

### NDA Multi-Disciplinary Review and Evaluation

<b>Application Type</b>	Efficacy Supplement
<b>Application Number(s)</b>	NDA 207925 S-016
<b>Priority or Standard</b>	Priority
<b>Submit Date(s)</b>	November 3, 2022
<b>Received Date(s)</b>	November 3, 2022
<b>PDUFA Goal Date</b>	May 3, 2023
<b>Division/Office</b>	Pulmonology, Allergy, and Critical Care (DPACC)/Immunology and Inflammation (OII)
<b>Review Completion Date</b>	May 2, 2023
<b>Established/Proper Name</b>	Ivacaftor
<b>(Proposed) Trade Name</b>	Kalydeco
<b>Pharmacologic Class</b>	Cystic fibrosis (CF) transmembrane conductance regulator (CFTR) potentiator
<b>Applicant</b>	Vertex Pharmaceuticals Incorporated
<b>Dosage form</b>	Oral Granules
<b>Applicant proposed Dosing Regimen</b>	<ul style="list-style-type: none"> <li>1 to &lt;2 months of age, weighing <math>\geq 3</math> kg: 5.8 mg q12h with fat-containing food or liquid</li> <li>2 to &lt;4 months of age, weighing <math>\geq 3</math> kg: 13.4 mg q12h with fat-containing food or liquid</li> </ul>
<b>Applicant Proposed Indication(s)/Population(s)</b>	Age 1 month to < 4 months
<b>Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication</b>	190905008  Cystic fibrosis (disorder)
<b>Recommendation on Regulatory Action</b>	Approval
<b>Recommended Indication(s)/Population(s) (if applicable)</b>	Expand CF indication to include patients 1 month to less than 4 months old and weighing $\geq 3$ kg
<b>Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)</b>	190905008  Cystic fibrosis (disorder)
<b>Recommended Dosing Regimen</b>	<ul style="list-style-type: none"> <li>1 to &lt;2 months of age, weighing <math>\geq 3</math> kg: 5.8 mg q12h with fat-containing food or liquid</li> <li>2 to &lt;4 months of age, weighing <math>&gt; 3</math> kg: 13.4 mg q12h with fat-containing food or liquid</li> </ul>

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

OPQ=Office of Pharmaceutical Quality

OPDP=Office of Prescription Drug Promotion





OSE= Office of Surveillance and Epidemiology

DMEPA=Division of Medication Error Prevention and Analysis

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NDA Multi-disciplinary Review and Evaluation {NDA 207925 S-016}  
{Kalydeco/ivacaftor Oral Granules}

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NDA Multi-disciplinary Review and Evaluation {NDA 207925 S-016}  
 {Kalydeco/ivacaftor Oral Granules}

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## Glossary

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AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonisation
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science

NDA Multi-disciplinary Review and Evaluation {NDA 207925 S-016}  
{Kalydeco/ivacaftor Oral Granules}

OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert (also known as Patient Information)
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event



## 1 Executive Summary

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### 1.1. Product Introduction

Ivacaftor is an orally bioavailable small molecule that potentiates CFTR protein chloride transport in patients with cystic fibrosis (CF) with mutations in the *CFTR* gene responsive to CFTR chloride channel potentiation. The chemical name for ivacaftor is N-(2,4 Di-tert-butyl-5-hydroxyphenyl)-1,4-dihydro-4-oxoquinoline-3-carboxymide.

Ivacaftor tablets (NDA 203188) were initially approved on January 31, 2012, for the treatment of CF in patients  $\geq 6$  years of age who have a G551D mutation in the *CFTR* gene at a dose of 150 mg every 12 hours (BID) with a fat-containing food.

- On February 21, 2014, the indication was expanded to include the following additional mutations: G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, or S549R.
- On December 29, 2014, the indication was again expanded to include patients with an R117H mutation.
- On March 17, 2015, a new granule formulation of ivacaftor was approved, which included approval for the 2 to 5-year-old age group at a dose of 75 mg BID for patients  $\geq 14$ kg and 50 mg BID for patients 7 to  $<14$ kg. The granule formulation was more age-appropriate, as the granules may be mixed with soft food or liquid for administration.
- On May 17, 2017, the indication statement was changed to include at least one mutation in the *CFTR* gene responsive to ivacaftor, rather than a list of mutations.
- On August 15, 2018, the indication was expanded to patients 1 year and older who have one mutation in the *CFTR* gene that is responsive to ivacaftor based on clinical and/or in vitro assay data, with dosing the same as for the 2-to 5-year-old age group.
- On April 29, 2019, the indication was again expanded to patients 6 months of age and older who have one mutation in the *CFTR* gene that is responsive to ivacaftor based on clinical and/or in vitro assay data. The dosing for 6 months to  $<6$  years of age is:
  - 5 kg to  $<7$  kg: one 25 mg packet of granules q12h
  - 7 kg to  $<14$  kg: one 50 mg packet of granules q12h
- On September 24, 2020, the indication was expanded to patients 4 months of age and older who have one mutation in the *CFTR* gene that is responsive to ivacaftor based on clinical and/or in vitro assay data. This is the current indication for ivacaftor. The approved dose for patients 4 months to less than 6 months of age and weighing  $\geq 5$  kg is one 25 mg packet of granules q12h.

In this supplemental NDA (sNDA) application, the Applicant proposes to expand the age range to include patients 1-month to less than 4 months old, with a proposed dosing regimen of:

(b) (4)

## 1.2. Conclusions on the Substantial Evidence of Effectiveness

The recommended regulatory action is **Approval** for ivacaftor granules for the treatment of CF in pediatric patients 1-month to <4 months of age who have one mutation in the CFTR gene that is responsive to ivacaftor based on clinical and/or in vitro assay data, with a revised dosing regimen of:

- 5.8 mg q12h for patients 1-month to less than 2-months-of age, and weighing  $\geq 3$  kg; and
- 13.4 mg q12h for patients 2-months to <4 months of age, and weighing  $\geq 3$  kg

This recommendation is based on the extrapolation of efficacy from the  $\geq 12$ -year-old patient population using ivacaftor tablets (NDA 203188) and review of safety data in the 1-month to less than 4-month-old population using the approved dosing.

In this sNDA, the Applicant has submitted an analysis from a pharmacokinetic (PK)/safety study (Trial 124) to support the use of ivacaftor in patients 1 to less than 4 months of age who have a CFTR mutation for which ivacaftor is indicated (Cohort 8). Trial 124 is a two-part, multiple age cohort, open-label, PK and safety trial in patients 1 to less than 24 months of age. The submitted interim analysis included patients 1 month to less than 4 months old. Seven patients were enrolled in Part A/B Cohort 8. Given that the disease process in the older population is the same as that in the 1 to <4-month-old population, efficacy in the proposed age group was extrapolated from the  $\geq 12$ -year-old age group, where efficacy had been demonstrated in clinical trials. Additionally, data from Part A/B in Cohort 8 showed a decrease in the pharmacodynamic (PD) endpoint of sweat chloride at Week 24 of -40.3 mmol/L, suggesting a PD response to ivacaftor treatment. Trial 124 did not reveal new safety signals.

### 1.3. Benefit-Risk Assessment

#### Benefit-Risk Summary and Assessment

Ivacaftor, in the tablet and granule formulation, is approved for the treatment of CF in patients 4 months and older who have one mutation in the CFTR gene that is responsive to ivacaftor based on clinical and/or in vitro assay data. In this sNDA, the Applicant has submitted data from an interim analysis of a pharmacokinetic/safety trial (Trial 124) to support the use of ivacaftor in patients (b) (4)

The recommended regulatory action is **Approval** for the proposed age group, but at a revised dose of 5.8 mg q12h for patients 1-month to less than 2-months-of age, and weighing  $\geq 3$  kg; and 13.4 mg q12h for patients 2-months to <4 months of age, and weighing  $\geq 3$  kg. The revised dosing is consistent with the doses studied in Trial 124, cohort 8.

Cystic fibrosis is a rare, progressive, usually fatal autosomal recessive genetic disease. CF affects roughly 30,000 children and adults in the U.S. Ivacaftor is indicated for the treatment of CF in patients aged 4 months and older who have one mutation in the CFTR gene that is responsive to ivacaftor based on clinical and/or in vitro assay data. For CF patients <4 months of age with this group of mutations, there are currently no FDA-approved therapies that treat the underlying cause of disease.

To support this supplemental NDA, the Applicant has submitted an interim analysis from patients 1 month to less than 4 months of age from cohort 8 of Trial 124. Trial 124 is a multiple-age, PK and safety trial in 1 to less than 24-month-old CF patients who have a CFTR mutation for which ivacaftor is indicated. This interim report included 7 patients from the PK and safety portion of the trial. Given that the disease process in the older population is the same as that in the 1 to <4-month-old population, efficacy in the proposed age group was extrapolated from the  $\geq 12$ -year-old age group where efficacy had been demonstrated in clinical trials. Additionally, data from part A/B in cohort 8 demonstrated a decrease in the pharmacodynamic (PD) endpoint of sweat chloride at Week 24 of -40.3 mmol/L, suggesting a PD response to ivacaftor treatment at the studied doses.

No new safety signals were identified based on analyses of deaths, SAEs, and AEs. No safety concerns were identified that would preclude approval or require a REMS. Known safety concerns for ivacaftor, including elevated hepatic transaminases, can be managed and/or monitored through routine pharmacovigilance and labeling.

In summary, the recommendation is **Approval** for ivacaftor for the treatment of CF in patients aged 1 month to less than 4 months of age who have one mutation in the CFTR gene that is responsive to ivacaftor based on clinical and/or in vitro assay data, based on extrapolation of efficacy, and based on acceptable safety risks with no new safety signals identified.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<a href="#">Analysis of Condition</a>	<ul style="list-style-type: none"> <li>• Cystic fibrosis is a rare, progressive, and usually fatal autosomal recessive genetic disease that affects roughly 30,000 children and adults in the US. CF results from mutations in the cystic fibrosis transmembrane conductance regulatory (CFTR) gene that lead to decreased or dysfunctional CFTR protein, which aids in the regulation of salt and water absorption and secretion throughout the body. Lack of properly functioning CFTR causes the clinical sequelae of CF disease: malabsorption of nutrients, inability to mobilize tenacious respiratory secretions, recurrent pulmonary infections, irreversible lung damage, and ultimately, respiratory failure. The median age of survival for a patient with CF is early-to-mid 40s.</li> <li>• Ivacaftor-responsive CFTR mutations account for roughly 13.6% of the US CF population. However, over 2,000 different mutations in the CFTR gene have been identified and have been classified based on a defect in CFTR chloride channel function.</li> </ul>	<p>Cystic fibrosis is a rare, progressive, and usually fatal genetic disease.</p> <p>The CFTR mutations included in this the ivacaftor indication represent approximately 13.6% of the US CF population.</p>
<a href="#">Current Treatment Options</a>	<ul style="list-style-type: none"> <li>• While no cure exists, ivacaftor is the only approved therapy aimed at the cause of CF (i.e. absent or defective CFTR ion channel at the cell surface) in the proposed mutation subpopulations (patients who have one mutation in the CFTR gene that is responsive to ivacaftor based on clinical and/or in vitro assay data). This therapy is currently approved for patients 4 months of age and older. The current</li> </ul>	<p>Ivacaftor is approved for the mutational subpopulation included in this application for patients with CF 4 months of age and older.</p> <p>Given that CF is a genetic disease, it is desirable to expand the population to a</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	application proposes to include patients 1 to <4 months of age for this indication. Other medications are used to treat the signs and symptoms of CF in 1 to <4-month old children with CF, but none are approved to specifically treat CF in this age range.	younger age group that may benefit from use of this drug earlier in life.
<a href="#">Benefit</a>	<ul style="list-style-type: none"> <li>• Efficacy in the proposed age group was extrapolated from the ivacaftor tablet development program in the <math>\geq 12</math>-year-old population where efficacy was demonstrated, because of the similar exposures (PK matching) and disease process.</li> <li>• Decreases in the pharmacodynamic endpoint of sweat chloride were observed in study patients, consistent with findings in the <math>\geq 12</math>-year-old population.</li> </ul>	<p>Ivacaftor granules provide a clinically relevant treatment benefit for CF patients 1 month to &lt;4 months old based on extrapolation of efficacy from the older population.</p> <p>Ivacaftor will be the first CFTR modulator approved for children <math>\geq 1</math> month of age with CF.</p>
<a href="#">Risk and Risk Management</a>	<ul style="list-style-type: none"> <li>• The safety program for ivacaftor in the 1 to less than 4-month-old age group demonstrated a safety profile consistent with the older approved age groups. Regarding known safety concerns (elevated transaminases and cataracts), there was one patient with elevated transaminases leading to treatment discontinuation. No cataracts were observed.</li> <li>• No new safety signals were identified in the proposed population.</li> <li>• No REMS is proposed.</li> </ul>	<p>No new safety signals were identified in this interim analysis of Trial 124.</p> <p>The potential risks of LFT elevation and cataracts can be managed through labeling and routine pharmacovigilance.</p>

#### 1.4. Patient Experience Data

**Patient Experience Data Relevant to this Application** (check all that apply)

<input type="checkbox"/>	<b>The patient experience data that were submitted as part of the application include:</b>	Section of review where discussed, if applicable
<input type="checkbox"/>	Clinical outcome assessment (COA) data, such as	
<input type="checkbox"/>	Patient reported outcome (PRO)	
<input type="checkbox"/>	Observer reported outcome (ObsRO)	
<input type="checkbox"/>	Clinician reported outcome (ClinRO)	
<input type="checkbox"/>	Performance outcome (PerfO)	
<input type="checkbox"/>	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
<input type="checkbox"/>	Patient-focused drug development or other stakeholder meeting summary reports	
<input type="checkbox"/>	Observational survey studies designed to capture patient experience data	
<input type="checkbox"/>	Natural history studies	
<input type="checkbox"/>	Patient preference studies (e.g., submitted studies or scientific publications)	
<input type="checkbox"/>	Other: (Please specify):	
<input type="checkbox"/>	<b>Patient experience data that were not submitted in the application, but were considered in this review:</b>	
<input type="checkbox"/>	Input informed from participation in meetings with patient stakeholders	
<input type="checkbox"/>	Patient-focused drug development or other stakeholder meeting summary reports	
<input type="checkbox"/>	Observational survey studies designed to capture patient experience data	
<input type="checkbox"/>	Other: (Please specify):	
<input checked="" type="checkbox"/>	<b>Patient experience data was not submitted as part of this application.</b>	



## 2 Therapeutic Context

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### 2.1. Analysis of Condition

Cystic fibrosis is an autosomal recessive, progressive, and usually fatal genetic disease most common in the Caucasian population. It occurs in approximately one out of every 3,500 children born in the United States, affecting roughly 30,000 children and adults in the U.S. CF results from mutations in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene that lead to decreased or dysfunctional CFTR protein. CFTR protein aids in the regulation of salt and water absorption and secretion throughout the body. Lack of a properly functioning CFTR ion channel is responsible for the clinical sequelae of CF, including malabsorption of nutrients, and the presence of tenacious respiratory secretions that are difficult to mobilize, leading to recurrent/chronic pneumonia, progressive lung damage, and ultimately respiratory failure. Over 2,000 different mutations in the *CFTR* gene have been identified, with 360 being most commonly associated with disease causation. *CFTR* variants have been classified based on the defect in CFTR chloride channel function. Ivacaftor is currently indicated for the treatment of CF patients in patients aged 4 months and older who have one mutation in the *CFTR* gene that is responsive to ivacaftor based on clinical and/or *in vitro* assay data. These patients have mutations with defective transport of chloride ion through the cell surface and may be class 3 or class 4 *CFTR* mutations. These patients comprise roughly 13.6% of the U.S. CF population. There is no cure for CF and, except for mutation-based subpopulations demonstrated to be responsive to ivacaftor, lumacaftor/ivacaftor, or tezacaftor/ivacaftor, treatment is limited to alleviation of symptoms and treatment of complications. Over the past several decades, with improved care, life expectancy has increased significantly, with the current median age of survival to the fifties.<sup>1</sup>

### 2.2. Analysis of Current Treatment Options

Current therapies used to manage patients with CF are listed in Table 1.

