the planned analysis but it is noticed that the SAP was finalised at the same time of study completion. The adverse event grading system that was used in study 108 was the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials which was considered more appropriate (than the Common Terminology Criteria for Adverse Events, CTCAE) for young children. The rationale seems to be that this system (which is mainly intended for preventive vaccine trials) is more appropriate for almost healthy children than the CTCAE.

Baseline data

Part A: Demographics and Baseline Characteristics, Safety Set

Variable	**Ivacaftor 50 mg N = 4**	**Ivacaftor 75 mg N = 5**
Age (years)		
-n (non-missing)	4	5
-Mean	2.3	3.8
-SD	0.50	1.10
-Median	2.0	3.0
-Range	2, 3	3, 5
Age category (years), n (%)		
2	3 (75%)	0
3	1 (25%)	3 (60%)
4 to 5	0	2 (22.2%)
Genotype, n (%)		
G551D/DELF508	3 (75.0)	4 (80.0)
G551D/3556INSAGTA	0	1 (20.0)
G551D/3905INST	1 (25.0)	0
Sweat chloride (mmol/L)		
-n (non-missing)	5	4
-Mean	105.88	106.20
-SD	5.893	6.852
-Median	105.50	106.50
-Range	99.5, 113.0	98.5, 115.0
Stature (cm)		
-n (non-missing)	4	5
-Mean	89.0	100.3
-SD	4.81	6.77
-Median	89.7	101.3
-Range (min, max)	83, 94	91, 107
Weight (kg)		

-n (non-missing)	4	5
-Mean	12.33	16.14
-SD	1.226	1.315
-Median	12.35	16.50
-Range (min, max)	10.8, 13.8	14.4, 17.6
BMI (kg/m²) -n (non-missing)	4	5
-Mean	15.550	16.116
-SD	0.3687	1.3308
-Median	15.655	15.660
-Range (min, max)	15.02, 15.87	14.85, 18.36
Stature-for-age z-score -n (non-missing)	4	5
-Mean	-0.8405	-0.8676
-SD	0.66774	0.59790
-Median	-0.8320	-0.9720
-Range (min, max)	-1.663, -0.035	-1.716, -0.152
Weight-for-age z-score -n (non-missing)	4	5
-Mean	-0.9683	-0.3306
-SD	0.54583	0.66630
-Median	-0.7850	-0.6730
-Range (min, max)	-1.767, -0.536	-0.990, 0.564
BMI-for-age z-score -n (non-missing)	4	5
-Mean	-0.4098	0.3476
-SD	0.54447	0.82625
-Median	-0.2950	0.3030
-Range (min, max)	-1.148, 0.099	-0.520, 1.682

Part B: Demographics and Baseline Characteristics, Safety Set

Variable	Ivacaftor 50 mg N = 10	Ivacaftor 75 mg N = 24	Overall N = 34
Gender, n (%)			
Male	6 (60.0)	22 (91.7)	28 (82.4)
Female	4 (40.0)	2 (8.3)	6 (17.6)
Race, n (%)			
White	10 (100.0)	24 (100.0)	34 (100.0)
Ethnicity, n (%)			
Hispanic or Latino	1 (10.0)	0	1 (2.9)
Not Hispanic or Latino	9 (90.0)	24 (100.0)	33 (97.1)
Geographic region, n (%)			
North America	9 (90.0)	17 (70.8)	26 (76.5)
Europe	1 (10.0)	7 (29.2)	8 (23.5)
Genotype, n (%)			
G551D/DELF508	7 (70.0)	19 (79.2)	26 (76.5)
G551D/1471DELA	0	1 (4.2)	1 (2.9)

G551D/1717-1G>A	1 (10.0)	0	1 (2.9)
G551D/3905INST	1 (10.0)	0	1 (2.9)
G551D/394DELTT	0	1 (4.2)	1 (2.9)
G551D/G551D	1 (10.0)	0	1 (2.9)
G551D/R117H	0	1 (4.2)	1 (2.9)
S549N/DELF508	0	1 (4.2)	1 (2.9)
S549N/R553X	0	1 (4.2)	1 (2.9)
Age (years)			
n (non-missing)	10	24	34
Mean	2.3	3.6	3.2
SD	0.48	0.82	0.96
Median	2.0	4.0	3.0
Minimum	2	2	2
Maximum	3	5	5
Age category (years), n (%)			
2	7 (70.0)	2 (8.3)	9 (26.5)
3	3 (30.0)	8 (33.3)	11 (32.4)
4 to 5	0	14 (58.3)	14 (41.2)
Percent predicted FEV1			
n (non-missing)	3	17	20
Mean	91.6	87.0	87.7
SD	11.55	17.79	16.83
Median	94.3	83.3	86.5
Minimum	79.0	44.4	44.4
Maximum	101.6	117.2	117.2
Percent predicted FEV1, n (%)			
<70%	0	2 (8.3)	2 (5.9)
≥70% to ≤90%	1 (10.0)	8 (33.3)	9 (26.5)
>90%	2 (20.0)	7 (29.2)	9 (26.5)
Not done	0	0	0
Sweat chloride (mmol/L)			
n (non-missing)	8	22	30
Mean	93.1	99.6	97.9
SD	15.04	13.55	14.00
Median	99.3	101.0	100.0
Minimum	66.0	75.0	66.0
Maximum	107.0	121.0	121.0
Weight (kg)			
n (non-missing)	10	24	34
Mean	12.5	16.8	15.5
SD	1.00	1.80	2.55
Median	12.8	16.3	15.8
Minimum	10.7	14.0	10.7

Maximum	13.8	21.0	21.0
BMI (kg/m2)			
n (non-missing)	10	24	34
Mean	15.79	16.06	15.98
SD	0.669	1.149	1.029
Median	15.70	15.91	15.89
Minimum	14.94	13.80	13.80
Maximum	16.87	18.11	18.11
Weight-for-age z-score			
n (non-missing)	10	24	34
Mean	-0.86	0.13	-0.16
SD	0.393	0.783	0.824
Median	-0.99	0.18	-0.30
Minimum	-1.29	-1.36	-1.36
Maximum	-0.11	1.43	1.43
BMI-for-age z-score			
n (non-missing)	10	24	34
Mean	-0.23	0.28	0.13
SD	0.567	0.839	0.797
Median	-0.10	0.38	0.13
Minimum	-1.06	-1.80	-1.80
Maximum	0.66	1.53	1.53
Fecal elastase-1 (µg/g)			
<200	5 (50.0)	21 (87.5)	26 (76.5)
≥200	0	1 (4.2)	1 (2.9)
Unknown	5 (50.0)	2 (8.3)	7 (20.6)

The most commonly reported concomitant medications were pancreatin, salbutamol, dornase alfa, and sodium chloride, which were taken by over 50% of subjects overall. Antibiotics such as tobramycin and colistin were administered to 11.8% (4/24) subjects.

Numbers analysed

Planned: Part A: A minimum of 8 subjects (minimum of 2 subjects in each of the following 3 age groups: 2, 3, and 4 or 5 [inclusive] years of age). Part B: A minimum of 20 subjects (minimum of 6 subjects 2 through 3 years of age)

Analysed: Part A: 9 subjects received at least 1 dose of ivacaftor and were included in the Safety Set. Part B: 34 subjects received at least 1 dose of ivacaftor and were included in the Safety Set.

Outcomes and estimation

- **Efficacy Endpoints**

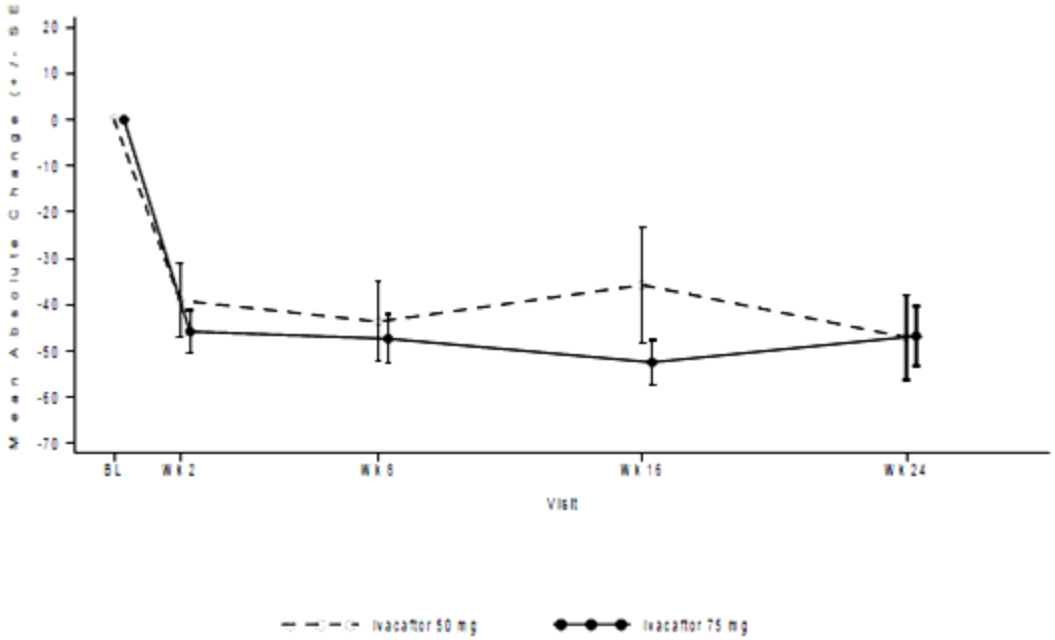
Sweat chloride

Mean (standard deviation [SD]) baseline sweat chloride levels (97.9 mmol/L [14.00]) decreased substantially by Week 2 and remained low at each time point through Week 24.

Absolute Changes From Baseline in Sweat Chloride (mmol/L), Part B, Safety Set

Time Point	Category or Statistic	Ivacaftor 50 mg (N = 10)	Ivacaftor 75 mg (N = 24)	Overall (N = 34)
Baseline	n	8	22	30
	Mean (SD) (mmol/L)	93.1 (15.04)	99.6 (13.55)	97.9 (14.00)
Week 24	n	8	20	28
	Mean (SD) (mmol/L)/n	47.8 (23.31)	55.2 (23.85)	53.1 (23.51)
	n	7	18	25
	Mean (SD) absolute change from baseline (mmol/L)	-47.1 (24.26)	-46.8 (27.58)	-46.9 (26.19)
	95% CI	(-69.50, -24.64)	(-60.50, -33.06)	(-57.67, -36.05)
	P value	0.0021	<0.0001	<0.0001

Mean Absolute Changes From Baseline in Sweat Chloride (mmol/L) by Ivacaftor Dose Group and Visit, Part B, Safety Set



There was a slight increase in sweat chloride in the 50 mg ivacaftor arm between week 8 and week 16 (by a mean value of 7.92 mmol/L).

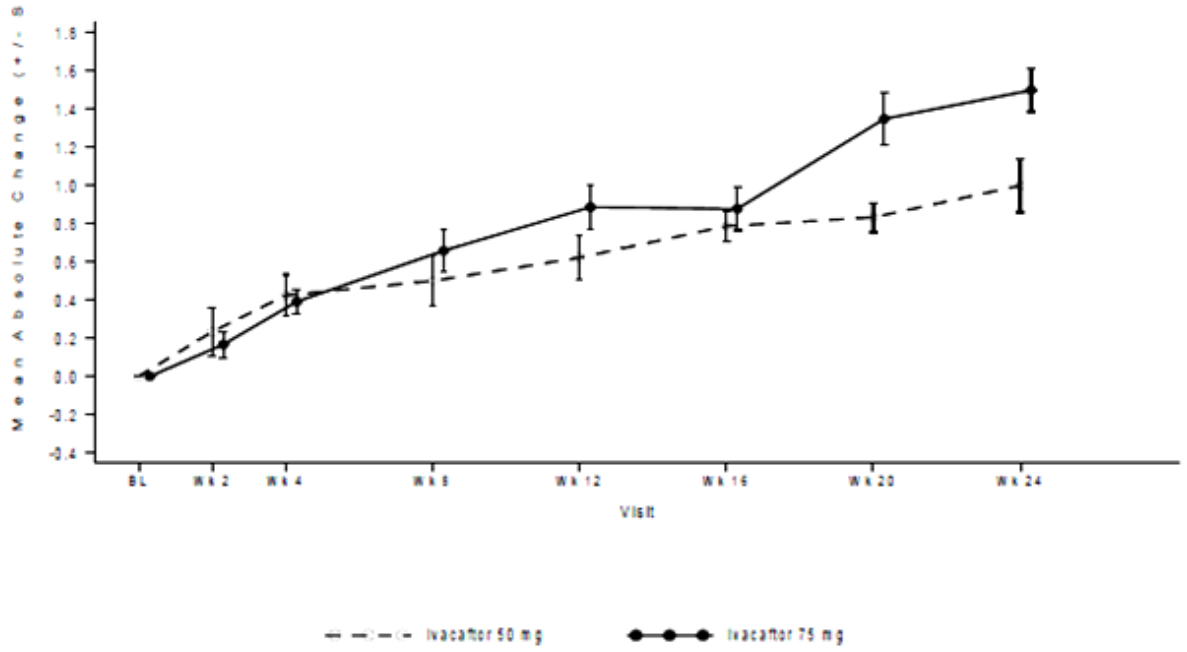
Weight

Mean (SD) baseline weight (15.5 kg [2.55]) increased by Week 2 and was sustained or increased at each time point to Week 24.]).

