

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA: NDA 207-925

Drug Name: Kalydeco (ivacaftor) Granules

Indication(s): Treatment of cystic fibrosis

Applicant: Vertex, Inc

Date(s): Received: September 17, 2014
PDUFA: March 17, 2015

Review Priority: Standard

Biometrics Division: Division of Biometrics II

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Keywords: NDA review, clinical studies, open-label

SUMMARY

Ivacaftor (IVA) tablets (NDA 203,188) was approved on January 31, 2012, for the treatment of cystic fibrous (CF) in patients 6 years of age or older who have a *G551D* mutation in the *CFTR* gene. On February 21, 2014, the indication was expanded to include the following additional mutations: *G1244E*, *G1349D*, *G178R*, *G551S*, *S1251N*, *S1255P*, *S549N*, or *S549R*. In December 2015, the *R117H* mutation was added. This application evaluates a new granule formulation of IVA and proposes to expand the indication to include children between 2 and 5 year of age. According to the applicant, the granule formulation is more pediatric friendly, as the granules may be mixed with soft food or liquid for administration.

Vertex submitted the results from a single study that evaluated children 2 to 5 years of age. Study VX11-770-108 (108) was an open-label, uncontrolled trial that was conducted in two parts. Part A evaluated the pharmacokinetics of IVA granules and part B evaluated the safety. Part B also evaluated some pharmacodynamic and efficacy-related endpoints during a 24-week open-label, uncontrolled treatment period. The efficacy endpoints evaluated in Part B included weight, stature, pulmonary function, and sweat chloride.

The IVA doses examined in this study were 50 mg twice daily for children weighing less than 14kg and 75mg twice daily for those weighing more than 14kg.

REVIEW

Since this was an open-label, uncontrolled, non-randomized, relatively small study (n=34), there were no formal statistical analyses with respect to the efficacy evaluated in Part B of study 108. Table 1 reports a descriptive summary for sweat chloride and weight at baseline, Week 24, and change from baseline to Week 24. I only reported information for those subjects that had values for baseline and Week 24.

Table 1. Summary of pharmacodynamic and efficacy data in Part B of study 108

endpoint	variable	dose of ivacaftor (bid)	
		50 mg	75 mg
	n	7	18
Sweat chloride, mmol/L mean, 95% CI	Baseline	93.1 (78.0, 108.1)	102.2 (96.0, 108.3)
	Week 24	46.0 (23.3, 68.7)	55.4 (43.7, 67.1)
	change	-47.1 (-69.5, -24.6)	-46.8 (-60.5, -33.1)
	n	9	24
Weight, kg Mean (95% CI)	Baseline	12.5 (11.7, 13.3)	16.8 (16.0, 17.6)
	Week 24	13.5 (12.7, 14.3)	18.3 (17.5, 19.1)
	Change	1.0 (0.7, 1.3)	1.5 (1.3, 1.7)

Source: Reviewer

With regard to weight, at week 24, both IVA dose groups demonstrated numerical 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 the study did not contain a placebo control and the age group studied 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. As such, the observed numerical increases in weight and stature may reflect normal development, rather than a treatment effect. With regard to BMI, the mean change from baseline was 0.33 kg/m² and 0.31 kg/m² for the IVA 50mg and 75mg groups, respectively.

Vertex also reported change from baseline in percent predicted FEV₁ (ppFEV₁) for those patients who could perform spirometry. Of the 34 patients evaluated, 20 could perform spirometry, and of these 17 were in the high dose group. At week 24, the change from baseline in ppFEV₁ was -12.5% and 4.3% in the IVA 50mg and IVA 75mg groups. Given the age of the patients and the relatively small sample size, the reliability of the spirometry data is questionable.

According to the clinical pharmacology review, the results from Part A of study 108 demonstrated that when IVA granules was administered every 12 hours for 4-days, systemic exposures matched that seen for ivacaftor tablets in the adolescent/adult population. In Part B, regardless of dose, after 24 weeks of treatment with IVA granules, the decrease in the pharmacodynamic endpoint sweat chloride was consistent with changes observed with the approved mutations.

The results from part B did not reveal any new safety signals.

CONCLUSION

Since this was an open-label, uncontrolled study, a formal statistical evaluation of efficacy was not conducted. Therefore, from a statistical perspective, based on the endpoints assessed, evidence of efficacy was not established in the current study. However, pharmacokinetic (exposure) and pharmacodynamic (sweat chloride) data support a biological effect for ivacaftor in CF patients 2 to 5 years of age that is similar to that observed for older CF patients for which ivacaftor is approved. Efficacy data collected in this uncontrolled study are in general insufficient to determine a real benefit attributable to ivacaftor either because of the lack of a placebo group (weight, stature) or because of the small amount and inherent variability of data (pulmonary function). Given the supportive pharmacokinetic and pharmacodynamic data, the clinical review team is recommending approval of ivacaftor granules for children between the ages of 2 and 5 based on the extrapolation of efficacy from existing data in an older patient population. There is no objection to this approach.

LABELING

There have been several internal discussions within the Office of New Drugs regarding the inclusion of open label (b) (4) safety data in product labels. Inclusion of open-label safety (b) (4) data is outlined in two current guidance's for industry.

- Clinical Studies Section of Labeling for Human Prescription Drugs and Biologic Products – Content and Format (June 2006)
- Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products – Content and Format (June 2006).

(b) (4)

(b) (4)

With respect to safety, the information obtained from this study is consistent with the safety information in the currently label which was obtained from double-blind, placebo-controlled clinical trials. (b) (4)

(b) (4)

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/s/

DAVID M PETULLO
02/24/2015

GREGORY P LEVIN
02/24/2015
I concur.