NDA/BLA Multi-Disciplinary Review and Evaluation

<table>
<tr><td>Application Type</td><td>sNDA</td></tr>
<tr><td>Application Number(s)</td><td>NDA 203188 S41
NDA 207925 S19</td></tr>
<tr><td>Priority or Standard</td><td>Priority</td></tr>
<tr><td>Submit Date(s)</td><td>December 9, 2024</td></tr>
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<tr><td>PDUFA Goal Date</td><td>June 6, 2025</td></tr>
<tr><td>Division/Office</td><td>Division of Pulmonology, Allergy, and Critical Care (DPACC)</td></tr>
<tr><td>Review Completion Date</td><td>May 21, 2025</td></tr>
<tr><td>Established/Proper Name</td><td>Ivacaftor</td></tr>
<tr><td>(Proposed) Trade Name</td><td>Kalydeco</td></tr>
<tr><td>Pharmacologic Class</td><td>Cystic Fibrosis Transmembrane Conductance Regulatory (CFTR) potentiator</td></tr>
<tr><td>Applicant</td><td>Vertex Pharmaceutical Incorporated</td></tr>
<tr><td>Doseage form</td><td>Oral tablets and granules</td></tr>
<tr><td>Applicant proposed Dosing Regimen</td><td>
<table>
<tr><th>Age</th><th>Weight</th><th>Dosage</th></tr>
<tr><td>1 month to less than 2 months</td><td>3 kg or greater</td><td>One 5.8 mg packet every 12 hours</td></tr>
<tr><td>2 months to less than 4 months</td><td>3 kg or greater</td><td>One 13.4 mg packet every 12 hours</td></tr>
<tr><td>4 months to less than 6 months</td><td>5 kg or greater</td><td>One 25 mg packet every 12 hours</td></tr>
<tr><td rowspan="3">6 months to less than 6 years</td><td>5 kg to less than 7 kg</td><td>One 25 mg packet every 12 hours</td></tr>
<tr><td>7 kg to less than 14 kg</td><td>One 50 mg packet every 12 hours</td></tr>
<tr><td>14 kg or greater</td><td>One 75 mg packet every 12 hours</td></tr>
<tr><td>6 years and older</td><td>-</td><td>One 150 mg tablet every 12 hours</td></tr>
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<tr><td>Applicant Proposed Indication(s)/Population(s)</td><td>Treatment of cystic fibrosis in patients aged 1 month and older who have at least one variant in the CFTR gene that is responsive to ivacaftor potentiation based on clinical and/or in vitro assay data.</td></tr>
<tr><td>Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication</td><td>190905008 |Cystic fibrosis (disorder)|</td></tr>
<tr><td>Recommendation on Regulatory Action</td><td>Approval</td></tr>
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<tr><td>Recommended Indication(s)/Population(s)
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	Signature: Elise M. Ferre -S Digitally signed by Elise M. Ferre -S Date: 2025.05.21 11:26:23 -04'00'			
Cross Discipline Team Leader	**Banu Karimi-Shah, MD**	OND/OII/DPACC	Sections: ALL	**Select one:** ___ Authored __X_ Approved
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Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AR	adverse reaction
AST	aspartate aminotransferase
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
CF	Cystic fibrosis
CFR	Code of Federal Regulations
CFTR	Cystic fibrosis transmembrane conductance regulator
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
FAS	full analysis set
F508del	deletion of amino acid phenylalanine at position 508 in the CFTR protein sequence
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
GGT	gamma-glutamyl transferase
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
IVA	Ivacaftor
LFT	liver function test
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
NISS	newly identified safety signal
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PEx	pulmonary exacerbation
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

1.1. Product Introduction

Ivacaftor (IVA) is an orally bioavailable small molecule that potentiates the cystic fibrosis transmembrane conductance regulator (CFTR) protein thereby increasing chloride transport in patients with cystic fibrosis (CF) who carry variants in the *CFTR* gene responsive to CFTR chloride channel potentiation. The chemical name for IVA is N-(2,4 Di-tert-butyl-5-hydroxylphenyl)-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 >6 years of age who have a G551D variant in the *CFTR* gene at a dose of 150 mg every 12 hours (BID) with a fat-containing food. The indication has since been expanded to include patients one month of age and older with at least one IVA-responsive *CFTR* variant. The current approved doses of IVA are summarized in Table 1. See Regulatory History (Section 3.1) for more detail.

Table 1: Approved Doses of Ivacaftor

Age	Weight	Dosage
1 month to less than 2 months	3 kg or greater	5.8mg every 12 hours
2 months to less than 4 months	3 kg or greater	13.4 mg every 12 hours
4 months to less than 6 months	5 kg or greater	25 mg ever 12 hours
6 months to less than 6 years	5 kg to less than 7 kg	25 mg every 12 hours
	7 kg to less than 14 kg	50 mg every 12 hours
	14 kg or greater	75 mg every 12 hours
6 years and older	-	150 mg every 12 hours

1.2. Conclusions on the Substantial Evidence of Effectiveness

Submitted in these supplements are the results of Study 126, the final study conducted in response to the Pediatric Written Request (PWR), issued by the Agency to the Applicant, amended last on March 29, 2021. Study 126 was a phase 3, open-label, rollover study that evaluated the long-term safety and tolerability of IVA treatment in pediatric patients aged 1 month to <24 months with CF who carry at least one IVA-responsive *CFTR* variant as indicated in the USPI. Study 126 was a rollover study to Study 124, which was an open label, 24-week, PK and safety study previously evaluated under multiple supplements (reviewed in 4 parts under NDA 203188-S028 and NDA2079525-S007 (part 1), NDA 203188-S029 and NDA 207925-S008

(part 2), NDA 203188-S033 and NDA 207925-S011 (part 3), and NDA 203188-S038 and 207925-S016 (part 4)). With this submission, the Applicant proposes the fulfillment of the PWR and requests pediatric exclusivity for the conducted pediatric studies.

Thirty-eight subjects rolled over from Study 124, and 48 subjects were IVA-naïve. With regard to safety, no deaths were reported, and 21 subjects experienced serious adverse events (SAEs), which were consistent with expected events for a CF population in a long-term safety study. Overall, the adverse events (AEs) seen in Study 126 were generally consistent with common manifestations of CF disease or common illnesses in patients 1 month to <24 months of age. Five subjects had liver transaminase increases of >3xULN, and one patient developed cataracts. Overall, the safety profile in the 1 month to <24 month age group was consistent with the previous studies of IVA in this age group. No new safety signals were identified in Study 126.

Both Studies 124 and 126 have met the criteria detailed in the PWR. The Pediatric Exclusivity Board took place on April 30, 2025, and it was determined that the Applicant has met the criteria outlined in the PWR. Therefore, the PWR has been fulfilled leading to issuance of Pediatric Exclusivity on May 20, 2025. The Applicant has proposed labeling changes to include the open label rollover study in the prescribing information (USPI). Although the Division typically would not include data from such an open-label rollover study, a brief description of this study will be included in section 8.4 of the label given that the results from this study fulfilled a PWR. The proposed regulatory action is Approval.

1.3. Benefit-Risk Assessment

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Benefit-Risk Summary and Assessment

Ivacaftor, in the tablet and granule formulation, is approved for the treatment of CF in patients 1 month and older who have one disease-causing variant in the *CFTR* gene that is responsive to IVA based on clinical and/or in vitro assay data. In these supplemental NDAs, the Applicant has submitted results from an open-label rollover study (Study 126).

Cystic fibrosis is a rare, progressive, usually fatal autosomal recessive genetic disease. Cystic fibrosis affects roughly 40,000 children and adults in the U.S. Ivacaftor is indicated for the treatment of CF in patients aged 1 month and older who have one variant in the *CFTR* gene that is responsive to IVA based on clinical and/or in vitro assay data.

Study 126 was an open-label, rollover, long-term (96 weeks) safety study in 86 CF subjects aged 1 month to <24 months who carry at least one IVA-responsive variant in the *CFTR* gene. This study was a rollover of the previous study (Study 124) which was an open-label, 24-week, PK and safety study. Thirty-eight subjects rolled over from Study 124, and 48 subjects were IVA-naïve subjects. With regard to safety, no deaths were reported, and 21 subjects experienced serious adverse events (SAEs) which were generally consistent with expected events in a CF population in a long-term safety study. Overall, the AEs were generally consistent with the known safety profile of IVA, common manifestations of CF disease, or common illnesses in patients aged 1 month to <24 months of age. Five subjects had liver transaminase increases of > 3xULN. Of these, two subjects had ALT or AST >8xULN and two subjects had ALT or AST >5xULN. None had elevations of total bilirubin >1xULN. Overall, the safety profile in the 1 month to <24-month-old age group was consistent with the previous study in this age range, as well as with previous clinical development of IVA in subjects 2 years of age and older. No new safety signals were identified in Study 126. Study 126 was not designed to assess efficacy. The efficacy of IVA has already been established.

