

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

212273Orig1s004

Trade Name: **Trikafta**

Generic or Proper Name: (elexacaftor, tezacaftor, and ivacaftor tablets)

Sponsor: Vertex Pharmaceuticals Inc

Approval Date: June 08, 2021

Indication: Trikafta is a combination of ivacaftor, a CFTR potentiator, tezacaftor, and elexacaftor indicated for the treatment of cystic fibrosis (CF) in patients aged 6 years and older who have at least one *F508del* mutation in the *CFTR* gene or a mutation in the *CFTR* gene that is responsive based on *in vitro* data. If the patient's genotype is unknown, an FDA-cleared CF mutation test should be used to confirm the presence of at least one *F508del* mutation or a mutation that is responsive based on *in vitro* data.

CENTER FOR DRUG EVALUATION AND RESEARCH

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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

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APPROVAL LETTER



NDA 212273/S-004

SUPPLEMENT APPROVAL

Vertex Pharmaceuticals
50 Northern Avenue
Boston, MA 02210

Attention: Barbara Balter, Ph.D.
Manager, Global regulatory Affairs

Dear Dr. Balter:

Please refer to your supplemental new drug application (sNDA) dated December 8, 2020, received December 8, 2020, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Trikafta (elixacaftor/tezacaftor/ivacaftor) tablet.

This Prior Approval supplemental new drug application provides for the treatment of cystic fibrosis (CF) in patients aged 6 through 11 years old with at least one F508del mutation in the CFTR gene or a mutation in the CFTR gene that is responsive based on in vitro data.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.¹ Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information, Patient Information), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.²

¹ <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>

² We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the enclosed carton and container labeling as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications. For administrative purposes, designate this submission “Final Printed Carton and Container Labeling for approved NDA 212273/S-004.” Approval of this submission by FDA is not required before the labeling is used.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs.³

³ For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/media/128163/download>.

You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at FDA.gov.⁴ Information and Instructions for completing the form can be found at FDA.gov.⁵

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Angela Ramsey, Senior Program Management Officer, at 301-796-2284.

Sincerely,

{See appended electronic signature page}

Sally Seymour, M.D
Director
Division of Pulmonology, Allergy, and Critical
Care
Office of Immunology and Inflammation
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
 - o Prescribing Information
 - o Patient Information
- Carton and Container Labeling

⁴ <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>

⁵ <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

BANU A KARIMI SHAH

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signing with the delegated authority of Dr. Sally Seymour, Director, DPACC

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

212273Orig1s004

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use TRIKAFTA safely and effectively. See full prescribing information for TRIKAFTA.

TRIKAFTA® (elixacaftor, tezacaftor, and ivacaftor tablets; ivacaftor tablets), co-packaged for oral use
Initial U.S. Approval: 2019

RECENT MAJOR CHANGES

- Indications and Usage (1) 06/2021
- Dosage and Administration (2) 06/2021

INDICATIONS AND USAGE

TRIKAFTA is a combination of ivacaftor, a CFTR potentiator, tezacaftor, and elixacaftor indicated for the treatment of cystic fibrosis (CF) in patients aged 6 years and older who have at least one *F508del* mutation in the *CFTR* gene or a mutation in the *CFTR* gene that is responsive based on *in vitro* data. If the patient's genotype is unknown, an FDA-cleared CF mutation test should be used to confirm the presence of at least one *F508del* mutation or a mutation that is responsive based on *in vitro* data. (1)

DOSAGE AND ADMINISTRATION

Recommended Dosage for Adult and Pediatric Patients aged 6 Years and Older		
Age	Morning Dose	Evening Dose
6 to less than 12 years weighing less than 30 kgs	Two tablets, each containing elixacaftor 50 mg/tezacaftor 25 mg/ivacaftor 37.5 mg	One tablet of ivacaftor 75 mg
6 to less than 12 years weighing 30 kgs or more	Two tablets, each containing elixacaftor 100 mg/tezacaftor 50 mg/ivacaftor 75 mg	One tablet of ivacaftor 150 mg
12 years and older	Two tablets, each containing elixacaftor 100 mg/tezacaftor 50 mg/ivacaftor 75 mg	One tablet of ivacaftor 150 mg

- TRIKAFTA should be taken with fat-containing food. (2.1, 12.3)
- Should not be used in patients with severe hepatic impairment. Use not recommended in patients with moderate hepatic impairment unless the benefit exceeds the risk. Reduce dose if used in patients with moderate hepatic impairment. Liver function tests should be closely monitored. (2.3, 5.1, 8.7, 12.3)
- See full prescribing information for dosage modifications due to drug interactions with TRIKAFTA. (2.4, 5.3, 7.2, 12.3)

DOSAGE FORMS AND STRENGTHS

Tablets:

- Fixed-dose combination containing elixacaftor 50 mg, tezacaftor 25 mg and ivacaftor 37.5 mg co-packaged with ivacaftor 75 mg. (3)

FULL PRESCRIBING INFORMATION: CONTENTS*

- INDICATIONS AND USAGE
- DOSAGE AND ADMINISTRATION
 - General Dosing Information
 - Recommended Dosage in Adults and Pediatric Patients Aged 6 Years and Older
 - Recommended Dosage for Patients with Hepatic Impairment
 - Dosage Adjustment for Patients Taking Drugs that are CYP3A Inhibitors
- DOSAGE FORMS AND STRENGTHS
- CONTRAINDICATIONS
- WARNINGS AND PRECAUTIONS
 - Liver Function Test Elevations
 - Concomitant Use with CYP3A Inducers
 - Concomitant Use with CYP3A Inhibitors
 - Cataracts
- ADVERSE REACTIONS
 - Clinical Trials Experience
- DRUG INTERACTIONS
 - Inducers of CYP3A
 - Inhibitors of CYP3A
 - Ciprofloxacin
 - CYP2C9 Substrates
 - Transporters
 - Hormonal Contraceptives

- Fixed-dose combination containing elixacaftor 100 mg, tezacaftor 50 mg, and ivacaftor 75 mg co-packaged with ivacaftor 150 mg. (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- Elevated liver function tests (ALT, AST or bilirubin): Liver function tests (ALT, AST, and bilirubin) should be assessed prior to initiating TRIKAFTA, every 3 months during the first year of treatment, and annually thereafter. Dosing should be interrupted in patients with ALT or AST >5 x upper limit of normal (ULN) or ALT or AST >3 x ULN with bilirubin >2 x ULN. Following resolution of transaminase elevations, consider the benefits and risks of resuming treatment. In patients with a history of hepatobiliary disease or liver function test elevations, more frequent monitoring should be considered. (5.1, 6, 8.7)
- Use with CYP3A inducers: Concomitant use with strong CYP3A inducers (e.g., rifampin, St. John's wort) significantly decrease ivacaftor exposure and are expected to decrease elixacaftor and tezacaftor exposure, which may reduce TRIKAFTA efficacy. Therefore, co-administration is not recommended. (5.2, 7.1, 12.3)
- Cataracts: Non-congenital lens opacities/cataracts have been reported in pediatric patients treated with ivacaftor-containing regimens. Baseline and follow-up examinations are recommended in pediatric patients initiating TRIKAFTA treatment. (5.4, 8.4)

ADVERSE REACTIONS

The most common adverse drug reactions to TRIKAFTA (≥5% of patients and at a frequency higher than placebo by ≥1%) were headache, upper respiratory tract infection, abdominal pain, diarrhea, rash, alanine aminotransferase increased, nasal congestion, blood creatine phosphokinase increased, aspartate aminotransferase increased, rhinorrhea, rhinitis, influenza, sinusitis and blood bilirubin increased. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Vertex Pharmaceuticals Incorporated at 1-877-634-8789 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Strong CYP3A inducers: Avoid co-administration. (5.2, 7.1, 12.3)
- Strong or moderate CYP3A inhibitors: Reduce TRIKAFTA dosage when co-administered. Avoid food or drink containing grapefruit. (2.4, 5.3, 7.2, 12.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 06/2021

8 USE IN SPECIFIC POPULATIONS

- Pregnancy
- Lactation
- Pediatric Use
- Geriatric Use
- Renal Impairment
- Hepatic Impairment
- Patients with Severe Lung Dysfunction

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- Mechanism of Action
- Pharmacodynamics
- Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

- Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES

- Trial 1
- Trial 2

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

TRIKAFTA is indicated for the treatment of cystic fibrosis (CF) in patients aged 6 years and older who have at least one *F508del* mutation in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene or a mutation in the *CFTR* gene that is responsive based on *in vitro* data [see *Clinical Pharmacology* (12.1)].

If the patient's genotype is unknown, an FDA-cleared CF mutation test should be used to confirm the presence of at least one *F508del* mutation or a mutation that is responsive based on *in vitro* data.

2 DOSAGE AND ADMINISTRATION

2.1 General Dosing Information

Swallow the tablets whole.

TRIKAFTA should be taken with fat-containing food. Examples of meals or snacks that contain fat are those prepared with butter or oils or those containing eggs, cheeses, nuts, whole milk, or meats [see *Clinical Pharmacology* (12.3)].

2.2 Recommended Dosage in Adults and Pediatric Patients Aged 6 Years and Older

Recommended dosage for adult and pediatric patients aged 6 years and older is provided in Table 1. The morning and the evening dose should be taken approximately 12 hours apart. TRIKAFTA is for oral use.

Table 1: Recommended Dosage for Adult and Pediatric Patients aged 6 Years and Older		
Age	Morning Dose	Evening Dose
6 to less than 12 years weighing less than 30 kgs	Two tablets, each containing elexacaftor 50 mg/tezacaftor 25 mg/ivacaftor 37.5 mg	One tablet of ivacaftor 75 mg
6 to less than 12 years weighing 30 kgs or more	Two tablets, each containing elexacaftor 100 mg/tezacaftor 50 mg/ivacaftor 75 mg	One tablet of ivacaftor 150 mg
12 years and older	Two tablets, each containing elexacaftor 100 mg/tezacaftor 50 mg/ivacaftor 75 mg	One tablet of ivacaftor 150 mg

Information for Missed Doses:

If 6 hours or less have passed since the missed morning or evening dose, the patient should take the missed dose as soon as possible and continue on the original schedule.

If more than 6 hours have passed since:

- the missed **morning** dose, the patient should take the missed dose as soon as possible and should **not** take the evening dose. The next scheduled morning dose should be taken at the usual time.
- the missed **evening** dose, the patient should **not** take the missed dose. The next scheduled morning dose should be taken at the usual time.

Morning and evening doses should not be taken at the same time.

2.3 Recommended Dosage for Patients with Hepatic Impairment

No dose adjustment is recommended for patients with mild hepatic impairment (Child-Pugh Class A) [see *Use in Specific Populations* (8.7), *Clinical Pharmacology* (12.3), and *Patient Counseling Information* (17)]. See Table 2. Liver function tests should be closely monitored [see *Warnings and Precautions* (5.1)].

Treatment is not recommended for patients with moderate hepatic impairment (Child-Pugh Class B). Use of TRIKAFTA in patients with moderate hepatic impairment should only be considered when there is a clear medical need and the benefit exceeds the risk. If used, TRIKAFTA should be used with caution at a reduced dose (see Table 2) [see *Use in Specific Populations* (8.7), *Clinical Pharmacology* (12.3) and *Patient Counseling Information* (17)]. Liver function tests should be closely monitored [see *Warnings and Precautions* (5.1)].

TRIKAFTA has not been studied in patients with severe hepatic impairment (Child-Pugh Class C), but the exposure is expected to be higher than in patients with moderate hepatic impairment. TRIKAFTA should not be used in patients with severe hepatic impairment.

Table 2: Recommended Dosage for use of TRIKAFTA in patients with hepatic impairment		
Mild (Child-Pugh Class A)	Moderate (Child-Pugh Class B)	Severe (Child-Pugh Class C)
No dose adjustment	Use of TRIKAFTA should only be considered when there is a clear medical need and the benefit exceeds the risk. If used, TRIKAFTA should be used with caution at a reduced dose, as follows: - Day 1: take two elexacaftor/tezacaftor/ivacaftor tablets in the morning - Day 2: take one elexacaftor/tezacaftor/ivacaftor tablet in the morning - Continue alternating Day 1 and Day 2 dosing thereafter. - No evening dose of ivacaftor tablet should be taken.	Should not be used

2.4 Dosage Adjustment for Patients Taking Drugs that are CYP3A Inhibitors

Table 3 describes the recommended dosage modification for TRIKAFTA when co-administered with strong (e.g., ketoconazole, itraconazole, posaconazole, voriconazole, telithromycin, and clarithromycin) or moderate (e.g., fluconazole, erythromycin) CYP3A inhibitors. Avoid food or drink containing grapefruit during TRIKAFTA treatment [see *Warnings and Precautions* (5.3), *Drug Interactions* (7.2), *Clinical Pharmacology* (12.3) and *Patient Counseling Information* (17)].

Table 3: Dosage Adjustment for Concomitant Use of TRIKAFTA with Moderate and Strong CYP3A Inhibitors				
Moderate CYP3A Inhibitors				
	Day 1	Day 2	Day 3	Day 4*
Morning Dose	Two elexacaftor/tezacaftor/ivacaftor tablets	One ivacaftor tablet	Two elexacaftor/tezacaftor/ivacaftor tablets	One ivacaftor tablet
Evening Dose [^]	No dose			
* Continue dosing with two elexacaftor/tezacaftor/ivacaftor tablets and one ivacaftor tablet on alternate days.				
[^] The evening dose of ivacaftor should not be taken.				
Strong CYP3A Inhibitors				
	Day 1	Day 2	Day 3	Day 4 [#]
Morning Dose	Two elexacaftor/tezacaftor/ivacaftor tablets	No dose	No dose	Two elexacaftor/tezacaftor/ivacaftor tablets
Evening Dose [^]	No dose			
[#] Continue dosing with two elexacaftor/tezacaftor/ivacaftor tablets twice a week, approximately 3 to 4 days apart.				
[^] The evening dose of ivacaftor tablet should not be taken.				

3 DOSAGE FORMS AND STRENGTHS

Tablets

Fixed-dose combination containing elexacaftor 50 mg, tezacaftor 25 mg, and ivacaftor 37.5 mg co-packaged with ivacaftor 75 mg:

- Elexacaftor, tezacaftor and ivacaftor tablets are light orange, capsule-shaped and debossed with “T50” on one side and plain on the other
- Ivacaftor tablets are light blue, capsule-shaped, and printed with “V 75” in black ink on one side and plain on the other

Fixed-dose combination containing elexacaftor 100 mg, tezacaftor 50 mg, and ivacaftor 75 mg co-packaged with ivacaftor 150 mg:

- Elexacaftor, tezacaftor and ivacaftor tablets are orange, capsule-shaped and debossed with “T100” on one side and plain on the other
- Ivacaftor tablets are light blue, capsule-shaped, and printed with “V 150” in black ink on one side and plain on the other

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Liver Function Test Elevations

Elevated transaminases have been observed in patients with CF treated with TRIKAFTA. Bilirubin elevations have also been observed with TRIKAFTA treatment. Assessments of liver function tests (ALT, AST, and bilirubin) are recommended for all patients prior to initiating TRIKAFTA, every 3 months during the first year of treatment, and annually thereafter. In the event of significant elevations in liver function tests, e.g. ALT or AST >5 x the upper limit of normal (ULN) or ALT or AST >3 x ULN with bilirubin >2 x ULN, dosing should be interrupted and laboratory tests closely followed until the abnormalities resolve. Following the resolution of liver function test elevations, consider the benefits and risks of resuming treatment. For patients with a history of hepatobiliary disease or liver function test elevations, more frequent monitoring should be considered [see *Adverse Reactions* (6.1) and *Use in Specific Populations* (8.7)].

5.2 Concomitant Use with CYP3A Inducers

Exposure to ivacaftor is significantly decreased and exposure to elexacaftor and tezacaftor are expected to decrease by the concomitant use of strong CYP3A inducers, which may reduce the therapeutic effectiveness of TRIKAFTA. Therefore, co-administration with strong CYP3A inducers is not recommended [see *Drug Interactions* (7.1), *Clinical Pharmacology* (12.3) and *Patient Counseling Information* (17)].

5.3 Concomitant Use with CYP3A Inhibitors

Exposure to elexacaftor, tezacaftor and ivacaftor are increased when co-administered with strong or moderate CYP3A inhibitors. Therefore, the dose of TRIKAFTA should be reduced when used concomitantly with moderate or strong CYP3A inhibitors [see *Dosage and Administration* (2.4), *Drug Interactions* (7.2), *Clinical Pharmacology* (12.3) and *Patient Counseling Information* (17)].

5.4 Cataracts

Cases of non-congenital lens opacities have been reported in pediatric patients treated with ivacaftor-containing regimens. Although other risk factors were present in some cases (such as corticosteroid use, exposure to radiation), a possible risk attributable to treatment with ivacaftor cannot be excluded. Baseline and follow-up ophthalmological examinations are recommended in pediatric patients initiating treatment with TRIKAFTA [see *Use in Specific Populations* (8.4) and *Patient Counseling Information* (17)].

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are discussed in greater detail in other sections of the labeling:

- Liver Function Test Elevations [see *Warnings and Precautions* (5.1)]
- Cataracts [see *Warnings and Precautions* (5.4)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The safety profile of TRIKAFTA is based on data from 510 CF patients aged 12 years and older in two double-blind, controlled trials of 24 weeks and 4 weeks treatment duration (Trials 1 and 2). Eligible patients were also able to participate in an open-label extension safety study (up to 96 weeks of TRIKAFTA). In the two controlled trials, a total of 257 patients aged 12 years and older received at least one dose of TRIKAFTA.

In addition, the following clinical trials have also been conducted [see *Use in Specific Population* (8.4) and *Clinical Pharmacology* (12.3)]:

- a 24-week open-label trial in 66 patients with CF aged 6 to less than 12 years who were either homozygous for the *F508del* mutation or heterozygous for the *F508del* mutation and a mutation on the second allele that results in either no CFTR protein or a CFTR protein that is not responsive to ivacaftor and tezacaftor/ivacaftor (Trial 3)

In Trial 1, the proportion of patients who discontinued study drug prematurely due to adverse events was 1% for TRIKAFTA-treated patients and 0% for placebo-treated patients.

In Trial 1, serious adverse reactions that occurred more frequently in TRIKAFTA-treated patients compared to placebo were rash (1% vs <1%) and influenza (1% vs 0). There were no deaths in Trials 1, 2 and 3.

Table 4 shows adverse reactions occurring in ≥5% of TRIKAFTA-treated patients and higher than placebo by ≥1% in the 24-week placebo-controlled, parallel-group trial (Trial 1).

Table 4: Adverse Drug Reactions in ≥5% of TRIKAFTA-Treated Patients and Higher than Placebo by ≥1% in Trial 1		
Adverse Drug Reactions (Preferred Term)	TRIKAFTA N=202 n (%)	Placebo N=201 n (%)
Headache	35 (17)	30 (15)
Upper respiratory tract infection ^a	32 (16)	25 (12)
Abdominal pain ^b	29 (14)	18 (9)
Diarrhea	26 (13)	14 (7)
Rash ^c	21 (10)	10 (5)
Alanine aminotransferase increased	20 (10)	7 (3)
Nasal congestion	19 (9)	15 (7)
Blood creatine phosphokinase increased	19 (9)	9 (4)
Aspartate aminotransferase increased	19 (9)	4 (2)
Rhinorrhea	17 (8)	6 (3)
Rhinitis	15 (7)	11 (5)
Influenza	14 (7)	3 (1)
Sinusitis	11 (5)	8 (4)
Blood bilirubin increased	10 (5)	2 (1)
a Includes upper respiratory tract infection and viral upper respiratory tract infection		
b Includes abdominal pain, abdominal pain upper, abdominal pain lower		
c Includes: rash, rash generalized, rash erythematous, rash macular, rash pruritic		

Additional adverse reactions that occurred in TRIKAFTA-treated patients at a frequency of 2 to <5% and higher than placebo by ≥1% include the following: Flatulence, abdominal distension, conjunctivitis, pharyngitis, respiratory tract infection, tonsillitis, urinary tract infection, c-reactive protein increased, hypoglycemia, dizziness, dysmenorrhea, acne, eczema and pruritus.

The safety profile for the CF patients enrolled in Trial 2 and Trial 3 was similar to that observed in Trial 1.

Rash Events

In Trial 1, the overall incidence of rash events was 10% in TRIKAFTA-treated and 5% in placebo-treated patients (see Table 4). The incidence of rash events was higher in female TRIKAFTA-treated patients (16%) than in male TRIKAFTA-treated patients (5%).

Hormonal contraceptives may play a role in the occurrence of rash. For patients taking hormonal contraceptives who develop rash, consider interrupting TRIKAFTA and hormonal contraceptives. Following the resolution of rash, consider resuming TRIKAFTA without the hormonal contraceptives. If rash does not recur, resumption of hormonal contraceptives can be considered.

Laboratory and Vital Sign Abnormalities

Liver Function Test Elevations

In Trial 1, the incidence of maximum transaminase (ALT or AST) >8, >5, or >3 x ULN was 1%, 2%, and 8% in TRIKAFTA-treated patients and 1%, 1%, and 5% in placebo-treated patients. The incidence of adverse reactions of transaminase elevations (AST and/or ALT) was 11% in TRIKAFTA-treated patients and 4% in placebo-treated patients.

In Trial 1, the incidence of maximum total bilirubin elevation >2 x ULN was 4% in TRIKAFTA-treated patients and <1% in placebo-treated patients. Maximum indirect and direct bilirubin elevations >1.5 x ULN occurred in 11% and 3% of TRIKAFTA-treated patients, respectively. No TRIKAFTA-treated patients developed maximum direct bilirubin elevation >2 x ULN.

During Trial 3, in patients aged 6 to less than 12 years, the incidence of maximum transaminase (ALT or AST) >8, >5, and >3 x ULN were 0%, 1.5%, and 10.6%, respectively. No TRIKAFTA-treated patients had transaminase elevation >3 x ULN associated with elevated total bilirubin >2 x ULN or discontinued treatment due to transaminase elevations.

Increased Creatine Phosphokinase

In Trial 1, the incidence of maximum creatine phosphokinase elevation >5 x ULN was 10% in TRIKAFTA-treated and 5% in placebo-treated patients. Among the TRIKAFTA-treated patients with creatine phosphokinase elevation >5 x ULN, 14% (3/21) required treatment interruption and none discontinued treatment.

Increased Blood Pressure

In Trial 1, the maximum increase from baseline in mean systolic and diastolic blood pressure was 3.5 mmHg and 1.9 mmHg, respectively for TRIKAFTA-treated patients (baseline: 113 mmHg systolic and 69 mmHg diastolic) and 0.9 mmHg and 0.5 mmHg, respectively for placebo-treated patients (baseline: 114 mmHg systolic and 70 mmHg diastolic).

The proportion of patients who had systolic blood pressure >140 mmHg and 10 mmHg increase from baseline on at least two occasions was 4% in TRIKAFTA-treated patients and 1% in placebo-treated patients. The proportion of patients who had diastolic blood pressure >90 mmHg and 5 mmHg increase from baseline on at least two occasions was 1% in TRIKAFTA-treated patients and 2% in placebo-treated patients.

With the exception of sex differences in rash, the safety profile of TRIKAFTA was generally similar across all subgroups of patients, including analysis by age, sex, baseline percent predicted FEV₁ (ppFEV₁) and geographic regions.

7 DRUG INTERACTIONS

Potential for other drugs to affect elexacaftor/tezacaftor/ivacaftor

7.1 Inducers of CYP3A

Elexacaftor, tezacaftor and ivacaftor are substrates of CYP3A (ivacaftor is a sensitive substrate of CYP3A). Concomitant use of CYP3A inducers may result in reduced exposures and thus reduced TRIKAFTA efficacy. Co-administration of ivacaftor with rifampin, a strong CYP3A inducer, significantly decreased ivacaftor area under the curve (AUC) by 89%. Elexacaftor and tezacaftor exposures are expected to decrease during co-administration with strong CYP3A inducers. Therefore, co-administration of TRIKAFTA with strong CYP3A inducers is not recommended [see *Warnings and Precautions* (5.2), *Clinical Pharmacology* (12.3) and *Patient Counseling Information* (17)].

Examples of strong CYP3A inducers include:

- rifampin, rifabutin, phenobarbital, carbamazepine, phenytoin and St. John's wort (*Hypericum perforatum*)

7.2 Inhibitors of CYP3A

Co-administration with itraconazole, a strong CYP3A inhibitor, increased elexacaftor AUC by 2.8-fold and tezacaftor AUC by 4.0 to 4.5-fold. When co-administered with itraconazole and ketoconazole, ivacaftor AUC increased by 15.6-fold and 8.5-fold, respectively. The dosage of TRIKAFTA should be reduced when co-administered with strong CYP3A inhibitors [see *Dosage and Administration* (2.4), *Warnings and Precautions* (5.3), *Clinical Pharmacology* (12.3) and *Patient Counseling Information* (17)].

Examples of strong CYP3A inhibitors include:

- ketoconazole, itraconazole, posaconazole and voriconazole
- telithromycin and clarithromycin

Simulations indicated that co-administration with moderate CYP3A inhibitors may increase elexacaftor and tezacaftor AUC by approximately 1.9 to 2.3-fold and 2.1-fold, respectively. Co-administration of fluconazole increased ivacaftor AUC by 2.9-fold. The dosage of TRIKAFTA should be reduced when co-administered with moderate CYP3A inhibitors [see *Dosage and Administration* (2.4), *Warnings and Precautions* (5.3), *Clinical Pharmacology* (12.3) and *Patient Counseling Information* (17)].

Examples of moderate CYP3A inhibitors include:

- fluconazole
- erythromycin

Co-administration of TRIKAFTA with grapefruit juice, which contains one or more components that moderately inhibit CYP3A, may increase exposure of elexacaftor, tezacaftor and ivacaftor; therefore, food or drink containing grapefruit should be avoided during treatment with TRIKAFTA [see *Dosage and Administration* (2.4) and *Patient Counseling Information* (17)].

7.3 Ciprofloxacin

Ciprofloxacin had no clinically relevant effect on the exposure of tezacaftor or ivacaftor and is not expected to affect the exposure of elexacaftor. Therefore, no dose adjustment is necessary during concomitant administration of TRIKAFTA with ciprofloxacin [see *Clinical Pharmacology* (12.3)].

Potential for elexacaftor/tezacaftor/ivacaftor to affect other drugs

7.4 CYP2C9 Substrates

Ivacaftor may inhibit CYP2C9; therefore, monitoring of the international normalized ratio (INR) during co-administration of TRIKAFTA with warfarin is recommended. Other medicinal products for which exposure may be increased by TRIKAFTA include glimepiride and glipizide; these medicinal products should be used with caution [see *Clinical Pharmacology* (12.3)].

7.5 Transporters

Co-administration of ivacaftor or tezacaftor/ivacaftor with digoxin, a sensitive P-gp substrate, increased digoxin AUC by 1.3-fold, consistent with weak inhibition of P-gp by ivacaftor. Administration of TRIKAFTA may increase systemic exposure of medicinal products that are sensitive substrates of P-gp, which may increase or prolong their therapeutic effect and adverse reactions. When used concomitantly with digoxin or other substrates of P-gp with a narrow therapeutic index such as cyclosporine, everolimus, sirolimus and tacrolimus, caution and appropriate monitoring should be used [see *Clinical Pharmacology* (12.3)].

Elexacaftor and M23-ELX inhibit uptake by OATP1B1 and OATP1B3 *in vitro*. Co-administration of TRIKAFTA may increase exposures of medicinal products that are substrates of these transporters, such as statins, glyburide, nateglinide and repaglinide. When used concomitantly with substrates of OATP1B1 or OATP1B3, caution and appropriate monitoring should be used [see *Clinical Pharmacology* (12.3)]. Bilirubin is an OATP1B1 and OATP1B3 substrate.

7.6 Hormonal Contraceptives

TRIKAFTA has been studied with ethinyl estradiol/levonorgestrel and was found to have no clinically relevant effect on the exposures of the oral contraceptive. TRIKAFTA is not expected to have an impact on the efficacy of oral contraceptives.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are limited and incomplete human data from clinical trials on the use of TRIKAFTA or its individual components, elexacaftor, tezacaftor and ivacaftor, in pregnant women to inform a drug-associated risk. Although there are no animal reproduction studies with the concomitant administration of elexacaftor, tezacaftor and ivacaftor, separate reproductive and developmental studies were conducted with each active component of TRIKAFTA in pregnant rats and rabbits.

In animal embryo fetal development (EFD) studies oral administration of elexacaftor to pregnant rats and rabbits during organogenesis demonstrated no teratogenicity or adverse developmental effects at doses that produced maternal exposures up to approximately 2 times the exposure at the maximum recommended human dose (MRHD) in rats and 4 times the MRHD in rabbits [based on summed AUCs of elexacaftor and its metabolite (for rat) and AUC of elexacaftor (for rabbit)]. Oral administration of tezacaftor to pregnant rats and rabbits during organogenesis demonstrated no teratogenicity or adverse developmental effects at doses that produced maternal exposures up to approximately 3 times the exposure at the MRHD in rats and 0.2 time the MRHD in rabbits (based on summed AUCs of tezacaftor and M1-TEZ). Oral administration of ivacaftor to pregnant rats and rabbits during organogenesis demonstrated no teratogenicity or adverse developmental effects at doses that produced maternal exposures up to approximately 5 and 14 times the exposure at the MRHD, respectively [based on summed AUCs of ivacaftor and its metabolites (for rat) and AUC of ivacaftor (for rabbit)]. No adverse developmental effects were observed after oral administration of elexacaftor, tezacaftor or ivacaftor to pregnant rats from the period of organogenesis through lactation at doses that produced maternal exposures approximately 1 time, approximately 1 time and 3 times the exposures at the MRHD, respectively [based on summed AUCs of parent and metabolite(s)] (*see Data*).

The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

Elexacaftor

In an EFD study in pregnant rats dosed during the period of organogenesis from gestation Days 6-17, elexacaftor was not teratogenic and did not affect fetal survival at exposures up to 9 times the MRHD (based on summed AUC for elexacaftor and its metabolite at maternal doses up to 40 mg/kg/day). Lower mean fetal body weights were observed at doses ≥ 25 mg/kg/day that produced maternal exposures ≥ 4 times the MRHD. In an EFD study in pregnant rabbits dosed during the period of organogenesis from gestation Days 7-20, elexacaftor was not teratogenic at exposures up to 4 times the MRHD (based on AUC of elexacaftor at maternal doses up to 125 mg/kg/day). In a pre- and postnatal development (PPND) study in pregnant rats dosed from gestation Day 6 through lactation Day 18, elexacaftor did not cause developmental defects in pups at maternal doses up to 10 mg/kg/day (approximately 1 time the MRHD based on summed AUCs of elexacaftor and its metabolite). Placental transfer of elexacaftor was observed in pregnant rats.

Tezacaftor

In an EFD study in pregnant rats dosed during the period of organogenesis from gestation Days 6-17 and in pregnant rabbits dosed during the period of organogenesis from gestation Days 7-20, tezacaftor was not teratogenic and did not affect fetal development or survival at exposures up to 3 and 0.2 times, respectively the MRHD (based on summed AUCs of tezacaftor and M1-TEZ). Lower fetal body weights were observed in rabbits at a maternally toxic dose that produced exposures approximately 1 time the MRHD (based on summed AUCs of tezacaftor and M1-TEZ at a maternal dose of 50 mg/kg/day). In a PPND study in pregnant rats dosed from gestation Day 6 through lactation Day 18, tezacaftor had no adverse developmental effects on pups at an exposure of approximately 1 time the MRHD (based on summed AUCs for tezacaftor and M1-TEZ at a maternal dose of 25 mg/kg/day). Decreased fetal body weights and early developmental delays in pinna detachment, eye opening and righting reflex occurred at a maternally toxic dose (based on maternal weight loss) that produced exposures approximately 1 time the exposure at the MRHD (based on summed AUCs for tezacaftor and M1-TEZ at a maternal oral dose of 50 mg/kg/day). Placental transfer of tezacaftor was observed in pregnant rats.

Ivacaftor

In an EFD study in pregnant rats dosed during the period of organogenesis from gestation Days 7-17 and in pregnant rabbits dosed during the period of organogenesis from gestation Days 7-19, ivacaftor was not teratogenic and did not affect fetal survival at exposures up to 5 and 14 times, respectively, the MRHD [based on summed AUCs of ivacaftor and its metabolites (for rat) and AUC of ivacaftor (for rabbit)]. In a PPND study in pregnant rats dosed from gestation Day 7 through lactation Day 20, ivacaftor had no effects on delivery or growth and development of offspring at exposures up to 3 times the MRHD (based on summed AUCs for ivacaftor and its metabolites at maternal oral doses up to 100 mg/kg/day). Decreased fetal body weights were observed at a maternally toxic dose that produced exposures 5 times the MRHD (based on summed AUCs of ivacaftor and its metabolites). Placental transfer of ivacaftor was observed in pregnant rats and rabbits.

8.2 Lactation

Risk Summary

There is no information regarding the presence of elexacaftor, tezacaftor, or ivacaftor in human milk, the effects on the breastfed infant, or the effects on milk production. Elexacaftor, tezacaftor, and ivacaftor are excreted into the milk of lactating rats (*see Data*). The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for TRIKAFTA and any potential adverse effects on the breastfed child from TRIKAFTA or from the underlying maternal condition.

Data

Elexacaftor

Lactal excretion of elexacaftor in rats was demonstrated following a single oral dose (10 mg/kg) of ^{14}C -elexacaftor administered 6 to 10 days postpartum to lactating dams. Exposure of ^{14}C -elexacaftor in milk was approximately 0.4 time the value observed in plasma (based on $\text{AUC}_{0-72\text{h}}$).

Tezacaftor

Lactal excretion of tezacaftor in rats was demonstrated following a single oral dose (30 mg/kg) of ^{14}C -tezacaftor administered 6 to 10 days postpartum to lactating dams. Exposure of ^{14}C -tezacaftor in milk was approximately 3 times higher than in plasma (based on $\text{AUC}_{0-72\text{h}}$).

Ivacaftor

Lactal excretion of ivacaftor in rats was demonstrated following a single oral dose (100 mg/kg) of ^{14}C -ivacaftor administered 9 to 10 days postpartum to lactating dams. Exposure of ^{14}C -ivacaftor in milk was approximately 1.5 times higher than in plasma (based on $\text{AUC}_{0-24\text{h}}$).

8.4 Pediatric Use

The safety and effectiveness of TRIKAFTA for the treatment of CF in patients aged 6 to less than 18 years who have at least one *F508del* mutation in the *CFTR* gene or a mutation in the *CFTR* gene that is responsive based on *in vitro* data has been established. Use of TRIKAFTA for this indication was supported by evidence from two adequate and well-controlled studies in CF patients aged 12 years and older (Trial 1 and Trial 2) and one open-label study in CF patients aged 6 to less than 12 years (Trial 3). In these trials, a total of 138 patients (aged 6 to less than 18 years) received TRIKAFTA, including:

- In Trial 1, 56 adolescents aged 12 to less than 18 years who had an *F508del* mutation on one allele and a mutation on the second allele that results in either no CFTR protein or a CFTR protein that is not responsive to ivacaftor and tezacaftor/ivacaftor [*see Adverse Reactions (6) and Clinical Studies (14)*].

- In Trial 2, 16 adolescents aged 12 to less than 18 years who were homozygous for the *F508del* mutation [see *Adverse Reactions (6) and Clinical Studies (14)*].
- In Trial 3, 66 children aged 6 to less than 12 years who were homozygous for the *F508del* mutation or heterozygous for the *F508del* mutation with a mutation on the second allele that results in either no CFTR protein or a CFTR protein that is not responsive to ivacaftor and tezacaftor/ivacaftor [see *Adverse Reactions (6) and Clinical Pharmacology (12.3)*].

The effectiveness of TRIKAFTA in patients aged 6 to less than 12 years was extrapolated from patients aged 12 years and older with support from population pharmacokinetic analyses showing elexacaftor, tezacaftor and ivacaftor exposure levels in patients aged 6 to less than 12 years within the range of exposures observed in patients aged 12 years and older [see *Clinical Pharmacology (12.3)*]. Safety of TRIKAFTA in this population was derived from a 24-week, open-label, clinical trial in 66 patients aged 6 to less than 12 years (mean age at baseline 9.3 years) administered either a total dose of elexacaftor 100 mg/tezacaftor 50 mg/ivacaftor 75 mg in the morning and ivacaftor 75 mg in the evening (for patients weighing less than 30 kgs) or a total dose of elexacaftor 200 mg/tezacaftor 100 mg/ivacaftor 150 mg in the morning and ivacaftor 150 mg in the evening (for patients weighing 30 kgs or more) (Trial 3). The safety profile of patients in this trial was similar to that observed in Trial 1 [see *Adverse Reactions (6)*].

The safety and effectiveness of TRIKAFTA in patients with CF younger than 6 years of age have not been established.

Juvenile Animal Toxicity Data

Findings of cataracts were observed in juvenile rats dosed from postnatal Day 7 through 35 with ivacaftor dose levels of 10 mg/kg/day and higher (0.21 time the MRHD based on systemic exposure of ivacaftor and its metabolites). This finding has not been observed in older animals [see *Warnings and Precautions (5.4) and Patient Counseling Information (17)*].

Studies were conducted with tezacaftor in juvenile rats starting at postnatal day (PND) 21 and ranging up to PNDs 35 to 49. Findings of convulsions and death were observed in juvenile rats that received a tezacaftor dose level of 100 mg/kg/day (approximately equivalent to 1.9 times the MRHD based on summed AUCs of tezacaftor and its metabolite, M1-TEZ). A no effect dose level was identified at 30 mg/kg/day (approximately equivalent to 0.8 times the MRHD based on summed AUCs of tezacaftor and its metabolite, M1-TEZ). Findings were dose related and generally more severe when dosing with tezacaftor was initiated earlier in the postnatal period (PND 7, which would be approximately equivalent to a human neonate). Tezacaftor and its metabolite, M1-TEZ, are substrates for P-glycoprotein. Lower brain levels of P-glycoprotein activity in younger rats resulted in higher brain levels of tezacaftor and M1-TEZ. These findings are not relevant for the indicated pediatric population 6 to 11 years of age, for whom levels of P-glycoprotein activity are equivalent to levels observed in adults.

8.5 Geriatric Use

Clinical studies of TRIKAFTA did not include any patients aged 65 years and older.

8.6 Renal Impairment

TRIKAFTA has not been studied in patients with severe renal impairment or end-stage renal disease. No dosage adjustment is recommended in patients with mild (eGFR 60 to <90 mL/min/1.73 m²) or moderate (eGFR 30 to <60 mL/min/1.73 m²) renal impairment. Use with caution in patients with severe (eGFR <30 mL/min/1.73 m²) renal impairment or end-stage renal disease [see *Clinical Pharmacology (12.3)*].

8.7 Hepatic Impairment

No dose modification is recommended for patients with mild hepatic impairment (Child-Pugh Class A). Treatment is not recommended for patients with moderate hepatic impairment (Child-Pugh Class B). In a clinical study of 11 subjects with moderate hepatic impairment, one subject developed total and direct bilirubin elevations >2 x ULN, and a second subject developed direct bilirubin elevation >4.5 x ULN. Use of TRIKAFTA in patients with moderate hepatic impairment should only be considered when there is a clear medical need and the benefit exceeds the risk. If used in patients with moderate hepatic impairment, TRIKAFTA should be used with caution at a reduced dose (see Table 2). Liver function tests should be closely monitored in patients with mild and moderate hepatic impairment. TRIKAFTA has not been studied in patients with severe hepatic impairment (Child-Pugh Class C), but the exposure is expected to be higher than in patients with moderate hepatic impairment. TRIKAFTA should not be used in patients with severe hepatic impairment [see *Dosage and Administration (2.3), Warnings and Precautions (5.1), Clinical Pharmacology (12.3) and Patient Counseling Information (17)*].

8.8 Patients with Severe Lung Dysfunction

Trial 1 included a total of 18 patients receiving TRIKAFTA with ppFEV₁ <40 at baseline. The safety and efficacy in this subgroup were comparable to those observed in the overall population.

10 OVERDOSAGE

No specific antidote is available for overdosage with TRIKAFTA. Treatment of overdosage consists of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient.

11 DESCRIPTION

TRIKAFTA is a co-package of elexacaftor, tezacaftor and ivacaftor fixed-dose combination tablets and ivacaftor tablets. Both tablets are for oral administration.

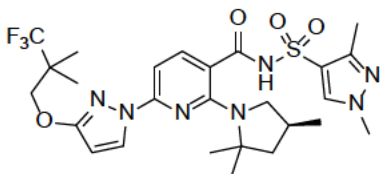
The elexacaftor, tezacaftor and ivacaftor fixed-dose combination tablets are available as: orange, capsule-shaped, film-coated tablet containing 100 mg of elexacaftor, 50 mg of tezacaftor, 75 mg of ivacaftor, or light-orange, capsule-shaped, film-coated tablet containing 50 mg of elexacaftor, 25 mg of tezacaftor, 37.5 mg of ivacaftor. The fixed-dose combination tablet contains the following inactive ingredients: hypromellose, hypromellose acetate succinate, sodium lauryl sulfate, croscarmellose sodium, microcrystalline cellulose and magnesium stearate. The tablet film coat contains hypromellose, hydroxypropyl cellulose, titanium dioxide, talc, iron oxide yellow and iron oxide red.

The ivacaftor tablet is available as a light blue, capsule-shaped, film-coated tablet containing 150 mg or 75 mg of ivacaftor and the following inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, hypromellose acetate succinate, lactose monohydrate, magnesium stearate, microcrystalline cellulose and sodium lauryl sulfate. The tablet film coat contains carnauba wax, FD&C Blue #2, PEG 3350, polyvinyl alcohol, talc and titanium dioxide. The printing ink contains ammonium hydroxide, iron oxide black, propylene glycol and shellac.

The active ingredients of TRIKAFTA are described below.

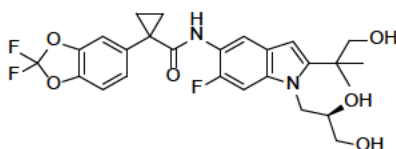
Elexacaftor

Elexacaftor is a white solid that is practically insoluble in water (<1 mg/mL). Its chemical name is N-(1,3-dimethyl-1H-pyrazole-4-sulfonyl)-6-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)-1H-pyrazol-1-yl]-2-[(4S)-2,2,4-trimethylpyrrolidin-1-yl]pyridine-3-carboxamide. Its molecular formula is C₂₆H₃₄N₇O₄SF₃ and its molecular weight is 597.66. Elexacaftor has the following structural formula:



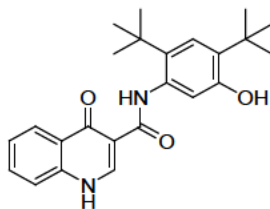
Tezacaftor

Tezacaftor is a white to off-white solid that is practically insoluble in water (<5 microgram/mL). Its chemical name is 1-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-N-{1-[(2R)-2,3-dihydroxypropyl]-6-fluoro-2-(1-hydroxy-2-methylpropan-2-yl)-1H-indol-5-yl}cyclopropane-1-carboxamide. Its molecular formula is C₂₆H₂₇N₂F₃O₆ and its molecular weight is 520.50. Tezacaftor has the following structural formula:



Ivacaftor

Ivacaftor is a white to off-white crystalline solid that is practically insoluble in water (<0.05 microgram/mL). Pharmacologically it is a CFTR potentiator. Its chemical name is N-(2,4-di-tert-butyl-5-hydroxyphenyl)-1,4-dihydro-4-oxoquinoline-3-carboxamide. Its molecular formula is C₂₄H₂₈N₂O₃ and its molecular weight is 392.49. Ivacaftor has the following structural formula:



12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Elexacaftor and tezacaftor bind to different sites on the CFTR protein and have an additive effect in facilitating the cellular processing and trafficking of select mutant forms of CFTR (including F508del-CFTR) to increase the amount of CFTR protein delivered to the cell surface compared to either molecule alone. Ivacaftor potentiates the channel open probability (or gating) of the CFTR protein at the cell surface.

The combined effect of elixacaftor, tezacaftor and ivacaftor is increased quantity and function of CFTR at the cell surface, resulting in increased CFTR activity as measured by CFTR mediated chloride transport.

CFTR Chloride Transport Assay in Fischer Rat Thyroid (FRT) cells expressing mutant CFTR

The chloride transport response of mutant CFTR protein to elixacaftor/tezacaftor/ivacaftor was determined in Ussing chamber electrophysiology studies using a panel of FRT cell lines transfected with individual *CFTR* mutations. Elexacaftor/tezacaftor/ivacaftor increased chloride transport in FRT cells expressing *CFTR* mutations that result in CFTR protein being delivered to the cell surface.

The *in vitro* CFTR chloride transport response threshold was designated as a net increase of at least 10% of normal over baseline because it is predictive or reasonably expected to predict clinical benefit. For individual mutations, the magnitude of the net change over baseline in CFTR-mediated chloride transport *in vitro* is not correlated with the magnitude of clinical response.

Table 5 lists responsive *CFTR* mutations based on *in vitro* data in FRT cells indicating that elixacaftor/tezacaftor/ivacaftor increases chloride transport to at least 10% of normal over baseline.

Table 5: List of CFTR Gene Mutations that are Responsive to TRIKAFTA					
3141del9	E822K	G1069R	L967S	R117L	S912L
546insCTA	F191V	G1244E	L997F	R117P	S945L
A46D	F311del	G1249R	L1077P	R170H	S977F
A120T	F311L	G1349D	L1324P	R258G	S1159F
A234D	F508C	H139R	L1335P	R334L	S1159P
A349V	F508C;S1251N [†]	H199Y	L1480P	R334Q	S1251N
A455E	F508del*	H939R	M152V	R347H	S1255P
A554E	F575Y	H1054D	M265R	R347L	T338I
A1006E	F1016S	H1085P	M952I	R347P	T1036N
A1067T	F1052V	H1085R	M952T	R352Q	T1053I
D110E	F1074L	H1375P	M1101K	R352W	V201M
D110H	F1099L	I148T	P5L	R553Q	V232D
D192G	G27R	I175V	P67L	R668C	V456A
D443Y	G85E	I336K	P205S	R751L	V456F
D443Y;G576A;R668C [†]	G126D	I502T	P574H	R792G	V562I
D579G	G178E	I601F	Q98R	R933G	V754M
D614G	G178R	I618T	Q237E	R1066H	V1153E
D836Y	G194R	I807M	Q237H	R1070Q	V1240G
D924N	G194V	I980K	Q359R	R1070W	V1293G
D979V	G314E	I1027T	Q1291R	R1162L	W361R
D1152H	G463V	I1139V	R31L	R1283M	W1098C
D1270N	G480C	I1269N	R74Q	R1283S	W1282R
E56K	G551D	I1366N	R74W	S13F	Y109N
E60K	G551S	K1060T	R74W;D1270N [†]	S341P	Y161D
E92K	G576A	L15P	R74W;V201M [†]	S364P	Y161S
E116K	G576A;R668C [†]	L165S	R74W;V201M;D1270N [†]	S492F	Y563N
E193K	G622D	L206W	R75Q	S549N	Y1014C
E403D	G628R	L320V	R117C	S549R	Y1032C
E474K	G970D	L346P	R117G	S589N	
E588V	G1061R	L453S	R117H	S737F	
* F508del is a responsive CFTR mutation based on both clinical and <i>in vitro</i> data [see Clinical Studies (14)].					
[†] Complex/compound mutations where a single allele of the CFTR gene has multiple mutations; these exist independent of the presence of mutations on the other allele.					

12.2 Pharmacodynamics

Sweat Chloride Evaluation

In Trial 1 (patients with an *F508del* mutation on one allele and a mutation on the second allele that results in either no CFTR protein or a CFTR protein that is not responsive ivacaftor and tezacaftor/ivacaftor), a reduction in sweat chloride was observed from baseline at Week 4 and sustained through the 24-week treatment period [see Clinical Studies (14.1)]. In Trial 2 (patients homozygous for the *F508del* mutation), a reduction in sweat chloride was observed from baseline at Week 4 [see Clinical Studies (14.2)]. In Trial 3 (patients aged 6 to less than 12 years who are homozygous for the *F508del* mutation or heterozygous for the *F508del* mutation and a mutation on the second allele that results in either no CFTR protein or a CFTR protein that is not responsive ivacaftor and tezacaftor/ivacaftor), the mean absolute change in sweat chloride from baseline through Week 24 was -60.9 mmol/L (95% CI: -63.7, -58.2).

Cardiac Electrophysiology

At doses up to 2 times the maximum recommended dose of elexacaftor and 3 times the maximum recommended dose of tezacaftor and ivacaftor, the QT/QTc interval in healthy subjects was not prolonged to any clinically relevant extent.

12.3 Pharmacokinetics

The pharmacokinetics of elexacaftor, tezacaftor and ivacaftor are similar between healthy adult subjects and patients with CF. The pharmacokinetic parameters for elexacaftor, tezacaftor and ivacaftor in patients with CF aged 12 years and older are shown in Table 6.

Table 6: Pharmacokinetic Parameters of TRIKAFTA Components			
	Elexacaftor	Tezacaftor	Ivacaftor
General Information			
AUC _{ss} (SD), mcg·h/mL ^a	162 (47.5) ^b	89.3 (23.2) ^b	11.7 (4.01) ^c
C _{max} (SD), mcg/mL ^a	9.2 (2.1)	7.7 (1.7)	1.2 (0.3)
Time to Steady State, days	Within 7 days	Within 8 days	Within 3-5 days
Accumulation Ratio	2.2	2.07	2.4
Absorption			
Absolute Bioavailability	80%	Not determined	Not determined
Median T _{max} (range), hours	6 (4 to 12)	3 (2 to 4)	4 (3 to 6)
Effect of Food	AUC increases 1.9- to 2.5-fold (moderate-fat meal)	No clinically significant effect	Exposure increases 2.5- to 4-fold
Distribution			
Mean (SD) Apparent Volume of Distribution, L ^d	53.7 (17.7)	82.0 (22.3)	293 (89.8)
Protein Binding ^e	>99%	approximately 99%	approximately 99%
Elimination			
Mean (SD) Effective Half-Life, hours ^f	27.4 (9.31)	25.1 (4.93)	15.0 (3.92)

Table 6: Pharmacokinetic Parameters of TRIKAFTA Components			
	Elexacaftor	Tezacaftor	Ivacaftor
Mean (SD) Apparent Clearance, L/hours	1 18 (0.29)	0.79 (0 10)	10.2 (3.13)
Metabolism			
Primary Pathway	CYP3A4/5	CYP3A4/5	CYP3A4/5
Active Metabolites	M23-ELX	M1-TEZ	M1-IVA
Metabolite Potency Relative to Parent	Similar	Similar	approximately 1/6 th of parent
Excretion^g			
Primary Pathway	- Feces: 87.3% (primarily as metabolites) - Urine: 0.23%	- Feces: 72% (unchanged or as M2-TEZ) - Urine: 14% (0.79% unchanged)	- Feces: 87.8% - Urine: 6.6%

^a Based on elexacaftor 200 mg and tezacaftor 100 mg once daily/ivacaftor 150 mg every 12 hours at steady state in patients with CF aged 12 year and older.

^b AUC_{0-24h}.

^c AUC_{0-12h}.

^d Elexacaftor, tezacaftor and ivacaftor do not partition preferentially into human red blood cells.

^e Elexacaftor and tezacaftor bind primarily to albumin. Ivacaftor primarily bind to albumin, alpha 1-acid glycoprotein and human gamma-globulin.

^f Mean (SD) terminal half-lives of elexacaftor, tezacaftor and ivacaftor are approximately 24.7 (4.87) hours, 60.3 (15.7) hours and 13.1 (2.98) hours, respectively.

^g Following radiolabeled doses.

AUC_{ss}: area under the concentration versus time curve at steady state; SD: Standard Deviation; C_{max}: maximum observed concentration; T_{max}: time of maximum concentration; AUC: area under the concentration versus time curve.

Specific Populations

Pediatric patients 6 to less than 12 years of age

Elexacaftor, tezacaftor and ivacaftor exposures observed in patients aged 6 to less than 12 years as determined using population PK analysis are presented by age group and dose administered in Table 7. Elexacaftor, tezacaftor and ivacaftor exposures in this patient population are within the range observed in patients aged 12 years and older.

Table 7: Mean (SD) Elexacaftor, Tezacaftor and Ivacaftor Exposures Observed at Steady State by Age Group and Dose Administered				
Age group	Dose	Elexacaftor AUC _{0-24h,ss} (mcg·h/mL)	Tezacaftor AUC _{0-24h,ss} (mcg·h/mL)	Ivacaftor AUC _{0-12h,ss} (mcg·h/mL)
Patients aged 6 to less than 12 years weighing less than 30 kgs (N=36)	elexacaftor 100 mg qd/ tezacaftor 50 mg qd/ ivacaftor 75 mg q12h	116 (39.4)	67.0 (22.3)	9.78 (4.50)
Patients aged 6 to less than 12 years weighing 30 kgs or more (N=30)	elexacaftor 200 mg qd/ tezacaftor 100 mg qd/ ivacaftor 150 mg q12h	195 (59.4)	103 (23.7)	17.5 (4.97)

SD: Standard Deviation; AUC_{ss}: area under the concentration versus time curve at steady state.

Pediatric patients 12 to less than 18 years of age

The following conclusions about exposures between adults and the pediatric population are based on population pharmacokinetic (PK) analyses. Following oral administration of TRIKAFTA to patients 12 to less than 18 years of age (elexacaftor 200 mg qd/tezacaftor 100 mg qd/ivacaftor 150 mg q12h), the mean (±SD) AUC_{ss} was 147 (36.8) mcg·h/mL, 88.8 (21.8) mcg·h/mL and 10.6 (3.35) mcg·h/mL, respectively for elexacaftor, tezacaftor and ivacaftor, similar to the AUC_{ss} in adult patients.

Patients with Renal Impairment

Renal excretion of elexacaftor, tezacaftor and ivacaftor is minimal. Elexacaftor alone or in combination with tezacaftor and ivacaftor has not been studied in subjects with severe (eGFR <30 mL/min/1.73 m²) renal impairment or end stage renal disease. Based on population PK analyses, the clearance of elexacaftor and tezacaftor was similar in subjects with mild (eGFR 60 to <90 mL/min/1.73 m²) or moderate (eGFR 30 to <60 mL/min/1.73 m²) renal impairment relative to patients with normal renal function [see Use in Specific Populations (8.6)].

Patients with Hepatic Impairment

Elexacaftor alone or in combination with tezacaftor and ivacaftor has not been studied in subjects with severe hepatic impairment (Child-Pugh Class C, score 10-15). In a clinical study, following multiple doses of elexacaftor, tezacaftor and ivacaftor for 10 days, subjects with moderately impaired hepatic function (Child-Pugh Class B, score 7 to 9) had 25% higher AUC and 12% higher C_{max} for elexacaftor, 73% higher AUC and 70% higher C_{max} for M23-ELX, 36% higher AUC and 24% higher C_{max} for combined elexacaftor and M23-ELX, 20% higher AUC but similar C_{max} for tezacaftor and 1.5-fold higher AUC and 10% higher C_{max} for ivacaftor compared with healthy subjects matched for demographics [see Dosage and Administration (2.3), Use in Specific Populations (8.7) and Patient Counseling Information (17)].

Tezacaftor and ivacaftor

Following multiple doses of tezacaftor and ivacaftor for 10 days, subjects with moderately impaired hepatic function had an approximately 36% higher AUC and a 10% higher in C_{max} for tezacaftor and a 1.5-fold higher AUC but similar C_{max} for ivacaftor compared with healthy subjects matched for demographics.

Ivacaftor

In a study with ivacaftor alone, subjects with moderately impaired hepatic function had similar ivacaftor C_{max}, but an approximately 2.0-fold higher ivacaftor AUC_{0-∞} compared with healthy subjects matched for demographics.

Male and Female Patients

Based on population PK analysis, the exposures of elexacaftor, tezacaftor and ivacaftor are similar in males and females.

Drug Interactions Studies

Drug interaction studies were performed with elexacaftor, tezacaftor and/or ivacaftor and other drugs likely to be co-administered or drugs commonly used as probes for pharmacokinetic interaction studies [see *Drug Interactions* (7)].

Potential for Elexacaftor, Tezacaftor and/or Ivacaftor to Affect Other Drugs

Based on *in vitro* results, elexacaftor and tezacaftor have a low potential to inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4, whereas ivacaftor has the potential to inhibit CYP2C8, CYP2C9 and CYP3A. However, clinical studies showed that the combination regimen of tezacaftor/ivacaftor is not an inhibitor of CYP3A and ivacaftor is not an inhibitor of CYP2C8 or CYP2D6.

Based on *in vitro* results, elexacaftor, tezacaftor and ivacaftor are not likely to induce CYP3A, CYP1A2 and CYP2B6.

Based on *in vitro* results, elexacaftor and tezacaftor have a low potential to inhibit the transporter P-gp, while ivacaftor has the potential to inhibit P-gp. Co-administration of tezacaftor/ivacaftor with digoxin, a sensitive P-gp substrate, increased digoxin exposure by 1.3-fold in a clinical study. Based on *in vitro* results, elexacaftor and M23-ELX may inhibit OATP1B1 and OATP1B3 uptake. Tezacaftor has a low potential to inhibit BCRP, OCT2, OAT1, or OAT3. Ivacaftor is not an inhibitor of the transporters OCT1, OCT2, OAT1, or OAT3.

The effects of elexacaftor, tezacaftor and/or ivacaftor on the exposure of co-administered drugs are shown in Table 8 [see *Drug Interactions* (7)].

Dose and Schedule		Effect on Other Drug PK	Geometric Mean Ratio (90% CI) of Other Drug No Effect=1.0	
			AUC	C _{max}
Midazolam 2 mg single oral dose	TEZ 100 mg qd/IVA 150 mg q12h	↔ Midazolam	1.12 (1.01, 1.25)	1.13 (1.01, 1.25)
Digoxin 0.5 mg single dose	TEZ 100 mg qd/IVA 150 mg q12h	↑ Digoxin	1.30 (1.17, 1.45)	1.32 (1.07, 1.64)
Oral Contraceptive Ethinyl estradiol 30 µg/Levonorgestrel 150 µg qd	ELX 200 mg qd/TEZ 100 mg qd/IVA 150 mg q12h	↑ Ethinyl estradiol*	1.33 (1.20, 1.49)	1.26 (1.14, 1.39)
		↑ Levonorgestrel*	1.23 (1.10, 1.37)	1.10 (0.985, 1.23)
Rosiglitazone 4 mg single oral dose	IVA 150 mg q12h	↔ Rosiglitazone	0.975 (0.897, 1.06)	0.928 (0.858, 1.00)
Desipramine 50 mg single dose	IVA 150 mg q12h	↔ Desipramine	1.04 (0.985, 1.10)	1.00 (0.939, 1.07)

↑ = increase, ↓ = decrease, ↔ = no change. CI = Confidence interval; ELX= elexacaftor; TEZ = tezacaftor; IVA = ivacaftor; PK = Pharmacokinetics
* Effect not clinically significant [see *Drug Interactions* (7.6)].

Potential for Other Drugs to Affect Elexacaftor, Tezacaftor and/or Ivacaftor

In vitro studies showed that elexacaftor, tezacaftor and ivacaftor are all metabolized by CYP3A. Exposure to elexacaftor, tezacaftor and ivacaftor may be reduced by concomitant CYP3A inducers and increased by concomitant CYP3A inhibitors.

In vitro studies showed that elexacaftor and tezacaftor are substrates for the efflux transporter P-gp, but ivacaftor is not. Elexacaftor and ivacaftor are not substrates for OATP1B1 or OATP1B3; tezacaftor is a substrate for OATP1B1, but not OATP1B3. Tezacaftor is a substrate for BCRP.

The effects of co-administered drugs on the exposure of elexacaftor, tezacaftor and/or ivacaftor are shown in Table 9 [see *Dosage and Administration* (2.4) and *Drug Interactions* (7)].

Dose and Schedule		Effect on ELX, TEZ and/or IVA PK	Geometric Mean Ratio (90% CI) of Elexacaftor, Tezacaftor and Ivacaftor No Effect = 1.0	
			AUC	C _{max}
Itraconazole 200 mg q12h on Day 1, followed by 200 mg qd	TEZ 25 mg qd + IVA 50 mg qd	↑ Tezacaftor	4.02 (3.71, 4.63)	2.83 (2.62, 3.07)
		↑ Ivacaftor	15.6 (13.4, 18.1)	8.60 (7.41, 9.98)
Itraconazole 200 mg qd	ELX 20 mg + TEZ 50 mg single dose	↑ Elexacaftor	2.83 (2.59, 3.10)	1.05 (0.977, 1.13)
		↑ Tezacaftor	4.51 (3.85, 5.29)	1.48 (1.33, 1.65)
Ketoconazole 400 mg qd	IVA 150 mg single dose	↑ Ivacaftor	8.45 (7.14, 10.0)	2.65 (2.21, 3.18)
Ciprofloxacin 750 mg q12h	TEZ 50 mg q12h + IVA 150 mg q12h	↔ Tezacaftor	1.08 (1.03, 1.13)	1.05 (0.99, 1.11)
		↑ Ivacaftor*	1.17 (1.06, 1.30)	1.18 (1.06, 1.31)

Table 9: Impact of Other Drugs on Elexacaftor, Tezacaftor and/or Ivacaftor

Dose and Schedule		Effect on ELX, TEZ and/or IVA PK	Geometric Mean Ratio (90% CI) of Elexacaftor, Tezacaftor and Ivacaftor No Effect = 1.0	
			AUC	C _{max}
Rifampin 600 mg qd	IVA 150 mg single dose	↓ Ivacaftor	0.114 (0.097, 0.136)	0.200 (0.168, 0.239)
Fluconazole 400 mg single dose on Day 1, followed by 200 mg qd	IVA 150 mg q12h	↑ Ivacaftor	2.95 (2.27, 3.82)	2.47 (1.93, 3.17)

↑ = increase, ↓ = decrease, ↔ = no change. CI = Confidence interval; ELX= elexacaftor; TEZ = tezacaftor; IVA = ivacaftor; PK = Pharmacokinetics
* Effect is not clinically significant [see *Drug Interactions (7.3)*].

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No studies of carcinogenicity, mutagenicity, or impairment of fertility were conducted with the combination of elexacaftor, tezacaftor and ivacaftor; however, separate studies of elexacaftor, tezacaftor and ivacaftor are described below.

Elexacaftor

A 6-month study in Tg.rasH2 transgenic mice showed no evidence of tumorigenicity at 50 mg/kg/day dose, the highest dose tested.

Elexacaftor was negative for genotoxicity in the following assays: Ames test for bacterial gene mutation, *in vitro* mammalian cell micronucleus assay in TK6 cells, and *in vivo* mouse micronucleus test.

Elexacaftor did not cause reproductive system toxicity in male rats at 55 mg/kg/day and female rats at 25 mg/kg/day, equivalent to approximately 6 times and 4 times the MRHD, respectively (based on summed AUCs of elexacaftor and its metabolite). Elexacaftor did not cause embryonic toxicity at 35 mg/kg/day which was the highest dose tested, equivalent to approximately 7 times the MHRD (based on summed AUCs of elexacaftor and its metabolite). Lower male and female fertility, male copulation and female conception indices were observed in males at 75 mg/kg/day and females at 35 mg/kg/day, equivalent to approximately 6 times and 7 times, respectively, the MRHD (based on summed AUCs of elexacaftor and its metabolite).

Tezacaftor

A 2-year study in Sprague-Dawley rats and a 6-month study in Tg.rasH2 transgenic mice were conducted to assess the carcinogenic potential of tezacaftor. No evidence of tumorigenicity from tezacaftor was observed in male and female rats at oral doses up to 50 and 75 mg/kg/day (approximately 1 and 2 times the MRHD based on summed AUCs of tezacaftor and its metabolites in males and females, respectively). No evidence of tumorigenicity was observed in male and female Tg.rasH2 transgenic mice at tezacaftor doses up to 500 mg/kg/day.

Tezacaftor was negative for genotoxicity in the following assays: Ames test for bacterial gene mutation, *in vitro* chromosomal aberration assay in Chinese hamster ovary cells and *in vivo* mouse micronucleus test.

There were no effects on male or female fertility and early embryonic development in rats at oral tezacaftor doses up to 100 mg/kg/day (approximately 3 times the MRHD based on summed AUC of tezacaftor and M1-TEZ).

Ivacaftor

Two-year studies were conducted in CD-1 mice and Sprague-Dawley rats to assess the carcinogenic potential of ivacaftor. No evidence of tumorigenicity from ivacaftor was observed in mice or rats at oral doses up to 200 mg/kg/day and 50 mg/kg/day, respectively (approximately equivalent to 2 and 7 times the MRHD, respectively, based on summed AUCs of ivacaftor and its metabolites).

Ivacaftor was negative for genotoxicity in the following assays: Ames test for bacterial gene mutation, *in vitro* chromosomal aberration assay in Chinese hamster ovary cells and *in vivo* mouse micronucleus test.

Ivacaftor impaired fertility and reproductive performance indices in male and female rats at 200 mg/kg/day (approximately 7 and 5 times, respectively, the MRHD based on summed AUCs of ivacaftor and its metabolites). Increases in prolonged diestrus were observed in females at 200 mg/kg/day. Ivacaftor also increased the number of females with all nonviable embryos and decreased corpora lutea, implantations and viable embryos in rats at 200 mg/kg/day (approximately 5 times the MRHD based on summed AUCs of ivacaftor and its metabolites) when dams were dosed prior to and during early pregnancy. These impairments of fertility and reproductive performance in male and female rats at 200 mg/kg/day were attributed to severe toxicity.

14 CLINICAL STUDIES

Efficacy:

The efficacy of TRIKAFTA in patients with CF aged 12 years and older was evaluated in two double blind, controlled trials (Trials 1 and 2).

Trial 1 was a 24-week, randomized, double-blind, placebo-controlled study in patients who had an *F508del* mutation on one allele and a mutation on the second allele that results in either no CFTR protein or a CFTR protein that is not responsive to ivacaftor and tezacaftor/ivacaftor. An interim analysis was planned when at least 140 patients completed Week 4 and at least 100 patients completed Week 12.

Trial 2 was a 4-week, randomized, double-blind, active-controlled study in patients who are homozygous for the *F508del* mutation. Patients received tezacaftor 100 mg qd/ivacaftor 150 mg q12h during a 4-week open-label run-in period and were then randomized and dosed to receive TRIKAFTA or tezacaftor 100 mg qd/ivacaftor 150 mg q12h during a 4-week double-blind treatment period.

Patients in Trials 1 and 2 had a confirmed diagnosis of CF and at least one *F508del* mutation. Patients discontinued any previous CFTR modulator therapies, but continued on their other standard-of-care CF therapies (e.g., bronchodilators, inhaled antibiotics, dornase alfa and hypertonic saline). Patients had a ppFEV₁ at screening between 40-90%. Patients with a history of colonization with organisms associated with a more rapid decline in pulmonary status, including but not limited to *Burkholderia cenocepacia*, *Burkholderia dolosa*, or *Mycobacterium abscessus*, or who had an abnormal liver function test at screening (ALT, AST, ALP,

or GGT $\geq 3 \times$ ULN, or total bilirubin $\geq 2 \times$ ULN), were excluded from the trials. Patients in Trials 1 and 2 were eligible to roll over into a 96-week open-label extension study.

14.1 Trial 1

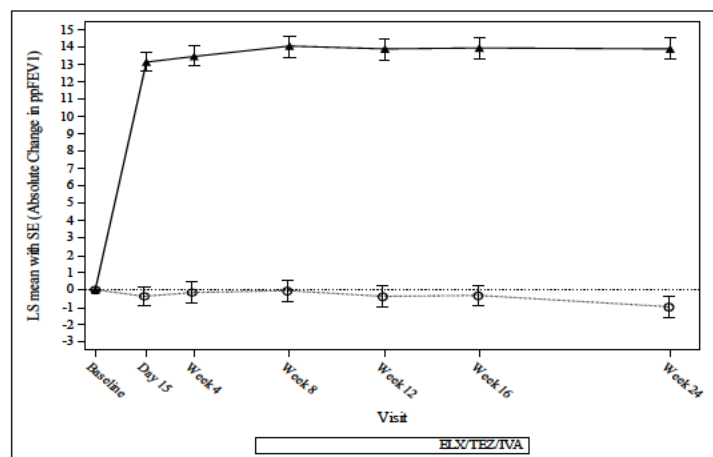
Trial 1 evaluated 403 patients (200 TRIKAFTA, 203 placebo) with CF aged 12 years and older (mean age 26.2 years). The mean ppFEV₁ at baseline was 61.4% (range: 32.3%, 97.1%). The primary endpoint assessed at the time of interim analysis was mean absolute change in ppFEV₁ from baseline at Week 4. The final analysis tested all key secondary endpoints in the 403 patients who completed the 24-week study participation, including absolute change in ppFEV₁ from baseline through Week 24; absolute change in sweat chloride from baseline at Week 4 and through Week 24; number of pulmonary exacerbations through Week 24; absolute change in BMI from baseline at Week 24, and absolute change in CFQ-R Respiratory Domain Score (a measure of respiratory symptoms relevant to patients with CF, such as cough, sputum production and difficulty breathing) from baseline at Week 4 and through Week 24.

Of the 403 patients included in the interim analysis, the treatment difference between TRIKAFTA and placebo for the mean absolute change from baseline in ppFEV₁ at Week 4 was 13.8 percentage points (95% CI: 12.1, 15.4; $P < 0.0001$).

The treatment difference between TRIKAFTA and placebo for mean absolute change in ppFEV₁ from baseline through Week 24 was 14.3 percentage points (95% CI: 12.7, 15.8; $P < 0.0001$). Mean improvement in ppFEV₁ was observed at the first assessment on Day 15 and sustained through the 24-week treatment period (see Figure 1). Improvements in ppFEV₁ were observed regardless of age, baseline ppFEV₁, sex and geographic region. See Table 10 for a summary of primary and key secondary outcomes in Trial 1.

Table 10: Primary and Key Secondary Efficacy Analyses (Trial 1)		
Analysis	Statistic	Treatment Difference* for TRIKAFTA (N=200) vs Placebo (N=203)
Primary (Interim Full Analysis Set)**		
Absolute change in ppFEV ₁ from baseline at Week 4 (percentage points)	Treatment difference (95% CI) P value	13.8 (12.1, 15.4) $P < 0.0001$
Key Secondary (Full Analysis Set)#		
Absolute change in ppFEV ₁ from baseline through Week 24 (percentage points)	Treatment difference (95% CI) P value	14.3 (12.7, 15.8) $P < 0.0001$
Number of pulmonary exacerbations from baseline through Week 24 ^{‡§}	Rate ratio (95% CI) P value	0.37 (0.25, 0.55) $P < 0.0001$
Absolute change in sweat chloride from baseline through Week 24 (mmol/L)	Treatment difference (95% CI) P value	-41.8 (-44.4, -39.3) $P < 0.0001$
Absolute change in CFQ-R respiratory domain score from baseline through Week 24 (points)	Treatment difference (95% CI) P value	20.2 (17.5, 23.0) $P < 0.0001$
Absolute change in BMI from baseline at Week 24 (kg/m ²)	Treatment difference (95% CI) P value	1.04 (0.85, 1.23) $P < 0.0001$
Absolute change in sweat chloride from baseline at Week 4 (mmol/L)	Treatment difference (95% CI) P value	-41.2 (-44.0, -38.5) $P < 0.0001$
Absolute change in CFQ-R respiratory domain score from baseline at Week 4 (points)	Treatment difference (95% CI) P value	20.1 (16.9, 23.2) $P < 0.0001$
ppFEV ₁ : percent predicted forced expiratory volume in 1 second; CI: confidence interval; CFQ-R: Cystic Fibrosis Questionnaire-Revised; BMI: body mass index. * Treatment difference provided as the outcome measure for changes in ppFEV ₁ , sweat chloride, CFQ-R and BMI; Rate ratio provided as the outcome measure for the number of pulmonary exacerbations. ** Primary endpoint was based on interim analysis in 403 patients. # Key secondary endpoints were tested at the final analysis in 403 patients. ‡ A pulmonary exacerbation was defined as a change in antibiotic therapy (IV, inhaled, or oral) as a result of 4 or more of 12 pre-specified sino-pulmonary signs/symptoms. § Number of pulmonary exacerbation events (event rate per year calculated based on 48 weeks per year) in the TRIKAFTA group were 41 (0.37) and 113 (0.98) in the placebo group.		

Figure 1: Absolute Change from Baseline in Percent Predicted FEV₁ at Each Visit in Trial 1



14.2 Trial 2

Trial 2 evaluated 107 patients with CF aged 12 years and older (mean age 28.4 years). The mean ppFEV₁ at baseline, following the 4-week open-label run-in period with tezacaftor/ivacaftor was 60.9% (range: 35.0%, 89.0%). The primary endpoint was mean absolute change in ppFEV₁ from baseline at Week 4 of the double-blind treatment period. The key secondary efficacy endpoints were absolute change in sweat chloride and CFQ-R Respiratory Domain Score from baseline at Week 4. Treatment with TRIKAFTA compared to tezacaftor/ivacaftor resulted in a statistically significant improvement in ppFEV₁ of 10.0 percentage points (95% CI: 7.4, 12.6; $P < 0.0001$). Mean improvement in ppFEV₁ was observed at the first assessment on Day 15. Improvements in ppFEV₁ were observed regardless of age, sex, baseline ppFEV₁ and geographic region. See Table 11 for a summary of primary and key secondary outcomes.

Table 11: Primary and Key Secondary Efficacy Analyses, Full Analysis Set (Trial 2)		
Analysis*	Statistic	Treatment Difference for TRIKAFTA (N=55) vs Tezacaftor/Ivacaftor [#] (N=52)
Primary		
Absolute change in ppFEV ₁ from baseline at Week 4 (percentage points)	Treatment difference (95% CI) <i>P</i> value	10.0 (7.4, 12.6) $P < 0.0001$
Key Secondary		
Absolute change in sweat chloride from baseline at Week 4 (mmol/L)	Treatment difference (95% CI) <i>P</i> value	-45.1 (-50.1, -40.1) $P < 0.0001$
Absolute change in CFQ-R respiratory domain score from baseline at Week 4 (points)	Treatment difference (95% CI) <i>P</i> value	17.4 (11.8, 23.0) $P < 0.0001$
ppFEV ₁ : percent predicted forced expiratory volume in 1 second; CI: confidence interval; CFQ-R: Cystic Fibrosis Questionnaire-Revised. * Baseline for primary and key secondary endpoints is defined as the end of the 4-week tezacaftor/ivacaftor run-in period. [#] Regimen of tezacaftor 100 mg qd/ivacaftor 150 mg q12h.		

16 HOW SUPPLIED/STORAGE AND HANDLING

TRIKAFTA is supplied as a co-packaged blister pack sealed into a printed wallet, containing elixacaftor, tezacaftor and ivacaftor fixed-dose combination tablets and ivacaftor tablets. Four such wallets are placed in a printed outer carton.

- The elixacaftor 50 mg, tezacaftor 25 mg and ivacaftor 37.5 mg tablets are supplied as light orange, capsule-shaped tablets; each containing 50 mg of elixacaftor, 25 mg of tezacaftor and 37.5 mg of ivacaftor. Each tablet is debossed with "T50" on one side and plain on the other. Ivacaftor 75 mg tablets are supplied as light blue, film-coated, capsule-shaped tablets; each containing 75 mg of ivacaftor. Each tablet is printed with the characters "V 75" in black ink on one side and plain on the other. TRIKAFTA is supplied as:

84-count tablet carton
(4 wallets, each wallet containing 14 tablets of elixacaftor, tezacaftor and ivacaftor and 7 tablets of ivacaftor)

NDC 51167-106-02
- The elixacaftor 100 mg, tezacaftor 50 mg and ivacaftor 75 mg tablets are supplied as orange, capsule-shaped tablets; each containing 100 mg of elixacaftor, 50 mg of tezacaftor and 75 mg of ivacaftor. Each tablet is debossed with "T100" on one side and plain on the other. Ivacaftor 150 mg tablets are supplied as light blue, film-coated, capsule-shaped tablets; each containing 150 mg of ivacaftor. Each tablet is printed with the characters "V 150" in black ink on one side and plain on the other. TRIKAFTA is supplied as:

84-count tablet carton
(4 wallets, each wallet containing 14 tablets of elixacaftor, tezacaftor and ivacaftor and 7 tablets of ivacaftor)

NDC 51167-331-01

Store at 68 F - 77 F (20 C - 25 C); excursions permitted to 59 F - 86 F (15 C - 30 C) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Liver Function Test Elevations and Monitoring

Inform patients that elevation in transaminases has occurred in patients treated with TRIKAFTA. Elevations in bilirubin have also been observed with TRIKAFTA treatment. Liver function tests (ALT, AST and bilirubin) should be assessed prior to initiating TRIKAFTA, every 3 months during the first year of treatment, and annually thereafter. More frequent monitoring should be considered in patients with a history of hepatobiliary disease or liver function test elevations [see *Warnings and Precautions* (5.1)].

Drug Interactions with CYP3A Inducers and Inhibitors

Ask patients to tell you all the medications they are taking including any herbal supplements or vitamins. Co-administration of TRIKAFTA with strong CYP3A inducers (e.g., rifampin, St. John's wort) is not recommended, as they may reduce the efficacy of TRIKAFTA. Dose reduction to two elexacaftor/tezacaftor/ivacaftor tablets twice a week, taken approximately 3 to 4 days apart is recommended when co-administered with strong CYP3A inhibitors, such as ketoconazole. Advise the patient not to take the evening dose of ivacaftor. Dose reduction to two elexacaftor/tezacaftor/ivacaftor tablets and one ivacaftor tablet taken on alternate days is recommended when co-administered with moderate CYP3A inhibitors, such as fluconazole. Advise the patient not to take the evening dose of ivacaftor. Food or drink containing grapefruit should be avoided [see *Dosage and Administration* (2), *Warnings and Precautions* (5), *Drug Interactions* (7) and *Clinical Pharmacology* (12.3)].

Use in Patients with Hepatic Impairment

No dose adjustment is recommended for patients with mild hepatic impairment (Child-Pugh Class A, score 5-6). See Table 2. Liver function tests should be closely monitored.

Treatment is not recommended for patients with moderate hepatic impairment (Child-Pugh Class B, score 7-9). Use of TRIKAFTA in patients with moderate hepatic impairment should only be considered when there is a clear medical need and the benefit exceeds the risk. If used in patients with moderate hepatic impairment, TRIKAFTA should be used with caution at a reduced dose (see Table 2). Liver function tests should be closely monitored.

TRIKAFTA has not been studied in patients with severe hepatic impairment (Child-Pugh Class C, score 10-15), but the exposure is expected to be higher than in patients with moderate hepatic impairment. TRIKAFTA should not be used in patients with severe hepatic impairment. Inquire and/or assess whether patients have liver impairment [see *Dosage and Administration* (2.3), *Warnings and Precautions* (5.1), *Use in Specific Populations* (8.7) and *Clinical Pharmacology* (12.3)].

Cataracts

Inform patients that abnormality of the eye lens (cataract) has been noted in some children and adolescents receiving ivacaftor-containing regimens. Baseline and follow-up ophthalmological examinations should be performed in pediatric patients initiating treatment with TRIKAFTA [see *Warnings and Precautions* (5.4) and *Use in Specific Populations* (8.4)].

Administration

Inform patients that TRIKAFTA is best absorbed by the body when taken with food that contains fat. A typical CF diet will satisfy this requirement. Examples include eggs, butter, peanut butter, whole-milk dairy products (such as whole milk, cheese and yogurt), etc. [see *Dosage and Administration* (2.1) and *Clinical Pharmacology* (12.3)].

Patients should be informed about what to do in the event they miss a dose of elexacaftor/tezacaftor/ivacaftor tablets or ivacaftor tablet:

- If 6 hours or less have passed since the missed morning or evening dose is usually taken, patients should be instructed to take the prescribed dose with fat-containing food as soon as possible.
- If more than 6 hours have passed since:
 - o the time the **morning** dose is usually taken, patients should be instructed to take the morning dose as soon as possible, and **not** take the evening dose. Patients should take the next scheduled morning dose at the usual time.
 - o the time the **evening** dose is usually taken, patients should be instructed to **not** take the missed evening dose. Patients should take the next scheduled morning dose at the usual time.
- Patients should be instructed to not take the morning and evening doses at the same time.
- Patients should be advised to contact their health care provider if they have questions.



Manufactured for
Vertex Pharmaceuticals Incorporated
50 Northern Avenue
Boston, MA 02210

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Patient Information is perforated for dispensing to the patient.