Study 108 Part B: Absolute Change From Baseline at Week 24 in Weight (kg), Safety Set

Time Point	Category or Statistic	Ivacaftor 50 mg (N = 10)	Ivacaftor 75 mg (N = 24)	Overall (N = 34)
Baseline	n	10	24	34
	Mean (SD) (kg)	12.5 (1.00)	16.8 (1.76)	15.5 (2.55)
Week 24	n	9	24	33
	Mean (SD) (kg)	13.5 (1.04)	18.3 (1.97)	17.0 (2.79)
	Mean (SD) absolute change from baseline (kg)	1.0 (0.42)	1.5 (0.55)	1.4 (0.56)
	95% CI	(0.68, 1.32)	(1.27, 1.73)	(1.16, 1.56)
	P value	<0.0001	<0.0001	<0.0001

Mean Absolute Changes From Baseline in Weight (kg) by Ivacaftor Dose Group and Visit, Part B, Safety Set



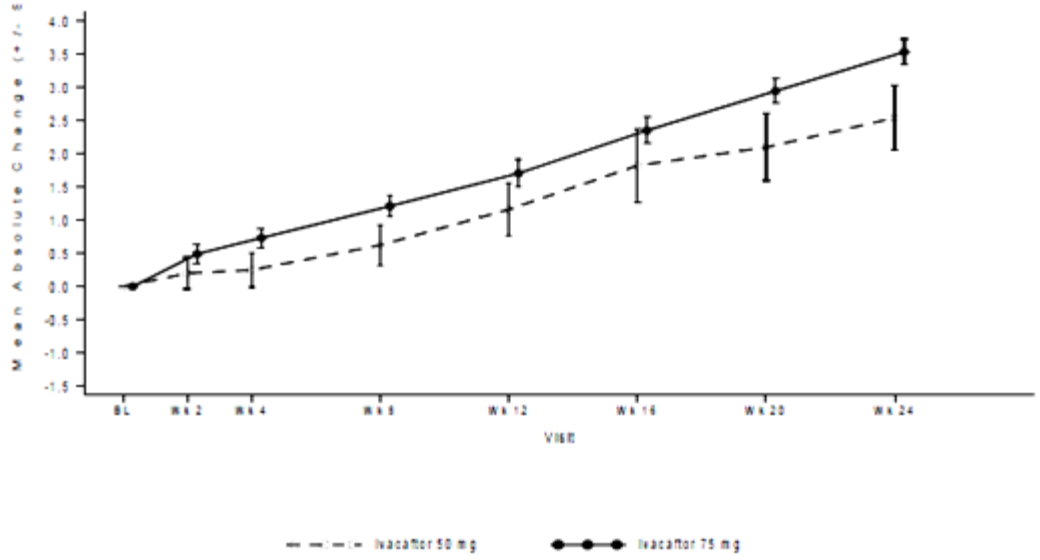
Stature

Mean (SD) baseline stature (98.4 cm [8.44]) increased at Week 24 (101.6 cm [8.64]; P < 0.0001 [overall]). Mean changes from baseline were 2.5 to 3.5 cm across the ivacaftor 50 mg and ivacaftor 75 mg groups.

Study 108 Part B: Absolute Change From Baseline at Week 24 in Stature (cm), Safety Set

Time Point	Category or Statistic	Ivacaftor 50 mg (N = 10)	Ivacaftor 75 mg (N = 24)	Overall (N = 34)
Baseline	n	10	24	34
	Mean (SD) (cm)	89.0 (4.05)	102.3 (6.44)	98.4 (8.44)
Week 24	n	9	23	32
	Mean (SD) (cm)	91.7 (4.26)	105.5 (6.53)	101.6 (8.64)
	Mean (SD) absolute change from baseline (cm)	2.5 (1.45)	3.5 (0.93)	3.3 (1.17)
	95% CI	(1.43, 3.66)	(3.14, 3.94)	(2.84, 3.68)
	P value	0.0008	<0.0001	<0.0001

Mean Absolute Changes From Baseline in Stature (cm) by Ivacaftor Dose Group and Visit, Part B, Safety Set



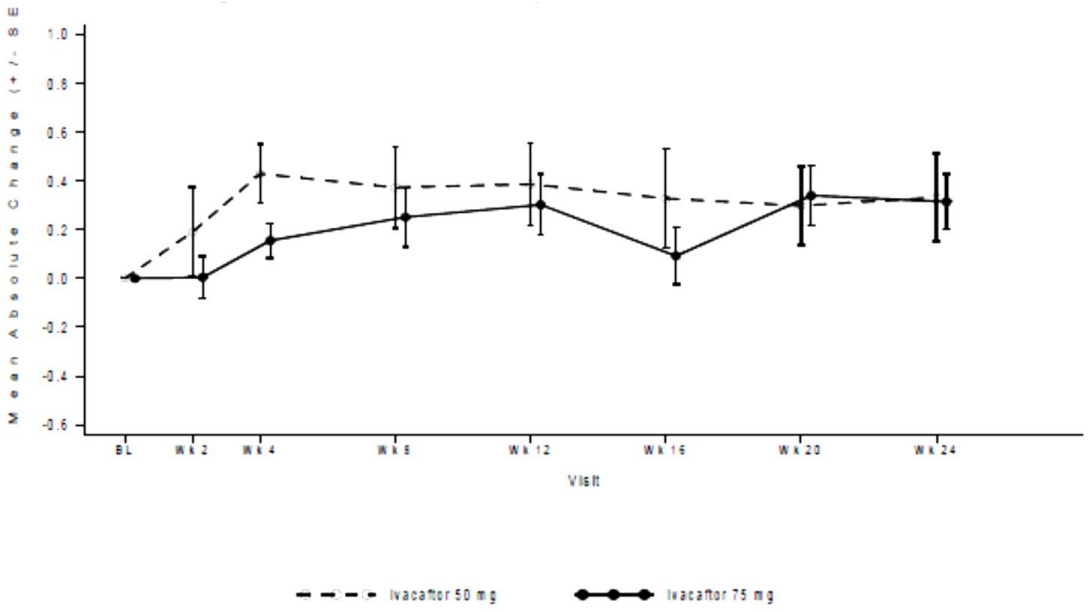
BMI

Mean (SD) baseline BMI (15.98 kg/m2 [1.029]) increased by Week 4 and generally increased or was sustained at each time point to Week 24.

Study 108 Part B: Absolute Change From Baseline at Week 24 in BMI (kg/m2), Safety Set

Time Point	Category or Statistic	Ivacaftor 50 mg (N = 10)	Ivacaftor 75 mg (N = 24)	Overall (N = 34)
Baseline	n	10	24	34
	Mean (SD) (kg/m2)	15.79 (0.669)	16.06 (1.149)	15.98 (1.029)
Week 24	n	9	23	32
	Mean (SD) (kg/m2)	16.07 (0.547)	16.40 (1.103)	16.30 (0.981)
	Mean (SD) absolute change from baseline (kg/m2)	0.33 (0.539)	0.31 (0.549)	0.32 (0.538)
	95% CI	(-0.08, 0.75)	(0.08, 0.55)	(0.13, 0.51)
	P value	0.1018	0.0118	0.0021

Mean Absolute Changes From Baseline in BMI (kg/m2) by Ivacaftor Dose Group and Visit, Part B, Safety Set



The improvements in weight and BMI were supported by the weight-for-age and BMI-for-age z-score results.

Tertiary Efficacy Endpoints

Weight-for-age z-scores

Mean (SD) baseline **weight-for-age z-scores** (-0.16 [0.824]) increased by Week 2 and were generally sustained or increased at each time point to Week 24 (0.07 [0.826]; P <0.0001 [overall]).

Table E-9 Study 108 Part B: Absolute Change From Baseline at Week 24 in Weight-for-age Z-score, Safety Set

Time Point	Category or Statistic	Ivacaftor 50 mg (N = 10)	Ivacaftor 75 mg (N = 24)	Overall (N = 34)
Baseline	n	10	24	34
	Mean (SD) (unit)	-0.86 (0.393)	0.13 (0.783)	-0.16 (0.824)
Week 24	n	9	24	33
	Mean (SD) (unit)	-0.65 (0.48)	0.34 (0.768)	0.07 (0.826)
	Mean (SD) absolute change from baseline (unit)	0.18 (0.317)	0.21 (0.228)	0.20 (0.250)
	95% CI	(-0.06, 0.43)	(0.11, 0.31)	(0.11, 0.29)
	P value	0.1192	0.0002	<0.0001

Notes: Baseline was defined as the most recent measurement before the first dose of study drug in Part B. Weight-for-age z-scores were calculated using National Center for Health Statistics (NCHS) growth chart equations for children and adolescents 2 to 20 years of age. P value was 2-sided, comparing mean absolute change from baseline at Week 24 with Week 0, based on a 1 sample T-test.

Stature-for-age z-scores

Mean (SD) baseline **stature-for-age z-scores** (-0.34 [0.823]) remained similar at each time point to Week 24 (-0.34 [0.939]; P = 0.8408).

Table E-10 Study 108 Part B: Absolute Change From Baseline at Week 24 in Stature-for-age Z-score, Safety Set

Time Point	Category or Statistic	Ivacaftor 50 mg (N = 10)	Ivacaftor 75 mg (N = 24)	Overall (N = 34)
Baseline	n	10	24	34
	Mean (SD) (unit)	-0.90 (0.787)	-0.11 (0.733)	-0.34 (0.823)
Week 24	n	9	23	32
	Mean (SD) (unit)	-1.07 (0.870)	-0.06 (0.817)	-0.34 (0.939)
	Mean (SD) absolute change from baseline (unit)	-0.25 (0.448)	0.08 (0.216)	-0.01 (0.327)
	95% CI	(-0.59, 0.10)	(-0.01, 0.17)	(-0.13, 0.11)

P value	0.1390	0.0907	0.8408

Notes: Baseline was defined as the most recent measurement before the first dose of study drug in Part B. Stature-for-age z-scores were calculated using National Center for Health Statistics (NCHS) growth chart equations for children and adolescents 2 to 20 years of age. P value was 2-sided, comparing mean absolute change from baseline at Week 24 with Week 0, based on a 1 sample T-test.

BMI-for-age z-scores

Mean (SD) baseline **BMI-for-age z-scores** (0.13 [0.797]) increased by Week 4 and generally increased or were sustained at each time point to Week 24 (0.51 [0.708]; P <0.0001 [overall]).

Table E-11 Study 108 Part B: Absolute Change From Baseline at Week 24 in BMI-for-age Z-score, Safety Set

Time Point	Category or Statistic	Ivacaftor 50 mg (N = 10)	Ivacaftor 75 mg (N = 24)	Overall (N = 34)
Baseline	n	10	24	34
	Mean (SD) (unit)	-0.23 (0.567)	0.28 (0.839)	0.13 (0.797)
Week 24	n	9	23	32
	Mean (SD) (unit)	0.19 (0.475)	0.63 (0.754)	0.51 (0.708)
	Mean (SD) absolute change from baseline (unit)	0.46 (0.456)	0.34 (0.417)	0.37 (0.424)
	95% CI	(0.11, 0.81)	(0.16, 0.52)	(0.22, 0.52)
	P value	0.0166	0.0008	<0.0001

Notes: Baseline was defined as the most recent measurement before the first dose of study drug in Part B. BMI-for-age z-scores were calculated using National Center for Health Statistics (NCHS) growth chart equations for children and adolescents 2 to 20 years of age. P value was 2-sided, comparing mean absolute change from baseline at Week 24 with Week 0, based on a 1 sample T-test.

Ancillary analyses

The results from the Phase 3, placebo-controlled studies in subjects with the *G551D-CFTR* mutation (Studies 102 and 103) and subjects with a non-*G551D-CFTR* mutation that causes *CFTR* gating defects (Study 111, Part 1) are summarized in the following table that shows the absolute mean changes from baseline of select efficacy endpoints to provide context for the efficacy results of Study 108.

Analysis at Week 24	Study 102 Patients ≥ 12 yo and with a G551D mutation	Study 103 Patients 6 to <12 yo and with a G551D mutation	Study 111 (Part 1) Patients ≥6 yo and with a non-G551D gating mutation	Study 108* Patients aged 2 to <6 years with a gating mutation
Absolute change from baseline in sweat chloride Mean (SD) (mmol/L)	-52.2. (16.92)	-58.6 (21.74)	-59.2 (32.57)	-46.9 (26.19)
Absolute change from baseline in weight-for-age z-score Mean (SD)	0.36 (0.31)	0.30 (0.26)	0.41 (0.19)	0.20 (0.25)
Absolute change from baseline in BMI Mean (SD) (Kg/m2)	0.93 (1.15)	1.11 (0.92)	1.26 (0.76)	0.33 (0.54)
Absolute change from baseline in BMI-for-age z-score Mean (SD)	0.36 (0.32)	0.33 (0.36)	0.42 (0.28)	0.37 (0.42)
Absolute change from baseline in PPFEV1 Mean (SD) (percentage points)	11.1 (8.92)	13.2 (13.51)	13.5 (10.18)	1.8 (17.81)

**Overall (both ivacaftor dosing groups combined) results*

It should be noticed that the above mean changes are not those corresponding to model-based treatment differences which seems adequate for the purpose of comparing these results to those of study 108 in which descriptive statistics have been used for the calculation of mean changes. The MAH also present the results corresponding to model-based differences (the primary analysis foreseen in the Statistical Analysis Plan of studies 102, 103 and 111). Model-based differences are generally of an inferior magnitude with respect to those calculated by means of descriptive statistics. Patient Reported Outcomes (PRO) (i.e. revised Cystic Fibrosis Questionnaire, CFQ-R) was not assessed in study 108. This is reasonable taking into account that no validated PRO instruments exist for children with CF <6 years of age. An alternative would have been the use of the parent version of the CFQ-R. The magnitude of the changes in the different endpoints assessed in studies 102, 103 and 111 is, in general, of a similar magnitude as that seen in study 108 with the exception of the mean change in percent predicted FEV1. Interpretation of the results in change in percent predicted FEV1 needs to consider the high degree of variability in the measurements due to the technical difficulties of conducting spirometry in small children and also the small number of patients with baseline and on-treatment spirometry data. The definitions of

pulmonary exacerbations in study 108 were different than the definition of pulmonary exacerbation in studies 103 and 111; therefore, the number and event rates for pulmonary exacerbations in study 108 cannot be compared to those in studies 103 and 111.

