18 October 2018
EMA/CHMP/799967/2018
Committee for Medicinal Products for Human Use (CHMP)

# Assessment report

## Kalydeco

International non-proprietary name: ivacaftor

Procedure No. EMEA/H/C/002494/II/0069

## Note

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

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# List of abbreviations

| | |
|---|---|
| ADR | adverse drug reaction |
| AE | adverse event |
| ALT | alanine transaminase |
| AST | aspartate transaminase |
| AUC | area under the concentration versus time curve |
| AUCss | AUC at steady-state |
| BMI | body mass index |
| CDC | Centers for Disease Control and Prevention |
| CF | cystic fibrosis |
| CFQ-R | Cystic Fibrosis Questionnaire-Revised |
| *CFTR* | CF transmembrane conductance regulator gene |
| CFTR | CF transmembrane conductance regulator protein |
| CHMP | Committee for Medicinal Products for Human Use |
| CL | clearance |
| Cmin | minimum observed concentration |
| Cmin,ss | Cmin at steady-state |
| CYP | cytochrome P450 |
| ECG | electrocardiogram |
| EU | European Union |
| FAS | Full Analysis Set |
| FDA | Food and Drug Administration |
| FE-1 | fecal elastase-1 |
| G551D | CFTR protein with a replacement of a glycine residue at position 551 with an aspartic acid residue |
| IAR | Interim Analysis Report |
| IRT | immunoreactive trypsin and/or trypsinogen |
| IVA | ivacaftor |
| LCI | lung clearance index |
| max | maximum |
| min | minimum |
| n | size of subsample |
| N | total sample size |
| *P* | probability |
| PD | pharmacodynamic, pharmacodynamics |
| PDCO | European Medicines Agency Pediatric Committee |
| PEx | pulmonary exacerbation |
| PIP | pediatric investigation plan |
| PK | pharmacokinetic, pharmacokinetics |
| ppFEV1 | percent predicted forced expiratory volume in 1 second |
| PT | Preferred Term |
| q12h | every 12 hours |
| qd | daily |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SD | standard deviation |
| SOC | System Organ Class |
| TEZ | tezacaftor |
| UK | United Kingdom |
| ULN | upper limit of normal |
| US | United States |
| WR | written request |

# 1. Background information on the procedure

## *1.1. Type II variation*

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Vertex Pharmaceuticals (Europe) Ltd. submitted to the European Medicines Agency on 12 March 2018 an application for a variation.

The following variation was requested:

| Variation requested | | Type | Annexes affected |
|---|---|---|---|
| C.I.6.a | Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one | Type II | I, IIIA and IIIB |

Extension of Indication to include treatment of cystic fibrosis in children age 12 to less than 24 months who have one of the currently approved gating mutations in the CFTR gene for Kalydeco 50 mg & 75 mg Granules; as a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. Relevant consequential changes are made to the Kalydeco 150 mg film-coated tablet Product Information. The Package Leaflet is updated in accordance. The RMP version 7.2 has also been submitted.

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

Kalydeco, was designated as an orphan medicinal product (EU/3/08/556) on 08 July 2007 in the following indication: Treatment of cystic fibrosis.

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

## *Information on paediatric requirements*

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0045/2018 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0045/2018 was not yet completed as some measures were deferred.

## *Information relating to orphan market exclusivity*

## Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the application included a critical report addressing the possible similarity with authorised orphan medicinal products.

## *Protocol assistance*

The applicant did not seek Protocol Assistance at the CHMP.

## *1.2. Steps taken for the assessment of the product*

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

Rapporteur: N/A Co-Rapporteur: Agnes Gyurasics

| Timetable | Actual dates |
|---|---|
| Submission date | 12 March 2018 |
| Start of procedure: | 31 March 2018 |
| CHMP Co-Rapporteur Assessment Report | 28 May 2018 |
| PRAC Rapporteur Assessment Report | 29 May 2018 |
| PRAC Outcome | 14 June 2018 |
| CHMP members comments | 18 June 2018 |
| Updated CHMP Co-Rapporteur Assessment Report | 25 June 2018 |
| 1st Request for supplementary information (RSI) | 28 June 2018 |
| MAH's responses submitted to the CHMP on: | 23 July 2018 |
| CHMP Co-Rapporteur Response Assessment Report | 21 August 2018 |
| PRAC Rapporteur Response Assessment Report | 28 August 2018 |
| PRAC members comments | 30 August 2018 |
| Updated PRAC Co-Rapporteur Response Assessment Report | n/a |
| PRAC Outcome | 6 September 2018 |
| CHMP members comments | 10 September 2018 |
| Updated CHMP Co-Rapporteur Response Assessment Report | 20 September 2018 |
| 2nd Request for supplementary information (RSI) | 20 September 2018 |
| MAH's responses submitted to the CHMP on: | 25 September 2018 |
| CHMP Co-Rapporteur Response Assessment Report | 3 October 2018 |
| CHMP members comments | 8 October 2018 |
| Updated CHMP Co-Rapporteur Response Assessment Report | 11 October 2018 |
| CHMP Opinion | 18 October 2018 |
| The CHMP adopted a report on similarity of Kalydeco with Bronchitol, Cayston, TOBI Podhaler and Symkevi (Appendix 1) | 18 October 2018 |

# 2. Scientific discussion

## *2.1. Introduction*

The underlying cause of cystic fibrosis (CF) is a defect in the gene encoding the CF transmembrane conductance regulator (CFTR) protein. The CFTR protein is an epithelial chloride channel that aids in regulating salt and water absorption and secretion in various tissues. This function is defective in patients with CF due to a loss of cell surface expression and/or function of CFTR protein. The failure of mutated CFTR protein to regulate chloride transport results in the multisystem pathology associated with CF.

Since the introduction and continued advances of newborn and antenatal screening, many patients with CF are identified through a positive screening test and subsequently diagnosed within the first year of life. Approximately 60% of patients with CF in the EU and 83% of patients with CF in the UK are diagnosed by 1 year of age. In the US, more than 80% of patients with CF are diagnosed by 2 years of age. CF affects the paediatric population and approximately half of the total CF patient population in the US, EU, and Australia and approximately 40% in Canada are less than 18 years of age.

Even before the widespread adoption of newborn screening, the majority of CF patients were diagnosed in infancy or early childhood due to manifestations of the disease. In patients with severe genotypes (with gating mutations such as *G551D*), pancreatic destruction leading to pancreatic exocrine insufficiency begins in utero, and lung involvement is manifested by pulmonary inflammation and infection that begins shortly after birth. Loss of lung function is the major cause of morbidity and mortality. CF patients as young as 1 month show the presence of lung disease. High-resolution computed tomography studies of infants with CF who were diagnosed by newborn screening but considered clinically healthy showed that structural lung damage is common even very early in disease progression. In a cohort of 81 well-treated CF patients in Australia, by the age of 3 years, 10% had *Pseudomonas aeruginosa* infection, and 84% had evidence of bronchiectasis. This is consistent with results of inflammatory marker studies that found that airway inflammation begins in infancy. Airway inflammation signals the beginning of the destructive cycles of chronic inflammation, infection, and irreversible lung damage that are characteristic of CF lung disease.

Exocrine pancreatic insufficiency and poor nutritional status are among the most significant clinical manifestations of CF in infants. These factors often lead to poor growth with subsequent growth delay, poorer cognitive development, and other clinical comorbidities such as decreased lung function and survival. Malnourishment is associated with worsening lung function in children with CF and is an independent predictor of mortality in this population.39 Fat malabsorption was present in 79% of infants tested at 6 months and 92% of infants by 12 months of age. Notably, 18% of children with CF fall below the US CDC's fifth percentile for weight and 16% of children fall below the CDC's fifth percentile for height. Additionally, increased energy expenditure and appetite suppression due to lung disease contribute to poor somatic growth and poor nutritional status in young CF patients.

Data in the literature suggest that early therapeutic intervention is beneficial to young children with CF; studies have demonstrated benefits such as improved measures of growth, nutrition, and lung disease through early intervention in children diagnosed by newborn screening. Moreover, treatments that target the functional defect of the mutated CFTR protein at a young age could postpone or even prevent the onset of clinical manifestations of CF, such as CF lung disease and impaired exocrine pancreatic function. However, this remains to be proven as long-term data may be needed to that end.

This application is for an extension of indication of Kalydeco (ivacaftor, IVA), to include treatment of cystic fibrosis in children age 12 to less than 24 months who have one of the currently approved gating mutations in the CFTR gene for Kalydeco 50 mg & 75 mg Granules. Submitted study 124 is included in the IVA pediatric investigation plan (PIP) in the EU. The PDCO agreed that the open-label roll-over Study 126 would be captured in the Kalydeco Risk Management Plan. The applicant received scientific advice from the CHMP on the development plan in patients <6 years of age.

## *2.2. Non-clinical aspects*

No new clinical data have been submitted in this application, apart from the Environmental Risk Assessment data, which was considered acceptable by the CHMP.

### 2.2.1. Ecotoxicity / environmental risk assessment

At the time of the initial Kalydeco (ivacaftor) marketing authorisation application (MAA), the Phase I ERA assessment was made based on market data, supported by published epidemiological data and by the prevalence adopted by the Committee for Orphan Medicinal Product (COMP). Since ivacaftor can now be used as monotherapy and in combination with lumacaftor or tezacaftor, the amount of ivacaftor present in the environment has increased. The ERA for ivacaftor has therefore undergone revision, with new experimental studies conducted and planned to assess the impact of ivacaftor in the environment, as recommended by the Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use. An updated ivacaftor ERA (Kalydeco Monotherapy and in combination with lumacaftor or tezacaftor Environmental Phase I and II Risk Assessment) will be provided in supportive Type II variation for tezacaftor/ivacaftor combination regimen indication. The report will provide a revised Fpen based on the prevalence of relevant CFTR mutations that ivacaftor is prescribed for in Kalydeco, Orkambi and Symkevi. The Fpen was refined by mutation only and was not restricted by age, thereby incorporating the proposed Kalydeco monotherapy indication extension. The Phase II Tier B assessments of ivacaftor are on-going and the final ivacaftor ERA will be available in 2019.

### 2.2.2. Conclusion on the non-clinical aspects

No new non-clinical data have been submitted in this application, which is considered acceptable apart from the studies of updated ERA. Final ivacaftor ERA will refer to monotherapy medicinal products (Kalydeco 150 mg film-coated tablets and Kalydeco 50 mg and 75 mg granules) and to combination therapy (Orkambi 100 mg/125 mg film-coated tablets and Orkambi 200 mg/125 mg film-coated tablets, Symkevy 100 mg/150 mg film coated tablets) and will be available in 2019.

## *2.3. Clinical aspects*

### 2.3.1. Introduction

There is potential for patients with CF who are 12 to <24 months to benefit from IVA treatment based on evidence of unmet medical need and data showing a favorable benefit risk profile in older patient cohorts:

- Evidence of efficacy in subjects ≥6 years of age with a G551D mutation (Studies 102, 103, and 105) or a non-G551D mutation (Studies 111 and 112);
- Comparable effects on PK and sweat chloride (measure of CFTR function) in subjects 2 through 5 years of age with a CFTR gating mutation (Study 108) and subjects ≥6 years of age;

- The well-characterized safety profile in subjects ≥2 years of age;
- Evidence of complications of CF starting very early in life, including impaired pancreatic exocrine function, lung inflammation and poor weight gain; and
- Evidence supporting the benefits of early therapeutic intervention.

In the 12- to <24-month population, the rationale for IVA treatment is supported by the importance of slowing disease progression and the prevention of the negative consequences of CF such as compromised lung and pancreatic function and impaired nutritional status, as claimed by the applicant. It is expected that the primary benefit of IVA treatment in these younger CF subjects would derive from the potential to reduce the progression of disease before sustaining irreversible damage.

## GCP

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

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

- Tabular overview of clinical studies

| Type of Study | Study Identifier/ Location | Objective(s) of the Study | Study Design and Type of Control | Test Product(s); Dosage Regimen; Route of Administration | Number of Subjects/ Healthy Subjects or Diagnosis of Patients | Duration of Treatment | Study Status; Type of Report |
|---|---|---|---|---|---|---|---|
| Phase 3<br>Safety, PK, and Efficacy | VX15-770-124<br>Module 5.3.5.2 | Part A:<br>• To evaluate the safety and PK of IVA treatment<br>Part B:<br>• To evaluate the safety, PK, PD, efficacy, and acceptability/ palatability of IVA treatment | Nonrandomized, open-label, multiple-dose | IVA 25-, 50-, or 75-mg granules; 25, 50, or 75 mg q12h; PO | Part A:<br>20 subjects<br>Part B:<br>15 subjects<br>male and female subjects<br><24 months of age and have a *CFTR* gating mutation | Part A:<br>Days 1 through 3, and morning dose on Day 4<br>Part B: 24 weeks | Ongoing<br>Cohort 1 and Cohort 5 are complete; (subjects 12 to <24 months of age) |
| Phase 3<br>Safety, PD, and Efficacy | VX15-770-126<br>Module 5.3.5.2 | IVA Arm<br>• To evaluate the safety of long-term IVA treatment in subjects with CF who are <24 months of age at treatment initiation and have a *CFTR* gating mutation<br>• To evaluate the PD of long-term IVA treatment in subjects with CF who are <24 months of age at treatment initiation and have a *CFTR* gating mutation<br>• To evaluate the efficacy of long-term IVA treatment in subjects with CF who are <24 months of age at treatment initiation and have a *CFTR* gating mutation<br>Observational Arm<br>• To evaluate long-term safety after discontinuation of IVA treatment in subjects with CF who were <24 months of age at treatment initiation and have a *CFTR* gating mutation | Open-label, 2-arm | 25-, 50-,or 75-mg granules, and others (to be determined based on safety and PK data from Study 770-124, age, and weight); PO | Approximately 75 male and female subjects who are <24 months of age and have a *CFTR* gating mutation on at least 1 allele | IVA Arm<br>128 weeks<br>Observational Arm<br>104 weeks | Ongoing |
| Phase 3b<br>Efficacy and Safety | VX15-770-123<br>Module 5.3.5.1 | • To evaluate the efficacy of IVA treatment, as measured by LCI<br>• To evaluate disease progression as measured by changes in CT scan and pancreatic function<br>• To evaluate the safety of IVA treatment | Randomized, double-blind, placebo-controlled crossover with a long-term open-label period | IVA 50-mg and 75-mg granules in capsules or sachets and matching placebo, and IVA 150-mg tablets; 50 mg, 75 mg, or 150 mg q12h; PO | 50 male and female subjects with CF, aged 3 through 5 years, with 1 of the specified *CFTR* gating mutations on at least 1 allele | Treatment Period 1:<br>8 weeks<br>Treatment Period 2:<br>8 weeks<br>Open-label Period:<br>120 weeks | Complete; Abbreviated [terminated early] |

## 2.3.2. Pharmacokinetics

The pharmacokinetics (PK) of IVA in the target age group was investigated in Study 124: An ongoing, Phase 3, 2-Part, open-label study in subjects <24 months of age. The study has multiple cohorts and cohorts 1 and 5, the cohorts that enrolled subjects 12 to <24 months of age, are complete. In each age cohort, safety and PK were evaluated in Part A (4 days of IVA treatment), and safety, PK, pharmacodynamics (PD), and efficacy were evaluated in Part B (24 weeks of IVA treatment). PK of IVA and its metabolites was a primary objective of Part A and a secondary objective for Part B.

*Dose:* IVA was supplied as granules packaged in a foil-laminated sachet/packet and was administered orally every 12 hours (q12h) at the following doses after mixing with 5 mL of age-appropriate soft food or liquid: 50 mg for subjects weighing 7 to <14 kg; 75 mg for subjects weighing 14 to <25 kg. At each study visit in Part B, the dose for each subject was adjusted based on body weight if necessary.

*Sampling*: The PK sampling schedule was as follows:

| | |
|---|---|
| Part A | Day 4: predose, between 2 and 4 hours, between 6 and 8 hours, and between 24 to 60 hours after the day 4 morning dosing |
| Part B | Week 2: predose, between 2 and 4 hours, and between 6 and 8 hours after the morning dose |
| | Week 8: predose, 1 hour, and 4 hours after the morning dose |
| | Week 18: predose and between 2 and 4 hours after the morning dose |
| | Week 24: predose and between 2 and 4 hours after the morning dose |

*Study population*: From Study 124 PK data was available for Part A (7 subjects, 28 PK observations) and Part B Cohort 5 (18 subjects, 108 PK observations). Study 124 data was added to a subset of the prior ivacaftor POP-PK data set that was previously constructed.

*Bioanalytics:* Validated LC/MS/MS methods were applied to quantify ivacaftor plasma concentrations in human plasma samples. The details are provided in two separate reports (Bioanalytical Report M315 and Method Validation Report N087). Two major metabolites were quantified besides ivacaftor. The stability of the samples was also checked by incurred sample reanalysis. Samples were analyzed by PPD Laboratories (US) which operates in accordance with the GPL principles.

*Results:* Mean IVA plasma concentrations observed in Cohort 1 were consistent with plasma concentrations previously observed in adult subjects (Study 102). The concentrations of IVA, M1-IVA, and M6-IVA, by nominal time point are summarized in Table 1 and Table 2 below.

