CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207925Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA	207925
Submission Date	9/17/2014
Brand Name	Kalydeco granules
Generic Name	Ivacaftor
Clinical Pharmacology Reviewer	Jianmeng Chen, M.D., Ph.D.
Pharmacometrics reviewer	Dinko Rekic, MSc, Ph.D.
Pharmacometrics Team Leader	Liang Zhao, Ph.D.
Clinical Pharmacology Team Leader	Satjit Brar, Pharm.D., Ph.D.
OCP Division	Clinical Pharmacology II
OND Division	Division of Pulmonary, Allergy, and Rheumatology Products
Sponsor/Authorized Applicant	Vertex
Submission Type; Code	pediatric supplement
Formulation; Strength(s)	Granules (50mg, 75mg/pack)
Indication	Treatment of Cystic Fibrosis in patients 2-5 yrs old with approved mutations
Dosage Regimen	Weight based dosing, 75 mg BID for patients ≥14kg; 50 mg BID for patients (b) (4) <14kg

1. Executive Summary ***2***
1.1 Recommendations ***2***
1.2 Phase IV Commitments ***3***
1.3 Summary of Clinical Pharmacology Findings ***3***
2. Question Based Review ***4***
2.1 General Attributes of the Drug and pediatric formulation ***4***
2.1.1 What is the proposed mechanism of action and therapeutic indication? *4*
2.1.2 What is the proposed dosing regimen and route of administration? *4*
2.1.3 What is the proposed formulation for pediatric patients for the pediatric trials and for marketing? *4*
2.1.3.1. Is this formulation appropriate for all proposed age groups? *4*
2.1.3.2. Is the bioavailability of this pediatric formulation similar to the original formulation (in adults)? *4*
2.1.3.3. Was the bioequivalence of the different strengths of the to-be-marketed formulation tested? If so, were they bioequivalent or not? *5*
2.2 General Clinical Pharmacology ***5***

Reference ID: 3704631

2.2.1 What are the design features of the clinical pharmacology and biopharmaceutics studies and the clinical studies used to support dosing or claims? ... 5
2.2.2 What is the basis for selecting the response endpoints and how are they measured in clinical pharmacology studies? ... 6
2.2.3 Are the active moieties in plasma and clinically relevant tissues appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships? ... 6
2.3 Ivacaftor Exposure in pediatric patients ... 7
2.4 Intrinsic and extrinsic factors ... 7
2.5 Analytical Section ... 7
2.5.1 How are parent drug and relevant metabolites identified and what are the analytical methods used to measure them in plasma and other matrices? ... 7
2.5.2 Which metabolites have been selected for analysis and why? ... 8
2.5.3 For all moieties measured, is free, bound, or total measured? ... 8
2.5.4 What bioanalytical methods are used to assess concentrations of the measured moieties? ... 8
2.5.5 What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques were used? ... 8
3. Detailed Labeling Recommendations ... 10
4. Appendix ... 12
4.1. Individual study review ... 12
4.2 Pharmacometrics review ... 18
4.3 New Drug Application Filing and Review Form ... 45

1. Executive Summary

Ivacaftor is a Cystic Fibrosis Transmembrane Regulator (CFTR) potentiator that is approved for the treatment of cystic fibrosis (CF) in subjects 6 years and older who possess at least one copy of one of the 10 mutations in the CFTR gene. The approved dosing regimen is for this age group is 150 mg BID. As CF is a genetic disorder, it is reasonable to assume that patients 2-5 years of age with the same CFTR gene mutations would have similar response to ivacaftor as patients 6 years and older. Therefore, the efficacy of KALYDECO in children 2-5 years of age could be extrapolated from efficacy in patients 6 years of age and older based on comparable ivacaftor exposure.

KALYDECO granules (2 x 75 mg) had a similar bioavailability as the 150 mg tablet when given with fat-containing food in adult subjects. The effect of food on ivacaftor absorption is similar for KALYDECO granules and the 150 mg tablet formulation.

The population pharmacokinetic analyses in our review demonstrated similar drug exposure levels in adults and children 2-5 years of age with the proposed dosing regimen. Also, we noted that in pediatric patients 6 to <12 years of age, the ivacaftor exposure (AUCss) is 87% higher than the mean AUC in adult patients administered KALYDECO tablets, 150 mg every 12 hours.

1.1 Recommendations

From the viewpoint of the Office of Clinical Pharmacology, NDA 207925 is approvable. The review of Clinical Pharmacology information supports the approval of ivacaftor in subjects age 2 and up who have one of the following mutations in the CFTR gene: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R, or R117H.

Reference ID: 3704631

1.2 Phase IV Commitments

None.

1.3 Summary of Clinical Pharmacology Findings

Background

Vertex has submitted the NDA207925 to expand the approved indications of KALYDECO (ivacaftor, NDA203188, initially approved on 31 January 2012) to include pediatric patients 2 to 5 years of age. Ivacaftor is a selective potentiator of the Cystic Fibrosis Transmembrane Regulator (CFTR) protein that is approved "for the treatment of cystic fibrosis in patients age 6 years and older who have one of the following mutations in the CFTR gene: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R or R117H" in the United States.

The proposed dose of ivacaftor granules for patients 2 to 5 years of age is 50 mg (<14kg) or 75 mg (≥14 kg) q12h administered with fat-containing food. Of note, the majority of the clinical pharmacology information for ivacaftor was reviewed with the original application (NDA 203188 by Dr. Lokesh Jain, DARRTs date 1/18/2012). The major findings for this Clinical Pharmacology review are as follows:

- KALYDECO granules (2 x 75 mg) had a similar bioavailability as the 150 mg tablet when given with fat-containing food in adult subjects. The effect of food on ivacaftor absorption is similar for KALYDECO granules and the 150 mg tablet formulation.
- Based on population PK analysis, in patients 2 to <6 years of are predicted to have similar exposure as adult patients following the proposed dosing regimen. The ivacaftor exposure (AUCss) in pediatric patients 6 to <12 years of age is 87% higher than the mean AUC in adult patients (Table 1).

Table 1. Ivacaftor exposure in different age groups

	Adult (≥18 yr)	**Pediatric (2 to <6 yrs, <14kg)**	**Pediatric (2 to <6 yrs, ≥14kg)**	**Pediatric (6 to <12 yrs)**	**Pediatric (12 to <18 yrs)**
Dose (mg, BID)	150	50	75	150	150
AUCss (ng/mL*h) mean (±SD)	10700 (4100)	10500 (4260)	11300 (3820)	20000 (8330)	9240 (3420)

- In an open-label Phase 3 clinical trial in 34 patients ages 2 to <6 years with G551D or S549N mutation, administered either 50 mg or 75 mg of ivacaftor twice daily (study 108), the mean absolute change from baseline in sweat chloride was -45 mmol/L (95% CI -53, -38) through Week 24.

Reference ID: 3704631

2. Question Based Review

Ivacaftor has been reviewed previously under NDA 203188 (submission date: October 18, 2011). For brevity purposes, only QBR questions relevant to this NDA207925 submission will be addressed. For additional information, see the clinical pharmacology review on the original NDA 203188 by Dr. Lokesh Jain (DARRTs date 1/18/2012).

2.1 General Attributes of the Drug and pediatric formulation

2.1.1 What is the proposed mechanism of action and therapeutic indication?

Ivacaftor is a CFTR modulator that acts by potentiating CFTR channel opening in specific types of mutations. Ivacaftor acts on the CFTR protein to increase the channel open probability (or gating) to enhance chloride transport.

2.1.2 What is the proposed dosing regimen and route of administration?

Pediatric patients 2 to <6 years of age and <14 kg: one 50 mg packet mixed with 1 teaspoon (5 mL) of soft food or liquid and administered orally every 12 hours with fat-containing food.

Pediatric patients 2 to <6 years of age and ≥14 kg: one 75 mg packet mixed with 1 teaspoon (5 mL) of soft food or liquid and administered orally every 12 hours with fat-containing food.

2.1.3 What is the proposed formulation for pediatric patients for the pediatric trials and for marketing?

KALYDECO granule is an immediate release granule dosage form for oral administration. The ivacaftor granules (b) (4) a target weight of 6.87 mg. Each (b) (4) contains a target of (b) (4) of ivacaftor. The (b) (4) are filled by count into the primary container closure (packet) to achieve the targeted strength of ivacaftor per packet. Each packet is equivalent to one unit dose (50 mg or 75 mg).

2.1.3.1. Is this formulation appropriate for all proposed age groups?

Yes. Neither an oral solution nor a suspension formulation is feasible for ivacaftor due to its low aqueous solubility. Therefore, a granule dosage form was developed and is appropriate for all proposed age groups.

2.1.3.2. Is the bioavailability of this pediatric formulation similar to the original formulation (in adults)?

Yes. KALYDECO granules (2 x 75 mg) had similar bioavailability as the 150 mg tablet when given with fat-containing food in adult subjects. The effect of food on ivacaftor absorption is similar for KALYDECO granules and the 150 mg tablet formulation.

Reference ID: 3704631

2.1.3.3. Was the bioequivalence of the different strengths of the to-be-marketed formulation tested? If so, were they bioequivalent or not?

There are two strengths of the to-be-marketed formulation, 50 mg and 75 mg packet. A dedicated bioequivalence study was conducted to assess the normalized exposure between the different strengths of ivacaftor granules. The data suggested that ivacaftor exposure was dose proportional from 50 mg to 150 mg (2 x 75 mg) ivacaftor granules (Table 2).

Table 2. Dose Proportionality Assessment for Ivacaftor Granule Formulation (150mg (T1F) VS 50mg (T2F), ANOVA Approach)

Comparison	Parameter	GLSMR	90% CIs (lower, upper)
T1F versus T2F	DN_C_{max}	1.18	0.959, 1.45
	DN_$AUC_{0-\infty}$	1.07	0.945, 1.22
	DN_$AUC_{0-tlast}$	1.09	0.952, 1.24

(Source – Table 11-3, Study VX12-770-015 report)

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and biopharmaceutics studies and the clinical studies used to support dosing or claims?

CF is caused by mutations in the CF transmembrane conductance regulator (CFTR) gene that result in absent or deficient function of the CFTR protein at the cell surface, and it is reasonable to assume that patients 2-5 years of age with the same CFTR gene mutations will have similar response to ivacaftor as patients 6 years and older. Therefore, the division agreed in previous interactions that the efficacy of ivacaftor in the 2-5 year old age group could be extrapolated from the 6 years and older data. This NDA contains the following clinical pharmacology studies:

- Study 012 was a Phase 1, randomized, open-label, 4-period, 4-sequence, 4-treatment crossover study in healthy adult male subjects to investigate the relative bioavailability of the 150-mg prototype granule formulation of ivacaftor. The study suggested that the bioavailability of the prototype granule was lower than the ivacaftor 150mg tablet.

- Study 015 was a Phase 1, randomized, open-label, 4-sequence, 4-period, crossover study in healthy male subjects designed to investigate (1) the relative bioavailability of 150 mg of ivacaftor dosed as the granule formulation (2 × 75-mg) 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 the 150-mg granule formulation (2 × 75-mg); and (3) the dose proportionality of the ivacaftor granule formulation between doses of 50 mg (1 × 50-mg) and 150 mg (2 × 75-mg) in the fed state. The formulation used in study 015 is the same as study 108 and the to-be-marketed formulation.

- Study 108 was a 2-part, open-label, single-arm, Phase 3 study designed to assess

Reference ID: 3704631

safety, PK, and PD of ivacaftor treatment (50-mg for subjects <14 kg; or 75-mg for subjects ≥14 kg; q12h) in subjects 2 through 5 years of age.

- A population PK model (pop PK report K199) that describes ivacaftor disposition was utilized for evaluation of sparse PK data obtained in Study 108.

2.2.2 What is the basis for selecting the response endpoints and how are they measured in clinical pharmacology studies?

As the efficacy of ivacaftor in the 2-5 year old age group was extrapolated from the 6 years and older data, the primary endpoint in phase 3 study 108 is safety and PK (part A). Efficacy endpoints such as spirometry, sweat chloride, weight, BMI and pulmonary exacerbation were also assessed. For safety and efficacy results, please refer to the clinical review by Dr. Robert Lim.

Sweat chloride is a biomarker of CF and is the most commonly used diagnostic tool for CF. In study 108, treatment with ivacaftor 50 and 75 mg in subjects 2 through 5 years of age led to rapid and substantial reductions in sweat chloride concentrations as early as Week 2 (first post-baseline time point measured), and the reductions seen at Week 2 were sustained throughout the 24-week treatment period. The reductions in sweat chloride were similar in both dose groups with an overall reduction from baseline of 45 mmol/L (95% CI -53, -38) through Week 24 (Figure 1).

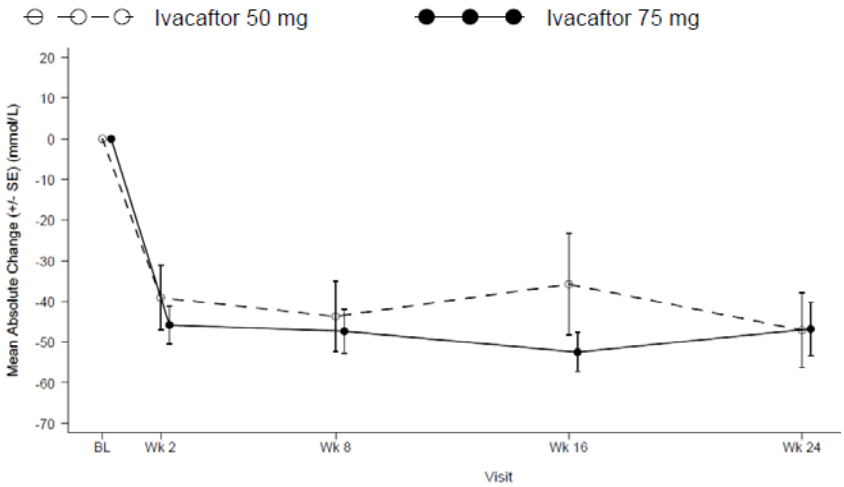


Figure 1. Mean Absolute Change from Baseline in Sweat Chloride by Treatment Group and Visit
(Source – Figure11-1, Study VX11-770-108 report)

2.2.3 Are the active moieties in plasma and clinically relevant tissues appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Yes. Ivacaftor concentrations were quantified in plasma for all studies using validated analytical methods. Ivacaftor's major metabolites, M1 and M6, were also quantified in plasma in study 108.

