CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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OFFICE DIRECTOR MEMO

Summary Basis for Regulatory Action

Date	January 30, 2012
From	Curtis J Rosebraugh, MD, MPH Director, Office of Drug Evaluation II
Subject	Summary Review
NDA/BLA # Supp #	203188
Applicant Name	Vertex pharmaceuticals, Inc.
Proprietary / Established (USAN) Names	Kalydeco (Ivacaftor)
Dosage Forms / Strength	150-mg tablets
Proposed Indication(s)	For the treatment of cystic fibrosis (CF) in patients age 6 years and older who have a G551D mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene
Action:	*Approval*

1. Introduction and Discussion

This review will be a brief summary of the basis for the regulatory action regarding ivacaftor and the reader should review the action package for more detail. Ivacaftor is a first in class new molecular entity for cystic fibrosis (CF) that potentiates the function of the cystic fibrosis transmembrane conductance regulator (CFTR) protein at the cell-surface membrane.

CF is a serious, debilitating, autosomal recessive genetic disease leading to premature mortality that affects ≈ 30,000 patients in the United States. Approximately one in every 3,500 children in the United States are born with CF each year. While the disease can be found in all ethnic and racial groups, it is most common in Caucasians. CF is caused by a defective gene (over 1800 known mutations) that code for the CFTR protein. The CFTR protein provides a cell-surface chloride ion channel that allows for the regulation of salt and water absorption. Lack of properly functioning CFTR protein leads to tenacious secretions that progressively affects mainly the pulmonary tract (infection, inflammation, bronchiectasis-leading to fibrosis and respiratory failure) and gastrointestinal tract (malabsorption of nutrients-poor weight gain). There is no cure for cystic fibrosis, affected patients have a median age of survival of the mid-30s. Present therapies only treat symptoms and sequelae of the disease and include antibiotics (both systemic and inhaled) for pulmonary infections, mucolytics to thin secretions, oral pancreatic enzymes to aid in nutrient absorption and bronchodilators to aid in breathing.

Mutations in the CFTR gene can result in reduced quantity and/or quality of the CFTR protein. As Dr. Witzmann discusses, the main mutations are of two varieties known as Class 2 or Class 3. Class 2 mutations (example F508-87% of all patients in United States have at least one allele) cause improper folding and processing of the protein leading to degradation in the endoplasmic reticulum and failure of the protein to reach the cell-surface membrane. Class 3

mutations (such as G551D) create proteins that reach the cell surface, but do not activate normally and are termed "gating mutations".

Ivacaftor acts to restoring some of the defective function of the CFTR protein that reaches the cell surface by increasing the probability of the channel being open, ultimately enhancing chloride transport. Ivacaftor's action is highly selective to the protein that has mutations in the G551D gene, and therefore it does not have any effect on CFTR function in patients that are homozygous for other mutations that do not reach the cell-surface (the most common of which is the F508-del mutation). The proposed dosage regimen is 150 mg orally every 12 hours with fat-containing food.

The efficacy of ivacaftor was demonstrated in two trials, one in children aged 6-11 years and a second in patients greater than 12 years old. Both trials were of 48 weeks duration and demonstrated improvement in lung function (FEV1) which was the primary endpoint. Clinically important secondary endpoints such as delayed time to first pulmonary exacerbation and improvement in weight gain were also demonstrated.

Adverse events were generally well-tolerated. Pre-clinical studies revealed dose-related hepatic toxicities in rodents with an adequate margin of safety. Clinical studies did not reveal overt hepatic toxicity, although the trials were small. The sponsor has proposed labeling to monitor hepatic function.

Overall, there is a robust clinical benefit for ivacaftor. It is premature to know if this will result in improved survival, but use of ivacaftor does have cause for optimism, at least in the small percentage of patients with CF for which it is intended. While there was not overt hepatic toxicity noted, there may be some subtle changes (increased shift of AST?) such that this issue may need further observation for the potential for rare liver toxicity. However, due to the limited population (N≈1200) that will receive this drug it is unlikely this issue could be further explored or defined before approval. Also, due to the limited population that will receive ivacaftor, there will be limited patients placed at risk should rare events be noted to occur associated with drug use. At present, available therapies only manage downstream consequences of CF (the result of diminished CFTR function) and there are not any other therapies that may actually treat the underlying cause of CF. As ivacaftor is targeted for the cause of CF, there clearly is a favorable risk:benefit consideration that allows approval and marketing.