**Table 1. Current Treatments for Cystic Fibrosis**

Active Ingredient	Trade Name	FDA Approved for CF Indication?
<b><i>CFTR Modulators</i></b>		
Ivacaftor	Kalydeco	Yes; patients with CF aged 4 months and older who have one of 97 specified

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<sup>1</sup> Cystic Fibrosis Foundation Patient Registry 2021 Annual Data Report

		mutations (not including <i>F508del</i> )
Lumacaftor/ivacaftor	Orkambi	Yes; patients with CF aged 1 year and older who are homozygous for <i>F508del</i> mutation
Tezacaftor/ivacaftor	Symdeko	Yes; patients with CF aged 6 years and older who have one of 154 specified mutations (including <i>F508del</i> )
Elexacaftor/tezacaftor/ivacaftor	Trikafta	Yes; patients with CF aged 2 years and older who have at least one copy of <i>F508del</i> mutation or at least one copy of 177 specified mutations
<b><i>Inhaled Antibiotics for the Treatment of Pseudomonas aeruginosa</i></b>		
Tobramycin (inhaled)	Bethkis	Yes
Tobramycin (inhaled)	Kitabis Pak	Yes
Tobramycin (inhaled)	TOBI	Yes
Aztreonam (inhaled)	Cayston	Yes
Polymyxin E (IV form given via nebulizer)	Colistin	No
<b><i>Mucolytics</i></b>		
Dornase alpha	Pulmozyme	Yes
Hypertonic saline (3%, 7%)	N/A	No
<b><i>Oral Pancreatic Enzyme Supplementation</i></b>		
Pancrease, pancrelipase	Creon, Pancreaze, Zenpep, Pancrelipase	Yes
<b><i>Inhaled Bronchodilators</i></b>		
Albuterol sulfate	Pro-Air, Ventolin, Proventil, Albuterol	Approved as bronchodilator



Levalbuterol hydrochloride	Xopenex	Approved as bronchodilator
<b>Oral Anti-Inflammatory Agents</b>		
Azithromycin	Zithromax	No
Ibuprofen (high-dose)	Motrin, Advil	No

### 3 Regulatory Background

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#### 3.1. U.S. Regulatory Actions and Marketing History

Ivacaftor tablets (NDA 203188) were initially approved on January 31, 2012, for the treatment of CF in patients  $\geq 6$  years of age who have a G551D mutation in the *CFTR* gene at a dose of 150 mg every 12 hours (BID) with a fat-containing food.

- On February 21, 2014, the indication was expanded to include the following additional mutations: G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, or S549R.
- On December 29, 2014, the indication was again expanded to include patients with an R117H mutation.
- On March 17, 2015, a new granule formulation of ivacaftor was approved, which included approval for the 2 to 5-year-old age group at a dose of 75 mg BID for patients  $\geq 14$ kg and 50 mg BID for patients 7 to  $<14$ kg. The granule formulation was more age-appropriate, as the granules may be mixed with soft food or liquid for administration.
- On May 17, 2017, the indication statement was changed to include at least one mutation in the *CFTR* gene responsive to ivacaftor, rather than a list of mutations.
- On August 15, 2018, the indication was expanded to patients 1 year and older who have one mutation in the *CFTR* gene that is responsive to ivacaftor based on clinical and/or in vitro assay data, with dosing the same as for the 2 to 5-year old age group.
- On April 29, 2019, the indication was again expanded to patients 6 months of age and older who have one mutation in the *CFTR* gene that is responsive to ivacaftor based on clinical and/or in vitro assay data. The dosing for 6 months to  $<6$  years of age is:
  - 5 kg to  $<7$  kg: one 25 mg packet of granules q12h
  - 7 kg to  $<14$  kg: one 50 mg packet of granules q12h
- On September 24, 2020, the indication was expanded to patients 4 months of age and older who have one mutation in the *CFTR* gene that is responsive to ivacaftor based on clinical and/or in vitro assay data. The approved dose for patients 4 months to less than 6 months of age and weighing  $\geq 5$  kg is one 25 mg packet of granules q12h. This is the current indication for ivacaftor.

With the current sNDA, the Sponsor proposes to expand the indication for ivacaftor granules to include the 1 to less than 4-month-old age group. Prior to submission of this sNDA, ivacaftor

has been the subject of multiple regulatory proceedings, as summarized in the following section.

### 3.2. Summary of Presubmission/Submission Regulatory Activity

Interactions between the Applicant and the Agency that are relevant to this sNDA submission are summarized below:

- A pediatric written request (WR), including 2 studies, was issued for ivacaftor on March 11, 2016.

(b) (4)



(b) (4)

- In February 2020, the Applicant submitted a type B meeting request to add an additional cohort, cohort 8, to Trial 124, which is the basis of the current sNDA submission.

## 4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

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### 4.1. Office of Scientific Investigations (OSI)

Given that the submitted data is from a small cohort of the larger Trial 124, the Applicant's data was accepted without repeat site inspections.

### 4.2. Product Quality

The product was reviewed by the Office of Lifecycle Drug Products, Division of Post-Marketing Activities I.

Executive Summary:

Vertex is submitting new dosages, 5.8 mg and 13.4 mg granules, supporting the treatment of CF in patients 1 month to less than 4 months who have at least one mutation in the CFTR gene that is responsive to ivacaftor based on clinical and/or in vitro assay data.

The 13.4 mg (and 5.8 mg) ivacaftor granules differ from the approved Kalydeco granules strengths of 25 mg, 50 mg, and 75 mg, (b) (4) (primary packaging; packets may also be referred to as sachets). 13.4 mg (and 5.8 mg) Kalydeco granules will use the same (b) (4) ivacaftor manufacturers and the same packaging sites as currently approved for Kalydeco granules (25 mg, 50 mg, and 75 mg). 13.4 mg (and 5.8 mg) Kalydeco granules will use the same IVA drug substance (b) (4) as the currently approved Kalydeco granules (25 mg, 50 mg, and 75 mg).

Conclusion and Recommendation:

This efficacy supplement is approvable from CMC perspective.

### 4.3. Clinical Microbiology

Not applicable.

#### **4.4. Devices and Companion Diagnostic Issues**

Not applicable.

## 5 Nonclinical Pharmacology/Toxicology

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### 5.1. Executive Summary

The Applicant submitted an efficacy supplement for Kalydeco (ivacaftor) granules and tablets. No new nonclinical studies were submitted. Nonclinical pharmacology and toxicology studies conducted with Kalydeco (ivacaftor) were reviewed with the original NDA 207925 and NDA 203188 submissions.

Juvenile animal studies with ivacaftor were previously reviewed under IND 74633. In the definitive juvenile rat study, animals received 0, 10, 25, or 50 mg/kg ivacaftor by oral gavage once daily from PND 7 to PND 35. The eye was identified as the target organ of toxicity. Opacity was observed in clinical observations starting at PND 15 in HD animals. Bilateral cataracts in the nucleus of the lens were observed 14/20 HD males and 12/20 HD females at the main study sacrifice. As expected for the finding of cataracts, there was no evidence of reversibility after a 4-week recovery period, and in fact there was evidence of progression. At the recovery sacrifice, cataracts were observed in 9/10 each HD males and females, as well as 2/7 MD females and 1/9 LD females. There was no NOAEL in the study due to the adverse finding of cataracts at all dose levels. However, there is extensive clinical experience with ivacaftor in older children and adults, there is appropriate clinical monitoring and disclosure of the risk of cataracts in place, and there is a significant unmet medical need for the CF indication.

## 6 Clinical Pharmacology

### 6.1. Executive Summary

In this 505b(b)(1) NDA efficacy supplement submission, the Applicant seeks the marketing approval for Kalydeco (ivacaftor) for “the treatment of cystic fibrosis (CF) in patients aged 1 month to less than 4 months old who have at least one mutation in the CFTR gene that is responsive to ivacaftor based on clinical and/or *in vitro* assay data.”

The proposed Kalydeco drug product is a granule dosage form of ivacaftor (IVA). The dosing strengths of IVA granules are 5.8 mg and 13.4 mg per packet. The Applicant proposed dosing regimens in children 1 to less than 4 months of age are listed in Table 2.

**Table 2 Proposed Ivacaftor Dose and Dosing Regimen in Pediatric Patients 1 to < 4 Months**

Age	Weight	Dose	Administration
1 month to less than 2 months	3 kg or greater	One 5.8 mg packet every 12 hours	Mixed with one teaspoon (5 ml) of soft food or liquid and administered orally every 12 hours with fat-containing food
2 months to less than 4 months	3 kg or greater	One 13.4 mg packet every 12 hours	

Given the similarities in the underlying pathophysiology and clinically presentation of CF in pediatrics and adults, it is reasonable to extrapolate efficacy of Kalydeco from older population to the proposed pediatric population based on comparable IVA systemic exposure.

The Clinical Pharmacology review team evaluated the pharmacokinetics (PK) data in Study VX15-770-124 and the population PK (PopPK) analysis in this sNDA submission and found that although the IVA systemic exposure in pediatric patients 1 to less than 4 months of age with the proposed dosing regimen is at the lower end, it is still within the range of systemic exposure of adults and pediatric patients 6 years and older. In addition, the systemic exposure achieved in children 1 to less than 4 months of age is comparable to the exposure in children 4 to 5 months weighing  $\geq 5$  kg and 6 to 11 months weighing 5 to  $<7$  kg following the approved 25 mg dose. Further, the proposed dose was either the studied dose in children 1 to  $<2$  months old (i.e., 5.8 mg), or within the range of studied dose in children 2 to  $<4$  months old (i.e., 13.4 mg) in Study VX15-770-124, which safety results were collected.

Of note, OSI inspection was requested for VX15-770-124 (analytical labs, validation reports and analytical study reports), and the Office of Study Integrity and Surveillance (OSIS) declined to conduct the inspections and concluded that the data from the reviewed studies were reliable based on the OSIS inspection histories in April 2019.

**Recommendations:** The Office of Clinical Pharmacology Division of Immune and Inflammation Pharmacology and Division of Pharmacometrics have reviewed the information submitted under NDA 207925/S016. This pediatric supplement and the proposed dosing regimen for pediatric CF patients 1 to less 4 months of age are approvable from a clinical pharmacology perspective.

## 6.2. Summary of Clinical Pharmacology Assessment

### 6.2.1. Pharmacology and Clinical Pharmacokinetics

The comparisons of systemic exposures (AUC) IVA between children 1 to <4 months of age on the proposed doses and older children/adult on the approved doses are listed in Table 3 based on population PK analysis.

**Table 3 Ivacaftor Exposure by Age Group, Mean (SD)**

Age Group	Dose	AUC <sub>τ, ss</sub> (ng·h/mL)
1 to less than 2 months (≥3 kg) *	5.8 mg q12h	5490 (1310)
2 to less than 4 months (≥3 kg) *	13.4 mg q12h	6730 (3650) †
4 to less than 6 months (≥3 kg) *	25 mg q12h	6480 (2520) ‡
6 to less than 12 months (3 kg to <7 kg) §	25 mg q12h	5360 ‡
6 to less than 12 months (7 kg to <14 kg)	50 mg q12h	9390 (3120) ‡
12 to less than 24 months (7 kg to <14 kg)	50 mg q12h	9050 (3050)
12 to less than 24 months (≥14 kg to <25 kg)	75 mg q12h	9600 (1800)
2 to less than 6 years (<14 kg)	50 mg q12h	10500 (4260)
2 to less than 6 years (≥14 kg to <25 kg)	75 mg q12h	11300 (3820)
6 to less than 12 years	150 mg q12h	20000 (8330)
12 to less than 18 years	150 mg q12h	9240 (3420)
Adults (≥18 years)	150 mg q12h	10700 (4100)
<p>* Patients 1 to less than 6 months of age were of ≥37 weeks gestational age.</p> <p>† Exposures for 2 to less than 4 months of age are predictions based on simulations from the population PK model incorporating data for this age group.</p> <p>‡ Values based on population PK modeling incorporating data from patients 4 to &lt; 6 months of age from Trial 8.</p> <p>§ Value based on data from a single patient; standard deviation not reported.</p>		

## 6.2.2. General Dosing and Therapeutic Individualization

### General Dosing

The proposed dose, dosing regimen, and dosage form for IVA in children 1 to <4 months of age are listed in Table 2.

The following two strengths of IVA granules are proposed to be used in children 1 to <4 months of age. The proposed dosage form (granule) is the identical granule approved in older children up to <6 years of age.

Strengths	(b) (4)
5.8 mg	
13.4 mg	

### Therapeutic Individualization

None.

- Concomitant use of moderate or strong CYP3A inhibitors is not recommended in patients below 1 to less than (b) (4) months of age.
- The use of ivacaftor is not recommended in children 1 to less than (b) (4) months old with hepatic impairment.

### Outstanding Issues

None.

## 6.3. Comprehensive Clinical Pharmacology Review

This sNDA submission contains the following clinical study:

VX15-770-124: A Phase 3, 2-Part, Open-label Study to Evaluate the Safety, Pharmacokinetics, and Pharmacodynamics of Ivacaftor in Subjects with Cystic Fibrosis Who Are Less Than 24 Months of Age at Treatment Initiation and Have an Ivacaftor-Responsive CFTR Mutation.

Analysis of Subjects 1 to <4 Months of Age (Part A/B Cohort 8)

Four PopPK analysis reports:

(b) (4)

(b) (4)



T096: Ivacaftor Simulations to Support Dose Selection for Subjects 1 to Less Than 4 Months of Age in Study VX15-770-124 Cohort 8 to Support the United States Prescribing Information

### 6.3.1. General Pharmacology and Pharmacokinetic Characteristics

General pharmacology and PK of ivacaftor has been reviewed with the original application (NDA 203188 by Dr. Lokesh Jain, archived on 1/18/2012 and NDA 207925 by Dr. Jianmeng Chen, M.D., Ph.D., archived on 11/26/2014).

