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*APPLICATION NUMBER:*

**207925Orig1s000**

**MEDICAL REVIEW(S)**

## CLINICAL REVIEW

Application Type	NDA
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Priority or Standard	Standard
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Division / Office	DPARP/ODE II
Reviewer Name(s)	Robert Lim
Review Completion Date	February 19, 2015
Established Name	Ivacaftor granules
(Proposed) Trade Name	Kalydeco granules
Therapeutic Class	CFTR Potentiator
Applicant	Vertex
Formulation(s)	50 and 75mg granules
Dosing Regimen	50mg for patients <14kg 75mg for patients ≥14kg
Indication(s)	Treatment of cystic fibrosis (CF) in patients 2 years and older who have one of the following mutations in the CFTR gene: <i>G551D</i> , <i>G1244E</i> , <i>G1349D</i> , <i>G178R</i> , <i>G551S</i> , <i>S1251N</i> , <i>S1255P</i> , <i>S549N</i> , <i>S549R</i> , and <i>R117H</i> .
Intended Population(s)	CF patients ≥2 years of age who have an approved mutation.

Template Version: [March 6, 2009](#)

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## **1 Recommendations/Risk Benefit Assessment**

### **1.1 Recommendation on Regulatory Action**

The recommended regulatory action from a clinical perspective is Approval of ivacaftor granules as an additional presentation of ivacaftor appropriate to use for the treatment of cystic fibrosis patients aged 2 to 5 years with *G551D*, *G1244E*, *G1349D*, *G178R*, *G551S*, *S1251N*, *S1255P*, *S549N*, *S549R*, or *R117H* mutation in the CFTR gene at a dose of 75mg q12 hours for patients  $\geq 14$ kg and 50mg q12 hours for patients  $< 14$ kg. This recommendation is based on the extrapolation of efficacy from existing data in older patient population using ivacaftor tablets (NDA 203,188) and review of safety data in the 2 to 5 year old population.

### **1.2 Risk Benefit Assessment**

Ivacaftor tablets (NDA 203,188) are approved for the treatment of CF patients aged 6 years and older with the *G551D*, *G1244E*, *G1349D*, *G178R*, *G551S*, *S1251N*, *S1255P*, *S549N*, *S549R*, or *R117H* mutation in the CFTR gene at a dose of 150mg once every 12 hours. In this NDA, Vertex has submitted data from a pharmacokinetic and safety study (study 108) to support the use of ivacaftor granules in patients 2 to 5 years in age. This formulation is more age appropriate than tablets, as the patients in this age group often cannot swallow tablets and this formulation can be administered mixed with food or liquid. Study 108 was an open-label, uncontrolled, two-part pharmacokinetic (PK, part A) and safety (part B) study in patients 2 to 5 years in age. In part A, results demonstrated that when ivacaftor was administered at 75mg for patients  $\geq 14$ kg and at 50mg for patients  $< 14$ kg every 12 hours for 4-days, systemic exposures matched that seen for ivacaftor tablets (150mg q12) in the adolescent/adult population. Because of the similar exposures and because the disease process in the older population is the same as that in the 2 to 5 year old population, efficacy in the proposed age group was extrapolated from the ivacaftor tablet development program. With regard to safety, based on analysis of deaths, SAEs, and AEs; no new safety signals were identified. With regard to lab evaluations, in the 2 to 5 year old population, transaminase elevations were observed more frequently in patients with baseline elevated transaminases.

### **1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies**

None beyond standard pharmacovigilance practices.

## 1.4 Recommendations for Postmarket Requirements and Commitments

None

## 2 Introduction and Regulatory Background

### 2.1 Product Information

The chemical name for ivacaftor is N-(2, 4-Di-tert-butyl-5-hydroxyphenyl)-1,4-dihydro-4-oxoquinoline-3-carboxamide. It is an orally-bioavailable small molecule that potentiates CFTR protein chloride transport in patients with cystic fibrosis (CF) with mutations in the *CFTR* gene responsive to CFTR chloride channel potentiation.. Ivacaftor tablets (NDA 203,188) was approved on January 31, 2012, for the treatment of CF in patients  $\geq 6$  years of age who have a *G551D* mutation in the *CFTR* gene at a dose of 150mg every 12 hours with a fat-containing food. On 2/21/14, the indication was expanded to include the following additional mutations: *G1244E*, *G1349D*, *G178R*, *G551S*, *S1251N*, *S1255P*, *S549N*, or *S549R*. On 12/30/15, the indication was again expanded to include patients with a *R117H* mutation. This NDA is for a new ivacaftor formulation (granules) and proposes to expand the indication to include the 2 to 5 year old age group at a dose of 75mg for patients  $\geq 14$ kg and 50mg for  $< 14$ kg. As this age group generally has difficulties swallowing tablets, the granule formulation is more pediatric friendly, as the granules may be mixed with soft food or liquid for administration.

### 2.2 Tables of Currently Available Treatments for Proposed Indications

Medications used to treat CF patients are summarized in Table 1. Note that not all are FDA approved for use in CF, and only ivacaftor treats the underlying cause of CF, whereas the others only treat symptoms of CF.

**Table 1. Treatments for CF**

Active Ingredient	Trade Name	FDA-approved for CF Indication?
<b>CFTR potentiator</b>		
Ivacaftor	Kalydeco	Yes; <i>G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R, and RT117H</i> mutations
<b>Inhaled Antibiotics for the Treatment of <i>Pseudomonas aeruginosa</i></b>		
Tobramycin (nebulized)	TOBI	Yes
Tobramycin (dry powder)	TIP	Yes
Aztreonam (nebulized)	Cayston	Yes
Polymyxin E (IV form given via nebulizer)	Colistin	No
<b>Inhaled Treatments used as Mucolytics</b>		
Dornase alpha (DNase)	Pulmozyme	Yes
Hypertonic Saline (7%)	----	No
<b>Oral Pancreatic Enzyme Supplementation</b>		
Pancrease, pancrelipase	Creon, Pancreaze, Zenpep, Pancrelipase™	Yes
<b>Inhaled Bronchodilators</b>		
Albuterol sulfate	Pro-Air, Ventolin, Proventil, Albuterol, etc.	Approved as bronchodilator
Levalbuterol hydrochloride	Xopenex	Approved as bronchodilator
<b>Anti-Inflammatory Agents</b>		
Oral azithromycin	Zithromax	No
Oral high-dose Ibuprofen	Motrin, Advil, etc.	No
[Source: Approved labeling data from Drugs@FDA, gov]		

### 2.3 Availability of Proposed Active Ingredient in the United States

The proposed granule formulation of ivacaftor is not approved anywhere in the world. However, ivacaftor tablets are currently approved for the treatment of CF patients aged 6 years and older with the *G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R, or R117H* mutation in the CFTR gene at a dose of 150mg once every 12 hours.

### 2.4 Important Safety Issues With Consideration to Related Drugs

There are no other approved drugs in this class. However, elevations in transaminases were noted in the *G551D CFTR* mutation development program for ivacaftor tablets (NDA 203188), and while they were observed in both placebo and active treatment

groups, there were more liver related SAEs in patients who received ivacaftor. Cataracts have also been observed in juvenile animal studies and in patients receiving ivacaftor.

## **2.5 Summary of Presubmission Regulatory Activity Related to Submission**

Ivacaftor was approved on 1/31/2012, for the treatment of CF in patients age 6 years and older who have a *G551D* mutation in the *CFTR* gene. On 2/21/14, the indication was expanded to include the following additional mutations: *G1244E*, *G1349D*, *G178R*, *G551S*, *S1251N*, *S1255P*, *S549N*, or *S549R*. On 12/30/14, the indication was expanded to include the *R117H* mutation. Prior to submission of this NDA, ivacaftor has been the subject of multiple regulatory proceedings. Interactions relevant to this sNDA are summarized below:

Communication dated March 1, 2012:

- Efficacy in the 2 to 5 year old population can be extrapolated from the older population
- To support safety in the proposed population, the Division encouraged Vertex to enroll at least 30 patients with at least 10 who were 2-3 years in age
- The Division also encouraged Vertex include non-*G551D* patients

## **2.6 Other Relevant Background Information**

None

## **3 Ethics and Good Clinical Practices**

### **3.1 Submission Quality and Integrity**

This NDA was submitted on 9/17/14. The submission was appropriately indexed and complete to allow for review. There were no issues with submission quality or data integrity.

### **3.2 Compliance with Good Clinical Practices**

A statement of compliance with Good Clinical Practices is located in the clinical study report, within the electronic submission.

### **3.3 Financial Disclosures**

See section 9      Appendices.

## 4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

### 4.1 Chemistry Manufacturing and Controls

The recommended regulatory action from the CMC review team is approval. See the review written by Dr. Edwin Jao for more details.

Ivacaftor is N-(2, 4-Di-tert-butyl-5-hydroxyphenyl)-1, 4-dihydro-4-oxoquinoline-3-carboxamide. The molecular formula of VX-770 is  $C_{24}H_{28}N_2O_3$  and its molecular weight is 392.49 grams per mole. The ivacaftor granules are white to off white in color with a <sup>(b) (4)</sup> weight of 6.87mg. Each granule contains <sup>(b) (4)</sup> of ivacaftor. The granules are packaged into a foil laminate packet with a dose of either 50mg or 75mg <sup>(b) (4)</sup>. The granules contain the following excipients: colloidal silicon dioxide, croscarmellose sodium, lactose monohydrate, mannitol, magnesium stearate, and sucralose. The ivacaftor drug substance used to produce the granules was previously described and reviewed under NDA 203188 for ivacaftor tablets (see Dr. Arthur Shaw's review).

### 4.2 Clinical Microbiology

Not applicable.

### 4.3 Preclinical Pharmacology/Toxicology

No new preclinical data was submitted with this NDA. For an in depth review of the preclinical pharmacology/toxicology data, see the review written by Dr. Marcie Wood for NDA 201,388.

