CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210491Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

CDTL Summary Review

Date	January 19, 2018
Authors	Anthony G. Durmowicz, M.D., CDTL
Subject	CDTL Review
NDA/BLA #	NDA 210491
Applicant	Vertex Pharmaceuticals
Date of Submission	June 28, 2017
PDUFA Goal Date	February 28, 2018
Proprietary Name **Established (USAN) names**	Symdeko tezacaftor-ivacaftor in combination
Dosage forms / Strength	Tezacaftor 100 mg/ivacaftor 150 mg tablet Ivacaftor 150 mg tablet (co-packaged)
Proposed Indication(s)	"… indicated for the treatment of cystic fibrosis in patients age 12 years and older who are homozygous for *F508del* mutation in the *CFTR* gene or with at least one *CFTR* mutation responsive to Symdeko based on in vitro assay and/or clinical data.
Recommended Regulatory Action:	Approval

1. 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 year 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 age 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. An IVA in combination with a second CFTR modulator, lumacaftor, combination product (Orkambi) was approved on July 2, 2015 for the treatment of CF patients homozygous for the *F508del* mutation but the product has limited efficacy due to significant pharmaceutical interaction between the 2 component drugs IVA and lumacaftor. For this application Vertex has combined IVA with a different CFTR modulator, TEZ, which possesses a similar mechanism of action as lumacaftor but lacks the drug-drug interaction issue IVA lumacaftor has with the hope of a better efficacy profile. 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 benefit.

2. Background

Cystic Fibrosis (CF)

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 and is an orphan drug population. 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 and lung damage. There is no cure for CF and, except for mutation-based subpopulations demonstrated to be responsive to IVA or IVA combined with lumacaftor, 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 early-mid thirties. Current therapies used by patients with CF to help manage their disease include mucolytics such as inhaled DNase, beta-agonist bronchodilators, inhaled antibiotics (tobramycin, aztreonam), and pancreatic enzyme supplements.

Ivacaftor:

IVA is a small molecule shown to increase chloride ion transport across the CFTR chloride channel in epithelial cell membranes and, as such, is classified as a "CFTR potentiator". It is currently approved in the USA as monotherapy for the treatment of CF in patients age 2 years and older who have one mutation in the *CFTR* gene that is responsive to IVA potentiation based on clinical and/or in vitro assay data (Kalydeco). It is also approved in combination with lumacaftor, another CFTR modulator that appears to work by facilitating the processing and intracellular transport of CFTR protein to the epithelial cell surface. This combination (Orkambi) is currently approved for the treatment of CF patients homozygous for the *F508del* mutation in the *CFTR* gene, a subpopulation of patients for which IVA monotherapy (Kalydeco) is not indicated.

Tezacaftor:

TEZ is another CFTR modulator similar in structure to lumacaftor that also facilitates cellular processing and intracellular transport of CFTR to increase the amount of CFTR protein delivered to the cell surface. It lacks the significant drug interaction with IVA that lumacaftor possesses and appears to have an improved safety profile compared to lumacaftor, suggesting it may have meaningful advantages when used in combination with IVA over Orkambi.

Regulatory Interactions

TEZ and the TEZ/IVA combination were developed under IND 108,105 which was opened on April 15, 2010. Fast Track, Breakthrough Therapy, and Orphan Drug designations were made on May 21, 2010, January 28, 2014, and April 24, 2014, respectively. 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.

September 9, 2013: Type C meeting

- Nonclinical findings of dilated lacteals were noted to be 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 tezacaftor-induced lacteal dilatation and its potential clinical significance in CF.

July 2, 2014: Type B meeting

- 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 or exacerbations were the preferred endpoints for determining efficacy for the TEZ/IVA combination. Other endpoints such as lung clearance index (LCI) and mucociliary clearance would be considered exploratory endpoints.

November 5, 2014: End of Phase 2 Meeting

- Based on results from study VX08-770-104 from the IVA monotherapy program 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 lumacaftor/ivacaftor arm in study 106 to obtain comparative safety data for the 2 closely related combination products.
- Vertex will need to demonstrate the ability for an in vitro test or other clinical parameters to predict whether or not 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%.