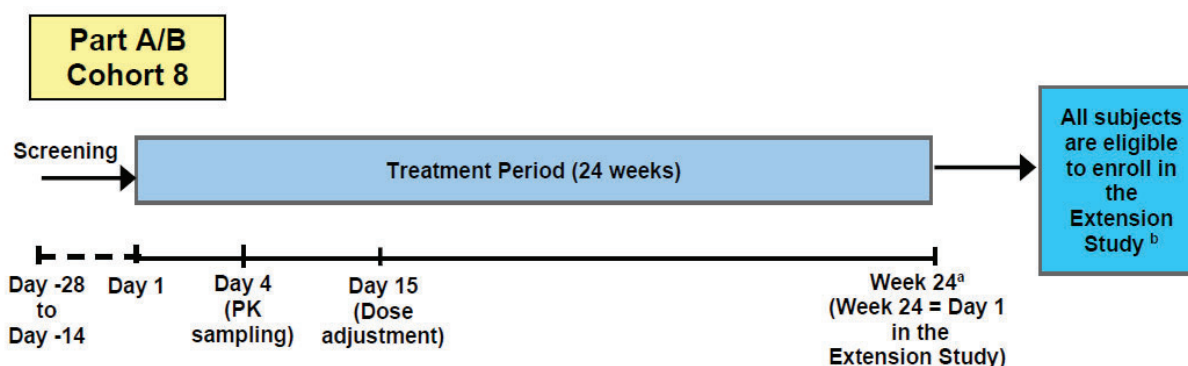
### 6.3.2. Clinical Pharmacology Questions

**Does the clinical pharmacology program provide supportive evidence of effectiveness?**

Yes. PK of IVA granules in children 1 to less than 4 months old were evaluated in Cohort 8 of Study VX15-770-124. Study VX15-770-124 was an open-label study to evaluate the safety, PK, and pharmacodynamics (PD) of IVA in children with CF who are less than 24 months of age at treatment initiation and have an IVA-responsive CFTR mutation (Figure 1).

Subjects received an initial low dose of IVA (based on their Day 1 age and weight) and continued that dose up to Day 15, at which point the dose could have been adjusted to better match the median adult exposure. Subjects were intended to remain on that dose until they were 4 months of age and at least 5 kg, after which the label-recommended age- and weight-appropriate dose(s) was administered.

**Figure 1 Schematic of Study Design (Part A/B Cohort 8)**



OE: ophthalmologic examination; PK: pharmacokinetics

a A Follow-up OE occurred approximately 12 weeks after last dose of study drug unless the subject enrolled in the Extension Study.

b All subjects who completed 24 weeks of study drug treatment were eligible to enroll in the open-label treatment arm of the Extension Study. All other subjects were eligible to enroll in the observational arm

of the Extension Study. Subjects who prematurely discontinued were required to have a Follow-up OE approximately 12 weeks after last dose of study drug.

Source: Figure 9-1 in Clinical Study Report S226 for Study VX15-770-124 Interim Analysis 4

On Days 1 through the morning dose of Day 15, subjects in Cohort 8 received an initial low dose of IVA ( (b) (4) or 11.4 mg, q12h) based on their age and weight at Day 1. (Table 4)

**Table 4 Cohort 8 Starting Doses (Day 1 up to Day 15)**

Age	Weight Range	Starting Dose
1 month	≥3 kg	(b) (4) q12h
2 months	≥3 to <5 kg	(b) (4) q12h
2 months	≥5 kg	11.4 mg q12h
3 months	≥5 kg	11.4 mg q12h

Note: All subjects must have been born within or beyond the 38th week of gestation.

Source: Table 9-1 in Clinical Study Report S226 for Study VX15-770-124 Interim Analysis 4

On Day 4, each subject provided PK samples to assess exposure. The samples were analyzed, and subject data was evaluated, and if appropriate, the dose was adjusted at Day 15 (evening) to (b) (4), 11.4, 17.1, 22.8, or 25 mg q12h to better match the adult median exposure. Subjects remained on this dose until the study visit after reaching 4 months of age and 5 kg, at which point subjects received the approved dose of 25 mg q12h.

A total of 7 subjects were enrolled and included in the Safety Set. Six (85.7%) subjects completed the 24 weeks of treatment. All subjects received an initial low dose of IVA ( (b) (4) or 11.4 mg, q12h) based on their age and weight at Day 1. On Day 4, each subject's exposure was evaluated, and if appropriate, the dose was adjusted on Day 15 (evening) to (b) (4), 11.4, 17.1, 22.8, or 25 mg q12h to better match the adult median exposure. Subjects received this dose until the study visit after reaching 4 months of age and 5 kg, at which point the approved age- and weight-based dosing was initiated. Six of the 7 subjects received an increased dose of 25 mg IVA q12h after reaching 4 months of age and 5 kg; and 1 subject discontinued study drug treatment prior to reaching 4 months of age. (Table 5)

**Table 5 Individual Subject Weight, Day 1 Dose, and Dose Administered Prior to Study Visit, Cohort 8, 1 to <4 Months**

Subject <sup>a</sup>	Day 1			Dose Administered Prior to Study Visit (mg IVA)					
	Age (months)	Weight (kg)	Dose (mg)	Day 15 <sup>b</sup>	Week 4	Week 8	Week 12	Week 18	Week 24
1	1	3.6	(b) (4)	(b) (4)	17.1	17.1	--	--	--
2	1	4.2			(b) (4)	(b) (4)	(b) (4)	25	25
3	1	4.3			11.4	11.4	11.4	25	25
4	2	5	11.4	11.4	17.1	17.1	25	25	50
5	2	6.1	11.4	11.4	22.8	22.8	25	25	50
6	3	5.3	11.4	11.4	22.8	25	25	50	50
7	3	6	11.4	11.4	25	25	25	25	50

a Subjects presented in ascending order of age and weight.

b Subjects received the Day 1 dose of IVA on the morning of Day 15, and received the adjusted dose from the evening of Day 15 and until the visit after reaching 4 months of age and 5 kg, at which point the approved IVA dosing was initiated.

Source: Table 10-2 in Clinical Study Report S226 for Study VX15-770-124 Interim Analysis 4

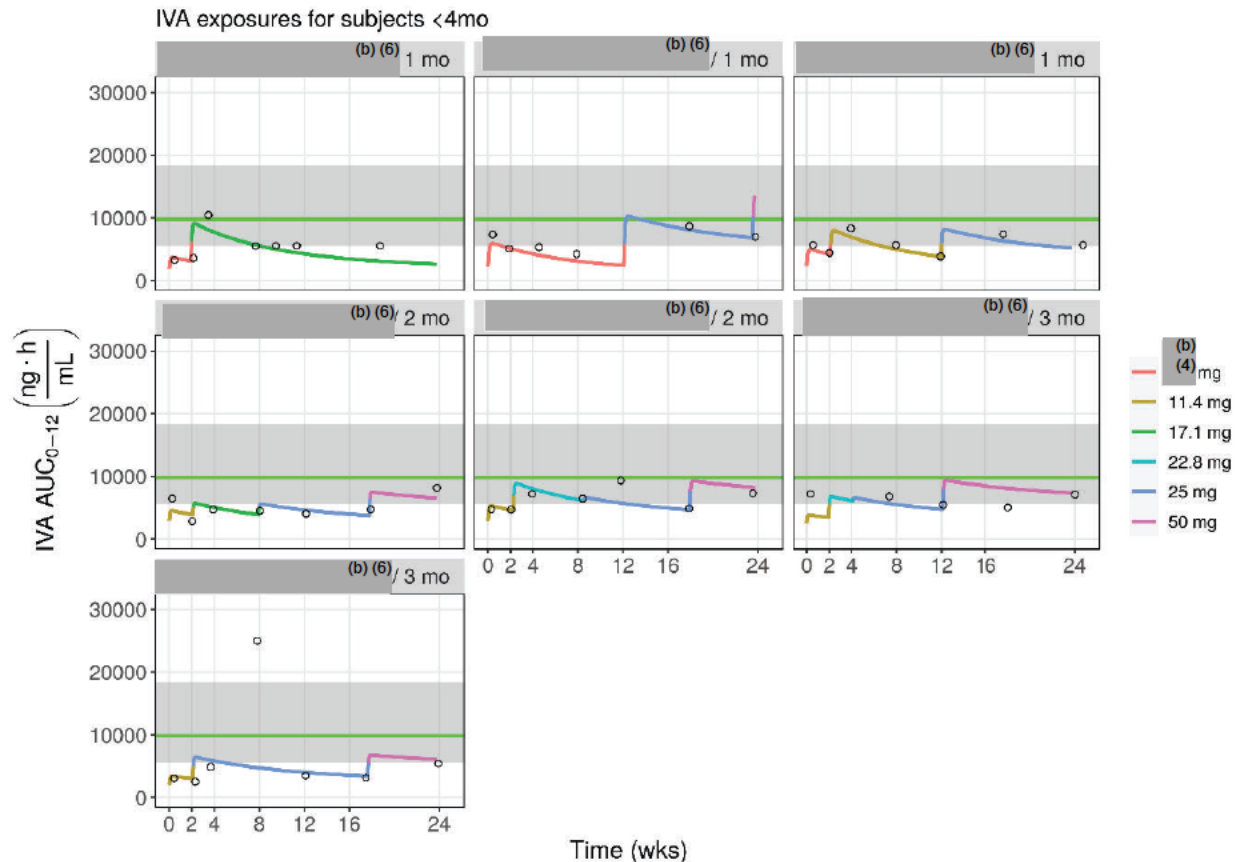
**Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?**

Yes. The proposed dose is reasonable from a clinical pharmacology perspective.

Although the IVA systemic exposure in pediatric patients 1 to less than 4 months of age with the proposed dosing regimen is at the lower end, it is still within the range of systemic exposure of adults and pediatric patients 6 years and older. In addition, the systemic exposure achieved in children 1 to less than 4 months of age is comparable to the exposure in children 4 to 5 months weighing  $\geq 5$  kg and 6 to 11 months weighing 5 to <7 kg following the approved 25 mg dose. Further, the proposed dose was either the studied dose in children 1 to <2 months old (i.e., 5.8 mg), or within the range of studied dose in children 2 to <4 months old (i.e., 13.4 mg) in Study VX15-770-124 (Table 5), which safety results were collected.

Following the studied initial doses in the 7 subjects in Cohort 8, the AUC was predicted using PopPK model and is depicted in Figure 2. The observed AUC in all the 7 subjects were consistently lower (about 40%) than the observed median in adults following the approved dosing regimen at steady state, and on average, the observed AUCs in the 7 subjects were comparable to the 5<sup>th</sup> percentile of the observed AUC in adults.

**Figure 2 Predicted IVA AUC<sub>0-12h</sub> Over Time for the Studied Dosing Regimens for CF Subjects 1 to <4 Months of Age in Cohort 8**



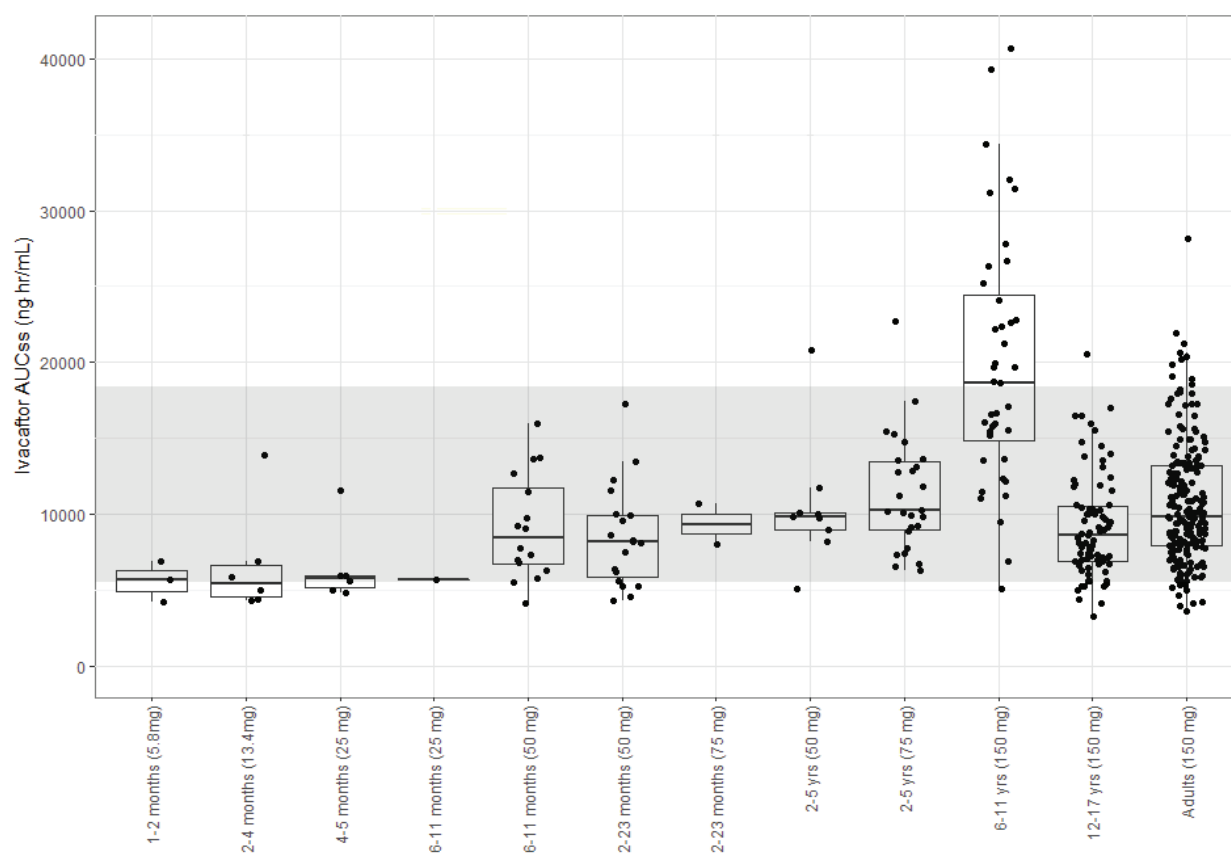
AUC<sub>0-12</sub>: area under the concentration vs time curve from dosing to 12 hours; CF: cystic fibrosis; IVA: ivacaftor; mo: month; wks: weeks

Notes: open circles represent the individual predicted exposures of subjects enrolled in Part B Cohort 8 receiving the dosing regimen listed to the right. Gray area represents the adult 5<sup>th</sup> to 95<sup>th</sup> percentile region of IVA AUC<sub>0-12h</sub> exposures with the median exposure shown as a green line.

Source: Figure 1 Panel B in Response to Information Request dated January 17, 2023

Based on the PopPK model predicted steady state IVA AUC following the proposed dosing regimens in children 1 to <4 months old, IVA exposure fell within the adult exposure range, with a 40% lower systemic exposure on average (Figure 3). See section 18.3.1 Pharmacometrics Review for details. In addition, the predicted steady state IVA AUC in children 1 to less than 4 months of age is comparable to the predicted steady state AUC in children 4 to 5 months weighing ≥ 5 kg and 6 to 11 months weighing 5 to <7 kg following the approved 25 mg dose.