### 4.4 Clinical Pharmacology

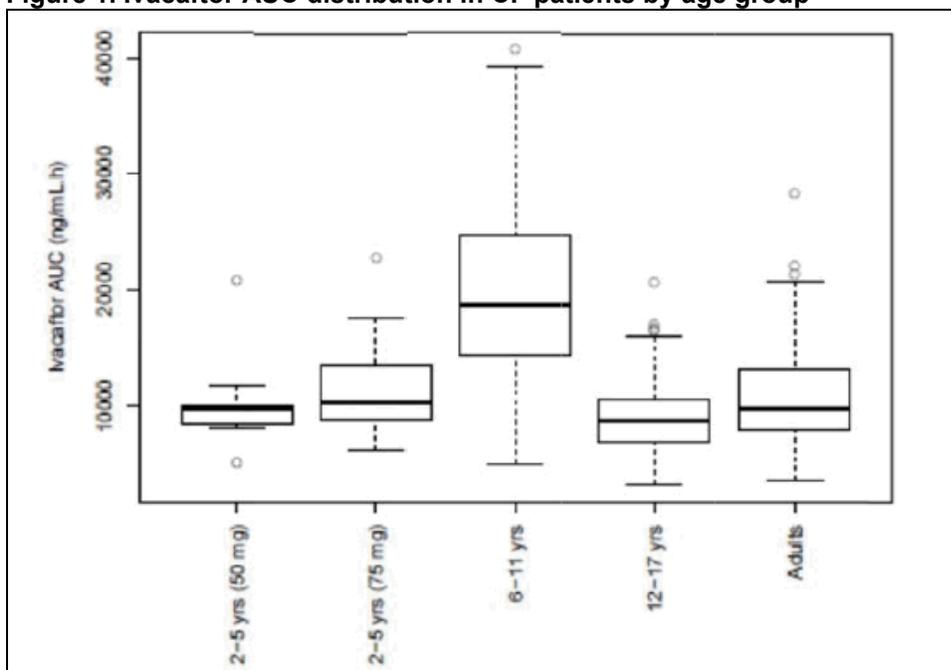
The recommended regulatory action from the Clinical Pharmacology review team is Approval. See the review written by Drs. Jianmeng Chen and Dinko Rebic for more details.

To support the proposed dosing in the 2 to 5 year old patient population, the Applicant submitted data from study 108. Study 108 was an open-label pharmacokinetic (PK) and safety study in patients 2 to 5 years of age where patients  $\geq 14$ kg received ivacaftor 75mg q12 and those  $< 14$ kg received 50mg q12. This study included two parts (A and B). Part A included a 4-day treatment period where the PK of ivacaftor granules was assessed and dosing confirmed based on exposure comparisons to the older population. Part B included an open-label 24-week treatment period where safety and PK parameters were assessed. Doses for this study were determined using a

population PK model generated from previously completed PK studies in the older population.

PK results from study 108 demonstrated that ivacaftor exposure was similar in the 2 to 5 year old age group (who received the appropriate weight-based ivacaftor 50 or 75 mg dose) compared to adolescents and adults ( $\geq 12$  years of age). These results are summarized in Figure 1. Note that the exposure in the 6-11 year old age group at the approved dose of 150mg q12 is higher than adults. However, this exposure was previously determined to be safe and efficacious in this age group (see NDA 203,188), although it is likely that exposure in the 6-11 year age group could have been lowered and efficacy retained.

**Figure 1. Ivacaftor AUC distribution in CF patients by age group**



Source: Summary of Clinical Pharmacology; figure 3-2; pg9.

Given the similarity in exposure between the 2 to 5 year old population and the adolescent/adult population and because the disease, CF, is the same, efficacy in the 2 to 5 year old population can be extrapolated from the older population.

## 5 Sources of Clinical Data

To support the proposed expansion of the indication to include the 2 to 5 year old population, the Applicant submitted clinical data from study 108.

## 5.1 Tables of Studies/Clinical Trials

Table 2. Summary of clinical studies included in this submission

Study Number	Study Type/Design	CF Mutation	Population	n	Treatment Arms	Countries
108	Open-label Safety and PK	"gating"	2 to 5 years	34	50mg BID (<14kg) 75mg BID (≥14kg)	N. America, United Kingdom

"gating"= G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R, or G970R

## 5.2 Review Strategy

The Applicant submitted clinical data from study 108 to support expansion of the indication to include patients 2 to 5 years in age. Study 108 was an open-label pharmacokinetic (PK) and safety study in patients 2 to 5 years in age. This study included two parts (A and B). Part A included a 4-day treatment period where the PK of ivacaftor granules was assessed and dosing determined. Part B included an open-label 24-week treatment period where safety was assessed. As Part A only included a 4-day treatment period compared to the 24-week treatment period in Part B, this review will focus on Part B only. While this study was a safety/PK study, Vertex also included pharmacodynamics (PD) and efficacy related endpoints.

The protocol for study 108 is discussed in section 5.3, the efficacy data in section 6, and the safety data in section 7.

## 5.3 Discussion of Individual Studies/Clinical Trials

### 5.3.1 Study 108

#### Administrative Information

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

- **Study start date:** January 8, 2013
- **Study completion:** March 18, 2014
- **Study report date:** August, 19, 2014
- **Study sites:** U.S.A., Canada, and United Kingdom

#### Objectives/Rationale

##### Part A:

- Primary
  - To evaluate the safety of ivacaftor granules in CF patients aged 2 to 5 years of age with an approved mutation

- To evaluate the PK of ivacaftor granules and its metabolites
- Exploratory
  - To evaluate the palatability of ivacaftor granules

**Part B:**

- Primary
  - To evaluate the safety of ivacaftor granules in CF patients aged 2 to 5 years of age with an approved mutation
- Secondary
  - To evaluate the PK and PD of ivacaftor granules in CF patients aged 2 to 5 years of age with an approved mutation
- Tertiary
  - To evaluate the efficacy of ivacaftor granules in CF patients aged 2 to 5 years of age with an approved mutation
  - To evaluate the palatability of ivacaftor granules

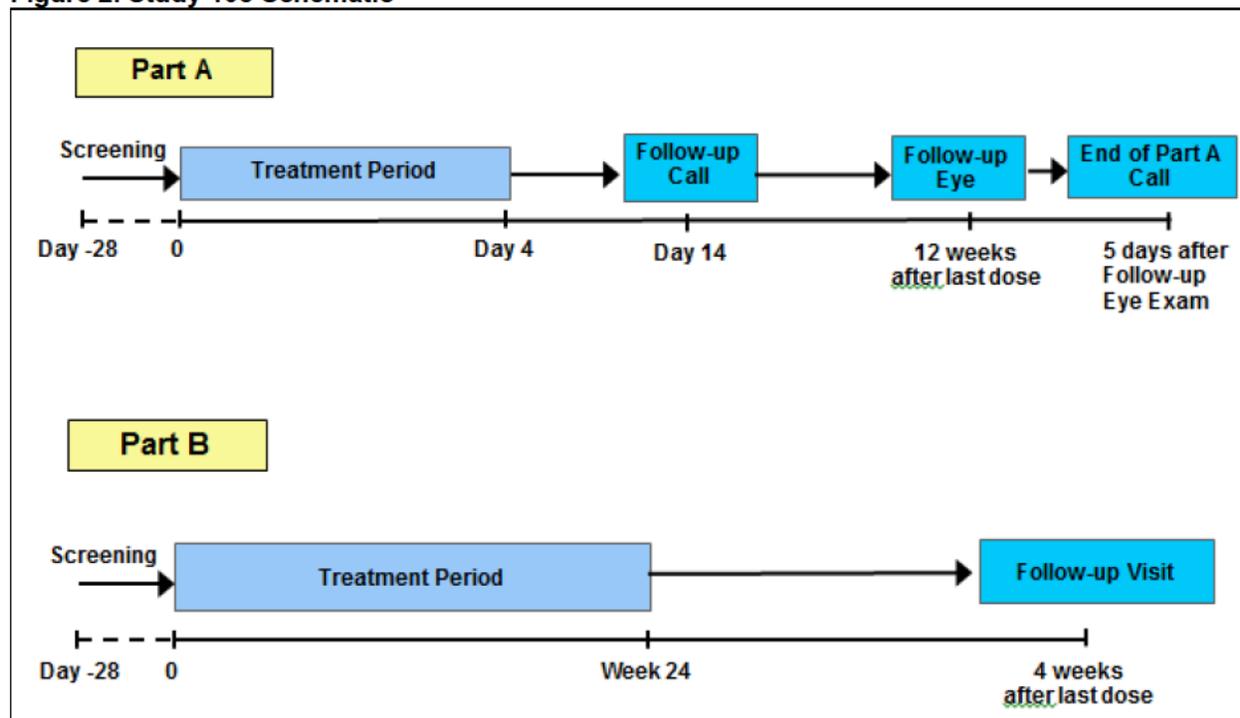
**Study Design and Conduct**

*Overview*

This was a 2-part (A and B) non-randomized, open-label study of ivacaftor granules in CF patients ages 2 to 5 years of age with a “gating” mutation in at least one allele. The following mutations were defined by the Applicant as “gating”: *G551D*, *G1244E*, *G1349D*, *G178R*, *G551S*, *S1251N*, *S1255P*, *S549N*, *S549R*, or *G970R*. It is worth noting that ivacaftor is not approved for use in the *G970R* mutation. In Part A, there was a 28-day screening period followed by a four day treatment period, where eligible patients received either 50mg (<14kg) or 75mg (≥14kg) of ivacaftor granules q12 hours. During the four day treatment period, PK samples were collected before the morning doses on day 1 and before the morning dose and at 2, 3, 6, 8, and 24-60 hours after the morning dose on day 4. Patients received an ophthalmologic exam prior the first dose and 12-weeks after the last dose.

In Part B, there was also a 28-day screening period. This was followed by a 24-week open-label treatment period where patients received IVA 75mg or 50mg depending on weight. Study visits occurred at day 1 and weeks 2, 4, 8, 12, 16, 20, 24, and 24+1 day. For patients who had not participated in part A, an ophthalmologic exam was performed prior to the initial dose and at week 12 and 24. Following the treatment period all patients were allowed to continue in the open-label extension study (109). The trial schematic for Parts A and B are summarized in Figure 2. See appendix 9.5 for assessment schedule.

Figure 2. Study 108 Schematic



### Trial population

This trial included 34 CF patients 2 to 5 years of age who had at least one “gating” *CFTR* mutation (as defined by Vertex).

### Key Inclusion Criteria

1. Male or female age 2-5 years with a confirmed diagnosis of CF, defined as a sweat chloride value of  $\geq 60$ mmol/L OR 2 CF-causing mutations.
2. A *CFTR* “gating” mutation on at least one allele.
3. Weight  $\geq 8$ kg at screening

### Key Exclusion Criteria

1. 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 ivacaftor to the subject
2. An acute upper or lower respiratory infection, or pulmonary exacerbation, or changes in therapy for pulmonary disease within 4-weeks before day 1.
3. Abnormal liver function, at screening, defined as  $\geq 3 \times$  upper limit of normal (ULN), of any 3 or more of the following: serum aspartate transaminase (AST), serum alanine transaminase (ALT), gamma-glutamyl transpeptidase (GGT), serum alkaline phosphatase, and total bilirubin

4. Colonization with organisms associated with more rapid decline in pulmonary status (e.g. *Burkholderia cenocepacia*, *Burkholderia dolosa*, and *Mycobacterium abscessus*)
5. Presence of a lens opacity or cataract identified at the screening ophthalmologic examination, or an inability to undergo an adequate slit lamp examination.