Summary of main study

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

<table>
<tr><td colspan="4">Title: A phase 3, 2-part, open-label study to evaluate the safety, pharmacokinetics, and pharmacodynamics of ivacaftor in subjects with cystic fibrosis who are 2 through 5 years of age and have a CFTR gating mutation</td></tr>
<tr><td>Study identifier</td><td colspan="3">VX11-770-108</td></tr>
<tr><td rowspan="2">Design</td><td colspan="3">Phase 3, 2-part, open-label</td></tr>
<tr><td colspan="2">Duration of Part A, screening:
Duration of Part A, treatment period:
Duration of Part A, follow-up:
Duration of Part B, screening:
Duration of Part B, treatment period:
Duration of Part B, follow-up:

Duration of extension phase (Study 109):</td><td>28 days
4 days
12 weeks after last dose +5 days
28 days
24 weeks
4 weeks ± 7 days after the last dose of study drug
ongoing</td></tr>
<tr><td>Hypothesis</td><td colspan="3">N/A</td></tr>
<tr><td rowspan="2">Treatment groups</td><td colspan="2">ivacaftor 50 mg</td><td>ivacaftor 50 mg BID, 4 days+24 weeks, N=10</td></tr>
<tr><td colspan="2">ivacaftor 75 mg</td><td>ivacaftor 75 mg BID, 4 days+24 weeks, N=24</td></tr>
<tr><td rowspan="2">Endpoints and definitions</td><td>Primary endpoint</td><td>Safety</td><td>-</td></tr>
<tr><td>Secondary endpoints</td><td>Sweat chloride (mmol/L)
Body weight (Kg)
Stature (m)
BMI (Kg/^{2})</td><td>Absolute change from baseline
Absolute change from baseline
Absolute change from baseline
Absolute change from baseline</td></tr>
</table>

	Tertiary endpoints	Weight-for-age z-score stature-for-age z-score BMI-for-age z-score Qualitative microbiological cultures Clinical events of interest including pulmonary exacerbations, unplanned antibiotic therapy, hospitalizations, and outpatient sick visits Spirometry parameters such as percent predicted FEV1 Fecal elastase-1 (µg/g) IRT (ng/mL)	Absolute change from baseline Absolute change from baseline Absolute change from baseline Shifts from baseline clinical events: • summarized by dose level • the number of days with event (cumulative duration) • the time-to-first event using the Kaplan-Meier method Absolute change from baseline Absolute change from baseline Absolute change from baseline

Database lock	2014.06.26 study end: 2014. 03.18			
Results and analysis				
Analysis description	Primary analysis			
Analysis population and time point description	Safety set (subjects received at least one dose)			
Descriptive statistics and estimate variability	Treatment group	ivacaftor 50 mg	ivacaftor 75 mg	Overall
	Number of subjects	10	24	34
	Sweat chloride Absolute change from baseline at week 24 mean (mmol/L) (SD)	-47.07 (24.256)/7	-47.07 (24.256)/7	-46.86 (26.193)/25
	SD 95%CI	see above (-69.50, -24.64)	see above (-60.50, -33.06)	see above (-57.67, -36.05)
	Body weight Absolute change from baseline at week 24 mean (kg) (SD)	1.00 (0.418)	1.50 (0.552)	1.36 (0.561)
	SD 95%CI	 (0.68, 1.32)	 (1.27, 1.73)	 (1.16, 1.56)
	Stature Absolute change from baseline at week 24 mean (cm) (SD)	2.5 (1.45)	3.5 (0.93)	3.3 (1.17)
	SD 95%CI	see above (1.43, 3.66)	see above (3.14, 3.94)	see above (2.84, 3.68)

	BMI Absoloute change from baseline at week 24 mean (kg/m^2) (SD)	0.332 (0.5393)	0.314 (0.5492)	0.319 (0.5378)
	SD 95%CI	see above (-0.08, 0.75)	see above (0.08, 0.55)	see above (0.13, 0.51)
	Weight-for-age z-score Absolute change from baseline at week 24 mean (SD)	0.1843 (0.31693)	0.2105 (0.22844)	0.2034 (0.25052)
	SD 95%CI	see above (-0.06, 0.43)	see above (0.11, 031)	see above (0.11, 0.29)
	Stature-for-age z-score Absolute change from baseline at week 24 mean (SD)	-0.2454 (0.44810)	0.0797 (0.21615)	-0.0117 (0.32717)
	SD 95%CI	see above (-0.59, 0.10)	see above (-0.01, 0.17)	see above (-0.13, 0.11)
	BMI-for-age z-score Absolute change from baseline at week 24 mean (SD)	0.4589 (0.45611)	0.3364 (0.41669)	0.3709 (0.42431)
	SD 95%CI	see above (0.11, 0.81)	see above (0.16, 0.52)	see above (0.22, 0.52)
	No. of subjects with pulmonary exacerbation events (%) Definition 1	2 (20.0)	13 (54.2)	15 (44.1)
	No. of subjects with pulmonary exacerbation events (%) Definition 2	1 (10.0)	4 (16.7)	5 (14.7)
	Event rate of pulmonary exacerbations (%) Definition 1	5 (0.54)	30 (1.24)	35 (1.04)
	Event rate of pulmonary exacerbation (%) Definition 2	2 (0.21)	4 (0.17)	6 (0.18)
	No. of subjects with pulmonary exacerbation requiring hospitalization (%) Definition 1	1 (10.0)	1 (4.2)	2 (5.9)

	No. of subjects with pulmonary exacerbation requiring hospitalization (%) Definition 2	0	0	0
	No. of subjects with pulmonary exacerbation requiring IV antibiotics (%) Definition 1	1 (10.0)	1 (4.2)	2 (5.9)
	No. of subjects with pulmonary exacerbation requiring IV antibiotics (%) Definition 2	0	0	0
	Percent Predicted FEV1 Absolute change from baseline at week 24 mean (%) (SD)	-12.5 (30.1)	4.3 (14.8)	1.8 (17.8)
	SD 95%CI	see above (-87.27, 62.35)	see above (-3.30, 11.90)	see above (-6.55, 10.12)
	Percent Predicted FEV0.75 Absolute change from baseline at week 24 mean (%) (SD)	-12.7 (23.0)	5.3 (16.2)	2.6 (17.9)
	SD 95%CI	see above (-69.70, 44.29)	see above (-3.04, 13.61)	see above (-5.78, 10.96)
	FEV1/FVC Absolute change from baseline at week 24 mean (SD)	-0.046 (0.02)	-0.002 (0.143)	-0.009 (0.132)
	Faecal elastase-1 Absolute change from baseline at week 24 mean (µg/g) (SD)	127.9 (191.84)	93.5 (128.28)	99.8 (138.35)
	Immunoreactive Trypsinogen Absolute change from baseline at week 24 (ng/mL) (SD)	-24.37 (21.71)	-19.54 (25.11)	-20.70 (23.99)

Supportive study

Palatability assessment was performed in Part A and Part B of the study following administration of the first dose of study drug. In Part A, all 9 subjects in the 2 ivacaftor dose groups fully consumed the first dose of study drug. In Part B, two patients (one per group) did not provide any palatability assessment, i.e. their assessments were missing. Eight and 23 patients in the ivacaftor 50- and 75-mg groups fully consumed the first dose of study drug. Seven and 11 respectively expressed that they like it very much while 3 patients in the ivacaftor 75-mg group dislike it very much. This was similar to the assessment made by the parents and also similar to the assessment made by

patients of 4 years of age and older using a visual analog scale with a 5-point facial hedonic scale. Therefore, it would appear that for the older children the formulation was not as palatable as for young children although for them parents are assumed to play an important role in the assessment.

The method of administration in the proposed SmPC states that "Each dose should be mixed with 5 mL of age-appropriate soft food or liquid". The size of the individual granules (2 mm) provides reasonable assurance that they can be swallowed with food without stimulating the urge to chew them. However, each granule contains 1.92 mg of ivacaftor. Therefore, the number of granules per sachet is 26 (50 mg) or 39 (75 mg). Swallowing them may create some difficulties for young children due to the high number of granules. In study 108, granules were provided in a capsule and parents were instructed on how to empty the capsules and administer ivacaftor with food. The MAH confirmed that the number of granules per capsule in study 108 is the same as in the case of the dosage form to be marketed, which is granules in sachet and that the volume of food or liquid used for administration is also identical to that used in the clinical trials. Instructions for age-appropriate soft food or liquid are included in the Product Information.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The application for the extension of the indication of Kalydeco to children aged 2 to 5 years is based on a single study VX11-770-108 (study 108): A phase 3, 2-part, open-label study to evaluate the safety, pharmacokinetics, and pharmacodynamics of ivacaftor in subjects with cystic fibrosis who are 2 through 5 years of age and have a *CFTR* gating mutation.

Part A was designed to evaluate the safety and PK of multiple-dose (for a 4-day period) administration of ivacaftor and to confirm (or adjust if necessary) the doses for Part B. Part B was designed to evaluate the safety, PK, PD, and efficacy of ivacaftor after 24 weeks of treatment. All patients who completed 24 weeks of study drug treatment were eligible to enrol in the open-label treatment arm of the extension study of ivacaftor (Study 109). Children aged 2 to less than 6 years with a diagnosis of cystic fibrosis as shown by the presence of a sweat chloride value ≥60 mmol/L by quantitative pilocarpine iontophoresis OR 2 CF-causing mutations and who had one of the following *CFTR* gating mutations in at least one allele (*G551D, G178R S549N, S549R G551S, G970R, G1244E, S1251N, S1255P, G1349D*) were eligible for enrolment.

The primary objectives of study 108 were safety and PK. Secondary efficacy endpoints were collected in part B as follows: absolute change from baseline in sweat chloride, weight, stature and BMI at week 24. There were also a number of tertiary (exploratory) endpoints such as pulmonary exacerbations, unplanned antibiotic therapy, hospitalisation, unscheduled visits to hospital and spirometry assessments. Palatability of the formulation in the target population was an exploratory endpoint.

A single population for analysis was defined, i.e. the safety set in both Part A and Part B defined as all subjects who received at least 1 dose of study drug (i.e., ivacaftor). Safety analyses of Part A and Part B were conducted separately. Efficacy analyses were only performed on Part B. Lack of randomisation is this study was justified on the basis that extrapolation of efficacy from adults and older children to these younger children was feasible. From this perspective, pharmacokinetics and safety of ivacaftor are the most appropriate primary endpoints for study 108. Change in percent predicted FEV1, the recommended primary endpoint to be used for registration studies as outlined in the CHMP guideline on the clinical development of medicinal products for the treatment of cystic fibrosis (EMEA/CHMP/EWP/9147/2008), is not feasible in children from birth through 5 years of age because FEV1 involves spirometry, which can only be performed in children 6 years of age and older. In addition, spirometry parameters are not sufficiently sensitive to detect early

manifestations of lung disease in young children with CF and for assessing drug effects. In study 108, preschool spirometry was conducted in accordance with American Thoracic Society and European Respiratory Society guidelines for patients ≥3 years of age.

In part A, all 9 patients completed the 4-day treatment period. In part B, a total of 34 enrolled and included in the safety set, of whom 10 patients received ivacaftor 50 mg q 12 hours and 24 patients received 75 mg q 12hours. Eight of the 9 patients who participated in Part A were enrolled in Part B. A total of 33 patients completed the 24-week treatment period. One patient, in the ivacaftor 50 mg dose group, prematurely discontinued study drug treatment due to an adverse event of increased transaminases and did not complete the follow-up visit. Baseline demographic and disease characteristics show that in Part A all children had a sweat chloride value well above the value considered as likely indicative of cystic fibrosis, i.e. >60 mmol/L. In part B, 28 (82.4%) were male patients and 6 (17.6%) were female patients; data from several cystic fibrosis registries do not show that in this age range there is a preponderance of male subjects. All children were diagnosed at either 0 or 1 month of age (newborn screening), with the exception of a single patient, who was diagnosed at the age of 2 years. Majority of children in the 50 mg group were 2 years old and weighted a mean of 12.5 kg. The majority of subjects in the 75 mg group were 4-5 years old with a mean body weight of 18.8 kg. The minimum values of weight/BMI suggest that some patients must have been undernourished. There were 32 patients with a *G551D* mutation and 2 patients with an *S549N* (i.e. non-*G551D*) gating mutation. Overall, 76.5% (26/34) had as a second *CFTR* mutation *F508del*. Second *CFTR* mutations other than *F508del* were as follows: *1471DELA* (n=1), *1717-1G>A* (n=1), *3905INST* (n=1), *394DELTT* (n=1), *G551D* (n=1, homozygous patient), *R117H* (n=1) and *R553X* (n=1). For the single patient with an *R117H-CFTR* mutation the poly-T status is *7T* in both alleles. Although patients with a *G970R* mutation were eligible for inclusion none was enrolled in study 108.

