CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207925Orig1s000

SUMMARY REVIEW

SUMMARY REVIEW OF REGULATORY ACTION

Date:	March 17, 2015
From:	Badrul A. Chowdhury, MD, PhD Director, Division of Pulmonary, Allergy, and Rheumatology Products, CDER, FDA
Subject:	Division Director Summary Review
NDA Number:	207925
Applicant Name:	Vertex Pharmaceuticals
Date of Submission:	September 17, 2014
PDUFA Goal Date:	March 17, 2015
Proprietary Name:	Kalydeco
Established Name:	Ivacaftor
Dosage form:	Oral granules
Strength:	50 mg and 75 mg
Proposed Indications:	Treatment of CF in patients 2 years and older who one of the following mutations in the CFTR gene: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R, or R117H.
Action:	Approval

1. Introduction

Vertex submitted this 505(b)(1) NDA to provide a new dosage form – oral granules, in order to modify the current label of Kalydeco (ivacaftor) to extend the currently approved indications to patients 2 to less than 6 years of age. The proposed dose is 50 mg every 12 hours for patients weighing less than 14 kg, and 75 mg every 12 hours for patients weighting 14 kg or greater. Kalydeco tablet was originally approved in January 2012 for the treatment of cystic fibrosis (CF) in patients 6 years of age and older who have the G551D mutation in the CFTR gene. Subsequently, Kalydeco tablet was approved in February 2014 for the treatment of CF in patients 6 years of age and older for 8 additional mutations in the CFTR gene that are functionally similar to the G551D mutation, and in December 2014 for the treatment of CF in patients 6 years and older who have a R117H mutation in the CFTR gene. The current application is primarily based on clinical pharmacology studies to support the appropriate Kalydeco weight-based dose in patients 2 to less than 6 years of age, and by extrapolating efficacy. This summary review will provide an overview of the application, with a focus on clinical pharmacology studies.

2. Background

Cystic fibrosis (CF) is an autosomal recessive, progressive, and usually fatal genetic disease most common in the Caucasian population. It occurs in approximately one out of every 3,500 children born in the United States and is an orphan disease. CF affects about 70,000 individuals worldwide including about 30,000 in the US. Lack of properly functioning CFTR chloride-conducting ion channel is responsible for the clinical sequelae of CF, including malabsorption of nutrients, and the inability to mobilize

tenacious respiratory secretions, leading to recurrent pneumonia and lung damage. There are about 2,000 mutations in the CFTR gene, some of which, when present in both CFTR alleles, results in the clinical constellation that is CF.

Ivacaftor tablet was originally approved in January 2012 to treat patients with CF with at least one copy of the G551D gene mutation. Patients with G551D mutation make up approximately 4% of the total CF patient population. Ivacaftor tablet was subsequently approved in February 2014 for 8 additional mutations in the CFTR gene that are functionally similar to the G551D mutation. The applicant identified 9 additional mutations for study: S1251N, G178R, S549N, G1244E, S549R, G551S, S1255P, G970R, and G1349D. Patients with these 9 mutations make up approximately 1% of the total cystic fibrosis patients. The clinical data and the pharmacodynamic sweat chloride data were supportive of efficacy of all the mutations studies, except G970R. In December 2014, ivacaftor tablet was approved for an additional mutation, the R117H mutation that is present in approximately 3% of patients with CF.

Relevant to this NDA, in communications with Vertex in March 2011 and in March 2012, the Division supported the development of an oral granule dosage form to extend the indication to lower ages, and stated that the efficacy in younger patients can be extrapolated from the older patients based on clinical pharmacology data showing similar systemic exposure.

3. Chemistry, Manufacturing, and Controls

Kalydeco is an approved marketed product. This NDA provides a new oral granule dosage form. The drug substance in the oral granule is the same in the marketed tablet dosage form. For the drug product, each granule is approximately (b) (4) a target weight of 6.87 mg of which (b) (4) mg is the drug substance, ivacaftor. The excipients are compendial and all are present in the marketed tablets, except for mannitol and sucralose that are added (b) (4). Two dosage strengths of the oral granule drug product are proposed to-be-marketed, 50 mg and 75 mg per packet, with each packet equivalent to one dose. Both strengths are filled with the same oral granules but with different fill weights. The drug product packet itself will be a printed, foil laminate packet (b) (4). The drug will be supplied as 56 packets in a carton. Stability data support a 24-month shelf life. All manufacturing and testing facilities associated with this application have acceptable inspection status.