Efficacy

Efficacy has been thoroughly covered by Drs. Hoberman, Durmowicz, Chowdhury and Witzmann and I will not present this in detail. There were two Phase 3 Trials, 102 (subjects 12 years and older) and 103 (subjects 6 to 11 years old) which had a primary endpoint of absolute change in percent predicted FEV1 through week 24. Important secondary endpoints evaluated included time to first pulmonary exacerbation (Trial 102 only) and change in weight, all measured through weeks 24 and 48. Also evaluated were CFQ-R scores (respiratory health domain only as the CFQ-R is not a validated PRO by the Agency) and change in sweat

chloride concentration. Below are two tables summarizing the results from Dr. Hoberman's review (Page 13-14).

Table 1: Study 102: Results for Primary and Secondary Efficacy Endpoints – Full Analysis Set

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

Source: Module 2.7.3 Summary of Clinical Efficacy page 25

Table 2: Study 103b: Results for Primary and Secondary Efficacy Endpoints – Full Analysis Set

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

Source: Module 2.7.3 Summary of Clinical Efficacy page 33

The primary method of analysis used by the sponsor was Mixed Model Repeated Measures (MMRM). There was little missing data and multiple other imputation methods demonstrated compared results (table below from Dr. Hoberman's review, Page 15). These analyses demonstrated that the results were robust regardless of the statistical methodology, removing any potential controversy over imputation method for this application.

Table 3: Study 102: Absolute Change From Baseline in Percent Predicted FEV_1, Week 24, Sensitivity Analysis, Full Analysis Set

		Overall Absolute Change From Baseline		Treatment Effect (VX-770 vs Placebo)	
Sensitivity Analysis	Treatment Group	n	LS Mean	Difference (95% CI)	*P*-value
MMRM With Toeplitz Covariance[a]	Placebo	78	-0.3971		
	VX-770	83	10.6010	10.9981 (9.0047, 12.9914)	< 0.0001
MMRM With Compound Symmetry Covariance[a]	Placebo	78	-0.4104		
	VX-770	83	10.6016	11.0120 (9.0179, 13.0060)	< 0.0001
MMRM With First Order Autoregressive Covariance[a]	Placebo	78	-0.3777		
	VX-770	83	10.6084	10.9861 (9.1214, 12.8509)	< 0.0001
ANCOVA[b]	Placebo	78	-0.3934		
	VX-770	83	10.5875	10.9809 (8.9795, 12.9822)	< 0.0001
ANCOVA With LOCF[c]	Placebo	78	-0.6482		
	VX-770	83	10.5511	11.1993 (9.1094, 13.2892)	< 0.0001
ANCOVA With Worst Case Imputation[c]	Placebo	78	-0.7317		
	VX-770	83	10.4302	11.1619 (9.0798, 13.2440)	< 0.0001
ANCOVA With Dropout Reason-based Imputation[c]	Placebo	78	-0.6602		
	VX-770	83	10.4500	11.1102 (9.0274, 13.1930)	< 0.0001
Stratified Wilcoxon[d]	Placebo	78	-0.0994		
	VX-770	83	9.3603		< 0.0001

Source: Table 14.2.1.2.3.1

ANCOVA: analysis of covariance; CI: confidence interval; FEV_1: forced expiratory volume in 1 second; LOCF: last observation carried forward; LS: least squares; MMRM: Mixed-Effects Model for Repeated Measures.

[a] Estimates were obtained from MMRM with dependent variable absolute change from baseline, fixed effects for categorical visit (Day 15, Week 8, Week 16, and Week 24) and treatment group, and adjustment for continuous baseline values of age and percent predicted FEV_1, using a Toeplitz, compound symmetric, and AR(1) covariance matrix, as indicated.

[b] ANCOVA on the mean change from baseline through Week 24, with treatment as the main effect, and adjustment for continuous baseline values of age and percent predicted FEV_1; missing values were not imputed.

[c] Identical ANCOVA model as (b) with missing values imputed by LOCF method, worst case method, and dropout reason based method, as indicated.

[d] Stratified (by baseline percent predicted FEV_1 severity and age group) Wilcoxon rank-sum test of the mean change from baseline. Medians are displayed in the LS Mean column.