Mean sweat chloride data at baseline was available for 8 patients in the ivacaftor 50mg group and for 22 patients in the 75mg group: 93.13 mmol/L and 99.61 mmol/L, respectively. Given that symptoms and signs of lung disease may be absent during early childhood and that the correlation between genotype and phenotype for lung disease is weak, the fact that most children enrolled in study 108 had a sweat chloride above 60 mmol/L is reassuring. In Part B, all patients in the ivacaftor 50-mg group had CF lung disease while this figure was 95.8% in the 75-mg group. As for pancreatic disease, all patients in the ivacaftor 50-mg group had pancreatic insufficiency while this figure for the 75-mg group was 87.5%. Baseline faecal elastase-1 values were as follows: 5 patients in the ivacaftor 50-mg group had a value below 200 μg/g indicative of pancreatic insufficiency while for the remaining 5 the value is unknown. In the 75-mg group, 21 patients had a value below 200 μg/g, 1 patient equal or above 200 μg/g and in 7 patients this value was unknown. Infective pulmonary exacerbation of CF was reported for two children, one in the ivacaftor 50-mg group and other in the 75-mg ivacaftor group. Symptoms and signs compatible with a clinical diagnosis of CF reported for children included in Part B of study 108 were nasal polyps, CF hepatic disease, CF related diabetes, failure to thrive, poor weight gain, and others. Children in study 108 continued to receive their usual, prescribed CF therapy in addition to ivacaftor. Most common concomitant medications were pancreatin/pacrelipase, salbutamol, dornase alfa, and sodium chloride, which were taken by over 50% of subjects overall.

Efficacy data and additional analyses

Absolute change from baseline through 24 week in sweat chloride

The mean (SD) absolute change from baseline through week 24 in sweat chloride was -47.07 mmol/L (24.26) in the ivacaftor 50mg group (n=7/10) and -46.78 mmol/L (27.58) in the 75mg group (n=18/24). The decrease in sweat chloride was already evident at week 2 (fist post-baseline measure) and was maintained until week 24. The above results are based on 25/34 children

(73.5%), i.e. 9 patients were excluded from the analysis, mainly due to lack of samples, since sampling sweat chloride in this young population is often difficult. The change from baseline in sweat chloride was calculated either as the change at week 24 or trough week 24. The average values of change through week 24 showed the same trend as the values at week 24 but with some exceptions, the degree of decrease from baseline is lower. The MAH clarified that both methods of analysis of change from baseline in sweat chloride were specified in the SAP and both analysis were presented. The mean (SD) baseline sweat chloride levels (97.9 [14.0] mmol/L) decreased at Week 24 (mean absolute change from baseline, -46.9 [26.2]). Consistent with the results at Week 24, overall, sweat chloride levels decreased from baseline through Week 24 (mean absolute change from baseline, -45.5 [21.0] mmol/L). The responder analysis of sweat chloride is based on 4 categories of change in sweat chloride through 24 week. There were 8 subjects in the ivacaftor 50-mg group and 21 in the 75-mg group. This analysis showed that 7 (70%) and 19 (79.2%) patients in the ivacaftor 50- and 75-mg groups had a decrease in sweat chloride through week 24 that was ≥ 20 mmol/L. A single patient in the 50-mg group had a decrease less than 20 mmol/L while this was the case for 2 patients in the 75-mg group. The three of them had the genotype *G551D*/*F508del*. While their average absolute change in sweat chloride value though week 24 was negative in the three cases, none of them exceed the threshold of 20 mmol/l. In addition, it is noticed that in the response provided, the change for these three patients is calculated as an average absolute change through week 24.

Absolute change from baseline in weight, BMI, BMI-for-age z score and weight-for-age z-score

The mean (SD) absolute change from baseline at week 24 in body weight was 1.00 Kg (0.42) in the ivacaftor 50-mg group (n=9/10) and 1.50 Kg (0.55) in the 75-mg group (n=24/24). These figures for BMI were as follows: 0.33 Kg/m^2 (0.54) and 0.31 Kg/m^2 (0.55). Regarding the corresponding z scores, the mean (SD) change in weight-for-age z-score at week 24 was 0.19 (0.32) in the 50-mg ivacaftor group and 0.21 (0.23) in the ivacaftor 75-mg group. The corresponding 95%CI was (-0.06, 0.43) and (0.11, 031). For BMI-for-age z-score these values were as follows: 0.46 (0.46) and 0.34 (0.42) respectively. The corresponding 95%CI were as follows: (0.11, 0.81) and (0.16, 052). The MAH compared the mean absolute change from baseline at week 24 with 0, based on a 1-sample test. The only difference that was not statistically significant was the mean change in weight-for-age z-score in the ivacaftor 50-mg group (p=0.1192).

Absolute change from baseline in height and in height-for-age z-score

The mean (SD) absolute change from baseline at week 24 in stature was 2.5 cm (1.45) in the ivacaftor 50-mg group (n=9/10) and 3.5 cm (0.93) in the 75-mg group (n=23/24). The mean (SD) change in stature-for-age z-score at week 24 was -0.25 (0.45) in the 50-mg ivacaftor group and 0.18 (0.22) in the ivacaftor 75-mg group. The 95%CI for the absolute change in stature was as follows: (1.43, 3.66) and (3.14, 3.94) for the 50- and 75-mg ivacaftor groups. For the change in stature-for-age z-score the 95%CI was (-0.59, 0.10) and (-0.01, 0.17) respectively. Height increase seems to be reduced compared to WHO data in the lower ivacaftor dose group (WHO data, median: 5 cm/6 months and 4.5 cm/6 months in girls and boys aged 2-3 years, respectively).

Nutritional status has a significant effect on pulmonary disease progression and survival in patients with cystic fibrosis. While acute malnutrition is associated with weight loss, chronic malnutrition also affects height. The Cystic Fibrosis Foundation recommends the use of BMI for children aged 2 years and above as indicator of their nutritional status. Data from CF registries show consistent pattern of lower BMI percentile values at higher ages. Children in the age range from 2 to 6 years are (as a group) usually above the 50th percentile for BMI. The 10 children enrolled in study 108 in the 50-mg ivacaftor group had at baseline a mean (SD) BMI-for-age z score of -0.23 (0.57) that at

week 24 increased up to 0.19 (0.48). However, the stature–for-age z score remained at week 24 below the median percentile as shown by a mean z-score of -0.25 (but from -0.90 at baseline). Overall, the assessment of nutritional status is incomplete and its interpretation difficult in the absence of information about specific interventions to improve the nutrition of children enrolled in study 108. Furthermore, due to the lack of placebo control, the magnitude of effect of ivacaftor treatment cannot be clearly assessed on nutritional status in this age group. In spite of this, the data provided show, in general, an improvement of the nutritional status of these young children that occurs in addition to the interventions aimed at improving growth and of the administration of pancreatic enzyme replacement therapy.

Qualitative Microbiology Cultures

The MAH conclusion that no obvious trends were observed in terms of new growths or shifts to higher or lower amounts of each microbe is, overall, acknowledged based on the data provided. The pattern of lung colonisation based on qualitative microbiology cultures from oropharyngeal swabs is consistent with that described for young children, with *S aureus* and *H influenzae* appearing in the early years and *P aeruginosa* usually later in life.

Pulmonary exacerbations

Two definitions of pulmonary exacerbations were used. Definition 2 was more conservative than Definition 1. The common criterion both definitions had to meet was the need for treatment with oral, inhaled or IV antibiotics. According to definition 1, 2 (20%) patients in the ivacaftor 50-mg group had 5 pulmonary exacerbations (event rate: 0.54) while in the 75-mg group 13 (54.2%) patients had 30 pulmonary exacerbations (event rate: 1.24). Of these, a patient in each group received IV antibiotics and required hospitalisation. Approximately 80% patients in the ivacaftor 50-mg group were event-free between Days 113 and 168. This figure in the 75-mg group was 45%. The apparent difference in time-to-first pulmonary exacerbation between the ivacaftor 50 mg and ivacaftor 75 mg groups may be explained by the low number of subjects (≤10 subjects) in the ivacaftor 50 mg group. According to definition 2, 5 subjects had a total of 6 pulmonary exacerbations: 1 subject with 2 pulmonary exacerbations in the ivacaftor 50-mg group and 4 subjects with 4 pulmonary exacerbations in the ivacaftor 75-mg group. No subjects were hospitalized or required IV antibiotic therapy due to pulmonary exacerbations. Overall, the interpretation of data of time-to-first pulmonary exacerbation is hampered by the small number of patients. In general, very few events are expected in this young population of CF patients.

Spirometry

Percent predicted FEV1 was measured in 20 children, 3 in the 50-mg ivacaftor group and 17 in the 75-mg group. The mean (SD) change from baseline in percent predicted FEV1 at week 24 was -12.47 (30.12) in the ivacaftor 50-mg group and 4.30 (14.78) in the 75-mg group. Percent predicted FEV1 decreased during the treatment period in the ivacaftor 50 mg group. The MAH clarified that these 3 patients had respiratory-related AEs during the treatment period that may have affected the spirometry measurements. Overall, interpretation of the results in change in percent predicted FEV1 needs to consider the high degree of variability in the measurements due to the technical difficulties of conducting spirometry in young children and also the small number of patients with baseline and on-treatment spirometry data. This is shown by the wide 95%CI that ranges from −87.27 to 62.35 in the ivacaftor 50-mg group. It has been suggested that for young children forced expiratory volumes at 0.75 second (FEV0.75) or at 0.5 second (FEV0.5) are more appropriate than (percent predicted) FEV1. The mean absolute change in percent predicted FEV0.75 shows the same trend of change as percent predicted FEV1.

Faecal Elastase-1

Faecal elastase-1 is used clinically to diagnose pancreatic exocrine insufficiency in CF patients. The diagnostic cut-offs for pancreatic exocrine function below 200 μg/g indicate pancreatic insufficiency.

Baseline faecal elastase-1 values were as follows: 5 patients in the ivacaftor 50-mg group had a value below 200 μg/g while for the remaining 5 the value was unknown. In the 75-mg group, 21 patients had a value below 200 μg/g, 1 patient equal to or above 200 μg/g and in 2 patients this value was unknown. The mean (SD) change from baseline in faecal elastase-1 at Week 24 was 127.9 μg/g (191.84) in the ivacaftor 50-mg group (n=5) and 93.5 μg/g (128.28) in the 75-mg ivacaftor group (n=22). The overall (both groups combined) mean (SD) absolute change from baseline in faecal elastase-1 was 99.8 μg/g (138.35). Although it is claimed that there was a substantial increase from baseline in this parameter, which may suggest an improved pancreatic function, it is not known how this translates clinically, e.g. if a reduction of the dose of pancreatic enzyme replacement therapy could be considered. In addition, levels of faecal elastase-1 are not available at baseline for 5 (50%) patients in the 50-mg ivacaftor group and for two patients in the 75-mg ivacaftor group. Additional data were requested for these 7 patients. Two of them do not have any value available either in study 108 or 109. Of the remaining 5 patients, 2 of them had at all available points in time in study 108 values well below 200 μg/g. Two additional patients had at week 24 and at week 48 of study 109 a value above 200 μg/g (as compared to values below 200 μg/g in prior visits in study 108). Finally, values for the last patient increased progressively during study 108 and study 109 but were still below 200 μg/g. A total of 6 patients with initial faecal elastase-1 values below 50 μg/g in study 108 experienced an increase at 24 weeks in study 108 that was ≥200 μg/g (indicative of pancreatic sufficiency). However, these values were maintained in study 109 only in two of them. Four patients with initial faecal elastase-1 values below 200 μg/g in study 108 had faecal elastase-1 values ≥200 μg/g during ivacaftor treatment in study 109. For three of them the first available measure in study 108 was below 15 μg/g.

In conclusion, it seems that faecal elastase-1 increased above the threshold of 200 μg/g (indicative of pancreatic sufficiency) in a very limited number of patients in study 108. It seems premature at this stage to conclude that ivacaftor is associated with an improvement in pancreatic function in these young children based on the current data.

Palatability of ivacaftor granules

Palatability assessment was performed in Part A and Part B of the study following administration of the first dose of study drug. In Part A, all 9 subjects in the 2 ivacaftor dose groups fully consumed the first dose. In Part B, two patients (one per group) did not provide any palatability assessment. Eight and 23 patients in the ivacaftor 50- and 75-mg groups fully consumed the first dose of study drug. Seven and 11 respectively expressed that they like it very much while 3 patients in the ivacaftor 75-mg group dislike it very much. This was similar to the assessment made by the parents and also similar to the assessment made by patients of 4 years of age and older using a visual analogue scale with a 5-point facial hedonic scale. Therefore, it appears that for the older children the formulation was not as palatable as for young children and parent play an important role in the assessment. In addition, an open-label taste profile study to characterize the sensory attributes of the ivacaftor paediatric granule formulation was performed in 5 healthy volunteers who tasted powder blends and the prototype granule formulation with foods or liquids. In conclusion, all evaluated foods and liquids were considered to be suitable dosing vehicles for the VX-770 granules from a flavour perspective. However, the gritty texture resulting from incomplete disintegration in low moisture foods products may be unacceptable to some patients, particularly infants. The method of administration is adequately reflected in the SmPC.

Subgroup analyses

Subgroup analysis have been performed for sweat chloride, weight, stature, and BMI by age group at baseline (2, 3, and 4 to 5 years of age), geographic region (North America and Europe), sex and

percent predicted FEV1 severity category at Baseline (<70%, ≥70% to ≤90%, >90%, and not done). The MAH conclude that the results of subgroup analyses were similar to those of the Safety Set overall. It is noticed that the number of patients per subgroup is small limiting any conclusions from these subgroup analyses. As an example only 6 female patients, 4 on ivacaftor 50 mg and 2 on 75 mg were enrolled in study 108. A review of the summary statistics provided for nutritional parameters by sex (given the preponderance of male patients in study 108) shows that the magnitude of the increase in weight- and BMI for-age z-scores was higher in female patients than in male patients. Regarding percent predicted FEV1, 8 patients and 7 patients in the 75-mg group had percent predicted FEV1 of ≥70% to ≤90% and >90% respectively. Two patients had percent predicted FEV1 <70%. These figures for patients on ivacaftor 50 mg were 1, 2 and none, respectively. With very few exceptions almost all subgroups showed an increase in their mean weight- and BMI-for-age z-scores.