#### *Key Patient Removal Criteria*

Patients were discontinued from the trial if any of the following criteria were met:

1. A subject had 1 of the following and no alternative etiology (e.g., viral hepatitis) for the elevated transaminase is identified, regardless of whether ALT or AST levels had improved:
  - An elevated ALT or AST of  $>8 \times \text{ULN}$
  - ALT or AST  $>5 \times \text{ULN}$  for more than 2 weeks
  - An elevation of ALT or AST  $>3 \times \text{ULN}$  in association with total bilirubin  $>2x \text{ULN}$  and/or clinical jaundice
2. Patient develops a lens opacity or cataract

Patients may have been discontinued from the trial after discussion with the Vertex medical monitor if any of the following criteria were met:

1. A patient developed a medical condition that required prolonged concomitant therapy with a prohibited medication or prolonged interruption of the study drug.
2. A patient developed a life-threatening adverse event, or a serious adverse event (SAE) that placed them at immediate risk.
3. A subject had an increase in liver function tests ([LFTs] ALT, AST, GGT, alkaline phosphatase, or total bilirubin) to  $3 \times \text{ULN}$  (if the baseline LFTs are normal) or an increase that exceeded an absolute value of  $5 \times \text{ULN}$  (regardless of whether baseline LFTs are normal on Day 1).

#### **Treatments**

The ivacaftor dose in study 108 was 50 mg q12 for patients  $<14\text{kg}$  and 75mg for those  $\geq 14\text{kg}$ .

#### *Concomitant Medications/Prohibited Medications:*

Restricted medications included any CYP3A inhibitors and inducers and grapefruit/grapefruit juice at least 14 days before day 1 of Part A or B and throughout the treatment period.

#### **Endpoint Parameters (Part B)**

##### *Primary endpoint (safety)*

This primary objective of this trial was evaluation of long-term safety. Safety was determined by adverse events (AE), clinical labs, ECGs, vital signs, ophthalmologic assessments, and physical exams.

Ophthalmologic assessments were performed during this study by a license ophthalmologist or optometrist. The assessment included the following:

- visual acuity each eye
- lens refracting power
- slit lamp exam
- fundoscopic exam
- Intraocular pressure

#### *Secondary endpoints*

*The secondary endpoints were as follows:*

- PK parameter estimation of ivacaftor and metabolites M1 and M6
- Absolute change from baseline in sweat chloride through 24-weeks of treatment.
- Absolute change from baseline in weight at 24-weeks of treatment
- Absolute change from baseline in stature at 24-weeks of treatment
- Absolute change from baseline in BMI at 24-weeks of treatment

#### Tertiary endpoints

The tertiary endpoints were as follows:

- Weight-for-age z-score
- Stature-for-age z-score
- BMI-for-age z-score
- Qualitative microbiology cultures
- Pulmonary exacerbations
- Unplanned antibiotic therapy
- Hospitalizations
- Outpatient sick visits
- Spirometry
- Fecal elastase-1
- Immunoreactive trypsinogen
- Palatability of the granules

For this study, there were two exacerbation definitions which were as follows:

Definition 1: Treatment with antibiotics (any route) and at least 1 or more of the criteria from List A or List B (below), within three days before antibiotic start date through antibiotic stop date.

Definition 2: Treatment with antibiotics (any route) and fulfillment of 1 criteria from List A or 2 from List B (below), within three days before antibiotic start date through antibiotic stop date.

List A

- Decrease in FEV<sub>1</sub> ≥10% change from highest value in the past 6 months before the first dose, unresponsive to albuterol (if applicable)
- Oxygen saturation <90% on room air or ≥5% decrease from baseline
- New lobar infiltrate(s) or atelectasis on chest x-ray
- Hemoptysis (more than streaks on more than 1 occasion in past week)

List B

- Increased work of breathing or respiratory rate (duration ≥3 days)
- New or increased adventitial sounds on lung exam (duration ≥3 days)
- Weight loss ≥5% decrease from highest value or decrease across 1 major percentile for age in past 6 months
- Increased cough (duration ≥3 days)
- Worked harder to breathe during physical activity (duration ≥3 days)
- Increased chest congestion or change in sputum (duration ≥3 days)

The definition for exacerbation in this study differs from that used in studies used to support previous ivacaftor approvals. The previous studies included similar types of symptoms, however included additional symptoms such as sinus tenderness, change in sinus discharge, and malaise/fatigue/lethargy. These were likely not included in this study's criteria given the age group studied. This age group lacks fully formed sinuses and malaise/lethargy/fatigue would likely be difficult to characterize. Additionally, to be defined as an exacerbation in the previous ivacaftor studies, a patient was required to have at least 4 symptoms which trigger antibiotic treatment as compared to just 1 (definition A) or 2 (definition B).

**Compliance:**

Compliance was assessed by calculating the percentage of medication packets consumed relative to the number of packets expected to be consumed.

**Ethics:**

This trial was conducted according to the principles of Good Clinical Practice, the World Medical Association Declaration of Helsinki (1989), and ICH guidelines. An institutional review board reviewed and approved this protocol. No changes were made without the IRB's approval.

**Statistical Analysis**

*Safety Analysis*

Analysis of safety was descriptive with no formal statistical testing.

*Efficacy Analysis*

The majority of the efficacy related variable were analyzed as continuous variables using descriptive summary statistics and presented by visit and treatment. For hospitalization and exacerbation, time to first event analysis was also performed.

Because all analyses were performed using open-label data and given the lack of a comparator arm, interpretation of the efficacy data is difficult.

### **Protocol Amendments**

This protocol was amended 4 times. Pertinent changes are summarized. The first amendment was dated August 7, 2012. The major changes in this amendment included the addition of ophthalmologic exams. The second and third amendments were submitted on November 2, 2012, and November 9, 2012. Major changes included requiring the ophthalmologic exam to be performed by an ophthalmologist and use of the Lens Opacities Classification System III grading scale. The final amendment submitted on May 8, 2013, removed the upper limit on the number of patients that could be enrolled and added text to specify that the Data Monitoring Committee would be notified if a lens opacity or cataract were identified.

## **6 Review of Efficacy**

### **Efficacy Summary**

Ivacaftor tablets (NDA 203,188) are approved for the treatment of CF patients aged 6 years and older with the *G551D*, *G1244E*, *G1349D*, *G178R*, *G551S*, *S1251N*, *S1255P*, *S549N*, *S549R*, or *R117H* mutation in the CFTR gene at a dose of 150mg once every 12 hours. In this NDA, Vertex has submitted data from a pharmacokinetic and safety study (study 108) to support the use of ivacaftor granules in patients 2 to 5 years in age. This formulation is more age appropriate than tablets, as the patients in this age group often cannot swallow tablets and this formulation can be administered mixed with food or liquid. Study 108 was an open-label, uncontrolled, two-part pharmacokinetic (PK, part A) and safety (part B) study in patients 2 to 5 years in age. In part A, results demonstrated that when ivacaftor was administered at 75mg for patients  $\geq 14$ kg and at 50mg for patients  $< 14$ kg every 12 hours for 4-days, systemic exposures matched that seen for ivacaftor tablets (150mg q12) in the adolescent/adult population. Because of the similar exposures and because the disease process in the older population is the same as that in the 2 to 5 year old population, efficacy in the proposed age group was extrapolated from the ivacaftor tablet development program.

### **6.1 Indication**

The proposed indication for ivacaftor granules is for the treatment of cystic fibrosis patients aged 2 to 5 years with *G551D*, *G1244E*, *G1349D*, *G178R*, *G551S*, *S1251N*, *S1255P*, *S549N*, *S549R*, or *R117H* mutation in the CFTR gene at a dose of 75mg q12 hours for patients  $\geq 14$ kg and 50mg q12 hours for patients  $< 14$ kg. Ivacaftor tablets (NDA 203-188) are currently approved to treat CF patients  $\geq 6$  years of age with the same mutations.

### 6.1.1 Methods

Because efficacy in the 2 to 5 year old age group can be extrapolated from the older age groups, study 108 was considered to be primarily a PK and safety study. However, the Applicant has submitted supportive efficacy data from study 108. Study 108 was a two-part, non-randomized, uncontrolled, open-label PK (part A) and safety (part B) study. Because the primary objective of part A was determination of PK and because the treatment period was only 4-days, this review will focus on part B. The primary endpoint in part B was safety. Secondary efficacy/pharmacodynamic endpoints included sweat chloride, weight, stature, BMI, exacerbations, and percent predicted FEV1 (PPFEV1) (in those patients who could perform spirometry).

### 6.1.2 Demographics

Patient demographic and baseline data for Part B of study 108 are summarized in Table 3.

**Table 3. Study 108. Baseline characteristics**

	IVA 50mg N=10	IVA 75mg N=24	Total N=34
Sex, n(%)			
Male	6 (60.0)	22 (91.7)	28 (82.4)
Female	4 (40.0)	2 (8.3)	6 (17.6)
Race			
White	10 (100.0)	24 (100.0)	24 (100.0)
Age			
Mean	2.3	3.6	3.2
Median	2	4	3
Age category			
Age 2	7 (70.0)	2 (8.3)	9 (26.5)
Age 3	3 (30.0)	8 (33.3)	11 (32.4)
Age 4-5	0	14 (58.3)	14 (41.2)
Percent Predicted FEV1*	91.6	87.0	87.7
Sweat Chloride	93.1	99.6	97.9
BMI	15.8	16.1	16.0

\*3 patients in the 50mg group and 17 in the 75mg group  
 Source: study 108 CSR; table 10-5; pp89-92

Of the 34 patients in Part B, all but 32 were *G551D* heterozygous. The remaining 2 were both *S549N* heterozygous. As such, while the inclusion criteria would have theoretically allowed for patients with the *G970R* mutation, for which ivacaftor is not approved, no such patients were enrolled.

### 6.1.3 Subject Disposition

A total of 34 patients were included in Part B, of these, 33 completed the 24-week treatment period. The one patient who did not complete the 24-week treatment discontinued due to an adverse event (see section 7.3.3 for discussion)

### 6.1.4 Analysis of Primary Endpoint(s)

The primary endpoint of this trial was safety and will be discussed in section 7.