4. Nonclinical Pharmacology and Toxicology

No new non-clinical toxicology studies were required or performed for this application. The pharmacology and toxicology data were reviewed with the original application.

5. Clinical Pharmacology and Biopharmaceutics

Vertex conducted a clinical pharmacology program to support the oral granule dosage form by linking to the tablet dosage form. This is appropriate as efficacy of ivacaftor can be extrapolated based on comparable ivacaftor exposure in CF patients 6 years of age and older to patients 2 to less than 6 years of age (extrapolation discussed in section 7 below).

The key components of the clinical pharmacology program were 2 studies, Study 015 and Study 108. These two studies used the to-be-marketed formulation. (b) (4) The conduct of the studies 015 and 108 is briefly reviewed below followed by review of the results.

Study 015 was a randomized, open-label, 4-sequence, 4-period, crossover study in healthy male subjects (n=20) designed to investigate (1) the relative bioavailability of the approved 150 mg of ivacaftor dosed as the oral granule formulation versus the 150 mg commercial tablet formulation in the fed state, (2) the effect of food (high-fat meal) on the bioavailability of ivacaftor dosed as 150 mg of the oral granule formulation, and (3) the dose proportionality of the ivacaftor granule formulation between doses of 50 mg and 150 mg in the fed state.

Study 108 was a 2-part, open-label, single-arm study of ivacaftor oral granule in CF patients 2 to less than 6 years of age (n=34, of which 32 had G551D mutation) at doses of 50 mg twice daily for subjects <14 kg and 75 mg twice for subjects ≥14 kg. This study was conducted in two parts, A and B. Part A included a 4-day treatment period where the PK of ivacaftor oral granules was assessed and dosing determined for Part B based on matching the PK of ivacaftor observed in the adult CF patient population. Part B included an open-label 24-week treatment period where safety, PK, pharmacodynamics (sweat chloride) and efficacy data were collected. Population PK modeling was applied in order to evaluate the sparse PK data obtained.

Study 015 showed that relative bioavailability between the tablet formulation and oral granule formulation was similar, and the oral granule formulation had a food effect with food increasing exposure about 3 fold (Table 1). The magnitude of the food effect for the granule formulation was similar to that observed with the commercial tablet formulation. Results of this study confirm similar bioavailability of the oral granule and tablet formulations, and justify using this oral granule formulation for further evaluation in Study 108.

Table 1. Study 015, Summary Analysis of relative bioavailability and food effect

	Parameter	Mean Ratio	90% CI
Kalydeco Tablets vs Oral Granules, Fed State	Cmax	0.92	0.75, 1.12
	$AUC_{0-\infty}$	0.95	0.84, 1.08
	$AUC_{0-tlast}$	0.95	0.84, 1.09
Kalydeco Oral Granules, Fed state vs Fasting state	Cmax	3.70	3.03, 4.54
	$AUC_{0-\infty}$	2.82	2.48, 3.20
	$AUC_{0-tlast}$	3.02	2.65, 3.44

Study 108 showed similar ivacaftor exposure levels in adults compared to CF patients 2 to less than 6 years of age with 50 mg and 75 mg oral granule formulation based on population PK analysis (AUC data are shown in Figure 1). The analysis also showed that CF patients 6-11 years of age had 87% higher mean AUC compared to adult patients administered ivacaftor 150 mg every 12 hours (Figure 1). On analyses of various covariates and predictors, body weight was the most important predictor of ivacaftor exposure. For patients 2 to less than 6 years of age and weighing less than 14 mg, 50 mg ivacaftor every 12 hours had similar exposure compared to adult administered ivacaftor at the approved dose of 150 mcg every 12 hours. For patients 2 to less than 6 years of age, but weighing 14 kg or greater, 75 mcg ivacaftor every 12 hours provided similar exposure compared to adult administered ivacaftor at the approved dose of 150 mcg every 12 hours. This analysis supports the age and weight based dosing regimen of ivacaftor.