**Table 1 Summary of Plasma Concentration by Nominal Time Point for IVA, M1-IVA, and M6-IVA in Part B/Cohort 1**

| Nominal Time (hr) | n | Mean (SD) (ng/mL) | | |
|---|---|---|---|---|
| | | IVA | M1-IVA | M6-IVA |
| 0 | 7 | 458 (244) | 1290 (466) | 1250 (632) |
| 2 to 4 | 7 | 815 (271) | 1640 (706) | 1150 (663) |
| 6 to 8 | 7 | 907 (383) | 2140 (692) | 1670 (896) |
| 24 to 60 | 7 | 148 (92.6) | 493 (201) | 551 (230) |

Source: Table 14.4.1.1
IVA: ivacaftor; n: size of subsample

**Table 2 Summary of Plasma Concentration by Nominal Time Point for IVA, M1-IVA, and M6-IVA in Part A/Cohort 5**

| Visit | Nominal Time (hr) | n | Mean (SD) (ng/mL) IVA | M1-IVA | M6-IVA |
|---|---|---|---|---|---|
| Week 2 | 0 | 18 | 430 (450) | 1130 (539) | 1490 (1000) |
| | 2 to 4 | 18 | 734 (595) | 1280 (616) | 1210 (817) |
| | 6 to 8 | 18 | 863 (392) | 1900 (705) | 1540 (923) |
| Week 8 | 0 | 18 | 347 (370) | 1110 (625) | 1510 (1170) |
| | 1 | 18 | 463 (357) | 1040 (603) | 1300 (885) |
| | 4 | 18 | 947 (513) | 2010 (948) | 1550 (1140) |
| Week 24 | 0 | 18 | 308 (181) | 1050 (352) | 1620 (750) |
| | 2 to 4 | 17 | 853 (479) | 1580 (802) | 1320 (530) |

Source: Table 14.4.1.1
IVA: ivacaftor; n: size of subsample

Results from the population PK model demonstrate that in subjects 12 to <24 months administered either 50 mg (7 to <14 kg) or 75 mg (14 to <25 kg) IVA granules in Study 124, IVA exposure, including both Cmin and AUC, was similar to that observed in 2- through 5-year-olds administered 50 mg (<14 kg) or 75 mg (≥14 kg) IVA granules in Study 108 and adults and adolescents in Phase 3 Studies 102 and 103, see Table 3 and Table 4 below.

**Table 3**

Table 8: Summary Statistics for Ivacaftor Cmin,ss (ng/mL) by Age Group

| Group | N | Min | Max | Median | Mean | SD | Q1 | Q3 |
|---|---|---|---|---|---|---|---|---|
| 12-23 months (50 mg) | 19 | 124 | 829 | 383 | 440 | 212 | 299 | 514 |
| 12-23 months (75 mg) | 2 | 363 | 540 | 451 | 451 | 125 | 407 | 495 |
| 2-5 years (50 mg) | 9 | 170 | 1310 | 536 | 577 | 317 | 466 | 623 |
| 2-5 years (75 mg) | 26 | 225 | 1540 | 580 | 629 | 296 | 438 | 774 |
| 6-11 years | 40 | 275 | 2840 | 1100 | 1240 | 594 | 836 | 1540 |
| 12-17 years | 78 | 141 | 1270 | 508 | 564 | 242 | 382 | 676 |
| Adults | 190 | 167 | 2080 | 634 | 701 | 317 | 471 | 864 |

**Table 4**

Table 9: Summary Statistics for Ivacaftor AUCss (ng/mL.h) by Age Group

| Group | N | Min | Max | Median | Mean | SD | Q1 | Q3 |
|---|---|---|---|---|---|---|---|---|
| 12-23 months (50 mg) | 19 | 4830 | 16400 | 8900 | 9050 | 3050 | 6510 | 10700 |
| 12-23 months years (75 mg) | 2 | 8330 | 10900 | 9600 | 9600 | 1800 | 8970 | 10200 |
| 2-5 years (50 mg) | 9 | 5120 | 20800 | 9840 | 10500 | 4260 | 8940 | 10100 |
| 2-5 years (75 mg) | 26 | 6260 | 22700 | 10200 | 11300 | 3820 | 8960 | 13500 |
| 6-11 years | 40 | 5060 | 40600 | 18700 | 20000 | 8330 | 14800 | 24400 |
| 12-17 years | 78 | 3280 | 20600 | 8670 | 9240 | 3420 | 6940 | 10500 |
| Adults | 190 | 3580 | 28200 | 9840 | 10700 | 4100 | 7920 | 13200 |

## *Absorption*

Absorption follows zero-order delivery to the absorption compartment and subsequent first order absorption. Although it was not possible to estimate the bioavailability, F was fixed to a value of 1 and random effects were described to characterise the inter-ocassion variability. For infants the SmPC recommends that ivacaftor granules should be mixed with 5 mL of age-appropriate soft food or liquid. The palatability of the food was checked on day 1 (Part B) and was assessed by the parent/caregiver. Regardless of the reaction of the patient (which was negative only in few cases) in all cases the whole amount (5 ml i.e. a teaspoon) was administered. Therefore, the granule formulation is palatable and acceptable in the target population.

## *Distribution*

The SmPC states that IVA is approximately 99% bound to plasma proteins, primarily to alpha 1-acid glycoprotein (AAG) and human serum albumin (HSA). Given that plasma binding protein levels are lower in the newborn than in the adult and gradually increase with age, the MAH was asked to discuss the plausibility of an age dependent shift in plasma protein binding (Free/Bound ratio) of ivacaftor and its metabolites taking also into account that a decreased plasma protein binding may be due not only to the reduction of the total amount of plasma proteins, but also to the diminished binding affinity and the high concentrations of endogenous competing substrates.

In response, it has been clarified that in *in vitro* experiments using a range of protein concentrations, ivacaftor, M1, and M6 were found to be highly protein bound (>99%) independent of the HSA concentration. The same was true for IVA and AAG, with IVA being highly protein bound (>97%) independent of AAG concentration. In addition, this high levels of protein binging makes it unlikely that changes in protein binding affinity or competition from endogenous substrates (such as bilirubin) have an impact on the free/bound ratio of IVA.

### *Elimination*

In adults after 150 mg q12h of the commercial tablet formulation in the fed state, the mean exposure ($AUC_T$ metabolite/$AUC_T$ ivacaftor) ratio was approximately 6 for M1 and 2 for M6 (Study 008 from the initial submission). The IVA/M1 and IVA/M6 concentration ratios in study 124 are lower, between 2 and 3. Therefore, the MAH was asked to address this issue. In response, it MAH clarified that the actual M1 plasma concentrations in Study 008 are only 39 % of the initially reported vales (refer to EMEA/H/C/002494/II/0026). Using this factor, the MAH re-estimated the previously reported AUC values. Due to the small sample size the results should be interpreted with caution. Nevertheless, the age-related metabolite difference after the correction disappeared.

### *Dose proportionality and time dependencies*

Ivacaftor does not inhibit neither induces the metabolic enzymes. When ivacaftor was administered as PEG solution formulation in the fasted state, over a single dose range of 25 to 800 mg in healthy male subjects, the AUC of ivacaftor from the time of dosing extrapolated to infinity ($AUC_{0-\infty}$) increased proportionally throughout the dose range, and maximum observed concentration (Cmax) increased proportionally between 25 and 375 mg, and less than proportionally at doses above 375 mg.

### *Special populations*

Although moderate hepatic impairment is relatively rare in children <24 months with CF, such a level of liver disease may occur. The recommended dose for patients 12 to <24 months with moderate hepatic impairment is the same as recommended for older CF patients with moderate hepatic impairment:

14 to <25 kg: one 75-mg sachet/packet of granules qd
7 to <14 kg: one 50-mg sachet/packet of granules qd

Studies have not been conducted in patients with severe hepatic impairment (Child-Pugh Class C), but exposure is expected to be higher than in patients with moderate hepatic impairment. The use of IVA in patients with severe hepatic impairment is therefore not recommended unless the benefits outweigh the risks. In such case, the starting dose should be 1 tablet or 1 sachet/packet of granules qd or less frequently. Dosing intervals should be modified according to the clinical response and tolerability.

### *Pharmacokinetic interaction studies*

There are no new experimental data, but it is known that ivacaftor is a sensitive CYP3A substrate. Medicinal products that modify CYP3A activity may modify the exposure of ivacaftor. Clinical studies showed that ivacaftor is a weak CYP3A inhibitor and is not a CYP2C8 or CYP2D6 inhibitor. *In vitro* studies suggested that ivacaftor is not a P-gp substrate but a P-gp inhibitor. A reduction in the IVA dose is recommended for coadministration with strong or moderate CYP3A inhibitors. The recommended IVA dose in patients ≥6 years of age and weighing at least 25 kg is 150 mg twice weekly with strong CYP3A inhibitors and 150 mg daily (qd) with moderate CYP3A inhibitors. The recommended IVA dose for 2- through 5-year-olds is 50 mg (<14 kg) or 75 mg (≥14 kg) twice weekly during concomitant dosing with strong CYP3A inhibitors and 50 mg (<14 kg) or 75 mg (≥14 kg) qd during concomitant dosing with moderate CYP3A inhibitors.

## 2.3.3. Pharmacodynamics

### *Mechanism of action*

Ivacaftor is a selective CFTR potentiator. Potentiators are pharmacological agents that increase the chloride ion transport properties of the channel in the presence of cyclic AMP-dependent protein kinase A (PKA) activation.

### *Primary and secondary pharmacology*

Loss of CFTR function in the sweat gland leads to an elevation in chloride concentration. In the epithelia of the lungs and pancreas, CFTR dysfunction causes aberrant ion and water movement leading to obstruction and eventual destruction of both organ systems. In the Phase 3 trials of IVA in subjects 2 through 5 and ≥6 years of age with CF, results showed that treatment with IVA improved CFTR function, as evidenced by improvements in sweat chloride levels. The pancreas is of the earliest and most seriously affected organs in patients with CF. Faecal elastase-1 (FE-1) and immunoreactive trypsin and/or trypsinogen (IRT) are two additional diagnostic measures which can be used to follow the effect effect of treatment although the interpretation of the results of IRT in the absence of a control group is difficult. Sweat chloride levels, FE-1 and IRT were measured in Study 124 to follow ivacaftor action in the 12-24-month-old patient group. All these parameters showed an improvement after 24 weeks of IVA treatment. Further details are provided in the efficacy section.

## 2.3.4. PK/PD modelling

A population PK model was used to evaluate IVA disposition in subjects 12 to <24 months from Study 124 (Part A/Cohort 1 and Part B/Cohort 5) and in subjects ≥2 years of age from an existing dataset that includes Studies 102, 103, 104, 108, 110, and 111. Consistent with previous iterations of the model, IVA PK was described by a 2-compartment model with zero-order delivery to the absorption compartment and subsequent first-order absorption. Goodness-of-fit criteria revealed that the final model was consistent with observed data and that no systematic bias remained when stratified by age groups down to 12 months of age. Allometric relationships were incorporated in the base model for all structural parameters to describe the effect of body weight on IVA PK. Although maturation models were explored, none of these models demonstrated improved fit when compared to the reduced allometric weight model. Additionally, population PK simulations that did not account for maturation effects demonstrated that subjects 12 to <24 months of age had similar exposure (AUCss) to older children administered 50-mg (<14 kg) or 75-mg doses (≥14 kg) q12h, and adult subjects administered 150 mg q12h. These results suggest that changes in IVA disposition due to maturation of clearance processes in children 12 to <24 months of age are minimal. However, due to the small sample size this point should be further assessed when new data from younger infants are available.

**Data**

Ivacaftor population PK in adults and paediatric subjects as young as two years old has been previously characterized in several analyses. The objectives of the population PK analysis were to characterize the PK of IVA in subjects with CF 12 to <24 months of age and to compare exposures to those previously obtained in older subjects. To achieve this goal data of Part A/Cohort 1 and Part B/Cohort 5 of Study 124, were integrated with an existing dataset of Phase 3 studies conducted in subjects with CF, including paediatric subjects ≥2 to 18 years of age. The ivacaftor PK data set comprised 197 patients contributing a total of 1797 plasma concentrations, dosing and covariate data. The study population

consisted of 106 males and 91 females with ages ranging from 6 months to 18 years and weights ranging from 6.70 to 87.0 kg, see Table 5 below.

**Table 5 Summary of Continuous Covariates (POP-PK data set)**

| Population | covariate | n | Mean | Median | SD | Min | Q25 | Q75 | Max | Missing | Pct.Miss |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 to 2 year olds | Age (months) | 31 | 18.7 | 21.0 | 4.92 | 12.0 | 13.5 | 24.0 | 24.0 | 0 | 0 |
| 1 to 2 year olds | Weight (kg) | 31 | 12.1 | 11.7 | 2.07 | 8.60 | 10.9 | 13.2 | 16.3 | 0 | 0 |

**Method**

Population PK analysis for repeated-measures endpoints was conducted via nonlinear mixed effects modelling with NONMEM (Version 7). The previously developed population PK model was used as the starting point for model fitting, which consisted of a two-compartment model with sequential zero and first order absorption and allometric scaling describe body size effects on ivacaftor. To investigate maturational effects on ivacaftor clearance, a model to describe the effects or age on clearance was also investigated. Model selection was guided by various goodness-of-fit criteria, including diagnostic scatter plots, convergence with at least 2 significant digits, plausibility of parameter estimates, precision of parameter estimates, correlation between model parameter estimation errors < 0.95, and the AIC, given the minimum objective function value and number of estimated parameters. The final population PK model was evaluated using a prediction-corrected visual predictive check (VPC).

**Model**

Consistent with the previous population PK model, IVA PK was described by a 2-compartment model with zero-order delivery to the absorption compartment and subsequent first-order absorption (Report N364). Allometric relationships using body weight were incorporated in the base model for all structural parameters to describe the effect of body size on IVA PK.

This model was further refined by testing different structural models and random effects models. To investigate maturational effects on ivacaftor clearance the following model was evaluated:

$$F_{MAT} = \frac{PMA^{Hill}}{TM_{50}^{Hill} + PMA^{Hill}}$$

$F_{MAT}$ is the fractional maturation of ivacaftor clearance, PMA is post menstrual age, TM50 is the maturation half-time, and Hill is the Hill coefficient.

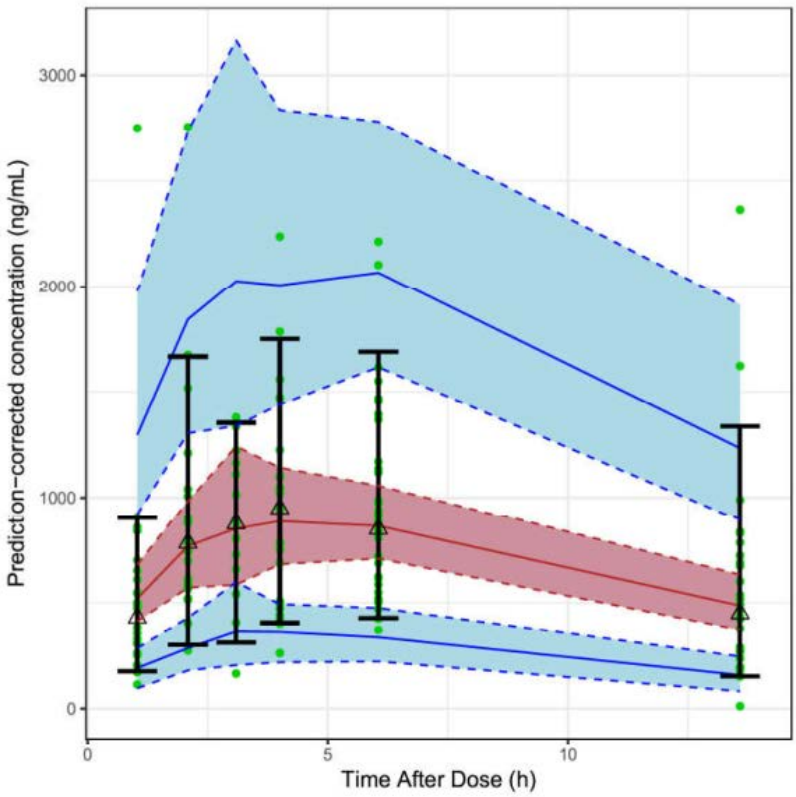
Once a final model was obtained, the same population PK model was fit to a subset of the data that did not include Study 124 subjects, to provide a simulation model that eliminated the impact of any maturation effects from these subjects. Five hundred subjects with body weights randomly sampled were simulated for each age group (up to 6 months, 7-12 months, 13-18 months, 19-24 months). Distributions of AUCss for each group, and also re-stratified by weight and dosing groups were compared to the individual predicted values for Study 124.

**Results**

The typical estimates of PK model parameters for the reference weight of 70 kg were 21.4 L/h for CL/F, 75.6 L for Vc/F, 76.5 L for Vp/F, 11.3 L/h for Q/F, 2.78 h for D1 and 0.160 h-1 for ka. Parameter estimates were relatively precise and were consistent with previously reported PK parameters for IVA. In prior population PK analyses, body weight was the most significant predictor of IVA disposition and other covariates (race, gender, and patient status [CF versus healthy subject]) did not explain a significant portion of the intersubject variability. After accounting for body weight, possible

maturational changes were explored for the 12- to <24-month-old subjects in Study 124. Plots of CL/F and Vc/F random effects showed no obvious trends with age that would indicate dispositional changes due to naturation. A two compartment model with allometric body weight provided an adequate description confirmed standard model checking methods, see Figure 1 below.

