CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210491Orig1s000

CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NME NDA
Application Number(s)	210491
Priority or Standard	Priority
Submit Date(s)	6/28/17
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PDUFA Goal Date	2/27/18
Division/Office	DPARP/ODEII
Reviewer Name(s)	Stacy Chin, MD
Review Completion Date	2/1/18
Established Name	Tezacaftor/Ivacaftor
(Proposed) Trade Name	Symdeko
Applicant	Vertex
Formulation(s)	Tezacaftor 100mg / Ivacaftor 150 mg Ivacaftor 150 mg
Dosing Regimen	Tezacaftor 100 mg / Ivacaftor 150 mg every morning Ivacaftor 150 mg every evening
Applicant Proposed Indication(s)/Population(s)	Treatment of patients with cystic fibrosis patients aged 12 years and older who are homozygous for the *F508del* mutation or who have at least 1 mutation in CFTR gene that is responsive to tezacaftor/ivacaftor based on *in vitro* data and/or clinical evidence
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	As proposed

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Glossary

AC	advisory committee
AE	adverse event
AESI	adverse event of special interest
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
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FAS	Full Analysis Set
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 Harmonization
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
IVA	Ivacaftor
LUM	Lumacaftor
LUM/IVA	Lumacaftor/Ivacaftor
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
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
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
PT	MedDRA preferred term
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	MedDRA system organ class
TEAE	treatment emergent adverse event
TEZ	Tezacaftor
TEZ/IVA	Tezacaftor/Ivacaftor

1 Executive Summary

1.1. Product Introduction

The Applicant, Vertex Pharmaceuticals Incorporated (Vertex) submitted a 505(b)(1) New Drug Application (NDA) for tezacaftor (TEZ)/ivacaftor (IVA) combination therapy for the treatment of cystic fibrosis (CF) in patients 12 years of age and older who are homozygous for the *F508del* mutation or who have at least one mutation in the CF transmembrane conductance regulator (CFTR) gene that is responsive to TEZ/IVA, based on *in vitro* data and/or clinical evidence. IVA monotherapy (Kalydeco) was approved for the treatment of CF patients with a *G551D* mutation in the *CFTR* gene on January 31, 2012. The indication was expanded over time to include treatment of CF in patients aged 2 years and older who have one mutation in the *CFTR* gene that is responsive to IVA based on clinical and/or *in vitro* assay data. A combination product consisting of IVA and a second CFTR modulator, lumacaftor (LUM/IVA, trade name Orkambi) was approved on July 2, 2015 for the treatment of CF patients homozygous for the *F508del* mutation. However, the LUM/IVA product has limited efficacy, in part due to significant pharmaceutical interaction between the IVA and LUM components. For this application, Vertex has combined IVA with a different CFTR modulator, TEZ, which possesses a similar mechanism of action as LUM but lacks the drug-drug interaction issue with IVA. This review will focus on the clinical efficacy and safety findings from the Phase 3 program as well as the assessment of a modified *in vitro* Ussing Chamber assay used to predict whether CF patients with specific mutations in the *CFTR* gene are likely to derive clinical benefit.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The recommended regulatory action from a clinical perspective is Approval for orally administered Tezacaftor 100 mg/Ivacaftor 150 mg qAM and Ivacaftor 150 mg qPM for the treatment of patients with cystic fibrosis (CF) aged 12 years and older who are homozygous for the *F508del* mutation or who have at least one mutation in the CFTR gene that is responsive to TEZ/IVA based on *in vitro* data and/or clinical evidence.

To support this application, Vertex has completed three phase 3 efficacy and safety trials in three different CFTR mutation subpopulations. These studies demonstrated substantial evidence of efficacy for the TEZ/IVA combination in CF patients who are homozygous for the *F508del* mutation (Trial 106), those with missense mutations predicted to be responsive to TEZ/IVA (Trial 108), and those with certain non-canonical splice mutations for which clinical data were available (Trial 108). Efficacy was not established for CFTR mutations predicted to be non-responsive to the TEZ/IVA combination (Trial 107). The determination of efficacy was primarily based on a statistically significant improvement in the primary endpoint of absolute

change from baseline in percent predicted forced expiratory volume in 1 second (ppFEV1) and supported by secondary endpoints showing benefits in the relative change from baseline in ppFEV1, the CFQ-R respiratory domain score, and pulmonary exacerbation reduction.

While efficacy of TEZ/IVA in the missense and non-canonical splice mutation subpopulations is not unexpected given that efficacy of IVA monotherapy has already been established for these mutations, it is notable that clinical data demonstrated that TEZ/IVA was superior to IVA alone, thus illustrating the contribution of TEZ to the combination. While the study in *F508del* homozygous patients did not include an IVA monotherapy treatment arm, cross-study comparisons, albeit limited, suggest that the TEZ/IVA combination is no worse, and possibly better, than the related marketed combination product, LUM/IVA (Orkambi), as well as better than IVA alone (Kalydeco), which is not approved for *F508del*/*F508del* mutations.

In addition to clinical data, *in vitro* assay data were also included in this application to support its use in determining whether certain, rare CFTR mutations, which would be difficult to evaluate clinically, may also be responsive to TEZ/IVA. While it appears that an *in vitro* assay response above a certain threshold may be reasonably predictive of a clinical benefit with TEZ/IVA therapy, the *in vitro* data can neither predict the magnitude of the clinical response nor whether TEZ confers an additional clinical benefit over IVA monotherapy; for this assessment, clinical data is needed.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Cystic fibrosis is a rare, progressive, usually fatal autosomal recessive genetic disease. While >1000 disease-causing mutations in the CFTR gene have been identified, most CF patients in the US carry at least one allele with the *F508del* CFTR mutation[1]. Two other approved therapies exist for the proposed subpopulation of CF patients who are either *F508del* homozygous or *F508del* heterozygous with a second missense or non-canonical splice mutation allele predicted to be responsive to TEZ/IVA therapy.

The efficacy and safety of TEZ/IVA was evaluated in three, well-controlled, adequately designed phase 3 trials in three CFTR mutation subgroup populations. In *F508del* homozygous patients, TEZ/IVA treatment for 24 weeks versus placebo and standard of care resulted in statistically significant improvements in lung function as measured by change in percent predicted FEV1 (ppFEV1), reduction in pulmonary exacerbations, and nominally significant improvements in the CFQ-R respiratory domain score, a well-established disease-specific quality of life measure. In CF patients with *F508del* and certain missense or non-canonical splice mutations, 8 weeks of TEZ/IVA treatment also resulted in statistically significant improvements in lung function (change in ppFEV1) and CFQ-R respiratory domain scores compared to placebo as well as IVA monotherapy. Efficacy was not established for patients with *F508del* and a second mutation predicted to be non-responsive to therapy following a 12-week treatment period. In addition to clinical data, *in vitro* assay data were submitted to support its use in determining whether certain, rare CFTR mutations may be responsive to TEZ/IVA. While it appears that *in vitro* assay above a certain threshold may be reasonably predictive of a clinical benefit with TEZ/IVA therapy, the *in vitro* data can neither predict the magnitude of the clinical response nor whether TEZ confers an additional clinical benefit over IVA monotherapy; for this, clinical data is needed. The clinical program also included an assessment of safety with a focus on known safety risks associated with IVA monotherapy, including LFT elevations and cataracts. No safety issues arose with the addition of TEZ that offset the efficacy benefits provided by the TEZ/IVA combination. Efficacy and safety results across various demographic and baseline disease characteristic subgroups were consistent with the overall findings.

The review recommends approval of TEZ/IVA for the treatment of CF patients aged 12 years and older who are homozygous for the *F508del* mutation or who have at least one mutation in the CFTR gene that is responsive to TEZ/IVA based on *in vitro* data and/or clinical evidence. Efficacy was demonstrated in the mutation subpopulations covered in the proposed indication with clinical data supporting the added benefit of TEZ/IVA therapy over IVA alone. No safety concerns were identified that should preclude approval or require a REMS.

[1] Ferec C and Cutting GR. Assessing the Disease-Liability of Mutations in the CFTR. Cold Spring Harb Perspect Med. 2012 Dec; 2(12): a009480

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Cystic fibrosis (CF) is a rare, progressive, and usually fatal autosomal recessive genetic disease that affects approximately 30,000 children and adults in the US. CF results from mutations to the cystic fibrosis transmembrane conductance regulator (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 function 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 CFTR mutation is *F508del* – in the US, approximately 90% of CF patients carry at least one allele and 50% are homozygous (carry two alleles). However, over 1,000 different disease-causing mutations in the CFTR gene have been identified.	Cystic fibrosis is a rare, progressive, and usually fatal genetic disease. The CFTR mutations included in the proposed indication represent most patients with CF in the US.
Current Treatment Options	• While no cure exists, there are two approved therapies aimed at the cause of CF (i.e., absent of defective CFTR ion channel at the cell surface) in the proposed mutation subpopulations, *F508del* homozygous patients and *F508del* heterozygotes with a second missense or non-canonical splice mutation allele predicted to be responsive based on clinical and/or *in vitro* assay data. • Other medications are used to treat the signs and symptoms of CF; however, not all are specifically approved to treat CF.	While there are two approved therapies to treat this specific subset of CF patients, the availability of additional treatment options for those unable to tolerate existing treatments or those with a suboptimal response to available therapies is desirable.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• The applicant has demonstrated substantial evidence of efficacy for the TEZ/IVA combination in CF patients who are homozygous for the *F508del* mutation (Trial 106), those who have missense mutations predicted to be responsive to TEZ/IVA (Trial 108), and those who have certain non-canonical splice mutations for which clinical data were available (Trial 108) based on improvements in lung function (change from baseline in ppFEV1), as well as improvements in an established quality of life measure (CFQ-R respiratory domain score) and reduction in pulmonary exacerbations. Efficacy was not established for CFTR mutations predicted to be non-responsive to the TEZ/IVA combination (Trial 107). • In the study evaluating missense and non-canonical splice mutations (Trial 108), clinical data demonstrated that TEZ/IVA was superior to IVA alone. • While the study in *F508del* homozygous patients did not include an IVA monotherapy treatment arm, cross-study comparisons, albeit limited, suggest that the TEZ/IVA combination is no worse, and possibly better, than the related marketed combination product, lumacaftor/ivacaftor (Orkambi), as well as better than IVA alone (Kalydeco), which is not approved for *F508del*/*F508del* mutations. • In addition to clinical data, *in vitro* assay data were also included in this application to support its use in determining whether certain, rare CFTR mutations may be responsive to TEZ/IVA. While it appears that *in vitro* assay above a certain threshold may be reasonably predictive of a clinical benefit with TEZ/IVA therapy, the *in vitro* data can neither predict the magnitude of the clinical response nor whether TEZ confers an additional clinical benefit over IVA monotherapy.	TEZ/IVA provides clinically relevant treatment benefits in CF patients with *F508del* homozygous CFTR mutations and *F508del* heterozygous patients with a second allele consisting of a missense or non-canonical splice mutation predicted to be responsive to TEZ/IVA treatment based on clinical and/or *in vitro* data. Clinical data in missense and non-canonical splice mutations demonstrated that treatment with TEZ/IVA was superior to IVA alone. Cross-study comparisons in *F508del* homozygous patients, while limited, suggest that TEZ/IVA is no worse and possibly better than a similar marketed combination product, Orkambi.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk	• The safety program for TEZ/IVA demonstrated potential risks that have been associated with IVA monotherapy: LFT elevation, drug-drug interactions, and cataracts. • No new safety signals were identified with the TEZ component.	No substantial safety findings were identified in the clinical development program that outweigh the potential benefit. The TEZ/IVA product appears to have fewer safety issues than the related Orkambi product.
Risk Management	• No REMS is proposed.	The potential risks of LFT elevation, cataracts, and drug-drug interactions can be managed through labeling and routine pharmacovigilance.

2 Therapeutic Context

2.1. Analysis of Condition

Cystic fibrosis is an autosomal recessive, progressive, and usually fatal genetic disease most common in the Caucasian population. It occurs in approximately one out of every 3,500 children born in the United States, affecting roughly 30,000 children and adults in the US, and is an orphan drug population. CF results from mutations to the cystic fibrosis transmembrane conductance regulator (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 which are difficult to mobilize, leading to recurrent/chronic pneumonia, progressive lung damage, and ultimately respiratory failure. While over 1,000 different disease-causing mutations in the CFTR gene have been identified, the most common CFTR mutation is *F508del*; in the US, approximately 90% of CF patients carry at least one allele and 50% are homozygous. There is no cure for CF and, except for mutation-based subpopulations demonstrated to be responsive to IVA or LUM/IVA, treatment is limited to alleviation of symptoms and treatment of complications. Over the past several decades, with improved care, life expectancy has increased significantly, with the current median age of survival to the mid-late thirties. Current therapies used by patients with CF to help manage their disease are listed in the table below.

2.2. Analysis of Current Treatment Options

In addition to the number of drugs used to treat the symptoms and sequelae of disease, there are FDA-approved products directed at the cause of CF (i.e., absent or defective CFTR ion channel) available for all the CFTR mutation subpopulations covered in the proposed indication. Medications used to treat CF patients are summarized in Table 1. Note that not all are FDA approved for use in CF.

Table 1. Summary of 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 CFTR gene that is responsive to ivacaftor potentiation based on clinical and/or *in vitro* assay*
Lumacaftor/Ivacaftor	Orkambi	Yes: *F508del* homozygous mutations
Inhaled Antibiotics for the Treatment of Pseudomonas aeruginosa		
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
Oral Pancreatic Enzyme Supplementation		
Pancrease, pancrelipase	Creon, Pancreaze, Zenpep, Pancrelipase™	Yes
Inhaled Bronchodilators		
Albuterol sulfate	Pro-Air, Ventolin, Proventil, Albuterol, etc.	Approved as bronchodilator
Levalbuterol hydrochloride	Xopenex	Approved as bronchodilator
Anti-Inflammatory Agents		
Oral azithromycin	Zithromax	No
Oral high-dose Ibuprofen	Motrin, Advil, etc.	No

Source: Approved labeling data from Drugs@FDA,.gov
**Includes G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R, R117H, E56K, P67L, R74W, D110E, D110H, R117C, E193K, L206W, R347H, R352Q, A455E, D579G, 711+3A→G, E831X, S945L, S977F, F1052V, K1060T, A1067T, G1069R, R1070Q, R1070W, 2789+5G→A, 3272-26A→G, 3849+10kbC→T* mutations

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Neither TEZ nor TEZ/IVA are approved or marketed in the US for any other indication. However, regulatory actions for related products also owned by the Applicant include:

- Approval of LUM/IVA (Orkambi®) for CF patients ages 12 years and older and between 6

and 11 years of age who are homozygous for the F580del CFTR mutation on 7/2/15 and 9/28/16, respectively.

- Approval of IVA (Kalydeco®) for CF patients with mutations in the CFTR gene that are responsive or predicted to be responsive to ivacaftor based on clinical and/or *in vitro* assay data (i.e., "residual function" mutations) on 5/17/17. *(Initial approval for G551D CFTR mutations on 1/31/12)*

3.2. Summary of Presubmission/Submission Regulatory Activity

TEZ and the TEZ/IVA combination was developed under IND 108,105, which was opened on 4/15/10. TEZ/IVA was granted fast track designation on 5/21/10, breakthrough therapy designation on 1/28/14, orphan therapy designation on 6/15/17, and priority review designation on 8/23/17. A summary of topics related to the clinical development program that were discussed during key interactions between the Applicant and the FDA is provided below. Additional CMC meetings between the Applicant and the FDA were held on separate occasions and are not included.

<u>September 9, 2013: Type C meeting, written responses only</u>
Nonclinical findings of dilated lacteals remained a significant clinical safety concern. But given the potential benefit of TEZ to treat patients with CF, the Division agreed to allow a clinical study to directly assess for TEZ-induced lacteal dilatation and its potential clinical significance in CF. The Division emphasized that the study should conduct endoscopy in a sufficient number of patients to effectively rule out the likelihood of lacteal dilatation after 3 months of treatment, and that study subjects should be limited to adults with CF.

<u>July 2, 2014: Type B meeting</u>

- FDA commented on the increased exposure of IVA in the presence of TEZ and noted that the Applicant will need to show that the synergistic clinical effect of the TEZ/IVA combination is not due to increased exposure of the two drugs.
- Agreement that data from study VX08-770-104 of IVA monotherapy in homozygous *F508del* patients in conjunction with data from study VX11-661 of TEZ monotherapy supports use of the combination in phase 3 trials and that monotherapy arms are not required.
- FEV1 as a surrogate endpoint for improved lung function remains the best, most expeditious path forward for determining efficacy for the TEZ/IVA combination since other endpoints such as lung clearance index (LCI) and mucociliary clearance (MCC) are considered exploratory endpoints and not reasonably predictive of a clinically meaningful benefit.

<u>November 5, 2014: End of Phase 2 Meeting</u>

- Based on results from study VX08-770-104, which showed minimal efficacy of IVA

monotherapy in *F508*/*F508del* patients, FDA recommended inclusion of IVA monotherapy arm in studies 106 and 107 (in lieu of placebo) to definitively show that the contribution of effect was from TEZ rather than IVA.

- Since study 106 was powered to detect relatively small differences in ppFEV1 (1.5% from placebo), it will be important to show a benefit on other clinically relevant secondary endpoints as well (exacerbations, CFQ-R, BMI, etc.).
- FDA recommended including a LUM/IVA arm in trial 106 to obtain comparative safety data.
- FDA disagreed with the mutations defined as "non-responsive".
- FDA cautioned that shorter studies limit evaluable efficacy endpoints.
- Vertex will need to demonstrate the ability for an *in vitro* test or other clinical parameters to predict whether a patient has "residual function" or is "nonresponsive".
- Regarding study 109 in heterozygous gating mutations, 8 weeks may not be long enough to determine if TEZ/IVA is better than IVA monotherapy. FDA expressed concern that it may be difficult to show either a statistical or clinically meaningful difference in FEV1 given that IVA monotherapy is known to increase ppFEV1 10-12%.
- Vertex will need to demonstrate that efficacy is not due to increased exposure of IVA or TEZ when combined.

November 4, 2015: Type B meeting – preliminary responses

- Vertex is not required to demonstrate the contribution of TEZ and IVA components to the combination for each type or subgroup of mutation being studied. They only need to demonstrate contribution of each component in one mutation subgroup, and FDA believes F508/*F508del* homozygotes may be the most appropriate population.
- Vertex assumes regulatory risk by not including an IVA monotherapy arm.

May 30, 2017: Pre-NDA meeting

- FDA will take a similar approach to the proposed indication as for IVA sNDA 203188/S-019, assuming the presence of similarly convincing supportive *in vitro* data for TEZ/IVA. (b) (4)
- Not all mutations approved for IVA alone will necessarily be approved for TEZ/IVA unless TEZ/IVA demonstrates added benefit above IVA. Vertex will need to carefully consider and justify what *in vitro* data (i.e., increase in chloride transport) can be considered sufficient to conclude that TEZ/IVA provides an added benefit over IVA alone.
- Agreement upon the clinical data to be submitted to the NDA will come from studies 101, 103, 106, 107, 108, and 110.
- An advisory committee meeting is not anticipated.
- Extension of indication to "residual function" mutations eligible for, but not enrolled in, study 108 will be a review issue. The rationale for extrapolating clinical safety and

efficacy from *in vitro* data should be included in the submission.

3.3. Foreign Regulatory Actions and Marketing History

Not applicable. Neither TEZ nor TEZ/IVA are approved for marketing in any country outside the US; however, TEZ/IVA is currently under review by the EMA.

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

4.1. Office of Scientific Investigations (OSI)

The following sites were inspected as part of FDA's Bioresearch Monitoring Program to evaluate the conduct of research:

Amparo Sole Jover, M.D. Hospital Universitario y Politecnico La Fe Valencia, 46026 Spain Site 533 in Trial 106	James Wallace, M.D. Sanford Children's Specialty Clinic Sioux Falls, SD Site 117 in Trial 106	Claire Keating, M.D. Columbia University Medical Center New York, NY Site 051 in Trial 107	Emily DiMango, M.D. Columbia University Medical Center New York, NY Site 051 in Trial 108	Jeffrey Leiden, M.D. Vertex Pharmaceuticals, Inc. Boston, MA sponsor

Although minor regulatory violations were observed at some of the clinical investigation sites, none were of magnitude that would significantly impact the efficacy or safety analyses or call into question the integrity of data. All inspections resulted in either NAI or VAI recommendations. Investigator responses to the inspection findings with plans to implement corrective actions and prevent future recurrence were found to be acceptable.

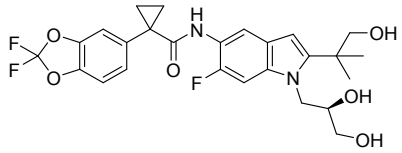
4.2. Product Quality

SYMDEKO is a co-packaged tezacaftor/ivacaftor fixed dose combination tablet and an ivacaftor tablet, both for oral administration. Tezacaftor is a new molecular entity (NME with BCS class II) while ivacaftor (BCS class II or IV) is already approved for treatment of CF as a single active ingredient (NDAs 203-188, 207-925) and in combination with lumacaftor (NDA 206-038).

The TEZ/IVA fixed dose combination tablet will be supplied as a yellow, capsule-shaped, film-coated tablet containing 100 mg of TEZ, 150 mg of IVA, and the following compendial excipients: hypromellose acetate succinate, sodium lauryl sulfate, hypromellose, microcrystalline cellulose, croscarmellose sodium, and magnesium stearate. The tablet film coat contains HPMC/hypromellose 2910, hydroxypropyl cellulose, titanium dioxide, talc, and iron oxide yellow.

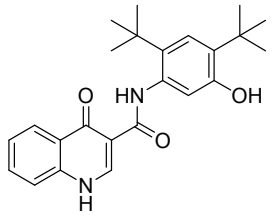
The IVA tablet will be supplied as a light blue, capsule-shaped, film-coated tablet containing 150 mg of IVA and the following compendial excipients: colloidal silicon dioxide, croscarmellose sodium, hypromellose acetate succinate, lactose monohydrate, magnesium stearate, microcrystalline cellulose, 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 chemical names and molecular structures are as follows:
Tezacaftor
The chemical name of tezacaftor 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)-1Hindol-5-yl}cyclopropane-1-carboxamide. Its molecular formula is C26H27N2F3O6 and its molecular weight is 520.50. Tezacaftor has the following structural formula:



Tezacaftor is a white to off white powder that is practically insoluble in water (<5 microgram/mL).

Ivacaftor
The chemical name of ivacaftor 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:



Ivacaftor is a white to off white powder that is practically insoluble in water (<0.05 microgram/mL).

The applicant uses similar Chemistry, Manufacturing, and Controls for production of the drug product at their Boston, MA site as was used for their approved NDA 206-038 (Orkambi), i.e., a fully continuous drug product manufacturing, process analytical technology, and real-time-release-testing as an alternative to regulatory end-product testing. Design spaces have been established for both the drug product manufacture and the tezacaftor synthesis. The

immediate container closure system is standard blister packaging for tablets. All batch analysis results met the proposed and acceptably justified specifications. Up to 18 months of real time stability data were provided with results indicating good product stability. Based on ICH Q1E, the information provided supports the applicant requested product expiry of 30 months.

Drug Master Files were not referenced for this application as all pertinent information was adequately provided within the application. The manufacturing facilities for NDA 210-491 are acceptable. There are no significant, outstanding manufacturing or facility risks that prevent approval. Thus, from a CMC perspective, the Applicant has provided sufficient CMC information to assure the identity, strength, quality, and purity of the drug product to recommend approval.

4.3. Clinical Microbiology

Not applicable.

4.4. Nonclinical Pharmacology/Toxicology

From the nonclinical Pharmacology/Toxicology perspective, the recommendation is for approval.

A full nonclinical development program, including lack of carcinogenic potential in rat and mouse studies, has been completed for IVA, which was approved as monotherapy for the treatment of CF on January 31, 2012. Key findings included bilateral cataracts in a juvenile rat study resulting in a Warning and Precaution in the Kalydeco label. Cataracts have been observed in CF patients receiving IVA but, because of confounding factors such as use of corticosteroid products, it is difficult to determine the strength of the association.

The nonclinical program for the TEZ/IVA combination was therefore focused on the nonclinical findings for TEZ, including carcinogenic potential.

General toxicity of TEZ was evaluated in rat and dog studies of up to 6 and 12 months' duration, respectively. Nonclinical findings of dilated lacteals in early rat studies were noted to be a significant clinical safety concern. These concerns were addressed by the conduct of a clinical study in adult CF patients to directly assess for TEZ-induced lacteal dilatation and its potential clinical significance in CF. Video capsule endoscopy (VCE) was performed on 39 subjects (21 active, 18 placebo) in study VX13-661-103 at screening and at Week 13 after 3 months of treatment. No treatment-emergent lymphangiectasias were detected by the blinded VCE assessments, thus alleviating the concern about this potential safety signal in humans.

Toxicology studies evaluating the TEZ/IVA combination were also conducted in rats. There were no novel toxicities attributed to the combination compared to the individual components.

Regarding genetic toxicity, TEZ was negative in gene toxicology tests including Ames test for bacterial gene mutation, *in vitro* mammalian chromosome aberration, and in vivo micronucleus assays.

TEZ was not associated with any adverse effects in developmental and reproductive toxicology studies, including male / female fertility, embryofetal survival, teratogenicity, and post-natal development and sexual maturation. Placental transfer of both TEZ and IVA were observed in pregnant rats.

The carcinogenicity evaluation of TEZ was evaluated in a 2-year rat study and a 26-week Tg.rasH2 mouse study. Doses and study designs were agreed upon with Executive Carcinogenicity Assessment Committee with Special Protocol Agreements dated December 18, 2013, and November 20, 2014. In studies for both rats and mice treated with maximum tolerated doses of TEZ, no statistically significant neoplastic findings were observed.

The nonclinical team is the lead discipline in the determination of the Established Pharmacological Class (EPC) of a product. IVA has previously been designated as a "CFTR Potentiator" based on its mechanism of action i.e., facilitates increased chloride transport by potentiating the channel-open probability of the CFTR protein at the cell surface.

TEZ, as a novel drug, does not belong to an EPC. However, in academic and drug development circles, TEZ, like lumacaftor, is referred to as a CFTR corrector, (b) (4) designating TEZ as a CFTR corrector was not fully justifiable based on what is known about its mechanism of action, i.e., to improve the conformational stability of mutant CFTR ion channel, resulting in increased cellular processing and trafficking of it to the cell surface. Thus, like lumacaftor, TEZ will be marketed without an EPC.

4.5. Clinical Pharmacology

From the clinical pharmacology perspective, the recommendation is for approval.

4.5.1. Mechanism of Action

Tezacaftor is a CFTR modulator that facilitates cellular processing and trafficking of normal or mutant forms of CFTR (including *F508del*-CFTR) to increase the amount of CFTR protein delivered to the cell surface, thereby enhancing chloride transport. IVA is a CFTR potentiator that potentiates the channel-open probability or gating of CFTR at the cell surface to enhance chloride transport. *In vitro* studies show that IVA can potentiate the CFTR protein delivered to the cell surface by TEZ, resulting in further enhancement of chloride transport than either agent alone.

4.5.2. Pharmacodynamics

Dose-ranging Studies
The clinical development program for TEZ/IVA included two dose-finding studies in CF patients, Studies 101 and 103.

Study 101
Results from Study 101 served as the primary basis for dose selection in phase 3. In this study, the effects of sequential dose increases of TEZ (10, 30, 100, and 150 mg) alone and in combination with the approved dose of IVA 150 mg q12h (given the lack of DDI between TEZ and IVA) on sweat chloride and percent predicted forced expiratory volume in 1 second (ppFEV1) were evaluated in 104 *F508del* homozygous subjects, the mutation subpopulation likely to be the least responsive to therapy. A mean reduction in sweat chloride on Day 28 was observed for all TEZ and TEZ/IVA dose groups (range: -2.63 to -20.43 mmol/L) except for the TEZ 10 mg QD group. Population PK/PD analyses were suggestive of a TEZ/IVA dose-response relationship for change in sweat chloride and estimated TEZ 100 mg QD/IVA 150 mg Q12 to be near the maximum achievable response. Increases in ppFEV1 were also observed with increasing TEZ exposure but did not appear to be dose-dependent based on data for the TEZ only groups (Table 18). At all TEZ doses above 10 mg, TEZ/IVA had a greater mean treatment effect than TEZ alone. The TEZ 100 mg QD/IVA 150 mg Q12h group showed the greatest mean improvement in ppFEV1 after 4 weeks of treatment compared to placebo (4.8, 95% CI 1.2-8.4). No additional benefit was observed at the higher TEZ dose of 150 mg QD. Study 101 also evaluated a lower dose of IVA (TEZ 100 mg QD/IVA 50 mg q12h), but this regimen resulted in a lower mean change in ppFEV1.

Table 2. Absolute change in ppFEV1 at Day 28 in *F508del* homozygous patients: Study 101

	Mean (95% CI) Absolute Change From Baseline at Day 28: $ppFEV_1$		Treatment Difference vs Placebo (95% CI)	
TEZ Dose	TEZ Monotherapy	TEZ + IVA 150 mg q12h	TEZ Monotherapy	TEZ + IVA 150 mg q12h
10 mg qd	N = 8	N = 18	N = 8	N = 18
	3.26	1.99	3.62	2.35
	(-0.79, 7.32)	(-0.65, 4.63)	(-1.03, 8.28)	(-1.14, 5.83)
	P = 0.1141	*P* = 0.1387	*P* = 0.1268	*P* = 0.1864
30 mg qd	N = 8	N = 19	N = 8	N = 19
	0.19	3.02	0.55	3.37
	(-3.70, 4.08)	(0.40, 5.63)	(-3.96, 5.06)	(-0.10, 6.84)
	P = 0.9237	*P* = 0.0240	*P* = 0.8115	*P* = 0.0567
100 mg qd	N = 8	N = 17	N = 8	N = 17
	1.55	4.44	1.91	4.80
	(-2.34, 5.45)	(1.66, 7.23)	(-2.61, 6.42)	(1.20, 8.39)
	P = 0.4339	*P* = 0.0019[b]	*P* = 0.4062	*P* = 0.0090
150 mg qd	N = 9	N = 17	N = 9	N = 17
	2.34	4.13	2.70	4.49
	(-1.33, 6.01)	(1.41, 6.86)	(-1.62, 7.01)	(0.94, 8.04)
	P = 0.2112	*P* = 0.0031	*P* = 0.2199	*P* = 0.0133

Source: Study 101 CSR/Table 14.2.5.2.1
Source: Module 2.7.2, Summary of Clinical Pharmacology Studies, Table 18, p56

The effect of TEZ 100 mg QD/IVA 150 mg Q12h was also evaluated in *F508del/G551D* subjects, the mutation subpopulation likely to show a larger therapeutic response. This patient cohort received either TEZ 100 mg QD or placebo on a background of physician prescribed Kalydeco. The TEZ/IVA group had decreases in mean sweat chloride of -7.02 mmol/L (difference vs placebo of -17.2 mmol/L) and increases in mean ppFEV1 of 4.60 percentage points (difference vs placebo of 3.20 percentage points) after 28 days of treatment. These results provided additional support for the dose selection of TEZ 100 mg QD/IVA 150 mg Q12h.

Study 103
Study 103 was conducted to confirm the dosing regimen of the TEZ component. In this study, 39 *F508del* homozygous patients received either TEZ 100 mg QD/IVA 150 mg Q12h, TEZ 50 mg Q12h/IVA 150 mg Q12h, or placebo. Absolute changes from baseline in ppFEV1 through Week 12 were 3.0 and 0.9 percentage points for TEZ 100 mg QD/IVA 150 mg Q12h versus TEZ 50 mg Q12h/IVA 150 mg q12h, respectively.

Results from these studies provided sufficient support for the selection of TEZ 100 mg QD/IVA 150mg Q12 to carry forward into phase 3 trials.

4.5.3. Pharmacokinetics

As IVA pharmacokinetics have already been extensively characterized, Vertex submitted results from a clinical pharmacology program that included studies to assess the pharmacokinetics and metabolism of TEZ and as well as the combination product.

Ivacaftor
Steady state concentration of IVA in CF patients was achieved in 3-5 days. Its absorption is improved (3-fold) when taken with fat-containing foods compared to the fasting state. IVA is extensively metabolized in humans with the majority excreted in the feces. *In vitro* and clinical studies indicate that IVA is primarily metabolized by CYP3A. As such, co-administration with strong CYP3A inhibitors increases IVA exposure (see drug-drug interactions below). The IVA effective half-life is approximately 20 hours.

Tezacaftor
Steady state concentration of TEZ in CF patients was achieved within 8 days. Food has no effect on TEZ absorption. TEZ is also extensively metabolized in humans, again by CYP3A with 3 major metabolites. Most of the drug is excreted in feces unchanged or as the M2 metabolite. The TEZ effective half-life is approximately 29 hours which supports a once daily dosing regimen.