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 IVA, including elevated transaminases, can be managed and monitored through routine pharmacovigilance and current USPI guidance.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• 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 variants in the *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. • Ivacaftor-responsive *CFTR* variants account for roughly 13.6% of the US CF population. However, over 2,000 different variants in the *CFTR* gene have been identified and have been classified based on a defect in CFTR chloride channel function.	Cystic fibrosis is a rare, progressive, and usually fatal genetic disease. The *CFTR* variants included in this the IVA indication represent approximately 13.6% of the US CF population.
Current Treatment Options	• While no cure exists, there are five (5)approved therapies that target the underlying cause of CF. Among these 5, only ivacaftor is approved for subjects less than 1 year of age. • Other available medications are used to treat the signs and symptoms of CF but not the underlying cause.	Ivacaftor is the only approved drug targeting CFTR proteinfor the age range included in this application for patients with CF 1 month of age and older.
Benefit	• While Study 126 was an open label rollover long term safety study and was not designed for efficacy, decreases in the pharmacodynamic endpoint of sweat chloride were observed.	CF patients will need long term therapy. Given the young age of the indicated population, safety data to support long term use of Ivacaftor are critical.
Risk and Risk Management	• The AEs observed in this study were consistent with common manifestations of CF disease or common illnesses in patients 1 to <2 years of age. No deaths were reported. 21 SAEs were reported but were not likely related to IVA. Specific safety analyses were done for	No new safety signals were identified in Trial 126. The risks of liver function test (LFT) elevation and development of cataracts are currently addressed through existing labeling

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	hepatic safety. Findings were similar to the previous 24 week study (Study 124) in the same age population as well as studies conducted in older populations.	and routine pharmacovigilance. A REMS is not required.

1.4. Patient Experience Data

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

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

2 Therapeutic Context

2.1. Analysis of Condition

Cystic fibrosis is an autosomal recessive, progressive, and usually fatal disease. It occurs in approximately one out of every 3,500 children born in the United States, affecting roughly 40,000 children and adults in the U.S. CF results from variants in the *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 infection, progressive lung damage, and respiratory failure. Over 2,000 different variants in the *CFTR* gene have been identified, with 360 most commonly associated with disease causation. Ivacaftor is currently indicated for the treatment of CF patients in patients aged 1 month and older who have one variant in the *CFTR* gene that is responsive to IVA based on clinical and/or *in vitro* assay data. These patients have variants that result in expression of CFTR protein at the cell surface membrane that is defective, with diminished transport of chloride ion through the cell surface. These patients comprise roughly 13.6% of the U.S. CF population. Although there is no cure for CF, over the past decade, with improved care largely related to the approval of drugs that directly affect CFTR processing or fuction, life expectancy has increased significantly for patients with CF, with the current median age of survival to the fifties.[1]

2.2. Analysis of Current Treatment Options

Table 2. Current Treatments for Cystic Fibrosis

Active Ingredient	Trade Name	FDA Approved for CF Indication?
***CFTR* Targeted Drugs**		
Ivacaftor	Kalydeco	Yes; patients with CF aged 1 month and older who have one of 97 specified variants (not including *F508del*)
Lumacaftor/ivacaftor	Orkambi	Yes; patients with CF aged 1 year and older who are homozygous for *F508del* variant
Tezacaftor/ivacaftor	Symdeko	Yes; patients with CF aged 6 years and older who have one of 154 specified variants (including *F508del*)
Elexacaftor/tezacaftor/ivacaftor	Trikafta	Yes; patients with CF aged 2 years and older who have at least one copy of *F508del* variant or at least one copy of 272 specified variants
Vanzacaftor/tezacaftor/deuterated ivacaftor	Alyftrek	Yes; patients with CF aged 6 years and older who have at least one copy of *F508del* variant or at least one copy of 303 specified variants
Inhaled Antibiotics for the Treatment of Pseudomonas aeruginosa		

[1] Cystic Fibrosis Foundation Patient Registry 2021 Annual Data Report

Tobramycin (inhaled)	Bethkis, Kitabis Pak, TOBI	Yes
Aztreonam (inhaled)	Cayston	Yes
Polymyxin E (IV form given via nebulizer)	Colisintin	No
Mucolytics		
Dornase alpha	Pulmozyme	Yes
Hypertonic saline (3%, 7%)	N/A	No
Oral Pancreatic Enzyme Supplementation		
Pancrease, pancrelipase	Creon, Pancreaze, Zenpep, Pancrelipase	Yes
Inhaled Bronchodilators		
Albuterol sulfate	Pro-Air, Ventolin, Proventil, Albuterol	Approved as bronchodilator
Levalbuterol hydrochloride	Xopenex	Approved as bronchodilator
Oral Anti-inflammatory Agents		
Azithromycin	Zithromax	No
Ibuprofen (high-dose)	Motrin, Advil	No
Source: Clinical Reviewer Abbreviations: F508del, deletion of amino aide phenylalanine at position 508 in the CFTR protein sequence		

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

- After its initial approval in 2012, the indication for IVA was first expanded on February 21, 2014, to include the following additional variants: G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, or S549R.
- On December 29, 2014, the indication was again expanded to include patients with an R117H variant.
- On March 17, 2015, a new granule formulation of IVA was approved, which included approval for the 2 to 5-year-old age group at a dose of 75 mg BID for patients >14kg and 50 mg BID for patients 7 to <14kg.
- On May 17, 2017, the indication statement was changed to include at least one variant in the *CFTR* gene responsive to IVA.
- On August 15, 2018, the indication was expanded to patients 1 year and older who have one variant in the *CFTR* gene that is responsive to IVA 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 expanded to patients 6 months of age and older who have one variant in the *CFTR* gene that is responsive to IVA 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 variant in the *CFTR* gene that is responsive to IVA 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.
- On May 3, 2023, the indication was expanded to patients 1-month to less than 4 months old who have at least one IVA-responsive *CFTR* variant. The approved dose for patients 1 month to less than 4 months of age is:
    - 5.8 mg q12h for patients 1 to <2 months of age, weighing $\geq$3 kg
    - 13.4 mg q12h for patients 2 to <4 months of age, weighing $\geq$3 kg.

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 PWR, including 2 studies, was issued for IVA on March 11, 2016.

- The pediatric WR issued on March 11, 2016, was amended on December 5, 2017 to:
    - Remove the age cohort 0 to <3 months for feasibility reasons
    - Permit the Sponsor to review PK data prior to initiating the corresponding cohort's safety study

  - Allow Study 2 to initiate after the first patient completes Part B of the respective cohort of Study 1

- A Type B meeting was held on May 5, 2017, to discuss clinical development plans for the <24-month-old age groups, with topics including:
  - 12 weeks of safety data for subjects 12 to <24 months old would be acceptable with justification
  - A waiver was discussed for 0 to <3-month-old cohort

- The Applicant submitted clinical information on July 27, 2018, requesting the Agency's feedback about a new proposed dosing regimen for Cohort 7 (subjects aged 3 to <6 months). Under the new dosing regimen, subjects aged 4 to <6 months, weighing 5 kg or more would receive IVA 25 mg every 12 hours due to a concern that one 3-month -old patient had exposure greater than the 95th percentile of the adult population; 3-month-old subjects would not be included in Cohort 7. On October 15, 2018, the Division confirmed that the Division had no objection to the new proposed dosing regimen. Therefore, Cohort 7 included only 4 to <6-month-old subjects.

- In February 2020, the Applicant submitted a Type B Meeting request to add an additional cohort, cohort 8 (subjects aged 1 month to <4 months), to Trial 124.

- A second amendment to the PWR was approved on March 29, 2021 that updated the timeframe for submitting reports of the studies from July 01, 2023 to July 01, 2025. The following studies were conducted by the Applicant to fulfill the PWR, as outlined in the amended PWR dated March 29, 2021:
  - WR Study 1 (Study VX15-770-124): A phase 3, two-part (A and B) open-label study to evaluate the safety, pharmacokinetic, and pharmacodynamics in subjects with cystic fibrosis (CF) subjects aged 1 month to <24 months who have an IVA-responsive *CFTR* variant. The study was divided into 8 cohorts as outlined below. Interim analyses were completed following each cohort and submitted as sNDA:
    - Part A
      - Cohort 1: Subjects aged 12 months to <24 months (n=7)
      - Cohort 2: Subjects aged 6 months to <12 months (n=6)
      - Cohort 3: Subjects aged 3 months to <6 months (n=6)
      - Cohort 4: was eliminated with the first amendment dated December 5, 2017
    - Part B
      - Cohort 5: Subjects aged 12 months to <24 months (n=19)
      - Cohort 6: Subjects aged 6 months to <12 months (n=11)
      - Cohort 7: Subjects aged 4 months to <6 months (n=6)
    - Parts A/B included Cohort 8: Subjects aged 1 month to <4 months of age (n=7)

        - The results of Study 124 had been reviewed in 4 parts under NDA 203188-S028 and NDA2079525-S007 (part 1), NDA 203188-S029 and NDA 207925-S008 (part 2), NDA 203188-S033 and NDA 207925-S011 (part 3), and NDA 203188-S038 and 207925-S016 (part 4) which collectively have supported the expansion of the indication down to 1-month of age. Refer to Section 3.1 for further details.
    - WR Study 2 (Study VX15-770-126) : A phase 3, open-label study to evaluate the safety and pharmacodynamics of long-term IVA treatment in subjects with cystic fibrosis who are less than 24 months of age at treatment initiation and have an approved IVA-responsive variant. The study enrolled two groups of subjects:
        - Rollover subjects: Subjects enrolled from Study 124 Part B who transitioned to Study 126 the same day they completed Study 124
        - IVA-naïve subjects: Subjects enrolled from Study 124 Part A or subjects who did not participate in Study 124.

With the current sNDAs, the Applicant submits the final required pediatric study as outlined in the PWR.

4 Nonclinical Pharmacology/Toxicology

4.1. Executive Summary

Nonclinical data was not submitted nor required for this supplement.

5 Clinical Pharmacology

5.1. Executive Summary

Clinical Pharmacology data was not submitted nor required for this supplement.