**Figure 1 Observed and predicted plasma concentrations in the 12-24-month-old patient group. The whiskers represent the observed 5th and 95th percentiles, solid blue lines are the simulated 5th and 95th percentiles, blue shaded regions are the 90 % CIs for the simulated 5th and 95th percentiles, solid red line is the simulated median, shaded red region is the 5th and 95th percentile for the simulated median. The green circles are the observed concentrations, the triangles are the observed median concentrations.**



The parameter estimates are provided in the following Table 6:

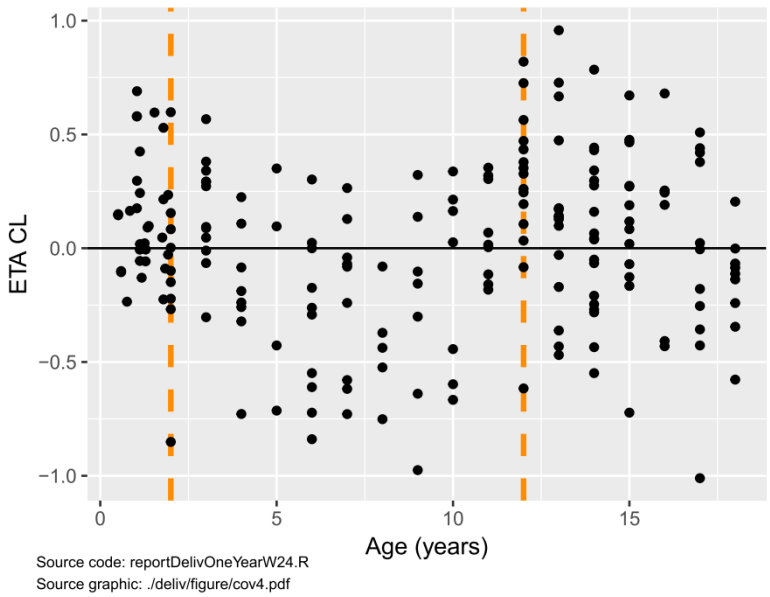
**Table 6**

Table 5: Population PK Parameter Estimates From the Final Model (Run 214).

| Description | Model | Estimate | RSE | Variability |
|---|---|---|---|---|
| apparent clearance | $CL \sim \theta_1 \cdot (WT/70)^{0.75} \cdot e^{\eta_1}$ | 21.4 $L/h$ | 3.86 | |
| apparent central volume | $V_c \sim \theta_2 \cdot (WT/70)^{1.0} \cdot e^{\eta_2}$ | 75.6 $L$ | 17.3 | |
| apparent peripheral volume | $V_p \sim \theta_3 \cdot (WT/70)^{1.0}$ | 76.5 $L$ | 19.1 | |
| apparent intercompartmental CL | $Q \sim \theta_4 \cdot (WT/70)^{0.75}$ | 11.3 $L/h$ | 23.9 | |
| first order absorption rate | $k_a \sim \theta_5$ | 0.160 $1/h$ | 11.6 | |
| zero order absorption time | $D1 \sim \theta_6 \cdot e^{\eta_3}$ | 2.78 $h$ | 4.69 | |
| interindividual variance of CL | $IIV_{CL} \sim \Omega_{1.1}$ | 0.180 | 16.5 | %CV = 44.4 |
| interindividual covariance of CL and Vc | $IIV_{CL-Vc} \sim \Omega_{2.1}$ | 0.0345 | 190 | CORR = 0.119 |
| interindividual variance of $V_c$ | $IIV_{Vc} \sim \Omega_{2.2}$ | 0.466 | 39.3 | %CV = 77.0 |
| interindividual covariance of CL and D1 | $IIV_{CL-D1} \sim \Omega_{3.1}$ | 0.0684 | 49.5 | CORR = 0.423 |
| interindividual covariance of Vc and D1 | $IIV_{Vc-D1} \sim \Omega_{3.2}$ | 0.130 | 70.4 | CORR = 0.501 |
| interindividual variance of D1 | $IIV_{D1} \sim \Omega_{3.3}$ | 0.145 | 52.2 | %CV = 39.5 |
| interoccasion variance of F1 | $IOV_{F1} \sim \Omega_{4.4}$ | 0.236 | 6.27 | %CV = 51.6 |
| proportional residual error | $err_{prop} \sim \Sigma_{1.1}$ | 0.0405 | 6.81 | %CV = 20.3 |
| additive residual error | $err_{add} \sim \Sigma_{2.2}$ | 4900 | 11.7 | SD = 70.0 |

Although the evaluation of the observations did not show any maturation effect (see Figure 2 below), an asymptotic maturation model was explored with both estimated and fixed parameters, but none of these models improved model fit. All tested models increased the objective function value with respect to the simplest model. The results of the pcVPC indicate that the model reasonably fit the data in one to two year old subjects.

**Figure 2 (CL/F random effect) values are plotted versus age with values indicated by solid circles and a dotted reference line at y=0. Vertical orange dashed lines represent age group cutoffs: Adolescents=> 12 - 18 years; Children= >2- 12 years; Infants= 6- 24 months (Study 124 subjects)**



Although results from this figure seem to indicate that no maturation effect affects clearance, results from the simulated subjects for each age group, do not completely exclude the maturation effect. The predicted $AUC_{ss}$ and $Cmin_{ss}$ show a clear age dependent exposure increase in the 1 – 11-year age interval, as depicted in Table 7 below.

**Table 7 Predicted IVA Exposure in Subjects with CF by Age (younger than 18-year-old)**

| | | $C_{min,ss}$ (ng/mL) | | $AUC_{ss}$ (ng·h/mL) | |
|---|---|---|---|---|---|
| Age Group | N | Median (min, max) | Mean (SD) | Median (min, max) | Mean (SD) |
| 12-24 months (50 mg) | 19 | 383 (124, 829) | 440 (212) | 8900 (4830, 16400) | 9050 (3050) |
| 12-24 months (75 mg) | 2 | 451 (363, 540) | 451 (125) | 9600 (8330, 10900) | 9600 (1800) |
| 2-5 years (50 mg) | 9 | 536 (170, 1310) | 577 (317) | 9840 (5120, 20800) | 10500 (4260) |
| 2-5 years (75 mg) | 26 | 580 (225, 1540) | 629 (296) | 10200 (6260, 22700) | 11300 (3820) |
| 6-11 years[a] | 40 | 1100 (275, 2840) | 1240 (594) | 18700 (5060, 40600) | 20000 (8330) |
| 12-17 years | 78 | 508 (141, 1270) | 564 (242) | 8670 (3280, 20600) | 9240 (3420) |

The predicted concentrations for the 12-24-month-old are similar to what was measured for adults.

## 2.3.5. Discussion on clinical pharmacology

The PK of ivacaftor in the target age group was investigated in Study 124. Study 124 was divided into initial part (part A) and maintenance part (Part B). PK data was available from both parts, from Part A {7 subjects, 28 PK observations) and from Part B Cohort 5 (18 subjects, 108 PK observations) as well. To carry out POP-PK analysis, the data from Study 124 data was added to a previously constructed POP-PK database. Therefore, with the results from the previous studies, plasma concentrations data from 31 subjects were available in the 12-24-month age group. Consistent with the previous population PK model, IVA PK was described by a 2-compartment model with zero-order delivery to the absorption compartment and subsequent first-order absorption. Algometric relationships using body weight were incorporated in the base model for all structural parameters to describe the effect of body size on ivacaftor PK. Model fit was not improved by incorporating maturational models. The results suggest that the maturation has no effect on the ivacaftor clearance. However, this needs to be further assessed when data from younger infants from study 124 become available. The observed and POP-PK predicted concentrations in the 12 to <24 age group was very similar what was observed in adults. Thus, the suggested dose recommendation is supported by the kinetic data.

However, there were some points which had to be clarified. In adults after 150 mg q12h of the commercial tablet formulation in the fed state, the mean exposure ($AUC_T$ metabolite/$AUC_T$ ivacaftor) ratio was approximately 6 for M1 and 2 for M6 (Study 008 from the initial submission). The IVA/M1 and IVA/M6 concentration ratios were lower, between 2 and 3 in study 124. Thus it seemed that the parent compound/metabolite concentration ratios in infants are different from what was observed in

adults. It was clarified that due to a bioanalytical error the metabolite concentration data in the initial MAA are incorrect. The MAH estimated that the actual M1 plasma concentrations in Study 008 are only 39% of the initially reported vales. Using this factor, the MAH re-estimated the previously reported AUC values. Due to the small sample size, the results should be interpreted with caution. Nevertheless, the age-related metabolite difference after the correction disappeared.

Different metabolism rate is only one of the factors which should be considered when PK processes between infants and adults are compared. Plasma binding protein levels are lower in the new-born than in the adult and gradually increase with age. At birth, human serum albumin (HSA) concentrations are close to adult levels (75%-80%), while alpha 1-acid glycoprotein (AAG) is initially half the adult concentration. The SmPC states that IVA is approximately 99% bound to plasma proteins, primarily to alpha 1-acid glycoprotein and HSA. This warranted further discussion about the possibility of altered plasma protein binding of ivacaftor and its metabolites in infants. In response to the CHMP's question, it has been clarified that in *in vitro* experiments using a range of HAS concentrations, ivacaftor and metabolites M1 and M6 were found to be highly protein bound (>99%) independent of the HSA concentration. The same was true for IVA and AAG, with IVA being highly protein bound (>97%) independent of AAG concentration. In addition, these high levels of protein binging make it unlikely that changes in protein binding affinity or competition from endogenous substrates (such as bilirubin) have an impact on the free/bound ratio of IVA.

Overall, the exposure is steadily increasing starting from age 1 up to age 12. The essential concern was not the safety of the patients, but rather an unknown, unexplained factor which has significant impact on the exposure in infants and children. This unknown age dependent factor was not well captured by the POP-PK model and quite apparent for 1-12-year-old patients. A POP-PK model is considered only partially validated if a random component shows dependence on a covariate. The MAH agreed that an unexplainable negative trend can be observed between Cl component and age. The reason remained unknown but currently considered as an unresolved methodological problem without clinical implications.

Hence, the SmPC, section 5.2, was adequately updated with the following PK data in this extended indication:

| **Mean (SD) ivacaftor exposure by age group** | | | |
|---|---|---|---|
| **Age group** | Dose | Cmin, ss (ng/mL) | $AUC_{\tau,ss}$ (ng.h/mL) |
| 12 months to less than 24 months (7 kg to <14 kg) | 50 mg q12h | 440 (212) | 9050 (3050) |
| 12 months to less than 24 months (≥14 kg to <25 kg) | 75 mg q12h | 451 (125) | 9600 (1800) |

The population approach is considered useful to extrapolate and analyse the available data including PD data. Serial sweat chloride measurements can be used to follow the effects of therapies directly affecting CFTR function. The sweat chloride response is influenced by several factors such as age gender, testing variability, recording biases, and the CFTR genotype itself. Previously the MAH developed POP-PK/PD models to characterize the effect between plasma concentration and FEV1. It is problematic to measure FEV1 under a certain young age. Therefore, the MAH was encouraged to develop a simple PK/PD model which makes connection between the POP-PK estimated AUC and the sweat chloride response parameters (EC50, Emax and T50 the time when EC50 is achieved). However, due to the sparsity of sweat chloride data in this study, there was insufficient information to

develop a linear or nonlinear exposure-response model. Instead, the MAH provided graphical analysis using the data of 10 children between age 1 and 2 years with sweat chloride values at baseline and at week 24. The plots did not reveal any trends between AUC and sweat chloride but this might be due to the small sample size (n=10) and high variability. The MAH focused on data in the 12 - 24-month age group but including data of older children would have been very useful.

### 2.3.6. Conclusions on clinical pharmacology

The recommended dose of IVA granules for patients 12 to <24 months is 50 mg for patients weighing 7 to <14 kg and 75 mg for patients weighing 14 to <25 kg, administered q12h with fat- containing food. This dose recommendation is supported by the measured plasma values in the 1-2-year-old age group and by the updated POP-PK model. Nevertheless, some observations pointed to the direction that the PK results obtained in adults cannot be fully extrapolated to children and infants. In the response the MAH clarified that plasma protein concentrations indeed might be lower than in older children but still in the normal range. However, there is no difference between the metabolite ratios, the reported difference was due to an already reported analytical error. Graphical analysis revealed no relationship between ivacaftor exposure and sweat chloride response. The observed trend between age and Cl remained unexplained but currently not considered clinically relevant problem. The updated wording of the SmPC is agreed by the CHMP.

## *2.4. Clinical efficacy*

The efficacy data presented for this current extension of indication is based on an interim analysis for Study 124, reporting data from subjects 12 to <24 months of age who completed Part A/Cohort 1 and/or Part B/Cohort 5 (through 24 weeks of IVA treatment).

Study 124 is an ongoing, Phase 3, 2-part, open-label study in subjects <24 months with 1 of the following mutations on at least 1 CFTR allele: G551D, G178R, S549N, S549R, G551S, G1244E, S1251N, S1255P, or G1349D. Patients with an R117H mutation are eligible to enrol in regions where IVA is approved for use in patients 2 through 5 years of age with an R117H mutation.

Given the underlying pathophysiology of CF and as outlined in the ICH guideline E11 (Clinical Investigation of Medicinal Products in the Paediatric Population), efficacy in subjects 12 to <24 months of age can also be extrapolated from data from older populations of subjects. Results from placebo-controlled Phase 3 studies in subjects with CF ≥6 years of age who had the G551D mutation (Studies 102 and 103) or a non-G551D gating mutation (Study 111) showed that IVA is effective in the treatment of subjects with CF, as evidenced by sustained improvements in CFTR channel function (measured by reduction in sweat chloride concentration) and corresponding substantial and durable improvements in lung function, pulmonary exacerbations, respiratory symptoms, and weight gain.

The safety, PK, PD and efficacy of IVA treatment in subjects 2 through 5 years of age with a gating mutation was evaluated in open-label Study 108. Results of Study 108 demonstrated the safety and PK of IVA treatment in subjects 2 through 5 years of age. Furthermore, results from Study 108 demonstrated that IVA improved CFTR function in subjects 2 through 5 years of age, with corresponding positive effects on pancreatic function, and nutritional status.

### 2.4.1. Dose response study

No formal dose-response study has been performed; however, selection of doses for Part A and Part B in Study 124 was supported by simulation exercise. Dosing regimen for 1-2 years olds is based on simulations performed to predict ivacaftor exposure in three weight groups of patients aged less than 2

years: 4.5 to <7 kg, 7 to <14 kg, and 14 to <25 kg. Previously developed population PK model was used, that included data from subjects 2 - 5 years of age. The same Cmin and AUC values were targeted as in adults. The simulations also incorporated a maturation function to determine the range of likely exposures given maturational changes in clearance. Based on results of these simulations, a lower weight bound of 5 kg was determined to be more appropriate for subjects receiving the 25-mg dose to maintain exposures within the targeted range. This approach was agreed by the CHMP.

### 2.4.2. Main study

#### Title of Study

**Study 124: A Phase 3, 2-Part, Open-label Study to Evaluate the Safety, Pharmacokinetics, and Pharmacodynamics of Ivacaftor in Subjects with Cystic Fibrosis Who Are Less Than 24 Months of Age at Treatment Initiation and Have a CFTR Gating Mutation**

#### *Methods*

This is an ongoing Phase 3, 2-part, open-label study of orally administered IVA in subjects with CF who were <24 months of age at treatment initiation (Day 1) and have a CFTR gating mutation or R117H (currently in the US only) on at least 1 allele. Part A was designed to evaluate the safety and PK of multiple-dose administration of IVA over 4 days of dosing, 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 IVA in subjects over 24 weeks. Subjects 12 to <24 months of age were enrolled in Cohort 1 of Part A and Cohort 5 of Part B. Younger subjects are enrolled in subsequent descending age cohorts following PK and safety assessments for each age cohort:

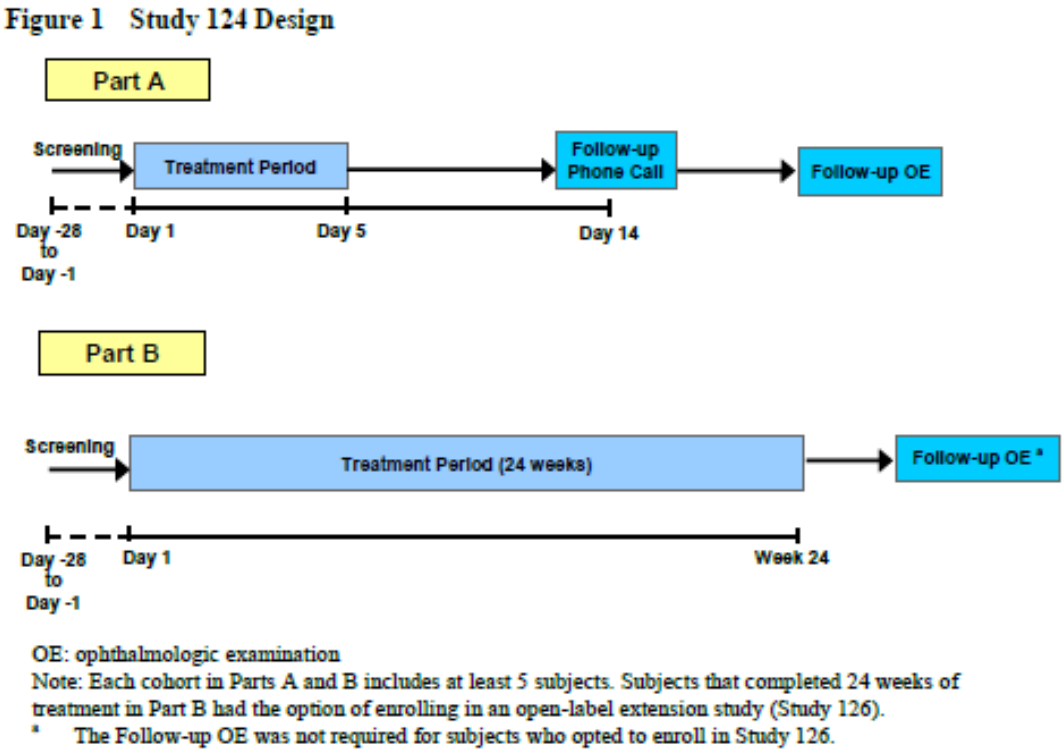
- Cohort 1: subjects aged 12 to <24 months
- Cohort 2: subjects aged 6 to <12 months
- Cohort 3: subjects aged 3 to <6 months
- Cohort 4: subjects aged 0 to <3 months

Subjects will be enrolled in Part B sequentially in the following cohorts based on age at Day 1 of Part B:

- Cohort 5: subjects aged 12 to <24 months
- Cohort 6: subjects aged 6 to <12 months
- Cohort 7: subjects aged 0 to <6 months

During the treatment periods of Parts A and B, 25 mg (for subjects 5 to <7 kg on Day 1), 50 mg (for subjects 7 to <14 kg on Day 1), or 75 mg (for subjects ≥14 to <25 kg on Day 1) IVA was to be administered every 12 hours (q12h). Part A consisted of a Screening Period (Day -28 to Day -1), a Treatment Period (Day 1 to Day 5), a Follow-up Telephone Call (Day 14), and a Follow-up Ophthalmologic Examination (OE, 8 weeks after the last dose). Part B consisted of a Screening Period (Day -28 to Day -1), a Treatment Period (Day 1 to Week 24), a Follow-up Visit (4 weeks after the last dose), and a Follow-up OE (24 weeks after the last dose). Subjects who completed 24 weeks of IVA treatment were eligible to enroll in the open-label treatment arm of an Extension Study, Study VX15-770-126. This interim analysis includes all data from subjects 12 to <24 months of age who completed Cohort 1/Part A and/or Cohort 5/Part B (through 24 weeks of treatment), see Figure 3 below.

**Figure 3**




## 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.
- Must have had 1 of the following 9 CFTR mutations on at least 1 allele: G551D, G178R, S549N, S549R, G551S, G1244E, S1251N, S1255P, or G1349D. Subjects who had an R117H-CFTR mutation were eligible in regions where IVA is approved for use in subjects 2 through 5 years of age with an R117H-CFTR mutation.
- Aged 0 to <24 months at Day 1; subjects who completed Part A who were ≥24 months of age on Day 1 in Part B were not eligible to enrol in Part B.