Tezacaftor/Ivacaftor
TEZ exposure, whether administered alone or in combination with IVA, increases in an approximately dose proportional manner with increasing doses from 10 mg to 150 mg once

daily. Although IVA exposure increases approximately 20% in the presence of TEZ, this is not expected to impact the clinical outcomes with the TEZ/IVA combination since IVA is already at the top of the dose-response curve at these exposure levels. Thus, one may consider any additional clinical benefit observed with the TEZ/IVA combination over IVA alone to originate from the TEZ component.

Drug-Drug Interaction
TEZ and IVA are substrates of CYP3A. Thus, concomitant use of CYP3A inducers such as rifampin, phenobarbital, and St. John's Wort, will result in reduced TEZ/IVA exposure that may affect efficacy. As such, co administration of TEZ/IVA with strong CYP3A inducers is not recommended, and this information will be conveyed in the PI.

Co-administration of TEZ/IVA with itraconazole, a strong CYP3A inhibitor, increased TEZ exposure (AUC) by 4.0-fold and IVA by 15.6-fold. Thus, when co-administered with moderate and strong CYP3A inhibitors, the dose of TEZ/IVA will need to be reduced. A table outlining the needed changes will be included in Section 7 of the PI.

TEZ/IVA has been studied with an estrogen/progesterone oral contraceptive and was found to have no significant effect on the exposures of the hormonal contraceptive.

4.5.4. *In vitro* Assay Assessment

Like the data submitted to support the 2017 expansion of the Kalydeco (NDA 203188) indication based on *in vitro* data, Vertex submitted Ussing Chamber assay data again using FRT cell lines stably expressing cDNAs from mutant *CFTR* genes supported by Western Blot analyses to predict clinical benefit for their proposed TEZ/IVA combination product. It is notable that the assay was modified: longer incubation times to account for the different mechanisms of action of TEZ and IVA, use of different ion channel inhibitors, and a different definition of baseline chloride transport value, among others. Thus, the data from this modified assay cannot be directly compared to the *in vitro* data presented in the Kalydeco prescribing information. That being said, a similar review process as previously was undertaken to evaluate the technical aspects of the assay, in particular, the validity of the modified Ussing Chamber assay, verification of *in vitro* data integrity and findings, and consistency of *in vitro* assay findings with clinical efficacy data for mutations in which clinical data were available.

The evaluation arrived at the following conclusions:

- The modified assay was conducted according to acceptable scientific standards and was adequate to determine the responsiveness in FRT cells with select CFTR mutations to the TEZ/IVA combination. While the assay reliably measures the same thing (chloride transport) as the assay for IVA (Kalydeco), because the methodology is somewhat

different to accommodate evaluation of a combination product, the values for chloride transport found in the Symdeko and Kalydeco labels can't be directly compared.

- The assay does not predict whether the addition of TEZ to IVA (Symdeko) will result in additional clinical benefit over that which may be provided by IVA (Kalydeco) alone. Clinical data are required for that assessment.
- Since it is unable to predict whether the addition of TEZ confers added clinical benefit, the primary intent of the assay is to determine whether change in Cl transport from exposure to TEZ/IVA for various CFTR mutations meets the net increase of at least 10% normal over baseline, the value that was previously determined to be reasonably predictive of clinical benefit. Because the assay has been modified, concern arose that the 10% cut-off value may no longer be valid. However, for all mutations submitted for this NDA, it is reassuring that for mutation groups for which there are positive clinical data, the TEZ/IVA combination *in vitro* result met or exceeded the 10% threshold and those that did not meet the 10% threshold failed to demonstrate clinical efficacy. Additionally, for the *F508del* mutation (for which IVA alone does not provide clinical benefit), the *in vitro* results for IVA did not meet the 10% threshold while they just met the 10% threshold for the TEZ/IVA combination, consistent with clinical data demonstrating efficacy (although less than more responsive mutations). Thus, the 10% of normal shift in chloride transport still appears to be a reasonable threshold to define a population with disease-causing mutations that may be amenable to treatment with TEZ/IVA. The 10% threshold likely errs on being more sensitive than specific but in this case that is desirable so as not to exclude CF patients with mutations that may respond clinically.

In summary, the assay methodology is technically solid and it reasonably predicts whether there may be a clinical benefit for the TEZ/IVA combination (Symdeko). It does not predict if the addition of TEZ to IVA (Kalydeco) will result in additional benefit, clinical data are required for such a determination. As such, while additional subpopulations of CF patients with less common disease-causing mutations in the *CFTR* gene may still be added to the label based on an *in vitro* response to TEZ/IVA, absent clinical trial data, clinical judgement should be used to determine whether response to IVA monotherapy (Kalydeco) should first be evaluated in these patients prior to the addition of a second CFTR modulator (TEZ in Symdeko). A figure like the one found in Section 12 of the Kalydeco label should be included in the Symdeko label accompanied by statements regarding its limitations (lack of ability to predict if Symdeko adds benefit over Kalydeco) to fully inform CF health care providers as to how to interpret the *in vitro* data.

5 Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

The sources of clinical data used in this review are summarized in Table 3.

Table 3. Listing of Clinical Trials Relevant to this NDA

Trial Identity/ *Dates*	Trial Design	Regimen (mg)*	Study Endpoints (1° and Key 2°)	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
Controlled Phase 3 Studies to Support Efficacy and Safety							
106 *01/15 – 01/17*	R, DB, PC, PG	• TEZ 100/IVA 150 qAM + IVA 150 qPM • Placebo BID	- Absolute Δ ppFEV1 through Wk 24 - Relative Δ ppFEV1 through Wk 24 - # pulmonary exacerbations through Wk 24 - Absolute Δ BMI at Wk 24 - Absolute Δ CFQ-R through Wk 24	24 weeks / 4 week FU or OLE	510 randomized 509 treated 477 completed	CF patients ≥ 12 years, homozygous F508 del-CFTR mutation	91 sites 12 countries: USA, Canada, Denmark, France, Germany, Ireland, Italy, Netherlands, Spain, Sweden, Switzerland, UK
107 *08/15 – 06/16*	R, DB, PC, PG	• TEZ 100/IVA 150 qAM + IVA 150 qPM • Placebo BID	- Absolute Δ ppFEV1 through Wk 12 - Absolute Δ CFQ-R through Wk 12 - # pulmonary exacerbations through Wk 12 - Absolute Δ BMI at Wk 12	12 weeks / 4 week FU or OLE	168 randomized 168 treated 166 completed	CF patients ≥ 12 years, heterozygous for *F508del*-CFTR mutation and 2nd CFTR mutation not likely to respond to TEZ and/or IVA therapy	38 sites 7 countries: USA, Australia, Austria, Canada, Spain, France, Israel
108 *03/15 – 02/17*	R, DB, PC, IXO	• TEZ 100/IVA 150 qAM + IVA 150 qPM • IVA 150 BID • Placebo BID	- Absolute Δ ppFEV1 (avg Wks 4 & 8) - Absolute Δ CFQ-R (avg Wks 4 & 8)	Two 8-week treatment periods with 8-week washout / 4 week FU or OLE	248 randomized 246 treated 234 completed	CF patients ≥ 12 years, heterozygous for *F508del*-CFTR mutation and 2nd CFTR mutation predicted to have residual function	81 sites 10 countries: USA, Australia, Belgium, Canada, Germany, France, UK, Israel, Italy, Netherlands
Uncontrolled Studies to Support Safety							
110 *08/15 – ongoing*	OLE	• TEZ 100/IVA 150 qAM + IVA 150 qPM	- Safety	96 weeks	870 enrolled 867 treated	Subjects who completed trials 103, 106, 107, 108, 109†, or 111‡	161 sites 16 countries: USA, Australia, Austria, Belgium, Canada, Germany, Denmark, Spain,

							France, Ireland UK, Israel, Italy, Switzerland, Sweden, Netherlands
Phase 2 Dose-ranging studies							
101 *02/12 – 03/14*	R, DB, PC, MAD	• TEZ 10 QD • TEZ 30 QD • TEZ 10 QD + IVA 150 BID • TEZ 100 QD • TEZ 30 QD + IVA 150 BID • TEZ 100 QD + IVA 150 BID • TEZ 150 QD • TEZ 100 QD + IVA 50 BID • TEZ 50 BID + IVA 150 BID • TEZ 100 QD + Kalydeco • Placebo	- Safety/tolerability - Δ sweat chloride through Day 28 & each visit - Δ ppFEV1 through Day 28 & each visit - Δ CFQ-R at each visit - PK parameters	28 days / 28 day FU	194 randomized 190 treated 179 completed	CF patients ≥ 18 years, homozygous for *F508del*-CFTR mutation or ≥12 years, heterozygous for *F508del* and G551D CFTR mutations	37 sites 4 countries: USA, Canada, Germany, UK
103 *03/14 – 05/16*	R, DB, PC	• TEZ 50 BID + IVA 150 BID • TEZ 100 QD + IVA 150 BID • Placebo	- Safety - Absolute and relative Δ ppFEV1 - Absolute Δ sweat chloride -Absolute Δ body weight - Absolute Δ BMI - Absolute Δ CFQ-R - PK	12 weeks / 28 day FU or OLE	40 randomized 39 treated 36 completed	CF patients ≥ 18 years, homozygous for *F508del*-CFTR mutation	16 sites 1 country: USA

BID=twice daily, BMI=body mass index, CF=cystic fibrosis, CFTR=cystic fibrosis transmembrane conductance regulator, CFQ-R=cystic fibrosis questionnaire-revised (respiratory domain), DB=double-blind, FU=follow up, IXO=incomplete crossover, IVA=ivacaftor, MAD=multiple ascending dose, OLE=open label extension, PC=placebo-controlled, PG=parallel group, PK=pharmacokinetic, ppFEV1=percent predicted forced expiratory volume in 1 second, qAM=every morning, QD=daily, qPM=every evening, R=randomized, TEZ=tezacaftor
*All doses administered orally
†Trial 109 enrolled adult and adolescent CF patients heterozygous for *F508del*-CFTR mutations and 2nd allele with gating mutation demonstrated to be clinically responsive to ivacaftor
‡Trial 111 enrolled adult CF patients homozygous for *F508del*-CFTR mutations

5.2. Review Strategy

Support for the efficacy and safety of TEZ/IVA in the proposed indication is based on two trials in different mutation subgroup populations: Trial VX14-661-106 in CF patients with *F508del* homozygous CFTR mutations and Trial VX14-661-108 in CF patients with the *F508del* CFTR mutation and a second allele with "residual function" (defined below in Section 6.2.1). In addition, Trial VX14-661-107 in CF patients with the *F508del* CFTR mutation and a second allele predicted to be unresponsive to TEZ/IVA was also reviewed. Despite failing to meet its primary endpoint and being terminated early for futility, the review team felt that it would be important to convey information from the failed study in the label. For the evaluation of efficacy, results from these three individual studies are presented in Section 6 while a discussion of the overall efficacy for the proposed indication is provided in Section 7. FDA biostatistician, Dr. Mingyu Xi confirmed the Applicant's efficacy analyses and generated tables and figures for this review. For the evaluation of safety, I analyzed data from the three phase 3 trials individually and pooled together using JMP, JMP Clinical, JReview, and MAED. The safety results presented in Section 8 represent my own analyses. In addition, the open label extension study VX14-661-110 will be discussed in Section 8 and was reviewed to evaluate the safety of chronic TEZ/IVA use. For brevity, trials will be referred to in this review by the last 3 digits of the trial name.

6 Review of Relevant Individual Trials Used to Support Efficacy

6.1. VX14-661-106

6.1.1. Study Design

Overview and Objective

Trial 106 was a multinational pivotal trial to provide evidence for the efficacy and safety of TEZ in combination with IVA in subjects with CF who are homozygous for the *F508del* mutation on the CFTR gene. The study was conducted from 1/30/15 through 1/20/17.

Study Title: A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group Study to Evaluate the Efficacy and Safety of VX-661 in Combination with IVA in Subjects Aged 12 Years and Older with Cystic Fibrosis, Homozygous for the *F508del*-CFTR Mutation

Primary Objective

- To evaluate the efficacy of TEZ/IVA through week 24 in CF patients homozygous for the *F508del* mutation

Secondary Objectives

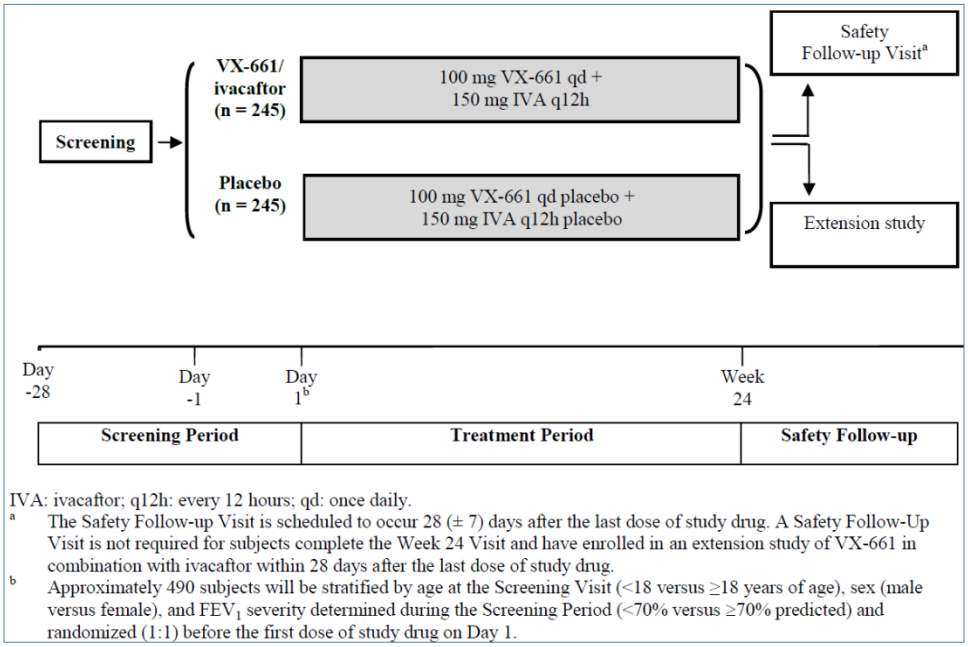
- To evaluate the safety of TEZ/IVA through week 24
- To investigate the PK of TEZ, IVA and their metabolites

Trial Design

Trial 106 had a randomized, double-blind, placebo-controlled, parallel group study design with a 24-week treatment period (Figure 1). The study included a 28-day screening period, 24-week treatment period, and 28 day follow up period. After screening, eligible subjects were randomized (1:1) to one of two treatment arms: active treatment with TEZ/IVA or placebo. The first dose of study drug was administered on Day 1. During the treatment period, study visits occurred on Days 1 and 15, and at weeks 4, 8, 12, 16, 20, and 24. For male subjects and female subjects not of childbearing potential, the week 20 study visit may have been conducted by phone. At the week 24 visit, subjects who completed the treatment period could enroll in extension study 110. If subjects declined to participate in the OLE study, safety follow-up visit occurred 28 (±7) days after the last dose of study drug. Subjects who discontinued treatment prematurely also had an early treatment termination visit as soon as possible after the decision to discontinue study drug treatment. Study assessments are summarized in Table 4.

The study design is adequate and typical of other trials for CFTR modulators; the longer treatment period also allows for an evaluation of less frequent events such as pulmonary exacerbations as well as parameters that respond more slowly to treatment such as weight/BMI. Dose selection for the TEZ/IVA combination was adequately explored in the dose ranging studies 101 and 103 as described in Section 4.5.2. Although IVA monotherapy has been shown to have minimal efficacy in the *F508del* homozygous population, the lack of an IVA only treatment arm in this study makes it difficult to demonstrate the contribution of each component to the combination product.

Figure 1. Study Design Schematic: Trial 106



IVA: ivacaftor; q12h: every 12 hours; qd: once daily.
[a] The Safety Follow-up Visit is scheduled to occur 28 (± 7) days after the last dose of study drug. A Safety Follow-Up Visit is not required for subjects complete the Week 24 Visit and have enrolled in an extension study of VX-661 in combination with ivacaftor within 28 days after the last dose of study drug.
[b] Approximately 490 subjects will be stratified by age at the Screening Visit (<18 versus ≥18 years of age), sex (male versus female), and FEV_1 severity determined during the Screening Period (<70% versus ≥70% predicted) and randomized (1:1) before the first dose of study drug on Day 1.

Source: Clinical Trial Protocol, VX14-661-106, Figure 8-1, p22

Table 4. Schedule of Assessments: Trial 106

Event/Assessment[a]	Day 1	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[b]	Safety Follow-up Visit 28 (± 7) days After the last dose of study drug (if applicable)[c]
Clinic visit	X	X	X	X	X	X	X[d]	X	X	X
Telephone contact							X[e]			
Inclusion and exclusion criteria review	X									
CFQ-R[f]	X		X	X	X	X		X	X	X
CFRSD[f]	X	X	X	X	X			X	X	
SF-12[f]	X		X	X	X			X	X	
PSQI[f]	X		X	X	X			X	X	
Actigraphy[g]	Continuous from Screening through Safety Follow-up Visit									
Weight and height[h]	X	X	X	X	X	X		X	X	X
Ophthalmologic exam								X[i]	X[j]	X[j]
Complete PE[k]	X							X	X	
Pregnancy test[l]	urine		urine	urine	urine	urine	urine	serum	serum	serum
Standard 12-lead ECG[m]	X	X	X	X	X	X		X	X	X
Vital signs[n]	X	X	X	X	X	X		X	X	X
Pulse oximetry[n]	X	X	X	X	X	X		X	X	X
Spirometry[o]	X	X	X	X	X	X		X	X	X
Sweat chloride[p]	X		X			X		X	X	
Urinalysis	X							X	X	X
Hematology	X	X	X	X	X	X		X	X	X
Coagulation	X							X	X	X

Serum chemistry	X[q]	X	X	X	X	X		X	X	X
Lipid panel[r]	X				X			X	X	
Vitamin levels	X				X			X	X	
PK sampling[s]	X				X	X			X	X
DNA Sample A and B (optional)		X								
Immunoreactive trypsinogen (IRT)	X							X		
Blood biomarker analysis	X							X		X
Sputum samples[t]	X							X		
Inflammatory mediators	X							X		
Other events related to outcome[u]	X	X	X	X	X	X	X	X	X	
Randomization[v]	X									
Meal(s) or snack(s) at site[w]	X	X	X	X	X	X				
Study drug dosing[x]	**Day 1 through Week 24**									
Study drug count		X	X	X	X	X		X	X	
Concomitant medications[y]	X	X	X	X	X	X	X	X	X	X
Concomitant treatments and procedures	X	X	X	X	X	X	X	X	X	X
AEs and SAEs[z]	**Continuous from signing of the ICF and Assent (where applicable) through the Safety Follow-up Visit**									

AE: adverse event; β-hCG: beta-human chorionic gonadotropin; CF: cystic fibrosis; CFQ-R: CF Questionnaire–Revised; CFRSD: CF Respiratory Symptom Diary; ECG: electrocardiogram; ETT: Early Treatment Termination; IWRS: interactive web response system; PE: physical examination; PK: pharmacokinetic; PSQI: Pittsburgh Sleep Quality Index; SAE: serious adverse event; SF-12: 12-Item Short Form Survey.

[a] All assessments will be performed before dosing unless noted otherwise. If study drug is not administered on the day of the visit (i.e., study drug interruption or premature discontinuation of study drug treatment), only 1 set of assessments will be collected. Subjects who discontinue treatment early will continue to complete all other scheduled study visits for assessments of efficacy (spirometry, CFQ-R, sweat chloride, height, and weight), other endpoints (PSQI, CFRSD, and SF-12), and other events related to outcome (hospitalizations, pulmonary exacerbations, etc.) as detailed in Section 8.1.4.

[b] If the subject prematurely discontinues study treatment, an Early Treatment Termination (ETT) Visit should be scheduled as soon as possible after the subject decides to terminate study treatment. Subjects who prematurely discontinue treatment will also be required to complete the Safety Follow-up Visit, approximately 28 (± 7) days after their last dose of study drug. If the ETT Visit occurs 3 weeks or later following the last dose of study drug, then the ETT Visit will replace the Safety Follow-up Visit, and a separate Safety Follow-up Visit will not be required. See Section 8.1.4.

[c] A Safety Follow-Up Visit is not required for subjects who complete the Week 24 Visit and have enrolled in a separate extension study of VX-661 in combination with ivacaftor within 28 days after the last dose of study drug.

[d] Females of childbearing potential will have a clinic visit for a urine pregnancy test. This clinic visit is not required for females who are **not** of childbearing potential or males.

[e] Telephone contact will be made for female subjects not of childbearing potential and males to assess the subject's status, any AEs, concomitant medications, treatments, and procedures.

[f] All questionnaires must be completed before the start of any other assessments scheduled at that visit. The CFQ-R must be completed first, followed by the CFRSD, SF-12, and PSQI (Section 11.1). Subjects will need to complete a CFQ-R, CFRSD, SF-12, and PSQI at the Early Treatment Termination Visit (Section 8.1.4).

[g] Actigraphy will be performed at select sites.

[h] Weight and height will be measured before dosing with shoes off. Height will be collected only for subjects 21 years of age or younger.

[i] All subjects will have an ophthalmologic examination conducted by a licensed ophthalmologist at Week 24. This exam may be completed within 4 weeks before the Week 24 Visit, but must be completed by the end of the Week 24 Visit. Subjects <18 years of age at the Screening Visit who complete an ophthalmologic exam at the ETT Visit will not be required to complete another ophthalmologic exam at the Week 24 Visit.

[j] Subjects <18 years of age at the Screening Visit who discontinue treatment after receiving at least 1 dose of study drug treatment, and subjects <18 years of age at the screening who complete treatment but do not enroll in a separate extension study of VX-661/ivacaftor within 28 days of the last dose of study drug will have an ophthalmologic exam conducted by a licensed ophthalmologist at the Safety Follow-up Visit or ETT Visit (see Section 11.7.8). The exam may be completed at either the ETT or Safety Follow-up Visit, but must be completed by the date of the Safety Follow-up Visit. Subjects who complete an ophthalmologic exam at the ETT Visit or Week 24 Visit will not be required to complete another ophthalmologic exam at a subsequent visit.

[k] Subjects will have a complete physical examination (as defined in Section 11.7.3) as noted. Symptom-targeted physical examinations will occur at any time during the study if triggered by AEs or if deemed necessary by the investigator.

[l] Pregnancy tests will be performed for all female subjects of childbearing potential. A urine β-hCG test will be performed on Day 1 (before first dose of study drug) and every 4 weeks thereafter.

[m] All standard 12-lead ECGs will be performed before dosing and after the subject has been supine for at least 5 minutes. At the Days 1 and 15 Visits, ECGs will be collected before dosing and at 1.5, 3, 4, and 6 hours after the morning dose; the 4-hour postdose ECG will be collected before the 4-hour postdose spirometry assessment. ECGs collected on Day 1 before dosing will be performed in triplicate. If study drug is not administered on the day of the visit (i.e., because of study drug interruption or permanent discontinuation of study drug), only 1 ECG will be collected.

[n] Vital signs and pulse oximetry will be collected before dosing and after the subject has been at rest (seated or supine) for at least 5 minutes.

[o] At all visits, spirometry must be performed for all subjects before dosing and should be performed prebronchodilator (Section 11.6.1). At Day 1 and Day 15, subjects <18 years of age at the Screening Visit will have additional spirometry performed at 2 and 4 hours postdose. If more than 1 spirometry assessment is required at a visit, bronchodilators should be withheld until the last scheduled spirometry assessment is completed.

[p] Sweat chloride collection will occur approximately 1 hour before the PK sample collection and before the morning dose of the study drugs. At each time point, 2 samples will be collected, 1 from each arm (left and right). Collection of sweat chloride will not overlap with any other study assessments.

[q] Blood samples will be collected before the first dose of study drug.

[r] Blood samples will be collected for the lipid panel following at least a 4-hour fast.

[s] PK samples will be collected on Day 1 at predose; at Week 12 (predose, 0.5, 3, and 6 hours after the morning dose); and at Week 16 (predose, 2, 4, and 8 hours after the morning dose). At the Safety Follow-up Visit and ETT Visit, a single blood sample for PK will be collected. If study drug is not administered on the visits of Weeks 12 and 16 (i.e., study drug interruption or permanent discontinuation of study drug), only 1 PK blood sample will be collected at each of these 2 visits.

[t] Sputum will be collected from subjects who can produce a sample spontaneously. An aliquot of the sputum sample will be used for microbiology culture, and the remaining sputum sample will be stored for use as described in Sections 11.5 and 11.6.9.

[u] Other events related to outcome include assessments relating to pulmonary exacerbations, administration of antibiotic therapy for sinopulmonary signs or symptoms, and hospitalizations (Section 11.6.12).

[v] Randomization must occur after all inclusion and exclusion criteria are met and before the first dose of study drug. Randomization will be done through IWRS. Randomization may occur on Day -1.

[w] Fat-containing food such as a standard "CF" high-fat, high-calorie meal or snack will be provided at the site to subjects after all predose assessments have occurred.

[x] The study drug should be administered every 12 hours (± 2 hours) within 30 minutes of starting a meal with fat-containing food such as a standard "CF" high-fat, high-calorie meal or snack. On days of scheduled visits, the morning dose of study drug will be administered at the site after predose assessments have been completed. The final dose of study drug will be administered the evening before the Week 24 Visit.

[y] All concomitant medications are collected through the Safety Follow-up Visit for all subjects. For subjects who discontinue treatment and are followed for certain efficacy assessments after the ETT Visit (see Section 8.1.4), concomitant antibiotic therapy for 'sinopulmonary signs and symptoms' are collected through the Week 24 Visit, as described in Section 11.6.12.1.

[z] SAEs that occur after the Safety Follow-Up Visit and are considered related to study drug(s) will be reported to Vertex GPS **within 24 hours** as described in Section 13.1.2.2.

Source: Clinical Trial Protocol, VX14-661-106, Table 3-2, p9

Trial Population
The study population included adults and adolescents (12 to 17 years of age) who are homozygous for the *F508del*-CFTR mutation, confirmed by genotyping. Subjects were stratified by age (< 18 vs ≥ 18 years), sex (male vs female), and FEV1 (< 70% vs ≥ 70% predicted). Given that weight, cytochrome P450 enzyme maturity, lung maturity and overall disease status in adolescent patients approaches that of adults, it was reasonable to include adolescent subjects in this study, and this has been the common practice in other CF programs.

Key inclusion criteria

1. Male or female patient aged ≥12 years with confirmed diagnosis of CF by sweat chloride value ≥ 60 mmol/L by quantitative pilocarpine iontophoresis
2. Homozygous for the *F508del*-CFTR mutation, genotype confirmed at screening
3. FEV1 ≥ 40% and ≤ 90% predicted normal for age, sex and height
4. Stable CF disease as judged by investigator

Key exclusion criteria

1. Significant comorbidity (e.g., cirrhosis with portal hypertension, cardiovascular disease, obesity, stroke)
2. Abnormal laboratory results:
    a. Hb < 10 g/dL
    b. elevated LFTs, 2 or more of the following – AST, ALT, GGT, or ALP ≥ 3x ULN, total bilirubin ≥ 2x ULN or ≥ 5x ULN of AST or ALT
    c. abnormal renal function defined as GFR≤ 50 mL/min/1.73m^2 for adults and ≤ 45 mL/min/1.73m^2 for adolescents
3. Acute upper/lower respiratory infection, pulmonary exacerbation, or change in therapy for pulmonary disease within 28 days before Day 1 (1st dose of study drug)
4. Prolonged QTc >450 msec at screening
5. History of solid organ or hematological transplantation
6. Clinically significant cataract, lens opacity, Y-suture, or lamellar rings on screening eye exam
7. Prior use of lumacaftor/ivacaftor in pivotal trials VX12-809-103 or VX12-809-104, extension study VX12-809-105, through early or extended access programs or by physician prescription of Orkambi (*Note: participants of dose-ranging study VX12-809-102 were not specifically excluded*)
8. Colonization with microorganisms associated with more rapid decline in pulmonary status such as *Burkholderia cenocepacia, Burkholderia dolosa, Mycobacterium abscessus*
9. Use of prohibited medications and foods metabolized by CYP3A4 (Table 5 below)

Subject removal criteria
Subjects were discontinued from study drug treatment for any of the following:

1. Pregnancy (female subjects or female partner of a male subject)
2. Unblinding by the investigator
3. Elevation in liver function tests (any one of the following) with no convincing alternative etiology, regardless of whether ALT or AST levels improve:
   - ALT or AST >8x ULN
   - ALT or AST >5x ULN for more than 2 weeks
   - ALT or AST >3x ULN in association with total bilirubin >2x ULN and/or clinical jaundice

Subjects could have been discontinued from study treatment after discussion between the investigator and medical monitor for any of the following:

1. Medical condition that required prolonged concomitant therapy with prohibited medication or prolonged interruption of study drug
2. Life-threatening AE or SAE that placed the subject at immediate risk and required discontinuation of study treatment and withdrawal from study
3. Noncompliance with study requirements
4. Increase in transaminases (as above) due to an alternative, reversible cause. Study drug could be resumed once transaminases returned to baseline or were ≤2x ULN with the approval of the medical monitor.
5. Increase in QTc >45 msec from the average of 3 pre-dose values on Day 1 or ≥500 msec on repeated measurement or on >2 occasions with no alternative etiology
6. Development of cataracts or lens opacity

Subjects who prematurely discontinued study treatment were required to complete the safety follow-up visit (approximately 28 ± 7 days after the last dose of study drug). If the subject had an early treatment termination visit 3 weeks or later following the last dose of study drug, a separate safety follow up visit was not required. Subjects were to complete all other scheduled study visits for assessments of efficacy and other events related to outcome as in Table 4. Subjects who withdrew or were withdrawn for non-safety reasons during the study treatment period could have been replaced at the sponsor's discretion.

Study treatments

TEZ/IVA

Single fixed dose combination tablet containing 100 mg TEZ and 150 mg IVA every morning and a single tablet of 150 mg IVA every evening.

Placebo

Visually matched tablets: TEZ/IVA matching placebo tablet every morning and IVA matching tablet every evening

Study drug was to be administered within 30 minutes of starting a fat-containing meal every 12

hours (±2 hours). Subjects were observed for 6 hours following the first morning dose of study drug on Day 1.

TEZ/IVA and matching placebo were supplied as light yellow film-coated tablets, similar in size and appearance containing 100 mg TEZ/150 mg IVA and 0 mg TEZ/0 mg IVA, respectively. IVA 150 mg and matching placebo were supplied as light blue film-coated tablets. Study drug tablets were supplied in blister cards that were returned by study subjects and inventoried by study monitors. Compliance was assessed by study drug count, supervised dosing at all study visits, and review with the subject.

Concomitant medications
Study drug was administered on a background of standard of care therapy. Stable medication and supplement regimens for CF were allowed if there were no changes from 28 days before Day 1 through the safety follow up visit. New chronic therapies could not be initiated during the study. Chronic antibiotic therapies (including inhaled or cyclic) were to remain on the same schedule throughout the study. Prednisone doses up to 10 mg/day chronically or 60 mg/day for up to 5 days were allowed without prior approval. Bronchodilators were allowed, but were to be withheld prior to spirometry assessments. Concomitant use of medications that could prolong the QT interval could be used with caution. A list of prohibited medications and foods are listed in Table 5.

Table 5. Study restrictions: Trial 106

	Study Period	
Restricted Medication/Food	**Screening Period**	**Treatment Period through Safety Follow-up Visit**
Certain fruits and fruit juices (Grapefruit, grapefruit juice, Seville oranges, marmalade)	None allowed within 14 days before the first dose of the study drug	None allowed through the Safety Follow-up Visit
Moderate and strong CYP3A inducers	None allowed within 14 days before the first dose of the study drug	None allowed through the Safety Follow-up Visit
Moderate and strong CYP3A inhibitors (except for ciprofloxacin)	None allowed within 14 days before the first dose of the study drug	None allowed through the Safety Follow-up Visit
Commercially available CFTR modulators (e.g., Kalydeco)	None allowed within 30 days before and during Screening	None allowed through the Safety Follow-up Visit

CYP: cytochrome P450.
Note: The use of restricted medication by subjects with medical needs will be addressed on a case-by-case basis with the medical monitor.

Source: Source: Clinical Trial Protocol, VX14-661-106, Table 9-1, p32

Blinding
An interactive web response system was used to assign subjects to treatment. All subjects and

site personnel (including investigator, site monitor, and study team) were blinded to study treatment. The independent data monitoring committee (IDMC) and vendors who prepared the unblinded analysis for the IDMC, analyzed PK samples and conducted population PK analysis were unblinded. In addition, the Vertex medical monitor may have unblinded individual subjects at any time for safety related concerns. Spirometry and sweat chloride data obtained post-dose remained blinded to the study team and subjects to minimize potential bias. Dummy data was used to develop statistical programs.