6 Sources of Clinical Data and Review Strategy

6.1. Table of Clinical Studies

Table 3. Summary of Clinical Study VX15-770-126 (Study 126)

Study Number	Study Type / Design	CF Variant	N, Population	Doses / Formulation	Treatment Arms	Countries
VX15-770-126 (Study 126)	Phase 3, 2-arm, Open-label study	Any IVA-responsive *CFTR* variant as stated in the USPI on at least 1 allele	86 adults and children with CF aged <24 months of age at treatment initiation	IVA 25 mg granules IVA 50 mg granules IVA 75 mg tablets	Rollover subjects from Study 124 IVA-naïve subjects (subjects not from Study 124)	29 sites in Australia, Canada, Germany, Ireland, UK, USA
Abbreviations: CF, cystic fibrosis, IVA, ivacaftor, q12h, every 12 hours. Source: Clinical Reviewer.						

6.2. Review Strategy

The Applicant submitted clinical data from Study VX15-770-126 (Study 126), which was the final study required under the Applicant's Pediatric Written Request. Study 126 was an open-label rollover, long-term (96 week) safety study in pedatric subjects aged 1 month to less than 24 months of age. The primary objective of Study 126 was to evaluate the safety and tolerability of long-term treatment with IVA. The Applicant also submitted exploratory data for the pharmacodynamic endpoint of sweat chloride concentrations and endpoints for growth, pancreatic function, pulmonary exacerbations, and CF-related hospitalizations. Note that efficacy in the 1-month to less than 2 year old population was previously extrapolated from the older population, as discussed in Section 3.1. The protocol for Study 126 is discussed in Section 7.1, and the safety data are discussed in Section 7.2

7 Statistical and Clinical and Evaluation

7.1. Review of Relevant Individual Trials Used to Support Efficacy

7.1.1. Study VX15-770-126 (Study 126)

Study Title
A Phase 3, 2-Arm, Open-label Study to Evaluate the Safety and Pharmacodynamics of Long-term IVA Treatment in Subjects With Cystic Fibrosis Who Are Less Than 24 Months of Age at Treatment Initiation and Have an Approved IVA-Responsive Variant

Study Dates
Study initiation (date first eligible subject signed the informed consent form): August 16, 2017
Study completion (date last subject completed the last visit): October 2, 2023
Clinical study report: February 14, 2024

Study Sites
Subjects were enrolled at 29 sites in Australia, Europe, and North America.

Study Objectives
Primary:
- To evaluate the safety of long-term IVA treatment in subjects with CF who were <24 months of age at treatment initiation and had an approved IVA-responsive variant
- To evaluate the long-term safety after discontinuation of IVA treatment in subjects with CF who were <24 months of age at treatment initiation and had an approved IVA-responsive variant

Secondary:
- To evaluate the pharmacodynamics (PD) of long-term IVA treatment in subjects with CF who were <24 months of age at treatment initiation and had an approved IVA-responsive variant

Tertiary:
- To evaluate the efficacy of long-term IVA treatment in subjects with CF who were <24 months of age at treatment initiation and had an approved IVA-responsive variant

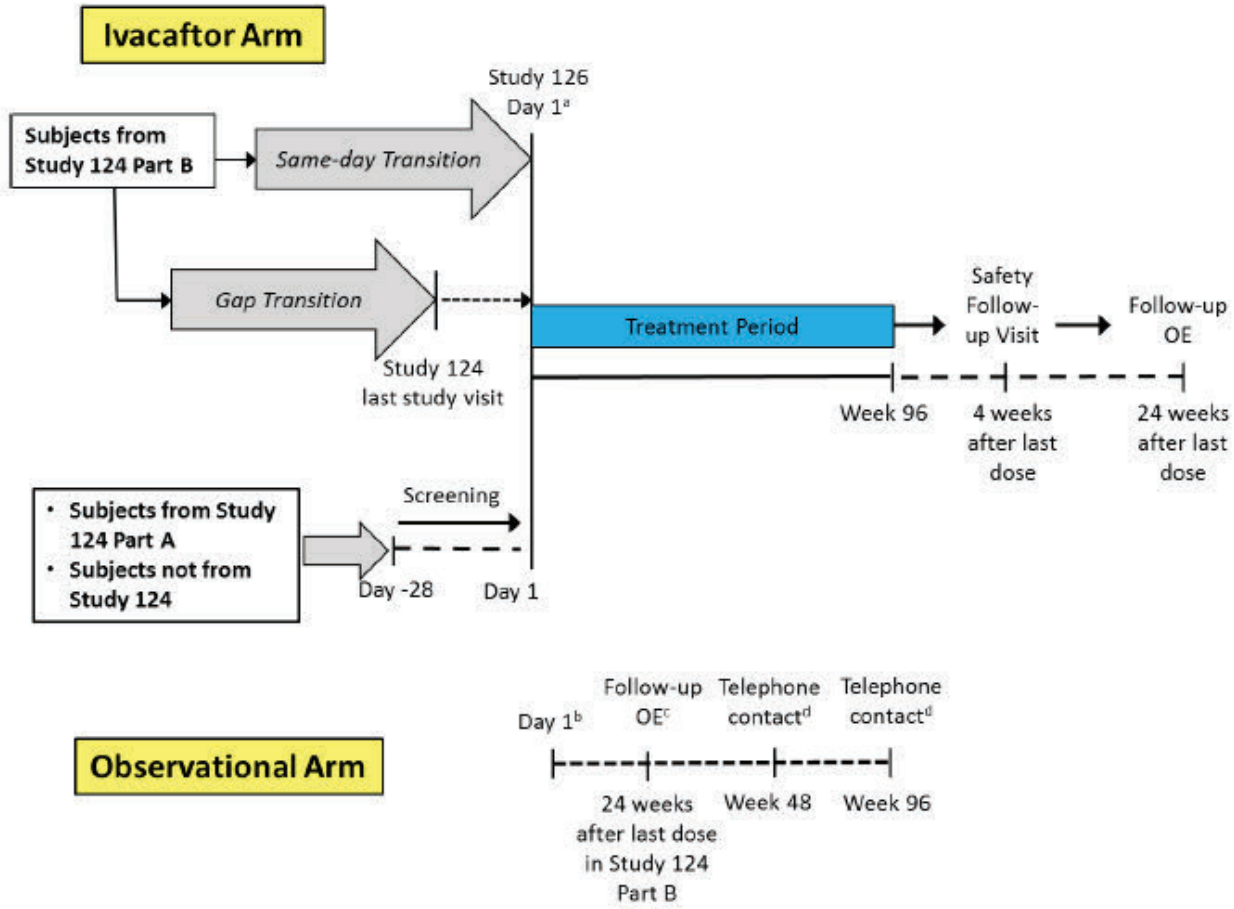
Study Design and Conduct

Study 126 was a phase 3, multicenter, multinational, open-label, two-arm (IVA arm and observational arm) study that evaluated the safety and PD of IVA treatment over a 96-week period in subjects who were <24 months of age at the initiation of IVA treatment and had an approved IVA-responsive variant.

The target enrollment for this study was about 75 subjects. The observational arm was to comprise subjects who completed IVA treatment in Study VX15-770-124 Part B (Study 124B) and elected not to enroll in the IVA arm in Study 126 or who received at least one dose of IVA during Study 124B and prematurely discontinued treatment.

Subjects enrolled in the IVA arm included rollover subjects who completed Study VX15-770-124 Part B or Part A/B (Study 124B or 124A/B) as well as IVA-naïve subjects who participated in Study VX15-770-124 Part A (Study 124A) only or who did not participate in Study 124 and were <24 months of age at Day 1 of Study 126. Subjects in the IVA arm received weight-based dosing: 25 mg IVA (5 to <7 kg), 50 mg IVA (7 to <14 kg), or 75 mg IVA (14 to <25 kg) every 12 hours. Subjects could have received IVA treatment for up to 120 weeks (for rollover subjects: 24 weeks in Study 124B or 124A/B and 96 weeks in Study 126; for IVA-naïve subjects: 96 weeks in Study 126). The Schedule of Assessments for rollover subjects and IVA-naïve subjects is provided in Table 13 and Table 14, respectively. The schematic for Study 126 is displayed in Figure 1.

Figure 1. Study Diagram (Study 126)



Source: Clinical Study Report (version 1.0), Figure 9-1, p. 21
Abbreviations: OE, ophthalmologic examination

Key Inclusion Criteria

- Aged <24 months at the Day 1 visit
- Confirmed diagnosis of CF, defined as a sweat chloride value ≥60 mmol/L by quantitative pilocarpine iontophoresis or 2 CF-causing variants
- An IVA-responsive *CFTR* variant on at least one allele (subjects will be eligible in countries/regions where IVA is approved for use in subjects 2 years of age and older)
- Hematology, serum chemistry, and vital sign results have no clinically significant abnormalities that would confound the study assessments, as judged by the investigator

Key Exclusion Criteria

- History of any illness or condition that, in the opinion of the investigator, may confound the results of the study or pose an additional risk in administering IVA to the subject
- An acute upper or lower respiratory infection, or pulmonary exacerbation, or changes in therapy (including antibiotics) for pulmonary disease within four weeks of Day 1
- Known colonization with organisms associated with a more rapid decline in pulmonary status, such as *Burkholderia cenocepacia*, *Burkholderia dolosa*, and *Mycobacterium abscessus* (a subject is excluded if they have a positive culture of one of these organisms)
- Abnormal liver function at screening or any prior history of clinically relevant elevated (>2 x upper limit of normal [ULN]) serum aspartate transaminase (AST), serum alanine transaminsase (ALT), or bilirubin (excluding newborn hyperbilirubinemia)
- Hemoglobin <9.5 g/dL at screening
- History of solid organ or hematological transplantation
- Any clinically significant "non-CF-related" illness within two weeks of Day 1, defined as an acute (serious or nonserious) condition (e.g., gastroenteritis)

Prohibited Medications

Subjects must have ended the use of moderate and strong inducers and inhibitors of CYP3A, including certain herbal medications and foods containing grapefruit or Seville oranges, at least 14 days before Day 1.