- For Cohorts 4 and 7 only, gestational age ≥38 weeks.
- Weight at screening within the weight limits as defined for the study drug dose levels

Key exclusion criteria

- History of any illness or condition that, in the opinion of the investigator, might have confounded the results of the study or posed an additional risk in administering study drug to the subject
- An acute upper or lower respiratory infection, or PEx, or changes in therapy (including antibiotics) for pulmonary disease within 4 weeks before Day 1
- Colonization with organisms associated with a more rapid decline in pulmonary status (e.g., Burkholderia cenocepacia, Burkholderia dolosa, and Mycobacterium abscessus) at screening.
- Abnormal liver function at screening or any prior history of clinically relevant elevated (>2 × upper limit of normal [ULN]) serum aspartate transaminase (AST), serum alanine transaminase (ALT), or bilirubin (excluding newborn hyperbilirubinemia)
- Any clinically significant "non-CF-related" illness within 2 weeks before Day 1. "Illness" was defined as an acute (serious or nonserious) condition (e.g., gastroenteritis)
- Use of any moderate or strong inducers or inhibitors of CYP3A within 2 weeks before Day 1
- Presence of a lens opacity or cataract identified at the screening OE (excluding those considered congenital and nonprogressive, such as a suture cataract)

In CHMP's view, inclusion and exclusion criteria were appropriate and in line with previous studies conducted with ivacaftor in children. Criteria did not include spirometry limits. This is agreed as spirometry usually cannot be performed in children aged less than 6 years old, due to compliance issues.

## Treatments

For Cohorts 1 and 5, IVA granules were administered orally at a dosage of 50 or 75 mg q12h based on their weight. In Part A, doses administered from the evening dose on Day 1 through the evening dose on Day 3 were administered q12h at home, and the Day 1 and Day 4 morning dose was administered in the clinic. On Day 1 of Part B, subjects received a single dose of 50 mg or 75 mg IVA (by weight) in the clinic. At each study visit, the IVA dose for each subject was reassessed based on body weight and adjusted if necessary. For Cohort 5, all subjects received 50 mg IVA based on their weight for the duration of the 24-week treatment period, with the exception of 1 subject who received 75 mg IVA at the Week 24 Visit. Each dose of granules was mixed with approximately 1 teaspoon (5 mL) of appropriate liquid or soft food and administered with an age-appropriate fat-containing meal or snack.

## Objectives

### Part A

*Primary:*

• To evaluate the safety of ivacaftor (IVA)

• To evaluate the pharmacokinetics (PK) of IVA and metabolites hydroxymethyl-ivacaftor (M1-IVA) and ivacaftor carboxylate (M6-IVA)

**Part B**

*Primary*

• To evaluate the safety of IVA

*Secondary*

• To evaluate the PK of IVA and metabolites M1-IVA and M6-IVA

• To evaluate the PD of IVA

*Tertiary*

• To evaluate the efficacy of IVA

• To evaluate the acceptability/palatability of IVA granules

## Outcomes / endpoints

Assessment of the safety of IVA treatment in subjects with CF who are less than 2 years of age and have a CFTR gating mutation was a primary objective of Parts A and B.

PK endpoints: refer to PK section of this report.

Primary safety endpoints: AEs, clinical laboratory values (haematology and serum chemistry), OEs, physical examinations, standard 12-lead ECGs, vital signs

Pharmacodynamic endpoint: sweat chloride test

Tertiary efficacy endpoints: Absolute change from baseline for weight, length, weight-for-length, weight-for-age z-score, length-for-age z-score, weight-for-length-for-age z-score, lung clearance index (LCI) at qualified study sites (based on mass spectrometry analysis), forced expiratory volume in 0.5 seconds, forced mid-expiratory flow rate, forced vital capacity, and functional residual capacity at qualified study sites, FE-1, IRT, markers of intestinal inflammation (calprotectin), qualitative microbiology cultures; pulmonary exacerbations (PEx), CF-related hospitalizations, acceptability/palatability.

## Sample size

A minimum of 5 subjects were planned to enrol in each of the cohorts for Parts A and B. In this interim analysis, the Full Analysis Set (FAS) and Safety Set included:

- Part A: 7 subjects who enrolled in Cohort 1 and received at least 1 dose of IVA
- Part B: 19 subjects who enrolled in Cohort 5 and received at least 1 dose of IVA

## Randomisation

This was a single-treatment-arm study.

## Blinding (masking)

This was an open-label study.

## Statistical methods

Study 124 is still ongoing study. The sample size of a minimum of 20 subjects in Part A and 15 subjects in Part B was based on the availability of the subject population and PK analysis considerations, and not on statistical consideration. Therefore, the study is not powered to detect a significant treatment effect. Continuous variables and categorical variables were summarized by standard descriptive statistics. The CHMP considered that the applied descriptive methods were adequate for the limited study goals set in protocol.

## *Results*

## Participant flow

**PART A:** A total of 7 subjects were enrolled and included in the Safety Set. All 7 subjects completed 4 days of treatment.

**PART B:** A total of 19 subjects were enrolled and included in the Safety Set. One subject participated in Part A and in Part B. Eighteen subjects (94.7%) completed the 24 weeks of treatment. One subject prematurely discontinued study drug treatment due to physician decision (due to difficulty in drawing blood), and consent was subsequently withdrawn.
Seventeen subjects rolled over into Study 126 and therefore did not have the Follow-up Visit, per protocol. One subject reached the age of 2 years and initiated treatment with commercial IVA after completing the 24-week treatment period.

## Recruitment

Subjects from Cohort 1 were enrolled at 7 sites in Australia, the UK, and the US. Subjects from Cohort 5 were enrolled at 13 sites in Australia, Canada, the UK, and the US.

## Conduct of the study

Study initiation: 25 August 2016 (date first eligible subject signed the informed consent form for Part A)

End of Interim Analysis: 01 November 2017 (date last subject from Cohort 5 completed Part B Week 24 Visit)

Study completion: Study is ongoing for subjects <12 months of age

Amendments:

| Protocol History |
|---|
| Version and Date of Protocol |
| Version 1.0, 19 October 2015 |
| Version 2.0, 09 March 2017 |

The protocol was amended twice but neither change can be considered compromise appropriate study conduct. Overall, the mean study drug compliance was 98.3%, and 100% of subjects were ≥80% compliant with study drug.

## Baseline data

### PART A

Demographics: The mean age of the 5 subjects in the 50-mg group was 18 months (range: 14 to 23 months). In the 75-mg group, the 2 subjects were aged 21 and 23 months. The number of male and female subjects was similar in the 50-mg group; both subjects in the 75-mg group were male. All subjects were White and of non-Hispanic or Latino ethnicity. All subjects had a G551D mutation, with the exception of 1 subject who had a G551S mutation. Overall, the most prevalent genotype was G551D/F508del (4/7).

Baseline characteristics: In general, weight, length, weight-for-length, and BMI values were similar among subjects within each dose group and, as expected from the weight-based dosing, generally greater in the 75-mg group than in the 50-mg group, see Table 8 below.

**Table 8**

**Table 10-3 Baseline Characteristics, Safety Set, Part A/Cohort 1**

| Characteristic | IVA 50 mg N = 5 | IVA 75 mg N = 2 | Total N = 7 |
|---|---|---|---|
| **Weight (kg)** | | | |
| n | 5 | 2 | 7 |
| Mean (SD) | 10.7 (1.5) | 15.3 (1.1) | 12.0 (2.6) |
| Median | 11.3 | 15.3 | 11.4 |
| [redacted] | | | |
| **Length (cm)** | | | |
| n | 5 | 2 | 7 |
| Mean (SD) | 79.3 (5.4) | 92.1 (1.1) | 82.9 (7.6) |
| Median | 80.0 | 92.1 | 84.0 |
| [redacted] | | | |
| **Weight-for-length (percentile)** | | | |
| n | 5 | 2 | 7 |
| Mean (SD) | 66.3 (28.8) | 94.6 (5.8) | 74.4 (27.4) |
| Median | 81.0 | 94.6 | 85.1 |
| [redacted] | | | |
| **BMI (kg/m²)** | | | |
| n | 5 | 2 | 7 |
| Mean (SD) | 16.90 (0.89) | 18.05 (0.92) | 17.23 (0.99) |
| Median | 17.06 | 18.05 | 17.40 |
| [redacted] | | | |

Source: Table 14.1.3.1.a1
BMI: body mass index; IVA: ivacaftor; n: size of subsample; N: total sample size
Notes: All results displayed are baseline results. Baseline was defined as the most recent non-missing measurement before the first dose of study drug.

Prior and concomitant medications: In general, concomitant medication use was typical of a CF population. The most commonly reported concomitant medications were salbutamol, pancreatin, dornase alfa, and sodium chloride, which were taken by over 50% of subjects overall.

### PART B

Demographics: All subjects weighed <14 kg (range: 7.5 to 12.4 kg) and therefore received IVA 50 mg q12h. The number of male and female subjects was similar. All subjects were White and the majority

were of non-Hispanic or Latino ethnicity. The majority (16/19) of subjects had a G551D mutation; 2 subjects had a S549N mutation; and 1 subject had a G178R mutation. The most prevalent genotype was G551D/F508del (11/19).

Baseline characteristics are summarised in Table 9 below.

**Table 9**

Table 10-7 Baseline Characteristics, Safety Set, Part B/Cohort 5

| Characteristic | IVA 50 mg N = 19 |
|---|---|
| **Weight (kg)** | |
| n | 19 |
| Mean (SD) | 10.5 (1.3) |
| Median | 10.8 |
| [redacted] | |
| **Length (cm)** | |
| n | 19 |
| Mean (SD) | 78.0 (3.7) |
| Median | 77.4 |
| [redacted] | |
| **Weight-for-length (percentile)** | |
| n | 19 |
| Mean (SD) | 68.2 (26.0) |
| Median | 82.4 |
| [redacted] | |
| **BMI (kg/m²)** | |
| n | 19 |
| Mean (SD) | 17.25 (1.40) |
| Median | 17.28 |
| [redacted] | |
| **Weight-for-age z-score** | |
| n | 19 |
| Mean (SD) | 0.31 (0.74) |
| Median | 0.25 |
| [redacted] | |
| **Length-for-age z-score** | |
| n | 19 |
| Mean (SD) | -0.30 (0.82) |
| Median | -0.38 |
| [redacted] | |
| **Weight-for-length-for-age z-score** | |
| n | 19 |
| Mean (SD) | 0.61 (0.90) |
| Median | 0.93 |
| [redacted] | |

Source: Table 14.1.3.1.b5

BMI: body mass index; IVA: ivacaftor; n: size of subsample; N: total sample size; WHO: World Health Organization

Notes: All results displayed are baseline results. Baseline was defined as the most recent non-missing measurement before the first dose of study drug. Z-scores are calculated using World Health Organization (WHO) Child Growth Standards for children 0 to 24 months of age.

Sweat chloride values were available only for 14 children at baseline. The mean (SD) sweat chloride value was 104.1 (12.8) mmol/l with a minimum value of 72.0 mmol/l. Of the 19 subjects in Cohort 5, 11 were considered to be pancreatic insufficient at baseline (based on a level of faecal elastase-1 [FE-1] values <200 µg/g) and 8 were considered pancreatic sufficient. Mean (SD) FE-1 values at baseline were 13.4 (12.3) µg/g for pancreatic insufficient subjects and 414.4 (120.9) µg/g for pancreatic sufficient subjects. Mean (SD) immunoreactive trypsinogen (IRT) values at baseline were 1122.2 (211.6) ng/mL for pancreatic insufficient subjects and 1200.0 (0.0) ng/mL for subjects who were pancreatic sufficient (upper limit of quantification of the assay was 1200 ng/ml).

Upon CHMP request the MAH provided baseline weight-, length-, and weight-for-length z-scores and percentiles by sex. These are summarised in Table 10 below.

**Table 10**

**Table 8 Baseline Data by Sex of Weight, Length, and Weight-for-length Z-scores and Percentiles, Study 124 FAS, Part B, Cohort 5**

| Parameter | Baseline Statistic | Male IVA 50 mg N = 11 | Female IVA 50 mg N = 8 |
|---|---|---|---|
| Weight-for-age z-score | n | 11 | 8 |
| | Mean (SD) | 0.45 (0.63) | 0.13 (0.87) |
| | Median | 0.27 | 0.13 |
| | [redacted] | | |
| Length-for-age z-score | n | 11 | 8 |
| | Mean (SD) | -0.38 (0.93) | -0.20 (0.68) |
| | Median | -0.69 | -0.12 |
| | [redacted] | | |
| Weight-for-length z-score | n | 11 | 8 |
| | Mean (SD) | 0.84 (0.72) | 0.29 (1.07) |
| | Median | 0.99 | 0.24 |
| | [redacted] | | |
| Weight-for-age percentile | n | 11 | 8 |
| | Mean (SD) | 64.3 (18.5) | 54.8 (27.9) |
| | Median | 60.6 | 55.3 |
| | [redacted] | | |
| Length-for-age percentile | n | 11 | 8 |
| | Mean (SD) | 37.2 (29.8) | 43.2 (23.2) |
| | Median | 24.6 | 45.5 |
| | [redacted] | | |
| Weight-for-length percentile | n | 11 | 8 |
| | Mean (SD) | 75.4 (20.0) | 58.3 (31.2) |
| | Median | 83.9 | 59.4 |
| | [redacted] | | |

Source: Table 3.1.b5
FAS: Full Analysis Set; IVA: ivacaftor; [redacted] n: size of subsample; N: total sample size
Note: Baseline is the most recent measurement before the first dose of study drug. Z-scores are calculated using World Health Organization (WHO) Child Growth Standards for children 0 to 48 months of age.

Medical history: the most frequent disease manifestation in these young children was lung disease followed by pancreatic failure and constipation.

Prior and concomitant medication: The most commonly reported concomitant medications were pancreatin, paracetamol, salbutamol, sodium chloride, dornase alfa, and pancrelipase, which were taken by over 30% of subjects.

## Outcomes and estimation

### *Secondary efficacy (pharmacodynamic) endpoint:*

**Sweat chloride**

The absolute changes from baseline in sweat chloride are summarised in Table 11 and Figure 4 below.

**Table 11**

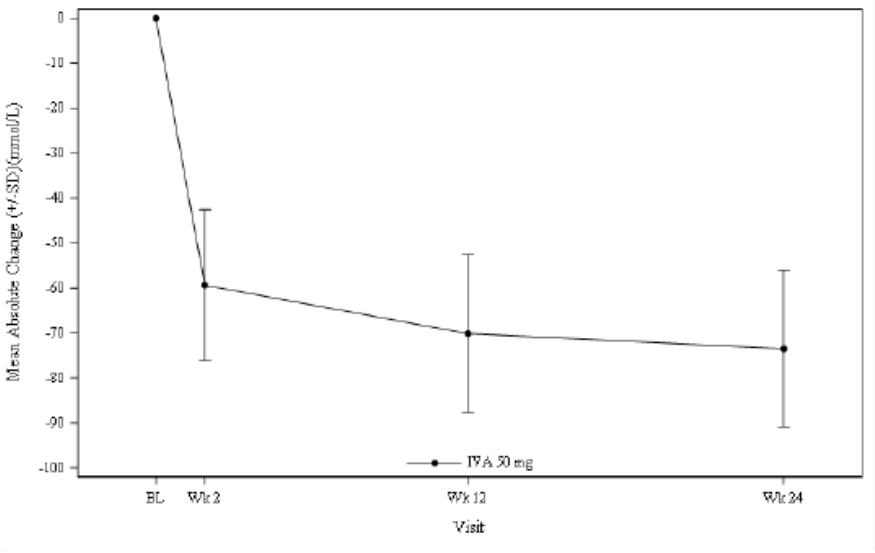
**Table 11-3 Absolute Changes From Baseline in Sweat Chloride (mmol/L), FAS, Part B/Cohort 5**

| | | IVA 50 mg N = 19 | |
|---|---|---|---|
| Visit | Statistic | Sweat Chloride (mmol/L) | Absolute Change From Baseline at Visit (mmol/L) |
| Baseline | n | 14 | NA |
| | Mean (SD) | 104.1 (12.8) | NA |
| | Median | 105.8 | NA |
| | Min, max | 72.0, 120.5 | NA |
| Week 2 | n | 15 | 11 |
| | Mean (SD) | 51.8 (25.9) | -59.4 (16.8) |
| | Median | 46.0 | -64.0 |
| | Min, max | 19.5, 96.0 | -77.0, -25.5 |
| Week 12 | n | 16 | 13 |
| | Mean (SD) | 35.2 (15.9) | -70.2 (17.5) |
| | Median | 32.5 | -70.5 |
| | Min, max | 16.5, 74.0 | -96.5, -40.0 |
| Week 24 | n | 14 | 10 |
| | Mean (SD) | 33.8 (10.8) | -73.5 (17.5) |
| | Median | 31.5 | -72.3 |
| | Min, max | 14.5, 52.0 | -97.5, -42.0 |

Source: Table 14.2.1.1.b5
FAS: Full Analysis Set; IVA: ivacaftor; n: size of subsample; N: total sample size; NA: not applicable
Notes: Baseline was defined as the most recent measurement before the first dose of study drug in Part B.

**Figure 4**

**Figure 2 Study 124 Part B/Cohort 5: Mean Absolute Changes From Baseline in Sweat Chloride (mmol/L) by Visit**

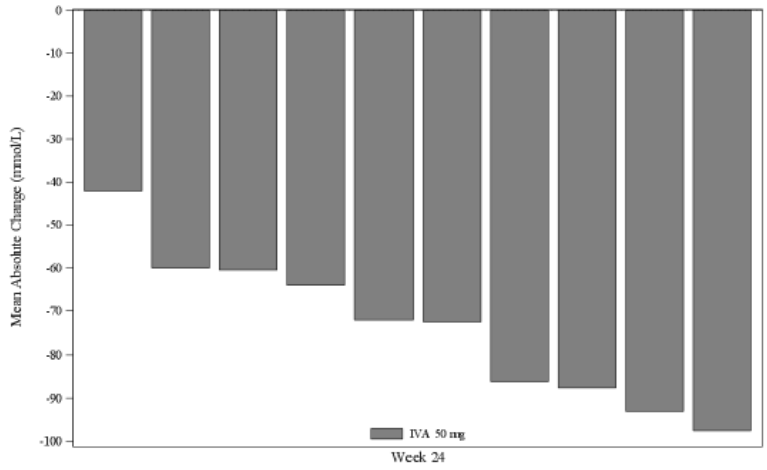



Source: Study 124 IAR/Figure 11-1
BL: baseline; IVA: ivacaftor; n: size of subsample; Wk: week
Notes: n for each visit was as follows: BL: n = 14; Wk 2: n = 11; Wk 12: n = 13; Wk 24: n = 10

The waterfall plot of change from baseline at week 24 in sweat chloride is presented in Figure 5 below.