**Figure 3 Predicted IVA AUC0-12h Distribution for Subjects 1 to <4 Months with CF Following the Proposed Dosing Regimens**



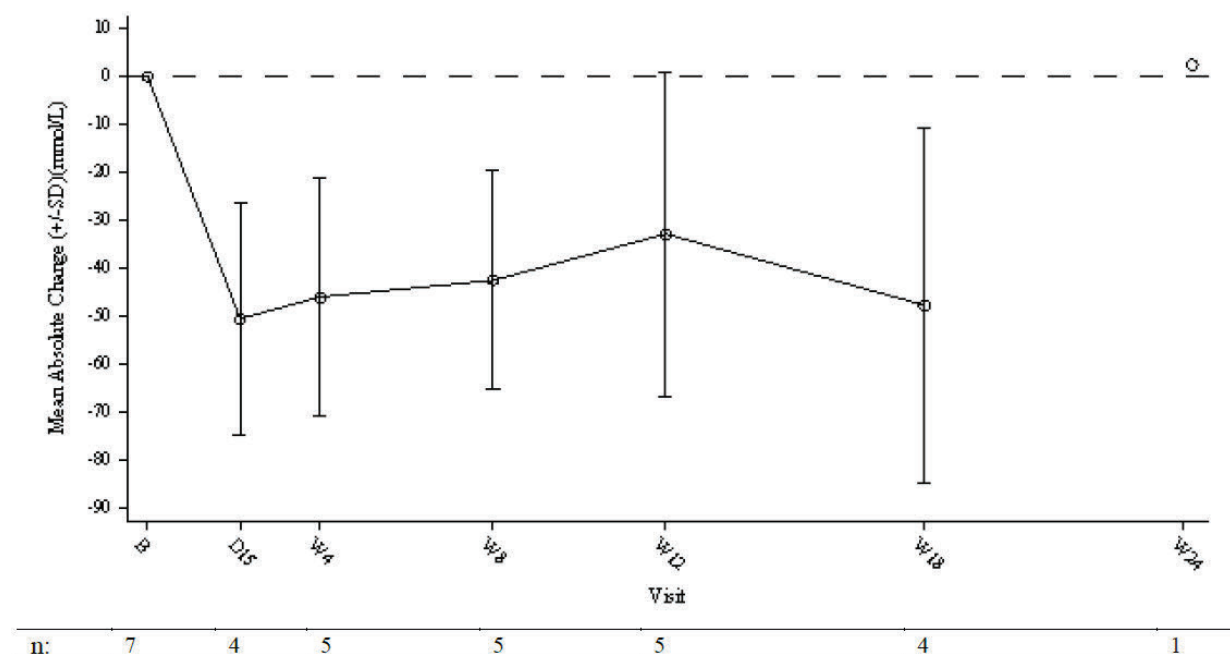
AUC: area under the curve; CF: cystic fibrosis; EBE: empirical Bayes estimate; IQR: interquartile range; IVA: ivacaftor; q12h: every 12 hours

Notes: Boxplots are simulated subjects 1 to <4 months of age, where black lines in the center of the box are medians, boxes are the IQR, and whiskers are the 0.5th to 99.5th percentile region. Circles represent the individual predicted exposures of subjects enrolled in Cohort 8 (blue) and in Part A Cohort 3 (orange) receiving the dosing regimen. Gray area represents the adult 5<sup>th</sup> to 95<sup>th</sup> percentile region of IVA AUC0-12h exposures with the median exposure shown as a green line.

Source: Reproduced by the reviewer based on Figure 1 in Abbreviated Modeling and Simulation Report T096 and Figure 37 in Population PK Analysis Report Q005

The mean (SD) absolute change from baseline in sweat chloride through 24 weeks for patients aged 1 to less than 4 months (n=5) was -40.3 (29.2) mmol/L with the mean (SD) absolute change from baseline in sweat chloride (n=4) as -50.6 (24.2) mmol/L on Day 15 (Figure 4), indicating that the initial low dose IVA treatment in this pediatric age group had similar effect on PD response compared to the relatively higher dose adjusted afterwards. In general, the change from baseline in sweat chloride observed in children 1 to <4 months of age was comparable to that observed in adult patients at the approved dosing regimen (Figure 5).

**Figure 4 Mean Absolute Change from Baseline in Sweat Chloride by Visit, FAS, Cohort 8, 1 to <4 Months**

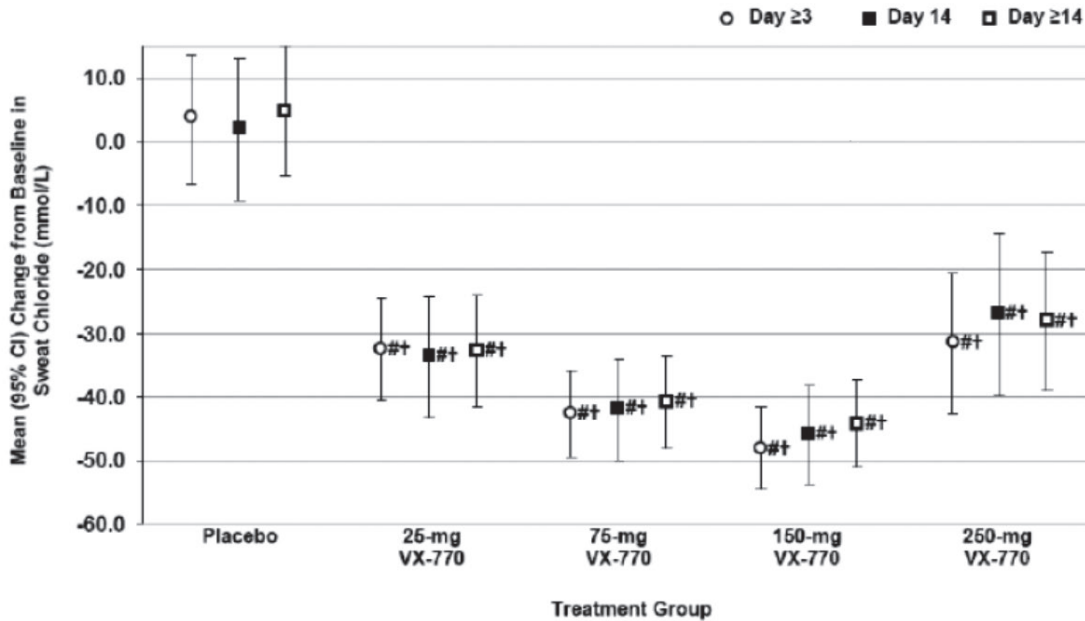


B: baseline; D: day; FAS: Full Analysis Set; IVA: ivacaftor; n: size of subsample; W: week

Notes: The W24 datapoint is not representative of the mean absolute change at W24 due to n = 1, so is not connected to the mean at W18. One subject discontinued study drug treatment at Week 9, but did not discontinue the study until Week 24. Data for this subject were included in the efficacy analyses.

Source; Figure 11-1 in Clinical Study Report S226 for Study VX15-770-124 Interim Analysis 4

**Figure 5 Mean (95% CI) change from baseline in sweat chloride for day ≥ 3, day 14, and day ≥ 14, full analysis set**

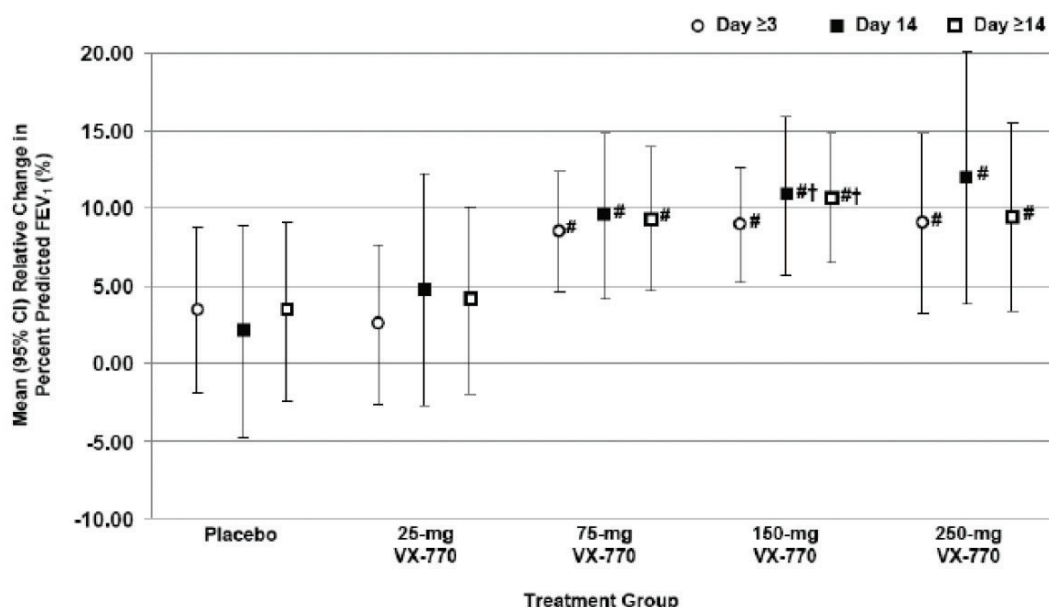


Source: Figure 6 in NDA 203188 Clinical Pharmacology Review by Dr. Lokesh Jain

In addition, the previously reviewed exposure-response analysis for lung function (percent predicted FEV1) change from baseline in adults demonstrated a flat relationship from 75 mg to 150 mg (the approved dose in adults and children 6 years of age and older) (Figure 6), indicating that approximately 50% lower in systemic exposure is unlikely to reduce the efficacy.



**Figure 6 Mean (95% CI) relative change from baseline in percent predicted FEV<sub>1</sub> for day ≥3, day 14, and day ≥14, full analysis data set**



Source: Figure 4 in NDA 203188 Clinical Pharmacology Review by Dr. Lokesh Jain

Considering the expected efficacy response and lack of safety data to support a dosing regimen higher than the observed ones in Study VX15-770-124, the proposed dosing regimens of 5.8 mg BID and 13.4 mg BID are reasonable.

Based on the totality of PK, PD, and limited safety results obtained from Cohort 8 of Study VX15-770-124 in seven children 1 to < 4 months of age, the PK and PD comparison between children in this age group and older patients, the established exposure-response relationship in adults, and the limited safety data collected from. The following proposed doses in children 1 to less than 4 months old by the Applicant is acceptable from a clinical pharmacology perspective:

- In children 1 month to less than 2 months and 3 kg or greater, one 5.8 mg packet every 12 hours
- In children 2 months to less than 4 months and 3 kg or greater, one 13.4 mg packet every 12 hours

**Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?**

No. Similar to the previously recommended management in children 4 to less than 6 months of age, the use of ivacaftor is not recommended in children 1 to less than <sup>(b)</sup><sub>(4)</sub> months old with hepatic impairment. See clinical pharmacology review by Dr. Tao Liu in DARRTS dated 09/24/2020.



**Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?**

Similar to the previously recommended instruction, Kalydeco should be taken with fat-containing food.

Similar to the previously recommended management in children 4 to less than 6 months of age, concomitant use of moderate or strong CYP3A inhibitors is not recommended in patients below 1 to less than (b) (4) months of age. See clinical pharmacology review by Dr. Tao Liu in DARRTS dated 09/24/2020.

## 7 Sources of Clinical Data and Review Strategy

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### 7.1. Table of Clinical Studies

Trial Number	Study Type/Design	CF Mutation	Population	N	Treatment Arms	Countries
VX15-770-124	Two-part open-label safety, PK/PD	“responsive”	1 month to less than 4 months	Part A: 7	3 to <5 kg:	US, Ireland
				Part B: 7	(b) (4) mg ≥5 kg: 11.4 mg	

Note: “responsive” includes *CFTR* mutations responsive to ivacaftor based on clinical and/or *in vitro* assay data as per the currently approved ivacaftor label (updated in December 2020)

## **7.2. Review Strategy**

For brevity, trial VX15-770-124, interim analysis 4, will be referred to in this review by the last 3 digits of the trial name (Trial 124). The Applicant submitted an interim analysis of clinical data from Trial 124, Cohort 8, to support expansion of the indication to include patients 1 month to less than 4 months of age. Trial 124 is a two-part, open-label, multi-cohort study evaluating ivacaftor (IVA) treatments in patients 1 month to <24 months of age. Trial 124 (interim analysis) included a 24-week open-label treatment period during which safety was assessed. While this trial was a safety/PK study, Vertex also included pharmacodynamic (PD) and efficacy-related endpoints. These data will be discussed descriptively since there is no comparator arm.

The protocol for Trial 124 is discussed in Section 8.1.1, trial results for Cohort 8 in Section 8.1.2, and safety data for Cohort 8 in Section 8.2.

## 8 Statistical and Clinical and Evaluation

### 8.1. Review of Relevant Individual Trials Used to Support Efficacy

#### 8.1.1. Trial VX-15-770-124 (Trial 124)

##### Trial Design

Title of trial: A Phase 3, 2-Part, Open-label Study to Evaluate the Safety, Pharmacokinetics, and Pharmacodynamics of Ivacaftor in Subjects with Cystic Fibrosis Who Are Less Than 24 Months of Age at Treatment Initiation and Have an Ivacaftor-Responsive *CFTR* Mutation. Analysis of Subjects 1 to <4 Months of Age (Cohort 8)

Trial start date: August 25, 2016

Trial end date: Ongoing

Interim analysis start date: January 27, 2021

Interim analysis end date: June 28, 2022

Report date: September 16, 2022

Trial 124 was a two-part, open-label, pharmacokinetic (PK) and safety trial in patients less than 24 months of age (Figure 7). Cohort 8 was designed to evaluate the safety, PK, PD, and efficacy of ivacaftor and its metabolites in patients 1 to <4 months of age who have an ivacaftor-responsive *CFTR* mutation. On Day 1 through the morning dose of Day 15, patients in Cohort 8 received an initial low dose of ivacaftor ( (b) (4) or 11.4 mg, q12h) based on their age and weight at Day 1:

Age	Weight Range	Starting Dose
1 month	≥3 kg	(b) (4) mg q12h
2 months	≥3 to <5 kg	(b) (4) mg q12h
2 months	≥5 kg	11.4 mg q12h
3 months	≥5 kg	11.4 mg q12h

At Day 4, each patient provided PK samples to assess exposure. The samples were analyzed and patient data evaluated, and if appropriate, the dose was adjusted at Day 15 (evening) for all cohorts to (b) (4), 11.4, 17.1, 22.8, or 25 mg q12h to better match the adult median exposure. For dosages <25 mg, doses were administered as multiples of (b) (4)-mg sachets. Patients remained on this dose until the study visit after reaching 4 months of age and 5 kg, at which point patients received the approved dose of 25 mg q12h.

After reaching 6 months of age, patients were dosed by weight according to the approved indication:

- 5 to <7 kg: 25 mg q12h
- 7 to <14 kg: 50 mg q12h
- 14 to <25 kg: 75 mg q12h

Each dose of granules was mixed with approximately 1 teaspoon (5 mL) of appropriate liquid or soft food and administered orally q12h with an age-appropriate fat-containing meal or snack.

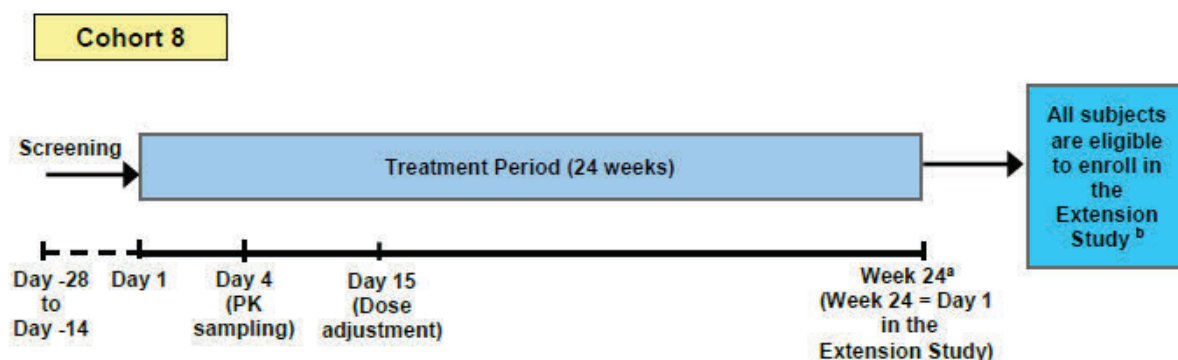
Patients who completed 24 weeks of study drug treatment were eligible to enroll in the open-label treatment arm of the Extension Study. All other patients were eligible to enroll in the observational arm of the Extension Study. Patients who prematurely discontinued were required to have a follow-up ophthalmologic examination approximately 12 weeks after last dosing of study drug.