Reference ID: 3704631

2.3 Ivacaftor Exposure in pediatric patients

2.3.1. Is the exposure in patients between 2 and 5 years similar to the exposure in adults folowing the proposed dosing regimen?

Yes. Predicted exposure in each age group is shown in Figure 2. Patients 2 to 5 years of age, below and above 14 kg, are predicted to have similar exposure as adult patients following the proposed dosing regimens. It should be noted that, following the approved dosing regimen, exposure in patients 6-11 years of age is estimated to be 87% higher than in adult patients, [see pharmacometrics review, appendix 4.2].

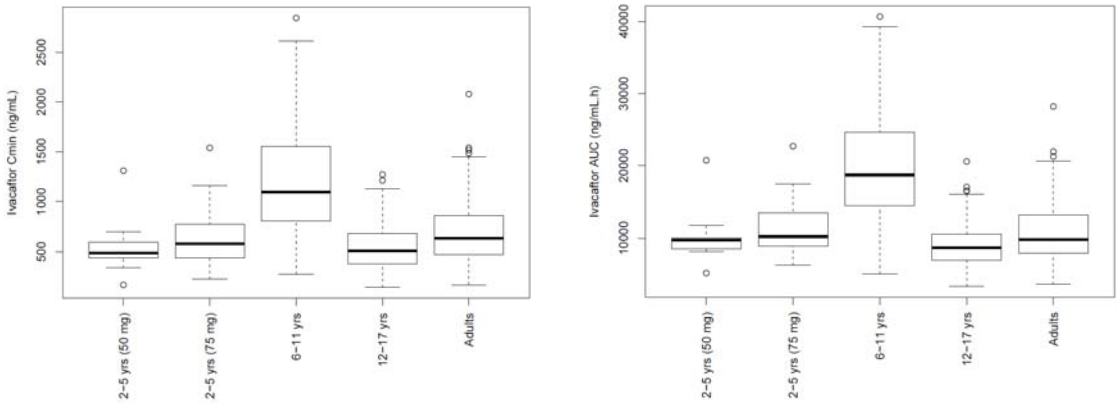


Figure 2. Predicted distribution of ivacaftor exposure across age-groups
Source k199 report, Figures 49 and 50.

2.4 Intrinsic and extrinsic factors

There are no DDI studies or renal and hepatic impairment studies done in pediatric patients. Dose adjustment in pediatric patients is based on what is known from adult data.

2.5 Analytical Section

2.5.1 How are parent drug and relevant metabolites identified and what are the analytical methods used to measure them in plasma and other matrices?

Ivacaftor concentrations were quantified in plasma in all studies using validated analytical methods. Ivacaftor's major metabolites, M1 and M6, were also quantified in plasma in study 108. Analytical methods used to measure the parent drug in different studies are listed in Table 3.

The reported lower limit of quantification (LLOQ) for ivacaftor is 2 ng/mL. Assays were developed and validated, and samples were analyzed in two sites: Vertex DMPK, Cambridge, MA, USA(in the following referred to as Vertex); and (b) (4) Cross validation was conducted to establish comparability of data generated in two different laboratories.

Reference ID: 3704631

Table 3. Analytical Method Validation Reports for Ivacaftor and Metabolites M1 and M6

Report Number Date of Report	Analyte/Matrix[a] Linear Range of Quantitation	Clinical Study Identifier (Abbrev.)
E053 VX-770-DMPK-VAL-033 20MAY2009	Ivacaftor/Human Plasma[b] 2.00 to 2000 ng/mL	012, 015, 108
J109 (b) (4)	Ivacaftor, M1, and M6/Human Plasma[b] 2.00 to 2000 ng/mL (ivacaftor and M1); 10.0 to 10000 ng/mL (M6)	108

M1: metabolite of ivacaftor, VRT-837018, hydroxymethyl-ivacaftor; M6: metabolite of ivacaftor, VRT-842917, ivacaftor carboxylate.

(Source – Table 3, Section 2.7.1, Summary of Biopharmaceutic Studies and Associated Analytical Methods)

2.5.2 Which metabolites have been selected for analysis and why?

Two major metabolites, M1 and M6 were analyzed in study 108.

2.5.3 For all moieties measured, is free, bound, or total measured?

Total (bound + unbound) concentrations were measured in plasma PK samples.

2.5.4 What bioanalytical methods are used to assess concentrations of the measured moieties?

Analytical method for ivacaftor, M1 and M6: report # E053

An analytical method was developed and validated for the determination of in K3 EDTA or K2 EDTA human plasma and used to quantify ivacaftor in biopharmaceutical studies (Studies 012 and 015).

The method was validated over the range of 2.00 to 2000 ng/mL for ivacaftor using HPLC-MS/MS. Sample preparation and analysis are based on a liquid-liquid extraction method using methyl tertiary butyl ether, chromatographic separation by reversed-phase HPLC using a 5.0-µm Symmetry C18 column (4.6 x 50 mm), a gradient mobile phase consisting of 0.1% formic acid in water and 0.1% formic acid in acetonitrile, followed by MS/MS detection in positive ESI mode. d4-Ivacaftor was used as the internal standard for quantification of ivacaftor and d4-M1 or d4-M6 as the internal standard for quantification of the ivacaftor metabolites.

Analytical method for ivacaftor, M1 and M6: report # J109

An analytical method was developed and validated for the determination of in K2 EDTA human plasma and used to quantify ivacaftor in biopharmaceutical studies (Studies 108). The method was validated over the range of 2.00 to 2000 ng/mL for ivacaftor using LC-MS/MS. Sample preparation and analysis are based on a liquid-liquid extraction method using methyl tertiary butyl ether, chromatographic separation by reversed-phase HPLC using a 5.0-µm Sunfire C18 column (2.1 x 50 mm), a gradient mobile phase consisting of 0.1% formic acid in water and 0.1% formic acid in acetonitrile, followed by MS/MS detection in positive ESI mode. d4-Ivacaftor was used as the internal standard for quantification of ivacaftor and d4-M1 or d4-M6 as the internal standard for quantification of the ivacaftor metabolites.

2.5.5 What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques were used?

Reference ID: 3704631

The standard curves were validated over the concentration range of 2 to 2000 ng/mL for ivacaftor and M1, and 10 to 10000 ng/mL for M6, respectively. Calibration curves were generated using a weighted ($1/x^2$) linear least-squares regression.

2.5.5.1 What are the lower and upper limits of quantitation for ivacaftor?

LLOQ and ULOQ for ivacaftor was 2 ng/mL and 2000 ng/mL, respectively, using sample volumes of 50 µL human plasma. A 10-fold dilution factor was validated for 10000 ng/mL concentration of ivacaftor.

2.5.5.2 What are the accuracy, precision, and selectivity at these limits?

All intra and inter-assay precision and accuracy values were within the acceptance criteria (≤15%; ≤20.0% at the LLOQ). All cross validation precision and accuracy values were within the acceptance criteria (≤15%).

In addition, the analyte response (peak area) at the LLOQ in the calibration standard sample was greater than five times the blank analyte response and meets the acceptance criteria stated in the protocol for the sensitivity experiment and cross validations.

The selectivity of all the methods was evaluated by extracting and analyzing blank human plasma from 6 individual sources (E053) or 5 CF donors (J109, one of the donors was on ivacaftor, therefore 4 of the 5 lots were used in analysis). All lots were free from significant interfering peaks in the drug and internal standard regions. Assessment of potential mutual interferences on the detection of the internal standards and the analytes was performed in blank matrix. No relevant interference between the analytes or the internal standards was observed.

2.5.5.3 What is the sample stability under conditions used in the study?

The stability characteristics of ivacaftor, M1, and M6 in human plasma are summarized in Table 4. Sample collection stability of ivacaftor, M1, and M6 in human whole blood was also confirmed at room temperature and under wet ice conditions for 2 hours, and it was demonstrated that the presence of hemolyzed red blood cells in the human plasma did not affect the quantification of ivacaftor, M1, and M6.

Table 4. Stability of Ivacaftor and Metabolites M1 and M6 in Human Plasma

	Demonstrated Stability of Ivacaftor and Metabolites in Plasma		
	Human Plasma		
Conditions	**Ivacaftor**	**M1**	**M6**
Bench-top stability (room temperature)	27 hours	27 hours	27 hours
Freeze-thaw stability (-60ºC or below)	6 cycles	6 cycles	6 cycles
Autosampler stability (4ºC)	118 hours	118 hours	118 hours
Long-term frozen stability (-60ºC or below)	633 days	633 days	633 days

(Source: Table 6, Summary of biopharm)

Reference ID: 3704631

3. Detailed Labeling Recommendations

The revised labeling language based on the preliminary review is as below. Based on the clinical pharmacology review, most revisions were on description of ivacaftor PK in pediatric population.

7 DRUG INTERACTIONS

7.1 Inhibitors of CYP3A

Ivacaftor is a sensitive CYP3A substrate. Co-administration with ketoconazole, a strong CYP3A inhibitor, (b) (4) significantly increased ivacaftor exposure [measured as area under the curve (AUC)] by 8.5-fold.

7.2 Inducers of CYP3A

Co-administration with rifampin, a strong CYP3A inducer, , (b) (4) significantly decreased ivacaftor exposure (AUC) by approximately 9-fold.

8 USE IN SPECIFIC POPULATIONS

8.4 Pediatric Use

The (b) (4) safety, and efficacy of KALYDECO in patients 6 to 17 years of age with CF who have a *G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, or S549R* mutation in the *CFTR* gene has been demonstrated [*see Adverse Reactions (6),* (b) (4) and *Clinical Studies (14)*].

The ~~pharmacokinetic profile,~~ safety and efficacy of KALYDECO in patients 6 to 17 years of age with CF who have an *R117H* mutation in the *CFTR* gene has been demonstrated [see *Adverse Reactions (6),* (b) (4) and *Clinical Studies (14)*].

The efficacy of KALYDECO in children 2-5 year of age is extrapolated from efficacy in patients 6 years of age and older with support from population pharmacokinetic analyses showing similar drug exposure levels in adults and children 2-5 year of age [see Clinical Pharmacology (12.3)].

12 CLINICAL PHARMACOLOGY

12.2 Pharmacodynamics

Sweat Chloride Evaluation

……..the mean absolute change from baseline in sweat chloride (b) (4)

12.3 Pharmacokinetics

(b) (4) **Specific populations**

Pediatric patients

The following conclusions about exposures between adults and the pediatric population are based on population PK analysis

Pediatric patients *2 to <6 years of age*

(b) (4)

(Weight <14 kg)
Following oral administration of KALYDECO granules, 50 mg every 12 hours, the mean (±SD) steady state AUC (AUCss) was 10500 (4260) ng/mL*h and is similar to the mean AUCss of 10700 (4100) ng/mL*h in adult patients administered KALYDECO tablets, 150 mg every 12 hours.

(Weight ≥14 kg)
Following oral administration of KALYDECO granules, 75 mg every 12 hours, the mean (±SD) AUCss was 11300 (3820) ng/mL*h ng/mL and is similar to the mean AUC in adult patients administered KALYDECO tablets, 150 mg every 12 hours.

Pediatric patients 6 to <12 years of age
Following oral administration of KALYDECO tablets, 150 mg every 12 hours, the mean (±SD) AUCss was 20000 (8330) ng/mL*h and is 87% higher than the mean AUC in adult patients administered KALYDECO tablets, 150 mg every 12 hours.

Pediatric patients 12 to <18 years of age
Following oral administration of KALYDECO tablets, 150 mg every 12 hours, the mean (±SD) AUCss was 9240 (3420) ng/mL*h and is similar to the mean AUSss in adult patients administered KALYDECO tablets, 150 mg every 12 hours.

14 CLINICAL STUDIES

14.1 Trials in Patients with CF who have a *G551D* Mutation in the *CFTR* Gene

Dose Ranging

Reference ID: 3704631

……The twice-daily dosing regimen was primarily based on an apparent terminal plasma half-life of approximately 12 hours. . (b) (4)

4. Appendix

4.1 Appendix 1

INDIVIDUAL STUDY REVIEW

1. Relative Bioavailability

Study VX10-770-012

Title: A Phase 1, Randomized, Open-Label Study to Evaluate the Bioavailability and Food Effect of (b) (4) Formulation of VX-770 Relative to Film-Coated Tablet Formulation of VX-770 in Healthy Male Subjects

Objective:
Primary: To evaluate bioavailability of 150-mg (b) (4) formulation (the prototype granule formulation) of VX-770 under fed conditions relative to 150-mg film-coated tablet formulation of VX-770 under fed conditions.
Secondary:

- To evaluate the food effect of 150-mg the prototype granule formulation of VX-770
- To assess the magnitude of food effect of 150-mg the prototype granule formulation relative to 150-mg film coated tablet formulation

Study design and treatment schedule:
This was a Phase 1, randomized, open-label, 4-period, 4-sequence, 4-treatment crossover study in healthy male subjects. Each subject was randomized to receive all 4 treatments in this study. There was to be a washout of at least 7 days between the doses administered in each period.

- Treatment 1: Film-coated tablet formulation under fasted condition (R)
- Treatment 2: The prototype granule formulation under fasted condition (T)
- Treatment 3: Film-coated tablet formulation under fed condition (RF)
- Treatment 4: The prototype granule formulation under fed condition (TF)

	Treatment Period			
Sequence	**1**	**2**	**3**	**4**
A	R	TF	T	RF
B	T	R	RF	TF
C	RF	T	TF	R
D	TF	RF	R	T

PK Sampling Schedule
Pharmacokinetic (PK) samples were collected in each of the 4 treatment periods for VX-770 analysis at pre-dose and 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 48, and 72 hours post-dose.