**Figure 5**

**Figure 3 Study 124 Part B/Cohort 5: Waterfall Plot of Change from Baseline at Week 24 in Sweat Chloride**




Source: Study 124 IAR/Figure 11-2
IVA: ivacaftor

In Part B, all subjects in Cohort 5 had very high sweat chloride values (around 100 mmol/L), as all subjects harboured gating (majority G551D) mutations which result generally in severe phenotype of CF. Following 2 weeks of treatment a robust decrease in sweat chloride was apparent (mean decrease 60 mmol/L), some patients must have had normal Cl values (suggested by minimum values). This robust improvement increased further on through week 24 visit.

The pre-specified analysis of sweat chloride as described in the protocol and the statistical analysis plan (SAP) was the mean absolute change at Week 24 from baseline in Part B only. No such analysis was planned for children in Part A and therefore these are not available.

Overall, the analysis of change from baseline in sweat chloride was conducted as pre-specified in the protocol and SAP. As a drawback of the present analysis, data at baseline and at week 24 are only available for 10 children (based on the waterfall plot provided). The descriptive analysis includes 14 subjects at baseline and 14 at week 24 (that are not the same subjects as otherwise the waterfall plot should have included data for 14 children). The MAH was asked to clarify the reason behind the decreased number of subjects in the analysis. In their response, it was stated that nineteen subjects were enrolled in part B of study 124. Out of these 19 subjects, 18 completed the 24 week treatment period. However, the data provided by the MAH show that for many of these children efficacy outcomes that allow calculating the change from baseline were not available. In this respect, for sweat chloride data at baseline and at week 24 were only available for 10 patients. The results quoted in section 5.1 of SmPC correspond to the change in sweat chloride observed for these 10 patients, which is agreeable.

### *Tertiary efficacy endpoints*

**Nutritional status**

The absolute change from baseline in weight-for-age-Z-score is presented in Table 12 below.

**Table 12**

**Table 11-4 Absolute Changes From Baseline in Weight-for-age Z-score (unit), FAS, Part B/Cohort 5**

| | | IVA 50 mg N = 19 | |
|---|---|---|---|
| Visit | Statistic | Weight-for-age Z-score | Absolute Change From Baseline at Visit |
| Baseline | n | 19 | NA |
| | Mean (SD) | 0.31 (0.74) | NA |
| | Median | 0.25 | NA |
| | [redacted] | | |
| Week 2 | n | 19 | 19 |
| | Mean (SD) | 0.38 (0.71) | 0.07 (0.20) |
| | Median | 0.33 | 0.08 |
| | [redacted] | | |
| Week 12 | n | 18 | 18 |
| | Mean (SD) | 0.43 (0.87) | 0.11 (0.36) |
| | Median | 0.14 | 0.01 |
| | [redacted] | | |
| Week 24 | n | 18 | 18 |
| | Mean (SD) | 0.48 (0.83) | 0.15 (0.42) |
| | Median | 0.35 | 0.09 |
| | [redacted] | | |

Source: Table 14.2.2.1.b5
FAS: Full Analysis Set; IVA: ivacaftor; n: size of subsample; N: total sample size; NA: not applicable; WHO: World Health Organization
Notes: Baseline was defined as the most recent measurement before the first dose of study drug in Part B. Z-scores were calculated using WHO Child Growth Standards for children 0 to 24 months of age.

The absolute change from baseline in length-for-age-Z-score is presented in Table 13 below.

**Table 13**

**Table 11-5 Absolute Changes From Baseline in Length-for-age Z-score (unit), FAS, Part B/Cohort 5**

| Visit | Statistic | IVA 50 mg N = 19 | |
|---|---|---|---|
| | | Length-for-Age Z-score | Absolute Change From Baseline at Visit |
| Baseline | n | 19 | NA |
| | Mean (SD) | -0.30 (0.82) | NA |
| | Median | -0.38 | NA |
| Week 2 | n | 19 | 19 |
| | Mean (SD) | -0.30 (0.74) | 0.00 (0.34) |
| | Median | -0.48 | -0.02 |
| Week 12 | n | 17 | 17 |
| | Mean (SD) | -0.01 (0.81) | 0.24 (0.48) |
| | Median | 0.23 | 0.23 |
| Week 24 | n | 17 | 17 |
| | Mean (SD) | 0.03 (0.91) | 0.28 (0.60) |
| | Median | 0.12 | 0.50 |

Source: Table 14.2.2.1.b5

FAS: Full Analysis Set; IVA: ivacaftor; n: size of subsample; N: total sample size; NA: not applicable

Notes: Baseline was defined as the most recent measurement before the first dose of study drug in Part B. Z-scores were calculated using WHO Child Growth Standards for children 0 to 24 months of age.

The absolute change from baseline in weight-for-length-for-age-Z-score is presented in Table 14 below.

**Table 14**

Table 11-6 Absolute Changes From Baseline in Weight-for-length-for-age Z-score, FAS, Part B/Cohort 5

| | | IVA 50 mg N = 19 | |
|---|---|---|---|
| Visit | Statistic | Weight-for-length-for-age Z-score | Absolute Change From Baseline at Visit |
| Baseline | n | 19 | NA |
| | Mean (SD) | 0.61 (0.90) | NA |
| | Median | 0.93 | NA |
| | [redacted] | | |
| Week 2 | n | 19 | 19 |
| | Mean (SD) | 0.70 (0.80) | 0.09 (0.40) |
| | Median | 0.85 | 0.18 |
| | [redacted] | | |
| Week 12 | n | 17 | 17 |
| | Mean (SD) | 0.65 (0.94) | 0.02 (0.54) |
| | Median | 0.55 | -0.08 |
| | [redacted] | | |
| Week 24 | n | 17 | 17 |
| | Mean (SD) | 0.69 (0.98) | 0.07 (0.65) |
| | Median | 0.67 | 0.17 |
| | [redacted] | | |

Source: Table 14.2.2.1.b5
FAS: Full Analysis Set; IVA: ivacaftor; n: size of subsample; N: total sample size; NA: not applicable
Notes: Baseline was defined as the most recent measurement before the first dose of study drug in Part B. Z-scores were calculated using WHO Child Growth Standards for children 0 to 24 months of age.

Small children with CF generally have normal lung function, as despite recurrent infections and small structural changes, lung compensates for a relatively long time. A more prominent sign of CF may be malnourishment (if any) in these children. However, growth parameters were normal or near-normal at baseline for most children enrolled in Cohort 5, part B of study 124. Pancreatic insufficient patients received enzyme-replacement therapy at baseline and during this study. Through week 24, all growth parameter increased. Considering that this population is normally a rapidly growing one, the MAH was requested to compare the change from baseline through week 24 in weight, length, BMI and respective z-scores of study subjects to historical values in those who were not treated with ivacaftor and had gating mutation at least on one allele and were at the same age. In addition, the MAH was also requested to provide the following:

- Descriptive statistics of change from baseline in weight-, length-, and weight-for-length z-scores by sex (part B) based on subjects with available data as well as restricted to subjects with both baseline and week 24 data available.

- Descriptive statistics of change from baseline in weight-for-age z-score restricted to subjects with weight-for-age z-scores below 0 (part B). The percentage of children who reach after 24 weeks a z-score equal or above 0 should be provided (by sex).

The requested comparison versus an age-matched historical cohort of children who were not treated with ivacaftor and had gating mutation in at least one allele was not provided. Instead, the MAH stated that patients with Class I to III CF mutations, including gating mutations, who were <2 years of age had a median weight percentile of 44.3, a median length percentile of 29.2, and a median weight-for-length percentile of 63.5 based on the 2016 Cystic Fibrosis Foundation (CFF) Patient Registry Annual Data Report. At study 124 baseline, children enrolled in Cohort 5, part B had a mean weight-for-age

percentile of 60.3, a mean length-for-age percentile of 39.8 and a mean weight-for-length percentile of 68.2 The mean (95% CI) change from baseline at week 24 in the above measures was 4.5 (-2.4, 11.4), 11.1 (2.1, 20.0), and 1.5 (-7.3, 10.3) respectively for the overall population of Cohort 5.

Regarding the requested data of change from baseline in weight-, length-, and weight-for-length Z-scores by sex, these are summarised in Table 15 below.

**Table 15**

**Table 6: Effect of ivacaftor on growth parameters in patients with baseline and Week 24 values**

| Endpoint | Overall | | Male * | | Female * | |
|---|---|---|---|---|---|---|
| | n | Mean (SD/CI) | n | Mean (SD/CI) | n | Mean (SD/CI) |
| Weight-for-age z-score | 18 | | 10 | | 8 | |
| - Baseline | | 0.32 (0.76) | | 0.48 (0.66) | | 0.13 (0.87) |
| - Week 24 | | 0.48 (0.83) | | 0.58 (0.87) | | 0.34 (0.81) |
| - Abs. change | | 0.15 (-0.05, 0.36) | | 0.10 (-0.11, 0.32) | | 0.22 (-0.24, 0.68) |
| Length-for-age z-score | 17 | | 9 | | 8 | |
| - Baseline | | -0.24 (0.83) | | -0.28 (0.99) | | -0.20 (0.68) |
| - Week 24 | | 0.03 (0.91) | | 0.09 (1.13) | | -0.03 (0.64) |
| - Abs. change | | 0.28 (-0.03, 0.58) | | 0.38 (-0.13, 0.88) | | 0.17 (-0.29, 0.62) |
| Weight-for-length z-score | 17 | | 9 | | 8 | |
| - Baseline | | 0.62 (0.94) | | 0.92 (0.75) | | 0.29 (1.07) |
| - Week 24 | | 0.69 (0.98) | | 0.86 (1.07) | | 0.50 (0.90) |
| - Abs. change | | 0.07 (-0.26, 0.40) | | -0.06 (-0.47, 0.36) | | 0.21 (-0.42, 0.85) |

* Post-hoc analysis by gender are based on small patient numbers and therefore definitive conclusions cannot be drawn with respect to differences in gender response.
SD: Standard Deviation; CI: 95% Confidence Intervals

Of the 6 subjects who had weight z-scores less than 0 at baseline, 3 (50%) had a z-score ≥0 after 24 weeks of treatment with IVA (1 of 3 males and 2 of 3 females). Overall, 14 of 19 (73.7%) subjects had a z-score ≥0 after 24 weeks of treatment with IVA. The mean (SD) change in weight-for-age Z-score from baseline to week 24 restricted to children with a weight-for-age Z-score below 0 at baseline was 0.12 (0.18) for boys and 0.51 (0.55) for girls.

When the results by sex are compared to those of the overall population it would appear that the change in weight-for-age z-score is driven by that observed in girls (0.22 vs. 0.10) while in the case of length-for-age z-score, boys experienced a change of 0.38 vs. 0.17 in girls. Regarding weight-for-length z-score, the change experienced by boys was -0.06 vs. 0.21 in girls. The MAH is of the opinion that there is no clinical rationale for the discrepancy in growth parameters by sex and the results observed are an artefact of the small sample size and high variability in ages within the cohort. This could lead to false assumptions and the potential for different treatment decisions between sexes, thus proposed to retain only the 'all patient' data in the label. In this respect, the results quoted in section 5.1, as agreed by the CHMP, are as follows:

For patients with both baseline and Week 24 values available, mean (SD) weight for age z score at baseline was 0.32 (0.76), with a mean (SD) absolute change of 0.15 (0.42) at 24 weeks; mean (SD)

length for age z score at baseline was -0.24 (0.83), with a mean (SD) absolute change of 0.28 (0.60) at 24 weeks; and mean (SD) weight for length z score at baseline was 0.62 (0.94), with a mean (SD) absolute change of 0.07 (0.65) at 24 weeks.

**Pancreatic function and inflammation**

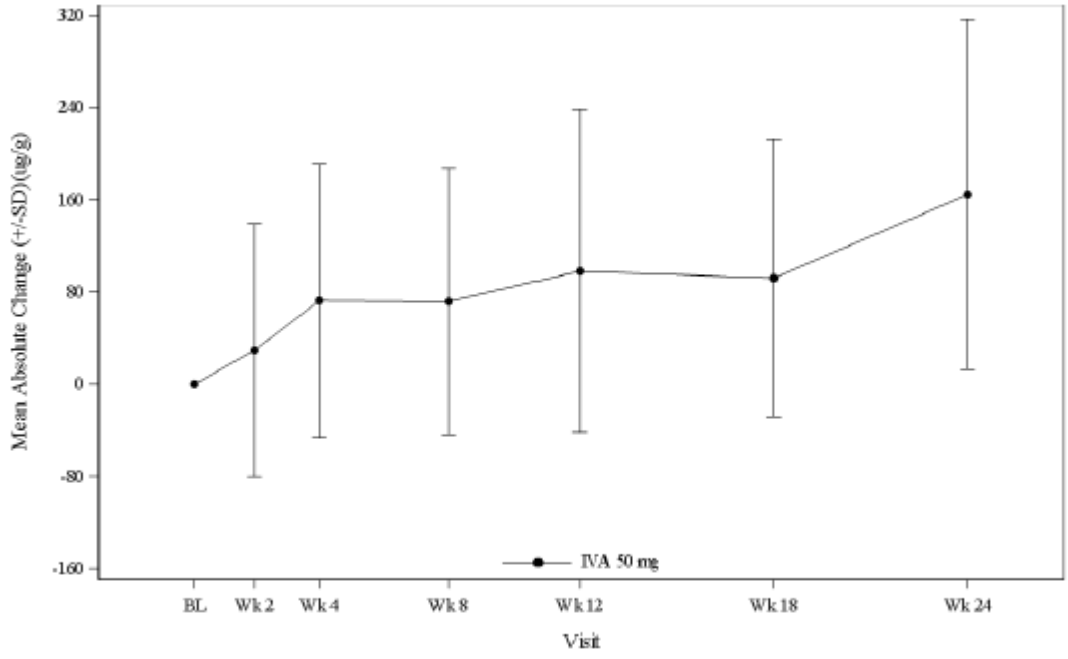
*Faecal elastase*

Increases in mean FE-1 were observed by Week 2 and sustained through Week 24, suggesting improvement in pancreatic function with IVA treatment (Figure 6 below). Mean FE-1 at Week 24 (326.9 µg/g) was nearly double that at baseline (182.2 µg/g). The mean (SD) absolute change from baseline was 29.4 (109.7) µg/g at Week 2 and 164.7 (151.9) µg/g at Week 24.

Subjects with CF that have FE-1 levels <200 µg/g are considered pancreatic insufficient. Of the 19 subjects in part B, cohort 5, 11 were considered to be pancreatic insufficient. Mean (SD) FE-1 values at baseline were 13.4 (12.3) µg/g for pancreatic insufficient subjects and 414.4 (120.9) µg/g for pancreatic sufficient subjects. Nine subjects with pancreatic insufficiency had values of FE-1 at both baseline and week 24. The mean (SD) change from baseline was 248.1 µg/g (132.9). These are the results quoted in section 5.1 of the SmPC. Six of these 9 subjects were pancreatic insufficient at baseline (FE-1 <200 µg/g) and had FE-1 >200 µg/g at Week 24, indicative of pancreatic sufficiency. No subject who was pancreatic sufficient at baseline became pancreatic insufficient after 24 weeks of treatment. Although these results are supportive, data beyond 24 weeks are needed to conclude whether this effect is kept in the long term.

**Figure 6**

**Figure 4 Study 124 Part B/Cohort 5: Mean Absolute Changes From Baseline in FE-1 by Visit**




Source: Study 124 IAR/Figure 11-6
BL: baseline; IVA: ivacaftor; Wk: week

*Immunoreactive trypsinogen*

There was a rapid decrease in mean IRT from baseline by Week 2 that was sustained through Week 24, suggesting a decrease in pancreatic inflammation. The mean (SD) absolute change from baseline was -444.1 (363.6) ng/mL at Week 2 and -647.1 (339.3) ng/mL at Week 24.

As previously stated, out of the 19 subjects in Cohort 5; 11 were considered to be pancreatic insufficient at baseline and 8 were considered pancreatic sufficient. Mean (SD) IRT values at baseline were 1122.2 (211.6) ng/mL for pancreatic insufficient subjects and 1200.0 (0.0) ng/mL for subjects who were pancreatic sufficient. All 8 pancreatic sufficient subjects had a value of 1200 ng/mL at baseline, which was the upper limit of quantification for this assay. The mean (SD) change from baseline at week 24 in IRT limited to subjects with pancreatic insufficiency who had values at both points in time was -533.1 (394.5) ng/ ml (n=10).

While improvements in IRT are not numerically comparable to results from prior studies due to the change in assay, the MAH states that the rapid and large improvement from baseline are clear and directionally consistent across IVA studies. However, data on IRT are difficult to interpret in the absence of a control group. As for FE-1, data beyond of 24 weeks are also needed.

*Lipase, amylase*

Part A/Cohort 1: Lipase and amylase levels showed a rapid decline after the start of IVA treatment in Part A. The mean lipase level was 125.7 U/L (normal range: 4 to 31 U/L) at baseline and decreased to 67.57 U/L at Day 5. The mean amylase level was 61.6 U/L baseline (normal range: 7 to 79 U/L) and decreased to 49.6 U/L at Day 5. The mean (SD) absolute change from baseline at Day 5 was -58.14 (58.35) U/L for lipase and -12.0 (16.4) U/L for amylase.