Study Endpoints

Primary endpoint
The primary efficacy endpoint was absolute change in percent predicted forced expiratory volume in 1 second (ppFEV1) from baseline through week 24. Percent predicted FEV1 is the ratio of FEV1 (L) to the predicted FEV1 (L) expressed as a percentage. Baseline was defined as the most recent non-missing measurement collected prior to or on the first dose of study drug. Absolute change from baseline was calculated as post-baseline value – baseline value.

Spirometry was performed per the American Thoracic Society guidelines at timepoints noted in Table 4. FEV1, FVC, FEV1/FVC, and $FEF_{25-75\%}$ values were normalized using standards of Wang et al for female subjects 12-15 years of age and male subjects 12-17 year of age, or Hankinson et al, for females ≥16 years of age and males ≥18 years of age to determine predicted values. For prebronchodilator spirometry, short-acting beta agonists and anticholinergics were withheld for 4 hours, LABAs such as salmeterol were withheld for 12 hours, and once daily long acting bronchodilators such as tiotropium were withheld for more than 24 hours prior to testing. During the screening period, spirometry assessments were performed either pre- or post-bronchodilator, but at all other visits, spirometry was conducted pre-bronchodilator (unless Day 1 spirometry was obtained postbronchodilator in which case all subsequent measurements were also to be obtained postbronchodilator). During the treatment period, spirometry was performed before study drug dosing. Adolescent subjects performed additional post-dose spirometry on Days 1 and 15. Spirometry data was transmitted to a centralized spirometry service for quality review.

Key secondary endpoints
- Relative change in ppFEV1 from baseline through Week 24
- Number of pulmonary exacerbations through week 24
- Absolute change in body mass index from baseline at week 24
- Absolute change in cystic fibrosis questionnaire – revised (CFQ-R) respiratory domain score from baseline through week 24

Baseline values for all parameters were defined as the most recent non-missing measurement collected prior to or on the first dose of study drug.

Absolute change from baseline was calculated as post-baseline value – baseline value. Relative change from baseline was calculated as [(post-baseline value – baseline value)/baseline value] x 100 and expressed as a percentage.

Pulmonary exacerbations were defined as new events or changes in antibiotic therapy (IV, inhaled, or oral) for 4 or more of the following signs/symptoms:

- Change in sputum
- New or increased hemoptysis
- Increased cough
- Increased dyspnea
- Malaise, fatigue, or lethargy
- Temperature > 38°C or 100.4°F
- Anorexia or weight loss
- Sinus pain or tenderness
- Change in sinus discharge
- Change in physical exam of the chest
- Decrease in pulmonary function by 10%
- Radiographic changes indicative of pulmonary infection

The exacerbation definition is consistent with that used in pivotal trials in the IVA monotherapy and LUM/IVA combination development programs.

Height and weight were measured with shoes off at time points noted in Table 4. During the treatment and safety follow up periods, repeat height measurements were only collected for subjects 21 years of age and younger.

The CFQ-R is a disease-specific health-related quality of life measure for CF. It consists of generic and CF-specific scales, grouped into 3 modules and 9 domains, that measure quality of life, health perception, and symptoms over a 2-week recall period. It is available in age-appropriate versions: child age 6-11 years (interview format), child age 12-13 years (self-reported format), adolescent/adult ages ≥14 years (self-reported), and a parent/caregiver proxy format. The respiratory domain of the CFQ-R has also been utilized independently to evaluate for respiratory symptoms relevant to patients with CF. The CFQ-R was completed in the subject's native language before the start of any other assessment at the timepoints noted in Table 4. Subjects who were 12 or 13 years of age on Day 1 completed the CFQ-R child version themselves and their parents/caregivers completed the CFQ-R parent version at all visits. Subjects who were 14 years of age or older on Day 1 completed the adolescent/adult version of the CFQ-R at all visits. All questions that contribute to a domain are scored on a scale of 1, 2, 3, or 4 with 1 representing the worst condition and 4 representing the best condition. The scaled score for each domain ranges from 0 (worst) to 100 (best) and is calculated as follows: 100 x

(mean (scores of all questions in that domain) – 1)/3. The respiratory domain for the child version of the CFQ-R consists of individual questions 31, 32, 33, and 34. The respiratory domain for the adolescent and adult version of the CFQ-R consists of individual questions 40, 41, 42, 44, 45, and 46. The minimum clinically important difference for the respiratory domain is a score change of 4.

Secondary efficacy endpoints

- Time to first pulmonary exacerbation through week 24
- Absolute change in sweat chloride from baseline through week 24
- Absolute change in BMI z-score from baseline at week 24 in subjects < 20 years of age at screening
- Absolute change in body weight from baseline at week 24

For sweat chloride, baseline was the mean of the values on the left and right arms prior to the first dose of study drug. Sweat samples were collected for sweat chloride testing using an approved collection device at the timepoints specified in Table 4, approximately 1 hour before PK sample collection and before the morning dose of study drug. At each time point, two samples were collected, one from each arm. Samples were sent to a central laboratory for testing and interpretation of results. Individual results were not disclosed to the study sites.

The BMI-z-score was BMI adjusted for age and sex, calculated using CDC growth charts for pediatric populations 2 to 20 years of age. The BMI-z-score was only calculated for subjects between 12 and <20 years of age at screening.

Other efficacy endpoints (not reviewed in detail)

- Absolute change in cystic fibrosis respiratory symptom diary (CFRSD) severity score from baseline through week 24
- Absolute change in duration for physical activity during the day from baseline through week 24
- Absolute change in duration of sleep time and sleep quality during the night from baseline through week 24
- Absolute change in Pittsburgh sleep quality index (PSQI) score from baseline through week 24 in subjects >18 years of age
- Absolute change in subjects' assessment of quality of life (SF-12) physical, mental, and utility component scores at weeks 12 and 24
- Absolute change in serum inflammatory mediators from baseline at week 24
- Absolute change in sputum microbiology from baseline at week 24
- Absolute change in serum immunoreactive trypsinogen (IRT) from baseline at week 24

Safety assessments
Safety evaluations included AEs, clinical laboratory assessments, pregnancy testing, vital signs, ECGs, pulse oximetry, spirometry, physical exams, and ophthalmologic exams, all of which were monitored as per the schedule in Table 4.

Statistical Analysis Plan

The following analysis sets were defined in the SAP:

- All Subjects Set – all subjects who were randomized or received at least one dose of study medication; this set was used in subject listing and the disposition table
- Randomized Set – all subjects who were randomized
- Full Analysis Set (FAS) – all randomized subjects who carry the intended CFTR allele mutation and received at least one dose of study drug (Note: this definition differs from the one in the protocol in that it only includes subjects with the intended CFTR allele mutation)
- Safety Set – all subjects who received at least one dose of study drug

All efficacy analyses were based on the FAS. Baseline values for all parameters were defined as the most recent non-missing measurement collected prior to or on the first dose of study drug. For ECGs, baseline was the average of the 3 pre-treatment measurements on Day 1. For sweat chloride, baseline was the mean of the values on the left and right arms prior to the first dose of study drug. Absolute change from baseline was calculated as post-baseline value – baseline value. Relative change from baseline was calculated as [(post-baseline value – baseline value)/baseline value] x 100 and expressed as a percentage. Treatment emergent was defined as the time from the first dose of study drug to the safety follow up visit or to 28 days after the last dose of study drug or to last participation date in the study for extension study participants.

Analysis of primary endpoint
The primary efficacy endpoint, absolute change from baseline in ppFEV1 through week 24, was analyzed based on a mixed model for repeated measures (MMRM). The null hypothesis was that the mean absolute change from baseline in ppFEV1 through week 24 is the same for TEZ/IVA and placebo. A p-value of 0.05 or less was interpreted as sufficient evidence to reject the null hypothesis. The model included absolute change from baseline in ppFEV1 at each post-baseline visit (Day 15, Weeks 4, 8, 12, 16, and 24) as dependent variables and the following fixed effects: treatment, visit, treatment-by-visit interaction, sex, age group (<18 vs ≥18 years) at screening, baseline ppFEV1, baseline ppFEV1-by-visit interaction. The LS Mean (SE) of the overall treatment difference between TEZ/IVA and placebo in absolute change from baseline in ppFEV1 from Day 15 through Week 24 were presented along with 95% confidence intervals and a 2-sided p value. Subgroup analyses of the primary endpoint were performed in a manner like that of the primary analysis within each of the following subgroups: age at screening (<18, ≥ 18 years), ppFEV1 at baseline (<40, 40 to <70, ≥70), sex, region (North America, Europe), inhaled

antibiotic use, inhaled bronchodilator use, inhaled hypertonic saline use, inhaled corticosteroid use, azithromycin use, and colonization of *P. aeruginosa* at baseline. The MMRM model included additional covariates of subgroup and subgroup x treatment interaction.

Analysis of key secondary endpoints
Key secondary endpoints of relative change in ppFEV1, absolute change in BMI, and absolute change in CFQ-R respiratory domain were analyzed similarly to the primary endpoint with baseline BMI or CFQ-R respiratory domain replacing baseline ppFEV1 and baseline BMI or CFQ-R respiratory domain-by-visit interaction replacing baseline ppFEV1-by-visit interaction in the MMRM model. The analysis for CFQ-R respiratory domain through week 24 pooled results from the "Children Ages 12 and 13" and the "Adolescents and Adults" versions of the questionnaire. For the key secondary endpoint of number of pulmonary exacerbations, a negative binomial generalized linear model was used to compare the rates of exacerbations over the 24-week treatment period for the two treatment groups. The number of pulmonary exacerbations was analyzed by comparing the annualized number of pulmonary exacerbation for each treatment group, calculated as 48 x (total number of pulmonary exacerbation/total duration of post-baseline assessment in weeks) obtained from all subjects in the same treatment group. BMI was calculated as weight (kg)/(height [m^2]).

Control for multiplicity
A hierarchical testing procedure was used to control overall Type I error for the multiple endpoints tested at α=0.05. For a test at any step to be considered statistically significant within the testing hierarchy, the test must be statistically significant at the 0.05 level, and all previous tests (if any) within the hierarchy must also be statistically significant. The testing hierarchy was as follows:

- Absolute change from baseline in ppFEV1 through week 24
- Relative change from baseline in ppFEV1 through week 24
- Number of pulmonary exacerbations through week 24
- Absolute change in body mass index from baseline at week 24
- Absolute change in CFQ-R respiratory domain score from baseline through week 24

Analyses of other secondary efficacy endpoints
Analysis of time to first pulmonary exacerbation through week 24 was based on a Cox regression model that included treatment, sex, age group at screening (< 18 vs ≥18 years), and baseline ppFEv1 as covariates. The Kaplan-Meier method was used to estimate the cumulative exacerbation-free rate. Subjects without a protocol defined exacerbation event by week 24 were censored at the date of the last visit (up to week 24).

Analysis of absolute change in sweat chloride from baseline through week 24 used a model like that used for the primary endpoint with baseline ppFEV1 replaced by baseline sweat chloride value and baseline ppFEV1-by-visit interaction replaced by baseline sweat chloride value by visit

interaction.

Analyses for absolute change in BMI z-score from baseline at week 24 and absolute change in body weight from baseline at week 24 were based on an MMRM model like that used for the analysis for the absolute change from baseline in BMI at week 24. Baseline BMI was replaced by baseline BMI z-score and weight, respectively, while baseline BMI-by-visit interaction was replaced by baseline BMI z-score or weight-by-visit interaction.

Summary statistics were used to present raw values and change from baseline for other spirometry endpoints by treatment group at each visit.

CFQ-R respiratory domain responders were defined as having a minimum 4-point increase in the absolute change from baseline in CFQ-R respiratory domain. A responder analysis was performed at each visit using generalized estimating equations. PROC GENMOD in SAS was used to fit a GEE model with covariates for treatment group, age, gender, ppFEV1 at baseline, baseline CFQ-R respiratory score, visit, and treatment group by visit interaction term, a logit link function, and an unstructured working correlation matrix. The odds ratio and 95% confidence interval for the odds ratio as well as the associated p-value were presented for each post-baseline visit.

No sensitivity, supportive, or subgroup analyses were planned for the key or other secondary endpoints. Refer to the biometrics statistical review by Dr. Mingyu Xi for a more detailed review of the sponsor's statistical analysis plan.

Protocol Amendments

The protocol was amended three times to add CFQ-R assessments at weeks 8, 16, and the safety follow up visit, to add post-dose spirometry and ophthalmologic exams in subjects < 18 years of age, and to exclude patients who have received commercial Orkambi following approval for marketing.

Modifications of the SAP from the last version of the protocol include:

- FAS definition – randomized subjects who received at least 1 dose of study drug must all carry the intended CFTR allele mutation since some subject's confirmatory genotype testing differed from historical records
- MMRM model for the primary endpoint changed ppFEV1 severity at screening (<70% vs ≥70%) variable to baseline ppFEV1 which the sponsor felt was a better predictor of the primary endpoint and added interaction term of baseline ppFEV1-by-visit
- MMRM model for key secondary endpoint of number of pulmonary exacerbations through week 24 changed ppFEV1 severity covariate to baseline ppFEV1
- Analysis of secondary efficacy endpoints absolute change in BMI and CFQ-R respiratory

domain score from baseline added baseline BMI/CFQ-R and baseline BMI/CFQ-R -by-visit interaction and removed ppFEV1 severity covariate for consistency with MMRM model for primary efficacy endpoint

Data Quality and Integrity: Sponsor's Assurance

Vertex conducted study site visits to verify investigator qualifications, inspect clinical study site facilities, and inform investigator of responsibilities and procedures for ensuring adequate and correct study documentation. Vertex had read-only access to site-entered clinical data in the web-based electronic data capture application for entry into the CRF. Missing, discrepant and uninterpretable data was queried with the investigator for resolution. An audit trail was maintained to show the user's identification information and date/time for any changes made to the study data and CRF.

6.1.2. Study Results

Compliance with Good Clinical Practices

The Applicant states that the study was conducted in accordance with GCP as described in ICH guidelines. The study protocol, amendments, informed consent, and other necessary documents were reviewed and approved by an independent ethics committee (IEC) or institutional review board (IRB) for each study site before initiation of the study at that site. Written informed consent was obtained from each subject before study participation. This study was conducted under IND 108,105.

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 13.1).

Patient Disposition

The disposition of patients is detailed in Table 6. The study had high overall completion rates, and there was no imbalance in the number of premature discontinuations between treatment groups.

Table 6. Subject Disposition: Trial 106

	Placebo	TEZ/IVA	Total
Randomized Set	259	251	510
Safety Set	258	251	509
Full Analysis Set (FAS)	256	248	504 (100)
Completed study	241 (93)	236 (94)	477 (94)
Completed treatment	240 (93)	235 (94)	475 (93)
Prematurely discontinued treatment	18 (7)	16 (6)	34 (7)
Adverse event	8 (3)	7 (3)	15 (3)
Subject refused further dosing (not due to AE)	5 2)	5 (2)	10 (2)
Did not meet eligibility criteria	3 (1)	3 (1)	6 (1)
Required prohibited medication	2 (1)	0	2 (0.4)
Physician decision	0	1 (0.4)	1 (0.3)
Source: Clinical Study Report, Trial VX14-661-106, Table 10-1, p64 and verified with ADSL dataset			

Protocol Violations/Deviations

Subjects who were randomized and later found not to be homozygous for the *F508del* CFTR mutation were not included in the FAS set which was used for all efficacy analyses. The remaining subjects who reported important protocol deviations were included in the FAS and safety analysis sets. However, none of the other violations were of a nature that would have had an impact on study outcome. Subjects not meeting eligibility criteria were primarily due to use of prohibited medications that are metabolized via the CYP3A pathway.

Table 7. Protocol violations and deviations in the FAS population: Trial 106

	Placebo N=256	TEZ/IVA N=248	Total N=504
Ineligible based on CFTR genotype testing, n (%)	2 (1)	3 (1)	5 (1)
Did not meet inclusion/exclusion criteria	3 (1)	2 (1)	5 (1)
Took prohibited medication	3 (1)	3 (1)	6 (1)
Less than 80% compliant with study drug	0	1 (<1)	1 (<1)
Pregnancy testing not performed at screening or Day 1	1 (<1)	0	1 (<1)
Genotype testing not performed at screening	0	1 (<1)	1 (<1)
Source: ADDV dataset analyzed in JMP (ADVCAT and ADVTERM by TRT01P)			

Patient Demographics

Patient demographic data is summarized in Table 8. Patients were predominantly young (mean/median age ~25-26 years) white adults from outside the US. Approximately 20% of the study population was adolescent (12-17 years of age), and both sexes were represented equally. The relatively low proportion of American subjects is likely due to the approval of LUM/IVA (Orkambi®) for this *F508del* homozygous patient population while the study was

taking place. There were no major differences in demographic characteristics between treatment groups.

Table 8. Demographic characteristics of FAS population: Trial 106

Demographic Parameters	Placebo N=256 n (%)	TEZ/IVA N=248 n (%)	Total N=504 n (%)
Sex			
Male	131 (51)	127 (49)	258 (51)
Female	125 (49)	121 (51)	246 (49)
Age			
Mean years (SD)	25.7 (10)	26.9 (11)	26.3 (10)
Median (years)	25	25	25
Min, max (years)	12, 61	12, 64	12, 64
Age Group			
12 to < 18 years	58 (23)	58 (23)	116 (23)
≥ 18 - < 65 years	198 (77)	190 (77)	388 (77)
Race			
White	254 (99)	245 (99)	499 (99)
Black or African American	0	1 (<1)	1 (<1)
Asian	2 (<1)	0	2 (<1)
Other[1]	0	2 (<1)	2 (<1)
Ethnicity			
Hispanic or Latino	3 (1)	9 (4)	12 (2)
Not Hispanic or Latino	250 (98)	234 (94)	484 (96)
Not reported	3 (1)	5 (2)	8 (2)
Region			
United States	51 (20)	51 (21)	102 (20)
Rest of the World	205 (80)	197 (79)	380 (80)
Canada	17 (7)	8 (3)	25 (5)
Europe	188 (73)	189 (76)	377 (75)

Source: Reviewer generated table using JMP; ADSL dataset, where (FASFL=Y) and TRT01P for treatment group
[1] Other='Father Indian' and 'Hispanic'

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

Overall, the two treatment groups were balanced with regard to various baseline disease characteristics and concomitant medication use as summarized in Table 9. The average ppFEV1 at baseline was 60% and roughly three quarters of patients were colonized with *Pseudomonas*.

Table 9. Baseline disease characteristics, FAS population: Trial 106

Baseline Disease Characteristics	Placebo N=256 n (%)	TEZ/IVA N=248 n (%)	Total N=504 n (%)
ppFEV1			
Mean (SD)	60 (16)	60 (15)	60 (15)
Median	60	59	59
Min, Max	28, 96	30, 91	28, 96
ppFEV1 by severity group			
< 40%	6 (9)	5 (9)	11 (9)
≥ 40 to < 70%	162 (59)	163 (64)	325 (61)
≥ 70 to < 90%	84 (29)	76 (26)	160 (27)
≥ 90%	1 (3)	1 (1)	2 (2)
Sweat chloride (mEq/L)			
Mean (SD)	101 (10)	101 (11)	101 (11)
Median	102	101	102
Min, Max	42, 126	39, 140	39, 140
Weight (kg)			
Mean (SD)	59 (12)	58 (12)	59 (12)
Median	58	57	58
BMI (kg/m^2)			
Mean (SD)	21 (3)	21 (3)	21 (3)
Median	21	21	21
Min, Max	15, 32	14, 30	14, 32
CFQ-R respiratory domain score			
Mean (SD)	70 (17)	70 (17)	70 (17)
Median	72	72	72
Background therapy			
Dornase alfa	185 (72)	165 (67)	350 (69)
Inhaled antibiotics	160 (63)	136 (55)	296 (59)
Inhaled corticosteroids	162 (63)	139 (56)	301 (60)
Inhaled bronchodilator	234 (91)	221 (89)	455 (90)
Short-acting only	68 (29)	78 (35)	146 (32)
Long-acting only	48 (21)	37 (17)	85 (19)
Short- and long-acting	118 (50)	106 (48)	224 (49)
Inhaled hypertonic saline	133 (52)	126 (51)	259 (52)
Azithromycin	141 (55)	135 (54)	276 (55)
Pseudomonas colonization			
Positive	182 (71)	185 (75)	367 (73)

Source: Reviewer generated table using JMP; ADSL dataset, where (FASFL=Y) and TRT01P for treatment group

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Only one subject in the study (in the TEZ/IVA group) had less than 80% treatment compliance. This subject (Subject 106-057-002) had 60% treatment compliance with 68 days missed to allow use of prohibited concomitant medication. Two other subjects in the TEZ/IVA group reported missing a total of 1 and 21 days, respectively, of study drug. In the placebo group, a total of 13 subjects reported dose interruptions ranging from 1 to 29 days. Overall treatment compliance was adequate to allow interpretation of study results.

Efficacy Results – Primary Endpoint

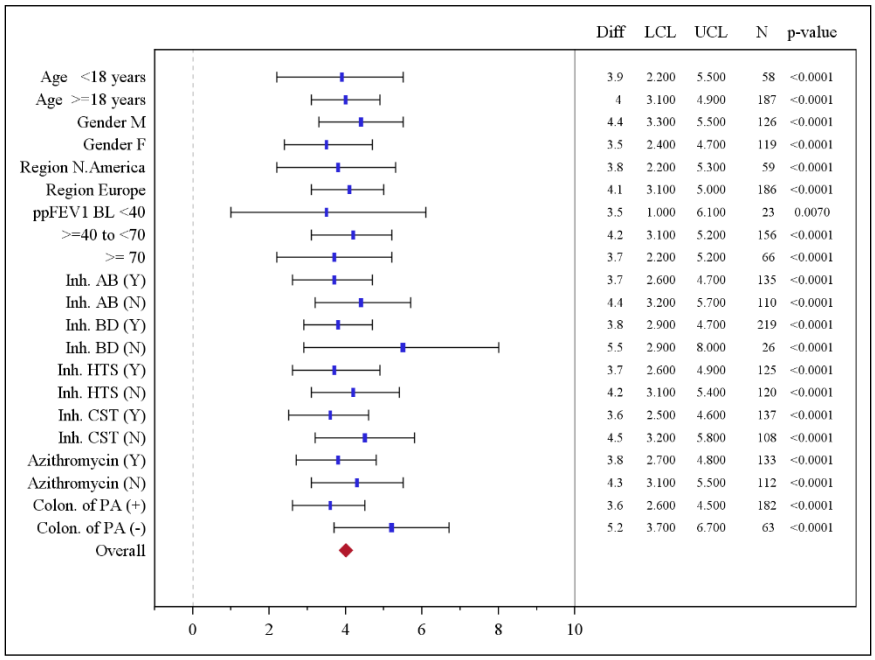
For the primary endpoint of absolute change from baseline in ppFEV1 through the end of treatment at Week 24, patients treated with TEZ 100 mg QD/IVA 150 mg Q12 had statistically significant improvements in ppFEV1 compared to placebo-treated patients (Table 10). Results were consistent regardless of age, sex, baseline ppFEV1, or colonization with *Pseudomonas* (Figure 2).

Table 10. Primary endpoint - Absolute change from baseline in percent predicted FEV1 (ppFEV1) through Week 24: Trial 106

ppFEV1	Placebo N=256	TEZ/IVA N=248
Baseline		
N	256	248
Mean (SD)	60.4 (16)	59.6 (15)
Absolute change from baseline through Week 24		
N	256	245
LS Mean (SE)	-0.6 (0.3)	3.4 (0.3)
p-value (95% CI)	0.06 (-1.3, 0)	<0.0001 (2.7, 4.0)
Difference from placebo (95% CI)	--	4.0 (3.1, 4.8)
p-value versus placebo	--	<0.0001
Absolute change from baseline through Week 24 in adolescent subjects (<18 years)		
N	58	58
LS Mean (SE)	-0.4 (0.6)	3.5 (0.6)
p-value (95% CI)	0.53 (-1.6, 0.8)	<0.0001 (2.3, 4.7)
Difference from placebo (95% CI)	--	3.9 (2.2, 5.5)
p-value versus placebo	--	<0.0001

Source: Biostatistics review by Dr. Mingyu Xi and CSR VX14-661-106, Table 11-2, p77 and Table 14.2.1.2.3, p359

Figure 2. Subgroup analyses of LS mean difference for absolute change from baseline in ppFEV1 through Week 24 in FAS population: Trial 106



Source: Biostatistics review by Dr. Mingyu Xi

Data Quality and Integrity – Reviewers' Assessment

This review did not reveal any inconsistencies in the data or issues with trial design or conduct which might influence the efficacy results.

Efficacy Results – Secondary and other relevant endpoints

Changes for key secondary endpoints relative change in ppFEV1 from baseline through week 24 and number of pulmonary exacerbations through week 24 were also significant while change in BMI at week 24 was not significant. Although the change in CFQ-R respiratory domain score was nominally positive, it was not statistically significant based on earlier failure for the BMI endpoint which was higher up in the statistical hierarchy. Mean change in sweat chloride through week 24 compared to placebo was -10.1 mmol/L (95% CI: -11.4, -8.8).

Table 11. Key secondary endpoint analyses: Trial 106

	Placebo N=256	TEZ/IVA N=248
Relative Δ from baseline in ppFEV1 through Week 24		
N	256	245
LS mean (SE)	-0.5 (0.6)	6.3 (0.6)
Difference from placebo (95% CI)	--	6.8 (5.3, 8.3)

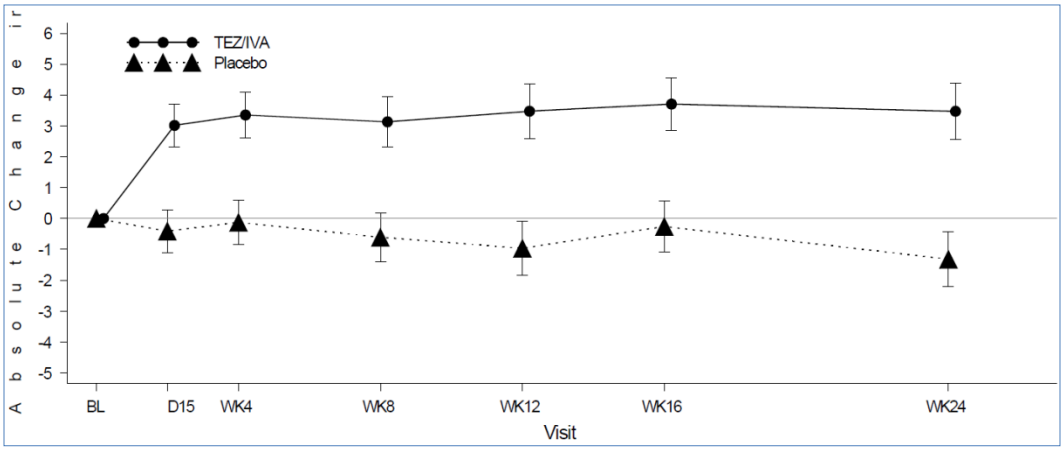
	Placebo N=256	TEZ/IVA N=248
p-value versus placebo	--	<0.0001
Number of pulmonary exacerbations		
Subjects with events, n (%)	88 (34)	62 (25)
Number of events	122	78
Estimated event rate/year	0.97	0.64
Rate ratio vs placebo (95% CI)	--	0.65 (0.48, 0.88)
p-value vs placebo	--	0.0054
Absolute Δ from baseline in BMI at Week 24		
N	245	237
LS mean (SE)	0.12 (0.05)	0.18 (0.05)
Difference from placebo (95% CI)	--	0.06 (-0.08, 0.19)
p-value versus placebo	--	0.41
Absolute Δ from baseline in CFQ-R respiratory domain score through Week 24		
N	256	246
LS mean (SE)	-0.1 (0.8)	5.0 (0.8)
Difference from placebo (95% CI)	--	5.1 (3.2, 7.0)
p-value versus placebo	--	<0.0001*

*nominal p-value due to earlier failure in analysis hierarchy
Source: Biostatistics review by Dr. Mingyu Xi and CSR VX14-661-106, Tables 11-4, 11-5, 11-6, 11-7, p80-84

Durability of Response

Treatment with TEZ/IVA resulted in sustained improvements in ppFEV1 over the entire 24-week treatment period as shown in Figure 3.

Figure 3. Absolute change from baseline in ppFEV1 at each visit: Trial 106



Source: CSR VX14-661-106, Figure 11-6, p79

6.2. VX14-661-108

6.2.1. Study Design

Overview and Objective

Trial 108 was a multinational pivotal trial to provide evidence for the efficacy and safety of IVA monotherapy and TEZ in combination with IVA in subjects with CF who are heterozygous for the *F508del* mutation on the CFTR gene and a second allele with a CFTR mutation predicted to have residual function. The study was conducted from 3/27/15 through 2/16/17.

Study Title: A Phase 3, Randomized, Double-blind, Placebo-controlled, Crossover Study to Evaluate the Efficacy and Safety of Ivacaftor and VX-661 in Combination with Ivacaftor in Subjects Aged 12 Years and Older with Cystic Fibrosis, Heterozygous for the *F508del*-CFTR Mutation, and a Second Allele with a CFTR Mutation Predicted to Have a Residual Function

Primary Objective

- To evaluate the efficacy of TEZ/IVA and IVA monotherapy through 8 weeks of treatment in CF patients heterozygous for the *F508del*-CFTR mutation and a second allele with a CFTR mutation predicted to have residual function

Secondary Objectives

- To evaluate the safety of TEZ/IVA through 8 weeks of treatment
- To evaluate the safety of IVA monotherapy through 8 weeks of treatment
- To investigate the PK of TEZ, IVA and their metabolites

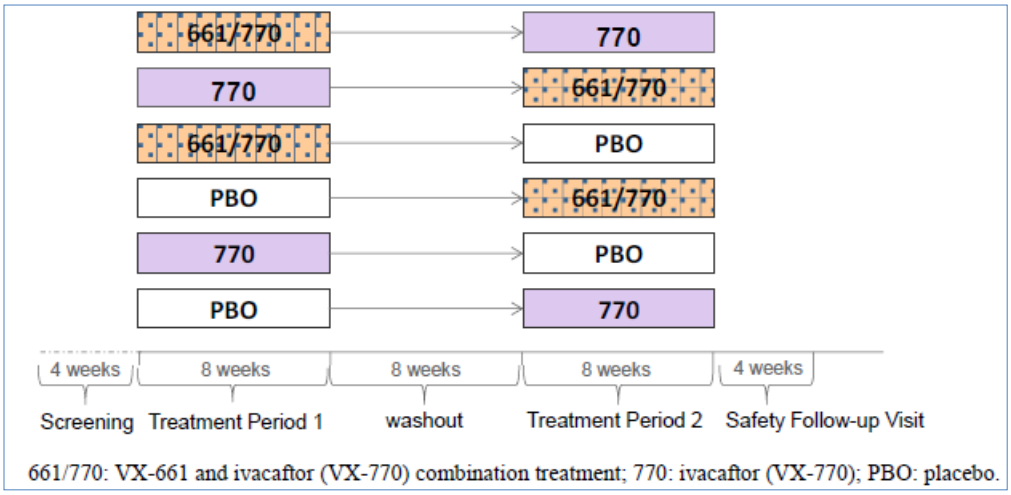
Trial Design

Trial 108 had a randomized, double-blind, placebo-controlled, 2-period, 3-treatment crossover study design with 8-week treatment periods (Figure 4). The study included a 28-day screening period, an 8-week treatment period (Treatment Period 1), an 8-week washout period, a second 8-week treatment period (Treatment Period 2) and a 28 day follow up period.

After screening, eligible subjects were randomized (1:1:1:1:1:1) to one of six treatment sequences as shown in Figure 4. The first dose of study drug was administered on Day 1 of each treatment period (Day 1 and Week 17 of the study). Study visits occurred on Days 1 and 15 and at weeks 4 and 8 during the first treatment period, week 12 during washout, weeks 17, 18, 20, 24. At the week 24 visit, subjects who completed the treatment period could enroll in extension study VX14-661-110. If subjects declined to participate in the OLE study, safety follow-up visit occurred 28 (±7) days after the last dose of study drug in treatment period 2. Subjects who discontinued treatment prematurely also had an early treatment termination visit as soon as

possible after the decision to discontinue study drug treatment. Study assessments are summarized in Table 12.