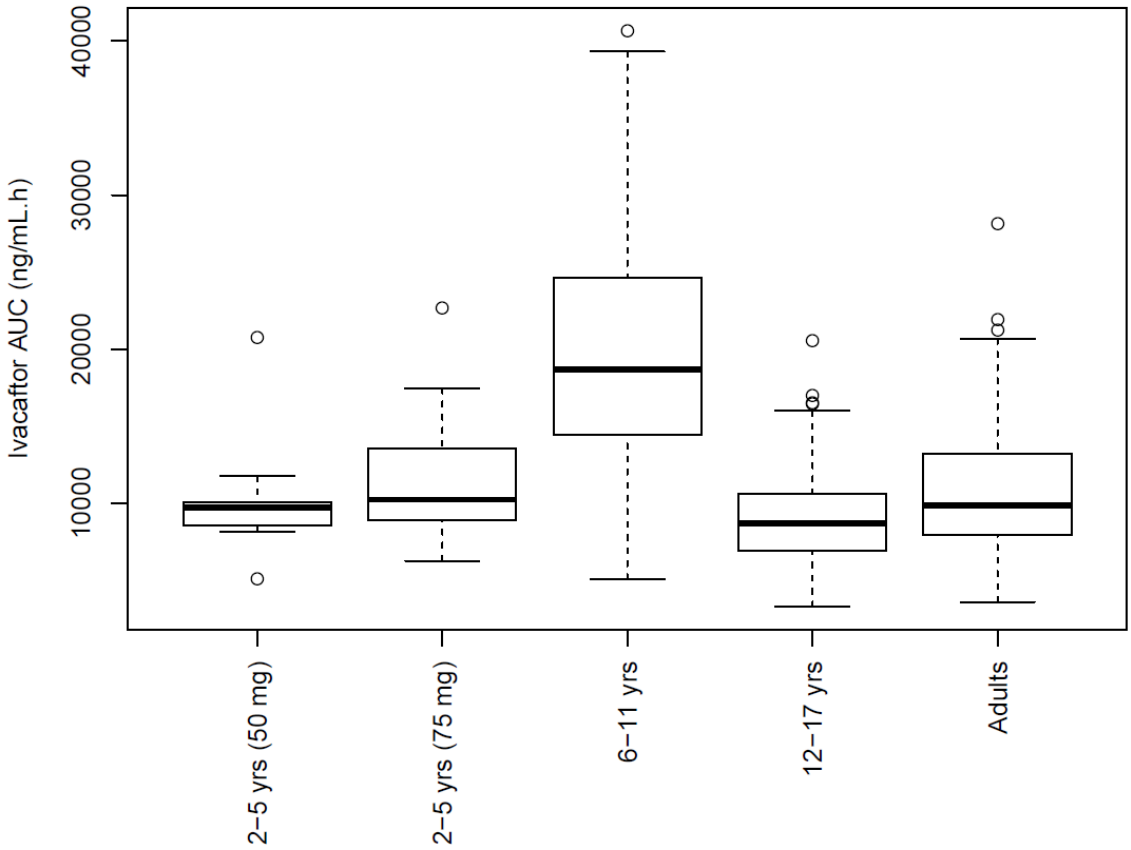

Figure 1. Study 108, Ivacaftor AUC distribution by age group.

Study 108 Part B collected pharmacodynamics (sweat chloride), efficacy, and safety data. Sweat chloride data showed positive effect (mean absolute change from baseline was -45 mmol/L). Exploratory efficacy assessment (weight gain, stature, fecal elastase, trypsinogen, spirometry, pulmonary exacerbation, etc.,) also showed numerical favorable response for some measures. A formal statistical evaluation was not warranted or appropriate for this open-label uncontrolled study. Safety assessment included recording of adverse events, clinical labs, ECGs, vital signs, ophthalmologic assessments, and physical exams.

6. Clinical Microbiology

There are no outstanding clinical microbiology issues.

7. Clinical and Statistical – Efficacy

a. Overview of the clinical program

No clinical study with efficacy measures as primary assessments were required or conducted for this application. The clinical program consists primarily of two studies (Study 015 and Study 108) as discussed in section 5 above. These were primarily clinical pharmacology studies.

b. Design and conduct of studies

As discussed in section 5 above, Study 108 Part B assessed sweat chloride (a pharmacodynamics measure of CFTR function), weight gain, stature, fecal elastase, trypsinogen, spirometry, pulmonary exacerbation, etc. In this study patients received ivacaftor at an age and weight based dosing (described in section 5 above) for a 24-week period. A total of 34 patients (32 had G551D mutation) participated in Study 108 Part B. One patient was discontinued from the study because of increase in liver enzyme (discussion in section 8 below).

c. Efficacy findings and conclusions

In Study 108 Part B, some of the efficacy measures showed favorable numerical response. Favorable efficacy is expected because ivacaftor exposure in these patients 2 to less than 6 years of age is similar to those with older patients with CF. A formal statistical evaluation was not warranted or appropriate for this open-label uncontrolled study.