Part B/Cohort 5: Rapid reductions in both lipase and amylase levels that persisted over the 24 weeks of IVA treatment were observed. Mean lipase was elevated at 285.26 U/L (normal range: 4 to 31 U/L) at baseline, and decreased to 67.44 U/L at Week 24. Mean amylase was also elevated at 102.2 U/L (normal range: 8 to 79 U/L) and decreased to 49.8 U/L at Week 24. All subjects with elevations in lipase and/or amylase at baseline were asymptomatic. Mean (SD) absolute changes in lipase from baseline were -224.06 (249.87) U/L at Week 2 and -228.39 (262.95) U/L at Week 24

Mean (SD) absolute changes in amylase from baseline were -46.4 (73.7) U/L at Week 2 and -54.8 (70.5) U/L at Week 24 (Study 124 IAR/Table 12-14). These results suggest an improvement in pancreatic inflammation.

## Ancillary analyses

No ancillary analyses were performed.

## *Summary of main study*

The following Table 16 summarises the efficacy results from the main study supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

**Table 16 Summary of Efficacy for trial Study VX15-770-124**

| **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 Less Than 24 Months of Age at Treatment Initiation and Have a CFTR Gating Mutation** | | | |
|---|---|---|---|
| Study identifier | VX15-770-124 | | |
| Design | phase 3, two-part, open-label | | |
| | Duration of main phase: | | treatment period in Part A: Day 1-Day5, follow-up phone call at Day 14, follow-up for ocular examination 8 weeks after last dose treatment period in Part B: Day 1-week24, rollover to Study 126 OR follow-up 4 weeks after last dose and follow-up for ocular examination 24 weeks after last dose |
| | Duration of Run-in phase: | | N/A |
| | Duration of Extension phase: | | from Part B at week 24 visit (Study 126) |
| Hypothesis | N/A | | |
| Treatments groups | ivacaftor 50 mg | | PART A: ivacaftor 50 mg, N=7, ivacaftor 75 mg N=2, duration: 4 days<br>PART B: ivacaftor 50 mg, N=19, duration: 24 weeks |
| Endpoints and definitions | Primary endpoint | safety | |
| | Secondary endpoint | sweat chloride | absolute change from baseline in sweat chloride concentration at week 24 (mmol/L) |
| | tertiary endpoints:<br>1. measures of nutritional status<br><br>2.measures of pancreatic function | 1.weight, length, weight-for-length, weight-for-age, length-for-age, and weight-for-length-for-age z-scores)<br>2.fecal elastase-1 | absolute change from baseline at week 24 |
| Database lock | ongoing | | |

**Results and Analysis**

| **Analysis description** | **Primary Analysis** | | | |
|---|---|---|---|---|
| Analysis population and time point description | Full Analysis Set (FAS) | | | |
| Descriptive statistics and estimate variability | Treatment group | ivacaftor | | |
| | Number of subject | 19 | | |

| | | | | |
|---|---|---|---|---|
| | abs. change from BL in sweat chloride mean (SD), mmol/L | -73.5 (17.5) | | |
| | Absolute Changes From Baseline in Weight-for-age Z-score mean (SD) unit | 0.15 (0.42) | | |
| | Absolute Changes From Baseline in Length-for-age Z-score (unit), mean (SD) | 0.28 (0.60) | | |
| | Absolute Changes From Baseline in Weight-for-length-for-age Z-score mean (SD) | 0.07 (0.65) | | |
| | Change From Baseline in Fecal Elastase-1 (µg/g), mean (SD) | 164.7 (151.9) | | |
| | Change From Baseline in IRT (ng/mL), mean (SD) | -647.1 (339.3) | | |
| | | | | |
| Notes | the study is currently ongoing | | | |
| **Analysis description** | **N/A** | | | |
| | | | | |

## *Supportive study*

### Study VX15-770-123

**A Phase 3b, 2-part, Randomized, Double-blind, Placebo-controlled Crossover Study With a Long-term Open-label Period to Investigate Ivacaftor in Subjects With Cystic Fibrosis Aged 3 Through 5 Years Who Have a Specified CFTR Gating Mutation**

Patients with 1 of the following *CFTR* gating mutations on at least 1 allele were eligible to enrol: *G551D, G178R, S549N, S549R, G551S, G1244E, S1251N, S1255P,* or *G1349D*.

During Part 1, subjects received 50 mg or 75 mg IVA (by body weight) or placebo q12h for 16 weeks: during Treatment Period 1 (Day 1 through Week 8), approximately half of the subjects received placebo, and the remaining subjects received IVA. Following an 8-week washout period, during Treatment Period 2 (Week 16 through Week 24), subjects who had received IVA in Treatment Period 1 received placebo, and subjects who had received placebo in Treatment Period 1 received IVA. The

primary endpoint was absolute change from baseline in $LCI_{2.5}$; secondary endpoints were absolute change from baseline in IRT, FE-1, weight, and body mass index (BMI) at 8 weeks of treatment in Part 1.

Approximately 50 subjects were planned to be enrolled. Following a review of study enrolment and assessment of the available number of potential subjects for the study, Vertex terminated the study early because of enrolment futility. Only 14 subjects were enrolled and therefore no efficacy conclusions can be made from this study.

### 2.4.3. Discussion on clinical efficacy

### Design and conduct of clinical studies

Study 124 is an ongoing, open-label, 2-part phase 3 study to assess safety, PK, PD and efficacy of ivacaftor in CF patients 1-2 years old, who have a gating type CFTR mutation in at least one allele. This submission is based on:

- previous evidence from well-controlled studies in CF subjects aged 6 years or older with gating mutations,
- results of study 108 (children aged 2-5 years),
- interim analysis of Cohort 1 and 5 data form study 124.

This approach is considered appropriate to support an extension of indication. Design of study 124, in principle, was supported by previous CHMP advice 2010 - EMEA/H/SA/1448/2/2010/PA/III, where CHMP indicated that a positive trend in clinical endpoints, such as z-scores for growth and height, may be sufficient to bridge efficacy to the less than 6-years-of-age population, though this should be supported by adequate safety data. CHMP further agreed that pulmonary function tests need not be used as an endpoint. Inclusion not only of patients with a G551D mutation, but also other non-G551D gating mutations was encouraged.

A dose-response study was not performed. The posology recommendation is based on the results of a simulation study. Previously developed population PK model was used, that included data from subjects 2 - 5 years of age. The same Cmin and AUC values were targeted that in adults. The simulations also incorporated a maturation function to determine the range of likely exposures given maturational changes in clearance. Based on results of simulations, a lower weight bound of 5 kg was determined to be more appropriate for subjects receiving the 25-mg dose to maintain exposures within the targeted range.

The inclusion and exclusion criteria in study 124 were very similar to studies previously conducted with ivacaftor (exc. of age). CF diagnosis was confirmed if the subject had a sweat chloride value ≥60 mmol/L (by quantitative pilocarpine iontophoresis) or 2 CF-causing mutations. The number of male and female subjects was similar. Subjects 12 to <24 months of age were enrolled in Cohort 1 of Part A and Cohort 5 of Part B. Younger subjects are enrolled in subsequent descending age cohorts in the study after PK and safety assessment for each preceding age cohort. The majority (16/19) of subjects had a G551D gating mutation; 2 subjects had the S549N gating mutation; and 1 subject had the G178R gating mutation at least in one allele.

It was recommended that subjects remained on a stable CF medication regimen; thus, ivacaftor was added to standard treatment.

In Part A, subjects received ivacaftor granules based on body weight (50 or 75 mg q12h) for 4 days. PK and safety were assessed. During Part B, study subjects received ivacaftor treatment for 24 weeks which is far long enough to detect short-term efficacy and short-term safety. In Part B, PD/efficacy and safety were evaluated.

Efficacy evaluation was tertiary objective in this study (Part B, Cohort 5). Efficacy was assessed by using nutritional parameters, biomarkers for pancreatic and intestinal inflammation, pulmonary exacerbation and hospitalisation due to CF. Lung function cannot be measured in this age group and if it could it was not informative for disease. To measure ventilation inhomogeneity, lung clearance index measure was performed. This is a multiple breath washout parameter detected by inert gas inhalation. LCI is an encouraged parameter to test small children's ventilation; however, the test requires specific centres.

## Efficacy data and additional analyses

Study population of Cohort 1 and 5 reflected well the targeted population. Study subject had G551D or other approved gating CFTR mutation at least in one allele. Boys and girls were roughly evenly included. Per protocol, subjects who had an R117H-CFTR mutation were eligible in regions where ivacaftor is approved for use in subjects 2 through 5 years of age with an R117H-CFTR mutation. However, no patient with R117H was enrolled into this study; thus, no data could be provided in young children with R117H CFTR mutation by this study.

In Cohort 5, part B of study 124 all subjects weighed <14 kg (range: 7.5 to 12.4 kg) and therefore received IVA 50 mg q12h. The number of male and female subjects was similar. All subjects were White and the majority were of non-Hispanic or Latino ethnicity. The majority (16/19) of subjects had a G551D mutation.

In Part B, all subjects with available baseline data (N=14) had very high sweat chloride values (around 100 mmol/L), as all subjects harboured gating mutations which result generally in severe phenotype of CF. For the remaining 5 subjects baseline data were not available as the amount of sweat collected was insufficient. Following 2 weeks of treatment a robust decrease in sweat chloride was apparent (mean decrease 60 mmol/L), some patients must have had normal Cl values (suggested by minimum values). This robust improvement increased further on through week 24 visit. Waterfall plot shows that even the smallest decrease in sweat chloride was 40 mmol/L, thus ivacaftor resulted in all subjects robust chloride decrease, which is a proof of pharmacodynamic effect in line with previous study results. It should be noted, however, that data of only 10 patients were displayed (who had available baseline and week 24 data). As the reason for not including all patients in the waterfall analysis the MAH clarified that only 10 of the 19 subjects had paired sweat chloride test results at both baseline and at Week 24, only these 10 patients were included in the analysis of change from baseline at Week 24. The mean change in sweat chloride in these 10 children was 73.5 mmol/L (95% CI 86.0, 61.0) at week 24.

Small children with CF generally have normal lung function, as despite recurrent infections and small structural changes, lung compensates for a relatively long time. A more prominent sign of CF may be malnourishment (if any) in these children. However, growth parameters were normal or near-normal at baseline for most children enrolled in Cohort 5, part B of study 124. Pancreatic insufficient patients received enzyme-replacement therapy at baseline and during this study. Through week 24, all growth parameter increased. Considering that this population is normally a rapidly growing one, the MAH was requested to compare the change from baseline through week 24 in weight, length, BMI and respective z-scores of study subjects to historical values in those who were not treated with ivacaftor and had gating mutation and were at the same age.

Instead of the requested comparison versus historical values, the MAH stated that patients with Class I to III CF mutations, including gating mutations, who were <2 years of age had a median weight percentile of 44.3, a median length percentile of 29.2, and a median weight-for-length percentile of 63.5 based on the 2016 Cystic Fibrosis Foundation (CFF) Patient Registry Annual Data Report. At study 124 baseline, children enrolled in Cohort 5, part B had a mean weight-for-age percentile of 60.3, a mean length-for-age percentile of 39.8, and a mean weight-for-length percentile of 68.2. The mean (95% CI) change from baseline at week 24 in the above measures was 4.5 (-2.4, 11.4), 11.1 (2.1, 20.0), and 1.5 (-7.3, 10.3) respectively for the overall population of Cohort 5.

Of the 6 subjects who had weight z-scores less than 0 at baseline, 3 (50%) had a z-score ≥0 after 24 weeks of treatment with IVA (1 of 3 males and 2 of 3 females). Overall, 14 of 19 (73.7%) subjects had a z-score ≥0 after 24 weeks of treatment with IVA. The mean (SD) change in weight-for-age Z-score from baseline to week 24 restricted to children with a weight-for-age Z-score below 0 at baseline was 0.12 (0.18) for boys and 0.51 (0.55) for girls.

When the results by sex are compared to those of the overall population it would appear that the change in weight-for-age z-score is driven by that observed in girls (0.22 vs. 0.10) while in the case of length-for-age z-score, boys experienced a change of 0.38 vs. 0.17 in girls. Regarding weight-for-length z-score, the change experienced by boys was -0.06 vs. 0.21 in girls. The MAH is of the opinion that there is no clinical rationale for the discrepancy in growth parameters by sex and the results observed are an artefact of the small sample size and high variability in ages within the cohort. This could lead to false assumptions and the potential for different treatment decisions between sexes, thus proposed to retain only the 'all patient' data in the label. This was agreed by CHMP and the results quoted in section 5.1 of Kalydeco granules are therefore those of the overall population for whom data were available at both baseline and week 24.

Faecal elastase-1 is a marker for pancreatic sufficiency/insufficiency. Values below 200 µg /g indicate pancreatic insufficiency. Out of the 19 subjects in part B, cohort 5, 11 were considered to be pancreatic insufficient. Mean (SD) FE-1 values at baseline were 13.4 (12.3) µg/g for pancreatic insufficient subjects and 414.4 (120.9) µg/g for pancreatic sufficient subjects. Nine subjects with pancreatic insufficiency had values of FE-1 at both baseline and week 24. The mean (SD) change from baseline was 248.1 (132.9) µg/g. These are the results quoted in section 5.1 of the SmPC. Six of these 9 subjects were pancreatic insufficient at baseline (FE-1 <200 µg/g) and had FE-1 >200 µg/g at Week 24, indicative of pancreatic sufficiency. No subject who was pancreatic sufficient at baseline became pancreatic insufficient after 24 weeks of treatment. Although these results are indicative of the potential for IVA treatment to improve and recover exocrine pancreatic function and protect against progressive exocrine pancreatic dysfunction in subjects 12 to <24 months old, data beyond 24 weeks are needed to conclude whether this effect is kept in the long term.

Immunoreactive trypsinogen (IRT) can be considered a marker for pancreatic duct obstruction. Consistently with study 108 data (Changes from baseline in IRT at Week 24 the mean (SD) absolute change from baseline in IRT was -20.70 ng/mL (23.991)), a rapid decrease in mean IRT from baseline by Week 2 that was sustained through Week 24, suggest an improvement of pancreatic status. The mean (SD) change from baseline at week 24 in IRT limited to subjects with pancreatic insufficiency (based on FE-1 values of less than 200 µg/g) who had values at both points in time was −533.1 (394.5) ng/ ml (n=10). While improvements in IRT are not numerically comparable to results from prior studies due to the change of the assay used (which was discontinued by the manufacturer), the MAH states that the rapid and large improvement from baseline are clear and directionally consistent across IVA studies. However, data on IRT are difficult to interpret in the absence of a control group. As

for FE-1, data beyond of 24 weeks are also needed. No statements or recommendations can be included in the SmPC for the prescribing physicians.

Enzyme values such as amylase and lipase showed substantial decrease by week 2 and was maintained through week 24, suggesting functional/structural improvement.

The lung clearance index (LCI) is a lung function parameter derived from the multiple-breath washout (MBW) test. LCI is sensitive to early CF lung disease in patients of all ages from infancy to adulthood. A workshop in January 2014 by the North American Cystic Fibrosis Foundation concluded that the MBW text is a valuable potential outcome measure for CF clinical trials in preschool-aged patients and in older patients with FEV1 in the normal range in multicenter clinical trials as well as clinical care (Subbarao, Ann Am Thorac Soc. 2015 Jun;12(6):932-9.). MBW test was performed in a single patient in Study 124 and the change from baseline to week 24 was -0.41 indicating improved ventilation.

At baseline, neither patients had positive culture with species of particular concern (P. aeruginosa, Burkholderia ssp, MRSA) at any time point, however, even at this low age group of children 8/18 had positive sputum microbiology (H. influenza) and2/18 subjects had methicillin-sensitive S. aureus) and 1/18 subject had both (H. influenza and methicillin-sensitive S (aureus), this is the usual pattern of lung colonisation at this age. From the results, no conclusion can be drawn regarding effect on pulmonary exacerbation or microbiology.

100% of the subjects fully consumed the dose. The majority of subjects (17 [89.5%]) liked the study drug very much or liked it a little as detected by study personnel/caregiver.

Regarding study 123, only 14 subjects were enrolled and therefore no efficacy conclusions can be made from this study. Efficacy data were available for these 14 subjects, but for some subjects there were incomplete efficacy measures. Changes from baseline in $LCI_{2.5}$ suggested a trend towards greater improvement in lung function with ivacaftor than with placebo. There were trends towards improvement with ivacaftor treatment in the secondary endpoints IRT, FE-1, BMI-for-age z-score, and weight-for-age z-score. Notably, efficacy and safety this population has been studied in study 108 already, although it was an open-label study, results could justify an extension of indication for children older than 2 years and who had gating mutation.

## 2.4.4. Conclusions on the clinical efficacy

Overall, the lack of appropriate efficacy endpoints in young children who are minimally symptomatic hampers a robust demonstration of efficacy. The potential benefit of initiating treatment with ivacaftor at an early age is thought to be related to halt disease progression and/or prevent organ damage. To that end long-term data are needed that are unlikely to be generated pre-authorisation due to the life-threatening nature of the disease. Given that there is an ongoing post-authorisation efficacy study starting ivacaftor at the age of 2 years, children from 12 to less than 24 months are strongly encouraged to be included too. The data provided in the ongoing study 124 support the notion that ivacaftor in the short-term is associated with an overall improvement of the disease in these young children. The CHMP considers therefore that the efficacy of ivacaftor in the extension to use for children aged 12 to less than 24 months has been demonstrated taking into account the similar decrease in sweat chloride that has been observed in these children, the data provided on growth parameters and faecal elastase-1 and the results obtained in older children and adult subjects.

## 2.5. Clinical safety

### Introduction

Ivacaftor is generally well tolerated; the majority of adverse events associated with ivacaftor are mild to moderate in severity. The number of subjects in some important subgroups of the target population (e.g. population from 2 to 11 years-old) is rather limited. The most common adverse events in the ivacaftor group were cough, CF lung (pulmonary exacerbation), headache, dizziness, URTI, nasal congestion, oropharyngeal pain, nausea, and rash. More patients in ivacaftor reported bacteria isolated in sputum. The mechanism of nervous system disorders is not known. Ear and labyrinths disorder and breast disorders have been observed with ivacaftor. The adverse events that are believed to have at least plausible causal relationship with the use of ivacaftor (adverse reactions) have been reflected in the SmPC. The most common adverse reactions are nasopharyngitis, upper respiratory tract infection, headache, nasal congestion, oropharyngeal pain, abdominal pain, diarrhoea and rash.