November 4, 2015: Type B meeting

- 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. FDA believes *F508/F508del* homozygotes may be the most appropriate population (Study 106).
- Vertex assumes regulatory risk by not including an IVA monotherapy arm in Study 106.

May 30, 2017: PreNDA meeting

- FDA will take a similar approach to the use of in vitro data 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. Vertex will need to carefully consider and justify how 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.

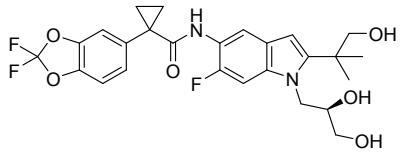
3. CMC

Symdeko is a co-packaged TEZ/IVA fixed dose combination tablet and an IVA tablet, both for oral administration. TEZ is a new molecular entity (NME with BCS class II) and IVA (BCS class II or IV) has already been approved for treatment of CF as a single active ingredient (NDAs 203188, 207925) and in combination with lumacaftor (NDA 206038).

The TEZ/IVA fixed dose combination tablet is available 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 is available 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:

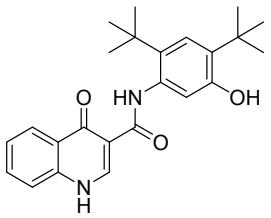
Tezacaftor
The chemical name of TEZ is 1-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-N-{1-[(2R)-2,3-dihydroxypropyl]-6-fluoro-2-(1-hydroxy-2-methylpropan-2-yl)-1Hindol-5-yl}cyclopropane-1-carboxamide. Its molecular formula is C26H27N2F3O6 and its molecular weight is 520.50. TEZ has the following structural formula:



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

Ivacaftor

The chemical name of IVA 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. IVA has the following structural formula:



IVA 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 206038 (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 TEZ 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 210491 are found to be 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. 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, both with negative findings, has been already 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.

A full nonclinical 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 studies in rats 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. The study included video capsule endoscopy examinations that were able to rule out the likelihood of lacteal dilatation/lymphangiectasis 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 genetic toxicology tests including Ames test for bacterial gene mutation, in vitro mammalian chromosome aberration, and in vivo micronucleus assays.

TEZ was also 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 although, like lumacaftor, in academic and drug development circles it has been 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. As a result, similar to lumacaftor, TEZ will be marketed without an EPC.

5. Clinical Pharmacology/Biopharmaceutics

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.

Drug-Drug Interaction

TEZ and IVA are substrates of CYP3A. As a result, 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 such as rifampin, phenobarbital, and St. John's Wort is not recommended.

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. As a result, 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 labelling.

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.

In Vitro Assay Assessment

Similar to 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. As a result, 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 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 set previously that would reasonably be expected to predict clinical benefit. Because the assay has been modified, concern arose that the 10% cut-off value may no longer be supportable. 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 *508del* 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 similar to 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) as a way to fully inform CF health

care providers as to how to interpret the in vitro data. In addition, consideration should be given to adding such a statement as a "Limitation of Use" to the Highlights and Indication sections of the Symdeko label.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

The key clinical studies submitted to support safety and efficacy of the TEZ/IVA FDC for the treatment of CF in patients age 12 years and older who are either homozygous for the *F508del* mutation in the *CFTR* or who have at least one mutation in the *CFTR* that is responsive to TEZ/IVA, based on in vitro data and/or clinical evidence are shown in Table 1 below. The design and conduct of these studies are briefly described below, followed by efficacy and safety findings and conclusions.