Patient Information TRIKAFTA® (tri-KAF-tuh) (elexacaftor/tezacaftor/ivacaftor tablets; ivacaftor tablets) for oral use
What is TRIKAFTA? • TRIKAFTA is a prescription medicine used for the treatment of cystic fibrosis (CF) in people aged 6 years and older who have at least one copy of the F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene or another mutation that is responsive to treatment with TRIKAFTA. • Talk to your doctor to learn if you have an indicated CF gene mutation. It is not known if TRIKAFTA is safe and effective in children under 6 years of age.
Who should not take TRIKAFTA? Do not take TRIKAFTA if you take certain medicines or herbal supplements such as: • antibiotics such as rifampin (RIFAMATE®, RIFATER®) or rifabutin (MYCOBUTIN®) • seizure medicines such as phenobarbital, carbamazepine (TEGRETOL®, CARBATROL®, EQUETRO®), or phenytoin (DILANTIN®, PHENYTEK®) • St. John's wort Talk to your doctor before taking TRIKAFTA if you take any of the medicines or herbal supplements listed above.
Before taking TRIKAFTA, tell your doctor about all of your medical conditions, including if you: • have kidney problems. • have or have had liver problems. • are pregnant or plan to become pregnant. It is not known if TRIKAFTA will harm your unborn baby. You and your doctor should decide if you will take TRIKAFTA while you are pregnant. • are breastfeeding or planning to breastfeed. It is not known if TRIKAFTA passes into your breast milk. You and your doctor should decide if you will take TRIKAFTA while you are breastfeeding. TRIKAFTA may affect the way other medicines work and other medicines may affect how TRIKAFTA works. Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins and herbal supplements. The dose of TRIKAFTA may need to be adjusted when taken with certain medicines. Ask your doctor or pharmacist for a list of these medicines if you are not sure. Especially tell your doctor if you take: • antifungal medicines including ketoconazole (such as NIZORAL®), itraconazole (such as SPORANOX®), posaconazole (such as NOXAFIL®), voriconazole (such as VFEND®), or fluconazole (such as DIFLUCAN®) • antibiotics including telithromycin (such as KETEK®), clarithromycin (such as BIAXIN®), or erythromycin (such as ERY-TAB®) • other medicines including rifampin, rifabutin, phenobarbital, carbamazepine, phenytoin and St. John's wort (see '<i>Who should not take TRIKAFTA</i>' section). Know the medicines you take. Keep a list of them to show your doctor and pharmacist when you get a new medicine.
How should I take TRIKAFTA? • Take TRIKAFTA exactly as your doctor tells you to take it. • Take TRIKAFTA by mouth only. • TRIKAFTA consists of 2 different tablets. • TRIKAFTA Tablets (age 6 to less than 12 years weighing less than 30 kgs): - o The light orange tablet is marked with 'T50' and each tablet contains the medicines elexacaftor, tezacaftor and ivacaftor. Take 2 light orange tablets in the morning. - o The light blue tablet is marked with 'V 75' and contains the medicine ivacaftor. Take 1 light blue tablet in the evening. • TRIKAFTA Tablets (age 6 to less than 12 years weighing 30 kgs or more, and age 12 years and older): - o The orange tablet is marked with 'T100' and each tablet contains the medicines elexacaftor, tezacaftor and ivacaftor. Take 2 orange tablets in the morning. - o The light blue tablet is marked with 'V 150' and contains the medicine ivacaftor. Take 1 light blue tablet in the evening. • Take the morning and the evening tablets about 12 hours apart.

- **Always take TRIKAFTA with food that contains fat.** Examples of fat-containing foods include butter, peanut butter, eggs, nuts, meat and whole-milk dairy products such as whole milk, cheese and yogurt.
- If you miss a dose of TRIKAFTA and:
 - o it is **6 hours or less** from the time you usually take the morning dose or the evening dose, **take the missed dose** with food that contains fat as soon as you can. Then take your next dose at your usual time.
 - o it is **more than 6 hours** from the time you usually take the morning dose, **take the missed dose** with food that contains fat as soon as you can. **Do not take the evening dose.**
 - o it is **more than 6 hours** from the time you usually take the evening dose, **do not take the missed dose.** Take your next morning dose at the usual time with food that contains fat.
- Do not take more than your usual dose of TRIKAFTA to make up for a missed dose.

What should I avoid while taking TRIKAFTA?

- TRIKAFTA can cause dizziness in some people who take it. Do not drive a car, use machinery, or do anything that needs you to be alert until you know how TRIKAFTA affects you.
- Avoid food or drink that contains grapefruit while you are taking TRIKAFTA.

What are the possible side effects of TRIKAFTA?

TRIKAFTA can cause serious side effects, including:

- **High liver enzymes in the blood** is a common side effect in people treated with TRIKAFTA. These can be serious and may be a sign of liver injury. Your doctor will do blood tests to check your liver:
 - o before you start TRIKAFTA
 - o every 3 months during your first year of taking TRIKAFTA
 - o then every year while you are taking TRIKAFTA

Your doctor may do blood tests to check the liver more often if you have had high liver enzymes in your blood in the past.

Call your doctor right away if you have any of the following symptoms of liver problems:

- o pain or discomfort in the upper right stomach (abdominal) area
- o nausea or vomiting
- o yellowing of your skin or the white part of your eyes
- o dark, amber-colored urine
- o loss of appetite

- **Abnormality of the eye lens (cataract)** has happened in some children and adolescents treated with TRIKAFTA. If you are a child or adolescent, your doctor should perform eye examinations before and during treatment with TRIKAFTA to look for cataracts.

The most common side effects of TRIKAFTA include:

- headache
- upper respiratory tract infection (common cold) including stuffy and runny nose
- stomach (abdominal) pain
- diarrhea
- rash
- increase in liver enzymes
- increase in a certain blood enzyme called creatine phosphokinase
- flu (influenza)
- inflamed sinuses
- increase in blood bilirubin

These are not all the possible side effects of TRIKAFTA.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store TRIKAFTA?

- Store TRIKAFTA at room temperature between 68°F to 77°F (20°C to 25°C).
- Do not use TRIKAFTA after the expiration date on the package.

Keep TRIKAFTA and all medicines out of the reach of children.

General information about the safe and effective use of TRIKAFTA.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use TRIKAFTA for a condition for which it was not prescribed. Do not give TRIKAFTA to other people, even if they have the same symptoms you have. It may harm them. You can ask your pharmacist or doctor for information about TRIKAFTA that is written for health professionals.

What are the ingredients in TRIKAFTA?

Elexacaftor/tezacaftor/ivacaftor tablets:

Active ingredients: elexacaftor, tezacaftor and ivacaftor.

Inactive ingredients: hypromellose, hypromellose acetate succinate, sodium lauryl sulfate, croscarmellose sodium, microcrystalline cellulose, magnesium stearate, hydroxypropyl cellulose, titanium dioxide, talc, iron oxide yellow and iron oxide red.

Ivacaftor tablets:

Active ingredients: ivacaftor.

Inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, hypromellose acetate succinate, lactose monohydrate, magnesium stearate, microcrystalline cellulose, sodium lauryl sulfate, carnauba wax, FD&C Blue #2, PEG 3350, polyvinyl alcohol, talc, titanium dioxide, ammonium hydroxide, iron oxide black, propylene glycol and shellac.



Manufactured for: Vertex Pharmaceuticals Incorporated; 50 Northern Avenue, Boston, MA 02210

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For more information, go to www.trikafta.com or call 1-877-752-5933.

This Patient Information has been approved by the U.S. Food and Drug Administration.

Revised 06/2021

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

212273Orig1s004

CROSS DISCIPLINE TEAM LEADER REVIEW

NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	sNDA
Application Number(s)	212273/S004
Priority or Standard	Priority
Submit Date(s)	December 8, 2020
Received Date(s)	December 8, 2020
PDUFA Goal Date	June 8, 2021
Division/Office	OII/DPACC
Review Completion Date	June 8, 2021
Established/Proper Name	Eluxacaftor (ELX) / tezacaftor (TEZ) / ivacaftor (IVA)
(Proposed) Trade Name	Trikafta
Pharmacologic Class	Unclassified / unclassified / Cystic Fibrosis Transmembrane Conductance Regulatory (CFTR) potentiator
Code name	VX-445 / VX-661 / VX-770
Applicant	Vertex Pharmaceuticals Incorporated
Dosage form	tablet
Applicant proposed Dosing Regimen	< 30 kg AM: 2 fixed-dose combination (FDC) tablets containing ELX 50 mg/ TEZ 25 mg/IVA 37.5 mg PM: 1 tablet containing 75 mg IVA ≥30 kg AM: 2 FDC tablets containing ELX 100 mg/ TEZ 50 mg/IVA 75 mg PM: 1 tablet containing 150 mg IVA
Applicant Proposed Indication(s)/Population(s)	Treatment of cystic fibrosis (CF) in patients aged 6 years and older who have at least one <i>F508del</i> mutation in the <i>CFTR</i> gene or a mutation in the <i>CFTR</i> gene that is responsive based on in vitro data.
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	Cystic Fibrosis
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of cystic fibrosis (CF) in patients aged 6 years and older who have at least one <i>F508del</i> mutation in the <i>CFTR</i> gene or a mutation in the <i>CFTR</i> gene that is responsive based on in vitro data.
Recommended SNOMED CT Indication Disease	190905008/Cystic fibrosis (disorder)

NDA/BLA Multi-disciplinary Review and Evaluation {NDA 212273}
{Trikafta (elexacaftor/tezacaftor/ivacaftor)}

Term for each Indication (if applicable)	
Recommended Dosing Regimen	≤30 kg AM: 2 FDC tablets containing ELX 50 mg/ TEZ 25 mg/IVA 37.5 mg PM: 1 tablet containing 75 mg IVA ≥30 kg AM: 2 FDC tablets containing ELX 100 mg/ TEZ 50 mg/IVA 75 mg PM: 1 tablet containing 150 mg IVA

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{Trikafta (elexacaftor/tezacaftor/ivacaftor)}

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Reviewers of Multi-Disciplinary Review and Evaluation

Senior Regulatory Project Manager	Angela Ramsey, MPH, MSN
Nonclinical Reviewer	Wei Sun, PhD
Nonclinical Team Leader	Timothy W. Robison, PhD, DABT
Nonclinical Division Director	Andrew Goodwin, PhD
Office of Clinical Pharmacology Reviewer(s)	Jie Cheng, PhD; Junshan Qiu PhD
Office of Clinical Pharmacology Team Leader(s)	Yunzhao Ren, MD, PhD; Jerry Yu, PhD
Clinical Reviewer	Courtney McGuire, MD
Clinical Team Leader	Stacy Chin, MD
Statistical Reviewer	Mingyu Xi, PhD
Statistical Team Leader	Yongman Kim, PhD
Cross-Disciplinary Team Leader	Stacy Chin, MD
Deputy Division Director (DPACC), signatory	Banu Karimi-Shah, MD

Additional Reviewers of Application

OPQ	Chong Ho Kim / Ramesh Raghavachari
OPDP	Kyle Snyder/Kathleen Klemm
OSE/DMEPA	Lissa Owens / Idalia Rychlik
OSE/RPM	Cristina Attinello / Nichelle Rashid
PLT	Maria Nguyen / Marcia Williams

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

RPM=Regulatory Project Management

PLT=Patient Labeling Team

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Nonclinical Reviewer	Wei Sun, PhD	OND/DPT-II	Sections: 5	Select one: ☒ Authored ☐ Approved
	Signature:			
Nonclinical Team Leader	Timothy W. Robison, PhD, DABT	OND/DPT-II	Sections: 5	Select one: ☐ Authored ☒ Approved
	Signature:			
Nonclinical Division Director	Andrew Goodwin, PhD	OND/DPT-II	Sections: 5	Select one: ☐ Authored ☒ Approved
	Signature:			
Clinical Pharmacology Reviewer	Jie Cheng, PhD	Division of Inflammation and Immune Pharmacology, Office of Clinical Pharmacology	Sections: 6, 15.2	Select one: ☒ Authored ☐ Approved
	Signature: (signed by Yunzhao Ren on behalf of Jie Cheng)			

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 {Trikafta (elexacaftor/tezacaftor/ivacaftor)}

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Pharmacology Team Leader	Yunzhao Ren, MD, PhD	Division of Inflammation and Immune Pharmacology, Office of Clinical Pharmacology	Section: 6, 15.2	Select one: ☒ Authored ☒ Approved
	Signature:			
Pharmacometrics Reviewer	Junshan Qiu, PhD	Division of Pharmacometrics, Office of Clinical Pharmacology	Section: 15.2	Select one: ☒ Authored ☐ Approved
	Signature:			
Pharmacometrics Team Leader	Jerry Yu, PhD	Division of Pharmacometrics, Office of Clinical Pharmacology	Section: 15.2	Select one: ☒ Authored ☒ Approved
	Signature:			
Clinical Reviewer	Courtney McGuire, MD	OND / OII / DPACC	Sections: 1, 2, 3, 4, 7, 8, 9, 10, 11, 12, 13, 15.3	Select one: ☐ Authored ☐ Approved
	Signature:			

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DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Team Leader	Stacy Chin, MD	OND / OII / DPACC	Sections: all	Select one: ☐ Authored ☒ Approved
	Signature:			
Deputy Division Director (Clinical)	Banu Karimi-Shah, MD	OND / OII / DPACC	Sections: all	Select one: ☐ Authored ☒ Approved
	Signature:			
Statistical Reviewer	Mingyu Xi, PhD	OB / DB3	Sections: 8.1, 8.3	Select one: ☒ Authored ☐ Approved
	Signature:			
Statistical Team Leader	Yongman Kim, PhD	OB / DB3	Sections: 8.1, 8.3	Select one: ☐ Authored ☒ Approved
	Signature:			

Glossary

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

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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

1.1. Product Introduction

The proposed product, Trikafta, is a fixed dose combination of elexacaftor, tezacaftor and ivacaftor (ETI). The chemical name for elexacaftor (ELX) is N-(1,3-dimethyl-1H-pyrazole-4-sulfonyl)-6-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)-1H-pyrazol-1-yl]-2-[(4S)-2,2,4-trimethylpyrrolidin-1-yl]pyridine-3-carboxamide. The chemical name for tezacaftor (TEZ) is 1-[2,2-difluoro-2H-1,3-benzodioxol-5-yl]-N-{1-[(2R)-2,3-dihydroxypropyl]-6-fluoro-2-[1-hydroxy-2-methylpropan-2-yl]-1H-indol-5-yl}cyclopropane-1-carboxamide. Both ELX and TEZ are orally-bioavailable small molecules that may facilitate the cellular processing and trafficking of defective cystic fibrosis transmembrane conductance regulator (CFTR) protein which allows it to reach the epithelial cell apical surface. The chemical name for ivacaftor (IVA) is N-(2, 4-Di-tert-butyl-5-hydroxyphenyl)-1,4-dihydro-4-oxoquinoline-3-carboxamide. IVA is an orally-bioavailable small molecule that is a potentiator of the CFTR chloride channel present on the epithelial cell membrane. IVA facilitates increased chloride transport by potentiating the channel-open probability of the CFTR.

ETI tablets (NDA 212273) were approved for the treatment of CF in patients 12 years of age and older who have at least one deletion of phenylalanine 508 mutation (*F508del*) in the *CFTR* gene on October 21, 2019. The indication was expanded on December 5, 2020 to also include treatment of CF in patients aged 12 years and older with 177 additional rare *CFTR* mutations based on in vitro assay data. This supplemental NDA for ETI combination therapy proposes to expand the indication to include cystic fibrosis (CF) in patients 6 to 11 years at an ETI dosage of 100 mg qd / 50 mg qd / 75 mg q12h for patients < 30 kg and an ETI dosage of 200 mg qd / 100 mg qd / 150 mg q12h for patients ≥ 30 kg.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The recommended regulatory action is Approval for orally administered Trikafta (elexacaftor/tezacaftor/ivacaftor [ETI]) for the treatment of CF patients aged 6 years and older with at least one *F508del* mutation or a mutation in the *CFTR* gene that is responsive based on in vitro data. This recommendation is based on the extrapolation of efficacy from existing data in the adolescent and adult population, supportive efficacy data in the 6 to 11 year old age group, and review of safety data in the 6 to 11 year old population.

ETI tablets (NDA 212273) are approved for the treatment of CF patients aged 12 years and older with at least one *F508del* mutation or a mutation in the *CFTR* gene that is responsive based on in vitro data. In this NDA, the Applicant submitted data from a pharmacokinetic (PK)/safety study (VX18-445-106, hereafter referred to as Trial 106) to support the use of ETI in patients 6

to 11 years of age with at least one *F508del* mutation or a mutation in the *CFTR* gene that is responsive based on in vitro data.

Trial 106 was a two-part, non-randomized, uncontrolled, open-label PK (Part A, 15-day duration, n=16) and safety (Part B, 24-week duration, n=66) study in patients 6 to 11 years of age. Results demonstrated that when ETI 100 mg qd / 50 mg qd / 75 mg q12h was administered to patients < 30 kg and ETI 200 mg qd / 100 mg qd / 150 mg q12h administered to patients ≥ 30 kg, systemic exposures were comparable to that observed in the adolescent/adult population at the approved dose. Because of the comparable systemic exposures and because the disease process in the adolescent/adult population is the same as that in the 6 to 11 year old population, efficacy in the proposed age group can be extrapolated from the adolescent/adult population where efficacy has been demonstrated in placebo-controlled clinical trials.

Additionally, Week 24 data from Part B demonstrated within group improvements in pulmonary function (ppFEV1), sweat chloride (SwCl), and Cystic Fibrosis Questionnaire-Revised Respiratory Domain (CFQ-R RD), suggesting a clinically meaningful response to the ETI treatment. Trial 106 did not reveal any new safety signals than that identified in the adolescent / adult clinical program.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

ETI tablets (NDA 212273), tradename Trikafta, are approved for the treatment of CF in patients ≥ 12 years of age who have at least one *F508del* mutation or a mutation in the *CFTR* gene that is responsive based on in vitro data. In this sNDA, the Applicant submitted data from a PK/safety study (Trial 106) to support the use of ETI in patients 6 to 11 years of age at an ETI dosage of 100 mg qd / 50 mg qd / 75 mg q12h in patients < 30 kg and an ETI dosage of 200 mg qd / 100 mg qd / 150 mg q12h in patients ≥ 30 kg. The recommended regulatory action is Approval of ETI for the treatment of CF patients aged 6 years and older with at least one *F508del* mutation or a mutation in the *CFTR* gene that is responsive based on in vitro data.

CF results from mutations to the *CFTR* gene which leads to decreased amount or abnormal function of CFTR protein. The most common *CFTR* mutation is *F508del*. In the United States, approximately 85% of patients carry at least one *F508del* allele, with approximately 45% of patients being homozygous for the *F508del* mutation.¹ Currently, in addition to the treatments of the symptoms and sequelae of the disease, in this age group, ETI is the only drug that is FDA approved for targeting the underlying cause of CF in patients who carry at least one *F508del* allele.

Trial 106 was a two-part, non-randomized, uncontrolled, open-label PK (Part A, 15-day duration, n=16) and safety (Part B, 24-week duration, n=66) study in patients 6 to 11 years of age. Results demonstrated that when ETI 100 mg qd / 50 mg qd / 75 mg q12h was administered to patients < 30 kg and ETI 200 mg qd / 100 mg qd / 150 mg q12h administered to patients ≥ 30 kg, systemic exposures were comparable to that observed in the adolescent/adult population at the approved dose. Because of the comparable systemic exposures and because the disease process in the adolescent/adult population is the same as that in the 6 to 11 year old population, efficacy in the proposed age group can be extrapolated from the adolescent/adult population where efficacy has been demonstrated in placebo-controlled clinical trials. In addition, in Part B, the within group improvements in ppFEV1, SwCl, and CFQ-R RD through 24 weeks support a clinically meaningful response to the ETI treatment and are consistent with that observed in previous ETI clinical trials.

With regard to safety, in Part B of Trial 106, no deaths were reported and 1 patient experienced three serious adverse events (preferred term: metapneumovirus infection, pneumonia, and rhinovirus infection). The three most common adverse events (AEs) were cough, upper respiratory tract infection, and headache. Overall, the AEs were generally consistent with common manifestations of CF disease, common illnesses in patients 6 to 11 years of age and AEs previously identified in the ETI development program. In the ETI tablet product label, the

¹ <https://www.cff.org/Research/Researcher-Resources/Patient-Registry/2019-Patient-Registry-Annual-Data-Report.pdf>, access on February 23, 2021.

listed Warnings and Precautions include liver-related events and cataracts, which were specifically evaluated in the safety analysis in Trial 106. Additional adverse events of special interest (AESI) identified in the clinical development program were creatine kinase (CK) elevation and rash. Seven (11%) patients had a maximum on-treatment liver transaminase (LFT) elevations of >3x ULN. Of these patients, 1 (2%) had values which were >5x ULN. None had elevations of total bilirubin greater than 2x ULN. Rash AEs occurred in 14 (21%) of patients. When considering data from unscheduled visits of the open label extension (OLE), 2 patients developed cataracts. Overall, the safety profile in the 6 to 11 year old age group was consistent with the older age group and no new safety signals were identified in Trial 106.

In summary, efficacy in the proposed age group was based on PK matching and extrapolation from the previous ETI trials in the older population. Efficacy was supported by improvements in clinical outcomes such as ppFEV1, CFQ-R RD, and SwCl in both weight groups following open-label treatment with ETI. With regard to safety, no new safety signals were identified in Trial 106. The demonstration of an acceptable safety profile along with the extrapolated efficacy and the change in ppFEV1, SwCl, and CFQ-R RD as a clinical and pharmacodynamic response to the treatment, and unmet need warrants the recommendation of Approval.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	- CF is a rare, progressive, and usually fatal autosomal recessive genetic disease that affects approximately 30,000 children and adults in the United States. CF results from mutations to the <i>CFTR</i> 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 infection, irreversible lung damage, and ultimately respiratory failure. The median age of survival for a patient with CF is in the mid-to-late 30's. - The most common <i>CFTR</i> mutation is <i>F508del</i> – in the United States, approximately 85% of CF patients carry at least one allele and 45.3% are homozygous (carry two alleles). - However, over 2,000 different disease-causing mutations in the <i>CFTR</i> gene have been identified.	CF is a rare, progressive, and usually fatal genetic disease. The <i>CFTR</i> mutation included in the proposed indication represents most patients with CF in the United States.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	- While no cure exists, there are three approved CFTR modulator therapies aimed at the cause of CF (i.e., absent or defective CFTR ion channel at the cell surface) in a subset of CF patients age 6 to less than 12 years of age with the following mutations in the <i>CFTR</i> gene: - Gating mutations (e.g., <i>G551D</i>, <i>S549N</i>) - Conduction mutations (e.g., <i>D1152H</i>, <i>R117H</i>) <i>F508del</i>/<i>F508del</i> homozygous mutations - Missense or non-canonical splice mutations predicted to be responsive based on clinical and/or in vitro assay data	There is an unmet medical need in those subpopulations not covered by any existing CFTR modulator therapy. While there are three approved therapies for specific subpopulations of CF patients, the treatment effect in some mutations (e.g. homozygous <i>F508del</i>) are modest. In these populations, there remains an unmet medical need for treatment options that may afford a greater treatment effect and modify the course of disease to slow or potentially prevent progression in younger patients.
Benefit	- Based on results from Trial 106, the Applicant demonstrated that when ETI was administered to CF patients aged 6 to 11 years of age homozygous for the <i>F508del</i> mutation or heterozygous for <i>F508del</i> and a MF mutation, systemic exposures were comparable to that observed in the adolescent/adult population. - Improvements in ppFEV1, CFQ-R RD, and the pharmacodynamic endpoint of SwCl were observed in study patients.	ETI provides a clinically relevant treatment benefit for patients with at least 1 <i>F508del</i> mutation in patients 6 to 11 years of age based on extrapolation of efficacy from the adolescent/adult population. Efficacy can be extrapolated as the disease process in this age group is similar to the older age group, efficacy has previously been demonstrated in the older age group, and systemic exposures are comparable between these age groups. Additionally, improvement in ppFEV1, CFQ-R RD, and decrease in SwCl level from baseline after ETI treatment provide supportive evidence of efficacy response.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	• The AEs observed in this study were consistent with common manifestations of CF disease or common illnesses in patients 6 to 11 years of age. One of 66 patients experienced three SAEs. No deaths were reported. Specific safety analyses were performed for the Warnings and Precautions listed in the approved ETI tablet label. One patient had a maximum on-treatment transaminase elevations of >5x ULN, but without bilirubin elevations; Fourteen patients had rash events/symptoms. Two patients developed cataracts during unscheduled visit obtained in the OLE. • No REMS is proposed.	No new safety signals were identified in Trial 106. The potential risks of LFT elevation, rash, CK elevation, cataracts, and drug-drug interactions can be managed through labeling and routine pharmacovigilance; a REMS is not required. No substantial safety findings were identified in the clinical development program that outweigh the potential benefit.

1.4. Patient Experience Data

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

X	The patient experience data that were submitted as part of the application include:		Section of review where discussed, if applicable
	X	Clinical outcome assessment (COA) data, such as	
	X	Patient reported outcome (PRO)	8.1.2
	☐	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	
	X	Patient preference studies (e.g., submitted studies or scientific publications)	8.2.6
	☐	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	

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☐	Observational survey studies designed to capture patient experience data	
☐	Other: (Please specify):	
☐	Patient experience data was not submitted as part of this application.	

2 Therapeutic Context

2.1. Analysis of Condition

CF is an autosomal recessive, progressive, and usually fatal genetic disease most common in the Caucasian population. In the United States, CF is an orphan disease which occurs in approximately one out of every 3,500 children born and affects roughly 30,000 children and adults.

CF results from mutations 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 ion channel is responsible for the clinical sequelae of CF, including malabsorption of nutrients, and the presence of tenacious respiratory secretions. Tenacious secretions are difficult to mobilize, leading to recurrent/chronic pneumonia, progressive lung damage, and ultimately respiratory failure which is the primary cause of death.

Over 2,000 different mutations in the *CFTR* gene have been identified, though not all are associated with disease causation.² The most prevalent CF-causing mutation is *F508del*; in the US Cystic Fibrosis Foundation Patient Registry, approximately 85% of CF patients carry at least one allele and 44.4% are homozygous for *F508del* (F/F).³ Historically, *CFTR* mutations have been categorized according to their functional impact on CFTR protein synthesis or function:

Table 1. *CFTR* Mutation Classes

Class	Description	Prevalence ¹
Class I (protein production mutations)	No functional CFTR created	22%

² United States Cystic Fibrosis Foundation, Johns Hopkins University, The Hospital for Sick Children, The Clinical and Functional Translation of CFTR (CFTR2). Accessed at <http://cfr2.org> on September 6, 2019

³ <https://www.cff.org/Research/Researcher-Resources/Patient-Registry/2019-Patient-Registry-Annual-Data-Report.pdf>, access on February 23, 2021.

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Class II (protein processing mutations)	CFTR protein created, but misfolded, keeping it from reaching the cell surface	88%
Class III (gating mutations)	CFTR protein created and reaches cell surface, but does not function properly	6%
Class IV (conduction mutations)	Opening in CFTR protein ion channel is faulty	6%
Class V (insufficient protein mutations)	CFTR created in insufficient quantities.	5%

³ Percent of people with CF who have at least one mutation in that class.
Source. Adapted from <https://www.cff.org/What-is-CF/Genetics/Types-of-CFTR-Mutations/> and <https://www.cff.org/What-is-CF/Genetics/Know-Your-CFTR-Mutations-Infographic.pdf> Accessed on April 14, 2021

This classification system can help understand the CFTR protein and potential disease severity but may be oversimplified. While not widely adapted, there is increasing interest in classifying mutations according to response to available therapies.⁴

2.2. Analysis of Current Treatment Options

Medications used to treat CF include drugs targeting the symptoms and sequelae of disease as well as those directed at the cause of CF, i.e. CFTR modulators. The FDA-approved CF products are only available for a subset of *CFTR* mutation subpopulations covered in the proposed indication. Table 2 summarizes the current treatment armamentarium for CF patients.

Table 2. Treatment Armamentarium Relevant to Proposed CF Indication

Active Ingredient	Trade Name	FDA-approved for CF Indication?
CFTR modulator		
Ivacaftor	Kalydeco	Yes: one mutation in the <i>CFTR</i> gene that is responsive to ivacaftor potentiation based on clinical and/or in vitro assay in patients age 4 months and older
Lumacaftor/ivacaftor	Orkambi	Yes: <i>F508del</i> /homozygous mutations in patients age 2 years and older

⁴ <https://www.cff.org/Research/Researcher-Resources/Patient-Registry/2019-Patient-Registry-Annual-Data-Report.pdf>, access on February 23, 2021.

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Tezacaftor/ivacaftor	Symdeko	Yes: <i>F508del</i> /homozygous mutations and one mutation in the <i>CFTR</i> gene that is responsive to tezacaftor/ivacaftor based on clinical and/or in vitro assay in patients age 6 years and older
Elexacaftor/tezacaftor/ivacaftor	Trikafta	Yes: <i>F508del</i> /homozygous mutations and one mutation in the <i>CFTR</i> gene that is responsive to elexacaftor/tezacaftor/ivacaftor based on in vitro assay in patients age 12 years and older
Inhaled Antibiotics for the Treatment of <i>Pseudomonas aeruginosa</i>		
Tobramycin (nebulized)	TOBI	Yes
Tobramycin (dry powder)	TIP	Yes
Aztreonam (nebulized)	Cayston	Yes
Polymyxin E (IV form given via nebulizer)	Colistin	No
Inhaled Treatments used as Mucolytics		
Dornase alpha (DNase)	Pulmozyme	Yes
Hypertonic Saline (7%)	----	No
Mannitol	Bronchitol	Yes
Oral Pancreatic Enzyme Supplementation		
Pancrease, pancrelipase	Creon, Pancreaze, Zenpep, Pancrelipase, Pertzye, Viokace, Ultresa	Yes
Inhaled Bronchodilators		
Albuterol sulfate	Pro-Air, Ventolin, Proventil, Albuterol, etc.	Approved as bronchodilator
Levalbuterol hydrochloride	Xopenex	Approved as bronchodilator
Oral azithromycin	Zithromax	No
Oral high-dose Ibuprofen	Motrin, Advil, etc.	No
Source: Approved labeling data from Drugs@FDA.gov (accessed on April 14, 2021)		

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

This sNDA proposes to expand the ETI indication to include the 6 to 11 year old age group. The Agency approved ETI tablets on October 21, 2019, for the treatment of CF in patients ≥ 12 years of age who at least on *F508del* mutation. On December 21, 2020, the Agency approved a supplement expanding the indication to include CF patients who have a mutation in the *CFTR* gene that is responsive based on in vitro data. The following table summarizes the approved indications for available CFTR modulators in the U.S.:

Table 3. Approved Pediatric Cystic Fibrosis (CF) Therapies Targeting the Cause of CF

Drug	CF Indication	Age / Approval date
IVA (Kalydeco®) NDAs 207925, 203188	One mutation in the <i>CFTR</i> gene that is responsive to ivacaftor potentiation based on clinical and/or in vitro assay ^a	≥ 6 yr.: 1/31/2012 2 to 6 yr.: 2/8/2017 12 m to 2 yr.: 8/15/2018 6 to 12 m: 4/29/2019 4 to 6 m: 9/24/2020
TEZ/IVA (Symdeko®) NDA 210491	<i>F508del</i> homozygous mutations and one mutation in the <i>CFTR</i> gene that is responsive to ivacaftor potentiation based on clinical and/or in vitro assay ^a	≥ 12 yr.: 2/12/2018 6 to 11 yr.: 6/21/2019
LUM/IVA (Orkambi®) NDA 206038	Homozygous <i>F508del</i> mutation	≥ 12 yr.: 7/2/2015 6 to 11 yr.: 9/28/2016
ETI (Trikafta®) NDA 217223	At least one <i>F508del</i> mutation or have a mutation in the <i>CFTR</i> gene that is responsive based on in vitro data ^a	≥ 12 yr.: 10/21/2019
m:months, yr.: years ^a See respective Prescribing Information for list of eligible mutations.		

3.2. Summary of Presubmission/Submission Regulatory Activity

Prior to submission of this sNDA, ETI was the subject of multiple regulatory proceedings. ELX and the ETI combination were developed under Investigational New Drug (IND) 132,547, which was opened on December 12, 2016. The Agency granted Fast Track Designation on February 8, 2017, Breakthrough Therapy Designation on May 15, 2018, and Orphan Drug Designation (ODD 18-6476)

on August 29, 2018. The Agency approved ETI on October 21, 2019 for the treatment of CF in patients 12 years of age and older with at least one *F508del* mutation. This approval was based on the demonstration of efficacy in two phase 3 efficacy/safety trials. On December 21, 2020, the Agency approved an expanded indication to include CF patients who have a mutation in the *CFTR* gene that is responsive based on in vitro data. This approval was based on results from in vitro assay studies.

There were no meetings to specifically discuss the development program for the 6 to 11 year old population. However, when the Applicant submitted the protocol for the PK/safety study included in this sNDA to IND 132547 (i.e. Trial 106), the Agency reviewed the protocol (see clinical review by Dr. Sarah Zaidi, dated 11/28/2018 under IND 132547).

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

4.1. Office of Scientific Investigations (OSI)

Due to the Agency's experience with the Applicant, including the recent approval of ETI (Trikafta), TEZ/IVA (Symdeko®) and the quality of the datasets as judged by the clinical and statistical review teams, and the unmet medical need for the rare, life-threatening disease, the multidisciplinary review team determined that an Office of Scientific Investigations audit was unnecessary for this submission. The small number of patients at each site made it unlikely that issues at any one site would substantially impact the efficacy or safety findings. In addition, the Division of New Drug Study Integrity within the Office of Study Integrity and Surveillance (OSIS) determined that inspections are not warranted at this time for the sites (b) (4) as OSIS inspected the analytical site in (b) (4) which falls within the surveillance interval.

4.2. Product Quality

This supplement is recommended for approval from the Chemistry, Manufacturing and Controls (CMC) perspective.

The ETI 50/25/37.5 mg drug product is a fixed dose combination (FDC) of the active ingredients ELX, TEZ, and IVA. (b) (4)

The ETI 50/25/37.5 mg core tablet is a weight multiple of the ETI 100/50/75 mg tablet. Both strengths are prepared from a common blend and use the same film coating components with minor differences in levels of colorants. All excipients used in the ETI 50/25/37.5 mg tablet have been previously used in formulations for pediatric populations, such as the Symdeko tablet. The ETI 50/25/37.5 mg tablet is manufactured using (b) (4) which is of similar or smaller size compared to other commercial products in this patient population, such as the Symdeko tablet.

The stability data show that the ETI 50/25/37.5 mg tablets are stable when packaged in the intended container closure system under all storage conditions. The stability data support proposed 24 months expiry.

Overall Manufacturing Inspection Recommendation is “APPROVE” (dated January 27, 2021).

CMC information provided for the ETI 50/25/37.5 mg tablet is adequate.

4.3. Clinical Microbiology

Not applicable.

4.4. Devices and Companion Diagnostic Issues

Not applicable.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

Vertex submitted the current efficacy supplement for Trikafta (elexacaftor/tezacaftor/ivacaftor) to extend treatment to CF subjects, 6 through 11 years of age with at least one F508del mutation in the CFTR gene or a mutation in the CFTR gene that is responsive based on in vitro data.

No new nonclinical studies were submitted in the current efficacy supplement; however, a decision was made to review the juvenile animal studies with elexacaftor and tezacaftor that had been submitted earlier. These juvenile animal studies are not pivotal to the pediatric age group under consideration (i.e., 6 through 11 years of age), which are generally covered by the standard toxicology program that was reviewed with the initial NDA submission. The juvenile rat studies were initiated on Postnatal Day (PND) 7 that corresponds to an infant at birth or PND 21 that corresponds to a 2- to 3-year old child. Pediatric patients represent a population different from adults when considering the rapid growth and postnatal development of several organ systems. Lung development in the juvenile rat parallels lung development in a child over the first 1 to 2 years of life (e.g., increases in alveolization and surface area that occur in this period). Potential concerns of neuropsychiatric AEs with the CFTR modulators have been reported in the literature and AE reporting, which is discussed below. Central nervous system (CNS) toxicity was evident in the juvenile rat toxicology studies with tezacaftor.

Elexacaftor (ELX)

The general toxicological profile of ELX was characterized in adult rats up to 26 weeks and adult dogs up to 39 weeks. These studies were previously reviewed under NDA 212273. The doses were 0, 7.5, 15, 40, and 75 mg/kg/day in males and 0, 4, 7.5, 15 and 30 mg/kg/day in females in rats and 0, 2.5, 6 or 14 mg/kg/day in dogs. In the 26-week study with adult rats, multiple deaths/euthanasia were noted in males at doses ≥ 40 mg/kg/day and females at 30 mg/kg/day with the findings of decreased food intake leading to lower body weight and declining clinical condition that were attributed to erosion of the glandular mucosa of the stomach. The No-Adverse-Effect-Level (NOAEL) was identified at 15 mg/kg/day in adult rats with corresponding AUC values that were 4 (males) and 12 (females) times the maximum recommended human dose (MRHD). In the 39-week study in adult dogs, test item-related microscopic changes were noted at 14 mg/kg/day that included hepatocellular hypertrophy, epithelium vacuolation in gallbladder, and testicular seminiferous tubule atrophy/degeneration. The testicular changes were not fully reversible and considered adverse. The NOAEL was identified at 6 mg/kg/day with a corresponding AUC value that was 6 times the maximum recommended human dose.

In the juvenile toxicology study, male and female rats received ELX from PNDs 7 to 70. Male rats received ELX at oral doses of 0, 7.5, 15, or 30 mg/kg/day. Female rats received ELX at oral doses of 0, 5, 7.5, or 15 mg/kg/day. Increases of mean TBIL concentration were observed in males of the HD group and in females of the mid-dose (MD) and high dose (HD) groups. Increases of mean ALT were observed in males and females in the HD group. Decreases of mean cholesterol concentration were observed in males and females in the HD group. There were no corresponding histopathological findings observed in the liver. Increases of mean CK activities were observed in males and females in the HD group. Mean ages and body weights for attainment of balanopreputial separation or vaginal patency were unaffected by ELX. There was no evidence of histopathological findings in the stomach as observed in adult rats or testes as observed in adult dogs. The NOAELs were identified at 30 mg/kg/day (AUC, 694 h•µg/mL) for males and 15 mg/kg/day (AUC, 976 h•µg/mL) for females. The AUC values of ELX were at least 4 times the ELX exposure at the maximum recommended dose of 200 mg in children 6 through 11 years of age. The AUCs of the metabolite M23-445 were 40.1 and 81.5 h•µg/mL for males and females, respectively. These AUC values were at least 0.4 times the M23-445 exposure at the maximum recommended dose of 200 mg in children 6 through 11 years of age.

Tezacaftor (TEZ)

The general toxicological profile of TEZ was characterized in studies with adult rats up to 6 months and adult dogs up to 1 year. These studies were previously reviewed under NDA 210491. Doses up to 100 mg/kg/day in rats and 200 mg/kg/day in dogs were evaluated. The major consistent finding was dilated terminal lymphatics of minimal to mild severity in the villi of the jejunum and ileum of males and females in both rats and dogs. There were no significant effects on the limited assessments of blood levels of absorbed nutrients (total protein, glucose, lipids, cholesterol, electrolytes), and no gastrointestinal pathology or signs of adverse function. The mechanism for dilated lymphatic terminals and its associated persistence following discontinuation of treatment was unknown. This finding was not associated with any detrimental health or nutritional effects in initially healthy rats or dogs and is currently considered a non-adverse finding.

TEZ was characterized in juvenile rats during PND 7-35, PND 14-35, PND 14-42, PND 21-35, and PND 21-49. The doses were 0, 10, 20, 30, 60, and 100 mg/kg/day. When administered starting at PND 7 (the equivalent of a human newborn) at doses of 10 to 100 mg/kg/day, multiple deaths/euthanasia, lower body weight, and adverse clinical signs including convulsions, hypoactivity, repetitive movement of the mouth, head tilt, small stature, and cool and/or thin body were observed at doses ≥30 mg/kg/day. When administered starting at postnatal day 21 (the equivalent of a human child, 2-3 years of age) at doses of 30 to 100 mg/kg/day, multiple deaths/euthanasia and convulsions occurred at a dose of 100 mg/kg/day and lower body weights occurred at doses ≥60 mg/kg/day, which were considered adverse. The effects on body weight and adverse clinical signs in juvenile rats were dose related

and generally more severe when administration was initiated earlier in the postnatal period. These adverse clinical signs including convulsions were observed at exposures that were at least 65% of the clinical exposure at the maximum recommended human dose of 100 mg daily in children 6 through 11 years of age as shown in Table 4.

Table 4. Convulsion in juvenile rats and exposure ratios to children 6-12

Juvenile Rat Studies	Doses, mg/kg/day	TEZ+ Metabolite, M1-TEZ,			Children 6-12, 100 mg		Children 6-12, 50 mg		Reference
		Adverse clinical signs/convulsion	C _{max} , µg/mL	AUC, µg*hr/mL	Ratio to C _{max} ^a	Ratio to AUC ^b	Ratio to C _{max} ^a	Ratio to AUC ^b	
					20.07 µg/mL	323 µg*hr/mL	14.18 µg/mL	220 µg*hr/mL	
PNDs 7-35	10 (NOAEL)	No	3.76	57.5	0.19	0.18	0.27	0.26	VX-661-TX-037
	30	Yes	11.35	208.9	0.57	0.65	0.80	0.95	
	60	Yes	21	447.8	1.05	1.39	1.48	2.04	
	100	Yes	28	641.3	1.40	1.99	1.97	2.92	
PNDs 21-35	30 (NOAEL)	No	10.01	141.7	0.50	0.44	0.71	0.64	VX-661-TX-069
	60	No	19.95	291.6	0.99	0.90	1.41	1.33	
	100	Yes	34.06	500	1.70	1.55	2.40	2.27	

^aClinical C_{max} Sources: Study 106 CSR/Table 14.4.1.4 and Table 14.4.1.6

^bClinical AUC Sources: Report Q075/Tables 7 and 8, Report Q076/Tables 7, 19, and 31;

In the Good Laboratory Practice (GLP) dose range-finding study in juvenile rats with doses of 0, 10, 30, 60, and 100 mg/kg/day administered from PND 7 to PND 35, multiple deaths/euthanasia, lower body weight, and adverse clinical signs including clonic convulsions, hypoactivity, repetitive movement of the mouth, head tilt, small stature, and cool and/or thin body were observed in both males and females at doses of 30, 60, and 100 mg/kg/day. All animals in the 30, 60, and 100 mg/kg/day groups were euthanized on PND 14-16, PND 10-11, and PND 9-10, respectively, due to adverse clonic convulsions and lower body weights. Lower body weight gains were observed in both males and females at doses ≥30 mg/kg/day. Histopathologic findings included decreases in lymphocytes in the spleen with higher incidences in the drug treated groups and minimal to mild hematopoiesis in the liver in the drug treated groups. The NOAEL from PND7 to PND 35 was identified as 10 mg/kg/day (AUC, 27.8 h•µg/mL) in juvenile rats. The AUC of metabolite M1-661 was 29.4 h•µg/mL.

In the GLP dose range-finding study in juvenile rats with doses of 0, 30, 60, and 100 mg/kg/day administered from PND 21 to PND 35, multiple deaths/euthanasia and convulsion were observed in both males and females at dose of 100 mg/kg/day. Lower body weight gain was observed in both males and females at doses ≥ 60 mg/kg/day. The NOAEL was identified as 30 mg/kg/day (AUC, 91.7 h• μ g/mL) during PND 21-35. The AUC of metabolite M1-661 was 79.1 h• μ g/mL.

In the GLP dose range-finding study in juvenile rats with doses of 0, 20, and 30 mg/kg/day administered from PND 14 to PND 35, no adverse findings were observed. Body weight gain was affected. The NOAELs was identified as 30 mg/kg/day (AUC, 90.3 h• μ g/mL) from PND 14-35. The AUC of metabolites M1-661 was 68.0 h• μ g/mL.

In the definitive GLP study, juvenile rats received oral doses of 0, 20, and 30 mg/kg/day from PND 14 to PND 42 or 0, 30, 30 (+10 mg/kg/day IVA), and 60 mg/kg/day from PND 21-49. No treatment-related deaths or adverse clinical signs were observed. For PND 14-42 and PND 21-49, body weights gains for male and female rats receiving doses up to 30 mg/kg/day were unaffected. However, for PND 21-49, body weight gain for males at 60 mg/kg/day was reduced to 89.5% of the control. Body weight gain was unaffected for females at 60 mg/kg/day. No adverse findings were identified in juvenile rats administered with the combination of 30 mg/kg/day TEZ and 10 mg/kg/day IVA. The NOAELs of TEZ were identified as 30 mg/kg/day (AUC₀₋₂₄: 107.8 h• μ g/mL) from PND 14-42 and 30 mg/kg/day (AUC₀₋₂₄: 106 h• μ g/mL) in juvenile rats from PND 21-49. In juvenile rats from PND 14-42, the AUC₀₋₂₄ of metabolites M1-661 and M2-661 were 47.4 h• μ g/mL and 4.35 h• μ g/mL, respectively. In juvenile rats from PND 21-35, the AUC₀₋₂₄ of metabolites M1-661 and M2-661 were 51.6 h• μ g/mL and 3.87 h• μ g/mL, respectively.

Increased brain levels of TEZ and metabolites

In a juvenile toxicokinetic (TK) study, female rats received TEZ at oral doses of 0 and 30 mg/kg/day for 3 days during PND 7–9, PND 14–16, PND 21–23, or PND 35–37. No treatment-related deaths or adverse clinical signs were observed. Plasma exposures to TEZ, M1-TEZ, and M2-TEZ were 2-3 fold higher in juvenile female rats on PND 9 and 16 as compared to PND 23 and 37. Brain exposures to TEZ, M1-TEZ, and M2-TEZ were much higher (18-24 fold) in juvenile female rats on PND 9 and 16 as compared to PND 23 and 37. Plasma exposures for M1-TEZ and M2-TEZ were approximately 36% to 100% and 2% to 10% of TEZ exposures, respectively. Brain tissue exposures of M1-TEZ and M2-TEZ were approximately 385% to 1190% and 36% to 73% of TEZ exposures, respectively. Increased brain exposures to TEZ and M1-TEZ were probably responsible for the CNS toxicity observed in juvenile rat studies initiated on PNDs 7 and 14.

Mechanism for high brain levels of TEZ and CNS-related toxicities

The increased brain levels of TEZ and its metabolite in the younger juvenile rats (treatment starting on PND 7 or PND 14) may be explained by the lower levels of the efflux transporter protein, P-glycoprotein (P-gp), in the brains of younger juvenile rats^{5,6}. TEZ and M1-661 are both substrates for P-gp. Toxicity observed in juvenile rats appeared to correlate to the developmental stage of the blood brain barrier in terms of low P-gp activity. The lower activity of P-gp in younger juvenile pups would lead to higher brain levels of TEZ, M1-661, and M2-661. The blood-brain barrier (BBB) in terms of levels of P-gp activity in rats is not fully developed until approximately PND 21 to PND 35, whereas in humans, the BBB in term of levels of G-gp activity reaches adult levels by approximately 3-6 months of age as measured by P-gp expression and function⁷⁸.

Table 5. Brain P-gp activity comparison in rats and humans

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⁵ Nicolas JM, de Lange ECM. Mind the Gaps: Ontogeny of Human Brain P-gp and Its Impact on Drug Toxicity. AAPS J. 2019; 21(4): 67.

⁶ C. Joakim Ek, Annamae Wong, Shane A. Liddelow, Pia A. Johansson, Katarzyna M. Dziegielewska, Norman R. Saunders. Efflux mechanisms at the developing brain barriers: ABC transporters in the fetal and postnatal rat. Toxicology Letters, 2010; 197: 51-59.

⁷ Jessica Lam, Stephanie Baello, Majid Iqbal, Lauren E. Kelly, Patrick T. Shannon, David Chitayat, Stephen G. Matthews, Gideon Korenff1. The ontogeny of P-glycoprotein in the developing human blood–brain barrier: implication for opioid toxicity in neonates. Pediatric Research, 2015; 78: 417-421.

⁸ Schmitt G., Parrott N., Prinssen E., Barrow P. The great barrier belief: The blood–brain barrier and considerations for juvenile toxicity studies. Reprod. Toxicol. 2017; 72: 129–135.

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Table 1. Effect of Age on Various Potential Readouts of Human Brain P-gp Activity

Species	Experimental approach	N	Age ^a	Conclusion
Human	Protein expression of brain P-gp by immunohistochemistry of post-mortem human brain cortex samples (13)	9	22–26 weeks ^b	Positive P-gp immunostaining of microvessel endothelial cells from 22 to 26 weeks gestation (brainstem, hindbrain, and thalamus) and from 27 to 32 weeks gestation (other regions of the forebrain). Lower signal at birth than in adults.
		10	27–32 weeks ^b	
		9	33–42 weeks ^b	
		3	adults	
	Protein expression of brain P-gp by immunohistochemistry of post-mortem human brain cortex samples (14)	8	0–3 months	Brain P-gp expression mature at 3–6 months of age
		7	3–6 months	
		8	54 ± 7 years	
	VCR concentration in CSF samples (15)	17	2.5–14 years	Brain P-gp function mature at ≤ 2.5 years
	Meta-analysis of CNS toxicity with loperamide (16)	1788	1 month–12 years	Increased frequency of CNS side effects with loperamide in children aged < 3 years vs older children or placebo
		146	5 months–18 years	Regression analysis identified age < 6 years as a risk factor for CNS side effects with CsA
Rat ^c	Brain distribution of oseltamivir, brain P-gp protein and mRNA levels (18)	na	3–42 days	Brain P-gp expression and function mature at 21 days
	Brain PET imaging with [¹¹ C]-oseltamivir (19)	na	7–44 days	Brain P-gp function mature at 21–24 days
	Brain distribution of digoxin, brain P-gp mRNA levels (20)	na	14–56 days	Brain P-gp expression and function mature at 21 days
		na	9 months–7 years	Brain P-gp function not fully mature in infant (9 months) or adolescent (24–27 months) monkeys
Monkey ^c	Brain PET imaging with [¹¹ C]-verapamil (21)	na	9 months–7 years	Brain P-gp function not fully mature in infant (9 months) or adolescent (24–27 months) monkeys
	Protein expression of brain P-gp levels by LC-MS/MS (22)	na	20-week fetus–50 years	Brain P-gp expression mature at 3–6 months

CNS central nervous system, CsA cyclosporine A, CSF cerebrospinal fluid, LC-MS/MS liquid chromatography-tandem mass spectrometry, mRNA messenger ribonucleic acid, na not applicable.

PET positron emission tomography, P-gp P-glycoprotein, VCR vincristine

^a Unless otherwise stated, postnatal age

^b Gestational age

^c 21 days of rat age reported to correspond to around 1–2 years of human age; 9 months of Rhesus monkey age reported to correspond to around 4 years of human age (33,34)

(Excerpted from Nicolas JM, de Lange ECM. Mind the Gaps: Ontogeny of Human Brain P-gp and Its Impact on Drug Toxicity. AAPS J. 2019; 21(4): 67.)

Ek et al. (Toxicology Letters 197 (2010): 51–59) used qPCR and immunocytochemistry to determine gene expression and localization of the four main barrier ABC-transporters (P-gp/ABCB1, MRP1/ABCC1, MRP4/ABCC4, and BCRP/ABCG2) in the fetal and neonatal rat brain cerebral blood vessels (site of blood–brain barrier) and choroid plexus (site of blood–CSF barrier). The study showed that the ABC transporters localize to the brain barriers even at early fetal stages and that P-gp expression in the forebrain and brainstem was the only transporter that was noted as being lower in the fetus; however, levels in the Lateral and 4th choroid plexus were comparable to adult levels. Levels of MRP1 and MRP4 were low in the Lateral and 4th choroid plexus. The other transporters were expressed at comparable levels in fetal and adult brains suggesting direct neuroprotection of the brain. Brain P-gp levels by PND 21 were approximately comparable to adult levels.

Figure 1. Forebrain/Brainstem

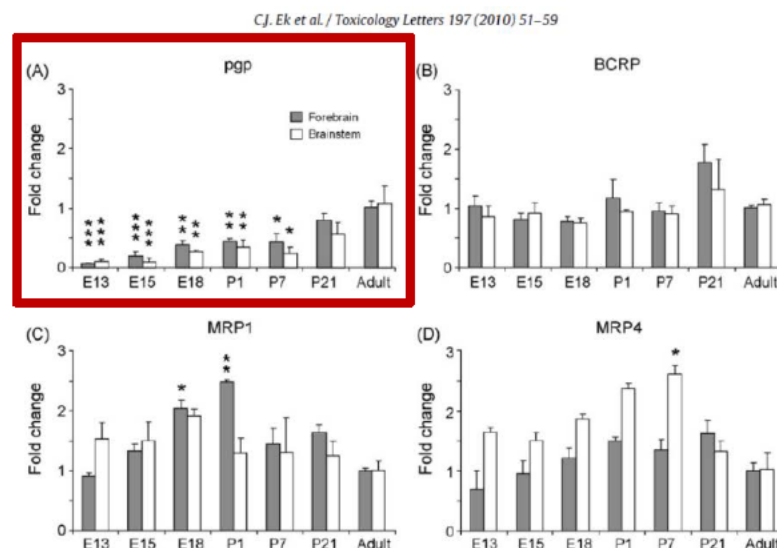
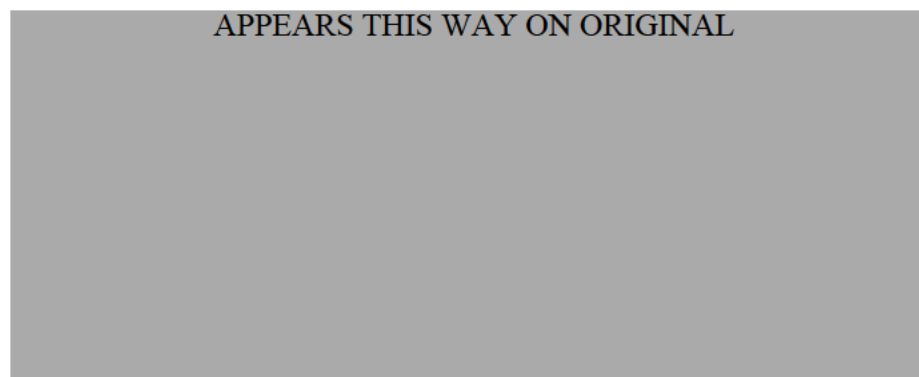


Fig. 1. Gene expression of pgp (A), BCRP (B), MRP1 (C) and MRP4 (D) in the rat forebrain and brainstem at different developmental stages between E13 and adulthood. Gene expression is calculated as fold change at each developmental age compared to the average adult value. Note that the tissue did not contain any choroid plexus since this was removed. Pgp expression progressively increased during development (about 10–12-fold) in both the forebrain and brainstem. BCRP showed similar gene expression at all ages and in both brain regions. MRP1 showed similar gene expression during development except at E18 and P1 when there was a 2–2.5-fold higher expression in the forebrain compared to the adult ($p < 0.05$). Likewise, MRP4 showed similar gene expression during development except at P7 when there is an almost 3-fold higher expression in the brainstem ($p < 0.05$). Thus each transporter shows a developmental peak, but the peak occurs at a different age. Data expressed as mean $\pm$ SEM, $n = 3$ at each age. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Excerpted from Ek *et al.*, Toxicology Letters 197 (2010): 51–59

Figure 2. Lateral Choroid Plexus/4th Choroid Plexus



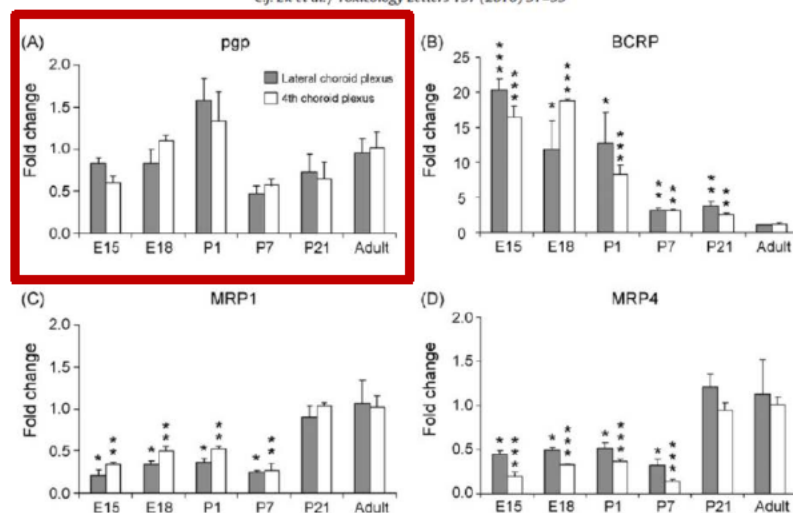


Fig. 2. Gene expression of pgp (A), BCRP (B), MRP1 (C) and MRP4 (D) in the rat lateral and 4th ventricular choroid plexus at different developmental stages from E15 to adulthood. The gene expression is calculated as fold change at each developmental age compared to the average adult value. Pgp did not show any statistically significant changes during development. BCRP was strikingly high at E15 (15–20-fold higher compared to adult) and then gradually decreased during development. The developmental pattern was similar for the lateral and 4th choroid plexuses and the expression levels of BCRP were statistically significantly higher than adult at all developmental ages in the 4th ventricular choroid plexus but only at E15 in the lateral ventricular plexus. MRP1 and MRP4 showed similar patterns of expression during development in the two different choroid plexuses. There was about 2–5-fold lower expression levels at developmental ages E15–P7 compared to adult whereas P21 showed similar expression to the adult. The developmental expression profile for the two plexuses appeared similar for both MRP1 and MRP4. Data are expressed as mean $\pm$ SEM, $n = 3$ at each age. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Excerpted from Ek *et al.*, Toxicology Letters 197 (2010): 51–59

High brain levels of TEZ and both metabolites in younger rats (dosed from PND 7–9 and PND 14–16) might explain the observed toxicity of TEZ in the juvenile rat dose range finding study (VX-661-TX-037), with initiation of dosing on PND 7, that included clonic convulsions and other CNS-related clinical observations. It was also noted that the M1-661 levels in brain tissue on PND 7–9, 14–16, 21–23, and 35–37 were significantly higher (3.8 to 11.9-fold) than TEZ level in brain tissues, while the plasma levels of these two compounds were relatively comparable (< 2-fold difference). $P_{app(A-B)}$ of TEZ and M1-TEZ were 0.3 and 7.6 cm/sec $\times 10^6$, respectively. Efflux Ratios of VX-661 and M1-TEZ were 31.5 and 4.18, respectively. P-gp was more efficient in blocking VX-661 than M1-TEZ in the BBB. These data might explain why significantly higher levels of M1-TEZ were observed in brain tissues. Brain P-gp activity appears to only be a safety concern for children less than 1 year of age and is unlikely to be a safety concern for children 6 through 11 years of age.

Neuropsychiatric events have been reported for the market-available CFTR modulators. Dagenais et al. (Journal of Clinical Medicine 2021, 10, 23; <https://dx.doi.org/10.3390/jcm10010023>) conducted a systematic review to summarize real-world Adverse Events (AEs) reported for market-available CFTR modulators (i.e., ivacaftor (IVA), lumacaftor/ivacaftor (LUM/IVA), tezacaftor/ivacaftor (TEZ/IVA), and elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA)). A signal for mental health and neurocognitive AEs was identified with all 4 CFTR modulators. Limited data were available regarding real-world AEs with TEZ/IVA; however, notable neuropsychiatric AEs were reported. In a cohort of 44 adults, 5 (11%) experienced neuropsychiatric AEs: out of body experience and visual hallucination; depersonalization and “brain fog”; severe migraine; and sleep pattern disturbance, which occurred in 2 individuals. The two individuals with sleep pattern disturbance remained on TEZ/IVA, but the other three individuals changed back to LUM/IVA and had resolution of symptoms thereafter. Another cohort study reported discontinuation due to unspecified mental health changes; the frequency was not reported. The results of juvenile rat studies with tezacaftor raise concerns for potential neuropsychiatric AEs. It is unclear if variations in brain levels of p-glycoprotein might be involved in these potential neuropsychiatric AEs.

Table 6. Safety Margins for ELX

Juvenile Rat Studies	NOAEL Dose (mg/kg/wk)	AUC μg*hr/mL	Safety margins for clinical dose		
			PND70		
			Adult, 200 mg 163.0	Children 6-12, 200 mg 195.0	Children 6-12, 100 mg 116.0
PNDs 7-70	M: 30 mg	694	4.26	3.56	5.98
	F: 15 mg	976	5.99	5.01	8.41

^cClinical AUC Sources: Report Q075/Tables 7 and 8, Report Q076/Tables 7, 19, and 31;

Table 7. Safety Margins for Metabolite, M23-ELX

Juvenile Rat Studies	NOAEL Dose (mg/kg/wk)	AUC μg*hr/mL	Safety margins for clinical dose		
			PND70		
			Adult, 200 mg 65.7	Children 6-12, 200 mg 104.0	Children 6-12, 100 mg 45.4

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PNDs 7-70	M: 30 mg	40.1	0.61	0.39	0.88
	F: 15 mg	81.5	1.24	0.78	1.80

^cClinical AUC Sources: Report Q075/Tables 7 and 8, Report Q076/Tables 7, 19, and 31;

Table 8. Safety Margins for TEZ + Metabolite, M1-TEZ

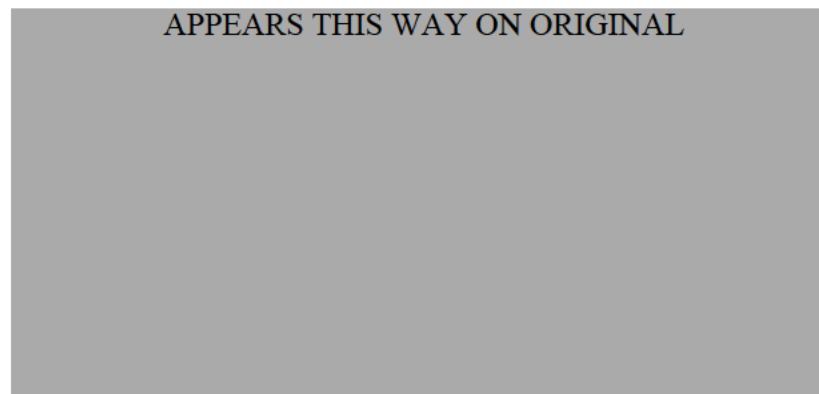
Juvenile Rat Studies	NOAEL Dose (mg/kg)	AUC (TEZ+Metabolite, M1-TEZ), $\mu\text{g} \cdot \text{hr}/\text{mL}$						Safety margins relative to 1st time point (PNDs 7, 14, or 21)			Safety margins relative to 2nd time point (PNDs 35, 42, or 49)		
		PND 7 ^a	PND 14	PND 21 ^b	PND 35	PND 42	PND 49	Adult, 100 mg ^c	Children 6-12, 100 mg ^c	Children 6-12, 50 mg ^c	Adult, 100 mg ^c	Children 6-12, 100 mg ^c	Children 6-12, 50 mg ^c
								220.4	323.0	220.0	220.4	323.0	220.0
PND 7-35	10	57.5			57.2			0.3	0.2	0.3	0.3	0.2	0.3
PND 14-35	30		232.6		158.3			1.1	0.7	1.1	0.7	0.5	0.7
PND 14-42	30		231.4			182.5		1.0	0.7	1.1	0.8	0.6	0.8
PND 21-35	30			141.7	170.8			0.6	0.4	0.6	0.8	0.5	0.8
PND 21-49	30			163			204	0.7	0.5	0.7	0.9	0.6	0.9
PND 21-49, +IVA	30			185.9			227.5	0.8	0.6	0.8	1.0	0.7	1.0

^aPND7 in rats is the equivalent of a human newborn;

^bPND 21 in rats is the equivalent of a human 2-3 years of age.

^cClinical AUC Sources: Report Q075/Tables 7 and 8, Report Q076/Tables 7, 19, and 31;

Table 9. Safety Margins for TEZ



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Juvenile Rat Studies	NOAEL Dose (mg/kg)	AUC, $\mu\text{g}\cdot\text{hr}/\text{mL}$						Safety margins relative to 1st time point (PNDs 7, 14, or 21)			Safety margins relative to 2nd time point (PNDs 35, 42, or 49)		
		PND 7	PND 14	PND 21 (weaning age)	PND 35	PND 42	PND 49	Adult, 100 mg	Children 6-12, 100 mg	Children 6-12, 50 mg	Adult, 100 mg	Children 6-12, 100 mg	Children 6-12, 50 mg
								86.4	103.0	67.0	86.4	103.0	67.0
PND 7-35	10	37.1			27.8			0.4	0.4	0.6	0.3	0.3	0.4
PND 14-35	30		186		90.3			2.2	1.8	2.8	1.0	0.9	1.3
PND 14-42	30		184			107.8		2.1	1.8	2.7	1.2	1.0	1.6
PND 21-35	30			90.1	91.7			1.0	0.9	1.3	1.1	0.9	1.4
PND 21-49	30			106			117.3	1.2	1.0	1.6	1.4	1.1	1.8
PND 21-49, +IVA	30			129.5			121.8	1.5	1.3	1.9	1.4	1.2	1.8

Table 10. Safety Margins for Metabolite, M1-TEZ

Juvenile Rat Studies	NOAEL Dose (mg/kg)	AUC, $\mu\text{g}\cdot\text{hr}/\text{mL}$						Safety margins relative to 1st time point (PNDs 7, 14, or 21)			Safety margins relative to 2nd time point (PNDs 35, 42, or 49)		
		PND 7	PND 14	PND 21 (weaning age)	PND 35	PND 42	PND 49	Adult, 100 mg	Children 6-12, 100 mg	Children 6-12, 50 mg	Adult, 100 mg	Children 6-12, 100 mg	Children 6-12, 50 mg
								134.0	220.0	153.0	134.0	220.0	153.0
PND 7-35	10	20.4			29.4			0.2	0.1	0.1	0.2	0.1	0.2
PND 14-35	30		46.6		68			0.3	0.2	0.3	0.5	0.3	0.4
PND 14-42	30		47.4			74.7		0.4	0.2	0.3	0.6	0.3	0.5
PND 21-35	30			51.6	79.1			0.4	0.2	0.3	0.6	0.4	0.5
PND 21-49	30			57			86.7	0.4	0.3	0.4	0.6	0.4	0.6
PND 21-49, +IVA	30			56.4			105.7	0.4	0.3	0.4	0.8	0.5	0.7

Table 11. Safety Margins for IVA

Juvenile Rat Studies	NOAEL Dose	AUC	Safety margins for clinical dose	Safety margins for clinical dose
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	(mg/kg/wk)	μg*hr/mL		PND7-21			PND35-49		
		PND 21	PND 49	Adult, 300 mg	Children 6-12, 300 mg	Children 6-12, 150 mg	Adult, 300 mg	Children 6-12, 300 mg	Children 6-12, 150 mg
				13.1	17.5	9.8	13.1	17.5	9.8
PND 21-49, +IVA	10	34.6	32.2	2.64	1.98	3.54	2.46	1.84	3.29

^cClinical AUC Sources: Report Q075/Tables 7 and 8, Report Q076/Tables 7, 19, and 31;

5.2. Referenced NDAs, BLAs, DMFs

Multi-Discipline Review of NDA 212273, Trikafta (elexacaftor/tezacaftor/ivacaftor) tablets dated October 21, 2018
Pharmacology & Toxicology Review of NDA 210491, Symdeko (ivacaftor, tezacaftor) tablets dated January 29, 2018

5.3. Pharmacology

Reviewed with the initial NDA submission

5.4. ADME/PK

Reviewed with the initial NDA submission

5.5. Toxicology

5.5.1. General Toxicology

Reviewed with the initial NDA submission

5.5.2. Genetic Toxicology

Reviewed with the initial NDA submission

5.5.3. Carcinogenicity

Reviewed with the initial NDA submission

5.5.4. Reproductive and Developmental Toxicology

Study Title: VX-445: An Oral (Gavage) Juvenile Toxicity and Toxicokinetics Study in Postnatal Day 7 through Postnatal Day 70 Sprague Dawley Rats (Study report #: VX-445-TX-021)

Key Study Findings

- In a juvenile toxicology study, male and female rats received VX-445 from PND 7 to PND 70. Male rats received VX-445 at oral doses of 0 [0.5% methylcellulose (400 cP), 0.1% sodium lauryl sulfate, 0.01% simethicone], 7.5, 15, or 30 mg/kg/day. Female rats received VX-445 at oral doses of 0 [0.5% methylcellulose (400 cP), 0.1% sodium lauryl sulfate, 0.01% simethicone], 5, 7.5, or 15 mg/kg/day.
- Increases of mean total bilirubin (TBIL) concentrations were observed in males of the HD group (mean was 0.03 mg/dL versus control group mean of 0.0 mg/dL), and in females of the MD and HD groups (means were 0.04 and 0.10 mg/dL, respectively, versus control group mean of 0.01 mg/dL). Increases of mean ALT were observed in males and females in the HD group (1.15x and 2.13x, respectively). Decreases of mean cholesterol concentration were observed in males and females in the HD group (0.67x and 0.76x, respectively). There were no corresponding histopathological findings were observed in the liver. Increases of mean creatine kinase (CK) activities were observed in males and females in the HD group (1.21x and 1.34x, respectively).
- Mean ages and body weights at attainment of balanopreputial separation or vaginal patency were unaffected.
- No potential target organs of toxicity were identified.
- The NOAELs were identified as the HDs of 30 mg/kg/day (AUC_{0-24} , 694 h•µg/mL) for males and 15 mg/kg/day (AUC_{0-24} , 976 h•µg/mL) for females, respectively. The AUC_{0-24} for the major human metabolite (M23-445) of VX-445 in males and females were 40.1 and 81.5 h•µg/mL, respectively.

Table 12. Histopathology findings in juvenile rats from PND 7 to PND 70

NDA/BLA Multi-disciplinary Review and Evaluation {NDA 212273}
 {Trikafta (elexacaftor/tezacaftor/ivacaftor)}

Organ/Tissue	Time	Males				Females			
		0	7	15	30	0	5	7.5	15
EYES									
-fold/rosette, retina		1/10			3/10	0/10			1/10
Minimal		1			2	0			1
Mild		0			1	0			0
Kidneys	Term								
-basophilic tubules, focal/multifocal		2/10			5/10	0/10			0/10
Minimal		1			4	0			0
Moderate		1			1	0			0
-fibrosis, cortical, focal		0/10			1/10	0/10			0/10
Mild		0			1	0			0
Lung	Term								
-hemorrhage, focal/multifocal		0/10			3/10	1/10			0/10
Minimal		0			3	1			0
-infiltration, mixed cell		0/10			1/10	1/10			0/10
Minimal		0			1	1			0
Spleen	Term								
-fibrosis, capsular, focal		0/10			1/10	0/10			0/10
Mild		0			1	0			0
Thymus	Term								
-hemorrhage, focal/multifocal		4/10		1/1	4/10	1/10			6/10
Minimal		4		0	4	1			3
Moderate		0		1	0				
Mild		0		0	0	0			3

Table 13. Toxicokinetic Parameters of VX-445 in rats on PND 70

NDA/BLA Multi-disciplinary Review and Evaluation {NDA 212273}
{Trikafta (elexacaftor/tezacaftor/ivacaftor)}

Text Table 15
VX-445 Toxicokinetic Parameters on PND 70

Group	Dose (mg/kg/day)	C _{max} (µg/mL)	t _{max} (hr)	AUC _{0-24hr} (hr•µg/mL)
Males				
2	7.5	10.6	4	161
3	15	23.6	4	416
4	30	41.9	8.27	694
Females				
2	5	9.38	4	168
3	7.5	16.2	2	300
4	15	45.4	8	976

(Excerpted from the Sponsor's submission)

Table 14. Toxicokinetic Parameters of M23-445 (VRT-1654548) in rats on PND 70

Text Table 16
VRT-1654548 Toxicokinetic Parameters on PND 70

Group	VX-445 Dose (mg/kg/day)	C _{max} (µg/mL)	t _{max} (hr)	AUC _{0-24hr} (hr•µg/mL)
Males				
2	7.5	0.407	0	6.61
3	15	1.27	12	23.5
4	30	2.33	8.27	40.1
Females				
2	5	0.533	12	10.1
3	7.5	0.989	2	20.2
4	15	3.73	12	81.5

(Excerpted from the Sponsor's submission)

Study Title: VX-661: An Oral (Gavage) Dose Range-Finding Study in Juvenile Rats (Study report #: VX-661-TX-037)

Key Study Findings

- In a juvenile toxicology study, rats received VX-661 at oral doses of 0 [0.5% methylcellulose (400 cP), 0.5% sodium lauryl sulfate, 0.01% simethicone], 10, 30, 60 or 100 mg/kg/day from PND 7 to PND 35.

- VX-661 was not tolerated at doses ≥ 30 mg/kg/day as rats in these groups were found dead or euthanized in extremis from PND 7 to PND 16. Adverse clinical observations prior to death included clonic convulsions, hypoactivity, and/or cool body as well as body weight losses. Probable causes of death could not be determined for a large number of animals based on anatomic pathology findings.
- Surviving main study phase males and females that received doses ≥ 30 mg/kg/day were noted with clonic convulsions at the daily examinations and/or following dose administration (beginning as early as approximately 1 minute through 4 hours following dose administration) as well as other adverse CNS-related clinical observations (including hypoactivity, repetitive movement of the mouth, head tilt, small stature, and cool and/or thin body) noted as early as PND 9 (3rd dose). All animals that received doses of 30, 60, and 90 mg/kg/day were euthanized on PND 14-16, PND 10-11, and PND 9-10, respectively, due to test-article related adverse clonic convulsions and reduced body weights.
- Statistically significant ($p < 0.05$ or $p < 0.01$) decreases of mean body weights were observed in both males and females in the mid-low dose (MLD), mid-high dose (MHD), and high dose (HD) groups (MLD: 36.1% and 35.4%, MHD: 31.1% and 31.9%, and HD: 30.6% and 35.5%, respectively) compared to the control group (MLD: PND 7–16, MHD: PND 7–11, and HD: PND 7–10).
- Decreases in lymphocytes in the spleen were observed with higher incidences in the drug treated groups. Minimal to mild hematopoiesis in the liver were observed in the drug treated groups. No microscopic brain/CNS related findings were observed.
- The NOAEL of Tezacaftor was identified as the low dose (LD) of 10 mg/kg/day (AUC_{0-24} , 27800 h•ng/mL) in juvenile rats. The AUC_{0-24} of metabolites, VRT-0996107 (M1-661) and VRT-1189001 (M2-661), were 29400 and 1830 h•ng/mL, respectively.

Table 15. Mortality in the juvenile rats from PND 7-16

Mortality	Males, mg/kg/day					Females, mg/kg/day				
	0	10	30	60	100	0	10	30	60	100
Total affected animal	2/10	1/10	11/11	10/10	10/10	0/10	0/10	10/10	10/10	10/10
-found dead	2	1	3	1	0	0	0	4	2	1
-sent to necropsy in extremis	0	0	0	0	1	0	0	1	0	0

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-early termination	0	0	8	9	9	0	0	5	8	9
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Table 16. Behavior/CNS clinical signs in the juvenile rats from PND 9-16

Clinical Signs (Behavior/CNS)	Time	Males, mg/kg/day					Females, mg/kg/day				
		0	10	30	60	100	0	10	30	60	100
Total affected animal		0	0	8	3	7	0	0	5	4	8
-Convulsions, clonic	Daily exam	0/0	0/0	15/8*	2/2	0/0	0/0	0/0	7/5	4/4	0/0
	Post-dose (0-210 min)	0/0	0/0	0/0	1/1	4/4	0/0	0/0	0/0	2/2	6/6
	4 hours post-dosing	0/0	0/0	9/7	0/0	3/3	0/0	0/0	4/2	1/1	5/5
-Hypoactivity	Daily exam	0/0	0/0	7/7	0/0	0/0	0/0	0/0	3/3	0/0	0/0
	4 hours post-dosing	0/0	0/0	0/0	0/0	1/1	-	-	-	-	-
-Repetitive movement of mouth	4 hours post-dosing	0/0	0/0	1/1	0/0	0/0	-	-	-	-	-
-Head tilt	Daily exam	-	-	-	-	-	0/0	0/0	1/1	0/0	0/0

*Expressed as number of observations / number of animals affected.

Table 17. Changes of Body Weight in rats from PND 7 to PND 35

Body weight	Males, mg/kg/day					Females, mg/kg/day				
Parameter	0	10	30	60	100	0	10	30	60	100
BW, PND 7	16.3	16.2	16.5	15.6	16.2	15.2	16.2	16.3	16.1	15.5
BW, PND 10	24.5	24.1	22.7	20.6	17.0	22.8	24.1	22.5	20.3	14.7
BW, PND 11	28.0	27.7	24.8	19.3	-	26.0	27.7	24.8	17.7	-
BW, PND 16	41.8	40.0	26.7	-	-	40.4	40.0	26.1	-	-
BW, PND 35	162.7	158.7	-	-	-	133.9	141.0	-	-	-
Δ BW 7-10	8.2				0.8	7.6				-0.8

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Δ BW 7-11	11.7			3.7		10.8			1.6	
Δ BW 7-16	25.5		10.2			25.2		9.8		
Δ BW 7-35	146.4	142.5				118.7	124.8			
Absolute BW, % of control	100.0	97.5	63.9	68.9	69.4	100.0	105.3	64.6	68.1	64.5
BW Gain, % of control	100.0	97.3	40.0	31.6	9.8	100.0	105.1	38.9	14.8	-10.5

-Further evaluation of body weight data at 30, 60, and 100 mg/kg/day was precluded by early group termination.

Table 18. Histopathology in rats from PND 7 to PND 35

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{Trikafta (elexacaftor/tezacaftor/ivacaftor)}

Text Table 18
Summary Incidence and Severity of Selected Microscopic Findings

Tissue/finding Sex	Males					Females				
VX-661 Dose (mg/kg/day)	0	10	30	60	100	0	10	30	60	100
Nasopharynx Number examined:	9	10	11	10	10	10	10	10	10	10
Exudate, lumen										
Total number affected	(0)	(0)	(3)	(1)	(0)	(0)	(0)	(5)	(0)	(0)
Minimal	0	0	0	1	0	0	0	3	0	0
Mild	0	0	2	0	0	0	0	1	0	0
Moderate	0	0	0	0	0	0	0	0	0	0
Marked	0	0	1	0	0	0	0	1	0	0
Spleen Number examined:	9	10	10	10	10	10	10	10	10	10
Lymphocytes, decreased										
Total number affected	(1)	(1)	(9)	(10)	(10)	(0)	(0)	(9)	(9)	(10)
Minimal	0	0	0	0	0	0	0	0	0	0
Mild	0	1	3	0	3	0	0	4	4	1
Moderate	1	0	6	9	6	0	0	3	5	5
Marked	0	0	0	1	1	0	0	2	0	4
Thymus Number examined:	10	10	11	10	10	10	10	10	10	10
Lymphocytes, decreased										
Total number affected	(0)	(0)	(1)	(0)	(0)	(0)	(0)	(1)	(0)	(0)
Minimal	0	0	0	0	0	0	0	0	0	0
Mild	0	0	1	0	0	0	0	1	0	0

(Excerpted from the Sponsor's submission)

Table 19. Toxicokinetic Parameters of VX-661 in rats on PND 7 and 35

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{Trikafta (elexacaftor/tezacaftor/ivacaftor)}

Text Table 19
VX-661 Toxicokinetic Parameters on PND 7 and 35 following Oral Gavage Administration of 10, 30, 60, and 100 mg/kg/day to Juvenile Male and Female Rats

VX-661 Dose (mg/kg/day)	10	30	60	100
Males				
PND 7				
AUC _{0-24h} (hr*ng/mL)	35800	162000	382000	543000
C _{max} (ng/mL)	2890	8880	22600	28600
t _{max} (hr)	4.00	4.00	4.00	4.00
PND 35				
AUC _{0-24h} (hr*ng/mL)	20600	NA	NA	NA
C _{max} (ng/mL)	2490	NA	NA	NA
t _{max} (hr)	4.00	NA	NA	NA
Females				
PND 7				
AUC _{0-24h} (hr*ng/mL)	38500	163000	363000	553000
C _{max} (ng/mL)	2220	8550	19400	28400
t _{max} (hr)	4.00	12.0	4.00	12.0
PND 35				
AUC _{0-24h} (hr*ng/mL)	35000	NA	NA	NA
C _{max} (ng/mL)	3460	NA	NA	NA
t _{max} (hr)	4.00	NA	NA	NA
Combined				
PND 7				
AUC _{0-24h} (hr*ng/mL)	37100	162000	372000	548000
C _{max} (ng/mL)	2550	8530	21000	28000
t _{max} (hr)	4.00	4.00	4.00	8.00
PND 35				
AUC _{0-24h} (hr*ng/mL)	27800	NA	NA	NA
C _{max} (ng/mL)	2970	NA	NA	NA
t _{max} (hr)	4.00	NA	NA	NA

NA = Not applicable.