Figure 4. Study Design Schematic: Trial 108



Source: Clinical Trial Protocol VX14-661-108, Figure 8-1, p27

Table 12. Schedule of Assessments: Trial 108

	Treatment Period 1				Washout[a]	Treatment Period 2					
Event/Assessment[b]	Week 1 (Day 1)	Week 2 (Day 15) (± 3 Days)	Week 4 (Day 29) (± 5 Days)	Week 8 (Day 57) (± 5 Days)	Safety Evaluation Visit Week 12 (Day 85) (± 5 Days)	Week 17[a] (Day 113)	Week 18 (Day 127) (± 3 Days)	Week 20 (Day 141) (± 5 Days)	Week 24 (Day 169) (± 5 Days)	ETT Visit[c]	Safety Follow-up Visit 28 days (± 7 days) After Last Dose[d]
Clinic visit	X	X	X	X	X	X	X	X	X	X	X
Inclusion and exclusion criteria review	X					X[e]					
CFQ-R[f]	X		X	X	X	X		X	X	X	X
SF-12[f]	X		X	X	X	X		X	X	X	X
Height and weight[g]	X	X	X	X	X	X	X	X	X	X	X
Ophthalmologic examination[h]										X	X
Complete PE[i]	X					X					
Pregnancy test[j]	urine	urine	urine	serum	urine	urine	urine	urine	serum	serum	serum
Standard digital ECG[k]	X	X	X	X	X	X	X	X	X	X	X
Vital signs[l]	X	X	X	X	X	X	X	X	X	X	X
Pulse oximetry[j]	X	X	X	X	X	X	X	X	X	X	X
Spirometry[m]	X	X	X	X	X	X	X	X	X	X	X
Sweat chloride[n]	X		X	X		X		X	X		
Urinalysis	X			X	X	X			X	X	X

Hematology[o]	X	X	X	X	X	X	X	X	X	X	X
Coagulation[o]	X			X	X	X			X	X	X
Serum chemistry[o]	X	X	X	X	X	X	X	X	X	X	X
Lipid panel[p]	X			X		X			X	X	
Vitamin levels (A, D, E, K, B12)	X			X		X			X	X	
NPD[q] (optional)	X[r]			X[s]		X[r]			X[s]		
IRT	X	X	X	X		X	X	X	X		
Fecal elastase-1[t]	X		X	X		X		X	X		
PK sampling[u]			X	X				X	X	X	X
DNA Sample A and B (optional)		X									
Nasal brushing (optional, in subset of subjects)		X									
Blood biomarker analysis	X			X		X			X		X
Other events related to outcome[v]	X	X	X	X	X	X	X	X	X	X	X
Randomization[w]	X										
Meal(s) or snack(s) at site[x]	X	X	X			X	X	X			
Study drug dosing[y]	X	X	X			X	X	X			
Study drug count		X	X	X			X	X	X	X	
Concomitant medications[z]	X	X	X	X	X	X	X	X	X	X	X
Concomitant treatments and procedures	X	X	X	X	X	X	X	X	X	X	X
AEs and SAEs	Continuous from signing of the ICF and assent (where applicable) through the Safety Follow-up Visit										

[a] The Washout Period starts the day after completion of the Week 8 Visit and continues for 8 weeks (+7 days). The Washout Period is considered to be complete when dosing has occurred at the Week 17 Visit.

[b] All assessments will be performed before dosing unless noted otherwise. If study drug is not administered on the day of the visit (i.e., study drug interruption or premature discontinuation of study drug treatment), only 1 set of assessments will be collected. Subjects who prematurely discontinue study drug treatment will continue to complete all other scheduled study visits for assessments of efficacy (spirometry, sweat chloride, and CFQ-R) and other endpoints (SF-12 and other events related to outcome [hospitalizations, pulmonary exacerbations, etc.]) through the end of the Treatment Period in which discontinuation occurred, as described in Section 8.1.6.

[c] If the subject prematurely discontinues study drug treatment, an ETT Visit should be scheduled as soon as possible after the decision to terminate study treatment. Subjects who prematurely discontinue study drug treatment will also be required to complete the Safety Follow-up Visit, approximately 28 (± 7) days after their last dose of study drug. If the ETT Visit occurs 3 weeks or later following the last dose of study drug, then the ETT Visit will replace the Safety Follow-up Visit, and a separate Safety Follow-up Visit will not be required. See Section 8.1.5 and 8.1.6.

[d] The Safety Follow-up Visit is not required for subjects who complete the Week 24 Visit and have enrolled in an extension study of VX-661 in combination with ivacaftor within 28 days after the last dose of study drug.

[e] In order to continue in Treatment Period 2, subjects must not have an acute upper or lower respiratory infection, pulmonary exacerbation, or changes in therapy (including antibiotics) for pulmonary disease within 4 weeks before the Week 17 Visit (first dose of study drug in Treatment Period 2) and must not have any "non-CF-related" illness within 2 weeks before the Week 17 Visit. "Illness" is defined as an acute (serious or nonserious) condition (e.g., gastroenteritis). If the subjects do not meet these criteria, then the continuation of the subjects into Treatment Period 2 must be discussed with the Medical Monitor.

[f] All questionnaires must be completed before the start of any other assessment scheduled for that visit. The CFQ-R must be completed first, followed by the SF-12. Subjects will need to complete a CFQ-R and SF-12 at the ETT Visit (Section 8.1.6).

[g] Weight and height will be measured before dosing with shoes off. Height will be collected only for subjects 21 years of age or younger.

[h] Subjects < 18 years of age at screening who discontinue study drug treatment after receiving at least 1 dose of study drug, and subjects < 18 years of age at screening who complete treatment but do not enroll in a separate extension study of VX-661/ivacaftor within 28 days after the last dose of study drug will have an ophthalmologic exam conducted by a licensed ophthalmologist (see Section 11.7.8). The exam may be completed at either the ETT or Safety Follow-up Visit, but must be completed by the date of the Safety Follow-up Visit. Subjects who have documented bilateral lens removal do no need an ophthalmologic exam.

[i] In addition to the complete PEs indicated, symptom-targeted PEs will occur at any time during the study if triggered by AEs or if deemed necessary by the investigator.

[j] Pregnancy tests will be performed for all female subjects of childbearing potential.

[k] All standard digital ECGs will be performed before dosing and after the subject has been supine for at least 5 minutes. At the Week 1, Week 2, Week 17, and Week 18 Visits, ECGs will be collected before dosing and at 1.5, 3, 4, and 6 hours after the morning dose. At the Week 1, Week 2, Week 17, and Week 18 visits the 4-hour postdose ECG will be collected before the 4-hour postdose spirometry assessment. The predose ECGs collected at the Week 1 (Day 1) visit will be performed in triplicate. If study drug is not administered on the day of the visit (i.e., because of study drug interruption or permanent discontinuation of study drug), only 1 ECG will be collected.

[l] Vital signs and pulse oximetry will be collected before dosing and after the subject has been at rest (seated or supine) for at least 5 minutes.

[m] At all visits, spirometry must be performed for all subjects before dosing and should be performed prebronchodilator (Section 11.6.1). At Week 1, Week 2, Week 17, and Week 18, subjects < 18 years of age at the Screening Visit will have additional spirometry performed at 2 and 4 hours after the morning dose. If more than 1 spirometry assessment is required at a visit, bronchodilators will be withheld until completion of the last scheduled spirometry assessment is completed.

[n] The Sweat collection on dosing visits should occur approximately 1 hour before the PK sample collection and before the morning dose of the study drugs. Sweat collection will not overlap with any other study assessments (Section 11.6.2).

[o] Blood samples will be collected before the first dose of study drug.

[p] Subjects will require 4 hours of fasting before the blood sample for the lipid panel is obtained.

[q] A subset of subjects at selected study sites will be assessed for NPD.

[r] NPD may be performed on the previous day (Day -1) of Treatment Period 1 or the day before the Week 17 Visit.

[s] NPD will be done predose and may be performed on the previous day. If done the previous day, the start of the NPD procedure must be no sooner than 6 hours after the morning dose of study drug.

[t] The samples may be collected at the study center during the study visit or may be collected by the subject at home and brought to the study visit.

[u] PK blood samples will be collected pre-morning-dose at Week 4, Week 8, Week 20, and Week 24. If study drug is not administered at the visit (i.e., study drug interruption or permanent discontinuation of study drug), a PK blood sample will still be collected. At the ETT and the Safety Follow-up Visit (as applicable), a PK blood sample will also be collected.

v Other events related to outcome include assessments relating to pulmonary exacerbations, administration of antibiotic therapy for sinopulmonary signs or symptoms, and hospitalizations (Section 11.6.4.5).
w Randomization must occur after all inclusion and exclusion criteria are met and before the first dose of study drug. Randomization will be done through IWRS. Randomization may occur on Day -1.
x Fat-containing food, such as a "standard CF" high-fat, high-calorie meal or snack, will be provided at the site to subjects after all predose assessments have occurred.
y The study drug should be administered every 12 hours (± 2 hours) within 30 minutes after starting a meal with fat-containing food such as a "standard CF" high-fat, high-calorie meal or snack. On days of scheduled visits, the morning dose of study drug will be administered at the site after predose assessments have been completed. The final dose of study drug in Treatment Period 1 will be administered the evening before the Week 8 Visit. The final dose of study drug in Treatment Period 2 will be administered the evening before the Week 24 Visit.
z All concomitant medications are collected through the Safety Follow-up Visit for all subjects. For subjects who prematurely discontinue study drug treatment and are followed for certain efficacy assessments after the ETT Visit (see Section 8.1.6), concomitant antibiotic therapy for 'sinopulmonary signs/symptoms' are collected through the Week 24 Visit, as described in Section 11.6.4.5.1.

Source: Clinical Trial Protocol, VX14-661-108, Table 3-2, p11

Trial Population

The eligibility criteria for trial 108 was like 106 except for the following key differences:

Key inclusion criteria

1. Heterozygous for *F508del*-CFTR mutations and a second allele with a CFTR mutation predicted to have residual function as defined in Table 13.
2. Either sweat chloride ≥60 mmol/L or evidence of chronic sinopulmonary disease manifested by at least 1 of the following if sweat chloride < 60 mmol/L (specific criteria to be discussed with and approved by medical monitor prior to randomization):
    a. Persistent colonization/infection with typical CF pathogens such as *Staphylococcus aureus, Haemophilus influenzae*, and *Pseudomonas aeruginosa*
    b. Chronic cough and sputum production
    c. Persistent chest radiograph abnormalities (e.g., bronchiectasis, atelectasis, infiltrates, hyperinflation)
    d. Nasal polyps, chronic sinusitis, radiographic or CT abnormalities of paranasal sinuses

Key exclusion criteria

1. Ongoing or prior participation in an investigational drug study (including studies for TEZ, lumacaftor, and ivacaftor) or use of commercially available CFTR modulators within 30 days of screening.

Table 13. CFTR mutations predicted to have residual function and responsiveness to IVA: Trial 108

2789+5G→A	R74W	R352Q	R1070W
3849+10kbC→T	D110E	A455E	F1074L
3272-26A→G	D110H	D579G	D1152H
711+3A→G	R117C	S945L	D1270N
E56K	E193K	S977F	
P67L	L206W	F1052V	
E831X	R347H	K1060T	

Source: Clinical Trial Protocol VX14-661-108, Appendix A, p89

Subject removal criteria

Subject removal criteria were the same as for Trial 106.

Study Endpoints

Efficacy endpoints in this trial were like those in Trial 106 with the main differences being position in the testing hierarchy and the analysis timepoint being change from baseline to the average of measurements obtained at weeks 4 and 8 for each treatment period.

Primary Endpoint

- Same as in Trial 106: absolute change in ppFEV1 from baseline to the average of week 4 and 8 measurements in each treatment period.

Key Secondary Endpoint

- Absolute change in CFQ-R respiratory domain score from baseline to the average of week 4 and 8 measurements in each treatment period

Secondary Endpoints

- Safety and tolerability assessments based on AEs, clinical lab values, ECGs, vital signs, pulse oximetry, and spirometry
- Relative change in ppFEV1 from baseline to the average of week 4 and 8 measurements in each treatment period
- Absolute change in sweat chloride from baseline to the average of week 4 and 8 measurements in each treatment period
- PK parameters of TEZ, IVA, and their metabolites

Other Endpoints – similar to trial 106, but not reviewed in detail

Efficacy and safety assessments and their methods of collection were the same as those described for Trial 106. The timing of assessments is outlined above in Table 12.

Statistical Analysis Plan

Analysis sets were defined as in Trial 106, and all efficacy analyses were performed on the FAS population.

The primary endpoint analysis was based on a mixed effects model using SAS procedure MIXED. The null hypotheses were that the mean absolute change from baseline in ppFEV1 to the average of week 4 and 8 measurements was the same for TEZ/IVA and placebo and for IVA monotherapy and placebo. The model included treatment, period, ppFEV1 at baseline as fixed effects and subject as a random effect. The within-subject covariance was assumed to have the same compound symmetry (CS) structure for sequences containing placebo treatment but were different from the CS structure for sequences containing active treatment in both periods. Denominator degrees of freedom for the F-test for fixed effects were estimated using the

Kenward-Roger approximation. No imputation of missing data was performed. Subjects with data for only one of the periods had a data structure similar to a parallel-group trial. Assuming that those subjects dropped out at random, an estimate of treatment effect based on those subjects was combined with the estimate from subjects with data from both treatment periods with weights based on the precision of these estimates.

In addition, an ANCOVA model analysis using absolute change from baseline in ppFEV1 to the average of week 4 and 8 measurements from treatment period 1 was performed to assess the treatment effect difference in case of a carryover effect. This model included treatment, age group at screening (< 18 vs ≥ 18 years), ppFEV1 at baseline, and category of residual function mutation (Class V vs Class II to IV).

The sponsor also performed planned sensitivity analyses of the primary endpoint which included an MMRM analysis and a multiple imputations-based repeat of the primary analysis. The MMRM approach was like that used for the primary endpoint analysis in Trial 106 with period as an additional fixed effect. The multiple imputation approach was used to assess the underlying assumption that data are missing at random, but was only to be performed if more than 10% of subjects were missing data for the absolute change in ppFEV1 from baseline from either treatment period 1 or 2. However, a missing value in period 2 due to treatment discontinuation in period 1 was not be imputed. A mixed effects model analogous to that for the primary analysis of the primary endpoint was to be applied to each imputed dataset and the combined result was used to obtain the multiple imputations estimates.

For the FAS, subgroup analyses of the primary endpoint were performed using a model similar to that for the primary analysis. The subgroups considered were the same as those analyzed in Trial 106 with the addition of residual function mutation (Class V non-canonical splice and Classes II to IV residual function).

Protocol Amendments

The sponsor amended the protocol two times. The first protocol amendment on 8/6/15 made the following key changes: incorporated additional spirometry assessments and an ophthalmologic exam at the early treatment termination (ETT) or safety follow up visit in subjects < 18 years of age, made sweat chloride test at screening optional, changed order of testing hierarchy – change in CFQ-R respiratory domain to key secondary endpoint and change in sweat chloride to secondary endpoint, added washout requirements for subjects who previously used commercially available CFTR modulators, updated criteria to determine eligible mutations to require that all mutations be potentially responsive to IVA monotherapy, removed P205S, A1067T and R1070Q as eligible mutations, and added E831X as eligible mutation. The second protocol amendment on 6/10/16 made the following key changes: reduced sample size from 300 to 204 subjects, moved relative change in ppFEV1 from key secondary to secondary

endpoint and removed from testing hierarchy, removed responder analysis for ppFEV1, required all subjects to have CFTR genotyping at screening, removed statistical comparison of TEZ/IVA and IVA from testing strategy and replaced with a single, stepwise, hierarchical approach. The main modification to the SAP was a revision of the testing strategy to control multiplicity in that the test of TEZ/IVA versus placebo for the key secondary endpoint was no longer gated by the test of IVA monotherapy versus placebo.

Data Quality and Integrity: Sponsor's Assurance

The sponsor's methods for assuring data quality and integrity were the same as in Trial 106.

6.2.2. Study Results

Compliance with Good Clinical Practices

The Applicant states that the study was conducted in accordance with GCP as described in ICH guidelines. The study protocol, amendments, informed consent, and other necessary documents were reviewed and approved by an independent ethics committee (IEC) or institutional review board (IRB) for each study site before initiation of the study at that site. Written informed consent was obtained from each subject before study participation. This study was conducted under IND 108,105.

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 13.1).

Patient Disposition

Patient disposition broken down by treatment sequence group is detailed in Table 14. Completion rates were relatively high, although somewhat lower in patients initially treated with placebo and those in the TEZ/IVA→IVA sequence; however, early treatment discontinuation was not driven by any one factor. Four subjects were excluded from the FAS population: two did not receive treatment (Subjects 108-301-010 and 108-510-001) and two subjects were randomized and received treatment but did not have eligible CFTR mutations (Subjects 108-036-004 and 108-051-009).

Table 14. Disposition of subjects: Trial 108

	Treatment sequence (Period 1 → Period 2)						
	TEZ/IVA→ IVA	TEZ/IVA → Placebo	IVA→ TEZ/IVA	IVA→ Placebo	Placebo→ TEZ/IVA	Placebo→ IVA	All Subjects

	Treatment sequence (Period 1 → Period 2)						
	TEZ/IVA→ IVA	**TEZ/IVA → Placebo**	**IVA→ TEZ/IVA**	**IVA→ Placebo**	**Placebo→ TEZ/IVA**	**Placebo→ IVA**	**All Subjects**
Randomized	41	43	42	40	41	41	248
Treated (Period 1 and overall)	41	43	42	39	40	41	246
Treated (Period 2)	38	43	41	38	37	38	235
FAS, n (% of total)	**40 (16)**	**43 (17)**	**42 (17)**	**39 (16)**	**39 (17)**	**41 (17)**	**244 (100)**
n, (% of FAS treatment sequence group)							
Completed study	38 (93)	43 (100)	41 (98)	38 (95)	37 (90)	38 (93)	235 (95)
Premature treatment discontinuation	4 (10)	1 (2)	1 (2)	0	2 (5)	3 (7)	11 (5)
Period 1							
Adverse event	0	0	1 (2)	0	0	1 (2)	2 (1)
Lost to follow-up	0	0	0	0	0	1 (2)	1 (<1)
Non-compliance	1 (3)	1 (2)	0	0	0	1 (2)	3 (1)
Withdrawal by subject	0	0	0	0	2 (5)	0	2 (1)
Other	1 (3)	0	0	0	0	0	1 (<1)
Washout							
Adverse event	1 (3)	0	0	0	0	0	1 (<1)
Period 2							
Adverse event	1 (3)	0	0	0	0	0	1 (<1)

Source: Reviewer generated table in JMP Clinical using ADSL dataset
FAS=Full Analysis Set

Protocol Violations/Deviations

As noted above, Subject 108-036-004 had N1303K/R1070W mutations and Subject 108-051-009 had W1282X/3849 + 10kbC→T mutations. There were 14 subjects with major or important protocol violations which included compliance <80%, excluded concomitant medications use, failure to perform pregnancy testing, and failure to obtain properly signed informed consent form for a minor.

Demographic Characteristics

Patient demographics are summarized in Table 15. The study population consisted predominantly of white adults (mean age 35 years) with slightly more females than males, and roughly half US and ex-US subjects. Approximately 15% of patients were adolescents. Reflecting the less severe nature of these "residual function" mutations, patients in this study tended to be older than those in trial 106.

Table 15. Subject demographics: Trial 108

	Treatment sequence (Period 1 → Period 2)						
	TEZ/IVA→ IVA	**TEZ/IVA → Placebo**	**IVA→ TEZ/IVA**	**IVA→ Placebo**	**Placebo→TEZ/IVA**	**Placebo→ IVA**	**All Subjects**
N (% of all subjects)	**40 (16)**	**43 (17)**	**42 (17)**	**39 (16)**	**39 (17)**	**41 (17)**	**244 (100)**
Sex, n (% of treatment sequence group)							

	Treatment sequence (Period 1 → Period 2)						
	TEZ/IVA→ IVA	TEZ/IVA → Placebo	IVA→ TEZ/IVA	IVA→ Placebo	Placebo→TEZ/IVA	Placebo→ IVA	All Subjects
Female	23 (57)	25 (58)	21 (50)	19 (49)	23 (58)	23 (56)	134 (55)
Male	17 (43)	18 (42)	21 (50)	20 (51)	16 (41)	18 (44)	110 (45)
Age (years)							
Mean (SD)	34 (13)	37 (14)	36 (15)	36 (16)	34 (16)	31 (12)	35 (14)
Median	35	35	38	40	30	30	34
Min, Max	12, 59	12, 68	13, 69	12, 63	12, 72	12, 60	12, 72
Age Groups, n (% of treatment sequence group)							
<18 Years	5 (13)	6 (14)	5 (12)	7 (18)	5 (13)	6 (15)	34 (14)
≥18 Years	35 (88)	37 (86)	37 (88)	32 (82)	34 (87)	35 (85)	210 (86)
40 to 64 Years	17 (43)	14 (33)	17 (40)	20 (51)	11 (28)	10 (24)	89 (37)
≥65 Years	0	2 (5)	2 (5)	0	2 (5)	0	6 (2)
Race, n (% of treatment sequence group)							
American Indian or Alaskan Native	0	0	0	0	0	1 (2)	1 (<1)
Black or African American	2 (5)	0	0	0	0	1 (2)	3 (1)
Not collected per local regulations	0	0	0	0	1 (3)	0	1 (<1)
Other	0	1 (2)	0	0	0	0	1 (<1)
White	38 (95)	42 (98)	42 (100)	39 (100)	38 (97)	39 (95)	238 (98)
Region, n (% of treatment sequence group)							
Europe	20 (50)	18 (42)	24 (57)	21 (54)	19 (49)	22 (54)	124 (51)
North America	20 (50)	25 (58)	18 (43)	18 (46)	20 (51)	19 (46)	120 (49)
USA	19 (48)	23 (53)	17 (40)	18 (46)	18 (46)	18 (44)	113 (46)
Ethnicity, n (% of treatment sequence group)							
Hispanic or Latino	1 (2)	0	3 (7)	1 (3)	2 (5)	2 (5)	9 (4)
Not Hispanic or Latino	39 (98)	43 (100)	39 (93)	38 (97)	36 (92)	39 (95)	234 (96)
Not reported	0	0	0	0	1 (3)	0	1 (<1)
Source: Reviewer generated table in JMP Clinical using ADSL dataset							

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

Treatment sequence groups were generally balanced with regard to various baseline disease characteristics and concomitant medication use as summarized in Table 16. The average ppFEV1 at baseline was ~62%. Patients possessing non-canonical splice mutations as the second CFTR mutation represent a larger proportion of the study population since these mutations are not amenable to assessing responsiveness to TEZ/IVA in the *in vitro* assays.

Table 16. Baseline disease characteristic: Trial 108

	Treatment sequence (Period 1 → Period 2)						
	TEZ/IVA→ IVA	TEZ/IVA → Placebo	IVA→ TEZ/IVA	IVA→ Placebo	Placebo→ TEZ/IVA	Placebo→ IVA	All Subjects
N	**40 (16)**	**43 (17)**	**42 (17)**	**39 (16)**	**39 (17)**	**41 (17)**	**244 (100)**
Baseline ppFEV1							
Mean (SD)	62 (15)	62 (15)	63 (15)	63 (14)	62 (13)	63 (15)	62 (14)

	Treatment sequence (Period 1 → Period 2)						
	TEZ/IVA→ IVA	TEZ/IVA → Placebo	IVA→ TEZ/IVA	IVA→ Placebo	Placebo→ TEZ/IVA	Placebo→ IVA	All Subjects
N	**40 (16)**	**43 (17)**	**42 (17)**	**39 (16)**	**39 (17)**	**41 (17)**	**244 (100)**
Median	61	60	61	63	61	64	62
Min, Max	38, 91	35, 91	35, 89	38, 92	35, 86	38, 93	35, 93
Baseline BMI (kg/m2)							
Mean (SD)	23 (3)	25 (5)	24 (5)	25 (6)	24 (5)	25 (5)	24 (5)
Median	22	23	24	24	24	23	23
Min, Max	16, 31	16, 42	15, 33	16, 50	16, 37	16, 34	15, 50
Baseline Weight (kg)							
Mean (SD)	64 (13)	72 (18)	71 (16)	71 (21)	69 (15)	71 (18)	69 (17)
Median	61	70	69	69	66	68	67
Min, Max	43, 93	44, 127	42, 102	40, 157	44, 112	42, 105	40, 157
Baseline Sweat Chloride,							
Mean (SD)	66 (29)	62 (29)	72 (25)	78 (23)	67 (23)	74 (25)	70 (26)
Median	71	58	74	85	69	75	74
Min, Max	15, 107	13, 119	11, 106	29, 113	21, 109	19, 135	11, 135
Baseline CFQ-R Resp Domain Score							
Mean (SD)	65 (17)	68 (19)	70 (16)	70 (20)	70 (19)	66 (16)	68 (18)
Median	67	72	72	72	72	67	72
Min, Max	28, 100	17, 100	33, 100	17, 100	17, 92	28, 94	17, 100
CF Genotyping, n (% of treatment sequence group)							
Non-canonical splice mutations							
F508del/2789+5G→A	6 (15)	5 (12)	10 (24)	8 (21)	4 (10)	4 (10)	37 (15)
F508del/3272-26A→G	7 (17)	8 (19)	5 (12)	5 (13)	4 (10)	7 (17)	36 (15)
F508del/3849+10kbC→T	11 (27)	13 (30)	9 (21)	9 (23)	14 (35)	13 (32)	69 (28)
F508del/711+3A→G	0	0	1 (2)	0	1 (3)	1 (2)	3 (1)
F508del/E831X	0	0	0	1 (3)	0	0	1 (<1)
Missense mutations							
F508del/A455E	3 (7)	3 (7)	2 (5)	7 (18)	3 (8)	2 (5)	20 (8)
F508del/D110H	0	1 (2)	0	0	0	0	1 (<1)
F508del/D1152H	6 (15)	7 (16)	5 (12)	3 (8)	3 (8)	2 (5)	26 (11)
F508del/D579G	0	1 (2)	1 (2)	1 (3)	0	0	3 (1)
F508del/L206W	0	1 (2)	1 (2)	0	2 (5)	1 (2)	5 (2)
F508del/P67L	4 (10)	1 (2)	3 (7)	0	3 (8)	6 (15)	17 (7)
F508del/R1070W	0	1 (2)	0	1 (3)	1 (3)	0	3 (1)
F508del/R117C	0	0	1 (2)	0	0	0	1 (<1)
F508del/R347H	1 (2)	1 (2)	0	1 (3)	0	1 (2)	4 (2)
F508del/R352Q	2 (5)	0	0	0	0	1 (2)	3 (1)
F508del/S945L	0	1 (2)	3 (7)	3 (8)	3 (8)	3 (7)	13 (5)
F508del/S977F	0	0	1 (2)	0	1 (3)	0	2 (1)
Dornase Alfa Use, n (% of treatment sequence group)							
Yes	21 (53)	26 (60)	24 (57)	25 (64)	27 (69)	27 (66)	150 (61)
Inhaled Antibiotic Use, n (% of treatment sequence group)							
Yes	13 (33)	13 (30)	13 (31)	14 (36)	11 (28)	12 (29)	76 (31)
Inhaled Corticosteroid Use, n (% of treatment sequence group)							
Yes	25 (63)	25 (58)	27 (64)	21 (54)	22 (56)	23 (56)	143 (59)
Inhaled Bronchodilator Use, n (% of treatment sequence group)							
Yes	35 (88)	39 (91)	35 (83)	32 (82)	35 (90)	36 (88)	213 (87)
Long-Acting only	7 (18)	2 (5)	9 (21)	4 (10)	8 (21)	3 (7)	33 (14)

	Treatment sequence (Period 1 → Period 2)						
	TEZ/IVA→ IVA	TEZ/IVA → Placebo	IVA→ TEZ/IVA	IVA→ Placebo	Placebo→ TEZ/IVA	Placebo→ IVA	All Subjects
N	**40 (16)**	**43 (17)**	**42 (17)**	**39 (16)**	**39 (17)**	**41 (17)**	**244 (100)**
Short-Acting and Long-Acting	15 (38)	24 (56)	15 (36)	14 (36)	17 (44)	15 (37)	100 (41)
Short-Acting only	13 (33)	13 (30)	11 (26)	14 (36)	11 (28)	18 (44)	79 (33)
Inhaled Hypertonic Saline Use, n (% of treatment sequence group)							
Yes	17 (43)	26 (60)	16 (38)	20 (51)	20 (51)	19 (46)	118 (48)
Azithromycin Use, n (% of treatment sequence group)							
Yes	16 (40)	16 (37)	15 (36)	16 (41)	17 (44)	21 (51)	101 (41)
***Pseudomonas aeruginosa* colonization, n (% of treatment sequence group)**							
Positive	30 (75)	22 (51)	23 (55)	22 (56)	24 (62)	24 (59)	145 (59)
Source: Reviewer generated table in JMP Clinical using ADSL dataset							

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Overall, 98% of subjects had treatment compliance ≥80% during Period 1 and only one subject had treatment compliance <80% during Period 2. Concomitant medications administered during the treatment periods consisted primarily of antibiotics and anti-inflammatory medications (ibuprofen, prednisone, and paracetamol).

Efficacy Results - Primary and Key Secondary Endpoints

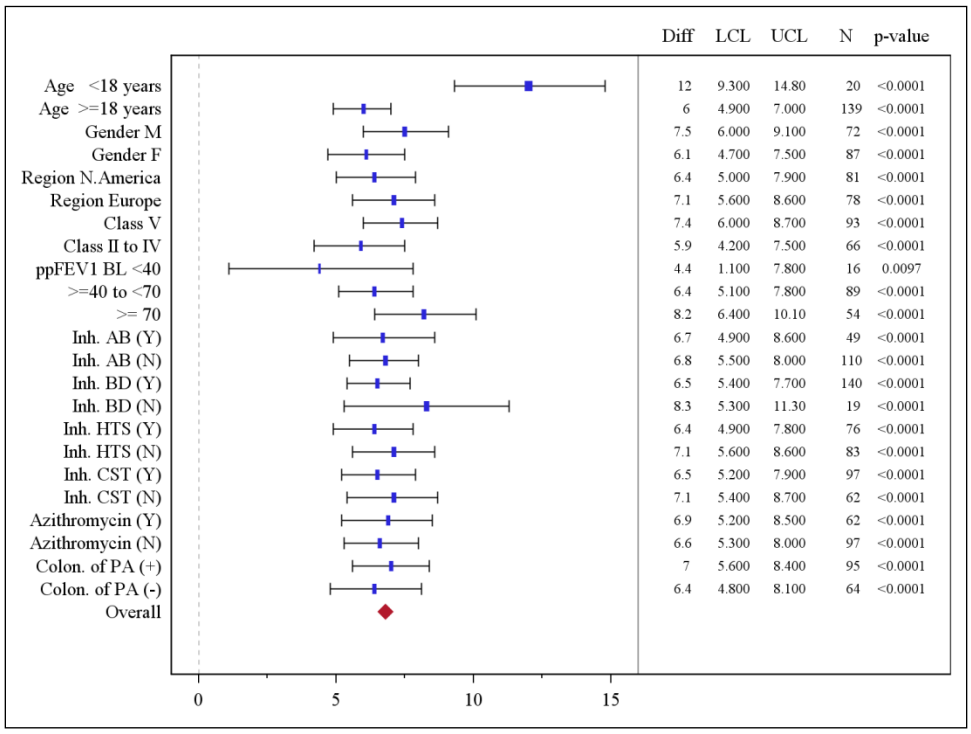
Efficacy analyses were conducted on the FAS population. For the purposes of this review, the efficacy results from Periods 1 and 2 were combined with treatment assignment based on planned treatment for each period. For the overall population, treatment with TEZ/IVA compared to placebo resulted in significant improvement in ppFEV1 [6.8% from study baseline to average of Week 4 and Week 8 (95% CI 5.7, 7.8)] and CFQ-R respiratory domain score [11.1 points from study baseline to average of Week 4 and Week 8 (95% CI 8.7, 13.6)]. In addition, TEZ/IVA treatment showed a numerical and statistical difference in ppFEV1 over IVA monotherapy (Table 17); thereby demonstrating the contribution of TEZ to the combination product. Subgroup analyses of the primary endpoint shown in Figure 5 were consistent with the overall treatment effect.

Table 17. Primary and key secondary endpoints, FAS population: Trial 108

Analysis	Statistic	Placebo N=161	IVA N=156	TEZ/IVA N=161
Absolute Δ in $ppFEV_1$ from baseline to the average of Week 4 and Week 8 (%)	Treatment difference versus placebo (95% CI)	NA NA	4.7 (3.7, 5.8)	6.8 (5.7, 7.8)
	Treatment difference versus IVA (95% CI)	NA NA	NA NA	2.1 (1.2, 2.9)
	Within-group change (SE)	-0.3 (0.5)	4.4 (0.5)	6.5 (0.4)

Analysis	Statistic	Placebo N=161	IVA N=156	TEZ/IVA N=161
Absolute Δ in CFQ-R respiratory domain score from baseline to the average of Week 4 and Week 8 (points)	Treatment difference versus placebo (95% CI)	NA NA	9.7 (7.2, 12.2)	11.1 (8.7, 13.6)
	Treatment difference versus IVA (95% CI)	NA NA	NA NA	1.4 (-1.0, 3.9)
	Within-group change (SE)	-1.0 (1.0)	8.7 (1.0)	10.1 (1.0)
CI: confidence interval; CFQ-R: Cystic Fibrosis Questionnaire-Revised; FEV_1: forced expiratory volume in 1 second; IVA: ivacaftor; TEZ/IVA: tezacaftor in combination with ivacaftor; NA: not applicable; SE: Standard Error.				