Study Drug Discontinuation Criteria

A subject was to be discontinued from study treatment if the subject was noncompliant with study protocol requirements, restrictions, and instructions, participated in another clinical study, or developed a new lens opacity or cataract. A subject may have been discontinued from study treatment for any of the following reasons:

- Developing a medical condition that requires prolonged concomitant therapy with a prohibited medication or prolonged interruption of IVA
- Developing a life-threatening AE or SAE that puts them at immediate risk
- An increase in LFT levels (e.g., AST or ALT levels)

- Clinically significant findings are observed in the slit-lamp examination

IVA treatment was to be interrupted immediately if any of the following criteria were met:

- ALT or AST >8 x ULN; or
- ALT or AST >5 x ULN for 2 weeks or more; or
- ALT or AST >3 x ULN in association with elevation of bilirubin >2 x ULN and/or jaundice

If a subject switched to commercially available IVA, the end of treatment (ETT) Visit was to be completed before dosing with commercial drug began, and the Safety Follow-up Visit would not be required. For subjects who discontinued from the study, their ETT Visit was to occur as soon as possible after their last dose of study drug, and their Safety Follow-up Visit was to occur within four weeks after their last dose of study drug.

Study Endpoints

Primary:

Safety, as determined by AEs, laboratory values (serum chemistry and hematology), 12-lead ECGs, vital signs, and OEs.

Secondary:

Absolute change from baseline in sweat chloride through Week 96.

Tertiary:

The tertiary endpoints for this study included absolute change from baseline through Week 96 in BMI, weight, FE-1, and markers of intestinal inflammation (e.g., fecal calprotectin). The annualized rates of pulmonary exacerbations and CF-related hospitalizations were also evaluated.

Statistical Analysis Plan (SAP)

The final SAP is dated April 25, 2023, and contains the information outlined below.

Analysis Sets:

All Subjects Set: All subjects who are enrolled in the current study. This analysis set will be used for all individual subject data listings and the disposition summary table, unless specified otherwise.

Full Analysis Set (FAS): All subjects who are enrolled and receive at least one post-baseline efficacy assessment in the current study. The FAS will be used for all efficacy analyses, unless

specified otherwise.

Safety Set: All subjects who receive at least one dose of study drug in the current study. This analysis set will be used for all safety analyses, unless specified otherwise.

Sample Size Considerations:

No formal sample size calculation was performed for this study, as the study was not powered to detect a significant treatment effect. The study aimed to enroll about 75 subjects.

Statistical Analyses:

All endpoints were analyzed descriptively with no formal statistical testing. Therefore, no multiplicity adjustment was performed.

Continuous variables were summarized using the following descriptive summary statistics: number of subjects (n), mean, standard deviation (SD), standard error (SE), median, minimum value (min), and maximum value (max). Categorical variables were summarized using counts and percentages.

Baseline value for rollover subjects was defined as the baseline measurement from Study 124B or 124A/B. That is, the most recent, non-missing measurement collected on or before the initial administration of study drug in Study 124B or 124A/B. Baseline value for IVA-naïve subjects was defined as the most recent, non-missing measurement collected on or before the initial administration of study drug in the current study, including both scheduled and unscheduled measurements.

Protocol Amendments

There was a single protocol amendment dated October 5, 2017. The major changes included a revised study population and inclusion criteria, the addition of information regarding IVA-responsive variants, and the removal of the Week 104 Visit. All other changes were minor.

7.1.2. Study Results

Compliance with Good Clinical Practices (GCP)

The Applicant states the following: This study was conducted in accordance with the current ICH E6 GCP guidelines, which are consistent with the ethical principles founded in the Declaration of Helsinki, and in accordance with local laws and regulations. Informed consent was obtained from each subject's legal representative before study participation, using a method compliant with ICH E6 GCP guidelines and applicable laws and regulations.

Financial Disclosure

Not applicable per 21 C.F.R. § 54.2(e)

Subject Disposition

All 86 enrolled subjects (38 rollover subjects from Study 124B or 124A/B and 48 IVA-naïve subjects) were included in the IVA arm (i.e., no subjects were included in the observational arm) and the All Subjects, Safety, and Full Analysis Sets. Of these 86 subjects, 60 subjects (70%) completed study drug treatment and 26 subjects (30%) prematurely discontinued treatment. The reasons for discontinuation were as follows: 20 subjects (23%) initiated commercial drug, 2 subjects (2%) were lost to follow-up, 2 subjects (3%) had AEs, 1 subject (1%%) was discontinued due to Applicant decision, and 1 subject (1%) was discontinued due to physician decision.

Additionally, all rollover subjects from Study 124B or 124A/B had a same-day transition to Study 126 (i.e., their Week 24 Visit in Study 124B was the same as their Day 1 Visit in Study 126); no rollover subjects had a time gap between Studies 124 and 126.

Protocol Deviations

There were three protocol deviations identified as important protocol deviations (IPDs): one was related to investigational product compliance (two kits were dispensed due to site error, but the correct dosage was dispensed), and two were related to inclusion/exclusion criteria (historical ALT, AST, or bilirubin levels were >2 x ULN prior to screening).

Baseline Demographics and Clinical Characteristics

Subject demographics at baseline are provided in Table 4. The study population included slightly more males (47%) than females (53%) and was predominantly white (95%), not Hispanic or Latino (92%), and located in North America (63%). Recorded baseline age reflect the age of entry to Study 124 among the rollover subjects (n=38) and Study 126 among the non-rollver subjects (n=48). Overall, the average age at baseline was 10 months with the average age of rollover subjects (15.9 months, range 6 to 27) greater than the non-rollover subjects (10.1 months, range 4 to 23). The baseline demographics of the study population were generally consistent with the target CF population in this age group.

Table 4. Baseline Demographics (Full Analysis Set, Study 126)

Demographic		IVA N=86
Sex, n (%)	Female	40 (46.5)
	Male	46 (53.5)
Age (months)	Mean (SD)	10.2 (5.2)
	Median (Min, Max)	9 (1, 23)
Race, n (%)	Asian	1 (1.2)
	White	82 (95.3)
	Not collected per local regulations	3 (3.5)
Ethnicity, n (%)	Hispanic or Latino	2 (2.3)
	Not Hispanic or Latino	79 (91.9)
	Not collected per local regulations	5 (5.8)
Site location, n (%)	Australia	4 (4.7)
	Europe	28 (32.6)
	North America	54 (62.8)
Genotype, n (%)	*G551D/DELF508*	46 (53.5)
	Other	40 (46.5)

Source: Statistical reviewer; Clinical Study Report (version 1.0), Table 10-2, p. 33-34
Abbreviations: IVA, ivacaftor; Max, maximum; Min, minimum; n, number of subjects in the respective category; SD, standard deviation

Subject clinical characteristics at baseline are summarized in Table 5. The average sweat chloride, BMI, and weight at baseline among all subjects with a baseline value was 95.1 mmol/L, 17.0 kg/m^2, and 8.9 kg, respectively. Additionally, the average FE-1 and fecal calprotectin levels at baseline were 213.4 µg/g and 153.7 µg/g, respectively, and a considerable portion of subjects had a history of pancreatic failure (62%), CF lung disease (53%), GERD (28%), and constipation (21%). The baseline clinical characteristics were generally consistent with the target CF population in this age group.

Table 5. Baseline Clinical Characteristics (Full Analysis Set, Study 126)

Clinical Characteristic	Statistic or Category	IVA N=86
Sweat chloride (mmol/L)	n (%)	85 (98.8)
	Mean (SD)	95.1 (17.9)
	Median (Min, Max)	100 (39.5, 120.5)
BMI (kg/m^2)	n (%)	86 (100)
	Mean (SD)	17.0 (1.6)
	Median (Min, Max)	16.8 (13.6, 22.0)
Weight (kg)	n (%)	86 (100)
	Mean (SD)	8.9 (2.0)
	Median (Min, Max)	8.8 (4.2, 13.7)
FE-1 level (µg/g)	n (%)	82 (95.3)
	Mean (SD)	213.4 (214.8)
	Median (Min, Max)	103.5 (7.5, 500)
Fecal calprotectin level (µg/g)	n (%)	80 (93)
	Mean (SD)	153.7 (155.4)
	Median (Min, Max)	96 (7.8, 718.9)
Medical history conditions[a] (%)	Pancreatic failure	53 (61.6)
	CF lung	46 (53.5)
	GERD	24 (27.9)
	Constipation	18 (20.9)

Source: Statistical reviewer; Clinical Study Report (version 1.0), Tables 10-3 (p. 34-35), 10-4 (p. 36), 11-3 (p. 47), and 14.2.2.7 (p. 247)

[a] Includes conditions in >20% of all enrolled subjects
Abbreviations: BMI, body mass index; CF, cystic fibrosis; FE-1, fecal elastase-1; g, grams; GERD, gastroesophageal reflux disease; IVA, ivacaftor; kg, kilograms; L, liters; m, meters; Max, maximum; Min, minimum; mmol, millimoles; n, number of subjects with a baseline value for the respective clinical characteristic; N, number of subjects in the Full Analysis Set; SD, standard deviation; µg, micrograms

Treatment Compliance

Study drug compliance was calculated as follows:

100 x (1 – [number of days of study drug interruption] /
[duration of study drug exposure in days])

In general, treatment compliance was high. The mean study drug compliance was 99.8%, and all subjects were >80% compliant.