(Excerpted from the Sponsor's submission)

Table 20. Toxicokinetic Parameters of VRT-0996107 and VRT-1189001 in rats on PND 7 and 35

NDA/BLA Multi-disciplinary Review and Evaluation {NDA 212273}
{Trikafta (elexacaftor/tezacaftor/ivacaftor)}

Text Table 20

VRT-0996107 Toxicokinetic Parameters on PND 7 and 35 following Oral Gavage Administration of 10, 30, 60, and 100 mg/kg/day to Juvenile Male and Female Rats

VX-661 Dose (mg/kg/day)	10	30	60	100
Males				
PND 7				
AUC _{0-24h} (hr*ng/mL)	18900	46100	75200	94800
C _{max} (ng/mL)	1220	2780	4580	6640
t _{max} (hr)	24.0	24.0	24.0	24.0
PND 35				
AUC _{0-24h} (hr*ng/mL)	33900	NA	NA	NA
C _{max} (ng/mL)	2090	NA	NA	NA
t _{max} (hr)	8.00	NA	NA	NA
Females				
PND 7				
AUC _{0-24h} (hr*ng/mL)	21900	47800	76500	91800
C _{max} (ng/mL)	1210	2850	4750	6010
t _{max} (hr)	24.0	24.0	24.0	24.0
PND 35				
AUC _{0-24h} (hr*ng/mL)	24900	NA	NA	NA
C _{max} (ng/mL)	1430	NA	NA	NA
t _{max} (hr)	4.00	NA	NA	NA
Combined				
PND 7				
AUC _{0-24h} (hr*ng/mL)	20400	46900	75800	93300
C _{max} (ng/mL)	1210	2820	4670	6330
t _{max} (hr)	24.0	24.0	24.0	24.0
PND 35				
AUC _{0-24h} (hr*ng/mL)	29400	NA	NA	NA
C _{max} (ng/mL)	1690	NA	NA	NA
t _{max} (hr)	8.00	NA	NA	NA

NA = Not applicable.

(Excerpted from the Sponsor's submission)

NDA/BLA Multi-disciplinary Review and Evaluation {NDA 212273}
{Trikafta (elexacaftor/tezacaftor/ivacaftor)}

Text Table 21

VRT-1189001 | Toxicokinetic Parameters on PND 7 and 35 following Oral Gavage Administration of 10, 30, 60, and 100 mg/kg/day to Juvenile Male and Female Rats

VX-661 Dose (mg/kg/day)	10	30	60	100
Males				
PND 7				
AUC _{0-24h} (hr*ng/mL)	3300	5970	6480	6640
C _{max} (ng/mL)	324	531	535	625
t _{max} (hr)	24.0	24.0	24.0	24.0
PND 35				
AUC _{0-24h} (hr*ng/mL)	2490	NA	NA	NA
C _{max} (ng/mL)	138	NA	NA	NA
t _{max} (hr)	12.0	NA	NA	NA
Females				
PND 7				
AUC _{0-24h} (hr*ng/mL)	4120	5220	6770	7140
C _{max} (ng/mL)	343	479	630	716
t _{max} (hr)	24.0	24.0	24.0	24.0
PND 35				
AUC _{0-24h} (hr*ng/mL)	1170	NA	NA	NA
C _{max} (ng/mL)	66.5	NA	NA	NA
t _{max} (hr)	12.0	NA	NA	NA
Combined				
PND 7				
AUC _{0-24h} (hr*ng/mL)	3710	5600	6620	6890
C _{max} (ng/mL)	334	505	583	670
t _{max} (hr)	24.0	24.0	24.0	24.0
PND 35				
AUC _{0-24h} (hr*ng/mL)	1830	NA	NA	NA
C _{max} (ng/mL)	102	NA	NA	NA
t _{max} (hr)	12.0	NA	NA	NA

NA = Not applicable.

(Excerpted from the Sponsor's submission)

Study Title: VX-661: An Oral (Gavage) Pharmacokinetic and Toxicity Study in Juvenile Sprague Dawley Rats (Study report #: VX-661-TX-065)

Key Study Findings

- In a juvenile TK study, female rats received TEZ at oral doses of 0 [0.5% methylcellulose (400 cP), 0.5% sodium lauryl sulfate, 0.01% simethicone] or 30 mg/kg/day for 3 days from PND 7–9, PND 14–16, PND 21–23, or PND 35–37. Additionally, female rats received TEZ at oral doses of 0 [0.5% methylcellulose (400 cP), 0.5% sodium lauryl sulfate, 0.01% simethicone] or 60 mg/kg/day for 3 days during PND 7–9.
- No treatment-related deaths or adverse clinical signs were observed in female rats during the TK study.
- In the TK study, systemic exposure to TEZ, M1-TEZ, and M2-TEZ were higher (2-3 fold) in juvenile female rats on PND 9 and PND 16 as compared to PND 23 and 37. M1-TEZ plasma levels were approximately 36% to 100% of the parent TEZ levels, while M2-TEZ plasma levels were approximately 2% to 10% of the parent TEZ levels.
- Brain exposures to TEZ, M1-TEZ, and M2-TEZ were higher (18-24 fold) in juvenile female rats on PND 9 and PND 16 as compared to PND 23 and PND 37. M1-TEZ brain tissue levels were approximately 385% to 1190% of the parent TEZ levels, while M2-TEZ brain tissue levels were approximately 36% to 73% of the parent TEZ levels.
- Higher brain levels of TEZ and its two metabolites in younger rats (dosed from PND 7-9 or PND 14-16) might explain the observed toxicity of TEZ in juvenile rats from Study #VX-661-TX-037 with initiation of dosing on PND 7 that included clonic convulsions and other CNS-related clinical observations.

Study Design

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{Trikafta (elexacaftor/tezacaftor/ivacaftor)}

Text Table 3
Study Group Assignments

Group Number	Treatment	Dosing Duration	Dose Level (mg/kg/day)	Dose Volume (mL/kg)	Number of Animals	
					Main Study Phase	Toxicokinetic Phase
1	Control Article	PND 7–10	0	10	10	NA
2	Control Article	PND 7–9	0	10	NA	5
3	Control Article	PND 14–16	0	10	NA	5
4	Control Article	PND 21–23	0	10	NA	5
5	Control Article	PND 35–37	0	10	NA	5
6	VX-661	PND 7–10	60	10	10	NA
7	VX-661	PND 7–9	30	10	NA	20
8	VX-661	PND 14–16	30	10	NA	20
9	VX-661	PND 21–23	30	10	NA	20
10	VX-661	PND 35–37	30	10	NA	20

NA = Not applicable.

(Excerpted from the Sponsor's submission)

Table 21. Changes of Body Weight in Female Rats from PND 7 to PND 11

Body weight	Females, mg/kg/day	
Parameter	0	60
BW, PND 7	16.7	16.6
BW, PND 8	18.5	18.7
BW, PND 9	20.4	19.8
BW, PND 10	22.5	20.8
BW, PND 11	24.3	18.7*
Δ BW	7.6	2.1*
Absolute BW	100.0	80.0
% of control		
BW Gain	100.0	27.6
% of control		

Table 22. Histopathology findings

Text Table 12
Incidence of Microscopic Findings - Scheduled Necropsy

	Females	
	1	6
	0	60
	9	10
Group		
Dose (mg/kg/day)		
Number Animals Examined		
Nasal Level I (Number Examined)	9	10
Exudate, lumen	(0) ^a	(1)
Minimal	0	1
Nasal Level II (Number Examined)	9	10
Exudate, lumen	(0)	(3)
Minimal	0	3
Nasal Level III (Number Examined)	9	10
Exudate, lumen	(1)	(0)
Minimal	0	0
Mild	1	0
Nasal Level IV (Number Examined)	9	10
Exudate, lumen	(0)	(2)
Minimal	0	1
Moderate	0	1
Nasopharynx (Number Examined)	8	9
Exudate, lumen	(0)	(1)
Minimal	0	1

^a Numbers in parentheses represent the number of animals with the finding.
(Excerpted from the Sponsor's submission)

Table 23. Toxicokinetic Parameters of TEZ, M1-661, and M2-661 in plasma in rats on PND 9, 16, 23, and 37

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 {Trikafta (elexacaftor/tezacaftor/ivacaftor)}

Text Table 13

VX-661, VRT-0996107, and VRT-1189001 Mean TK Parameters on PND 9, 16, 23, and 37 Following Oral Gavage Administration of 30 mg/kg/day VX-661 to Female Juvenile Sprague-Dawley Rats

Analyte	Group	PND	t _{max} (hr)	C _{max} (ng/g)	AUC _{0-24h} (hr*ng/g)
VX-661	7	9	4.00	13,000	232,000
	8	16	4.00	16,100	259,000
	9	23	4.00	6270	71,100
	10	37	2.00	9310	133,000
VRT-0996107	7	9	8.00	5140	110,000
	8	16	8.00	5760	129,000
	9	23	8.00	4100	76,700
	10	37	4.00	3550	64,300
VRT-1189001	7	9	24.0	1160	19,300
	8	16	24.0	800	13,700
	9	23	8.00	329	6850
	10	37	8.00	172	3700

PND = Postnatal Day

(Excerpted from the Sponsor's submission)

Table 24. Toxicokinetic Parameters of TEZ, M1-661, and M2-661 in brain tissues in rats on PND 9, 16, 23, and 37

NDA/BLA Multi-disciplinary Review and Evaluation {NDA 212273}
{Trikafta (elexacaftor/tezacaftor/ivacaftor)}

Text Table 14

VX-661, VRT-0996107, and VRT-1189001 Mean TK Parameters in Brain Tissues on PND 9, 16, 23, and 37 Following Oral Gavage Administration of 30 mg/kg/day VX-661 to Female Juvenile Sprague-Dawley Rats

Analyte	Group	PND	t _{max} (hr)	C _{max} (ng/g)	AUC _{0-24h} (hr*ng/g)
VX-661	7	9	8.00	7130	138,000
	8	16	8.00	7900	144,000
	9	23	24.00	845	18,200
	10	37	8.00	428	7770
VRT-0996107	7	9	24.00	26,600	532,000
	8	16	24.00	54,900	1,180,000
	9	23	24.00	10,100	217,000
	10	37	8.00	2390	48,400
VRT-1189001	7	9	24.0	3570	55,700
	8	16	24.0	2840	52,200
	9	23	8.00	590	13,200
	10	37	8.00	176	3540

PND = Postnatal Day
(Excerpted from the Sponsor's submission)

Table 25. Plasma and Brain levels of TEZ and M1-TEZ Comparison in Rats during PND 7-9, 14-16, 21-23, and 35-37

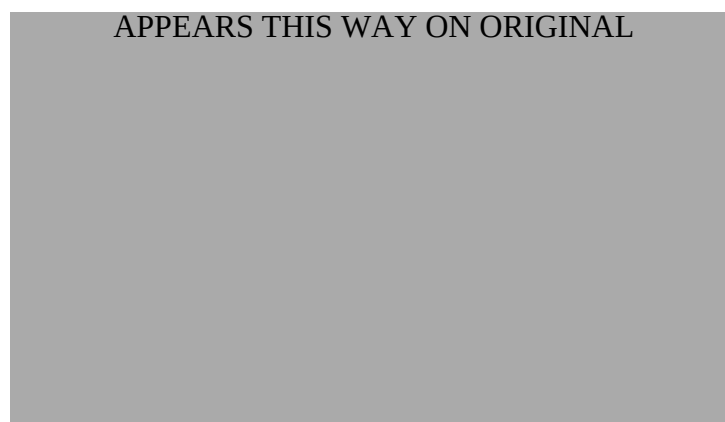


Table 22 TEZ Plasma and Brain Levels Following 3 Days of Dosing With 30 mg/kg/day TEZ

Dosing Period	Analyte	PK After 3 Days of Dosing		
		Mean Plasma AUC _{0-24h} (µg·h/mL)	Mean Brain AUC _{0-24h} (µg·h/mL)	Brain:Fold over PND 35-37
PND 7-9	TEZ	232	138	17.7
PND 14-16	TEZ	259	144	18.5
PND 21-23	TEZ	71.1	18.2	2.3
PND 35-37	TEZ	133	7.8	-

Table 23 M1-661 Plasma and Brain Levels Following 3 Days of Dosing With 30 mg/kg/day TEZ

Dosing Period	Analyte	PK After 3 Days of Dosing		
		Mean Plasma AUC _{0-24h} (µg·h/mL)	Mean Brain AUC _{0-24h} (µg·h/mL)	Brain:Fold over PND 35-37
PND 7-9	M1-661	110	532	11.0
PND 14-16	M1-661	129	1180	24.4
PND 21-23	M1-661	76.7	217	4.5
PND 35-37	M1-661	64.3	48.4	-

(Excerpted from the Sponsor's submission)

Study Title: VX-661: VX-661: An Oral (Gavage) Dose Range-Finding Study from Postnatal Day (PND) 14 or 21 to PND 35 in Juvenile Sprague Dawley Rats (Study report #: VX-661-TX-069)

Key Study Findings

- In a juvenile toxicology study, rats received VX-661 at oral doses of 0 [0.5% methylcellulose (400 cP), 0.5% sodium lauryl sulfate, 0.01% simethicone], 20, or 30 mg/kg/day from PND 14-35 or 0, 30, 60, or 100 mg/kg/day from PND 21-35.

- VX-661 was not tolerated in the 100 mg/kg/day group (Started on PND 21) as mortality was observed for both sexes (1 main study male, 1 TK male, and 1 main study female) on PNDs 25-30. All remaining animals in the 100 mg/kg/day group were euthanized on PNDs 26–30 due to test-article related lower mean body weights (up to 51.5%). Probable causes of death could not be determined based on anatomic pathology findings. Five of 9 males and 6 of 9 females in the HD group had increased K⁺ levels (2.6- and 1.5x the UL of respective control ranges).
- One male and one female in the 100 mg/kg/day group each had a single episode of clonic convulsion approximately 4 hours postdosing on PND 27.
- Statistically significant decreases of mean body weights were observed in both males and females in the 60 mg/kg/day (12.5% and 13%, respectively) and 100 mg/kg/day (51.2% and 32.5%, respectively) compared to the control group during the entire dosing period (PND 21–35). Body weight gains for males and females in the 60 mg/kg/day group were decreased by 18.3% and 19.5% relative to controls, respectively.
- No treatment-related adverse histopathology findings were identified.
- The NOAELs of VX-661 were identified as 30 mg/kg/day (AUC₀₋₂₄, 90.3 h•µg/mL) in juvenile rats from PND 14-35 and 30 mg/kg/day (AUC₀₋₂₄, 91.7 h•µg/mL) from PND 21-35 due to mortality and decreased body weight. The AUC₀₋₂₄ of metabolites M1-661 and M2-661 were 68.0 h•µg/mL and 4.56 h•µg/mL, respectively, in juvenile rats from PND 14-35. The AUC₀₋₂₄ of metabolites M1-661 and M2-661 were 79.1 h•µg/mL and 5.16 h•µg/mL, respectively, in juvenile rats from PND 21-35.

Study Design:

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{Trikafta (elexacaftor/tezacaftor/ivacaftor)}

Text Table 3
Experimental Design – Main Study

Group Number	Treatment	Dosing Duration	Dose Level ^a (mg/kg/day)	Concentration (mg/mL)	Dose Volume (mL/kg)	Number of Animals/Sex
1	Vehicle Control ^b	PND 14–35	0	0	10	10
2	Vehicle Control ^b	PND 21–35	0	0	10	10
3	VX-661	PND 21–35	30	3	10	10
4	VX-661	PND 21–35	60	6	10	10
5	VX-661	PND 21–35	100	10	10	10
6	VX-661	PND 14–35	20	2	10	10
7	VX-661	PND 14–35	30	3	10	10

^a A correction factor of 2.0 was used for VX-661 formulation.

^b Control article, hypromellose acetate succinate, was added to the vehicle at approximately the highest concentration within the VX-661 test article groups, 10 mg/mL.

Table 26. Changes of Body Weight in Rats from PND 21 to PND 35

Body weight	Males, mg/kg/day				Females, mg/kg/day			
Parameter	0	30	60	100	0	30	60	100
BW, PND 21	56.9	57.6	57.4	57.0	52.5	52.4	51.2	51.5
BW, PND 30	116.9	113.1	98.6	57.1	101.8	99.3	84.8	68.7
BW, PND 35	160.9	156.9	142.4	-	136.6	135.9	118.9	-
Abs. BW % of control	100.0	97.5	88.5	48.8	100.0	99.5	87.0	67.5
Δ BW 30-21	60.0	55.5	41.2	0.1	49.3	46.9	33.6	17.2
Δ BW 35-21	104.0	99.3	85.0		84.1	83.5	67.7	
BW Gain % of control	100.0	95.5	81.7	-	100.0	99.2	80.5	-

-Further evaluation of body weight data at 100 mg/kg/day was precluded by early group termination.

Table 27. Toxicokinetic Parameters of VX-661 in rats on PND 14, 21, and 35

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Text Table 18
VX-661 Mean Toxicokinetic Parameters on PND 14, 21, and 35 Following Oral Administration to Male and Female Juvenile Rats

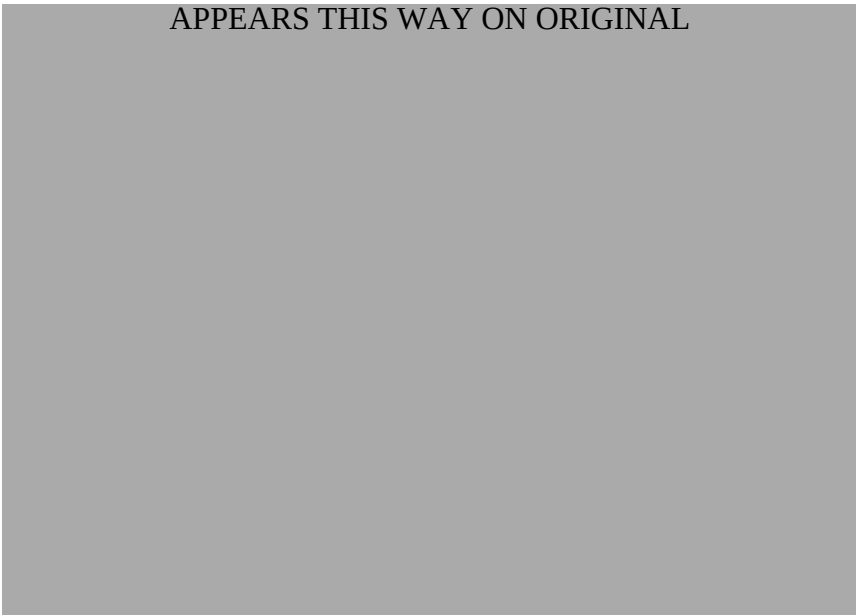
VX-661 Dose (mg/kg/day)	30 (PND 21–35)	60 (PND 21–35)	100 (PND 21–35)	20 (PND 14–35)	30 (PND 14–35)
Males					
PND 14					
AUC _{0-24h} (hr*µg/mL)	NA	NA	NA	101	180
C _{max} (µg/mL)	NA	NA	NA	7.22	11.7
t _{max} (hr)	NA	NA	NA	2.00	4.00
PND 21					
AUC _{0-24h} (hr*µg/mL)	90.5	215	337	NA	NA
C _{max} (µg/mL)	7.48	16.0	25.2	NA	NA
t _{max} (hr)	4.00	4.00	4.00	NA	NA
PND 35					
AUC _{0-24h} (hr*µg/mL)	78.8	159	NA	48.1	82.8
C _{max} (µg/mL)	8.63	16.8	NA	5.27	8.34
t _{max} (hr)	2.00	2.00	NA	4.00	2.00
Females					
PND 14					
AUC _{0-24h} (hr*µg/mL)	NA	NA	NA	116	192
C _{max} (µg/mL)	NA	NA	NA	7.28	1.26
t _{max} (hr)	NA	NA	NA	2.00	4.00
PND 21					
AUC _{0-24h} (hr*µg/mL)	89.6	191	359	NA	NA
C _{max} (µg/mL)	6.79	15.0	24.7	NA	NA
t _{max} (hr)	4.00	2.00	8.00	NA	NA
PND 35					
AUC _{0-24h} (hr*µg/mL)	105	175	NA	61.5	97.9
C _{max} (µg/mL)	8.99	14.6	NA	5.76	8.02
t _{max} (hr)	4.00	4.00	NA	4.00	4.00
Combined					
PND 14					
AUC _{0-24h} (hr*µg/mL)	NA	NA	NA	109	186
C _{max} (µg/mL)	NA	NA	NA	7.25	12.1
t _{max} (hr)	NA	NA	NA	2.00	4.00
PND 21					
AUC _{0-24h} (hr*µg/mL)	90.1	203	348	NA	NA
C _{max} (µg/mL)	7.14	15.4	24.6	NA	NA
t _{max} (hr)	4.00	4.00	4.00	NA	NA
PND 35					
AUC _{0-24h} (hr*µg/mL)	91.7	167	NA	55	90.3
C _{max} (µg/mL)	8.50	14.7	NA	5.52	8.18
t _{max} (hr)	4.00	4.00	NA	4.00	4.00

NA = Not applicable.

(Excerpted from the Sponsor's submission)

Table 28. Toxicokinetic Parameters of VRT-0996107 and VRT-1189001 in rats on PND 14, 21, and 35

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Text Table 19

VRT-0996107 Toxicokinetic Parameters on PND 14, 21, and 35 Following Oral Administration of VX-661 to Male and Female Juvenile Rats

VX-661 Dose (mg/kg/day)	30 (PND 21–35)	60 (PND 21–35)	100 (PND 21–35)	20 (PND 14–35)	30 (PND 14–35)
Males					
PND 14					
AUC _{0-24h} (hr*µg/mL)	NA	NA	NA	36.9	45.0
C _{max} (µg/mL)	NA	NA	NA	1.93	2.60
t _{max} (hr)	NA	NA	NA	24.0	12.0
PND 21					
AUC _{0-24h} (hr*µg/mL)	54.6	88.2	142	NA	NA
C _{max} (µg/mL)	3.14	4.47	9.06	NA	NA
t _{max} (hr)	12.0	12.0	24.0	NA	NA
PND 35					
AUC _{0-24h} (hr*µg/mL)	82.4	152	NA	45.8	74.4
C _{max} (µg/mL)	4.60	8.45	NA	2.37	3.81
t _{max} (hr)	12.0	12.0	NA	8.00	12.0
Females					
PND 14					
AUC _{0-24h} (hr*µg/mL)	NA	NA	NA	39.3	48.1
C _{max} (µg/mL)	NA	NA	NA	2.20	2.55
t _{max} (hr)	NA	NA	NA	24.0	24.0
PND 21					
AUC _{0-24h} (hr*µg/mL)	48.5	89.1	162	NA	NA
C _{max} (µg/mL)	2.61	4.63	9.86	NA	NA
t _{max} (hr)	12.0	12.0	24.0	NA	NA
PND 35					
AUC _{0-24h} (hr*µg/mL)	76.3	127	NA	34.8	61.6
C _{max} (µg/mL)	3.80	6.41	NA	1.68	2.73
t _{max} (hr)	12.0	12.0	NA	4.00	12.0
Combined					
PND 14					
AUC _{0-24h} (hr*µg/mL)	NA	NA	NA	38.1	46.6
C _{max} (µg/mL)	NA	NA	NA	2.08	2.48
t _{max} (hr)	NA	NA	NA	24.0	12.0
PND 21					
AUC _{0-24h} (hr*µg/mL)	51.6	88.6	152	NA	NA
C _{max} (µg/mL)	2.87	4.55	9.46	NA	NA
t _{max} (hr)	12.0	12.0	24.0	NA	NA
PND 35					
AUC _{0-24h} (hr*µg/mL)	79.1	140	NA	40.5	68.0
C _{max} (µg/mL)	4.20	7.43	NA	2.01	3.27
t _{max} (hr)	12.0	12.0	NA	4.00	12.0

NA = Not applicable.

(Excerpted from the Sponsor's submission)

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Text Table 20
VRT-1189001 Toxicokinetic Parameters on PND 14, 21, and 35 Following Oral Administration of VX-661 to Male and Female Juvenile Rats

VX-661 Dose (mg/kg/day)	30 (PND 21–35)	60 (PND 21–35)	100 (PND 21–35)	20 (PND 14–35)	30 (PND 14–35)
Males					
PND 14					
AUC _{0-24h} (hr*µg/mL)	NA	NA	NA	3.43	4.12
C _{max} (µg/mL)	NA	NA	NA	0.301	0.251
t _{max} (hr)	NA	NA	NA	24.0	12.0
PND 21					
AUC _{0-24h} (hr*µg/mL)	4.35	5.01	8.61	NA	NA
C _{max} (µg/mL)	0.288	0.352	0.857	NA	NA
t _{max} (hr)	24.0	24.0	24.0	NA	NA
PND 35					
AUC _{0-24h} (hr*µg/mL)	5.74	12.7	NA	3.99	5.47
C _{max} (µg/mL)	0.296	0.585	NA	0.217	0.307
t _{max} (hr)	8.00	12.0	NA	12.0	4.00
Females					
PND 14					
AUC _{0-24h} (hr*µg/mL)	NA	NA	NA	3.32	3.55
C _{max} (µg/mL)	NA	NA	NA	0.274	0.292
t _{max} (hr)	NA	NA	NA	24.0	24.0
PND 21					
AUC _{0-24h} (hr*µg/mL)	3.38	5.29	7.43	NA	NA
C _{max} (µg/mL)	0.216	0.404	0.702	NA	NA
t _{max} (hr)	24.0	24.0	24.0	NA	NA
PND 35					
AUC _{0-24h} (hr*µg/mL)	4.49	8.42	NA	2.63	3.65
C _{max} (µg/mL)	0.218	0.463	NA	0.131	0.176
t _{max} (hr)	12.0	4.00	NA	12.0	12.0
Combined					
PND 14					
AUC _{0-24h} (hr*µg/mL)	NA	NA	NA	3.37	3.83
C _{max} (µg/mL)	NA	NA	NA	0.288	0.261
t _{max} (hr)	NA	NA	NA	24.0	24.0
PND 21					
AUC _{0-24h} (hr*µg/mL)	3.87	5.15	8.02	NA	NA
C _{max} (µg/mL)	0.252	0.378	0.780	NA	NA
t _{max} (hr)	24.0	24.0	24.0	NA	NA
PND 35					
AUC _{0-24h} (hr*µg/mL)	5.16	10.6	NA	3.33	4.56
C _{max} (µg/mL)	0.252	0.482	NA	0.174	0.216
t _{max} (hr)	8.00	12.0	NA	12.0	12.0

NA = Not applicable.

(Excerpted from the Sponsor's submission)

Study Title: VX-661: An Oral (Gavage) Juvenile Toxicity Study with a Combination Arm of VX-661 and VX-770 from Postnatal Day (PND) 14 to 42 or PND 21 to 49 in Juvenile Sprague Dawley Rats (Study report #: VX-661-TX-038)

Key Study Findings

- In a juvenile toxicology study, rats received VX-661 at oral doses of 0 [0.5% methylcellulose (400 cP), 0.5% sodium lauryl sulfate, 0.01% simethicone], 20, and 30 mg/kg/day during PND 14-42. Another set of rats received VX-661 at oral doses of 0, 30, 30 (+10 mg/kg/day IVA), and 60 mg/kg/day during PND 21-49.
- No treatment-related deaths or adverse clinical signs were observed for main and TK study rats.
- Body weight gains were unaffected for male and female juvenile rats treated with doses up to 30 mg/kg/day from PND 14-42. Body weight gain for males at 60 mg/kg/day treated from PND 21-49 was reduced to 89.5% of the control; however, body weight gain for females at 60 mg/kg/day was unaffected.
- Increases of mean ALT (1.25x), AST (1.19x), CK (1.82x), urea nitrogen (1.18x), creatine (1.39x), and phosphorous (1.17x) were observed in males in the HD group (60 mg/kg/day) during the PND 21-49 study. There were no corresponding histopathology findings.
- No adverse histopathological findings were identified in rats.
- Systemic exposure to VX-661 tended to be lower (~38%-78%) in juvenile male and female rats on PND 42, following repeated administration of VX-661, compared to PND 14. The decreases were more pronounced in males comparing to females. No differences of systemic exposure were observed between VX-661 alone and in combination with VX-770. Systemic exposure to VRT-0996107 (M1-661) were approximately 26% to 127% of the parent VX-661 levels, while exposures to VRT-1189001 (M2-661) were less than 10% of the parent VX-661 levels.
- The NOAELs of VX-661 in juvenile rats were identified as 30 mg/kg/day (AUC_{0-24} : 107.8 h• μ g/mL) from PND 14-42 and 30 mg/kg/day (AUC_{0-24} : 106 h• μ g/mL) from PND 21-49, respectively. No adverse findings were identified in juvenile rats administered with the combination of 30 mg/kg/day TEZ and 10 mg/kg/day IVA. The AUC_{0-24} of metabolites M1-661 and M2-661

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were 47.4 h•µg/mL and 4.35 h•µg/mL, respectively, in juvenile rats from PND 14-42. The AUC₀₋₂₄ of metabolites M1-661 and M2-661 were 51.6 h•µg/mL and 3.87 h•µg/mL, respectively, in juvenile rats from PND 21-35.

Study Design

Text Table 1
Experimental Design

Group Number	Test Article	Dosing Duration	VX-661/VX-770 Dose Level (mg/kg/day)*	VX-661/VX-770 Dose Concentration (mg/mL)*	Dose Volume (mL/kg)	Number of Animals/Sex	
						Main ^b	TK ^b
1	Vehicle Control ^a	PND 14-42	0/-	0/-	10	20	27
2	Vehicle Control ^a	PND 21-49	0/-	0/-	10	20	27
3	VX-661	PND 21-49	30/-	3/-	10	20	27
4	VX-661 and VX-770	PND 21-49	30/10	3/1	10	20	27
5	VX-661	PND 21-49	60/-	6/-	10	20	27
6	VX-661	PND 14-42	20/-	2/-	10	20	27
7	VX-661	PND 14-42	30/-	3/-	10	20	27

Main = Main phase; TK = Toxicokinetic phase.

* A correction factor of 2.0 was used for VX-661 test article formulations. A correction factor of 1.25 was used for VX-770 test article formulations.

^a Control article, hypromellose acetate succinate, was added to the vehicle at approximately the highest concentration within the VX-661 test article groups, at 3 mg/mL for Group 1 and at 6 mg/mL for Group 2.

^b Main phase: at scheduled necropsy; TK phase: PND 14, 21, 42, and 49 collection intervals.

(Excerpted from the Sponsor's submission)

Table 29. Changes of Body Weight in Rats from PND 21 to PND 49

Body weight Parameter	Males, mg/kg/day				Females, mg/kg/day			
	0	30 TEZ	30 TEZ + 10 IVA	60 TEZ	0	30 TEZ	30 TEZ + 10 IVA	60 TEZ
BW, PND 21	51.0	51.0	51.5	51.7	50.0	49.8	50.5	50.0
BW, PND 35	162.4	159.7	157.1	143.0	139.1	136.9	139.7	127.5
BW, PND 49	293.0	294.7	290.0	268.4	203.3	202.1	206.4	199.1
Δ BW 35-21	111.4	108.7	105.6	91.3	89.1	87.1	89.2	77.5
Δ BW 49-21	242.0	243.7	238.5	216.7	153.3	152.3	155.9	149.1

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Absolute BW % of control	100.0	100.6	99.0	91.6	100.0	99.4	101.5	97.9
BW Gain % of control	100.0	100.7	98.6	89.5	100.0	99.3	101.7	97.2

Table 30. Toxicokinetic Parameters of TEZ, M1-661 (VRT-0996107), M2-661 (VRT-1189001), and IVA (VX-770) in plasma in rats on PND 14, 42, 21, and 49

Text Table 15
TK Parameters for VX-661 (Males and Females Separate)

Gender	VX-661 Dose (mg/kg/day)	PND	Group	C _{max} (µg/mL)	t _{max} (hr)	AUC _{0-24hr} (µg·hr/mL)
Female	30	21	3	8.89	4	105
Female	30	49	3	11.7	4	138
Female	30	21	4	10.0	4	139
Female	30	49	4	15.5	2	153
Female	60	21	5	17.4	2	217
Female	60	49	5	15.3	4	205
Female	20	14	6	8.27	8	123
Female	20	42	6	5.86	4	76.2
Female	30	14	7	12.6	4	170
Female	30	42	7	10.0	4	133
Male	30	21	3	8.97	4	107
Male	30	49	3	10.3	4	96.6
Male	30	21	4	7.88	4	120
Male	30	49	4	10.0	4	90.5
Male	60	21	5	15.9	8	220
Male	60	49	5	18.5	4	191
Male	20	14	6	10.3	4	124

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Gender	VX-661 Dose (mg/kg/day)	PND	Group	C _{max} (µg/mL)	t _{max} (hr)	AUC _{0-24hr} (µg·hr/mL)
Male	20	42	6	6.09	4	46.9
Male	30	14	7	11.3	12	198
Male	30	42	7	9.49	4	82.5

Text Table 16
TK Parameters for VRT-0996107 (Males and Females Separate)

Gender	VX-661 Dose (mg/kg/day)	PND	Group	C _{max} (µg/mL)	t _{max} (hr)	AUC _{0-24hr} (µg·hr/mL)
Female	30	21	3	3.16	12	59.1
Female	30	49	3	4.14	8	84.1
Female	30	21	4	3.37	24	59.3
Female	30	49	4	4.94	12	96.4
Female	60	21	5	4.76	24	87.3
Female	60	49	5	8.26	8	158
Female	20	14	6	2.14	12	41.8
Female	20	42	6	2.36	12	45.0
Female	30	14	7	2.43	24	44.2
Female	30	42	7	3.81	8	74.3
Male	30	21	3	3.07	12	54.8
Male	30	49	3	4.74	4	89.3
Male	30	21	4	2.99	12	53.5
Male	30	49	4	5.52	12	115
Male	60	21	5	5.39	12	93.7
Male	60	49	5	9.75	8	171
Male	20	14	6	1.87	12	37.3
Male	20	42	6	3.30	4	54.9
Male	30	14	7	2.76	12	50.6
Male	30	42	7	4.22	8	75.1

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Text Table 17
TK Parameters for VRT-1189001 (Males and Females Separate)

Gender	VX-661 Dose (mg/kg/day)	PND	Group	C _{max} (µg/mL)	t _{max} (hr)	AUC _{0-24hr} (µg·hr/mL)
Female	30	21	3	0.209	24	3.51
Female	30	49	3	0.174	4	2.53
Female	30	21	4	0.334	24	3.74
Female	30	49	4	0.175	8	3.02
Female	60	21	5	0.361	12	5.79
Female	60	49	5	0.256	12	5.91
Female	20	14	6	0.462	24	5.29
Female	20	42	6	0.107	8	1.63
Female	30	14	7	0.244	24	3.27
Female	30	42	7	0.197	12	3.45
Male	30	21	3	0.127	12	2.40
Male	30	49	3	0.272	8	5.60
Male	30	21	4	0.262	24	3.81
Male	30	49	4	0.282	8	5.13
Male	60	21	5	0.454	12	6.75

Gender	VX-661 Dose (mg/kg/day)	PND	Group	C _{max} (µg/mL)	t _{max} (hr)	AUC _{0-24hr} (µg·hr/mL)
Male	60	49	5	0.386	24	8.16
Male	20	14	6	0.265	24	4.08
Male	20	42	6	0.140	4	2.67
Male	30	14	7	0.502	24	5.43
Male	30	42	7	0.241	8	4.47

Text Table 18
TK Parameters for VX-770 (Males and Females Separate)

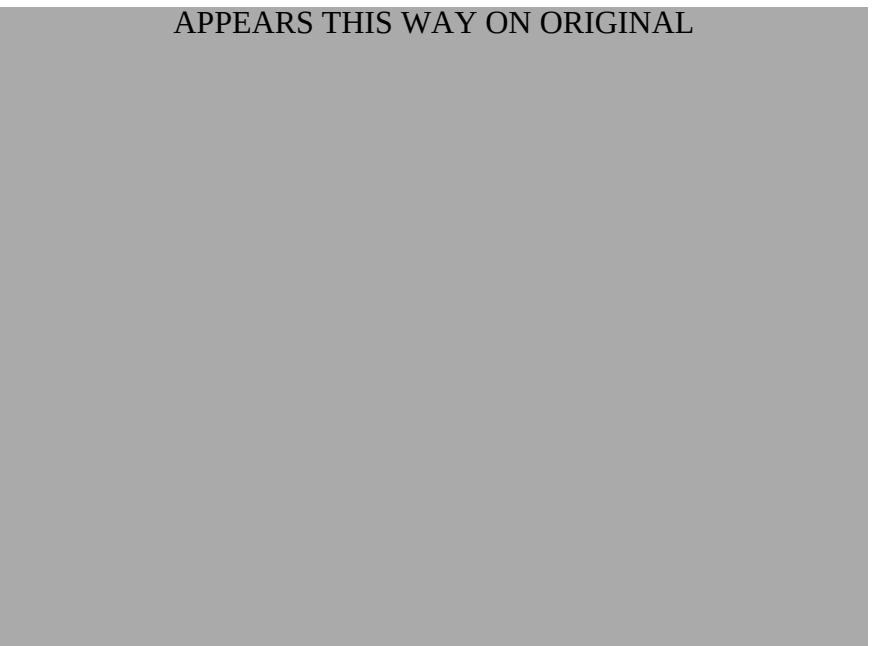
Gender	VX-770 Dose (mg/kg/day)	PND	Group	C _{max} (µg/mL)	t _{max} (hr)	AUC _{0-24hr} (µg·hr/mL)
Female	10	21	4	2.05	4	38.3
Female	10	49	4	1.74	2	32.3
Male	10	21	4	1.88	8	30.9
Male	10	49	4	1.84	4	32.0

(Excerpted from the Sponsor's submission)

5.5.5. **Other Toxicology Studies**

Reviewed with the initial NDA submission

APPEARS THIS WAY ON ORIGINAL



6 Clinical Pharmacology

6.1. Executive Summary

Vertex submitted pediatric supplement (NDA 212273, Supplement 4, SDN0067) on Dec. 8, 2020 seeking the marketing approval of Trikafta (ETI, a combination drug of ELX, TEZ and IVA) for the treatment of CF in patients aged 6 to less than 12 years of age who have at least one *F508del* mutation in the CFTR gene or a mutation in the CFTR gene that is responsive based on in vitro data. The proposed oral dose is based on body weight:

- < 30 kg: Two tablets in the morning each containing ELX 50 mg, TEZ 25 mg and IVA 37.5 mg, and one tablet in the evening containing IVA 75 mg, taken approximately 12 hours apart.
- ≥ 30 kg: Two tablets in the morning: each containing ELX 100 mg, TEZ 50 mg and IVA 75 mg tablets, and one tablet in the evening containing IVA 150 mg, taken approximately 12 hours apart.

Recommendations: The Office of Clinical Pharmacology Division of Immune and Inflammation Pharmacology and Division of Pharmacometrics have reviewed the information submitted under sNDA 212273/S-04. This pediatric supplement and the proposed dosing regimen for pediatric CF patients are approvable from a clinical pharmacology perspective.

One pediatric study (Trial 106) conducted in pediatric subjects 6 through 11 years of age, with F (*F508del*)/MF (minimal function mutation) and F/F genotypes, and one relative bioavailability study (Trial 011) conducted in healthy adult subjects, and two pharmacometrics reports for study VX18-445-016 were submitted in this pediatric supplement.

The evaluation of key review items with specific recommendations/comments are summarized below:

Review Items	Recommendations and Comments
Comparison of systemic exposure of ETI and their metabolites M23-ELX/M1-TEZ in younger children with CF to those from adolescents and adults with CF	Observed and population PK model-estimated steady state AUC, C_{max}, C_{trough} values of ELX, M23-ELX, TEZ, IVA, and M1-IVA in pediatric subjects aged 6 to 12 years following the proposed dose in Study VX18-445-106 are generally within the 5th and 95th percentile of the adult reference range. However, M1-TEZ mean systemic exposure in children aged 6 to 11 years with body weight greater than or equal to 30 kg and on 100 mg TEZ QD regimen is about 40% and 60% higher than that of adolescents and adults who were on the same dosing regimen, respectively. Based on totality of clinical pharmacology

	assessment, this moderate increase of M1-TEZ systemic exposure does not strongly support a dose adjustment of TEZ in this pediatric population.
Evaluation of popPK model	In general, the applicant's population PK analysis is considered acceptable for the purpose of supporting analyses objectives.
Relative bioavailability of low-dose tested FDC with reference FDC	The systemic exposures of ELX, TEZ, and IVA are comparable between two low-dosing strength FDC (fixed-dose combination) tablets (ELX 50 mg/TEZ 25 mg/IVA 37.5 mg) or one reference FDC tablet (ELX 100 mg/TEZ 50 mg/IVA 75 mg) following single dose administration in healthy adults.
Bioanalytical assay for measuring ELX/TEZ/IVA and M23-ELX, M1-TEZ, M1-IVA plasma concentration	The bioanalytical methods are validated, and the in-study bioanalysis study reports are acceptable.
Overall clinical pharmacology conclusion of Trikafta dosing in pediatric patients with CF	The following proposed doses are reasonable: ▪ <30 kg: Two tablets in the morning each containing ELX 50 mg, TEZ 25 mg and IVA 37.5 mg, and one tablet in the evening containing IVA 75 mg, taken approximately 12 hours apart. ▪ ≥ 30 kg: Two tablets in the morning: each containing ELX 100 mg, TEZ 50 mg and IVA 75 mg tablets, and one tablet in the evening containing IVA 150 mg, taken approximately 12 hours apart.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Pediatric PK summary from Trial 106

Trial 106 was divided into two parts. Part A was a pilot study with low dose treatment in subjects for only 15 days; Part B was a pivotal study with the proposed dosing regimen in subjects for 24 weeks. The following review regarding observed PK, population PK, and graphical exploration of exposure-response relationship on efficacy are mostly focused on the results from part B.

The mean observed trough and maximum concentrations of ELX, M23-ELX, TEZ, IVA, and M1-IVA in CF subjects 6 through 11 years of age in Part B were shown in table, the drug exposure was proportionally increased for three components and their metabolites, regardless of the differences of body weight for two low and dosing group.

Table 31. Observed Ranges of Mean Ctrough (from Day 15 to Week 24) and Cmax (Week 4) values of ELX, M23-ELX, TEZ, M1-TEZ, IVA, and M1-IVA from Trial 106

	Mean Ctrough (µg/mL) through Day 15 to week 24		Mean Cmax (µg/mL) at week 4	
	ETI Low dose	ETI High dose	ETI Low dose	ETI High dose
ELX	2.67-3.02	4.99-6.53	6.79	11.7
M23-ELX	1.31-1.76	3.78-4.41	2.01	5.02
TEZ	1.18-1.46	2.31-2.73	6.97	9.97
M1-TEZ	5.30-5.68	7.88-8.37	7.21	10.1
IVA	0.288-0.455	0.77-0.96	1.15	2.13
M1-IVA	0.787-1.05	1.97-2.55	2.42	4.47

Source: Adapted by reviewer per table 11-2 from Trial 106 CSR, pg. 81.

PK comparability between low-dose fixed-dose combination (FDC) and reference FDC tablet

Since the low-dose FDC tablet (ELX 50 mg/TEZ 25 mg/IVA 37.5 mg) was used in Trial 106 to treat pediatric patients aged from 6 to 12 with body weight less than 30 kg, the relative bioavailability were compared between single dose administration of 2 low-dose FDC tablets and 1 reference FDC tablet (ELX 100 mg/TEZ 50 mg/IVA 75 mg) in healthy adults in Study VX18-445-011. The results showed that the exposures (AUC_{0-∞} and C_{max}) of ELX, TEZ, and IVA were comparable between two dosing strengths with 90% CI of geometric mean ratios between 0.8-1.25 (Table 32).

Table 32. Relative BA Assessment of ELX, TEZ, and IVA Exposures After Administration of ETI as 2 Low-dose or 1 Reference FDC Tablets from Trial 011

Analyte	PK Parameter	Test GLSM (Low-dose FDC)	Reference GLSM (Reference FDC)	GLSM Ratio (Test:Reference)	90% CI	
					Lower	Upper
ELX	AUC _{0-∞} (h·µg/mL)	68.4	66.9	1.02	0.956	1.09
	C _{max} (µg/mL)	2.41	2.38	1.01	0.922	1.11
TEZ	AUC _{0-∞} (h·µg/mL)	45.1	45.3	0.996	0.936	1.06
	C _{max} (µg/mL)	2.45	2.63	0.931	0.831	1.04
IVA	AUC _{0-∞} (h·µg/mL)	4.88	4.75	1.03	0.955	1.10
	C _{max} (µg/mL)	0.401	0.390	1.03	0.899	1.18

Source: Table 11-2 of study 011 CSR, pg. 38

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The approved dose and dosing regimen for ETI in adults and adolescents are:

- Morning dose: two ELX 100 mg, TEZ 50 mg and IVA 75 mg tablets.
- Evening dose: one IVA 150 mg tablet.
- Morning and evening dose should be taken approximately 12 hours apart with fat-containing food.

Therapeutic Individualization

The proposed dosing regimen for pediatric patients aged 6 to less than 12 years with body weight greater than or equal to 30 kg is the same as the dosing regimen approved in adult CF patients, which is two tablets of ETI in the morning each containing ELX 100 mg, TEZ 50 mg, and IVA 75 mg, and one tablet in the evening containing IVA 150 mg, taken approximately 12 hours apart with fat-containing food.

The proposed dosing regimen for pediatric patients aged 6 to less than 12 years with body weight less than 30 kg, is two tablets of lower-dosing strength in the morning that each containing ELX 50 mg, TEZ 25 mg, and IVA 37.5 mg, and one tablet in the evening containing IVA 75 mg in the evening, taken approximately 12 hours apart with fat-containing food. The proposed dose in this pediatric population is half of the dose for adult patients and pediatric patients with body weight over 30 kg.

Outstanding Issues

None.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

Yes. The overall results of Trial 106, including the observed PK, population PK, and graphical exploration of exposure-response on efficacy, provide supportive evidence of effectiveness.

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

Yes. The following proposed dosing regimen for pediatric subjects is acceptable

- <30 kg: Two tablets in the morning each containing ELX 50 mg, TEZ 25 mg, and IVA 37.5 mg, and one tablet in the evening containing IVA 75 mg, taken approximately 12 hours apart with fat-containing food.
- ≥ 30 kg: Two tablets in the morning: each containing ELX 100 mg, TEZ 50 mg and IVA 75 mg, and one tablet in the evening containing IVA 150 mg, taken approximately 12 hours apart with fat-containing food.

Dose Selection Rationale

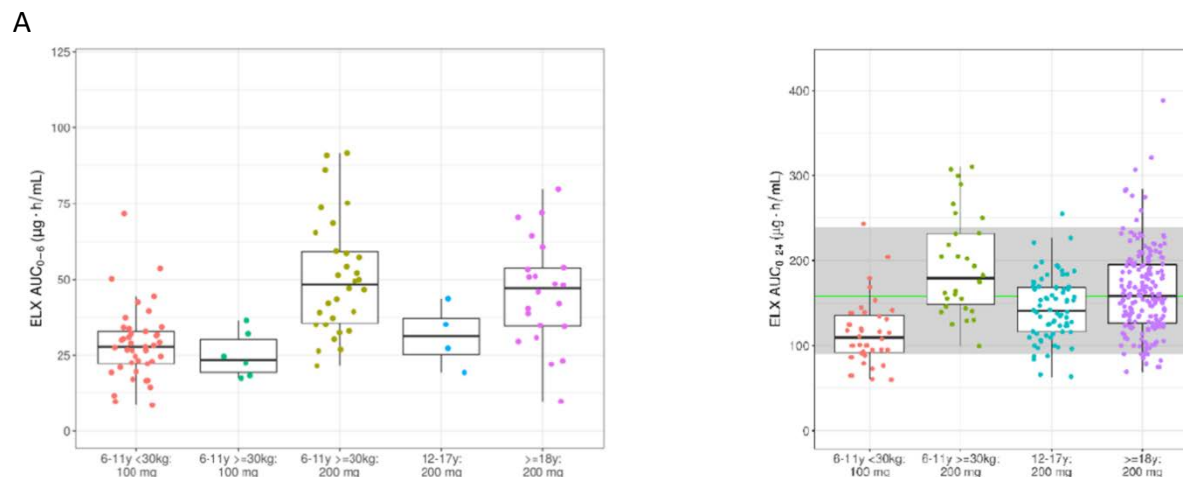
The pediatric dose and body weight cutoff in Part B of Trial 106 was determined based on population-PK modeling that was updated with preliminary PK data from Part A and PK results of TEZ/IVA in CF children 6 to 11 years of age in approved NDA 210491 (SYMDEKO, TEZ/IVA combination drugs, same Applicant).

Comparison of PK parameters across younger children, adolescent and adults

- ELX and M23-ELX PK comparison between children aged 6 to less than 12 years, adolescents, and adults.

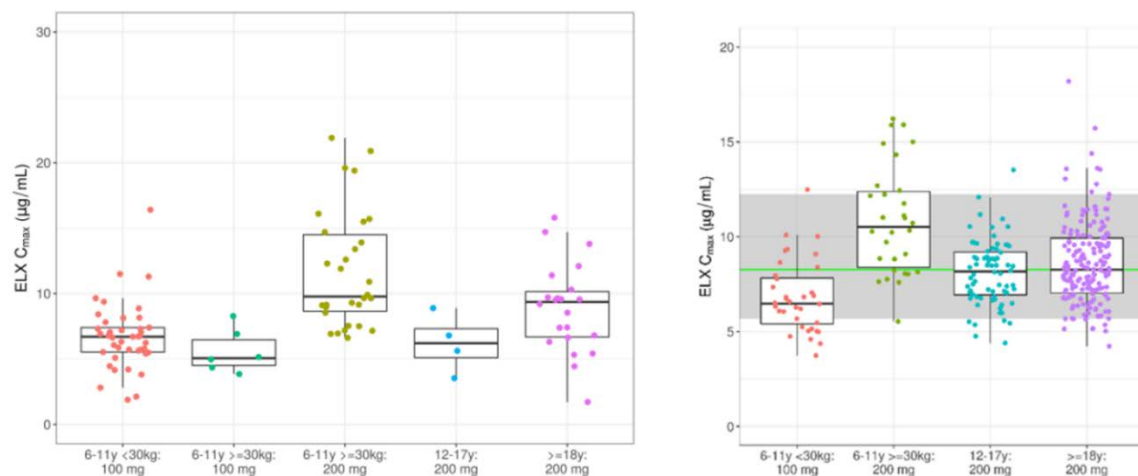
For ELX, the population PK model-estimated and the observed steady state AUC, C_{max}, and C_{min} values (Figure 3) from majority of children on the proposed doses were within the 5th and 95th percentiles of the adult reference values.

Figure 3. Boxplot comparison of ELX steady state AUC (A), C_{max} (B), and C_{min} (C) between younger children, adolescents, and adults

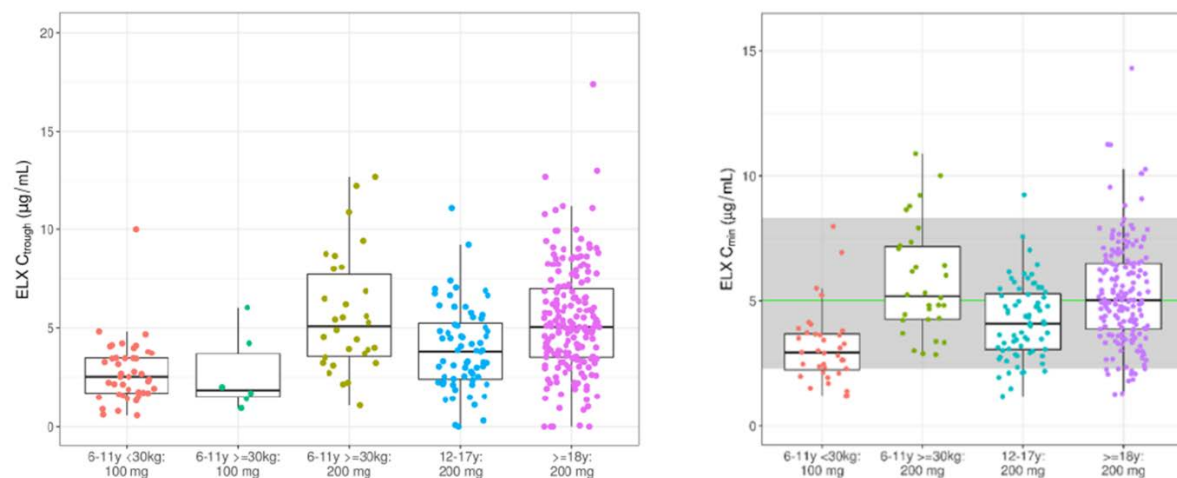


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{Trikafta (elexacaftor/tezacaftor/ivacaftor)}

B



C

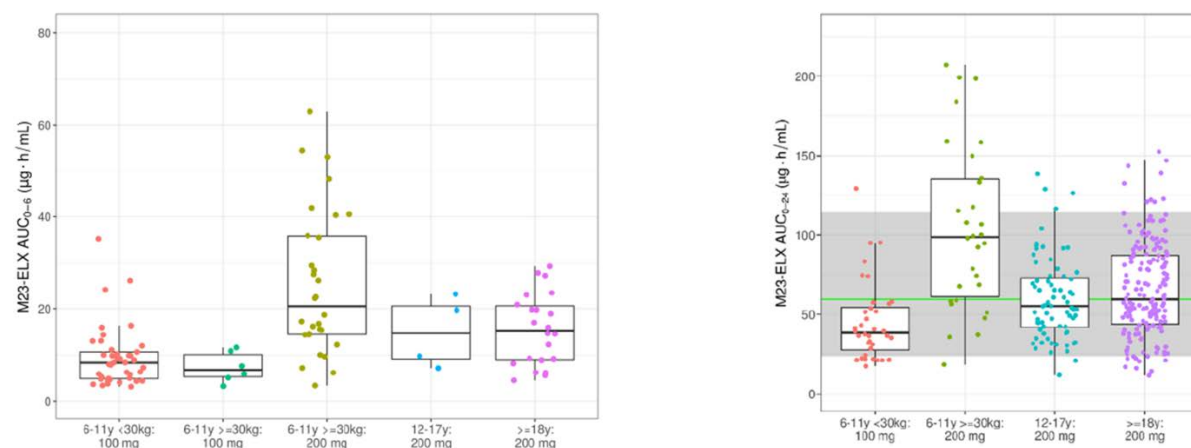


The left column is from observed values and the right column is from population PK-estimated values. The gray shaded area indicates the 5th and 95th percentiles of the adult reference values. Source: Figure 1, 2, 3 from clin-info-amend-response-ir-dated-28-jan-2021.pdf, page 3 to 9.

Similarly, the population PK model-estimated and the observed steady state AUC, C_{max}, and C_{min} values of M23-ELX (Figure 4) from majority of children on the proposed doses were within the 5th and 95th percentiles of the adult reference values. Of note, M23-ELX is an active metabolite of ELX with similar pharmacologic potency.

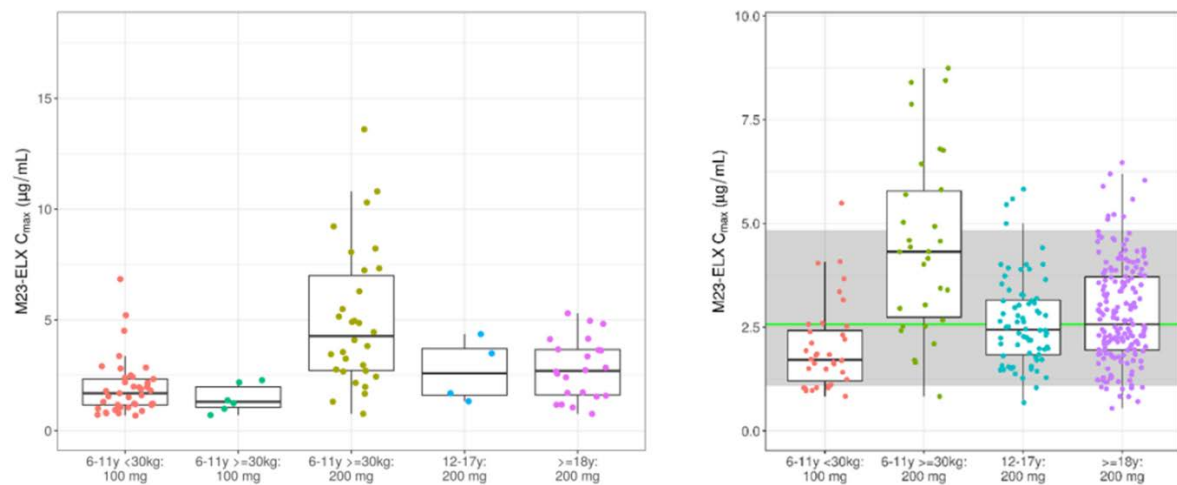
Figure 4. Boxplot comparison of M23-ELX steady state AUC (A), C_{max} (B), and C_{min} (C) between younger children, adolescents, and adults

A

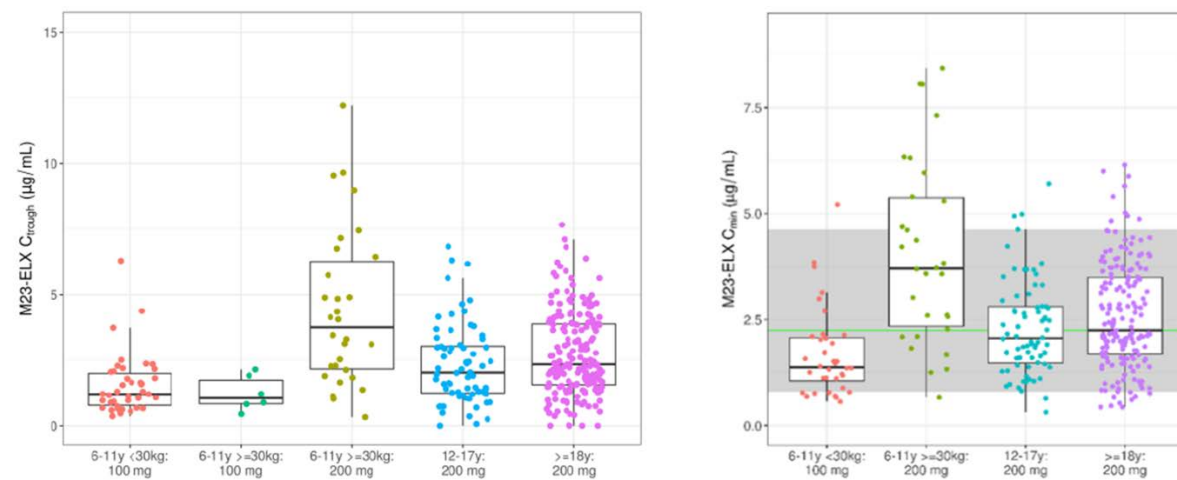


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B



C



The left column is from observed values and the right column is from population PK-estimated values. The gray shaded area indicates the 5th and 95th percentiles of the adult reference values. Source: Figure 1, 2, 3 from clin-info-amend-response-ir-dated-28-jan-2021.pdf, page 3 to 9.

The population PK-estimated mean values of C_{min} , C_{max} , and AUC_{τ} of ELX and M23-ELX at steady state in children, adolescents, and adults are listed in Table 33.

Table 33. Summary of Population PK Model-Predicted PK parameters of ELX, M23-ELX, TEZ, M1-TEZ and IVA

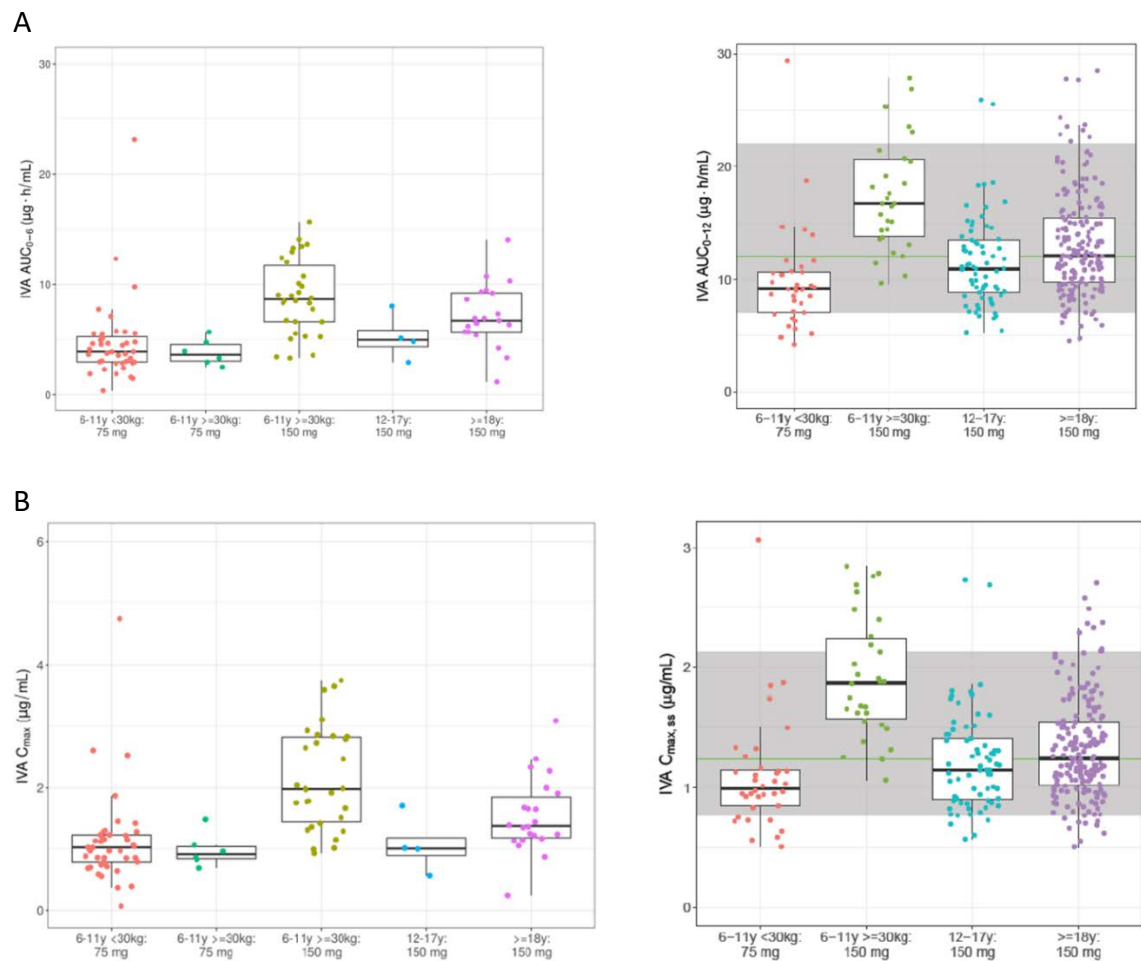
PK	Cmin ($\mu\text{g/mL}$) (Mean (CV%))				Cmax ($\mu\text{g/mL}$) (Mean (CV%))				AUCss ($\mu\text{g}\cdot\text{h/mL}$) (Mean (CV%))			
	<30 kg (6-11yo)	≥ 30 kg (6-11yo)	adolescent	adult	<30 kg (6-11yo)	≥ 30 kg (6-11yo)	adolescent	adult	<30 kg (6-11yo)	≥ 30 kg (6-11yo)	adolescent	adult
ELX	3.15 (46.4)	5.69 (39.1)	4.2 (40.3)	5.25 (42.7)	6.82 (27)	10.9 (27.2)	8.11 (21.7)	8.59 (24.9)	116 (32.8)	195 (30.8)	144 (27.9)	163 (31.5)
M23-ELX	1.69 (59.4)	4.05 (68.1)	2.29 (56.5)	2.59 (60.1)	2.02 (49.8)	4.48 (59.7)	2.64 (43.2)	2.83 (49.7)	45.4 (53.2)	104 (62.6)	60.1 (47.9)	65.7 (53.4)
TEZ	1.39 (47.1)	2.19 (36.0)	1.94 (38.8)	2.01 (45.3)	6.12 (21.6)	8.97 (20.6)	7.32 (21.8)	6.71 (19.7)	67.0 (30.2)	103 (24.0)	88.9 (25.2)	86.4 (28.5)
M1-TEZ	5.55 (25.4)	8.06 (18.4)	5.82 (29.2)	5.00 (37.2)	6.96 (23.4)	9.99 (18.4)	7.09 (24.3)	5.99 (30.1)	153 (24.0)	220 (18.1)	157 (26.0)	134 (32.5)
IVA	0.478 (48.0)	0.900 (37.9)	0.644 (42.6)	0.789 (44.3)	1.09 (37.3)	1.92 (26.9)	1.22 (32.4)	1.33 (32.1)	9.78 (39.4)	17.5 (29.0)	11.6 (34.0)	13.1 (35.3)

Source: Q075 population PK report of Trial 106, table 7-12, pg. 72-74; Q076 population PK report of Trial 106: table 19-21, pg. 66-68, table 31-33, pg78-80

- IVA PK comparison between children aged 6 to less than 12 years, adolescents, and adults.

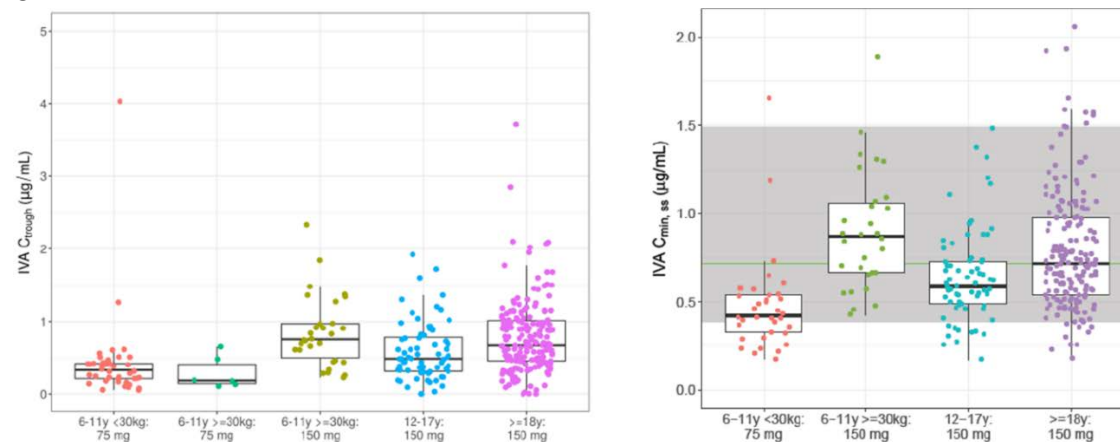
For IVA, the population PK model-estimated steady state AUC, C_{max} , and C_{min} values (Figure 5) from majority of children on the proposed doses were within the 5th and 95th percentiles of the adult reference values. The population PK-estimated mean values of C_{min} , C_{max} , and AUC_{τ} of IVA at steady state in children, adolescents, and adults are listed in Table 33.

Figure 5. Boxplot comparison of steady state AUC (A), C_{max} (B), and C_{min} (C) of IVA between younger children, adolescents, and adults.



NDA/BLA Multi-disciplinary Review and Evaluation {NDA 212273}
{Trikafta (elexacaftor/tezacaftor/ivacaftor)}

C

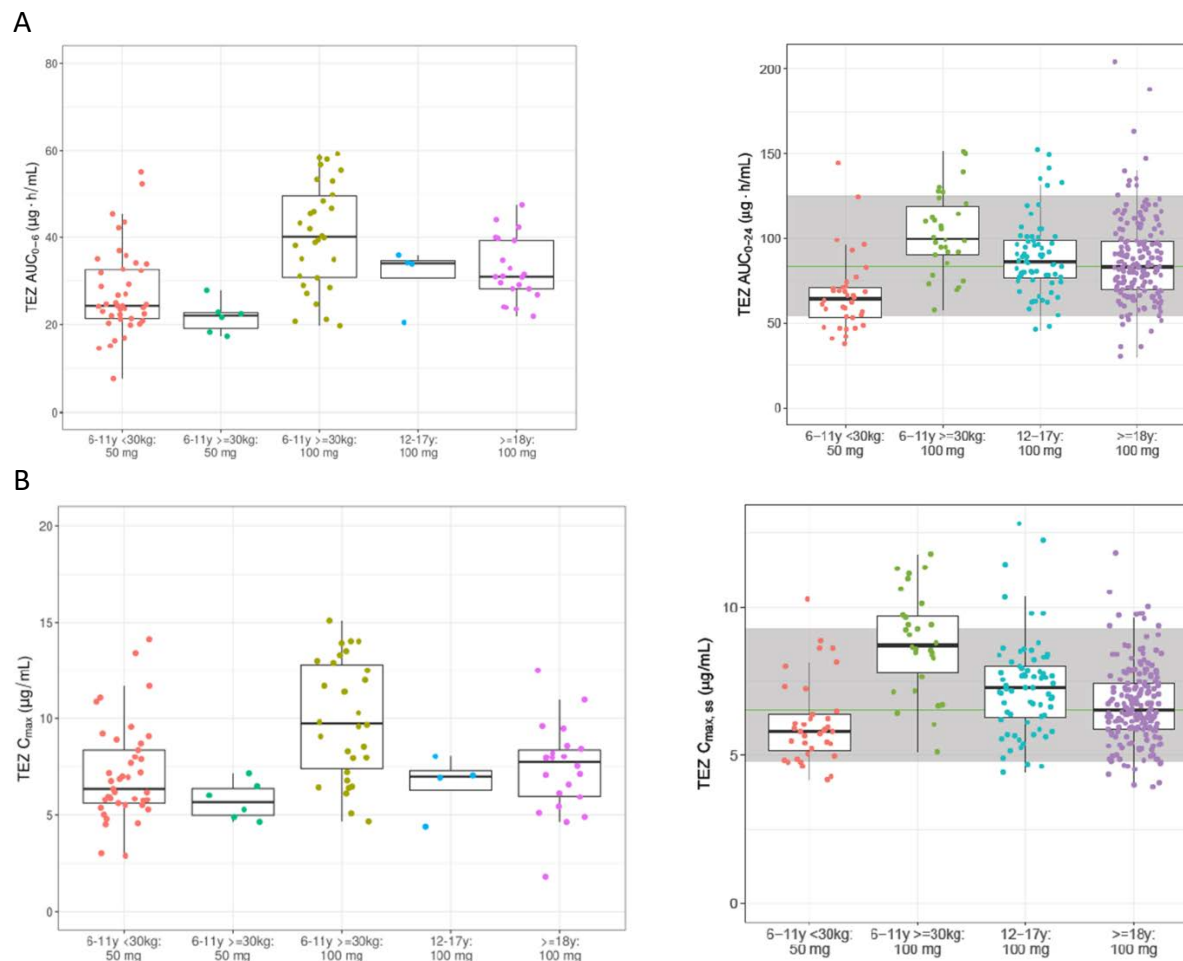


The gray shaded area indicates the 5th and 95th percentiles of the adult reference values. Source: Figure 1, 2, and 3 from clin-info-amend-response-ir-dated-28-jan-2021.pdf, page 3 and 4.

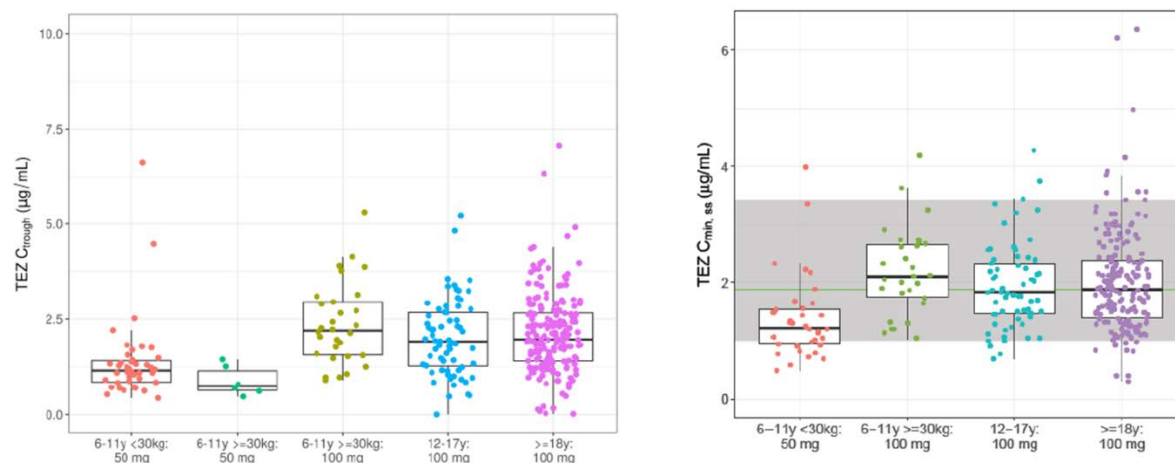
- TEZ and M1-TEZ PK comparison between children aged 6 to less than 12 years, adolescents, and adults.

For TEZ, the population PK model-estimated and the observed steady state AUC, Cmax, and Cmin values (Figure 6) from majority of children on the proposed doses were within the 5th and 95th percentiles of the adult reference values.

Figure 6. Boxplot comparison of TEZ steady state AUC (A), C_{max} (B), and C_{min} (C) between younger children, adolescents, and adults.



C

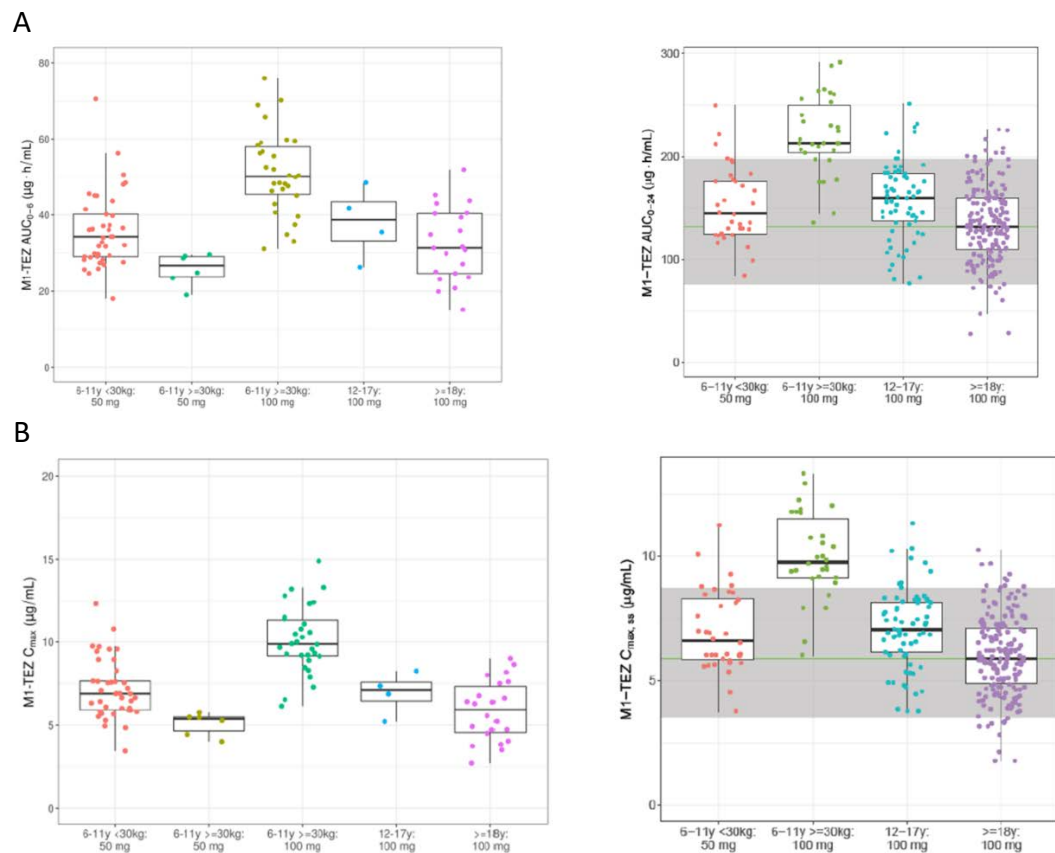


The left column is from observed values and the right column is from population PK-estimated values. The gray shaded area indicates the 5th and 95th percentiles of the adult reference values. Source: Figure 1, 2, 3 from clin-info-amend-response-ir-dated-28-jan-2021.pdf, page 3 to 9.

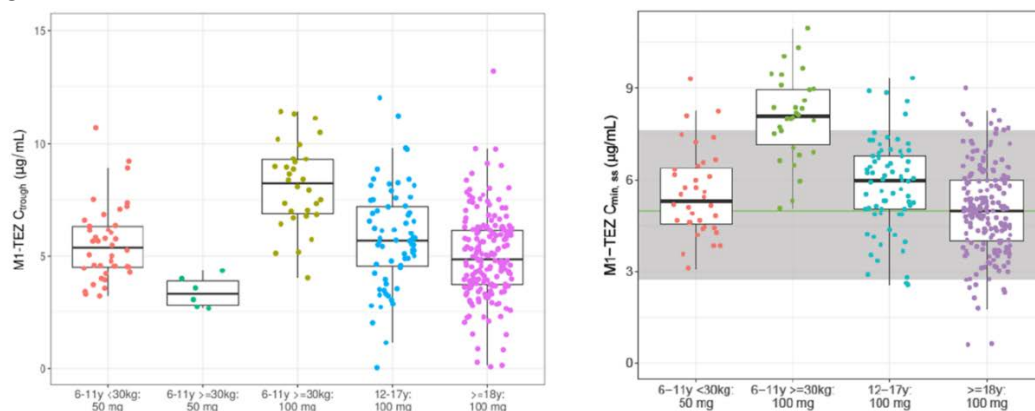
For M1-TEZ, the population PK model-estimated and the observed steady state AUC, Cmax, and Cmin values (Figure 7) from majority of children aged 6 to 11 years with body weight less than 30 kg and on 50 mg TEZ QD regimen were within the 5th and 95th percentiles of the adult reference values. Of note, M1-TEZ is an active metabolite of TEZ with similar pharmacologic potency.

However, the population PK model-estimated and the observed steady state AUC, Cmax, and Cmin values (Figure 7) from majority of children aged 6 to 11 years with body weight greater than or equal to 30 kg and on 100 mg TEZ QD regimen were above the 95th percentiles of the adult reference values.

Figure 7. Boxplot comparison of M1-TEZ steady state AUC (A), Cmax (B), and Cmin (C) between younger children, adolescents, and adults.



C



The left column is from observed values and the right column is from population PK-estimated values. The gray shaded area indicates the 5th and 95th percentiles of the adult reference values. Source: Figure 1, 2, 3 from clin-info-amend-response-ir-dated-28-jan-2021.pdf, page 3 to 9.

The population PK-estimated that M1-TEZ mean values of C_{min}, C_{max}, and AUC_t (Table 33) in children aged 6 to 11 years with body weight greater than or equal to 30 kg and on 100 mg TEZ QD regimen was about 40% and 60% higher than that of adolescents and adults who were on the same dosing regimen, respectively. In addition, the estimated AUC_t of M1-TEZ in children aged 6 to 11 years with body weight greater than or equal to 30 kg and on 100 mg TEZ QD regimen in Trial 106 was also higher than the estimated AUC_t (131 µg·h/mL, Table 15 from O350.pdf, page 55) of M1-TEZ in children aged 6 to 11 years with body weight greater than or equal to 40 kg and on 100 mg TEZ QD regimen from NDA 210491.

The cause of moderately increase of M1-TEZ in children aged 6 to 11 years with body weight greater than or equal to 30 kg and on 100 mg TEZ QD regimen from Trial 106 is unclear. However, by considering following justifications, there is a lack of compelling rationale for dose adjustment of TEZ in children aged 6 to 11 years with body weight greater than or equal to 30 kg on ETI treatment:

- 1) The increase of systemic exposure of M1-TEZ in this pediatric population is moderate (~40% to 60%) when compared to adolescents and adults on the same dosing regimen.
- 2) The systemic exposure of M1-TEZ only accounts for 21.6% of the orally administered TEZ dose (Table 11.3 from vx06-770-003-csr.pdf, page 51).

- 3) TEZ was not identified as an active ingredient with narrow therapeutic index in the CF clinical program (both NDAs 210491 and 212273).
- 4) There is no clear relationship between systemic exposure of M1-TEZ and liver enzyme elevation (Table 35).
- 5) A higher dose (300 mg QD) of TEZ with higher M1-TEZ systemic exposure was previously investigated in adults' program (Table 34).
- 6) A dose reduction of TEZ to match the exposure of M1-TEZ in this pediatric population with that of adolescents/adults will inevitably reduce the TEZ systemic exposure, which may reduce the efficacy of TEZ.

Table 34. Comparison of values of M1-TEZ AUC_{ss} and C_{max,ss} (observed or predicted) across different studies

Studies	TEZ Dosing regimen	Mean AUC _{ss} (µg·h/mL)	Mean C _{max,ss} (µg/mL)
NDA 210491, Study 010 (phase 1 study on healthy subjects)	200 mg QD for 7 days	244	11.5
	300 mg QD for 14 days	366	17.6
NDA 210491, Study 101 (phase 2 dose ranging study on adult patients)	150 mg QD for 28 days	193*	9.33*
NDA 210491, Study 113 (Pediatric Study)	100 mg QD for 24 weeks (≥ 40 kg children)	131*	6.08*
NDA 212273, Trial 106, Current pediatric study using ELX/TEZ/IVA	100 mg QD for 24 weeks (≥ 30 kg children)	220*	9.99*
	100 mg QD for adolescent	157*	7.09*
	100 mg for adult	134*	5.99*

* Predicted values per modeling and simulation.

Source: Table 11-2 (pg. 56), and Table 11-4 (pg. 60) of Trial 010; Table 11-4 (pg. 94) of Trial 101; Table 15 and 16 (pg. 55-56) of Pop-PK report O350 of NDA 210491, and Q076 population PK report of Trial 106: table 20, pg. 67

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

None.

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

Refer to previously approved drug label of NDA 212273.