Reference ID: 3704631

Results

• In the fed state, the prototype granule formulation had lower exposures than the film-coated tablet formulation with AUC0-∞ being 32% lower and Cmax being 41% lower.
• In the fasted state, the prototype granule formulation had lower exposures than film-coated tablet formulation with AUC0-∞ being 39% lower and Cmax being 34% lower. (Table 5)

Table 5. Statistical Comparison of (b) (4) Formulation to Film-Coated Tablet Formulation Under Fasted and Fed Conditions

Comparison	N	Parameter	Ref GLSM (ng*hr/mL)	Test GLSM (ng*hr/mL)	GLSM Ratio	90% CI Lower	90% CI Upper
(b) (4) vs. Film-coated tablet (fasted condition)	16	C_{max}	198.4877	130.5159	0.6576	0.5283	0.8184
	16	$AUC_{0-\infty}$	3388.4213	2065.3746	0.6095	0.5181	0.7171
(b) (4) vs. Film-coated tablet (fed condition)	18	C_{max}	728.8427	428.2740	0.5876	0.4749	0.7270
	18	$AUC_{0-\infty}$	9594.4907	6567.3866	0.6845	0.5876	0.7974

(Source – Table 11-2, Study VX10-770-012 report)

Conclusions

The prototype granule formulation had lower exposure compared to the commercial 150 mg tablet. Therefore, this formulation was not used in the later pediatric studies.

2. Relative Bioavailability

Study VX12-770-015

Title: A Phase 1, Randomized, Open-Label Study to Evaluate the Relative Bioavailability, Food Effect, and Dose Proportionality of a (b) (4) Formulation of Ivacaftor in Healthy Adult Male Subjects

Objective:

Primary: To evaluate the relative bioavailability (BA) of the ivacaftor (b) (4) formulation (KALYDECO granules) compared to the film-coated ivacaftor tablet formulation in the fed condition as a single 150-mg dose

Secondary:

- To evaluate the food effect on the ivacaftor (b) (4) (KALYDECO granules) formulation as a single 150-mg dose
- To evaluate the dose proportionality of the (b) (4) (KALYDECO granules) formulation between 50- and 150-mg doses
- To assess the safety and tolerability of the 50-mg and 150-mg ivacaftor single doses given to healthy, adult subjects

Study design and treatment schedule:

This was a Phase 1, randomized, open-label, 4-sequence, 4-period, crossover study using a Williams' design. Each of the 20 subjects was randomized to receive all 4 treatments in this study (Table 6). There was to be a washout of at least 7 days between the doses administered in each period.

Reference ID: 3704631

Table 6. Dosing sequences (William's design)

Sequence	Dosing Periods			
	1	2	3	4
1 (N = 5)	150-mg Film-coated tablet (fed) (RF)	150-mg (b) (4) Dose (fasted) (T1)	150-mg (b) (4) Dose (fed) (T1F)	50-mg (b) (4) Dose (fed) (T2F)
2 (N = 5)	150-mg (b) (4) Dose (fed) (T1F)	150-mg Film-coated tablet (fed) (RF)	50-mg (b) (4) Dose (fed) (T2F)	150-mg (b) (4) Dose (fasted) (T1)
3 (N = 5)	50-mg (b) (4) Dose (fed) (T2F)	150-mg (b) (4) Dose (fed) (T1F)	150-mg (b) (4) Dose (fasted) (T1)	150-mg Film-coated tablet (fed) (RF)
4 (N = 5)	150-mg (b) (4) Dose (fasted) (T1)	50-mg (b) (4) Dose (fed) (T2F)	150-mg Film-coated tablet (fed)(RF)	150-mg (b) (4) Dose (fed) (T1F)

Notes: RF = reference formulation (one 150-mg film-coated tablet) administered in the fed state; T1F = 150-mg (b) (4) dose (two 75-mg capsules) administered in the fed state; T1 = 150-mg (b) (4) dose (two 75-mg capsules) administered in the fasted state; T2F = one 50-mg (b) (4) dose administered in the fed state.

PK Sampling Schedule

Pharmacokinetic (PK) samples were collected in each of the 4 treatment periods for VX-770 analysis at pre-dose and 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 48, and 72 hours post-dose.

Results

• Results from the relative BA assessment found that, compared to the film-coated 150-mg tablet formulation, C_{max}, $AUC_{0\text{-tlast}}$ and $AUC_{0\text{-}\infty}$ was similar with (b) (4) (KALYDECO granules) formulation.

Table 7. Summary of Statistical Analysis on Relative Bioavailability of Ivacaftor (b) (4) Formulation (KALYDECO granules, T1F) Versus Reference Formulation (KALYDECO tablets, RF) Following a 150-mg Single-Dose of Ivacaftor Administered in the Fed State

Comparison	Parameter	GLSMR	90% CIs (lower, upper)
T1F versus RF	C_{max}	0.918	0.750, 1.12
	$AUC_{0\text{-}\infty}$	0.951	0.839, 1.08
	$AUC_{0\text{-tlast}}$	0.954	0.837, 1.09

(Source – Table 11-2, Study VX12-770-015 report)

• Food effect: The Cmax of ivacaftor was approximately 3.70 times higher, AUC0-∞ was 2.82 times higher, and the AUC0-tlast was 3.02 times higher when (b) (4) (KALYDECO granules) was administered in the fed state as compared with the fasted state. (Table 8)

Table 8. Effect of Food on Relative Bioavailability of (b) (4) Formulation (KALYDECO granules, T1F, fed; T1, fast)

Comparison	Parameter	GLSMR	90% CIs (lower, upper)
T1F versus T1	C_{max}	3.70	3.03, 4.54
	$AUC_{0\text{-}\infty}$	2.82	2.48, 3.20
	$AUC_{0\text{-tlast}}$	3.02	2.65, 3.44

(Source – Table 11-3, Study VX12-770-015 report)

Reference ID: 3704631

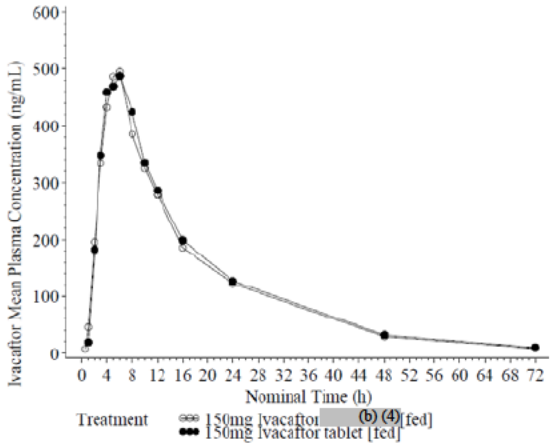


Figure 3. Mean Plasma Concentrations of Ivacaftor Versus Time
(Source – Figure11-1, Study VX12-770-015 report)

• For the (b) (4) (KALYDECO granules) formulation administered in the fed state, the increase in ivacaftor exposure from 50 mg to 150 mg was generally dose proportional.

Table 9. Dose Proportionality Assessment for (b) (4) Formulation (KALYDECO granules, 150mg (T1F) VS 50mg (T2F), ANOVA Approach)

Comparison	Parameter	GLSMR	90% CIs (lower, upper)
T1F versus T2F	DN_C_{max}	1.18	0.959, 1.45
	DN_$AUC_{0-\infty}$	1.07	0.945, 1.22
	DN_$AUC_{0-tlast}$	1.09	0.952, 1.24

(Source – Table 11-3, Study VX12-770-015 report)

Conclusions
This reviewer performed an independent analysis and was in agreement with the sponsor's results. The (b) (4) formulation (KALYDECO granules) had comparable exposure to the 150 mg KALYDECO tablets under fed state. The increase in ivacaftor exposure is dose proportional from 50 mg to 150 mg KALYDECO granules.

3. Phase 3 study in 2-5 yrs CF patients

Study VX11-770-108 part B

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

Objective:
To evaluate the PD (sweat chloride) of ivacaftor treatment in subjects with CF who are 2 through 5 years of age and have a CFTR gating mutation.

Only results related to sweat chloride are reviewed here. For safety and efficacy results, please refer to the clinical review by Dr. Robert Lim. For PK comparison, please refer to pharmacometics review (Appendix 4.2)

Reference ID: 3704631

Study design and treatment schedule:
This was a Phase 3, open-label, 2-part study as depicted in Figure 4. 34 subjects were enrolled in the study and 33 subjects completed the 24-week treatment period. Doses were 50-mg ivacaftor q12h for subjects weighing <14 kg on Day 1 and 75-mg ivacaftor q12h for subjects weighing ≥14 kg on Day 1. No individual dose adjustments were allowed throughout the duration of dosing in Part B, regardless of change in body weight or age. After a Screening Period, subjects received 50- or 75-mg ivacaftor q12h during the 24-week treatment period.

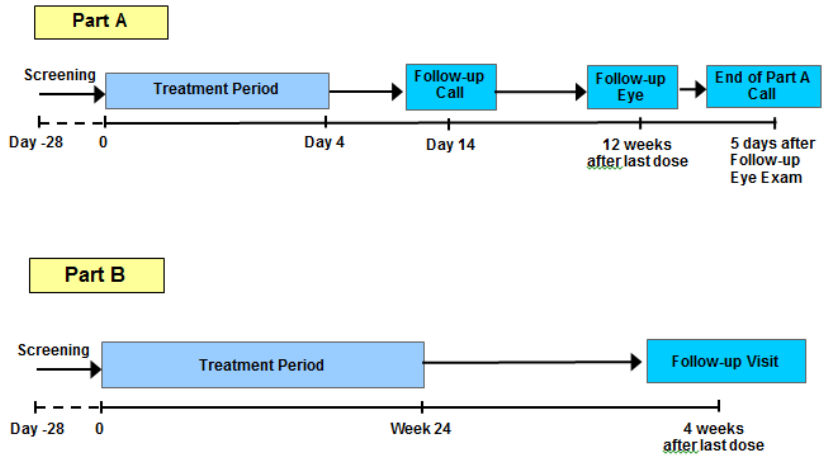


Figure 4. Schematic of study design
(Source – Figure9-1, Study VX11-770-108 report)

PD (sweat chloride) Sampling Schedule
At the Day 1 Visit in Part B, the sweat chloride test was performed before the morning dose. At the Weeks 2, 8, 16, and 24 Visits, the sweat chloride test was performed within a window of ± 2 hours relative to the morning dose of the study drug.

Results and Conclusions
The overall mean change from baseline in sweat chloride at Week 24 was -46.86 mmol/L. Reductions in sweat chloride of approximately 40 mmol/L were observed at Week 2, and these reductions were sustained throughout the 24-week treatment period. Changes from baseline in sweat chloride were consistent across the ivacaftor 50 mg and ivacaftor 75 mg groups (Table 10).

Reference ID: 3704631

Table 10. Absolute Changes From Baseline in Sweat Chloride (mmol/L), Part B, Safety Set

Time Point	Category or Statistic	Ivacaftor 50 mg (N = 10)	Ivacaftor 75 mg (N = 24)	Overall (N = 34)
Baseline				
	Mean (SD) (mmol/L)/n	93.13 (15.040)/8	99.61 (13.551)/22	97.88 (14.003)/30
Week 2				
	Mean (SD) (mmol/L)/n	52.38 (24.061)/8	53.95 (18.805)/21	53.52 (19.946)/29
	Mean (SD) absolute change from baseline (mmol/L)/n	-39.07 (21.015)/7	-45.79 (20.319)/19	-43.98 (20.310)/26
Week 8				
	Mean (SD) (mmol/L)/n	59.79 (26.374)/7	54.29 (17.409)/21	55.66 (19.620)/28
	Mean (SD) absolute change from baseline (mmol/L)/n	-43.67 (21.160)/6	-47.34 (23.440)/19	-46.46 (22.537)/25
Week 16				
	Mean (SD) (mmol/L)/n	63.21 (30.174)/7	46.53 (15.767)/19	51.02 (21.319)/26
	Mean (SD) absolute change from baseline (mmol/L)/n	-35.75 (30.586)/6	-52.44 (20.507)/18	-48.27 (23.848)/24
Week 24				
	Mean (SD) (mmol/L)/n	47.81 (23.305)/8	55.23 (23.845)/20	53.11 (23.507)/28
	Mean (SD) absolute change from baseline (mmol/L)/n	-47.07 (24.256)/7	-46.78 (27.584)/18	-46.86 (26.193)/25
	95% CI	(-69.50, -24.64)	(-60.50, -33.06)	(-57.67, -36.05)
	P value	0.0021	<0.0001	<0.0001

(Source – Table 11-1, Study VX11-770-108 report)

By reviewer's analysis, the mean absolute change from baseline in sweat chloride was -45 mmol/L (95% CI -53, -38) through Week 24. Datasets used for this review analysis are summarized in Table 11.

Table 11. Analysis Data Sets

Data Source	Dataset Names	Link to EDR
Analysis dataset of Study 108	adsw.xpt	\\cdsesub1\evsprod\nda207925\0000\m5\datasets\vx11-770-108b\analysis\adam\datasets\adsw.xpt

Reference ID: 3704631

4.2 APPENDIX 2

OFFICE OF CLINICAL PHARMACOLOGY: PHARMACOMETRIC REVIEW

Application Number	NDA207925
Submission Date	9/17/2014
Compound	Ivacaftor
Dosing regimen (route of administration)	Weight based dosing, 75 mg BID for patients ≥14kg; 50 mg BID for patients 7 to <14kg. (Oral)
Indication	Cystic Fibrosis patients 2-5 yrs old with approved mutations
Clinical Division	Division of Pulmonary, Allergy, and Rheumatology Products
Primary PM Reviewer	Dinko Rekić, MSc, Ph.D.
Secondary PM Reviewer	Liang Zhao, Ph.D.