2.5.4. Conclusions on the clinical efficacy

Studies performed in CF children diagnosed by newborn screening suggest that early intervention is associated with an improvement in nutritional status and lung disease. It is therefore postulated that initiation of treatment with ivacaftor at a young age could postpone or even prevent the onset of clinical manifestation of CF. The MAH conducted study 108 to provide data on the safety and benefit of ivacaftor administered to children younger than 6 years. Study 108 was an uncontrolled study, which raises uncertainties regarding the accuracy of the effect of ivacaftor in the target population. Acceptance of this study design is made on the basis that extrapolation of efficacy from older children and adults to the younger children enrolled in study 108 may be feasible as efficacy has been proven in older age groups of patients with CF carrying *G551D* and several other gating mutations of the *CFTR* gene. The ICH guideline E11 (Clinical Investigation of Medicinal Products in the Paediatric Population) states that when a medicinal product is to be used in younger paediatric patients for the same indication as that studied in older paediatric patients, the disease process is similar, and the outcome of therapy is likely to be comparable, extrapolation of efficacy from older to younger paediatric patients may be possible. In such cases, pharmacokinetic studies in the relevant age groups of paediatric patients likely to receive the medicinal product, together with safety studies, may be sufficient to provide adequate information for paediatric use.

In the particular case of ivacaftor, although the underlying cause of CF is the same in childhood and adulthood, the heterogeneity of target organs and the progression of the disease over time lead to clinical manifestations that vary according to age. Sweat chloride changes are comparable across younger and older children. This is reassuring but insufficient given that sweat chloride cannot be considered as a surrogate for clinical outcome. No attempts have been performed to validate other possible pharmacodynamic endpoints. The assessment of secondary efficacy endpoints in study 108 shows, in general, consistency with the results of the prior registration studies of ivacaftor in older patients. The main exception refers to lung function in the 50-mg ivacaftor group but this observation is based on data from 3 children only, and, consequently, it should be viewed with caution. In an attempt to gain additional certainty, the CHMP requested two comparative analyses between the results seen in children enrolled in study 108 and patients with CF with pancreatic insufficiency receiving pancreatic enzymes, of the same age range and with *CFTR* gating mutations who had not been treated with ivacaftor and were followed in existing registries. However, the MAH was unable to provide the requested information during this procedure, but stated that these data can be captured in the ongoing long-term safety study (ANX-001).

The MAH was also requested to discuss what data of relevance for long term efficacy and safety could be extracted from existing registries and address feasibility issues, e.g. in terms of coverage of the target population, availability and completeness of data in relevant disease registries needed

to define exposure, appropriate comparator treatment, relevant outcomes, and potential confounders related to the conduct of such study. This should have also included expectations regarding what size of exposed study population is achievable. In this respect the MAH argued that registry data may be of limited value due to the fact that the size of the target population is small and there is limited scope to demonstrate an impact on lung function due to both feasibility of assessments in very young children and their relatively well preserved lung function. However, as above mentioned, the MAH was of the opinion that these data could be captured in the ongoing long-term safety study (ANX-001). However, this study is already ongoing and the value of a follow-up that is less than that of older patients is dubious. Therefore, the MAH was requested to discuss concrete alternatives to gather data on long-term efficacy of ivacaftor in the post-authorisation setting. Length of follow up should be sufficient to provide insight on the evolution of the manifestations of the disease (including lung disease) and a control group should be constructed to facilitate interpretation of the results. Since the proposed ivacaftor treatment of children with CF is long-term, the CHMP considered that efficacy and safety data to be obtained from the post-authorisation study regarding such long-term treatment would be key for the benefit-risk balance of ivacaftor in the newly granted extension of indication. Therefore, such study is to be included as an obligation in Annex II of the marketing authorisation.

The applicant accepted to perform a post-authorisation efficacy study within the US Cystic Fibrosis Foundation (CFF) registry and the UK Cystic Fibrosis registry (this latter one as supportive data given the low number of patients). A protocol synopsis capturing the key elements of the design of this study was provided. The main objective of this study is to compare disease progression among children with CF who have a specified CF transmembrane conductance regulator gene (*CFTR*) gating mutation and are 2 through 5 years of age at the time of Kalydeco treatment initiation (142 patients 2 through 5 years of age with 1 of the *CFTR* gating mutations of interest in the US CF CFF Patient Registry) versus disease progression in a concurrent comparator cohort of children who are homozygous for the *F508del-CFTR* mutation, have never received Kalydeco therapy or any other *CFTR* modulator therapy.

Two additional (supportive) cohorts will be used for comparison: 1) historical data from an earlier time period of children with CF who have a specified *CFTR* gating mutation, aged 2 to 5 years and had never been exposed to Kalydeco; and 2) relevant data from the ongoing Kalydeco PASS study on children aged 6 to 11 years at the time of Kalydeco initiation. Potentially, the cohort of children who initiated treatment at the age of 6 to 11 years would enable indirect comparison of outcomes (included in the current PASS protocol) between cohorts starting Kalydeco earlier and later in life although it was acknowledged that these cohorts are not concurrent and they are inherently different raising a concern for channeling bias.

Power estimations were provided to detect a difference in pulmonary exacerbation risk and changes in nutritional parameters under 2 scenarios (100% product uptake in the target population and 75% product uptake in the target population). Based on changes from baseline after 24 weeks of ivacaftor treatment in study 108 and assuming effect size is maintained, the MAH anticipate that the study will be sufficiently powered to detect changes in nutritional status.

The effectiveness of ivacaftor with respect to lung function in young children will be assessed by following them for 6 years, allowing them to reach the age when lung function measurements are routinely performed and are more reliable. Children aged 2 years will be followed until they are 9 years old while children aged 5 will be followed until the age of 12 years old. The following timelines were agreed for providing CHMP with interim analysis: Interim Analysis 1 (IA1) will be performed after the "enrolment" period closes (31 December 2016) and will include the description of baseline characteristics of patients in US and UK Kalydeco and Concurrent Comparator Cohorts as well as the US and UK Historical Cohort analyses and summary of relevant data from the ongoing PASS study on children 6 to 12 years of age at the time of Kalydeco initiation. The IA1

report will be submitted by 31 December 2017. Interim Analysis 2 (IA2) will be performed after completion of the second year of follow-up (31 December 2018), when all patients in the Kalydeco and Comparator Cohorts would have reached at least 4 years of age. The IA2 report will be submitted by 31 December 2019. Interim Analysis 3 (IA3) will be performed after completion of the fourth year of follow-up (31 December 2020), when all patients in the Kalydeco and Comparator Cohorts would have reached at least 6 years of age. The IA3 report will be submitted by 31 December 2021. The final analysis will be performed after completion of the sixth year of follow-up (31 December 2022), when all patients in the Kalydeco and Comparator Cohorts would have reached at least 8 years of age. The final report will be submitted by 31 December 2023.

This study will be considered as a condition of the Marketing Authorisation in the Annex II.

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

Long-term effectiveness study. To compare disease progression among children with CF who have a specified CFTR gating mutation and are aged 2 through 5 years at the time of Kalydeco treatment initiation versus disease progression among concurrent matched cohort of children with CF who have never received Kalydeco treatment. Final report: December 2023. This study is considered to be a study imposed in accordance with Article 34 of Regulation (EC) No 1901/2006.

2.6. Clinical safety

Short-term safety data from study 108 including children with CF aged 2 to 5 years and having a *CFTR* mutation were presented. Children who completed the 24-week treatment period in Study 108 were offered the opportunity to continue onto the ivacaftor treatment arm of Study VX11-770-109, currently ongoing. In addition, safety data from 2 completed Phase 1 studies (Studies 012 and 015) and from 2 completed taste profiling studies (Studies 004 and 014) are also presented, although their findings were considered less relevant.

Patient exposure

Study 108: Data from 35 children who received at least 1 dose of ivacaftor are presented. This includes 1 subject who was enrolled only in Part A, 8 subjects who were enrolled in both Part A and Part B, and 26 subjects who were enrolled only in Part B. The mean treatment duration (standard deviation [SD]) was 156.4 (48.90) days in the 50-mg group and 169.4 (2.64) days in the 75-mg group. All but 1 subject received at least 16 weeks of treatment; 1 subject in the 50-mg group received treatment for <4 weeks. Table below provides a summary of part B exposure to ivacaftor.

Study 108 Part B: Study Drug Exposure, Safety Set

Exposure Summary	Category or Statistic	Ivacaftor 50 mg (N = 10)	Ivacaftor 75 mg (N = 24)	Overall (N = 34)
Exposure to Study Drug (Days)	n	10	24	34
	Mean (SD)	156.4 (48.90)	169.4 (2.64)	165.6 (26.33)
	Median (Min, Max)	170.0 (18, 184)	169.0 (161, 75)	169.0 (18, 184)
Exposure Classification (Weeks)	0 to <2	0	0	0
	2 to <4	1 (10.0)	0	1 (2.9)
	4 to <8	0	0	0

8 to <12	0	0	0
12 to <16	0	0	0
16 to <24	2 (20.0)	2 (8.3)	4 (11.8)
≥24	7 (70.0)	22 (91.7)	29 (85.3)

Phase I studies: Safety data for 20 adults from study 012 (4-single-dose period), 20 adults from study 015 (4-single-dose period), 4 adults from study 004 (taste profiling studies) and 5 adults from study 014 (taste profiling studies) are also presented.

Adverse events

Adverse events (AEs) were classified using Medical Dictionary for Regulatory Activities (MedDRA) preferred terms (PTs). The grading scale "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials"5 was used in Study 108 by the investigator to assign a severity to each adverse event.

Study 108, part A

- Overall, 8 (88.9%) of the 9 subjects in the Safety Set had adverse events. The SOC with the greatest incidence of adverse events was general disorders and administration site conditions, with 55.6% of subjects overall with adverse events in this SOC. The most commonly reported adverse events in this SOC was pyrexia, which occurred in 4 subjects (44.4%) overall.

- Of the 8 subjects with adverse events, 6 subjects had mild adverse events and 2 subjects had moderate adverse events. No severe or life-threatening adverse events occurred. The most frequent adverse events were pyrexia (4 subjects), vomiting (2 subjects), rhinorrhea (2 subjects), and ecchymosis (2 subjects).

- There were no SAEs or deaths.

- There were no AEs that led to permanent discontinuation of study drug. One subject had adverse events (fever, abdominal bloating, abdominal pain, vomiting, and mild pancreatic enzymes increased) that led to temporary interruption of study drug for 1 day.

- The majority of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels were ≤2 × upper limit of normal (ULN) and there were no bilirubin elevations. Two subjects with pre-existing liver function test (LFT) elevations, 1 in each dose group, had maximum on-treatment ALT elevations >3 x to ≤5 x ULN.

- There were no other clinically meaningful trends in clinical laboratory evaluations, vital signs, ECGs, or physical examination findings during the study.

- Based on slit lamp examination, no subjects developed lens opacities and there were no clinically meaningful changes in LOCS III grading.

Study 108, part B

Table below summarizes the incidence of children with adverse events in study 108.

Study 108 Part B: Integrated Summary of Adverse Events, Safety Set

Category	Ivacaftor 50 mg (N = 10) n (%)	Ivacaftor 75 mg (N = 24) n (%)	Overall (N = 34) n (%)
Subjects With Any Adverse Events	**10 (100.0)**	**23 (95.8)**	**33 (97.1)**
Subjects with related adverse events	3 (30.0)	8 (33.3)	11 (32.4)
Subjects with adverse events leading to death	0	0	0
Subjects with serious adverse events	3 (30.0)	3 (12.5)	6 (17.6)
Subjects with related serious adverse events	1 (10.0)	0	1 (2.9)
Subjects with adverse events leading to study drug interruption	4 (40.0)	7 (29.2)	11 (32.4)
Subjects with related adverse events leading to study drug interruption	1 (10.0)	1 (4.2)	2 (5.9)
Subjects with adverse events leading to study drug withdrawal	1 (10.0)	0	1 (2.9)
Subjects with related adverse events leading to study drug withdrawal	1 (10.0)	0	1 (2.9)

Overall, 33 (97.1%) of the 34 subjects in the Safety Set had adverse events. Overall, 11 subjects (32.4%) had related adverse events: 3 subjects (30.0%) in the ivacaftor 50 mg group and 8 subjects (33.3%) in the ivacaftor 75 mg group. No deaths occurred in this study. Overall, 6 subjects (17.6%) had SAEs, 3 subjects in each dose group, only 1 of which (in the ivacaftor 50 mg group) was assessed as related to study drug and also resulted in permanent discontinuation of study drug. A total of 11 subjects, 4 subjects (40.0%) in the ivacaftor 50 mg group and 7 subjects (29.2%) in the ivacaftor 75 mg group, had adverse events that resulted in study drug interruption.

Adverse events with an incidence of at least 10% subjects in either dose group were presented by SOC and PT. The SOC with the greatest incidence of adverse events was respiratory, thoracic, and mediastinal disorders, with over 80% of subjects overall with adverse events in this SOC. The most commonly reported adverse event in this SOC was cough, which occurred in 55.9% subjects overall (40% subjects in the ivacaftor 50 mg group and 62.5% subjects in the ivacaftor 75 mg group).

The following SOCs also had adverse events with an incidence of at least 20% of subjects overall:

- Infections and infestations: 58.8% subjects overall
- Gastrointestinal disorders: 44.1% subjects overall
- Investigations: 35.3% subjects overall
- Skin and subcutaneous tissue disorders: 23.5% subjects overall
- General disorders and administrative site conditions: 20.6% subjects overall

By Preferred Term, the adverse events with the greatest incidence were generally respiratory and gastrointestinal in nature. The most common adverse events by PT (10% of subjects overall) were cough (55.9%), vomiting (29.4%), nasal congestion (26.5%), upper respiratory tract infection (23.5%), rhinorrhea (20.6%), pyrexia (17.6%), infective pulmonary exacerbation of CF (14.7%), constipation (11.8%), and rash (11.8%).