Question on clinically relevant specifications?

In Part B of Trial 106, seven pediatric subjects experienced an increase in ALT $>3 \times$ ULN. Based on this finding, an Information Request was conveyed to the Applicant on March 4, 2021 requesting an evaluation between the ALT elevation and PK of ETI.

The Applicant provided a response on March 12, 2021 showing that there is no clear trend between ALT elevation and PK of ELX, M23-ELX, TEZ, M1-TEZ, and IVA. The distribution of systemic exposure of ELX, M23-ELX, TEZ, M1-TEZ, and IVA in those seven subjects with elevated ALT substantially overlapped with the distribution in other subjects without elevated ALT (Table 35).

Table 35. Observed Steady State Exposure Parameters based on Noncompartmental Analysis for Subjects with ALT >3 × ULN Compared to Subjects with ALT ≤3 × ULN

Analyte	Group	N	AUC _{0-6h} ^a (µg.h/mL)		C _{max} ^b (µg/mL)		N	C _{min} ^b (µg/mL)	
			Mean	Median (min, max)	Mean	Median (min, max)		Mean	Median (min, max)
ELX	ALT >3 × ULN	7	48.2	39.1 (21.4, 91.8)	11	9.3 (6.62, 19.4)	7	5.32	4.01 (2.39, 9.99)
	ALT ≤3 × ULN	55	38.3	32.7 (8.42, 91)	8.94	7.5 (1.88, 21.9)	56	3.98	3.44 (0.562, 12.7)
M23-ELX	ALT >3 × ULN	7	20.6	16.2 (4.02, 42)	4.26	3.55 (0.818, 8.22)	7	3.75	3.3 (0.541, 7.44)
	ALT ≤3 × ULN	55	17	11.1 (3.07, 62.9)	3.36	2.39 (0.685, 13.6)	56	2.83	1.85 (0.327, 12.2)
TEZ	ALT >3 × ULN	7	43.5	53.4 (19.7, 59.2)	10.8	13.5 (5.51, 14.1)	7	2.82	2.23 (0.714, 6.62)
	ALT ≤3 × ULN	55	32.5	29 (7.69, 57.9)	8.12	7.18 (2.88, 15.1)	56	1.75	1.4 (0.426, 5.31)
M1-TEZ	ALT >3 × ULN	7	46.7	45.1 (29.7, 69)	9.83	9.28 (5.9, 14.9)	7	7.68	7.08 (3.23, 11.3)
	ALT ≤3 × ULN	55	42.8	41.5 (18.1, 75.9)	8.47	8.31 (3.43, 13.3)	56	6.67	6.48 (3.31, 11.4)
IVA	ALT >3 × ULN	7	10.6	8.96 (2.86, 23.1)	2.38	1.99 (0.641, 4.74)	7	1.25	0.962 (0.104, 4.03)
	ALT ≤3 × ULN	55	6.32	5.22 (0.357, 14.1)	1.53	1.29 (0.0671, 3.65)	56	0.568	0.423 (0.0539, 2.33)

Source: Table 4, page 13 from clin-info-amend-response-ir-04mar2021.pdf

7 Sources of Clinical Data and Review Strategy

Table 36. Table of Clinical Studies

Trial Identity (Dates)	NCT no.	Trial Design	Regimen/schedule/route	Study Endpoints	Treatment Duration	No. enrolled	Study Population	No. of Centers and Countries
VX18-445-106 (Trial 106) 10/2/2018 to 8/7/2020	NCT03691779	Part A: OL, single arm	<u>ETI low dose</u> (all subjects): ELX 100 mg qd/TEZ 50 mg qd /IVA 75 mg q12h Oral administration	Primary: -PK of VX-445, TEZ, and IVA Secondary: -PK parameters of VX-445, TEZ, and IVA metabolites -Safety and tolerability	15 days	12 planned/ 16 enrolled	CF 6 to 11 years F/MF or F/F	US Sites: 6
		Part B: OL, single arm	<u>ETI low dose</u> (<30 kg): ELX 100 mg qd/ TEZ 50 mg qd / IVA 75 mg q12h <u>ETI high dose</u> (≥30 kg): ELX 200 mg qd/ TEZ 100 mg qd/ IVA 150 mg q12h Oral administration	Primary: -Safety and tolerability Secondary: -Absolute Δ ppFEV1 through Wk. 24 -Absolute Δ SwCl through Wk. 24 -Absolute Δ CFQ-R RD through Wk. 24 -Absolute Δ BMI, weight, height and z-scores at Wk. 24 -Number of PEx and CF-related hospitalizations through Wk. 24 -PK parameters of VX-445, TEZ, IVA, and relevant metabolites -Absolute Δ LCI _{2.5} through Wk. 24	24 weeks	56 planned/ 66 enrolled	CF 6 to 11 years F/MF or F/F	US, Canada, Ireland, UK, and Australia Sites: 21
VX19-445-107 (Study 107) ongoing	NCT04183790	OL study Single arm Multicenter	<u>ETI low dose</u> (<30 kg): ELX 100 mg qd/ TEZ 50 mg qd / IVA 75 mg q12h		Up to 96 weeks	66 Planned/ 64 enrolled	CF 6 to 11 years F/MF or F/F	US, Canada, Ireland, UK, and Australia

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{Trikafta (elexacaftor/tezacaftor/ivacaftor)}

			ETI high dose (≥30 kg): ELX 200 mg qd/ TEZ 100 mg qd/ IVA 150 mg q12h Oral administration				Subjects enrolled from Trial 106 Part B	
BMI: body mass index, CF: cystic fibrosis, CFQ-R: cystic fibrosis questionnaire-revised (respiratory domain), ETI: elexacaftor/ tezacaftor/ ivacaftor, ELX: elexacaftor, F/F: homozygous F508 del-<i>CFTR</i> mutation, F/MF: heterozygous F508 del-<i>CFTR</i> mutation and 2nd minimal function <i>CFTR</i> mutation; IVA: ivacaftor, , kg: kilogram, mg: milligrams, OL: open label, PEx: pulmonary exacerbations, PK: pharmacokinetic, ppFEV1: percent predicted forced expiratory volume in 1 second, qd: daily, q12h: every 12 hours , S: safety, T: tolerability, TEZ: tezacaftor, US: United States, UK: United Kingdom, wk.: week, Δ: change								

7.1. Review Strategy

The Applicant submitted clinical data from Study VX18-445-106 (Trial 106) to support expansion of the indication to include patients 6 to 11 years in age. Trial 106 was an open-label PK and safety study in patients 6 to 11 years in age with either a single *F508del* mutation and a second MF mutation (F/MF genotype; MF defined below in Section 8.1.1) or homozygous for the *F508del* mutation (F/F genotype). This study included two parts (A and B). Part A included a 15-day treatment period where the PK of ETI was assessed. Part B assessed PK, safety and efficacy in an open-label 24-week treatment period. Section 8.1.1 reviews the protocol for Trial 106.

For the evaluation of efficacy, the Applicant extrapolated efficacy from the adolescent and adult populations. However, while Trial 106 was primarily a safety/PK study, the Applicant included pharmacodynamic and efficacy-related endpoints. These data are presented in Sections 8.1.2, and a discussion of the overall efficacy for the proposed indication appears in Section 8.1.3. The statistical reviewer, Dr. Mingyu Xi, conducted efficacy analyses using methods pre-specified in the statistical analysis plan (SAP) and generated tables and figures for the efficacy review. Section 8.3 presents the statistical issues and considerations.

Section 8.2 presents the safety data. The clinical reviewer, Dr. Courtney McGuire, conducted analyses of safety data from the Phase 3 trial using JMP 15.0, JMP clinical and MAED. While the safety review considered safety data from Parts A and B, as Part A only included a 15-day treatment period compared to the 24-week treatment period in Part B, the clinical review focuses on Part B only.

Finally, Section 8.4 provides overall conclusions and recommendations.

For brevity, trials will be referred to in this review by the last 3 digits of the trial name.

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Trial 106 Study Design

Trial Design

Administrative information

Trial 106 was a multinational, pediatric safety study to provide evidence of efficacy and safety of ETI in patients with CF aged 6 to 11 years who are homozygous for *F508del* mutation on the *CFTR* gene or heterozygous for *F508del* mutation on the *CFTR* gene and a second MF mutation. The study was conducted from October 2, 2018 to August 7, 2020.

Study Title: A Phase 3 Study Evaluating the Pharmacokinetics, Safety, and Tolerability of VX-445/TEZ/IVA Triple Combination Therapy in Cystic Fibrosis Subjects 6 Through 11 Years of Age

- o **Study start date:** October 2, 2018
- o **Study completion:** August 7, 2020
- o **Study report date:** November 11, 2020
- o **Study sites:** Part A: 6 sites in US, Part B: 21 sites in North America, Europe and Australia.

Objectives/Rationale

Part A:

- *Primary*
 - o To evaluate the PK of ETI when dosed in TC
- *Secondary*
 - o To evaluate the PK of ETI metabolites
 - o To evaluate the safety and tolerability of ETI

Part B:

- *Primary*
 - o To evaluate the safety and tolerability of ETI through Week 24
- *Secondary Objectives:*
 - o To evaluate the efficacy of ETI through Week 24
 - o To evaluate the PK of ETI
 - o To evaluate the PK of ETI metabolites

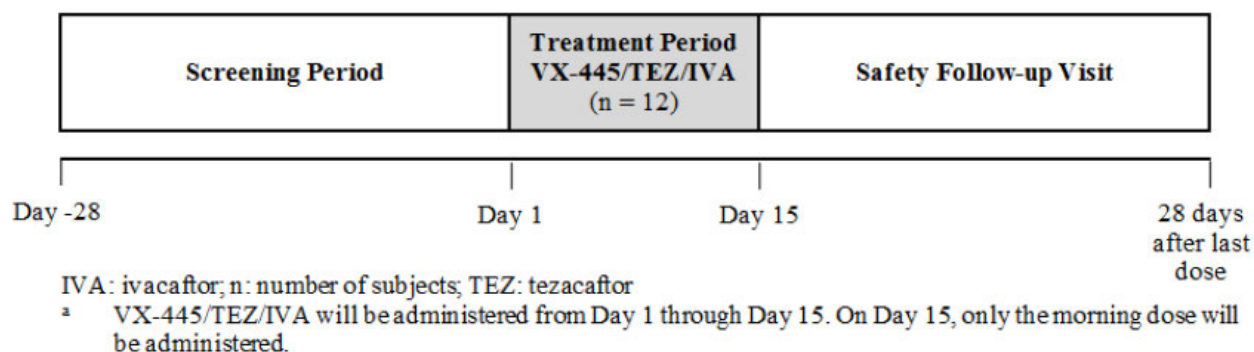
Study Design and Conduct

Overview

Trial 106 Part A was an open label, multicenter, PK study with a planned enrollment of approximately 12 patients. Part B was a 24-week open label, multicenter, single arm, single cohort study with a planned enrollment of approximately 56 patients. The trial required approximately 25 subjects to enroll with a F/MF genotype.

In Part A, following a 28-day screening period, eligible patients received ETI in a 15-day treatment period. Part A evaluated a single dose level of ETI. During the 15-day treatment period, PK samples were collected according to the Schedule of Assessments. Final follow-up occurred 28 days after the last dose. See Clinical Appendix Section 15.3.1 for the assessment schedule. The trial schematic for Part A appears in Figure 8.

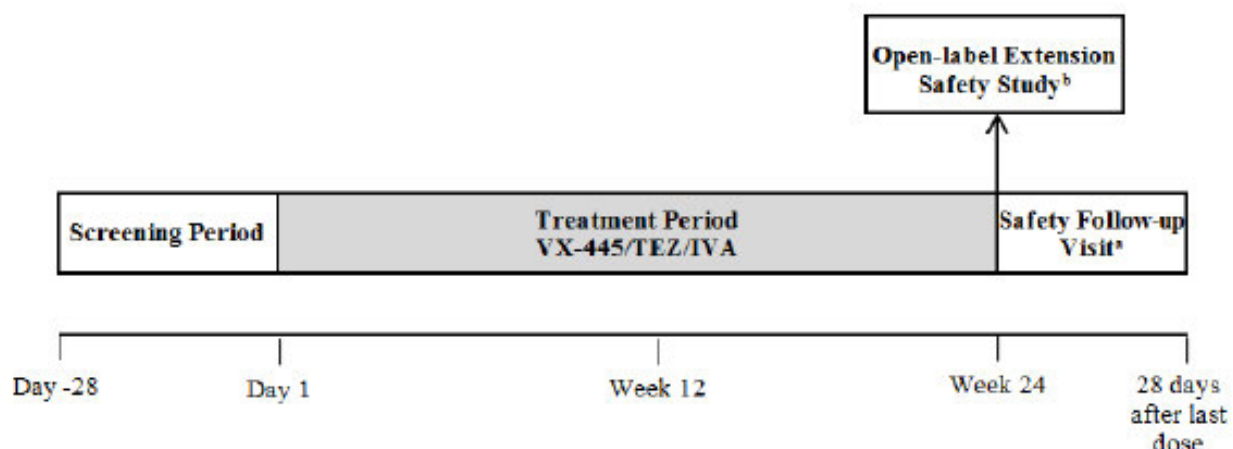
Figure 8. Study Schematic, Part A



Source. Clinical Trial Protocol VX18-445-106-16-1-1, Figure 9-1

Part B included a 28-day screening period, 24-week treatment period, and a 28-day follow-up period. During the treatment period, patients received weight based dosing with ETI for 24-weeks (see Table 37). Study visits occurred at Days 1, 3, 15 and Weeks 4, 8, 12, 16, 20, 24, and 26-weeks. For patients who had not participated in Part A, an ophthalmologic exam (OE) was performed prior to the initial dose and at Week 24. Following the treatment period all patients were allowed to continue in the open-label extension (OLE) study (Study 107). The trial schematic for Part B appears in Figure 9. See Clinical Appendix Section 15.3.1 for assessment schedule.

Figure 9. Study Schematic, Part B



IVA: ivacaftor; TEZ: tezacaftor

- ^a The Safety Follow-up Visit is scheduled to occur 4 weeks (± 7 days) after the last dose. This visit is not required for subjects who enroll in an optional open-label extension safety study within 28 days of the last dose.
- ^b Subjects who complete the visits in the Treatment Period, regardless of whether they are on a treatment interruption, will be offered the opportunity to enroll in an optional open-label extension safety study evaluating VX-445 in a triple combination regimen.

Source: Clinical Trial Protocol VX18-445-106-16-1-1, Figure 9-2

Reviewer comment: This was an open label study with no placebo or comparator arm. This was primarily a PK and safety study, and efficacy-related endpoints were secondary. While a placebo-controlled study would yield data that is clearer to interpret, an open label study was reasonable given that efficacy is primarily based on PK matching due to the same underlying pathophysiology of disease with adults/adolescents. Overall, the study design is typical of other pediatric trials with CF products.

Study Population

Key inclusion criteria:

1. Male and/or females, 6 through 11 years of age, inclusive, on the date of informed consent
2. Confirmed diagnosis of CF
3. Weight ≥ 15 kg
4. FEV1 $\geq 40\%$ of predicted normal for age, sex, and height using equations of the Global Lung Function Initiative (GLI)⁹ at the Screening Visit.
5. Stable CF disease at the start of the Treatment Period as deemed by the investigator

⁹ Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall GL, Culver BH, et al. Multi-ethnic reference values for spirometry for the 3–95-yr age range: the global lung function 2012 equations. *Eur Respir J.* 2012;40(6):1324-43.

6. Willing to remain on a stable CF medication regimen (other than CFTR modulators) through Day 15 (Part A) or through Week 24 (Part B) or, if applicable, through the Safety Follow-up Visit.
7. Able to swallow tablets
8. *F508del* homozygotes (F/F genotype) or heterozygous for *F508del* and a MF that is not responsive to IVA and TEZ/IVA. Refer to Section 15.3.2 Definition and Listing of Eligible Minimal Function Mutations for more details.

Key exclusion criteria

1. History of any illness or any clinical condition that, in the opinion of the investigator, might confound the results of the study or pose an additional risk in administering study drug(s) to the subject, including, but not limited to the following:
 - a. Clinically significant cirrhosis with or without portal hypertension
 - b. Solid organ or hematological transplantation.
 - c. Alcohol or drug abuse in the past year, including, but not limited to, cannabis, cocaine, and opiates, as deemed by the investigator.
 - d. Cancer, except for squamous cell skin cancer, basal cell skin cancer, and Stage 0 cervical carcinoma in situ (all 3 with no recurrence for the last 5 years)
2. Any clinically significant laboratory abnormalities at the Screening Visit that would interfere with the study assessments or pose an undue risk for the subject (as deemed by the investigator).
3. Any of the following abnormal laboratory values:
 - a. Any of the following abnormal laboratory values at screening:
 - b. Hemoglobin <10 g/dL
 - c. Total bilirubin $\geq 2 \times$ upper limit of normal (ULN)
 - d. Aspartate transaminase (AST), alanine transaminase (ALT), gamma-glutamyl transferase (GGT), or alkaline phosphatase (ALP) $\geq 3 \times$ ULN
 - e. Abnormal renal function defined as glomerular filtration rate ≤ 45 mL/min/1.73 m² (calculated by the Counahan-Barratt equation)¹⁰
4. An acute upper or lower respiratory infection, pulmonary exacerbation, or changes in therapy (including antibiotics) for pulmonary disease within 28 days before Day 1.
5. Treatment for or evidence of acute lung infection within 28 days of screening
6. Lung infection with organisms associated with a more rapid decline in pulmonary status (including, but not limited to, *Burkholderia cenocepacia*, *Burkholderia dolosa*, and *Mycobacterium abscessus*). For subjects who have had a history of a positive culture, the

¹⁰ Counahan R, Chantler C, Ghazali S, Kirkwood B, Rose F, Barratt TM. Estimation of glomerular filtration rate from plasma creatinine concentration in children. Arch Dis Child. 1976;51(11):875-78.

investigator will apply the following criteria to establish whether the subject is free of infection with such organisms:

- a. The subject has not had a respiratory tract culture positive for these organisms within the 12 months before the date of informed consent and assent.
 - b. The subject has had at least 2 respiratory tract cultures negative for such organisms within the 12 months before the date of informed consent, with the first and last of these separated by at least 3 months, and the most recent one within the 6 months before the date of informed consent and assent.
7. An acute illness not related to CF (e.g., gastroenteritis) within 14 days before Day 1.

Reviewer comment: Overall the inclusion and exclusion criteria were generally reasonable to define the study population and support the proposed indication. The inclusion and exclusion criteria are similar to that used in the ETI and TEZ/IVA Phase 3 studies.

Dose and Duration of Treatment

The ETI dosage for Parts A and B appears in the following table:

Table 37. Investigational Drug Dosage, Trial 106 Part A and B

Part Subject weight	Ellexacaftor	Tezacaftor	Ivacaftor
Part A All weights	100 mg qd	50 mg qd	75 mg q12h
Part B Patients < 30 kg Patients ≥ 30 kg	100 mg qd 200 mg qd	50 mg qd 100 mg qd	75 mg q12h 150 mg q12h

q12hr: every 12 hours; qd: once daily

Compliance was assessed by calculating the percentage of tablets consumed relative to the number of tablets expected to be consumed.

Reviewer comment. The ETI dosage is reasonable. The TEZ/IVA weight-based dosage in Part B is the approved pediatric dose under NDA 210491. With respect to ELX, the dose of 200 mg (≥ 30 kg) is the approved dose in CF patients aged ≥ 12 years old with F/MF or F/F genotype in phase 3 studies. The ELX dose of 100 mg (< 30 kg) was selected based on population-PK modeling using adult data; the 100 mg dose is predicted to provide exposures equivalent to adult exposures over a range of weights from 15 to 50 kg. Further discussion of the PK and dosing regimen appears in Section 6.

Concomitant medications

The trial allowed administration of study drug on a background of standard-of-care CF therapy. Stable medication and supplement regimens for CF were allowed if there were no changes from 28 days before Day 1 through completion of study participation, but new chronic therapies

could not be initiated from 28 days before Day 1 visit through completion of study participation. Subjects taking chronically inhaled tobramycin or other chronically inhaled antibiotics remained on the regimen throughout the study; subjects who cycle on and off an antibiotic or who alternate between two different inhaled antibiotics were to continue the prior schedule. Subjects could receive doses of prednisone or prednisolone up to 10 mg/day chronically, or up to 60 mg daily for up to 5 days. Bronchodilators were allowed but were to be withheld prior to spirometry assessments. Prohibited medications appear in Table 38.

Table 38. Prohibited Medications

Medication	Start Restriction	End Restriction
Moderate and strong CYP3A inducers	None allowed within 14 days before the first dose of the study drug on Day 1	None allowed through completion of study participation
Moderate and strong CYP3A inhibitors (except ciprofloxacin)		
CFTR modulators (investigational or approved), except for study drugs	None allowed within 28 days before the first dose of the study drug on Day 1	None allowed until after the last dose of study drug
CYP: cytochrome P450; IVA: ivacaftor Source. Adapted from Table 9.2 Protocol VX18-445-106-1-1, Version 3.0		

Reviewer comment: Overall, the handling of concomitant and prohibited medications is reasonable. Similar to the prior TEZ/IVA and ETI studies, hypertonic saline was not a prohibited medication.

Study Drug Interruption Rules

Rash

The protocol stated that study drug should be interrupted if a subject develops a generalized rash of Grade 3 or higher, or a rash that is considered a SAE. The investigator would notify the medical monitor of any rash that results in interruption of study drug, is Grade 3 or higher or is a SAE. Investigators should consider additional evaluation including laboratory testing (e.g., complete blood count with differential, LFTs), photographs of the rash, and dermatology consultation. The investigator could consider resumption of study drug if considered clinically appropriate.

Liver Function Tests

The protocol stated that study drug administration must be interrupted immediately (prior to confirmatory testing) if any of the following criteria were met:

- ALT or AST $>8 \times$ upper limit of normal (ULN)
 - ALT or AST $>5 \times$ ULN for more than 2 weeks
 - ALT or AST $>3 \times$ ULN, in association with total bilirubin $>2 \times$ ULN and/or clinical jaundice
- A thorough investigation of potential causes should be conducted, and the subject should be followed closely for clinical progression.

Study drug administration must be discontinued if the following criterion was met:

- Subsequent ALT or AST values confirm the initial elevation that satisfied the interruption rule (above), and no convincing alternative etiology (e.g., acetaminophen use, viral hepatitis, alcohol ingestion) was identified, regardless of whether transaminase levels have improved

All subjects in whom treatment was discontinued for elevated transaminases (and bilirubin, as applicable) should have these levels monitored closely until levels normalize or return to baseline.

If an alternative, reversible cause of transaminase elevation with or without increased bilirubin or clinical jaundice has been identified, study drug administration may be resumed once transaminases return to baseline or are $\leq 2 \times \text{ULN}$, whichever was higher. Upon resumption of study drug, transaminases and bilirubin were to be assessed weekly for 4 weeks. If a protocol-defined transaminase elevation interruption threshold recurs within 4 weeks of rechallenge with the study drug (with confirmation of the initial elevation by repeat testing within 48 to 72 hours), then the study drug was to be permanently discontinued, regardless of the presumed etiology.

Subject Removal Criteria

Subjects were withdrawn from the study for any of the following:

- Anytime at the discretion of the investigator or the Applicant for safety, behavior, noncompliance with study procedures, or administrative reasons.
- Pregnancy
- Screening *CFTR* genotype that does not confirm study eligibility
- Meets any study discontinuation criteria (see above)

Subjects that discontinued study medication were to be followed, provided that the subject did not withdraw consent (or assent where applicable).

Study Endpoints

Primary endpoint (safety)

The primary endpoint was safety and tolerability assessments as determined by AEs, clinical laboratory values, standard 12-lead ECGs, vital signs (VS), pulse oximetry, and OE, collected per the assessment schedule (see Clinical Appendix Section 19.6.1 for assessment schedule).

Secondary endpoints:

Part B included the following secondary endpoints:

- Absolute change in ppFEV1 from baseline through Week 24
- Absolute change in SwCl from baseline through Week 24

- Absolute change in CFQ-RD score from baseline through Week 24
- Absolute change in body mass index (BMI) and BMI-for-age z-score from baseline at Week 24
- Absolute change in weight and weight-for-age z-score from baseline at Week 24
- Absolute change in height and height-for-age z-score from baseline at Week 24
- Drug acceptability assessment using Modified Facial Hedonic Scale
- Number of pulmonary exacerbations (PEx) and CF-related hospitalizations through Week 24
- PK parameters of ELX, TEZ, IVA, and relevant metabolites
- Absolute change in lung clearance index 2.5 (LCI2.5) from baseline through Week 24

Reviewer comment: Overall, the secondary efficacy endpoints in Part B evaluate a number of factors considered to be clinically meaningful to patients with CF (i.e. ppFEV1, CFQ-R RD, BMI, SwCl, weight, and PExs).

Statistical Analysis Plan

Safety Analysis

Analysis of safety was descriptive with no formal statistical testing.

Efficacy Analysis

For Part B, efficacy is a secondary objective of the study, there was no multiplicity adjustment; all *P*-values are considered nominal.

The main efficacy analyses were based on the full analysis set which was defined as all enrolled subjects who carry the intended *CFTR* allele mutation and received at least 1 dose of study drug. Each continuous efficacy endpoint was analyzed using a mixed-effects model for repeated measures that included visit as the fixed effect, with baseline value of the efficacy variable and genotype group (F/F or F/MF) as covariates. The model included all measurements of the efficacy variable up to week 24, whether assessed on treatment or after treatment discontinuation.

Reviewer comment: Because all analyses were performed using open-label data and given the lack of a comparator arm, caution should be exercised in the interpretation of any efficacy data.

Protocol Amendments

This protocol was amended 2 times. Pertinent changes are summarized below.

Amendment 1, dated June 7, 2019, incorporated updates to the study design for Part B, including addition of dose justification for Part B based on data from Part A.

- Removed G6PD deficiency and history of hemolysis as exclusion criteria for Part B.
- Updated inclusion criterion 7 to require subjects to have stable CF disease before entering the Treatment Period.
- Based on further in vitro characterization, OATP1B1 substrates were removed from the prohibited medications list
- Removed herbal and dietary supplements from the list of prohibited medications for consistency with concomitant medication guidance in other studies evaluating this study drug regimen.
- Provided additional guidance on cycling antibiotics, P-gp and CYP2C9 substrates, prednisone, and bronchodilator use.
- Updated baseline definition and analysis for secondary efficacy and pharmacodynamic endpoints in Part B to provide more details on the planned analysis.
- Updated guidance on missed doses to ensure subjects prioritize taking their triple combination dose rather than the IVA tablet.

Amendment 2, dated December 18, 2019, incorporated the following changes:

- Removed 120 minute predose assessment window due to feedback about feasibility from clinical sites.
- Removed restriction against performing blood collection at the same time as sweat chloride collection in Part B
- Clarified text regarding timing of ophthalmologic examinations.
- Removed requirement for subjects with QTcF above threshold value to discontinue study drug treatment.

Reviewer comment. In general, the amendments are unlikely to impact the interpretation of the study results.

The Applicant also incorporated measures to minimize unnecessary risk to COVID-19 exposure through travel to study sites. Operational adjustments were implemented to align with Health Authority guidance ensuring the protection of subjects, investigators, and site personnel while maintaining compliance with GCP and minimizing impact to the integrity of the studies. The key changes appear below:

Addendum 1.0, dated April 24, 2020

Safety Assessments:

- Study visits may be conducted as in-home visits by qualified personnel as requested by participating sites on a per-subject basis. In addition, all subjects may be contacted by site personnel by telephone or video call, irrespective of in-home visits.
- Blood and/or urine samples for safety assessments may be collected and analyzed at local laboratories for subjects who do not have in-home visits, but do not complete the assessment at the site.
- In addition, safety assessments will be evaluated by telephone (AEs, signs and symptoms for CF, medications, planned or unplanned hospitalizations for CF, study drug administration, outcomes related to PEx, outcomes related to antibiotic treatment)
- Investigators will review results (in-home and telephone) and contact subjects for follow-up as needed.
- All data will continue to be retained in the subject's source files.
- Any clinically significant finding (e.g., AE, SAE, laboratory abnormalities) will continue to be reported as indicated per protocol.

Efficacy Assessments

- Efficacy and other assessments, as indicated per protocol, may be performed by qualified personnel conducting the in-home visits. These assessments may include the following, as indicated per protocol, and per local regulation.
 - A spirometry device may be provided to subjects for in-home assessments of lung function as indicated per protocol. Sites and subjects will receive training and guidance as needed.
 - CFQ-R questionnaires may be provided to subjects (electronically or post mail) to be completed at home as indicated per protocol. Subjects will return these questionnaires to the site via post mail
 - Other assessments (ECGs, SwCl, etc.)

Addendum 2.0, dated May 15, 2020

- Weight and height/length/stature may be assessed by subjects or their caregivers using medical grade scales and stadiometers, as indicated per protocol and per local regulation. Sites and subjects will receive training and guidance as needed on these devices.
- Subjects or caregivers will provide these measurements to site personnel by telephone or video call. Investigators will review results and contact subjects for follow-up as needed. All data will continue to be retained in the subject's source files.

Addendum 3.0, dated July 29, 2020

- Unscheduled visit(s) will be permissible at the discretion of the investigator(s) or Vertex. The unscheduled visit(s) may be conducted at any time during the study (including after the protocol defined last study visit) in the event assessments specified to be collected at a

scheduled visit were not collected due to COVID-19.

Reviewer comment. In general, the changes made due to the COVID-19 impact were reasonable to minimize risk to study subjects and study personnel. As discussed in Section 8.1.2 and 8.2.3, these changes were unlikely to impact the interpretation of the study results.

8.1.2. Study Results

Compliance with Good Clinical Practices

The Applicant states that the study was conducted in accordance with Good Clinical Practices as described in Integrated Addendum to ICH Guideline E6 (R2), Good Clinical Practice (November 2016). The study protocol, amendments, informed consent, and other necessary documents were reviewed and approved by an independent ethics committee or institutional review board for each study site before initiation of the study at that site. Written informed consent was obtained from each subject / guardian before study participation. This study was conducted under IND 132,547.

Financial Disclosure

The Applicant has adequately disclosed financial interests and arrangements with clinical investigators as recommended in the guidance for industry Financial Disclosure by Clinical Investigators (Section 15.1).

Patient Disposition

Trial 106 had high completion rates. In Part B, 97% of subjects completed study treatment (Table 39)

Table 39. Subject Disposition, Trial 106 Part B

Disposition Reason	ETI Low Dose N=36	ETI High Dose N=30	Total N=66
All Subjects Set	36	30	66
Randomized	36	30	66
FAS	36	30	66
Safety Set	36	30	66
Completed treatment	35 (97)	29 (97)	64 (97)
Prematurely discontinued treatment	1 (3)	1 (3)	2 (3)
Adverse event	1 (3)	0	1 (1.5)
Other ⁴	0	1 (3)	1 (1.5)
Completed study	35 (97)	29 (97)	64 (97)
Prematurely discontinued study	1 (3)	1 (3)	2 (3)

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Adverse event	1 (3)	0	1 (1.5)
Withdrawal of consent (not due to AE)	0	1 (3)	1 (1.5)
Rollover to the extension study	35 (97)	29 (97)	64 (97)

AE: adverse event; COVID-19: coronavirus disease; ETI Low Dose: elexacaftor 100 mg qd / tezacaftor 50 mg qd / ivacaftor 75 mg q12h; ETI High Dose: elexacaftor 200 mg qd / tezacaftor 100 mg qd / ivacaftor 150 mg q12h; FAS: Full Analysis Set; n: size of subsample,
¹All Subjects Set included all subjects who were enrolled or received at least 1 dose of study drug (in Part B
²FAS included all enrolled subjects who carry the intended *CFTR* allele mutation and received at least 1 dose of study drug.
³Safety Set included all subjects who received at least 1 dose of study drug.
⁴The subject did not want to leave home due to the COVID-19 pandemic and therefore switched to commercially available drug.
Source: Reviewer calculated in JMP 15.0 using ADSL dataset and the following parameters: EOSSTT, DCSREAS, EOTSTT, DCTREA1, ALLFL, SAFFL, FASFL, WTBGR1.

Protocol Violations/Deviations

The Applicant defined an important protocol deviation (IPD) as a deviation that may have significantly affected the completeness, accuracy, and/or reliability of the study data, or that may have significantly affected the subject's rights, safety, or well-being. Two (3%) subjects had IPDs in which the screening ppFEV1 assessment was completed before informed consent/screening.

Reviewer comment. The number and type of IPDs are unlikely to impact the outcome of the trial.

Table of Demographic Characteristics

Subjects in Trial 106 were predominately white and non-Hispanic with a mean age of 9 years (Table 40).

Table 40. Demographic Characteristics, Trial 106 Part B, FAS

Characteristic	ETI Low Dose N=36 n(%)	ETI High Dose N=30 n(%)	Total N=66 n(%)
Sex			
Male	10 (28)	13 (43)	27 (41)
Female	26 (72)	17 (57)	39 (59)
Age			
Mean years (SD)	8.0 (1.3)	10.9 (1.0)	9.3 (1.9)
Median (years)	7.8	10.9	9.6
Min, max (years)	6.1, 10.6	8.1, 12.1	6, 11
Age Group			
6 to 9 years	33 (92)	5 (17)	38 (58)
10 to 12 years	3 (8)	25 (83)	28 (42)
Race			
White	31 (86)	27 ^a (90)	58 ^a (88)
Black or African American	0	0	0
Asian	0	1 ^a (3)	1 ^a (2)

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Not collected per local regulations ^b	5 (14)	3 (10)	8 (12)
Ethnicity			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	31 (86)	27 (90)	59 (88)
Not collected per local regulations	5 (14)	3 (10)	8 (12)
Region			
North America	24 (67)	23 (77)	47 (71)
Europe and Australia	12 (33)	7 (23)	19 (29)
ETI Low Dose: elexacaftor 100 mg qd / tezacaftor 50 mg qd / ivacaftor 75 mg q12h; ETI High Dose: elexacaftor 200 mg qd / tezacaftor 100 mg qd / ivacaftor 150 mg q12h; n: size of subsample; FAS: Full Analysis Set; SD: standard deviation			
^a A single subject reported race as both white and Asian.			
^b Data on race and/or ethnicity were not collected because of local regulations.			
Source. Reviewer calculated with Part B datasets ADSL.xpt in JMP 15.0 selecting FASFL(Y) and variables analysis age, sex, analysis race, analysis ethnicity, and geographic region 1.			

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

Overall, the baseline disease characteristics and background therapy were consistent with a pediatric CF population. Fewer than half of the enrolled patients were colonized by pseudomonas (39%). The trial population had a mean (SD) baseline ppFEV1 of 88.8% (18) and a CFQ-R RD score of 80.3 (15). Baseline characteristics appear in Table 41.

Table 41. Baseline Characteristics, Trial 106 Part B, FAS

Parameter	ETI Low Dose N=36 n(%)	ETI High Dose N=30 n(%)	Total N=66 n(%)
CFTR genotype group, n (%)			
F/F	16 (44)	13 (43)	29 (44)
F/MF	20 (56)	17 (57)	37 (56)
ppFEV1			
n	35	27	62
Mean (SD)	84.9 (18.6)	93.7 (15.5)	88.8 (18)
Median	89.0	95.0	89.3
Min, max	39.0, 113.8	69.4, 127.1	39.0, 127.1
ppFEV1 category at baseline, n (%)			
<70%	9 (25)	1 (3)	10 (15)
≥70 to <90%	10 (28)	12 (40)	22 (33)
>90%	16 (44)	14 (47)	30 (45)
Missing	1 (3)	3 (10)	4 (6)
SwCl (mmol/L)			
n	33	29	62
Mean (SD)	102.4 (10.6)	102.1 (7.3)	102.2 (9)
Median	103.5	101	101.5
Min, max	75.5, 122	90, 119	75.5, 122.0

NDA/BLA Multi-disciplinary Review and Evaluation {NDA 212273}
{Trikafta (elexacaftor/tezacaftor/ivacaftor)}

Weight group, n (%)			
<30 kg	36 (100)	0	36 (54)
≥30 kg	0	30 (100)	30 (46)
Weight (kg)			
Mean (SD)	24.3 (3.4)	36.8 (5.8)	30.0 (7.7)
Median	24.1	35.1	29
Min, max	18.1 29.5	30.1, 53.6	18.1, 53.6
BMI (kg/m²)¹			
Mean (SD)	15.4 (1.2)	17.6 (1.4)	16.4 (1.7)
Median	15.4	17.3	16.3
Min, max	13.4, 17.8	15.5, 20.9	13.4, 20.9
CFQ-R respiratory domain score (points)			
n	35	30	65
Mean (SD)	79.5 (15.3)	81.1 (15.3)	80.3 (15)
Median	83.3	83.3	83.3
Min, max	33.3, 100	50, 100	33.3, 100
LCI2.5 at baseline			
n	28	25	53
Mean (SD)	9.6 (2.3)	10.0 (3.1)	9.8 (3)
Median	9.4	9.0	9.21
Min, max	6.9, 16.7	6.9, 20.1	6.9, 20.1
Background therapy,² n (%)			
CFTR modulator	7 (19)	7 (23)	14 (21)
Dornase alfa	30 (83)	24 (80)	54 (82)
Azithromycin	10 (28)	9 (30)	19 (29)
Inhaled antibiotic	3 (8)	5 (17)	8 (12)
Inhaled Bronchodilator	31 (86)	30 (100)	61 (92)
Inhaled hypertonic saline	26 (72)	26 (87)	52 (79)
Pseudomonas colonization within 2 years			
Positive	14 (39)	12 (40)	26 (39)
BMI: body mass index; CFQ-R: Cystic Fibrosis Questionnaire-Revised; ETI Low Dose: elexacaftor 100 mg qd / tezacaftor 50 mg qd / ivacaftor 75 mg q12h; ETI High Dose: elexacaftor 200 mg qd / tezacaftor 100 mg qd / ivacaftor 150 mg q12h; FAS: Full Analysis Set; F/F: homozygous for <i>F508del</i>; F/MF: heterozygous for <i>F508del</i> and a <i>CFTR</i> minimal function mutation; LCI2.5: number of lung turnovers required to reduce the end tidal inert gas concentration to 1/40th of its starting value; n: size of subsample; N: total sample size; ppFEV1: percent predicted forced expiratory volume in 1 second Notes: Baseline was defined as the most recent non-missing measurement before the first dose of study drug in Part B. ¹ BMI = weight / (height × height) (kg/m²). ² Includes medications administered during the 56 days before the first dose of study drug in Part B. Source: Source. Reviewer calculated with Part B datasets ADSL.xpt in JMP 15.0 selecting FASFL(Y) and variables analysis by Baseline weight, Baseline weight group 1, baseline body mass index, BL percent predicted FEV1 Group 1, BL percent predicted FEV1 Group 1 (N) Baseline Sweat Chloride, Baseline LCI2.5, Baseline CFQ-R Respiratory Domain Score, Prior use flags. Pr Pseudomonas aeruginosa Status Group 1, actual arm code.			

Reviewer comment. The baseline characteristics reflect a CF population. Consistent with a younger population, subjects enrolled in Trial 106 had a higher ppFEV1 (88.8%) than that of both adult trials 102 and 103 (approximately 61%).

The enrolled population in Part B included 44% subjects with a F/F genotype and 56% with a F/MF genotype. Among the MF subgroup, there were 16 different MF mutations. G542X was the most common MF mutation (13, 20%). Specific mutations reported in at least 1 subject appear in Table 42.

Table 42. Genotype Distribution for Mutations, Trial 106 Part B, FAS

Genotype	ETI Low Dose N=36 n(%)	ETI High Dose N=30 n(%)	Total N=66 n(%)
<i>F508del / F508del</i>	16 (44)	13 (43)	29 (44)
<i>F508del / minimal function mutation</i>	20 (56)	17 (57)	37 (56)
<i>F508del / G542X</i>	7 (19)	6 (20)	13 (20)
<i>F508del / N1303K</i>	3 (8)	1 (3)	4 (6)
<i>F508del / 1078delT</i>	2 (6)	1 (3)	3 (4)
<i>F508del / R560T</i>	2 (6)	1 (3)	3 (4)
<i>F508del / 3659delC</i>	1 (3)	1 (3)	2 (3)
<i>F508del / E60X</i>	1 (3)	1 (3)	2 (3)
<i>F508del / R553X</i>	2 (6)	0	2 (3)
<i>F508del / 621+1G>T</i>	0	1 (3)	1 (2)
<i>F508del / 1154insTC</i>	1 (3)	0	1 (2)
<i>F508del / 1811+1.6kb A>G</i>	0	1 (3)	1 (2)
<i>F508del / 1898+1G>A</i>	0	1 (3)	1 (2)
<i>F508del / CFTR dele2, 3</i>	0	1 (3)	1 (2)
<i>F508del / CFTRdele17a,17b</i>	0	1 (3)	1 (2)
<i>F508del / E379X</i>	0	1 (3)	1 (2)
<i>F508del / V520F</i>	1 (3)	0	1 (2)
ETI Low Dose: elexacaftor 100 mg qd / tezacaftor 50 mg qd / ivacaftor 75 mg q12h; ETI High Dose: elexacaftor 200 mg qd / tezacaftor 100 mg qd / ivacaftor 150 mg q12h; n: size of subsample; N: total sample size; Source: Reviewer calculated in JMP 15.0 using Part B ADSL/xpt datasets and CF Genotyping variable			

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Investigators formally assessed compliance by ongoing study drug count. The Applicant calculated the compliance rate using the following formula:

$$100 \times \left(1 - \frac{\text{total number of days of study drug interruption}}{\text{duration of study drug exposure in days}} \right)$$

In addition, percentage of tablets taken was calculated using the following formula:

$$100 \times \frac{\text{total number of tables dispensed} - \text{total number of tablets returned}}{\text{total number of tablets planned per day} \times \text{duration of study drug exposure in days}}$$

In Part B, the mean compliance rate was great than or equal to 99.4% for all subjects. All subjects reported >89.5% of tablets taken, with a mean of approximately 99%.

Concomitant medication use, defined as medication that was continued or newly received during the Treatment Emergent Period (TE Period), reflected a CF population. Individual medications with greater than 15 subjects appear in Table 43.

Table 43. Concomitant Medications in ≥15 subjects, Trial 106 Part B, FAS

Medication (Preferred name)	ETI Low Dose N=36 n (%)	ETI High Dose N=30 n (%)	Total (N=66) n (%)
Subjects with any concomitant medication	36 (100)	30 (100)	66 (100)
Sodium chloride	30 (80)	27 (90)	57 (86)
Dornase alfa	30 (80)	25 (83)	55 (83)
Salbutamol	26 (72)	27 (90)	53 (80)
Pancreatin	26 (72)	20 (67)	46 (70)
Fluticasone propionate	14 (39)	9 (30)	23 (35)
Multivitamin ¹	7 (19)	13 (43)	20 (30)
Azithromycin	11 (31)	9 (30)	20 (30)
Ibuprofen	10 (28)	10 (33)	20 (30)
Pancrelipase	9 (25)	10 (33)	19 (29)
Macrogol 3350	10 (28)	8 (27)	18 (27)
Paracetamol	10 (28)	7 (23)	17 (26)
Omeprazole	6 (17)	10 (33)	16 (24)

ETI Low Dose: elexacaftor 100 mg qd / tezacaftor 50 mg qd / ivacaftor 75 mg q12h; ETI High Dose: elexacaftor 200 mg qd / tezacaftor 100 mg qd / ivacaftor 150 mg q12h; FAS: Full Analysis Set; n: size of subsample; N: total sample size

¹Standardized medication name: Ascorbic acid/ beta carotene/ biotin/ calcium pantothenate/ cholecalciferol/ cyanocobalamin/ folic acid/ nicotinamide/ phytomenadione/ pyridoxine hydrochloride/ retinol palmitate/ riboflavin/ thiamine mononitrate/ tocopherol/ zinc ascorbate

Notes: Medications were coded using WHODrug Global, version March 2020, format B3. PNs were sorted in descending order of frequency. A subject with multiple medications with the same PN was counted only once for that PN. Concomitant medication was defined as medication that was continued or newly received during the TE Period of Part B.

Source: Table 14.1.6.2b. Reviewer confirmed using ADAM dataset in JMP 12.0 selecting for FASFL(Y), ONTRTFL(Y) by CMDECOD, WTBLGR1.

Efficacy Results – Primary Endpoint

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

Data Quality and Integrity

This NDA was submitted on 12/8/20. The submission was appropriately indexed and complete

to allow for review. This review did not reveal any inconsistencies in the data or issues with trial design or conduct which might influence the efficacy results. However, the review team identified a higher rate of missing efficacy data for Trial 106 Part B compared to previous IVA and TEZ/IVA pediatric trials. The majority of missing data was due to the COVID-19 pandemic, either because the subject did not have an in-clinic visit or because the subject had an in-clinic visit which was impacted by COVID-19 and some assessments were not performed; many clinical sites had restrictions in place to avoid exposure to COVID-19 which meant that these efficacy assessments were not feasible. The remaining reasons for missing data included subjects who discontinued treatment in Trial 106 Part B, and assessments that were collected but were considered missing for analysis purposes (assessment not meeting ATS criteria for ppFEV1, sweat volume insufficient or results out of range for SwCl, or greater than half of questions with answers missing for CFQ-R RD score). These missing data were consistent (both in frequency and the reasons for the missing data) with previous experience of efficacy assessments performed in trials of subjects with CF 6 through 11 years of age.

The Applicant provided reasons for missing data at each visit for ppFEV1, SwCl, CFQ-R, BMI, and weight, and a summary of data collected at unscheduled visits due to COVID-19. To evaluate the impact of missing data to the study result, the statistical reviewer conducted additional analyses. Results and discussions will be presented in Section 8.3 Statistical Issues.

Efficacy Results – Secondary and other relevant endpoints

Trial 106 evaluated multiple secondary efficacy endpoints, but did not control for multiplicity, thus p values are considered nominal. This section focuses on the following non-PK related secondary endpoints:

- Absolute change in ppFEV1 from baseline through Week 24
- Absolute change in SwCl from baseline through Week 24
- Absolute change in CFQ-R respiratory domain score from baseline through Week 24
- Absolute change in BMI and BMI-for-age z-score from baseline at Week 24
- Absolute change in weight and weight-for-age z-score from baseline at Week 24
- Absolute change in height and height-for-age z-score from baseline at Week 24

ppFEV1

Treatment with ETI resulted in nominal within subject improvements in ppFEV1 through Week 24. The LS mean within subject change from baseline in ppFEV1 through Week 24 was 10.2% (95% CI: 7.9, 12.6), representing a clinically meaningful improvement in ppFEV1 consistent with the within group ETI treatment effect seen in the adult studies. These data are summarized in Table 44.

Table 44. MMRM Analysis of Absolute Change from Baseline in ppFEV1 (%) through Week 24 (Trial 106 Part B, FAS)

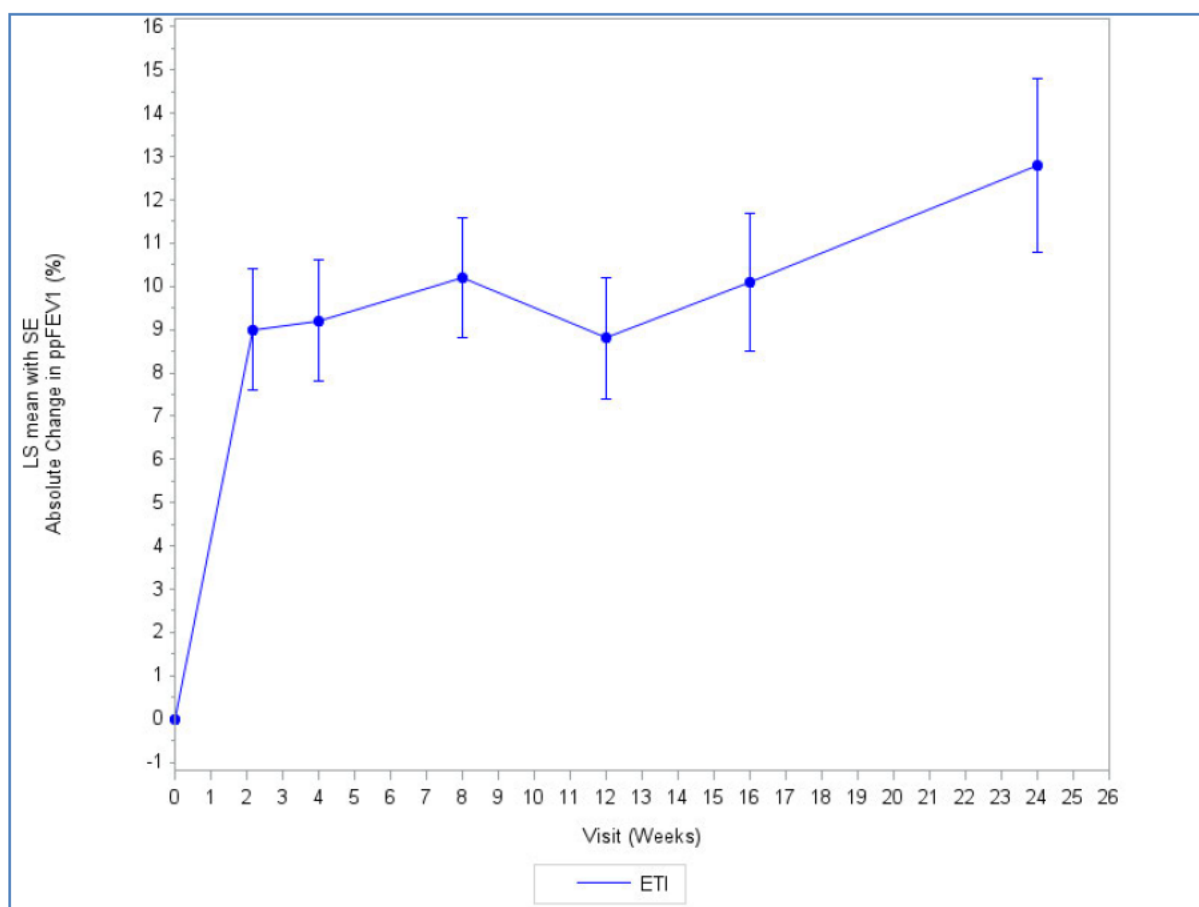
NDA/BLA Multi-disciplinary Review and Evaluation {NDA 212273}
{Trikafta (elexacaftor/tezacaftor/ivacaftor)}

Parameter	ETI N = 66
Baseline	
n	62
Mean (SD)	88.8 (18)
Absolute change through Week 24	
n	59
LS mean (SE)	10.2 (1.2)
95% CI of LS mean	(7.9, 12.6)
P value	<0.0001
ETI Low Dose: elexacaftor 100 mg qd / tezacaftor 50 mg qd / ivacaftor 75 mg q12h; ETI High Dose: elexacaftor 200 mg qd / tezacaftor 100 mg qd / ivacaftor 150 mg q12h; FAS: Full Analysis Set; F/F: homozygous for <i>F508del</i> ; F/MF: heterozygous for <i>F508del</i> and a CFTR minimal function mutation; LS: least squares; MMRM: mixed-effects model for repeated measures; n: size of subsample; N: total sample size; ppFEV1: percent predicted forced expiratory volume in 1 second; Note: Baseline was defined as the most recent non-missing measurement before the first dose of study drug in Part B. MMRM included clinic-assessed data up to Week 24, with visit as fixed effect and baseline ppFEV1 and genotype group (F/F or F/MF) as covariates. However, the Day 15 Visit was not included in the estimation of the average treatment effect through Week 24. A Kenward-Roger approximation was used for denominator degrees of freedom. A compound symmetry covariance structure was used to model the within-subject errors. Source: Clinical and Statistical Reviewers	

Reviewer comment. While cross study comparisons are limited by different populations, the magnitude of the observed within group absolute change from baseline change is similar to that observed in the adult ETI trial in F/F patients. This is particularly notable given that the enrolled population, had a higher mean baseline ppFEV1 (ppFEV1 88.8%) than that of both adult trials 102 and 103 (ppFEV1 approximately 61%).

Treatment with ETI resulted in sustained improvements in ppFEV1 over the 24-week treatment period. These changes were also observed at earlier weeks, indicating that the drug response was durable while on drug (Figure 10).

Figure 10. MMRM Analysis of Absolute Change From Baseline in ppFEV1 (Percentage Points) by Visit (Trial 106 Part B, FAS)



Source: Statistical Reviewer

Reviewer comment. These results suggest that in 6 to 11 year old population, two weeks is sufficient time for both onset of the ETI treatment effect.

Sweat Chloride

Treatment with ETI resulted in nominal within subject improvements in SwCl through Week 24. The LS mean within subject change from baseline in SwCl through Week 24 was -60.9 (95% CI: -63.7, -58.2). These data are summarized in Table 45.

Table 45. MMRM Analysis of Absolute Change from Baseline in SwCl (mmol/L) through Week 24 (Trial 106 Part B, FAS)

Parameter	ETI N = 66
Baseline	
n	62
Mean (SD)	102.2 (9.1)

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{Trikafta (elexacaftor/tezacaftor/ivacaftor)}

Absolute change through Week 24	
n	60
LS mean (SE)	-60.9 (1.4)
95% CI of LS mean	(-63.7, -58.2)
P value	<0.0001

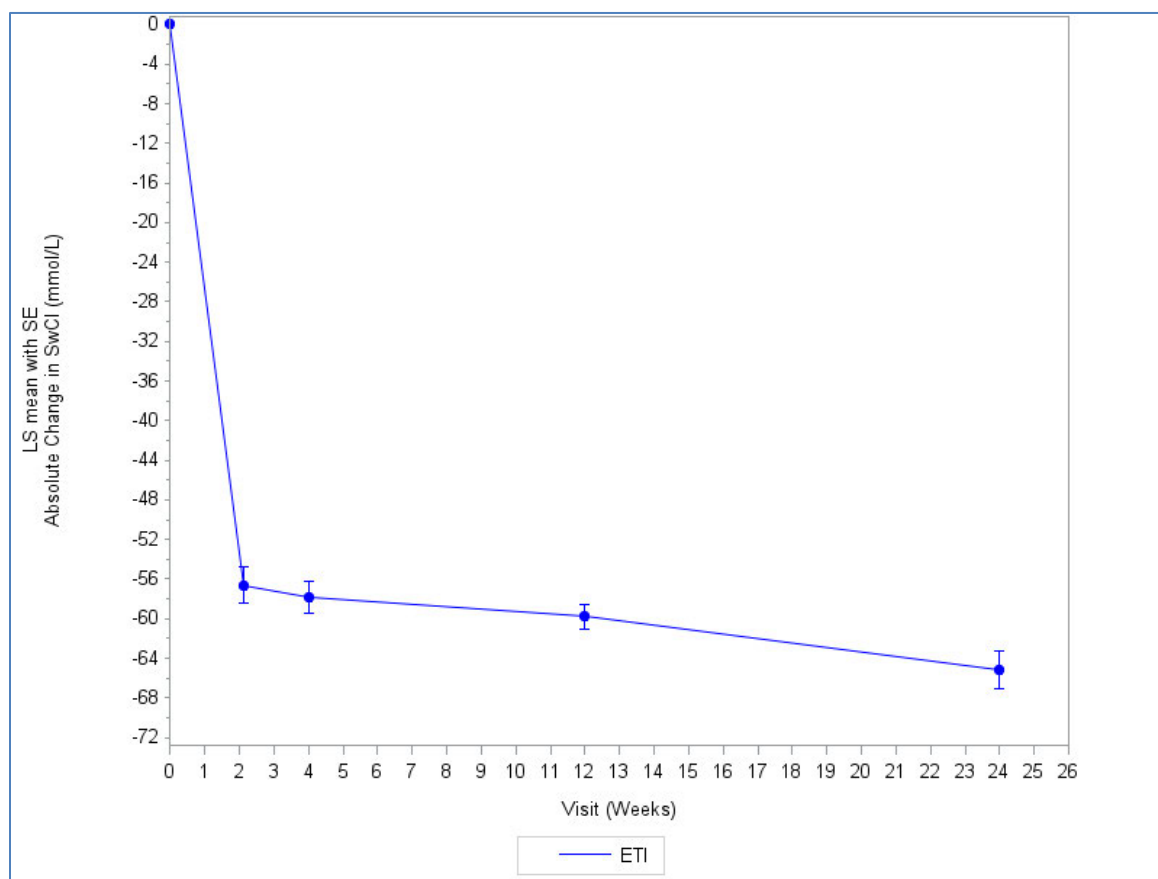
ETI Low Dose: elexacaftor 100 mg qd / tezacaftor 50 mg qd / ivacaftor 75 mg q12h; ETI High Dose: elexacaftor 200 mg qd / tezacaftor 100 mg qd / ivacaftor 150 mg q12h ; FAS: Full Analysis Set; F/F: homozygous for *F508del*; F/MF: heterozygous for *F508del* and a *CFTR* minimal function mutation; LS: least squares; MMRM: mixed-effects model for repeated measures; n: size of subsample; N: total sample size; SwCl: sweat chloride

Note: Baseline was defined as the most recent non-missing measurement before the first dose of study drug in Part B. MMRM included data up to Week 24, with visit as fixed effect and baseline SwCl and genotype group (F/F or F/MF) as covariates. However, the Day 15 Visit was not included in the estimation of the average treatment effect through Week 24. A Kenward-Roger approximation was used for denominator degrees of freedom. An unstructured covariance structure was used to model the within-subject errors.

Source: Clinical and Statistical Reviewers

With respect to additional secondary endpoints, there were sustained effects for absolute changes in SwCl (Figure 11) over the entire 24 week treatment period.

Figure 11. MMRM Analysis of Absolute Change From Baseline in SwCl (mmol/L) by Visit (Trial 106 Part B, FAS)



NDA/BLA Multi-disciplinary Review and Evaluation {NDA 212273}
{Trikafta (elexacaftor/tezacaftor/ivacaftor)}

Source: Statistical Reviewer

Reviewer comment. The onset of treatment effect was approximately 2 weeks and the within group absolute mean change from baseline was approximately 50% greater than that observed in the adult ETI trials. This is somewhat surprising in that one would expect SwCl response to be similar between age groups given that the disease process is similar between age groups. However, a similar observation was seen in the lumacaftor/ivacaftor program. Acknowledging that the actual reason is unknown, the differences could be related to different ivacaftor exposure and/or the inherent variability of the sweat chloride measure.

CFQ-R Respiratory Domain

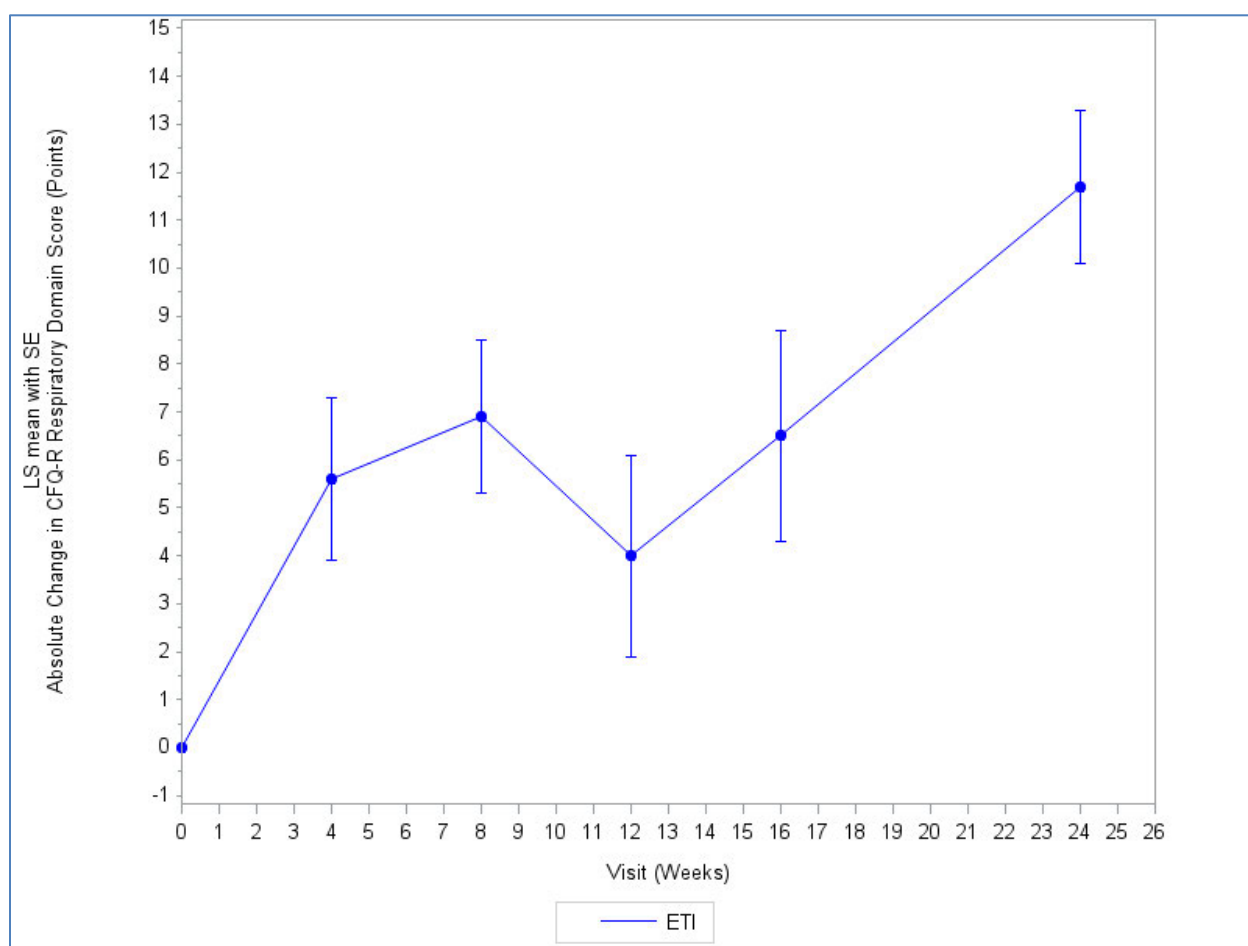
Treatment with ETI resulted in nominal within subject improvements in CFQ-R RD through Week 24. The LS mean within subject change from baseline in CFQ-R RD through Week 24 was 7.0 points (95% CI: 4.7, 9.2). These data are summarized in Table 46.

Table 46. MMRM Analysis of Absolute Change from Baseline in CFQ-R RD (Points) through Week 24 (Trial 106 Part B, FAS)

Parameter	ETI N = 66
Baseline	
n	65
Mean (SD)	80.3 (15.2)
Absolute change through Week 24	
n	65
LS mean (SE)	7.0 (1.1)
95% CI of LS mean	(4.7, 9.2)
P value	<0.0001
ETI Low Dose: elexacaftor 100 mg qd / tezacaftor 50 mg qd / ivacaftor 75 mg q12h; ETI High Dose: elexacaftor 200 mg qd / tezacaftor 100 mg qd / ivacaftor 150 mg q12h; FAS: Full Analysis Set; F/F: homozygous for <i>F508del</i> ; F/MF: heterozygous for <i>F508del</i> and a <i>CFTR</i> minimal function mutation; LS: least squares; MMRM: mixed-effects model for repeated measures; n: size of subsample; N: total sample size; RD: respiratory domain Note: Baseline was defined as the most recent non-missing measurement before the first dose of study drug in Part B. MMRM included clinic-assessed data from all available visits, with visit as fixed effect and baseline CFQ-R RD score (Child's Version) and genotype group (F/F or F/MF) as covariates. A Kenward-Roger approximation was used for denominator degrees of freedom. An unstructured covariance structure was used to model the within-subject errors. Source: Clinical and Statistical Reviewers	

There were sustained effects for absolute changes in CFQ-R RD (Figure 12) over the 24 week treatment period.

Figure 12. MMRM Analysis of Absolute Change From Baseline in CFQ-R RD Score (Child's Version; Points) Visit (Trial 106 Part B, FAS)



Source: Statistical Reviewer

Reviewer comment. The within group magnitude of absolute mean change from baseline is smaller than that of the changes observed with the adult population, but the subject population started with a higher baseline CFQ-R RD score. Furthermore, while smaller in magnitude, the observed improvement in CFQ-R RD is greater than the minimal clinically important difference (i.e. 4) and supports a clinical benefit in this population.

Weight, Height and BMI

Treatment with ETI resulted in within subject increases in absolute change from baseline for weight (3.0 kg), stature (2.3 cm), BMI (1.02 kg/m²) and weight/height/BMI z-scores (0.25, 0.05, 0.27, respectively) at Week 24 (Table 47).

Table 47. MMRM Analysis of Absolute Change from Baseline in BMI (kg/m²) and Weight (kg) at Week 24 (Trial 106 Part B, FAS)

NDA/BLA Multi-disciplinary Review and Evaluation {NDA 212273}
{Trikafta (elixacaftor/tezacaftor/ivacaftor)}

Parameter	ETI N = 66
BMI (kg/m²)	
Baseline	
n	66
Mean (SD)	16.39 (1.69)
Absolute change at Week 24	
n	33
LS mean (SE)	1.02 (0.13)
95% CI of LS mean	(0.76, 1.28)
P value	<0.0001
Weight (kg)	
Baseline	
n	66
Mean (SD)	30.0 (7.7)
Absolute change through Week 24	
n	33
LS mean (SE)	3.0 (0.2)
95% CI of LS mean	(2.5, 3.5)
P value	<0.0001
Height (cm)	
Baseline	
n	66
Mean (SD)	134.1 (12.3)
Absolute change through Week 24	
n	33
LS mean (SE)	2.3 (0.2)
95% CI of LS mean	(1.9, 2.7)
P value	<0.0001
ETI Low Dose: elixacaftor 100 mg qd / tezacaftor 50 mg qd / ivacaftor 75 mg q12h; ETI High Dose: elixacaftor 200 mg qd / tezacaftor 100 mg qd / ivacaftor 150 mg q12h; FAS: Full Analysis Set; F/F: homozygous for <i>F508del</i> ; F/MF: heterozygous for <i>F508del</i> and a <i>CFTR</i> minimal function mutation; LS: least squares; MMRM: mixed-effects model for repeated measures; n: size of subsample; N: total sample size; RD: respiratory domain Note: Baseline was defined as the most recent non-missing measurement before the first dose of study drug in Part B. MMRM included data from all available visits up to Week 24, with visit as fixed effect and baseline value of the relevant growth parameter (BMI, weight, height, or associated z-score) and genotype group (F/F or F/MF) as covariates. A Kenward-Roger approximation was used for denominator degrees of freedom. An unstructured covariance structure was used to model the within-subject errors. Source: Clinical and Statistical Reviewers	

Reviewer comment. The assessment is limited given the absence of a comparator arm. Based on CDC growth charts for healthy children, the average weight gain during every 6-month period for children between the age of 6 to 11 years is approximately 1 to 2 kg and for stature approximately 3-4 cm. While the observed change in stature is below the CDC growth chart for healthy children, the absence of a comparator arm creates difficulty drawing conclusions. Whether or not the observed changes were related to treatment is uncertain, as there was no

placebo group and as the studied age group is actively growing. In addition, data were missing for approximately half of the subjects at Week 24. As such, the observed absolute increases in weight and stature may reflect normal development, rather than a treatment effect.

Other Endpoints

The Applicant also analyzed other secondary endpoints including exacerbation, CF-related hospitalizations, and LCI. While these results were reported, it is difficult to make any definitive conclusions given the lack of a placebo, active, or historical control group. The Applicant also assessed the change from baseline in qualitative microbiology cultures, and no trends for increased or decreased growth were noted.

Dose/Dose Response

Trial 106 was not designed to evaluate a dose response. Trial 106 included a single dosage level for each weight category. The dose in subjects ≥ 30 kg was extrapolated from the adult program. The proposed dose in the population with weight < 30 kg is half of that approved in the ≥ 12 year old population, and selected by PK modeling and data from Part A. PK results from Trial 106 Part A and B demonstrated that the range of ETI exposure were comparable in the 6 to 11 year old age group following administration of ETI 200 mg qd / 100 mg qd / 150 mg q12h (patients ≥ 30 kg) and ETI 100 mg qd / 50 mg qd / 75 mg q12h (patients < 30 kg) compared to adolescents and adults (≥ 12 years of age) following administration of ETI 200 mg qd / 100 mg qd / 150 mg q12h, supporting the proposed dosages.

Durability of Response

With respect to secondary endpoints, there were sustained effects for absolute changes in ppFEV1 (Figure 10), SwCl (Figure 11), and CFQ-R RD (Figure 12) over the entire 24 week treatment period.

Persistence of Effect

Efficacy was extrapolated from the ≥ 12 year old population. In the clinical trials in the ≥ 12 year old population, effects on ppFEV1 persisted throughout the 24-week treatment period.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

See discussion of CFQ-R Respiratory Domain.

Additional Analyses Conducted on the Individual Trial

No additional subpopulation analyses were performed as subpopulation analyses were performed in the initial NDA submission.

Integrated Review of Effectiveness

Only one study was included to assess efficacy in this NDA. Refer to Section 8.1.1 and 8.1.2 for the review of effectiveness.

8.1.3. Integrated Assessment of Effectiveness

In this NDA, the Applicant has submitted data from a pharmacokinetic (PK) and safety study (Trial 106) to support the use of ETI in patients 6 to 11 years of age who have at least one *F508del* mutation in the *CFTR* gene or a mutation in the *CFTR* gene that is responsive based on in vitro data.

Trial 106 was a two-part, non-randomized, uncontrolled, open-label PK (part A, 15-day duration, n=12) and safety (part B, 24-week duration, n=66) study in patients 6 to 11 years of age. Week 24 data from Part B demonstrated clinically significant improvements in ppFEV₁, SwCl, and CFQ-R RD through Week 24. The observed changes are consistent with previous ETI studies in which ETI demonstrated efficacy.

In Part B, PK data demonstrated that when ETI 200 mg qd / 100 mg qd / 150 mg q12h was administered to patients ≥30kg and ETI 100 mg qd / 50 mg qd / 75 mg q12h administered to patients <30kg, systemic exposures were comparable to that observed in the adolescent/adult population. Because of the similar systemic exposures and because the disease process in the older population is the same as that in the 6 to less than 12 year old population, efficacy in the proposed age group was extrapolated from the ETI adolescent/adult development program.

In summary, efficacy of ETI in CF patients aged 6 to 11 years who have at least one *F508del* mutation in the *CFTR* gene or a mutation in the *CFTR* gene that is responsive based on in vitro data has been demonstrated based on extrapolation from the adolescent/adult population.

8.2. Review of Safety

8.2.1. Safety Review Approach

The clinical safety review is based on the clinical data from Trial 106 that was a 2-part (A and B) open-label, non-randomized study in CF patients who were homozygous for the *F508del* mutation or heterozygous for *F508del* and a second minimal function mutation. As Part A only included a 15-day treatment period, this section will only include a discussion of safety data from Part B which included a 24-week treatment period. Safety analyses were conducted on the safety analysis set (SAS), defined as all subjects that received at least 1 dose of study drug. This review completed safety analyses for the overall population and by weight group / ETI

dosage where “ETI high dose” includes patients ≥ 30 kg receiving ETI 200 mg qd / 100 mg qd / 150 mg q12h in and “ETI Low Dose” includes subjects < 30 kg receiving ETI 100 mg qd / 50 mg qd / 75 mg q12h. This review used MAED and JMP to independently analyze safety data.

Section 8.2.4 discusses the safety data from Trial 106, including but not limited to AEs, laboratory parameters, VS, and ECGs.

Section 8.2.5 discusses Submission-Specific Safety issues from Trials 106 that were either pre-specified adverse events of special interest (AESI), potential safety issues identified in the pre-NDA and NDA review of ETI or known safety issues with related CFTR modulator products. Specifically, the Applicant identified liver enzyme elevation and rash as AESI in the original ETI development program, and blood creatine phosphokinase elevation emerged as a safety signal during the ETI pre-NDA review. Cataracts are known safety signals with IVA monotherapy, TEZ/IVA and the related CFTR modulator product lumacaftor/ivacaftor. For a detailed summary of the Trial 106 protocol, refer to Section 8.1.1.

Section 8.2.7 discusses safety from the ongoing long term extension safety study, Trial 107.

8.2.2. Review of the Safety Database

Overall Exposure

The safety database includes 66 pediatric CF patients aged 6 to 11 years receiving ETI combination therapy. Thirty-six patients who weighed less than 30 kg were administered the ETI low dose with a mean (SD) exposure of 23.4 (4.0) weeks, while 30 patients who weighed 30 kg or greater received ETI high dose for a mean (SD) duration of 24.2 (0.4) weeks. The duration of exposure to ETI in Trial 106 Part B appears in Table 48.

Table 48. Duration of Exposure to ETI, Trial 106 Part B, SAS

	ETI Low Dose N=36	ETI High Dose N=30	Total N=66
Extent of Exposure (days)			
Mean (SD)	164.1 (28.1)	169.6 (3.0)	166.6 (20.9)
Median (min, max)	169 (1, 174)	169 (162, 174)	169 (1, 174)
Duration of Exposure, n(%)			
>0 to ≤ 2 weeks	1	0	1
>2 to ≤ 4 weeks	0	0	0
>4 to ≤ 8 weeks	0	0	0
>8 to ≤ 16 weeks	0	0	0
>16 to ≤ 24 weeks	15	12	27
>24 weeks	20	18	38
ETI Low Dose: elexacaftor 100 mg qd, tezacaftor 50 mg qd, ivacaftor 75 mg q12h given to patients < 30 kg. ETI High Dose: elexacaftor 200 mg qd, tezacaftor 100 mg qd, ivacaftor 150 mg q12h given to patients ≥ 30 kg.			

Source: Reviewer calculated in JMP 15.0 using ADSL dataset for Part B using variables TRTDURD by WTBLGR1. Duration of study drug exposure (weeks) = TRTDURD (days)/7, regardless of study drug interruption.
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Adequacy of the safety database:

Part B of Trial 106 included a 24-week treatment period where safety was assessed. The safety database was adequate to review the safety of ETI in pediatric patients 6 to 11 years of age.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The review of the NDA identified a higher rate of missing safety data compared to previous pediatric trials with IVA and/or TEZ/IVA. The study was conducted during the COVID-19 pandemic, and the majority of missing safety data was due to the COVID-19 pandemic, either because the subject did not have an in-clinic visit (due to COVID-19), or because the subject had an in-clinic visit which was impacted by COVID-19 and some assessments were not performed. The Applicant addressed the missing data by completing laboratory safety assessments in an unscheduled visit in Trial 106 Part B, and by obtaining ECGs, VS, and ophthalmic examinations (OEs) in an unscheduled visit during the OLE Study 107. The number of subjects impacted by parameter appears below:

- LFT data for 19 of 22 subjects with missing Week 24 data were collected in an unscheduled visit in Trial 106.
- Hematology data for 19 of 24 subjects with missing Week 24 data were collected in an unscheduled visit in Trial 106.
- Hematology data for 14 of 25 subjects with missing Week 24 data were collected in an unscheduled visit in Trial 106.
- VS data for 27 of 31 subjects with Week 24 missing data who rolled over into the OLE were collected in an unscheduled visit in Study 107.
- ECG data for 24 of 31 subjects with missing Week 24 data who rolled over into the OLE were collected in an unscheduled visit in Study 107.
- OE data for 46 of 46 subjects with missing Week 24 data who rolled over into the OLE were collected in an unscheduled visit in Study 107.

No other data quality issues were identified in the review of this NDA.

Due to the Agency's experience with the Applicant, including the recent approval of ETI, TEZ/IVA (Symdeko®) and quality of the datasets as judged by the clinical and statistical review teams, and the unmet medical need for the rare, life-threatening disease, Office of Scientific Investigations audits were deemed unnecessary for this submission.

Reviewer comment. Overall, the totality of the safety database including the unscheduled visits from 106 and the OLE were sufficient for the safety analysis.

Categorization of Adverse Events

The Applicant provided accurate definitions of AEs and SAEs consistent with 21 CFR 312.32.

Investigators captured AEs from the time the informed consent form (ICF) was signed and through the TE Period for each study (i.e., premature discontinuation or 28 days after last study drug exposure). TEAEs were defined as any AE that worsened (either in severity or seriousness) or that was newly developed at or after the first dose date of study drug through the end of the TE Period. For purposes of this review, summary tables present TEAEs.

The Applicant coded AEs in Trial 106 Part B using the MedDRA dictionary version 23.0. The Applicant graded AE severity using the Common Terminology Criteria for Adverse Events version 5.0 toxicity scale or as mild/moderate/severe/life-threatening.

The Applicant assessed AE frequency, rather than rate, a method appropriate for trials of this duration.

Reviewer comment: The Applicant's coding of verbatim terms to PTs was acceptable. The Common Terminology Criteria for Adverse Events severity scale is consistent with other CF development programs and appropriate for the enrolled subject population.

Routine Clinical Tests

Routine clinical tests included laboratory tests, ECGs, PEs, VS, pulse oximetry, and OE.

8.2.4. Safety Results

Deaths

There were no deaths in Trial 106.

Serious Adverse Events

In general, the SAEs reported were what would be expected in a pediatric CF population. A single subject (1.5%) reported three SAEs (PT: metapneumovirus infection, pneumonia, and rhinovirus infection). Investigators assessed these SAEs as moderate in severity. The subject was in the <30 kg group. SAE data did not reveal new safety concerns.

Dropouts and/or Discontinuations Due to Adverse Effects

Sixty-six patients were enrolled and received at least 1 dose of ETI. Sixty-four (97%) completed the ETI treatment and completed the study. One (1.5%) subject in the ETI low dose group had

an AE of rash erythematous that led to treatment discontinuation. Investigator's assessed the AE as moderate in severity and related to study drug. Study drug was withdrawn, a single dose of cetirizine was administered, and the event resolved the next day. No patients in the ETI high dose group discontinued from the study for AEs.

One (1.5%) subject in the ETI high dose group reported AEs of diarrhea, vomiting, and pyrexia that led to treatment interruption. All 3 AEs were assessed by the investigator as moderate in severity and unlikely related to study drug. The dose of IVA was interrupted for 1 day, and the events resolved.

Significant Adverse Events

In Trial 106, 1 (1.5%) subject reported a grade 3 (severe) AE. The single subject (ETI low dose) had severe AEs of constipation and shoulder pain, assessed as likely referred pain from constipation. No grade 4 life-threatening TEAEs were reported. No new safety signals were identified.

Treatment Emergent Adverse Events and Adverse Reactions

In Trial 106, 65 (98%) subjects reported at least 1 AE. Most AEs were mild and moderate in severity. In the overall study population, the most common AEs were cough (42%), headache (24%), rash (21%), and pyrexia (21%). The distribution of AEs was generally similar between those subjects receiving the ETI low and high dose with the exception of ALT increase, which occurred in 6 (20%) subjects receiving the high dose group compared to 1 (3%) subject in the low dose group. Subjects reporting cough were generally distributed across baseline ppFEV1 categories. Common AEs occurring in at least 4 patients overall appear in Table 49.

Table 49. AEs Occurring in At Least 4 Subjects by Preferred Term, Trial 106 Part B, SAS

Preferred Term	ETI Low Dose N=36 n (%)	ETI High Dose N=30 n (%)	Total N = 66 n (%)
Subjects with any AEs	35 (97)	30 (100)	65 (98)
Cough ^a	20 (56)	11 (37)	31 (42)
Upper respiratory tract infection ^b	8 (22)	10 (33)	18 (27)
Headache	9 (25)	7 (23)	16 (24)
Rash ^c	6 (17)	8 (27)	14 (21)
Pyrexia	6 (17)	6 (20)	14 (21)
Abdominal pain ^d	7 (19)	6 (20)	13 (20)
Oropharyngeal pain	6 (17)	6 (20)	12 (18)
Nasal congestion	4 (11)	6 (20)	10 (15)
Rhinorrhea	5 (14)	3 (10)	8 (12)
ALT increased	1 (3)	6 (20)	7 (11)
Diarrhea	4 (11)	3 (10)	7 (11)

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Influenza	4 (11)	3 (10)	7 (11)
Vomiting	4 (11)	3 (10)	7 (11)
Fatigue	3 (8)	2 (7)	5 (7.6)
Constipation	3 (8)	1 (3)	4 (6.1)
Ear infection	2 (6)	2 (7)	4 (6.1)

AE: adverse event; ALT: alanine transaminase; ETI Low Dose: elexacaftor 100 mg qd, tezacaftor 50 mg qd, ivacaftor 75 mg q12h given to patients < 30 kg. ETI High Dose: elexacaftor 200 mg qd, tezacaftor 100 mg qd, ivacaftor 150 mg q12h given to patients ≥ 30 kg; n: size of subsample; N: total sample size; PT: Preferred Term
ETI Low Dose is ELX 100 mg qd, TEZ 50 mg qd, IVA 75 mg q12h given to patients < 30 kg. ETI High Dose is ELX 200 mg qd, TEZ 100 mg qd, IVA 150 mg q12h given to patients ≥ 30 kg.

^aIncludes PT cough and productive cough. Note 2 subjects (106-083-402 and 106-083-404) with Verbatim Term “sputum” coded to PT “productive cough” not included.

^bIncludes PT upper respiratory infection and viral upper respiratory tract infection

^cIncludes PTs: rash papular, rash maculo-papular, rash, rash erythematous

^dAbdominal pain includes PT abdominal pain and abdominal pain upper

Notes: AEs were coded using MedDRA version 23.0. A subject with multiple events within a category was counted only once in that category.