1. SUMMARY OF FINDINGS

1.1 Key Review Questions

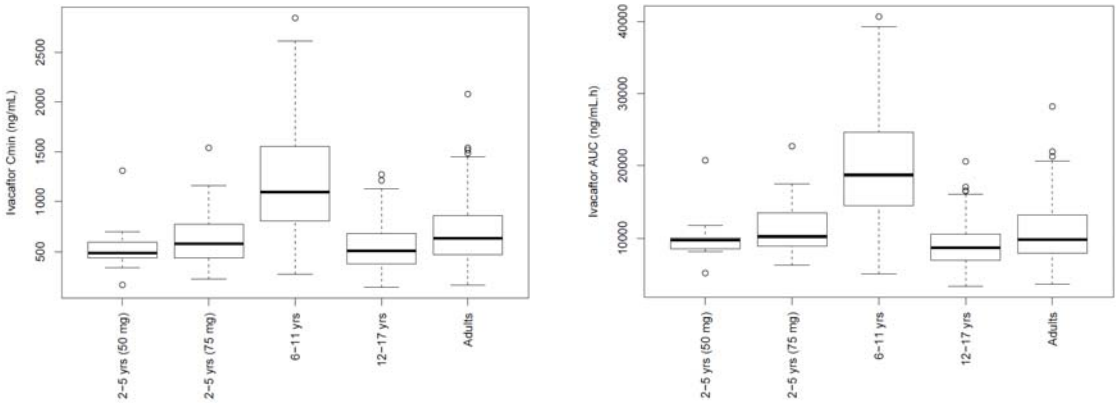
The purpose of this review is to address the following key questions.

1.1.1 Is the exposure in patients between 2 and 5 years similar to the exposure in adults following the proposed dosing regimen?

Yes. Exposure in each age group is shown in Figure 5, Table 12 and Table 13 Patients 2 to 5 years of age, below and above 14 kg, have similar exposure to adult patients following the proposed dosing regimen. It should be noted that, following the approved dosing regimen, area under the curve (AUC) in patients 6-11 years of age is 86% higher than in adult patients, [Sponsors report: Table 6]. The analysis dataset consisted of 426 subjects that contributed 5386 PK samples. Out of those subjects, 33 belong to the target population (2-5 years of age). On average, each individual contributed ~9 PK samples in the target population. Given the indication, the collected covariate and PK data is of sufficient quality and quantity to support sponsor's model.

Reference ID: 3704631

Figure 5. Predicted distribution of ivacaftor exposure across age-groups



Source k199 report, Figures 49 and 50.

Table 12. Summary Statistics for Ivacaftor Cmin,ss (ng/mL) by Age Group

Group	N	Min	Max	Median	Mean	SD	Q1	Q3
2-5 years (50 mg)	9	170	1310	536	577	317	466	623
2-5 years (75 mg)	26	225	1540	580	629	296	438	774
6-11 years	40	275	2840	1100	1240	594	836	1540
12-17 years	78	141	1270	508	564	242	382	676
Adults	190	167	2080	634	701	317	471	864

Table 13. Summary Statistics for Ivacaftor AUCss (ng/mL.h) by Age Group

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

Source k199 report, tables 6 and 7.

Reference ID: 3704631

1.2 Recommendations

Division of Pharmacometrics finds NDA 207925 acceptable from a Pharmacometrics perspective.

APPEARS THIS WAY ON ORIGINAL

Reference ID: 3704631

1.3 Label Statements
Section 8.4 Pediatric use

The [redacted] (b) (4), safety, and efficacy of KALYDECO in patients [redacted] (b) (4) 6 to 17 years of age with CF who have a *G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N,* or *S549R* mutation in the *CFTR* gene has been demonstrated [*see Adverse Reactions (6)*; [redacted] and *Clinical Studies (14)*].

The efficacy of KALYDECO in children 2-5 year of age is extrapolated from efficacy in patients 6 years of age and older with support from population pharmacokinetic analyses showing similar drug exposure levels in adults and children 2-5 year of age [see Clinical Pharmacology (12.3) and Clinical Studies (14)].

Section 12.3 Special populations

Pediatric patients [redacted] (b) (4)

[redacted] (b) (4)

Pediatric patients

The following conclusions about exposures between adults and the pediatric population are based on population PK analysis:

Pediatric patients *2 to <6 years of age*

(Weight <14 kg)

Following oral administration of KALYDECO granules, 50 mg every 12 hours, the mean (±SD) steady state AUC (AUCss) was 10500 (4260) ng/mL*h and is similar to the mean AUCss of 10700 (4100) ng/mL*h in adult patients administered KALYDECO tablets, 150 mg every 12 hours.

(Weight ≥14 kg)

Following oral administration of KALYDECO granules, 75 mg every 12 hours, the mean (±SD) AUCss was 11300 (3820) ng/mL*h ng/mL and is similar to the mean AUC in adult patients administered KALYDECO tablets, 150 mg every 12 hours.

Pediatric patients 6 to <12 years of age

Following oral administration of KALYDECO tablets, 150 mg every 12 hours, the mean (±SD) AUCss was 20000 (8330) ng/mL*h and is 87% higher than the mean AUC in adult patients administered KALYDECO tablets, 150 mg every 12 hours.

Reference ID: 3704631

Pediatric patients 12 to <18 years of age

Following oral administration of KALYDECO tablets, 150 mg every 12 hours, the mean (±SD) AUCss was 9240 (3420) ng/mL*h and is similar to the mean AUSss in adult patients administered KALYDECO tablets, 150 mg every 12 hours.

2 PERTINENT REGULATORY BACKGROUND

Ivacaftor (KALYDECI ®) is approved for treatment of cystic fibrosis in patients 6 years and older with the following mutations: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, or S549R. The approved dosage is 150 mg every 12 hr. for all approved ages and mutations. The current applications propose to extend the approved age range to include patients down to 2 years of age. The proposed doses are 75 mg and 50 mg every 12 hours in patients ≥14 or <14 kg of body weight. The basis of approval is extrapolation of efficacy from patients 6 years and older, based on exposure matching and observed accepted safety profile in the target population.

3 RESULTS OF SPONSOR'S POPULATION PK ANALYSIS

Sponsor has submitted a population PK model describing ivacaftor pharmacokinetic in children, adolescents, and adults. The sponsor intends to use the model to justify doses in patients 2-5 years of age by demonstrating similar exposure to adults.

Reviewer's comments: The reviewer was able to confirm the applicant's parameter estimates by rerunning the model. However, in order to converge, initial estimates had to be updated based on the output of applicant's final model.

3.1 Data

The dataset used in applicant's population PK analysis included 426 subjects that contributed with 5386 PK samples, Table 14. Out of those subjects, 33 belong to the target population for this NDA supplement (2-5 years of age). On average, each individual contributed with ~9 PK samples in the target population. Number of subjects stratified for study and age group is shown in Table 15. The distribution of age and weight in the PK dataset is shown in Figure 6. Observed plasma concentrations versus time are shown in Figure 7.

Reviewer's comments: The lowest dosage-group (2-5 year olds, below 14 kg.) is only supported by PK data in 9 patients. However, considering the prevalence of the disease in the patient population, these 9 subjects represent a considerable proportion of the total target population.

Reference ID: 3704631

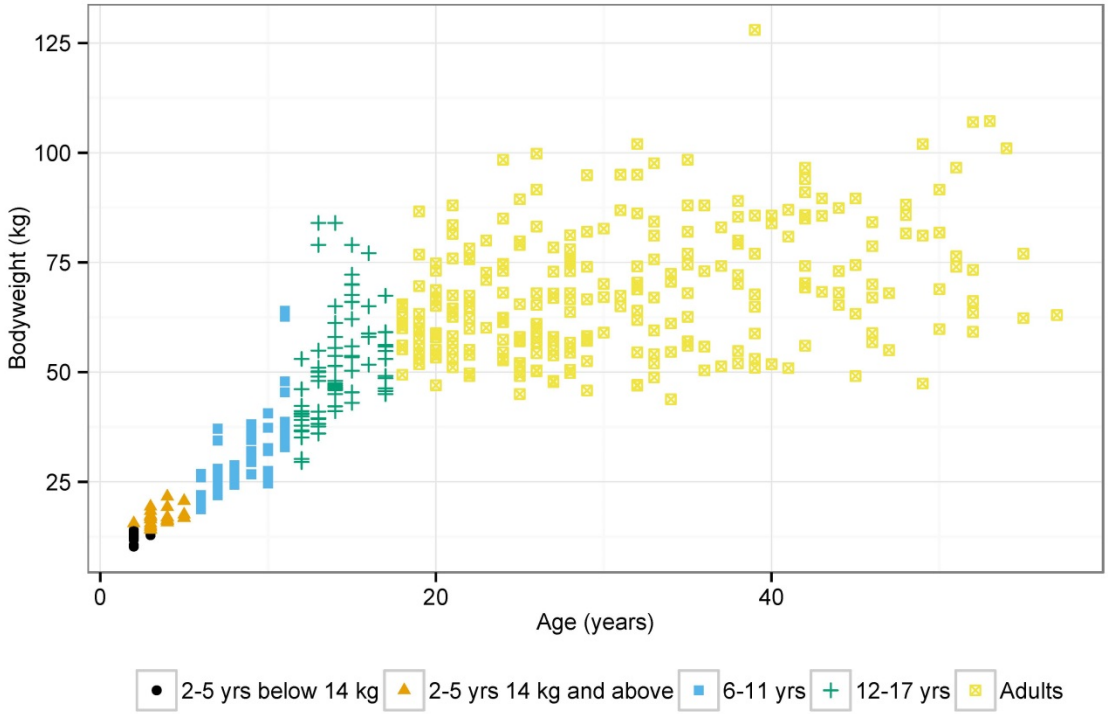
Table 14. Number of subjects per age group at baseline

Study	Age group	Number of Subjects
Total	2-5 yrs below 14 kg	9
Total	2-5 yrs 14 kg and above	24
Total	12-17 yrs	78
Total	6-11 yrs	47
Total	Adults	264
7	Adults	17
10	Adults	24
16	Adults	20
101	Adults	31
102	12-17 yrs	19
102	Adults	61
103	12-17 yrs	3
103	6-11 yrs	30
104	12-17 yrs	44
104	Adults	68
108	2-5 yrs below 14 kg	9
108	2-5 yrs 14 kg and above	24
110	12-17 yrs	1
110	6-11 yrs	9
110	Adults	24
111	12-17 yrs	11
111	6-11 yrs	8
111	Adults	19

Source: reviewer derived from sdtab1017

Reference ID: 3704631

Figure 6. Distribution of age and bodyweight in the applicant's PK dataset at baseline



Source: derived from applicant's dataset sdtab1017

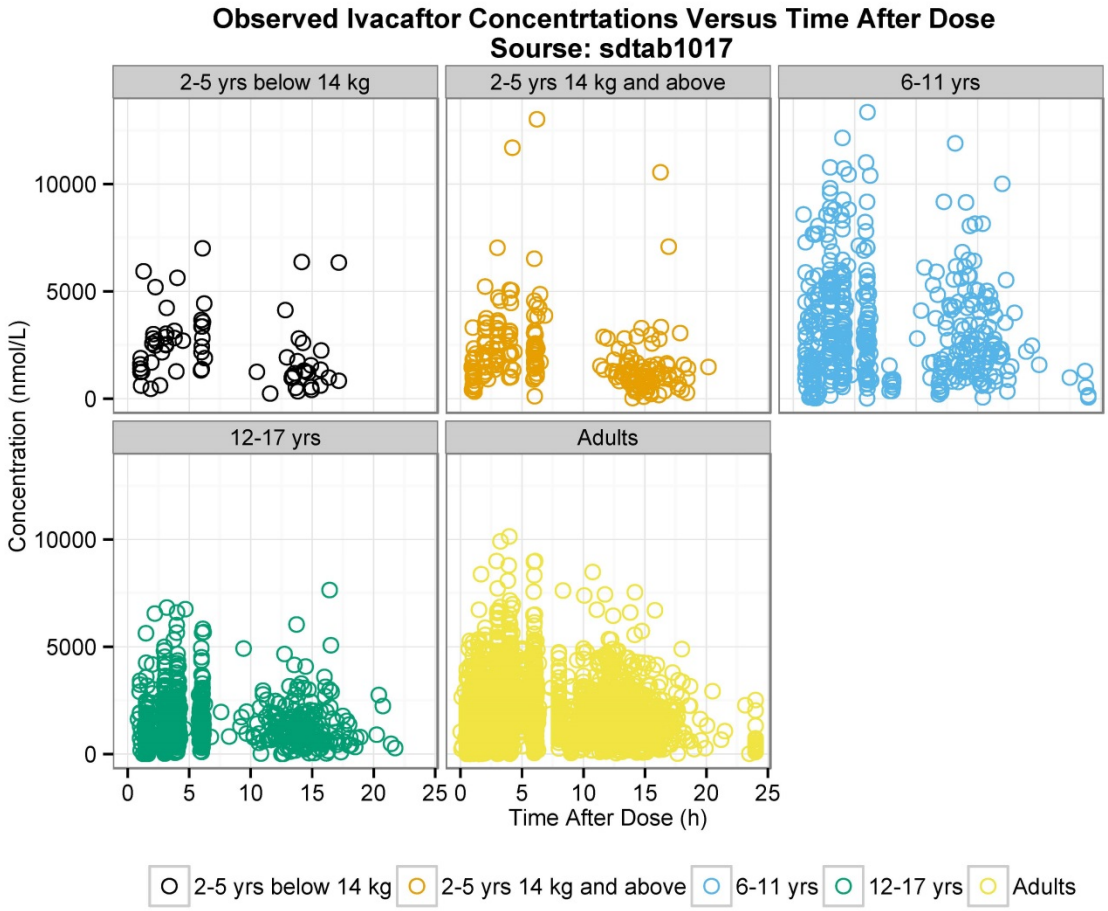
Table 15. Distribution of bodyweights and age in the applicant's PK dataset at baseline

Age group	Mean Age	Age SD	Age max	Age min	Mean Bodyweight	Bodyweight SD	Bodyweight max	Bodyweight min	n
2-5 yrs below 14 kg	2.1	0.3	3	2	12.4	1.3	14.0	10.3	9
2-5 yrs 14 kg and above	3.6	0.8	5	2	17.0	1.9	21.7	14.1	24
6-11 yrs	8.4	1.8	11	6	30.7	9.7	64.0	18.8	47
12-17 yrs	14.2	1.6	17	12	51.4	12.2	84.0	29.5	78
Adults	31.3	9.9	57	18	68.1	14.4	128.0	43.8	264

Source: derived from applicant's dataset sdtab1017

Reference ID: 3704631

Figure 7. Pharmacokinetic data used to derive the applicants population PK model



The X axis has been restricted to 25 h., resulting in omission of 79 observations. Most (82%) of the omitted observations were from adult patients.