Figure 5. Subgroup analyses for absolute change in $ppFEV_1$, average of Week 4 and 8 values (TEZ/IVA vs PBO): Trial 108



Source: Biostatistics review by Dr. Mingyu Xi
ppFEV1 results reflect the average of Week 4 and 8 measurements

Data Quality and Integrity - Reviewers' Assessment

This review did not reveal any inconsistencies in the data or issues with trial design or conduct which might influence the efficacy results.

Efficacy Results - Secondary and other relevant endpoints

Results for the exploratory BMI endpoint at Week 8 demonstrated an increase in BMI of 0.2 kg/m^2 (95% CI 0.0, 0.3), 0.1 kg/m^2 [95% CI (-0.1, 0.3)], and 0.3 kg/m^2 [95% CI (0.1, 0.5)] versus

placebo for the overall, non-canonical splice, and missense mutation populations of patients, respectively.

Durability of Response

The absolute change in ppFEV1 over baseline was consistent over the limited 8-week treatment duration.

Additional Analyses Conducted on the Individual Trial

As was done for the review of the IVA monotherapy component of this study (NDAs 203-188/207-925, supplements 26 and 5), the efficacy results were also evaluated by non-canonical splice and missense mutation subpopulations and at the individual mutation level. While the number of patients with any individual mutation is relatively small, it is reassuring that efficacy results at this granular level generally track with and support the overall results. Furthermore, efficacy results by individual mutation also generally support the added benefit of TEZ to the TEZ/IVA combination. That being said, a few individual mutations, such as R347H, did not clearly demonstrate an improvement in ppFEV1 response to TEZ/IVA treatment vs IVA alone; however, the study was not powered nor expected to show a difference at the individual mutation level when represented by such a small number of patients. Thus, while Vertex had initially excluded the R347H mutation from the list of indicated mutations in Section 12 of the proposed label, the review division prefers to err on the side of being more inclusive. Given the overall results, the knowledge that IVA monotherapy is efficacious and therefore TEZ/IVA should be as well, and the rationale provided above, we will extend the indication to all mutations evaluated in the study.

Table 18. Effect of TEZ/IVA for Efficacy Variables in Non-canonical splice and Missense CFTR Mutation Subgroups: Trial 108

Mutation (n)	Absolute Change in $ppFEV_1$[*†]	Absolute Change in CFQ-R Respiratory Domain Score (Points) [*‡]	Absolute Change in Sweat Chloride (mmol/L) [*‡]
Non-canonical splice mutations (n=93 for TEZ/IVA and n=97 for PBO) **Results shown as difference in mean (95% CI) change from study baseline for TEZ/IVA vs. placebo-treated patients:**			
	7.4 (6.0, 8.7)	9.5 (6.3, 12.7)	-5.4 (-8.0, -2.7)

By individual non-canonical splice mutation (n). Results shown as mean (minimum, maximum) for change from study baseline for TEZ/IVA-treated patients			
2789+5G→A (25)	8.6 (-1.5, 23.4)	12.0 (-8.3, 38.9)	-3.2 (-16.5, 9.0)
3272-26A→G (23)	5.7 (-2.1, 25.9)	5.7 (-22.2, 44.4)	-3.8 (-22.3, 16.5)
3849+10kBc→T (43)	5.8 (-7.2, 22.3)	8.2 (-25.0, 47.2)	-5.6 (-27.0, 8.5)
711+3A→G (2)	4.3 (2.0, 6.7)	-4.2 (-5.6, -2.8)	-15.4 (-21.0, -9.8)
E831X (0)	NA	NA	NA
Missense mutations (n=66 for TEZ/IVA and n=63 for PBO) Results shown as difference in mean (95% CI) change from study baseline for TEZ/IVA vs. placebo-treated patients:			
	5.9 (4.2, 7.5)	13.4 (9.6, 17.3)	-16.3 (-19.7, -12.9)
By individual non-canonical splice mutation (n). Results shown as mean (minimum, maximum) for change from study baseline for TEZ/IVA-treated patients			
D579G (2)	8.1 (-0.2, 16.4)	11.1 (5.6, 16.7)	-23.1 (-24.8, -21.5)
D110H (1)	-1.0 (-1.0, -1.0)	-11.1 (-11.1, -11.1)	-22.5 (-22.5, -22.5)
D1152H (21)	3.8 (-2.5, 12.5)	15.2 (-8.3, 55.6)	-4.1 (-15.0, 11.5)
A455E (11)	8.5 (2.6, 16.1)	11.6 (-11.1, 44.4)	-0.3 (-8.8, 14.0)
L206W (4)	3.0 (-4.5, 10.2)	12.5 (-2.8, 38.9)	-36.1 (-44.5, -27.5)
P67L (11)	9.4 (0.0, 31.9)	11.7 (-12.5, 72.2)	-29.3 (-50.0, 0.8)
R1070W (2)	6.1 (2.0, 10.1)	29.2 (16.7, 41.7)	-13.8 (-26.8, -0.8)
R117C (1)	2.9 (2.9, 2.9)	16.7 (16.7, 16.7)	-38.8 (-38.8, -38.8)
R347H (2)	-0.5 (-2.8, 1.7)	5.6 (-5.6, 16.7)	-13.8 (-19.0, -8.5)
R352Q (2)	4.9 (2.6, 7.1)	8.3 (8.3, 8.3)	-43.3 (-49.8, -36.8)
S945L (7)	9.6 (0.7, 19.5)	11.3 (-4.2, 25.0)	-29.0 (-42.5, -8.0)
S977F (2)	10.1 (5.5, 14.7)	-1.4 (-8.3, 5.6)	-13.9 (-22.3, -5.5)

* Average of Week 4 and 8 values
† Absolute change in $ppFEV_1$ by individual mutation is an ad hoc analysis
‡ Absolute change in CFQ-R respiratory domain score and absolute change in sweat chloride by individual mutation subgroups and by individual mutations are ad hoc analyses.
Source: Generated by biostatistical reviewer, Dr. Mingyu Xi

6.3. **VX14-661-107**

6.3.1. **Study Design**

Overview and Objective

Trial 107 was a multinational trial to evaluate the efficacy and safety of TEZ in combination with IVA in subjects with CF who are heterozygous for the *F508del* mutation on the CFTR gene and a second CFTR mutation predicted to be unresponsive to TEZ and/or IVA therapy. The study was conducted from 8/15/15 through 6/7/16.

Study Title: A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group Study to Evaluate the Efficacy and Safety of Ivacaftor and VX-661 in Combination with Ivacaftor in Subjects Aged 12 Years and Older with Cystic Fibrosis, Heterozygous for the *F508del*-CFTR Mutation, and with a Second CFTR Mutation That Is Not Likely to Respond to VX-661 and/or Ivacaftor Therapy (*F508del*/NR)

Primary Objective

- To evaluate the efficacy of TEZ/IVA through Week 12 in CF patients heterozygous for the *F508del*-CFTR mutation and a second CFTR mutation not likely to respond to TEZ and/or

IVA therapy

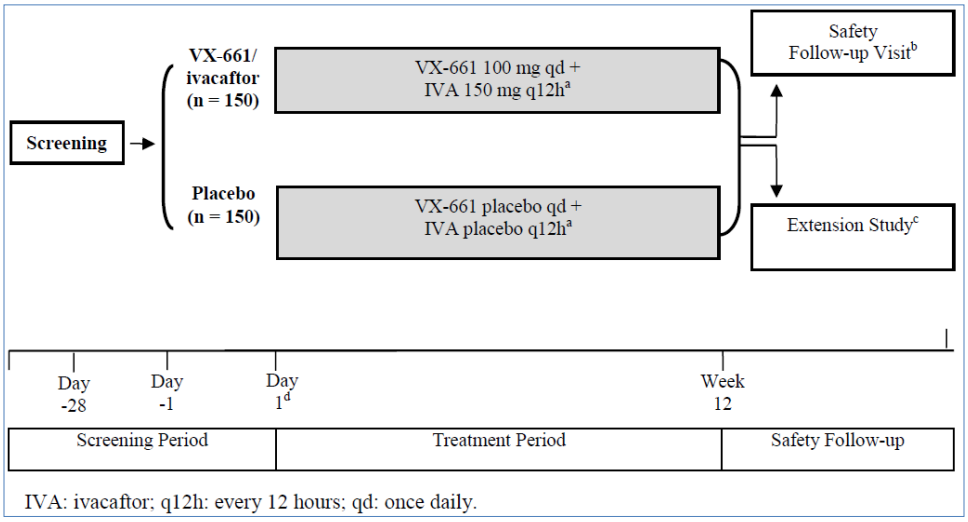
Secondary Objectives

- To evaluate the safety of TEZ/IVA through week 12
- To investigate the PK of TEZ, IVA and their metabolites

Trial Design

Apart from a 12 rather than 24-week treatment period, the design of Trial 107 was the same as Trial 106. The study schematic and study assessments are shown in Figure 6 and Table 19, respectively.

Figure 6. Study Design Schematic: Trial 107



Source: Clinical Trial Protocol VX14-661-107, Figure 8-1, p24

Table 19. Schedule of Assessments: Trial 107

Event/Assessment[a]	Day 1	Day 15 (± 3 days)	Week 4 (Day 29) (± 5 days)	Week 8 (Day 57) (± 5 days)	Week 12 (Day 85) (± 5 days)	Early Treatment Termination Visit[b]	Safety Follow-up Visit 28 (± 7) days After Last Dose[c]
Clinic visit	X[d]	X	X	X	X	X	X
Inclusion and exclusion criteria review	X						
CFQ-R[e]	X	X	X	X	X	X	X
CFRSD[e]	X	X	X	X	X	X	
SF-12[e]	X	X	X	X	X	X	X
PSQI[e]	X		X	X	X	X	X
Weight and height[f]	X	X	X	X	X	X	X
Ophthalmologic examination[g]						X	X
Complete physical examination[h]	X						
Pregnancy test[i]	X		X	X	X	X	X
Standard digital ECG[j]	X	X	X	X	X	X	X
Vital signs[k]	X	X	X	X	X	X	X
Pulse oximetry[k]	X	X	X	X	X	X	X
Spirometry[l]	X	X	X	X	X	X	X
Sweat chloride[m]	X		X	X	X	X	
Urinalysis	X				X	X	X
Hematology	X	X	X	X	X	X	X
Coagulation	X				X	X	X
Serum chemistry	X	X	X	X	X	X	X
Lipid panel[n]	X		X		X	X	
Vitamin levels	X		X		X	X	
PK sampling[o]		X	X	X	X	X	X
DNA Sample A and B (optional)		X					
Blood biomarker analysis	X				X		X
Sputum samples[p]	X				X		
Inflammatory mediators	X				X		
Other events related to outcome[q]	X	X	X	X	X	X	
Randomization[r]	X						
Meal(s) or snack(s) at site[s]	X	X	X	X			
Study drug dosing[t]		Day 1 through Week 12					
Study drug count		X	X	X	X	X	
Concomitant medications	X	X	X	X	X	X	X
Concomitant treatments and procedures	X	X	X	X	X	X	X
AEs and SAEs	Continuous from signing of the ICF and assent (where applicable) through the Safety Follow-up Visit[u]						

AE: adverse event; CF: cystic fibrosis; CFQ-R: CF Questionnaire–Revised; CFRSD: CF Respiratory Symptom Diary; *CFTR: cystic fibrosis transmembrane conductance regulator* gene; ECG: electrocardiogram; ETT: Early Treatment Termination; FSH: follicle-stimulating hormone; ICF: informed consent form; PK: pharmacokinetics; PSQI: Pittsburgh Sleep Quality Index; SAE: serious adverse event; SF-12: 12-Item Short Form Survey; US: United States.

[a] All assessments will be performed before dosing unless noted otherwise. Where repeats of the same assessment are required at a given visit, if study drug is not administered on the day of the visit (i.e., study drug interruption or premature discontinuation of study drug treatment), only 1 set of assessments will be collected.

[b] If the subject prematurely discontinues study drug treatment, an Early Treatment Termination (ETT) Visit should be scheduled as soon as possible after the last dose of study drug. Subjects who prematurely discontinue study drug treatment will also be required to complete the Safety Follow-up Visit, approximately 28 (± 7) days after their last dose of study drug. If the ETT Visit occurs 3 weeks or later following the last dose of study drug, then the ETT Visit will replace the Safety Follow-up Visit, and a separate Safety Follow-up Visit will not be required. See Section 8.1.3.

[c] Subjects who completed the whole duration of treatment with study drug in this study and have enrolled in the extension study within 28 days after the last dose of study drug will not have a Safety Follow-up Visit.

[d] Subjects will be observed in the clinic for 6 hours after the morning dose of study drug.

[e] All questionnaires must be completed before the start of any other assessments scheduled at that visit. The CFQ-R must be completed first, followed by the CFRSD, SF-12, and the PSQI (Section 11.7). Subjects will fill out the CFRSD daily at home for Days 2 through 14 and Days 16 through 28 after 05:00 PM each day, as per the instrument instructions. On Days 1 and 15, and Weeks 4, 8, and 12, subjects will fill out the CFRSD in the clinic. Subjects will need to complete the CFRSD, CFQ-R, SF-12, and PSQI at the ETT Visit if it has been 2 weeks or more since their last visit.

[f] Weight and height will be measured before dosing with shoes off. Height will be collected only for subjects 21 years of age or younger.

[g] Subjects < 18 years of age at screening who discontinue study drug treatment after receiving at least 1 dose of study drug treatment, and subjects < 18 years of age at screening who complete study drug treatment but do not enroll in a separate extension study of VX-661/ivacaftor within 28 days of the last dose of study drug will have an ophthalmologic exam conducted by a licensed ophthalmologist at the Safety Follow-up Visit or ETT Visit (see Section 11.8.8). The exam may be completed at either the ETT or Safety Follow-up Visit, but must be completed by the date of the Safety Follow-up Visit. Subjects who have documentation of bilateral lens removal do not need an ophthalmologic examination.

[h] Symptom-targeted physical examinations will occur at any time during the study if triggered by AEs or if deemed necessary by the investigator.

[i] Pregnancy tests will be performed for all female subjects of childbearing potential. A urine β-hCG test will be performed on Day 1 (before first dose of study drug), Week 4, and Week 8. A serum pregnancy test will be performed at the Week 12 Visit, the ETT Visit, and the Safety Follow-up Visit.

[j] All standard digital ECGs will be performed before dosing and after the subject has been supine for at least 5 minutes. At the Days 1 and 15 Visits, ECGs will be collected before dosing and at 1.5, 3, 4, and 6 hours after the morning dose. On Days 1 and 15, the 4 hour postdose ECG will be collected before the 4 hour postdose spirometry assessment. ECGs collected on Day 1 before dosing will be performed in triplicate. If study drug is not administered on the day of the visit (i.e., because of study drug interruption or permanent discontinuation of study drug), only 1 ECG will be collected.

[k] Vital signs and pulse oximetry will be collected before dosing after the subject has been at rest (seated or supine) for at least 5 minutes.

[l] At all visits, spirometry must be performed for all subjects before dosing and should be performed pre-bronchodilator (Section 11.7.1). On Days 1 and 15, subjects < 18 years of age at the Screening Visit will have additional spirometry performed at 2 and 4 hours after the morning dose. If more than 1 spirometry assessment is required at a visit, bronchodilators will be withheld until completion of the last scheduled spirometry assessment is completed.

[m] Sweat collection must be completed before the predose PK sample collection and before the morning dose of study drug. Sweat collection will not overlap with any other study assessments (Section 11.7.2).

[n] Blood samples will be collected for the lipid panel following at least a 4-hour fast.

[o] PK blood samples will be collected before the morning dose on Day 15, Week 4, and Week 8. A PK blood sample will also be collected at the Week 12, Safety Follow-up, and the ETT Visits.

[p] Sputum will be collected from subjects who can produce a sample spontaneously. A part of the required sputum sample will be used for microbiology culture, and the remaining sputum sample will be stored for pharmacogenomics use.

[q] Other events related to outcome include assessments relating to pulmonary exacerbations, administration of antibiotic therapy for sinopulmonary signs or symptoms, and hospitalizations (Section 11.7.10).

[r] Randomization must occur after all inclusion and exclusion criteria are met and before the first dose of study drug. Randomization will be done through the interactive web response system (IWRS). Randomization may occur on Day -1.

[s] Fat-containing food such as a "standard CF" high-fat, high-calorie meal or snack will be provided at the site to subjects after all predose assessments have occurred.

[t] The study drug should be administered every 12 hours (± 2 hours) within 30 minutes of starting a fat-containing meal such as a "standard CF" high-fat, high-calorie meal or snack. On days of scheduled visits, the morning dose of study drug will be administered at the site after predose assessments have been completed. The final dose of study drug will be administered the evening before the Week 12 Visit.

[u] For enrolled subjects who do not have a Safety Follow-up Visit, AEs and SAEs will be collected through the earliest of either 28 days after the last dose of study drug, the ETT Visit (if that visit is 3 weeks or later following the last dose of study drug; see Section 8.1.4), or prior to the first dose of study drug in the extension study.

Source: Clinical Trial Protocol VX14-661-107, Table 3-2, p11

Trial Population
The eligibility criteria were the same as for Trials 106 and 108 with the following key difference:

Key Inclusion Criteria

1. Heterozygous for the *F508del*-CFTR mutation and with a second CFTR mutation that is not likely to respond to TEZ and/or IVA therapy (Table 20). *Note: previous CFTR genotype lab results may have been used to establish eligibility if screening genotype results were not received before randomization. However, if the screening genotype did not confirm study eligibility, subjects were discontinued from the study.*

Table 20. CFTR mutations not likely to respond to TEZ and/or IVA therapy: Trial 107

Criteria	Mutation				
Truncation mutations • %PI >50% and/or $SwCl^-$ >86 mmol/L • no full-length protein	Q39X	Q290X	G542X	R792X	R1162X
	W57X	G330X	Q552X	E822X	S1196X
	E60X	W401X	R553X	W846X	W1204X
	R75X	Q414X	E585X	R851X	S1255X
	E92X	S434X	G673X	Q890X	W1282X
	Q98X	S466X	R709X	S912X	Q1313X
	Y122X	S489X	K710X	W1089X	
	L218X	Q493X	L732X	Y1092X	
	Q220X	W496X	R764X	E1104X	
	C276X	Q525X	R785X	R1158X	
Canonical splice mutations • %PI >50% and/or $SwCl^-$ >86 mmol/L • no or little mature mRNA	621+1G→T	405+3A→C	1717-1G→A	2622+1G→A	4374+1G→T
	711+1G→T	406-1G→A	1811+1.6kbA→G	3120+1G→A	
	711+5G→A	621+1G→T	1811+1G→C	3120G→A	
	712-1G→T	1248+1G→A	1812-1G→A	3850-1G→A	
	405+1G→A	1341+1G→A	1898+1G→A	4005+1G→A	
Frameshift mutations • %PI >50% and/or $SwCl^-$ >86 mmol/L • garbled or truncated protein	663delT	3905insT	1677delTA	3007delG	2043delG
	2183AA→G	2184delA	3876delA	574delA	2869insG
	CFTRdele2,3	1078delT	2307insA	2711delT	3600+2insT
	3659delC	1154insTC	4382delA[a]	3791delC	3737delA
	394delTT	2183delAA	4016insT	CFTRdele22,23	4040delA
	2184insA	2143delT	2347delG	457TAT→G	541delC
Class II, III, IV mutations not responsive to ivacaftor or VX-661 • %PI >50% and/or $SwCl^-$ >86 mmol/L OR • not responsive in vitro to ivacaftor and VX-661)	A46D[b]	S341P[b]	R560T	R1066C	N1303K
	T338I[c]	L467P[b]	R560S	R1066M	
	R347P	I507del	A561E	L1077P[b]	
	L927P	V520F	Y569D[b]	H1085R[b]	
	G85E	A559T[b]	L1065P	M1101K	

%PI: percentage of subjects who are pancreatic insufficient; $SwCl^-$: sweat chloride
[a] PI frequency is consistent with a residual function mutation, but this mutation is included because of $SwCl^-$ data and biological rationale, which suggests that this type of mutation should be severe and not responsive.
[b] Unpublished data.
[c] PI frequency is consistent with a residual function mutation, but this mutation is included because of $SwCl^-$ data, low baseline in vitro conductance, and failure for ivacaftor to improve conductance by at least 10% over baseline.

Source: Clinical Trial Protocol VX14-661-107, Appendix 1, p85

Vertex took three factors into account to identify and define mutations that were unlikely to respond to TEZ and/or IVA therapy: biological plausibility (i.e., mutation class), clinical severity on a population basis from patient registry data (average sweat chloride > 86 mmol/L,

percentage of patients with pancreatic insufficiency > 50%), and *in vitro* testing (mutations that responded with chloride transport < 10% of wild-type CFTR). Of note, the clinical severity criteria did not specifically apply to individual subjects in the study.

Subject Removal Criteria
Criteria for removal were the same as in Trial 106.

Study Treatments
Study drug and administration were the same as in Trial 106.

Concomitant Medications
Prohibited and allowed medications during the study were the same as for Trial 106.

Blinding
Methods of assigning subjects to treatment groups and to maintain the blind were the same as for Trial 106.

Study Endpoints

Primary Endpoint
The primary endpoint was the same as in Trial 106 (absolute change in ppFEV1 from baseline) except through week 12.

Key Secondary Endpoints

- Absolute change in CFQR-respiratory domain score from baseline through week 12
- Number of pulmonary exacerbations through week 12
- Absolute change in BMI from baseline at week 12

Secondary and other endpoints were not reviewed in detail.

Efficacy and safety assessments and their methods of collection were the same as those described for Trial 106. The timing of assessments is outlined above in Table 19.

Statistical Analysis Plan

Analysis sets were defined in the same manner as in Trial 106, and all efficacy analyses were based on the FAS population.

Analysis of the primary endpoint was similar to Trial 106. An MMRM with absolute change in ppFEV1 at each post baseline visit (Week 2, 4, 8 and 12) was the dependent variable using SAS PROC MIXED. The null hypothesis was that the mean change from baseline in ppFEV1 through week 12 was the same for the two treatment arms. A p-value of ≤0.05 was considered sufficient

evidence to reject the null hypothesis. Variables in the model were the same except for ppFEV1 severity (<70 or ≥70) in place of baseline ppFEV1. There were no planned subgroup analyses of the primary endpoint.

A futility interim analysis was planned when approximately 50% (150 subjects) of the planned number of subjects had completed 12 weeks of treatment. At the interim analysis, the primary endpoint was analyzed using the same MMRM as specified for the primary analysis method. The 1-sided 80% upper confidence bounds (UCB) for the treatment difference and for the within-treatment change for the TEZ/IVA arm were estimated from the MMRM model and evaluated using the following futility rules:

- The 80% UCB for the treatment difference is less than 2.5 percentage points
  OR
- The 80% UCB for the within-treatment change from baseline through week 12 for the TEZ/IVA treatment arm is less than 1.75 percentage points

To protect the integrity of the treatment assignment and study data for the interim analysis, the sponsor used blinded data to program tables, figures and listings based on the SAP for the interim analysis. An independent biostatistical group used the SAS program provided by Vertex and unblinded data to perform the unblinded analyses to provide the unblinded results to the independent data monitoring committee (IDMC). After review of the interim results for futility/efficacy as well as safety results and key secondary efficacy results as needed, the IDMC made their recommendation to a small senior level sponsor group via communication with the Vertex CMO. If the IDMC recommended to continue the study, the group remained blinded. If the IDMC recommended stopping the trial for futility, the group was unblinded to review interim results to decide whether to accept the IDMC recommendation. However, the study team, subjects, and site personnel were not unblinded to the interim analysis results until after the trial was complete and the database locked.

As in Trial 106, a hierarchical testing procedure was used to control the Type I error for multiple endpoints tested at α=0.05. The testing hierarchy was as follows:

1. Absolute change in ppFEV1 from baseline through week 12
2. Absolute change in CFQ-R respiratory domain score from baseline through week 12
3. Number of pulmonary exacerbations through week 12
4. Absolute change in BMI from baseline at week 12

Analysis of key secondary and secondary endpoints was the same as in Trial 106. No sensitivity, supportive, or subgroup analyses were planned for the key or other secondary endpoints. Refer to the biometrics statistical review for a more detailed review of the sponsor's statistical analysis plan.

Protocol Amendments

The sponsor amended the protocol on two occasions. Key changes made in the first protocol amendment included additional post-dose spirometry assessments and an ophthalmologic examination at the ETT or safety follow up visit for adolescent subjects, increased sample size (278 to 300 subjects) to account for an interim analysis for futility, washout requirements for subjects who previously received commercial CFTR modulators, and criteria used to define CFTR mutations not likely to respond to TEZ and/or IVA therapy. Key changes made in the second protocol amendment included a change to the order of secondary and key secondary endpoints in the testing hierarchy, permission to use previous CFTR genotype results for eligibility screening, and making sweat chloride test at screening optional if the medical record was used to establish eligibility. In addition, the SAP noted that the CFTR mutation G970R, which was not listed in the protocol Appendix I, was re-categorized as a genotype to be enrolled in Trial 107 and included in the FAS, based on emerging data (previously G970R was thought to represent a simple gating mutation and thus was included in the list of eligible genotypes for Trial VX14-661-109). There were no modifications to the SAP.

Data Quality and Integrity: Sponsor's Assurance

The sponsor's methods for assuring data quality and integrity were the same as in Trial 106.

6.3.2. Study Results

Compliance with Good Clinical Practices

The sponsor states that the study was conducted in accordance with GCP as described in ICH guidelines. The study protocol, amendments, informed consent, and other necessary documents were reviewed and approved by an independent ethics committee (IEC) or institutional review board (IRB) for each study site before initiation of the study at that site. Written informed consent was obtained from each subject before study participation. This study was conducted under IND 108,105.

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 13.1).

Patient Disposition

Nearly all subjects completed the study, and all treated subjects were included in the FAS.

Table 21. Subject Disposition: Trial 107

	Placebo N=85	TEZ/IVA N=83	Total N=168
Randomized Set	85	83	168
Safety Set	85	83	168
Full Analysis Set (FAS), n (%)	85 (100)	83 (100)	168 (100)
Completed study	85 (100)	81 (98)	166 (99)
Completed treatment	84 (99)	81 (98)	165 (98)
Prematurely discontinued treatment			
Adverse event	1 (<1)	1 (<1)	2 (<1)
Hemoptysis	1 (<1)	0	1 (<1)
Adenocarcinoma, colon	0	0	1 (<1)
Withdrawal by subject	0	1 (<1)	1 (<1)
Source: Reviewer generated table using ADSL dataset in JMP (TRT01P for treatment arm)			

Protocol Violations/Deviations

Major protocol violations were reported for eight subjects: three with study drug compliance <80%, four with prohibited concomitant medication use, and one with failure to meet all eligibility criteria (specifically exclusion criterion #3 – recent pulmonary/respiratory infection or change in therapy).

Table of Demographic Characteristics

Patient demographics were like the other trials: predominantly young, white adults with mean/median age of 25-26 years and roughly equal numbers of males and females. Approximately 20% of subjects were adolescent and about half of subjects were from the US.

Table 22. Subject Demographics: Trial 107

Demographic parameters, n (%)	Placebo N=85	TEZ/IVA N=83	All Subjects N=168
Sex			
Female	42 (49)	39(47)	81(48)
Male	43 (51)	44 (53)	87 (52)
Age			
Mean (SD)	26 (9)	26 (10)	26 (9)
Median	25	25	25
Min, Max	13, 50	13, 52	13, 52
Age Group			
<18 years	18 (21)	19 (23)	37 (22)
≥18 years	67 (79)	64 (77)	131 (78)
40 to 64 years	8 (9)	8 (10)	16 (10)
Race			
Black or African American	2 (2)	1 (1)	3 (2)
White	76 (89)	78 (94)	154 (92)
Other	3 (4)	0	3 (2)

Demographic parameters, n (%)	Placebo N=85	TEZ/IVA N=83	All Subjects N=168
Not collected per local regulations	4 (5)	4 (5)	8 (5)
Ethnicity			
Hispanic or Latino	5 (6)	1 (1)	6 (4)
Not Hispanic or Latino	76 (89)	78 (94)	154 (92)
Not collected per local regulations	4 (5)	4 (5)	8 (5)
Region			
Australia	7 (8)	10 (12)	17 (10)
Europe	13 (15)	21 (25)	34 (20)
Israel	14 (16)	10 (12)	24 (14)
North America	51 (60)	42 (51)	93 (55)
USA	51 (60)	38 (46)	89 (53)
Roll-over to Extension Study			
Y	81 (95)	79 (95)	160 (95)
Source: Reviewer generated table in JMP Clinical using ADSL dataset (TRT01P for treatment group)			

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

Overall, the two treatment groups were balanced with regard to various baseline disease characteristics and concomitant medication use as summarized in Table 23. Baseline disease characteristics: Trial 107 The average ppFEV1 at baseline was 56%; however, the TEZ/IVA group had a larger proportion of patients with ppFEV1<40 at baseline. CF patients with the *F508del* mutation and one of the following mutations in the CFTR gene were enrolled in the study (listed in decreasing frequency): W1282X, G542X, N1303K, 621+1G>T, 1717-1G>A, 1898+1G>A, CFTRdele2,3, 2183delAA>G, 2184insA, R1162X, R553X, 3659delC, 3905insT, G970R, I507del, R1066C, R347P, 1154insTC, 1811+1.6kbA>G, 2184delA, 405+1G>A, E60X, G85E, L1077P, Q39X, S466X, Y1092X, 1078delT, 1248+1G>A, 1677delTA, 1812-1G>A, 2869insG, 3120+1G>A, 394delTT, 457TAT>G, 711+1G>T, 711+5G>A, 712-1G>T, G673x, L1065P, Q220X, Q493X, R709X, V520F.

Table 23. Baseline disease characteristics: Trial 107

	Placebo N=85	TEZ/IVA N=83	All Subjects N=168
Baseline ppFEV1			
Mean (SD)	58 (13)	57 (15)	58 (14)
Median	56	55	56
Min, Max	31, 83	33,97	31, 97
Baseline ppFEV1			
<40%	4 (5)	10 (12)	14 (8)
40 to <70%	61 (72)	54 (65)	115 (68)
70 to 90%	20 (24)	18 (22)	38 (23)
>90%	0	1 (1)	1 (1)
Baseline Body Mass Index (kg/m2)			
Mean	21 (3)	21 (3)	21 (3)
Median	21	21	21
Min, Max	15, 27	14, 29	14, 29

	Placebo N=85	TEZ/IVA N=83	All Subjects N=168
Baseline Sweat Chloride, n	84	80	164
Mean (SD)	103 (10)	101 (13)	102 (11)
Median	104	103	103
Min, Max	65, 125	33, 118	33, 125
Baseline CFQ-R Respiratory Domain Score			
Mean (SD)	64 (21)	68 (16)	66 (19)
Median	61	67	67
Min, Max	0, 100	22, 100	0, 100
Baseline Weight (kg)			
Mean (SD)	57 (11)	60 (13)	59 (12)
Median	56	58	57
Min, Max	32, 78	31, 90	31, 90
Prior Dornase Alfa Use			
Yes	70 (82)	63 (76)	133 (79)
Prior Inhaled Antibiotic Use			
Yes	54 (64)	53 (64)	107 (64)
Prior Inhaled Corticosteroid Use			
Yes	50 (59)	42 (51)	92 (55)
Prior Inhaled Bronchodilator Use			
Yes	76 (89)	77 (93)	153 (91)
Prior Inhaled Hypertonic Saline Use			
Yes	63 (74)	60 (72)	123 (73)
***Pseudomonas aeruginosa* colonization**			
Positive	63 (74)	60 (72)	123 (73)
Source: Reviewer generated table in JMP Clinical using ADSL dataset (TRT01P for treatment group)			

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Most concomitant medications administered during the treatment period were antibiotic and anti-inflammatory (prednisone and ibuprofen) drugs with slightly greater use overall in the placebo arm with study start days relatively evenly distributed across the entire treatment period.

Efficacy Results - Primary Endpoint

The primary endpoint was absolute change in ppFEV1 from baseline through week 12. While there was a numerical improvement in ppFEV1 with TEZ/IVA treatment, suggestive perhaps of minimal efficacy, the difference from placebo failed to achieve statistical significance (Table 24). The study was terminated prematurely based on an interim futility analysis.

Table 24. Primary endpoint, absolute change in ppFEV1 through week 12: Trial 107

ppFEV1	Placebo	TEZ/IVA

ppFEV1	Placebo	TEZ/IVA
Baseline		
N	85	83
Mean (SD)	58 (13)	57 (15)
Absolute change from baseline through Week 12		
N	85	82
LS Mean (SE)	-0.1 (0.6)	1.4 (5)
p-value (95% CI)	0.8 (-1.3, 1.0)	0.1 (-0.1, 2.2)
Difference from placebo (95% CI)	--	1.2 (-0.3, 2.6)
p-value versus placebo	--	0.1
Source: CSR Table 11-2, p59		

Data Quality and Integrity - Reviewers' Assessment

This review did not reveal any inconsistencies in the data or issues with trial design or conduct which might influence the efficacy results.