When both dosing groups of study 108 are compared the incidence of related serious AEs was higher for the 50-mg group (10% versus 0%) and for drug-related AEs leading to interruption (10% versus 4.2%). Also the incidence of most AEs by SOC was higher for the ivacaftor 50-mg group, i.e., respiratory, thoracic and mediastinal disorders (80% and 83.3%), gastrointestinal disorders (50% versus 41.7%), Investigations (50% versus 29.2%) and Infections and Infestations (60% and 58.3%). By preferred terms, the AEs with the highest incidence were cough (40% and 63% for the ivacaftor 50-mg and 75-mg groups, respectively), nasal congestion (40% and 21%) and vomiting

(30% and 29%). Exacerbations of CF were reported in 10% and 17% of patients on ivacaftor 50 mg and 75 mg, respectively. The majority of subjects had adverse events that were mild or moderate in severity. Of the 33 subjects with adverse events, 15 subjects had mild adverse events and 16 subjects had moderate adverse events. Overall, the incidence of mild and moderate adverse events was similar across the ivacaftor 50 mg and ivacaftor 75 mg groups.

Approximately one-third of subjects overall had adverse events that were considered possibly related to study drug. All adverse events that were considered possibly related to study drug occurred in only 1 subject, except rash, which was reported in 2 subjects (both in the 75-mg group).

Study 108 Part B: Related and Possibly Related Adverse Events by Preferred Term and Dose Group, Safety Set

Preferred Term	Ivacaftor 50 mg N = 10 n (%)	Ivacaftor 75 mg N = 24 n (%)	Overall N = 34 n (%)
Subjects With Possibly Related Adverse Events	**3 (30.0)**	**8 (33.3)**	**11 (32.4)**
Alanine aminotransferase increased	0	1 (4.2)	1 (2.9)
Aspartate aminotransferase increased	0	1 (4.2)	1 (2.9)
Blood creatine increased	0	1 (4.2)	1 (2.9)
Hepatic enzyme increased	1 (10.0)	0	1 (2.9)
Transaminases increased	1 (10.0)	0	1 (2.9)
Constipation	0	1 (4.2)	1 (2.9)
Eructation	0	1 (4.2)	1 (2.9)
Vomiting	0	1 (4.2)	1 (2.9)
Rash	0	2 (8.3)	2 (5.9)
Acne	0	1 (4.2)	1 (2.9)
Petechiae	0	1 (4.2)	1 (2.9)
Cough	1 (10.0)	0	1 (2.9)
Productive cough	0	1 (4.2)	1 (2.9)
Snoring	0	1 (4.2)	1 (2.9)
Pyrexia	0	1 (4.2)	1 (2.9)

Serious adverse event/deaths/other significant events

There were no life-threatening adverse events or deaths in this study. Two subjects, both in the 50-mg dose group, had severe adverse events (transaminases increased [2 years old] and device-related sepsis [3 years old]). Both of the severe adverse events were considered SAEs and were resolved.

The below table presents the incidence of SAEs by SOC, PT, and age (2 years, 3 years, and 4 to 5 years of age). A total of 7 SAEs occurred: 3 in subjects 2 years of age; 3 in subjects 3 years of age; and 1 in a subject 4 years of age.

By PT, the most common SAE was infective pulmonary exacerbation of CF, which occurred in 2 subjects who were both 3 years of age. All other SAEs occurred in no more than 1 subject overall. One subject who was 3 years of age had 2 SAEs (infective pulmonary exacerbation of CF and device-related sepsis).

Study 108 Part B: Serious Adverse Events by System Organ Class, Preferred Term, and Age, Safety Set

	2 Years			3 Years			4 to 5 Years		
System Organ Class Preferred Term	Ivacaftor 50 mg (N = 7) n (%)	Ivacaftor 75 mg (N = 2) n (%)	Overall (N = 9) n (%)	Ivacaftor 50 mg (N = 3) n (%)	Ivacaftor 75 mg (N = 8) n (%)	Overall (N = 11) n (%)	Ivacaftor 50 mg (N = 0) n (%)	Ivacaftor 75 mg (N = 14) n (%)	Overall (N = 14) n (%)
Subjects With Serious Adverse Events	**2 (28.6)**	**1 (50.0)**	**3 (33.3)**	**1 (33.3)**	**1 (12.5)**	**2 (18.2)**	**0**	**1 (7.1)**	**1 (7.1)**
Infections and infestations	--	--	--	**1 (33.3)**	**1 (12.5)**	**2 (18.2)**	--	--	--
Infective pulmonary exacerbation of CF	--	--	--	1 (33.3)	1 (12.5)	2 (18.2)	--	--	--
Device-related sepsis	--	--	--	1 (33.3)	0	1 (9.1)	--	--	--
Investigations	**2 (28.6)**	**0**	**2 (22.2)**	--	--	--	--	--	--
Pseudomonas test positive	1 (14.3)	0	1 (11.1)	--	--	--	--	--	--
Transaminases increased	1 (14.3)	0	1 (11.1)	--	--	--	--	--	--
Gastrointestinal disorders	**0**	**1**	**1 (11.1)**	--	--	--	--	--	--
Vomiting	0	1 (50.0)	1 (11.1)	--	--	--	--	--	--
Nervous system disorders	--	--	--	--	--	--	0	1 (7.1)	1 (7.1)
Convulsion	--	--	--	--	--	--	0	1 (7.1)	1 (7.1)

Laboratory findings

Adverse events associated with LFTs occurred in 3 subjects in the 50-mg group and 2 subjects in the 75-mg group. In one subject (2 years old), an SAE of transaminases increased led to permanent discontinuation of study drug.

Mean absolute changes from baseline to Week 24 for LFT parameters of alkaline phosphatase, ALT, AST, total bilirubin, and gamma-glutamyl transferase (GGT) are summarized in table below.

Study 108 Part B: Liver Function Test Parameters Absolute Changes From Baseline to Week 24, Safety Set

	Ivacaftor 50 mg N = 10				Ivacaftor 75 mg N = 24			
Parameter	n	Mean Change (SD)	Median Change	Min/Max	n	Mean Change (SD)	Median Change	Min/Max
Alanine aminotransferase (U/L)	9	-13.7 (33.96)	-3.0	−100/19	22	14.9 (68.30)	-1.0	−11/319
Aspartate aminotransferase (U/L)	9	13.00 (52.096)	-4.00	−25.0/149.0	22	11.64 (54.098)	-1.00	−13.0/252.0
Alkaline phosphatase (U/L)	9	-30.3 (30.40)	-35.0	−78/32	22	-4.8 (26.43)	2.0	−48/40
Gamma-glutamyl transferase (U/L)	9	−5.89 (13.815)	1.00	−30.0/7.0	22	2.07 (6.987)	1.00	−8.0/24.0
Total bilirubin (µmol/L)	9	0.7 (1.50)	0.0	−1/4	22	0.8 (1.66)	0.0	−1/5

Overall (both dosing groups combined), 5 subjects (14.7%) had a maximum on-treatment ALT or AST of >8 × ULN. Moderate transaminase elevations seem to be frequent in subjects with CF and according to the MAH, published information suggests that transaminase elevations are more common in younger patients than in adults and particularly frequent in the first 2 to 3 years of life. Overall, most children in study 108 had maximum on-treatment ALT, AST, and total bilirubin values that were ≤2 × ULN (82.4%, 82.4%, and 100.0%, respectively). However, while these values were under this threshold for almost all children on ivacaftor 75 mg (i.e., 91%, 91% and 100%), these percentages were reduced to 60% for transaminase levels in children receiving ivacaftor 50 mg. In this dosing group 3 children (30%) had ALT >8 × ULN and 1 of them (10%) also had AST >8 × ULN. One child with history of previous transaminase increase during a viral illness had elevations on LTFs after starting ivacaftor that led to discontinuation. Two children on ivacaftor 75 mg (8.3%) had also ALT >8 × ULN. One child had AST>5 to ≤8 x ULN.

The incidence of transaminase elevations across different ranges was similar for ivacaftor and placebo groups in moderate liver abnormalities. Study 108 shows a higher incidence of transaminase levels >8 x ULN in children weighing less than 14 kg that was 10 times the one seen in study 103 (30% versus 3.8% for ALT increase). Although it is acknowledged that the absence of

a control arm in study 108 makes it impossible to know whether a similar pattern had been observed in young children with CF who do not receive ivacaftor, close monitoring of liver function in younger children should be recommended in section 4.4 of the SmPC.

There were no abnormal or potentially clinically significant ECG findings during the 24-week treatment period, and there were no adverse events associated with ECG abnormalities.

Due to the finding of an increase in cataracts in juvenile rats in a nonclinical study (see section 2.3 of this report), ophthalmologic examinations were performed at baseline, Week 12, and Week 24. Changes from baseline were minimal, and no clinically important trends attributable to ivacaftor treatment were observed. No subjects developed lens opacities during the study. One subject in the 75-mg group was included in the study despite a screening ophthalmological examination revealing Mittendorf opacity. This finding was considered congenital, nonprogressive, clinically insignificant, and the subject continued on treatment without any changes from baseline in respect to lens characteristics. Visual acuity of the left and right eyes was also measured at baseline, Week 12, and Week 24. Changes from baseline to Week 12 and Week 24 were minimal in both dose groups, and no clinically important trends attributable to ivacaftor treatment were observed.

No relevant change has been observed in coagulation parameters or in haematological parameters.

Safety in special populations

Data form study 108 show that the majority AEs were reported in youngest children (2 and 3 years old), most of them weighing less than 14 kg. It appears that AEs are more common in males than in females. Regarding baseline FEV1, the patients with FEV1<70% reported, more AEs except for cough, vomiting, upper respiratory tract infections and pulmonary exacerbations that were more frequent in children with FEV1>90%. The analysis for geographical regions shows that AEs were more common in European than in North American children. There is a significant difference between the two regions in exacerbations of CF (50% in Europe versus 3.8% in North America). This has been observed in previous trials of ivacaftor and is usually attributed to chance findings, however, it cannot be ruled out that other (unknown) factors could also contribute.

Safety related to drug-drug interactions and other interactions

Ivacaftor is a substrate of cytochrome P450 (CYP) 3A4 and 3A5 isoenzymes. As a consequence, any medicinal product that modifies CYP3A activity may impact the PK of ivacaftor. A reduction of the ivacaftor dose from twice a day to twice a week is recommended for coadministration with strong CYP3A inhibitors (150 mg twice a week for patients ≥6 years of age, 75 mg twice a week for patients 2 to <6 years of age with a body weight ≥14 kg, and 50 mg twice a week for patients 2 to <6 years of age with a body weight <14 kg). A reduction in the ivacaftor dose from twice daily to once daily is recommended for coadministration with moderate CYP3A inhibitors (150 mg once daily for patients ≥6 years of age, 75 mg once daily for patients 2 to <6 years of age with a body weight ≥14 kg, and 50 mg once daily for patients 2 to <6 years of age with a body weight <14 kg). Coadministration with strong CYP3A inducers is not recommended.

Ivacaftor is also a weak CYP3A and permeability glycoprotein (P-gp) inhibitor and may therefore modify the PK of medicinal products that are substrates for CYP3A and/or P-gp. In vitro studies indicated that ivacaftor has the potential to inhibit CYP2C9. Therefore, CYP3A and P-gp substrates such as benzodiazepines, tacrolimus, digoxin, and cyclosporine should be used with caution and appropriate monitoring. In addition, warfarin should be used with caution and appropriate monitoring. The SmPC includes the above information.

Discontinuation due to adverse events

In part A of study 108, nine subjects were enrolled and received at least 1 dose of ivacaftor. There were no adverse events that led to permanent discontinuation of study drug. A child had an

adverse event of fever, abdominal bloating, abdominal pain, vomiting, and mild pancreatic enzymes increase that led to a temporary interruption of study drug. In part B, a child in the 50-mg dosing group discontinued due to an adverse event oftransaminase increase while all children in the 75-mg group completed the follow-up visit.

Adverse events leading to temporary interruption of ivacaftor were reported in 11 children (32.4%) overall, 4 (40%) in the ivacaftor 50-mg group and 7 (29.2%9 in the 75-mg group. All adverse events that caused temporary withdrawal of study drug were resolved by the end of the study. Two of these adverse vents (one per dosing group) were considered drug-related.

Post marketing experience

Ivacaftor is approved in the US, European Union (EU), Canada, Australia, New Zealand, Switzerland, and Liechtenstein. A cumulative and interval summary tabulation of serious and nonserious adverse reactions was provided and covers a total of 1954 patients (747970 person-days) who received at least 1 dose of ivacaftor during the time period from the International Birth Date of ivacaftor
(31 January 2012) to 23 January 2014.

2.6.1. Discussion on clinical safety

The most relevant safety data for this extension of marketing authorisation originate from study 108, which enrolled CF children aged 2 to less than 6 years with a *CFTR* gating mutation; one child was enrolled only in part A, 8 children were enrolled in parts A and B and 26 only in part B of the study.
In addition, safety data from 40 adults included in bioavailability studies as well as 9 included in the taste profiling studies were also presented although the relevance of these data is limited as these were healthy adults. As a consequence, discussion on safety data focuses on study 108.

The AEs grading system used in study 108 was the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials which was considered more appropriate than the Common Terminology Criteria for Adverse Events (CTCAE) for young children.