Concomitant Medications

The most commonly reported concomitant medications were vitamins (88%), medications related to pancreatic enzyme replacement therapy (71%), sodium chloride (57%), salbutamol

(55%), amoxicillin/clavulanate potassium (50%), paracetamol (45%), amoxicillin (34%), ibuprofen (28%), dornase alfa (27%), flucloxacillin (27%), and cefdinir (22%). These medications are typically used for CF management in younger age groups.

Efficacy Results – Primary Endpoint

Study 126 was a long-term, open-label safety study; the primary endpoint evaluated safety, not efficacy. The safety findings are discussed in Section 7.2.

Efficacy Results – Secondary and other relevant endpoints

Other relevant endpoints included the absolute change from baseline to Week 96 in sweat chloride (secondary) and the absolute change from baseline to Week 96 in BMI, weight, and FE-1 and fecal calprotectin levels (tertiary). Mean decreases in sweat chloride (-55.3 mmol/L), BMI (-0.84 kg/m^2), and fecal calprotectin (-75 µg/g) from baseline were observed at Week 96, as well as mean increases in weight (5.9 kg) and FE-1 (225.6 µg/g), as shown in Table 6. Although assessment is limited without a comparator arm, there did not appear to be detrimental effects on growth. There were observed changes in FE-1 and fecal calprotectin levels, but the clinical relevance of these changes is unknown.

Table 6. Change from Baseline to Week 96 in Sweat Chloride, BMI, Weight, FE-1, and Fecal Calprotectin (Full Analysis Set, Study 126)

Parameter	Statistic	IVA N=86
Sweat Chloride (mmol/L)	n (%)	33 (38.4)
	Mean (SD)	-55.3 (25)
	95% CI	-64.2, -46.5
	Median (Min, Max)	-60.5 (-93, 0)
BMI (kg/m^2)	n (%)	51 (59.3)
	Mean (SD)	-0.84 (1.33)
	95% CI	-1.21, -0.46
	Median (Min, Max)	-0.98 (-3.4, 2.35)
Weight (kg)	n (%)	51 (59.3)
	Mean (SD)	5.9 (1.6)
	95% CI	5.4, 6.4
	Median (Min, Max)	5.9 (2.5, 11.7)
FE-1 level (µg/g)	n (%)	33 (38.4)
	Mean (SD)	225.6 (202.4)
	95% CI	213.1, 238.1
	Median (Min, Max)	272 (-94, 492.5)
Fecal calprotectin level (µg/g)	n (%)	32 (37.2)
	Mean (SD)	-75 (202.7)
	95% CI	-88, -62.1
	Median (Min, Max)	-79.1 (-506.2, 756.5)

Source: Statistical Reviewer; Clinical Study Report (version 1.0), Tables 11-1 (p. 39), 11-2 (p. 41), 11-3 (p. 47), and 14.2.2.7 (p. 251)
Abbreviations: BMI, body mass index; CI, confidence interval; FE-1, fecal elastase-1; g, grams; IVA, ivacaftor; kg, kilograms; L, liters; m, meters; Max, maximum; Min, minimum; mmol, millimoles; n, size of subsample; N, number of subjects in the Full Analysis Set; SD, standard deviation; µg, micrograms

Data Quality and Integrity

This NDA was submitted on December 6, 2024. The application was appropriately indexed and complete to allow for review.

Durability of Response

There was a change in mean sweat chloride (an important PD marker) from baseline to the end of the treatment period (Week 96) that was initially observed in the early weeks after initiating therapy, thus suggesting durability of drug response while on treatment.

7.1.3. Assessment of Efficacy Across Trials

Study 126 was not designed to evaluate efficacy; therefore, this section is not applicable.

7.2. Review of Safety

7.2.1. Safety Review Approach

The clinical safety review is based on clinical data from Study 126, which was a 96-week open-label rollover study from the previous Study 124 reviewed under NDA 203188 and NDA 207925.

7.2.2. Review of the Safety Database

Overall Exposure

The safety database includes a total of 86 subjects who were exposed to IVA granules in Study 126 at the following doses:

- 6 subjects received IVA 25 mg
- 79 subjects received IVA 50 mg
- 1 subject received IVA 75 mg

Half of the subjects were exposed to IVA granules for >96 weeks and the majority were exposed to >72 weeks. The extent of exposure is summarized in Table 7.

Table 7: Summary of Exposure, Study 126, Safety Set

Exposure Duration	IVACAFTOR (N=86)
Exposure Duration (Weeks)	
Mean (SD)	80.0 (27.57)
SE	3.00
Median	96.1
Min, Max	5.1, 99.1
Exposure Duration Category (Weeks), n (%)	
>12 to <=24 Weeks	5 (5.8)
>24 to <=48 Weeks	10 (11.6)
>4 to <=8 Weeks	1 (1.2)
>48 to <=72 Weeks	6 (7.0)
>72 to <=96 Weeks	21 (24.4)
>96 Weeks	43 (50.0)

Source: OCS Analysis Studio, Custom Table Tool.
Columns - Dataset: Demographics; Filter: SAFFL = 'Y'.
Exposure Duration (Weeks) - Dataset: Demographics; Filter: None.
Exposure Duration Category - Dataset: Demographics; Filter: None.
Abbreviations: Min, minimum; Max, maximum; SD, Standard Deviation; SE, standard error.

Adequacy of the safety database:

Study 126 included a 96-week treatment period during which safety was assessed. The safety database was adequate in the context of the overall program and for the purposes of this review.

7.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

None.

Categorization of Adverse Events

The Applicant defined an adverse event (AE) as any untoward medical occurrence in a subject during the study that does not necessarily have a causal relationship with the treatment. This definition included any newly occurring event or worsening of a pre-existing condition after the informed consent form was signed. Any abnormal laboratory tests, ECGs, physical exams, or vital signs that were deemed to have clinically significant worsening from baseline was considered an AE. Adverse events were classified using MeDRA Version 26.1.

The treatment emergent period started from the first dose date of study drug in Study 126 to the Safety Follow-up visit or the last dose date plus 28 days for those who did not have a Safety Follow-up Visit.

The Applicant graded AE severity using the FDA Guidance for Industry, Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (September 2007).

Routine Clinical Tests

Routine clinical tests included AEs, clinical laboratory measurements, standard 12-lead ECGs, Vital Signs, physical examinations, pulse oximetry, and ophthalmology examinations.

7.2.4. Safety Results

Deaths

There were no deaths in Study 126.

Serious Adverse Events

A total of 21 (24.4%) subjects experienced a serious adverse event (SAE) in Study 126. These events are summarized in **Table 8**.

Table 8: Summary of Serious Adverse Events (SAEs), Safety Set, Study 126

System Organ Class, n (%) Preferred term, n (%)	IVA (N=86)
Number of subjects with at least 1 SAE, n (%)	21 (24.4)
Infections and infestations	16 (18.6)
Infective pulmonary exacerbation of cystic fibrosis	9 (10.5)
Bronchiolitis	1 (1.2)
Bronchitis	1 (1.2)
Gastroenteritis	1 (1.2)
Gastroenteritis viral	1 (1.2)
Lower respiratory tract infection viral	1 (1.2)
Parainfluenzae virus infection	1 (1.2)
Periorbital cellulitis	1 (1.2)
Respiratory syncytial virus infection	1 (1.2)
Rhinovirus infection	1 (1.2)
Viral infection	1 (1.2)
Viral rash	1 (1.2)
Viral upper respiratory tract infection	1 (1.2)
Investigations	4 (4.7)
Pseudomonas test positive	2 (2.3)
Electrocardiogram QT shortened	1 (1.2)
Electroencephalogram abnormal	1 (1.2)
Gastrointestinal disorders	3 (3.5)
Constipation	2 (2.3)
Distal intestinal obstruction syndrome	1 (1.2)
Metabolism and nutrition disorders	2 (2.3)
Dehydration	1 (1.2)
Malnutrition	1 (1.2)
Endocrine disorders	1 (1.2)
Adrenocortical insufficiency acute	1 (1.2)
General disorders and administration site conditions	1 (1.2)
Pyrexia	1 (1.2)
Product issues	1 (1.2)
Device dislocation	1 (1.2)

Source: OCS Analysis Studio, Custom Table Tool.
Columns - Dataset: Demographics; Filter: SAFFL = 'Y'.
SAEs - Dataset: Adverse Events; Filter: SAFFL = 'Y', TRTEMFL = 'Y', AESER = 'Y'.

There were two SAEs that were unexpected for the population. The first was an SAE of shortened QT in a 13-month old male rolled over to Study 126 from Study 124 Part B, during which time he had a stable QTcF of 336 msec. On study day 174, the subject experienced an

asymptomiatic shortened QTcF of 339 msec with repeat assessments of 343 msec. The subject had a second episode of asymptomatic shortened QTcF 3 months later. At an unspecified time during the subject's treatment period, there was study drug interruption for a total of 25 days. After each episode, the subject underwent cardiology consultation by an electrophysiology cardiologist. Cardiology's final assessment considered these QTcF changes to be minimal, not clinically significant, not substantially different when on or off study drug, and not consistent with short QT syndrome. Given cardiology's assessment, this SAE was deemed by the Applicant as not related to study drug which appears reasonable based on the submitted clinical data.