The schedule of assessment is displayed in Figure 8.

While Trial 124 was a safety/PK study, the Applicant also included pharmacodynamics (PD) and efficacy-related endpoints.

*Reviewer Comment: The trial design is adequate and similar to the PK/safety trial used to support expansion of the ivacaftor indication to the 2 to less than 6-year-old age group. Interim analyses of Cohorts 1, 2, 3, 4, 5, 6, and 7 of Trial 124 were used to support expansion of the ivacaftor indication down to 12 months, then 6 months, then 4 months of age. The 24-week treatment period allows for evaluation of longer-term safety and other parameters that respond more slowly to treatment, such as somatic growth as measured by weight and length. Dose selection was made by matching PK exposures to the older population.*

Figure 7. Trial Design VX-15-770-124 Cohort 8



OE: ophthalmologic examination; PK: pharmacokinetics

- <sup>a</sup> A Follow-up OE occurred approximately 12 weeks after last dose of study drug unless the subject enrolled in the Extension Study.
- <sup>b</sup> All subjects who completed 24 weeks of study drug treatment were eligible to enroll in the open-label treatment arm of the Extension Study. All other subjects were eligible to enroll in the observational arm of the Extension Study. Subjects who prematurely discontinued were required to have a Follow-up OE approximately 12 weeks after last dose of study drug.

**Figure 8. Schedule of Assessments**

Event/Assessment	Screening Period	Treatment Period (Day 1 to Week 24)							Early Termination of Treatment Visit <sup>a</sup>	Follow-up Visit <sup>b</sup>	Follow-up Ophthalmologic Examination <sup>c</sup>
	Day -28 to Day -14	Day 1	Day 4	Day 15 (± 1 Day)	Day 17 (± 1 Day)	Week 4 (± 5 Days)	Week 8 (± 5 Days)	Weeks 12, 18, and 24 (± 5 Days)	As Soon as Possible After the Last Dose of Study Drug	4 Weeks (± 7 Days) After Last Dose of Study Drug	12 Weeks (± 14 Days) After Last Dose of Study Drug
Informed consent <sup>d</sup>	X										
Inclusion/exclusion criteria review	X	X									
Clinic visit/ Assessment contact	X	X	X	X		X	X	X	X	X	
Telephone contact		pm			X						
Demographics	X										
Medical history	X										
Length and weight <sup>e</sup>	X	X	X	X		X	X	X	X	X	
Physical examination <sup>f</sup>	X	X	X	X		X	X	X	X	X	
Vital signs <sup>g</sup>	X	X	X	X		X	X	X	X	X	
12-lead ECGs <sup>h</sup>	X		X			X		X	X		
Ophthalmologic examinations <sup>i</sup>	X							X <sup>j</sup>	X		X
Serum chemistry <sup>k</sup>	X	X	X	X		X	X	X	X	X	
Hematology <sup>k</sup>	X			X		X		X	X	X	
PK blood collection <sup>l</sup>			X <sup>m</sup>	X		X	X <sup>j</sup>	X	X <sup>n</sup>		
Sweat chloride test <sup>o</sup>	X	X		X		X	X	X	X		
Fecal sample collection <sup>p</sup>	X		X	X		X	X	X	X		
IRT		X						X			
Qualitative microbiology cultures		X						X			
Study drug administration <sup>q</sup>		X	X	X		X	X	X			

Event/Assessment	Screening Period	Treatment Period (Day 1 to Week 24)							Early Termination of Treatment Visit <sup>a</sup>	Follow-up Visit <sup>b</sup>	Follow-up Ophthalmologic Examination <sup>c</sup>
	Day -28 to Day -14	Day 1	Day 4	Day 15 (± 1 Day)	Day 17 (± 1 Day)	Week 4 (± 5 Days)	Week 8 (± 5 Days)	Weeks 12, 18, and 24 (± 5 Days)	As Soon as Possible After the Last Dose of Study Drug	4 Weeks (± 7 Days) After Last Dose of Study Drug	12 Weeks (± 14 Days) After Last Dose of Study Drug
In-clinic observation for 4 hours after administration of the first dose of study drug		X									
Study drug count		X		X		X	X	X	X		
Study drug dispensing		X		X		X	X	X <sup>r</sup>			
Pulmonary exacerbations, CF-related hospitalizations	Continuous from signing of ICF through last dose of study drug										
Adverse events	Continuous from signing of ICF through ETT and Follow-up Visit (if required; see Section 14.1.1.3)										Ocular adverse events only
Medications and procedures review	Continuous from 28 days before the Screening Visit (or from birth, as relevant) through the ETT and Follow-up Visit (if required; see Section 10.3.1)										

CF: cystic fibrosis; ECG: electrocardiogram; ETT: early termination of treatment; ICF: informed consent form; IRT: immunoreactive trypsin and/or trypsinogen; OE: ophthalmologic examination; PK: pharmacokinetic; q12h: every 12 hours



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- <sup>a</sup> Subjects who prematurely discontinue treatment before their last scheduled dose will be required to complete the ETT Visit as soon as possible after the last dose of study drug and the Follow-up Visit. All subjects who prematurely discontinue from study drug treatment in Part A/B Cohort 8 will be eligible to enroll in an observational arm of the Extension Study.
- <sup>b</sup> The Follow-up Visit is not required if the subject completes the Part A/B Cohort 8 treatment period and enrolls in the treatment arm of the Extension Study. For all other subjects, the Follow-up Visit is not required if the ETT Visit occurs 3 weeks or later after the last dose of study drug (ivacaftor) or in the event that the subject initiates treatment with commercially available ivacaftor within 3 weeks of the final scheduled treatment visit or ETT Visit.
- <sup>c</sup> Subjects who prematurely discontinue ivacaftor treatment in Part A/B Cohort 8 and received at least 1 dose of ivacaftor treatment in Part A/B Cohort 8 will have a Follow-up OE 12 weeks after the last dose of study drug. Subjects enrolling into the Extension Study within 12 weeks after the last dose of study drug are not required to have the Follow-up OE (the OE will be performed in the Extension Study instead). Subjects who initiate treatment with commercially available ivacaftor within 3 weeks of the ETT Visit will not have the Follow-up OE.
- <sup>d</sup> Informed consent may be obtained before the Screening Visit and must be obtained before any screening assessment is performed.
- <sup>e</sup> Length and weight must be measured with the subject in a dry diaper or dry underclothes only (see Section 12.5.1 for details). Length and weight measurements will be made before the morning dose on Day 1.
- <sup>f</sup> Full physical examinations will occur at the Screening, Week 24, and Early Termination of Treatment (ETT) Visits; abbreviated physical examinations will occur at all other study visits.
- <sup>g</sup> Vital signs include blood pressure (systolic and diastolic), temperature, heart rate, respiration rate, and pulse oximetry. The subject should rest for at least 5 minutes, if possible, before having vital signs measured. Day 1 vital sign measurements will be collected before the morning dose. Temperature must be obtained by the same method throughout the study.
- <sup>h</sup> All 12-lead ECGs will be performed before the morning dose. The subject should rest for at least 5 minutes, if possible, before having the ECG performed. The ECG will be performed before any other procedures that may affect heart rate, such as blood draws.
- <sup>i</sup> The screening OE may be performed at any time from screening until before the first dose on Day 1. If an adequate slit-lamp examination cannot be conducted at screening, subjects will not be enrolled until an adequate repeat slit-lamp examination is completed (within 4 weeks of the Screening Period). Eligibility criteria regarding the ophthalmologic findings must be met prior to dosing.
- <sup>j</sup> OE to be performed at the Week 12 and Week 24 Visits.
- <sup>k</sup> To minimize the volume of blood drawn on Day 1, clinical laboratory assessments will be determined from a single blood draw taken during the Screening Period Day -28 to Day -14. The results must be received and reviewed before the first dose of study drug. All blood samples will be collected while subjects are in a seated or supine position.
- <sup>l</sup> PK samples will be collected before the morning dose and between 2 to 4 hours and between 6 to 8 hours after the morning dose on Day 4 and the Week 8 Visit. PK samples will be collected before the morning dose on Day 15, and on the Week 4, 12, 18, and 24 Visits.
- <sup>m</sup> If all PK samples collected on Day 4 are missing or cannot be analyzed, PK samples collected on Day 15 will be used to assess whether the initial dose should be adjusted at the Week 4 Visit.
- <sup>n</sup> Assessment will be performed only if within 3 days of last dose of study drug.
- <sup>o</sup> At Screening a sweat chloride test must be performed if the sweat chloride value is not available in the subject's medical records and the value is needed to establish eligibility. For subjects with sweat chloride values documented in their medical records and for whom it is not needed to establish eligibility, the sweat chloride test at screening is not required. At the Day 1 Visit, the sweat chloride test must be performed before the morning dose. At the Day 15 and Week 4, 8, 12, 18 and 24 Visits, the sweat chloride test must be performed within a window of  $\pm 2$  hours relative to the morning dose of the study drug.
- <sup>p</sup> Samples will be analyzed for fecal elastase-1 and fecal calprotectin. The fecal sample may be collected at any time from screening until before the first dose at Day 1.
- <sup>q</sup> Study drug will be administered q12h. Each dose of granules will be mixed with approximately 1 teaspoon (5 mL) of appropriate liquid or soft food (as listed in the study manual). Details of dose preparation and dose administration will be provided in the study manual. The dose administration dates and times, occurrence and time of regurgitation within 1 hour after dosing, and their timing with respect to food intake, will be recorded for the 2 doses prior to each PK clinic visit in each subject's dosing diary. In addition, the time of administration of study drug and occurrence and time of regurgitation within 1 hour after dosing in clinic on the day of the visit will be recorded.
- <sup>r</sup> Week 12 and Week 18 Visits only. Study drug will only be dispensed at Week 24 to subjects enrolling in the open-label treatment arm of the Extension Study.

### Study Endpoints

#### Primary Endpoints

- To evaluate the safety of ivacaftor treatment in patients with CF who are 1 to <4 months of age at treatment initiation and have an ivacaftor-responsive *CFTR* mutation (consistent with the approved mutations in the region).
- To evaluate the pharmacokinetics (PK) of ivacaftor and the ivacaftor metabolites M1 and M6 in patients with CF who are 1 to <4 months of age at treatment initiation and have an ivacaftor-responsive *CFTR* mutation (consistent with the approved mutations in the region).

#### Secondary Endpoint

- To evaluate the PD of ivacaftor treatment in patients with CF who are 1 to <4 months of



age at treatment initiation and have an ivacaftor-responsive *CFTR* mutation (consistent with the approved mutations in the region).

#### *Tertiary Endpoint*

- To evaluate the efficacy of ivacaftor treatment in patients with CF who are 1 to <4 months of age at treatment initiation and have an ivacaftor-responsive *CFTR* mutation (consistent with the approved mutations in the region).

#### **Statistical Analysis Plan**

Since the results reported are from an open-label, single arm study, they are descriptive. As a result, a Statistical Analysis Plan was not included with the submission.

#### **Protocol Amendments**

The original protocol was amended four times.

In Version 2.0 (March 9, 2017), the following key changes were included:

- Added follow-up ophthalmologic examination 24 weeks after last dose of study drug in Part B for patients who prematurely discontinue treatment before the extension study was open for enrollment.
- Clarified that patients will be enrolled in Part B sequentially in Cohorts 5, 6, and 7 “based on age at Day 1 of Part B.” Also clarified that patients from a Part A cohort who age out of the corresponding age cohort in Part B at Day 1 may enroll in an older age cohort in Part B. Otherwise, those patients who will age out of the corresponding age cohort may enroll in the extension study (Study 126).
- Added inclusion criterion 6 that the patient’s weight at screening must be within the weight limits as defined for the study drug dose levels.
- Adjusted exclusion criterion 9 to exclude hemoglobin threshold of <9.5 g/dL at screening.
- Exclusion criteria 11 and 12 were split into 2 separate criteria to clarify that patients will be ineligible if an adequate slit-lamp examination cannot be conducted at the screening ophthalmologic exam.
- Added EKG assessments at the Week 4 and Week 12 visits of Part B.
- Updated LCI and infant pulmonary function test assessments.
- Clarified that patients will not be dosed if *CFTR* genotype is not confirmed by 1 of the following before the first dose of the study drug: a) historic genotype result and approval of medical monitor; or b) a genotype test result at screening.

In Version 3.0 (June 9, 2020), the following key changes were included:

- Added Part A/B Cohort 8 to study patients 1 to <4 months of age; removed Cohort 4.
- Revised lower age and weight bounds for Part B Cohort 7 and revised dosing guidance.
- Expanded Part A/B Cohort 8 eligible mutations to ivacaftor-responsive *CFTR* mutations.

In Version 3.1 (June 29, 2020), the strengths and route of administration were clarified.

In Version 4.0 (April 1, 2021), an additional 59 eligible ivacaftor-responsive *CFTR* mutations were added in regions where ivacaftor is approved for use with these mutations.

### **8.1.2. Study Results**

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

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

#### **Financial Disclosure**

Financial disclosures were provided and are documented in Section 19.2.

#### **Patient Disposition**

A total of 7 patients were enrolled in Cohort 8. Six (85.7%) patients completed the 24 weeks of treatment. One patient discontinued study drug treatment prematurely; the primary reason for study discontinuation was physician decision (patient's ALT value never returned to a stable baseline after initial elevation at Week 8 Visit to meet protocol resumption criteria).

#### **Protocol Violations/Deviations**

An important protocol deviation was defined as a deviation that had the potential to affect the interpretation of study results (i.e., completeness, accuracy, and/or reliability of the study data) and/or to significantly affect a patient's rights, safety, or well-being. There were no important protocol deviations for Cohort 8.

#### **Table of Demographic Characteristics**

Patient demographic data were derived from the safety set, which included all seven patients from Cohort 8. Patient demographic data are summarized in Figure 9. There were 3 males and 4 females in this interim analysis of Trial 124. The median age at baseline was 1.3 months. All patients were non-Hispanic White. Three (3) patients were from North America, while 4 patients were from Europe.

**Figure 9. Demographic characteristics of the safety set, Cohort 8**

Demographic Parameters	Ivacaftor <sup>(b)</sup> <sub>(4)</sub> or 11.4 mg (N=7)
<b>Sex, n (%)</b>	
Male	3 (42.9)
Female	4 (57.1)
<b>Age at Screening (months)</b>	
Mean years (SD)	1.3 (0.49)
Median	1.0
Min, max	1, 2
<b>Race, n (%)</b>	
White	7 (100)
<b>Ethnicity, n (%)</b>	
Not Hispanic or Latino	7 (100)
<b>Geographical Region, n (%)</b>	
North America	3 (42.9)
Europe	4 (57.1)
<b>Genotype, n (%)</b>	
G551D/DEL508	2 (28.6)
DEL508/R117H	1 (14.3)
G551D/3197G>A	1 (14.3)
G551D/R117H	1 (14.3)
N1303K/S945L	1 (14.3)
R117C/W1282X	1 (14.3)
<b>Baseline Growth Parameters</b>	
Weight, mean (SD) in kg	4.9 (0.9)
Length, mean (SD) in cm	57.8 (4.1)
Weight-for-length (percentile)	22.4 (20.4)
BMI (kg/m <sup>2</sup> ), mean (SD)	14.62 (1.04)

Notes: Percentages are calculated relative to the number of patients in the Safety Set.