### 6.1.5 Analysis of Secondary Endpoints(s)

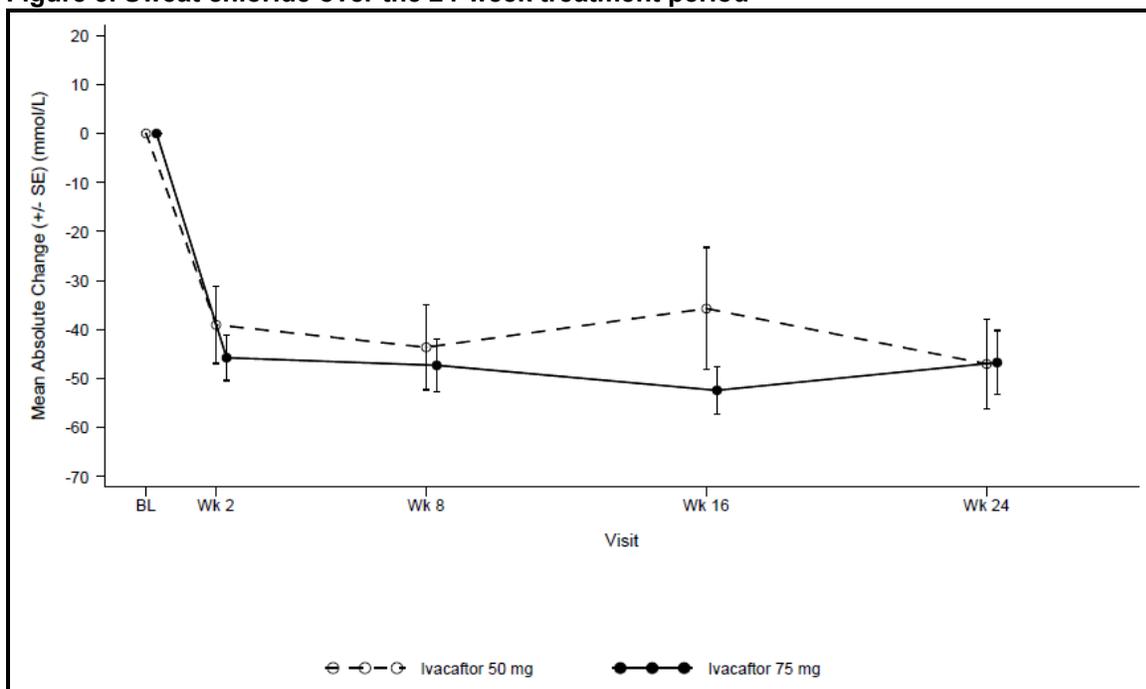
The non-PK related secondary endpoints were as follows:

- Absolute change from baseline in sweat chloride through 24-weeks of treatment.
- Absolute change from baseline in weight at 24-weeks of treatment

- Absolute change from baseline in stature at 24-weeks of treatment
- Absolute change from baseline in BMI at 24-weeks of treatment

For sweat chloride, decreases from baseline were seen in both ivacaftor treatment groups within 2-weeks of treatment (IVA 50mg=  $\bar{39}$ mmol/L; IVA 75mg=  $\bar{45.8}$ mmol/L). This initial decrease was sustained over the 24-week treatment period. Sweat chloride results are summarized in Figure 3.

**Figure 3. Sweat chloride over the 24-week treatment period**



Source: Study 108 CSR; figure 14.2.1.1b; pg656

While there is no placebo control for comparison, these data would imply that IVA in this age group has a pharmacodynamic effect within 2-weeks of treatment. This is consistent with previous IVA studies in which ivacaftor demonstrated efficacy, where similar sweat chloride responses were observed within 2-weeks of treatment and sustained for up to 48-week treatment periods.

With regard to absolute change from baseline in weight, at week 24, both IVA dose groups demonstrated absolute increases in weight compared to their own baseline (IVA 50mg= 1.0kg; IVA 75mg= 1.5kg). At week 24, absolute increases in stature were also observed (IVA 50mg=2.5cm; IVA 75mg=3.5cm). However, whether or not this was related to treatment is uncertain, as there was no placebo group and as the studied age group is actively growing. Based on CDC growth charts for healthy children, the average weight gain during every 6-month period for children between the age of 2-6

years is approximately 1 kg and for stature approximately 3-4 cm<sup>1</sup>. As such, the observed absolute increases in weight and stature may reflect normal development, rather than a treatment effect. With regard to BMI, the mean change from baseline was 0.33kg/m<sup>2</sup> and 0.31kg/m<sup>2</sup> for the IVA 50mg and 75mg groups, respectively.

### 6.1.6 Other Endpoints

Vertex also evaluated weight, stature, and BMI in terms of age adjusted z-scores. At baseline, mean values in both IVA dose groups demonstrated weight, stature, and BMI that were within one standard deviation of normal as evidenced by baseline z-scores bounded by -1 and 1. At week 24 of treatment, results were generally similar with z-scores still bounded by -1 and 1. This would suggest that during the 24-week treatment period, growth was similar to what one would expect in this age group. The results at baseline and week 24 are summarized in Table 4.

**Table 4. Weight, stature, and BMI for age z-scores**

	Weight for age z-score		Stature for age z-score		BMI for age z-score	
	Baseline	Week 24	Baseline	Week 24	Baseline	Week 24
<b>IVA 50mg (N=10)</b>	-0.86	-0.65	-0.9	-1.07	-0.23	0.19
<b>IVA 75 mg (N=24)</b>	0.13	0.34	-0.11	-0.06	0.63	0.34
<b>Total (N=34)</b>	-0.16	0.07	-0.34	-0.01	0.13	0.51

Source: SCE; tables 11, 12, 13, pg 31, 33, 34

The Applicant also reported absolute change from baseline for z-scores. Change from baseline in weight for age z-score at week 24 was 0.18 and 0.21 for the IVA 50mg and 75mg groups, respectively. Change from baseline in stature for age z-scores were -0.25 and 0.08 for the IVA 50mg and 75mg groups, respectively. For BMI, they were 0.46 and 0.34 for the IVA 50mg and 75mg groups, respectively. Overall, the changes in z-scores were small which may imply that the changes were related to normal growth. However, without a placebo group for comparison these data are difficult to interpret as these data represent change from baseline in z-scores rather than z-scores for change from baseline. As such, the change from baseline cannot be interpreted in relationship to normal values.

The Applicant also analyzed a number of other tertiary endpoints including exacerbation, unplanned antibiotic therapy, hospitalizations, outpatient sick visits, and spirometry. While the number of events and rates were reported, it is difficult to make any definitive efficacy conclusions given the lack of a placebo, active, or historical control group.

Vertex also reported change from baseline in PPFEV1 for those patients who could perform spirometry. Of the 34 patients, 20 could perform spirometry, and of these 17

<sup>1</sup> [http://www.cdc.gov/growthcharts/clinical\\_charts.htm](http://www.cdc.gov/growthcharts/clinical_charts.htm)

were in the 75mg group. At week 24, the change from baseline in PPFV1 was -12.5% and 4.3% in the IVA 50mg and IVA 75mg groups. Given the age of the patients, the reliability of the spirometry data is questionable, especially in the IVA 50mg group.

Vertex also reported change from baseline in qualitative microbiology cultures, fecal elastase, and immunoreactive trypsinogen (IRT). For qualitative microbiology cultures, no trends for increased or decreased growth were noted. For fecal elastase, values were increased at week 24, and for IRT values were decreased at week 24. While there were changes in these values, the clinical relevance of these changes are unknown.

#### 6.1.7 Subpopulations

The Applicant performed subgroup analysis based on baseline PPFV1 severity, geographic region, age, and sex. Subgroup analyses were non-informative.

#### 6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Dosing for ivacaftor granules in this age group was determined based on PK data from Part A of this trial. The proposed per kilogram dosing resulted in similar systemic exposure compared to the adult/adolescent population. See the Clinical Pharmacology Review for a more in depth discussion of dosing.

#### 6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

While sweat chloride is not a surrogate for efficacy, changes in sweat chloride demonstrate a pharmacodynamic effect. The persistence of sweat chloride changes over the 24-week treatment period in both IVA treatment groups, demonstrate that tolerance to IVA would likely not develop over time. This is consistent with data from the older population.

#### 6.1.10 Additional Efficacy Issues/Analyses

none

## 7 Review of Safety

### **Safety Summary**

Vertex has submitted data from study 108 to support the safety of ivacaftor granules in CF patients 2 to 5 years in age. In the ivacaftor tablet (NDA 203188) initial clinical trials, elevations in transaminases were observed, and while they were occurred in both placebo and active treatment groups, there were more liver related SAEs in patients who received ivacaftor. Concerns were also raised regarding significant drug-drug

interactions with CYP3A inducers, inhibitors, and substrates. Based on analysis of deaths, SAEs, and AEs; no new safety signals were identified. With regard to lab evaluations, in the 2 to 5 year old population, transaminase elevations were observed more frequently in patients with baseline elevated transaminases.

## **7.1 Methods**

### **7.1.1 Studies/Clinical Trials Used to Evaluate Safety**

Study 108 was used to evaluate safety in the 2 to 5 year old age group. This study was a 2-part (A and B) open-label, non-randomized study in CF patients with “gating” mutations. As Part A only included a 4 day treatment period, this section will only include a discussion of safety data from Part B which included a 24-week treatment period.

### **7.1.2 Categorization of Adverse Events**

The sponsor defined an adverse event (AE) as any untoward medical occurrence in a patient during the study, which does not require a causal relationship with study drug. Any abnormal laboratory assessment, ECG, vital sign or physical exam finding that was judged by the investigator as clinically significant worsening from baseline were to be reported as adverse events. Adverse events were classified using MedDRA Version 15.1.

### **7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence**

No pooling of data was performed as only a single study was evaluated.

## **7.2 Adequacy of Safety Assessments**

### **7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations**

A total of 34 patients were exposed to IVA in study 108. The majority of patients were exposed to ivacaftor for  $\geq 24$  weeks. The extent of exposure in study 108 is summarized in Table 5.

**Table 5. Extent of exposure in study 105 and cumulatively**

	IVA 50mg N=10	IVA 75mg N=24	IVA total N=34
Extent of Exposure (days)			
Mean (SD)	156.4 (48.9)	169.4 (2.6)	165.6 (26.33)
Median (min, max)	170 (18, 184)	169 (161, 175)	169 (18, 184)
Duration of Exposure [N (%)]			
<2 weeks	0	0	0
2 to <4 weeks	1 (10.0)	0	1 (2.9)
4 to <8 weeks	0	0	0
8 to <12 weeks	0	0	0
12 to <16weeks	0	0	0
16 to <24 weeks	2 (20.0)	2 (8.3)	4 (11.8)
≥24 weeks	7 (70.0)	22 (91.7)	29 (85.3)

Source: Study 108 CSR; table 12-8; pp135

### 7.2.2 Explorations for Dose Response

While this trial included two doses of IVA, both doses yielded similar systemic exposures. As such, exploration for dose response was not possible.

### 7.2.3 Special Animal and/or In Vitro Testing

Not applicable.

### 7.2.4 Routine Clinical Testing

Clinical laboratory testing was performed as summarized in section 9.5 Study 108 assessment schedule.

### 7.2.5 Metabolic, Clearance, and Interaction Workup

Not applicable.

### 7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

There are no other drugs in this class. However, elevations in LFTs were noted in the *G551D CFTR* mutation development program, and while they were observed in both placebo and active treatment groups, there were more liver related SAEs in patients who received ivacaftor. In juvenile animal studies, lens opacities/cataracts were also noted. Study 108 regularly monitored LFTs and incorporated ophthalmologic evaluations during the treatment period.

### 7.3 Major Safety Results

#### 7.3.1 Deaths

There were no deaths reported.

#### 7.3.2 Nonfatal Serious Adverse Events

In general, the serious adverse events (SAE) reported were what would be expected in a CF population. A total of 6 patients experienced SAEs. The events were isolated in nature. Based on preferred term (PT), the only event that occurred in  $\geq 2$  patients was exacerbation of CF. These results are summarized in Table 6. SAE data did not reveal new safety concerns.