Table 1: Studies Relevant to the TEZ/IVA Program

Study/ Years conducted	Study Type	Study Duration	CF Mutation	Pt age (yr)	Endpoints	Treatment groups	N	Countries
Dose-ranging and Proof of Concept								
Study 101 Years: 2/2012-3/2014	Dose-ranging, PK, PD	Multiple part, each 4 week Rxment periods	Homo or heterozygous for *F508del*	≥ 18	- Safety - Δ sweat Cl - Δ ppFEV1 - Δ CFQ-R	- TEZ 10 mg, 30 mg, 100mg, 150 Qd -TEZ 10, 30, 100 mg Qd, and 50 mg bid on background of IVA 150 bid -TEZ 100 mg qD + IVA 50 mg bid -Placebo	194 total	North America (USA)
Phase 3 and Supportive Studies								
Study 106 Years: 1/2015-1/2017	Safety and Efficacy	24 weeks	*F508del/ F508del*	≥ 12	- Absolute Δ ppFEV1 -Relative Δ ppFEV1 -pulmonary exacerbation - Δ BMI - Δ CFQ-R	-TEZ 100/IVA 150 qam + IVA 150 qpm -Placebo bid	510	North America, EU
Study 107 Years: 8/2015-6/2016	Safety and Efficacy	12 weeks	*F508del/ NR**	≥ 12	- Absolute Δ ppFEV1 - Δ CFQ-R -pulmonary exacerbation - Δ BMI - Absolute Δ ppFEV1 (avg wks 4 & 8) - Absolute Δ CFQ-R (avg wks 4 & 8)	-TEZ 100/IVA 150 qam + IVA 150 qpm -Placebo bid	168	North America, EU, Israel, Australia
Study 108 Years: 3/2015-2/2017	Safety and Efficacy	16 weeks	*F508/ F508*	≥ 12	≥ 40%	VX-770 150 mg Placebo	112 28	North America, EU, Israel, Australia
Study 110 Years: 8/2015-Ongoing	Safety OLE	Up to 96 weeks	All eligible	≥ 12	≥ 40%	TEZ 100/IVA 150 qam + IVA 150 qpm (open label)	870	North America, EU, Israel, Australia

*NR=CFTR mutation predicted to be nonresponsive to TEZ/IVA therapy
bid=twice daily, BMI=body mass index, CF=cystic fibrosis, CFTR=cystic fibrosis transmembrane conductance regulator, CFQ-R=cystic fibrosis questionnaire-revised (respiratory domain), IVA=ivacaftor, OLE=open label extension, PK=pharmacokinetic, PD=pharmacodynamic, ppFEV=percent predicted forced expiratory volume in 1 second, qam=every morning, Qd=daily, qpm=every evening

Tezacaftor/Ivacaftor Dose-ranging

Study 101 formed the primary basis for dose selection for the TEZ/IVA combination product program. Because of the lack of any drug-drug interactions between TEZ and IVA which had been an issue with the lumacaftor/ivacaftor (Orkambi) program, the approved 150 mg twice daily dose of IVA served as a background on top of which varying doses of TEZ were assessed.

Study 101

Study 101 was a randomized, double-blind placebo-controlled, multi-cohort study that evaluated multiple doses of TEZ (10, 30, 100, and 150 mg) once daily alone and in

combination with the approved dose of 150 mg of IVA administered twice daily. CF patients homozygous for the *F508del* mutation (those likely to be least responsive) were the primary study population. Patients heterozygous for *F508del* with a *G551D* mutation as the other allele (those most likely to be responsive) were also evaluated at the TEZ 100 mg qd/IVA 150 mg q12h dose combination.

One hundred four CF patients homozygous for *F508del* were evaluated over a 28-day treatment period (Table 2). Increases in ppFEV1 were observed with increasing TEZ exposure but were not dose-dependent. However, in combination with IVA 150 mg q12h, a dose-dependent increase in mean ppFEV1 change from baseline was observed with TEZ doses ranging from 10 mg to 150 mg qd. At all TEZ doses above 10 mg, TEZ/IVA had a greater mean treatment effect than TEZ alone. The group that received TEZ 100 mg qd/IVA 150 mg q12h showed the greatest mean improvement in ppFEV1 compared to placebo (4.8 percentage points difference, 95% CI (1.20, 8.39). No additional benefit was observed at the higher TEZ dose of 150 mg qd.

For sweat chloride on Day 28, a reduction 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 suggested an exposure-response relationship for change in sweat chloride as a function of TEZ exposure at a fixed IVA dose of 150 mg q12h and estimated TEZ 100 mg qd/IVA 150 mg q12 to be near the maximum achievable response.