In part A of the study 108, 3 and 5 patients on ivacaftor 50mg and 75mg, respectively, reported at least an adverse event (AE) indicating that safety issues start very soon after treatment. Nine patients in part A reported a total of 42 AEs (36 by 5 patients receiving 75mg and 6 by 4 patients receiving 50mg). Pyrexia and rash were reported by 2 patients and a single patient respectively in the 50mg dose group. For the 75mg dose gastrointestinal events, pyrexia and rhinorrhoea were the most commonly reported AEs. Two cases of transaminase level elevations and a case of pancreatic enzymes increased occurred. A patient on 75mg reported an AE of fever, abdominal bloating, abdominal pain, vomiting and pancreatic enzymes increased that led to drug interruption. The CHMP requested the MAH to provide the narrative of this patient including the values of pancreatic enzymes because the clinical picture resembled that of an acute pancreatitis. Pancreatic enzyme elevations were mild although the exact values were not given. It was clarified that only a single ivacaftor dose was missed due to this event and, therefore, no further issues were raised in this respect. Elevations of pancreatic enzymes are subject to reporting via PSURs. In the 50 mg dosing group an additional child was reported to have an increase in transaminases. This child had a serious adverse event in part B of increased transaminases that led to permanent discontinuation of study drug. In part A, both children had a maximum on-treatment ALT value of >3 to ≤5 x ULN.

In part B, almost all patients reported at least an AE (100% and 95.8% for ivacaftor 50 mg and 75 mg dosing groups, respectively). By preferred term, adverse events with the highest incidence were cough (40% and 63%), nasal congestion (40% and 21%) and vomiting (30% and 29%). Exacerbations of CF were reported in 10% and 17% of patients on ivacaftor 50mg and 75mg,

respectively. Vomiting seems particularly frequent with 3 (30.0%) and 7 (29.2%) patients in the 50-mg and 75-mg dosing groups reporting this adverse event. Vomiting resulted in interruption of ivacaftor dosing in 2 children in the 75-mg group and in a child in the 50-mg group. However, vomiting was considered possibly related to ivacaftor and serious only in a child treated with 75 mg.

In all, 11 patients (32.4%) had possibly related AEs, with only 1 of them considered as serious, two patients had drug-related AEs leading to study drug interruption and an additional one leading to permanent withdrawal. When both treatment groups are compared it can be seen that in the ivacaftor 50-mg group three children (30%) had possibly related AEs, 1 of them (10%) had serious drug-related AEs, 1 (10%) had AEs leading to drug discontinuation and another one (10%) had AEs leading to drug withdrawal. In the group receiving ivacaftor 75 mg although a similar percentage of patients had possibly related AEs (8 [33.3%]), no patients had serious drug-related AEs or drug-related AEs leading to study drug withdrawal. A single patient reported drug-related AEs leading to study drug interruption. These data would suggest a less favourable safety profile for children weighing less than 14kg and treated with ivacaftor 50mg. No deaths occurred in the study.

During the evaluation, the CHMP made an indirect comparison with study 103, in which children aged 6 to 11 years with a G551D gating mutation and treated with ivacaftor 150mg BID were included. Comparing to the safety data from study 103, the incidence of AEs by SOC seems similar to that of study 108 except for "Respiratory, Thoracic and Mediastinal Disorders" (65.4%) that was lower for patients in study 103. For other AEs, percentages are quite close to those for patients on ivacaftor 50mg: 69.2% in "Infections and Infestations", 46.2% in "Gastrointestinal Disorders", 50% in "Investigations, and 30.8% in "General Disorders and Administrative Site Conditions". While it seems that the percentage of patients reporting at least one AE, or AEs related to study drug was similar or lower in study 103, no patients reported either serious AEs or related AEs leading to discontinuations or to drug withdrawal. Although the limitations of indirect comparisons are acknowledged the MAH was invited to comment on the apparently worse safety profile observed in the youngest children. The MAH stated that in study 108, the safety profile was consistent across the 50- and 75-mg groups and that any differences in the incidence of adverse events were likely artefacts of the small number of patients in the subgroups. However, the question also included a request to compare the safety profile of very young children in study 108 versus that of patients enrolled in studies 102 and 103. The response provided focused on liver function tests which were not the goal of the question as the frequency of liver enzymes increases was addressed in additional questions.

An update of section 4.8 of the SmPC was also requested in line with the principles of the SmPC guideline. The MAH's updated proposal for section 4.8 includes a single table on adverse reactions covering all age groups and types of mutations on the basis that the safety profile does not markedly differ between adults, adolescents, children aged 6 to less than 12 years and children aged 2 to less than 6 years. However, a justification was lacking in terms of comparative data of adverse drug reactions across the studies that served as a basis for the approval of ivacaftor in patients with *G551-CFTR* mutations, non-*G551D* gating mutations and *R117H* mutations (the latter being assessed in parallel with the current procedure) as requested above. This information has been provided and is the basis for the current proposal of section 4.8 of the SmPC which is considered acceptable now.

Laboratory parameters, including liver function testing, were monitored. In study 108 overall, most subjects had maximum on-treatment ALT, AST, and total bilirubin results ≤2 × ULN. In the group treated with ivacaftor 50mg, three children had ALT >8 × ULN and one of them also had AST >8 × ULN. Two subjects on ivacaftor 75mg had ALT >8 × ULN. The MAH considered that some cases of hepatic enzyme increase are confounded by several factors such as the underlying CF-related

hepatic injury, pre-treatment elevation of transaminases, antibiotic treatment, non-compliance with Ursodiol-treatment, or pyrexia. Indeed, confounded cases are noted by the CHMP, but several positive dechallenge and rechallenge suggest that ivacaftor may cause hepatocellular damage. It was also discussed that liver disease is a known clinical manifestation of CF and is thought to be a result of *CFTR* dysfunction in biliary tract cells. The reported prevalence of liver disease varies widely (from 2% to 68% in children and adolescents), which is likely to be due to the different definitions used, ages studied, and whether the analysis is cross-sectional versus longitudinal. Among patients with CF liver disease, approximately 70% have elevated liver enzymes. Annual patient registry data from different countries report that transaminase elevations occur in up to 16% of patients with CF across all ages. However, the natural history of transaminase elevations in patients with CF is not well described in the literature, particularly for younger patients. The available information indicates that transaminase elevations are more common in younger patients with CF than in adults. A retrospective cohort study showed that abnormal transaminase levels were present in 84% of patients <18 years of age, compared to 16% in patients ≥18 years of age. Transaminase elevations in patients with CF are particularly common in the first 2 to 3 years of life (occurring in 38% to 53% of patients), and levels tend to normalise by 4 to 5 years of age. In these studies, clinically significant elevations were uncommon. The literature data refer to several factors that may contribute to transaminase elevations in patients with CF, such as pulmonary exacerbations, medications, and concurrent viral infections.

The absence of a control arm in study 108 makes it difficult to determine whether a similar pattern would have been seen in young children with CF who do not receive ivacaftor. Hence, the CHMP requested the MAH to provide an analysis of liver function parameters by age groups based on data from previous Phase II/III studies, postmarketing cases and study 108. Furthermore, the MAH was asked to assess the temporal relationship between ivacaftor dosing and the onset/offset of LFT elevations, to clarify the maximum elevation of transaminases in studies 102, 103, 108, 111, and 110 by age group and to analyse the relationship between baseline liver function tests and on-treatment changes in liver function tests in the subset of patients with transaminase elevations by age groups according to the available data. Based on the response received, it appears that transaminase elevations >3 x ULN occurred in 15% of children of 6-11 years of age in studies 103, 110 and 111 (placebo-controlled studies) and in 14.7% of children of 2-5 years of age in study 108. The data by Sokol et al (1994) show that the proportion of patients of 2-5 years of age with elevated AST/ALT vary between 38-15% and 25-15% for AST and ALT values respectively as observed in CF-patients in the Colorado CF program. All clinical study data are in line with the literature findings; i.e. elevated LFTs are more common at lower years of age and elevated LFTs decline or are normalised as children grow up, whilst the registry data from UK, IE, FR and Australia show the opposite: the proportion of patients with elevated LFTs is higher in older children (10-14/12-17 years of age) compared to younger patients and the overall incidences are smaller than those reported from literature or ivacaftor-studies. The MAH also state that the registry data should be interpreted with caution since it may underestimate the true prevalence of LFT elevations because the majority of registries only collect a single annual LFT measurement from the enrolled patients. The CHMP agreed with this explanation.

The provided data also show that there is a preferential increase of ALT compared to AST. In addition, while ALT elevations occurred in patients with pre-treatment elevations of liver enzymes, this is not the case of AST elevations, which occurred mainly in patients with no pre-treatment elevations. While the ALT increase seems to be of limited magnitude in older patients, the five patients in study 108 had elevations in ALT above 8 x ULN (with one of them having ALT of 18.15 x ULN and AST of 6 x ULN). Elevations of this magnitude were seen only in a child and an adolescent treated in the placebo controlled studies. One of the major markers of hepatocellular damage is precisely ALT increase which is more liver-specific than AST. The MAH concluded that the overall pattern of the occurrence of transaminase elevations does not suggest an association with

ivacaftor. However, gating *CFTR* mutations are rare, the sample size and the number of cases were low and therefore incidence data should be interpreted with caution.

Given the uncertainties related to the increase in transaminases and the role that ivacaftor or its metabolites may play, the MAH was requested to include transaminase elevations in the table of adverse reactions of section 4.8 of the SmPC, which has been agreed. This is also consistent with the FDA labelling, in which this abnormality is considered an adverse reaction. Risk minimisation measures are also included in section 4.4 of the SmPC and patients who develop increased transaminase levels should be closely monitored until the abnormalities resolve. Dosing should be interrupted in patients with ALT or AST of greater than 5 times the upper limit of normal (ULN).

There were no clinically important trends attributable to ivacaftor treatment identified in the standard digital ECGs. Given the existing concerns related to the findings in juvenile rats, ophthalmological examinations were performed at baseline, week 12 and week 24. No subjects developed opacities. Changes in visual acuity seem minimal and without clinical relevance. No relevant change has been observed in coagulation parameters or in haematological parameters.

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

2.6.2. Conclusions on the clinical safety

No new adverse events have been identified following the revision of safety data of study 108. Quantitative data suggest, however, that some adverse events such as vomiting may be more frequently reported by young patients. Regarding whether the data provided show that the safety profile is worse in the subset of children receiving ivacaftor 50 mg (i.e. with a lower body weight), it is concluded that this may be influenced by the small number of patients enrolled in study 108 in this dosing group. Cross-comparison of study 108 versus studies in older children, adolescents and adults with gating mutations suggest that the safety profile of ivacaftor is similar justifying that a single table of adverse reactions is included in section 4.8 of the SmPC. The main difference in the safety profile refers to the increase in liver transaminases in younger children (see below).

Five cases of ALT or AST increase above 8 x ULN occurred in this study. One of them required ivacaftor permanent discontinuation but the remaining 4 could resume ivacaftor dosing and rolled over to study 109 in which 3 of them remain. The comparative data provided for liver function tests in the ivacaftor studies show that transaminase elevations >3 x ULN occurred in 15% of children of 6-11 years of age in studies 103, 110, and 111 (placebo-controlled studies) and in 14.7% of children of 2-5 years of age in study 108. Clinical study data are in line with the literature finding that elevated LFTs are more common at lower years of age and elevated LFTs decline or are normalised as children grow up. Furthermore, the overall pattern of the occurrence of transaminase increases does not suggest an association with ivacaftor. However, assessment of individual cases suggests positive dechallenge and rechallenge events. In addition, gating *CFTR* mutations are rare, the sample size and the number of cases were limited and therefore incidence data should be interpreted with caution. From a safety perspective as a potential causal relationship with ivacaftor cannot be completely ruled out, the CHMP requested that liver function tests increase should be included in the table of section 4.8 of the SmPC displaying adverse reactions to ivacaftor. In conclusion, it is considered by the CHMP that potential liver toxicity can be managed trough appropriate monitoring as also advised in section 4.4. of the SmPC.

Based on the overall review of the clinical efficacy data, the CHMP granted the following extended indications:

Kalydeco 50 mg and 75 mg granules:

Kalydeco granules are indicated for the treatment of children with cystic fibrosis (CF) aged 2 years and older and weighing less than 25 kg who have one of the following gating (class III) mutations in the CFTR gene: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N or S549R (see sections 4.4 and 5.1).

Kalydeco 150 mg tablets:

Kalydeco tablets are indicated for the treatment of patients with cystic fibrosis (CF) aged 6 years and older and weighing 25 kg or more who have one of the following gating (class III) mutations in the CFTR gene: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N or S549R (see sections 4.4 and 5.1).

2.7. Risk Management Plan

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

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

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

Safety concerns

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

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

Pharmacovigilance plan

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

Risk minimisation measures

No changes to the additional risk minimisation measures are necessary.

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the MAH fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8. Product information

2.8.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the MAH 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.*

2.8.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Kalydeco (IVACAFTOR) is included in the additional monitoring list. Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

Benefits

Beneficial effects
Studies performed in children diagnosed by newborn screening suggest that early intervention is associated with an improvement in nutritional status. Overall, results of the analysis of secondary efficacy endpoints assessed in study 108 are supportive of the short-term efficacy of ivacaftor in this population of young children (2-6 years) with CF, in particular when sweat chloride and endpoints related to nutritional status (weight-for-age z-score and BMI-for-age z-score) are considered.

The mean (SD) absolute change from baseline through week 24 in sweat chloride was -47.07 mmol/L (24.256) in the ivacaftor 50-mg group (n=7/10) and -46.78 mmol/L (27.584) in the 75-mg group (n=18/24). The decrease in sweat chloride was already evident at week 2 (first post-baseline measure) and was kept until week 24. Regarding weight-for-age z-score, the mean (SD) change at week 24 was 0.19 (0.32) in the 50-mg ivacaftor group and 0.21 (0.23) in the ivacaftor 75-mg group. The corresponding 95%CI were (-0.06, 0.43) and (0.11, 031) respectively. For BMI-for-age z-score these values were as follows: 0.46 (0.46) and 0.34 (0.42) respectively. The corresponding 95%CI were as follows: (0.11, 0.81) and (0.16, 052). Nutritional improvement has been demonstrated in addition to the effect of pancreatic enzyme substitution and to the nutritional interventions that children with CF undergo to keep growth as normal as possible. The magnitude of the changes in sweat chloride and weight- and BMI-for-age z-scores is similar to that seen in studies 102, 103 and 111.