**Table 6. Study 108. Nonfatal serious adverse events.**

	2-years		3-years		4-5 years		Overall		
	IVA 50mg N=7	IVA 75mg N=2	IVA 50mg N=3	IVA 75mg N=8	IVA 50mg N=0	IVA 75mg N=14	IVA 50mg N=10	IVA 75mg N=24	Total N=34
<b>Subjects With Serious Adverse Events</b>	2 (28.6)	1 (50.0)	1 (33.3)	1 (12.5)	0	1 (7.1)	3 (30.0)	2 (8.3)	6 (17.6)
<b>Infections and infestations</b>	0	0	1 (33.3)	1 (12.5)	0	0	1 (10.0)	1 (4.2)	2 (5.9)
Infective pulmonary exacerbation of CF	0	0	1 (33.3)	1 (12.5)	0	0	1 (10.0)	1 (4.2)	2 (5.9)
Device-related sepsis	0	0	1 (33.3)	0	0	0	1 (10.0)	0	1 (2.9)
<b>Investigations</b>	2 (28.6)	0	0	0	0	0	2 (20.0)	0	2 (5.9)
<i>Pseudomonas</i> test positive	1 (14.3)	0	0	0	0	0	1 (10.0)	0	1 (2.9)
Transaminases increased	1 (14.3)	0	0	0	0	0	1 (10.0)	0	1 (2.9)
<b>Gastrointestinal disorders</b>	0	1	0	0	0	0	0	1 (4.2)	2 (2.9)
Vomiting	0	1 (50.0)	0	0	0	0	0	1 (4.2)	1 (2.9)
<b>Nervous system disorders</b>	0	0	0	0	0	1 (7.1)	0	1 (4.2)	1 (2.9)
Convulsion	0	0	0	0	0	1 (7.1)	0	1 (4.2)	1 (2.9)

Source: study 108 CSR; table 14; pg31

#### 7.3.3 Dropouts and/or Discontinuations

One patient dropped out due to an adverse event. This was a two year old male (08-028-03) in the IVA 50mg group. This patient also had a history of elevated LFTs. At baseline in Part B, the patient had an elevated ALT ( $>3x$  ULN) and after two weeks of dosing, the ALT had increased to  $>8x$  ULN. This was reported as an SAE and study drug was permanently discontinued. A liver biopsy was performed 3-weeks after study withdrawal, which showed non-specific findings. At that time, ALT had decreased to  $>3x$  ULN. Approximately 2 months later the patient's ALT was 58 U/L.

Eleven patients (32.4%) temporarily interrupted study drug treatment due to adverse events. In the 50mg group, this is included 2 for LFT elevations, 1 for croup, and one for device-related sepsis. In the 75mg group, this included 1 for LFT elevation, 2 for vomiting, one for gastroenteritis, 1 for retching, 1 for rash, and one for increased cough. Following resolution of the AE, all patients restarted study drug.

### 7.3.4 Significant Adverse Events

See section 7.3.5

### 7.3.5 Submission Specific Primary Safety Concerns

In the *G551D CFTR* mutation phase 3 trials, while increases in AST and ALT were observed in patients both in the placebo and active treatment groups, there were more liver-related SAEs in patients who received ivacaftor. As such, in study 108, AE and clinical lab data were specifically assessed for liver function test (LFT) abnormalities. In study 108, 6 patients (18%) had a maximum on-treatment LFT of >2x ULN. Of these patients 5 had values which were >8x ULN. It is also worth noting that all these patients had a baseline LFTs >2x ULN. No patients with baseline LFTs ≤2x ULN had maximum LFT elevations of greater than 2x ULN. These results are summarized in Table 7.

**Table 7. Study 108. Maximum on-treatment liver function test (LFT) results by baseline**

Baseline	Maximum on-treatment	Liver Function Test	IVA 50mg N=10 n(%)	IVA 75mg N=24 n(%)	Total N=34 n(%)
≤2x ULN	≤2x ULN	ALT / AST (U/L)	5 (50.0)	21 (87.5)	26 (76.5)
	>2x ULN to ≤3x ULN		0	0	0
	>3x ULN to ≤5x ULN		0	0	0
	>5x ULN to ≤8x ULN		0	0	0
	>8x ULN		0	0	0
>2x ULN	≤2x ULN	ALT / AST (U/L)	1 (10.0)	1 (4.2)	2 (5.9)
	>2x ULN to ≤3x ULN		1 (10.0)	0	1 (2.9)
	>3x ULN to ≤5x ULN		0	0	0
	>5x ULN to ≤8x ULN		0	0	0
	>8x ULN		3 (30.0)	2 (8.3)	5 (14.7)

Source: study 108 CSR; table 12-22; pg150

While there is no placebo group for comparison, the relative number of IVA treated patients who developed elevations in LFTs appears higher compared to that seen in the original *G551D* program. For example, in the *G551D* development program, a total of 4 ivacaftor treated patients out of 221 had maximum on-treatment LFTs >8x ULN (of which 3 had a history of elevated LFTs) (see table 26 of Dr. Witzmann's clinical review dated 1/17/12).

The five cases of LFT elevations >8x ULN are reviewed below:

Patient 08-002-03:

This was a 2 year old male (wt. 11.9kg) assigned to the IVA 50mg treatment group. This patient also had a history of elevated LFTs during viral infections with ALT elevations of 8x ULN. At screening (8/15/1013) this patient had an ALT >3x ULN (113 U/L). On 8/26/13, baseline LFTs were repeated and the patient was started on IVA 50mg, however, IVA was discontinued two days later as baseline ALT was found to be elevated [ALT>8x ULN (244 U/L)]. When LFTs were reassessed on 9/03/13, the ALT continued to be elevated (366 U/L). The patient also reported the AE of cough. The patient remained off of ivacaftor. When LFTs were reassessed on 10/25/13, the ALT was reported at normal (57 U/L) and ivacaftor was restarted. Following resumption of dosing, there was some increase in ALT, but not to the extent that was previously observed.

Patient 08-021-01:

This patient was a 4 year-old male (14.4kg) with a history of elevated LFTs. In Part B, at baseline (8/01/13), the patient was noted to have an ALT of 100 U/L (5x ULN), with a normal AST. After approximately 20-weeks of treatment, the patient's ALT was noted to be 327 U/L (>8x ULN) and dosing was interrupted. Within approximately 2-weeks, the patient's ALT returned to baseline. A hepatologist was consulted who concluded that IVA related elevation could not be ruled out, but that the elevations could have also been related to underlying CF.

Patient 08-028-03:

This patient was a 2 year old male (12.4 kg) with a history of LFT elevations since 6-months of age. At Part B baseline, the patient was noted to have an ALT of 144 U/L (>3x ULN) and an AST of 78 U/L. Following 2-weeks of treatment, the ALT had risen to 389 U/L (>8x ULN) and the AST to 231 U/L (3x ULN). IVA was permanently discontinued. A liver biopsy was performed which showed non-specific findings. Approximately 2 months after discontinuation, the patient's ALT returned to normal range.

Patient 08-074-01:

This patient was a 5 year old male (16kg) with a history of mild LFT elevations. At baseline LFTs were normal. After 24-weeks of treatment, both the patient's ALT and AST were elevated at >8x ULN and >5x ULN, respectively.

Patient 08-203-01:

This was a 3-year old female (13.3kg) with a history of CF-related liver disease who was on Ursodiol. This patient had an ALT of 209 U/L at Part B baseline. During the 24-week treatment period, IVA dosing was interrupted and restarted 3 times due to changes in patient LFTs.

Note that in all 5 cases of LFT elevations >8x ULN in this study, associated increases in bilirubin, alkaline phosphatase, or GGT were not observed. While there was a higher

percentage of patients with LFT elevations >8x ULN in study 108 compared to the original *G551D* program, the case descriptions were similar in that the patients who developed elevations had baseline elevated LFTs or a history of elevated LFTs. As such, it is uncertain if these findings represent a unique risk to this age group.

Additionally, as lens opacities/cataracts were noted in juvenile animal studies, study 108 included ophthalmologic evaluations pre-dose, at week 12, and at week 24. No patients developed lens opacities during the study.

## 7.4 Supportive Safety Results

### 7.4.1 Common Adverse Events

Common adverse events are summarized in Table 8. The AEs reported are generally consistent with the AE observed in the ivacaftor tablet program. No new safety signals have been identified.

**Table 8. Study 108. Adverse events occurring in ≥10% of patients in any IVA group**

	IVA 50mg N=10 n(%)	IVA 75mg N=24 n(%)	Total N=34 n(%)
<b>Any adverse event</b>	<b>10 (100.0)</b>	<b>23 (95.8)</b>	<b>33 (97.1)</b>
<b>Respiratory, thoracic, and mediastinal disorders</b>	<b>8 (80.0)</b>	<b>20 (83.3)</b>	<b>28 (82.4)</b>
Cough	4 (40.0)	15 (62.5)	19 (55.9)
Nasal congestion	4 (40.0)	5 (20.8)	9 (26.5)
Rhinorrhea	2 (20.0)	5 (20.8)	7 (20.6)
Productive cough	0	3 (12.5)	3 (8.8)
Dyspnea exertional	1 (10.0)	0	1 (2.9)
<b>Infections and infestations</b>	<b>6 (60.0)</b>	<b>14 (58.3)</b>	<b>20 (58.8)</b>
Upper respiratory tract infection	1 (10.0)	7 (29.2)	8 (23.5)
Infective pulmonary exacerbation of CF	1 (10.0)	4 (16.7)	5 (14.7)
Croup infectious	2 (20.0)	1 (4.2)	3 (8.8)
Otitis media	2 (20.0)	1 (4.2)	3 (8.8)
Sinusitis	2 (20.0)	1 (4.2)	3 (8.8)
Device related sepsis	1 (10.0)	0	1 (2.9)
Genital candidiasis	1 (10.0)	0	1 (2.9)
Infectious mononucleosis	1 (10.0)	0	1 (2.9)
Pharyngitis streptococcal	1 (10.0)	0	1 (2.9)
Viral rash	1 (10.0)	0	1 (2.9)
<b>Gastrointestinal disorders</b>	<b>5 (50.0)</b>	<b>10 (41.7)</b>	<b>15 (44.1)</b>
Vomiting	3 (30.0)	7 (29.2)	10 (29.4)
Constipation	0	4 (16.7)	4 (11.8)
Abdominal distension	1 (10.0)	0	1 (2.9)
Teething	1 (10.0)	0	1 (2.9)
<b>Investigations</b>	<b>5 (50.0)</b>	<b>7 (29.2)</b>	<b>12 (35.3)</b>
Bacterial test positive	0	3 (12.5)	3 (8.8)
Hemophilus test positive	0	3 (12.5)	3 (8.8)