Source: Reviewer calculated using JMP 15.0.0 analysis datasets adae and adsl selecting SAFFL(Y) and TRTEMFL(Y) by USUBJID, AEDECOD and WTBLGR1.

Reviewer comment. Overall, the AEs reported were generally consistent with common manifestations of CF disease, labeled AEs for ETI, or common illnesses in patients 6 to less than 12 years of age. No new safety signals were identified. With respect to LFT AEs, the clinical pharmacology review team determined that the distribution of systemic exposure of ELX, M23-ELX, TEZ, M1-TEZ, and IVA in those 7 subjects with elevated ALT substantially overlapped with the distribution in other subjects without elevated ALT (see also Sections 6 and 8.25)

Laboratory Findings

Routine clinical testing for this safety program included evaluations of hematology, serum chemistries, coagulation studies, and urinalyses. This reviewer analyzed chemistry (inclusive of LFT, non-LFT, and CK), hematology, coagulation, and urinalysis results in Trial 106, inclusive of unscheduled visits, and where relevant, considered potential lab-related AEs. A discussion of LFT and CK-related laboratory changes appears in [Section 8.2.5](#).

Analysis of non-LFT and non-CK chemistry parameters, inclusive of mean changes and individual subject shift from baseline threshold analyses, did not identify any clinically significant findings.

Mean concentrations of hematology parameters varied over time. While not below the normal range, decreases from baseline were observed for mean platelets (maximum change -18.4 (65.0) × 10⁹/L at Week 16), leukocytes (maximum change of -1.63 (2.70) × 10⁹/L at Week 16), and neutrophils (maximum change of -1.25 (2.35) × 10⁹/L at Week 16). No clinically significant changes were identified on post-baseline threshold analysis.

There were no trends observed with respect to coagulation factors. Analysis of coagulation factors by individual subject identified no subjects with treatment emergent post-baseline elevations of partial thromboplastin time (PTT), prothrombin time (PT), or international normalized ratio (INR) greater than 1.5x ULN. Three subjects had AEs related to coagulation findings (PT: PT, aPTT and INR increased), but none of these subjects developed shifts in post-baseline PT, aPTT, or INR values from normal to greater than 1.5 xULN and no bleeding events occurred in those subjects with elevation in coagulation factors.

Reviewer comment. While small trends were observed with respect to hematology, the changes do not appear to be clinically significant and additional labeling is not recommended.

Vital Signs

The Applicant presented mean values for heart rate, blood pressure, body temperature, and oxygen saturations for the overall population as well as individual shifts from baseline.

With respect to heart rate, decreases from baseline in heart rate were observed, ranging from a mean (SD) decrease of -1.8 (10.9) bpm at Week 16 to -4.8 (13.6) bpm at Week 4. There were no clinically significant individual changes in heart rate.

With respect to blood pressure, there were no clinically significant mean changes from baseline. Examination of individual subject shifts from baseline were notable for 10 (15%) subjects with shifts in SBP >120 mmHg and > 10 mmHg increase from baseline of which 7 were administered ETI high dose. Four (6%) had shifts in SBP >120 mmHg and > 20 mmHg increase from baseline of which 3 were administered ETI high dose. With respect to DBP, three subjects administered the ETI developed DBP >80 mmHg and change from baseline > 20 mmHg, and all were administered the ETI low dose. Three subjects administered the ETI developed DBP <50 mmHg and change from baseline > 20 mmHg, of which 2 were administered the ETI low dose.

There were no clinically significant changes in other VS parameters.

No subjects had AEs related to the VS.

Review of additional data from the OLE unscheduled visits identified no trends in these additional vital signs parameters.

Reviewer comment. Section 6 of the ETI PI already describes increased blood pressure.

Electrocardiograms (ECGs)

The Applicant provided summary statistics of heart rate, PR interval, RR interval, QRS duration, QT and QTcF for ETI.

Examination of post-baseline ECGs identified no clinically significant mean trends in RR interval, PR interval, QRS duration, and heart rate (HR). Evaluation of individual post-baseline values and individual subject relative changes from baseline identified no subjects with bradycardia (HR < 50 beats/min) or tachycardia (≥ 140 beats/min).

A single subject administered the ETI low dose reported an AE of 'defect conduction intraventricular' on Day 16 that was nonserious and did not lead to treatment discontinuation or interruption. The AE resolved without intervention. There were no other subjects with AEs related to ECG findings or cardiac disorders.

Review of the additional data from unscheduled OLE visits identified no clinically relevant findings.

QT

This reviewer examined post-baseline QTcF changes by relative change from baseline (>30 , >40 , and >60 msec) and absolute post-baseline values (>450 to <500 msec (male) or >470 to <500 msec (female) and >500 msec). Three (4%) and 1 (2%) subjects reported maximum changes in the QTcF interval of > 30 msec and > 40 msec, respectively. No subjects developed relative increase from baseline in the QTcF interval of >60 msec. With respect to absolute post-baseline values, no subjects developed absolute post-baseline values >450 (male) or >470 (female).

Review of the additional data from unscheduled OLE visits identified no clinically relevant findings and no AEs related to QT findings.

Immunogenicity

Not applicable

8.2.5. Analysis of Submission-Specific Safety Issues

Hepatobiliary-Related Labs and Adverse Events

The Applicant prespecified LFT elevations as an AESI, as LFT abnormalities have been seen with IVA, TEZ/IVA, LUM/IVA, and the adult / adolescent ETI clinical development program. This reviewer analyzed LFT laboratory changes (mean changes and maximum on-treatment elevations) as well as relevant AE PTs in the Investigations SOC and Hepatobiliary SOC in Trial 106 for the overall trial population and by dosage group.

In the overall population, increases from baseline in mean total bilirubin were observed, with a greater increase in indirect bilirubin than in direct bilirubin. In the overall population, the mean (SD) changes from baseline were 3.3 (4.3) $\mu\text{mol/L}$ for total bilirubin, 1.4 (1.5) $\mu\text{mol/L}$ for direct bilirubin, and 2.1 (3.3) $\mu\text{mol/L}$ for indirect bilirubin at Week 24 (inclusive of unscheduled visits). There were no clinically meaningful mean differences in change from baseline with respect to total bilirubin, direct bilirubin, or indirect bilirubin by weight group.

In the overall population, 7 (11%) subjects had ALT or AST $>3 \times$ ULN, and 1 (2%) subject had ALT or AST $>5 \times$ ULN; no subjects had ALT or AST $>8 \times$ ULN. The majority of subjects had bilirubin values that remained within the normal range; no subjects had total bilirubin $>2 \times$ ULN. More subjects in the ETI high dose group had AST or ALT elevations $>3 \times$ ULN (5, 17%) than subjects in the ETI low dose group (2, 6%). However, the exposures of ELX, M23-ELX, TEZ, M1-TEZ, and IVA in the subjects with ALT $>3 \times$ ULN were generally within the range of exposures observed across the Trial 106 Part B population (see Table 35). Table 50 summarizes LFT changes.

Table 50. Maximum Liver Function Test Elevations During Treatment Emergent Period, Trial 106 Part B, SAS

Lab parameter	ETI Low Dose N=36 n (%)	ETI High Dose N=30 n (%)	Total N=66 n (%)
ALT (U/L), n (%)			
>3x to $\leq 5x$ ULN	2 (6)	4 (13)	6 (9)
>5x to $\leq 8x$ ULN	0	1 (3)	1 (2)
>8x to $\leq 20x$ ULN	0	0	0
AST (U/L), n (%)			
>3x to $\leq 5x$ ULN	0	0	0
>5x to $\leq 8x$ ULN	0	0	0
>8x to $\leq 20x$ ULN	0	0	0
AST or ALT (U/L), n (%)			
>3x ULN	2 (6)	5 (17)	7 (11)
>5x ULN	0	1 (3)	1 (2)
>8x ULN	0	0	0
>20x ULN	0	0	0
Alkaline phosphatase (U/L), n (%)			
>1.5x ULN to $\leq 2.5x$ ULN	1 (3)	1 (3)	2 (3)
>2.5x to $\leq 5x$ ULN	0	0	0
GGT (U/L), n (%)			
>2.5x ULN to $\leq 3x$ ULN	0	1 (3)	1 (2)
>5x to $\leq 20x$ ULN	0	0	0
Total Bilirubin ($\mu\text{mol/L}$), n (%)			
>1.5x ULN to $\leq 2x$ ULN	2 (3)	2 (7)	4 (6.1)
>2x ULN	0	0	0
ALT or AST and total bilirubin, n (%) (ALT or AST $>3x$ ULN) and bilirubin $>2x$ ULN	0	0	0
ALT: alanine aminotransferase, AST: aspartate aminotransferase, ETI Low Dose: elexacaftor 100 mg qd, tezacaftor 50 mg qd, ivacaftor 75 mg q12h given to patients < 30 kg. ETI High Dose: elexacaftor 200 mg qd, tezacaftor 100 mg qd, ivacaftor 150 mg q12h given to patients ≥ 30 kg; ULN: upper limit of normal, GGT: gamma-glutamyl transferase; n: number of subjects in subset, N: total subjects in trial arm, U: units. Source: Reviewer calculated using ADLB, ADLBEP and ADSL datasets in JMP 15.0 selecting SAFFL(Y), ONTRTFL(Y) by PARAMCD, USUBJID, MCRIT1ML, and WTBLGR1.			

This reviewer queried the AE database for hepatobiliary-related AEs in the Investigations and Hepatobiliary Disorders SOC for the overall subject population and by administered dosage. One (1.5%) subject administered ETI low dose had 2 AEs of blood bilirubin increased, neither of which were serious or led to treatment discontinuation or interruption. No AEs of bilirubin elevation occurred in those administered ETI high dose. A total of 7 (11%) subjects reported at least one AE of ALT increased, including 6 (20%) administered ETI high dose and 1 (3%) administered ETI low dose. A total of 2 (3%) subjects reported an AE of AST increased, including one administered ETI low dose and ETI high dose, respectively.

Reviewer comment. Given the small sample size, it is difficult to draw conclusions related to the increased LFT events in those administered the high dose. The distribution of systemic exposure for ETI and its metabolites in subjects with significant elevations overlapped with subjects without elevated ALT (see also Sections 6). Overall, the observed elevations in LFTs are consistent with that identified in the adult and adolescent studies.

Skin-Related Adverse Events

Following identification of rash as a potential safety issue early in the original clinical development program, the Applicant defined rash as an AESI in the adult Phase 3 trials and in Trial 106. The following section discusses rash AEs from Trial 106.

Review of the AE database for Trial 106 included exploration by Higher Level Term and PT to identify trends in related clinical events. Fourteen (21%) subjects reported a rash AE, including the following PTs: rash, rash papular, rash maculo-papular, and rash erythematous. No subjects reported SAEs related to skin AEs. All rash AE were mild or moderate in severity. Exploration by sex was notable for 9 (64%) of rash events occurring in female subjects. There were no cases of Steven Johnson Syndrome reported or identified on query of the AE database. Table 51 summarizes the incidence of skin-related AEs by higher level term and PT.

Table 51. Incidence of Skin-Related Adverse Events, Trial 106 Part B, SAS

Higher Level Term Preferred term	ETI Low Dose N=36 n (%)	ETI High Dose N=30 n (%)	Total N= 66 N(%)
Subjects with at least 1 skin-related AE	9 (25)	10 (33)	19 (29)
Rashes, eruptions, and exanthems	6 (17)	8 (27)	14 (21)
Rash	3 (8)	5 (17)	8 (12)
Rash erythematous	2 (6)	1 (3)	3 (4)
Rash maculo-papular	0	2 (7)	2 (3)
Rash papular	1 (3)	1 (3)	2 (3)
Pruritus NEC	0	0	0
Pruritus generalized	0	0	0
Acnes	1 (3)	0	1 (1)

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Acne	1 (3)	0	1 (1)
Dermatitis and eczema	2 (6)	0	2 (3)
Dermatitis contact	2 (6)	0	2 (3)
Urticarias	0	1 (3)	1 (1)
Urticaria	0	1 (3)	1 (1)
Exfoliative conditions	0	1 (3)	1 (1)
Skin exfoliation	0	1 (3)	1 (1)
AE: adverse event, ETI Low Dose: elexacaftor 100 mg qd, tezacaftor 50 mg qd, ivacaftor 75 mg q12h given to patients < 30 kg. ETI High Dose: elexacaftor 200 mg qd, tezacaftor 100 mg qd, ivacaftor 150 mg q12h given to patients ≥ 30 kg; n: number of subjects in subset, N: total subjects in trial arm. Subjects counted once for each category. Source: Reviewer calculated in JMP 15.0.0 using ADAE dataset VX18-445-106-PartB selecting subjects by SAFFL(Y), TRTEMFL(Y),) by USUBJID, AEDECOD, AEHLT and WTBLGR1			

Reviewer comment. Because the overall incidence of rash is higher than the adult program, we had proposed including the exact frequencies in the PI. However, during labeling negotiations, the Applicant noted the lack of a control arm creates difficulty interpreting these data in the pediatric population for which viral rashes are common. Furthermore, the Applicant stated that several rash AEs were mild, resolved without drug interruption, and were consistent with possible viral exanthem. We accepted the Applicant's rationale for removing FDA's proposed language and concluded that overall, the observed rash AEs are consistent with that observed in the original development program and already captured in the PI.

Creatinine Kinase Elevations

This review explored the Trial 106 AE database by PT to identify trends in creatine kinase (CK) related clinical events. AEs of CK elevation occurred in 2 (3%) of subjects. Neither AE was serious or led to study drug discontinuation or interruption, and both AEs resolved without treatment. Exploration of the laboratory database was notable for a mean (SD) increase in CK ranging from 30.2 (32.7) U/L at Week 12 to 53.3 (63.8) U/L at Week 24 / unscheduled visit. Four (6%) subjects in the ETI low dose group had CK levels >2.5 × ULN, and no subjects had CK levels >5 × ULN. No CK changes > 2.5 x ULN were observed in the ETI high dose group. There were no cases of rhabdomyolysis reported.

Cataracts

Cataracts have been observed in patients, particularly pediatric patients, treated with IVA monotherapy and in juvenile rat toxicology studies with IVA. Trial 106 required OEs at screening/baseline, and at Week 24 for enrolled subjects. Of the 18 subjects with OEs at Week 24, no subjects developed new treatment emergent cataract or lens opacity. Of the 46 subjects with OE at unscheduled visits in Study 107, 2 subjects had treatment emergent lens findings, including one subject with a nuclear cataract on Day 175 and a second subject with multiple posterior nuclear cataracts on Day 422. Two additional subjects had lens findings at baseline and follow-up examination.

Reviewer comment. Cataracts are a labeled warning and precaution for IVA. Due to the extensive pediatric experience with IVA, the database is acceptable for this application. No changes to the label are recommended.

Neuropsychiatric Events

Given reports of neuropsychiatric events in the postmarketing setting (NISS (b) (4) this review explored AEs in the Psychiatric Disorders and Nervous System SOC explored by PT. The most common PT in the Nervous System SOC was headache (16, 24%), and anxiety (2, 3%) and depressed mood (2, 3%) in the Psychiatric Disorders SOC.

Table 52. Incidence of Neuropsychiatric Adverse Events, Trial 106 Part B, SAS

SOC Preferred term	ETI Low Dose N=36 n (%)	ETI High Dose N=30 n (%)	Total N= 66 N(%)
Nervous System	9 (25)	7 (23)	16 (24)
Headache	9 (25)	7 (23)	16 (24)
Presyncope	1 (3)	0	1 (2)
Psychiatric Disorders	4 (11)	3 (10)	7 (11)
Anxiety	1 (3)	1 (3)	2 (3)
Depressed Mood	1 (3)	1 (3)	2 (3)
Mood Swings	1 (3)	0	1 (2)
Sleep disorder	1 (3)	0	1 (2)
Aggression	0	1 (3)	1 (2)
Attention deficient hyperactivity disorder	0	1 (3)	1 (2)

AE: adverse event; ETI Low Dose: elexacaftor 100 mg qd, tezacaftor 50 mg qd, ivacaftor 75 mg q12h given to patients < 30 kg. ETI High Dose: elexacaftor 200 mg qd, tezacaftor 100 mg qd, ivacaftor 150 mg q12h given to patients ≥ 30 kg; n: number of subjects in subset; N: total subjects in trial arm. Subjects counted once for each category.

ETI Low Dose is ELX 100 mg qd, TEZ 50 mg qd, IVA 75 mg q12h given to patients < 30 kg. ETI Low Dose is ELX 200 mg qd, TEZ 100 mg qd, IVA 150 mg q12h given to patients ≥ 30 kg.

Source. Reviewer calculated in JMP 15.0.0 using ADAE dataset VX18-445-106-PartB selecting subjects by SAFFL(Y), TRTEMFL(Y),) by USUBJID, AEDECOD, AESOC and WTLGR1

Reviewer comment. In general, events aside from headache were infrequent. Given the absence of a control arm and the known background incidence of anxiety / depression in CF patients, it is difficult to make conclusions about the events.

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

Review of trends in CFQ-R scores identified no additional safety concerns.

The Applicant completed drug acceptability assessments using the Modified Facial Hedonic Scale in 33 subjects at Week 24. The majority of subjects with “liked it very much” (16, 48.5%)

or “liked it a little” (6, 18.2%). Only 1 (3%) subject “disliked it a little” and no subjects “disliked it very much.”

Reviewer comment. In general, most subjects’ reaction found the drug acceptable.

8.2.7. Safety Analyses by Demographic Subgroups

This reviewer explored the safety database by sex, age, race, and region. There were too few subjects to provide a meaningful assessment by race. Exploration of events by sex was notable for cough, abdominal pain, and vomiting occurring more often in females than males and at $\geq 15\%$ difference in incidence, while pyrexia occurred more often in males than females and at $\geq 15\%$ difference in incidence (see Table 53).

Table 53. TEAE by sex with $\geq 8\%$ difference between male and female, Trial 106 Part B, SAS

Preferred Term	Female N = 39 n (%)	Male N = 27 n (%)
Subjects with any AEs	39 (100)	26 (96)
Cough ^a	24 (62)	7 (26)
Headache	11 (28)	5 (19)
Abdominal pain ^b	10 (27)	3 (11)
Vomiting	7 (18)	0
Pyrexia	6 (15)	8 (30)
Rhinorrhea	6 (15)	2 (7)
Diarrhea	6 (15)	1 (4)
ALT increased	2 (5)	5 (19)

AE: adverse event; ALT: alanine transaminase; ELX: elexacaftor; IVA: ivacaftor; n: size of subsample; N: total sample size; PT: Preferred Term; TEZ: tezacaftor
ETI Low Dose is ELX 100 mg qd, TEZ 50 mg qd, IVA 75 mg q12h given to patients < 30 kg. ETI Low Dose is ELX 200 mg qd, TEZ 100 mg qd, IVA 150 mg q12h given to patients ≥ 30 kg.
^aIncludes PT cough and productive cough. Note 2 subjects (106-083-402 and 106-083-404) with Verbatim Term “sputum” coded to PT “productive cough” not included.
^bAbdominal pain includes PT abdominal pain and abdominal pain upper
Notes: AEs were coded using MedDRA version 23.0. A subject with multiple events within a category was counted only once in that category.
Source: Reviewer calculated using JMP 15.0.0 analysis dataset adae VX18-445-106-PartB selecting SAFFL(Y) and TRTEMFL(Y) by USUBJID, AEDECOD and SEX.

Reviewer comment. Given the absence of a comparator control arm and the small number of subjects, it is difficult to draw conclusions regarding the sex difference. In addition, based on the known mechanism of action and pharmacological effect of ETI, there is no biologically plausible reason to have a significant difference in incidence between male and female subjects. In the larger studies of ETI in subjects ≥ 12 years of age, the incidence of events was generally similar between male and female subjects, with the exception of headache and rash. At this

time, we do not believe there is enough evidence to include the sex differences from Trial 106 in the label.

8.2.8. Specific Safety Studies/Clinical Trials

The Applicant also submitted safety data from an ongoing OLE, Trial VX19-445-107 (Trial 107) on March 8, 2021 covering the period of February 17, 2020 through February 12, 2021. Trial 107 is a Phase 3, open-label, multicenter, rollover study evaluating the long-term (approximately 96 weeks) safety and efficacy of ETI in subjects with CF who are 6 years and older and have completed Trial 106 Part B. A total of 64 subjects received at least 1 dose of study drug in Trial 107. The Applicant identified 2 SAEs during the reporting period, including a case of anaphylaxis to accidental peanut exposure and a case of idiopathic intracranial hypertension. A narrative for the case of idiopathic intracranial hypertension appears below:

- **Subject 106** (b) (6) was a 9-year-old female with F/F genotype with a medical history of allergies. The subject previously enrolled in Trial 106 Part B and received open label treatment in Trial 107 for 24 weeks. During Trial 106, the subject had 3 non-serious AEs of vomiting and 1 non-serious AE of headache; these events were mild or moderate and considered by the investigator as not related to study drug. At the Trial 106 Week 24 Visit (Trial 107 Day 1 Visit, (b) (6)) the subject had an SAE of idiopathic intracranial hypertension. An OE showed mild bilateral optic nerve swelling with small optic disc hemorrhage, and magnetic resonance imaging (MRI) scan revealed bilateral narrowing of the transverse sinuses, which in the context of funduscopy papilledema was suggestive of idiopathic intracranial hypertension. The subject's blood pressure was normal. The subject had intermittent headaches that were treated with acetaminophen and not considered to be clinically significant, and intermittent vomiting, which the investigator considered retrospectively to be possibly linked to an increase in intracranial pressure. The subject reported no hearing changes or blurred vision. The subject's medications at the time of SAE were acetaminophen, hypertonic saline, fluticasone propionate, cholecalciferol, azithromycin, ursodiol, fluticasone furoate, and EpiPen.

On (b) (6) a lumbar puncture showed an opening pressure of (b) (6) (reference range ≤ 28 cm H₂O). Cerebrospinal fluid appeared clear, and cell count, protein, and glucose levels were all within normal limits. The subject started treatment with acetazolamide.

On (b) (6) a follow-up OE was performed. Visual acuity (both eyes) was 20/20. Slit lamp exam and fundus exam were normal; papilledema was slightly worse, but still in the mild range. The subject did not have any headaches or nausea but had occasional pulsatile tinnitus.

Study drug was subsequently interrupted on (b) (6) and the acetazolamide was slowly increased with improved symptoms. The subject resumed treatment with ETI on (b) (6) and subsequently OE on (b) (6) showed resolution of papilledema.

On (b) (6) the subject had an OE demonstrating resolution of papilledema and had no symptoms of high intracranial pressure. The subject continued treatment with acetazolamide. The SAE of idiopathic intracranial hypertension was considered by the investigator to be possibly related to study drug.

Reviewer comment. The use of acetazolamide and timing of study drug interruption create difficulty interpreting whether the case is spontaneous or related to study drug. At this time, the single case does not change the risk benefit for Trikafta or warrant labeling.

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

No human carcinogenicity studies have been performed for ETI.

Human Reproduction and Pregnancy

The use of ETI during pregnancy or lactation has not been evaluated in well-controlled trials. No additional findings were reported in this study. There were no pregnancies.

Pediatrics and Assessment of Effects on Growth

This trial included pediatric patients of 6 to less than 12 year old. As height and weight were secondary efficacy endpoints, a discussion of growth appears in Section 8.1.2.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

The Applicant did not complete studies on potential withdrawal, rebound effects, or systemic examination of abuse potential of ETI, nor were such studies required. Given the mechanism of action and intended use (chronic, life-long), ETI is anticipated to have minimal to no abuse potential.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

ETI was initially approved on 10/21/2019 for CF patients aged 12 years and older with at least 1 mutation. Following identification of hepatic events of increased severity in the postmarketing setting, the Applicant submitted a labeling supplement on April 8, 2021 to include additional language in the Prescribing Information (PI). This supplement remains under Agency review.

Expectations on Safety in the Postmarket Setting

The patient population included in Trial 106 who received ETI is similar to the target population.

Given this fact and the postmarketing experience with ETI, no substantial differences are anticipated.

8.2.11. Integrated Assessment of Safety

The safety data submitted with this application in conjunction with the known safety profile of ETI, were sufficient to assess the safety of ETI in the CF patient population aged 6 to 11 years of age. In Trial 106 Part B, which included 66 patients all treated with ETI, no deaths were reported. The observed SAEs were infrequent and generally consistent with the disease process in a pediatric population. Given the previous clinical experience with ETI tablets, this review explored the clinical safety database to assess for liver-related toxicity, rash, CPK elevation, and cataract formation. These safety analyses did not identify new safety concerns, and the safety findings were consistent with the known safety profile of ETI. Overall, the ETI safety profile in CF patients aged 6 to 11 years of age is favorable.

8.3. Statistical Issues

Substantial evidence of effectiveness

The approval of ETI in the 6 to 11 years age group is based on extrapolation of efficacy from the adolescent /adult studies.

In Part B of Trial 106, PK data demonstrated that when ETI 200 mg qd / 100 mg qd / 150 mg q12h was administered to patients ≥ 30 kg and ETI 100 mg qd / 50 mg qd / 75 mg q12h administered to patients < 30 kg, systemic exposures were comparable to those observed in the adolescent/adult population (see Section 6). Because of the similar systemic exposures and because the disease process in the 6 to less than 12 year old population is the same as that in the older CF population, efficacy in the proposed age group was extrapolated from the ETI adolescent/adult development program.

Under the original NDA application, the totality of the clinical efficacy data in adolescent and adult populations supported an indication for CF patients with at least one *F508del* mutation through a robust lung function benefit (ppFEV1) as well as improvement in all clinically meaningful key secondary endpoints (i.e. number of PEx, BMI, SwCl, and CFQ-R RD for Trial 102; SwCl and CFQ-R RD for Trial 103 ; see original NDA review “REV-SUMMARY-13 (Unireview)” dated 10/21/2019 under NDA 212273). Efficacy findings were generally consistent in both study populations, inclusive of CF subjects with 1 or 2 *F508del* mutant alleles. Although Trial 106 Part B did not have a placebo arm, the study demonstrated clinically significant improvements in ppFEV1, SwCl, and CFQ-R RD through Week 24 from patients’ baseline.

In addition, the Applicant examined endpoints of ppFEV1, SwCl, CFQ-R RD, BMI, and weight in Trial 106 Part B as secondary objectives to support the effectiveness. However, Trial 106 was an open label study without a comparator. The study had a 24-week treatment duration. All the efficacy measurements were compared to itself at baseline value. For all the endpoints

examined, they showed substantial improvement through Week 24 (Please refer to Section 8.1.2 for efficacy results.). This reviewer concludes that the substantial evidence of effectiveness was reasonably demonstrated although caution should be taken to interpret the efficacy results.

Open label without comparator

Trial 106 Part B evaluated change from baseline value through Week 24 for several efficacy endpoints including ppFEV1, SwCl, CFQ-R, BMI and weight. The interpretation of the efficacy results is limited due to lack of a comparator.

For the CF patients without any treatment, patient's ppFEV1 and CFQ-R RD value will decrease over the time. Acknowledging the lack of a placebo group control, observing a significant increase in ppFEV1 and CFQ-R or decrease in SwCl from a subject's baseline through week 24 suggests that the drug is contributing to the treatment effect; however, definitive conclusions can't be drawn due to lack of a comparator in the study.

Missing data and impact to the analysis results

For the endpoints of ppFEV1, SwCl, and CFQ-R RD, this reviewer analyzed change from baseline through Week 24 using a MMRM model and data collected at the following timepoints: baseline, Day 15, Week 4, Week 8, Week 12, Week 16, and Week 24. However, during the review, the reviewer identified unusually high missing data rate (exceeding 50%) at the Week 16 and Week 24 time points. Table 54 tabulated the number of subjects with data by visit for the endpoints of ppFEV1, SwCl, CFQ-R RD, BMI, and weight. As shown in Table 54, most of the missing data occurred at Week 16 and Week 24:

Table 54. Number of Subjects with Data by Visit (Trial 106, Part B)

Endpoints	Baseline	Day 15	Week 4	Week 8	Week 12	Week 16	Week 24
ppFEV1	62	51	52	51	43	29	15
SwCl	62	56	56	n/a*	50	n/a*	28
CFQ-R RD	65	n/a*	64	62	57	43	36
BMI	66	65	65	63	58	45	33
Weight	66	65	65	63	58	45	33

* n/a = not applicable, data was not collected at this time point. Source: Statistical Reviewer

To evaluate the impact of these missing data, the statistical reviewer conducted post-hoc exploratory analyses on ppFEV1 and SwCl by excluding Week 16 and Week 24 data. A comparison of efficacy results for change from baseline through Week 12 with the efficacy results for change from baseline through Week 24 appears in the last column of Table 57 and Table 58.

Table 55. Analysis and Subgroup Analysis of Absolute Change from Baseline in ppFEV1 (%) through Week 24 by Baseline Body Weight (Trial 106 Part B, FAS)

Endpoints	ETI Low Dose N = 33	ETI High Dose N = 29	Total N = 62
CFB* in ppFEV1 through Week 24 (%): LS mean (SE) 95% CI p-value	7.0 (1.7) (3.5, 10.5) 0.0003	14.7 (1.5) (11.6, 17.7) <0.0001	10.2 (1.2) (7.9, 12.6) <0.0001
CFB* in ppFEV1 through Week 12 (%): LS mean (SE) 95% CI p-value	6.9 (1.8) (3.3, 10.5) 0.0005	13.0 (1.5) (10.0, 16.0) 0.0001	9.5 (1.1) (7.2, 11.8) <0.0001

* CFB = change from baseline
Source: Statistical Reviewer

Table 56. Analysis and Subgroup Analysis of Absolute Change from Baseline in SwCl (mmol/L) through Week 24 by Baseline Body Weight (Trial 106 Part B, FAS)

Endpoints	ETI Low Dose N = 33	ETI High Dose N = 29	Total N = 62
CFB* in SwCl through Week 24 (mmol/L): LS mean (SE) 95% CI p-value	-61.7 (1.8) (-65.3, -58.1) <0.0001	-60.4 (2.1) (-64.8, -56.0) <0.0001	-60.9 (1.4) (-63.7, -58.2) <0.0001
CFB* in SwCl through Week 12 (mmol/L): LS mean (SE) 95% CI p-value	-58.9 (1.6) (-62.2, -55.7) <0.0001	-58.4 (1.7) (-62.0, -54.9) <0.0001	-58.6 (1.3) (-61.1, -56.1) <0.0001

* CFB = change from baseline
Source: Statistical Reviewer

Comparing absolute changes from baseline in ppFEV1 and SwCl through Weeks 12 and 24, the significant improvements in these efficacy parameters through Week 12 persists through Week 24 despite the high rate of data missing at Week 16 and Week 24.

Following an information request to the Applicant to clarify the reason for data missing at each time point, the Applicant indicated that the majority of the data missing at Weeks 16 and 24 was due to impact of COVID-19 on data collection (see discussion in Section 8.1.1). Treating data missing as missing at random due to COVID-19 is consistent with Agency's current practice. The analyses using MMRM model treating data missing as missing at random,

therefore, are aligned to estimate the treatment effect of interest in the presence of COVID-19 related missing data. Thus, this reviewer concludes that the analyses of change from baseline through Week 24 were reasonable despite high missing data rate at Week 16 and Week 24.

Subgroup analysis by baseline body weight

Since subjects with baseline body weight <30 kg and ≥30 kg were treated with different ETI dosage, it is important to examine whether the overall efficacy came from one subgroup or both groups. This reviewer conducted post-hoc subgroup analyses on the ppFEV1 and SwCl endpoints by baseline body weight group for change from baseline through Week 24 and Week 12, respectively. Results are presented in Table 57 and Table 58:

Table 57. Subgroup Analysis of Absolute Change from Baseline in ppFEV1 (%) through Week 24 or 12 by Baseline Body Weight (Trial 106 Part B, FAS)

Endpoints	Baseline Weight < 30 Kg N = 33	Baseline Weight ≥ 30 Kg N = 29	All N = 62
CFB* in ppFEV1 through Week 24 (%): LS mean (SE) 95% CI p-value	7.0 (1.7) (3.5, 10.5) 0.0003	14.7 (1.5) (11.6, 17.7) <0.0001	10.2 (1.2) (7.9, 12.6) <0.0001
CFB* in ppFEV1 through Week 12 (%): LS mean (SE) 95% CI p-value	6.9 (1.8) (3.3, 10.5) 0.0005	13.0 (1.5) (10.0, 16.0) 0.0001	9.5 (1.1) (7.2, 11.8) <0.0001

* CFB = change from baseline
Source: Statistical Reviewer

Table 58. Subgroup Analysis of Absolute Change from Baseline in SwCl (mmol/L) through Week 24 or 12 by Baseline Body Weight (Trial 106 Part B, FAS)

Endpoints	Baseline Weight < 30 Kg N = 33	Baseline Weight ≥ 30 Kg N = 29	All N = 62
CFB* in SwCl through Week 24 (mmol/L): LS mean (SE) 95% CI p-value	-61.7 (1.8) (-65.3, -58.1) <0.0001	-60.4 (2.1) (-64.8, -56.0) <0.0001	-60.9 (1.4) (-63.7, -58.2) <0.0001
CFB* in SwCl through Week 12 (mmol/L): LS mean (SE)	-58.9 (1.6) (-62.2, -55.7) <0.0001	-58.4 (1.7) (-62.0, -54.9) <0.0001	-58.6 (1.3) (-61.1, -56.1) <0.0001

95% CI p-value			
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*CFB = change from baseline
Source: Statistical Reviewer

Table 57 and Table 58 demonstrate that changes from baseline through Weeks 12 and 24 for both ppFEV1 and SwCl endpoints were similar for both weight subgroups despite the different ETI treatment dosages (see Table 37) and despite large missing data at Weeks 16 and 24. Therefore, this reviewer concludes that efficacy was demonstrated for both subgroups of baseline body weight <30 kg and baseline body weight ≥30 kg for the endpoints examined (ppFEV1 and SwCl).

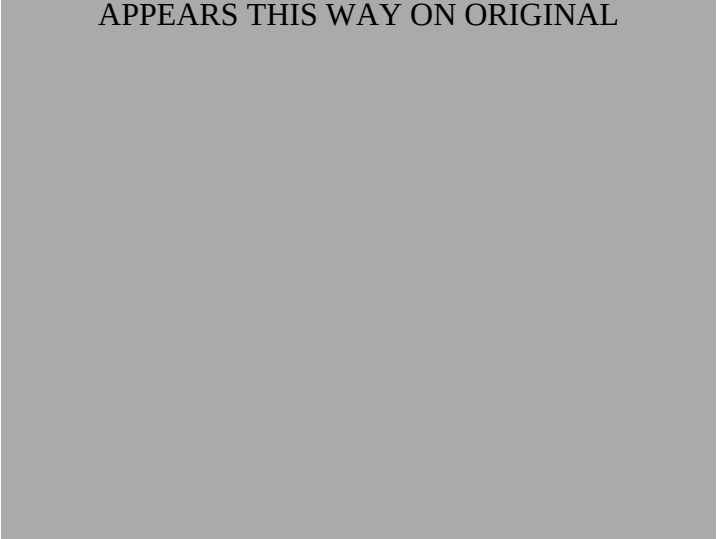
8.4. Conclusions and Recommendations

The Applicant has demonstrated substantial evidence of safety and effectiveness for ETI for the treatment of CF in patients ≥ 6 years of age with at least one *F508del* mutation in the *CFTR* gene. The recommended regulatory action is Approval.

9 Advisory Committee Meeting and Other External Consultations

A Pulmonary and Allergy Drug Advisory Committee (PADAC) meeting was considered for this supplement. However, given the persuasiveness of the clinical trial results, the Division decided that the evidence supporting the original approval for the indicated populations were sufficiently robust that discussion by an Advisory Committee was not necessary.

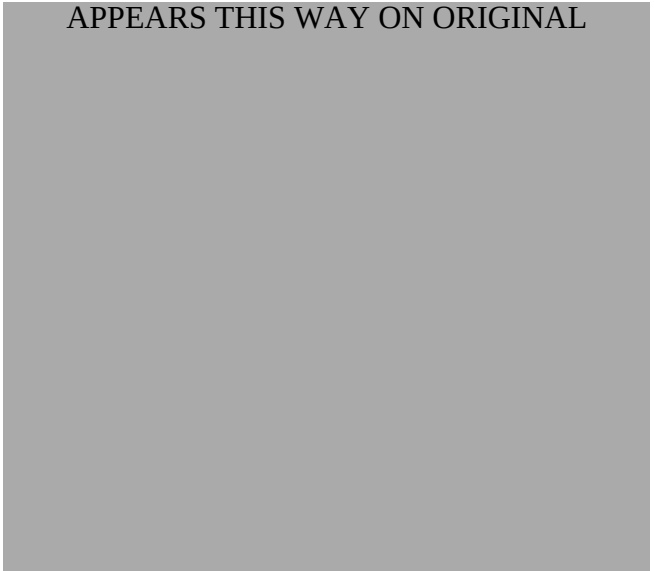
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10 **Pediatrics**

CF is a rare, orphan disease and thus is not subject to pediatric study requirements as defined under PREA. However, both phase 3 trials included CF patients 12 to 17 years of age (inclusive) and the present supplement included CF patients 6 to 11 years of age (inclusive). Efficacy and safety data in the 6 to 11 year age group and adolescents were consistent with the overall results.

APPEARS THIS WAY ON ORIGINAL



11 Labeling Recommendations

11.1. Prescription Drug Labeling

The Applicant submitted proposed Prescribing Information, Patient Information, and carton and container labeling for the ETI combination that included the tradename TRIKAFTA.

The Division of Medication Error Prevention and Analysis reviewed the proposed PI, container labels, and carton labeling for areas of vulnerability that were conveyed to the Applicant.

Table 59. Summary of Significant Labeling Changes

Section	Proposed Labeling	Approved Labeling	Rationale
Section 8.4. Juvenile Animal Toxicity Data	(b) (4)	Recommended to add findings of convulsions and death in juvenile rats dosed from postnatal days (PND) 21 through 35 at a tezacaftor dose level of 100 mg/kg/day, and findings of decreased body weight gains observed in juvenile rats dosed from PND 21 to PND 49 at a tezacaftor dose level of 60 mg/kg/day. Noted that these findings are not thought to be of concern for the indicated pediatric patients (6 through 11 years of age) where levels of P-glycoprotein activity are approximately equivalent to levels observed in adults.	Vertex conducted 4 juvenile rat studies with tezacaftor and the findings were very reproducible in terms of CNS toxicity. There are concerns for younger children less than of approximately 1 (or 2) year of age in terms of potential CNS toxicity. Even though the findings are not thought to be pertinent to the indicated pediatric population of 6 to 11 year olds, this safety information should be included in the product labeling to discourage off-label use. These findings may also be related to reports of neuropsychiatric events with the CFTR modulators.

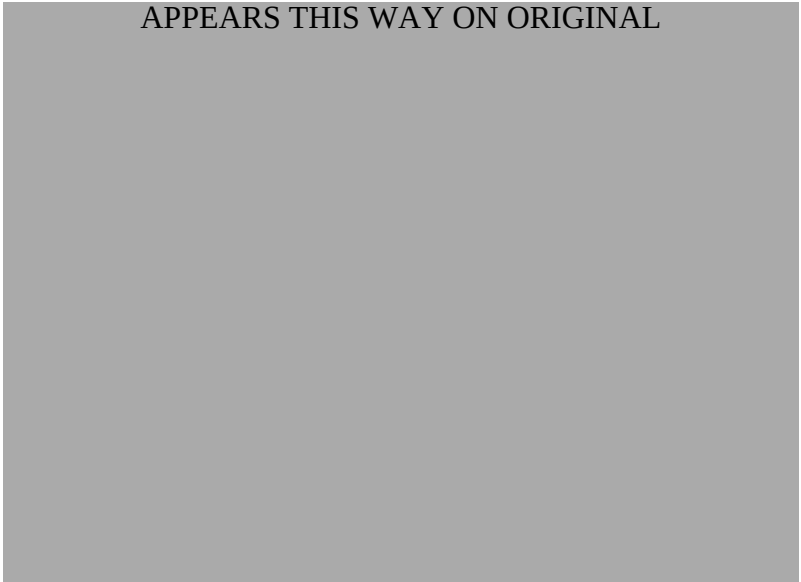
12 Risk Evaluation and Mitigation Strategies (REMS)

A REMS was not deemed necessary for this application.

13 Postmarketing Requirements and Commitment

PREA requirements do not apply to this orphan drug product; however, Vertex is voluntarily conducting clinical studies in CF patients less than 6 years of age. No PMRs or PMCs will be issued with this supplement.

APPEARS THIS WAY ON ORIGINAL



14 Deputy Division Director (DPACC) Comments

Trikafta is a fixed-dose combination of elexacaftor (ELX), tezacaftor (TEZ), and ivacaftor (IVA) [ETI]. IVA is a potentiator of the CFTR chloride channel present on the epithelial cell membrane; ELX and TEZ facilitate the cellular processing and trafficking of defective CFTR protein to the epithelial cell apical surface. Trikafta was approved under NDA 212273 in October 2019 for the treatment of CF in patients 12 years of age and older who have at least one *F508del* mutation in the CFTR gene. In December 2020, based on in vitro assay data, the indication was expanded to include 177 additional rare CFTR gene mutations. In this supplemental NDA (sNDA), the Applicant proposed to expand the indication to include CF patients 6 to 11 years of age. The proposed doses are:

- For patients < 30 kg:
 - AM: 2 fixed-dose combination (FDC) tablets containing ELX 50 mg/ TEZ 25 mg/IVA 37.5 mg
 - PM: 1 tablet containing 75 mg IVA
- For patients ≥ 30 kg:
 - AM: 2 FDC tablets containing ELX 100 mg/ TEZ 50 mg/IVA 75 mg
 - PM: 1 tablet containing 150 mg IVA

In this sNDA, the Applicant submitted data from a PK/safety study – Trial 106 to support the use of ETI in patients 6 to 11 years of age. Trial 106 was a two-part, non-randomized, uncontrolled, open-label, PK (part A, 15 day duration, n=16) and safety (part B, 24-week duration, n=66) study in patients 6 to 11 years of age. Results demonstrated systemic exposures comparable to those observed in the adult/adolescent program when dosed according to the dosing regimen described above. Week 24 data from Part B demonstrated within group improvements in pulmonary function (ppFEV1), sweat chloride (SwCl), and Cystic Fibrosis Questionnaire-Revised Respiratory Domain (CFQ-R RD), suggesting a clinically meaningful response to the ETI treatment.

Because of the comparable systemic exposures and because the disease process in the older population is the same as that in the ≥ 12 year old population, efficacy in the proposed age group was extrapolated from the ≥ 12 year old age group where efficacy had been demonstrated in clinical trials. No new safety signals were identified. Language regarding neurotoxicity noted in juvenile toxicity studies of tezacaftor was added to the package insert. There are no outstanding issues from any review disciplines. I concur with the content of the various discipline assessments and recommendation of approval. The Agency and the Applicant have also agreed upon the final labeling language. The submitted clinical program is adequate to support the efficacy and safety of ETI for the treatment of patients 6 years of age and older with at least one *F508del* mutation or a mutation in the *CFTR* gene that is responsive based on in vitro data. The action for this application will be **Approval**.

15 Appendices

15.1. Financial Disclosure

Application Number: NDA 212273, supplement 4

Submission Date(s): 12/8/2020

Applicant: Vertex

Product: Trikafta (elexacaftor, tezacaftor, ivacaftor)

Reviewer: Courtney McGuire, MD

Date of Review: 2/25/2021

Covered Clinical Study (Name and/or Number): VX18-445-106

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>152</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>1</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>1</u> Proprietary interest in the product tested held by investigator: <u>0</u> Significant equity interest held by investigator in Sponsor of covered study: <u>0</u>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (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 ☐	No ☐ (Request explanation from Applicant)

15.2. OCP Appendices (Technical documents supporting OCP recommendations)

15.2.1. Clinical PK/PD Assessments

Following the proposed dosing regimen in Par B of Study VX18-445-106, the absolute mean change of sweat chloride concentration from baseline through Week 24 was -60.9 mM (Table 60). By genotype, the absolute mean change of sweat chloride concentration from baseline through Week 24 was -67.3 ± 9.6 mM and -55.1 ± 11.1 mM for F/F and F/MF, respectively.

Table 60. MMRM Analysis of Absolute Change from Baseline in Sweat Chloride Concentration (mM) Through Week 24 (FAS, Part B)

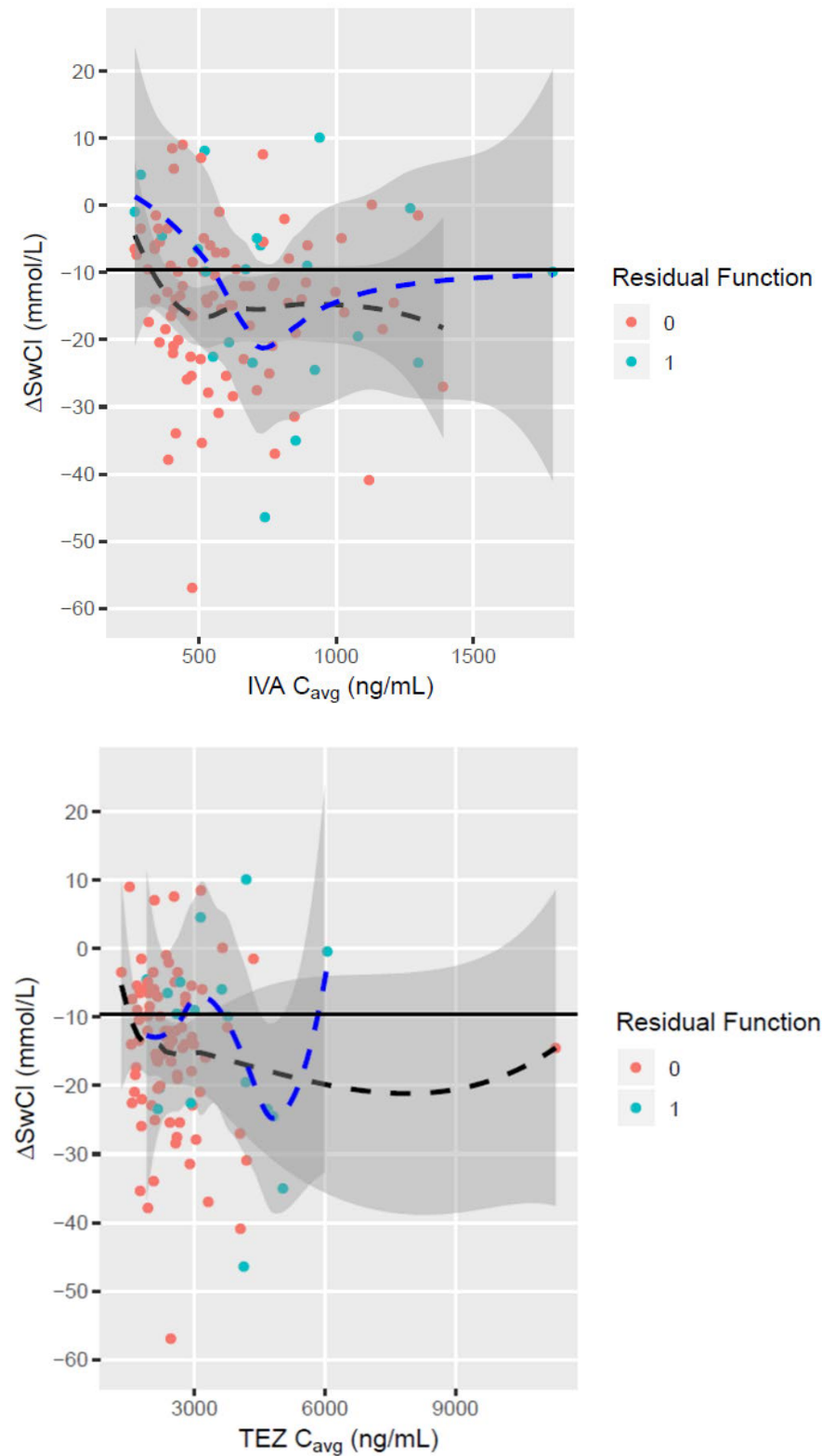
	ELX/TEZ/IVA N = 66
Baseline	
n	62
Mean (SD)	102.2 (9.1)
Absolute change through Week 24	
n	60
LS mean (SE)	-60.9 (1.4)
95% CI of LS mean	(-63.7, -58.2)
P value	<0.0001

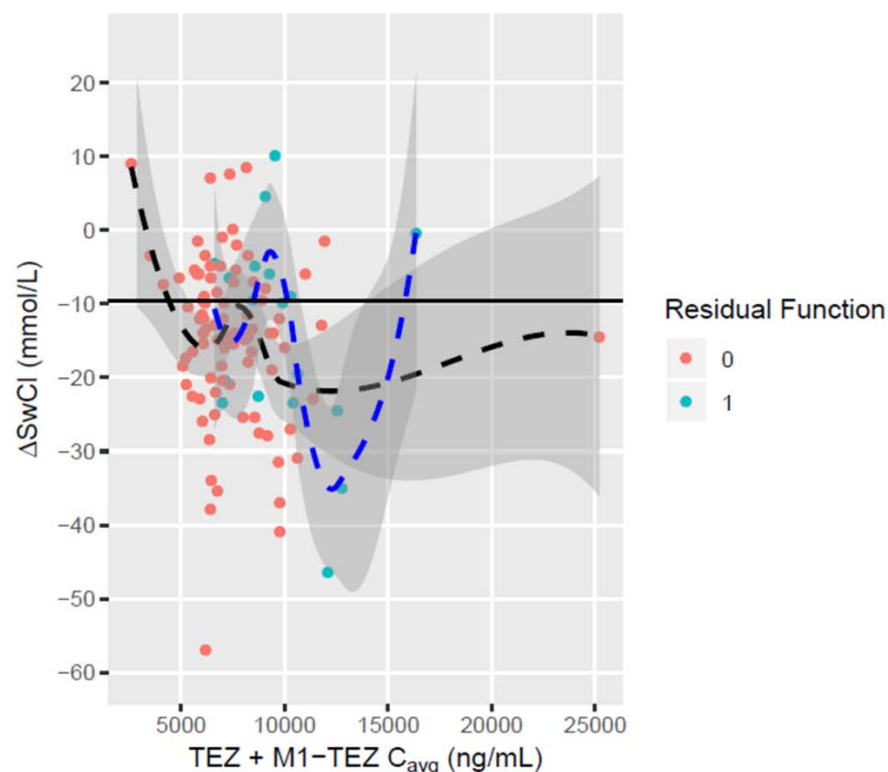
Source: CSR of Trial 106, table 11-5, pg. 86.

15.2.2. Exposure-Response

No formal ER analyses were performed for review based on the pivotal pediatric study 106. Graphical approach was used to evaluate the relationship between sweat chloride concentrations and average IVA, TEZ, and M1-TEZ concentration in pediatric subjects from Trials 113 and 115 (under NDA 210491) around their sweat chloride evaluation at the end of treatment (Week 24 or Week 8, respectively). Figure 13 indicated (1) no major differences in response between average concentration quartiles, (2) similar responses between adult and pediatric subjects, and (3) similar responses between F/F and F/RF subjects.

Figure 13. Relationship between sweat chloride concentrations and average IVA, TEZ, and M1-TEZ concentration in pediatric subjects from Studies 113 and 115.





The change in sweat chloride concentration at 24 weeks for Study 113 and 8 weeks for Study 115 is plotted versus average concentration for each subject. Subjects with the F/F genotype are shown in pink and those with the RF genotype are shown in green. A solid line at -9.9 mmol/L represents the average change in sweat chloride for adult subjects. The dotted lines represent a loess fit through the data points, with a gray shaded 95% CI surrounding it. The black line represents the fit of the F/F subjects and blue line represents the fit of the RF subjects.

Source: Figure 188 (pg. 289), 190 (pg. 291) and 192 (pg. 293) from report P133.

15.2.3. Population PK Analysis

Aim: 1) Evaluate the final population pharmacokinetic (PK) models of elexacaftor (ELX) and its M23 metabolite (M23-ELX) in subjects 6 through 11 years of age (6-11y) based on the final data from Study VX18-445-106 (Study 106); and characterize the exposures of ELX and M23-ELX exposures in 6-11y subjects with the proposed dosing regimen of ELX in combination with tezacaftor (TEZ) and ivacaftor (IVA), also known as ELX/TEZ/IVA at different weight cutoffs. 2) Evaluate the population PK of TEZ, M1-TEZ, and IVA in CF subjects receiving the combination of ELX/TEZ/IVA, including those who are 6 through 11 years of age, with a focus on describing the impact of body weight on clearance and volume related parameters.

PopPK Data: There are 4 studies included in the analyses including one phase 1 study (VX16-445-001 (001)) and three phase 3 studies (VX17-445-102 (102), VX17-445-103 (103) and VX18-445-106 (106). These studies are summarized in Table 61. The final ELX dataset used for model development included 2333 ELX plasma concentration measurements from adult and adolescent CF subjects, and 799 ELX plasma concentration measurements from 71 unique CF

subjects 6-11 years of age. The final M23-ELX dataset used for model development included 2255 M23-ELX plasma concentration measurements from adult and adolescent CF subjects, and 777 M23-ELX plasma concentration measurements from 71 unique CF subjects 6-11 years of age. In summary, there were a total of 3,132 ELX and 3,032 M23-ELX observed concentrations from 417 subjects. The baseline covariates are summarized in Table 62.

Table 61. Summary of the Studies Included in the ELX Population PK Analysis

Study	Phase	Cohort	ELX Dose (mg)	Concomitant Drug	PK Sampling Scheme	*Number of subjects	Population
001	1/2	A (Single dose)	20, 60, 120, 240, and 360	Monotherapy	Predose	8	Healthy
		B	60 qd, 120 qd, 240 qd, 340 qd		From 0.25 up to ≤12 hours after study drug dosing	8	
		C	100 qd, 200 qd, and 280 qd		From >12 up to ≤24 hours after study drug dosing	8	
				100mg qd TEZ/150mg q12h IVA	From >24 up to ≤48 hours after study drug dosing		
					From >48 up to ≤120 hours after study drug dosing		
		D1	100 qd	100mg qd TEZ/150mg q12h IVA	Predose	6	F/MF CF
		D2	50 qd, 100 qd, 200 qd		From 1 up to ≤8 hours after study drug dosing	39	
102	3	E	200 qd	100mg qd TEZ/150mg q12h IVA	Predose	18	F/F CF
		F	200 qd	100mg qd TEZ/150mg qd IVA	Predose	18	F/MF CF
					From 1 up to ≤8 hours after study drug dosing		
					Predose on Day 1, Week 4, Week 8, Week 12, and Week 16.		
103	3		200 qd	100mg qd TEZ/150mg q12h IVA	Approximately 40 subjects enrolled in the study will have 4 postdose samples taken at 2, 4, 6, and 8 hours after the morning dose at Week 4. All remaining subjects will have 1 postdose sample taken at 1 hour after the morning dose at Week 4.	180	F/MF CF
106	3	Part A	100 qd	50mg qd TEZ/75mg q12h IVA	Predose on Day 1, Day 15, and Week 4	50	F/F CF
106	3	Part B	100 qd for <30 kg	50 mg qd TEZ/ 75mg q12h IVA for <30 kg	Day 1: before the AM dose, and at 1, 2, 4, and 6 hours after the AM dose Day 8: before the AM dose Day 15: before the AM dose, and at 1, 2, 4, and 6 hours after the AM dose	16	F/F or F/MF CF
			200 qd for ≥30 kg	100mg qd TEZ/ 150mg q12h IVA for ≥30 kg	Day 15, Week 12, and Week 24. Serial sampling will be performed on Day 1 at 2, 4, and 6h postdose; and on Week 4 before dosing, and 1, 2, 4, and 6 hours after the morning dose.	66	F/F or F/MF CF

Source: Table 1 in the PopPK report Q075, pg. 15.

Table 62. Summary of Baseline Covariates

Study	001	102	103	106A	106B	Overall
N	95	199	52	16	66	417
Male	52	103	22	5	27	205
Female	43	96	30	11	39	212
CF, F/MF	74	199	0	9	37	312
CF, F/F	21	0	52	7	29	105
White	92	184	51	16	57	389
Black or African American	1	3	0	0	0	4
Asian	0	0	0	0	0	0
Multiple	0	1	0	0	1	2
Other	2	11	1	0	8	22
Age, years (median [min, max])	30 [18, 58]	24 [12, 59]	27 [12, 53]	8.5 [6, 11]	9 [6, 11]	23 [6, 59]
Age, years (mean [SD])	30.8 [8.8]	25.1 [9.7]	28.3 [11.8]	8.4 [1.9]	8.7 [1.8]	24 [11.5]
Body weight, kg (median [min, max])	63 [44, 111.1]	58 [29, 108]	59.5 [36, 83]	28.5 [18.1, 42.8]	29 [18.1, 53.6]	56 [18.1, 111.1]
Body weight, kg (mean [SD])	63.1 [11.1]	59.8 [12.9]	59.6 [12.2]	29.3 [6.7]	30 [7.7]	55.5 [16.4]

max: maximum value; min: minimum value; N: total sample size; SD: standard deviation. Note: 11 subjects were enrolled in both Parts A and B in Study 106, their baseline covariates were counted separately in each part. In the overall, these crossover subject covariates were only counted once.

Source: Table 2 in the PopPK report Q075, pg. 24.

ELX Final Model: The ELX final model is a linear, two-compartment popPK model with four-transit compartments; first-order absorption; IIV on CL, V2 and KTR; and additive and proportional errors. The model had the following covariate effects: weight on CL, Q, V2 and V3; formulation on KA; and age on KTR. The final model parameter estimates are summarized in Table 63. The formulation effect on KA showed that there was less than 20% difference in the parameter estimates between monotherapy tablets versus FDC which is still the range of the PK variability. The KTR values were 26.3% lower for subjects less than 21 years of age comparing to population value. This age effect on KTR only impacted the time to reach maximum concentration after dosing and did not impact ELX exposures. Weight was the only covariate that had a clinically meaningful impact on ELX disposition. The final model was further assessed via goodness of fit plots (e.g., see Figure 14).

Table 63. ELX Final Model Parameter Estimates.

Parameters	Unit	Estimate	Relative Standard Error (%)	95% CI	IIV (%CV)
Central clearance, CL	L/h	1.09	26.3	[1.04,1.14]	34 (CV% ^a)
Central volume, V2	L	34.9	1.46	[31.5,38.6]	35.4 (CV% ^a)
Absorption rate, KA	h ⁻¹	0.684	15.9	[0.471,0.896]	
Total bioavailability, F (fixed)		0.802			
Inter-compartmental clearance, Q	L/h	2.52	19.1	[1.78,3.57]	
Peripheral volume, V3	L	13.8	12.6	[7.24,26.4]	
Transit rate constant, KTR	h ⁻¹	3.58	6.52	[3.04,4.22]	56.3 (CV% ^a)
Weight saturation on CL and Q	Kg	44.9	0.0283	[44.8,45]	
Allometric exponent for CL and Q (fixed)		0.75			
Allometric exponent for V2 and V3		0.944	5.76	[0.838,1.05]	
Formulation on KA, KATABLET		0.836	32.9	[0.297,1.38]	
Age effect on transit rate constant, AGEKTR		-0.263	20.6	[-0.37,-0.157]	
ω^2_{CL}		0.115	9.28	[0.0943,0.136]	
ω^2_{V2}		0.126	33.9	[0.0421,0.209]	
ω^2_{KTR}		0.317	13.9	[0.23,0.403]	
$\sigma^2_{proportional}$		0.0582	10.8	[0.0459,0.0705]	24.1 (CV% ^a)
$\sigma^2_{additive}$	(ng/ml) ²	94600	52.1	[0.191000]	308 (SD ^b)

Notes: Estimates are for a reference subject: a 70 kg CF subject). Inter-individual variability and residual error estimates are reported as variances ω^2 , σ^2 respectively. The model has 4 transit compartments.

Model: run90000.mod

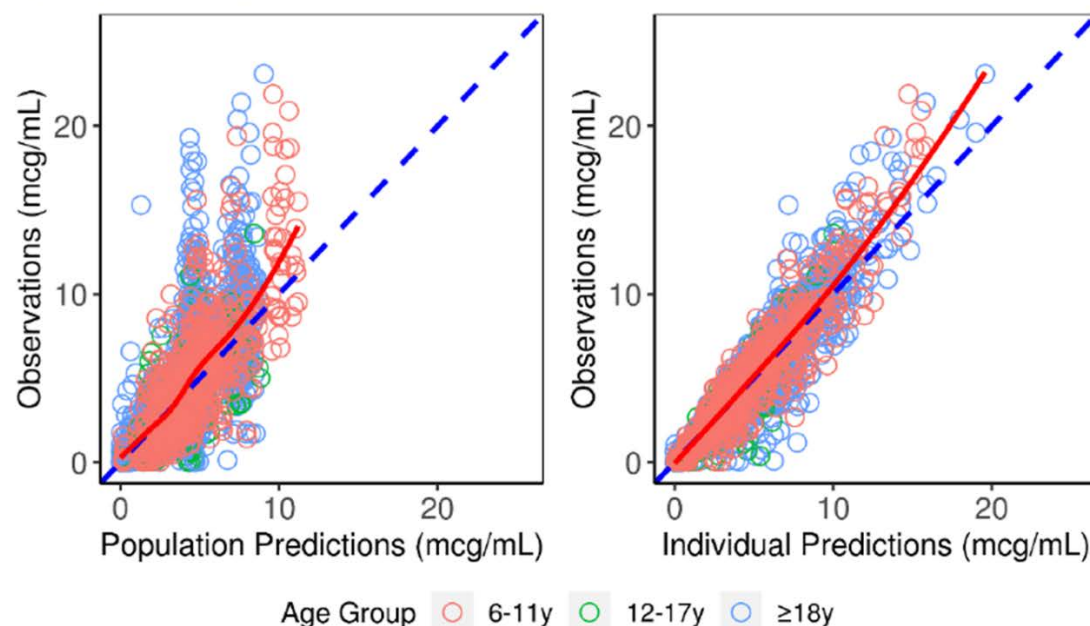
^a Parameter IIV CV% = square root of the parameter IIV * 100

^b Additive Error SD = square root of the additive error variance

Source: Table 3 in the PopPK report Q075, pg. 41-42.

Figure 14. Goodness-of-Fit Plots for the Final ELX Model by Age.

Panel A: Observed Versus Population Prediction (left) and Observed Versus Individual Prediction (right) (All CF subjects)



Source: Figure 7-5, Part A in the PopPK report Q075, pg. 27

M23-FLX Final Model: The M23-ELX final model is a linear, two compartment popPK model with IIV on CLM and V2M, additive and proportional errors, and the following covariate effects: weight on CLM, QM, V2M, and V3M; and female and 6-11y male gender on CLM. Female and 6-11y male gender on CLM covariate was kept in final model to remove trends in the final model diagnostics. This covariate does not impact the 23-ELX exposures in the clinically meaningful manner. Weight was the only clinically meaningful covariates those impact M23-ELX disposition. The final M-23 ELX model parameter estimates are summarized in Table 64. The model was further assessed via goodness of fit plots (e.g., see Figure 15). DV versus PRED plots indicated a slight bias at higher concentrations. There was no systemic bias on IPRED versus DV plots, which implies that the individual EBEs were reasonably estimated to describe the 6-11y exposures for subjects participating in the clinical study.

Table 64. M23-ELX Final Model Parameter Estimates.

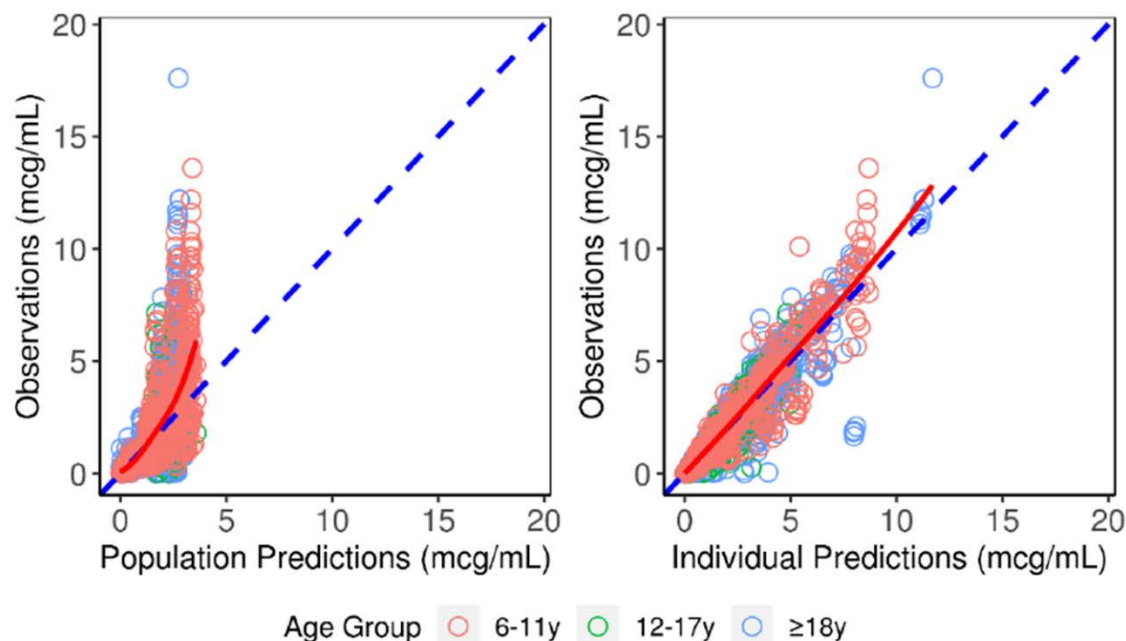
Parameters	Unit	Estimate	Relative Standard Error (%)	95% CI	IIV (%CV)
Central clearance, CLM	L/h	1.77	7.7	[1.62,1.93]	54.6 (CV% ^a)
Central volume, V2M	L	12	2.61	[10.6,13.6]	58.3 (CV% ^a)
Inter-compartmental clearance, QM	L/h	7.8	9.03	[5.42,11.2]	
Peripheral volume, V3M	L	20.4	4.11	[16,25.9]	
Fraction metabolized to M23-ELX (fixed)		0.574			
Weight saturation on CLM and QM	kg	29.5	0.181	[29.1,29.9]	
Allometric exponent for CLM and QM (fixed)		0.75			
Allometric exponent for V2M and V3M		0.765	12.7	[0.575,0.955]	
Female effect on CLM		-0.248	16.3	[-0.327,-0.169]	
Male effect on CLM for 6-11y		-0.381	19.8	[-0.529,-0.233]	
ω^2_{CLM}		0.298	10.1	[0.239,0.357]	
ω^2_{V2M}		0.34	20	[0.206,0.474]	
$\sigma^2_{\text{proportional CF}}$		0.0681	6.43	[0.0595,0.0766]	26.1 (CV% ^a)
$\sigma^2_{\text{additive CF}}$		16.2	32.9	[0,26.7]	4.03 (SD ^b)

Notes: Estimates are for a reference subject: a 70 kg male CF subject. Inter-individual variability and residual error estimates are reported as variances ω^2 , σ^2 respectively.

Source: Table 5 in the PopPK report Q075, pg. 63.

Figure 15. Goodness-of-Fit Plots for M23-ELX Model by Age.

Panel A: Observed Versus Population Prediction (left) and Observed Versus Individual Prediction (right) for All CF Subjects



Source: Figure 7-9, Part A in the PopPK report Q075, pg. 49.

Final TEZ Model: The PK of TEZ was well described using a two-compartment model with first-order absorption. Covariate-parameter relationships in the final TEZ population PK model included: weight on apparent clearance after oral dosing (CL/F), apparent central volume of distribution after oral dosing (Vc/F), apparent peripheral volume of distribution after oral dosing (Vp/F), and apparent intercompartmental clearance after oral dosing (Q/F). The weight effect on clearance terms (CL/F, Q/F) and volume terms (Vc/F, Vp/F) was described using an allometric model with an estimated exponent. Separate exponents were estimated for the clearance and volume terms. The final TEZ model parameter estimates are summarized in Table 65. The final model was further assessed via goodness of fit plots (e.g., see

Figure 16).

Table 65. Final TEZ Model Parameter Estimates.

			Estimate	95% CI	%RSE
Structural model parameters					
CL/F (L/hr)	θ_1	Apparent clearance	1.38	1.28, 1.47	3.38
Vc/F (L)	θ_2	Apparent central volume	18.1	15.5, 20.7	7.27
Vp/F (L)	θ_3	Apparent peripheral volume	65.4	39.5, 91.3	20.2
Q/F (L/hr)	θ_4	Apparent intercompartmental clearance	1.20	0.786, 1.61	17.5
k_a (1/hr)	θ_5	First order absorption rate constant	1.17	0.719, 1.62	19.7
Covariate effect parameters					
CL _{WT}	θ_6	Weight effect on clearance terms	0.563	0.458, 0.667	9.46
V _{WT}	θ_7	Weight effect on volume terms	0.834	0.733, 0.935	6.18
Interindividual variability parameters					
IIV-CL/F	$\Omega_{1,1}$	Variance of CL/F	0.0886 [CV%=30.4]	0.0703, 0.107	10.5
IIV-Vc/F	$\Omega_{2,2}$	Variance of Vc/F	0.0771 [CV%=28.3]	0.0231, 0.131	35.8
Covariance parameters					
CL/F-Vc/F	$\Omega_{2,1}$	Covariance: CL/F-Vc/F	0.0177 [Corr=0.214]	0.00408, 0.0312	39.2
Residual variability					
Proportional	$\Sigma_{1,1}$	Variance	0.111 [CV%=33.3]	0.0992, 0.122	5.25
Additive	$\Sigma_{2,2}$	Variance	17100 [SD=131]	3550, 30700	40.4

Abbreviations: CI = confidence intervals; Corr = Correlation coefficient; CV = coefficient of variation; SD = standard deviation; SE = standard error; %RSE = residual standard error (%)

Confidence intervals = estimate $\pm$ 1.96 * SE

CV% of omegas = $\sqrt{\exp(\text{estimate}) - 1} * 100$

CV% of sigma = $\sqrt{\text{estimate}} * 100$

RSE% = SE/estimate * 100

Source: Table 5 in the PopPK report Q076, pg. 52.

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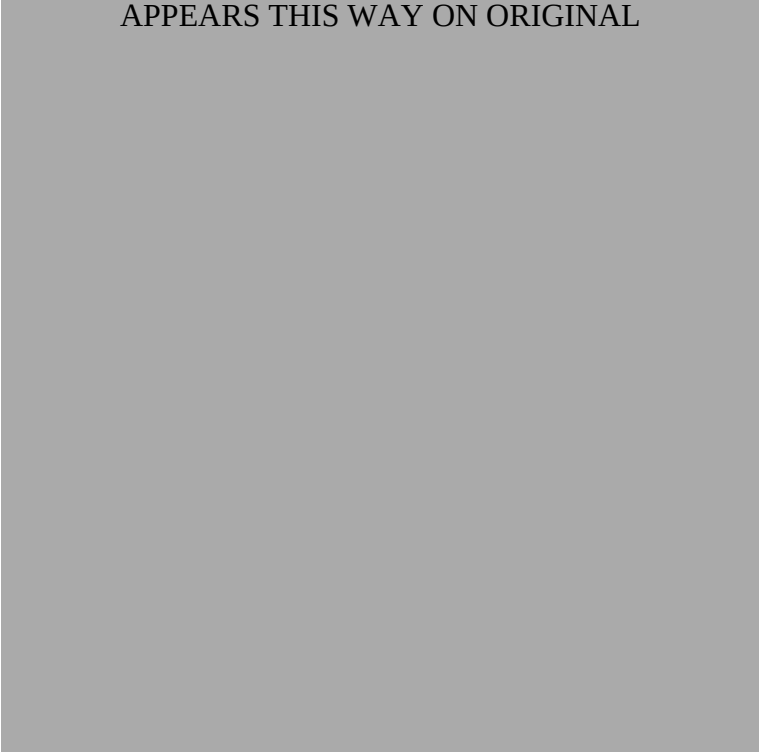
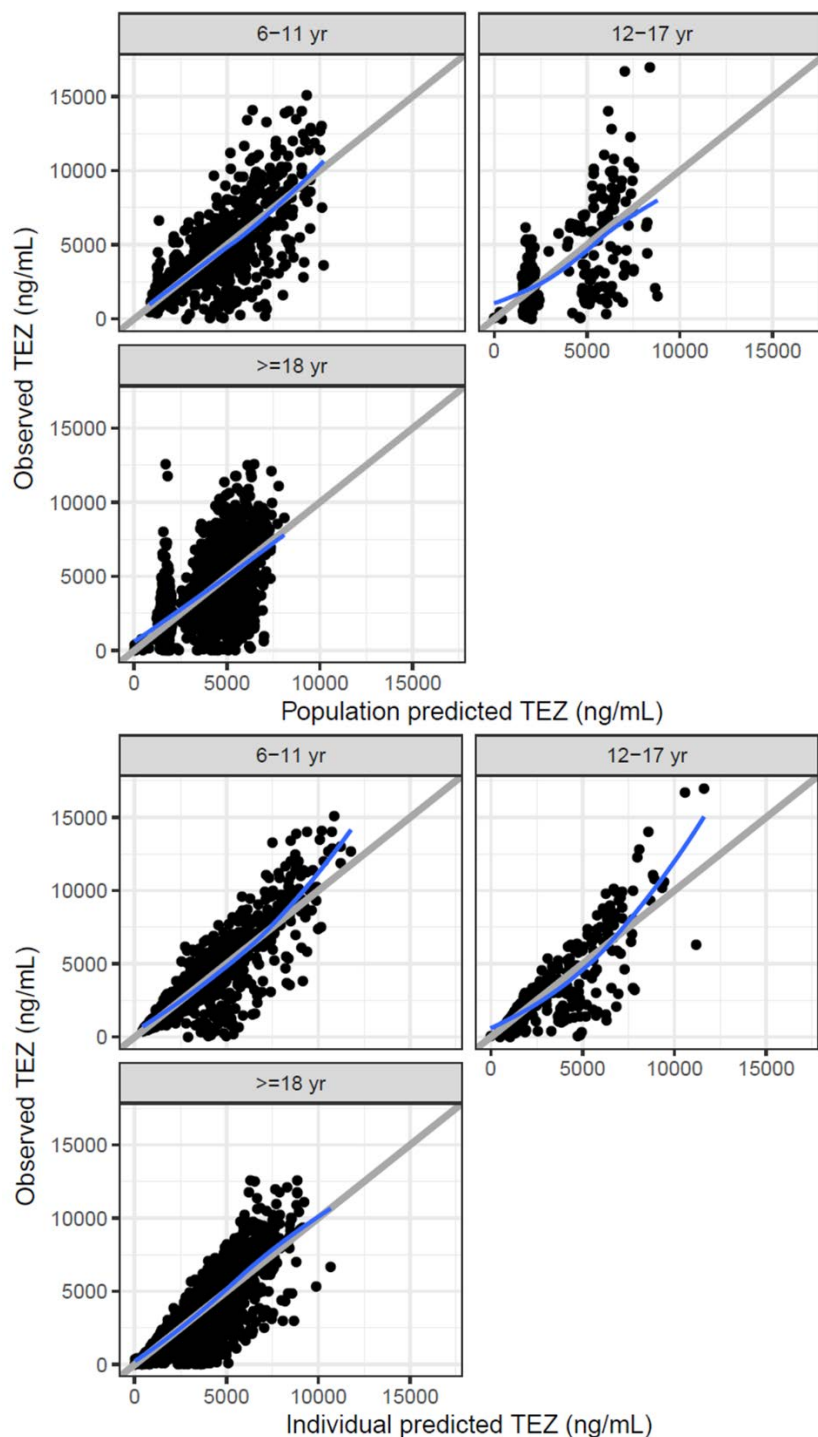


Figure 16. Goodness of Fit Plots for Final TEZ model by Age.



Values are indicated by black circles with a LOESS smooth trend line (solid blue) through the data. The line of identity (solid gray) is included as a reference.

Source: Figures 4 (pg. 88) and 7 (pg. 91) in the PopPK report Q076.

M-1 TEZ Final Model: The PK of M1-TEZ was well described using a two-compartment model. Covariate-parameter relationships in the final M1-TEZ population PK model included: weight on CL/F, Vc/F, Vp/F, and Q/F. The weight effect on clearance terms (CL/F, Q/F) and volume terms (Vc/F, Vp/F) was described using an allometric model. The allometric exponent was estimated for the clearance terms and fixed to 1.0 for the volume terms. The M-1 TEZ final model parameter estimates are summarized in Table 66. The M-1 TEZ final model was further assessed via goodness of fit plots (e.g., see

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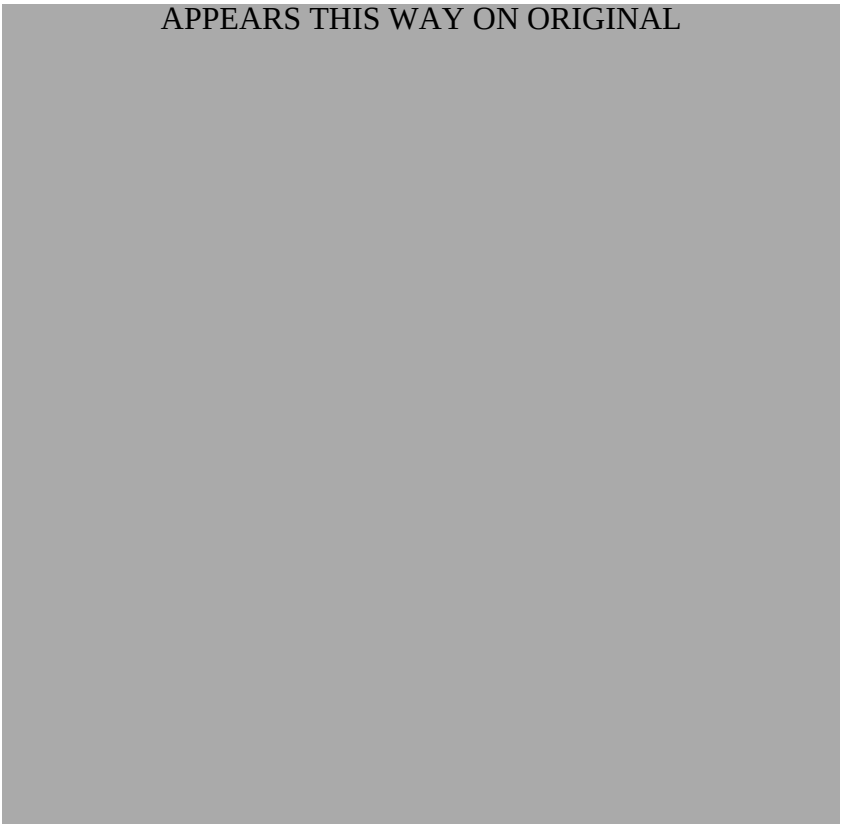


Figure 17).

Table 66. M-1 TEZ Final Model Parameter Estimates.