Uncertainty in the knowledge about the beneficial effects
While there seems to be evidence that earlier intervention improves growth and nutritional status in children with CF, data seems to be scanter regarding lung disease. Theoretically speaking, however, it is expected that correcting the function of the defective *CFTR* protein in CF will be most successful in patients with no irreversibly fixed lung abnormalities. As a consequence, early administration of ivacaftor to young children with structural lung disease (in the absence of clinical manifestations) makes sense provided that no deleterious effects are associated with ivacaftor in this young population.

In study 108, a decrease from baseline was seen in percent predicted FEV1 in children receiving ivacaftor 50 mg and weighing less than 14 kg, for whom the mean absolute change was −12.47 percentage points based on the results from 3 children. This result in the 50-mg ivacaftor group

needs to take into consideration the high degree of variability in the measurements due to the technical difficulties of conducting spirometry in small children. Furthermore, this observation is based on a small number of patients. In addition, the overall mean baseline stature-for-age z-score remained similar at each time point to Week 24. The mean changes from baseline in stature-for-age z-scores were -0.2454 to 0.0797 across the ivacaftor 50 mg and ivacaftor 75 mg groups. It is claimed that the observed increase seen in faecal elastase-1 values suggests the possibility that CF patients in this age group may retain some pancreatic function, which can be improved by ivacaftor treatment. However, whether this is clinically meaningful and a reduction of pancreatic enzyme replacement therapy dose could be considered remains unexplored. In addition, levels of faecal elastase-1 were unknown for 5 (50%) patients in the 50-mg ivacafor group and hence, the conclusion may be influenced by the unknown values. Overall, it seems that in study 108, faecal elastase-1 levels increased above the threshold of 200 µg/g (indicative of pancreatic sufficiency) in a limited number of patients. The CHMP considers it premature to conclude on ivacaftor's association with an improvement in pancreatic function in these young children.

It is acknowledged that the major deficiency of study 108 is the lack of a placebo control arm. However, considering that efficacy has been shown in older patients with cystic fibrosis and the same type of *CFTR* mutation, it seems reasonable to accept that the results of study 108 are compatible with the benefit in the short-term in young children with cystic fibrosis. Nevertheless there is a need of factual confirmation of this assumption, which should be obtained in a post-marketing setting conducting a long-term observation study in the relevant patient population as outlined in the RMP and Annex II of the marketing authorisation.

Furthermore, it should be considered that most patients enrolled in study 108 carried the *G551D-CFTR* mutation; there were only two patients with a non-*G551D* mutation. Based on the effect shown at the level of in vivo sweat chloride, which is a marker of *CFTR* activity, it is believed that this should not preclude covering non-*G551D* gating mutations in the indication.

The effect of discontinuing prescribed therapies for CF while remaining on ivacaftor treatment has not been evaluated. During study 108, subjects continued on their prescribed CF therapies. Thus, ivacaftor will remain recommended for use in addition to other prescribed therapies for CF, as it was evaluated in the Phase 3 studies.

Risks

Unfavourable effects

The safety profile of ivacaftor in children aged 2 to 5 years with a *CFTR* gating mutation in study 108 was consistent with that observed in previous studies recruiting older children and adolescents as no new adverse events (AE) have been identified following the review of safety data.

In part B, almost all patients reported at least an AE. AEs with the highest incidence were cough, nasal congestion and vomiting. Exacerbations of CF were reported in 10% and 17% of patients on ivacaftor 50 mg and 75 mg, respectively. Vomiting seems particularly frequent with 30.0% and 29.2% of patients in the 50-mg and 75-mg dosing groups respectively. Vomiting resulted in interruption of ivacaftor dosing in 2 children in the 75-mg group and in a child in the 50-mg group. However, vomiting was considered possibly related to ivacaftor and as a serious AE only in a child treated with 75 mg. In part A, a patient on 75 mg ivacaftor reported fever, abdominal bloating, abdominal pain, vomiting and pancreatic enzymes increased, which led to omitting one dose of ivacaftor. Elevations of pancreatic enzymes are being monitored via PSURs.

In study 108, 14.7% children had an elevation of ALT or AST that was > 8 x ULN with one of them having also AST >8 × ULN. All of them had pre-treatment ALT or AST elevations > 2 x ULN Fifteen percent (6/40) of ivacaftor-treated children aged 6 to less than 12 years in studies 103, 110 and

111 (cross-over portion) had an ALT/AST elevation > 3 x ULN. Out of these 6 patients, one had an ALT and AST elevation > 8 x ULN. As for ivacaftor-treated adolescents, 5.1% (4/78) had ALT/AST elevations > 3 x ULN. Out of these 4, one (1.3%) had an ALT and AST elevation > 8 x ULN. Regarding ivacaftor-treated adult patients these figures are as follows: 2.9% (5/175) and 1.1% (2 patients, both of them with an isolated AST elevation > 8 x ULN). The maximum ALT increase in the ivacaftor group in study 108 was seen in a child aged 4 to 5 years who had an ALT increase of 18.15 x ULN. The maximum AST increase in study 108 was 11.51 x ULN that was seen in a child aged 2 to 3 years. Overall, considering the data from controlled-placebo studies (including study 110) the maximum ALT or AST elevations were always seen in paediatric patients as compared to adult patients. Similarly, maximum ALT elevations were seen in ivacaftor-treated paediatric patients as compared to placebo-treated patients. Of the 5 children who in study 108 had ALT or AST elevations above 8 x ULN, 4 of them rolled over to study 109. One of them discontinued this study due to another elevation following study drug restart. Of the remaining three, two of them did not have any further significant elevations while a single patient has had additional significant elevations with alternative aetiologies but is now continuing treatment. Since the initial submission, 3 additional subjects in study 109 have had ALT elevations >8 × ULN. All 3 subjects have resumed ivacaftor dosing without any further elevations. The time to initial LFT-increase and the duration of LFT elevations was highly variable in 2-5 year-old children justifying the timing for monitoring as added to section 4.4 of the SmPC for all patients, i.e. prior to initiating ivacaftor, every 3 months during the first year of treatment, and annually thereafter with a more frequent monitoring to be considered for patients with a history of transaminase elevations. This measure was considered appropriate by the CHMP.

Uncertainty in the knowledge about the unfavourable effects

In study 108, ivacaftor was administered for the first time to children aged 2 to less than 6 years. In general, it appears that the safety profile of ivacaftor might be worse in these young children, especially in those with less body weight, at least from a quantitative point of view. This may, however, be driven by the small number of patients enrolled in this study, particularly in the 50-mg dosing group.

Marked transaminase elevations appeared to be more common in this age group than in older patients, although the clinical features and outcomes appeared to be comparable. Due to the lack of control group in the study, it is not known whether the elevations in LFT observed in this age group are related to ivacaftor treatment, underlying CF liver disease or to any additional factors. In study 108, liver enzyme elevations were reversible. Nevertheless, the mechanisms behind this apparently increased hepatic damage, and how ivacaftor and/or its metabolites may contribute to it, remain unexplained. Various factors may contribute to liver toxicity, which is likely to be of multifactorial origin. Furthermore, data from follow up study 109 are still limited but certainly long term safety data in this population is needed and hence, a post-authorisation study will be conducted. It is likely that the small number of patients (n=34) included in study 108 and the short length of therapy (24 weeks) limit the number of adverse events reported. In addition, it is also expected that their young age impacts the ability to report adverse events. The Package Leaflet includes advice on reporting adverse events by the parents to the physicians.

Despite the nearly normal pulmonary function as measured by FEV1, structural lung damage is present in CF patients even in the very early years according to high-resolution computer tomography (HRCT) studies. Possible earliest intervention and treatment of CF are considered important due to the progressive nature of the disease but it remains to be shown whether ivacaftor is able to postpone or prevent disease progression or to stabilise clinical disease, in particular lung disease. Due to the progressive nature of CF, long-term data are needed to establish efficacy of ivacaftor on lung function. Data from study 108 and 109 provided limited data

pertaining to effects on sweat chloride and endpoints related to nutritional status and growth. This gives sufficient certainty on beneficial effects but long term data are needed to demonstrate efficacy on more robust clinical endpoints. Hence, it is unlikely that this question can be addressed in a registration clinical study, due to the fact that an extensive and long follow-up would be needed. Given the unmet medical need in cystic fibrosis and the already demonstrated positive effects of ivacaftor in the conducted clinical trials, the CHMP is of the opinion that it would be unreasonable to wait for such data before granting the authorisation in this age population. Nevertheless, the CHMP also considered that a post-authorisation study was needed to address long-term efficacy of ivacaftor in children who initiated treatment at such an early age.

Importance of favourable and unfavourable effects

CF lung disease is the primary cause of morbidity and mortality in CF. Patients with CF typically experience a progressive loss of lung function ultimately resulting in respiratory failure and death. The rate of decline in FEV1 may be variable depending on several factors such as genotype and environmental factors. Studies performed in children diagnosed by newborn screening suggest that early intervention is associated to an improvement in nutritional status while for lung disease data seem to be scanter. Very young children with CF present structural changes in the lung although conventional tests of lung function (such as spirometry) are not sufficiently sensitive to detect them. Demonstration of favourable effect on nutritional status and pancreatic function is considered particularly important for this population, since most CF patients with gating mutation suffer from pancreatic insufficiency. However, the magnitude of the observed effect cannot be fully established due to the lack of a control arm. In addition, complete data set is not available for all patients enrolled in study 108 and this fact may interfere with the conclusions reached, in particular with that derived from the change in faecal elastase-1 values from baseline. Ivacaftor showed positive effect on main efficacy endpoints, i.e. sweat chloride levels, weight, BMI.

While malnutrition and poor somatic growth are prominent signs of CF in young children, lung function assessment by spirometry cannot be easily performed. Furthermore, pulmonary function changes are not always demonstrated at this age (compared to later in life) and consequently, the magnitude of change from baseline in lung function parameters are generally smaller and difficult to show, unless alternative methods of lung function assessment are used, such as Lung Clearance Index (LCI). As a consequence, there is no solid biomarker or surrogate endpoint that can be used to bridge efficacy from adult patients to young children. Extrapolation of efficacy was deemed feasible because of the beneficial effects in improving *CFTR* function and it can be accepted that the results of study 108 are compatible with the short-term benefit in the young CF children, considering also the efficacy shown in older CF patients, and the comparable results seen in sweat chloride across all age ranges studied.

The uncertainties of the clinical use of ivacaftor will be addressed with a post-authorization efficacy study (PAES) to evaluate the long-term effectiveness and safety of Kalydeco treatment in young children with cystic fibrosis (CF) who have a specified gating mutation using the US Cystic Fibrosis Foundation (CFF) registry and the UK Cystic Fibrosis registry -based data capture as described in the RMP and outlined in Annex II of the marketing authorisation.

No new AEs were identified in study 108 and the safety profile was consistent with that known for patients with a *G551D* gating mutation for whom data on medium term are available. However, the safety profile seems worse in youngest children. In particular, there is a concern that in young children hepatocellular injury occurs more frequently and is of a higher magnitude as compared to older age groups. However, liver toxicity can be managed trough appropriate monitoring in clinical practice and to that end, appropriate recommendations are given in the SmPC (section 4.4). Furthermore, elevations in transaminases are listed in 4.8 of the SmPC for the awareness of the prescriber.

Benefit-risk balance

Discussion on the benefit-risk balance

Cystic fibrosis represents an area with a high-unmet medical need for specific targeted therapies. In patients with cystic fibrosis lung function declines with age and is a significant predictor of mortality.

While there exist clear evidence that earlier intervention with ivacraftor improves growth and nutritional status in children with cystic fibrosis data is scanter regarding lung disease. Nevertheless it is expected that correcting the function of the defective CFTR protein in cystic fibrosis may be beneficial particularly for patients with virtually no irreversibly fixed lung abnormalities as ivacaftor could postpone or prevent disease progression or stabilise clinical disease. Consequently, early administration of ivacaftor to young children with structural lung disease (in the absence of clinical manifestations) is considered reasonable and unfavourable effects can be controlled with the adopted risk minimisation measures.

Demonstration of long term beneficial effects in very young patients with CF, including CF lung disease in a registration trial cannot reasonably be expected due to the duration such a trial would require. Therefore, a post authorisation efficacy study will be performed as described in Annex II of the marketing authorisation. This study is considered to be a study imposed in accordance with Article 34 of Regulation (EC) No 1901/2006.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Kalydeco is not similar to Bronchitol 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 that the risk-benefit balance of Kalydeco in the treatment of

Kalydeco 50 mg and 75 mg granules:

children with cystic fibrosis (CF) aged 2 years and older and weighing less than 25 kg who have one of the following gating (class III) mutations in the CFTR gene: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N or S549R (see sections 4.4 and 5.1).

Kalydeco 150 mg tablets:

patients with cystic fibrosis (CF) aged 6 years and older and weighing 25 kg or more who have one of the following gating (class III) mutations in the CFTR gene: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, or S549R,

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

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

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

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

N/A

- **Obligation to complete post-authorisation measures**

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

Description	**Due date**
Long-term effectiveness study. To compare disease progression among children with CF who have a specified *CFTR* gating mutation and are aged 2 through 5 years at the time of Kalydeco treatment initiation versus disease progression among concurrent matched cohort of children with CF who have never received Kalydeco treatment.	Due date: Interim analysis 1: December 2017 Interim analysis 2: December 2019 Interim analysis 3: December 2021 Final report: December 2023.

Additional Data/Market exclusivity

Furthermore, the CHMP reviewed the data submitted by the Vertex Pharmaceuticals (Europe) Ltd., taking into account the provisions of Article 14(11) of Regulation (EC) No 726/2004 and considers by consensus that the new therapeutic indication brings significant clinical benefit in comparison with existing therapies.