Efficacy for CF patients 2 to less than 6 years of age is being partially extrapolated for this application. The extrapolation is partial because the dose is not extrapolated; dose for patients 2 to less than 6 years of age is based on clinical pharmacology data. Also, safety is not extrapolated. Extrapolation of efficacy for this application is appropriate, as the pathophysiology of CF and the effect or ivacaftor on CFTR are the same regardless of age such that CF patients 2 to less than 6 years of age who possess one of the mutations in the CFTR gene for which ivacaftor is indicated would be expected to obtain benefit. For this application, extrapolation is based on similar ivacaftor exposure in patients 2 to less than 6 years of age compared to older patients (discussed in section 5 above), expected similar pharmacodynamics effect that is supported by sweat chloride data, and

supportive efficacy and safety data from study 108 Part 8. Separate confirmatory efficacy data for various age groups and for different CFTR mutations is not necessary. This use of extrapolation for this application is consistent with Agency precedence. [1]

(b) (4)

The Agency policy on Clinical Studies Section of Labeling is outlined in Guidance for Industry on Clinical Studies Section issued in 2006.[2] As detailed in the Guidance, the Clinical Studies Section of the label is expected to identify and include studies that facilitate safe and effective use of drugs and provide a concise summary of such studies. This section is not intended to describe all available data. Studies that reach the same conclusion should be omitted. Clinical Studies Section should include adequate and well-controlled studies that: (1) Provide primary support of effectiveness, (2) Provide other important information about effectiveness not provided in the primary support of effectiveness, such as differential effect in population subsets, lack of effectiveness in situations or on endpoints where effectiveness is expected, information on dose selection or adjustment, information on the nature and size of a treatment effect where the effect is small, and (3) Studies that prospectively evaluate safety.

(b) (4)

[1] Dunne J, Rodriguez WJ, Murphy D, et al., Extrapolation of adult data and other data in pediatric drug-development programs. Pediatrics 2011; 128:1242-9 (Epub 2011 October 24)
[2] Guidance for Industry: Clinical Studies Section of Labeling for Human Prescription Drugs and Biologic Products – Content and Format. Issued by CDER and CBER in January 2006

(b) (4)

8. Safety

a. Safety database

The safety assessment of ivacaftor for CF patients 2 to less than 6 years of age is based on studies described in Section 5 above, and safety data from other sources. The primary safety issues of interest are liver injury, and lens opacification.

b. Safety findings and conclusion

The safety data submitted and reviewed with this submission do not raise any new safety concerns in the CF patients 2 to less than 6 years of age.

There were no deaths reported in CF studies in patients 2 to less than 6 years of age.

Serious Adverse Events (SAE) reported were those expected of patients with CF. There were a total of six SAEs reported that included CF exacerbation, device-related sepsis, live enzyme elevation, positive pseudomonas culture, vomiting, and convulsion. None of these raise new safety concerns for CF patients 2 to less than 6 years of age.

One patient permanently discontinued treatment due to an adverse event. The patient was a 2 year old male who developed an increase in ALT > 8 times the upper limit of normal. Notably, the child had an ALT that was > 3 times the upper limit of normal at baseline. A liver biopsy was performed 3-weeks which showed non-specific findings. Approximately 2 months after discontinuation the patient's ALT had decreased to 58 U/L.

Eleven patients temporarily interrupted ivacaftor treatment due to adverse events; 3 for LFT elevations, 2 for vomiting, and 1 for croup, device-related sepsis, gastroenteritis, retching, rash, and increased cough.

Common adverse events for both the 50 and 75 mg ivacaftor treatment groups were consistent with those commonly observed in the CF population and in young children

such as increased cough, nasal congestion, rhinorrhea, upper respiratory tract infection, vomiting, pyrexia, and CF exacerbation.