This extension is mainly based on an interim analysis of Study 124, reporting data from subjects 12 to <24 months of age who completed Part A/Cohort 1 and/or Part B/Cohort 5 (through 24 weeks of IVA treatment). Study 124 is an ongoing, Phase 3, 2-part, open-label study in subjects <24 months of age who have 1 of the following mutations on at least 1 CFTR allele: G551D, G178R, S549N, S549R, G551S, G1244E, S1251N, S1255P, or G1349D. Subjects with an R117H-CFTR mutation on at least 1 allele are eligible to enrol in regions where IVA is approved for use in patients 2 through 5 years of age with an R117H mutation. Safety data from study 123 were also analysed.

### Patient exposure

Subjects 12 to <24 months of age were enrolled in Cohort 1 of Part A (4 days of IVA treatment), with a goal to select a dose for Cohort 5 of Part B (24 weeks of IVA treatment). Safety is a primary objective in Parts A and B. IVA granules were administered orally every 12 hours (q12h) at the following doses, after mixing with 5 mL of age appropriate soft food or liquid:

- 50 mg for subjects weighing 7 to <14 kg
- 75 mg for subjects weighing 14 to <25 kg

At each study visit in Part B, the dose for each subject was adjusted based on body weight, if necessary.

Part A/Cohort 1: Seven subjects were enrolled and included in the Safety Set. One subject continued into Part B/Cohort 5; the remaining 6 subjects all aged out of the eligible age range for Part B/Cohort 5.

Part B/Cohort 5: Subject disposition data for Part B are presented in Table 17 below. Nineteen subjects were enrolled and included in the safety set. The mean treatment duration (SD) was 22.9 (5.06) weeks (range: 2 to 25 weeks). Eighteen subjects received >18 weeks of treatment.

**Table 17**

**Table 1 Subject Disposition, All Subjects Set, Study 124 Part B/Cohort 5**

| Disposition Category | IVA 50 mg n (%) |
|---|---|
| Safety Set | 19 (100) |
| Never dosed | 0 |
| Study ongoing* | 1 (5.3) |
| Completed study drug treatment | 18 (94.7) |
| Failed to complete treatment period | 1 (5.3) |
| Reason for discontinuation of study drug treatment/discontinuation from study | |
| Physician decision/withdrawal of consent (not due to AE) | 1 (5.3) |

Source: Study 124 IAR/Table 14.1.1.1.b5
AE: adverse event; IVA: ivacaftor; n: size of subsample; OE: ophthalmologic examination
Notes: Percentages were calculated relative to the number of subjects in the Full Analysis Set. Safety Set was defined as all subjects who received at least 1 dose of study drug. Full Analysis Set was defined as all subjects who were eligible for study enrollment and received at least 1 dose of study drug.
* At the time of the data-cut, this subject had completed dosing but had not yet had a follow-up OE.

## *Adverse events*

### Study 124

Eighteen (94.7%) of the 19 subjects had a total of 133 AEs, see Table 18 below.

**Table 18**

**Table 8 Study 124 Part B/Cohort 5: Overview of Adverse Events, Safety Set**

| Category | IVA 50 mg (N = 19) |
|---|---|
| Subjects with any AEs, n (%) | 18 (94.7) |
| Subjects with related AEs, n (%) | 7 (36.8) |
| Subjects with AEs leading to treatment discontinuation, n (%) | 0 |
| Subjects with AEs leading to treatment interruption, n (%) | 2 (10.5) |
| Subjects with SAEs, n (%) | 2 (10.5) |
| Subjects with AEs leading to death, n (%) | 0 |

Source: Study 124 IAR/Table 12-5
AE: adverse event; IVA: ivacaftor; n: size of subsample; N: total sample size; SAE: serious adverse event
Notes: When summarizing number and % of subjects, a subject with multiple events within a category was counted only once in that category. Related AEs included related, possibly related, and missing categories.

The most common AEs (>20% incidence) included cough, alanine transaminase (ALT) or aspartate transaminase (AST) elevations, pyrexia, rhinorrhea, otitis media, and upper respiratory tract infection (Table 19 below). The majority of subjects had AEs that were mild or moderate in severity and were considered unlikely to be related or not related to study drug.

**Table 19**

**Table 9 Study 124 Part B/Cohort 5: Adverse Events Occurring in At Least 2 Subjects by System Organ Class and Preferred Term, Safety Set**

| System Organ Class[a]<br>Preferred Term | IVA 50 mg<br>(N = 19)<br>n (%) |
|---|---|
| **Subjects with any AEs** | 18 (94.7) |
| **Respiratory, thoracic and mediastinal disorders** | **16 ( 84.2)** |
| Cough | 14 ( 73.7) |
| Rhinorrhoea | 6 ( 31.6) |
| **Infections and infestations** | **10 ( 52.6)** |
| Otitis media | 4 ( 21.1) |
| Upper respiratory tract infection | 4 ( 21.1) |
| Conjunctivitis | 2 ( 10.5) |
| Rhinitis | 2 ( 10.5) |
| **Investigations** | **10 ( 52.6)** |
| Aspartate aminotransferase increased | 7 ( 36.8) |
| Alanine aminotransferase increased | 6 ( 31.6) |
| Blood pressure increased | 3 ( 15.8) |
| Gamma-glutamyl transferase increased | 3 ( 15.8) |
| Pseudomonas test positive | 3 ( 15.8) |
| Blood lactate dehydrogenase increased | 2 ( 10.5) |
| **General disorders and administration site conditions** | **7 ( 36.8)** |
| Pyrexia | 7 ( 36.8) |
| **Gastrointestinal disorders** | **6 ( 31.6)** |
| Constipation | 3 ( 15.8) |
| Vomiting | 3 ( 15.8) |
| **Metabolism and nutrition disorders** | **2 ( 10.5)** |
| Dehydration | 2 ( 10.5) |

Source: Study 124 IAR/Table 12-6

AE: adverse event; IVA: ivacaftor; n: size of subsample; N: total sample size; PT: Preferred Term; SOC: System Organ Class

[a] A subject with multiple events within a category (Any, SOC, or PT) was counted only once in that category. Table is sorted in descending order of Total column by SOC, and by PT within each SOC.

Two subjects had a total of 4 SAEs. All but one (constipation) were considered unlikely or unrelated to study drug.

Five subjects had transaminase elevations (ALT or AST) >3 × upper limit of normal (ULN). Three subjects had transaminase elevations (ALT) >3 to ≤5 × ULN and remained on study drug continuously. Two subjects had transaminase elevations (ALT) >8 × ULN, both had alternative etiologies (concurrent infections) and resumed treatment following a short period of study drug interruption with no further elevations. No subjects had total bilirubin levels above the normal range. No treatment-emergent cataracts (lens opacities) were observed. There were no notable safety trends in other clinical laboratory, vital sign, or ECG parameters.

The majority of subjects had AEs that were mild to moderate in severity. There were no AEs that were considered to be life-threatening in severity. Two subjects had AEs that were considered severe.

One subject had 3 severe AEs of eczema herpeticum, distal intestinal obstruction syndrome (DIOS), and constipation. The AE of eczema herpeticum resolved after treatment and was considered unlikely related to study drug. The AE of DIOS was considered unlikely related to study drug, and the AE of constipation was considered possibly related to study drug; both AEs resolved. All 3 severe AEs were considered serious.

Another subject had 3 severe AEs that occurred at the same time of ALT increased (>3 × ULN), AST increased (>2 × ULN), and gamma-glutamyltransferase (GGT) increased (>2 × ULN). The AEs of AST

increased and GGT increased were considered unlikely related to study drug. The AE of ALT increased was considered possibly related to study drug. All 3 AEs resolved without treatment.

ALT and AST increased were the only AEs considered related or possibly related to study drug by the investigator to occur in ≥5 subjects.

**Study 123**

Treatment with IVA for 8 weeks in Part 1 and up to approximately 31 weeks in Part 2 in Study 123 was well tolerated in this population of 3- through 5-year-old subjects with CFTR gating mutations. The most common AEs among the 14 subjects were cough, infective pulmonary exacerbation of CF, and vomiting.

All AEs were assessed as mild or moderate in severity and not related or unlikely related to study drug. There were no deaths and no treatment-emergent SAEs. No AEs led to discontinuation or interruption of study drug. No subject had an ALT level above 3 × ULN, an alkaline phosphatase level above 1.5 × ULN, or an AST, gamma-glutamyl transferase, or total bilirubin level above the ULN. Liver function test levels above the ULN did not occur more commonly during the IVA treatment periods than during the placebo treatment period. There were no notable safety trends in other clinical laboratory or vital sign parameters. No treatment-emergent cataracts (lens opacities) were observed during the study.

No new adverse drug reactions (ADRs) were identified in Study 124 Part A/Cohort 1, Part B/Cohort 5, or Study 123.

## *Serious adverse event / deaths / other significant events*

There were no deaths, serious adverse events (SAEs), treatment interruptions or discontinuations.

## *Laboratory findings*

There were no notable findings from clinical laboratory, vital sign, and ECG parameters. For liver function test results, please see Table 20 below.

**Table 20**

**Table 12-11 Liver Function Test Parameters: Changes From Baseline to Week 24, Safety Set, Part B/Cohort 5**

| | IVA 50 mg N = 19 | | | |
|---|---|---|---|---|
| Parameter | n* | Mean (SD) Change | Median Change | Min, Max |
| Alanine transaminase (U/L) | 18 | -1.8 (15.4) | -5.0 | -16, 42 |
| Alkaline phosphatase (U/L) | 18 | -17.9 (62.8) | -15.0 | -216, 54 |
| Aspartate transaminase (U/L) | 18 | 0.3 (11.2) | -2.5 | -16, 24 |
| Gamma-glutamyl transferase (U/L) | 18 | 2.6 (5.2) | 1.0 | -2, 16 |
| Total bilirubin (µmol/L) | 18 | 1.2 (1.7) | 1.0 | -0.8, 5.8 |

Source: Table 14.3.4.2.b5
IVA: ivacaftor; N: total sample size; n: size of subsample
Notes: Baseline was the most recent measurement before the first dose of study drug in Part B. Alanine transaminase = alanine aminotransferase; aspartate transaminase = aspartate aminotransferase.
* One subject who withdrew from the study, did not have any LFT assessments after taking the first dose of study drug.

The majority of subjects had maximum on-treatment ALT or AST ≤2 × ULN. Five subjects had transaminase elevations (ALT or AST) >3 x ULN. Three subjects had transaminase elevations (ALT) >3

to ≤5 × ULN and remained on study drug continuously. Two subjects had transaminase elevations (ALT) >8 × ULN, both had alternative etiologies (concurrent infections) and resumed treatment following a short period of study drug interruption with no further elevations. No subjects had AST and/or ALT elevations >5 to ≤8 x ULN. No subjects had total bilirubin levels above the ULN.

### *Safety related to drug-drug interactions and other interactions*

Assessment of drug-drug and other interactions was conducted and there were no unique findings due to age to suggest a safety concern. There were no AEs identified caused by DDI in Study 124. The DDI profile in children 12 to <24 months of age is expected to be the same as that in older subjects based on the following:

- CYP3A maturation has reached full adult activity by 12 months of age.
- Population PK analyses support that changes in IVA disposition can be accounted for by changes in body weight and that the impact of CYP maturation on IVA disposition in this age group are minimal.
- IVA exposures were comparable to adults in this age group.

The current SmPC adequately reflects necessary information for this age group.

### *Discontinuation due to adverse event*

No such events were reported.

### *Post marketing experience*

The ADRs identified from previously completed studies include nasopharyngitis, upper respiratory tract infection, headache, nasal congestion, oropharyngeal pain, rash, abdominal pain, and diarrhoea. Most of these ADRs are mild to moderate in severity and resolved with continued IVA treatment. Other potential risks include elevated transaminases, drug-drug interactions, and cataracts (lens opacities). These risks are adequately managed through product labelling, including recommendation of close monitoring of unexplained elevations in transaminase levels until resolution and proper dose adjustments when IVA is used concomitantly with moderate or strong CYP3A inhibitors.

Ophthalmologic examinations will be conducted as part of the safety study 126 included in the pharmacovigilance plan to further characterise the risk of chataract as in the postmarketing experience reports of lens abnormalities have been received.

## 2.5.1. Discussion on clinical safety

Ivacaftor was well tolerated during the 4 days, 24 days or 8 weeks of in study 124, part A, part B and study 123, respectively. Of note, study 124 was conducted in 1-2 years old children, while study 123 in 3-5 years olds. According to available data (interim analysis of two cohorts or incomplete study results) both studies, AEs were generally those that are typical for CF patients of this age group. The most common AEs were cough, ALT or AST elevations, pyrexia, rhinorrhea, otitis media, and upper respiratory tract infection (or vomiting in study 123). The majority of subjects had AEs mild or moderate in severity. There were no deaths or treatment discontinuations due to AEs. No treatment-emergent cataracts (lens opacities) were observed. There were no notable safety trends in other clinical laboratory, vital sign, or ECG parameters.In study 124, part B, Cohort 5, two subjects had a total of 4 SAEs. Seven subjects reported related AEs.

Five subjects had transaminase elevations (ALT) >3 × ULN. Three subjects had transaminase elevations (ALT) >3 to ⩽5 x ULN and remained on study drug continuously. Two subjects had transaminase elevations (ALT) >8 x ULN, both had alternative etiologies (concurrent infections) and resumed treatment following a short period of study drug interruption with no further elevations. No subjects had total bilirubin levels above the normal range. The hypothesis that elevated LTFs could rather be attributed to amoxicillin is not agreed for the first case, as ivacaftor treatment, interruption and resolution of laboratory parameters are paralleled. However, CF itself can cause liver injury and this is also a well-identified risk with ivacaftor treatment. This case was fully managed with treatment interruption and further LFTs were not detected. No further action was required. The risk of hepatotoxicity will be further characterised in a safety study in the post-marketing setting (i.e. study 126). This study will also allow for the characterisation of use in children aged 12 months to 11 years due to the limited number of patients evaluated in study 124.

No new adverse drug reactions (ADRs) were identified in Study 124 Part A/Cohort 1, Part B/Cohort 5, or Study 123.

### 2.5.2. Conclusions on clinical safety

Acknowledging the shortcomings of the trial design, such as the lack of control, relative short duration of study 124 (interim analysis of completed cohorts) and small sample size due to the rarity of the disease, a full safety evaluation of ivacaftor in 1-2 years old children with CF carrying gating mutations is limited. However, all available data suggest similar safety profile in the new target population compared to the already approved one. This is considered reassuring. In addition, further data will be generated in the ongoing studies with ivacaftor.

Overall, no new adverse event or adverse drug reaction were identified. The adverse events, incidence and relatedness are comparable to that in previous Phase 3 studies conducted for the already approved indications.

### 2.5.3. PSUR cycle

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

## *2.6. Risk management plan*

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

The PRAC considered that the risk management plan version 8.1 is acceptable. The PRAC endorsed PRAC Rapporteur assessment report is attached.

The MAH is reminded that, within 30 calendar days of the receipt of the Opinion, an updated version of Annex I of the RMP template, reflecting the final RMP agreed at the time of the Opinion should be submitted to h-eurmp-evinterface@emea.europa.eu.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 8.1 with the following content:

## *Safety concerns*

| | |
|---|---|
| **Important identified risks** | None |
| **Important potential risks** | • Hepatotoxicity<br>• Cataract<br>• Concomitant use of IVA with strong CYP3A inhibitors or inducers<br>• Cardiac arrhythmias |
| **Missing information** | • Use in pregnant and lactating women<br>• Use in children aged 12 months to 11 years<br>• Safety in patients with cardiac diseases<br>• Patients with moderate or severe hepatic impairment |

CYP: cytochrome P450

The summary of safety concerns has been updated to rename the missing information of "Use in children aged 2 years to 11 years" as "Use in children aged 12 months to 11 years" given the limited study size (26 subjects total) supporting the expanded indication. No new adverse event or adverse drug reaction were identified.

## *Pharmacovigilance plan*

| Study / Status | Summary of Objectives | Safety Concerns Addressed | Milestones | Due Dates |
|---|---|---|---|---|
| **Category 1 – Imposed mandatory additional PV activities which are Conditions of the MA (key to benefit risk)** | | | | |
| None | | | | |
| **Category 2 – Imposed mandatory additional PV activities which are Specific Obligations in the context of a conditional MA under exceptional circumstances (key to benefit risk)** | | | | |
| None | | | | |
| **Category 3 – Required additional PV activities (by the competent authority)** | | | | |
| Study 126<br><br>Ongoing | <u>IVA Arm</u><br>In subjects with CF who are <24 months of age at treatment initiation and have an approved IVA-responsive mutation:<br>• To evaluate the safety of long-term IVA treatment<br>• To evaluate the PD of long-term IVA treatment<br>• To evaluate the efficacy of long-term IVA treatment<br><u>Observational Arm</u> | • Hepatotoxicity<br>• Cataract<br>• Use in children aged 12 to <24 months old at initiation | Final Report | March 2022 |

| Study / Status | Summary of Objectives | Safety Concerns Addressed | Milestones | Due Dates |
|---|---|---|---|---|
| | To evaluate long-term safety after discontinuation of IVA treatment in subjects with CF who were <24 months of age at treatment initiation and have an approved IVA-responsive mutation | | | |

CF: cystic fibrosis; IVA: ivacaftor; PD: pharmacodynamics
Note: Study 126 addresses a subpopulation of the Missing Information of "Use in children aged 12 months to 11 years.

Study 126 has been included in the Pharmacovigilance plan to address the safety concerns of hepatotoxicity, cataracts and use in children aged 12 to less than 24 months old at initiation.

Study 126 is a Phase 3, 2-arm, multicenter study with an open-label IVA arm and an observational arm.

-The IVA ARM comprises subjects who completed IVA treatment in Study 124 Part B and subjects who are <24 months of age at Day 1 of Study 126. The 96-week IVA Treatment Period includes safety evaluations of adverse events, clinical laboratory assessments (serum chemistry and hematology), electrocardiographs, vital signs, physical examinations, and ophthalmological examinations.

-The non-treatment Observational Arm comprises subjects who completed IVA treatment in Study 124 Part B and elected not to enroll in the IVA Arm of Study 126 and subjects who received at least 1 dose of IVA and prematurely discontinued IVA treatment in Study 124 Part B. The 96-week study period include an ophthalmological examination and telephone contacts.