Source: Interim Analysis Clinical Study Report, Table 14.1.3.1.ab8. Verified by reviewer.

### **Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)**

Weight, length, weight-for-length, and BMI values were within the normal range. Mean (SD) weight-for-age z-score at baseline was -0.88 (1.00). Mean (SD) length-for-age z-score at baseline was -0.23 (1.58). Medical history at baseline was consistent with CF.

### **Treatment Compliance, Concomitant Medications, and Rescue Medication Use**

Mean trial drug compliance was 100%. Concomitant medications were generally typical for CF treatment. The most commonly reported (more than 30% of patients) medications were vitamins, sodium chloride, flucloxacillin, and pancreatin.

### **Efficacy Results – Primary Endpoint**

The primary endpoint of this trial was safety and will be discussed in Section 8.2.

### **Data Quality and Integrity**

There were no issues with data quality or integrity.

### **Efficacy Results – Secondary and other relevant endpoints**

The non-PK related endpoints include the following:

- Absolute change from baseline in sweat chloride through 24 weeks of treatment
- Absolute change from baseline in the following parameters at 24 weeks of treatment:
  - Weight
  - Length
  - Weight-for-length percentile
  - Weight-for-age z-score
  - Length-for-age z-score
  - Weight-for-length z-score
  - FE-1
  - Serum IRT
  - Fecal calprotectin
  - Microbiology cultures
  - Number of pulmonary exacerbations and CF-related hospitalizations

### *Sweat Chloride*

Though sweat chloride is not a surrogate for efficacy, changes in sweat chloride demonstrate a pharmacodynamic effect. Treatment with ivacaftor resulted in improvement in sweat chloride by Day 15 (Figure 10). Sweat chloride decreased from a mean baseline of 73.8 mmol/L (n=7) to 29.8 mmol/L on Day 15 (n=4), to 35.4 mmol/L at Week 18 (n=4). Three patients did not have a Day 15 sweat chloride measurement (sample volumes were insufficient). Six patients did not have sweat chloride measurements at Week 24. One patient discontinued the study at Week

24; sample volumes were insufficient for five patients. Due to the large number of missing samples at Week 24, an ad hoc analysis of the average change from baseline in sweat chloride through Week 24 was performed for all post-baseline visits. The mean (SD) average change from baseline through Week 24 was -40.3 (29.2) mmol/L (n=5). Mean absolute changes from baseline in sweat chloride concentration are summarized in Figure 4. While there is no placebo group for comparison, these data imply that ivacaftor in this age group has a pharmacodynamic effect within 2 weeks of treatment. This is consistent with previous studies in which ivacaftor demonstrated efficacy, where similar sweat chloride responses were observed within 2 weeks of treatment and sustained for up to 48-week treatment periods.

**Figure 10. Absolute Change from Baseline in Sweat Chloride (mmol/L), FAS, Part A/B, Cohort 8, 1 to <4 Months**

Visit	Statistic	Cohort 8 Ivacaftor <sup>(b)</sup> <sub>(4)</sub> or 11.4 mg N=7	
		Sweat Chloride (mmol/L)	Absolute change from baseline at visit (mmol/L)
Baseline	n	7	N/A
	Mean (SD)	73.8 (19.1)	N/A
	Median	69.0	N/A
	Min, max	49.0, 103.0	N/A
Day 15	n	4	4
	Mean (SD)	29.8 (8.7)	-50.6 (24.2)
	Median	32.8	-58.0
	Min, max	17.0, 36.5	-71.0, -15.5
Week 4	n	5	5
	Mean (SD)	30.3 (6.2)	-46.0 (24.8)
	Median	32.0	-55.0
	Min, max	19.5, 35.0	-72.0, -14.0
Week 8	n	5	5
	Mean (SD)	33.8 (11.8)	-42.5 (22.9)
	Median	39.0	-56.0
	Min, max	14.5, 44.0	-60.0, -8.5
Week 12	n	5	5
	Mean (SD)	43.4 (17.9)	-32.9 (33.8)
	Median	43.0	-56.0
	Min, max	18.0, 67.5	-60.0, 7.5
Week 18	n	4	4
	Mean (SD)	35.4 (21.6)	-47.8 (37.0)
	Median	29.0	-60.8

	Min, max	17.0, 66.5	-76.0, 6.5
Week 24	n	1	1
	Mean (SD)	51.5	2.5
	Median	51.5	2.5
	Min, max	51.5, 51.5	2.5, 2.5

Source: Interim Analysis Clinical Study Report, Table 11-2, p. 46. Source Table 14.2.1.1.ab8. Verified by reviewer.

### *Weight, length, weight-for-length and z-scores*

Absolute changes from baseline in weight, length, weight-for-length, and the corresponding z-scores were reported at 24 weeks (Figure 11). The mean (SD) absolute change in weight from baseline at Week 24 was 3.5 (0.9) kg. The mean (SD) absolute change from baseline in length from baseline at Week 24 was 13.2 (1.8) cm.

**Figure 11. Baseline and Absolute Change from Baseline in Nutritional/Growth Parameters at Week 24, Cohort 8**

Parameter Statistic	Cohort 8 Ivacaftor <sup>(b)</sup> <sub>(4)</sub> or 11.4 mg N = 7	
	Baseline	Absolute Change from Baseline at Week 24
<b>Weight (kg)</b>		
n	7	6
Mean (SD)	4.9 (0.9)	3.5 (0.9)
Median	5.0	3.4
Min, max	3.6, 6.1	2.5, 4.9
<b>Length (cm)</b>		
n	7	6
Mean (SD)	57.8 (4.1)	13.2 (1.8)
Median	56.0	13.0
Min, max	52.5, 63.4	11.5, 16.0
<b>Weight-for-length Z-score</b>		
n	7	6
Mean (SD)	-0.87 (0.66)	0.75 (1.05)
Median	-0.92	0.48
Min, max	-1.70, 0.41	-0.61, 2.18
<b>Weight-for-age Z-score</b>		
n	7	6
Mean (SD)	-0.88 (1.00)	1.14 (0.89)
Median	-1.32	1.01
Min, max	-1.93, 0.70	0.14, 2.66

<b>Length-for-age Z-score</b>		
n	7	6
Mean (SD)	-0.23 (1.58)	1.12 (0.61)
Median	-1.06	1.15
Min, max	-1.57, 2.15	0.18, 2.06
<b>Weight-for-length (percentile)</b>		
n	7	6
Mean (SD)	22.4 (20.4)	22.2 (35.9)
Median	17.8	11.5
Min, max	4, 66	-24, 67

Source: Interim Analysis Clinical Study Report, Table 11-3, p. 48. Source Table 14.2.2.1.ab8. Verified by reviewer.

### *Pulmonary exacerbations*

Two definitions of pulmonary exacerbation were used for analysis:

- Definition 1: Treatment with oral, inhaled, or intravenous (IV) antibiotics and fulfillment of 1 or more of the criteria from List A or List B below, within 3 days before antibiotic start date through antibiotic stop date.
- Definition 2: Treatment with oral, inhaled, or IV antibiotics and fulfillment of 1 criterion from List A or 2 criteria from List B, within the period 3 days before antibiotic start date through antibiotic stop date.
- List A:
  - Oxygen saturation <90% on room air or  $\geq 5\%$  decrease from baseline
  - New lobar infiltrate(s) or atelectasis on chest x-ray
  - Hemoptysis (more than streaks on more than 1 occasion in past week)
- List B:
  - Increased work of breathing or respiratory rate (duration  $\geq 3$  days)
  - New or increased adventitial sounds on lung exam (duration  $\geq 3$  days)
  - Weight loss  $\geq 5\%$  decrease from highest value or decrease across 1 major percentile for age in past 6 months
  - Increased cough (duration  $\geq 3$  days)
  - Worked harder to breathe during physical activity (duration  $\geq 3$  days)
  - Increased chest congestion or change in sputum (duration  $\geq 3$  days)

No patient had an event that met the criteria for either definition of pulmonary exacerbation.

### *CF-related hospitalizations*

There were no CF-related hospitalizations.

### *Other endpoints*

Fecal elastase-1 levels increased (improved) over the treatment period (baseline mean value of 344.8 µg/g increased to a Week 24 mean value of 417.2 µg/g). The mean IRT level decrease from a baseline mean of 1094.9 ng/mL to a Week 24 mean value of 781.0 ng/mL. Mean fecal calprotectin levels decreased from a baseline mean of 272.0 µg/g to a Week 24 mean of 46.0 µg/g. The clinical significance of these findings, especially in the absence of a placebo arm group, is unclear. There were no identifiable trends in amylase and lipase levels over 24 weeks of treatment.

### **Dose/Dose Response**

Dose pharmacokinetics in this age group match the exposures in the ≥12-year-old age group. No dose exploration was conducted once PK exposures were matched.

Although the IVA systemic exposure in pediatric patients 1 to less than 4 months of age with the proposed dosing regimen is at the lower end (the mean value is about 40% lower than that of adults), it is still within the range of systemic exposure of adults and pediatric patients 6 years and older. In addition, the previously reviewed exposure-response analysis for lung function (percent predicted FEV1) change from baseline in adults demonstrated a flat relationship from 75 mg to 150 mg (the approved dose in adults and children 6 years of age and older) (Figure 6), indicating that approximately 40% lower in systemic exposure unlikely to reduce the efficacy.

### **Persistence of Effect**

Decreases in the pharmacodynamic parameter of sweat chloride were seen on Day 15 and generally maintained at Weeks 12 and 18. Mean baseline sweat chloride was 73.8 mmol/L and this decreased on Day 15 to a mean of 29.8 mmol/L. At Week 12, the mean sweat chloride value was 43.4 mmol/L and at Week 18, the mean sweat chloride value was 35.4 mmol/L.

### **Integrated Review of Effectiveness**

#### **8.1.3. Assessment of Efficacy Across Trials**

The Applicant provided data from a single trial. Efficacy in the proposed age group was extrapolated from the ivacaftor tablet development program in patients 12 years of age and older.

#### **8.1.4. Integrated Assessment of Effectiveness**

In this supplemental NDA, Vertex submitted safety and PK data from an interim analysis of Trial 124 (Cohort 8) to support the use of ivacaftor granules in CF patients 1 month to less than 4 months of age with an indicated mutation. Trial 124 is an open-label, multiple-age cohort, uncontrolled, PK and safety trial. In this interim analysis, Trial 124 assessed ivacaftor granules at



doses (b) (4), 11.4, 17.1, 22.8, or 25 mg q12h) based on the patient's age and weight. Efficacy in the proposed age group was extrapolated from the ivacaftor tablet development program because of the comparable exposures and similarity in the disease process compared to the  $\geq 12$ -year-old population, where efficacy had been previously demonstrated in placebo-controlled clinical trials. Sweat chloride, a pharmacodynamic assessment, demonstrated a mean change from baseline of -40.3 mmol/L at Week 24, which suggests a pharmacodynamic effect of the drug and generally supports the extrapolation of efficacy.

## **8.2. Review of Safety**

### **8.2.1. Safety Review Approach**

Trial 124, part B was evaluated for safety. This review will focus on the interim analysis for Cohort 8 only. Sponsor data was verified by the clinical reviewer using JMP software.

### **8.2.2. Review of the Safety Database**

#### **Overall Exposure**

In the interim analysis of Cohort 8 in Trial 124, patients were exposed to study drug at a mean exposure of 22.0 weeks. 6 patients received at least 24 weeks of treatment. 1 patient received only 9 weeks of treatment due to study drug treatment discontinuation. Overall, exposure was acceptable to assess safety.

#### **Adequacy of the safety database:**

Overall, the safety database is of sufficient size and duration for an infant population in a rare disease to assess the safety of the proposed dose of ivacaftor when taken chronically in the 1 to less than 4-month-old age group. Ivacaftor is already approved for CF patients ages 4 months and older; adequate safety in the older population has been previously established. Safety data in the older population allow for a targeted review of known safety issues for the current population (1 to less than 4 months).

### **8.2.3. Adequacy of Applicant's Clinical Safety Assessments**

#### **Issues Regarding Data Integrity and Submission Quality**

No data quality issues were identified in the review of this supplemental NDA. There were no site inspections.

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

The Applicant provided accurate definitions of adverse events (AEs) and serious adverse events (SAEs) in the protocol. AEs were captured from signing of informed consent through the Week 24 visit. Treatment emergent adverse events (TEAEs) were defined as adverse events with start date or increased severity on or after the first dose of study drug through the end of

participation. TEAEs were the key safety assessment. TEAEs were summarized by treatment (dose level). TEAE summaries were presented by MedDRA system organ class and preferred term using frequency counts and percentages. TEAEs were referred to as adverse events in the interim analysis of the Clinical Study Report. AEs were coded using the MedDRA dictionary version 25.0. Grading of AE severity was based on the “Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials” (September 2007, CBER), or as mild/moderate/severe/life-threatening. The same adverse event occurring in the same patient multiple times, or continuing, was counted once. The Applicant analyzed laboratory data for LFT elevations.

### **Routine Clinical Tests**

Laboratory tests were obtained according to the schedule of assessments. PK, clinical laboratory, and sweat chloride samples were collected at the individual trial sites and mailed to a centralized laboratory for processing.

#### **8.2.4. Safety Results**

##### **Deaths**

No deaths were reported.

##### **Serious Adverse Events**

There were no treatment-emergent serious adverse events.

##### **Dropouts and/or Discontinuations Due to Adverse Effects**

One patient discontinued study drug treatment due to an AE of elevated alanine transaminase (ALT).

A summary of safety results is provided in Figure 12.

**Figure 12. Overview of Adverse Events**

Category	Cohort 8 Ivacaftor (b) (4) or 11.4 mg N = 7
Number of AEs, n	14
Number of SAEs, n	0
Number of non-serious AEs, n	14
Patients with any AEs, n (%)	4 (57.1)
Patients with related AEs, n (%)	0
Patients with AEs leading to treatment discontinuation, n (%)	1 (14.3)
Patients with AEs leading to treatment interruption, n (%)	0
Patients with SAEs, n (%)	0
Patients with AEs leading to death, n (%)	0

Source: Interim Analysis Clinical Study Report, Table 12-2, p. 60. Source Table 14.3.1.1.ab8. Verified by reviewer.

### Significant Adverse Events

There were no AEs graded as severe (grade 3) or life-threatening (grade 4).

### Treatment Emergent Adverse Events and Adverse Reactions

There were a total of 14 TEAEs in four patients. Adverse events are displayed by preferred term in Figure 13. The incidence of AEs and the type of AEs were generally as expected for this population and were similar to those seen in the ivacaftor studies in older CF patients.