Source: Study 102 Study Report page 114

As can be seen above in the first two tables, the absolute change in per cent predicted FEV1 was about 10-12% depending upon the trial. This change was apparent by Day 15 and for the most part maintained through Week 48. Using Trial 102 as an example, this equates to a mean absolute change in per cent predicted FEV1 from baseline through Week 24 of 10.4% for the ivacaftor group compared to -0.2% for the placebo group (Patients with CF typically have declines of 1-4% per year). Trial 103 demonstrated similar results. This is an impressive increase in FEV1 and would be considered by most to be clinically important. Secondary endpoints for both trials were supportive of the primary endpoint and represented clinically important findings. As an example, Study 102 the pulmonary exacerbation-free rate was 78% and 67% in the ivacaftor groups through Week 24 and Week 48, compared to 51% and 41% in

the placebo group for the same time periods. Mean change in weight was 3.1 kg in the ivacaftor group compared to 0.4 kg in the placebo group at Week 48. While perhaps not an indication of a clinically important endpoint, it is provocative that the mean change in sweat chloride concentration was -48.7 mmol/L in the ivacaftor group versus -0.6 mmol/L in the placebo group (baseline median values were ≈100) from baseline through Week 48 (>60 mmol/L positive for CF, < 40 mmol/L for older children and adults and <30 mmol/L for infants considered normal). As mentioned, while the changes in sweat chloride demonstrate pharmacodynamic relevance, it is also instructive that that there is not a correlation between FEV1 improvement and sweat chloride change as noted in the graph below (Dr. Chowdhury's review, page 6).

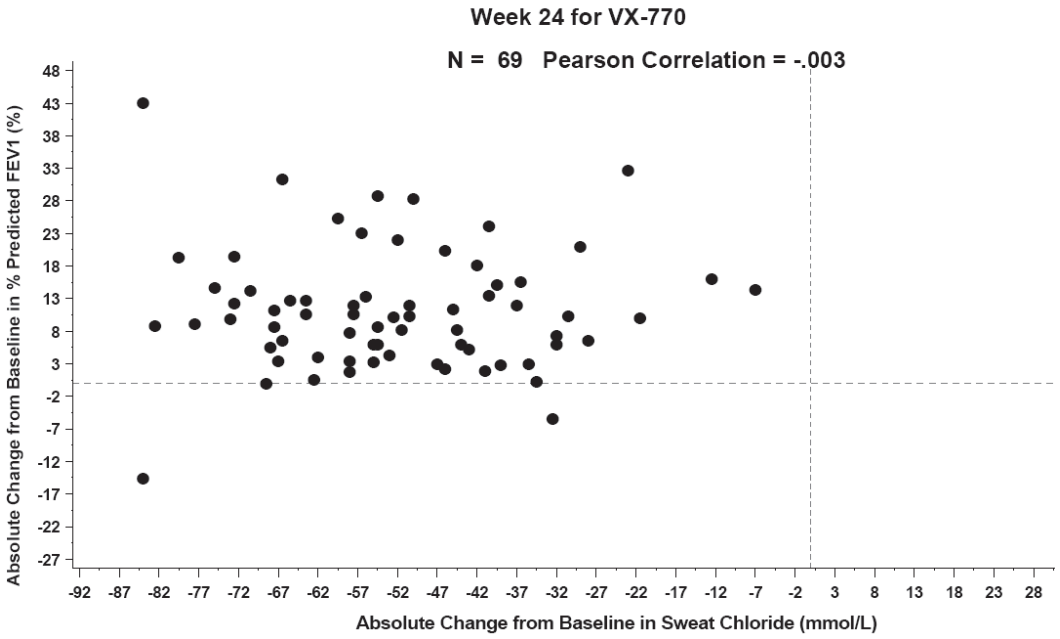

Figure 1. Scatter plot of absolute change from baseline in percent predicted FEV1 and absolute change from baseline in sweat chloride for study 102.

Therefore, change in sweat chloride, while of interest, may not be predictive of outcome. There was a positive correlation between FEV1 function and change in weight (although weak). There were 18 subjects that received ivacaftor while not achieving a change from baseline in FEV1 of at least 5% at Week 24. For the "non-responders" to ivacaftor use as measured by FEV1, an examination of covariates did not reveal any patterns. However, within this group, 13 subjects did have a weight gain greater than the mean of the overall group and also had the same improvement in pulmonary exacerbation rates as the drug treated group. This indicates that if the subject had an improvement in FEV1, or a weight increase, the rate of pulmonary exacerbation rates improved as well.