The second SAE of abnormal EEG occurred in a 7-month old male with no prior history of seizures who underwent evaluation after report of "eyes rolling back" suspicious for tonic upward gaze of infancy. The EEG was notable for left temporal focal voltage attenuation suspicious for left temporal focal cerebral dysfunction. The subject was hospitalized to undergo further work-up with a 48-hour video EEG and MRI. Although the video EEG was normal, the MRI revealed nonspecific mild T2 FLAIR hyperintensities within bilateral hippocampi. Pediatric neurologist evaluation considered the presentation to be consistent with benign tonic upgaze syndrome but also noted the imaging to be consistent with mesial temporal sclerosis, a finding associated with temporal lobe seizures. The subject had no further events on study. Although the SAE was considered to be possibly related to study treatment, there is not insufficient data on the subjects history or sufficient longitudinal follow-up to make a meaningful assessment of relatedness.

Aside from these two cases, the SAEs reported were otherwise generally what would be expected in a CF population in a long-term safety study and did not revewal new safety concerns.

Dropouts and/or Discontinuations Due to Adverse Effects

Overall, 26 (30.2%) subjects discontinued study, amongst which 20 did so due to the commercial availability of the study drug. Two subjects (2.3%) discontinued due to AEs of increased transaminases and are discussed in Section 7.2.5.1. There were few (8 subjects, 9.3%) treatment interruptions, the majority of which were secondary to vomiting (5 subjects) followed by viral gastroenteritis (1 subject), viral rash (1 subject) and shortened QT syndrome (1 subject).

Significant Adverse Events

In Study 126, a total of 10 subjects had Grade 3 treatment emergenty adverse events (TEAEs). Of these 10, 2 subjects developed infective pulmonary exacerbation (PEx) of CF and increased alanine transaminase (ALT) and aspartate transaminase (AST). For the remaining eight subjects, the following TEAEs occurred in one subject each: respiratory syncytial virus infection, viral rash, periorbital cellulitis, obstructive sleep apnea syndrome, abdominal pain, distal intestinal obstruction syndrome, *Pseudomonas* test positive, increased alkaline phosphatase (ALP), and pyrexia. There were no Grade 4/5 TEAEs.

Treatment Emergent Adverse Events and Adverse Reactions

TEAEs occurring in >10% of subjects are summarized in **Table 9**. The TEAEs reported were generally consistent with the known safety profile of IVA consisting of either common manifestations of CF disease or common illnesses in this population age. No new safety signals were identified.

Table 9: TEAEs occurring in >10% of Subjects by Preferred Term, Study 126, Safety Set

Preferred Term	IVA (N=86)
Cough	60 (69.8)
Pyrexia	35 (40.7)
Rhinorrhoea	33 (38.4)
Upper respiratory tract infection	24 (27.9)
Vomiting	22 (25.6)
Rash	21 (24.4)
Ear infection	19 (22.1)
Infective pulmonary exacerbation of cystic fibrosis	18 (20.9)
Diarrhoea	15 (17.4)
Constipation	14 (16.3)
Nasal congestion	13 (15.1)
Rhinitis	11 (12.8)
Nasopharyngitis	10 (11.6)
Otitis media	10 (11.6)
Conjunctivitis	9 (10.5)
Gastroenteritis	9 (10.5)
Pseudomonas test positive	9 (10.5)

Source: OCS Analysis Studio, Custom Table Tool.
Columns - Dataset: Demographics; Filter: SAFFL = 'Y'.
AEs occuring in >10% of Subjects by PT, Safety Set - Dataset: Adverse Events; Filter: SAFFL = 'Y', TRTEMFL = 'Y'; Percent Threshold: >= 10%.

Laboratory Findings

Routine clinical testing for this safety study included evaluations of hematology and serum chemistries, including liver transaminases. Excluding transaminases, no laboratory abnormalities resulted in treatment interruptions or discontinuations. See Section for a more detailed evaluation of liver transaminases.

Vital Signs

The Applicant presented mean values for heart rate, blood pressure, body temperature, and oxygen saturations. No clinically relevant changes from baseline were noted.

Electrocardiograms (ECGs)

Summary statistics of heart rate, PR interval, QRS duration, QTcF interval, QT interval, and RR interval were provided by the Applicant. There was one subject with an SAE of shortened QT as shown in Table 8 and discussed under Serious Adverse Events above. Otherwise, there were no clinically relevant changes from baseline noted.

7.2.5. Analysis of Submission-Specific Safety Issues

Given the listed Warnings and Precautions included in the approved IVA label, specific safety analyses were performed for transaminase elevations, hypersensitivity reactions, and cataracts. Safety analysis for rash was also included.

Transaminase elevations

Given the know incidences of transaminase increases for IVA and IVA-containing drugs, the Applicant assessed clinical lab data and AEs for transaminase abnormalities in Study 126, which are summarized in Table 10. Overall, 5 subjects had an ALT or AST >3 times the upper limit of normal (ULN), among which 2 had an ALT or AST > 5xULN and another 2 had and ALT or AST >8xULN. No subjects had total bilirubin elevations.

Table 10: Maximum On-Treatment Liver Function Test Results, Study 126, Safety Set

Maximum On-Treatment Result, n (%)	IVA (N=86)
Alanine Aminotransferase (ALT) (U/L)	
<=1xULN	56 (65.1)
>1xULN to <=2xULN	24 (27.9)
>2xULN to <=3xULN	1 (1.2)
>3xULN to <=5xULN	1 (1.2)
>5xULN to <=8xULN	2 (2.3)
>8xULN	2 (2.3)
Aspartate Aminotransferase (ALT) (U/L)	
<=1xULN	75 (98.8)
>1xULN to <=2xULN	9 (10.5)
>2xULN to <=3xULN	2 (2.3)
ALT or AST	
<=1xULN	54 (62.8)
>1xULN to <=2xULN	26 (30.2)
>2xULN to <=3xULN	1 (1.2)
>3xULN to <=5xULN	1 (1.2)
>5xULN to <=8xULN	2 (2.3)
>8xULN	2 (2.3)
Total Bilirubin (umol/L)	
<=1xULN	86 (100.0)
Maximum ALT or AST >3xULN and Total Bilirubin>2xULN During Treatment-Emergent Period	0 (0)

Source: OCS Analysis Studio, Custom Table Tool.
Columns - Dataset: Demographics; Filter: SAFFL = 'Y'.
Table Section 1 - Dataset: Laboratory; Filter: SAFFL = 'Y', PARAM = 'Alanine Aminotransferase (U/L)' or 'Aspartate Aminotransferase (U/L)' or 'Bilirubin (umol/L)' or 'Direct Bilirubin (umol/L)' or 'Maximum ALT>3xULN and Total Bilirubin>2xULN During Treatment-Emergent Period' or 'Maximum AST>3xULN and Total Bilirubin>2xULN During Treatment-Emergent Period', APHASE = 'TREATMENT'.
Abbreviations: ALT, alanine transferase; AST, aspartate transferase; IVA, ivacaftor; L, liter; U, units; ULN, upper limit of normal

Although no subjects were reported to have discontinued the study because of transaminase elevations, two subjects experienced treatment withdrawal because of ALT, AST and gamma-glutamyl transferase (GGT) >8xULN and >5xULN, each occurring in a single male subject aged 21 months. Both subjects experienced improvement in transaminase elevations but ultimately discontinued the study because of the commercial availability of the drug. The remaining subjects with and ALT or AST 5>X or >8xULN had displayed a history of waxing and waning transaminase elevations prior to these events, which resolved without study drug interruption or other intervention. Similarly the maximal elevations of >5x or >8xULN also resolved without study drug interruption or other intervention.

Cataracts

All subjects had ophthalmological examinations for cataracts at screening, during treatment at weeks 24, 48, 72, and 96, and at the 24-week follow-up visit. The Applicant reported there were no adverse events of cataracts identified during the 96-week treatment. However, review of the case narratives identified a 6-month old subject who had no evidence of cataracts or lens opacity at screening but did have an ophthalmologic examination at week 48 significant for lens opacity (cataract-related) in the left eye, with posterior polar cataract. These findings were present and unchanged at the week 96 visit. In a response dated February 3, 2025 to the Agency's information request for clarification of the case dated January 29, 2025, the Applicant stated that the lens opacity and cataract were not considered by the Investigator to be clinically significant and, therefore, did not meet the per protocol definition of an advese event. Cataracts is a well-described adverse reaction of IVA and is included under Warnings and Precautions of the USPI. This event is consistent with the knonwn safety profile of IVA.

Rash

As displayed in the adverse reactions table (Table 9) in Section 7.2.4, rash events occurred in 24.4% of subjects in Study 126. Given that rash is a well-described adverse reaction of IVA and other IVA-containing products and the USPI reports a rash frequency of 13% from the pivotal trial, this review aimed to explore all rash-related events, which are summarized in Table 11.

Table 11: Summary of Rash Events, Study 126, Safety Set

Preferred Term	IVACAFTOR (N=86)
All Rash-related Events	28 (32.6)
Rash	21 (24.4)
Rash papular	2 (2.3)
Urticaria	2 (2.3)
Rash erythematous	1 (1.2)
Rash macular	1 (1.2)
Erythema	1 (1.2)

Source: OCS Analysis Studio, Custom Table Tool.
Columns - Dataset: Demographics; Filter: SAFFL = 'Y'.
Table Section - Dataset: Adverse Events; Filter: SAFFL = 'Y', TRTEMFL = 'Y', AEBODSYS = 'Skin and subcutaneous tissue disorders'.