**Figure 13. Adverse events by preferred term, Cohort 8**

Preferred Term	Cohort 8 Ivacaftor <sup>(b)</sup> <sub>(4)</sub> or 11.4 mg N = 7 n (%)
Patients with any AEs	4 (57.1)
Accidental overdose	1 (14.3)
ALT increased	1 (14.3)
Bronchiolitis	1 (14.3)
Constipation	1 (14.3)
Contusion	1 (14.3)
Diarrhea	1 (14.3)
Enterovirus test positive	1 (14.3)
Feces discolored	1 (14.3)
Human rhinovirus test positive	1 (14.3)
Irritability	1 (14.3)
Nasal congestion	1 (14.3)
Rhinorrhea	1 (14.3)
Vomiting	1 (14.3)

Source: Interim Analysis Clinical Study Report, Table 12-3, p. 61. Source Table 14.3.1.3.ab8. Verified by reviewer.

## Laboratory Findings

Clinical safety testing included hematology and serum chemistry with liver function tests. Liver function test abnormalities are a known safety issue with ivacaftor. Maximum on-treatment liver function test results for Trial 124 Cohort 8 are shown in Figure 14. One patient had an AE of ALT increased. This patient had a maximum ALT of >8x ULN and a maximum AST of >3 to ≤5x ULN. Study drug treatment was discontinued due to the event of ALT increased. No patient had a transaminase elevation (ALT or AST>3x ULN) concurrent with a bilirubin elevation>2x ULN.

**Figure 14. Maximum On-Treatment Liver Function Test Results, Cohort 8**

Maximum On-treatment Results	Cohort 8 Ivacaftor <sup>(b) (4)</sup> or 11.4 mg N = 7 n (%)
<b>ALT or AST</b>	
≤1 x ULN	2 (28.6)
>1 to ≤2 x ULN	3 (42.9)
>2 to ≤3 x ULN	1 (14.3)
>8 x ULN	1 (14.3)
<b>ALT (U/L)</b>	
≤1 x ULN	2 (28.6)
>1 to ≤2 x ULN	3 (42.9)
>2 to ≤3 x ULN	1 (14.3)
>8 x ULN	1 (14.3)
<b>AST (U/L)</b>	
≤1 x ULN	6 (85.7)
>3 to ≤5 x ULN	1 (14.3)
<b>Total Bilirubin (μmol/L)</b>	
≤1 x ULN	6 (85.7)
>2 to ≤3 x ULN	1 (14.3)
<b>ALT (or AST) &gt;3 x ULN and Total Bilirubin &gt;2 x ULN</b>	0

Source: Interim Analysis Clinical Study Report, Table 12-4, p. 64. Source Table 14.3.4.3.1.ab8. Verified by reviewer.

### Vital Signs

Vital signs were generally normal at baseline and stayed normal through the treatment period. There were no clinically significant trends or changes noted over the treatment period for pulse rate, oxygen saturation, temperature, respiratory rate, or blood pressure (BP).

### Electrocardiograms (ECGs)

No clinically important trends were identified in ECG results. There were no major differences between baseline values and end-of-treatment values. All patients had a maximum QTcF interval of ≤450 msec. No patient had an increase in QTcF of >60 msec.

### QT

See section on Electrocardiograms above. No new Interdisciplinary Review Team QT reviews were requested for this supplemental NDA.

### Immunogenicity

Not applicable.

### **8.2.5. Analysis of Submission-Specific Safety Issues**

Cataracts and elevation of liver enzymes are considered AEs of special interest due to the known safety profile of ivacaftor. Please refer to the heading “Laboratory findings” in the Safety Results section 8.2.4 for discussion of LFTs.

#### **8.2.5.1. Cataracts**

All patients had ophthalmological examinations for cataracts at screening and at Week 24. No treatment-emergent cataracts were identified during the 24-week treatment period.

### **8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability**

This trial did not include clinical outcome assessments.

### **8.2.7. Safety Analyses by Demographic Subgroups**

Given the limited number of patients included, all of whom were 1 to less than 4 months of age, no safety analyses by demographic subgroups were performed.

### **8.2.8. Specific Safety Studies/Clinical Trials**

Trial 124, Part A/B Cohort 8 was a PK and safety study. The results of the safety study have been discussed.

### **8.2.9. Additional Safety Explorations**

#### **Human Carcinogenicity or Tumor Development**

Not applicable.

#### **Human Reproduction and Pregnancy**

Not applicable.

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

This trial included pediatric patients 1 month to less than 4 months of age. Compared to historical controls (WHO growth charts), there did not appear to be any detrimental effects on growth. PREA requirements do not apply to this orphan drug product; however, the Applicant is voluntarily conducting studies in pediatric age groups.

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

Not applicable.

### 8.2.10. Safety in the Postmarket Setting

#### Safety Concerns Identified Through Postmarket Experience

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

#### Expectations on Safety in the Postmarket Setting

Ivacaftor is subject to standard post-marketing safety reporting prior to the submission of this supplemental NDA. The Applicant has been providing adequate reporting, including annual safety reports. No new safety signals have been identified. The patient population included in Trial 124 who received ivacaftor granules is generally similar to the target population. Given this fact and the post-marketing experience with ivacaftor, no substantial differences are anticipated.

### 8.2.11. Integrated Assessment of Safety

The safety data submitted with this supplemental NDA was sufficient to assess the safety of ivacaftor in the proposed CF population. The safety information for ivacaftor granules in the 1 to less than 4-month-old age group is primarily derived from an interim analysis of Trial 124, an open-label phase 3 PK/safety trial in patients 1 to less than 24 months of age. This interim analysis of Cohort 8 included 7 patients 1 to less than 4 months of age. No deaths occurred. There was one patient who discontinued study drug treatment due to an AE of ALT increased. The AEs were typical for a pediatric CF population and consistent with the known safety profile of ivacaftor. Overall, no new safety signals were identified for ivacaftor. The ivacaftor safety profile in the 1 to less than 4-month-old age group with the rare and serious disease of cystic fibrosis with a CFTR gating mutation is favorable.

## 8.3. Statistical Issues

There were no statistical issues.

## 8.4. Conclusions and Recommendations

The recommended regulatory action is **Approval** for ivacaftor granules for the treatment of CF in patients who have one mutation in the CFTR gene that is responsive to ivacaftor based on clinical and/or in vitro assay data, for pediatric patients 1 month to less than 4 months old, according to the following dosing regimen:

- For patients 1 to <2 months old and  $\geq 3$  kg: 5.8 mg q12h
- For patients 2 to <4 months old and  $\geq 3$  kg: 13.4 mg q12h

In this supplemental NDA, the Applicant has submitted an interim analysis from a

pharmacokinetic (PK)/safety study (Trial 124) to support the use of ivacaftor in patients 1 to less than 4 months of age who have a CFTR mutation for which ivacaftor is indicated (Cohort 8). Trial 124 is a two-part, multiple-age cohort, open-label, PK and safety trial in patients 1 to less than 24 months of age. The submitted interim analysis included 7 patients from the 1 to <4-month-old age cohort. Because of the comparable systemic exposures and because the disease process in the older population is the same as that in the 1 to <4-month-old population, efficacy in the proposed aged group was extrapolated from the  $\geq 12$ -year-old age group where efficacy had been demonstrated in clinical trials. Additionally, data from Cohort 8 demonstrated a decrease in the pharmacodynamic (PD) endpoint of sweat chloride at Week 24 of -40.3 mmol/L, suggesting a PD response to ivacaftor treatment. Trial 124 did not reveal new safety signals. One subject discontinued treatment due to elevation of ALT, however, this is a monitorable finding and is included in labeling. The overall risk-benefit assessment supports approval of ivacaftor granules. The clinical recommendation is Approval.



## **9 Advisory Committee Meeting and Other External Consultations**

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An advisory committee meeting was not necessary for this supplemental NDA.

## 10 **Pediatrics**

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Pediatric Research Equity Act requirements do not apply to this orphan drug product. Further, the trial was conducted in pediatric patients pursuant to a written request for pediatric studies, issued on March 14, 2016.

## 11 Labeling Recommendations

### 11.1. Prescription Drug Labeling

Full Prescribing Information Sections <sup>1</sup>	Rationale for Major Changes Incorporated into the Finalized Prescribing Information (PI)
1 INDICATIONS AND USAGE	<ul style="list-style-type: none"> <li>Indication expansion to 1 month and older from previous indication of 4 months and older:</li> </ul> <p><i>KALYDECO is indicated for the treatment of cystic fibrosis (CF) in patients age 1 month and older who have at least one mutation in the CFTR gene that is responsive to ivacaftor potentiation based on clinical and/or in vitro assay data [see Clinical Pharmacology (12.1) and Clinical Studies (14)].</i></p>
2 DOSAGE AND ADMINISTRATION	<ul style="list-style-type: none"> <li>Section 2 has been revised and reformatted consistent with Dosage and Administration Section of Labeling (draft guidance). <a href="https://www.fda.gov/media/72142/download">https://www.fda.gov/media/72142/download</a></li> <li>Added recommended dosage for 1 month to less than 2 months (≥ 3 kg): 5.8 mg ivacaftor every 12 hours</li> <li>Added recommended dosage for 2 months to less than 4 months (≥ 3 kg): 13.4 mg ivacaftor every 12 hours</li> </ul>
6 ADVERSE REACTIONS	Addition of 1 month to less than 4 month patient cohort and the effect on ALT or AST among these patients.
8 USE IN SPECIFIC POPULATIONS (e.g., Pregnancy, Lactation, Females and Males of Reproductive Potential, Pediatric Use, Geriatric Use, Renal Impairment, Hepatic Impairment)	Updated 8.4 Pediatric Use subsection to support the use of Kalydeco in patients as young as 1 month from extrapolation of population pharmacokinetic analyses of patients 1 month to less than 24 months and patients 6 years and older.
12 CLINICAL PHARMACOLOGY	<ul style="list-style-type: none"> <li>Pharmacodynamics subsection updated with inclusion of sweat chloride mean absolute change from baseline for patients aged 1 month to less than 4 months.</li> <li>Table 4: Ivacaftor Exposure by Age Group, Mean (SD) updated with inclusion of new age group 1 to less than 2 months and 2 to less than 4 months.</li> </ul>
Product Quality Sections (i.e., DOSAGE FORMS AND	Product Quality sections updated with addition of new strengths, 5.8 mg and 13.4 mg, for Oral Granules.

STRENGTHS, DESCRIPTION, HOW SUPPLIED/STORAGE AND HANDLING)	
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## **12 Risk Evaluation and Mitigation Strategies (REMS)**

No REMS is proposed.

### **13 Postmarketing Requirements and Commitment**

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No postmarketing requirement or commitment is proposed.

## 14 Division Director (Clinical) Comments

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The submitted clinical program is adequate to support the efficacy and safety of ivacaftor granules for the treatment of CF in patients who have one mutation in the *CFTR* gene that is responsive to ivacaftor based on clinical and/or *in vitro* assay data, for pediatric patients 1 to less than 4 months of age, at a dose of:

- 5.8 mg orally administered every 12 hours for patients 1 to <2 months of age, and weighing  $\geq 3$  kg
- 13.4 mg orally administered every 12 hours for patients 2 to <4 months of age, and weighing  $\geq 3$  kg

Of note, the approved dosing differs from that initially proposed by the Applicant and reflects the doses studied in Trial 124.

The submitted clinical program consisted primarily of an analysis from a pharmacokinetic (PK)/safety study (Trial 124, Cohort 8) to support the use of ivacaftor in patients who have a *CFTR* mutation for which ivacaftor is indicated. Trial 124 was a two-part, multiple age cohort, open-label, PK (part A, 4 days duration) and safety (part B, 24-week duration) trial in patients 1 to less than 24 months in age. The submitted analysis included patients from the 1 to <4-month age cohort (Cohort 8). This included 7 patients from the PK portion (part A, cohort 3) and 7 patients from the safety portion (part B, cohort 7). The PK portion enrolled 1-month old to less than 4-month-old patients with CF. Because of the comparable systemic exposures at the studied doses and because the disease process in the older population is the same as that in the 1 to <4-month-old population, efficacy in the proposed age group was extrapolated from the  $\geq 12$ -year-old age group where efficacy had been demonstrated in clinical trials. Additionally, data from part B demonstrated a decrease in the pharmacodynamic (PD) endpoint of sweat chloride, suggesting a PD response to ivacaftor treatment. Although 1 patient discontinued treatment at Week 9 due to elevation of ALT, this finding is consistent with known toxicity of ivacaftor, is monitorable, and is included in labeling. No new safety signals were identified.

No new product quality information was submitted with this supplement. There are no outstanding issues from any review disciplines.

I concur with the content of various discipline assessments and the recommendation of approval. The Agency and the Applicant have also agreed upon final labeling language. The action for this application will be **Approval**.

## 15 Appendices

### 15.1. References

None.

### 15.2. Financial Disclosure

**Covered Clinical Study (Name and/or Number): Protocol VX15-770-124**

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from Applicant)
Total number of investigators identified: <u>132</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>13</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):  Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>0</u>  Significant payments of other sorts: <u>13</u>  Proprietary interest in the product tested held by investigator: <u>0</u>  Significant equity interest held by investigator in S  Sponsor of covered study: <u>0</u>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		
Is an attachment provided with the reason:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request explanation from Applicant)

### 15.3. OCP Appendices (Technical documents supporting OCP recommendations)

#### 15.3.1. Pharmacometrics Review

The PK of IVA in pediatric patients 1 to less than 4 months of age were characterized in Study VX15-770-124 Cohort 8. A PopPK model was developed by the Applicant to describe the PK characteristics.

The final IVA dataset used for model development included 2023 IVA plasma concentration measurements from 227 CF subjects, including 74 IVA plasma concentration measurements from 7 unique 1 to <4 months CF subjects in Cohort 8.

Table 6 summarizes the baseline continuous and categorical covariates by study. Data from Study 124 (subjects <24 months) is also summarized for Cohort 8 (subjects 1 to < 4 months). The mean age for Cohort 8 was 1.9 months. All subjects were of  $\geq 37$  weeks gestational age and weighed  $\geq 3$  kg on Day 1.

**Table 6 Summary of Covariates in the PK Analysis Dataset**

Study	101	102	103	104	108	110	111	124	124 Cohort 8	Overall
N	1	21	33	49	33	11	19	60	7	227
Age, year	18	15	9	14	3	9	13	0.79	0.17	8
(median [min, max])	[18, 18]	[12, 18]	[6, 12]	[12, 18]	[2, 5]	[6, 18]	[6, 17]	[0.08, 1.92]	[0.08, 0.25]	[0.08, 18]
Age, year	15.19	8.88	14.43	10	3.21 [0.99]	10	11.32 [3.71]	0.82 [0.51]	0.15	8.01
(mean [SD])	18 [NA]	[1.89]	[2.01]	[1.97]	[3.41]	11.32 [3.71]	0.82 [0.51]	[0.07]	[6]	[6]
Age, mo	216	180	108	168	36	108	156	9.5	2	96
(median [min, max])	[216, 216]	[144, 216]	[72, 144]	[144, 216]	[24, 60]	[72, 216]	[72, 204]	[1, 23]	[1, 3]	[1, 216]
Age, mo	182.3	106.5	173.1	120	38.5 [11.9]	120	135.8 [44.6]	9.8 [6.1]	1.9 [0.9]	96.1
(mean [SD])	216 [NA]	[22.6]	[24.1]	[23.6]	[40.9]	135.8 [44.6]	9.8 [6.1]	1.9 [0.9]	[72]	[72]
Body weight, kg	60.7	50	29.5	49.4	15.8	33	46	8.6	5	26.8
(median [min, max])	[60.7, 60.7]	[30.2, 79]	[18.8, 62.6]	[35.1, 69.9]	[10.7, 21]	[20, 84]	[20, 83]	[3.6, 16.1]	[3.6, 6.1]	[3.6, 84]
Body weight, kg	53.4	31.9	50	15.5	39.8	44.8 [20.1]	8.7 [2.5]	4.9 [0.9]	30.9	30.9
(mean [SD])	60.7 [NA]	[13.3]	[9.3]	[8.9]	[2.6]	44.8 [20.1]	8.7 [2.5]	4.9 [0.9]	[20.3]	[20.3]
Gestational Age, wk	40	40	40	40	40	40	40	40	38	40
(median [min, max])	[40, 40]	[40, 40]	[40, 40]	[40, 40]	[40, 40]	[40, 40]	[40, 40]	[31, 41]	[37, 39]	[31, 41]
Gestational Age, wk	39	38.1	39.7	39.7	39.7	39.7	39.7	39.7	39.7	39.7
(mean [SD])	40 [NA]	40 [0]	40 [0]	40 [0]	40 [0]	40 [0]	40 [0]	[1.9]	[0.7]	[1.1]

max: maximum value; min: minimum value; N: total sample size; SD: standard deviation.