Source derived from applicant's dataset sdtab1017

3.2 Method

The structural component of the model consisted of two compartments with linear elimination using the PREDPP subroutines ADVAN4 and TRANS4 in NONMEM version 7 level 1.0. Absorption delay was modeled as a sequential zero to first order process. Inter individual variability (IIV) was estimated for CL/F, K1, and D1 with exponential variance models, as a full covariance matrix. No IIV vas estimated for Vc/F, Vp/F, or Q/F. Inter occasion variability was estimated on CL/F, ka, and F. The residual error structure consisted of combined additive and proportional components.

The full model was presented as the final model, with all of the following covariates: bodyweight, gender, age, healthy status, and race. Effect of bodyweight on all structural parameters was accounted for via allometric scaling, with clearance terms scaled by an

Reference ID: 3704631

exponent of 0.75 and volumes scaled by an exponent of 1.0. The applicant has also presented a base model that incorporated allometric scaling as described above without including any covariates.

Reviewer comments:

- *The full model approach focuses primarily on parameter estimation and not on hypothesis testing. There is no consensus in the scientific literature whether the full model approach incorporating all available covariates is preferred over the stepwise covariate selection approach. For the purpose of this analysis the full covariate approach appears acceptable.*

- *Allometric scaling based on fixed exponents (0.75 and 1 for clearance and volume terms, respectively) has strong theoretical support in literature* [1]*. However, based on the purpose of this review (to match the exposure of pediatric patients to adults) this is a major assumption that should be checked with a sensitivity analysis.*

3.3 Results

Parameter estimates for the full model are shown in Table 16. Parameters were generally estimated with high precision. The applicant concludes: "body weight was a clinically important predictor for ivacaftor PK. None of the other covariates studied were clinically important predictors".

Reviewer comments:

- *Inclusion of the covariates to the base model did not lower the unexplained variability in clearance (IIV for CL/F) to a great extent (45.3 %CV versus 44.4 %CV). (Source: k199 report, tables 4 and 5). Typically IIV should be reduced by addition of covariates. Both the base and the final model accounted for the influence of bodyweight and CL/F, which is arguably the most influential covariate. This offers some explanation to small reduction in IIV. In other words: when accounting for differences in bodyweight, other covariates do not explain the IIV to a large extent.*

3.3.1Evaluation of model fit

Selected goodness of fit (GOF) plots submitted by the applicant are shown in in Figure 8. Applicant has submitted other variations of GOF plots, suggesting adequate model fit. An information request was sent to the sponsor on November 6, 2014 asking for additional goodness of fit plots, including the │IWRES│ vs. IPRED plot. Sponsor provided the agency with the requested information on the 20th of November 2014. The content in the information request has been reviewed along with the original submission.

Reviewer's comments:

- *The plots presented by the applicant evaluate how the model fit the overall PK data. However, the primary goal of the analysis is to support the dosing regimen in the 2-5 year old population. Stratifying the plots by age-group allows evaluation of model fit in the target population. This is shown in reviewer's analysis.*

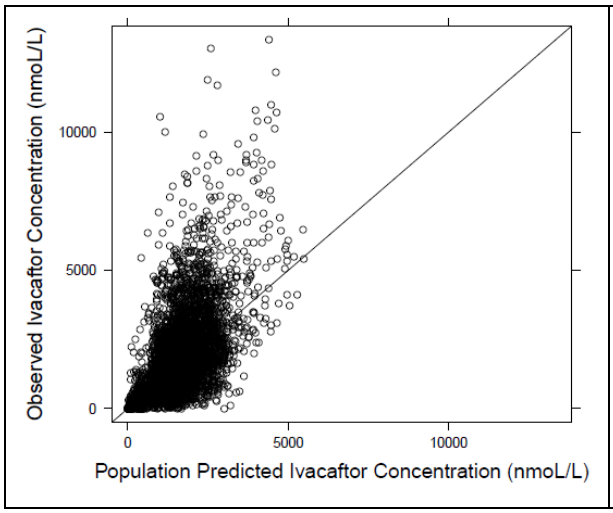
Reference ID: 3704631

- *Simulation based diagnostics are a useful tool to evaluate if the model can describe the data. Such diagnostics are shown in the reviewer's analysis.*
- *Utility of GOF plots that are based on empirical bayes estimates (EBE) e.g. IPRED vs. DV, is conditioned on low ETA shrinkage*[2]*. Based on applicant's submitted NONMEM output file (run107.lst) for the final model (run1007), CL shrinkage is estimated to 13%. This is considered to be moderate to low shrinkage.*
- *The presented plots do not appear to show major trends. However, the DV vs. PRED plot is difficult to evaluate due to lack of a non-parametric smoother line that would show trends (if any) in the plot. The lower right quadrant of Figure 8 show conditional weighted residuals (CWRES) versus time after dose (TAD). The non-parametric smoother suggests some trends; however, within the relevant time frame (0-24 h) the trend disappears. This is shown in the reviewer's analysis.*
- *The* $|IWRES|$ *vs. IPRED shows significant trends. This plot is discussed in the reviewer's analysis.*

Reference ID: 3704631

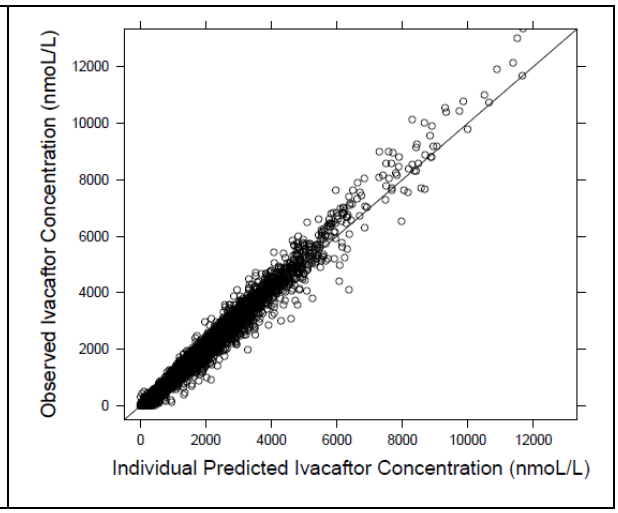
Figure 8. Selected goodness of fit plots

observations versus population prediction
DV vs. PRED



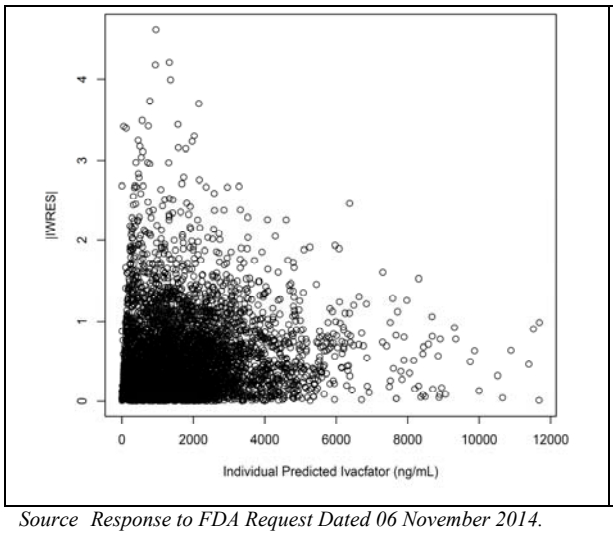
Source k199 report, figure 15 (left)

observations versus individual prediction
DV vs. IPRED



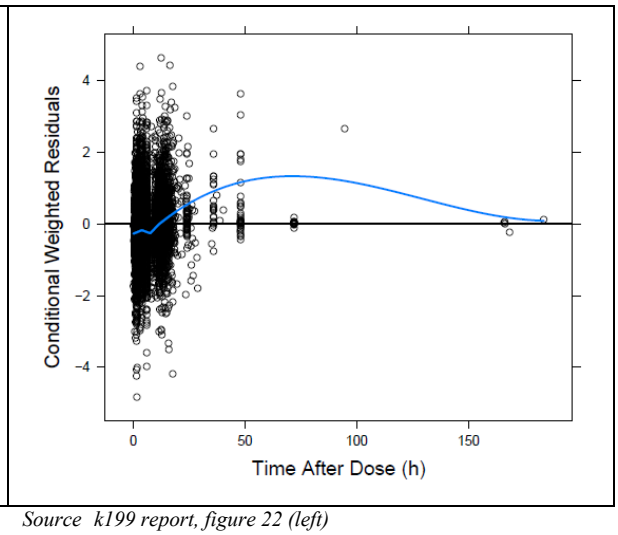
Source k199 report, figure 16 (left)

Absolute Individual Weighted residuals versus Individual predictions
|IWRES| vs. IPRED



Source Response to FDA Request Dated 06 November 2014.

Conditional weighted residuals versus Time after dose
CWRES vs. TAD



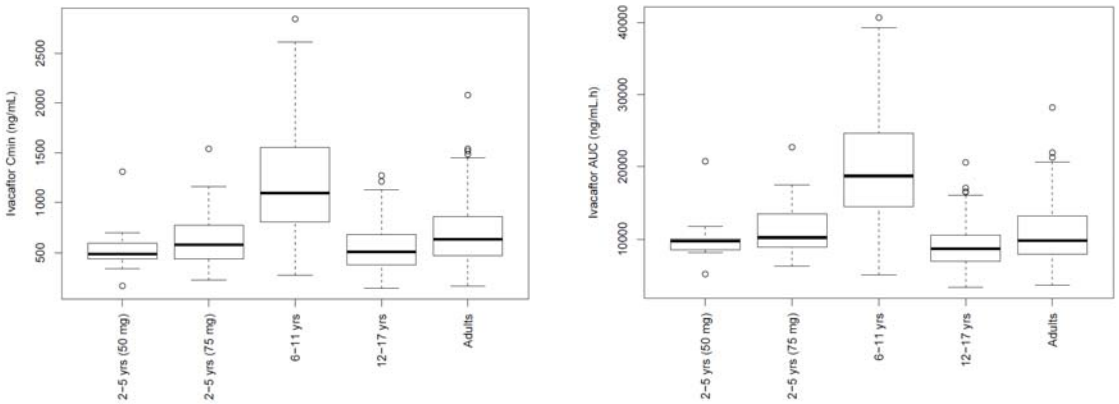
Source k199 report, figure 22 (left)

Reference ID: 3704631

3.4 Model based estimates of exposure

Simulations based on the model and the observed dataset show similar exposure in the pediatric populations and adults, Figure 9.

Figure 9. Predicted distribution of ivacaftor exposure across age-groups



Source k199 report, figures 49 and 50.

Reviewer's comments:

- *The simulation study provided by the sponsor is based on one simulation of the observed dataset. This approach does not utilize the Monte Carlo simulations to their full extent. Therefore, a simulation study was undertaken by the reviewer to assess the robustness of the applicant's conclusions. The original submission did not include NONMEM control stream and dataset used for the simulation study. This issue was resolved in the response to information request dated Dec 10, 2014.*
- *It should be noted that exposure (AUCss) in patients 6-11 years of age is estimated to be 1.87 fold higher than in adult patients, following the approved dosing regimen.*

Reference ID: 3704631

Table 16. Final parameter estimates for the final model (run 1007)

Description	Model	Estimate	%RSE	90% CI	Variability
apparent oral clearance	$CL/F \sim \theta_1 \cdot (WT/70)^{0.75} \cdot \theta_8^{FEMALE} \cdot (AGE/18)^{\theta 9} \cdot \theta_{10}^{HEALTHY} \cdot \theta_{11}^{RACE} \cdot e^{\eta_1}$	16.4 L/h	3.34	(15.5,17.4)	
central volume of distribution	$V_c/F \sim \theta_2 \cdot (WT/70)^{1.0} \cdot e^{\eta_2}$	165 L	4.93	(150,181)	
peripheral volume of distribution	$V_p/F \sim \theta_3 \cdot (WT/70)^{1.0}$	81.7 L	9.19	(59.7,99.0)	
intercompartmental clearance	$Q/F \sim \theta_4 \cdot (WT/70)^{0.75}$	12.1 L/h	21.8	(9.24,14.2)	
first-order absorption rate constant	$K_a \sim \theta_5 \cdot e^{\eta_3}$	0.483 $h^{-}1$	7.69	(0.402,0.557)	
zero-order absorption rate constant	$D1 \sim \theta_6$	3.09 h	3.83	(2.94,3.21)	
female effect on clearance	$FEMALE_{CL/F} \sim \theta_7$	1.08	4.53	(0.997,1.16)	
age effect on clearance	$AGE_{CL/F} \sim \theta_8$	-0.102	29.2	(-0.155,-0.0488)	
disease status (healthy) on clearance	$HEALTHY_{CL/F} \sim \theta_9$	1.31	9.41	(1.16,1.46)	
effect of non-white race on clearance	$RACE_{CL/F} \sim \theta_{10}$	0.964	11.5	(0.869,1.08)	
interindividual variability of clearance	$IIV_{CL/F} \sim \Omega_{1.1}$	0.180	9.66	(0.152,0.216)	%CV = 44.4
interindividual CL-Ka covariance	$cov_{CL,Ka} \sim \Omega_{2.1}$	-0.112	27.3	(-0.168,-0.0670)	CORR = -0.546
interindividual variability of Ka	$IIV_{Ka} \sim \Omega_{2.2}$	0.233	39.0	(0.155,0.544)	%CV = 51.2
interindividual CL-D1 covariance	$cov_{CL,Ka} \sim \Omega_{3.1}$	0.00646	225	(-0.0166,0.0301)	CORR = 0.0477
interindividual Ka-D1 covariance	$cov_{Ka,D1} \sim \Omega_{3.2}$	-0.0332	96.2	(-0.0807,0.0222)	CORR = -0.215
interindividual variability of zero-order absorption	$IIV_{D1} \sim \Omega_{3.3}$	0.102	23.0	(0.0794,0.147)	%CV = 32.8
interoccasion variability in bioavailability	$IOV_{F1} \sim \Omega_{4.4}$	0.105	6.69	(0.0697,0.128)	%CV = 33.3
interoccasion variability in first-order absorption	$IOV_{Ka} \sim \Omega_{22.22}$	0.680	10.3	(0.545,0.903)	%CV = 98.7
interoccasion variability in clearance	$IOV_{CL} \sim \Omega_{40.40}$	0.0818	6.09	(0.0615,0.101)	%CV = 29.2
proportional error	$err_{prop} \sim \Sigma_{1.1}$	0.0207	2.99	(0.0180,0.0298)	%CV = 14.4
additive error	$err_{add} \sim \Sigma_{2.2}$	13000	4.08	(8930,16400)	SD = 114

Source k199 report, table 5.