			Estimate	95% CI	%RSE
Structural model parameters					
CL/F (L/hr)	θ_1	Apparent clearance	0.662	0.639, 0.686	1.81
Vc/F (L)	θ_2	Apparent central volume	8.80	7.11, 10.5	9.81
Q/F (L/hr)	θ_3	Apparent intercompartmental clearance	3.33	1.57, 5.10	27.0
Vp/F (L)	θ_4	Apparent peripheral volume	13.5	9.17, 17.9	16.4
FM1	-	Fraction of TEZ converted to M1-TEZ	0.8 [Fixed]	-	-
Covariate effect parameters					
CL _{WT}	θ_5	Weight effect on clearance terms	0.823	0.762, 0.884	3.80
V _{WT}	θ_6	Weight effect on volume terms	1.00 [Fixed]	-	-
Interindividual variability parameters					
BC for IIV – CL/F	θ_7	Box-Cox transformation factor	1.36	0.895, 1.82	17.4
IIV-CL/F	$\Omega_{1,1}$	Variance of CL/F	0.0678 [CV%=26.5]	0.0533, 0.0823	10.9
IIV-Vc/F	$\Omega_{2,2}$	Variance of Vc/F	0.263 [CV%=54.8]	0.169, 0.357	18.2
Covariance parameters					
CL/F-Vc/F	$\Omega_{2,1}$	Covariance: CL/F-Vc/F	0.0746 [Corr=0.559]	0.0490, 0.100	17.5
Residual variability					
Proportional	$\Sigma_{1,1}$	Variance	0.0190 [CV%=13.8]	0.0152, 0.0229	10.3
Additive	$\Sigma_{2,2}$	Variance	4.56e+05 [SD=675]	2.68e+05, 6.43e+05	21.0

Abbreviations: CI = confidence intervals; Corr = Correlation coefficient; CV = coefficient of variation; SD = standard deviation;

SE = standard error; %RSE = residual standard error (%)

Confidence intervals = estimate $\pm$ 1.96 * SE

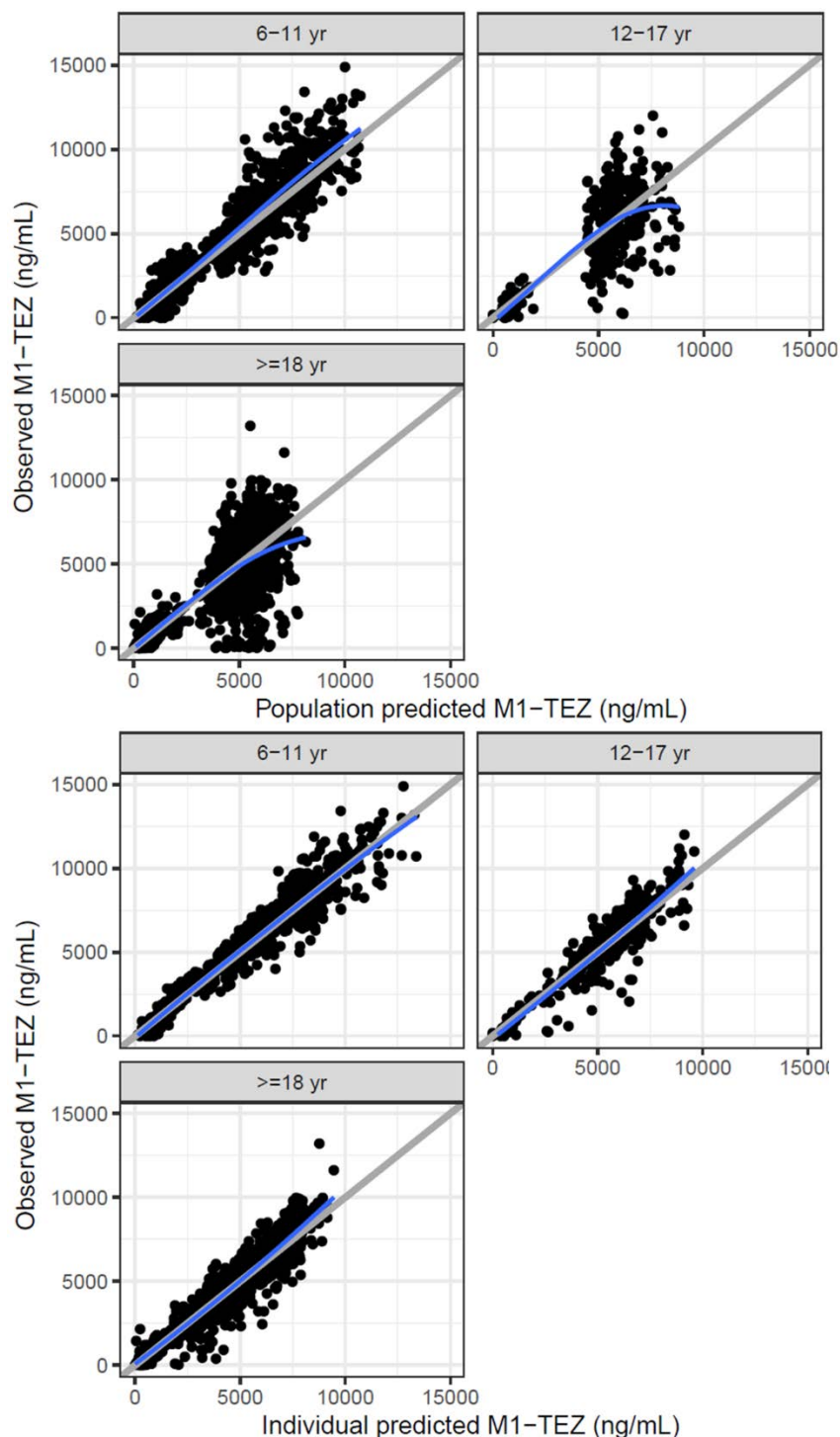
CV% of omegas = $\sqrt{\exp(\text{estimate}) - 1} * 100$

CV% of sigma = $\sqrt{\text{estimate}} * 100$

RSE% = SE/estimate * 100

Source: Table 17 in the PopPK report Q076, pg. 64.

Figure 17. Goodness of Fit Plots for Final M1-TEZ model by Age.



Values are indicated by black circles with a LOESS smooth trend line (solid blue) through the data. The line of identity (solid gray) is included as a reference.

Source: Figures 59 (pg. 143) and 62 (pg. 146) in the PopPK report Q076.

Final IVA Model: The PK of IVA was well described using a one-compartment model with first-order absorption. Covariate parameter relationships in the final IVA population PK model included: weight on CL/F and apparent volume of distribution after oral dosing (V/F), first dose adjustment on CL/F, and an adjustment on relative bioavailability for subjects 6-11 years old at steady-state. The weight effect on CL/F was described using a weight cut point model with a fixed exponent of 0.75. The estimate (95% CI) of the weight cut point was 29.8 kg (29.7, 29.9 kg); the weight effect was turned off (set to the null value of 1) for subjects with a weight greater than or equal to the cut point. The weight effect on V/F was described using an allometric model with an estimated exponent. The final IVA model parameter estimates are summarized in Table 67. The final IVA model was further assessed via goodness of fit plots (e.g., see

Figure 18).

Table 67. Final IVA Model Parameter Estimates

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			Estimate	95% CI	%RSE
Structural model parameters					
CL/F (L/hr)	θ_1	Apparent clearance	13.2	12.4, 13.9	2.89
V/F (L)	θ_2	Apparent volume	206	179, 233	6.73
k_a (1/hr)	θ_3	First order absorption rate constant	0.688	0.556, 0.821	9.83
ALAG (hr)	θ_4	Oral absorption lag time	0.668	0.600, 0.737	5.25
Covariate effect parameters					
CL _{WT}	θ_5	Weight effect on CL/F	0.750 [Fixed]	-	-
V _{WT}	θ_6	Weight effect on V/F	0.646	0.514, 0.778	10.4
CL _{WTC} (kg)	θ_7	Weight cut-point for CL/F	29.5	28.9, 30.1	1.11
CL _{FD}	θ_8	First dose effect on CL/F	1.25	1.11, 1.39	5.81
F _{age,ss}	θ_9	6-11yr, steady-state Frel adjustment	1.35	1.21, 1.49	5.26
Interindividual variability parameters					
IIV-CL/F	$\Omega_{1,1}$	Variance of CL/F	0.179 [CV%=44.3]	0.142, 0.216	10.6
IIV-V/F	$\Omega_{2,2}$	Variance of V/F	0.207 [CV%=47.9]	0.140, 0.274	16.5
Interoccasion variability parameters					
IOV-Frel	$\Omega_{3,3}$	Variance: IOV-Frel	0.119 [CV%=35.6]	0.0762, 0.162	18.4
Covariance parameters					
CL/F-V/F	$\Omega_{2,1}$	Covariance: CL/F-V/F	0.113 [Corr=0.588]	0.0765, 0.150	16.6
Residual variability					
Proportional	$\Sigma_{1,1}$	Variance	0.0362 [CV%=19.0]	0.0244, 0.0479	16.6
Additive	$\Sigma_{2,2}$	Variance	17500 [SD=132]	13400, 21700	12.0

Abbreviations: CI = confidence intervals; Corr = Correlation coefficient; CV = coefficient of variation; SD = standard deviation;

SE = standard error; %RSE = residual standard error (%)

Confidence intervals = estimate $\pm$ 1.96 * SE

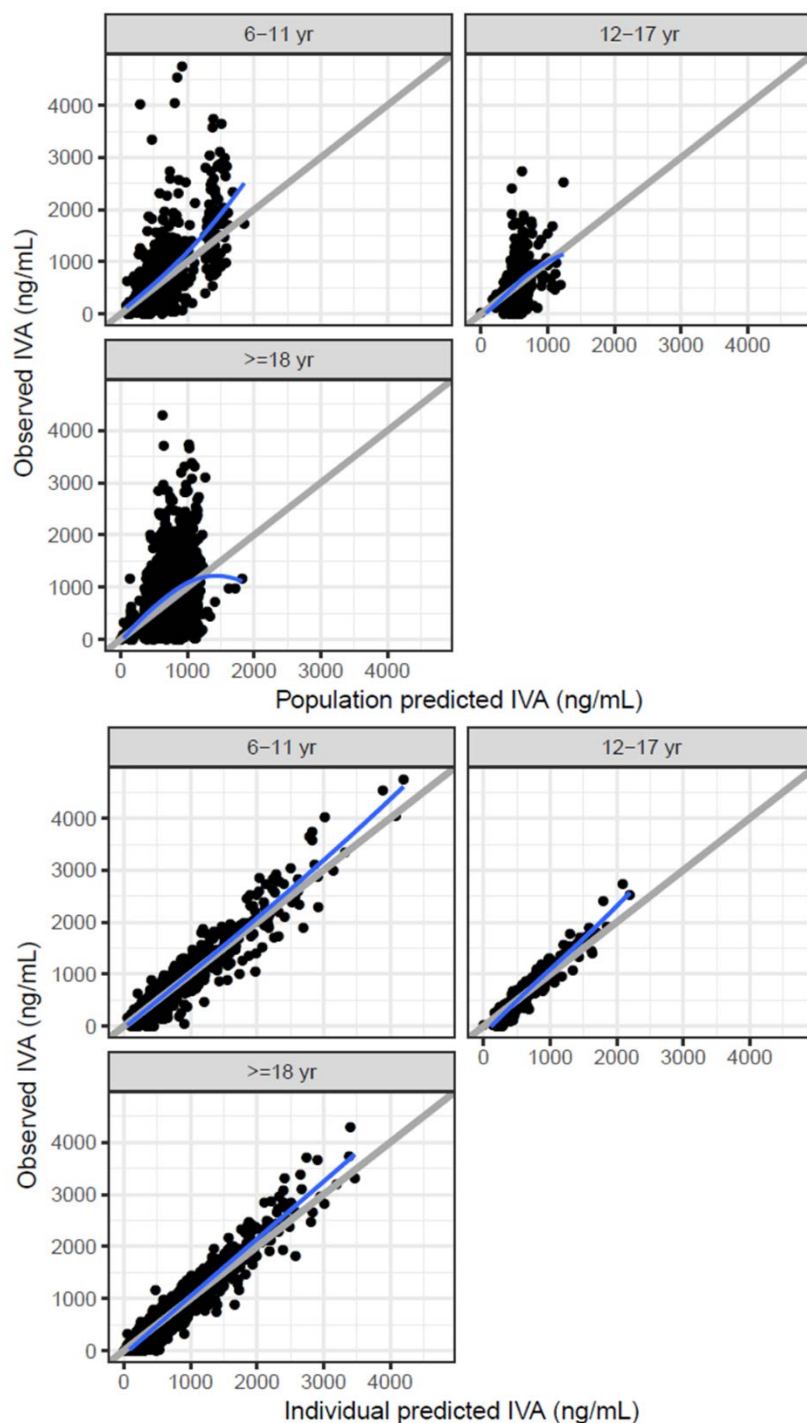
CV% of omegas = $\sqrt{\exp(\text{estimate}) - 1} * 100$

CV% of sigma = $\sqrt{\text{estimate}} * 100$

RSE% = SE/estimate * 100

Source: Table 29 in the PopPK report Q076, pg 76.

Figure 18. Goodness of Fit Plots for Final IVA Model by Age.



Values are indicated by black circles with a LOESS smooth trend line (solid blue) through the data. The line of identity (solid gray) is included as a reference.

Source: Figures 114 (pg. 198) and 117 (pg. 201) in the PopPK report Q076.

Simulations: The empirical Bayes estimates (EBEs) from the final models for ELX, M23-ELX, TEZ, M1-TEZ and IVA were used to derive individual predicted exposures at steady state for all subjects in the Phase 3 studies (102, 103, and 106 Part B). The exposure metrics of interest

were: area under the concentration time curve (AUC) over the dosing interval at steady state, maximum concentration (C_{max}) in the dosing interval at steady state, and minimum concentration (C_{min}) in the dosing interval at steady state. Steady-state AUCs were reported and calculated using the equation: $AUC = \text{Dose}/(CL/F)$. Subjects enrolled in Study 106 Part A were excluded from the exposure summaries unless they also participated in Part B, in which case, their data from Part B was retained for the summaries. Results of ELX, M23-ELX, TEZ, M1-TEZ and IVA steady-state exposures derived from EBEs simulations for different age and dose(weight) groups for AUC, C_{max}, and C_{min} are shown in Figure 19,

Figure 20, Figure 21,

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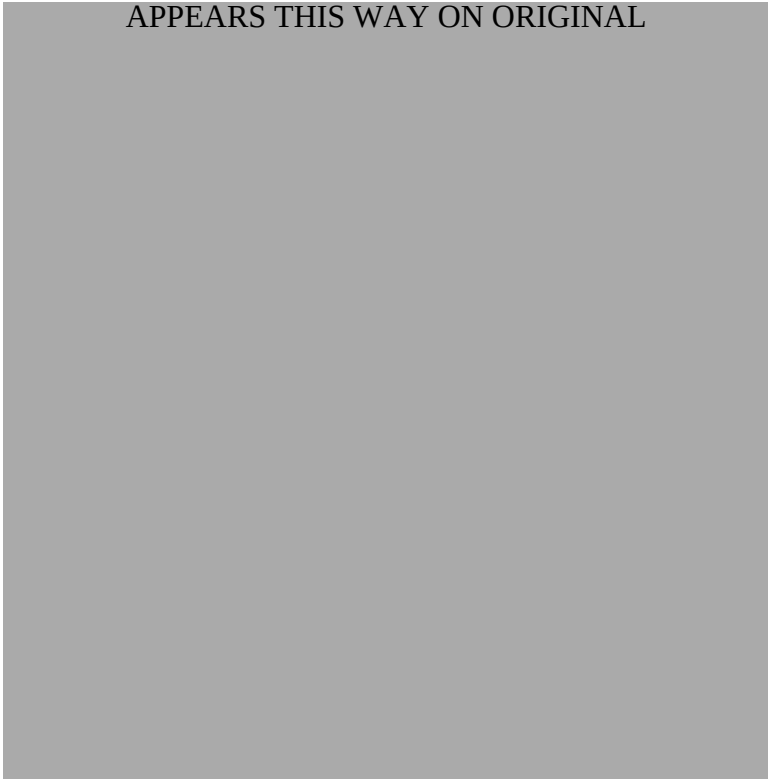


Figure 22, and

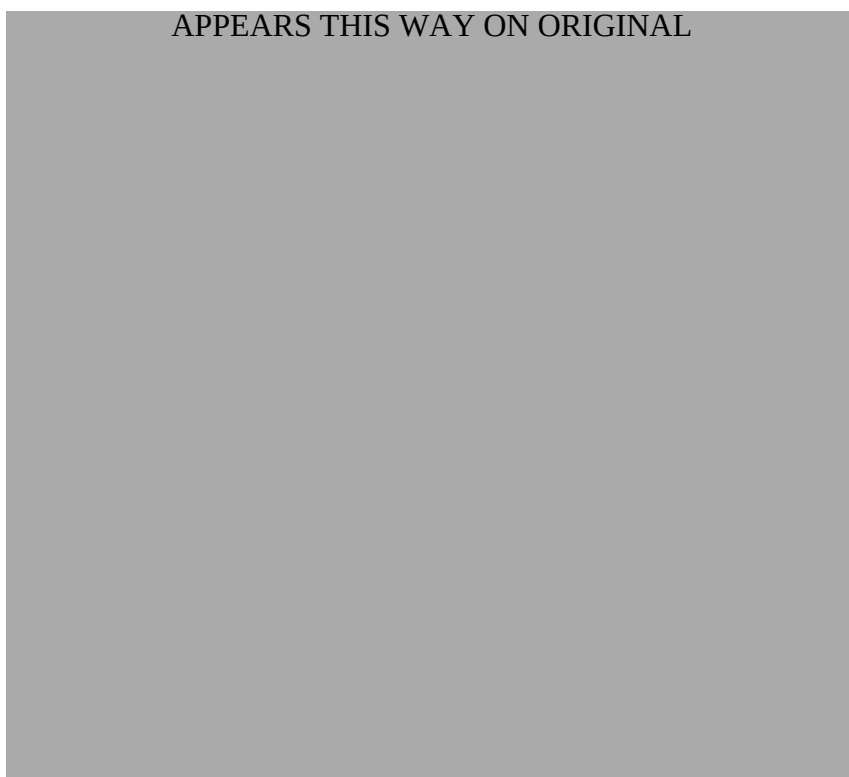
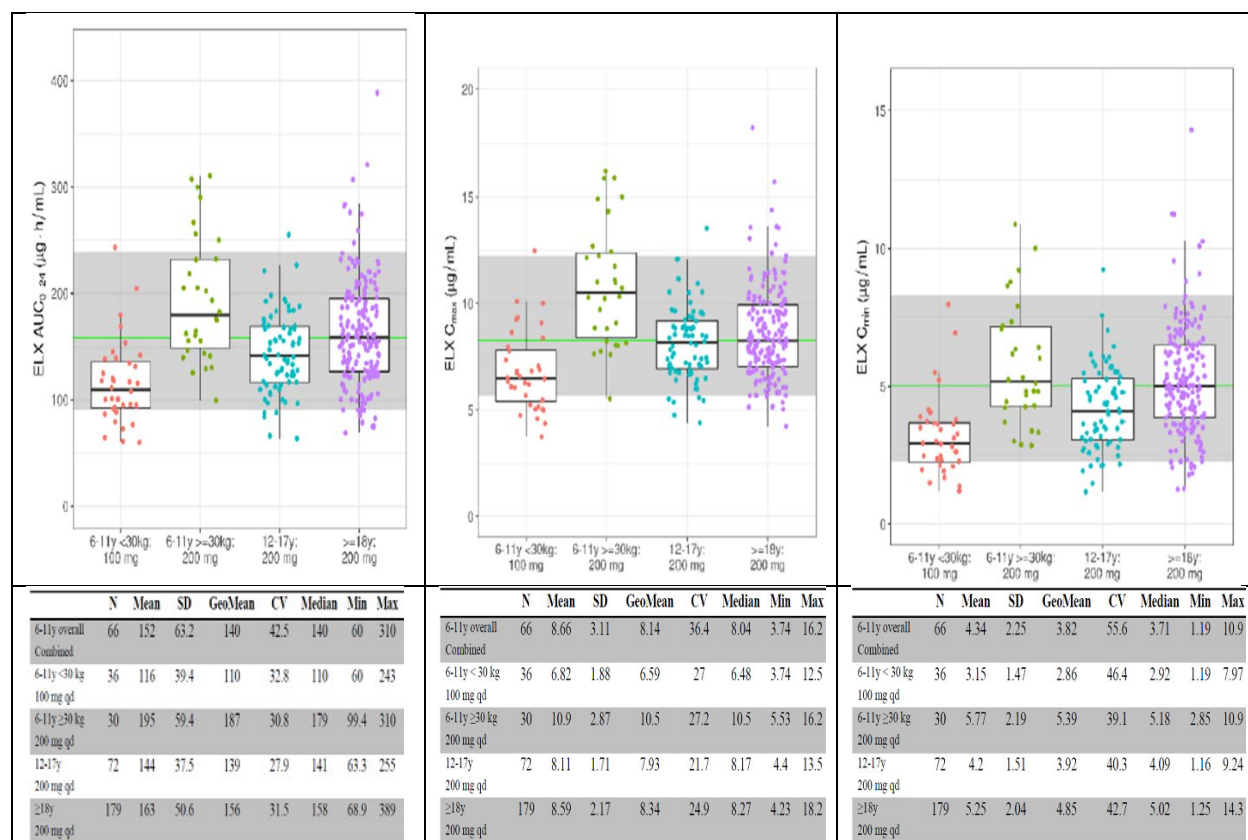


Figure 23. As shown in the Figures, the desired principles of exposure matching were met under the proposed dosing regimen with a 30 kg weight cutoff. That is, exposures of ELX, M23-ELX, TEZ and IVA were within the adult (>18 years) exposure range previously shown to be safe and efficacious (i.e., the grey zone in the figures and M1-TEZ exposures were outside the grey zone but still within the range of previous clinical experience. Overall, the following dosing regimen is appropriate for CF subjects 6 through 11 years of age:

- Subjects weighing <30 kg: ELX 100 mg qd/TEZ 50 mg qd/IVA 75 mg q12h
- Subjects weighing ≥30 kg: ELX 200 mg qd/TEZ 100 mg qd/IVA 150 mg q12h

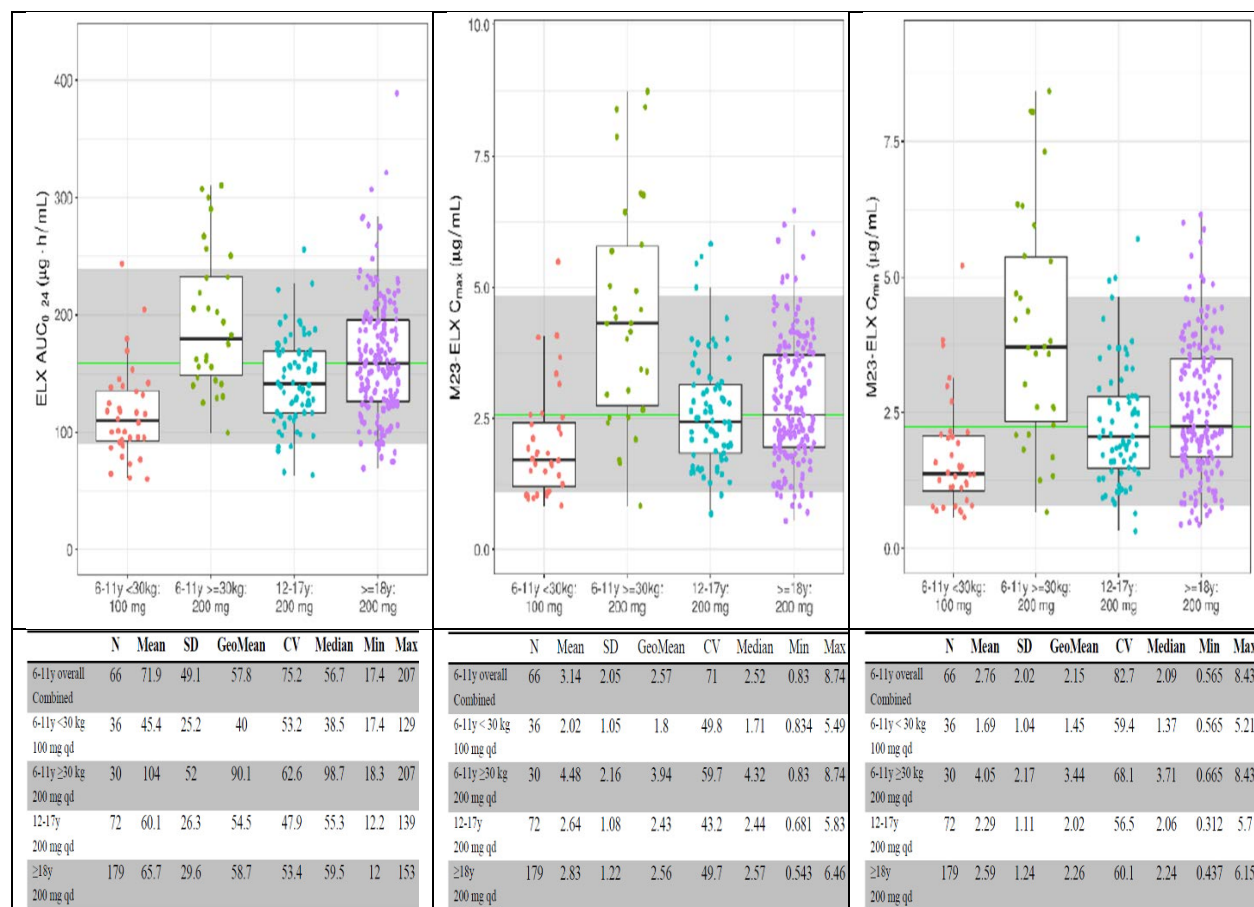
Figure 19. Summary of ELX Steady-state Exposures by Age and Dose Groups.



Source: Figures 7-12 (pg. 70), 10-4 (pg. 84), 10-5 (pg. 85) and Tables 7 (pg. 72), 9 (pg. 73) and 11 (pg. 74) in the PopPK report Q075.

Figure 20. Summary of M23-ELX Steady-state Exposures by Age and Dose Groups

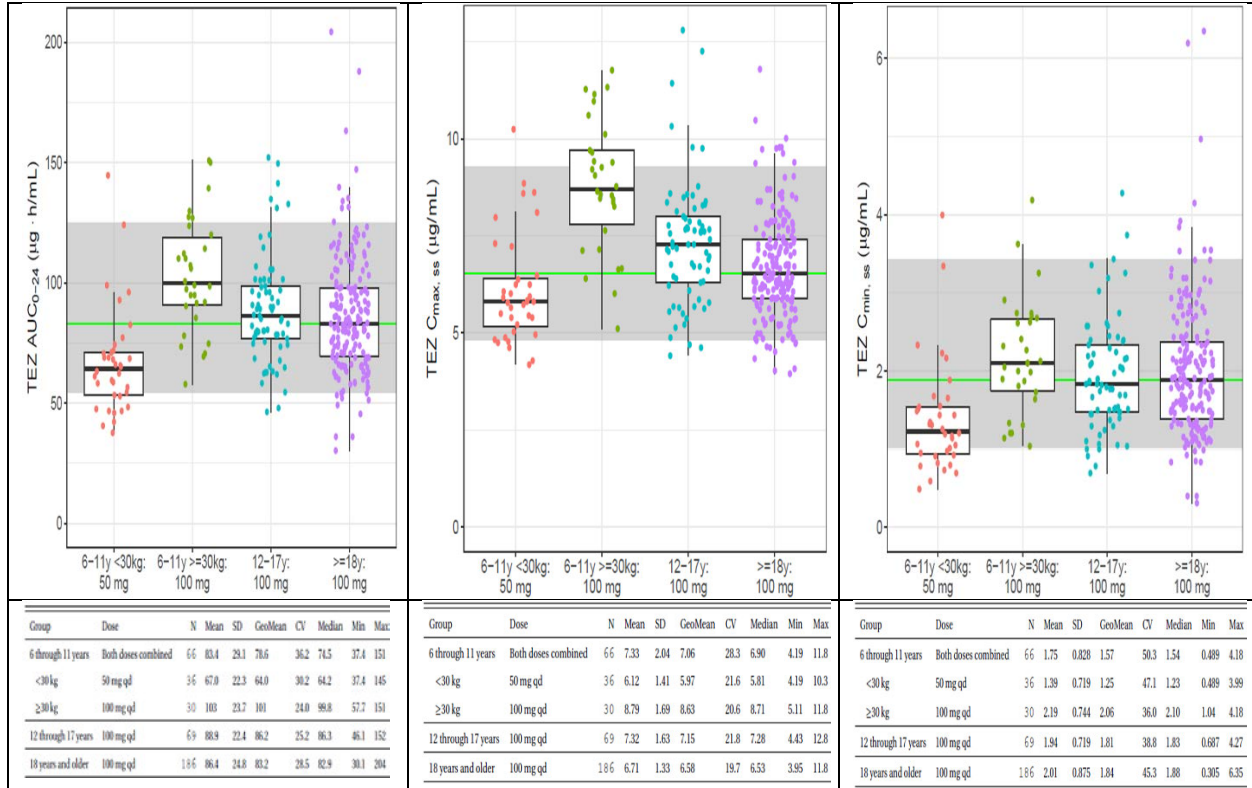
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Source: Figures 7-12 (pg. 70), 10-4 (pg. 84), 10-5 (pg. 85) and Tables 8 (pg. 72), 10 (pg. 73) and 12 in the PopPK report Q075.

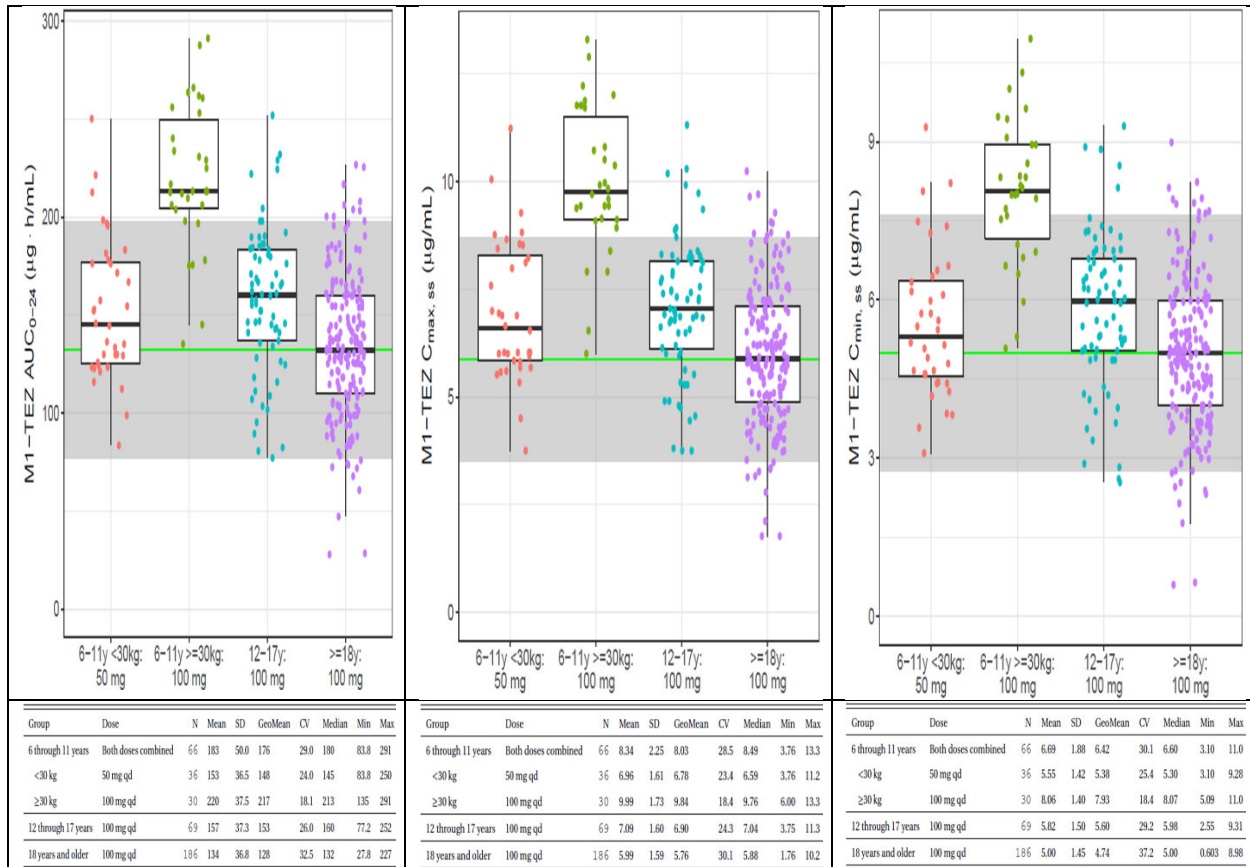
Figure 21. Summary of TEZ Steady-state Exposures by Age and Dose Groups

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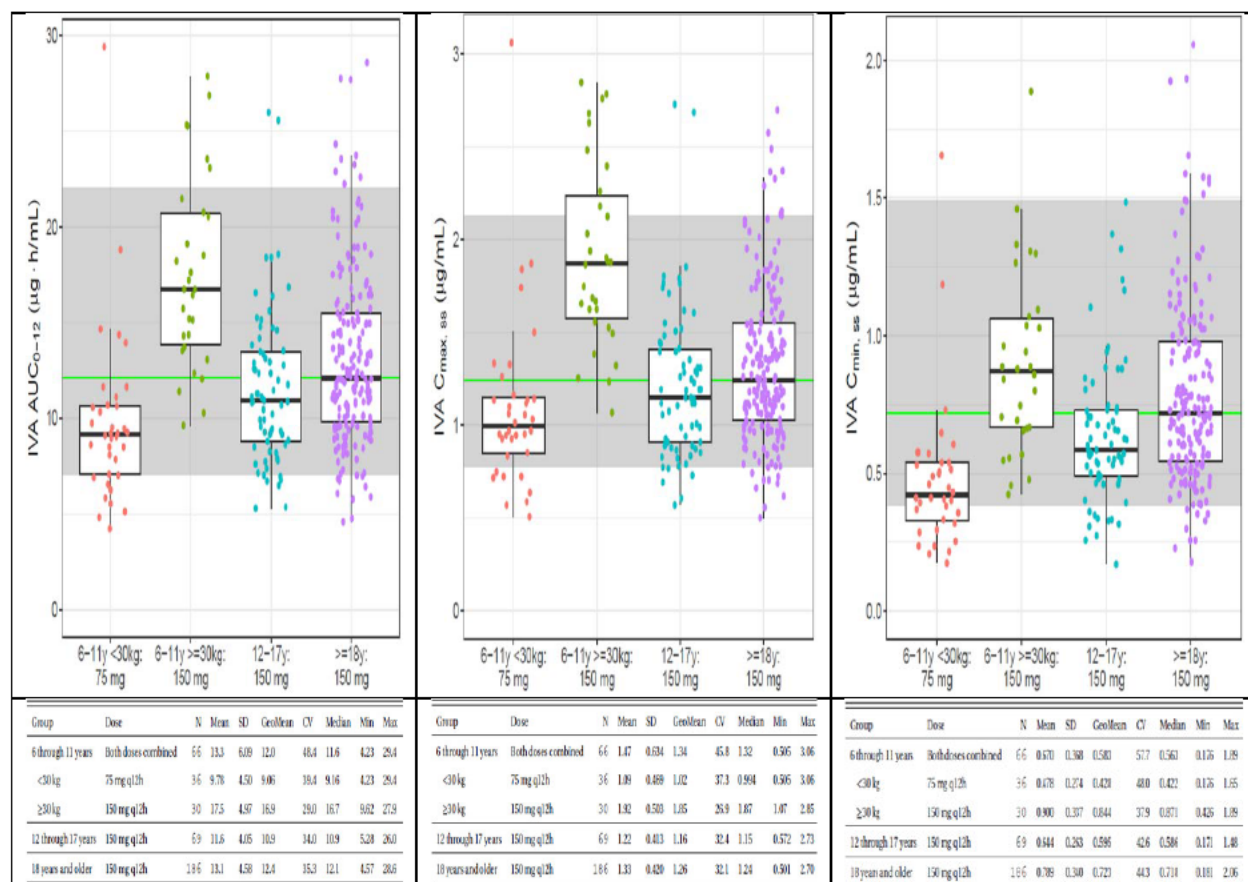
Source Tables 7 (pg. 54), 8 (pg. 55), 9 and Figures 43 (pg. 127), 46 (pg. 130), 48 (pg. 132) in the PopPK report Q076.

Figure 22. Summary of M1-TEZ Steady-state Exposures by Age and Dose Groups.



Source: Tables 19 (pg. 66), 20 (pg. 67), 21 (pg. 68) and Figures 98 (pg. 182), 101 (pg. 185), 103 (pg. 187) in the PopPK report Q076.

Figure 23. Summary of IVA Steady-state Exposures by Age and Dose Groups.



Source: Tables 31 (pg. 78), 32 (pg. 79), 33 (pg. 80) and Figures 153 (pg. 237), 156 (pg. 240), 158 (pg. 242) in the PopPK report Q076.

15.2.4. Bioanalytical Method Report

The bioanalytical methods are validated for ELX, M23-ELX, TEZ, M1-TEZ, IVA, and M1-IVA. Calibration curves in human plasma ranged from 10.0 to 10000 ng/mL for ELX; 5.00 to 5000 ng/mL for M23-ELX; 10.0 to 10000 ng/mL for TEZ and M1-TEZ; and 2.0 to 2000 ng/mL for IVA and M1-IVA. The in-study report below showed that the bioanalytical results were reliable for PK analysis.

Table 68. Summary of Bioanalytical Assays

Study No.	Bioanalysis Report No.	Stability	Incurred sample reanalysis
Trial 106	P039 for ELX and M23-ELX	103 days (part B analysis: 03/12/2020-06/23/2020)	Total of 823 pediatric human plasma samples, 78 samples (9.4%) were analyzed for ISR. 78 out of 78 samples (100%) for ELX and 77 out of

			78 samples (98.72%) for M23-ELX met the acceptance criteria.
	Q108 for TEZ and M1-TEZ, IVA and M1-IVA	402 days (analysis: 11/21/2018-07/23/2020)	Total of 821 pediatric human plasma samples, 84 samples were analyzed for ISR (10.2%). 80 out of 84 samples (95.2%) for IVA, 79 out of 84 samples (96.3%) for M1-IVA and 82 out of 84 samples (97.6%) for TEZ and 81 out of 84 samples (96.4%) for M1-TEZ met the acceptance criteria.
Study 011	P243 for ELZ and TEZ	336 days (analysis: 07/31/2019-08/07/2019)	Total of 496 adult plasma samples, 50 samples were analyzed for ISR (10%). 50 out of 50 (100%) samples met the acceptance criteria.
	P244 for IVA	409 days (analysis: 07/12/2019-08/08/2019)	Total of 496 adult plasma samples, 50 samples were analyzed for ISR (10%). 49 out of 50 (98%) samples met the acceptance criteria.

15.2.5. Individual Study Summary

15.2.5.1. Study VX18-445-106 (Trial 106)

Title

A Phase 3 Study Evaluating the Pharmacokinetics, Safety, and Tolerability of VX-445/TEZ/IVA Triple Combination Therapy in Cystic Fibrosis Subjects 6 Through 11 Years of Age

Study Date

Oct 02, 2018-Aug 07, 2020

Study Design

This was a Phase 3, 2-part (Parts A and B), multicenter study evaluating the PK, safety, and tolerability of ELX/TEZ/IVA in subjects with cystic fibrosis (CF; homozygous for F508del [F/F] genotype or heterozygous for F508del and a CFTR minimal function mutation [F/MF] genotypes) 6 through 11 years of age (inclusive). Subjects who participated in Part A could participate in Part B. Part A (Oct 02, 2018-Jan 16, 2019), Part B (Aug 05, 2019-Aug 07, 2020)

Table 69. Study design of Trial 106

Study Number	Study Purpose
Trial 106	Phase 3, open-label, 2-part (Parts A and B), multicenter study in subjects 6 through 11 years of age, with F/MF and F/F genotypes

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	Part A: ELX 100 mg qd/TEZ 50 mg qd/IVA 75 mg q12h with fat-containing food for 15 days. Minimum BW $\geq$ 15 kg	Part B (no subjects were carried over from part A to B): <30 kg ELX 100 mg qd/TEZ 50 mg qd/IVA 75 mg q12h $\geq$ 30 kg ELX 200 mg qd/TEZ 100 mg qd/IVA 150 mg q12h 24 weeks - Minimum BW $\geq$ 15 kg
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- Study population
Male and female CF subjects 6 through 11 years of age with F/F or F/MF genotypes.
Subject Demographics (Part B)

Table 70. Demographic information of Part B in Trial 106

Demographic	ELX/TEZ/IVA N = 66
Sex, n (%)	
Male	27 (40.9)
Female	39 (59.1)
Childbearing potential ^a , n (%)	
Yes	39 (100.0)
No	0
Age at baseline (years)	
n	66
Mean (SD)	9.3 (1.9)
Median	9.6
Min, max	6.1, 12.1 ^b
Ethnicity, n (%)	
Hispanic or Latino	0
Not Hispanic or Latino	58 (87.9)
Not collected per local regulations	8 (12.1)
Race, n (%)	
White	58 (87.9)
Asian	1 (1.5)
Not collected per local regulations	8 (12.1)
Geographic region, n (%)	
North America	47 (71.2)
Europe and Australia	19 (28.8)
CFTR genotype group, n (%)	
F/F	29 (43.9)
F/MF	37 (56.1)
Weight group, n (%)	
<30 kg	36 (54.5)
$\geq$ 30 kg	30 (45.5)
Weight (kg)	
n	66
Mean (SD)	30.0 (7.7)
Median	29.0
Min, max	18.1, 53.6

Source: CSR of Trial 106, table 10-6, pg. 75.

- Investigational drug
Part A (all subjects): ELX/TEZ/IVA 100-mg/50-mg/75-mg fixed-dose combination (FDC) tablet (batch/lot 2018019) and IVA 75-mg tablet (batch/lot 2016058) for oral administration.
Part B (subjects <30 kg at Day 1): ELX/TEZ/IVA 50-mg/25-mg/37.5-mg FDC tablet (batch/lot 2019016) and IVA 75-mg tablet (batch/lot 2018024) for oral administration.
Part B (subjects ≥30 kg at Day 1): ELX/TEZ/IVA 100-mg/50-mg/75-mg FDC tablet (batch/lot 2019015) and IVA 150-mg tablet (batch/lot 3175095R) for oral administration.
- PK sampling scheme:
Blood samples were collected on Day 1, 15, week 4, week 12 and week 24. On day 1, blood samples were collected at 2, 4 and 6 hours after the morning dose; on week 4, Blood samples were collected pre-dose and 1, 2, 4, and 6 hours after the morning dose. Single PK samples were collected on the rest days of day 15, week 12 and 24.
- PK results:
The mean observed trough and maximum concentrations of ELX, M23-ELX, TEZ, IVA, and M1-IVA in CF subjects 6 through 11 years of age in Part B (Table 71) were within the range of exposures seen in CF subjects 12 years of age and older. M1-TEZ exposures, while higher, were within the expected range of exposures seen in previous clinical studies with TEZ/IVA and ELX/TEZ/IVA.

Table 71. Mean (%CV) C_{trough} and C_{max} Observed in CF Subjects 6 Through 11 Years of Age (Part B)

Dose Level Analyte	C _{trough} (µg/mL) Mean (%CV)				C _{max} (µg/mL) Mean (%CV)
	Day 15	Week 4	Week 12	Week 24	Week 4
ELX 100 mg qd/TEZ 50 mg qd/IVA 75 mg q12h	N = 35	N = 33	N = 30	N = 19	N = 32
ELX	3.02 (61.3)	2.71 (65.4)	2.67 (45.6)	2.73 (40.8)	6.79 (41.9)
M23-ELX	1.76 (72.6)	1.59 (78)	1.58 (60.4)	1.31 (40.5)	2.01 (68.3)
TEZ	1.46 (63.8)	1.43 (83.8)	1.30 (55.2)	1.18 (58)	6.97 (37.3)
M1-TEZ	5.68 (29)	5.57 (31.9)	5.30 (29)	5.40 (33.8)	7.21 (26.1)
IVA	0.407 (87.2)	0.455 (149.7)	0.356 (67.4)	0.288 (63.2)	1.15 (72.8)
M1-IVA	1.05 (65.6)	1.00 (63)	0.974 (50.2)	0.787 (49.4)	2.42 (49.7)
ELX 200 mg qd/TEZ 100 mg qd/IVA 150 mg q12h	N = 30	N = 30	N = 27	N = 19	N = 30
ELX	4.99 (48.3)	5.69 (52.7)	6.16 (50)	6.53 (44.4)	11.7 (38.1)
M23-ELX	3.78 (59.9)	4.41 (67.4)	4.32 (56.6)	4.33 (48)	5.02 (62.2)
TEZ	2.39 (64.7)	2.37 (45.2)	2.31 (44.6)	2.73 (66.6)	9.97 (30.5)
M1-TEZ	8.21 (23.2)	8.12 (23.1)	7.88 (21.4)	8.37 (22.9)	10.1 (19.9)
IVA	0.766 (62.9)	0.851 (57.5)	0.800 (69.3)	0.965 (51)	2.13 (38.8)
M1-IVA	1.97 (58.4)	2.18 (47.7)	2.11 (54.7)	2.55 (36.6)	4.47 (34.0)

Source: CSR of Trial 106, table 11-2, pg. 81.

15.2.5.2. Study VX18-445-011 (Trial 011)

Title

A Phase 1, Open-label, Randomized, Crossover Study to Evaluate the Relative Bioavailability of a Fixed-dose Combination Tablet of VX-445, Tezacaftor, and Ivacaftor in Healthy Adult Subjects

Study Date

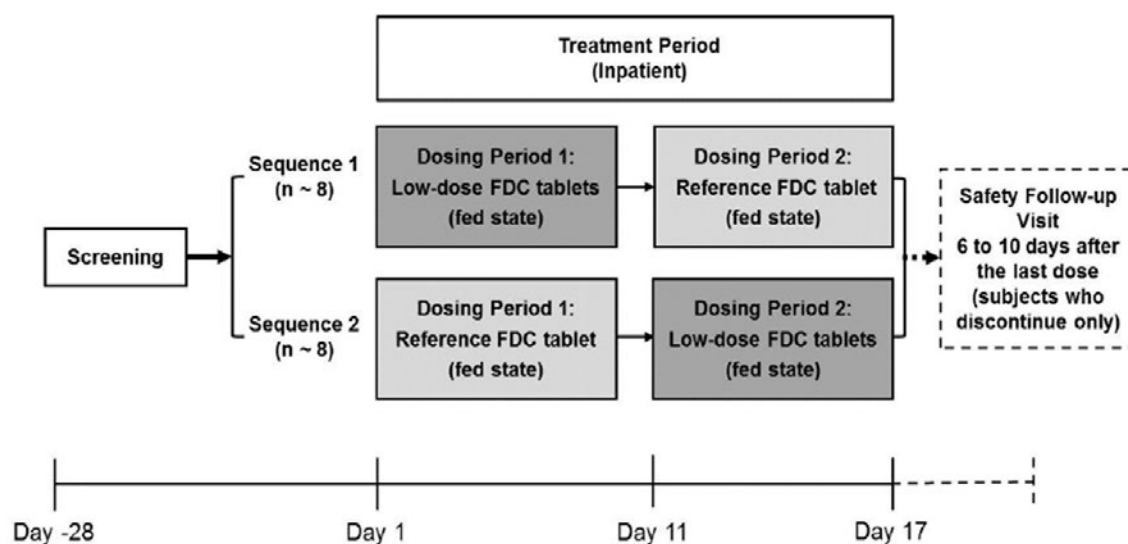
June 14, 2019-July 28, 2019

Study Design

This was a Phase 1, open-label, randomized, 2-sequence, 2-period crossover study to evaluate the relative BA of a low-dose FDC tablet formulation compared to a reference FDC tablet formulation.

At the start of each dosing period, healthy subjects received ELX 100 mg/TEZ 50 mg/IVA 75 mg orally in the fed state, either as 2 low-dose FDC tablets or as 1 reference FDC tablet.

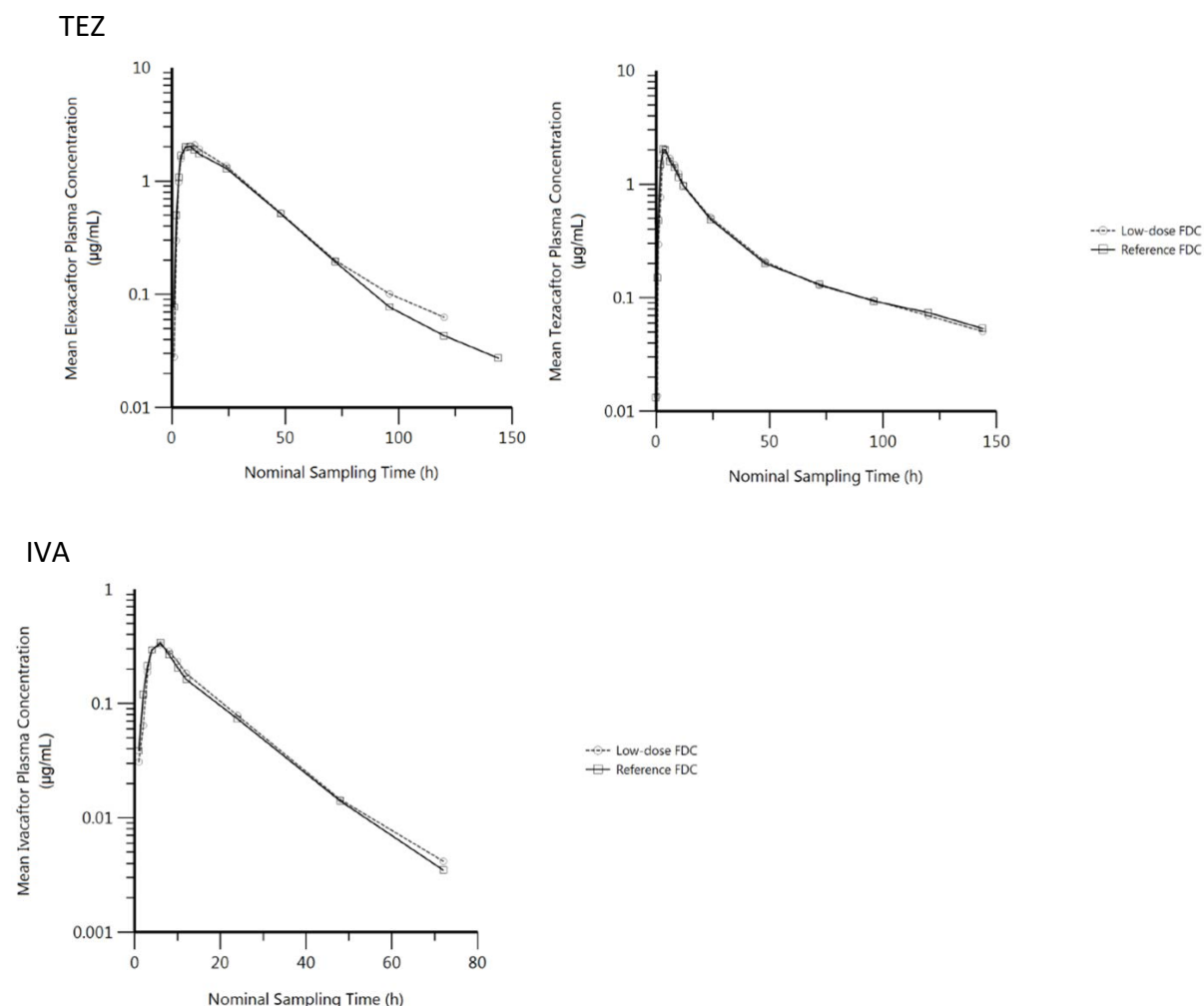
Figure 24. Study design of Trail 011



- Study population
16 healthy male and female subjects 18 to 55 years of age, 8 subjects were in each sequence group.
Overall, 68.8% of subjects were Black or African American, 68.8% were male, and the median age was 36.5 years.
- Investigational drug
ELX 50-mg/TEZ 25-mg/IVA 37.5-mg low-dose FDC tablets (Lot 2019016) and ELX 100-mg/TEZ 50-mg/IVA 75-mg reference FDC tablets (Lot 2018027) were administered orally.

- Pharmacokinetics (PK):
Blood samples were collected on predose, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 24, 48, 72, 96, 120 and 144 hrs. post dose for each treatment.
- PK results:
The concentration-time profile of ELX, TEZ, and IVA following single dose administration of two low-dosing strength FDC tablet (ELX 50 mg/TEZ 25 mg/IVA 37.5 mg) or one reference FDC tablet (ELX 100 mg/TEZ 50 mg/IVA 75 mg) in healthy adults is listed in Figure 25.

Figure 25. Mean plasma concentration-time profile of ELX, TEZ, and IVA following single dose administration of two low-dosing strength FDC tablet (ELX 50 mg/TEZ 25 mg/IVA 37.5 mg) or one reference FDC tablet (ELX 100 mg/TEZ 50 mg/IVA 75 mg) in healthy adults



Source: CSR of study 011, Figure 11-1, pg. 35

The PK parameters of ELX, TEZ, and IVA following single dose administration of two low-dosing strength FDC tablet (ELX 50 mg/TEZ 25 mg/IVA 37.5 mg) or one reference FDC tablet (ELX 100 mg/TEZ 50 mg/IVA 75 mg) in healthy adults is listed in Table 72.

Table 72. Summary of ELX, TEZ, and IVA PK Parameters Following Single Dose Administration of two low-dosing strength FDC tablet (ELX 50 mg/TEZ 25 mg/IVA 37.5 mg) or one reference FDC tablet (ELX 100 mg/TEZ 50 mg/IVA 75 mg) in healthy adults

Analyte	Treatment	N	Median (Min, Max)	Mean (SD) CV%			
			t _{max} (h)	C _{max} (µg/mL)	AUC _{0-∞} (h·µg/mL)	AUC _{0-tlast} (h·µg/mL)	t _{1/2} (h)
ELX	Low-dose FDC	15	6.00 (4.00, 12.0)	2.46 (0.567) 23.1%	72.5 (26.0) 35.9%	71.5 (24.9) 34.9%	16.9 (4.59) 27.2%
	Reference FDC	15	6.00 (4.00, 12.0)	2.40 (0.412) 17.1%	69.1 (18.7) 27.0%	68.5 (18.2) 26.6%	17.3 (4.17) 24.0%
TEZ	Low-dose FDC	15	4.00 (3.00, 8.02)	2.49 (0.459) 18.4%	46.1 (10.1) 21.9%	42.2 (8.78) 20.8%	51.5 (10.5) 20.5%
	Reference FDC	15	3.00 (1.00, 8.00)	2.74 (0.764) 27.9%	46.5 (9.62) 20.7%	42.4 (8.91) 21.0%	54.3 (9.65) 17.8%
IVA	Low-dose FDC	15	6.00 (2.00, 8.02)	0.418 (0.114) 27.2%	5.17 (1.75) 33.9%	5.10 (1.76) 34.6%	9.64 (1.20) 12.4%
	Reference FDC	15	4.00 (1.00, 8.00)	0.410 (0.120) 29.1%	4.95 (1.50) 30.3%	4.87 (1.51) 31.0%	10.1 (0.921) 9.14%

Source: CSR of study 011, Table 11-1, pg. 37

The relative bioavailability statistical analysis comparing the AUC_{0-∞} and C_{max} of TEZ, and IVA following single dose administration of two low-dosing strength FDC tablet (ELX 50 mg/TEZ 25 mg/IVA 37.5 mg) or one reference FDC tablet (ELX 100 mg/TEZ 50 mg/IVA 75 mg) in healthy adults is listed in Table 73.

Table 73. Relative Bioavailability Statistical Analysis Comparing the AUC_{0-∞} and C_{max} of ELX, TEZ, and IVA Following Single Dose Administration of two low-dosing strength FDC tablet (ELX 50 mg/TEZ 25 mg/IVA 37.5 mg) or one reference FDC tablet (ELX 100 mg/TEZ 50 mg/IVA 75 mg) in healthy adults

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Analyte	PK Parameter	Test GLSM (Low-dose FDC)	Reference GLSM (Reference FDC)	GLSM Ratio (Test:Reference)	90% CI	
					Lower	Upper
ELX	AUC _{0-∞} (h·µg/mL)	68.4	66.9	1.02	0.956	1.09
	C _{max} (µg/mL)	2.41	2.38	1.01	0.922	1.11
TEZ	AUC _{0-∞} (h·µg/mL)	45.1	45.3	0.996	0.936	1.06
	C _{max} (µg/mL)	2.45	2.63	0.931	0.831	1.04
IVA	AUC _{0-∞} (h·µg/mL)	4.88	4.75	1.03	0.955	1.10
	C _{max} (µg/mL)	0.401	0.390	1.03	0.899	1.18

Source: CSR of study 011, Table 11-2, pg. 38

15.3. Clinical Appendix

15.3.1. Schedule of Assessments

Table 74. Schedule of Assessments Trial 106 Part A

Assessment	Day 1	Day 2	Day 4 (± 1 Day)	Day 8 (± 1 Day)	Day 15 (± 1 Day)	ETT Visit	Safety Follow-up Visit 28 (± 7) Days After the Last Dose of Study Drug
Clinic Visit	X	X		X	X	X	X
Telephone Contact			X				
Inclusion and Exclusion Criteria Review	X						
Full Physical Examination ¹	X				X	X	X
Weight, Height, and BMI ²	X				X	X	X
Vital Signs ³	X	X		X	X	X	X
Pulse Oximetry ⁴	X	X		X	X	X	X
Standard 12-lead ECG ⁵	X (triplicate)	X			X	X	X
Spirometry ⁶	X	X		X	X	X	X
Sweat chloride ⁷	X				X		
Pregnancy Test ⁸ (females of childbearing potential)	X (urine)				X (urine)	X (urine)	X (urine)
Serum Chemistry	X			X	X	X	X
Hematology	X			X	X	X	X
Coagulation	X				X		
Drug Test (urine)	X						
Alcohol Test (urine)	X						
Observation 4 hours After the Morning Dose	X						
Concomitant Medications	Continuous, From Signing of ICF (and Assent Form) Through Completion of Study Participation						
Concomitant Treatments and Procedures	Continuous, From Signing of ICF (and Assent Form) Through Completion of Study Participation						
AEs and SAEs	Continuous, From Signing of ICF (and Assent Form) Through Completion of Study Participation						
PK Sampling ⁹	X			X	X		
Meal(s) or Snack(s) at Site ¹⁰	X	X		X	X		
VX-445/TEZ/IVA ¹¹	Day 1 Through Day 15 (morning dose only on Day 15)						
1. Symptom-directed physical examinations will occur at any time during the study if deemed necessary by the investigator. 2. Weight and height will be measured before study drug dosing with shoes off 3. Collected after the subject has been at rest for at least 5 minutes 4. Collected after the subject has been at rest for at least 5 minutes 5. Day 1 and 2: before the AM dose. Day 15: before the AM dose and 4 hours (+/- 30 min) after the AM dose Performed after the subject has been at rest for at least 5 minutes							

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6. Should be performed pre-bronchodilator, before the AM dose, and at approximately the same time at each visit
7. Collection will be done approximately at the same time as predose blood collections; however, they may not be done at exactly the same time
8. Females of childbearing potential is defined as females 10 years of age and older
9. Day 1: before the AM dose, and at 1, 2, 4, and 6 hours after the AM dose. Day 8: before the AM dose. Day 15: before the AM dose, and at 1, 2, 4, and 6 hours after the AM dose. If study drug is not administered on the day of the visit (i.e., study drug interruption or permanent discontinuation of study drug), only 1 PK blood sample will be collected.
10. Fat-containing food such as a standard "CF" meal or snack will be provided at the site to subjects after all predose assessments have occurred.
11. Administered within approximately 30 minutes of consuming fat-containing food (e.g., standard "CF" meal or snack) (Section 9.6.1). On scheduled visits, the AM dose of study drug will be administered at the site after predose assessments have been completed (food to be provided by site on these days).

Source. Adapted from Table 3-2, Protocol VX18-445-106, Version 3.0

Table 75. Schedule of Assessments Trial 106 Part B

Event/ Assessment	Day 1	Day 3 (± 1 day)	Day 15 (± 3 days)	Week 4 (± 5 days)	Week 8 (± 5 days)	Week 12 (± 5 days)	Week 16 (± 5 days)	Week 20 (± 5 days)	Week 24 (± 5 days)	ETT Visit	Safety Follow-up Visit 28 (± 7) Days After the Last Dose of Study Drug ^b
Clinic Visit	X		X	X	X	X	X		X	X	X
Telephone Contact ¹		X						X			
Inclusion and Exclusion Criteria Review	X										
CFQ-R ²	X			X	X	X	X		X	X	X
Modified Facial Hedonic Scale ³	X		X	X	X	X	X		X	X	X
Ophthalmologic Examination									X at or up to 4 weeks before	X	
Full Physical Examination ⁴	X					X			X	X	
Weight, Height, and BMI ⁵	X		X	X	X	X	X		X	X	X
Vital Signs ⁶	X		X	X	X	X	X		X	X	X
Pulse Oximetry ⁶	X		X	X	X	X	X		X	X	X
Standard 12-lead ECG ⁷	X		X			X	X		X	X	X
Spirometry ⁸	X		X	X	X	X	X		X	X	X
Sweat chloride	X		X	X		X			X	X	
Pregnancy Test (all female subjects) ⁹	X (urine)			X (serum)	X (serum)	X (serum)	X (serum)	X (serum)	X (serum)	X (serum)	X (serum)

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Serum Chemistry ¹⁰	X		X	X	X	X	X	X	X	X	X
Hematology	X		X	X	X	X	X		X	X	X
Coagulation	X								X	X	X
Urinalysis	X								X	X	
Multiple-breath Washout	X		X	X		X			X	X	
Observation 4 Hours After the Morning Dose	X										
Study Drug Count			X	X	X	X	X		X	X	
Concomitant Medications	Continuous, From Signing of ICF (and Assent Form) Through Completion of Study Participation										
Concomitant Treatments and Procedures	Continuous, From Signing of ICF (and Assent Form) Through Completion of Study Participation										
AEs and SAEs	Continuous, From Signing of ICF (and Assent Form) Through Completion of Study Participation										
DNA sample (optional)			X								
Blood Biomarker Samples	X								X	X	
FE-1	X		X	X		X			X	X	
IRT	X		X	X		X			X	X	
Single PK Sampling			X			X			X		
Serial PK Sampling	X			X							
VX-445/TEZ/IVA	VX-445/TEZ/IVA (Day 1 through evening before Week 24 Visit)										
1. Assess the subject's status, any AEs, concomitant medications, treatments, and procedures. 2. Completed before the start of any other assessments 3. Completed immediately after dosing with study drug 4. Symptom-directed physical examinations will occur at any time during the study if deemed necessary by the investigator. 5. Weight and height will be measured before study drug dosing with shoes off 6. Collected after the subject has been at rest for at least 5 minutes 7. Performed after the subject has been at rest for at least 5 minutes and before the AM dose 8. Should be performed pre-bronchodilator, before the AM dose, and at approximately the same time at each visit 9. A local laboratory may be used for the Week 20 sample if a subject cannot return to the study site for the blood draw 10. Liver function testing (ALT, AST, GGT, ALP, and total bilirubin) must be performed at the scheduled visits and at Week 20 (a minimum of every 4 weeks after Week 4). A local laboratory may be used for the Week 20 sample if a subject cannot return to the study site for the blood draw.											
Source. Adapted from Table 3-4, Protocol VX18-445-106, Version 3.0											

15.3.2. Definition and Listing of Eligible Minimal Function Mutations

The protocol defined “MF” mutations as a subset of minimal function mutations that are non-responsive to IVA and TEZ/IVA. MF mutations met at least 1 of the following 2 criteria:

- (1) No biological plausibility of translated protein (genetic sequence predicts the complete absence of CFTR protein), or

- (2) In vitro testing that supports lack of responsiveness to IVA and TEZ/IVA, where MF mutations based on in vitro testing met the following criteria in in vitro experiments:
- o Baseline chloride transport that was <10% of wildtype *CFTR*
 - o An increase in chloride transport of <10% over baseline following the addition of IVA and TEZ/IVA in the assay

A list of eligible MF mutations as provided in the protocol appears in Table 76.

Table 76. Eligible MF *CFTR* Mutations

Non-exhaustive List of Minimal Function *CFTR* Mutations Eligible for VX18-445-106

Q2X	L218X	Q525X	R792X	E1104X
S4X	Q220X	G542X	E822X	W1145X
W19X	Y275X	G550X	W882X	R1158X
G27X	C276X	Q552X	W846X	R1162X
Q39X	Q290X	R553X	Y849X	S1196X
W57X	G330X	E585X	R851X	W1204X
E60X	W401X	G673X	Q890X	L1254X
R75X	Q414X	Q685X	S912X	S1255X
L88X	S434X	R709X	Y913X	W1282X
E92X	S466X	K710X	Q1042X	Q1313X
Q98X	S489X	Q715X	W1089X	Q1330X
Y122X	Q493X	L732X	Y1092X	E1371X
E193X	W496X	R764X	W1098X	Q1382X
W216X	C524X	R785X	R1102X	Q1411X
185+1G>T	711+5G>A	1717-8G>A	2622+1G>A	3121-1G>A
296+1G>A	712-1G>T	1717-1G>A	2790-1G>C	3500-2A>G
296+1G>T	1248+1G>A	1811+1G>C	3040G>C (G970R)	3600+2insT
405+1G>A	1249-1G>A	1811+1.6kbA>G		3850-1G>A
405+3A>C	1341+1G>A	1811+1643G>T	3120G>A	4005+1G>A
406-1G>A	1525-2A>G	1812-1G>A	3120+1G>A	4374+1G>T
621+1G>T	1525-1G>A	1898+1G>A	3121-2A>G	
711+1G>T		1898+1G>C		
182delT	1119delA	1782delA	2732insA	3791delC
306insA	1138insG	1824delA	2869insG	3821delT
365-366insT	1154insTC	1833delT	2896insAG	3876delA
394delTT	1161delC	2043delG	2942insT	3878delG
442delA	1213delT	2143delT	2957delT	3905insT
444delA	1259insA	2183AA>G*	3007delG	4016insT
457TAT>G	1288insTA	2184delA	3028delA	4021dupT
541delC	1343delG	2184insA	3171delC	4022insT
574delA	1471delA	2307insA	3171insC	4040delA
663delT	1497delGG	2347delG	3271delGG	4279insA
849delG	1548delG	2585delT	3349insT	4326delTC
935delA	1609delCA	2594delGT	3659delC	
1078delT	1677delTA	2711delT	3737delA	

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CFTRdele1	CFTRdele16-17b	991del5
CFTRdele2	CFTRdele17a,17b	1461ins4
CFTRdele2,3	CFTRdele17a-18	1924del7
CFTRdele2-4	CFTRdele19	2055del9>A
CFTRdele3-10,14b-16	CFTRdele19-21	2105-2117del13insAGAAA
CFTRdele4-7	CFTRdele21	2372del8
CFTRdele4-11	CFTRdele22-24	2721del11
CFTR50kdel	CFTRdele22,23	2991del32
CFTRdup6b-10	124del23bp	3121-977_3499+248del2515
CFTRdele11	306delTAGA	3667ins4
CFTRdele13,14a	602del14	4010del4
CFTRdele14b-17b	852del22	4209TGTT>AA

A46D	V520F	Y569D	N1303K
G85E	A559T	L1065P	
R347P	R560T	R1066C	
L467P	R560S	L1077P	
I507del	A561E	M1101K	

CFTR: cystic fibrosis transmembrane conductance regulator; IVA: ivacaftor; SwCl: sweat chloride; TEZ: tezacaftor
Source: CFTR2.org [Internet]. Baltimore (MD): Clinical and functional translation of CFTR. The Clinical and Functional Translation of CFTR (CFTR2), US Cystic Fibrosis Foundation, Johns Hopkins University, the Hospital for Sick Children. Available at: <http://www.cfr2.org/>. Accessed 15 February 2016.

Notes: %PI: percentage of *F508del*-CFTR heterozygous patients in the CFTR2 patient registry who are pancreatic insufficient; SwCl: mean sweat chloride of *F508del*-CFTR heterozygous patients in the CFTR2 patient registry.

* Also known as 2183delAA>G.

Source. Appendix A, Protocol VX18-445-106, Version 3.0

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/s/

STACY J CHIN
06/07/2021 04:08:45 PM

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

212273Orig1s004

NON-CLINICAL REVIEW(S)

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number: NDA212273-S004

Supporting document/s: NDA212273-S001 SD#1: VX-445-TX-021 (ELX),
VX-661-TX-037 (TEZ), VX-661-TX-065 (TEZ),
and VX-661-TX-069 (TEZ)
IND 108105 SD#539: VX-661-TX-038 (TEZ/IVA)

Applicant's letter date: 12/8/2020

CDER stamp date: 07/19/2019 for VX-445-TX-021 (ELX), VX-661-
TX-037 (TEZ), VX-661-TX-065 (TEZ), and VX-
661-TX-069 (TEZ)
05/06/2020 for VX-661-TX-038 (TEZ/IVA)

Product: Trikafta (elexacaftor/tezacaftor/ivacaftor)

Indication: Cystic Fibrosis

Applicant: Vertex Pharmaceuticals Incorporated

Review Division: Division of Pulmonology, Allergy and Critical
Care (DPACC)

Reviewer: Wei Sun, Ph.D.

Supervisor/Team Leader: Timothy Robison, Ph.D., D.A.B.T.

Division Director: Sally Seymour, MD

Project Manager: Angela Ramsey, PharmD

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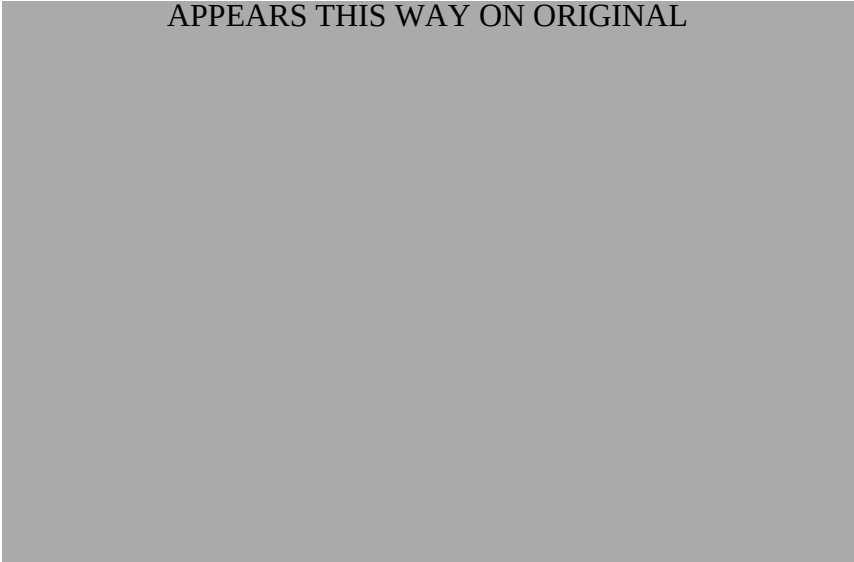


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1 Executive Summary

1.1 Introduction

Vertex submitted the current efficacy supplement for Trikafta (elexacaftor/tezacaftor/ivacaftor) to extend treatment to cystic fibrosis (CF) patients, 6 through 11 years of age, with at least one F508del mutation in the CFTR gene. Pediatric patients, 6 to 11 years of age, are generally covered by the standard nonclinical program. This review evaluated the juvenile animal studies with elexacaftor and tezacaftor. These juvenile rat studies can assess potential toxicity that might be relevant to pediatric patients (e.g., treatment starting on postnatal day (PND) 7 corresponds to an infant at birth and on PND 21 corresponds to a 2- to 3-year old child). Pediatric patients represent a population different from adults when considering the rapid growth and postnatal development of several organ systems. Lung development in the juvenile rat parallels lung development over the first 1 to 2 years of life for a child (e.g., increased alveolization and surface area that occur in both species). Potential concerns of neuropsychiatric adverse events (AEs) with the CFTR modulators have been reported in the literature and AE reporting, which is discussed below. CNS toxicity was evident in the juvenile rat toxicology studies with tezacaftor.

1.2 Brief Discussion of Nonclinical Findings

In the toxicology study with juvenile rats treated with elexacaftor (ELX) from PND 7 to PND 70, findings were limited to small increases of total bilirubin and ALT and CK activities without correlating histopathological findings.

Tezacaftor (TEZ) was characterized in juvenile rats starting from PND 7, PND 14, or PND 21 and ending on PND 35, PND 42, or PND 49, respectively. The doses evaluated were 0, 10, 20, 30, 60, and/or 100 mg/kg/day.

When administered starting at PND 7 (the equivalent of a human newborn) at doses of 10 to 100 mg/kg/day, multiple deaths/euthanasia, lower body weight gains, and adverse central nervous system (CNS) clinical signs including convulsions, hypoactivity, repetitive movement of the mouth, head tilt, small stature, and cool and/or thin body were observed at doses ≥ 30 mg/kg/day. The NOAEL was identified at 10 mg/kg/day.

When administered starting at PND 21 (the equivalent of a human 2-3 years of age) at doses of 30 to 100 mg/kg/day, multiple deaths/euthanasia and convulsions occurred at doses of 100 mg/kg/day and lower body weight gains occurred at doses ≥ 60 mg/kg/day, which were considered adverse. The NOAEL was identified at 30 mg/kg/day. The effects on body weight and adverse CNS-related clinical signs in juvenile rats were dose related and generally more severe when administration was initiated earlier in the postnatal period.

In the definitive GLP definitive study, juvenile rats received oral doses of 0, 20, and 30 mg/kg/day from PND 14 to PND 42 or 0, 30, 30 (+10 mg/kg/day IVA), and 60 mg/kg/day from PND 21 to PND 49. No treatment-related deaths or adverse clinical signs were

observed. For PND 14-42 and PND 21-49, body weight gains for male and female rats receiving doses up to 30 mg/kg/day were unaffected. However, for PND 21-49, body weight gain for males at 60 mg/kg/day was reduced to 89.5% of the control. Body weight gain was unaffected for females at 60 mg/kg/day. No adverse findings were identified in juvenile rats administered with the combination of 30 mg/kg/day TEZ and 10 mg/kg/day IVA. The NOAELs of TEZ in juvenile rats were identified as 30 mg/kg/day (AUC_{0-24} : 107.8 h•µg/mL) from PND 14-42 and 30 mg/kg/day (AUC_{0-24} : 106 h•µg/mL) from PND 21-49. In juvenile rats from PND 14-42, the AUC_{0-24} of metabolites M1-661 and M2-661 were 47.4 h•µg/mL and 4.35 h•µg/mL, respectively. In juvenile rats from PND 21-35, the AUC_{0-24} of metabolites M1-661 and M2-661 were 51.6 h•µg/mL and 3.87 h•µg/mL, respectively.

Higher brain levels of TEZ and its two metabolites in younger rats dosed starting from PND 7-9 and PND 14-16 might explain the observed CNS toxicity (clonic convulsions and other CNS-related clinical observations) of TEZ. The increased brain levels of TEZ and its metabolite in the younger juvenile rats may be explained by the lower activity levels of the efflux transporter protein, P-glycoprotein (P-gp), in the brain of younger juvenile rats. TEZ and M1-661 are both substrates for P-gp. Toxicity observed in juvenile rats appeared to correlate to the developmental stage of the blood brain barrier (i.e., P-gp activity). The decreased activity of P-gp in younger juvenile pups would lead to higher brain levels of TEZ, M1-661, and M2-661. The blood-brain barrier (BBB) in rats in terms of P-gp activity is not fully developed until approximately PND 21 - PND 35, whereas in humans the BBB in term of P-gp activity reaches adult levels at approximate 3-6 months of age as measured by P-gp activity and expression. In general, P-gp activity appears to only be a safety concern for children less than 1 year of age and is unlikely to be a concern for children 6 through 11 years of age.

Neuropsychiatric events have been reported for the market-available CFTR modulators. Dagenais et al. (Journal of Clinical Medicine 2021, 10, 23; <https://dx.doi.org/10.3390/jcm10010023>) conducted a systematic review to summarize real-world Adverse Events (AEs) reported for market-available CFTR modulators (i.e., ivacaftor (IVA), lumacaftor/ivacaftor (LUM/IVA), tezacaftor/ivacaftor (TEZ/IVA), and elxacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA)). A signal for mental health and neurocognitive AEs was identified with all 4 CFTR modulators. Limited data were available regarding real-world AEs with TEZ/IVA: however, notable neuropsychiatric AEs were reported. In a cohort of 44 adults, 5 (11%) experienced neuropsychiatric AEs. The results of juvenile rat studies with tezacaftor raise concerns for potential neuropsychiatric AEs. It is unclear if variations in brain levels of p-glycoprotein might be involved in these potential neuropsychiatric AEs.

The supplement (NDA 212273-S004) is recommended for approval from the nonclinical perspective.

1.3 Recommendations

1.3.1 Approvability

The supplement (NDA 212273-S004) is recommended for approval from the nonclinical perspective.

1.3.2 Additional Nonclinical Recommendations

None.

1.3.3 Labeling

The nonclinical review of the proposed product label recommends changes in Sections 8.4 (Pediatric Use; Juvenile Animal Toxicity Data) and 13.1 (Carcinogenesis, Mutagenesis, Impairment of Fertility) to describe juvenile rat studies with tezacaftor and elexacaftor, respectively, as shown below. Additions are shown as underlined text and deletions are shown as ~~strikeout text~~.

Reviewer's recommended changes:

8.4 Pediatric Use

Juvenile Animal Toxicity Data

Findings of cataracts were observed in juvenile rats dosed from postnatal Day 7 through 35 with ivacaftor dose levels of 10 mg/kg/day and higher (0.24 times the MRHD based on systemic exposure of ivacaftor and its metabolites). This finding has not been observed in older animals [see Warnings and Precautions (5.4) and Patient Counseling Information (17)].

(b) (4)

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No studies of carcinogenicity, mutagenicity, or impairment of fertility were conducted with the combination of elexacaftor, tezacaftor and ivacaftor; however, separate studies of elexacaftor, tezacaftor and ivacaftor are described below.

Elexacaftor

A 6-month study in Tg.rasH2 transgenic mice showed no evidence of tumorigenicity at 50 mg/kg/day dose, the highest dose tested.

Elexacaftor was negative for genotoxicity in the following assays: Ames test for bacterial gene mutation, in vitro mammalian cell micronucleus assay in TK6 cells, and in vivo mouse micronucleus test.

Elexacaftor did not cause reproductive system toxicity in male rats at 55 mg/kg/day and female rats at 25 mg/kg/day, equivalent to approximately 6 times and 4 times the MRHD, respectively (based on summed AUCs of elexacaftor and its metabolite). Elexacaftor did not cause embryonic toxicity at 35 mg/kg/day which was the highest dose tested, equivalent to approximately 7 times the MHRD (based on summed AUCs of elexacaftor and its metabolite). Lower male and female fertility, male copulation, and female conception indices were observed in males at 75 mg/kg/day and females at 35 mg/kg/day, equivalent to approximately 6 times and 7 times, respectively, the MRHD (based on summed AUCs of elexacaftor and its metabolite).

(b) (4)

Tezacaftor

A 2 year study in Sprague-Dawley rats and a 6-month study in Tg.rasH2 transgenic mice were conducted to assess the carcinogenic potential of tezacaftor. No evidence of tumorigenicity from tezacaftor was observed in male and female rats at oral doses up to 50 and 75 mg/kg/day (approximately 1 and 2 times the MRHD based on summed AUCs of tezacaftor and its metabolites in males and females, respectively). No evidence of tumorigenicity was observed in male and female Tg.rasH2 transgenic mice at tezacaftor doses up to 500 mg/kg/day.

Tezacaftor was negative for genotoxicity in the following assays: Ames test for bacterial gene mutation, in vitro chromosomal aberration assay in Chinese hamster ovary cells, and in vivo mouse micronucleus test.

There were no effects on male or female fertility and early embryonic development in rats at oral tezacaftor doses up to 100 mg/kg/day (approximately 3 times the MRHD based on summed AUC of tezacaftor and M1 TEZ).

Ivacaftor

Two year studies were conducted in CD-1 mice and Sprague-Dawley rats to assess the carcinogenic potential of ivacaftor. No evidence of tumorigenicity from ivacaftor was observed in mice or rats at oral doses up to 200 mg/kg/day and 50 mg/kg/day, respectively (approximately equivalent to 2 and 7 times the MRHD, respectively, based on summed AUCs of ivacaftor and its metabolites).

Ivacaftor was negative for genotoxicity in the following assays: Ames test for bacterial gene mutation, in vitro chromosomal aberration assay in Chinese hamster ovary cells, and in vivo mouse micronucleus test.

Ivacaftor impaired fertility and reproductive performance indices in male and female rats at 200 mg/kg/day (approximately 7 and 5 times, respectively, the MRHD based on summed AUCs of ivacaftor and its metabolites). Increases in prolonged diestrus were observed in females at 200 mg/kg/day. Ivacaftor also increased the number of females with all nonviable embryos and decreased corpora lutea, implantations, and viable embryos in rats at 200 mg/kg/day (approximately 5 times the MRHD based on summed AUCs of ivacaftor and its metabolites) when dams were dosed prior to and during early pregnancy. These impairments of fertility and reproductive performance in male and female rats at 200 mg/kg/day were attributed to severe toxicity.

2 Drug Information

2.1 Drug

Elexacaftor/tezacaftor/ivacaftor (co-packaged)/tablets.