In total, there were 28 (32.6%) events, none of which resulted in treatment interruption or study discontinuation and all resolved spontaneously. In the absence of a comparator arm, clinical trial data was reviewed from two 24-week, open-label studies: Study 124, the predecessor to Study 126, and Study 108, which enrolled subjects aged 2 to <6 years and supported the initial approval of IVA granules. Collectively, among the 43 children aged 1

month to <24 months in Study 124 there were 5 (11.6%) rash events. Similarly, among the 34 children aged 2 to <6 years in Study 108, there were 4 (11.8%) rash events.

Although the assessment of this signal is limited without a comparator arm, it is possible that the higher frequency of rash events in Study 126 is reflective of the epidemiology of viral exanthems common in this age range and the long-term follow-up period that allowed more time to capture such events. No changes to the USPI are warranted based on these findings.

7.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

This study did not include clinical outcome assessments.

7.2.7. Safety Analyses by Demographic Subgroups

Given the limited size of this study, additional safety analyses by demographic subgroup were not performed.

7.2.8. Additional Safety Explorations

Pediatrics and Assessment of Effects on Growth

This trial included pediatric subjects of 1 month of age to less than 2 years old. Height, weight, and BMI were included as exploratory endpoints (discussed in Section 8.1.1). The mean change (and standard deviation) at 96 weeks from baseline were as follows in (Table reference below)

Table 12: Mean Change from Baseline in Growth Parameters, Study 126, Safety Set

	IVA (N=86) Mean Change (SD)
BMI	16.5 (1.95)
BMI-for-age z score	0.2 (1.18)
Weight (kg)	9.8 (3.54)
Weight-for-age z-score	0.0 (1.18)
Length (cm)	76.5 (13.29)
Length-for-age z-score	-0.2 (1.37)

Source: OCS Analysis Studio, Custom Table Tool.
Columns - Dataset: Demographics; Filter: SAFFL = 'Y'.
Table Section - Dataset: Other 1; Filter: SAFFL = 'Y'.
SD = Standard Deviation.

Although the assessment is limited without a comparator arm, compared to CDC growth charts for healthy children (average weight gain is 2.27 kg per 1 year and average length increases is

10-12 cm per year), there did not appear to be detrimental effects on growth.

7.2.9. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Ivacaftor was initially approved on January 31, 2012, for the G551D variant. At the time of this review, there are currently two ongoing NISS evaluations for psychiatric disorders and intracranial disorders (NISS 1005257, NISS 1005337). There were no events of intracranial disorders in Study 126 and neuropsychiatric disorders were not assessable in this population.

Expectations on Safety in the Postmarket Setting

The patient population (1 month to <2 years of age) included in Study 126 is already indicated for IVA since May 3, 2023. Therefore, no substantial differences in post marketing experience are anticipated.

7.2.10. Integrated Assessment of Safety

The safety data submitted with this application for the IVA granules in subjects 1 month to <24 months of age, in conjunction with the known safety profile of IVA granules and tablets in patients ≥2years of age, was sufficient to assess the safety of IVA granules in the CF patient population aged 1 month to <24 months. In Study 126, which included 86 subjects all treated with IVA, no deaths were reported, and the observed SAEs were infrequent and consistent with the underlying CF disease process. Given the previous clinical experience with IVA granules and tablets, specific safety analyses were also performed to assess for liver-related toxicity, rash, and cataracts. These safety analyses did not reveal new safety concerns and were consistent with the known safety profile of IVA that is adequately characterized in the USPI; therefore, no safety related changes are recommended . Overall, the IVA granule safety profile in CF patients aged 1 month to <24 months confirms a favorable benefit risk assessment.

7.3. Statistical Issues

There were no statistical issues, as all results were descriptive.

7.4. Conclusions and Recommendations

The recommended regulatory action is Approval. In these current supplements (NDA 203188 S041 and NDA 207925 S019), the Applicant has submitted the results of the final pediatric study (Study 2 of 2) outlined in the PWR and proposes the fulfillment of the PWR, as well as pediatric exclusivity for the conducted pediatric studies. Study 1 was previously completed and submitted as interim analyses each of which were reviewed in 4 parts under NDA 203188-S028 and NDA2079525-S007 (part 1), NDA 203188-S029 and NDA 207925-S008 (part 2), NDA 203188-S033 and NDA 207925-S011 (part 3), and NDA 203188-S038 and 207925-S016 (part 4).

Both pediatric studies have met the criteria detailed in the PWR. Therefore, the PWR has been fulfilled. The Applicant has proposed labeling changes to include a brief, high level summary of the open label rollover study in the USPI. The proposed regulatory action is Approval.

8 Advisory Committee Meeting and Other External Consultations

Not applicable.

9 Pediatrics

Ivacaftor was granted Orphan Drug Designation on December 20, 2006. Pediatric Research Equity Act (PREA) requirements do not apply to this orphan drug product. The trial reviewed in this submission was conducted in pediatric patients pursuant to a PWR, issued on March 14, 2016.

10 Labeling Recommendations

10.1. Prescription Drug Labeling

The Applicant proposed the following addition to 8.4:

- "Safety of KALYDECO in patients aged 1 month and older was also evaluated in a 96-week, open-label study (Trial 9) in 86 patients (38 rolled over from Trial 8 and 48 KALYDECO-naïve)."

The Division typically does not include data from open label studies in the USPI; however, since this product is already approved for this population and the data from this study were obtained in response to a PWR, it is reasonable to include this brief descriptive sentence in section 8.4 of of the USPI. Furthermore, as Study 126 (Trial 9) did not identify new safety issues and the adverse reactions observed are consistent with previous studies including Study 124 (Trial 8), we will add the following additional statement to the Applicant's proposed language:

- "Adverse reactions from Trial 9 were generally similar to those reported in Trial 8."

11 Risk Evaluation and Mitigation Strategies (REMS)

A REMS was not deemed necessary for this application.

12 Postmarketing Requirements and Commitment

No postmarketing requirements and commitments are requested.

13 Deputy Director (designated signatory authority) Comments

Vertex Pharmaceuticals has submitted results of the final study (Study 126) as outlined in the Pediatric Written Request for ivacaftor. The results of this study were submitted as supplemental NDAs for the granule and tablet formulations (NDA 203188/S-41 and NDA 207925/S-19). With completion of this study, the Applicant proposes fulfullment of the PWR and requests pediatric exclusivity.

Study 126 was a phase 3, open-label, rollover study that evaluated the long-term safety and tolerability of IVA treatment in pediatric patients aged 1 month to <24 months with CF who carry at least one IVA-responsive *CFTR* variant as indicated in the USPI. Study 126 was a rollover study to Study 124, which was an open label, 24-week, PK and safety study. Thirty eight

subjects rolled over from Study 124, and 48 subjects were IVA-naïve. Overall, no new safety signals were identified in study 126 and the safety profile was consistent with the known saety profile of ivacaftor.

Study 126 was the second of the two studies conducted under the PWR. With submission of results from this study, the PWR is fulfilled. There are no outstanding issues from any review disciplines. I concur with the content of the various discipline assessments and the recommendation of approval. The Agency and the Applicant have also agreed upon the final labeling language. The action for this application will be Approval.

14 Appendices

14.1. Schedule of Assessments, Study 126

Table 13. Schedule of Assessments (Rollover Subjects, Study 126)

		Treatment Period (Day 1 Through Week 96)		ETT Visit[a]	Safety Follow-up Visit[b]	24-Week Follow-up OE
Event/Assessment	Day 1[c]	Weeks 12, 36, 60, and 84 (± 7 Days)	Weeks 24, 48, 72, and 96 (± 7 Days)	As Soon as Possible After the Last Dose	4 Weeks (± 7 Days) After the Last Dose	24 Weeks (+ 14 Days) After the Last Dose
Informed consent	X					
Confirm eligibility	X					
Clinic visit	X	X	X	X	X	
Study drug dose determination[d]	X	X	X			
Length and weight[e]	X	X	X	X	X	
Physical examination[f]	X	X	X	X	X	
Vital signs[g]	X	X	X	X	X	
12-lead ECGs[g, h]	X		X	X	X	
Serum chemistry and hematology	X	X	X	X	X	
Ophthalmologic examination[i]	X		X	X[j]		X
Fecal sample collection[k]	X		X	X		
Sweat chloride test[l]	X		X			
Qualitative microbiology cultures	X		X			
Multiple breath washout (optional)[m]	X		X[n]			
Study drug administration[o]	X	X	X			
Study drug count	X	X	X	X		
Pulmonary exacerbations, CF-related hospitalizations	*Continuous from signing of ICF through the last dose of study drug*					
Adverse events	*Continuous from signing ICF through the Safety Follow-up Visit (see Section 13.1.1.3)*					*Ocular adverse events only*
Medications and procedures review	*Continuous from signing of ICF through the Safety Follow-up Visit*					

Source: Clinical Study Protocol (version 2.0), Table 3-1, p. 9-10

[a] The ETT Visit is to be scheduled as soon as possible after the last dose of ivacaftor. If the ETT Visit occurs 3 weeks or later after the last dose of ivacaftor, the Safety Follow-up Visit will not be required. Subjects who elect to receive commercially available ivacaftor will be discontinued from ivacaftor dosing and will complete the ETT Visit and Follow-up OE.

[b] For subjects who elect to receive commercially available ivacaftor, the Safety Follow-up Visit will not be required.

[c] The Day 1 Visit will be the same day as the Week 24 Visit of Study 124 Part B. Any Study 126 Day 1 assessments performed at the Week 24 Visit of Study 124 Part B do not need to be repeated. Day 1 results should be taken from the Week 24 Visit in Study 124 (if applicable) on which these data are available (including demographics and medical history), except for the signing of informed consent, confirmation of eligibility, and IVRS/IWRS contact.