Efficacy Results - Secondary and other relevant endpoints

Key secondary endpoints included absolute change in CFQ-R respiratory domain score from baseline through week 12, number of pulmonary exacerbations through week 12, and absolute change in BMI from baseline at week 12. The number of subjects who experienced pulmonary exacerbations through week 12 was similar between treatment groups (21 placebo and 19 TEZ/IVA) as was absolute change in BMI at week 12 (difference from placebo -0.08). Results for CFQ-R respiratory domain score and sweat chloride are shown in the table below. Secondary endpoints were consistent with the primary endpoint demonstrating minimal efficacy of TEZ/IVA treatment in this group of mutations.

Table 25. Secondary endpoints: Trial 107

	Placebo	TEZ/IVA
CFQ-R respiratory domain score		
Baseline		
N	85	83
Mean (SD)	64 (21)	68 (16)
Absolute change from baseline through Week 12		
N	85	83
LS Mean (SE)	3.8 (1)	3.0 (14)
p-value (95% CI)	0.005 (1.1, 6.4)	<0.0001 (3.2, 8.5)
Difference from placebo (95% CI)	--	2.1 (-1.2, 5.4)
p-value versus placebo	--	0.2
Sweat chloride		

	Placebo	TEZ/IVA
Baseline		
N	84	80
Mean (SD)	103 (10)	101 (13)
Absolute change from baseline through Week 12		
N	84	79
LS Mean (SE)	-1.2 (6)	-4.7 (1)
p-value (95% CI)	0.2 (-3.1, 0.7)	<0.0001 (-6.6, -2.8)
Difference from placebo (95% CI)	--	-3.5 (-5.9, -1.2)
p-value versus placebo	--	0.003
Source: CSR Table 11-4, p62 and Table 11-8, p66		

7 Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

7.1.1. Primary Endpoints

For the proposed population of CF patients homozygous for the *F508del* CFTR mutation or with *F508del* and a second CFTR mutation that is responsive to TEZ/IVA based on *in vitro* and/or clinical evidence, treatment with TEZ/IVA has demonstrated statistically significant improvements in ppFEV1 over placebo (trials 106 and 108).

7.1.2. Secondary and Other Endpoints

In trials 106 and 108, other clinically meaningful secondary endpoints such as pulmonary exacerbations and CFQ-R respiratory domain score also showed improvements with TEZ/IVA treatment providing additional support for efficacy in the proposed population. While changes in BMI revealed no statistical difference between treatment groups in either study, this is not surprising given the relatively limited treatment durations.

7.1.3. Subpopulations

Subgroup analyses in trials 106 and 108 revealed consistent efficacy results regardless of age, sex, region, baseline ppFEV1, concomitant CF medications or *Pseudomonas* colonization.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

While clinical data is not available for all the CFTR mutations encompassed in the proposed indication (as discussed in Section 4.5), basing the indication on *in vitro* and/or clinical evidence errs on the side of including CF patients with rare mutations that may respond clinically. In

addition, given the lack of drug-drug interaction between TEZ and IVA, one would expect mutations which respond clinically to IVA monotherapy to respond to TEZ/IVA as well, even if the added benefit of TEZ may be uncertain.

7.2.2. Other Relevant Benefits

Although approved therapies exist for the proposed indication in this application (Orkambi for *F508del* homozygous patients and Kalydeco for *F508del* heterozygous patients with a second allele responsive to IVA based on *in vitro* and/or clinical evidence), TEZ/IVA could offer additional benefits: fewer drug-drug interactions and drug-related adverse reactions than Orkambi and potentially improved efficacy over IVA (Kalydeco) monotherapy.

7.3. Integrated Assessment of Effectiveness

Evidence of the efficacy of TEZ/IVA (tezacaftor 100 mg QD/ivacaftor 150 mg q12) in CF patients ≥ 12 years of age with *F508del* homozygous CFTR mutations or with heterozygous *F508del* mutations with a second allele predicted to be responsive based on *in vitro* and/or clinical evidence has been demonstrated with respect to statistically significant improvements in ppFEV1. Lung function improvements were supported by clinically relevant secondary endpoints: rate of CF pulmonary exacerbations, relative change in ppFEV1, CFQ-R respiratory domain, and sweat chloride. Furthermore, efficacy findings were consistent within trials 106 and 108 of the two CF populations.

Regarding the regulatory requirement to demonstrate the contribution of the individual components to the combination product, this requirement has been fulfilled. Trial 108 which included both TEZ/IVA and IVA only treatment arms clearly demonstrated the added benefit of TEZ to the TEZ/IVA combination with statistical different improvements in the primary endpoint of absolute change from baseline ppFEV1 between TEZ/IVA and IVA as well as numerical differences in the secondary endpoints. Indirectly, one can infer an added benefit of TEZ to the TEZ/IVA combination in the *F508del* homozygous population even though trial 106 did not include an IVA monotherapy arm by referring to historical data from previously conducted studies. In trial 106, the difference from placebo in absolute change from baseline in ppFEV1 was 4%. In replicate pivotal trials for LUM/IVA (Orkambi), the difference from placebo for absolute change in ppFEV1 was 2.6-3%. In study 770-104, conducted for the Kalydeco program with IVA only, the absolute change in ppFEV1 was 1.7%. Although cross study comparisons are fraught with limitations, these data do show that TEZ/IVA provides some lung function benefit in *F508del* homozygous patients while IVA monotherapy has minimal effect.

8 Review of Safety

8.1. Safety Review Approach

All clinical studies conducted as part of the TEZ/IVA development program were evaluated for safety; however, given the short exposure periods and absence of additional safety findings in the phase 1 and 2 studies, the focus of this safety review is on the phase 3 trials: 106, 107, and 108. Pooling the safety populations from all three phase 3 studies did not reveal safety signals or rare adverse reactions not already identified in the individual studies; therefore, to minimize distortion of safety results, safety data in this review will be presented from trial 106, which exposed the largest number of patients for the longest period and did not involve treatment crossover. However, additional data from trials 107 and 108 will be presented to explore specific safety signals or to point out any differences. The review tools used to conduct independent reviewer analyses included MAED, JMP Clinical, JMP, and JReview.

Safety issues identified *a priori* include liver enzyme elevation, respiratory symptoms, and cataracts due to known safety signals observed with IVA monotherapy and with the related CFTR modulator product lumacaftor/ivacaftor (Orkambi®).

8.2. Review of the Safety Database

8.2.1. Overall Exposure

Table 26 shows the entire population of subjects exposed to TEZ/IVA in the development program for CF. However, as noted above, the focus of this safety review is on phase 3 trials 106, 107, and 108 given the short exposure periods in the phase 1 and 2 studies.

Table 26. Safety database for TEZ/IVA

Safety Database for TEZ/IVA[1] Individuals exposed to the study drug in this development program for the indication under review N=1461 (N is the sum of all available numbers from the columns below)				
Clinical Trial Groups	**TEZ/IVA (n=1129)**	**TEZ only (n=168)**	**IVA only (n=161)**	**Placebo (n=622)**
Healthy Volunteers[2]	102	135	--	72
Controlled trials conducted for this indication				
Phase 2 Trials				
101	120	33	4	33
103	21	--	--	12
Phase 3 Trials	**TEZ/IVA**	**TEZ only**	**IVA only**	**Placebo**
106	251	--	--	258
107	83	--	--	85

108[3]	162	--	157	162
Period 1	84	--	81	81
Period 2	78	--	76	81
Uncontrolled trials conducted for this indication[4]				
Study 110	390	--	--	--

[1] *study drug* means the drug being considered for approval.
[2] Excludes subjects who received TEZ monoproduct, but includes subjects who received any dose of TEZ/IVA including in DDI studies
[3] Incomplete crossover design in which patients received different study drug in each treatment period; therefore, some patients are double counted
[4] Number of placebo arm patients who switched to study drug in the open label extension; rollover subjects who received active treatment in the parent study are not double counted

Exposure to TEZ/IVA in phase 3 is shown in the tables below. Most patients were exposed to TEZ/IVA for ≥12 to ≤24 weeks in a controlled trial, and over 300 patients have been exposed to TEZ/IVA for at least 1 year in controlled and uncontrolled studies.

Table 27. Duration of exposure in controlled trials

	Number of patients exposed to TEZ/IVA in controlled studies:			
Study	**<8 weeks**	**>=8 weeks**	**>=12 weeks**	**>=24 weeks**
103	0	6	15	0
106	9	1	95	146
107	1	15	67	0
108	60	102	0	0
Total	**70**	**124**	**177**	**146**

Reviewer generated tables in JMP using ADSL datasets for studies 103, 106, 107, 108 and ISS phase 2 and 3 with exposure calculated as follows:
≥8 weeks if TR01DURN ≥56 to <84
≥12 weeks if TR01DURN ≥84 to <168
≥24 weeks if TR01DURN ≥168 to <336
≥48 weeks if TR01DURN ≥336 to <504
≥ 72 weeks if TR01DURN ≥504 to <672
≥96 weeks if TR01DURN ≥672

Table 28. Duration of exposure in controlled and OLE studies

	Number of patients exposed to TEZ/IVA in controlled studies + OLE[1]			
Study	**>=24 weeks**	**>=48 weeks**	**>=72 weeks**	**>= 96 weeks or longer**
103	1	1	4	19
106	146	172	80	4
107	96	0	0	0
108 (period 2)	106	43	3	0
Total	**349**	**216**	**87**	**23**

[1]Includes placebo rollover subjects who only received open label TEZ/IVA. Exposure in controlled parent study prior to washout (i.e., Study 103 and Period 1 of Study 108) not counted. ADSL ISS phase 2 and 3 dataset used, where ANLCAT=DB+EXT

8.2.2. Relevant characteristics of the safety population:

The safety population is essentially the same as the efficacy population. For demographics and

baseline disease characteristics, refer to Table 8, Table 15, Table 22, and Table 23 in Section 6. Of note, CF patients with clinically significant renal impairment (GFR <50 in adults or <45 in adolescents), hepatic dysfunction (cirrhosis with portal hypertension, or LFT elevations >3x ULN or total bilirubin >2x ULN), pre-existing cataracts, ppFEV1 <40, colonization with microorganisms associated with more rapid respiratory decline, or concomitant use of moderate and strong CYP3A substrates were excluded from the studies. While the study population is generally reflective of the broader target CF population, safety results in these studies may not be directly applicable to sicker CF patients with additional co-morbidities.

8.2.3. Adequacy of the safety database:

Overall, the safety database is of sufficient size and duration for a rare disease such as CF to assess the safety of the proposed dose of TEZ/IVA when taken chronically.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

No data quality issues were identified in the review of this NDA. OSI audits of study sites 533 and 117 from trial 106, site 051 from trials 107 and 108, and site 020 from trial 108 did not reveal any substantial issues related to data integrity.

8.3.2. Categorization of Adverse Events

The Applicant provided accurate definitions of adverse events (AEs) and serious adverse events (SAEs) in the protocols. AEs were captured from signing of informed consent to through the safety follow up visit or alternatively 28 days after the last dose of study drug, the early trial termination visit if ≥3 weeks after last dose of study drug, or prior to the first dose of study drug in the extension study. Treatment emergent adverse events (TEAEs) were defined as any AE that increased in severity or that was newly developed at or after the first dose of study drug through the end of the treatment emergent period, i.e., safety follow-up visit or 28 days after last dose of study drug or day right before the first dose of study drug in the extension study. AEs were coded using the MedDRA dictionary version 19.1. Grading of AE severity was based on the CTCAE version 4.0 toxicity scale or as mild/moderate/severe/life-threatening. The Applicant's coding of verbatim terms to preferred terms (PTs) was appropriate. AEs were assessed by frequency, rather than rate, a method appropriate for trials of this duration. To analyze adverse events of special interest (AESI), the Applicant analyzed laboratory data for LFTs elevations and relied on ophthalmology exams for reporting of cataracts.

8.3.3. Routine Clinical Tests

Laboratory tests were obtained at time points specified in the schedule of assessments

provided for each trial. Except for urine pregnancy tests, lab specimens were sent to a central laboratory for processing. 12-lead ECGs were manually read at the study site. AST or ALT elevations >3x ULN with associated clinical symptoms were repeated by the central laboratory within 48-72 hours of the initial finding. For AST/ALT elevations >5x ULN, repeat follow-up levels were obtained within 7 ± 2days. Only clinically significant abnormalities (as determined by the investigator) in lab values, physical exam findings, or vital signs were reported as AEs. A study assessment was considered clinically significant if the subject had one or more of the following: concomitant sign or symptom related to the abnormal assessment, further testing or medical/surgical intervention, change in dose of study drug or discontinuation from study.

8.4. Safety Results

8.4.1. Deaths

No deaths were reported in the placebo controlled phase 3 trials; however, there was one death due to respiratory failure included in the 120-day safety update from OLE study 110. Subject 109-031-003 was a 62-year-old female heterozygous for *F508del* and a gating mutation with Crohn's disease. On day 329 of study 110, she developed a CF exacerbation requiring hospitalization with *Pseudomonas aeruginosa* and *Candida albicans* on sputum culture. TEZ/IVA was discontinued on Day 338 due to use of prohibited medication (itraconazole). She was discharged on Day 347 and never resumed TEZ/IVA. She was hospitalized again on Day 371 for worsening GI symptoms and hypoxia and developed respiratory failure on Day 376 and was discovered to have *Influenza A*. She was unable to wean off mechanical ventilation, and her condition progressively worsened so comfort measures were put in place. She was disconnected from ventilator and life support on Day 388 and died later that day.

Reviewer's comment: CF exacerbations and hospitalization are typical in this patient population. Her underlying CF disease and recent exacerbation likely made her more susceptible to influenza infection, which appears to be the ultimate cause of her respiratory failure leading to death. There are no factors suggesting a causal link to TEZ/IVA which had been discontinued several weeks prior to the re-hospitalization and respiratory failure.

8.4.2. Serious Adverse Events

In general, the SAEs reported in the phase 3 trials were typical of events one might expect to occur in CF patients. Across studies, the overall number of patients with an SAE was higher in the placebo group than the TEZ/IVA group. The most common SAEs by MedDRA system organ class (SOC) were 'Infections and Infestations' driven primarily by infective pulmonary exacerbations of CF. However, in all three trials, including 107, serious CF exacerbations occurred more frequently in placebo-treated patients, a finding consistent with the efficacy results. Most reported SAEs were single occurrences and associated with underlying CF disease. However, two single events which occurred in the TEZ/IVA group only and could potentially be

drug-related include benign intracranial hypertension and generalized tonic-clonic seizure; while narratives of these events do not clearly implicate TEZ/IVA treatment, a potential causal relationship cannot be ruled out.

The SAEs which occurred in more than one patient in Trial 106 are shown in the table below. SAEs reported in trials 108 and 107 were generally similar in type and frequency. In trial 108, numerically more CF exacerbations occurred on placebo > IVA > TEZ/IVA. Two subjects in the IVA group experienced SAEs of increased blood CPK levels, one event occurring during each period. Otherwise, the remainder of SAEs were events typical of CF disease that occurred in no more than one patient in the active treatment groups. In trial 107, one TEZ/IVA subject was diagnosed on study day 13 with adenocarcinoma of the colon (invasive, moderately differentiated). Other events were typical of CF.

Table 29. SAEs occurring in ≥2 patients in any treatment group: Trial 106

SOC/PT	Placebo N=258	TEZ/IVA N=251	Total Subjects N=509
Any SAE	47 (18)	31 (12)	78
Gastrointestinal disorders			
Constipation	2 (1)	0	2 (0.4)
Infections and infestations			
Infective pulmonary exacerbation of cystic fibrosis	32 (12)	23 (9)	55 (11)
Pneumonia	1 (0.4)	2 (1)	3 (1)
Investigations			
Blood creatinine phosphokinase increased	1 (0.4)	1 (0.4)	2 (0.4)
Renal and urinary disorders			
Acute kidney injury	2 (1)	0	2 (0.4)
Respiratory, thoracic and mediastinal disorders			
Haemoptysis	3 (1)	3 (1)	6 (1)
Source: Reviewer generated table in JReview using ADSL and ADAE where SAFFL=Y, TRTEMFL=Y, AESER=Y and TRT01A for treatment group			

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

In the phase 3 trials, a total of 8 (1.6%) TEZ/IVA subjects and 10 (2%) placebo subjects discontinued treatment prematurely. Most adverse dropouts occurred during the 24-week trial 106; the TEAEs by PT leading to early treatment discontinuation are shown in the table below. Most events were single occurrences, and more placebo-treated subjects discontinued treatment due to LFT elevations.

From trial 107, two subjects dropped out early due to an adverse event: one placebo subject due to CF exacerbation and hemoptysis, and one TEZ/IVA subject due to adenocarcinoma of the colon; both were also considered SAEs. From trial 108, no subjects discontinued treatment

prematurely due to an AE while receiving TEZ/IVA. Three subjects dropped out early due to an AE while receiving IVA treatment: two due to elevated CPK (also categorized as SAEs) and one due to fatigue. Two subjects had treatment interrupted due to CPK elevation, one during TEZ/IVA treatment and one during IVA treatment. There were no treatment interruptions due to LFT elevations in any treatment group.

Table 30. Premature Discontinuations due to TEAEs: Trial 106

SOC/PT	Placebo N=258	TEZ/IVA N=251
Total # of premature discontinuations due to an AE	**8 (3)**	**7 (3)**
Cardiac disorders		
Palpitations	1 (0.4)	0
Eye disorders		
Cataract	1 (0.4)	0
Gastrointestinal disorders		
Abdominal discomfort	1 (0.4)	0
Abdominal pain	0	2 (1)
Nausea	1 (0.4)	0
General disorders and administration site conditions		
Fatigue	2 (1)	0
Malaise	1 (0.4)	0
Hepatobiliary disorders		
Cholangitis	1 (0.4)	0
Infections and infestations		
Infective pulmonary exacerbation of cystic fibrosis	0	1 (0.4)
Lower respiratory tract infection	0	1 (0.4)
Investigations		
Alanine aminotransferase increased	2 (1)	1 (0.4)
Aspartate aminotransferase increased	1 (0.4)	1 (0.4)
Blood alkaline phosphatase increased	2 (1)	1 (0.4)
Blood creatinine phosphokinase increased	0	1 (0.4)
Electrocardiogram ST segment elevation	1 (0.4)	0
Gamma-glutamyltransferase increased	1 (0.4)	0
Weight decreased	0	1 (0.4)
Nervous system disorders		
Generalised tonic-clonic seizure	0	1 (0.4)
Headache	2 (1)	0
Respiratory, thoracic and mediastinal disorders		
Oropharyngeal pain	1 (0.4)	0

Source: Reviewer generated table in JReview using ADSL and ADAE datasets where SAFFL=Y, TRTEMFL=Y, and AEDSTRFL=Y

8.4.4. Significant Adverse Events

Regarding other significant AEs, there were only a handful of TEAEs grade 3 or 4 in severity. In trial 106, one grade 4 TEAE of hemoptysis occurred in the TEZ/IVA group; none in the placebo group. The most common severe grade 3 TEAE was CF exacerbation which occurred with equal frequency in both treatment groups (n=11, 4%). Other events were reported in 1 or 2 subjects and were typical of CF disease with more events reported in the placebo group.

In trial 108, grade 4 life-threatening TEAEs of mental status change, acute respiratory failure, pneumothorax, CF exacerbation, and pneumonia occurred in one placebo subject. Severe (grade 3) TEAEs occurred in half the number of TEZ/IVA vs IVA or placebo-treated subjects; the following severe events occurred in 4 TEZ/IVA subjects: CF exacerbation (x2), extremity pain, and pneumothorax.

In trial 107, no grade 4 life-threatening TEAEs occurred. Severe grade 3 TEAEs were reported at roughly the same rate between treatment groups and primarily reflected CF disease-related events such as CF exacerbation, hemoptysis, PFTs decreased and DIOS. Other severe events that occurred in single TEZ/IVA-treated patients include decreased weight/adenocarcinoma of the colon (withdrew from study) and blood CK increased (resolved, dose not changed).

Overall, no new safety signals were identified that are not covered elsewhere in this review.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

To assess common adverse events, subjects from the 12 and 24-week trials 107 and 106 were pooled, while subjects from trial 108 were omitted due to the shorter 8-week treatment period and crossover design. The TEAEs occurring with ≥3% frequency and greater than placebo are shown in Table 31, listed by PT.

Table 31. Common TEAEs occurring with ≥3% frequency and greater than placebo in 12 and 24-week parallel group studies: Trials 106 and 107

Preferred Term	Placebo N=343	TEZ/IVA N=334
Headache/ Sinus headache	44 (13) 1 (<1)	49 (15) 0
Nausea	24 (7)	29 (9)
Dizziness	8 (3)	13 (4)
Sinus congestion	6 (2)	13 (4)
Reviewer generated table in JMP using ADSL and ADAE datasets, where SAFFL=Y, TRTEMFL=Y		

While the reported frequency of “Forced expiratory volume decreased” showed a slight imbalance between TEZ/IVA and placebo subjects (4% vs 3%), grouping these events with the synonymous preferred term of “PFT decreased” (<1% vs 2%) eliminated the imbalance. The common TEAEs in trial 108 were similar with the additional PTs of diarrhea, sputum increased

and elevated blood CPK occurring more often in the TEZ/IVA group. An evaluation of CK elevation is discussed in Section 8.5.

Notably, respiratory-related TEAEs such as dyspnea, cough, respiration abnormal, and bronchospasm/wheeze that were observed with the initiation of lumacaftor dosing in clinical trials, occurred with similar and/or decreased frequency in the TEZ/IVA group compared to placebo across studies. Furthermore, certain CF disease-related TEAEs (e.g., CF exacerbations/lower respiratory tract infections, bronchitis hemoptysis, constipation, fatigue) were reported more often in the placebo group, thereby providing additional support to the primary efficacy results that demonstrated a therapeutic benefit with TEZ/IVA treatment.

8.4.6. Laboratory Findings

Routine clinical testing included hematology, serum chemistry with liver function tests, and urinalysis. Liver function tests and creatinine kinase are discussed in detail in Section 8.5. Otherwise, there were no clinically significant differences between TEZ/IVA and placebo groups in other laboratory parameters measured during the trials.

8.4.7. Vital Signs

No substantial or clinically meaningful shifts from baseline in mean or median vital signs (SBP, DBP, pulse, respiratory rate, oxygen saturation, or temperature) were observed with TEZ/IVA treatment across visits in any of the trials. Although rare, there was no substantial difference among treatment groups in the frequency of hypertension or increased blood pressure TEAEs reported in the phase 3 trials.

8.4.8. Electrocardiograms (ECGs)

No substantial or clinically meaningful ECG trends associated with TEZ/IVA treatment were identified in phase 3 trials. The sponsor analyzed ECGs by visit during the treatment period using reasonable threshold criteria, and no safety signals emerged. Cardiovascular TEAEs related to ECG findings were rare and generally balanced between treatment groups.

8.4.9. QT

There was no apparent QTcF prolongation identified through ECG monitoring in the phase 3 trials. In addition, the Interdisciplinary Review Team for QT studies consult review (dated 10/10/17) revealed no significant QTc prolongation effect from TEZ 100 mg or 300 mg QD in the Applicant's thorough QT study.

8.4.10. Immunogenicity

Not applicable.

8.5. Analysis of Submission-Specific Safety Issues

Liver function tests (LFTs)

While CF disease is associated with underlying abnormalities in liver function tests (LFTs), IVA monotherapy as well as the related LUM/IVA product may also cause elevations in LFTs; therefore, LFT lab findings in the TEZ/IVA program are also of interest. Subjects' maximum elevation in AST, ALT, and total bilirubin were identified from the ADLB1 laboratory datasets and evaluated based on the cutoffs outlined in the Agency's guidance on drug-induced liver injury in the pre-marketing setting.[2] The incidence of LFT elevations was generally similar between the TEZ/IVA and placebo-treated patients; a total of 18 unique placebo patients compared to 16 unique TEZ/IVA patients are represented in Table 32 below. Only one placebo-treated subject (VX14-661-106-813-006) had concurrent elevations in total bilirubin >2x ULN and AST (>5x ULN) during the treatment period (ALP also elevated); however, one TEZ/IVA subject (VX14-661-106-528-003) had concurrent elevation of bilirubin and AST/ALT prior to starting treatment. One subject (VX14-661-106-604-009) had bilirubin >2x ULN on day 58 (visit 8) during TEZ/IVA treatment with normal ALT and ALP, but missing AST; however, he had normal transaminases at all subsequent visits. Three TEZ/IVA patients had concurrent elevations in AST and ALT, only one of whom had ALT elevated >5x ULN. Five placebo patients had concurrent elevations in AST and ALT, two of whom had concurrent AST/ALT elevations ≥5xULN.

Table 32. LFT elevations: Trial 106

Lab parameter (maximum elevation)	Placebo N=258	TEZ/IVA N=251
ALT, n (%)		
>3x to ≤5x ULN	9 (3)	7 (3)
>5x to ≤8x ULN	3 (1)	1 (<1)
>8x ULN	0	0
AST, n (%)		
>3x to ≤5x ULN	3 (1)	7 (3)
>5x to ≤8x ULN	2 (1)	0
>8x to ≤10x ULN	2 (1)	0
>10x ULN	0	0
Total Bilirubin, n (%)		
>2x ULN	6 (2)	4 (2)
ALT or AST and total bilirubin, n (%)		
ALT or AST >3x ULN and bilirubin >2x ULN	1 (<1)	0

Source: Reviewer generated table using JMP analyses of ADLB1 dataset. Findings confirmed results provided in CSR.
ULN=upper limit of normal

In trials 107 and 108, there were no Hy's law cases. In trial 107, four TEZ/IVA and four placebo

[2] https://www.fda.gov/downloads/Guidances/UCM174090.pdf

subjects had transaminase elevations >3x ULN. One placebo subject had elevated total bilirubin in the absence of transaminase elevation. In trial 108, one placebo, one TEZ/IVA, and three IVA subjects had transaminase elevations >3x ULN, two of whom (both IVA only) had transaminase elevations >5x ULN. No subjects had LFT elevations >8x ULN. One subject (IVA→TEZ/IVA) had elevations in both transaminase levels and bilirubin, but not concurrently. These results support the findings in trial 106.

In addition, the occurrence of hepatobiliary TEAEs was more common in placebo than TEZ/IVA patients. Results from trial 106 are shown below. In studies 107 and 108, slightly more TEZ/IVA patients had TEAEs of AST or ALT increased; however, based on the laboratory data, there was no clinically meaningful difference between groups.

Table 33. Hepatobiliary TEAEs: Trial 106

SOC/PT	Placebo		TEZ/IVA	
	Count	%	Count	%
Investigations				
Alanine aminotransferase increased	13	5.0%	8	3.2%
Aspartate aminotransferase increased	12	4.7%	7	2.8%
Gamma-glutamyltransferase increased	3	1.2%	3	1.2%
Blood bilirubin increased	1	0.4%	2	0.8%
Activated partial thromboplastin time prolonged	1	0.4%	.	.
International normalized ratio increased	1	0.4%	.	.
Prothrombin time prolonged	1	0.4%	.	.
Hepatobiliary disorders				
Cholelithiasis	1	0.4%	1	0.4%
Cholangitis	1	0.4%	.	.
Hepatic fibrosis	1	0.4%	.	.
Hepatic lesion	1	0.4%	.	.
Hepatomegaly	1	0.4%	.	.
Hypertransaminasaemia	.	.	1	0.4%

Source: Reviewer generated table in JMP Clinical using ADSL and ADAE datasets, where SAFFL=Y, TRTEMFL=Y, and Primary System Organ Class = Hepatobiliary disorders, Investigations and High Level Term = Bile duct infections and inflammations, Cholecystitis and cholelithiasis, Coagulation and bleeding analyses, Hepatic and hepatobiliary disorders NEC, Hepatic enzymes and function abnormalities, Hepatic fibrosis and cirrhosis, Hepatobiliary signs and symptoms, Liver function analyses

Respiratory-related adverse events

Off-target respiratory events (such as abnormal respiration, dyspnea, and chest tightness) were observed in the LUM/IVA program, particularly with initiation of therapy; therefore, respiratory events were pre-specified as an AESI in the TEZ/IVA trials as well. Respiratory TEAEs in the TEZ/IVA program were more common in patients treated with placebo than TEZ/IVA as shown in Table 34. Results from trials 107 and 108 were similar. This safety issue does not appear to apply to the TEZ/IVA product.

Table 34. Respiratory-related TEAEs: Trial 106

Respiratory, thoracic and mediastinal disorders SOC	Placebo N=258		TEZ/IVA N=251	
Preferred Term	Count	%	Count	%
Cough	84	32.6%	66	26.3%
Sputum increased	42	16.3%	36	14.3%
Haemoptysis	35	13.6%	26	10.4%
Dyspnea	18	7.0%	16	6.4%
Productive cough	11	4.3%	11	4.4%
Respiration abnormal	11	4.3%	11	4.4%
Wheezing	10	3.9%	4	1.6%
Sputum discolored	6	2.3%	7	2.8%
Asthma	3	1.2%	4	1.6%
Bronchospasm	2	0.8%	1	0.4%
Allergic cough	1	0.4%	1	0.4%
Bronchial obstruction	1	0.4%	1	0.4%
Asthma exercise induced	-	-	1	0.4%
Dyspnea exertional	1	0.4%	-	-
Sputum retention	-	-	1	0.4%

Reviewer generated table in JMP Clinical using ADSL and ADAE datasets where SAFFL=Y, TRTEMFL=Y, and Primary System Organ Class = Respiratory, thoracic and mediastinal disorders and High Level Term = Breathing abnormalities, Bronchospasm and obstruction, Coughing and associated symptoms and High Level Group Term = Bronchial disorders (excl neoplasms), Lower respiratory tract disorders (excl obstruction and infection), Respiratory disorders NEC)

Blood creatinine kinase (CK)

To further explore the number of blood CK elevations reported as TEAEs and SAEs, this review analyzed CK results from the ADLB1 laboratory datasets alongside corresponding related TEAEs. The overall number and incidence of elevated CK-related events reported as TEAEs as well as highly elevated CK lab results from each phase 3 trial are provided in Table 35. Since normal CK levels can vary by race, sex, or other demographic factors, cutoffs of >1000 and >10x ULN were chosen to restrict elevations to those which might be clinically meaningful or more likely to reflect a drug-induced event or result in associated rhabdomyolysis. Across trials, roughly the same number of subjects from each treatment group reported TEAEs of blood CK increased or potentially CK elevation-related TEAEs. In trial 106, there was one SAE of CK elevation per treatment group (peak elevation of 5214 in placebo and 2651 in TEZ/IVA); neither subject reported myalgia symptoms. While six (2%) subjects from each treatment group in trial 106 reported myalgia, only one event in a TEZ/IVA-treated subject corresponded temporally to an elevated CK level (957 at week 8). Similarly, myalgia TEAEs sporadically occurred in the presence of mildly elevated CK levels in the other trials.

CK elevations primarily occurred in adult patients. There was no apparent difference in CK elevations between treatment groups. Furthermore, the CK elevation does not appear to be drug-related because subsequent labs reveal that CK returned to normal levels with no change in treatment. No cases of rhabdomyolysis were reported in the program.

Table 35. CK elevations: Trials 106, 107, and 108

Trial 106	Placebo N=258	TEZ/IVA N=251
Elevated CK-related TEAEs, n (%)		
Blood CK increased	12 (5)	11 (4)
SAE of blood CK increased[1]	1 (<1)	1 (<1)
Myalgia	6 (2)	6 (2)
Myositis	0	1 (<1)
CK lab results, n (%)		
>10x ULN	6 (2)	5 (2)
>1000[2]	10 (4)	9 (4)
with normal baseline[3]	9 (3)	8 (3)
Trial 107	**Placebo N=85**	**TEZ/IVA N=83**
Elevated CK-related TEAEs, n (%)		
Blood CK increased	0	2 (2)
Myalgia	1 (1)	0
CK lab results, n (%)		
>1000	2 (2)	2 (2)
with normal baseline[3]	2 (2)	1 (1)

Trial 108	Placebo N=162	TEZ/IVA N=162	IVA N=157
Elevated CK-related TEAEs, n (%)			
Blood CK increased	5 (3)	6 (4)	8 (5)
Myalgia	0	2 (1)	2 (1)
CK lab results, n (%)			
>1000	5 (3)	2 (1)	9 (6)
with normal baseline[3]	2 (1)	1 (1)	5 (3)

Reviewer generated table using analysis of ADSL, ADAE, and ADLB1 datasets in JMP and JReview. TRTA for treatment group in Study 108. LBSTRN for CK level and BASCAT to define normal baseline

[1]Neither subject reported concurrent TEAE of myalgia symptoms

[2]Median day of onset for CK levels >1000 was study day 84 in the placebo group and study day 28 in the TEZ/IVA group. None of the subjects reported myalgia, myositis, or rhabdomyolysis.

[3]Subset of subjects with CK elevations >1000 who had normal CK levels at baseline

Cataracts

Cataracts have been observed in patients, particularly pediatric patients, treated with IVA monotherapy and were identified *a priori* as an AESI.