Reference ID: 3704631

4 REVIEWER'S ANALYSIS

The overall objectives of the reviewer's analysis are to evaluate if the applicant's model can describe the PK data in pediatric patients 2 through 5 years of age and to conduct a sensitivity analysis on the applicant's assumptions about the fixed allometric relationship between bodyweight and exposure. Furthermore, the robustness of the applicant's conclusions are assessed by an independent simulation study. Issues identified in the applicants submission and the corresponding reviewer's work used to address the issues are outlined in Table 17.

Table 17. Motivation for independent analysis

Identified deficiencies in the applicants analysis	Reviewer's analysis to address the identified deficiencies
Model diagnostics submitted to this application were not designed to evaluate the model fit in specific age- and dose-groups.	The reviewer generated standard goodness of fit plots, including |IWRES| vs. IPRED for the overall population and stratified by dose-group. Age-group stratified visual predictive checks have been generated.
The goodness of fit plot (|IWRES| vs. IPRED) used to evaluate the residual model was not submitted in the original submission. However, this was addressed in an IR request.	
A common simulation based diagnostic (Visual predictive check) was not submitted in the original submission. However, this was addressed in an IR request.	
Applicant did not submit the control stream and the dataset for the simulations used to confirmed similar exposure in adult and patients 2-5 years of age. (The control stream and dataset were submitted following an information request)	Applicant's model was used to estimate the exposures in the different age group as outlined in the applicant's simulation plan.
Applicant has utilized fixed allometric relationships between bodyweight and clearance and volume terms without a sensitivity analysis.	A model was developed with estimated allometric components on all clearance and volume terms.
Applicant's simulations study was only based on one simulation of the observed patients.	An independent simulation study was undertaken to assess the robustness of the applicant's conclusions from their simulations.

Reference ID: 3704631

4.1 Methods

4.2 Methods - Reviewers evaluation of the applicant's model

Applicant's NONMEM control stream and dataset were amended to generate output form the applicant's model needed to assess the model fit in the target and the reference population.

An age-group variable was added to the applicant's dataset that would allow generation of stratified GOF plots. Furthermore, time after dose (TAD) was calculated for all individuals and added as a variable in the analysis dataset. The applicants NONMEM control stream was amended to allow calculation of individual weighted residuals as outlined in Table 18.

Table 18. Modifications to the applicants code

Reviewer's code	Applicants original code
Run 1017	Run 1007
(b) (4)	

4.2.1 Methods - Sensitive analysis to assess the allometric scaling assumption in applicant's model

The applicant's model was amended so that the fixed exponents of all clearance and volume parameters were estimated. Goodness of fit for the target and the reference population was assessed by stratified visual predictive check and standard goodness of fit plots. The influence of fixing versus fitting the allometric exponents was evaluated on Empirical Bayes Estimates (EBE) for CL/F. Furthermore, the individual objective function value as well as the objective function value for each age group was evaluated.

4.2.2 Methods - Assessment of robustness of applicant's simulation study

A simulation study was conducted in a simulated population consisting of 500 subjects in 5 age categories (2-5 years <14 kg, 2-5 years ≥14 kg, 6-11 years, 12-17 years, and adults). Each category consisted of 50 male and female subjects. Bodyweight and age were simulated based on reported mean and standard deviation for each age group.

4.2.3 Datasets

Data sets used are summarized in Table 19.

Reference ID: 3704631

Table 19. Analysis Datasets

Study Number	Name	Link to EDR
VX08-770-007 VX09-770-010 VX06-770-101 VX08-770-102 VX08-770-103 VX08-770-104 VX11-770-110 VX11-770-111 VX11-770-108 VX12-770-016	tranmaster.xpt	//Cdsesub1/evsprod/NDA207925/0000/m5/datasets/k199/analysis/legacy/datasets/tranmaster.xpt
Input dataset for run505001.mod	expsim.xpt	//Cdsesub1/evsprod/NDA207925/0004/m5/datasets/k199/analysis/adam/datasets/expsim.xpt

4.2.4 Software

Statistical software R version 3.1.1 was used for data handling and visualization. R package Xpose4 version 4.5 was used for generation of VPC plots. Xpose [3] and Pirana [4,5] version 2.9.0 were used for handling of model and model output files. PSN version 3.6.2 was used for model execution, and for generation of data for the VPC plots.

4.3 Results

4.3.1 Results - Reviewers evaluation of applicants model

The stratified basic goodness of fit plots are shown in Figure 10 A-D. Individual predictions and observations versus time after dose for the target populations are shown in Figure 10 E. Stratified visual predictive checks are shown in Figure 11. Data appears to be well described for all patients except for patients 12 to 17 years of age. The model appears to overestimate the exposure in that age group. The average (min-max) over-prediction of exposure in the 12 to 17 years patient population is estimated to 40 (27-69) %.

Diagnostic plots suggest that the applicant's model is able to describe the data in the targeted (2-5 years of age) population as well as the reference population (adults).

4.3.2 Results - Sensitive analysis to assess the allometric scaling assumption in applicant's model

Estimating the allometric components for clearance and volume terms reduced the objective function (OBJ) value by 21 points (Table 20, (run1015.mod)). However, the largest decrease in OBJ occurred in the adult population (Δ14), while the OBJ increased by 1 point in the patients 2-5 years below 14 kg and decreased by 7 points in patients 2-5 years above 14 kg. The 90% CI interval of the estimated allometric coefficients contained

Reference ID: 3704631

the fixed coefficient in the applicant's model. A stratified VPC shows no apparent improvement in prediction for the reviewer's model (run1015.mod). Simulations illustrating the estimated apparent oral clearance for each individual using the sponsor's model (run1017.mod) and the reviewer's model (run1015.mod) show no apparent difference in prediction Figure 12.

Applicant's conclusions are not sensitive to assumptions of the allometric coefficients for body weight.

4.3.3 Results - Assessment of robustness of applicants simulation study

Based on the empirical bayes estimates of primary pharmacokinetic parameters, the applicant estimated exposures for different age groups. These are shown in Figure 5 and Tables 1 and 2. Given the relative low shrinkage of CL (13%), applicant´s estimate of AUC is viewed as reliable.

The applicant's model was used by reviewer for a Monte Carlo simulation study to assess the exposure in the target population and the reference population. Results of the applicant's and the reviewer's simulation studies are shown in Figure 13. The projected exposure at 12 hr. is nearly identical in the reviewer's and the applicant's simulation studies for the target and the reference populations.

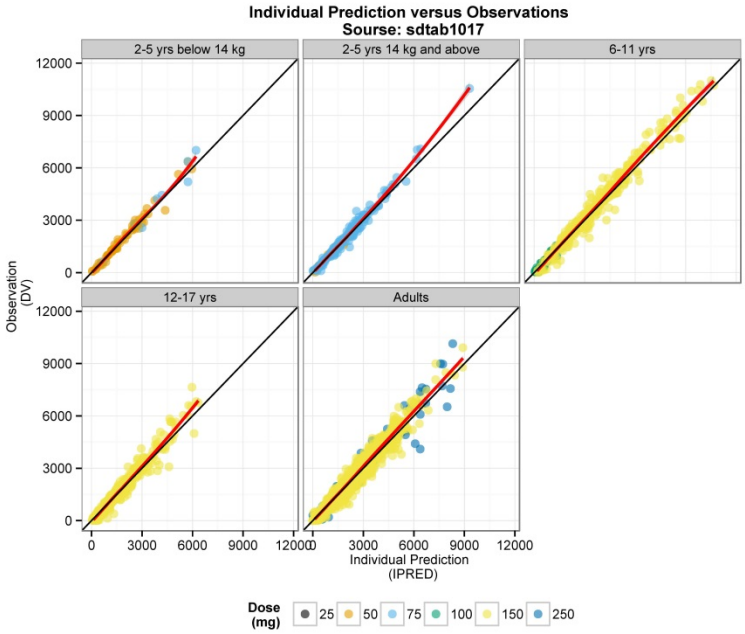
There are some discrepancies in the 6-11 age group as well as in the 12-17 age group, these discrepancies are relatively small. As indicted by visual predictive check in Figure 10, applicant's model shows some degree of overprediction across the entire concentration time range in the 12-17 age group. A comparison of observed and predicted concentration for each binned time interval is shown in Table 10.

The reason for the discreptancy between observed and simulated exposure in the 12-17 age group is not known. However, the purpose of the model is to support approval in the 2-5 age group based on exposure matching. Based on the review of the applicant's submission and independent analysis, the model is deemed qualified for that purpose.

Reference ID: 3704631

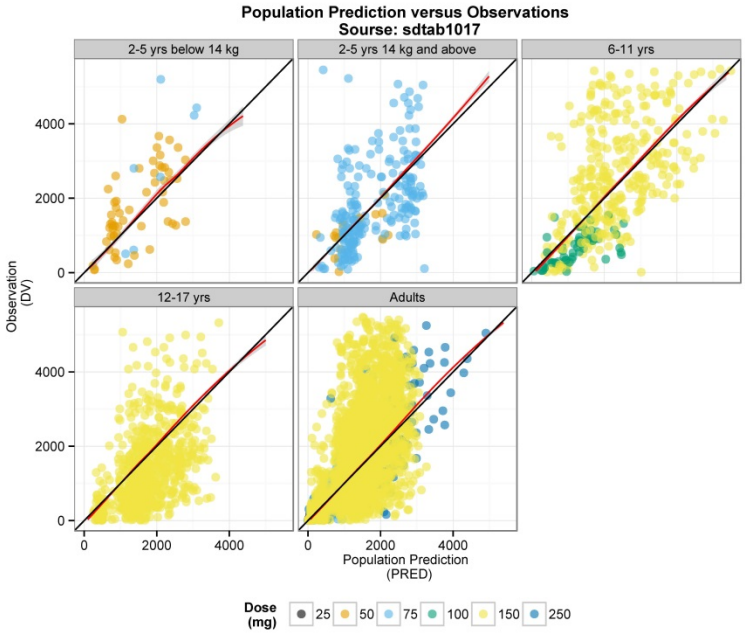
Figure 10 Reviewer generated goodness of fit plots based on the applicant's model.

A



Reviewer's comment No apparent trends are visible.

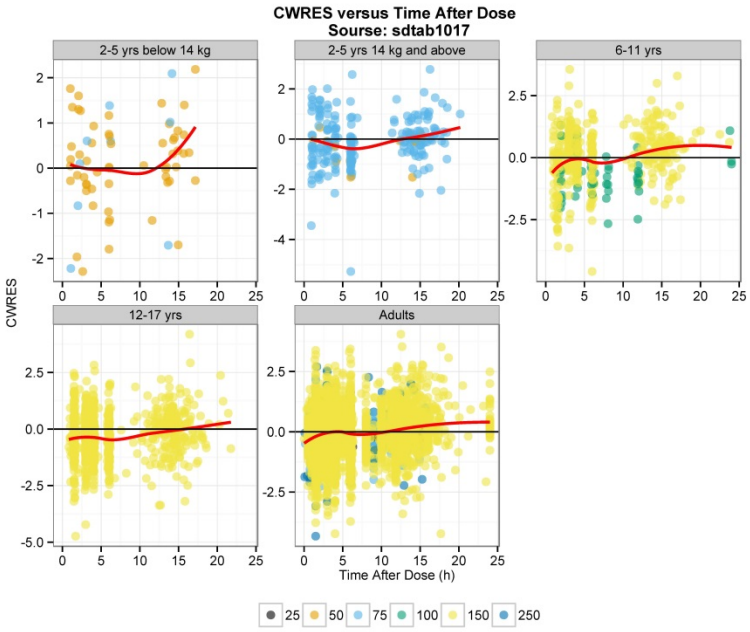
B



Reviewer's comment No apparent trends are visible. However, there are some high observations that are not captured by the model.

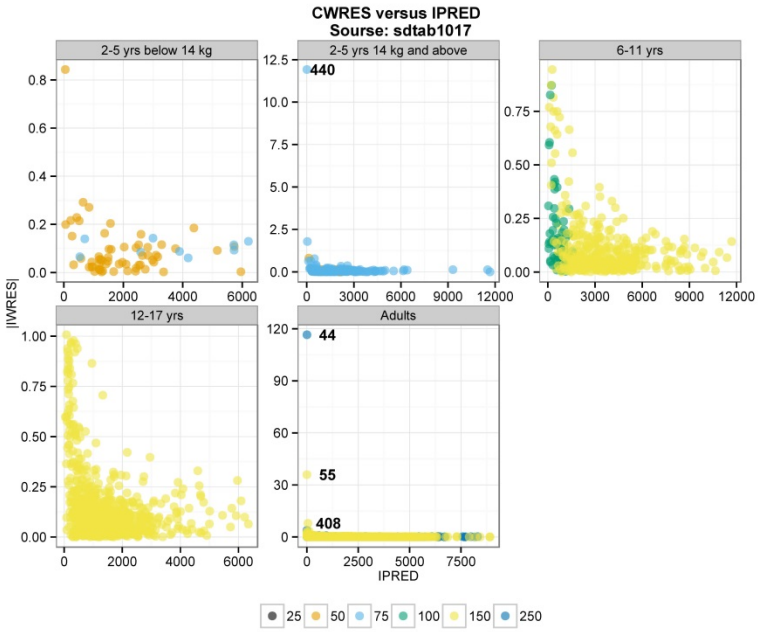
Reference ID: 3704631

C



Reviewer's comment Some trends are visible, especially in the 2-5 yrs, 14 kg and above where a u-shape is visible. This may suggest a need for additional PK compartments in this population.