[d] The ivacaftor dose for each subject will be reassessed based on body weight and adjusted if necessary (see Section 9.4).

[e] Length and weight measurements will be performed predose through the Week 24 Visit (see Section 11.5.1).

[f] Full physical examinations will be performed at the ETT and Safety Follow-up Visits; abbreviated physical examinations will be performed at all other study visits.

[g] Vital signs and ECGs will be taken predose through the Week 24 Visit. Following the Week 24 Visit, vital signs and ECGs may be taken pre- or post-dose. Vital signs include blood pressure (systolic and diastolic), temperature, heart rate, respiratory rate, and pulse oximetry (see Section 11.6.3).

[h] All 12-lead ECGs will be taken predose at the Day 1, Week 12 and Week 24 Clinic Visits. At all visits, ECGs will be taken before any other procedures that may affect heart rate, such as blood draws (see Section 11.6.4).

[i] The OE will be conducted by a licensed ophthalmologist, preferably a pediatric ophthalmologist. The OE may be performed at the study visit or ± 14 days of the clinic visit.

[j] The OE for the ETT Visit will be conducted for all subjects who prematurely discontinue ivacaftor dosing (for any reason) unless performed in the last 12 weeks.

[k] Samples will be analyzed for fecal elastase-1 and other markers of intestinal inflammation, including fecal calprotectin. Samples may be collected up to 24 hours before the study visit (e.g., at home) and brought to the clinic. If the sample is collected in the clinic, the sample may be collected pre- or postdose.

[l] The sweat chloride test must be performed on Day 1 before the ivacaftor dose. At all other visits up to the Week 24 Visit, the sweat chloride test must be performed within ± 2 hours of the ivacaftor dose. After the Week 24 Visit, the sweat chloride test may be performed at any time during the visit.

[m] MBW will be performed on subjects for whom additional or separate informed consent was obtained for the procedures, and only at sites that are adequately trained and qualified to perform MBW (see Section 11.5.6). The Day 1 MBW must be performed within 1 week before the Day 1 Visit. The Week 96 MBW must be performed within 1 week before the last dose. Detailed procedures will be supplied in a separate study manual.

[n] MBW will be performed at the Week 24 and 48 Visits (± 7 days).

[o] The morning dose of study drug will be administered at the Day 1, Week 12 and Week 24 Clinic Visits. After the Week 24 Visit, the morning dose need not be administered at the Clinic Visit. Additional guidance for preparation and administration of study drug is provided in Section 9.4 and the study manual.

Abbreviations: CF, cystic fibrosis; ECG, electrocardiogram; ETT, early termination of treatment; ICF, informed consent form; IVA, ivacaftor; MBW, multiple breath washout; OE, ophthalmologic examination

Table 14. Schedule of Assessments (IVA-naïve Subjects, Study 126)

	Screening Period[a]	Treatment Period (Day 1 through Week 96)								ETT Visit[b]	Safety Follow-up Visit[c]	24-Week Follow-up OE
Event/Assessment	Day -28 to Day -1	Day 1	Day 3 (± 1 Day)	Week 2 (± 1 Day)	Week 4 (± 5 Days)	Weeks 8 and 18 (± 7 Days)	Weeks 12 and 24 (± 7 Days)	Weeks 36, 60, and 84 (± 7 Days)	Weeks 48, 72, and 96 (± 7 Days)	As Soon as Possible After the Last Dose	4 Weeks (± 7 Days) After the Last Dose	24 Weeks (+ 14 Days) After the Last Dose
Informed consent	X											
Inclusion/exclusion criteria review	X	X										
Clinic visit	X	X		X	X	X	X	X	X	X	X	
Telephone contact			X									
Demographics	X											
Medical history	X											
Historical data	X[d]											
CFTR genotype[e]	X											
Study drug dose determination		X		X	X	X	X	X	X			
Length and weight[f]	X	X		X	X	X	X	X	X	X	X	
Physical examination[g]	X	X		X	X	X	X	X	X	X	X	
Vital signs[h]	X	X		X	X	X	X	X	X	X	X	
12-lead ECGs[h, i]	X	X			X		X	X	X	X	X	
Serum chemistry and hematology[j]	X			Chem-istry only	LFTs and hema-tology only	X	X	X	X	X	X	
Ophthalmologic examination[k]	X[l]						X		X	X[m]		X
Fecal sample collection[n]	X[o]			X	X	X	X		X	X		
Sweat chloride test[p]	X	X		X			X		X			
Qualitative microbiology cultures		X					X		X			
Multiple breath washout (optional)[q]		X					X		X[r]			
Study drug administration[s]		X		X	X	X	X	X	X			
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	X		
Pulmonary exacerbations, CF-related hospitalizations	*Continuous from signing of ICF through the last dose of study drug*											
Adverse events	*Continuous from signing ICF through the Safety Follow-up Visit (see Section 13.1.1.3)*											*Ocular adverse events only*
Medications and procedures review	*Continuous from signing of ICF through the Safety Follow-up Visit*											

Source: Clinical Study Protocol (version 2.0), Table 3-3, p. 14-17

[a] Subjects will only be allowed to enroll in Study 126 after an adequate number of subjects have completed the corresponding age cohort in Study 124, in conjunction with feedback from regulatory authorities.
[b] The ETT Visit is to be scheduled as soon as possible after the last dose of ivacaftor. If the ETT Visit occurs 3 weeks or later after the last dose of ivacaftor, the Safety Follow-up Visit will not be required. Subjects who elect to receive commercially available ivacaftor will be discontinued from ivacaftor dosing and will complete the ETT Visit.
[c] For subjects who elect to receive commercially available ivacaftor, the Safety Follow-up Visit will not be required.
[d] Historical data from birth to screening will also be collected before (i.e., at screening) or at Day 1 (see Section 11.2).
[e] For subjects who participated in Study 124 Part A, the *CFTR* genotype result can be taken from Study 124. For all other subjects, the genotype results must be available before the first dose of study drug. If a genotype test has been performed previously and is documented in the subject's medical record, the subject's eligibility must be approved by the Vertex medical monitor. If a historic genotype result is not available at screening or if the historic genotype result is not approved by the Vertex medical monitor, subjects will be tested for *CFTR* genotype and the results must be reviewed before the first dose of study drug.
[f] Length and weight measurements will be performed predose through the Week 24 Visit (see Section 11.5.1).
[g] Full physical examinations will be performed at the Screening, ETT, and Safety Follow-up Visits; abbreviated physical examinations will be performed at all other study visits.
[h] Vital signs and ECGs will be taken predose through the Week 24 Visit. Following the Week 24 Visit, vital signs and ECGs may be taken pre- or post-dose. Vital signs include blood pressure (systolic and diastolic), temperature, heart rate, respiratory rate, and pulse oximetry (see Section 11.6.3).
[i] All 12-lead ECGs will be performed predose at the Day 1, Week 12 and Week 24 Clinic Visits. At all visits, ECGs will be taken before any other procedures that may affect heart rate, such as blood draws (see Section 11.6.4).
[j] To minimize blood draws, the Screening Visit and Day 1 clinical laboratory assessments can be combined into a single blood draw taken up to 9 days before the Day 1 dosing. The results must be received and reviewed before the first dose of study drug.
[k] The OE will be conducted by a licensed ophthalmologist, preferably a pediatric ophthalmologist. The OE may be performed at the study visit or ± 14 days of the clinic visit.
[l] If an OE was conducted in Study 124 Part A within 12 weeks of the Day 1 Visit, the Day 1 Visit OE does not need to be repeated.
[m] The OE for the ETT Visit will be conducted for all subjects who prematurely discontinue ivacaftor dosing in the ivacaftor arm, regardless of the reason for discontinuation. If the ETT Visit occurs within 12 weeks of the subject's last OE, the OE at the ETT Visit will not be required.
[n] Samples will be analyzed for fecal elastase-1 and other markers of intestinal inflammation, including fecal calprotectin. Samples may be collected (e.g., at home) up to 24 hours before the study visit (e.g., at home) and brought to the clinic. If the sample is collected in the clinic, the sample may be collected pre- or postdose.
[o] The fecal sample may be collected at any time during screening.
[p] 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. For all subjects, except those that completed a baseline sweat chloride test at screening, a Day 1 sweat chloride test will be performed predose. At all other visits up to the Week 24 Visit, the test must be performed within a window of ± 2 hours relative to the ivacaftor dose. After the Week 24 Visit, the sweat chloride test may be performed at any time during the visit.
[q] MBW will be performed on subjects for whom additional or separate informed consent was obtained for the procedures, and only at sites that are adequately trained and qualified to perform this assessment (Section 11.5.6). The Day 1 MBW must be performed within 1 week before the first dose, not postdose. The Week 96 MBW must be performed within 1 week before the last dose, not after the last dose. Detailed procedures will be supplied in a separate study manual.
[r] MBW will be performed at the Week 48 and Week 72 Visits (± 7 days).
[s] The morning dose of study drug will be administered at the Day 1, and 2-, 4-, 8-, 12-, 18-, and 24-Week Clinic Visits. After the Week 24 Visit, the morning dose need not be administered at the Clinic Visit. Additional guidance for preparation and administration of study drug is provided in Section 9.4 and the study manual.

Abbreviations: CF, cystic fibrosis; CFTR, CF transmembrane conductance regulator gene; ECG, electrocardiogram; ETT, early termination of treatment; ICF, informed consent form; IVA, ivacaftor; LFT, liver function test; MBW, multiple breath washout; OE, ophthalmologic examination

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