Source: Table 6-2 in Population PK Analysis Report R269

The IVA final model was a linear, two-compartment PopPK model with first-order absorption and a zero-order infusion duration. IIV was included on CL/F, Vc/F, and D1, and IOV was included on F1. The model used a combined additive and proportional residual error. The following covariate effects were included:

- Allometric exponent (weight effect) on apparent clearance (Q) was fixed to 0.75 and to 1 on volumes (Vc and Vp); and
- Empirical functions accounting for the effects of age and weight on CL/F.

In total, this model was governed by:



$$CL/F_i = \left[ \theta_{CL/F} \cdot F_{mat,i} + \frac{(\theta_{CLmax/F} \cdot WT_i^{\theta_{hcm}})}{(\theta_{WT50}^{\theta_{hcm}} + WT_i^{\theta_{hcm}})} \right] \cdot \exp^{\eta_{CL/F_i}}$$

$$Vc/F_i = \theta_{Vc/F} \cdot \left( \frac{WT_i}{70(\text{kg})} \right)^{1.0} \cdot \exp^{\eta_{Vc/F_i}}$$

$$Vp/F_i = \theta_{Vp/F} \cdot \left( \frac{WT_i}{70(\text{kg})} \right)^{1.0}$$

$$Q/F_i = \theta_{Q/F} \cdot \left( \frac{WT_i}{70(\text{kg})} \right)^{0.75}$$

$$k_{a,i} = \theta_{k_a}$$

$$DI_i = \theta_{DI} \cdot \exp^{\eta_{DI_i}}$$

$$FI_i = 1 \cdot \exp^{\eta_{FI,JOV,i}}$$

where:

- TVCL/F<sub>i</sub> is the typical value of CL/F for individual i and is described as a function of individual body weight (WT<sub>i</sub>) (kg),
- CL<sub>i</sub>/F is the apparent initial clearance excluding contributions due to weight (CL<sub>i</sub>/F),
- CL<sub>max</sub>/F is the maximum apparent clearance for weight range (CL<sub>max</sub>/F), h<sub>cm</sub> is the Hill coefficient for body weight scaling (h<sub>cm</sub>),
- WT<sub>50</sub> is the body weight (kg) to achieve half maximum clearance (WT<sub>50</sub>),
- WT<sub>i</sub> is individual body weight (kg), and
- F<sub>mat,i</sub> is the fraction of mature CL/F for individual i and is described as a function of individual post-menstrual age in weeks (PMA).
- F<sub>mat,i</sub> is defined as

$$F_{mat,i} = \frac{PMA_i^{hcm}}{TM_{50}^{hcm} + PMA_i^{hcm}}$$

where:

- PMA is the postmenstrual age in weeks and was calculated as: GAGE + AGE\*30/7 where AGE is in months and GAGE refers to gestational age in weeks,
- h<sub>cm</sub> is the Hill coefficient for maturation effect,
- TM<sub>50</sub> is the time to reach half mature clearance in weeks, and
- individual PK parameters are denoted with the subscript i.

The final PK parameter estimates

**Table 7 IVA Population Pharmacokinetic Final Model Parameter Estimates**

Description	Parameter	Units	Estimate	RSE (%)	95% CI	Derived
Apparent initial clearance	CL/F	L/h	7.10	6.30	[6.23,7.98]	
Apparent central volume	V <sub>c</sub> /F	L	94.9	26.00	[46.6,143]	
Apparent peripheral volume	V <sub>p</sub> /F	L	97.7	37.90	[25.1,170]	
Apparent intercompartmental clearance	Q/F	L/h	14.1	40.00	[3.04,25.1]	
First order absorption rate	k <sub>a</sub>	1/h	0.191	25.50	[0.0956,0.286]	
Zero order absorption rate	D1	h	2.80	3.02	[2.63,2.96]	
Maximum apparent clearance for weight range	CL <sub>max</sub> /F	L/h	11.9	11.80	[9.17,14.7]	
Hill coefficient for body weight scaling	hcw		12.2	61.00	[-2.39,26.9]	
Body weight to achieve half maximum clearance	WT <sub>50</sub>	kg	35.8	4.08	[32.9,38.7]	
Weight effect on V <sub>c</sub> /F (fixed)	WTV2		1.00			
Weight effect on V <sub>p</sub> /F (fixed)	WTV3		1.00			
Weight effect on Q/F (fixed)	WTQ		0.750			
Hill coefficient for maturation	H <sub>cm</sub>		5.59	14.20	[4.03,7.15]	
Time to reach half mature clearance	TM <sub>50</sub>	wks	57.3	5.67	[50.9,63.6]	
Interindividual variance of CL/F	IIV <sub>CL/F</sub>		0.164	12.70	[0.123,0.204]	40.4 (CV% <sup>a</sup> )
Interindividual covariance of CL/F and V <sub>c</sub> /F	IIV <sub>CL/F-V<sub>c</sub>/F</sub>		0.0133	249.00	[-0.0517,0.0784]	
Interindividual variance of V <sub>c</sub> /F	IIV <sub>V<sub>c</sub>/F</sub>		0.426	42.50	[0.0708,0.781]	65.3 (CV% <sup>a</sup> )
Interindividual covariance of CL/F and D1	IIV <sub>CL/F-D1</sub>		0.0577	27.80	[0.0263,0.0891]	
Interindividual covariance of V <sub>c</sub> /F and D1	IIV <sub>V<sub>c</sub>/F-D1</sub>		0.0917	49.90	[0.00203,0.181]	
Interindividual variance of D1	IIV <sub>D1</sub>		0.169	14.30	[0.122,0.217]	41.2 (CV% <sup>a</sup> )
Interoccasion variance of F1	IOV <sub>F1</sub>		0.209	16.10	[0.143,0.275]	
Proportional residual error	err <sub>prop</sub>		0.0480	14.00	[0.0348,0.0611]	21.9 (CV% <sup>a</sup> )
Additive Residual error	err <sub>add</sub>	(ng/ml) <sup>2</sup>	4120.	22.80	[0.5950]	64.1 (SD <sup>b</sup> )

Notes: Inter-individual variability and residual error estimates are reported as variances  $\omega^2$ ,  $\sigma^2$  respectively. Parameter values are for a reference subject weighing 70 kg.

CI: Confidence Interval; IIV: Inter-Individual Variability; CV: Coefficient of Variation; RSE: relative standard error

Model: 120.mod

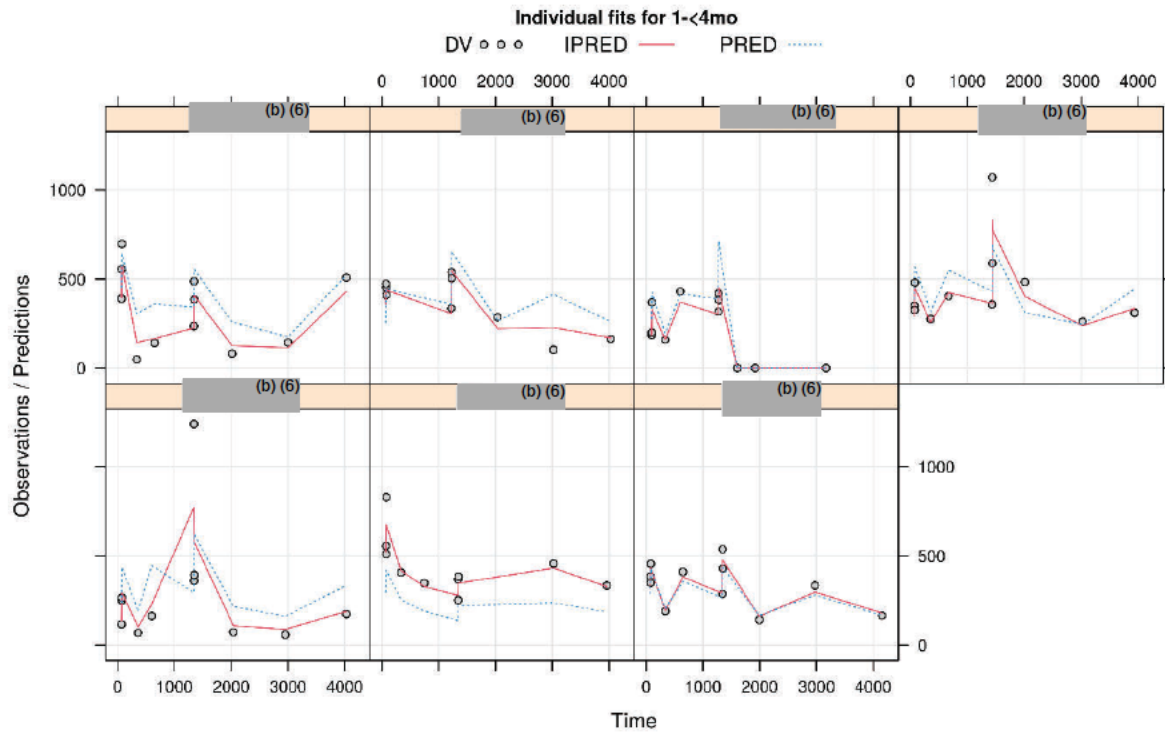
<sup>a</sup> Parameter IIV CV% = square-root of the parameter IIV \* 100

<sup>b</sup> Proportional Error SD = square-root of the proportional error variance.

Source: Table 6-5 in Population PK Analysis Report R269

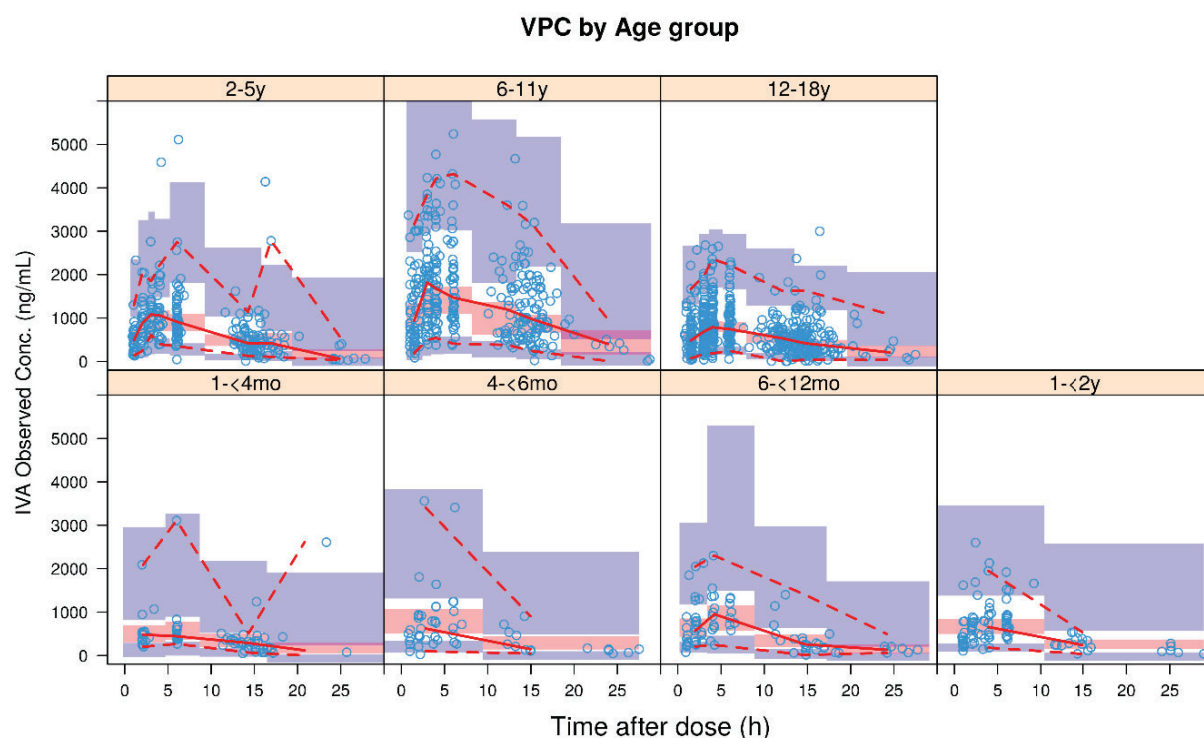
The model diagnostic plots are depicted in Figure 15 below.

Figure 15 Individual Fits for Subjects in Cohort 8 (1 to <4 months of age)



Source: Figure 6-9 in Population PK Analysis Report R269

**Figure 16 Visual Predictive Checks (VPCs) of the IVA Final Population PK Model**



Source: Figure 6-13 Panel B in Population PK Analysis Report R269

The parameter estimates and model diagnostic plots supported the final IVA PopPK model as a validated model and for the simulation to support the proposed dosing regimens in pediatric patients 1 to less than 4 months old.

Based on the final PopPK model, the Applicant simulated the PK profiles in pediatric patients 1 to less than 4 months of age to support the proposed dosing regimens which are different from the studied dosing regimen in Study VX15-770-124 Cohort 8. The simulation was based on the individual PK parameter estimates in 7 pediatric patients in Cohort 8 and 2 pediatric patients 3 months old at baseline in Cohort 7. The model predicted AUC and Cmin are given in Table 8. See section 6.3 Comprehensive Clinical Pharmacology Review for additional information.

**Table 8 Model-predicted Steady-State IVA PK exposures by Age Group (Cohorts 3 and 8)**

Age Group	Dose <sup>a</sup>	N	Median	Min	Max	Mean	SD	Parameter
1-<2mo (b) (4) mg q12h)	(b) (4)	3	5570.	4150.	6760.	5490.	1310.	AUC <sub>0-12h</sub> (ng·hr/mL)
2-<4mo (13.4 mg q12h)	13.4	6	5400.	4350.	13900.	6730.	3650.	AUC <sub>0-12h</sub> (ng·hr/mL)
1-<2mo (b) (4) mg q12h)	(b) (4)	3	367.	274.	484.	375.	105.	C <sub>min</sub> (ng/mL)
2-<4mo (13.4 mg q12h)	13.4	6	295.	203.	1080.	426.	327.	C <sub>min</sub> (ng/mL)

N: number of subjects in the summary, SD: standard deviation, Min: minimum, Max: maximum.

Notes: Exposure metrics were derived from individual EBEs from the final population PK model.

(b) (4)

Source: Table 1 in Abbreviated Modeling and Simulation Report T096

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/s/  
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