D



Reviewer's comment The general shape appears to be triangular with a descending slope. This usually suggests that a proportional error model was used when the appropriate model should be an additive error model. The reviewer has fitted sponsors model with only an additive model as opposed to the combined additive and proportional error model used in the applicant's analysis. The objective function increased significantly and the trend in plot was still present.

Reference ID: 3704631

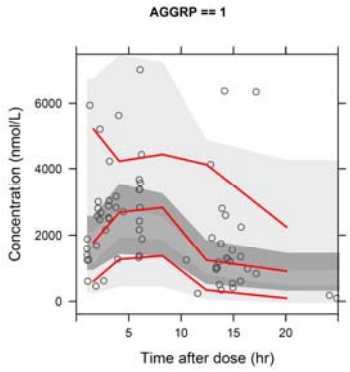
E

Reviewer's comment bodyweight is treated as a time variant covariate. The individual concentrations time profiles are captured adequate by the applicant's model in the target population.

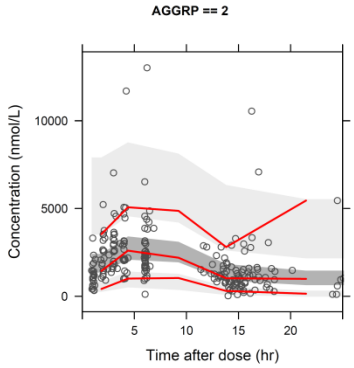
Reference ID: 3704631

F

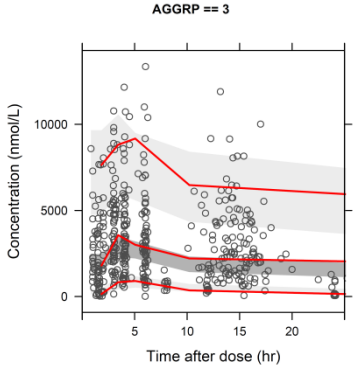
VPC run1017
2-5 yrs. below 14 kg



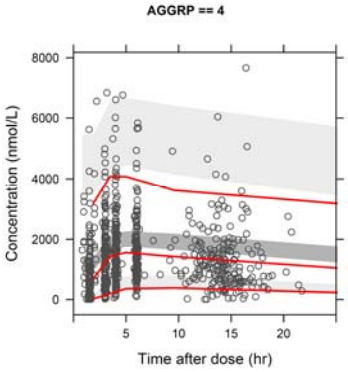
VPC run1017
2-5 yrs. 14 kg and above



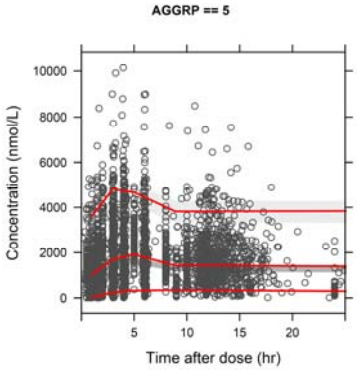
VPC run1017
6-11 yrs.



VPC run1017
12-17 yrs.



VPC run1017
Adults



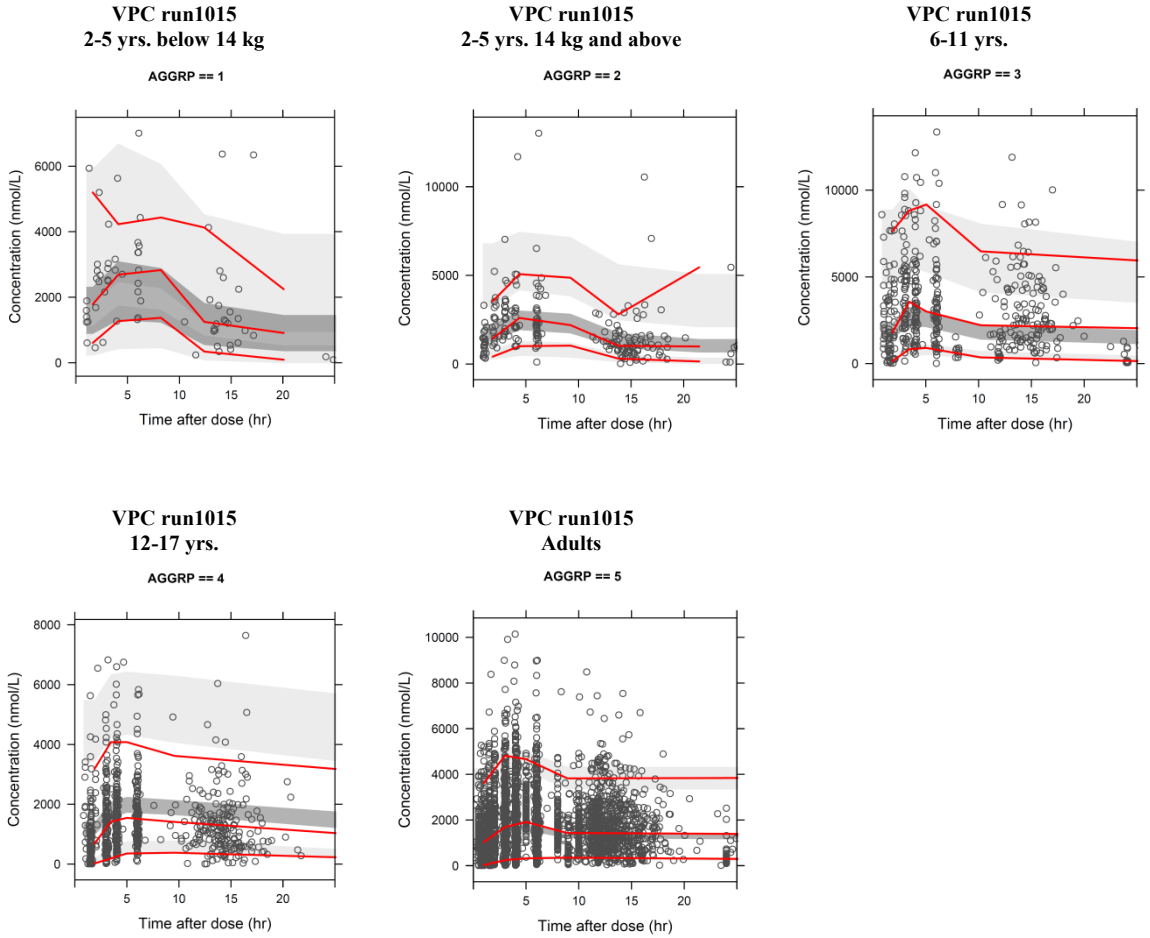
Reviewer's comment There is good agreement between observed and predicted data with the exception to subjects 12-17 years of age. The model generally predicts higher concentrations than what is observed (the prediction interval [shaded areas] of the simulated data is completely above the observed data [red lines]).

The X axis in the VPCs has been restricted to 25 h., resulting in omission of 79 observations. Most (82%) of the omitted observations were from adult patients.

PsN code vpc -samples=2000 -no_of_bins=5 -bin_by_count=1 -dir=vpc_1017.3 1017.mod -lst_file=1017.lst -stratify_on=AGGRP -threads=8 -idv=TAD

Reference ID: 3704631

Figure 11. Visual predictive check for the reviewer derived model (run1015)



Reviewer's comment There is good agreement between observed and predicted data with the exception to subjects 12-17 years of age. The model generally predicts higher concentrations than what is observed (the prediction interval [shaded areas] of the simulated data is completely above the observed data [red lines]). Reviewer's model did not visually improve the fit in patients 12-17 years of age.

The X axis in the VPCs has been restricted to 25 h., resulting in omission of 79 observations. Most (82%) of the omitted observations were from adult patients.

PsN code vpc -samples=2000 -no_of_bins=5 -bin_by_count=1 -dir=vpc_1015 1015.mod -lst_file=1015.lst -stratify_on=AGGRP -threads=8 -idv=TAD

Reference ID: 3704631

Table 20. Objective function value (OBJ) for the applicant's and the reviewer's models.

	Reviewer Run 1015[5]		Sponsor Run 1017[6]		Run1015-Run1017	
Age group	**OBJ[1]**	**Contribution[2] (%)**	**OBJ[1]**	**Contribution[2] (%)**	**ΔOBJ[3]**	**Contribution[4] (%)**
2-5 yrs. below 14 kg	1155	2	1154	2	1	-4
2-5 yrs. 14 kg and above	3094	4	3101	4	-7	35
6-11 yrs.	6790	9	6789	9	2	-8
12-17 yrs.	10371	14	10373	14	-2	10
Adults	50340	70	50354	70	-14	68
Total	**71749**	**100**	**71770**	**100**	**-21**	**100**

[1] *Lower is better.*

[2] *Contribution of age group to overall OBJ.*

[3] *Negative numbers Run1015 is better than run1017. Positive number Run1015 is worse than Run1017.*

[4] *Contribution of age group to overall ΔOBJ. Large positive number more contribution to improvement in OBJ*

[5] *Reviewer's model estimates allometric exponent for all clearance and volume parameters in the model*

[6] *Applicant's model includes fixed allometric exponents of 0.75 and 1 for all clearance and volume parameters in the model.*

Source derived from 1017.phi and 1015.phi

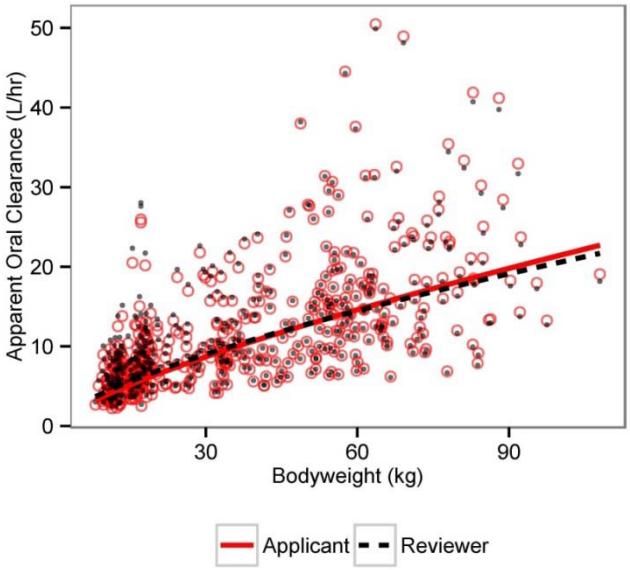
Table 21. Observed and predicted exposure in the 12-17 age group.

Time after dose in hr. (range of bin)		Number of observations per bin	Median observed data (nmol/mL)	Median simulated data (nmol/mL)	95%CI for simulated data (nmol/mL)		Mean bias (%)
0.83	2.95	155	688	1161	957	1397	69
2.95	3.99	147	1419	1808	1538	2093	27
3.99	5.99	150	1544	1985	1740	2268	29
5.99	13.15	164	1410	1892	1638	2186	34
13.15	40.25	153	996	1419	1177	1727	42

Source vpc_results_1017.csv

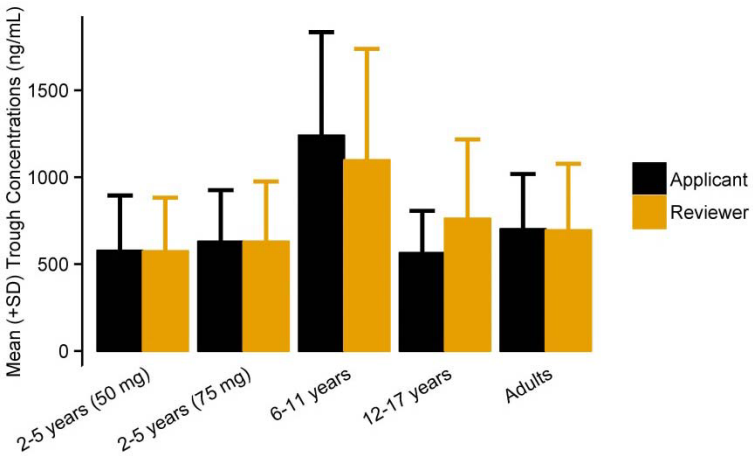
Reference ID: 3704631

Figure 12. Predicted apparent oral clearance based on a fixed allometric exponent of 0.75 (Applicant's model) and an estimated allometric exponent of 0.687 (Reviewer's model)



Sourse sdtab1021 and sdtab1022

Figure 13. Predicted distribution of ivacaftor exposure across age-groups based on the applicant's and the reviewer's model



Source sdtab1021 and k199 report, table 6.

Reviewer's comment Applicants simulation results were recreated by the reviewer. Reviewer's model did not result in any meaningful difference in exposure at steady state. It should be noted that subjects age 6 through 11 have approximately 1.77 times the exposure of adult population.

Reference ID: 3704631

5 LISTING OF ANALYSES CODES AND OUTPUT FILES

Table 22. List of NONMEM datasets, output files and control streams.

NONMEM control stream	Dataset	Output	Description	Location in \\cdsnas\pharmacometrics\
run1005 mod	Transmaster.csv		Applicant's base model	
run1007 mod	Transmaster.csv		Applicant's final model	
run1015 mod	Transmaster2.csv	sdtab1015 1015.phi	Model with estimated allometric exponent	
run1017 mod	Transmaster2.csv	sdtab1017 1017.phi	Applicant's final model used by reviewer to generate GOF plots	
run1018 mod	Transmaster2.csv	sdtab1017	Applicant's final model with additive error only	
run1021 mod	SimData.csv	sdtab1021	Simulation control-stream to for model run1017 mod	
run1022 mod	SimData.csv	Sdtab1022	Simulation control-stream to for model run1015 mod	
run505001 mod	Expsim.csv	505001-tab.txt	Applicants simulation control stream for model run1005.mod	

Reference ID: 3704631

Table 23. List of R programs and datasets used for post processing and generation of figures and tables

R program	Dataset	Output	Description	Location in \\cdsnas\pharmacometrics\
Data.R	transmaster xpt.	transpaster2.csv	R code to generate transmaster2.csv from	
model.check.R	sdtab1017	Figure 2 Figure 3 Figure 6 A-E Table 1 Table 2	R code and data to generate Figure 2, Figure 3, Figure 10 A-E and Table 14 and Table 15.	
VPC_run1015.R	vpc_results_1015	Figure 11 Figure 10	R code and data to generate Figure 11 and data for Figure 10	
VPC_run1017.R	vpc_results_1017	Figure 10 F.	R code and data to generate Figure 10 F.	
PHI.R	1017.phi 1015.phi	Table 20.	R code and data to generate data in Table 20.	
SimData.R		SimData.csv Figure 8 Figure 9	R code to generate SimData.csv and generate Figure 7 and Figure 9.	