100 mg VX-445/50 mg tezacaftor/75 mg ivacaftor per tablet & 150 mg ivacaftor per tablet

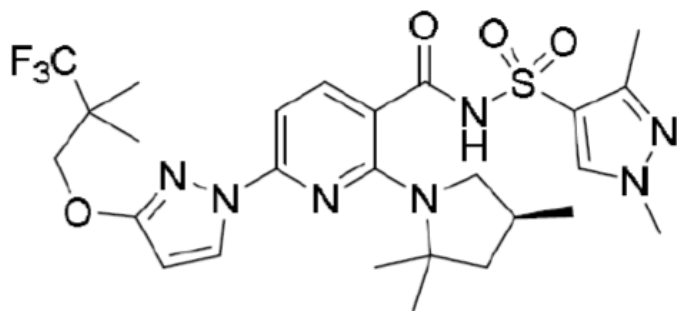
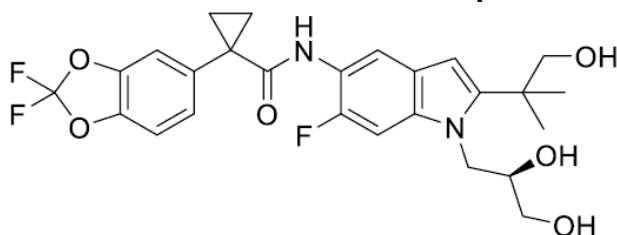
Elexacaftor

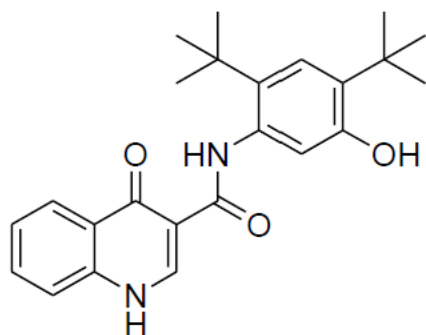
CAS Registry Number: 2216712-66-0

Generic Name: VX-445, VRT-1651445

Chemical Name: N-(1,3-dimethyl-1H-pyrazole-4-sulfonyl)-6-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)-1H-pyrazol-1-yl]-2-[(4S)-2,2,4-trimethylpyrrolidin-1-yl]pyridine-3-carboxamide

Molecular Formula/Molecular Weight: C₂₆H₃₄F₃N₇O₄S / 597.66 g/mol

Structure or Biochemical Description:**Pharmacologic Class:****Tezacaftor****CAS Registry Number:** 1152311-62-0**Generic Name:** VX-661**Chemical Name:** (R)-1-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-N-(1-(2,3-dihydroxypropyl)-6-fluoro-2-(1-hydroxy-2-methylpropan-2-yl)-1H-indol-5-yl)cyclopropanecarboxamide**Molecular Formula/Molecular Weight:** C₂₆H₂₇F₃N₂O₆/ 520.505 g/mol**Structure or Biochemical Description:****Pharmacologic Class:****Ivacaftor****CAS Registry Number:** 873054-44-5**Generic Name:** VX-770**Chemical Name:** N-(2,4-ditert-butyl-5-hydroxyphenyl)-4-oxo-1H-quinoline-3-carboxamide**Molecular Formula/Molecular Weight:** C₂₄H₂₈N₂O₃/ 392.499 g/mol

Structure or Biochemical Description:

Pharmacologic Class: cystic fibrosis transmembrane conductance regulator (CFTR) potentiator

2.2 Relevant INDs, NDAs, BLAs and DMFs

The following is a list of relevant INDs and NDAs:

NDA 212273, Trikafta (elexacaftor/tezacaftor/ivacaftor) tablets

NDA 203188, Kalydeco (ivacaftor) tablets

NDA 207925, Kalydeco (ivacaftor) granules

NDA 206038, Orkambi (ivacaftor, lumacaftor) tablets

NDA 210491, Symdeko (ivacaftor, tezacaftor) tablets

NDA 211358, Orkambi (ivacaftor, lumacaftor) granules

2.3 Drug Formulation

The elexacaftor/tezacaftor/ivacaftor FDC tablet contains 50 mg of elexacaftor, 25 mg of tezacaftor, and 37.5 mg of ivacaftor (b) (4). It is a light orange film coated tablet, (b) (4).

(b) (4) The composition of the elexacaftor/tezacaftor/ivacaftor 50/25/37.5 mg tablet, which consists of the core tablet and film coat, is provided in Table 1.

Table 1 Quantitative Composition of Trikafta (elexacaftor/tezacaftor/ivacaftor)**Table 1 Composition of Elexacaftor/Tezacaftor/Ivacaftor 50/25/37.5 mg Fixed Dose Combination Tablet**

Component	Quality Standard	Component Function	Amount per Tablet (mg)	Content (% w/w)
Core Tablet				
<i>Intragranular</i>				
Elexacaftor drug substance	Internal standard	Active ingredient	(b) (4)	(b) (4)
Tezacaftor SDD ^a				
Tezacaftor drug substance	Internal standard	Active ingredient		
Hypromellose (HPMC)	USP/NF/Ph.Eur.	(b) (4)		
Ivacaftor SDD ^b				
Ivacaftor drug substance	Internal Standard	Active ingredient		
Hypromellose acetate succinate (HPMCAS)	USP/NF	(b) (4)		
Sodium lauryl sulfate (SLS)	USP/NF/Ph.Eur.			
Croscarmellose sodium	USP/NF/Ph.Eur.			
Microcrystalline cellulose	USP/NF/Ph.Eur.			
<i>Extragranular</i>				
Microcrystalline cellulose	USP/NF/Ph.Eur.			
Magnesium stearate	USP/NF/Ph.Eur.			
Core Tablet Total				
Film Coat				
Component	Quality Standard	Component Function	Amount per Tablet (mg)	Content (% w/w)
(b) (4)				
Water ^c	USP/Ph.Eur			(b) (4)
Total Tablet Weight			(b) (4)	

^a Content of tezacaftor SDD and intragranular excipients are adjusted when the tezacaftor SDD assay is outside of 97.0-103.0%

^b Content of ivacaftor SDD and intragranular excipients are adjusted when the ivacaftor SDD assay is outside of 98.0-102.0%

^c Removed during the manufacturing process

(Excerpted from the Sponsor's submission)

2.4 Comments on Novel Excipients

None.

2.5 Comments on Impurities/Degradants of Concern

None.

2.6 Proposed Clinical Population and Dosing Regimen

Trikafta® was approved in October of 2019 for the treatment of cystic fibrosis (CF) patients, aged 12 years and older, with at least one F508del mutation in the CFTR gene. The current efficacy supplement is indicated for the treatment of CF subjects 6 through 11 years of age.

The recommended total daily dose of ELX/TEZ/IVA for patients 6 through 11 years of age is as follows:

- Patients weighing ≥ 30 kg: ELX 200 mg/TEZ 100 mg/IVA 300 mg
- Patients weighing < 30 kg: ELX 100 mg/TEZ 50 mg/IVA 150 mg

Table 2 Dosing Regimen of Trikafta in Children 6-11 years old

Table 2 Tablets in the ELX/TEZ/IVA Regimen Recommended for CF Patients 6 Through 11 Years of Age

Patient Weight	ELX/TEZ/IVA (Morning Dose = 2 tablets)	IVA (Evening Dose = 1 tablet)
≥ 30 kg ^a	ELX 100 mg/TEZ 50 mg/IVA 75 mg (film-coated tablets)	IVA 150 mg (film-coated tablets)
< 30 kg	ELX 50 mg/TEZ 25 mg/IVA 37.5 mg (film-coated tablets)	IVA 75 mg (film-coated tablets)

CF: cystic fibrosis; ELX: elexacaftor; IVA: ivacaftor; TEZ: tezacaftor

^a These patients would receive the same ELX/TEZ/IVA regimen and formulation as the currently approved commercial product for patients ≥ 12 years of age

(Excerpted from the Sponsor's submission)

2.7 Regulatory Background

The efficacy supplement NDA was submitted on December 8, 2020, and the application was filed on January 21, 2021 for standard review.

3 Studies Submitted

3.1 Studies Reviewed

General Toxicology Study	GLP	Report Number
Rats		
VX-445: An Oral (Gavage) Range-Finding Toxicity and Toxicokinetics Study in Juvenile Sprague Dawley Rats from Postnatal Days 7 or 21 through 35 Doses: Males: 0, 7.5, 15, or 30 mg/kg/day from PND 7 or PND 21 to PND 35; Females: 0, 5, 7.5, or 10 mg/kg/day from PND 7 or PND 21 to PND 35, 10/sex/group *This non-GLP DRF study was briefly reviewed and summarized under the review of the GLP definitive study.	No	VX-445-TX-013
VX-445: An Oral (Gavage) Juvenile Toxicity and Toxicokinetics Study in Postnatal Day 7 through Postnatal Day 70 Sprague Dawley Rats Doses: Males: 0, 7.5, 15, or 30 mg/kg/day; Females: 0, 5, 7.5, or 15 mg/kg/day, 10/sex/group	Yes	VX-445-TX-021
VX-661: An Oral (Gavage) Dose Range-Finding Study in Juvenile Rats Doses: 0, 10, 30, 60, or 100 from PND 7 to 35; 10/sex/group	Yes	VX-661-TX-037
VX-661: An Oral (Gavage) Pharmacokinetic and Toxicity Study in Juvenile Sprague Dawley Rats Doses: TK study: 0 and 30 mg/kg/day on PND 7–9, PND 14–16, PND 21–23, or PND 35–37, 5 females for control, and 20 females for 30 mg/kg/day VX-661 treated groups Additional toxicology study on PND 7–9: 0 and 60 mg/kg/day, 10 females /group	Yes	VX-661-TX-065
VX-661: An Oral (Gavage) Dose Range-Finding Study from Postnatal Day (PND) 14 or 21 to PND 35 in Juvenile Sprague Dawley Rats Doses: 0, 20, or 30 mg/kg/day from PND 14-35, 10/sex/group Doses: 0, 30, 60, or 100 mg/kg/day from PND 21-35, 10/sex/group	Yes	VX-661-TX-069
VX-661: An Oral (Gavage) Juvenile Toxicity Study with a Combination Arm of VX-661 and VX-770 from Postnatal Day (PND) 14 to 42 or PND 21 to 49 in Juvenile Sprague Dawley Rats Doses: VX-661 alone study: 0, 20 and 30 mg/kg/day, 20/sex/group VX-661 in combination with VX-770 study: 0, 30, 30 combined with VX-770 at 10 mg/kg/day, and 60 mg/kg/day, 20/sex/group	Yes	VX-661-TX-038

3.2 Studies Not Reviewed

None.

3.3 Previous Reviews Referenced

1. Multi-Discipline Review of NDA 212273, Trikafta (elexacaftor/tezacaftor/ivacaftor) tablets dated October 21, 2018
2. Pharmacology and Toxicology Review of NDA 210491, Symdeko (ivacaftor/tezacaftor) tablets dated January 29, 2018

9 Reproductive and Developmental Toxicology

9.4 Juvenile Animal Studies⁺

9.4.1 Study Title: VX-445: An Oral (Gavage) Juvenile Toxicity and Toxicokinetics Study in Postnatal Day 7 through Postnatal Day 70 Sprague Dawley Rats (Study report #: VX-445-TX-021)

Study no.:	VX-445-TX-021
Study report location:	NDA212273-S001-SD1-M4-2354
Conducting laboratory and location:	 (b) (4)
Duration:	9
Duration Units:	Week
GLP compliance:	Y
Drug, lot #, and % purity:	VX-445 (also known as VRT-1651445), GMP111-154-M, and 100.0%

Key Findings:

- In a juvenile toxicology study, male and female rats received VX-445 from PND 7 to PND 70. Male rats received VX-445 at oral doses of 0 [0.5% methylcellulose (400 cP), 0.1% sodium lauryl sulfate, 0.01% simethicone], 7.5, 15, or 30 mg/kg/day. Female rats received VX-445 at oral doses of 0 [0.5% methylcellulose (400 cP), 0.1% sodium lauryl sulfate, 0.01% simethicone], 5, 7.5, or 15 mg/kg/day.
- Increases of mean total bilirubin (TBIL) concentrations were observed in males of the high dose (HD) group (mean was 0.03 mg/dL versus control group mean of 0.0 mg/dL), and in females of the mid dose (MD) and HD groups (means were 0.04 and 0.10 mg/dL, respectively, versus control group mean of 0.01 mg/dL). Increases of mean ALT were observed in males and females in the HD group (1.15x and 2.13x, respectively). Decreases of mean cholesterol concentration were observed in males and females in the HD group (0.67x and 0.76x, respectively). There were no corresponding histopathological findings were observed in the liver. Increases of mean creatine kinase (CK) activities were observed in males and females in the HD group (1.21x and 1.34x, respectively).

- Mean ages and body weights at attainment of balanopreputial separation or vaginal patency were unaffected.
- No potential target organs of toxicity were identified.
- The NOAELs were identified as the HDs of 30 mg/kg/day (AUC_{0-24} , 694 h• μ g/mL) for males and 15 mg/kg/day (AUC_{0-24} , 976 h• μ g/mL) for females, respectively. The AUC_{0-24} for the major human metabolite (M23-445) of VX-445 in males and females were 40.1 and 81.5 h• μ g/mL, respectively.

Methods

Doses:	Males: 0, 7.5, 15, or 30 mg/kg/day Females: 0, 5, 7.5, or 15 mg/kg/day
Frequency of dosing:	Daily
Number/Sex/Group:	Main: 10/sex/group TK: 3/sex for control, and 6/sex for low dose (LD), MD, and HD groups
Dose volume:	10 mL/kg
Formulation/Vehicle:	Group 2F (0.5 mg/mL), Group 2M/3F (0.75 mg/mL), Group 3M/4F (1.5 mg/mL), and Group 4M (3.0 mg/mL) / Vehicle = 0.5% methylcellulose (400 cP), 0.1% sodium lauryl sulfate, 0.01% simethicone in deionized water
Route of administration:	ORAL GAVAGE
Species:	Rats
Strain:	Sprague Dawley Crl:CD(SD)
Age at start of experiment:	Postnatal day 7
Period of development studied:	Postnatal Day (PND) 7 through PND 70
Comment on Study Design and Conduct:	A non-GLP dose range-finding juvenile toxicology study was conducted (Study# VX-445-TX-013). Males received oral doses of VX-445 at 7.5, 15, or 30 mg/kg/day from PND 7 to PND 35. Females received oral doses of VX-445 at 5, 7.5, or 10 mg/kg/day from PND 7 to PND 35. Increases of ALT, AST and creatine kinase (CK) activities were observed in males at ≥ 7.5 mg/kg/day (up to 1.21X, 1.28X, and 2.02X, respectively) and females at 10 mg/kg/day (1.26X, 1.28X, and 3.62X, respectively). No dose-limiting toxicities were identified.
Parameters and Key Endpoints Evaluated:	Clinical signs, body weights, food consumption, developmental landmarks,

ophthalmology, clinical pathology (hematology, serum chemistry, urinalysis, and urine chemistry), toxicokinetic parameters, gross necropsy findings, spermatogenesis endpoints, organ weights, and histopathology

Dosing Solution Analysis: The results were within the specified range (85% to 115%).

Observations and Results

Mortality: Animals were checked twice daily for mortality and signs of morbidity.

There were no treatment-related deaths.

Clinical Signs: Animals were examined daily for clinical signs.

There were no treatment-related clinical signs.

Body Weight: Animals were weighed individually daily from PND 7 through PND 21 and twice weekly thereafter until euthanasia (PND 71).

There were no treatment-related changes of body weight at the end of study (PND 7 to PND 71). Transient decreased body weight gains were observed in males of the HD group starting from PND 11 to PND 12 and lasting through PND 24 to PND 28 (0.31X to 0.87X).

Feed Consumption: Food consumption was measured twice weekly following weaning from PND 21 until euthanasia.

Transient decreased food consumption was observed in males in the HD group starting from PND 21 to PND 28 interval (0.56X and 0.85X), corresponding to the decreased body weight gains.

Ophthalmoscopy: Ophthalmic examinations were conducted during the last week (PND 64 to PND 67).

There were no treatment-related ophthalmic findings.

Hematology: Hematology and Coagulation parameters were determined on PND 71.

There were no treatment-related changes of hematology and coagulation parameters.

Clinical Chemistry: Clinical chemistry parameters were determined on PND 71.

Changes in clinical chemistry may be test item-related but were not considered adverse due to the small magnitude of change and the lack of corresponding histopathological

findings. Statistically significant increases of mean TBIL concentration were observed in males in the HD group (mean was 0.03 mg/dL versus control group mean of 0.0 mg/dL), and in females of the MD and HD groups (means were 0.04 and 0.10 mg/dL, respectively, versus control group mean of 0.01 mg/dL). Increases of mean ALT were observed in males and females in the HD group (1.15x and 2.13x, respectively). Decreases of mean cholesterol concentration were observed in males and females in the HD group (0.67x and 0.76x control mean, respectively). There were no corresponding histopathological findings were observed in the liver. Increases of mean CK activities were observed in males and females in the HD group (1.21x and 1.34x, respectively).

Urinalysis: Urine samples were collected on PND 71.

There were no treatment-related changes of urinalysis parameters.

Sexual Maturation:

Balanopreputial Separation

Each male pup was observed for balanopreputial separation beginning on PND 35. The age at which balanopreputial separation was first observed was recorded for each pup. Examination of the males continued daily until balanopreputial separation was present. Body weights were recorded at the age of attainment of this landmark.

There were no treatment-related changes of mean ages of attainment of balanopreputial separation and mean body weights at the age of attainment.

Vaginal Patency

Each female pup was observed for vaginal perforation beginning on PND 25. The age at which vaginal patency was first observed was recorded for each pup. Examination of the females continued daily until vaginal patency was present. Body weights were recorded at the age of attainment of this landmark.

There were no treatment-related changes of mean ages of attainment of vaginal patency and mean body weights at the age of attainment.

Reproductive Capacity: Immediately upon euthanasia, the reproductive tract of each male was exposed via a ventral mid-line incision. The right cauda epididymis was excised and weighed. Analysis of a minimum of 200 motile and nonmotile spermatozoa per animal (if possible) in all groups was performed by the analyzer.

There were no treatment-related changes of spermatogenesis endpoints (mean testicular and cauda epididymal sperm numbers and sperm production rate, motility, and morphology).

Gross Pathology: On completion of treatment, all main animals were killed on PND 71 by carbon dioxide inhalation. Each animal was weighed and subsequently exsanguinated. Main study animals were subjected to a complete necropsy

examination, which included examination of the external surface, all orifices, the cranial cavity, the external surfaces of the brain and spinal cord, and the thoracic, abdominal, and pelvic cavities, including viscera. Gross lesions were examined from all animals in all groups.

There were no treatment-related gross pathological changes.

Organ Weights: The organs identified in Table 1 were weighed at necropsy for all scheduled euthanasia animals.

There were no treatment-related changes of organ weights.

Table 3 Organ weighed

Text Table 11
Organs Weighed at Necropsy

Adrenal glands	Prostate gland
Brain	Seminal vesicles with coagulating glands (with accessory fluids)
Epididymides (total and cauda) ^a	Spleen
Kidneys	Testes ^a
Liver	Thymus
Lungs	Thyroid with parathyroids
Ovaries	Uterus (with oviducts and cervix)
Pituitary gland	

^a These paired organs were weighed separately.

(Excerpted from the Sponsor's submission)

Histopathology:

Adequate Battery: An adequate battery of organs and tissues was submitted to histopathological examination. Organs or parts of organs of all animals were fixed in 10% neutral buffered formalin, dehydrated and embedded in paraffin wax and sectioned at approximately 4-6 µm thickness and stained with hematoxylin and eosin (H&E). Tissues identified in Table 2 for microscopic examination were evaluated from all animals in the control and high-dose groups. Findings were assigned one of the following four severity grades: minimal, mild, moderate and marked. In addition, PAS staining was used for the testes and epididymides.

Table 4 Tissue collection list

Text Table 12
Tissue Collection and Preservation

Adrenal glands (2) Aorta Bone with marrow (sternebrae) Bone with marrow (distal femur, collected and processed as femorotibial joint) Brain (8 levels) Coagulating gland (2) Eyes with optic nerve (2)^a Gastrointestinal tract Esophagus Stomach Duodenum Jejunum Ileum Cecum Colon Rectum^b Heart Kidneys (2) Liver (sections of 2 lobes) Lymph nodes (mandibular [2], mesenteric) Larynx Lungs (including bronchi, fixed by inflation with fixative)	Ovaries with oviducts (2) Pancreas Peripheral nerve (sciatic) Pituitary Prostate Salivary glands [mandibular (2)] Nasal cavity^c Nasopharynx Seminal vesicles (2) Skeletal muscle (rectus femoris) Skin (with mammary gland)^d Spinal cord (cervical, thoracic, lumbar) Spleen Testes with epididymides (1)^e and vas deferens Thymus Thyroid (with parathyroids, if present [2]) Trachea Urinary bladder Ureter (2) Uterus with cervix and vagina Gross lesions (all groups)^f
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^a Fixed in Davidson's solution.

^b Collected and preserved longitudinally so that the histology specimen included the recto-anal junction.

^c Four nasal cavity sections were prepared according to the method of Kittel et al.⁸

^d For females; a corresponding section of skin was taken from the same anatomic area for males.

^e Testis (right) and epididymis (right and remainder of left) were fixed in modified Davidson's solution. Care was taken to ensure separation between the left and right organs.

^f Representative sections of corresponding organs from a sufficient number of controls was retained for comparison, if possible.

(Excerpted from the Sponsor's submission)

Peer Review: The histopathology peer review was performed by Kathryn E. Bowenkamp, DVM, PhD, DACVP, Vertex Pharmaceuticals Incorporated.

No potential target organs of toxicity were identified. The following findings were observed with low incidence and the relationship of those changes to the administration of VX-445 was unclear.

Table 5 Histopathology findings in juvenile rats from PND 7 to PND 70

Organ/Tissue	Time	Males				Females			
		0	7	15	30	0	5	7.5	15
EYES									
-fold/rosette, retina		1/10			3/10	0/10			1/10
Minimal		1			2	0			1
Mild		0			1	0			0

Organ/Tissue	Time	Males				Females			
		0	7	15	30	0	5	7.5	15
Kidneys -basophilic tubules, focal/multifocal Minimal Moderate -fibrosis, cortical, focal Mild	Term	2/10 1 1 0/10 0			5/10 4 1 1/10 1	0/10 0 0 0/10 0			0/10 0 0 0/10 0
Lung -hemorrhage, focal/multifocal Minimal -infiltration, mixed cell Minimal	Term	0/10 0 0/10 0			3/10 3 1/10 1	1/10 1 1/10 1			0/10 0 0/10 0
Spleen -fibrosis, capsular, focal Mild	Term	0/10 0			1/10 1	0/10 0			0/10 0
Thymus -hemorrhage, focal/multifocal Minimal Moderate Mild	Term	4/10 4 0 0		1/1 0 1 0	4/10 4 0 0	1/10 1 0			6/10 3 3

Toxicokinetics: Blood samples for measurement of serum VX-445 and major human metabolite, M23-445, concentrations were collected from each animal. Samples (for serum concentrations) were collected predose, 2-hour, 4-hour, 8-hour, 12-hour, and 24-hour postdosing on PND70. Serum samples were stored frozen at -70°C. Serum concentrations of VX-445 were analyzed at (b) (4) using an LC-MS/MS assay with detection limits between 50.0 to 50000 ng/mL.

Overall, serum C_{max} and AUC values in males generally increased in an approximately dose proportional manner on PND 70. Serum C_{max} and AUC values of VX-445 in females generally increased in a greater than dose proportional manner on PND 70. In males, T_{max} values were 4 hours postdose at 7.5 and 15 mg/kg and 8.27 hours postdose at 30 mg/kg. In females, T_{max} values were 4 hours postdose at 5 mg/kg, 2 hours postdose at 7.5 mg/kg, and 8 hours postdose at 15 mg/kg. At the same doses (7.5 mg/kg and 15 mg/kg), systemic exposures (AUC) of VX-445 in females were approximately 2 times greater than in males on PND 70.

Table 6 Toxicokinetic Parameters of VX-445 in rats on PND 70

Text Table 15
VX-445 Toxicokinetic Parameters on PND 70

Group	Dose (mg/kg/day)	C _{max} (µg/mL)	t _{max} (hr)	AUC _{0-24hr} (hr•µg/mL)
Males				
2	7.5	10.6	4	161
3	15	23.6	4	416
4	30	41.9	8.27	694
Females				
2	5	9.38	4	168
3	7.5	16.2	2	300
4	15	45.4	8	976

(Excerpted from the Sponsor's submission)

AUCs of M23-445 (VRT-1654548), a major human metabolite (M23) of VX-445, were 4-8% of AUCs of VX-445 in males and females on PND 70. Serum C_{max} and AUC values of the metabolite, M23-445, in males generally increased in an approximately dose proportional manner on PND 70. Serum C_{max} and AUC values of the metabolite, M23-445, in females generally increased in a greater than dose proportional manner on PND 70. In males, T_{max} values were 0 hr postdose at 7.5 mg/kg, 12 hours postdose at 15 mg/kg, and 8.27 hours postdose at 30 mg/kg. In females, T_{max} values were 12 hours postdose at 5 and 15 mg/kg and 2 hours postdose at 7.5 mg/kg. At the same dose (7.5 mg/kg and 15 mg/kg), the systemic exposure (AUC) of the metabolite M23-445 in females were approximately 3-4 times of that in males on PND 70.

Table 7 Toxicokinetic Parameters of M23-445 (VRT-1654548) in rats on PND 70

Text Table 16
VRT-1654548 Toxicokinetic Parameters on PND 70

Group	VX-445 Dose (mg/kg/day)	C _{max} (µg/mL)	t _{max} (hr)	AUC _{0-24hr} (hr•µg/mL)
Males				
2	7.5	0.407	0	6.61
3	15	1.27	12	23.5
4	30	2.33	8.27	40.1
Females				
2	5	0.533	12	10.1
3	7.5	0.989	2	20.2
4	15	3.73	12	81.5

(Excerpted from the Sponsor's submission)

9.4.2 Study Title: VX-661: An Oral (Gavage) Dose Range-Finding Study in Juvenile Rats (Study report #: VX-661-TX-037)

Study no.: VX-661-TX-037
Study report location: NDA212273-S001-SD1-M42354
Conducting laboratory and location:  (b) (4)

Duration: 28
Duration Units: Day
GLP compliance: Y
Drug, lot #, and % purity: VX-661, 19QB10A-50.NJ00001, and 98.0%

Key Findings:

- In a juvenile toxicology study, rats received VX-661 at oral doses of 0 [0.5% methylcellulose (400 cP), 0.5% sodium lauryl sulfate, 0.01% simethicone], 10, 30, 60 or 100 mg/kg/day from PND 7 to PND 35.
- VX-661 was not tolerated at doses ≥ 30 mg/kg/day as rats in these groups were found dead or euthanized in extremis from PND 7 to PND 16. Adverse clinical observations prior to death included clonic convulsions, hypoactivity, and/or cool body as well as body weight losses. Probable causes of death could not be determined for a large number of animals based on anatomic pathology findings.
- Surviving main study phase males and females that received doses ≥ 30 mg/kg/day were noted with clonic convulsions at the daily examinations and/or following dose administration (beginning as early as approximately 1 minute through 4 hours following dose administration) as well as other adverse CNS-related clinical observations (including hypoactivity, repetitive movement of the mouth, head tilt, small stature, and cool and/or thin body) noted as early as PND 9 (3rd dose). All animals that received doses of 30, 60, and 90 mg/kg/day were euthanized on PND 14-16, PND 10-11, and PND 9-10, respectively, due to test-article related adverse clonic convulsions and reduced body weights.
- Statistically significant ($p < 0.05$ or $p < 0.01$) decreases of mean body weights were observed in both males and females in the mid-low dose (MLD), mid-high dose (MHD), and high dose (HD) groups (MLD: 36.1% and 35.4%, MHD: 31.1% and 31.9%, and HD: 30.6% and 35.5%, respectively) compared to the control group (MLD: PND 7–16, MHD: PND 7–11, and HD: PND 7–10).
- Decreases in lymphocytes in the spleen were observed with higher incidences in the drug treated groups. Minimal to mild hematopoiesis in the liver were observed in the drug treated groups. No microscopic brain/CNS related findings were observed.

- The NOAEL of Tezacaftor was identified as the LD of 10 mg/kg/day (AUC_{0-24} , 27800 h•ng/mL) in juvenile rats. The AUC_{0-24} of metabolites VRT-0996107 (M1-661) and VRT-1189001 (M2-661) were 29400 and 1830 h•ng/mL, respectively.

Methods

Doses:	0, 10, 30, 60, or 100 mg/kg/day
Frequency of dosing:	Daily
Number/Sex/Group:	Main: 10/sex/group TK: 9/sex for control, and 54/sex for LD, MLD, MHD, and HD groups
Dose volume:	10 mL/kg
Formulation/Vehicle:	LD (1 mg/mL), MLD (3 mg/mL), MHD (6 mg/mL), and HD (10 mg/mL) /vehicle = 0.5% methylcellulose (400 cP), 0.5% sodium lauryl sulfate, 0.01% simethicone in deionized water
Route of administration:	ORAL GAVAGE
Species:	Rats
Strain:	Sprague Dawley Crl:CD(SD)
Age at start of experiment:	Postnatal day 7
Period of development studied:	Postnatal Day (PND) 7 through PND 35
Comment on Study Design and Conduct:	None.
Parameters and Key Endpoints Evaluated:	Clinical signs, body weights, food consumption, ophthalmology, clinical pathology (hematology and serum chemistry), toxicokinetic parameters, gross necropsy findings, organ weights, and histopathology
Dosing Solution Analysis:	The results were within the specified range (85% to 115%).

Observations and Results

Mortality: Animals were checked twice daily for mortality and signs of morbidity.

Test-article related mortality was observed at doses ≥ 30 mg/kg/day from PND 7 to PND 16. Due to test-article related adverse clonic convulsions and reduced body weights, all animals in the MLD, MHD, and HD groups were euthanized on PND 14-16, PND 10-11, and PND 9-10, respectively. Adverse clinical observations prior to death included clonic convulsions, hypoactivity, and/or cool body as well as body weight losses. Probable causes of death could not be determined for a large number of animals based on anatomic pathology findings.

HD: one male and one female in the HD group were euthanized on PND 10. The HD male had adverse clinical observations of clonic convulsions approximately 10 minutes

following dose administration and hypoactivity and cool body at approximately 4 hours following dose administration on the day of euthanasia, and body weight loss (19.1%) during PND 8–10. There were no macroscopic findings noted for this male at necropsy. The HD female had a cool body at the daily examinations on the day of death and a body weight loss (17.2%) during PND 9–10. No macroscopic findings were observed for this female.

Remaining HD animals were euthanized on PND 9-10.

MHD: one male and two females in the MHD group were found dead between PND 8-11. Dark red discoloration was observed in the lungs in one MHD female. No clinical or macroscopic findings were observed for the other two animals.

Remaining MHD animals were euthanized on PND 10-11.

MLD: three males and 5 females in the MLD group were euthanized or found dead between PND 8-16. One MLD female had adverse clinical observations of clonic convulsions and/or cool body at approximately 4 hours following dose administration 1–2 days prior to euthanasia, and clonic convulsions, hypoactivity, cool and thin body, and small stature at the daily examination on the day of euthanasia (PND 16). Cool body was also observed for this female on PND 13–15 at the daily examinations. No macroscopic findings were noted for this female. Brain trauma was observed in one MLD male. Dark red discoloration was observed in the lungs at necropsy in the other MLD males and females.

Remaining MLD animals were euthanized on PND 14-16.

LD: one male was found dead one PND 18. Congestion and dark red discoloration were observed in the lung. The cause of death was not determined by the Sponsor, although it was likely due to gavage-error.

Table 8 Mortality in the juvenile rats from PND 7-16

Mortality	Males, mg/kg/day					Females, mg/kg/day				
	0	10	30	60	100	0	10	30	60	100
Total affected animal	2/10	1/10	11/11	10/10	10/10	0/10	0/10	10/10	10/10	10/10
-found dead	2	1	3	1	0	0	0	4	2	1
-sent to necropsy in extremis	0	0	0	0	1	0	0	1	0	0
-early termination	0	0	8	9	9	0	0	5	8	9

Of the 21 early termination/unscheduled deaths from Group 3 (30 mg/kg/day), 8 were considered consistent with sequelae of gavage-related reflux, as evidenced by the presence of exudate in nasopharynx microscopically. A single male administered VX-661 at 60 mg/kg/day (Number 5229-04) also had luminal exudate in the nasopharynx

microscopically, which was consistent with gavage-related reflux, and was considered a probable cause of death. One 30 mg/kg/day male (Number 5237-05) had macroscopic evidence of accidental trauma unrelated to VX-661 administration and was replaced on PND 7 with male Number 5267-05. The probable causes of death/poor clinical condition could not be determined for the remaining animals in the 60 mg/kg/day dose group or any of the animals in the 100 mg/kg/day dose groups.

Clinical Signs: Animals were examined daily for clinical signs.

Clonic convulsions were observed for males in MLD (8/10), MHD (3/10), and HD (7/10) groups and for females in the MLD (5/10), MHD (4/10), and HD (8/10) groups, during PND 9–16. This observation occurred at the daily examinations and/or 1 minute to 4 hours following dose administration.

Other remarkable clinical observations noted for surviving males and females at all dose levels included hypoactivity, repetitive movement of the mouth, head tilt, small stature, and cool and/or thin body. These observations occurred at the daily examinations and/or approximately 4 hours following dose administration beginning on the third day of dose administration (PND 9).

Table 9 Behavior/CNS clinical signs in the juvenile rats from PND 9-16

Clinical Signs (Behavior/CNS)	Time	Males, mg/kg/day					Females, mg/kg/day				
		0	10	30	60	100	0	10	30	60	100
Total affected animal		0	0	8	3	7	0	0	5	4	8
-Convulsions, clonic	Daily exam	0/0	0/0	15/8*	2/2	0/0	0/0	0/0	7/5	4/4	0/0
	Post-dose (0-210 min)	0/0	0/0	0/0	1/1	4/4	0/0	0/0	0/0	2/2	6/6
	4 hours post-dosing	0/0	0/0	9/7	0/0	3/3	0/0	0/0	4/2	1/1	5/5
-Hypoactivity	Daily exam	0/0	0/0	7/7	0/0	0/0	0/0	0/0	3/3	0/0	0/0
	4 hours post-dosing	0/0	0/0	0/0	0/0	1/1	-	-	-	-	-
-Repetitive movement of mouth	4 hours post-dosing	0/0	0/0	1/1	0/0	0/0	-	-	-	-	-
-Head tilt	Daily exam	-	-	-	-	-	0/0	0/0	1/1	0/0	0/0

*Expressed as number of observations / number of animals affected.

Body Weight: Animals were weighed individually daily from PND 7 through PND 36.

Statistically significant ($p < 0.05$ or $p < 0.01$) decreases of mean absolute body weights were observed in both males and females in the MLD, MHD, and HD groups (36.1% and 35.4%, 31.1% and 31.9%, and 30.6% and 35.5%, respectively) compared to the control group (MLD: PND 7–16, MHD: PND 7–11, and HD: PND 7–10). Body weight gains were significantly reduced at doses ≥ 30 mg/kg/day.

Table 10 Changes of Body Weight in rats from PND 7 to PND 35

Body weight	Males, mg/kg/day					Females, mg/kg/day				
Parameter	0	10	30	60	100	0	10	30	60	100
BW, PND 7	16.3	16.2	16.5	15.6	16.2	15.2	16.2	16.3	16.1	15.5
BW, PND 10	24.5	24.1	22.7	20.6	17.0	22.8	24.1	22.5	20.3	14.7
BW, PND 11	28.0	27.7	24.8	19.3	-	26.0	27.7	24.8	17.7	-
BW, PND 16	41.8	40.0	26.7	-	-	40.4	40.0	26.1	-	-
BW, PND 35	162.7	158.7	-	-	-	133.9	141.0	-	-	-
Δ BW 7-10	8.2				0.8	7.6				-0.8
Δ BW 7-11	11.7			3.7		10.8			1.6	
Δ BW 7-16	25.5		10.2			25.2		9.8		
Δ BW 7-35	146.4	142.5				118.7	124.8			
Absolute BW, % of control	100.0	97.5	63.9	68.9	69.4	100.0	105.3	64.6	68.1	64.5
BW Gain, % of control	100.0	97.3	40.0	31.6	9.8	100.0	105.1	38.9	14.8	-10.5

-Further evaluation of body weight data at 30, 60, and 100 mg/kg/day was precluded by early group termination.

Ophthalmoscopy: Ophthalmic examinations were conducted during the last week (week 3).

There were no treatment-related ophthalmic findings.

Hematology: Hematology and Coagulation parameters were determined on PND 36.

Decreased mean RBC mass, increased mean corpuscular volume (MCV), decreased white blood cell (WBC) counts, and decreased lymphocyte were observed in MLD, MHD, and HD groups on days of sacrifice at PND 16, PND 11 and PND 10, respectively, comparing to controls on PND 36. The Sponsor contended that these changes were due to age difference at the time of sampling and immune system immaturity rather than a direct VX-661-related effect; however, decreases of RBC and WBC counts were noted to have correlating histopathological findings. Additional differences were attributed to stress. Decreased lymphocytes appeared to correlate with histopathological findings in the spleen. Decreased RBC mass appeared to correlate with compensatory minimal to mild hematopoiesis in the liver.

Clinical Chemistry: Clinical chemistry parameters were determined on PND 36.

Decreased ALT, increased urea nitrogen, decreased mean albumin, decreased total protein concentrations, decreased sodium concentration, increased total bilirubin, increased cholesterol and glucose were observed in MLD, MHD, and HD groups on PND 16, PND 11 and PND 10, respectively, comparing to controls on PND 36. The

Sponsor contended that these changes were due to age difference at the time of sampling and food intake rather than a direct VX-661-related effect. Additional differences were attributed to dehydration.

Gross Pathology: A complete necropsy was conducted on all animals that were found dead, euthanized due to early group termination (both phases), or at the scheduled termination by carbon dioxide inhalation on PND 36. Each animal was weighed and subsequently exsanguinated. Main study animals were subjected to a complete necropsy examination, which included examination of the external surface, all orifices, the cranial cavity, the external surfaces of the brain and spinal cord, and the thoracic, abdominal, and pelvic cavities, including viscera. Gross lesions were examined from all animals in all groups.

There were no treatment-related changes of gross pathology.

Organ Weights: The organs identified in Table 11 were weighed at necropsy for all scheduled euthanasia animals.

There were no treatment-related changes of organ weights in the LD group. Organ weights were not recorded from animals in the MLD, MHD, and HD dose groups at the early terminations of these dose levels (concurrent control animals were not available at early termination time points).

Table 11 Organ weighed

Text Table 7
Organs Weighed at Necropsy

Adrenal glands	Pituitary
Brain	Prostate
Epididymides	Seminal vesicles
Heart	Spleen
Kidneys	Testes
Liver	Thymus
Lungs	Thyroids
Ovaries (with oviducts)	Uterus

(Excerpted from the Sponsor's submission)

Histopathology:

Adequate Battery: An adequate battery of organs and tissues was submitted to histopathological examination. Organs or parts of organs of all animals were fixed in 10% neutral buffered formalin, dehydrated and embedded in paraffin wax and sectioned at approximately 4-6 µm thickness and stained with hematoxylin and eosin (H&E). Tissues identified in Table 2 for microscopic examination were evaluated from all animals that were found dead or euthanized in extremis or due to early group termination, and all animals in the control and 10 mg/kg/day groups. Findings were assigned one of the following four severity grades: minimal, mild, moderate and severe.

Table 12 Tissue collection listText Table 6
Tissue Collection

Adrenal glands Aorta Bone marrow smear (femur) Bone with marrow (femur and sternbrae) Brain (7 levels) Eyes with optic nerve ^a Femur Gut-associated lymphoid tissue (GALT; Peyer's patch) Gastrointestinal tract Esophagus Stomach Duodenum Jejunum Ileum Cecum Colon Rectum Heart Kidneys Liver (sections of 2 lobes) Lungs	Lymph nodes (mandibular and mesenteric) Mammary gland Ovaries with oviducts (2) Pancreas Sciatic nerve Pituitary Prostate Salivary glands (mandibular) Seminal vesicles Skeletal muscle (rectus femoris) Skin Spinal cord (cervical) Spleen Sternum Testes with epididymides ^b Thymus Thyroid [with parathyroids, if present] Tongue Trachea Urinary bladder Uterus with cervix and vagina Gross lesions
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^a Fixed in Davidson's solution.^b Fixed in modified Davidson's solution.

(Excerpted from the Sponsor's submission)

Peer Review: The histopathology peer review was performed by Kathryn E. Bowenkamp, DVM, PhD, DACVP, Vertex Pharmaceuticals Incorporated.

Decreases in lymphocytes in the spleen were observed with higher incidences in the drug treated groups and appeared to correlate with decreases of circulating lymphocytes. Minimal to mild hematopoiesis in the liver were observed in the drug treated groups and appeared to be a compensatory response to decreased RBC mass. No microscopic treatment-related brain findings were observed. The other findings were observed with low incidence and the relationship of those changes to the administration of VX-661 was unclear.

Table 13 Histopathology in rats from PND 7 to PND 35Text Table 18
Summary Incidence and Severity of Selected Microscopic Findings

Tissue/finding Sex	Males					Females				
VX-661 Dose (mg/kg/day)	0	10	30	60	100	0	10	30	60	100
Nasopharynx Number examined:	9	10	11	10	10	10	10	10	10	10
Exudate, lumen										
Total number affected	(0)	(0)	(3)	(1)	(0)	(0)	(0)	(5)	(0)	(0)
Minimal	0	0	0	1	0	0	0	3	0	0
Mild	0	0	2	0	0	0	0	1	0	0
Moderate	0	0	0	0	0	0	0	0	0	0
Marked	0	0	1	0	0	0	0	1	0	0
Spleen Number examined:	9	10	10	10	10	10	10	10	10	10
Lymphocytes, decreased										
Total number affected	(1)	(1)	(9)	(10)	(10)	(0)	(0)	(9)	(9)	(10)
Minimal	0	0	0	0	0	0	0	0	0	0
Mild	0	1	3	0	3	0	0	4	4	1
Moderate	1	0	6	9	6	0	0	3	5	5
Marked	0	0	0	1	1	0	0	2	0	4
Thymus Number examined:	10	10	11	10	10	10	10	10	10	10
Lymphocytes, decreased										
Total number affected	(0)	(0)	(1)	(0)	(0)	(0)	(0)	(1)	(0)	(0)
Minimal	0	0	0	0	0	0	0	0	0	0
Mild	0	0	1	0	0	0	0	1	0	0

(Excerpted from the Sponsor's submission)

Toxicokinetics: Blood samples for measurement of serum concentrations of VX-661 and its two metabolites, M1-661 and M2-661, were collected from each animal. Samples (for serum concentrations) were collected at predose, 2-hour, 4-hour, 8-hour, 12-hour, and 24-hour postdosing on PND70. Serum samples were stored frozen at -70°C. Serum concentrations of VX-661 were analyzed at (b) (4) using an LC-MS/MS assay with detection limits between 25.0 to 25000 ng/mL.

Overall, serum C_{max} and AUC values of VX-661 in males and females generally increased in a greater than dose proportional manner from 10 to 100 mg/kg/day on PND 7. No sex-related differences were observed for systemic exposure to VX-661. AUC values for 10 mg/kg VX-661 in males and females were slightly lower (< 0.5-fold) on PND 35 compared to PND 7.

Table 14 Toxicokinetic Parameters of VX-661 in rats on PND 7 and 35

Text Table 19

VX-661 Toxicokinetic Parameters on PND 7 and 35 following Oral Gavage Administration of 10, 30, 60, and 100 mg/kg/day to Juvenile Male and Female Rats

VX-661 Dose (mg/kg/day)	10	30	60	100
Males				
PND 7				
AUC _{0-24h} (hr*ng/mL)	35800	162000	382000	543000
C _{max} (ng/mL)	2890	8880	22600	28600
t _{max} (hr)	4.00	4.00	4.00	4.00
PND 35				
AUC _{0-24h} (hr*ng/mL)	20600	NA	NA	NA
C _{max} (ng/mL)	2490	NA	NA	NA
t _{max} (hr)	4.00	NA	NA	NA
Females				
PND 7				
AUC _{0-24h} (hr*ng/mL)	38500	163000	363000	553000
C _{max} (ng/mL)	2220	8550	19400	28400
t _{max} (hr)	4.00	12.0	4.00	12.0
PND 35				
AUC _{0-24h} (hr*ng/mL)	35000	NA	NA	NA
C _{max} (ng/mL)	3460	NA	NA	NA
t _{max} (hr)	4.00	NA	NA	NA
Combined				
PND 7				
AUC _{0-24h} (hr*ng/mL)	37100	162000	372000	548000
C _{max} (ng/mL)	2550	8530	21000	28000
t _{max} (hr)	4.00	4.00	4.00	8.00
PND 35				
AUC _{0-24h} (hr*ng/mL)	27800	NA	NA	NA
C _{max} (ng/mL)	2970	NA	NA	NA
t _{max} (hr)	4.00	NA	NA	NA

NA = Not applicable.

(Excerpted from the Sponsor's submission)

Serum C_{max} and AUC values of the metabolites VRT-0996107 (M1-661) and VRT-1189001 (M2-661) generally increased in a less than dose proportional manner from 10 to 100 mg/kg/day on PND 7. Systemic formation of VRT-0996107 and VRT-1189001 tended to be higher in juvenile male rats following multiple administrations. At 10 mg/kg, AUC values for VRT-0996107 on PND 7 and PND 35 were approximately 55% and 100% of VX-661, respectively. At 10 mg/kg, AUC values for VRT-1189001 on PND 7 and PND 35 were approximately 10% and 7.5% (male: 12%; female 3%) of VX-661, respectively.

Table 15 Toxicokinetic Parameters of VRT-0996107 and VRT-1189001 in rats on PND 7 and 35

Text Table 20

VRT-0996107 Toxicokinetic Parameters on PND 7 and 35 following Oral Gavage Administration of 10, 30, 60, and 100 mg/kg/day to Juvenile Male and Female Rats

VX-661 Dose (mg/kg/day)	10	30	60	100
Males				
PND 7				
AUC _{0-24h} (hr*ng/mL)	18900	46100	75200	94800
C _{max} (ng/mL)	1220	2780	4580	6640
t _{max} (hr)	24.0	24.0	24.0	24.0
PND 35				
AUC _{0-24h} (hr*ng/mL)	33900	NA	NA	NA
C _{max} (ng/mL)	2090	NA	NA	NA
t _{max} (hr)	8.00	NA	NA	NA
Females				
PND 7				
AUC _{0-24h} (hr*ng/mL)	21900	47800	76500	91800
C _{max} (ng/mL)	1210	2850	4750	6010
t _{max} (hr)	24.0	24.0	24.0	24.0
PND 35				
AUC _{0-24h} (hr*ng/mL)	24900	NA	NA	NA
C _{max} (ng/mL)	1430	NA	NA	NA
t _{max} (hr)	4.00	NA	NA	NA
Combined				
PND 7				
AUC _{0-24h} (hr*ng/mL)	20400	46900	75800	93300
C _{max} (ng/mL)	1210	2820	4670	6330
t _{max} (hr)	24.0	24.0	24.0	24.0
PND 35				
AUC _{0-24h} (hr*ng/mL)	29400	NA	NA	NA
C _{max} (ng/mL)	1690	NA	NA	NA
t _{max} (hr)	8.00	NA	NA	NA

NA = Not applicable.

(Excerpted from the Sponsor's submission)

Text Table 21

VRT-1189001 | Toxicokinetic Parameters on PND 7 and 35 following Oral Gavage Administration of 10, 30, 60, and 100 mg/kg/day to Juvenile Male and Female Rats

VX-661 Dose (mg/kg/day)	10	30	60	100
Males				
PND 7				
AUC _{0-24h} (hr*ng/mL)	3300	5970	6480	6640
C _{max} (ng/mL)	324	531	535	625
t _{max} (hr)	24.0	24.0	24.0	24.0
PND 35				
AUC _{0-24h} (hr*ng/mL)	2490	NA	NA	NA
C _{max} (ng/mL)	138	NA	NA	NA
t _{max} (hr)	12.0	NA	NA	NA
Females				
PND 7				
AUC _{0-24h} (hr*ng/mL)	4120	5220	6770	7140
C _{max} (ng/mL)	343	479	630	716
t _{max} (hr)	24.0	24.0	24.0	24.0
PND 35				
AUC _{0-24h} (hr*ng/mL)	1170	NA	NA	NA
C _{max} (ng/mL)	66.5	NA	NA	NA
t _{max} (hr)	12.0	NA	NA	NA
Combined				
PND 7				
AUC _{0-24h} (hr*ng/mL)	3710	5600	6620	6890
C _{max} (ng/mL)	334	505	583	670
t _{max} (hr)	24.0	24.0	24.0	24.0
PND 35				
AUC _{0-24h} (hr*ng/mL)	1830	NA	NA	NA
C _{max} (ng/mL)	102	NA	NA	NA
t _{max} (hr)	12.0	NA	NA	NA

NA = Not applicable.

(Excerpted from the Sponsor's submission)

9.4.3 Study Title: VX-661: An Oral (Gavage) Pharmacokinetic and Toxicity Study in Juvenile Sprague Dawley Rats (Study report #: VX-661-TX-065)

Study no.: VX-661-TX-065

Study report location: NDA212273-S001-SD1-M42354

Conducting laboratory and location:

(b) (4)

Duration: VX-661 was administered for three days from PND 7–9, 14–16, 21–23, or 35–37 (Groups 7, 8, 9, and 10, respectively).

Duration Units: Day

GLP compliance: Y

Drug, lot #, and % purity: VX-661, 19QB10A-50.NJ00001, and 98.0%

Key Findings:

- In a juvenile TK study, female rats received TEZ at oral doses of 0 [0.5% methylcellulose (400 cP), 0.5% sodium lauryl sulfate, 0.01% simethicone] or 30 mg/kg/day for 3 days from PND 7–9, PND 14–16, PND 21–23, or PND 35–37. Additionally, female rats received TEZ at oral doses of 0 [0.5% methylcellulose (400 cP), 0.5% sodium lauryl sulfate, 0.01% simethicone] or 60 mg/kg/day for 3 days during PND 7–9.
- No treatment-related deaths or adverse clinical signs were observed in female rats during the TK study.
- In the TK study, systemic exposure to TEZ, M1-TEZ, and M2-TEZ were higher (2-3 fold) in juvenile female rats on PND 9 and PND 16 as compared to PND 23 and 37. M1-TEZ plasma levels were approximately 36% to 100% of the parent TEZ levels, while M2-TEZ plasma levels were approximately 2% to 10% of the parent TEZ levels.
- Brain exposures to TEZ, M1-TEZ, and M2-TEZ were higher (18-24 fold) in juvenile female rats on PND 9 and PND 16 as compared to PND 23 and PND 37. M1-TEZ brain tissue levels were approximately 385% to 1190% of the parent TEZ levels, while M2-TEZ brain tissue levels were approximately 36% to 73% of the parent TEZ levels.
- Higher brain levels of TEZ and its two metabolites in younger rats (dosed from PND 7-9 or PND 14-16) might explain the observed toxicity of TEZ in juvenile rats from Study #VX-661-TX-037 with initiation of dosing on PND 7 that included clonic convulsions and other CNS-related clinical observations.

Methods

Doses:	TK: 0 and 30 mg/kg/day Toxicology study: 0 and 60 mg/kg/day
Frequency of dosing:	Daily
Number/Sex/Group:	Toxicology: 10 females /group TK: 5 females for control, and 20 females for 30 mg/kg/day VX-661 treated groups
Dose volume:	10 mL/kg
Formulation/Vehicle:	60 mg/kg/day (6 mg/mL), 30 mg/kg/day (3 mg/mL)/0.5% methylcellulose (400 cP), Vehicle = 0.5% sodium lauryl sulfate, 0.01% simethicone in deionized water
Route of administration:	ORAL GAVAGE
Species:	Rats
Strain:	Sprague Dawley Crl:CD(SD)
Age at start of experiment:	Postnatal day 7

Period of development studied: Postnatal Day (PND) 7 through PND 10
Comment on Study Design and Conduct: The objective of this study was to determine the toxicokinetic profile of TEZ and its metabolites in both plasma and brain following oral administration of TEZ to female Sprague-Dawley rats dosed at 30 mg/kg/day during PND 7–9, PND 14–16, PND 21–23, or PND 35–37.

The toxicokinetic profile of TEZ and its metabolites in both plasma and brain were evaluated following oral administration of TEZ to female juvenile Sprague-Dawley rats dosed at 30 mg/kg/day for 3 days from PND 7–9, PND 14–16, PND 21–23, or PND 35–37.

Dose levels were selected based on the results of a previously conducted GLP dose range-finding study in juvenile male and female rats at 10, 30, 60, and 100 mg/kg/day from PND 7–35 (#VX-661-TX-037). In the DRF study, drug-related mortality and clonic convulsions were observed at doses of 30, 60, and 100 mg/kg/day.

Parameters and Key Endpoints Evaluated: For the main study animals, clinical signs, body weights, food consumption, clinical pathology (hematology and serum chemistry), toxicokinetic parameters, gross necropsy findings, organ weights, and histopathology were evaluated.

For the TK study animals, the toxicokinetic profile of TEZ and its metabolites in both plasma and brain were evaluated.

Dosing Solution Analysis: The results were within the specified range (85% to 115%).

Study Design

Text Table 3
Study Group Assignments

Group Number	Treatment	Dosing Duration	Dose Level (mg/kg/day)	Dose Volume (mL/kg)	Number of Animals	
					Main Study Phase	Toxicokinetic Phase
1	Control Article	PND 7–10	0	10	10	NA
2	Control Article	PND 7–9	0	10	NA	5
3	Control Article	PND 14–16	0	10	NA	5
4	Control Article	PND 21–23	0	10	NA	5
5	Control Article	PND 35–37	0	10	NA	5
6	VX-661	PND 7–10	60	10	10	NA
7	VX-661	PND 7–9	30	10	NA	20
8	VX-661	PND 14–16	30	10	NA	20
9	VX-661	PND 21–23	30	10	NA	20
10	VX-661	PND 35–37	30	10	NA	20

NA = Not applicable.

(Excerpted from the Sponsor's submission)

Observations and Results**Mortality:** Animals were checked twice daily for mortality and signs of morbidity.

There were no treatment-related deaths.

Clinical Signs: Animals were examined daily for clinical signs.

There were no treatment-related clinical signs.

Body Weight: Animals were weighed individually daily from PND 7 through PND 11.Statistically significant ($p < 0.05$ or $p < 0.01$) decreases (up to 23.0%) of mean absolute body weights were observed in females in drug-treated group compared to the control group on PND 11. Body weight gain was reduced by 72.4%.**Table 16 Changes of Body Weight in Female Rats from PND 7 to PND 11**

Body weight	Females, mg/kg/day	
Parameter	0	60
BW, PND 7	16.7	16.6
BW, PND 8	18.5	18.7
BW, PND 9	20.4	19.8
BW, PND 10	22.5	20.8
BW, PND 11	24.3	18.7*
Δ BW	7.6	2.1*
Absolute BW % of control	100.0	80.0

BW Gain % of control	100.0	27.6
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Hematology: Hematology and Coagulation parameters were determined on PND11.

Increased red blood cell count, increased hemoglobin concentration, and increased hematocrit (up to 1.21X), decreased mean reticulocyte counts (0.70X), decreased mean white blood cell count, and decreased mean lymphocyte count (0.59X) were observed in drug-treated females at 60 mg/kg. These changes were considered due to dehydration or stress.

Clinical Chemistry: Clinical chemistry parameters were determined on PND 11.

Statistically significant ($p < 0.05$ or $p < 0.01$) decreases in mean phosphorus (0.80X), potassium (0.78X), and triglycerides (0.08X) concentration and increases in glucose (1.31X) concentration were observed in drug-treated females at 60 mg/kg.

Gross Pathology: A complete necropsy was conducted on all main study animals at the scheduled termination by carbon dioxide inhalation on PND 11. Each animal was weighed and subsequently exsanguinated. Main study animals were subjected to a complete necropsy examination, which included examination of the external surface, all orifices, the cranial cavity, the external surfaces of the brain and spinal cord, and the thoracic, abdominal, and pelvic cavities, including viscera. Gross lesions were examined from all animals in all groups.

There were no treatment-related gross pathological changes.

Organ Weights: The organs identified in Table 17 were weighed at necropsy for all scheduled euthanasia animals.

Statistically significant ($p < 0.05$ or $p < 0.01$) decreases of mean absolute and relative (to body and brain weight) spleen weights (approximately -29% to -47%) were observed for drug-treated females at 60 mg/kg. Microscopic examination of the spleen was not performed per protocol.

Table 17 Organ weighed

Text Table 7
Organs Weighed at Necropsy

Brain	Liver
Heart	Spleen
Kidneys	Thymus

(Excerpted from the Sponsor's submission)

Histopathology:

Adequate Battery: No. Examination was confined to the nasal cavities and nasopharynx; this was not a pivotal study as treatment was limited to PNDs 7 to 10 for rats in the control and 60 mg/kg/day groups. Microscopic examination of routinely prepared hematoxylin-eosin stained paraffin sections was performed on the nasal cavities and nasopharynx collected at necropsy from all animals in the control and 60 mg/kg/day groups and from all animals dying spontaneously. Microscopic examination of the 4 standard nasal cavity sections in this study included examination of the following primary nasal cavity structures: nasoturbinates, maxilloturbinates, ethmoturbinates, nasal meatuses, maxillary sinus, vomeronasal organ, nasopharyngeal duct, and nasal septum; and the following nasal epithelial types: squamous, transitional, respiratory, and olfactory.

Table 18 Tissue collection listText Table 6
Tissue Collection

Adrenal glands (2)	Lymph nodes
Animal Identification	Mandibular (2)
Aorta	Mesenteric
Bone with marrow (femur and sternum)	Nasal cavity (4 levels) ^d
Bone marrow smear (femur) ^a	Nasopharynx
Brain ^b	Ovaries with oviducts (2)
Cervix	Pancreas
Eyes with optic nerve (2) ^c	Peripheral nerve (sciatic)
Gastrointestinal tract	Pituitary
Esophagus	Salivary glands [mandibular (2)]
Stomach	Skeletal muscle (rectus femoris)
Duodenum	Skin (with mammary gland)
Jejunum	Spinal cord (cervical, thoracic, lumbar)
Ileum	Spleen
Cecum	Thymus
Colon	Thyroid with parathyroids (2)]
Rectum	Tongue
Gut-associated lymphoid tissue	Trachea
Heart	Urinary bladder
Kidneys (2)	Uterus
Liver (sections of 2 lobes)	Vagina
Lungs	Gross lesions (when possible)

^a Bone marrow slides were not placed in formalin; slides were not examined.

^b Histologic trimming of the brain was performed per Experimental Pathology Laboratories, Inc. SOP such that 7 cross (coronal) sections of the brain were taken.

^c Fixed in Davidson's solution.

^d Sectioning of the nasal cavity was in accordance with the method of Young.⁴

(Excerpted from the Sponsor's submission)

Peer Review: The histopathology peer review was performed by Kathryn E. Bowenkamp, DVM, PhD, DACVP, Vertex Pharmaceuticals Incorporated.

Minimal or mild exudate accumulation in the nasal cavity and nasopharynx were observed in both control and drug-treated groups.

In animals administered the vehicle, minimal or mild exudate accumulation in 1 or more levels of the nasal cavity was present in 2 of 10 animals examined. In vehicle control group Animal Number 7352-05 (found dead on Postnatal Day 11), exudate in Levels II-IV of the nasal cavity was considered sufficient to result in the death of this animal (gavage-related reflux). Vehicle control group Animal Number 7349-09 had mild exudate accumulation in Level II of the nasal cavity, but survived until scheduled euthanasia.

In animals administered VX-661, exudate in the lumina of 1 or more levels of the nasal cavity or nasopharynx was noted in 5 of 10 animals. These included Animal Numbers 7352-04 (minimal luminal exudate, nasopharynx), 7347-09 (minimal luminal exudate, Nasal Levels II and IV), 7345-10 (severe luminal exudate, Nasal Level IV), 7377-09 (minimal luminal exudate, Nasal Level II), and 7346-09 (minimal luminal exudate, Nasal Levels I and II). All survived until scheduled euthanasia.

Table 19 Histopathology findings

Text Table 12
Incidence of Microscopic Findings - Scheduled Necropsy

	Females	
	1	6
	0	60
	9	10
Nasal Level I (Number Examined)	9	10
Exudate, lumen	(0) ^a	(1)
Minimal	0	1
Nasal Level II (Number Examined)	9	10
Exudate, lumen	(0)	(3)
Minimal	0	3
Nasal Level III (Number Examined)	9	10
Exudate, lumen	(1)	(0)
Minimal	0	0
Mild	1	0
Nasal Level IV (Number Examined)	9	10
Exudate, lumen	(0)	(2)
Minimal	0	1
Moderate	0	1
Nasopharynx (Number Examined)	8	9
Exudate, lumen	(0)	(1)
Minimal	0	1

^a Numbers in parentheses represent the number of animals with the finding.

(Excerpted from the Sponsor's submission)

Toxicokinetics: Blood samples for measurement of serum TEZ (VX-661), VRT-0996107 (M1-661), and VRT-1189001 (M2-661) concentrations were collected from each animal. Samples (for serum concentrations) were collected predose, 2-hour, 4-hour, 8-hour, and 24-hour postdosing on PND 9, 16, 23, and 37. Serum samples were

stored frozen at -65°C to -85°C. Serum concentrations of VX-661 were analyzed at (b) (4) using an LC-MS/MS assay with detection limits between 25.0 to 25000 ng/mL.

Following blood collection, all VX-661-treated animals were perfused with phosphate buffered saline (PBS) to remove all blood. The brain was removed, rinsed in PBS, and transferred into sample tubes. Brain samples were maintained at room temperature prior to being weighed and stored at -65°C to -85°C until shipped for analysis. Brain samples were shipped on dry ice to (b) (4) for analysis. An LC-MS/MS method was used for the determination of TEZ, M1-TEZ, and M2-TEZ in rat brain tissue. Detection ranges for TEZ, M1-TEZ, and M2-TEZ were 25.0 to 5000 ng/g.

Systemic exposure to TEZ, M1-661, and M2-661 tended to be lower in juvenile female rats on PND 23 and 37 compared to PND 9 and 16 following 3 days of repeated administration of VX-661 at a dose of 30 mg/kg/day. M1-661 plasma levels were approximately 36% to 100% of the parent TEZ levels, while M2-661 plasma levels were approximately 2% to 10% of the parent TEZ levels.

Brain exposures to TEZ, M1-661, and M2-661 were higher in juvenile female rats on PND 9 and 16 as compared to PND 23 and 37 following 3 days of repeated administration of TEZ at a dose of 30 mg/kg/day. M1-661 brain tissue levels were approximately 385% to 1190% of the parent TEZ levels, while M2-661 brain tissue levels were approximately 36% to 73% of the parent TEZ levels. High brain levels of TEZ and both metabolites in younger rats (dosed from PND 7-9 and PND 14-16) might explain the observed toxicity of TEZ in the juvenile rat DRF study (VX-661-TX-037) with initiation of dosing on PND 7 that included clonic convulsions and other CNS-related clinical observations.

Brain AUC_{0-24h} comparison ratios of TEZ for PND 16, 23, or 37 relative to PND 9 were 1.04, 0.132, and 0.0563, respectively. Brain to Plasma AUC_{0-24h} ratios of TEZ were 0.595, 0.556, 0.256, and 0.0584 for PND 9, 16, 23, and 37 in juvenile female rats, respectively.

Brain AUC_{0-24h} comparison ratios of M1-661 for PND 16, 23, or 37 relative to PND 9 were 2.22, 0.407, and 0.0908, respectively. Brain to Plasma AUC_{0-24h} ratios of M1-661 were 4.84, 9.15, 2.83, and 0.753 for PND 9, 16, 23, and 37 in juvenile female rats, respectively. M1-661: TEZ brain AUC_{0-24h} and brain C_{max} ratios in juvenile female rats ranged from 3.73 to 11.9.

Brain AUC_{0-24h} ratios of M2-661 for PND 16, 23, or 37 relative to PND 9 were 0.937, 0.237, and 0.0636, respectively. Brain to Plasma AUC_{0-24h} ratios of M2-661 were 2.89, 3.81, 1.93, and 0.957 for PND 9, 16, 23, and 37, respectively. M2-661: TEZ brain AUC_{0-24h} and brain C_{max} ratios in juvenile female rats ranged from 0.359 to 0.725.

Table 20 Toxicokinetic Parameters of TEZ, M1-661, and M2-661 in plasma in rats on PND 9, 16, 23, and 37

Text Table 13

VX-661, VRT-0996107, and VRT-1189001 Mean TK Parameters on PND 9, 16, 23, and 37 Following Oral Gavage Administration of 30 mg/kg/day VX-661 to Female Juvenile Sprague-Dawley Rats

Analyte	Group	PND	t _{max} (hr)	C _{max} (ng/g)	AUC _{0-24h} (hr*ng/g)
VX-661	7	9	4.00	13,000	232,000
	8	16	4.00	16,100	259,000
	9	23	4.00	6270	71,100
	10	37	2.00	9310	133,000
VRT-0996107	7	9	8.00	5140	110,000
	8	16	8.00	5760	129,000
	9	23	8.00	4100	76,700
	10	37	4.00	3550	64,300
VRT-1189001	7	9	24.0	1160	19,300
	8	16	24.0	800	13,700
	9	23	8.00	329	6850
	10	37	8.00	172	3700

PND = Postnatal Day

(Excerpted from the Sponsor's submission)

Table 21 Toxicokinetic Parameters of TEZ, M1-661, and M2-661 in brain tissues in rats on PND 9, 16, 23, and 37

Text Table 14

VX-661, VRT-0996107, and VRT-1189001 Mean TK Parameters in Brain Tissues on PND 9, 16, 23, and 37 Following Oral Gavage Administration of 30 mg/kg/day VX-661 to Female Juvenile Sprague-Dawley Rats

Analyte	Group	PND	t _{max} (hr)	C _{max} (ng/g)	AUC _{0-24h} (hr*ng/g)
VX-661	7	9	8.00	7130	138,000
	8	16	8.00	7900	144,000
	9	23	24.00	845	18,200
	10	37	8.00	428	7770
VRT-0996107	7	9	24.00	26,600	532,000
	8	16	24.00	54,900	1,180,000
	9	23	24.00	10,100	217,000
	10	37	8.00	2390	48,400
VRT-1189001	7	9	24.0	3570	55,700
	8	16	24.0	2840	52,200
	9	23	8.00	590	13,200
	10	37	8.00	176	3540

PND = Postnatal Day

(Excerpted from the Sponsor's submission)

Table 22 Plasma and Brain levels of TEZ and M1-TEZ Comparison in Rats during PND 7-9, 14-16, 21-23, and 35-37

Table 22 TEZ Plasma and Brain Levels Following 3 Days of Dosing With 30 mg/kg/day TEZ

Dosing Period	Analyte	PK After 3 Days of Dosing		
		Mean Plasma AUC _{0-24h} (µg·h/mL)	Mean Brain AUC _{0-24h} (µg·h/mL)	Brain:Fold over PND 35-37
PND 7-9	TEZ	232	138	17.7
PND 14-16	TEZ	259	144	18.5
PND 21-23	TEZ	71.1	18.2	2.3
PND 35-37	TEZ	133	7.8	-

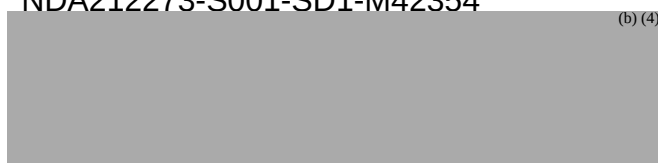
Table 23 M1-661 Plasma and Brain Levels Following 3 Days of Dosing With 30 mg/kg/day TEZ

Dosing Period	Analyte	PK After 3 Days of Dosing		
		Mean Plasma AUC _{0-24h} (µg·h/mL)	Mean Brain AUC _{0-24h} (µg·h/mL)	Brain:Fold over PND 35-37
PND 7-9	M1-661	110	532	11.0
PND 14-16	M1-661	129	1180	24.4
PND 21-23	M1-661	76.7	217	4.5
PND 35-37	M1-661	64.3	48.4	-

(Excerpted from the Sponsor's submission)

9.4.4 Study Title: VX-661: VX-661: An Oral (Gavage) Dose Range-Finding Study from Postnatal Day (PND) 14 or 21 to PND 35 in Juvenile Sprague Dawley Rats (Study report #: VX-661-TX-069)

Study no.: VX-661-TX-069
Study report location: NDA212273-S001-SD1-M42354
Conducting laboratory and location:



Duration: 21 (PND 14-35) or 14 (PND 21-35)
Duration Units: Day
GLP compliance: Y
Drug, lot #, and % purity: VX-661, 19QB10A-50.NJ00001, and 98.0%

Key Findings:

- In a juvenile toxicology study, rats received VX-661 at oral doses of 0 [0.5% methylcellulose (400 cP), 0.5% sodium lauryl sulfate, 0.01% simethicone], 20, or 30 mg/kg/day from PND 14-35 or 0, 30, 60, or 100 mg/kg/day from PND 21-35.

- VX-661 was not tolerated in the 100 mg/kg/day group (Started on PND 21) as mortality was observed for both sexes (1 main study male, 1 TK male, and 1 main study female) on PNDs 25-30. All remaining animals in the 100 mg/kg/day group were euthanized on PNDs 26–30 due to test-article related lower mean body weights (up to 51.5%). Probable causes of death could not be determined based on anatomic pathology findings. Five of 9 males and 6 of 9 females in the HD group had increased K⁺ levels (2.6- and 1.5x the UL of respective control ranges).
- One male and one female in the 100 mg/kg/day group each had a single episode of clonic convulsion approximately 4 hours postdosing on PND 27.
- Statistically significant decreases of mean body weights were observed in both males and females in the 60 mg/kg/day (12.5% and 13%, respectively) and 100 mg/kg/day (51.2% and 32.5%, respectively) compared to the control group during the entire dosing period (PND 21–35). Body weight gains for males and females in the 60 mg/kg/day group were decreased by 18.3% and 19.5% relative to controls, respectively.
- No treatment-related adverse histopathology findings were identified.
- The NOAELs of VX-661 were identified as 30 mg/kg/day (AUC₀₋₂₄, 90.3 h•µg/mL) in juvenile rats from PND 14-35 and 30 mg/kg/day (AUC₀₋₂₄, 91.7 h•µg/mL) from PND 21-35 due to mortality and decreased body weight. The AUC₀₋₂₄ of metabolites M1-661 and M2-661 were 68.0 h•µg/mL and 4.56 h•µg/mL, respectively, in juvenile rats from PND 14-35. The AUC₀₋₂₄ of metabolites M1-661 and M2-661 were 79.1 h•µg/mL and 5.16 h•µg/mL, respectively, in juvenile rats from PND 21-35.

Methods

Doses:	PND 14-35: 0, 20, or 30 mg/kg/day; PND 21-35: 0, 30, 60, or 100 mg/kg/day
Frequency of dosing:	Daily
Number/Sex/Group:	Main: 10/sex/group TK: 0/sex for control, and 36/sex for VX-661 treated groups
Dose volume:	10 mL/kg
Formulation/Vehicle:	2 mg/mL for 20 mg/kg, 3 mg/mL for 30 mg/kg, 6 mg/mL for 60 mg/kg, and 10 mg/mL for 100 mg/kg group /Vehicle = 0.5% methylcellulose (400 cP), 0.5% sodium lauryl sulfate, 0.01% simethicone in deionized water
Route of administration:	ORAL GAVAGE
Species:	Rats
Strain:	Sprague Dawley Crl:CD(SD)
Age at start of experiment:	PND 14 or 21

Period of development studied: PND 14-35 or PND 21-35
 Comment on Study Design and Conduct: None
 Parameters and Key Endpoints Evaluated: Clinical signs, body weights, clinical pathology (hematology, coagulation, and serum chemistry), toxicokinetic parameters, gross necropsy findings, organ weights, and histopathology
 Dosing Solution Analysis: The results were within the specified range (85% to 115%).

Study Design:

Text Table 3
 Experimental Design – Main Study

Group Number	Treatment	Dosing Duration	Dose Level ^a (mg/kg/day)	Concentration (mg/mL)	Dose Volume (mL/kg)	Number of Animals/Sex
1	Vehicle Control ^b	PND 14–35	0	0	10	10
2	Vehicle Control ^b	PND 21–35	0	0	10	10
3	VX-661	PND 21–35	30	3	10	10
4	VX-661	PND 21–35	60	6	10	10
5	VX-661	PND 21–35	100	10	10	10
6	VX-661	PND 14–35	20	2	10	10
7	VX-661	PND 14–35	30	3	10	10

^a A correction factor of 2.0 was used for VX-661 formulation.

^b Control article, hypromellose acetate succinate, was added to the vehicle at approximately the highest concentration within the VX-661 test article groups, 10 mg/mL.

Text Table 4
 Experimental Design – Toxicokinetic Phase

Group Number	Treatment	Dosing Duration	Dose Level ^a (mg/kg/day)	Concentration (mg/mL)	Dose Volume (mL/kg)	Number of Animals/Sex
1	Vehicle Control ^b	PND 14–35	0	0	10	0
2	Vehicle Control ^b	PND 21–35	0	0	10	0
3	VX-661	PND 21–35	30	3	10	36
4	VX-661	PND 21–35	60	6	10	36
5	VX-661	PND 21–35	100	10	10	36
6	VX-661	PND 14–35	20	2	10	36
7	VX-661	PND 14–35	30	3	10	36

^a A correction factor of 2.0 was used for VX-661 formulation.

^b Control article, hypromellose acetate succinate, was added to the vehicle at approximately the highest concentration within the VX-661 test article groups, 10 mg/mL.

Observations and Results

Mortality: Animals were checked twice daily for mortality and signs of morbidity.

PND 14-35 study: there were no treatment-related deaths with doses of 20 or 30 mg/kg/day.

PND 21-35 study: mortality was observed in the HD group (100 mg/kg/day) for both sexes (1 main study male, 1 TK male, and 1 main study female) on PNDs 25-30. All remaining animals in the HD group were euthanized on PNDs 26–30 due to test-article related lower mean body weights (up to 51.5%) compared to controls. Probable causes of death could not be determined based on anatomic pathology findings.

5 of 9 males and 6 of 9 females in the HD group had increased K⁺ levels (2.6x and 1.5x the UL of respective control ranges, respectively).

Microscopic findings in the HD group (100 mg/kg/day) of lymphoid depletion in spleen and thymus and bone marrow cellular depletion (sternum and femur) with serous atrophy of fat were consistent with stress and/or loss of body condition.

Clinical Signs: Animals were examined daily for clinical signs.

PND 21-35 study: one HD male (8166-03) and 1 HD female (8160-08) each had a single episode of clonic convulsion approximately 4 hours postdosing on PND 27.

Body Weight: Animals were weighed individually daily.

PND 14-35 study: With doses of 20 or 30 mg/kg/day, there were no treatment-related changes of body weight on PND 35.

PND 21-35 study: statistically significant ($p < 0.05$ or $p < 0.01$) decreases of mean body weights were observed in both males and females in the MD of 60 mg/kg/day (11.5% and 13%, respectively) and HD of 100 mg/kg/day (51.2% and 32.5%, respectively) compared to the control group during the entire dosing period (PND 21–35). Body weight gains for males and females in the MD group were 81.7 and 80.5% of control, respectively.

Table 23 Changes of Body Weight in Rats from PND 21 to PND 35

Body weight	Males, mg/kg/day				Females, mg/kg/day			
Parameter	0	30	60	100	0	30	60	100
BW, PND 21	56.9	57.6	57.4	57.0	52.5	52.4	51.2	51.5
BW, PND 30	116.9	113.1	98.6	57.1	101.8	99.3	84.8	68.7
BW, PND 35	160.9	156.9	142.4	-	136.6	135.9	118.9	-
Abs. BW % of control	100.0	97.5	88.5	48.8	100.0	99.5	87.0	67.5
Δ BW 30-21	60.0	55.5	41.2	0.1	49.3	46.9	33.6	17.2
Δ BW 35-21	104.0	99.3	85.0		84.1	83.5	67.7	
BW Gain % of control	100.0	95.5	81.7	-	100.0	99.2	80.5	-

-Further evaluation of body weight data at 100 mg/kg/day was precluded by early group termination.

Hematology: Hematology and Coagulation parameters were determined on PND 36.

Changes of hematology parameters (e.g., RBC count, HGB concentration, and HCT) were generally small (<10%) on PND 35.

There were no treatment-related changes of the coagulation parameters.

Clinical Chemistry: Clinical chemistry parameters were determined on PND 36.

There were no treatment-related changes of the clinical chemistry parameters in surviving animals.

Gross Pathology: A complete necropsy was conducted on all animals that were found dead, euthanized due to early group termination, or at the scheduled termination by carbon dioxide inhalation on PND 36. Each animal was weighed and subsequently exsanguinated. Main study animals were subjected to a complete necropsy examination, which included examination of the external surface, all orifices, the cranial cavity, the external surfaces of the brain and spinal cord, and the thoracic, abdominal, and pelvic cavities, including viscera. Gross lesions were examined from all animals in all groups.

There were no treatment-related gross pathological findings in surviving animals.

Organ Weights: The organs identified in Table 1 were weighed at necropsy for all scheduled euthanasia animals.

There were no treatment-related changes of organ weights in surviving animals.

Table 24 Organ weighed

Text Table 12
Organs Weighed at Necropsy

Adrenal glands	Pituitary
Brain	Prostate
Epididymides	Seminal vesicles with coagulating glands
Heart	Spleen
Kidneys	Testes
Liver	Thymus
Lung	Thyroid glands (with parathyroids, if present) ^a
Ovaries and oviducts	Uterus (with cervix)

^a Weighed after fixation.

(Excerpted from the Sponsor's submission)

Histopathology:

Adequate Battery: An adequate battery of organs and tissues was submitted to histopathological examination. Organs or parts of organs of all animals were fixed in 10% neutral buffered formalin, dehydrated and embedded in paraffin wax and sectioned at approximately 4-6 µm thickness and stained with hematoxylin and eosin (H&E).

Tissues identified in Table 2 for microscopic examination were evaluated from all animals in the control and high-dose groups (i.e., Control 1 (PND 14-35), Control 2 (PND 21-35), 60 mg/kg/day, 100 mg/kg/day, and 30 mg/kg/day) and from all animals found dead and euthanized in extremis. In addition, tissues were examined from all animals in the 60 mg/kg/day group as the 100 mg/kg/day group was terminated early and the 60 mg/kg/day became the high-dose group.

Table 25 Tissue collection list

Text Table 13
Tissue Collection and Preservation

Adrenal glands (2)	Nasal cavities (4 levels) ^f
Aorta	Nasopharynx
Bone with marrow (sternebrae and femur)	Optic nerve ^c
Bone marrow smear (from femur) ^a	Ovaries with oviducts (2)
Brain	Pancreas
Epididymides (2) ^b	Peripheral nerve (sciatic)
Eyes (2) ^c	Pituitary
Gastrointestinal tract	Prostate
Esophagus	Salivary glands [mandibular (2)]
Stomach	Seminal vesicles (2)
Duodenum	Skeletal muscle (rectus femoris)
Jejunum	Skin
Ileum	Spinal cord (cervical, thoracic, and lumbar)
Cecum	Spleen
Colon	Testes (2) ^d
Rectum ^d	Vas deferens
Gut-associated lymphoid tissue	Thymus
Heart	Tongue
Kidneys (2)	Thyroid (with parathyroids, if present [2])
Liver (sections of 2 lobes)	Trachea
Lungs	Urinary bladder
Lymph nodes (mandibular [2] and mesenteric)	Uterus
Mammary gland (females only) ^e	Vagina
	Gross lesions/masses

^a Bone marrow smears not collected from animals found dead or euthanized in extremis and were not placed in formalin.

^b Fixed in modified Davidson's solution.

^c Fixed in Davidson's solution.

^d Prepared as longitudinal section to include ano-rectal junction.

^e Equivalent region of skin in males.

^f Sectioned in accordance with the method of Young.⁵

(Excerpted from the Sponsor's submission)

Peer Review: The histopathology peer review was performed by Kathryn E. Bowenkamp, DVM, PhD, DACVP, Vertex Pharmaceuticals Incorporated.

There were no treatment-related histopathological findings.

Toxicokinetics: Blood samples for measurement of serum concentrations of VX-661 and human metabolites M1-661 and M2-661 were collected from each animal. Samples (for serum concentrations) were collected on PND70 at predose, 2-hour, 4-hour, 8-hour,

12-hour, and 24-hour postdosing. Serum samples were stored frozen at -70 °C. Serum concentrations of VX-661 were analyzed at (b) (4) using an LC-MS/MS assay with detection limits between 25.0 to 25000 ng/mL.

Following single dose administration on PND 14 or PND 21, serum C_{max} and AUC values of VX-661 in males and females generally increased in a less than dose proportional manner from 20 to 100 mg/kg/day. On PND 35, serum C_{max} and AUC values of VX-661 in males and females generally increased in an approximately dose proportional manner from 20 to 60 mg/kg/day. No sex-related differences were observed for systemic exposures to VX-661. AUC values for VX-661 in males and females were slightly lower (< 0.5-fold) following repeated administration of VX-661 to juvenile rats. VRT-0996107 (M1-661) plasma levels were approximately 20% to 105% of the parent VX-661 levels following single administration of VX-661 while VRT-1189001 (M2-661) plasma levels were approximately 2% to 8% of the parent VX-661 levels.