## Clinical Review

Robert Lim

NDA 207,925

Trade Name: Kalydeco Granules, Generic Name: ivacaftor

Hepatic enzyme increased	2 (20.0)	0	2 (5.9)
Activated partial thromboplastin time prolonged	1 (10.0)	0	1 (2.9)
Antibiotic resistant <i>Staphylococcus</i> test positive	1 (10.0)	0	1 (2.9)
Pseudomonas test positive	1 (10.0)	0	1 (2.9)
Respiratory rate increased	1 (10.0)	0	1 (2.9)
Transaminases increased	1 (10.0)	0	1 (2.9)
<b>Skin and subcutaneous tissue disorders</b>	<b>5 (50.0)</b>	<b>3 (12.5)</b>	<b>8 (23.5)</b>
Rash	2 (20.0)	2 (8.3)	4 (11.8)
Dermatitis contact	1 (10.0)	0	1 (2.9)
Skin irritation	1 (10.0)	0	1 (2.9)
Urticaria	1 (10.0)	0	1 (2.9)
<b>General disorders and administrative site conditions</b>	<b>4 (40.0)</b>	<b>3 (12.5)</b>	<b>7 (20.6)</b>
Pyrexia	4 (40.0)	2 (8.3)	6 (17.6)
<b>Metabolism and nutrition disorders</b>	<b>1 (10.0)</b>	<b>2 (8.3)</b>	<b>3 (8.8)</b>
Decreased appetite	1 (10.0)	1 (4.2)	2 (5.9)
<b>Renal and urinary disorders</b>	<b>1 (10.0)</b>	<b>1 (4.2)</b>	<b>2 (5.9)</b>
Chromaturia	1 (10.0)	0	1 (2.9)
<b>Blood and lymphatic system disorders</b>	<b>1 (10.0)</b>	<b>0</b>	<b>1 (2.9)</b>
Lymphadenopathy	1 (10.0)	0	1 (2.9)

Source: study 108 CSR; table 12-10; pp137-138

### 7.4.2 Laboratory Findings

Routine clinical testing for this safety program included evaluations of hematology, serum chemistries including liver transaminases (discussed in section 7.3.5), coagulation studies, and urinalyses. No laboratory abnormalities resulted in study drug discontinuation, aside from the single discontinuation due to LFT elevations described in section 7.3.3.

### 7.4.3 Vital Signs

Vertex presented mean values for heart rate, blood pressure, body temperature, and oxygen saturations for both IVA groups. No clinically relevant changes from baseline were noted.

### 7.4.4 Electrocardiograms (ECGs)

Summary statistics of heart rate, PR interval, RR interval, QRS duration, QT, QTcF, and QTcB for each IVA treatment group was provided by the sponsor. Differences between treatment groups were minimal. Shift table analysis was also unrevealing.

#### 7.4.5 Special Safety Studies/Clinical Trials

Not performed

#### 7.4.6 Immunogenicity

Not performed

### 7.5 Other Safety Explorations

#### 7.5.1 Dose Dependency for Adverse Events

While this study included two doses, systemic exposure was similar between the two dose groups. As such, conclusions regarding dose dependent effects cannot be made.

#### 7.5.2 Time Dependency for Adverse Events

No formal analysis was performed.

#### 7.5.3 Drug-Demographic Interactions

The sponsor compared adverse event data between subgroups based on age, sex, and baseline FEV1. In general, the pattern of adverse events between subgroups was similar to that of the overall population.

#### 7.5.4 Drug-Disease Interactions

Drug-Disease interaction data for ivacaftor is summarized in section 8 and 12 of the approved label. Drug-disease interactions were not studied in study 108

#### 7.5.5 Drug-Drug Interactions

Drug-Drug interaction data for ivacaftor is summarized in sections 7 and 12 of the approved label. Drug-Drug interactions were not studied in study 108

### 7.6 Additional Safety Evaluations

#### 7.6.1 Human Carcinogenicity

No human carcinogenicity studies have been performed for ivacaftor

#### 7.6.2 Human Reproduction and Pregnancy Data

Not applicable

#### 7.6.3 Pediatrics and Assessment of Effects on Growth

This trial included pediatric patients (2 to 5 years in age). Compared to historical controls (CDC growth charts), there did not appear to be detrimental effects on growth.

#### 7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Not applicable

### 7.7 Additional Submissions / Safety Issues

None

## 8 Postmarket Experience

Ivacaftor was initially approved on January 31, 2012 for the *G551D* mutation. Since that time until the date of this review, no new issues have been identified that would alter the risk-benefit profile in the approved indication.

## **9 Appendices**

### **9.1 Literature Review/References**

This reviewer searched PubMed with the search terms “cystic fibrosis,” “ivacaftor,” and “pediatric.” A total of 26 articles were retrieved. No new safety signals were identified from this literature search.

### **9.2 Labeling Recommendations**

Labeling negotiations are ongoing at the time of this review. Identified issues with the label include the presentation of open-label efficacy data in 2 to 5 year olds in Section 14. As efficacy was extrapolated from the older population and not based on the open-label data, inclusion in the label is not recommended. Additionally, as there is no comparator group, interpretation of this data is difficult. Further, the weight and stature data were consistent with normal growth and PPFEV1 data is generally not dependable in this age group. Additionally, in the 2 to 5 year old population, transaminase elevations were observed more frequently in patients with baseline elevated transaminases. Because of this Vertex includes in the label specific LFT monitoring for the 2 to 5 year old population. However, this observation may also be applicable to the general population and not specific to the 2 to 5 year population. As such, it is recommended that the proposed wording regarding LFT monitoring be edited to apply to the general population.

### **9.3 Advisory Committee Meeting**

An advisory committee meeting is not necessary for this NDA.

### **9.4 Clinical Investigator Financial Disclosure Review Template**

#### Clinical Investigator Financial Disclosure Review Template

Application Number: 206756

Submission Date(s): 9/17/1014

Applicant: Vertex

Product: Ivacaftor

Reviewer: Robert Lim

Clinical Review  
 Robert Lim  
 NDA 207,925  
 Trade Name: Kalydeco Granules, Generic Name: ivacaftor

Date of Review: 2/20/15

Covered Clinical Study (Name and/or Number): 108

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from applicant)
Total number of investigators identified: 90 (Primary and sub-investigators)		
Number of investigators who are sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>3</u>		
<p>If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):</p> <p>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study:</p> <p>Significant payments of other sorts: <u>3</u></p> <p>Proprietary interest in the product tested held by investigator: <u>0</u></p> <p>Significant equity interest held by investigator in sponsor of covered study: <u>0</u></p>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3)		
Is an attachment provided with the reason:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request explanation from applicant)

From study 108, Vertex certified the absence of financial arrangements for 87 of the primary investigators and sub-investigators. In study 108, there was one principle and two sub-investigators with significant payments of other sorts: Drs. (b) (6). These significant payments of other sorts were determined to not have a significant impact upon the conduct of this study. Enrollment at any particular site was relatively small compared to the overall number of patients. Additionally, removal of patients from these sites would not have affected interpretation of safety and efficacy was based on extrapolation from the older population.

## 9.5 Study 108 assessment schedule

Event/Assessment	Screening Period		Treatment Period								Week 24 + 1 Day <sup>a</sup>	Early Termination Visit	Follow-up Visit
	Day -28	Day -1	Day 1	Week 2 (± 1 day)	Week 4 (± 5 days)	Week 8 (± 5 days)	Week 12 (± 5 days)	Week 16 (± 5 days)	Week 20 (± 5 days)	Week 24 (± 5 days)		As Soon as Possible After Last Dose of Study Drug <sup>b</sup>	4 Weeks (± 7 Days) After Last Dose <sup>b</sup>
Clinic visit	X	X	X	X	X	X	X	X	X	X	X	X	
Informed consent/assent <sup>c</sup>	X												
Inclusion/exclusion criteria review	X	X											
Demographics	X												
Medical history	X												
CFTR genotype <sup>d</sup>	X												
Stature and weight <sup>e</sup>	X	X	X	X	X	X	X	X	X	X	X	X	
Physical examination <sup>f</sup>	X	X	X	X	X	X	X	X	X	X	X	X	
Vital signs <sup>g</sup>	X	X	X	X	X	X	X	X	X	X	X	X	
12-lead ECGs <sup>h</sup>	X	X	X								X	X	
Serum chemistry and hematology	X	X	X							X	X	X	
Coagulation studies	X	X								X	X	X	
Urinalysis	X												
Ophthalmologic examinations <sup>i</sup>	X					X				X			
PK blood collection			X <sup>j</sup>	X <sup>k</sup>		X <sup>l</sup>		X <sup>m</sup>		X <sup>n</sup>	X <sup>o</sup>	X	
Sweat chloride test <sup>p</sup>	X	X	X			X		X		X			
Fecal elastase-1 <sup>q</sup>		X				X		X		X			
Immunoreactive trypsinogen		X	X			X		X		X			
Qualitative microbiology cultures	X	X	X			X		X		X	X	X	
Spirometry <sup>r</sup>	X	X	X			X		X		X			
Palatability assessment <sup>s</sup>		X											
Study drug administration <sup>t</sup>		X	X	X	X	X	X	X	X	X			
Study drug count		X	X	X	X	X	X	X	X	X	X		
TVRS/TWRS contact	X	X	X	X	X	X	X	X	X	X			
DNA analysis (optional) <sup>v</sup>		X											
Pulmonary exacerbations, hospitalizations, outpatient sick visits, and unplanned antibiotic therapy	Continuous from Screening through the last dose of study drug												
Adverse events, and prior and concomitant treatment and procedures	Continuous from signing of ICF through end of study participation												

<sup>a</sup> The Week 24 + 1 Day Visit occurred 24 hours after the last dose of study drug, which was the morning dose of the Week 24 Visit.

<sup>b</sup> All subjects who prematurely discontinued study drug treatment during the Treatment Period were required to complete the Early Termination Visit and the Follow-up Visit. If the Early Termination Visit occurred 3 weeks or later after the last dose of ivacaftor, the Follow-up Visit was not required. Subjects who prematurely discontinued treatment were eligible to enroll in the observational arm of Study 109. The Follow-up Visit was not required for subjects who enrolled in the treatment arm of Study 109.

<sup>c</sup> Informed consent/assent was to be obtained before the Screening Visit and was to have been obtained before any screening assessment was performed.

<sup>d</sup> All subjects were tested for CFTR genotype to confirm the CFTR genotype documented in the subject's medical record. Subjects must have had a gating CFTR mutation in at least 1 allele to meet inclusion criteria. Subjects who had CFTR genotyping completed in Part A of the study were not required to have repeat testing upon entry into Part B. If a presence of CFTR gating mutation was not confirmed, the subject was discontinued from study drug dosing.

<sup>e</sup> At 2 years of age and older, if children could stand unassisted and follow directions, stature was measured as height; otherwise, stature was measured as length. Stature and weight were measured with shoes off and light clothing. Day 1 stature and weight measurements were made before dosing.