Cataract TEAEs reported in the three trials were relatively rare with numerically more cases

reported in the active treatment groups. However, this numerical difference is like what has been observed in the IVA and LUM/IVA programs.

In trial 106, four subjects (2 placebo and 2 TEZ/IVA) experienced a cataract TEAE:

- 30 yr old male (placebo) diagnosed with a mild cataract on study day 142; he was withdrawn from treatment and the cataract did not resolve.
- 12 yr old male (placebo) diagnosed with subcapsular cataract of moderate severity on study day 170. He continued treatment, and the cataract did not resolve.
- 13 yr old male (TEZ/IVA) diagnosed with mild cataract and cortical cataract on study day 169. He continued study drug and the cataract did not resolve.
- 38 yr old male (TEZ/IVA) diagnosed with a mild subcapsular cataract on study day 142; he also continued study drug.

In trial 107, a 29 yr old male (TEZ/IVA) was diagnosed with a mild cataract on study day 84; he had history of CF-related diabetes and extended steroid use (>2 wks). In trial 108, a 59 yr old female (TEZ/IVA) was diagnosed with a mild cataract during period 2 on study day 56. She had received IVA treatment during period 1.

Trial 106 was the only study to perform ophthalmologic exams at screening and during/after treatment. The table below summarizes the cataract findings at baseline and during/after the treatment emergent period. Of note, all adolescents with TE cataracts rolled over into OLE study 110.

Table 36. Ophthalmologic exams: Trial 106

Statistic	Placebo n/N (%)	TEZ/IVA n/N (%)
Subjects with cataracts at baseline[a]	11/258 (4.3)	15/251 (6.0)
TE cataracts[b]		
Subjects ≥12 to <18 years old	1/54 (1.9)	2/51 (3.9)[c]
Subjects ≥18 years old	10/158 (6.3)	12/152 (7.9)
Total	11/212 (5.2)	14/203 (6.9)[c]
Resolved cataracts[d]		
Subjects ≥12 to <18 years old	1/2 (50.0)[e]	2/3 (66.7)
Subjects ≥18 years old	1/6 (16.7)	2/9 (22.2)
Total	2/8 (25.0)[e]	4/12 (33.3)

Sources: Table 14.3.5.4, Listing 16.2.8.4.1, Listing 16.2.8.4.2.1, and additional data on file
IVA: ivacaftor; n: size of subsample; TE: treatment-emergent; TEZ: tezacaftor
[a] N includes subjects who had ophthalmologic examinations at screening.
[b] N includes subjects who had no cataract at screening and had at least 1 ophthalmologic examination during or after the TE Period.
[c] Includes 1 subject whose TE cataract resolved while receiving TEZ/IVA in Study 110 (interim analysis).
[d] N includes subjects who had a cataract in at least 1 eye at screening and had at least 1 ophthalmologic examination during or after the TE Period.
[e] Includes 1 subject with clarification post data-lock that cataract was incorrectly recorded as resolved.

CSR Trial VX14-661-106, Table 12-21, p123

Menstrual abnormalities

While not designated as an AESI in the trials, menstrual abnormalities are listed as adverse drug reactions in the LUM/IVA (Orkambi®) label. Therefore, TEAEs potentially related to menstrual abnormalities were specifically evaluated in the TEZ/IVA trials as well. The imbalance seen in

the LUM/IVA program (10% vs 2%) was not observed in the TEZ program. In trial 106, 10 (4%) TEZ/IVA patients compared to 8 (3%) placebo patients reported the following PTs: dysmenorrhea, metrorrhagia, menorrhagia, vaginal hemorrhage, and delayed menstruation. In trial 107, two TEZ/IVA experienced dysmenorrhea and delayed menstruation compared to zero placebo patients. Finally, in trial 108, three TEZ/IVA and 2 placebo patients reported dysmenorrhea, menorrhagia, and oligomenorrhea.

8.6. Safety Analyses by Demographic Subgroups

In trial 106, adolescent patients (n=117) treated with TEZ/IVA experienced slightly more CF exacerbations (24 (41%) vs 21 (36%)) as well as increased/discolored sputum compared to placebo, but there were fewer serious CF exacerbations in the TEZ/IVA group. Regardless, efficacy was similar between adult and adolescent patient subgroups. Otherwise, no substantial differences in safety results were observed in subgroups by age (<18 vs >18), region (N. America vs Europe), sex (Male vs Female), race (white vs Asian, Black/AA, other), or baseline ppFEV1 (<40, ≥40 to <70, ≥70 to <90, ≥90). In addition, there were no substantial differences in TEAEs or SAEs by demographic subgroups in trials 107 and 108. However, the number of non-white subjects was quite small, as one would expect in CF; therefore, any evaluation of results by racial subgroups is limited.

8.7. Specific Safety Studies/Clinical Trials

Study VX14-661-110 is the open label extension (OLE) study for subjects who completed phase 2 and 3 trials and is currently ongoing. Uncontrolled safety data from this study provides support for the long-term use of TEZ/IVA. An overview of the study protocol and safety results thus far are provided below.

Title: A Phase 3, Open-label, Rollover Study to Evaluate the Safety and Efficacy of Long-term Treatment with VX-661 in Combination with Ivacaftor in Subjects Aged 12 Years and Older with Cystic Fibrosis, Homozygous or Heterozygous for the *F508del*-CFTR Mutation

Primary objective: To evaluate the long-term safety and tolerability of TEZ/IVA in subjects with CF, homozygous or heterozygous for the *F508del* CFTR mutation who are in the treatment cohort

Secondary objectives: to evaluate the long-term efficacy of TEZ/IVA for subjects in the treatment cohort and to evaluate the post-treatment safety of TEZ/IVA for subjects in the observational cohort

Study design
Subjects who participated in Vertex studies investigating TEZ in combination with IVA, including studies 103, 106, 107, 108, 109, and 111 were eligible for enrollment. Subjects who completed

study drug treatment during the treatment period in the parent study and who met eligibility criteria were offered enrollment into the treatment cohort. Subjects who permanently discontinued study drug treatment or who withdrew their consent during the parent study were not eligible for enrollment in the treatment cohort.

Subjects in the treatment cohort received open label TEZ/IVA (100mg TEZ/150 mg IVA qam and 150mg IVA qpm) for 96 weeks. However, subjects who completed at least 4 weeks of treatment in Study 110, could screen for and participate in another qualified Vertex study and to subsequently re-enroll and resume TEZ/IVA treatment in study 110 after completion.

Subjects who were not eligible for the treatment cohort or who elected not to enroll in the treatment cohort were offered the opportunity to enroll in the observational cohort. These subjects did not receive study drug, but received regular phone call follow-up for 2 years after their last dose of study drug in the parent study. This review will focus on subjects in the treatment cohort.

Day 1 of the study could have been on the same day as the last scheduled visit of the parent study. Subjects who did not complete the Day 1 study visit within 28 days after the last dose of study drug in the parent study were required to complete the safety follow-up visit in the parent study before receiving the first dose of study drug in Study 110. Study visits were scheduled on Day 15, weeks 8, 16, 24, 36, 48, 60, 72, 84, and 96 with safety follow-up 28 days after the last dose. Subjects who prematurely discontinued treatment had an early treatment termination visit, optimally within 7 days after the last dose of study drug, in addition to the safety follow-up visit; however, the two visits may have been combined if the early treatment termination visit occurred 3 weeks or more after the last dose of study drug.

Study population (Treatment Cohort)
Key inclusion criteria

1. Did not withdraw consent from parent study
2. Completed study drug treatment during the treatment period in an eligible parent study of TEZ/IVA (103, 106, 107, 108, 109, 111). Studies VX11-661-101, VX15-661-11, and VX15-661-113 are not eligible studies.

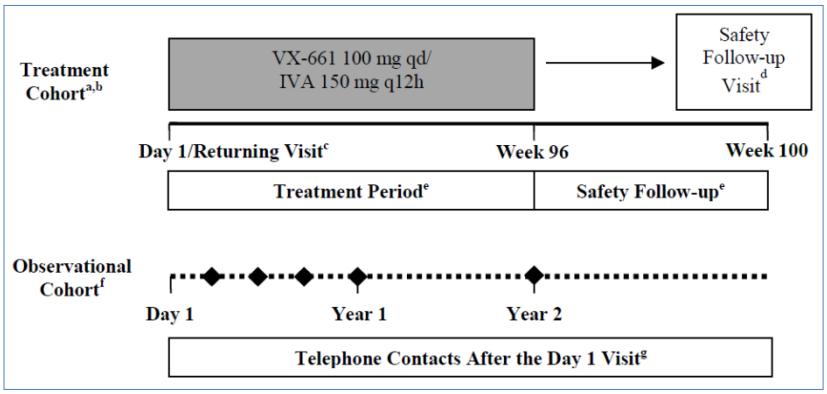
Key exclusion criteria

1. History of any comorbidity that might confound the results of the study or pose an additional risk in administering study drug
2. Pregnancy and nursing
3. Unwilling to follow the contraception requirements
4. History of drug intolerance in parent study or other qualified Vertex study (e.g., hypersensitivity to study drug, LFT or ECG abnormality requiring permanent study drug discontinuation, other severe of life-threatening reaction to study drug)

5. History of poor compliance with study drug/procedures in parent study
6. Participation in investigational drug trial (other than qualified studies) or use of commercially available CFTR modulator
7. Previous re-enrollment in treatment cohort of study 110

Prohibited/restricted medications were the same as in parent studies.

Figure 7. Study design schematic: Study 110



Source: VX14-661-110 Protocol, Figure 8-1, p26

Table 37. Schedule of assessments (Treatment Cohort): OLE Study 110

Event/Assessment[a]	Day –28 to Day -1	Treatment Period[b]						ETT Visit (Within 7 Days of Last Dose of Study Drug)[b,c,d,e]	Safety Follow-up Visit 28 (± 7) Days After Last Dose[c,d,e]
		Day 1[f]/ Returning Visit[b,g]	Day 15 (± 3 days)	Weeks 8, 16, 24, 36 (± 5 days)	Week 48 (± 5 days)	Weeks 60, 72, 84 (± 5 days)	Week 96 (± 5 days)		
Informed consent/assent	X[h]	X[h]							
Inclusion and exclusion criteria review		X							
CFQ-R[i]		X	X	X	X	X	X	X	X
SF-12[i]		X		X	X	X	X	X	
Weight and height[j]		X		X	X	X	X	X	X
Ophthalmological history[k]		Day 1							
Ophthalmologic examination[l]	X[h,m]	X[n]			X		X	X°	X°
Complete physical examination[p]		X			X		X	X	
Pregnancy test[q]		urine		urine	urine	urine	serum	serum	serum
Standard 12-lead ECG[r]		X	X	Weeks 8, 16, 24	X	Week 72	X	X	X
Vital signs[s]		X	X	X	X	X	X	X	X
Pulse oximetry[s]		X	X	X	X	X	X	X	X
Spirometry[t]		X	X	X	X	X	X	X	X
Hematology[u]		X[v]	X	X	X	X	X	X	X
Coagulation[u]		X[v]		X	X	X	X	X	X
Serum chemistry[u]		X[v]	X	X	X	X	X	X	X
Lipid panel[u]		X[v]		X	X	X	X	X	X
Vitamin levels[u]		X[v]		X	X	X	X	X	X
Urinalysis		X		X	X	X	X	X	X
PK sampling				Week 24[w]				X	
Other events related to outcome[x]		X	X	X	X	X	X	X	X
Meal(s) or snack(s) at site[y]		X	X	X	X	X			
Study drug count			X	X	X	X	X	X	

Study drug dosing[z]		*Day 1 to Week 96*		
Retrospective CF Ecology Data Collection (Optional)[aa]		*Continuous from signing of ICF through END OF TREATMENT (Retrospective data collection through registry review or through chart review to occur minimally every 6 months)*		
Concomitant medications		*Continuous from signing of the ICF and Assent (where applicable) through the Safety Follow-up Visit*		
Concomitant treatments and procedures		*Continuous from signing of the ICF and Assent (where applicable) through the Safety Follow-up Visit*		
AEs and SAEs[bb]		*Continuous from signing of the ICF and Assent (where applicable) through the Safety Follow-up Visit*		

AE: adverse event; CF: cystic fibrosis; CFQ-R: CF Questionnaire–Revised; ECG: electrocardiogram; ETT: Early Treatment Termination; ICF: informed consent form; PK: pharmacokinetic; SAE: serious adverse event; SF-12: 12-Item Short Form Survey.

h If the baseline ophthalmologic examination (see Footnote m) is not conducted as a parent study assessment but is conducted during the Day -28 to Day -1 period of Study VX14-661-110, informed consent/assent will be obtained before this examination and will not be obtained again on Day 1 of Study VX14-661-110.
i Questionnaires must be completed before the start of any other assessments scheduled at that visit (Section 11.1). The CFQ-R must be completed first, followed by the SF-12.
j Weight and height will be measured before dosing with shoes off (Section 11.7.2). Height will be collected only for subjects ≤21 years of age (age on the date of informed consent/assent in the parent study).
k Required on Day 1 for all subjects without a documented ophthalmological history from the parent study. Not required at the Returning Visit.
l Ophthalmologic examinations will be conducted on subjects <18 years of age (age on the date of informed consent/assent in the parent study) by a licensed ophthalmologist.
m An ophthalmologic examination will be conducted on subjects <18 years of age (age on the date of informed consent/assent in the parent study) by a licensed ophthalmologist within 28 days before enrollment on Day 1 (Section 11.8.7). This examination may be conducted while the subject is participating in the parent study. If this examination is not conducted during the Day -28 to Day -1 period, subjects are required to complete the Day 1 ophthalmologic examination.
n The Day 1 ophthalmologic examination is not required for subjects who complete the baseline ophthalmologic examination during the Day -28 to Day -1 period (this examination may be conducted while the subject is participating in the parent study).
o Subjects <18 years of age (age on the date of informed consent/assent in the parent study) who discontinue treatment after receiving at least 1 dose of study drug will have an ophthalmologic examination conducted by a licensed ophthalmologist at the ETT or Safety Follow-Up Visit (Section 8.1.1.3). The examination may be completed at either the ETT or Safety Follow-Up Visit, but must be completed by the date of the Safety Follow-Up Visit.
p Symptom-targeted physical examinations will occur at any time during the study if triggered by AEs or if deemed necessary by the investigator (Section 11.8.3).
q Pregnancy tests will be performed for all female subjects of childbearing potential. All urine pregnancy tests will be performed at the site.
r All standard 12-lead ECGs will be performed before dosing and after the subject has been supine for at least 5 minutes (Section 11.8.4). At the Day 1 and 15 Visits, ECGs will be collected before dosing and at 1.5 and 4 hours after the morning dose. A window of ± 15 minutes will be allowed around the nominal times for all postdose ECG assessments. ECGs collected on Day 1 before dosing will be performed in triplicate. If study drug is not administered on the day of the visit (i.e., because of study drug interruption), only 1 ECG will be collected.
s Vital signs and pulse oximetry will be collected before dosing and after the subject has been at rest (seated or supine) for at least 5 minutes (Sections 11.8.3 and 11.8.5).
t Spirometry must be performed for all subjects before dosing and should be performed pre-bronchodilator (Section 11.7.1).
u With the exception of Day 15, all blood samples will require a 4-hour fast before collection.
v Blood samples will be collected before the first dose of study drug.
w A single blood sample for PK will be collected within 60 minutes before dosing (Section 11.5.1).
x Other events related to outcome include assessments relating to pulmonary exacerbations, administration of antibiotic therapy for sinopulmonary signs or symptoms, and hospitalizations (Section 11.7.5).
y Fat-containing food such as a standard CF high-fat, high-calorie meal or snack will be provided at the site to subjects after all predose assessments have occurred.
z The study drug should be administered every 12 hours (± 2 hours) within 30 minutes of starting a meal with fat-containing food such as a standard CF high-fat, high-calorie meal or snack (Section 10.2). On days of scheduled visits, the morning dose of study drug will be administered at the site after predose assessments have been completed. The final dose of study drug will be administered the evening before the Week 96 Visit.
aa An optional, noninterventional, retrospective data collection will take place, if the subject agrees, for all clinically obtained respiratory culture results (throat swab, sputum, or bronchoalveolar lavage) from 12 months before the first dose in the parent study through to the end of the Treatment Period of Study VX14-661-110 (Section 11.6).
bb SAEs that occur after the Safety Follow-Up Visit and are considered related to study drug(s) will be reported to Vertex GPS **within 24 hours** as described in Section 13.1.2.2.

Source: CTP VX14-661-110, Table 3-1, p10

Endpoints: AEs, ophthalmologic exams, clinical labs, ECGs, vital signs, and pulse oximetry

Results

Overall demographics of study 110 population are reflective of demographics in the parent studies: primarily young adults (mean age 28 years) with ~ 20% adolescents, equally male and female, primarily white and non-Hispanic/Latino, and a majority from Europe. Disposition of subjects is provided in Table 38 while exposure is provided in Table 39.

Table 38. Subject disposition: Study 110

	Placebo→ TEZ/IVA	Active → TEZ/IVA	All Subjects
All subjects set	391	479	870
Safety set	390	477	867
Parent study			
103	0	23 (5)	23 (3)
106	232 (60)	230 (48)	462 (53)
107	80 (21)	79 (17)	159 (18)

108	78 (20)	145 (30)	223 (26)
Prematurely discontinued treatment	95 (24)	90 (19)	185 (21)
Adverse event	5 (1)	1(<1)	6 (1)
Refused further dosing (not due to AE)	4 (1)	6 (1)	10 (1)
Lost to follow-up	1 (<1)	2 (<1)	3 (<1)
Did not meet eligibility criteria	0	1 (<1)	1 (<1)
Other noncompliance	0	1 (<1)	1 (<1)
Physician decision	1 (<1)	1 (<1)	2 (<1)
Required prohibited medication	1 (<1)	0	1 (<1)
Pregnancy (self or partner)	2 (1)	1 (<1)	4 (1)
Study termination by sponsor*	78 (20)	76 (16)	154 (18)
Other	3 (1)	2 (<1)	4 (1)

Source: CSR VX14-661-110, Table 10-1, p75. Confirmed by reviewer in JMP.
*Subjects from parent study 107 were discontinued after 107 was terminated early for futility

Table 39. Exposure in Study 110, Safety Set*

	Placebo→ TEZ/IVA N=390	**Active → TEZ/IVA N=477**	**All Subjects N=867**
Total exposure (patient years)	243	314	557
Exposure duration in weeks			
Mean (SD)	33 (19)	34 (19)	34 (19)
Median	29	33	31
Exposure duration interval, n (%)			
0 to ≤8 weeks	33 (9)	35 (7)	68 (8)
>8 to ≤16 weeks	65 (17)	62 (13)	127 (15)
>16 to ≤24 weeks	61 (16)	72 (15)	165 (19)
>24 to ≤36 weeks	75 (19)	90 (19)	165 (19)
>36 to ≤48 weeks	67 (17)	86 (18)	153 (18)
>48 to ≤60 weeks	44 (11)	83 (17)	127 (15)
>60 weeks	45 (12)	49 (10)	94 (11)

Source: CSR VX14-661-110, Table 12-1, p111. Confirmed by reviewer in JMP.
*Data reflects exposure in Study 110 only and does not include exposure from the parent study.

Adverse Events

One death due to respiratory failure and influenza infection was reported in the 120-day safety update and is described in Section 8.4.1.

SAEs

Most SAEs occurred in 1-2 subjects. The most commonly reported SAE was CF exacerbation in 117 (14%) of subjects followed by hemoptysis in 16 (2%) of subjects, and distal intestinal obstruction syndrome in 7 (1%) of subjects. Additional SAEs reported in two or more subjects are briefly described below.

Drug hypersensitivity and anaphylactic reaction: Events of were clearly due to other drugs and to existing walnut allergy.

CK elevation and/or rhabdomyolysis:

- Subject 106-131-004 is a 31 yr old male who had elevated CK of 253 U/L upon enrollment; he experienced onset of rhabdomyolysis on study day 172 that ended on study day 225. Peak CK level was 4512. He was found to have positive SRP antibodies and negative anti-DNA. Rheumatologist suspected necrotizing autoimmune myopathy. The event resolved, and he continued TEZ/IVA treatment
- Subject 106-522-011 is a 23 yr old female with increased blood CK. The narrative only includes information about a hemoptysis SAE, thus it is unclear why increased CK was considered a serious event.
- Subject 107-075-005 is a 30 yr old white female who experienced elevated CK (3166 U/L) on study day 106. She denied any symptoms (muscle pain, dark urine, strenuous exercise), and after increasing hydration, her CK normalized.

Psychiatric disorders: Several subjects, including one adolescent, experienced suicidal ideation/attempt, depression, panic attack, and anxiety. All events appear to be related to pre-existing psychiatric conditions.

AEs leading to discontinuation

Adverse events leading to study drug discontinuation were primarily single events: CK elevation, urticarial vasculitis, cataracts, and abdominal pain/DIOS (all adolescent subjects). The subject diagnosed with urticarial vasculitis and extremity pain was not evaluated by a dermatologist and did not have a skin biopsy; although CRP was elevated, characteristic lab findings such as hypocomplementemia and positive ANA/dsDNA were not present. In addition, three patients discontinued due to CF exacerbations (and perceived lack of efficacy).

Common TEAEs

AEs by preferred term that were reported in ≥5% of subjects were like those observed in phase 3 trials and included (in decreasing frequency): CF exacerbations, cough, hemoptysis, nasopharyngitis, sputum increased, headache, pyrexia, fatigue, dyspnea, oropharyngeal pain, upper respiratory tract infection, abdominal pain, and nausea.

The degree and frequency of LFT elevations was generally similar to the trends observed in the controlled phase 3 trials. Approximately 2% of subjects had elevations in AST or ALT >3x ULN; transaminase elevations >5x ULN were relatively rare. One subject had a single AST measurement >20x ULN which resolved after temporary study drug interruption, and TEZ/IVA was continued. One subject had a transient concurrent elevation in total bilirubin >2x ULN and AST >3x ULN, but he had a history of mildly elevated bilirubin and transaminases throughout the studies as well as a history of CF liver disease.

In conclusion, the OLE included a sufficient number of patients exposed for an adequate duration to support chronic TEZ/IVA use. There were no new safety signals identified with long term exposure in the OLE study.

Safety Update

The 120-day safety update was submitted on 9/21/17. The submission included all new SAEs reported from 3/6/17 through 7/1/17 for all studies in the TEZ/IVA program as well as studies of TEZ/IVA in combination with another CFTR modulator. In addition, SAEs reported before 3/6/17 for studies that were ongoing and still blinded at the time of the NDA data cutoff were included.

Table 40. Studies included in the 120-day safety update

Study	Population	# Enrolled	Duration	Status
VX14-661-109	*F508del*/gating defect	156	12 weeks	Ongoing, blinded
VX14-661-110	Homozygous/heterozygous *F508del*	1034	96 week	Ongoing, OLE
VX14-661-111	*F508del*/*F508del*, ≥18 years	34	29 days	Ongoing, blinded
VX15-661-112	*F508del*/*F508del*	41	72 weeks	Ongoing, blinded
VX15-661-113	Homozygous/heterozygous *F508del*, 6-11 years	Part A: 13 Part B: 56	14 days 24 weeks	Part A: complete Part B: planned
VX16-661-114	*F508del*/*F508del*	45	8 weeks	Enrolling, blinded
Studies of TEZ in combination with other CFTR modulators				
VX15-152-001	Healthy adults	18	14 days	Dosing complete
VX16-152-102	CF adults	72	2-10 weeks	Enrolling
VX15-440-002	Healthy adults	12 TEZ/IVA	14 days	Complete
VX15-440-101	CF ≥12 years of age	198	12 weeks	Enrolling
VX16-445-001	Healthy adults CF	Part C: 16 Part D: 56 Part E: 24	2 weeks 5 weeks 12 weeks	Enrolling
VX16-659-001	Healthy adults CF	Part C/D: 40 (TEZ/IVA) Part E: 8	14 days	Enrolling

Source: Adapted from TEZ/IVA safety update, Table 1, p3

One death was reported as described in Section 8.4.1. During the reporting period, a total of 125 subjects reported 183 SAEs, the most common of which were CF exacerbation (89 subjects with 106 events) and hemoptysis (6 subjects with 7 events). Additional events of elevated CK and elevated LFTs leading to TEZ/IVA discontinuation were reported. These subjects appear to have had pre-existing disease/abnormal lab values as well as confounding factors such as strenuous exercise and cholelithiasis/alcohol abuse, respectively. Brief summary narratives of rare events, not usually associated with CF, which could potentially be drug-related are provided below. While it is not possible to eliminate TEZ/IVA as a potential cause of these AEs, each case involves confounding factors or too little information to draw conclusions about

causality. Overall, the risk-benefit assessment and safety profile of TEZ/IVA for the proposed CF indication is unchanged by the information in the 120-day safety update.

Subject 106-813-002 is a 27 yr old female homozygous for *F508del* mutations. She has a family history of autoimmune disease and medical history of elevated hepatic enzymes, focal biliary cirrhosis, portal fibrosis and pericellular fibrosis. She received placebo in trial 106 and had normal LFTs throughout the trial and through week 36 of study 110. On study day 335 of the OLE, she developed elevated AST, ALT, ALP and GGT with normal bilirubin; at the time, she was also being treated with IV ceftazidime at that time for deteriorating lung function. In the week prior, she had also been treated for influenza. Serial liver ultrasounds were normal. She stopped TEZ/IVA permanently on study day 393. A liver biopsy obtained about 3 months after onset of elevated LFTs showed heavy inflammation with lobular and portal lymphocyte infiltration and clear interphase activity suggestive of autoimmune hepatitis; however, all liver antibodies were negative. An MRI of the liver showed discrete irregularity with tendency of nodular pattern, slight edema, and contrast loaded septa, discrete fat storage and no dilated bile ducts. She started tacrolimus for autoimmune hepatitis ~4 months after onset after which her transaminases normalized.

Subject 108-802-004 is a 25 yr old female, heterozygous for *F508del* mutation. She had no history of liver disease or family history of autoimmune disease. She received TEZ/IVA → IVA in trial 108 and had normal LFTs on day 1 of study 110 through week 36. On study day 112, she developed elevated ALT and AST with normal bilirubin and ALP. She denied concomitant alcohol or drug abuse. Her liver ultrasound was normal; however, IgG and IgM levels along with ANA and TSH were elevated. Other autoimmune tests and serology for viral hepatitis were all negative. GI suggested potential etiologies of drug reaction or autoimmune hepatitis.

Subject 109-029-002 is a 20 yr old female who was diagnosed with metastatic colon adenocarcinoma on day 339 following biopsy on colonoscopy for DIOS. Immunohistochemistry revealed loss of Msh6 gene expression and probable lynch syndrome. She was scheduled for chemotherapy and chose to withdraw from the study and TEZ/IVA permanently.

Subject 108-703-003 is a 67 yr old male with history of GERD. He received IVA→TEZ/IVA in study 108. He had a history of weight loss, nausea/vomiting, and dysphagia during study 108. On day 5 of study 110, he was hospitalized for gastroscopy and gastric emptying study, results of which revealed Barrett's esophagus and gastritis. He was re-hospitalized on study day 56 for nausea/vomiting and dysphagia. A biopsy confirmed esophageal carcinoma, and TEZ/IVA was permanently discontinued.

Subject 106-134-009 is a 49 yr old male who developed LV dysfunction. He had a history of CF related diabetes, CF hepatic disease, pancreatic insufficiency and depression. He received TEZ/IVA in trail 106. During the trial, he underwent echocardiogram for fatigue that revealed

normal LV function but signs of cor pulmonale. His ECG was unremarkable on day 1 of study 110, but a repeat echo on day 12 showed normal RV function and LV dysfunction. Cardiac MRI on Day 58 showed an ejection fraction of 50%, and a repeat echo on Day 72 showed LVEF of 48% (hypertrophic cardiomyopathy criteria not met). He was immediately started on metoprolol and Ramipril; TEZ/IVA was permanently discontinued on the same day.

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

No human carcinogenicity studies have been performed for TEZ/IVA.

8.8.2. Human Reproduction and Pregnancy

The use of TEZ/IVA during pregnancy or lactation has not been evaluated in well-controlled trials. Three pregnancies were reported in 2 female subjects and 1 partner of a male subject. The outcome of two pregnancies reported from study 110 are unknown. One subject from trial 108 gave birth to a live healthy female infant.

8.8.3. Pediatrics and Assessment of Effects on Growth

CF is a rare, orphan disease and thus is not subject to pediatric study requirements as defined under the Pediatric Research Equity Act (PREA). However, all phase 3 trials included CF patients 12-17 years of age (inclusive). Efficacy and safety data in this adolescent age group was consistent with the overall results.

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Not applicable.

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

There is no postmarketing experience with TEZ/IVA. However, postmarketing experience with IVA monotherapy since approval on 1/31/12 has not identified additional safety concerns that alter the risk-benefit profile of TEZ/IVA combination therapy.

8.9.2. Expectations on Safety in the Postmarket Setting

Since phase 3 trials excluded patients with certain co-morbidities and more severe disease, it is possible that sicker CF patients may experience side effects not observed in clinical trials. However, given the postmarketing experience with the IVA component and the relatively safe

profile of TEZ, no substantial differences are anticipated.

8.10. Integrated Assessment of Safety

The safety data submitted with the NDA was sufficient to assess the safety of TEZ/IVA in the proposed CF patient population. The safety information for TEZ/IVA is primarily derived from three placebo-controlled phase 3 trials (106, 107, and 108). In total, these trials included 690 adolescent and adult CF subjects, 496 of whom received at least one dose of the proposed dose of TEZ/IVA. (100 mg TEZ/150 mg IVA in the morning and 150 mg IVA in the evening). Given the varying treatment durations (8, 12, and 24 weeks) and study designs (parallel group and crossover), most safety data presented in this review is from trial 106, the 24-week parallel group study, with safety findings or differences from the other two studies noted where applicable. Additional support for long-term safety comes from open label extension (OLE) study 110.

No deaths occurred in the placebo controlled studies; however, a single death due to respiratory failure in the setting of recent CF exacerbation and concurrent influenza infection occurred in the OLE. SAEs and AEs leading to premature treatment discontinuation occurred more frequently in placebo patients compared to TEZ/IVA patients. Safety analyses were performed for AESIs identified *a priori* and potential safety signals identified during the review. Liver-related toxicity, which has been observed with IVA monotherapy and LUM/IVA was evaluated as an AESI. Hepatobiliary TEAEs as well as transaminase or total bilirubin elevations occurred more frequently in placebo patients than TEZ/IVA patients. Furthermore, transaminase elevations >3x ULN were more common in the placebo group. In contrast to the LUM/IVA program, respiratory symptom-related TEAEs occurred more often in the placebo group and do not appear to be a drug-related side effect of TEZ/IVA. Cataracts are a potential risk associated with IVA monotherapy and were reported with TEZ/IVA as well. While the numbers were small, numerically more TEZ/IVA patients were found to have treatment emergent cataracts on ophthalmologic exam than placebo patients; therefore, cataracts remains a potential safety risk and will be conveyed in product labeling. Other adverse reactions associated with LUM/IVA such as menstrual abnormalities and hypertension were evaluated; however, TEZ/IVA patients did not appear to be at increased risk of these events in the controlled clinical trials. Finally, CK elevation emerged as a potential safety signal as several SAEs and AEs were reported in the controlled and OLE studies. However, upon further evaluation of the laboratory data alongside CK-related TEAEs from all three studies, there was no apparent difference between placebo and TEZ/IVA treated patients. In general, safety data from OLE study 110 was consistent with the placebo controlled data and supports chronic TEZ/IVA use. Overall, the TEZ/IVA safety profile for the treatment of a rare, serious disease such as cystic fibrosis is favorable.

9 Advisory Committee Meeting and Other External Consultations

A pulmonary allergy drug advisory committee (PADAC) meeting was considered for this supplement. However, given the results of the studies submitted, including demonstration in clinical studies of the contribution of TEZ to the effect of IVA alone, the Division decided that the evidence supporting approval for the indicated populations were sufficiently robust that discussion at an AC was not necessary.

10 Labeling Recommendations

10.1. Prescribing Information

Vertex submitted proposed prescribing information, patient instruction sheet, and carton and container labeling for the TEZ/IVA combination that included the tradename "Symdeko". The label was reviewed by the appropriate disciplines within the Division and labeling consultants who recommended various changes to the prescribing information and patient information sheet to correct formatting errors and to better describe the drug product and indicated population to healthcare providers and fully inform patients. Edits were also made to harmonize, where appropriate, the proposed Symdeko label to the label of the currently approved products, Kalydeco (the IVA component of the combination) and Orkambi (the lumacaftor/ivacaftor combination). Specific issues identified in the proposed label included:

- (b) (4)
- Pooling of safety data from parallel and crossover trials
- Omission of death from OLE study 110
- Exclusion of R347H mutation from study 108 in Section 12
- (b) (4) without corresponding clinical data
- Absence of language to qualify the interpretation of *in vitro* assay results
- Lack of data from dose-ranging study 101
- Lack of efficacy data by individual mutation from trial 108 in Section 14
- Absence of efficacy results from trial 107

10.2. Patient Labeling

DMPP and OPDP reviewed the proposed patient package insert (PPI) submitted to the NDA. Revisions to reduce redundancy, make patient information more consistent with the PI and concise, and harmonize with Kalydeco and Orkambi labels were conveyed to and accepted by Vertex.