Table 26 Toxicokinetic Parameters of VX-661 in rats on PND 14, 21, and 35

Text Table 18

VX-661 Mean Toxicokinetic Parameters on PND 14, 21, and 35 Following Oral Administration to Male and Female Juvenile Rats

VX-661 Dose (mg/kg/day)	30 (PND 21–35)	60 (PND 21–35)	100 (PND 21–35)	20 (PND 14–35)	30 (PND 14–35)
Males					
PND 14					
AUC _{0-24h} (hr*µg/mL)	NA	NA	NA	101	180
C _{max} (µg/mL)	NA	NA	NA	7.22	11.7
t _{max} (hr)	NA	NA	NA	2.00	4.00
PND 21					
AUC _{0-24h} (hr*µg/mL)	90.5	215	337	NA	NA
C _{max} (µg/mL)	7.48	16.0	25.2	NA	NA
t _{max} (hr)	4.00	4.00	4.00	NA	NA
PND 35					
AUC _{0-24h} (hr*µg/mL)	78.8	159	NA	48.1	82.8
C _{max} (µg/mL)	8.63	16.8	NA	5.27	8.34
t _{max} (hr)	2.00	2.00	NA	4.00	2.00
Females					
PND 14					
AUC _{0-24h} (hr*µg/mL)	NA	NA	NA	116	192
C _{max} (µg/mL)	NA	NA	NA	7.28	1.26
t _{max} (hr)	NA	NA	NA	2.00	4.00
PND 21					
AUC _{0-24h} (hr*µg/mL)	89.6	191	359	NA	NA
C _{max} (µg/mL)	6.79	15.0	24.7	NA	NA
t _{max} (hr)	4.00	2.00	8.00	NA	NA
PND 35					
AUC _{0-24h} (hr*µg/mL)	105	175	NA	61.5	97.9
C _{max} (µg/mL)	8.99	14.6	NA	5.76	8.02
t _{max} (hr)	4.00	4.00	NA	4.00	4.00
Combined					
PND 14					
AUC _{0-24h} (hr*µg/mL)	NA	NA	NA	109	186
C _{max} (µg/mL)	NA	NA	NA	7.25	12.1
t _{max} (hr)	NA	NA	NA	2.00	4.00
PND 21					
AUC _{0-24h} (hr*µg/mL)	90.1	203	348	NA	NA
C _{max} (µg/mL)	7.14	15.4	24.6	NA	NA
t _{max} (hr)	4.00	4.00	4.00	NA	NA
PND 35					
AUC _{0-24h} (hr*µg/mL)	91.7	167	NA	55	90.3
C _{max} (µg/mL)	8.50	14.7	NA	5.52	8.18
t _{max} (hr)	4.00	4.00	NA	4.00	4.00

NA = Not applicable.

(Excerpted from the Sponsor's submission)

Serum C_{max} and AUC values of the metabolite VRT-0996107 generally increased in an approximately dose proportional manner. Serum C_{max} and AUC values of the metabolite VRT-1189001 generally increased in a less than dose proportional manner from 10 to

100 mg/kg/day on PND 7. Systemic formation of VRT-0996107 and VRT-1189001 tended to be higher in both juvenile male and female rats following repeat dosing (relative to a single dose).

Table 27 Toxicokinetic Parameters of VRT-0996107 and VRT-1189001 in rats on PND 14, 21, and 35

Text Table 19

VRT-0996107 Toxicokinetic Parameters on PND 14, 21, and 35 Following Oral Administration of VX-661 to Male and Female Juvenile Rats

VX-661 Dose (mg/kg/day)	30 (PND 21–35)	60 (PND 21–35)	100 (PND 21–35)	20 (PND 14–35)	30 (PND 14–35)
Males					
PND 14					
AUC _{0-24h} (hr*µg/mL)	NA	NA	NA	36.9	45.0
C _{max} (µg/mL)	NA	NA	NA	1.93	2.60
t _{max} (hr)	NA	NA	NA	24.0	12.0
PND 21					
AUC _{0-24h} (hr*µg/mL)	54.6	88.2	142	NA	NA
C _{max} (µg/mL)	3.14	4.47	9.06	NA	NA
t _{max} (hr)	12.0	12.0	24.0	NA	NA
PND 35					
AUC _{0-24h} (hr*µg/mL)	82.4	152	NA	45.8	74.4
C _{max} (µg/mL)	4.60	8.45	NA	2.37	3.81
t _{max} (hr)	12.0	12.0	NA	8.00	12.0
Females					
PND 14					
AUC _{0-24h} (hr*µg/mL)	NA	NA	NA	39.3	48.1
C _{max} (µg/mL)	NA	NA	NA	2.20	2.55
t _{max} (hr)	NA	NA	NA	24.0	24.0
PND 21					
AUC _{0-24h} (hr*µg/mL)	48.5	89.1	162	NA	NA
C _{max} (µg/mL)	2.61	4.63	9.86	NA	NA
t _{max} (hr)	12.0	12.0	24.0	NA	NA
PND 35					
AUC _{0-24h} (hr*µg/mL)	76.3	127	NA	34.8	61.6
C _{max} (µg/mL)	3.80	6.41	NA	1.68	2.73
t _{max} (hr)	12.0	12.0	NA	4.00	12.0
Combined					
PND 14					
AUC _{0-24h} (hr*µg/mL)	NA	NA	NA	38.1	46.6
C _{max} (µg/mL)	NA	NA	NA	2.08	2.48
t _{max} (hr)	NA	NA	NA	24.0	12.0
PND 21					
AUC _{0-24h} (hr*µg/mL)	51.6	88.6	152	NA	NA
C _{max} (µg/mL)	2.87	4.55	9.46	NA	NA
t _{max} (hr)	12.0	12.0	24.0	NA	NA
PND 35					
AUC _{0-24h} (hr*µg/mL)	79.1	140	NA	40.5	68.0
C _{max} (µg/mL)	4.20	7.43	NA	2.01	3.27
t _{max} (hr)	12.0	12.0	NA	4.00	12.0

NA = Not applicable.

(Excerpted from the Sponsor's submission)

Text Table 20
 VRT-1189001 Toxicokinetic Parameters on PND 14, 21, and 35 Following Oral Administration of VX-661 to Male and Female Juvenile Rats

VX-661 Dose (mg/kg/day)	30 (PND 21–35)	60 (PND 21–35)	100 (PND 21–35)	20 (PND 14–35)	30 (PND 14–35)
Males					
PND 14					
AUC _{0-24h} (hr*µg/mL)	NA	NA	NA	3.43	4.12
C _{max} (µg/mL)	NA	NA	NA	0.301	0.251
t _{max} (hr)	NA	NA	NA	24.0	12.0
PND 21					
AUC _{0-24h} (hr*µg/mL)	4.35	5.01	8.61	NA	NA
C _{max} (µg/mL)	0.288	0.352	0.857	NA	NA
t _{max} (hr)	24.0	24.0	24.0	NA	NA
PND 35					
AUC _{0-24h} (hr*µg/mL)	5.74	12.7	NA	3.99	5.47
C _{max} (µg/mL)	0.296	0.585	NA	0.217	0.307
t _{max} (hr)	8.00	12.0	NA	12.0	4.00
Females					
PND 14					
AUC _{0-24h} (hr*µg/mL)	NA	NA	NA	3.32	3.55
C _{max} (µg/mL)	NA	NA	NA	0.274	0.292
t _{max} (hr)	NA	NA	NA	24.0	24.0
PND 21					
AUC _{0-24h} (hr*µg/mL)	3.38	5.29	7.43	NA	NA
C _{max} (µg/mL)	0.216	0.404	0.702	NA	NA
t _{max} (hr)	24.0	24.0	24.0	NA	NA
PND 35					
AUC _{0-24h} (hr*µg/mL)	4.49	8.42	NA	2.63	3.65
C _{max} (µg/mL)	0.218	0.463	NA	0.131	0.176
t _{max} (hr)	12.0	4.00	NA	12.0	12.0
Combined					
PND 14					
AUC _{0-24h} (hr*µg/mL)	NA	NA	NA	3.37	3.83
C _{max} (µg/mL)	NA	NA	NA	0.288	0.261
t _{max} (hr)	NA	NA	NA	24.0	24.0
PND 21					
AUC _{0-24h} (hr*µg/mL)	3.87	5.15	8.02	NA	NA
C _{max} (µg/mL)	0.252	0.378	0.780	NA	NA
t _{max} (hr)	24.0	24.0	24.0	NA	NA
PND 35					
AUC _{0-24h} (hr*µg/mL)	5.16	10.6	NA	3.33	4.56
C _{max} (µg/mL)	0.252	0.482	NA	0.174	0.216
t _{max} (hr)	8.00	12.0	NA	12.0	12.0

NA = Not applicable.

(Excerpted from the Sponsor's submission)

9.4.5 Study Title: VX-661: An Oral (Gavage) Juvenile Toxicity Study with a Combination Arm of VX-661 and VX-770 from Postnatal Day (PND) 14 to 42

or PND 21 to 49 in Juvenile Sprague Dawley Rats (Study report #: VX-661-TX-038)

Study no.: VX-661-TX-038
Study report location: IND 108105-SD# 539-M42353
Conducting laboratory and location:  (b) (4)

Duration: VX-661 alone during PND 14-42;
VX-661 in combination with VX-770
during PND 21-49.

Duration Units: Day
GLP compliance: Y
Drug, lot #, and % purity: VX-661, 19QB10A-50.NJ00001, and
98.0%;
VX-770, 19QB07A-80.HQ00090, and
99.1%.

Key Findings:

- In a juvenile toxicology study, rats received VX-661 at oral doses of 0 [0.5% methylcellulose (400 cP), 0.5% sodium lauryl sulfate, 0.01% simethicone], 20, and 30 mg/kg/day during PND 14-42. Another set of rats received VX-661 at oral doses of 0, 30, 30 (+10 mg/kg/day IVA), and 60 mg/kg/day during PND 21-49.
- No treatment-related deaths or adverse clinical signs were observed for main and TK study rats.
- Body weight gains were unaffected for male and female juvenile rats treated with doses up to 30 mg/kg/day from PND 14-42. Body weight gain for males at 60 mg/kg/day treated from PND 21-49 was reduced to 89.5% of the control; however, body weight gain for females at 60 mg/kg/day was unaffected.
- Increases of mean ALT (1.25x), AST (1.19x), CK (1.82x), urea nitrogen (1.18x), creatine (1.39x), and phosphorous (1.17x) were observed in males in the HD group (60 mg/kg/day) during the PND 21-49 study. There were no corresponding histopathology findings.
- No adverse histopathological findings were identified in rats.
- Systemic exposure to VX-661 tended to be lower (~38%-78%) in juvenile male and female rats on PND 42, following repeated administration of VX-661, compared to PND 14. The decreases were more pronounced in males comparing to females. No differences of systemic exposure were observed between VX-661 alone and in combination with VX-770. Systemic exposure to VRT-0996107 (M1-661) were

approximately 26% to 127% of the parent VX-661 levels, while exposures to VRT-1189001 (M2-661) were less than 10% of the parent VX-661 levels.

- The NOAELs of VX-661 were identified as 30 mg/kg/day (AUC_{0-24} : 106 h•µg/mL) in juvenile rats from PND 21-49 and 30 mg/kg/day (AUC_{0-24} : 107.8 h•µg/mL) from PND 14-42, respectively. No adverse findings were identified in juvenile rats administered with the combination of 30 mg/kg/day TEZ and 10 mg/kg/day IVA. The AUC_{0-24} of metabolites M1-661 and M2-661 were 47.4 h•µg/mL and 4.35 h•µg/mL, respectively, in juvenile rats from PND 14-42. The AUC_{0-24} of metabolites M1-661 and M2-661 were 51.6 h•µg/mL and 3.87 h•µg/mL, respectively, in juvenile rats from PND 21-35.

Methods

Doses:	PND 14-42 VX-661 alone study: 0, 20 and 30 mg/kg/day PND 21-49 VX-661 in combination with VX-770 study: group 2 (0), group 3 (VX-661 at 30 mg/kg/day), group 4 (VX-661 at 30 mg/kg/day combined with VX-770 at 10 mg/kg/day), and group 5 (VX-661 at 60 mg/kg/day)
Frequency of dosing:	Daily
Number/Sex/Group:	Main: 20 animals/sex/group TK: 27 animals/sex/group
Dose volume:	10 mL/kg
Formulation/Vehicle:	VX-661: 20 mg/kg/day (2 mg/mL), 30 mg/kg/day (3 mg/mL), 60 mg/kg/day (6 mg/mL); VX-770: 10 mg/kg/day (1 mg/mL) /Vehicle = 0.5% methylcellulose (400 cP), 0.5% sodium lauryl sulfate, 0.01% simethicone in deionized water
Route of administration:	ORAL GAVAGE
Species:	Rats
Strain:	Sprague Dawley CrI:CD(SD)
Age at start of experiment:	PND 14 or PND 21
Period of development studied:	PND 14-42 and PND 21-49
Comment on Study Design and Conduct:	None
Parameters and Key Endpoints Evaluated:	For the main study animals, clinical signs, body weights, food consumption, ophthalmology, clinical pathology (hematology, coagulation, and serum chemistry), toxicokinetic parameters, gross

necropsy findings, organ weights, and histopathology were evaluated.

For the TK study animals, the toxicokinetic profiles of TEZ and IVA and their metabolites in plasma were evaluated.

Dosing Solution Analysis: The results were within the specified range (85% to 115%).

Study Design

Text Table 1
Experimental Design

Group Number	Test Article	Dosing Duration	VX-661/VX-770 Dose Level (mg/kg/day)*	VX-661/VX-770 Dose Concentration (mg/mL)*	Dose Volume (mL/kg)	Number of Animals/Sex	
						Main ^b	TK ^b
1	Vehicle Control ^a	PND 14-42	0/-	0/-	10	20	27
2	Vehicle Control ^a	PND 21-49	0/-	0/-	10	20	27
3	VX-661	PND 21-49	30/-	3/-	10	20	27
4	VX-661 and VX-770	PND 21-49	30/10	3/1	10	20	27
5	VX-661	PND 21-49	60/-	6/-	10	20	27
6	VX-661	PND 14-42	20/-	2/-	10	20	27
7	VX-661	PND 14-42	30/-	3/-	10	20	27

Main = Main phase; TK = Toxicokinetic phase.

* A correction factor of 2.0 was used for VX-661 test article formulations. A correction factor of 1.25 was used for VX-770 test article formulations.

^a Control article, hypromellose acetate succinate, was added to the vehicle at approximately the highest concentration within the VX-661 test article groups, at 3 mg/mL for Group 1 and at 6 mg/mL for Group 2.

^b Main phase: at scheduled necropsy; TK phase: PND 14, 21, 42, and 49 collection intervals.

(Excerpted from the Sponsor's submission)

Observations and Results

Mortality: Animals were checked twice daily for mortality and signs of morbidity.

There were no treatment-related deaths.

Clinical Signs: Animals were examined daily for clinical signs.

There were no treatment-related clinical signs.

Body Weight: Animals were weighed individually daily.

PND 14-42: there were no treatment-related changes of body weight or body weight gain with doses up to 30 mg/kg/day following treatment from PND 14-42.

PND 21-49: there were no treatment-related changes of body weight at the end of the study on PND 49. Body weight gain for males at 60 mg/kg/day was reduced to 89.5% of the control. However, bodyweight gain was unaffected for females at 60 mg/kg/day.

Table 28 Changes of Body Weight in Rats from PND 21 to PND 49

Body weight	Males, mg/kg/day				Females, mg/kg/day			
Parameter	0	30 TEZ	30 TEZ + 10 IVA	60 TEZ	0	30 TEZ	30 TEZ + 10 IVA	60 TEZ
BW, PND 21	51.0	51.0	51.5	51.7	50.0	49.8	50.5	50.0
BW, PND 35	162.4	159.7	157.1	143.0	139.1	136.9	139.7	127.5
BW, PND 49	293.0	294.7	290.0	268.4	203.3	202.1	206.4	199.1
Δ BW 35-21	111.4	108.7	105.6	91.3	89.1	87.1	89.2	77.5
Δ BW 49-21	242.0	243.7	238.5	216.7	153.3	152.3	155.9	149.1
Absolute BW % of control	100.0	100.6	99.0	91.6	100.0	99.4	101.5	97.9
BW Gain % of control	100.0	100.7	98.6	89.5	100.0	99.3	101.7	97.2

Feed Consumption: Food consumption was measured twice weekly following weaning from PND 21 until euthanasia.

PND 14-42: Transient decreased food consumption was observed in males and females in the HD group (30 mg/kg/day) between from PND 21-24, corresponding to the decreased body weight gains.

PND 21-49: Decreased food consumption was observed for males in the HD group (60 mg/kg/day) during the dosing period PND 21-49, which corresponded to decreased BW gain. Females in the HD group (60 mg/kg/day) were observed with decreased food consumption from PND 21-38; however, body weight gain was not affected.

Ophthalmoscopy: Ophthalmic examinations were conducted during PND 38-40 for the PND 14-42 dosing group and PND 41-45 for the PND 21-49 dosing group.

There were no treatment-related ophthalmic findings.

Hematology: Hematology and Coagulation parameters were determined on PND 43 (PND 14-42 dosing group) or PND 50 (PND 21-49 dosing group).

There were no treatment-related hematology or coagulation findings.

Clinical Chemistry: Clinical chemistry parameters were determined on PND 43 (PND 14-42 dosing group) or PND 50 (PND 21-49 dosing group).

PND 14-42: There were no treatment-related changes of clinical chemistry parameters with doses up to 30 mg/kg/day.

PND 21-49: Increases of mean ALT (1.25x), AST (1.19x), CK (1.82x), urea nitrogen (1.18x), creatine (1.39x), and phosphorous (1.17x) were observed in males in the HD group (60 mg/kg/day). There were no corresponding histopathology findings.

Gross Pathology: A complete necropsy was conducted on all main study animals at the scheduled termination by carbon dioxide inhalation on PND 43 (PND 14-42 dosing group) or PND 50 (PND 21-49 dosing group). Each animal was weighed and subsequently exsanguinated. Main study animals were subjected to a complete necropsy examination, which included examination of the external surface, all orifices, the cranial cavity, the external surfaces of the brain and spinal cord, and the thoracic, abdominal, and pelvic cavities, including viscera. Gross lesions were examined from all animals in all groups.

There were no treatment-related gross pathological findings.

Organ Weights: The organs identified in Table 28 were weighed at necropsy for all scheduled euthanasia animals.

There were no treatment-related changes of organ weights.

Table 29 Organ weighed

Text Table 12
Organs Weighed at Necropsy

Adrenal glands	Prostate
Brain	Seminal vesicles with coagulating glands (with accessory fluids)
Epididymides (total)	Spleen
Heart	Testes
Kidneys	Thymus
Liver	Thyroids (with parathyroids)
Lungs	Uterus (with cervix)
Ovaries (with oviducts)	
Pituitary	

(Excerpted from the Sponsor's submission)

Histopathology:

Adequate Battery: An adequate battery of organs and tissues was submitted to histopathological examination. Organs or parts of organs of all animals were fixed in 10% neutral buffered formalin, dehydrated and embedded in paraffin wax and sectioned at approximately 4-6 µm thickness and stained with hematoxylin and eosin (H&E). Tissues identified in Table 28 for microscopic examination were evaluated from all animals in the control and HD groups. Findings were assigned one of the following four severity grades: minimal, mild, moderate and severe.

Table 30 Tissue collection list

Text Table 13
Tissue Collection and Preservation

Animal identification^a Artery, aorta Bone marrow smear (femur)^a Bone marrow (femur and sternum) Bone, femur Bone, sternum Brain (7 levels) Cervix Epididymis^{b,g} Esophagus Eye^c Gland, adrenal (2) Gland, mammary^d Gland, pituitary Gland, prostate Gland, salivary (mandibular) Gland, seminal vesicle Gland, thyroid with parathyroid Gross lesions/masses Gut-associated lymphoid tissue Heart Kidney(2) Large intestine, cecum Large intestine, colon	Large intestine, rectum Liver Lung Lymph node, mandibular Lymph node, mesenteric Muscle, skeletal (rectus femoris) Nasal Cavities^e Nasopharynx Nerve, optic Nerve, sciatic Ovary and Oviducts (2) Pancreas Skin Small Intestine, duodenum Small Intestine, ileum Small Intestine, jejunum Spinal cord Spleen Stomach^f Testis^{b,g} Thymus Tongue Trachea Urinary Bladder Uterus Vagina
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^a = Not examined.

^b = Fixed in modified Davidson's solution.

^c = Fixed in Davidson's solution.

^d = For females; the same anatomic area was examined for males.

^e = Sectioning of the nasal cavity was in accordance with the method of Young (1981).⁴

^f = Section of stomach was in 5 sections.

^g = Pair weighed together.

(Excerpted from the Sponsor's submission)

Peer Review: The histopathology peer review was performed by Kathryn E. Bowenkamp, DVM, PhD, DACVP, Vertex Pharmaceuticals Incorporated.

No adverse histopathological findings were identified in rats.

Toxicokinetics: Blood samples for measurement of serum concentrations of VX-661, VRT-0996107 (M1-661), VRT-1189001 (M2-661), and (VX-770), VRT-0837018 (M1), and VRT-0842917 (M6) were collected from each animal. Samples (for serum concentrations) were collected on PND 9, 16, 23, and 37 at predose, 2-hour, 4-hour, 8-hour, and 24-hour postdosing. Serum samples were stored frozen at -65°C to -85°C. Serum concentrations were analyzed at (b) (4) using an LC-MS/MS assay with LLOQ (20.0 ng/mL for VX-661, 5.0 ng/mL for VRT-0996107, and 2.0 ng/mL for VRT-1189001, VX-770, VRT-0837018, and VRT-0842917).

Serum C_{max} and AUC values of VX-661 in males and females generally increased in an approximately dose proportional manner from 20 to 60 mg/kg/day on PND 14 and PND

42 or PND 21 and PND 49. No sex-related differences were observed for systemic exposure to VX-661. Systemic exposure to VX-661 tended to be lower (~38%-78%) in juvenile male and female rats on PND 42 following repeated administration of VX-661 as compared to PND 14. The decreases were more pronounced in males comparing to females. No differences of systemic exposure were observed between VX-661 alone and in combination with VX-770. Systemic exposures to VRT-0996107 (M1-661) were approximately 26% to 127% of the parent VX-661 levels, while exposures to VRT-1189001 (M2-661) were less than 10% of the parent VX-661 levels.

There were no differences in systemic exposure to IVA on PND 21 and 49 following repeated administration of IVA to juvenile rats.

Table 31 Toxicokinetic Parameters of TEZ, M1-661 (VRT-0996107), M2-661 (VRT-1189001), and IVA (VX-770) in plasma in rats on PND 14, 42, 21, and 49

Text Table 15
TK Parameters for VX-661 (Males and Females Separate)

Gender	VX-661 Dose (mg/kg/day)	PND	Group	C _{max} (µg/mL)	t _{max} (hr)	AUC _{0-24hr} (µg·hr/mL)
Female	30	21	3	8.89	4	105
Female	30	49	3	11.7	4	138
Female	30	21	4	10.0	4	139
Female	30	49	4	15.5	2	153
Female	60	21	5	17.4	2	217
Female	60	49	5	15.3	4	205
Female	20	14	6	8.27	8	123
Female	20	42	6	5.86	4	76.2
Female	30	14	7	12.6	4	170
Female	30	42	7	10.0	4	133
Male	30	21	3	8.97	4	107
Male	30	49	3	10.3	4	96.6
Male	30	21	4	7.88	4	120
Male	30	49	4	10.0	4	90.5
Male	60	21	5	15.9	8	220
Male	60	49	5	18.5	4	191
Male	20	14	6	10.3	4	124

Gender	VX-661 Dose (mg/kg/day)	PND	Group	C _{max} (µg/mL)	t _{max} (hr)	AUC _{0-24hr} (µg·hr/mL)
Male	20	42	6	6.09	4	46.9
Male	30	14	7	11.3	12	198
Male	30	42	7	9.49	4	82.5

Text Table 16
TK Parameters for VRT-0996107 (Males and Females Separate)

Gender	VX-661 Dose (mg/kg/day)	PND	Group	C _{max} (µg/mL)	t _{max} (hr)	AUC _{0-24hr} (µg·hr/mL)
Female	30	21	3	3.16	12	59.1
Female	30	49	3	4.14	8	84.1
Female	30	21	4	3.37	24	59.3
Female	30	49	4	4.94	12	96.4
Female	60	21	5	4.76	24	87.3
Female	60	49	5	8.26	8	158
Female	20	14	6	2.14	12	41.8
Female	20	42	6	2.36	12	45.0
Female	30	14	7	2.43	24	44.2
Female	30	42	7	3.81	8	74.3
Male	30	21	3	3.07	12	54.8
Male	30	49	3	4.74	4	89.3
Male	30	21	4	2.99	12	53.5
Male	30	49	4	5.52	12	115
Male	60	21	5	5.39	12	93.7
Male	60	49	5	9.75	8	171
Male	20	14	6	1.87	12	37.3
Male	20	42	6	3.30	4	54.9
Male	30	14	7	2.76	12	50.6
Male	30	42	7	4.22	8	75.1

Text Table 17
TK Parameters for VRT-1189001 (Males and Females Separate)

Gender	VX-661 Dose (mg/kg/day)	PND	Group	C _{max} (µg/mL)	t _{max} (hr)	AUC _{0-24hr} (µg·hr/mL)
Female	30	21	3	0.209	24	3.51
Female	30	49	3	0.174	4	2.53
Female	30	21	4	0.334	24	3.74
Female	30	49	4	0.175	8	3.02
Female	60	21	5	0.361	12	5.79
Female	60	49	5	0.256	12	5.91
Female	20	14	6	0.462	24	5.29
Female	20	42	6	0.107	8	1.63
Female	30	14	7	0.244	24	3.27
Female	30	42	7	0.197	12	3.45
Male	30	21	3	0.127	12	2.40
Male	30	49	3	0.272	8	5.60
Male	30	21	4	0.262	24	3.81
Male	30	49	4	0.282	8	5.13
Male	60	21	5	0.454	12	6.75

Gender	VX-661 Dose (mg/kg/day)	PND	Group	C _{max} (µg/mL)	t _{max} (hr)	AUC _{0-24hr} (µg·hr/mL)
Male	60	49	5	0.386	24	8.16
Male	20	14	6	0.265	24	4.08
Male	20	42	6	0.140	4	2.67
Male	30	14	7	0.502	24	5.43
Male	30	42	7	0.241	8	4.47

Text Table 18
TK Parameters for VX-770 (Males and Females Separate)

Gender	VX-770 Dose (mg/kg/day)	PND	Group	C _{max} (µg/mL)	t _{max} (hr)	AUC _{0-24hr} (µg·hr/mL)
Female	10	21	4	2.05	4	38.3
Female	10	49	4	1.74	2	32.3
Male	10	21	4	1.88	8	30.9
Male	10	49	4	1.84	4	32.0

(Excerpted from the Sponsor's submission)

APPEARS THIS WAY ON ORIGINAL

11 Integrated Summary and Safety Evaluation

Vertex submitted the current efficacy supplement for Trikafta (elexacaftor/tezacaftor/ivacaftor) to extend treatment to CF subjects, 6 through 11 years of age, with at least one F508del mutation in the CFTR gene.

No new nonclinical studies were submitted in the current efficacy supplement; however, a decision was made to review the juvenile animal studies with elexacaftor and tezacaftor that had been submitted earlier. These juvenile animal studies are not pivotal to the pediatric age group under consideration (i.e., 6 through 11 years of age), which are generally covered by the standard toxicology program that was reviewed with the initial NDA submission. The juvenile rat studies were initiated on postnatal (PND) 7 that corresponds to an infant at birth or PND 21 that corresponds to a 2- to 3-year old child. Pediatric patients represent a population different from adults when considering the rapid growth and postnatal development of several organ systems. Lung development in the juvenile rat parallels lung development in a child over the first 1 to 2 years of life (e.g., increases in alveolization and surface area that occur in this period). Potential concerns of neuropsychiatric adverse events (AEs) with the CFTR modulators have been reported in the literature and AE reporting, which is discussed below. Central nervous system (CNS) toxicity was evident in the juvenile rat toxicology studies with tezacaftor.

Elexacaftor (ELX)

General toxicological profiles of ELX were characterized in adult rats up to 26 weeks and adult dogs up to 39 weeks. These studies were previously reviewed under NDA 212273. The doses were 0, 7.5, 15, 40, and 75 mg/kg/day in males and 0, 4, 7.5, 15 and 30 mg/kg/day in females in rats and 0, 2.5, 6 or 14 mg/kg/day in dogs. In the 26-week study with adult rats, multiple deaths/euthanasia were noted in males at doses ≥ 40 mg/kg/day and females at 30 mg/kg/day with the findings of decreased food intake leading to lower body weight and declining clinical condition that were attributed to erosion of the glandular mucosa of the stomach. The NOAEL was identified at 15 mg/kg/day in adult rats with corresponding AUC values that were 4 (males) and 12 (females) times the maximum recommended human dose (MRHD). In the 39-week study in adult dogs, test item-related microscopic changes were noted at 14 mg/kg/day that included hepatocellular hypertrophy, epithelium vacuolation in gallbladder, and testicular seminiferous tubule atrophy/degeneration. The testicular changes were not fully reversible and considered adverse. The NOAEL was identified at 6 mg/kg/day with a corresponding AUC value that was 6 times the maximum recommended human dose.

In the juvenile toxicology study, male and female rats ELX from PNDs 7 to 70. Male rats received ELX at oral doses of 0, 7.5, 15, or 30 mg/kg/day. Female rats received ELX at oral doses of 0, 5, 7.5, or 15 mg/kg/day. Increases in mean TBIL concentration were observed in males in the HD group and in females in the MD and HD groups. Increases of mean ALT were observed in males and females in the HD group. Decreases of mean cholesterol concentration were observed in males and females in the HD group. There were no corresponding histopathological findings observed in the liver. Increases of mean CK activities was observed in males and females in the HD group. Mean ages

and body weights for attainment of balanopreputial separation or vaginal patency were unaffected by ELX. There was no evidence of histopathological findings in the stomach as observed in adult rats or testes as observed in adult dogs. The NOAELs were identified at 30 mg/kg/day (AUC, 694 h•µg/mL) for males and 15 mg/kg/day (AUC, 976 h•µg/mL) for females. The AUC values of ELX were at least 4 times the ELX exposure at the maximum recommended dose of 200 mg in children 6 through 11 years of age. The AUCs of the metabolite M23-445 were 40.1 and 81.5 h•µg/mL for males and females, respectively. These AUC values were at least 0.4 times the M23-445 exposure at the maximum recommended dose of 200 mg in children 6 through 11 years of age.

Tezacaftor (TEZ)

The general toxicological profile of TEZ was characterized in studies with adult rats up to 6 months and adult dogs up to 1 year. These studies were previously reviewed under NDA 210491. Doses up to 100 mg/kg/day in rats and 200 mg/kg/day in dogs were evaluated. The major consistent finding was dilated terminal lymphatics of minimal to mild severity in the villi of the jejunum and ileum of males and females of both rats and dogs. There were no significant effects on the limited assessments of blood levels of absorbed nutrients (total protein, glucose, lipids, cholesterol, electrolytes), and no gastrointestinal pathology or signs of adverse function. The mechanism for dilated lymphatic terminals and its associated persistence following discontinuation of treatment was unknown. This finding was not associated with any detrimental health or nutritional effects in initially healthy rats or dogs and is currently considered a non-adverse finding.

TEZ was characterized in juvenile rats during PND 7-35, PND 14-35, PND 14-42, PND 21-35, and PND 21-49. The doses were 0, 10, 20, 30, 60, and 100 mg/kg/day. When administered starting at PND 7 (the equivalent of a human newborn) at doses of 10 to 100 mg/kg/day, multiple deaths/euthanasia, lower body weight, and adverse clinical signs including convulsions, hypoactivity, repetitive movement of the mouth, head tilt, small stature, and cool and/or thin body were observed at doses ≥30 mg/kg/day. When administered starting at postnatal day 21 (the equivalent of a human child, 2-3 years of age) at doses of 30 to 100 mg/kg/day, multiple deaths/euthanasia and convulsions occurred at a dose of 100 mg/kg/day and lower body weights occurred at doses ≥60 mg/kg/day, which were considered adverse. The effects on body weight and adverse clinical signs in juvenile rats were dose related and generally more severe when administration was initiated earlier in the postnatal period. These adverse clinical signs including convulsions were observed at exposures that were at least 65% of the clinical exposure at the maximum recommended human dose of 100 mg daily in children 6 through 11 years of age as shown in Table 31.

Table 32 Convulsion in juvenile rats and exposure ratios to children 6-12

Juvenile Rat Studies	TEZ+M1-TEZ,				Children 6-12, 100 mg		Children 6-12, 50 mg		Reference
	Doses, mg/kg/day	Adverse clinical signs/convulsion	C _{max} , µg/mL	AUC, µg*hr/mL	Ratio to C _{max} ^a	Ratio to AUC ^b	Ratio to C _{max} ^a	Ratio to AUC ^b	

					20.07 µg/mL	323 µg*hr/mL	14.18 µg/mL	220 µg*hr/mL	
PNDs 7-35	10 (NOAEL)	No	3.76	57.5	0.19	0.18	0.27	0.26	VX-661- TX-037
	30	Yes	11.35	208.9	0.57	0.65	0.80	0.95	
	60	Yes	21	447.8	1.05	1.39	1.48	2.04	
	100	Yes	28	641.3	1.40	1.99	1.97	2.92	
PNDs 21-35	30 (NOAEL)	No	10.01	141.7	0.50	0.44	0.71	0.64	VX-661- TX-069
	60	No	19.95	291.6	0.99	0.90	1.41	1.33	
	100	Yes	34.06	500	1.70	1.55	2.40	2.27	

^aClinical C_{max} Sources: Study 106 CSR/Table 14.4.1.4 and Table 14.4.1.6

^bClinical AUC Sources: Report Q075/Tables 7 and 8, Report Q076/Tables 7, 19, and 31;

In the GLP dose range-finding study in juvenile rats with doses of 0, 10, 30, 60, and 100 mg/kg/day administered from PND 7 to PND 35, multiple deaths/euthanasia, lower body weight, and adverse clinical signs including clonic convulsions, hypoactivity, repetitive movement of the mouth, head tilt, small stature, and cool and/or thin body were observed in both males and females at doses of 30, 60, and 100 mg/kg/day. All animals in the 30, 60, and 100 mg/kg/day groups were euthanized on PND 14-16, PND 10-11, and PND 9-10, respectively, due to adverse clonic convulsions and lower body weights. Lower body weight gain was observed in both males and females at doses $\geq$ 30 mg/kg/day. Histopathologic findings included decreases in lymphocytes in the spleen with higher incidences in the drug treated groups and minimal to mild hematopoiesis in the liver in the drug treated groups. The NOAEL from PND7 to PND 35 was identified as 10 mg/kg/day (AUC, 27.8 h•µg/mL) in juvenile rats. The AUC of metabolite M1-661 was 29.4 h•µg/mL.

In the GLP dose range-finding study in juvenile rats with doses of 0, 30, 60, and 100 mg/kg/day administered from PND 21 to PND 35, multiple deaths/euthanasia and convulsion were observed in both males and females at dose of 100 mg/kg/day. Lower body weight gain was observed in both males and females at doses $\geq$ 60 mg/kg/day. The NOAEL was identified as 30 mg/kg/day (AUC, 91.7 h•µg/mL) during PND 21-35. The AUC of metabolite M1-661 was 79.1 h•µg/mL.

In the GLP dose range-finding study in juvenile rats with doses of 0, 20, and 30 mg/kg/day administered from PND 14 to PND 35, no adverse findings were observed. Body weight gain was affected. The NOAELs was identified as 30 mg/kg/day (AUC, 90.3 h•µg/mL) from PND 14-35. The AUC of metabolites M1-661 was 68.0 h•µg/mL.

In the definitive GLP study, juvenile rats received oral doses of 0, 20, and 30 mg/kg/day from PND 14 to PND 42 or 0, 30, 30 (+10 mg/kg/day IVA), and 60 mg/kg/day from PND 21-49. No treatment-related deaths or adverse clinical signs were observed. For PND 14-42 and PND 21-49, body weights gains for male and female rats receiving doses up to 30 mg/kg/day were unaffected. However, for PND 21-49, body weight gain for males at 60 mg/kg/day was reduced to 89.5% of the control. Body weight gain was unaffected for females at 60 mg/kg/day. No adverse findings were identified in juvenile rats administered with the combination of 30 mg/kg/day TEZ and 10 mg/kg/day IVA. The

NOAELs of TEZ were identified as 30 mg/kg/day (AUC_{0-24} : 107.8 h• μ g/mL) from PND 14-42 and 30 mg/kg/day (AUC_{0-24} : 106 h• μ g/mL) in juvenile rats from PND 21-49. In juvenile rats from PND 14-42, the AUC_{0-24} of metabolites M1-661 and M2-661 were 47.4 h• μ g/mL and 4.35 h• μ g/mL, respectively. In juvenile rats from PND 21-35, the AUC_{0-24} of metabolites M1-661 and M2-661 were 51.6 h• μ g/mL and 3.87 h• μ g/mL, respectively.

Increased brain levels of TEZ and metabolites

In a juvenile toxicokinetic (TK) study, female rats received TEZ at oral doses of 0 and 30 mg/kg/day for 3 days during PND 7–9, PND 14–16, PND 21–23, or PND 35–37. No treatment-related deaths or adverse clinical signs were observed. Plasma exposures to TEZ, M1-TEZ, and M2-TEZ were 2-3 fold higher in juvenile female rats on PND 9 and 16 as compared to PND 23 and 37. Brain exposures to TEZ, M1-TEZ, and M2-TEZ were much higher (18-24 fold) in juvenile female rats on PND 9 and 16 as compared to PND 23 and 37. Plasma exposures for M1-TEZ and M2-TEZ were approximately 36% to 100% and 2% to 10% of TEZ exposures, respectively. Brain tissue exposures of M1-TEZ and M2-TEZ were approximately 385% to 1190% and 36% to 73% of TEZ exposures, respectively. Increased brain exposures to TEZ and M1-TEZ were probably responsible for the CNS toxicity observed in juvenile rat studies initiated on PNDs 7 and 14.

Mechanism for high brain levels of TEZ and CNS-related toxicities

The increased brain levels of TEZ and its metabolite in the younger juvenile rats (treatment starting on PND 7 or PND 14) may be explained by the lower levels of the efflux transporter protein, P-glycoprotein (P-gp), in the brains of younger juvenile rats¹². TEZ and M1-661 are both substrates for P-gp. Toxicity observed in juvenile rats appeared to correlate to the developmental stage of the blood brain barrier in terms of low P-gp activity. The lower activity of P-gp in younger juvenile pups would lead to higher brain levels of TEZ, M1-661, and M2-661. The blood-brain barrier (BBB) in terms of levels of P-gp activity in rats is not fully developed until approximately PND 21 to PND 35, whereas in humans, the BBB in term of levels of G-gp activity reaches adult levels by approximately 3-6 months of age as measured by P-gp expression and function³⁴.

¹ Nicolas JM, de Lange ECM. Mind the Gaps: Ontogeny of Human Brain P-gp and Its Impact on Drug Toxicity. AAPS J. 2019; 21(4): 67.

² C. Joakim Ek, Annamae Wong, Shane A. Liddelow, Pia A. Johansson, Katarzyna M. Dziegielewska, Norman R. Saunders. Efflux mechanisms at the developing brain barriers: ABC transporters in the fetal and postnatal rat. Toxicology Letters, 2010; 197: 51-59.

³ Jessica Lam, Stephanie Baello, Majid Iqbal, Lauren E. Kelly, Patrick T. Shannon, David Chitayat, Stephen G. Matthews, Gideon Korenff1. The ontogeny of P-glycoprotein in the developing human blood–brain barrier: implication for opioid toxicity in neonates. Pediatric Research, 2015; 78: 417-421.

⁴ Schmitt G., Parrott N., Prinssen E., Barrow P. The great barrier belief: The blood–brain barrier and considerations for juvenile toxicity studies. Reprod. Toxicol. 2017; 72: 129–135.

Table 33 Brain P-gp activity comparison in rats and humans**Table 1. Effect of Age on Various Potential Readouts of Human Brain P-gp Activity**

Species	Experimental approach	N	Age ^a	Conclusion
Human	Protein expression of brain P-gp by immunohistochemistry of post-mortem human brain cortex samples (13)	9	22–26 weeks ^b	Positive P-gp immunostaining of microvessel endothelial cells from 22 to 26 weeks gestation (brainstem, hindbrain, and thalamus) and from 27 to 32 weeks gestation (other regions of the forebrain). Lower signal at birth than in adults.
		10	27–32 weeks ^b	
		9	33–42 weeks ^b	
		3	adults	
	Protein expression of brain P-gp by immunohistochemistry of post-mortem human brain cortex samples (14)	8	0–3 months	Brain P-gp expression mature at 3–6 months of age
		7	3–6 months	
		8	54 ± 7 years	
	VCR concentration in CSF samples (15)	17	2.5–14 years	Brain P-gp function mature at ≤ 2.5 years
	Meta-analysis of CNS toxicity with loperamide (16)	1788	1 month–12 years	Increased frequency of CNS side effects with loperamide in children aged < 3 years vs older children or placebo
		146	5 months–18 years	Regression analysis identified age < 6 years as a risk factor for CNS side effects with CsA
Rat ^c	Brain distribution of oseltamivir, brain P-gp protein and mRNA levels (18)	na	3–42 days	Brain P-gp expression and function mature at 21 days
	Brain PET imaging with [¹¹ C]-oseltamivir (19)	na	7–44 days	Brain P-gp function mature at 21–24 days
	Brain distribution of digoxin, brain P-gp mRNA levels (20)	na	14–56 days	Brain P-gp expression and function mature at 21 days
Monkey ^c	Brain PET imaging with [¹¹ C]-verapamil (21)	na	9 months–7 years	Brain P-gp function not fully mature in infant (9 months) or adolescent (24–27 months) monkeys
	Protein expression of brain P-gp levels by LC-MS/MS (22)	na	20-week fetus–50 years	Brain P-gp expression mature at 3–6 months

CNS central nervous system, CsA cyclosporine A, CSF cerebrospinal fluid, LC-MS/MS liquid chromatography-tandem mass spectrometry, mRNA messenger ribonucleic acid, na not applicable.

PET positron emission tomography, P-gp P-glycoprotein, VCR vincristine

^a Unless otherwise stated, postnatal age

^b Gestational age

^c 21 days of rat age reported to correspond to around 1–2 years of human age; 9 months of Rhesus monkey age reported to correspond to around 4 years of human age (33,34)

(Excerpted from Nicolas JM, de Lange ECM. Mind the Gaps: Ontogeny of Human Brain P-gp and Its Impact on Drug Toxicity. AAPS J. 2019; 21(4): 67.)

Ek et al. (Toxicology Letters 197 (2010): 51–59) used qPCR and immunocytochemistry to determine gene expression and localization of the four main barrier ABC-transporters (P-gp/ABCB1, MRP1/ABCC1, MRP4/ABCC4 and BCRP/ABCG2) in the fetal and neonatal rat brain cerebral blood vessels (site of blood–brain barrier) and choroid plexus (site of blood–CSF barrier). The study showed that the ABC transporters localize to the brain barriers even at early fetal stages and that P-gp expression in the forebrain and brainstem was the only transporter that was noted as being lower in the fetus; however, levels in the Lateral and 4th choroid plexus were comparable to adult levels. Levels of MRP1 and MRP4 were low in the Lateral and 4th choroid plexus. The other transporters were expressed at comparable levels in fetal and adult brains suggesting direct neuroprotection of the brain. Brain P-gp levels by PND 21 were approximately comparable to adult levels.

Figure 1 Forebrain/Brainstem

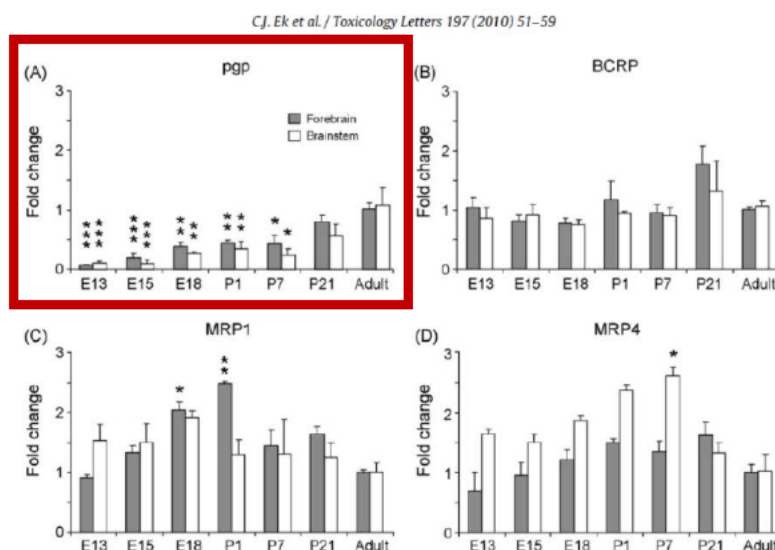


Fig. 1. Gene expression of pgp (A), BCRP (B), MRP1 (C) and MRP4 (D) in the rat forebrain and brainstem at different developmental stages between E13 and adulthood. Gene expression is calculated as fold change at each developmental age compared to the average adult value. Note that the tissue did not contain any choroid plexus since this was removed. Pgp expression progressively increased during development (about 10–12-fold) in both the forebrain and brainstem. BCRP showed similar gene expression at all ages and in both brain regions. MRP1 showed similar gene expression during development except at E18 and P1 when there was a 2–2.5-fold higher expression in the forebrain compared to the adult ($p < 0.05$). Likewise, MRP4 showed similar gene expression during development except at P7 when there is an almost 3-fold higher expression in the brainstem ($p < 0.05$). Thus each transporter shows a developmental peak, but the peak occurs at a different age. Data expressed as mean $\pm$ SEM, $n = 3$ at each age. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Excerpted from Ek *et al.*, Toxicology Letters 197 (2010): 51–59

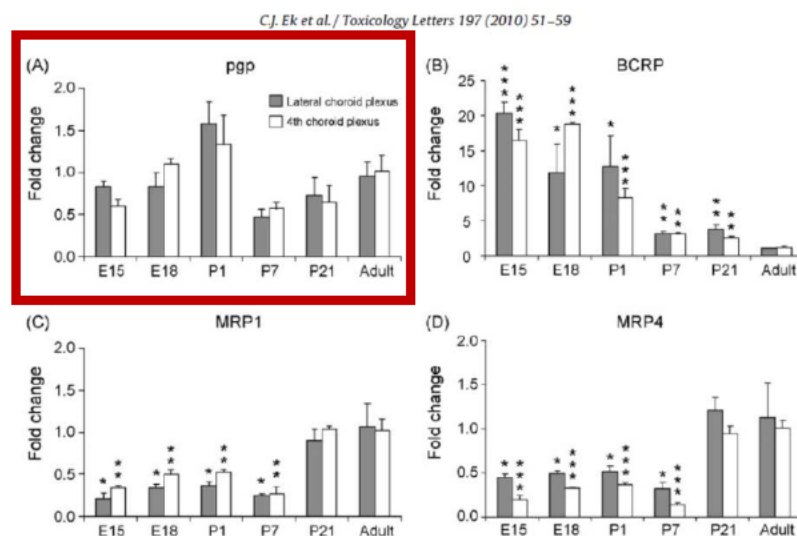
Figure 2 Lateral Choroid Plexus/4th Choroid Plexus

Fig. 2. Gene expression of pgp (A), BCRP (B), MRP1 (C) and MRP4 (D) in the rat lateral and 4th ventricular choroid plexus at different developmental stages from E15 to adulthood. The gene expression is calculated as fold change at each developmental age compared to the average adult value. Pgp did not show any statistically significant changes during development. BCRP was strikingly high at E15 (15–20-fold higher compared to adult) and then gradually decreased during development. The developmental pattern was similar for the lateral and 4th choroid plexuses and the expression levels of BCRP were statistically significantly higher than adult at all developmental ages in the 4th ventricular choroid plexus but only at E15 in the lateral ventricular plexus. MRP1 and MRP4 showed similar patterns of expression during development in the two different choroid plexuses. There was about 2–5-fold lower expression levels at developmental ages E15–P7 compared to adult whereas P21 showed similar expression to the adult. The developmental expression profile for the two plexuses appeared similar for both MRP1 and MRP4. Data are expressed as mean $\pm$ SEM, $n = 3$ at each age. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Excerpted from Ek *et al.*, Toxicology Letters 197 (2010): 51–59

High brain levels of TEZ and both metabolites in younger rats (dosed from PND 7-9 and PND 14-16) might explain the observed toxicity of TEZ in the juvenile rat dose range finding study (VX-661-TX-037), with initiation of dosing on PND 7, that included clonic convulsions and other CNS-related clinical observations. It was also noted that the M1-661 levels in brain tissue on PND 7-9, 14-16, 21-23, and 35-37 were significantly higher (3.8 to 11.9-fold) than TEZ level in brain tissues, while the plasma levels of these two compounds were relatively comparable (< 2-fold difference). $P_{app(A-B)}$ of TEZ and M1-TEZ were 0.3 and 7.6 cm/sec $\times 10^6$, respectively. Efflux Ratios of VX-661 and M1-TEZ were 31.5 and 4.18, respectively. P-gp was more efficient in blocking VX-661 than M1-TEZ in BBB. These data might explain why significantly higher levels of M1-TEZ were observed in brain tissues. Brain P-gp activity appears to only be a safety concern for children less than 1 year of age and is unlikely to be a safety concern for children 6 through 11 years of age.

Neuropsychiatric events have been reported for the market-available CFTR modulators. Dagenais et al. (Journal of Clinical Medicine 2021, 10, 23; <https://dx.doi.org/10.3390/jcm10010023>) conducted a systematic review to summarize real-world Adverse Events (AEs) reported for market-available CFTR modulators (i.e., ivacaftor (IVA), lumacaftor/ivacaftor (LUM/IVA), tezacaftor/ivacaftor (TEZ/IVA), and elxacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA)). A signal for mental health and neurocognitive AEs was identified with all 4 CFTR modulators. Limited data were available regarding real-world AEs with TEZ/IVA; however, notable neuropsychiatric AEs were reported. In a cohort of 44 adults, 5 (11%) experienced neuropsychiatric AEs: out of body experience and visual hallucination; depersonalization and “brain fog”; severe migraine; and sleep pattern disturbance, which occurred in 2 individuals. The two individuals with sleep pattern disturbance remained on TEZ/IVA, but the other three individuals changed back to LUM/IVA and had resolution of symptoms thereafter. Another cohort study reported discontinuation due to unspecified mental health changes; the frequency was not reported. The results of juvenile rat studies with tezacaftor raise concerns for potential neuropsychiatric AEs. It is unclear if variations in brain levels of p-glycoprotein might be involved in these potential neuropsychiatric AEs.

Table 34 Safety Margin for ELX

Juvenile Rat Studies	NOAEL Dose (mg/kg/wk)	AUC $\mu\text{g}\cdot\text{hr/mL}$	Safety margins for clinical dose		
			PND70		
			Adult, 200 mg 163.0	Children 6-12, 200 mg 195.0	Children 6-12, 100 mg 116.0
PNDs 7-70	M: 30 mg	694	4.26	3.56	5.98
	F: 15 mg	976	5.99	5.01	8.41

^cClinical AUC Sources: Report Q075/Tables 7 and 8, Report Q076/Tables 7, 19, and 31;

Table 35 Safety Margin for M23-ELX

Juvenile Rat Studies	NOAEL Dose (mg/kg/wk)	AUC $\mu\text{g}\cdot\text{hr}/\text{mL}$	Safety margins for clinical dose		
			PND70		
			Adult, 200 mg 65.7	Children 6-12, 200 mg 104.0	Children 6-12, 100 mg 45.4
PNDs 7-70	M: 30 mg	40.1	0.61	0.39	0.88
	F: 15 mg	81.5	1.24	0.78	1.80

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^cClinical AUC Sources: Report Q075/Tables 7 and 8, Report Q076/Tables 7, 19, and 31;

Table 36 Safety Margin for TEZ+M1-TEZ

Juvenile Rat Studies	NOAEL Dose (mg/kg)	AUC (TEZ+M1-TEZ), $\mu\text{g}\cdot\text{hr}/\text{mL}$						Safety margins relative to 1st time point (PND 7, 14, or 21)			Safety margins relative to 2nd time point (PND 35, 42, or 49)		
		PND 7 ^a	PND 14	PND 21 ^b	PND 35	PND 42	PND 49	Adult, 100 mg ^c	Children 6-12, 100 mg ^c	Children 6-12, 50 mg ^c	Adult, 100 mg ^c	Children 6-12, 100 mg ^c	Children 6-12, 50 mg ^c
								220.4	323.0	220.0	220.4	323.0	220.0
PND 7-35	10	57.5			57.2			0.3	0.2	0.3	0.3	0.2	0.3
PND 14-35	30		232.6		158.3			1.1	0.7	1.1	0.7	0.5	0.7
PND 14-42	30		231.4			182.5		1.0	0.7	1.1	0.8	0.6	0.8
PND 21-35	30			141.7	170.8			0.6	0.4	0.6	0.8	0.5	0.8
PND 21-49	30			163			204	0.7	0.5	0.7	0.9	0.6	0.9
PND 21-49, +IVA	30			185.9			227.5	0.8	0.6	0.8	1.0	0.7	1.0

^aPND 7 in rats is the equivalent of a human newborn;

^bPND 21 in rats is the equivalent of a human 2-3 years of age.

^cClinical AUC Sources: Report Q075/Tables 7 and 8, Report Q076/Tables 7, 19, and 31;

Table 37 Safety Margin for TEZ

Juvenile Rat Studies	NOAEL Dose (mg/kg)	AUC, $\mu\text{g}\cdot\text{hr}/\text{mL}$						Safety margins relative to 1st time point (PND 7, 14, or 21)			Safety margins relative to 2nd time point (PND 35, 42, or 49)		
		PND 7	PND 14	PND 21 (weaning age)	PND 35	PND 42	PND 49	Adult, 100 mg	Children 6-12, 100 mg	Children 6-12, 50 mg	Adult, 100 mg	Children 6-12, 100 mg	Children 6-12, 50 mg
								86.4	103.0	67.0	86.4	103.0	67.0
PND 7-35	10	37.1			27.8			0.4	0.4	0.6	0.3	0.3	0.4
PND 14-35	30		186		90.3			2.2	1.8	2.8	1.0	0.9	1.3
PND 14-42	30		184			107.8		2.1	1.8	2.7	1.2	1.0	1.6
PND 21-35	30			90.1	91.7			1.0	0.9	1.3	1.1	0.9	1.4
PND 21-49	30			106			117.3	1.2	1.0	1.6	1.4	1.1	1.8
PND 21-49, +IVA	30			129.5			121.8	1.5	1.3	1.9	1.4	1.2	1.8

Table 38 Safety Margin for M1-TEZ

Juvenile Rat Studies	NOAEL Dose (mg/kg)	AUC, $\mu\text{g}\cdot\text{hr}/\text{mL}$						Safety margins relative to 1st time point (PND 7, 14, or 21)			Safety margins relative to 2nd time point (PND 35, 42, or 49)		
		PND 7	PND 14	PND 21 (weaning age)	PND 35	PND 42	PND 49	Adult, 100 mg	Children 6-12, 100 mg	Children 6-12, 50 mg	Adult, 100 mg	Children 6-12, 100 mg	Children 6-12, 50 mg
								134.0	220.0	153.0	134.0	220.0	153.0
PND 7-35	10	20.4			29.4			0.2	0.1	0.1	0.2	0.1	0.2
PND 14-35	30		46.6		68			0.3	0.2	0.3	0.5	0.3	0.4
PND 14-42	30		47.4			74.7		0.4	0.2	0.3	0.6	0.3	0.5
PND 21-35	30			51.6	79.1			0.4	0.2	0.3	0.6	0.4	0.5
PND 21-49	30			57			86.7	0.4	0.3	0.4	0.6	0.4	0.6
PND 21-49, +IVA	30			56.4			105.7	0.4	0.3	0.4	0.8	0.5	0.7

Table 39 Safety Margin for IVA

Juvenile Rat Studies	NOAEL Dose (mg/kg/wk)	AUC $\mu\text{g}\cdot\text{hr}/\text{mL}$		Safety margins for clinical dose PND7-21			Safety margins for clinical dose PND35-49		
		PND 21	PND 49	Adult, 300 mg	Children 6-12, 300 mg	Children 6-12, 150 mg	Adult, 300 mg	Children 6-12, 300 mg	Children 6-12, 150 mg
				13.1	17.5	9.8	13.1	17.5	9.8
PND 21-49, +IVA	10	34.6	32.2	2.64	1.98	3.54	2.46	1.84	3.29

^cClinical AUC Sources: Report Q075/Tables 7 and 8, Report Q076/Tables 7, 19, and 31;

The nonclinical review of the proposed product label recommended changes for labeling in Sections 8.4 (Pediatric Use), and 13.1 (Carcinogenesis, Mutagenesis, Impairment of Fertility) to describe juvenile animal studies with tezacaftor and elexacaftor, respectively, that are described below. Additions are shown as underlined text and deletions are shown as ~~strikeout text~~.

Recommended labeling:

Current Labeling:	Reviewer's Recommended Labeling:
Section 8.4 Pediatric Use	
Juvenile Animal Toxicity Data Findings of cataracts were observed in juvenile rats dosed from postnatal Day 7	Juvenile Animal Toxicity Data Findings of cataracts were observed in juvenile rats dosed from postnatal Day 7

through 35 with ivacaftor dose levels of 10 mg/kg/day and higher (0.24 times the MRHD based on systemic exposure of ivacaftor and its metabolites). This finding has not been observed in older animals [see Warnings and Precautions (5.4) and Patient Counseling Information (17)].	through 35 with ivacaftor dose levels of 10 mg/kg/day and higher (0.24 times the MRHD based on systemic exposure of ivacaftor and its metabolites). This finding has not been observed in older animals [see Warnings and Precautions (5.4) and Patient Counseling Information (17)]. (b) (4)
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(b) (4)

Section 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility	
No studies of carcinogenicity, mutagenicity, or impairment of fertility were conducted with the combination of elexacaftor, tezacaftor and ivacaftor; however, separate studies of elexacaftor, tezacaftor and ivacaftor are described below. Elxacaftor A 6-month study in Tg.rasH2 transgenic mice showed no evidence of tumorigenicity at 50 mg/kg/day dose, the highest dose tested. Elxacaftor was negative for genotoxicity in the following assays: Ames test for bacterial gene mutation, in vitro mammalian cell micronucleus assay in TK6 cells, and in vivo mouse micronucleus test. Elxacaftor did not cause reproductive system toxicity in male rats at 55 mg/kg/day and female rats at 25 mg/kg/day, equivalent to approximately 6 times and 4 times the MRHD, respectively (based on summed AUCs of elxacaftor and its metabolite).	No studies of carcinogenicity, mutagenicity, or impairment of fertility were conducted with the combination of elexacaftor, tezacaftor and ivacaftor; however, separate studies of elexacaftor, tezacaftor and ivacaftor are described below. Elxacaftor A 6-month study in Tg.rasH2 transgenic mice showed no evidence of tumorigenicity at 50 mg/kg/day dose, the highest dose tested. Elxacaftor was negative for genotoxicity in the following assays: Ames test for bacterial gene mutation, in vitro mammalian cell micronucleus assay in TK6 cells, and in vivo mouse micronucleus test. Elxacaftor did not cause reproductive system toxicity in male rats at 55 mg/kg/day and female rats at 25 mg/kg/day, equivalent to approximately 6 times and 4 times the MRHD, respectively (based on summed AUCs of elxacaftor and its metabolite).

Elxacaftor did not cause embryonic toxicity at 35 mg/kg/day which was the highest dose tested, equivalent to approximately 7 times the MHRD (based on summed AUCs of elxacaftor and its metabolite). Lower male and female fertility, male copulation, and female conception indices were observed in males at 75 mg/kg/day and females at 35 mg/kg/day, equivalent to approximately 6 times and 7 times, respectively, the MRHD (based on summed AUCs of elxacaftor and its metabolite).	Elxacaftor did not cause embryonic toxicity at 35 mg/kg/day which was the highest dose tested, equivalent to approximately 7 times the MHRD (based on summed AUCs of elxacaftor and its metabolite). Lower male and female fertility, male copulation, and female conception indices were observed in males at 75 mg/kg/day and females at 35 mg/kg/day, equivalent to approximately 6 times and 7 times, respectively, the MRHD (based on summed AUCs of elxacaftor and its metabolite).
	(b) (4)
Tezacaftor A 2 year study in Sprague-Dawley rats and a 6-month study in Tg.rasH2 transgenic mice were conducted to assess the carcinogenic potential of tezacaftor. No evidence of tumorigenicity from tezacaftor was observed in male and female rats at oral doses up to 50 and 75 mg/kg/day (approximately 1 and 2 times the MRHD based on summed AUCs of tezacaftor and its metabolites in males and females, respectively). No evidence of tumorigenicity was observed in male and female Tg.rasH2 transgenic mice at tezacaftor doses up to 500 mg/kg/day. Tezacaftor was negative for genotoxicity in the following assays: Ames test for bacterial gene mutation, in vitro chromosomal aberration assay in	Tezacaftor A 2 year study in Sprague-Dawley rats and a 6-month study in Tg.rasH2 transgenic mice were conducted to assess the carcinogenic potential of tezacaftor. No evidence of tumorigenicity from tezacaftor was observed in male and female rats at oral doses up to 50 and 75 mg/kg/day (approximately 1 and 2 times the MRHD based on summed AUCs of tezacaftor and its metabolites in males and females, respectively). No evidence of tumorigenicity was observed in male and female Tg.rasH2 transgenic mice at tezacaftor doses up to 500 mg/kg/day. Tezacaftor was negative for genotoxicity in the following assays: Ames test for bacterial gene mutation, in vitro chromosomal aberration assay in

Chinese hamster ovary cells, and in vivo mouse micronucleus test. There were no effects on male or female fertility and early embryonic development in rats at oral tezacaftor doses up to 100 mg/kg/day (approximately 3 times the MRHD based on summed AUC of tezacaftor and M1 TEZ). Ivacaftor Two year studies were conducted in CD-1 mice and Sprague-Dawley rats to assess the carcinogenic potential of ivacaftor. No evidence of tumorigenicity from ivacaftor was observed in mice or rats at oral doses up to 200 mg/kg/day and 50 mg/kg/day, respectively (approximately equivalent to 2 and 7 times the MRHD, respectively, based on summed AUCs of ivacaftor and its metabolites). Ivacaftor was negative for genotoxicity in the following assays: Ames test for bacterial gene mutation, in vitro chromosomal aberration assay in Chinese hamster ovary cells, and in vivo mouse micronucleus test. Ivacaftor impaired fertility and reproductive performance indices in male and female rats at 200 mg/kg/day (approximately 7 and 5 times, respectively, the MRHD based on summed AUCs of ivacaftor and its metabolites). Increases in prolonged diestrus were observed in females at 200 mg/kg/day. Ivacaftor also increased the number of females with all nonviable embryos and decreased corpora lutea, implantations, and viable embryos in rats at 200 mg/kg/day (approximately 5 times the MRHD based on summed AUCs of ivacaftor and its metabolites) when dams were dosed prior to and during early pregnancy. These impairments of fertility	Chinese hamster ovary cells, and in vivo mouse micronucleus test. There were no effects on male or female fertility and early embryonic development in rats at oral tezacaftor doses up to 100 mg/kg/day (approximately 3 times the MRHD based on summed AUC of tezacaftor and M1 TEZ). Ivacaftor Two year studies were conducted in CD-1 mice and Sprague-Dawley rats to assess the carcinogenic potential of ivacaftor. No evidence of tumorigenicity from ivacaftor was observed in mice or rats at oral doses up to 200 mg/kg/day and 50 mg/kg/day, respectively (approximately equivalent to 2 and 7 times the MRHD, respectively, based on summed AUCs of ivacaftor and its metabolites). Ivacaftor was negative for genotoxicity in the following assays: Ames test for bacterial gene mutation, in vitro chromosomal aberration assay in Chinese hamster ovary cells, and in vivo mouse micronucleus test. Ivacaftor impaired fertility and reproductive performance indices in male and female rats at 200 mg/kg/day (approximately 7 and 5 times, respectively, the MRHD based on summed AUCs of ivacaftor and its metabolites). Increases in prolonged diestrus were observed in females at 200 mg/kg/day. Ivacaftor also increased the number of females with all nonviable embryos and decreased corpora lutea, implantations, and viable embryos in rats at 200 mg/kg/day (approximately 5 times the MRHD based on summed AUCs of ivacaftor and its metabolites) when dams were dosed prior to and during early pregnancy. These impairments of fertility
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and reproductive performance in male and female rats at 200 mg/kg/day were attributed to severe toxicity.	and reproductive performance in male and female rats at 200 mg/kg/day were attributed to severe toxicity.
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Recommendation

This efficacy supplement application for NDA 212273-S004 is recommended for approval from the nonclinical perspective.

12 Appendix/Attachments

Table 5 Summary of ELX, M23-ELX, TEZ, M1-TEZ, and IVA Observed Steady-state AUC by Age Group, 30-kg Weight Cutoff

Age Group, Weight	Dose Regimen (ELX/TEZ/IVA)	ELX AUC _{0-24h} (µg·h/mL)			M23-ELX AUC _{0-24h} (µg·h/mL)			TEZ AUC _{0-24h} (µg·h/mL)			M1-TEZ AUC _{0-24h} (µg·h/mL)			IVA AUC _{0-12h} (µg·h/mL)		
		N	Mean (SD)	Min, Max	N	Mean (SD)	Min, Max	N	Mean (SD)	Min, Max	N	Mean (SD)	Min, Max	N	Mean (SD)	Min, Max
6 through 11 years	(Both doses combined)	66	152 (63.2)	60, 310	66	71.9 (49.1)	17.4, 207	66	83.4 (29.1)	37.4, 151	66	183 (50.0)	83.8, 291	66	13.3 (6.09)	4.23, 29.4
<30 kg	100 mg qd/ 50 mg qd/ 75 mg q12h	36	116 (39.4)	60, 243	36	45.4 (25.2)	17.4, 129	36	67.0 (22.3)	37.4, 145	36	153 (36.5)	83.8, 250	36	9.78 (4.50)	4.23, 29.4
≥30 kg	200 mg qd/ 100 mg qd/ 150 mg q12h	30	195 (59.4)	99.4, 310	30	104 (52)	18.3, 207	30	103 (23.7)	57.7, 151	30	220 (37.5)	135, 291	30	17.5 (4.97)	9.62, 27.9
12 through 17 years	200 mg qd/ 100 mg qd/ 150 mg q12h	72	144 (37.5)	63.3, 255	72	60.1 (26.3)	12.2, 139	69	88.9 (22.4)	46.1, 152	69	157 (37.3)	77.2, 252	69	11.6 (4.05)	5.28, 26.0
≥18 years	200 mg qd/ 100 mg qd/ 150 mg q12h	179	163 (50.6)	68.9, 389	179	65.7 (29.6)	12, 153	186	86.4 (24.8)	30.1, 204	186	134 (36.8)	27.8, 227	186	13.1 (4.58)	4.57, 28.6

Sources: Report Q075/Tables 7 and 8, Report Q076/Tables 7, 19, and 31

ELX: elexacaftor; IVA: ivacaftor; N: total sample size; q12h: every 12 hours; qd: once daily; TEZ: tezacaftor

Table 9 Mean (%CV) C_{trough} and C_{max} Observed in CF Subjects 6 Through 11 Years of Age (Study 106 Part B)

Dose Level Analyte	C_{trough} ($\mu\text{g/mL}$) Mean (%CV)				C_{max} ($\mu\text{g/mL}$) Mean (%CV)
	Day 15	Week 4	Week 12	Week 24	Week 4
ELX 100 mg qd/TEZ 50 mg qd/IVA 75 mg q12h	N = 35	N = 33	N = 30	N = 19	N = 32
ELX	3.02 (61.3)	2.71 (65.4)	2.67 (45.6)	2.73 (40.8)	6.79 (41.9)
M23-ELX	1.76 (72.6)	1.59 (78)	1.58 (60.4)	1.31 (40.5)	2.01 (68.3)
TEZ	1.46 (63.8)	1.43 (83.8)	1.30 (55.2)	1.18 (58)	6.97 (37.3)
M1-TEZ	5.68 (29)	5.57 (31.9)	5.30 (29)	5.40 (33.8)	7.21 (26.1)
IVA	0.407 (87.2)	0.455 (149.7)	0.356 (67.4)	0.288 (63.2)	1.15 (72.8)
M1-IVA	1.05 (65.6)	1.00 (63)	0.974 (50.2)	0.787 (49.4)	2.42 (49.7)
ELX 200 mg qd/TEZ 100 mg qd/IVA 150 mg q12h	N = 30	N = 30	N = 27	N = 19	N = 30
ELX	4.99 (48.3)	5.69 (52.7)	6.16 (50)	6.53 (44.4)	11.7 (38.1)
M23-ELX	3.78 (59.9)	4.41 (67.4)	4.32 (56.6)	4.33 (48)	5.02 (62.2)
TEZ	2.39 (64.7)	2.37 (45.2)	2.31 (44.6)	2.73 (66.6)	9.97 (30.5)
M1-TEZ	8.21 (23.2)	8.12 (23.1)	7.88 (21.4)	8.37 (22.9)	10.1 (19.9)
IVA	0.766 (62.9)	0.851 (57.5)	0.800 (69.3)	0.965 (51)	2.13 (38.8)
M1-IVA	1.97 (58.4)	2.18 (47.7)	2.11 (54.7)	2.55 (36.6)	4.47 (34.0)

Sources: Study 106 CSR/Table 14.4.1.4 and Table 14.4.1.6

CF: cystic fibrosis; CV: coefficient of variation; ELX: ellexacaftor; IVA: ivacaftor; N: total sample size; q12h: every 12 hours; qd: once daily; TEZ: tezacaftor

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TIMOTHY W ROBISON
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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

212273Orig1s004

OTHER REVIEW(S)

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: May 3, 2021

To: Angela Ramsey, Senior Regulatory Project Manager
Division of Pulmonology, Allergy, and Critical Care (DPACC)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Sharon Williams, MSN, BSN, RN
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

From: Maria Nguyen, MSHS, BSN, RN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Kyle Snyder, Pharm.D.
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Patient Package Insert (PPI)

Drug Name (established name): TRIKAFTA (elexacaftor/tezacaftor/ivacaftor) tablets; (ivacaftor) tablets

Dosage Form and Route: elexacaftor/tezacaftor/ivacaftor tablets, for oral use; co-packaged with ivacaftor tablets, for oral use

Application Type/Number: NDA 212273

Supplement Number: S-004

Applicant: Vertex Pharmaceuticals, Incorporated

1 INTRODUCTION

On December 8, 2020, Vertex Pharmaceuticals, Incorporated, submitted for the Agency's review a prior Approval Supplement (PAS)-Efficacy for approved New Drug Application (NDA) #212273/S-004 for TRIKAFTA (elexacaftor/tezacaftor/ivacaftor) tablets; (ivacaftor) tablets, for oral use. This supplemental application proposes the expansion of treatment of cystic fibrosis (CF) in patients ages 6 through 11 years old with at least one F508del mutation in the CFTR gene.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Pulmonology, Allergy, and Critical Care (DPACC) on December 9, 2020, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for TRIKAFTA (elexacaftor/tezacaftor/ivacaftor) tablets; (ivacaftor) tablets, for oral use.

2 MATERIAL REVIEWED

- Draft TRIKAFTA (elexacaftor/tezacaftor/ivacaftor) tablets; (ivacaftor) tablets, for oral use PPI received on December 8, 2020, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on April 26, 2021.
- Draft TRIKAFTA (elexacaftor/tezacaftor/ivacaftor) tablets; (ivacaftor) tablets, for oral use Prescribing Information (PI) received on December 9, 2020, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on April 26, 2021.
- Approved TRIKAFTA (elexacaftor/tezacaftor/ivacaftor) tablets; (ivacaftor) tablets, for oral use labeling dated December 21, 2020.
- Approved KALYDECO comparator labeling dated December 21, 2020.
- Approved SYMDEKO comparator labeling dated December 21, 2020.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APhont to make medical information more accessible for patients with vision loss. We reformatted the PPI document using the Arial font, size 10.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible

- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the PPI is consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI are appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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/s/

MARIA T NGUYEN

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DMPP-OPDP Review of elexacaftor.tezacaftor.ivacaftor (TRIKAFTA) NDA 212273 S-004 PPI

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LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	May 5, 2021
Requesting Office or Division:	Division of Pulmonology, Allergy, and Critical Care (DPACC)
Application Type and Number:	NDA 212273/S-004
Product Name and Strength:	Trikafta (elexacaftor/tezacaftor/ivacaftor) Tablets, 50 mg/25 mg/37.5 mg and 75 mg of ivacaftor
Product Type:	Multi-Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Vertex Pharmaceuticals Inc.
FDA Received Date:	December 8, 2020
OSE RCM #:	2020-2638
DMEPA Safety Evaluator:	Lissa C. Owens, PharmD
DMEPA Team Leader:	Idalia E. Rychlik, PharmD

1 REASON FOR REVIEW

Vertex Pharmaceuticals Inc. submitted a supplement for Trikafta (elexacaftor/tezacaftor/ivacaftor) Tablets to support a label expansion for the treatment of cystic fibrosis (CF) in patients aged 6 through 11 years old with at least one F508del mutation in the CFTR gene. Additionally, Vertex is submitting a new dosage of elexacaftor 50mg/ tezacaftor 25mg/ ivacaftor 37.5 mg tablet, supporting the treatment of CF in patients 6 through 11 years old with at least one F508del mutation in the CFTR gene. Subsequently, the Division of Pulmonology, Allergy, and Critical Care (DPACC) requested that we review the proposed Trikafta prescribing information (PI), container labels and carton labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
ISMP Newsletters*	C-N/A
FDA Adverse Event Reporting System (FAERS)*	D
Other	E-N/A
Labels and Labeling	F

N/A=not applicable for this review

*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 FINDINGS AND RECOMMENDATIONS

Tables 2 and 3 below include the identified medication error issues with the submitted prescribing information (PI), container labels and carton labeling, our rationale for concern, and the proposed recommendation to minimize the risk for medication error.

The following table (Table 2) outlines issues and recommendations for the Division:

Table 2. Identified Issues and Recommendations for Division of Pulmonology, Allergy, and Critical Care (DPACC)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Prescribing Information – General Issues			

Table 2. Identified Issues and Recommendations for Division of Pulmonology, Allergy, and Critical Care (DPACC)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
1.	As presented both age and weight are in the same column.	Presenting two different metrics for discernment within the same column may lead to confusion and dosing errors.	 (b) (4)
Highlights of Prescribing Information			
1.	Use of confusing symbols (e.g., ">" and "<")	These symbols may be mistaken as opposite of intended.	Replace the symbols "<" and "≥" with their intended meanings to prevent misinterpretation and confusion.
Full Prescribing Information – Section 2 Dosage and Administration			
1.	Use of confusing symbols (e.g., ">" and "<")	These symbols may be mistaken as opposite of intended.	Replace the symbols "<" and "≥" with their intended meanings to prevent misinterpretation and confusion.

The following table (Table 3) outlines issues and recommendations to convey to the Applicant:

Table 3. Identified Issues and Recommendations for Vertex Pharmaceuticals Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label(s) and Carton Labeling			
1.	As presented the circular bubble graphic contains the strengths without the drug name and appears in the form of an equation	The graphic is misleading as it appears as an equation as the strengths would equal the number below (i.e. 75 mg). It also appears without the established names the strengths represent. This	Remove circular bubble graphic containing: 50 mg 25 mg <u>37.5 mg</u> 75 mg

Table 3. Identified Issues and Recommendations for Vertex Pharmaceuticals Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		may lead to confusion. The strength is currently listed appropriately under the proprietary name.	
2.	The current color scheme used on the container labels (PDP) and carton labeling does not provide adequate differentiation when compared to the currently marketed higher strength (100 mg/50 mg/75 mg and 150 mg) product.	With similar color schemes, there is the potential for wrong strength errors to occur.	Revise the color scheme to a distinct color to adequately differentiate it from the 100 mg/50 mg/75 mg and 150 mg dosage strength.

4 CONCLUSION

Our evaluation of the proposed Trikafta prescribing information (PI), container labels, and carton labeling identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in Table 2 for the Division and Table 3 for the Applicant. We ask that the Division convey Table 3 in its entirety to Vertex Pharmaceuticals Inc. so that recommendations are implemented prior to approval of this NDA Supplement.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for Trikafta that Vertex Pharmaceuticals Inc. submitted on December 8, 2020 and the SCPI provided by DPACC as of May 3, 2021

Table 4. Relevant Product Information for Trikafta			
Initial Approval Date	October 21, 2019 for the 100 mg/50 mg/75 mg and 150 mg		
Active Ingredient	Elexacaftor, tezacaftor, and ivacaftor		
Indication	The treatment of cystic fibrosis (CF) in adult and pediatric patients aged 6 years and older who have at least one F508del mutation in the CFTR gene or a mutation in the CFTR gene that is responsive based on in vitro data		
Route of Administration	Oral		
Dosage Form	Tablets		
Strength	50 mg/25 mg/37.5 mg and 75 mg		
Dose and Frequency	Recommended Dosage for Adult and Pediatric Patients aged 6 Years and Older		
	Age	Morning Dose	Evening Dose
	6 to <12 years weighing <30 kg	Two tablets, each containing elexacaftor 50 mg/tezacaftor 25 mg/ivacaftor 37.5 mg	One tablet of ivacaftor 75 mg
	6 to <12 years weighing ≥30 kg	Two tablets, each containing elexacaftor 100 mg/tezacaftor 50 mg/ivacaftor 75 mg	One tablet of ivacaftor 150 mg
	≥12 years	Two tablets, each containing elexacaftor 100 mg/tezacaftor 50 mg/ivacaftor 75 mg	One tablet of ivacaftor 150 mg
How Supplied	Supplied as a co-packaged blister pack sealed into a printed wallet, containing elexacaftor, tezacaftor and ivacaftor fixed-dose combination tablets and ivacaftor tablets. Four such wallets are placed in a printed outer carton		
Storage	68°F - 77°F (20°C - 25°C); excursions permitted to 59°F - 86°F (15°C - 30°C)		

APPENDIX B. PREVIOUS DMEPA REVIEWS

On May 3, 2021, we searched for previous DMEPA reviews relevant to this current review using the terms, Trikafta. Our search identified 2 previous reviews^{a,b}, and we considered our previous recommendations to see if they are applicable for this current review.

^a Owens, L. Label and Labeling Review for Trikafta (NDA 212273/S-001). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 OCT 05. RCM No.: 2020-1952.

^b Owens, L. Label and Labeling Review for Trikafta (NDA 212273). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 SEP 16. RCM No.: 2019-15445.

APPENDIX D. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

D.1 Methods

On May 3, 2021, we searched FAERS using the criteria in the table below and identified 11 cases. We individually reviewed the cases and limited our analysis to cases that described errors possibly associated with the label and labeling. We used the NCC MERP Taxonomy of Medication Errors to code the type and factors contributing to the errors when sufficient information was provided by the reporter.^c We excluded all 11 cases because they were not relevant to this review.

Table 5. Criteria Used to Search FAERS	
Initial FDA Receive Dates:	September 25, 2020 (date of our last search) – May 3, 2021
Product Name:	Trikafta
Product Active Ingredient (PAI):	elexacaftor, tezacaftor, ivacaftor
Event:	SMQ <i>Medication errors</i> (Narrow)
Country (Derived):	USA

D.4 Description of FAERS

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's postmarket safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. FDA's Office of Surveillance and Epidemiology codes adverse events and medication errors to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Product names are coded using the FAERS Product Dictionary. More information about FAERS can be found at: <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm>.

^c The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website <http://www.nccmerp.org/pdf/taxo2001-07-31.pdf>.

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^d along with postmarket medication error data, we reviewed the following Trikafta labels and labeling submitted by Vertex Pharmaceuticals Inc.

- Container label(s) received on December 8, 2020
- Carton labeling received on December 8, 2020
- Prescribing Information (Image not shown) received on December 8, 2020 and the SCPI provided by DPACC as of May 3, 2021.

F.2 Label and Labeling Images

Container label(s)

Inside



(b) (4)

^d Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: April 28, 2021

To: Angela Ramsey, Regulatory Project Manager
Division of Pulmonology, Allergy, and Critical Care (DPACC)

From: Kyle Snyder, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Kathleen Klemm, Team Leader, OPDP

Subject: OPDP Labeling Comments for Trikafta® (elexacaftor, tezacaftor, and ivacaftor tablets; ivacaftor tablets), co-packaged for oral use (Trikafta)

NDA: 212273/S-004

In response to DPACC's consult request dated December 9, 2020, OPDP has reviewed the proposed Prescribing Information (PI), Patient Package Insert (PPI), and carton and container labeling for Trikafta. This supplement provides for a new dosage strength and expansion of the indicated population to include patients 6 to 11 years of age with at least one *F508del* mutation in the *CFTR* gene.

Labeling: OPDP has reviewed the proposed PI received by electronic mail from DPACC on April 26, 2021, and we have no additional comments at this time.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed for the PPI and comments will be sent under separate cover.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling received by electronic mail from DPACC on April 28, 2021, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Kyle Snyder at (240) 402-8792 or kyle.snyder@fda.hhs.gov.

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/s/

KYLE SNYDER
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MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 2/16/2021

TO: Division of Pulmonology, Allergy, and Critical Care (DPACC)
Office of Immunology and Inflammation (OII)

FROM: Division of New Drug Study Integrity (DNDSI)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Decline to conduct an on-site inspection**

RE: NDA 212273/S-004

The Division of New Drug Study Integrity (DNDSI) within the Office of Study Integrity and Surveillance (OSIS) determined that inspections are not warranted at this time for the sites listed below. The rationale for this decision is noted below.

Rationale

(b) (4) OSIS inspected the analytical site in May 2019, which falls within the surveillance interval. The inspection was conducted under the following submission: (b) (4).

(b) (4) OSIS inspected the analytical site in April 2019, which falls within the surveillance interval. The inspection was conducted under the following submission: NDA (b) (4).

The final classification for the inspections was No Action Indicated (NAI).

Therefore, based on the rationale described above, inspections are not warranted at this time.

Inspection Sites

Facility Type	Facility Name	Facility Address
Analytical	(b) (4)	
Analytical		

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