### *Risk minimisation measures*

| Safety Concern | Risk Minimisation Measures | Pharmacovigilance Activities |
|---|---|---|
| **Hepatotoxicity** | **Routine risk minimisation measure:**<br>SmPC Section 4.4 where advice is given on monitoring LFTs.<br>SmPC Section 4.8<br>PL Section 4<br><br>**Additional risk minimisation measures:**<br>None | **Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection**<br>Prescription only<br><br>**Additional PV activities:**<br>Study 126 |
| **Cataract** | **Routine risk minimisation measure:**<br>SmPC Section 4.4 where advice is given on recommended ophthalmological examinations<br>SmPC Section 5.3<br>PL Section 2<br><br>**Additional risk minimisation measures:**<br>None | **Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection**<br>Prescription only<br><br>**Additional PV activities:**<br>Study 126 |

| Safety Concern | Risk Minimisation Measures | Pharmacovigilance Activities |
|---|---|---|
| **Concomitant use of IVA with strong CYP3A inhibitors or inducers** | **Routine risk minimisation measure:**<br>SmPC Section 4.2 where dose reductions are recommended when co-administered with a strong inhibitor of CYP3A.<br>SmPC Section 4.4<br>PL Section 2<br><br>**Additional risk minimisation measures:**<br>None | **Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection**<br>Prescription only<br><br>**Additional PV activities:**<br>None |
| **Cardiac arrhythmias** | **Routine risk minimisation measure:**<br>SmPC Section 5.3<br><br>**Additional risk minimisation measures:**<br>None | **Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection**<br>Prescription only<br><br>**Additional PV activities:**<br>None |
| **Use in pregnant and lactating women** | **Routine risk minimisation measure:**<br>SmPC Section 4.6 where advice is given on to use Kalydeco during pregnancy only if clearly needed and during breastfeeding if the potential benefit outweighs the potential risks.<br>PL Section 2<br><br>**Additional risk minimisation measures:**<br>None | **Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection**<br>Prescription only<br>Pregnancy follow-up form<br><br>**Additional PV activities:**<br>None |
| **Use in children aged 12 months to 11 years** | **Routine risk minimisation measure:**<br>SmPC Section 4.2 where the posology is described<br>SmPC Sections 4.8 and 5.2<br>PL Section 2<br><br>**Additional risk minimisation measures:**<br>No risk minimisation measures | **Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection**<br>Prescription only<br><br>**Additional PV activities:**<br>Study 126 |
| **Safety in patients with cardiac disease** | **Routine risk minimisation measure:**<br>SmPC Section 5.3<br><br>**Additional risk minimisation measures:**<br>None | **Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection**<br>Prescription only<br><br>**Additional PV activities:**<br>None |
| **Patients with moderate or severe hepatic impairment** | **Routine risk minimisation measure:**<br>SmPC Section 4.2 where advice is given on dose adjustment based on severity of hepatic impairment<br>SmPC Section 5.2<br>PL Section 3<br><br>**Additional risk minimisation measures:**<br>None | **Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection**<br>Prescription only<br><br>**Additional PV activities:**<br>None |

| Safety Concern | Risk Minimisation Measures | Pharmacovigilance Activities |
|---|---|---|

CYP: cytochrome P450, PL: Patient Leaflet; SmPC: Summary of Product Characteristics

### *2.7. Update of the Product information*

As a consequence of this new indication, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

#### 2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons: updates made to the package leaflets are minimal, and the structure and guidance for caregivers remains aligned to the principles agreed on in procedure EMEA/H/C/002494/X/0034/G

#### 2.7.2. Additional monitoring

Pursuant to Article 23(3) of Regulation No (EU) 726/2004, Kalydeco (ivacaftor) is removed from the additional monitoring list as the imposed PASS (i.e. 5-year long term observational study) which is a condition to the marketing authorisation has been fulfilled.

Therefore the statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information, preceded by an inverted equilateral black triangle, is removed from the summary of product characteristics and the package leaflet.

## 3. Benefit-Risk Balance

### *3.1. Therapeutic Context*

#### 3.1.1. Disease or condition

CF is an autosomal recessive disease with serious, chronically debilitating morbidities and high premature mortality and, at present, has no cure. CF affects approximately 78,000 individuals worldwide, with approximately 29,000 individuals in the US; 42,000 individuals in the EU; 4,200 individuals in Canada; and 3,200 individuals in Australia. CF greatly affects the paediatric population, as approximately half of the total population with CF is <18 years of age. Pancreatic destruction leading to pancreatic exocrine insufficiency begins in utero, and lung involvement is manifested by pulmonary inflammation and infection that begins shortly after birth. Despite progress in the treatment of CF with antibiotics and mucolytics, the predicted median age of survival for a person with CF is 41.6 years. Although the disease affects multiple organs, progressive loss of lung function is the leading cause of mortality.

#### 3.1.2. Available therapies and unmet medical need

There is currently no fully effective cure for CF. Hence, the goals of current CF therapies are to slow or reverse disease progression, manage symptoms and complications such as pancreatic insufficiency and respiratory infections, and improve quality of life. The majority of CF therapies currently available, including nutritional supplements, antibiotics, and mucolytics, target the downstream consequences

and symptoms of the disease. The CFTR modulators (i.e., correctors and potentiators) target the underlying cause of CF with the potential to alter the course of the disease. These CFTR modulators are not a cure for CF and must be taken chronically for the patient to maintain treatment benefits.

Kalydeco (IVA), Orkambi (lumacaftor/IVA), and Symdeko (tezacaftor [TEZ]/IVA + IVA) are the CFTR modulators currently approved for CF patients. Kalydeco is approved in the US, Canada, EU, and other regions for treatment in patients ≥2 years of age with certain IVA-responsive mutations. Orkambi is approved in the US, Canada, and EU for treatment in patients ≥6 years of age, homozygous for F508del, and is approved in other regions for treatment in older populations. Symdeko is approved in the US for treatment in patients ≥12 years of age, homozygous for F508del or with a TEZ/IVA-responsive mutation.

At this time, there is no approved CFTR modulator therapy available for CF patients <2 years of age.

### 3.1.3. Main clinical studies

Previously evaluated studies:

Studies 102, 103, 110 and 111 were performed in subjects with gating or R117H mutation in at least one allele of CFTR gene (≥6 years of age).

Study 108 was an uncontrolled OL study in subjects 2 through 5 years of age

Studies 105, 112 and 109 were OL-long term studies in subjects ≥6 years of age and in subjects 2 through 5 years of age, respectively (Study 109)

Registry studies: Long-term Safety Study (all patients with a record of Kalydeco use in the US and UK CF registries).

Recently submitted study:

Study 124 is an OL, ongoing study in patients aged <24 months, interim (week 24) analysis was submitted in two cohorts of this study.

## *3.2. Favourable effects*

Treatment with ivacaftor targets the functional defect of the mutated CFTR protein and improves CFTR function, resulting in clinically relevant and statistically significant improvements in PPFEV1, Cystic Fibrosis Questionnaire-Revised respiratory domain, weight/BMI, and commensurate changes in sweat chloride for subjects ≥6 years of age (Studies 102, 103, and 111).

Results from Study 108 demonstrated that ivacaftor improves CFTR function in subjects 2 through 5 years of age, resulting in positive effects on nutritional status and pancreatic function.

Sustained, long-term benefits of IVA treatment were demonstrated in clinical studies of ivacaftor in subjects ≥6 years of age (Studies 105 and 112) and in subjects 2 through 5 years of age (Study 109). Furthermore, up to 5 years of data in the Long-term Safety Study (all patients with a record of Kalydeco use in the US and UK CF registries) showed lower risks for death, organ transplantation, hospitalizations, PEx, and serious safety outcomes in IVA-treated patients relative to untreated comparators.

Interim analysis of Cohort A and B of Study 124 demonstrated the ability of ivacaftor to increase CFTR function in subjects 12 to <24 months, as evidenced by an absolute change from baseline in sweat chloride of -73.5(17.5) [mean (SD)], mmol/L. This provides additional support for extrapolation of

efficacy. For children with available data at both baseline and week 24, the mean (95% CI) change from baseline at week 24 in weight-, length-, and weight-for-length percentiles was 4.5 (-2.4, 11.4), 11.1 (2.1, 20.0), and 1.5 (-7.3, 10.3) respectively for the overall population of Cohort 5. In nine children who were pancreatic insufficient at baseline, the mean (SD) change at week 24 in faecal elastase-1 was 248.1 (132.9) µg/g. In six of them, the level at week 24 was above 200 µg/g.

Overall, the clinical benefits of ivacaftor treatment may be supported in children 12 to less than 24 months by numerically positive effects on markers of pancreatic function and pancreatic inflammation (by measuring IRT and FE-1 and IRT, serum lipase and serum amylase levels) as well as maintained generally good nutritional status, as measured by growth parameters, such as absolute change from baseline in weight-for-age Z-score (0.15 units) and absolute changes from baseline in length-for-age Z-score (0.28 units).

## *3.3. Uncertainties and limitations about favourable effects*

The level of evidence of an interim analysis in two cohorts of an open-label study is limited. However, it can be considered sufficient for support extrapolation efficacy and safety from already approved population to 1-2 years old children, based on previous experience. The duration of study is rather short and there is uncertainty whether the improvement is maintained.

Lung function correlates with mortality in CF patients. There are no firm data to support lung function improvement (as spirometry cannot be performed at this age and LCI could not be systematically measured in this study) or slower rate of decline of lung function when starting treatment as early as of 1 year. This can be, however, hypothesised based on already existing long-term data, but needs further confirmation. Long term data are needed to establish a beneficial effect of ivacaftor on lung function and microbiological endpoints and to confirm positive results on nutrition in this age group.

Graphical analysis revealed no relationship between ivacaftor exposure and sweat chloride response. Thus, the claimed efficacy claim is not directly supported by exposure-response (POP-PK/PD) analysis. Additionally, there appears to be a negative trend between age and clearance. The reason of age dependent clearance remained unclarified but currently not considered as a clinically significant problem.

Data at baseline and week 24 for some endpoints were not available for all children enrolled in Cohort 5, part B of study 124. Appropriate explanation has been given by the MAH (e.g., the volume of sweat collected at baseline was insufficient in 5 children to determine sweat chloride which is not uncommon in young children). The SmPC only quotes results for children with both values available.

The lack of a control group somehow hampers the appropriate interpretation of the efficacy data provided, but the consistency seen in all parameters measured is reassuring. Regarding faecal calprotectin levels, results may be indicative of reduction of inflammation, however, elevated faecal calprotectin naturally declines from birth to its nadir at 4 years and therefore the interpretation of the above results is confounded by this issue in the absence of a control group. The very similar consideration applies for IRT levels. Based on FE-1 levels (with a cut-off at 200 µg/g), the MAH states that 6 children became pancreatic sufficient. However, none of them apparently could stop pancreatic enzyme supplementation as this possibility was not pre-specified in the study protocol. Furthermore, data beyond 24 weeks of treatment are needed to confirm that the results in FE-1, IRT etc. are maintained.

The effect of discontinuing prescribed therapies for CF while remaining on ivacaftor treatment has not been evaluated. During Study 124, subjects continued on their prescribed CF therapies. Thus, as is the

case for patients ≥24 months of age, ivacaftor will be recommended for use in addition to other prescribed therapies for CF.

## 3.4. Unfavourable effects

The safety profile of ivacaftor has been well characterised. Adverse drug reactions identified from previously completed studies include nasopharyngitis, upper respiratory tract infection, headache, nasal congestion, oropharyngeal pain, rash, abdominal pain, and diarrhoea. Most of these ADRs are mild to moderate in severity and resolved with continued ivacaftor treatment. Other potential risks include elevated transaminases, drug-drug interactions, and cataracts (lens opacities). These risks are properly managed through product labeling, including recommendation of close monitoring of unexplained elevations in transaminase levels until resolution and proper dose adjustments when IVA is used concomitantly with moderate or strong CYP3A inhibitors. In addition, baseline and follow-up ophthalmological examinations are recommended in paediatric patients treated with IVA. Safety results in subjects 12 to <24 months in Study 124 were generally consistent with those in subjects ≥2 years of age, with no new safety concerns identified. Transaminase elevations were observed; however, all subjects were able to either maintain or successfully resume ivacaftor treatment following interruption.

## 3.5. Uncertainties and limitations about unfavourable effects

The safety of long-term ivacaftor treatment in subjects 12 to <24 months is being evaluated in the 96-week open-label extension Study 126, final results of which are due in March 2022 as stated in the RMP .

## 3.6. Effects Table

| Effect | Short description | Unit | Treatment | Control | Uncertainties / Strength of evidence | References |
|---|---|---|---|---|---|---|
| **Favourable Effects** | | | | | | |
| sweat chloride | Absolute Change From Baseline at week 24 | (mmol/L), mean, SD | -73.5 (17.5) | none | robust and clinically relevant change, secondary endpoint, open-label, uncontrolled study, indirect comparison suggest consistency with previous results | Study 124, Cohort 5 |
| weight-for-age z-score | Absolute Change From Baseline in Weight-for-age Z-score at week 24 | unit mean, SD | 0.15 (0.42) | none | improvement, but tertiary endpoint, uncontrolled data | Study 124, Cohort 5 |
| Length-for-age Z-score | Absolute Change From Baseline in Length-for-age Z-score at week 24 | unit, mean, SD | 0.28 (0.60) | none | improvement, but tertiary endpoint, uncontrolled data | Study 124, Cohort 5 |
| Weight-for-length-for-age Z-score | Absolute Change From Baseline in Weight-for-length-for-age Z-score at week 24 | unit, mean, SD | 0.07 (0.65) | none | maintained, but tertiary endpoint, uncontrolled data, | Study 124, Cohort 5 |

| Effect | Short description | Unit | Treatment | Control | Uncertainties / Strength of evidence | References |
|---|---|---|---|---|---|---|
| FE-1 | Change From Baseline in Faecal Elastase-1 | (µg/g), mean, SD | 248.1 [132.9]) | none | increased levels in subjects with pancreatic insufficiency at baseline, but uncontrolled data. Evidence of maintenance of effect needed. | Study 124, Cohort 5 |
| IRT | Change From Baseline in IRT | (ng/mL), mean, SD | -533.1 (394.5) | none | Decreased levels in subjects with pancreatic insufficiency at baseline but uncontrolled data, particularly difficult to interpret in this situation as the levels are expected to decrease naturally. Evidence of maintenance of effect needed. | Study 124, Cohort 5 |
| **Unfavourable Effects** | | | | | | |
| AEs | | Subjects with any AEs, n (%) | 18 (94.7) | none | uncontrolled data, low sample size, indirect comparison to previous study results suggest comparable safety | Study 124, Cohort 5 |
| AEs | | total No. of AEs | 133 | none | uncontrolled data, low sample size, indirect comparison to previous study results suggest comparable safety | Study 124, Cohort 5 |
| Related AEs | | Subjects with related AEs, n (%) | 7 (36.8) | none | uncontrolled data, low sample size, indirect comparison to previous study results suggest comparable safety | Study 124, Cohort 5 |
| SAEs | | Subjects with SAEs, n (%) | 2 (10.5) | none | uncontrolled data, low sample size, indirect comparison to previous study results suggest comparable safety | Study 124, Cohort 5 |

## *3.7. Benefit-risk assessment and discussion*

### 3.7.1. Importance of favourable and unfavourable effects

Reduction in decline in FEV1 correlates with mortality in CF. In young children, however, spirometry cannot be performed, as they have generally well-preserved lung function at this age, in addition, small children cannot cooperate properly. In small children, nutritional status is more indicative about disease burden.

### 3.7.2. Balance of benefits and risks

Interim results from Study 124 demonstrated that ivacaftor improves CFTR function in subjects 1 through 2 years of age who have a mutation that causes CFTR gating defects, with positive effects on

sweat chloride, nutritional status and pancreatic function. According to ICH E11 (Clinical Investigation of Medicinal Products in the Paediatric Population) “when a medicinal product is to be used in younger paediatric patients for the same indication(s) as those 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.” Although the underlying defect in cystic fibrosis is the same across all ages, the heterogeneity of disease effects in target organs and the progression of the disease over time lead to clinical manifestations that vary according to age. The implementation of newborn screening programmes has shown that early interventions such as nutritional support, eradication of early lung colonisation/infection etc. are associated to improved health outcomes and quality of life. It can be assumed that drugs targeting the basic defect of the mutant CFTR protein such as CFTR modulators may have the potential to slow disease progression and earlier treatment would result in better outcomes. Some uncertainties regarding PK were identified that do not preclude the use of ivacaftor for these young children.

Based on the principles of paediatric extrapolation, the benefits of ivacaftor treatment could be extended to patients with all approved gating CFTR mutations as some “other concerns” raised during evaluation have been resolved.

### *3.8. Conclusions*

The overall B/R of Kalydeco is positive.

# 4. Recommendations

### *Outcome*

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

| **Variation accepted** | | **Type** | **Annexes affected** |
|---|---|---|---|
| C.I.6.a | C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one | Type II | I, IIIA and IIIB |

Extension of Indication to include treatment of cystic fibrosis in children age 12 to less than 24 months who have one of the currently approved gating mutations in the CFTR gene for Kalydeco 50 mg & 75 mg Granules; as a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. Relevant consequential changes are made to the Kalydeco 150 mg film-coated tablet Product Information. The Package Leaflet is updated in accordance.
The RMP version 8.1 has also been submitted.

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

### *Conditions and requirements of the marketing authorisation*

### Periodic Safety Update Reports

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) ) provided for under Article 107c(7) of Directive 2001/83/EC and 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.

In addition, 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.

### *Paediatric data*

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0045/2018 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

### *Similarity with authorised orphan medicinal products*

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

## 5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

### *Scope*

Extension of Indication to include treatment of cystic fibrosis in children age 12 to less than 24 months who have one of the currently approved gating mutations in the CFTR gene for Kalydeco 50 mg & 75 mg Granules; as a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. Relevant consequential changes are made to the Kalydeco 150 mg film-coated tablet Product Information. The Package Leaflet is updated in accordance.
The RMP version 8.1 has also been submitted.

### *Summary*

Please refer to Scientific Discussion ‘Kalydeco-H-C-2494-II-69’

## Attachments

1. SmPC, Labelling, Package Leaflet (changes highlighted) adopted by the CHMP on 20 September 2018.

## Appendix

1. CHMP AR on similarity dated 18 October 2018.