11 Risk Evaluation and Mitigation Strategies (REMS)

A REMS was not deemed necessary for this application.

12 Postmarketing Requirements and Commitments

None. PREA requirements do not apply to this orphan drug product; (b) (4)

13 Appendices

13.1. Financial Disclosure

The financial disclosure checklist for the clinical studies submitted to this NDA is provided below. Although there were several significant payments of other sorts (primarily small research grants), these were unlikely to have had a significant impact upon the conduct of the clinical trials, given that each investigator site enrolled a small number of patients and the efficacy studies were randomized, double-blinded, and placebo controlled with objective spirometric, nutritional and exacerbation related endpoints.

Covered Clinical Studies: VX11-661-101, VX13-661-103, VX14-661-106, VX14-661-107, VX14-661-108, VX14-661-110

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 2198		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 61		
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: 2 (study 106) Significant payments of other sorts: 59 (12 from study 106, 9 from study 107, 16 from study 108, and 22 from study 110) Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Sponsor of covered study: 0		
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) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

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/s/

STACY J CHIN
02/01/2018

BADRUL A CHOWDHURY
02/01/2018
I concur

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA Number: 210491 Applicant: Vertex Pharmaceuticals Inc. Stamp Date: 6/28/17

Drug Name: tezacaftor/ivacaftor (Symdeko - proposed proprietary) NDA/BLA Type: original

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic common technical document (eCTD).				eCTD
2.	Is the clinical section legible and organized in a manner to allow substantive review to begin?	x			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	x			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	x			
5.	Are all documents submitted in English or are English translations provided when necessary?	x			
LABELING					
6.	Has the applicant submitted a draft prescribing information that appears to be consistent with the Physician Labeling Rule (PLR) regulations and guidances (see http://www.fda.gov/Drugs/GuidanceComplianceRegulatory Information/LawsActsandRules/ucm084159 htm	x			
SUMMARIES					
7.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	x			
8.	Has the applicant submitted the integrated summary of safety (ISS)?	x			
9.	Has the applicant submitted the integrated summary of efficacy (ISE)?	x			
10.	Has the applicant submitted a benefit-risk analysis for the product?	X			Module 2.5 Clinical Overview, Section 6
11.	Indicate if the Application is a 505(b)(1) or a 505(b)(2).				505(b)(1)
505(b)(2) Applications					
12.	If appropriate, what is the relied upon listed drug(s)?			x	
13.	Did the applicant provide a scientific bridge demonstrating the relationship between the proposed product and the listed drug(s)/published literature?			x	
14.	Describe the scientific bridge (e.g., BA/BE studies)			x	
DOSAGE					
15.	If needed, has the applicant made an appropriate attempt to determine the correct dosage regimen for this product (e.g., appropriately designed dose-ranging studies)? Study Number: VX11-661-101 Study Title: A Phase 2, Multicenter, Double-Blind, Placebo-Controlled Study to Evaluate Safety, Efficacy, Pharmacokinetics, and Pharmacodynamics of VX-661 and VX-661/Ivacaftor cotherapy in cystic fibrosis patients homozygous or heterozygous for the F508del CFTR mutations	x			

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Sample Size: 190 CF patients Treatment Arms: TEZ 10, 30, 100, 150 mg QD ± IVA 50 or 150 mg Q12 or placebo; TEZ 50 mg Q12, IVA 150 mg Q12, TEZ 100 mg QD + IVA 150 mg Q12 Location in submission: Module 5.3.4.2				
EFFICACY					
16.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1: VX14-661-106 Indication: F508/F508del Pivotal Study #2: VX14-661-107 Indication: F508del/Nonresponsive mutation Pivotal Study #3: VX14-661-108 Indication: F508del/residual function mutation	X			
17.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
18.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
19.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?	X			All studies included US and non-US sites. Non-US sites required to study orphan population.
SAFETY					
20.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
21.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?	X			Study VX09-770-008 Study VX15-661-010
22.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
23.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dosage (or dosage range) believed to be efficacious?	X			Adequate safety database for orphan indication
24.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

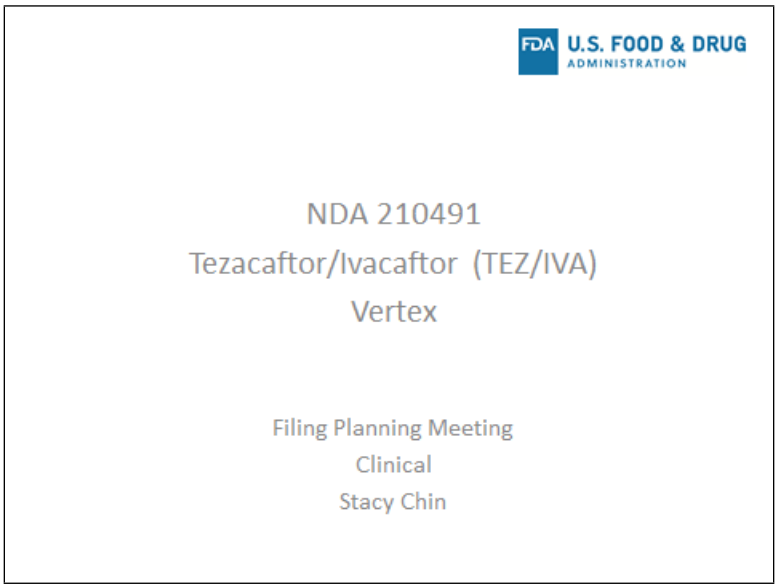
	Content Parameter	Yes	No	NA	Comment
25.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	X			MedDRA v12.0 (study 770-104) MedDRA v14.1 (study 661-101) MedDRA v19.0 (study 661-103) MedDRA v19.1 (phase 3 studies)
26.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
27.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
28.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			X	
29.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
30.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			Orphan product designation
PREGNANCY, LACTATION, AND FEMALES AND MALES OF REPRODUCTIVE POTENTIAL USE					
31.	For applications with labeling required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, has the applicant submitted a review of the available information regarding use in pregnant, lactating women, and females and males of reproductive potential (e.g., published literature, pharmacovigilance database, pregnancy registry) in Module 1 (see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307 htm)?	X			
ABUSE LIABILITY					
32.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
33.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	US sites represented in all efficacy/safety studies. Orphan disease
DATASETS					
34.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
35.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
36.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
37.	Are all datasets to support the critical safety analyses available and complete?	X			
38.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
39.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	x			
40.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			x	
FINANCIAL DISCLOSURE					
41.	Has the applicant submitted the required Financial Disclosure information?	x			
GOOD CLINICAL PRACTICE					
42.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	x			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? __YES_____



Regulatory Background

- Breakthrough Therapy Designation granted (1/28/14)
- EOP2 meeting (11/5/14)
  - IVA monotherapy arm needed (in place of placebo)
  - Comparative safety data to LUM/IVA
  - Disagreement w/mutations defined as NR
  - Shorter studies limit evaluable efficacy endpoints
- Type B meeting (11/4/15)
  - Only need to demonstrate contribution of each component in one mutation subgroup (F508/F508)
  - Assuming risk by not including IVA only arm
- PreNDA meeting (5/30/17)
  - Similar approach to proposed indication as for ivacaftor sNDA 203188/S-019
  - AC meeting not anticipated
  - Inclusion of RF mutations not studied, a review issue

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Tezacaftor/Ivacaftor (SYMDEKO)

- Proposed indication:
  - Treatment of CF patients ≥12 years homozygous for F508del mutation or with at least one CFTR mutation responsive to TEV/IVA based on in vitro data and/or clinical evidence
- Mechanism of Action:
  - Tezacaftor – "corrector", facilitates trafficking to cell surface
  - Ivacaftor – potentiator, increases open-channel probability once at cell surface
- Proposed dose: TEZ 100mg/IVA 150 mg qAM, IVA 150 mg qPM
- Conclusion: Fileable

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Trial	Design	Population	Treatment	N	Duration	Endpoints
Phase 2						
101	R, DB, PC	Adults F508/F508 F508/G551D	TEZ 10 QD (+IVA 150 Q12) TEZ 30 QD (+IVA 150 Q12) TEZ 100 QD (+IVA 150 Q12) TEZ 150 QD (+IVA 150 Q12) TEZ 100 QD + IVA 50 Q12 TEZ 50 Q12 + IVA 150 Q12 TEZ 100 QD + Kalydeco Placebo	8 (18) 8 (18) 8 (17) 9 (17) 19 16 14 39	28 days	Sweat chloride ppFEV1 CFQ-R resp
103	R, DB, PC + OLE	Adults F508/F508	TEZ 50 Q12 + IVA 150 Q12 TEZ 100 QD + IVA 150 Q12 Placebo	6 15 19	12 weeks 40 week OLE	ppFEV1
Phase 3						
106	R, DB, PC, PG	≥ 12 yrs F508/F508	TEZ 100 QD + IVA 150 Q12 Placebo	251 258	24 weeks	Abs/Rel Δ ppFEV1 Exacerbations BMI CFQ-R resp
107	R, DB, PC, PG	≥ 12 yrs F508/NR	TEZ 100 QD + IVA 150 Q12 Placebo	83 85	12 weeks	Abs Δ ppFEV1 CFQ-R resp Exacerbations BMI
108	R, DB, PC, XO	≥ 12 yrs F508/RF	TEZ 100 QD + IVA 150 Q12 IVA 150 Q12 Placebo	162 157 162	16 weeks (8 wk periods)	Abs/Rel Δ ppFEV1 CFQ-R resp
110	OLE	Completion of study 103, 106, 107, 108, 109, 111	TEZ 100 QD + IVA 150 Q12		96 weeks	ppFEV1 Exacerbations BMI/Weight

Study 109 (ongoing): F508/gating mutation, IVA and TEZ/IVA arms, 8 wks

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Efficacy: Study 106 (F508/F508)

FDA

Endpoint Δ from baseline (Wk 24)	Placebo N=256	TEZ/IVA N=248
ppFEV1 (absolute)	-0.6	3.4
Difference from placebo (overall)		4.0 (3.1-4.8)
Difference from placebo (<18y)		3.9 (2.2, 5.5)
# Exacerbations (event rate/yr)	122 (0.97)	78 (0.64)
Rate ratio vs placebo		0.65 (0.48, 0.88)
BMI	0.12	0.18
Difference from placebo		0.06 (-0.08, 0.19)
CFQ-R	-0.1	5.0
Difference from placebo		5.1 (3.2, 7.0)
Sweat chloride	0.2	-9.9
Difference from placebo		-10.1* (-11.4, -8.8)

LUM/IVA in F508/F508, ppFEV1 = 2.6-3%, RR exacerbation 0.6-0.7
IVA in F508/F508, ppFEV1 = 1.7%, RR exacerbation 0.68
IVA in G551D hetero, ppFEV1 = 10.6-12.5%, HR exacerbation 0.4-0.46

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Efficacy: Study 108 (F508/RF)

Endpoint Δ from baseline (Wk 4&8)	Placebo N=161	IVA N=156	TEZ/IVA N=161
ppFEV1 (absolute)	-0.3	4.4	6.5
Difference from placebo (overall)		4.7 (3.7,5.8)	6.8 (5.7, 7.8)
Difference from placebo (< 18y)		8.0 (5.2, 10.7)	12 (9.3, 14.8)
vs IVA			2.1 (1.2, 2.9)
CFQ-R	-1.0	8.7	10.1
Difference from placebo		9.7 (7.2, 12.2)	11.1 (8.7, 13.6)
vs IVA			1.4 (-1.0, 3.9)
Sweat chloride	-0.4	-4.9	-9.9
Difference from placebo		-4.5 (-6.7, -2.3)	-9.5 (-11.7, -7.3)
vs IVA			-5.1 (-7.0, -3.1)

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Study 107 (F508/NR)

Endpoint Δ from baseline (Wk 12)	Placebo N=85	TEZ/IVA N=82
ppFEV1 (absolute)	-0.1	1.0
Difference from placebo		1.2 (-0.3, 2.6)
CFQ-R	3.8	5.9
Difference from placebo		2.1 (-1.2, 5.4)
# Exacerbations	23	22
Rate ratio		0.98 (0.55, 1.76)
BMI	0.22	0.14
Difference from placebo		-0.08 (-0.27, 0.11)
Sweat chloride	-1.2	-4.7
Difference from placebo		-3.5 (-5.9, -1.2)

Study terminated early for futility

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Safety: Exposure
Pooled PC studies (106, 107, 108)

Duration of Exposure	Statistic	Placebo N = 505	TEZ/IVA N = 496
Total exposure	Patient years	157.3	154.2
Exposure duration (weeks)	Mean (SD)	16.3 (7.5)	16.2 (7.7)
	Median	12.7	12.6
	Min, max	1.9, 25.0	0.3, 26.4
Exposure duration by interval, n (%)			
≤2 weeks		2 (0.4)	6 (1.2)
>2 to ≤4 weeks		5 (1.0)	2 (0.4)
>4 to ≤8 weeks		113 (22.4)	113 (22.8)
>8 to ≤16 weeks		140 (27.7)	137 (27.6)
>16 to ≤24 weeks		174 (34.5)	155 (31.3)
>24 weeks		71 (14.1)	83 (16.7)
Number of subjects by study			
Study 106		258	251
Study 107		85	83
Study 108		162	162

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Safety: Exposure
OLE interim analysis
(103, 106, 107, 108)

Duration of Exposure	Statistic	Placebo-TEZ/IVA N = 390	Active-TEZ/IVA N = 477	Total N = 867
Total exposure	Patient years	242.6	314.0	556.6
Exposure duration (weeks)	Mean (SD)	32.5 (19.3)	34.3 (18.8)	33.5 (19.0)
	Median	29.0	33.0	30.7
	Min, max	0.1, 79.1	1.7, 76.1	0.1, 79.1
Exposure duration by interval, n (%)				
>0 to ≤8 weeks		33 (8.5)	35 (7.3)	68 (7.8)
>8 to ≤16 weeks		65 (16.7)	62 (13.0)	127 (14.6)
>16 to ≤24 weeks		61 (15.6)	72 (15.1)	133 (15.3)
>24 to ≤36 weeks		75 (19.2)	90 (18.9)	165 (19.0)
>36 to ≤48 weeks		67 (17.2)	86 (18.0)	153 (17.6)
>48 to ≤60 weeks		44 (11.3)	83 (17.4)	127 (14.6)
>60 weeks		45 (11.5)	49 (10.3)	94 (10.8)

Source: Study 110 IA CSR/Table 14.1.7

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Safety: Adverse Events

Pooled PC studies	Placebo N=505 (%)	TEZ/IVA N=496 (%)
Completed	484 (96)	477 (96)
Discontinued due to AE	10 (2)	8 (2)
Deaths	0	0
SAEs	75 (15)	50 (10)
Any AE	439 (87)	408 (82)
Elevated transaminases	18 (4)	17 (3)
CF exacerbation	153 (30)	117 (24)
Respiratory events	74 (15)	56 (11)
Study 106	**Placebo N=212 (%)**	**TEZ/IVA N=203 (%)**
Treatment emergent cataracts	11 (5)	14 (7)

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DSI Audit

- High enrollers
- Large treatment effect

Label

- (b) (4)
- Safety: pooled studies 106, 107, 108
- Section 14:
  - No dose ranging data; primarily studies 106 & 107
  - Endpoints: absolute & relative chg ppFEV1, exacerbations, BMI, CFQ-R respiratory domain score
  - Chg in ppFEV1 over time figure (Day 15)
  - Study 107 (F508/NR) described in Section 14 without results
- OLE mentioned in sections 6 and 14, but no data included – intend to update later in review cycle?

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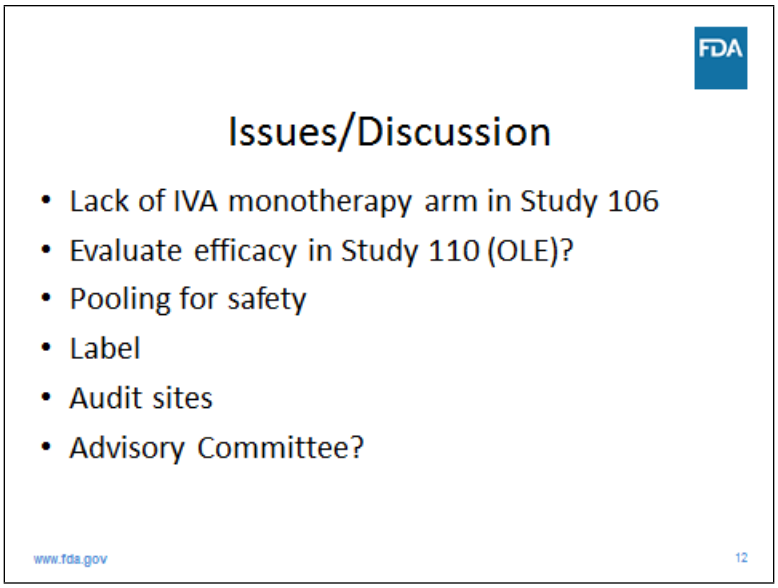
FDA
Issues/Discussion
• Lack of IVA monotherapy arm in Study 106
• Evaluate efficacy in Study 110 (OLE)?
• Pooling for safety
• Label
• Audit sites
• Advisory Committee?
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/s/

STACY J CHIN
08/04/2017

ANTHONY G DURMOWICZ
08/04/2017

MEDICAL OFFICER REVIEW

Division of Pulmonary, Allergy and Rheumatology Drug Products (HFD-570)

Application #:	**108,105**	**Application Type:**	IND
Sponsor:	Vertex Pharmaceuticals	**Proprietary Name:**	VX-661
Category:	CFTR modifier	**Route of Administration:**	oral
Reviewer:	K. Witzmann, MD	**Review Date:**	January 15, 2014

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date	CDER Stamp Date	Submission Type	Comments
12-03-2013	12-03-2013	Breakthrough Designation Request	SD-51, e050

REVIEW SUMMARY:

On December 03, 2013, Vertex Pharmaceuticals submitted a request for designation of their chloride channel modifier, VX-661, as a "Breakthrough therapy" as defined in section 902 of the Food and Drug Administration Safety and Innovation Act (FDASIA). Specifically, and in accordance with the definition of Breakthrough therapy, the company believes that VX-661, alone or in combination with one or more other drugs, treats a serious or life-threatening disease or condition (cystic fibrosis) and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies. CF is a life-threatening autosomal recessive disease which affects about 70, 000 individuals world-wide (30,000 in US). It is caused by mutations in the *CFTR* gene that results in lack of or inadequate function of the CFTR protein on the surface of epithelial cells. The CFTR is a chloride channel that helps regulate salt and water absorption and secretion across epithelial cells. While over 1800 mutations in *CFTR* have been identified, approximately 50% of patients with CF are homozygous for the *F508del CFTR* mutation and about 90% of CF patients have it on at least 1 allele. VX-661, termed a "corrector" of CFTR protein function in CF patients with the *F508del-CFTR* mutation, is proposed to work by promoting the proper folding of the *F508del* CFTR protein during its translation and processing in the endoplasmic reticulum, allowing it to exit the endoplasmic reticulum and traffic to the cell surface where it is normally active. Ivacaftor (tradename Kalydeco), classified as a CFTR potentiator, was approved on January 31, 2012, for the treatment of CF in patients age 6 years and older who have a *G551D* in the *CFTR* gene. It works by increasing chloride transport in CFTR protein already present at the cell surface. Clinical studies conducted by Vertex have demonstrated that ivacaftor alone does not have a beneficial effect in patients homozygous for *F508del-CFTR*. However, Vertex has submitted preliminary clinical evidence to suggest that VX-661 in combination with ivacaftor has the potential for efficacy in this patient population, presumably by allowing misfolded CFTR protein to reach the cell surface and subsequently increasing its chloride transport activity.

The Division, therefore, is of the opinion that VX-661 in combination with ivacaftor meets the definition of a "breakthrough therapy" for the treatment of CF as outlined in Section 902 of the Food and Drug Administration Safety and Innovation Act and recommends that the combination be given breakthrough therapy designation.

RECOMMENDED REGULATORY ACTION:

Breakthrough Designation Request: **__X___** **Grant Breakthrough Designation**

Medical Reviewer: K. Witzmann, MD, DPARP

Medical Team Leader: A. Durmowicz, MD, DPARP

Introduction

This purpose of this expanded medical policy council meeting is to discuss the request by Vertex Pharmaceuticals for designation of their chloride channel corrector, VX-661, to be designated as a "breakthrough therapy" as defined in Section 903 of the Food and Drug Administration Safety and Innovation Act, which became effective October 1, 2012. Specifically, in accordance with the definition of breakthrough therapy, the company believes that VX-661 treats a serious or life-threatening disease or condition (cystic fibrosis) and that preliminary clinical evidence for the use of VX-661 in combination with the currently marketed CFTR potentiator therapy, ivacaftor, indicates that the drug may demonstrate substantial improvement over existing symptom-based therapies on 1 or more clinically significant endpoints.

Breakthrough designation was granted for ivacaftor (chloride channel potentiator) on November 13, 2012, for "the treatment of cystic fibrosis in patients with CFTR gene mutations that result in CFTR protein gating defects or residual baseline CFTR protein function."

Breakthrough designation was granted for lumacaftor (another chloride channel "corrector") in combination with ivacaftor on December 07, 2012, for "development in cystic fibrosis patients homozygous for the *F508del-CFTR* mutation." Of note is that a lumacaftor/ivacaftor combination product is currently in Phase 3 development, so no approved treatment is yet available for this CF population.

Cystic Fibrosis (CF) Background

Cystic fibrosis (CF) is a life-threatening autosomal recessive disease which affects about 70, 000 individuals world-wide (30,000 in US). Clinical manifestations of CF are most apparent in the lungs, GI system (intestines, pancreas, liver), and reproductive systems. Death is usually due to respiratory failure as a result of obstructive lung disease and chronic pulmonary infection. The mean age of death is the mid to late 30's.

CF is the result of mutations in the *CFTR* gene that results in lack of or inadequate function of the CFTR protein on the surface of epithelial cells. The CFTR protein is a chloride channel that helps regulate salt and water absorption and secretion across epithelial cells. While over 1800 mutations in the CFTR have been identified, approximately 50% of patients with CF are homozygous for the *F508del CFTR* mutation and about 90% of CF patients have it on at least 1 allele. This mutation, termed a processing mutation, results in improperly folded CFTR protein that is degraded intracellularly, and, as a result, does not reach the apical cell membrane where the CFTR is active. In general, patients with CF homozygous for the *F508del* mutation in the *CFTR* gene have more severe CF-related disease. Currently, there are no therapies that target the underlying cause of CF in the majority of patients who have the *F508del CFTR* mutation, including those homozygous for the *F508del* mutation.

Clinical evidence that VX-661 in combination with ivacaftor has the potential to be a substantial improvement over existing treatments in CF patients homozygous for the *F508del-CFTR* mutation

VX-661 is a small molecule drug being developed by Vertex as a CFTR "corrector" of the F508del mutated CFTR protein in patients with CF. Its proposed mechanism of action is to promote the proper folding of the F508del mutated CFTR protein during its translation and processing in the endoplasmic reticulum, thereby allowing it to exit the endoplasmic reticulum and move to the cell surface where it would be active. VX-661 received Fast Track designation in May 2010.

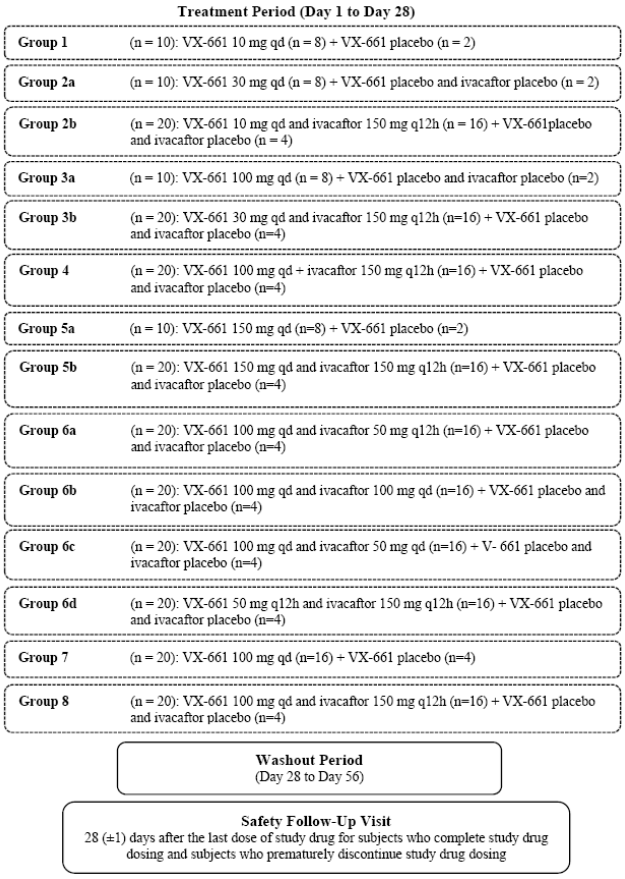
Ivacaftor (tradename Kalydeco) was approved on January 31, 2012, for the treatment of CF in patients age 6 years and older who have a G551D mutation in the CFTR gene. However, ivacaftor

alone is not beneficial to CF patients homozygous for the *F508del* mutation as was demonstrated in Study 770-104 conducted as part of the ivacaftor development program (see Kalydeco PI).

Vertex has conducted one clinical study to date investigating the potential efficacy of either VX-661 alone and in combination with the marketed CFTR potentiator therapy, ivacaftor (study 101). Study 101 is an ongoing Phase 2, multicenter, double-blinded, placebo-controlled, multiple-dose study of lumacaftor administered alone and in combination with the CFTR potentiator ivacaftor, in CF patients who are homozygous for the *F508del CFTR* mutation. The primary objective of Study 101 is to assess the efficacy, safety, dose-ranging, and tolerability of VX-661 monotherapy as well as VX-661-ivacaftor co-therapy in subjects who are homozygous for the *F508del-CFTR* mutation. As with the other CF development programs conducted by the company, the main clinical efficacy endpoint assessed is improvement in pulmonary function measured by change in FEV1. Change in sweat chloride once again was assessed as a pharmacodynamic endpoint. The study consists of two main cohorts of patients, the first randomized to receive either VX-661 (10, 30, 100 and 150 mg once daily [qd]) or placebo as monotherapy for 28 days. A second group of patients was randomized to receive the combination of VX-661 (10, 30, 100, and 150 mg qd) with ivacaftor (150 mg every 12 hours [q12h]), or placebo, for 28 days. (Other groups are being evaluated, including those with a lower dose of ivacaftor, but data presented here represents those treated with the currently approved dose of ivacaftor 150mg q12h).

Of note is that the company's Breakthrough Therapy request package does not include efficacy results for the VX-661 monotherapy groups or the results for the pharmacodynamic endpoint, change in sweat chloride. The results for the improvement in lung function endpoint, FEV1, obtained from combination therapy at varying doses of VX-661are outlined below.

Figure 1: Overview of Study 101 Design



[Vertex Breakthrough Designation Package, submitted 12-03-2013 to IND 108,105, SD-51, page 8]

The FEV1 results provided for absolute and relative changes in lung function in the combination (VX-661 + ivacaftor) dosing groups showed that improvements in lung function were observed in all combination dosing groups (10, 30, 100, and 150 mg), both within group and versus placebo. The improvements in lung function appear to be dose dependent, with the greatest improvements observed in the groups that received the 2 highest doses of VX-661 in combination with ivacaftor. Subjects in the 2 highest combination dose groups (100 or 150 mg of VX-661 in combination with ivacaftor 150 mg) showed statistically significant mean absolute improvements in lung function versus placebo of 4.8% (P = 0.01) and 4.5% (P = 0.01), respectively, at Day 28. Table 1 displays these results in tabular format, below:

Table 1: Mean Changes in Absolute and Relative % predicted FEV1 for VX-661+ ivacaftor combination therapy v. placebo

	Mean relative change in percent predicted FEV_1 from baseline		Mean absolute change in percent predicted FEV_1 from baseline	
	Day 0-28	28 days post-treatment (within-group mean)[a]	Day 0-28	28 days post-treatment (within-group mean)[a]
Placebo (n = 23) (within group)	0.03 (NS)	1.6	-0.4 (NS)	0.6
Combination treatment arms	**versus placebo**		**versus placebo**	
10 mg VX-661 + 150 mg ivacaftor (n = 17)	4.1 (NS)	1.7	2.3 (NS)	0.8
30 mg VX-661 + 150 mg ivacaftor (n = 17)	5.4 (NS)	1.2	3.4 (NS)	0.5
100 mg VX-661 + 150 mg ivacaftor (n = 15)	9.0 (*P* = 0.01)	1.7	4.8 (*P* = 0.01)	0.5
150 mg VX-661 + 150 mg ivacaftor (n = 16)	7.5 (*P* = 0.02)	1.4	4.5 (*P* = 0.01)	0.7

Source: Study 101/Table 14.2.2.2.1.1.A, Table 14.2.2.2.2.1.A, and Table 14.2.2.2.6.1.A.(Interim analysis 4)
NS: not statistically significant
[a] The statistical analysis plan for Study 101 did not include statistical comparisons for the 28-day washout period

[Vertex Breakthrough Designation Package, submitted 12-03-2013 to IND 108,105, SD-51, page 9]

Vertex also notes that a within-subject improvement in *relative* percent predicted FEV1 of 5% or greater at Day 28 occurred as described in Table 2 below; responder data regarding *absolute* change in FEV1 of 5% or greater was not provided.

Table 2: Responder Data of 5% or greater relative improvement in FEV1 at Day 28

Treatment Group	% Responders	N of responders
Placebo	21.7%	5 of 23
100mgQD VX-661 +iva 150mg BID	66.7%	10 of 15
150mg QD VX-661 +iva 150mg BID	56.3%	9 of 16
Vertex Breakthrough Designation Package, submitted 12-03-2013 to IND 108,105, SD-51, page 9		

Summary

Cystic fibrosis is a life-threatening autosomal recessive disease. While over 1800 mutations in the CFTR have been identified, approximately 50% of patients with CF are homozygous for the *F508del CFTR* mutation and about 90% of CF patients have it on at least 1 allele. This mutation,

termed a processing mutation, results in improperly folded CFTR protein that is degraded intracellularly, and as a result, does not reach the apical cell membrane where the CFTR is active. In general, patients with CF homozygous for the *F508del* mutation in the *CFTR* gene have more severe CF-related disease.

VX-661, termed a "corrector" of CFTR protein function in CF patients with the *F508del* mutation in the *CFTR* gene, is proposed to work by promoting the proper folding of the F508del-CFTR protein during its translation and processing in the endoplasmic reticulum, allowing it to exit the endoplasmic reticulum and traffic to the cell surface,. This is similar to lumacaftor, which received Breakthrough designation in combination with ivacaftor for the same proposed patient population.

Ivacaftor (tradename Kalydeco), classified as a CFTR potentiator, was approved on January 31, 2012, for the treatment of CF in patients age 6 years and older who have a G551D in the CFTR gene. It works by increasing chloride transport in CFTR protein already present at the cell surface.

Clinical studies have demonstrated that neither ivacaftor nor lumacaftor alone have a beneficial effect in patients with CF homozygous for the *F508del* mutation. Vertex has submitted preliminary clinical evidence to suggest that VX-661 in combination with ivacaftor has potential for efficacy in patients with CF homozygous for the *F508de*l mutation in *CFTR*, presumably by allowing the misfolded CFTR protein to reach the cell surface, and subsequently increase its chloride transport activity.

The Sponsor, Vertex Pharmaceuticals, has requested breakthrough therapy designation for VX-661 in combination with ivacaftor, under Section 902 of the Food and Drug Administration Safety and Innovation Act in order to expedite development of VX-661 for the treatment of CF. (No clinical evidence has been presented that might suggest VX-661 as a monotherapy has the potential to be a beneficial therapy in CF patients). Based on the preliminary demonstration of clinical efficacy outlined above for the combination of VX-661with the CFTR potentiator, ivacaftor, in CF patients homozygous for the *F508del* mutation, DPARP believes that clinical evidence exists that VX-661 in combination with ivacaftor has the potential for efficacy, and would represent a substantial improvement over existing CF therapies for patients homozygous for the *F508del* mutation in the CFTR. As a result, DPARP believes the VX-661/ivacaftor combination should be designated a breakthrough therapy.

Medical Policy Council

The MPC discussed this request via virtual meeting, and the decision was made to grant designation of VX-661 in combination with ivacaftor, as a breakthrough therapy for development in cystic fibrosis patients homozygous for the *F508del-CFTR* mutation.

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/s/

KIMBERLY A WITZMANN
01/17/2014

ANTHONY G DURMOWICZ
01/17/2014

BADRUL A CHOWDHURY
01/17/2014
I concur