<sup>f</sup> Full physical examinations occurred at the Screening Visit, Week 24 Visit, and the Early Termination and Follow-up Visits; abbreviated physical examinations occurred at the all other study visits.

<sup>g</sup> Vital signs included blood pressure, temperature, heart rate, respiratory rate, and pulse oximetry. Vital signs were collected after the subject had been resting for at least 5 minutes. Day 1 vital signs were collected before dosing.

<sup>h</sup> All 12-lead ECGs were performed before the morning dose after the subject had been resting for at least 5 minutes.

<sup>i</sup> The Screening Ophthalmologic Examination may have been performed pre-dose on Day 1. If an adequate slit-lamp examination was not conducted at the Week 12 Visit, the subject continued to receive study drug until an adequate repeat examination was completed (within 4 weeks); if an adequate slit-lamp examination could not be conducted at the second examination or a lens opacity or cataract was identified, study drug dosing was discontinued and the subject was eligible to enroll in the observational arm of Study 109. If an adequate slit-lamp examination was not able to be conducted at the Week 24 Visit, the subject was not eligible for enrollment into the treatment arm of Study 109 until a repeat exam was performed (within 4 weeks). If the second examination was successful and no lens opacity or cataract was identified, the subject resumed study drug treatment in the treatment arm in Study 109; if the slit-lamp examination could not be performed or if a lens opacity or cataract was identified at the second examination, the subject was eligible to enroll in the observational arm of Study 109. See the protocol in Appendix 16.1.1, Section 12.7.6 for details.

<sup>j</sup> A PK sample was collected before the morning dose on Day 1.

<sup>k</sup> For subjects who did not participate in Part A, PK samples were collected before the morning dose and 2 hours, 3 hours, and between 6 and 8 hours after dosing on Week 2. For subjects who participated in Part A, a PK sample was collected before the morning dose only on Week 2.

<sup>l</sup> PK samples were collected before the morning dose and 1 hour after dosing on Week 8.

<sup>m</sup> PK samples were collected before the morning dose and 4 and 6 to 8 hours after dosing on Week 16.

<sup>n</sup> The last dose of study drug in Part B was the morning dose at the Week 24 Visit; PK samples were collected before the morning dose on Week 24 and on the morning of the day after the Week 24 Visit.

<sup>o</sup> At the Day 1 Visit in Part B, the sweat chloride test was to have been performed before the morning dose. At the Weeks 2, 8, 16, and 24 Visits, the sweat chloride test was to have been performed within a window of ± 2 hours relative to the morning dose of the study drug.

<sup>p</sup> The stool sample for the Day 1 fecal elastase-1 assessment was to have been obtained at any time from screening until before the first dose on Day 1. The sample was to have been collected at the study center during the study visit or was to have been collected by the subject at home and brought to the study visit.

<sup>q</sup> Spirometry assessments were performed at qualified study sites for subjects ≥ 3 years of age; see the protocol in Appendix 16.1.1, Section 12.6.7 for details.

<sup>r</sup> All subjects had their acceptance of the dose administered and the volume consumed recorded. All subjects were also to be observed by their facial expressions and any spontaneous comments in regards to likes or dislikes, which were noted. Palatability of ivacaftor minitablets was further assessed in subjects 4 years of age and older in the study using a visual analog scale that incorporated a 5-point facial hedonic scale; subjects 4 through 5 years of age were asked to rate their degree of liking using the visual analog scale. See the protocol in Appendix 16.1.1, Section 12.6.10 for details.

<sup>s</sup> Study drug was administered every 12 hours (q12h). Each dose of minitablets was mixed with approximately 1 teaspoon (5 mL) applesauce (or other appropriate food listed in the study manual) and administered orally with fit-containing food such as a standard "CF" high-calorie, high-fat meal or snack. Details of dose preparation and dose administration were provided in the study manual (see the protocol in Appendix 16.1.1, Section 11.2). For 3 days preceding the Week 2, Week 8, Week 16, and Week 24 Visits, the administration dates and times and their timing with respect to food intake of all study drug doses administered outside the clinic was to have been recorded in each subject's dosing diary. The last dose of study drug in Part B was the morning dose at the Week 24 Visit.

<sup>t</sup> Optional DNA sample (buccal mucosa swab) was obtained for exploratory analyses; see the protocol in Appendix 16.1.1, Section 12.5 for details.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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ROBERT H LIM  
02/19/2015

ANTHONY G DURMOWICZ  
02/19/2015

**MEDICAL OFFICER REVIEW**  
**Division Of Pulmonary and Allergy Drug Products (HFD-570)**

<b>APPLICATION:</b> NDA 207925	<b>CODE NAME:</b> Kalydeco granules
<b>APPLICANT/SPONSOR:</b> Vertex	<b>USAN NAME:</b> ivacaftor
<b>MEDICAL OFFICER:</b> Robert Lim, MD	
<b>TEAM LEADER:</b> Anthony Durmowicz, MD	<b>CATEGORY:</b> CFTR potentiator
<b>DUE DATE:</b>	<b>ROUTE:</b> oral

**SUBMISSIONS REVIEWED IN THIS DOCUMENT**

<u>Document Date</u>	<u>CDER Stamp Date</u>	<u>Submission</u>	<u>Comments</u>
09/17/14	09/17/14	NDA	

**RELATED APPLICATIONS**

<u>Document Date</u>	<u>Application Type</u>	<u>Comments</u>

**REVIEW SUMMARY:**

Vertex has submitted a new NDA (207925) for ivacaftor granules which proposes to expand the indication for ivacaftor tablets (NDA 203188) to include the 2-5 year old age group (50mg q12 for <14 kg, 75mg q12 for ≥14 kg). Ivacaftor tablets were approved on January 31, 2012, for the treatment of CF in patients ≥6 years of age who have a *G551D* mutation in the *CFTR* gene at a dose of 150mg every 12 hours with a fat-containing food. On February 21, 2014 in a subsequent sNDA (supplement 004), the indication was expanded to include the following additional mutations: *G1244E*, *G1349D*, *G178R*, *G551S*, *S1251N*, *S1255P*, *S549N*, or *S549R*. Regulatory action for the *R117H* mutation is currently pending. In previous review cycles for ivacaftor there have been safety concerns regarding LFT elevations observed in the clinical studies, as well as cataracts observed in juvenile animal studies. In previous regulatory interactions, the Division agreed that efficacy in the 2-5 year old age group could be extrapolated from the ≥6 year old data from the ivacaftor tablet program, and that dosing for ivacaftor granules could be determined using systemic exposures. As such, the development program for ivacaftor granules consists primarily of a PK/PD/safety study (108) in the targeted age group. Study 108 included 2-parts (A and B). In part A, Vertex determined dosing by assessing PK parameters. Part B consisted of a 24-week open-label treatment period with the dosing determined in part A. The primary objective of part B was to demonstrate safety, although there were some efficacy related secondary endpoints. This submission was adequately indexed, organized, and complete to allow for review. The filing checklist and slides from the filing meeting held on 10/20/14 are attached.

**OUTSTANDING ISSUES:**

Comment to sponsor:

“Efficacy for the 2-5 year old population is extrapolated from the existing data in the older population. As such, the inclusion of data from study 108 in section 14 of the label will be a review issue.”

**RECOMMENDED REGULATORY ACTION**

<b>IND/NEW STUDIES:</b> <input type="checkbox"/>	<b>SAFE TO PROCEED</b> <input type="checkbox"/>	<b>CLINICAL HOLD</b> <input type="checkbox"/>
<b>NDA/SUPPLEMENTS:</b> <input checked="" type="checkbox"/>	<b>FILEABLE</b> <input type="checkbox"/>	<b>NOT FILEABLE</b> <input type="checkbox"/>
<b>OTHER ACTION:</b> <input type="checkbox"/>	<b>APPROVAL</b> <input type="checkbox"/>	<b>APPROVABLE</b> <input type="checkbox"/> <b>NOT APPROVABLE</b> <input type="checkbox"/>

**1. Filing checklist****NDA/BLA Number: 207925****Applicant: Vertex****Stamp Date: 9/17/14****Drug Name: Ivacaftor Granules NDA/BLA Type: New**

On initial overview of the NDA/BLA application for filing:

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>NA</b>	<b>Comment</b>
<b>FORMAT/ORGANIZATION/LEGIBILITY</b>					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	XX			eCTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	XX			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	XX			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?	XX			
5.	Are all documents submitted in English or are English translations provided when necessary?	XX			
6.	Is the clinical section legible so that substantive review can begin?	XX			
<b>LABELING</b>					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	XX			
<b>SUMMARIES</b>					
8.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?	XX			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	XX			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	XX			
11.	Has the applicant submitted a benefit-risk analysis for the product?	XX			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?				505 (b)(2). Ivacaftor tablets (NDA 203188)

	Content Parameter	Yes	No	NA	Comment
<b>DOSE</b>					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product ( <i>i.e.</i> , appropriately designed dose-ranging studies)?  Study Number:	XX			
<b>EFFICACY</b>					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application?	XX			
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?			XX	Efficacy is extrapolated from the ivacaftor tablet (NDA 203188) efficacy data in the $\geq 6$ year old population
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.			XX	
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?				This is a subset of an orphan population. As such use of non-U.S. sites was required.
<b>SAFETY</b>					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	XX			
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product ( <i>e.g.</i> , QT interval studies, if needed)?			XX	This was assessed in the NDA 203188 (ivacaftor tablets)
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	XX			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure <sup>1</sup> ) been exposed at the dose (or dose range) believed to be efficacious?	XX			Given the fact that this is for an orphan indication, an adequate safety database has been established.
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been			XX	Drug is chronically administered.

<sup>1</sup> For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>NA</b>	<b>Comment</b>
	exposed as requested by the Division?				
23.	Has the applicant submitted the coding dictionary <sup>2</sup> used for mapping investigator verbatim terms to preferred terms?	XX			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	XX			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	XX			
<b>OTHER STUDIES</b>					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			XX	
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included ( <i>e.g.</i> , label comprehension, self selection and/or actual use)?			XX	
<b>PEDIATRIC USE</b>					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?			XX	This is an Orphan disease
<b>ABUSE LIABILITY</b>					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			XX	
<b>FOREIGN STUDIES</b>					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?	XX			Orphan disease
<b>DATASETS</b>					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	XX			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	XX			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	XX			
34.	Are all datasets to support the critical safety analyses available and complete?	XX			
35.	For the major derived or composite endpoints, are all of the	XX			

<sup>2</sup> The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>NA</b>	<b>Comment</b>
	raw data needed to derive these endpoints included?				
<b>CASE REPORT FORMS</b>					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	XX			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	XX			
<b>FINANCIAL DISCLOSURE</b>					
38.	Has the applicant submitted the required Financial Disclosure information?	XX			
<b>GOOD CLINICAL PRACTICE</b>					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	XX			Included in the CSR

**IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? \_\_\_yes\_\_\_**

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

*Comments to the Applicant:*

*Efficacy for the 2-5 year old population is extrapolated from the existing data in the older population. As such, the inclusion of data from study 108 in section 14 of the label will be a review issue.*

---

Reviewing Medical Officer

Date

---

Clinical Team Leader

Date

## 2. Filing meeting slides

The image displays two slides from a filing meeting. The top slide is a title slide with a blue header containing the FDA logo and the text 'U.S. Food and Drug Administration Protecting and Promoting Public Health www.fda.gov'. The main content of the slide lists 'NDA 207925', 'Ivacaftor Granules', and 'Vertex'. Below this, it identifies 'Bob Lim' as the presenter for the 'Filing Meeting'. The bottom slide also features the same blue header. The title of this slide is 'General Information'. It contains a bulleted list of key information: Name: Ivacaftor Granules; Class: CFTR potentiator; Approved indication (tablet) - Cystic Fibrosis with "gating" mutation; Proposed Expanded Indication - 2-5 year old population; Dose: 50mg (<14kg), 75mg (≥14 kg) every 12 hours; and Conclusion: Fileable. Both slides have a blue decorative bar at the bottom.