Safety

Safety data is limited (N=221 subjects dosed 150 mg every 12 hours), but this is to be expected considering the size of the population for which ivacaftor is indicated. While there were dose-related findings of liver toxicity in rodent studies, an adequate margin exists and there were not findings consistent with hepatotoxicity in the clinical trials. Dr. Witzmann has two tables reproduced below summarizing transaminase elevations.

Table 4: Adverse Events of Transaminase Elevations, G551D Safety Set

	Phase 3 Safety Data, Adverse Events (Studies 102, 103 Part B)		
Preferred Term	**Placebo N=104 n (%)**	**VX-770 N=109 n (%)**	**Difference %**
AST Increased	4 (3.8)	8 (7.3)	+ 3.5
Hepatic Enzyme Increased	3 (2.9)	5 (4.6)	+1.7
ALT Increased	8 (7.7)	7 (6.4)	-1.3
[Source: Module 5.3.5.3.28, ISS, Table 2.3.3.3]			

Table 5: Cumulative Incidence of Maximum On-Treatment Transaminase Values, Safety Set

	Cumulative Incidence[a] in Safety Set (Studies 102, 103B, 104A)									
	<2 x ULN n (%)		≥2 to <3 x ULN n (%)		≥3 to <5 x ULN n (%)		≥5 to <8 x ULN n (%)		≥8 x ULN n (%)	
Parameter	**Plcbo N=131**	**VX-770 N=221**	**Plcbo N=131**	**VX-770 N=221**	**Plcbo N=131**	**VX-770 N=221**	**Plcbo N=131**	**VX-770 N=221**	**Plcbo N=131**	**VX-770 N=221**
ALT	115 (88)	191 (86)	16 (12)	30 (14)	8 (6)	12 (5)	3 (2)	4 (2)	2 (2)	2 (1)
AST	119 (91)	203 (92)	12 (9)	18 (8)	5 (4)	7 (3)	2 (2)	5 (2)	1 (1)	4 (2)
ALT or AST[b]	109 (83)	185 (84)	22 (17)	36 (16)	11 (8)	14 (6)	3 (2)	6 (3)	2 (2)	4 (2)

a= Cumulative Incidence describes each patient tabulated for every category, such that a patient with AST >8x ULN is calculated in each of the categories, from ≥2 to <3 x ULN through the last ≥8 x ULN
b= each patient tabulated only once according to level of maximum on-treatment transaminase, except for the <2 ULN column, which included patient for whom both maximum AST and ALT were <2 x ULN

[Source: Module 5.3.5.3.28, ISS, Table 2.2.4.8, and Module 2.7.4, Summary of Clinical Safety, Table 25]

Transaminitis by itself certainly does not mean that a drug will be hepatotoxic as there are many drugs that increase liver function tests without compromising liver function. I do not find the above data compelling that there is a liver toxicity finding or even disturbing transaminitis shifts. It is also difficult to evaluate this data as most CF patients have some pre-existing liver dysfunction due to cholestasis. However, due to the limited size of the database,

it would be reasonable to recommend monitoring of liver function as the sponsor has suggested (because of the pre-clinical finding) during treatment with ivacaftor.

Other common adverse events more common with ivacaftor use than placebo use included headache, rash, dizziness and upper respiratory tract.

Ivacaftor is metabolized by CYP 3A, and has the potential to interact with several classes of drugs that interact with this pathway.

Advisory Committee Meeting

An Advisory Committee Meeting was deemed unnecessary as outside expertise was not necessary; there were no controversial issues that would benefit from advisory committee discussion. Also, ivacaftor use did not raise significant public health questions regarding its use in the approximately 1200 patients for which it is indicated.

Conclusions and Recommendations

Ivacaftor has demonstrate robust efficacy as measured by lung function and supported by secondary endpoints such as decreased pulmonary exacerbations and improved weight gain. While it is premature to know if ivacaftor will alter the course and outcome of CF in patients with the G551D genetic defect, based on its action at the 'root' of the problem there is great potential that this therapy may be a 'game-changer' in the small subgroup of patients with at least one G551D allele defect. As is always the case, no drug therapy is without risk, some known and some theoretical. Such is also the case with ivacaftor. While most of the adverse events were common, non-serious and reversible, there is a small, but real, concern regarding potential for hepatic toxicity. The database is too small for ivacaftor to know if this concern is real. However, given the clear benefit, lack of any other therapy that may alter the long-term outcome of CF, and limited exposure to the population (≈1200 patients), there clearly exists a favorable risk:benefit calculation that allows marketing with adequate clinical monitoring.

I recommend Approval with appropriate labeling.

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/s/

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