Reference ID: 3704631

6 LITERATURE REFERENCES

1. Anderson, B. J. & Holford, N. H. Mechanistic basis of using body size and maturation to predict clearance in humans. *Drug Metab. Pharmacokinet.* **24**, 25–36 (2009).
2. Savic, R. M. & Karlsson, M. O. Importance of shrinkage in empirical bayes estimates for diagnostics: problems and solutions. *AAPS J* **11**, 558–69 (2009).
3. Jonsson, E. N. & Karlsson, M. O. Xpose--an S-PLUS based population pharmacokinetic/pharmacodynamic model building aid for NONMEM. *Comput Methods Programs Biomed* **58**, 51–64 (1999).
4. Keizer, R. J., Benten, M. van, Beijnen, J. H., Schellens, J. H. & Huitema, A. D. Piraña and PCluster: a modeling environment and cluster infrastructure for NONMEM. *Comput Methods Programs Biomed* **101**, 72–9 (2011).
5. Keizer, R. J., Karlsson, M. O. & Hooker, A. Modeling and Simulation Workbench for NONMEM: Tutorial on Pirana, PsN, and Xpose. *CPT Pharmacometrics Syst Pharmacol* **2**, e50 (2013).

Reference ID: 3704631

4.3 Appendix 3 – New Drug Application Filing and Review Form

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information about the Submission

	Information		Information
NDA/BLA Number	**207925**	**Brand Name**	**Kalydeco granules**
OCP Division (I, II, III, IV, V)	**II**	**Generic Name**	**Ivacaftor**
Medical Division	**Pulmonary, Allergy, and Rheumatology Products**	**Drug Class**	**Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) potentiator**
OCP Reviewer	**Jianmeng Chen**	**Indication(s)**	**CF patients 2-5 yr with approved mutations**
OCP Team Leader	**Brar Satjit**	**Dosage Form**	**Granules (50mg, 75mg/pack)**
Pharmacometrics Reviewer	**Dinko Rekic**	**Dosing Regimen**	**Weight based dosing, 75 mg BID for patients ≥14kg; 50 mg BID for patients 7 to <14kg**
Pharmacometrics Team Leader	**Liang Zhao**		
Date of Submission	**9/17/2014**	**Route of Administration**	**Oral**
Estimated Due Date of OCP Review	**2/21/2015**	**Sponsor**	**Vertex**
PDUFA Due Date	**3/17/2015**	**Priority Classification**	**P**

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**x**			
Tabular Listing of All Human Studies	**x**			
HPK Summary	**x**			
Labeling	**x**			
Reference Bioanalytical and Analytical Methods		**1**		
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Transporter specificity:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	**X**	**2**		Study 012 and 015
multiple dose:				
Patients-				
single dose:				
multiple dose:	**X**	**1**		Study 108
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				

Reference ID: 3704631

In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:	**X**	**1**		Study 108
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:	**X**	**1**		K199 with data in study 108
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies	**X**			Mutations in CFTR was characterized in subjects in study 108
QT studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		**3**		

Reference ID: 3704631

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JIANMENG CHEN
02/20/2015

DINKO REKIC
02/20/2015

LIANG ZHAO
02/20/2015

SATJIT S BRAR
02/20/2015

BIOPHARMACEUTICS REVIEW Office of New Drug Quality Assessment			
Application No.:	NDA 207-925	**Reviewer:** Kareen Riviere, Ph.D.	
Submission Date:	9/17/2014		
Division:	DPARP	**Team Leader:** Tapash Ghosh, Ph.D.	
Applicant:	Vertex Pharmaceuticals Incorporated	**Acting Supervisor:** Paul Seo, Ph.D.	
Trade Name:	Kalydeco®	**Date Assigned:**	9/19/2014
Generic Name:	ivacaftor	**Date of Review:**	1/7/2015
Indication:	Treatment of cystic fibrosis (CF) in patients 2 years of age and older who have one of the following mutations in the CFTR gene: *G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N,* or *S549R*	**Type of Submission:** 505(b)(2) NDA	
Formulation/strengths:	IR granules; 50 mg and 75 mg		
Route of Administration:	Oral		

SUMMARY:

This submission is a 505(b)(2) New Drug Application for Kalydeco® (ivacaftor) 50 mg and 75 mg immediate release granules. The proposed indication is for the treatment of cystic fibrosis (CF) in patients 2 years of age and older who have one of the following mutations in the CFTR gene: *G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N,* or *S549R.*

The Biopharmaceutics review for this NDA is focused on the evaluation and acceptability of the proposed dissolution method and acceptance criterion.

A. Dissolution Method

The proposed dissolution method is:

USP Apparatus	Rotation Speed	Media Volume	Temp	Medium
2	65 rpm	900 ml	37 °C	50 mM phosphate buffer (pH 6.8) w/ 0.4% SLS

The dissolution method is deemed acceptable.

B. Dissolution Acceptance Criterion

The proposed dissolution acceptance criterion is:

Acceptance Criterion
Q = (b)(4)% at 20 min

The dissolution acceptance criterion is deemed acceptable.

RECOMMENDATION:

1. NDA 207-925 for Kalydeco® (ivacaftor) 50 mg and 75 mg immediate release granules is recommended for approval from a Biopharmaceutics perspective.

2. The following dissolution method and acceptance criteria are recommended for both strengths.
   i. Dissolution Method: Apparatus 2, 65 rpm agitation rate, 900 mL media volume, 37 °C, 50 mM potassium phosphate buffer, pH 6.8 with 0.4% SLS.
   ii. Dissolution acceptance criterion: (b)(4)% at 20 minutes.

Kareen Riviere, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Tapash Ghosh, Ph.D.
Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

cc: Dr. Paul Seo

ASSESSMENT OF BIOPHARMACEUTICS INFORMATION

1. Background

Drug Substance

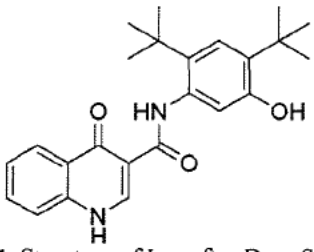


Figure 1. Structure of Ivacaftor Drug Substance

Drug Product

Ivacaftor drug product is an immediate release granule dosage form for oral administration. The ivacaftor granules have a diameter of [redacted] (b) (4) a target weight of 6.87 mg. The Applicant states that individual ivacaftor granules do not exceed the maximum [redacted] (b) (4) stated in FDA Guidance for Industry: Size of [redacted] (b) (4) for Drug Product Labeled for Sprinkle (2012). Each granule contains a target of [redacted] (b) (4) of ivacaftor. The composition of the proposed 50 mg and 75 mg strength ivacaftor granules is shown in Table 1.

Table 1. Composition of Ivacaftor Granules

Component	Quality Standard	Component Function	Amount per 50 mg unit dose (mg)	Amount per 75 mg unit dose (mg)	Content (% w/w)
Ivacaftor (b) (4)	NDA 203188	Active	[redacted]	[redacted]	[redacted] (b) (4)
Lactose monohydrate	USP/NF	[redacted]	[redacted]	[redacted]	[redacted] (b) (4)
Mannitol	USP/NF	[redacted]	[redacted]	[redacted]	[redacted]
Sucralose	USP/NF	[redacted]	[redacted]	[redacted]	[redacted]
Croscarmellose sodium	USP/NF	[redacted]	[redacted]	[redacted]	[redacted]
Colloidal silicon dioxide	USP/NF	[redacted]	[redacted]	[redacted]	[redacted]
Magnesium stearate	USP/NF	[redacted]	[redacted]	[redacted]	[redacted]
Total	---	---	**178.6**	**268.0**	**100.0**

[redacted] (b) (4)

2. Dissolution Method

The proposed dissolution method is shown below.

USP Apparatus	Rotation Speed	Media Volume	Temp	Medium
2	65 rpm	900 ml	37 °C	50 mM phosphate buffer (pH 6.8) w/ 0.4% SLS

3 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

[redacted]

3. Dissolution Acceptance Criterion

The proposed dissolution acceptance criterion is shown below.

Acceptance Criterion
Q = (b) (4)% at 20 min

These representative lots show acceptable release of ivacaftor at 20 minutes through 12 months as shown in Figure 8 below.

Figure 8. Dissolution Results at the 20 Minute Time-Point

(b) (4)

[redacted]

Reviewer's Assessment:

The proposed acceptance criterion was shown to have adequate discriminating ability and would be able to reject batches that resulted in lower bioavailability (refer to Figure 5 above). Additionally, the stability data in Figure 8 further supports that the proposed acceptance criterion is adequate. Thus, the proposed acceptance criterion is deemed acceptable.

Kareen Riviere -S

Digitally signed by Kareen Riviere -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Kareen Riviere -S, 0.9.2342.19200300.100.1.1=2000386237
Date: 2015.01.07 15:28:48 -05'00'

Tapash K. Ghosh -S

Digitally signed by Tapash K. Ghosh -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300148262, cn=Tapash K. Ghosh -S
Date: 2015.01.07 15:35:39 -05'00'

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information about the Submission

	Information		Information
NDA/BLA Number	**207925**	**Brand Name**	**Kalydeco granules**
OCP Division (I, II, III, IV, V)	**II**	**Generic Name**	**Ivacaftor**
Medical Division	**Pulmonary, Allergy, and Rheumatology Products**	**Drug Class**	**Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) potentiator**
OCP Reviewer	**Jianmeng Chen**	**Indication(s)**	**CF patients 2-5 yr with approved mutations**
OCP Team Leader	**Brar Satjit**	**Dosage Form**	**Tablet**
Pharmacometrics Reviewer	**Dinko Rekic**	**Dosing Regimen**	**Weight based dosing, 75 mg BID for patients ≥14kg; 50 mg BID for patients 7 to <14kg**
Pharmacometrics Team Leader	**Liang Zhao**		
Date of Submission	**9/17/2014**	**Route of Administration**	**Oral**
Estimated Due Date of OCP Review	**2/21/2015**	**Sponsor**	**Vertex**
PDUFA Due Date	**3/17/2015**	**Priority Classification**	**P**

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**x**			
Tabular Listing of All Human Studies	**x**			
HPK Summary	**x**			
Labeling	**x**			
Reference Bioanalytical and Analytical Methods		**1**		
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Transporter specificity:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	**X**	**2**		Study 012 and 015
multiple dose:				
Patients-				
single dose:				
multiple dose:	**X**	**1**		Study 108
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				

Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:	**X**	**1**		Study 108
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:	**X**	**1**		K199 with data in study 108
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies	**X**			Mutations in CFTR was characterized in subjects in study 108
QT studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		**3**		

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	
2	Has the applicant provided metabolism and drug-drug interaction information?			X	No update
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	X			
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	X			
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			X	The efficacy was extrapolated from data >6 years old. No E-R analysis was done in 2-5 year old group.
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	The pediatric studies were done w/o an WR
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	The pediatric studies were done w/o an WR

17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?		X		

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
_____Yes__

If the NDA/BLA is not fileable from the clinical pharmacology 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.
- None

Submission in brief:

Indication and mechanism of action

This is a new NDA to expand the approved indications of Kalydeco (ivacaftor, NDA203188, initially approved on 31 January 2012) to include pediatric patients 2 to 5 years of age. Ivacaftor is a selective potentiator of the CFTR protein that was approved "for the treatment of cystic fibrosis in patients age 6 years and older who have one of the following mutations in the CFTR gene: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, or S549R" in the United States.

The proposed dose of ivacaftor granules for patients 2 to 5 years of age is 50 mg (<14kg) or 75 mg (≥14 kg) q12h administered with fat-containing food. Ivacaftor received an orphan drug designation, fast track designation, and breakthrough therapy designation.

Summary of information submitted

Cystic fibrosis is a genetic disorder, and it is reasonable to assume that patients 2-5 years of age would have similar disease and similar response to ivacaftor. Therefore, the division agreed in previous interactions that the efficacy of ivacaftor in the 2-5 year old age group could be extrapolated from the 6 years and older data. This NDA contains the following clinical studies:

1. Study 012 was a Phase 1, randomized, open-label, 4-period, 4-sequence, 4-treatment crossover study in healthy adult male subjects to investigate the relative bioavailability of the 150-mg prototype granule formulation of ivacaftor. The study suggested that the bioavailability of the prototype granule was lower than the ivacaftor 150mg tablet.
2. Study 015 was a Phase 1, randomized, open-label, 4-sequence, 4-period, crossover study in healthy male subjects designed to investigate (1) the relative bioavailability of 150 mg of ivacaftor dosed as the granule formulation (2 × 75-mg) 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 the 150-mg granule formulation (2 × 75-mg); and (3) the dose

proportionality of the ivacaftor granule formulation between doses of 50 mg (1 × 50-mg) and 150 mg (2 × 75-mg) in the fed state. The formulation used in study 015 is the same as study 108 and the to-be-marketed formulation.

3. Study 108 was a 2-part, open-label, single-arm, Phase 3 study designed to assess safety, PK, and PD of ivacaftor treatment (50-mg for subjects <14 kg; or 75-mg for subjects ≥14 kg; q12h) in subjects 2 through 5 years of age.
4. A population PK model (pop PK report K199) that describes ivacaftor disposition was utilized for evaluation of sparse PK data obtained in Study 108.
5. All subjects who completed 24 weeks of study drug treatment in Part B were eligible to enroll in the open-label treatment arm of Study 109.

The clinical pharmacology review will focus on the first 4 studies listed above, and assess the doses for patients 2-5 years old.

OSI inspection

OSI inspection was requested for study 015 and study 108.

Mid-Cycle Deliverables

- Review of dose selection in CF patients 2-5 years old
- High level labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JIANMENG CHEN
11/25/2014

SATJIT S BRAR
11/26/2014