Liver injury is a safety finding of interest because increase AST and ALT and liver-related adverse events were observed in the prior ivacaftor studies, and increase in transaminases are included in the Warning and Precautions section of the Kalydeco label. It has been difficult to ascertain causality to ivacaftor because CF-related liver-disease is common in CF patients and occurred in both ivacaftor and placebo treatment arms in previous studies. In Study 108, a total of five adverse events (one SAE described above, and 4 non-serious adverse events) were related to increased transaminases. During protocol specified monitoring of transaminases, 5 patients out of 34 (14.7%) had increased transaminases, most of these were in patients who also had transaminases higher than normal at baseline. The lack of placebo arm in Study 108 makes it difficult to relate the liver related adverse events to ivacaftor. The nature and magnitude of liver related adverse events in CF patients 2 to less than 6 years of age generally is similar to those that were observed in older children. The current Warning and Precaution labeling on transaminases are adequate to convey this safety risk.

Lens opacification is a safety finding of interest because of findings of cataracts or lens opacification as an ivacaftor-related toxicity in a juvenile rat nonclinical study. Ophthalmological evaluation were conducted at baseline, and during and after the 24-week ivacaftor treatment in the 34 patients enrolled in Study 108 Part B. No cataracts or lens opacifications were identified.

c. REMS/RiskMAP

No post-marketing risk evaluation and mitigation strategies are recommended.

9. Advisory Committee Meeting

An advisory committee meeting was not convened for this application. The data submitted in this NDA are straightforward and did not warrant discussion at an Advisory Committee meeting.

10. Pediatric

CF is an orphan disease and not subject to PREA. Based on the knowledge that CF is a genetic disease, which can manifest at birth, the applicant is appropriately addressing dosing of ivacaftor in younger CF patients primarily by PK data, with supporting safety data.

11. Other Relevant Regulatory Issues

a. DSI Audits

DSI audits were not conducted for this submission. No irregularities were identified that would impact data integrity. During review of this application, the review team did not

identify any irregularities that would raise concerns regarding data integrity. All studies were conducted in accordance with accepted ethical standards.

b. Financial Disclosure

The applicant submitted acceptable financial disclosure statements. No investigators with significant equity interest in Vertex were involved in studies used to support this NDA.

c. Other

There are no outstanding issues with consults received from the OPDP, DMEPA, or from other groups in CDER. The CDRH was consulted during earlier review of Kalydeco applications to help address the adequacy of available tests for identification of specific CF gene mutation identification. CDRH noted that there are several FDA-cleared diagnostic tests available that can detect various mutations that are subject of this application. Furthermore, identification of specific CFTR genotype in patients with CF is now almost a standard of care of CF patients.

12. Labeling

a. Proprietary Name

The proposed proprietary name Kalydeco was previously reviewed by DMEPA and found to be acceptable.

b. Physician Labeling

Vertex submitted a label that contained information from studies submitted with this application. (b) (4) For reasons discussed in section 7 above, no new language will be added to Section 14 of the label based on Study 108. Various other sections of the label will be modified to include findings from the submitted studies to inform use of the granule dosage form in patients 2 to less than 6 years of age.

c. Carton and Immediate Container Labels

These were reviewed by various disciplines of this Division and DMEPA, and found to be acceptable.

d. Patient Labeling and Medication Guide

There is a Patient Counseling Information (Instruction for Use and Patient Package Insert) that has been reviewed previously by the Division, OMPP, and other groups within the Center and found to be acceptable. There is no Medication Guide for this product.

13. Action and Risk Benefit Assessment

a. Regulatory Action

Vertex has submitted adequate data to support approval of the oral granule dosage form for CF patients 2 to less than 6 years of age at a dose of 50 mg every 12 hours for patients weighing less than 14 kg, and 75 mg every 12 hours for patients weighting 14 kg or greater. The action on this NDA will be Approval.

b. Risk Benefit Assessment

The overall risk-benefit assessment of ivacaftor supports approval of the oral granule dosage form and extending the currently approved indications to patients 2 to less than 6 years of age. The submitted safety data show that the risk of ivacaftor in patients 2 to less than 6 years of age was consistent with the known safety profile in older patients. The dose of ivacaftor for patients 2 to less than 6 years of age was based on clinical pharmacology data, and efficacy for this age group is extrapolated from older patients. The principles of extrapolation of efficacy (discussed in section 7 above), dose selection based on clinical pharmacology program (discussed in section 5 above), and the submitted safety data show favorable risk-benefit for ivacaftor in patients 2 to less than 6 years of age.

c. Post-marketing Risk Management Activities

No post-marketing risk evaluation and management strategies are recommended.

d. Post-marketing Study Commitments

No PMR or PMC studies are recommended.

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BADRUL A CHOWDHURY
03/17/2015