**NDA 207925**  
**Ivacaftor Granules**  
**Vertex**

Bob Lim  
Filing Meeting

**General Information**

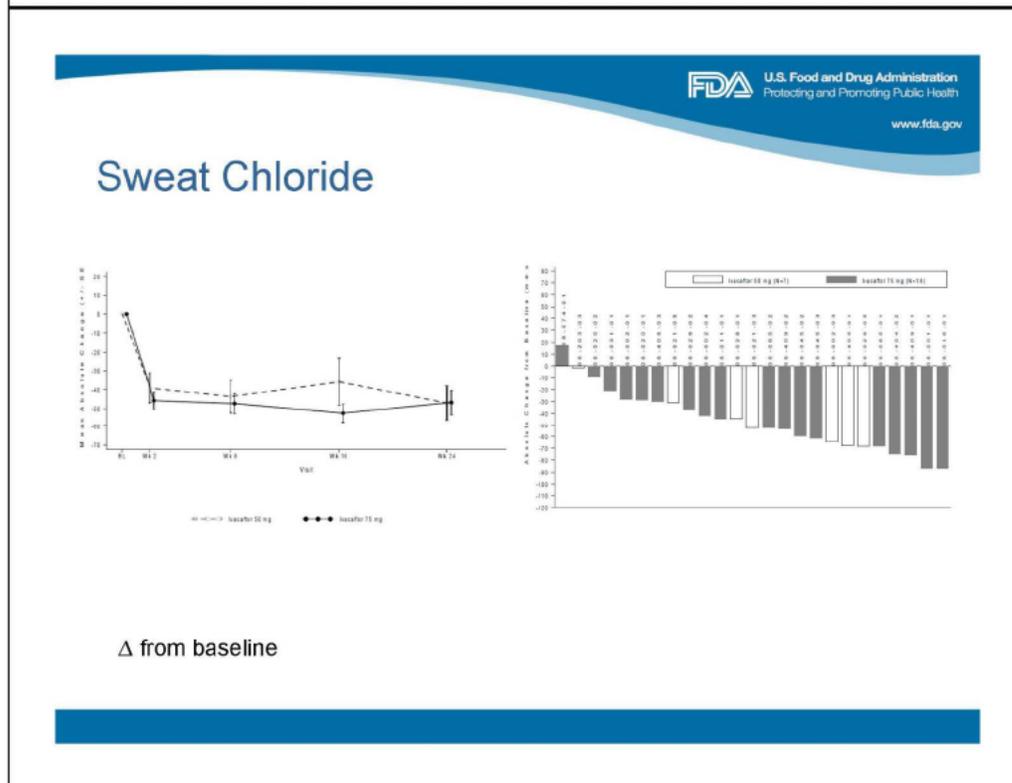
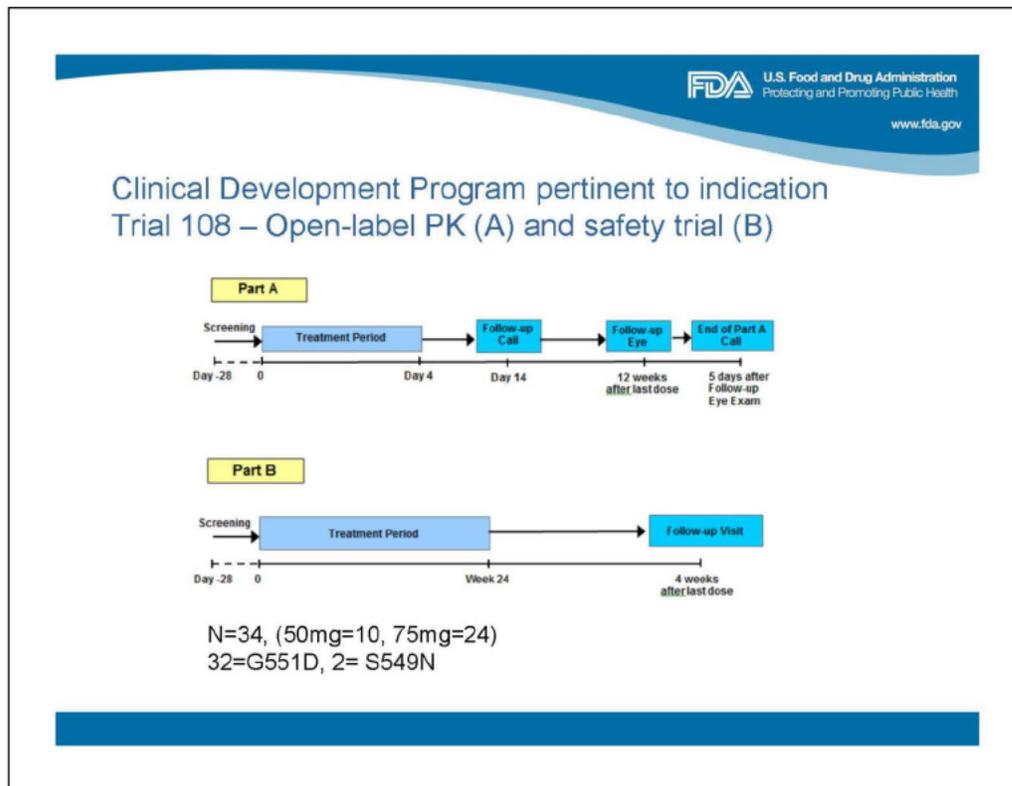
- Name: Ivacaftor Granules
- Class: CFTR potentiator
- Approved indication (tablet)
  - Cystic Fibrosis with "gating" mutation
- Proposed Expanded Indication
  - 2-5 year old population
- Dose: 50mg (<14kg), 75mg (≥14 kg) every 12 hours
- Conclusion: Fileable

## Background

- Ivacaftor tablets
  - approved 1/31/12 for G551D
  - approved 2/21/14 for 8 additional mutations
- Safety Concerns
  - LFT elevations
  - Cataracts in juvenile animal study
- Relevant Interactions
  - Efficacy in 2-5 year olds to be extrapolated from  $\geq 6$  yo
  - Encouraged to enroll at least 30 patients
    - at least 10 who were 2-3 years
  - Encouraged to include non-G551D

## Contents of Submission

- Trial 108:
  - A: PK trial for dosing
  - B: OL safety trial. Included “efficacy endpoints”



## Efficacy Variables

- $\Delta$  from baseline in height, weight, BMI, fecal elastase, and IRT
- $\Delta$  from baseline in height, weight, and BMI for age z-scores
  - Some improvement in weight and BMI z-scores

## Safety

	IVA 50mg N(%)	IVA 75mg N(%)	Total N(%)
Number of patients	10	24	34
Patients with AEs	10 (100)	23 (96)	33 (97)
Patients with AEs leading to death	0	0	0
Patients with SAEs	3 (30)	3 (13)	6 (18)
Patients with AEs leading to dose interruption	4 (40)	7 (29)	11 (32)

- No deaths
- SAEs consistent with CF
- 5 patients with LFT  $\geq 8x$  ULN
  - All with baseline  $\geq 2x$  ULN

## Review Issues

- Review timeline: Request Priority
- Efficacy: no issues
- Safety: no major issues identified
- Label:

Table 5: Effect of KALYDECO on Efficacy Endpoints in Trial 5

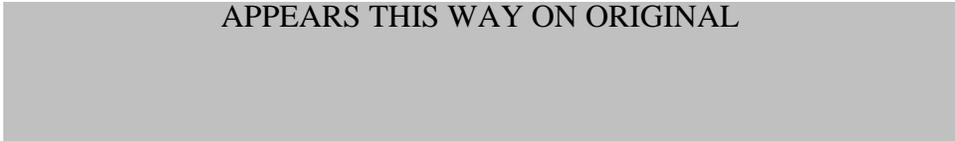
Endpoint	Week 24 Mean (SD) Absolute Changes from Baseline		
	Ivacaftor 50 mg (N = 10)	Ivacaftor 75 mg (N = 24)	Overall (N = 34)
<b>Secondary Endpoints</b>			
Sweat chloride (mmol/L) <sup>45</sup>	-47 (24.26)	-47 (27.58)	-47 (26.19)
Weight (kg) <sup>42</sup>	1.0 (0.42)	1.5 (0.55)	1.4 (0.56)
BMI (kg/m <sup>2</sup> ) <sup>43</sup>	0.33 (0.539)	0.31 (0.549)	0.32 (0.538)
Stature (cm) <sup>44</sup>	2.5 (1.45)	3.5 (0.83)	3.3 (1.17)
<b>Other Endpoints</b>			
Weight-for-age z-score (unit) <sup>46</sup>	0.18 (0.317)	0.21 (0.228)	0.20 (0.251)
BMI-for-age z-score (unit) <sup>46</sup>	0.46 (0.456)	0.34 (0.417)	0.37 (0.424)
Stature-for-age z-score (unit) <sup>47</sup>	-0.2454 (0.44810)	0.0797 (0.21615)	-0.0117 (0.32717)
Fecal Elastase-1 (µg/g) <sup>48</sup>	128 (191.84)	93.5 (128.28)	99.8 (138.35)
Immunoreactive Trypsinogen (IR <sup>2</sup> ) <sup>49</sup>	-24.37 (21.714)	-19.54 (25.111)	-20.70 (23.991)

<sup>45</sup> N=5, ivacaftor 50 mg; N=22, ivacaftor 75 mg; N=27 overall<sup>45</sup>  
<sup>46</sup> N=5, ivacaftor 50 mg; N=21 ivacaftor 75 mg; N=28 overall<sup>46</sup>  
<sup>47</sup> N=7, ivacaftor 50 mg; N=21 ivacaftor 75 mg; N=28 overall<sup>47</sup>

## Review Logistics/Timeline

- PDUFA deadline: 3/17/2015
- Primary clinical review: prior to 2/21/2015

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/s/  
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ROBERT H LIM  
11/19/2014

ANTHONY G DURMOWICZ  
11/19/2014