Table 2. Absolute Change in ppFEV1 at Day 28 in *F508del/F508del* Patients (Study 101)

	TEZ 10mg qd	**TEZ 30mg qd**	**TEZ 100mg qd**	**TEZ 150mg qd**
TEZ Monotherapy Δ ppFEV1 (95% CI)	N=8 3.26 (-0.79, 7.32)	N=8 0.19 (-3.70, 4.08)	N=8 1.55 (-.34, 5.45)	N=9 2.34 (-1.33, 6.01)
Difference vs Placebo (95% CI)	3.62 (-1.03, 8.28	0.55 (-3.96, 5.06)	1.91 (-2.61, 6.42)	2.70 -1.62, 7.01
TEZ + IVA 150mg q12h Δ ppFEV1 (95% CI)	N=18 1.99 (-0.65, 4.63)	N=19 3.02 (0.40, 5.63)	N=17 4.44 (1.66, 7.23)	N=17 4.13 (1.41, 6.86)
Difference vs Placebo (95% CI)	2.35 (-1.14, 5.83)	3.37 (-0.10, 6.84)	4.80 (1.20, 8.39)	4.49 (0.94, 8.04)

For the *F508del/G551D* patients, TEZ 100 mg qd/IVA 150 mg q12h resulted in decreases in mean sweat chloride of -7.02 mmol/L with a treatment difference of -17.2 mmol/L compared to placebo that was statistically significant. The TEZ/IVA treatment group also had increases in mean ppFEV1 of 4.60% within-group that was statistically significant and a treatment difference of 3.20% compared to placebo that was not significant.

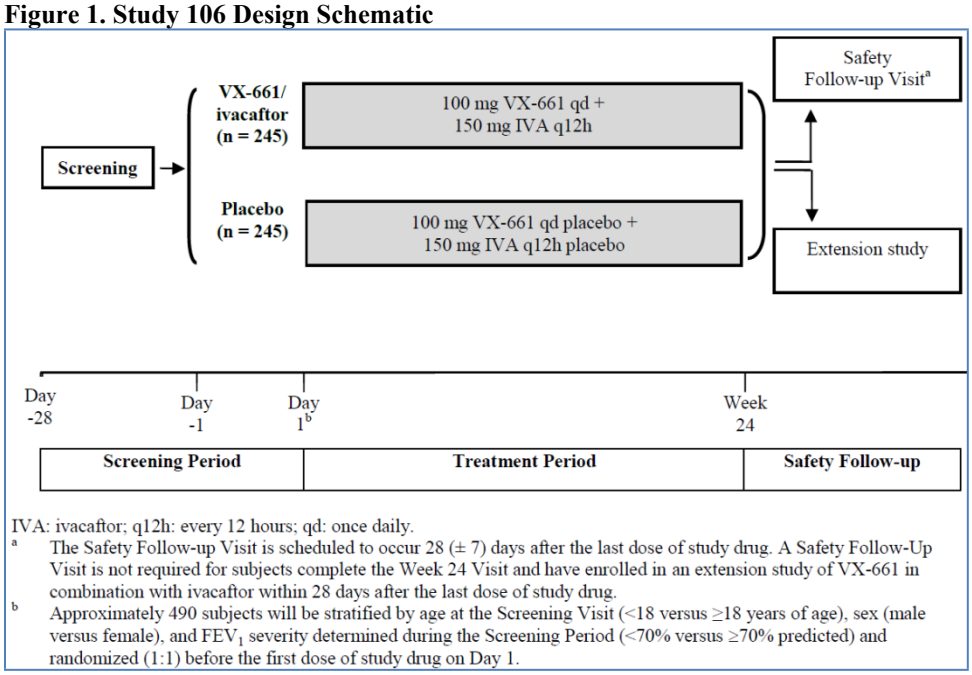
Overall, the data suggest the dose of TEZ 100mg qd is at the top of the FEV1 dose response curve and support the contribution of TEZ to the combination.

Tezacaftor/Ivacaftor Phase 3 Program
Studies 106, 107, and 108

Study 106

Study 106 was a Phase 3, 24-week randomized, double-blind, placebo-controlled study parallel-group study conducted to assess the efficacy and safety of TEZ 100 mg qd/IVA 150 mg q12h in CF patients ≥12 years of age homozygous for the *F508del* mutation in the *CFTR* gene. After a 4-week screening period patients entered the 24-week treatment period followed by a 4-week follow-up period (Figure 1). Approximately 504 patients were randomized 1:1 to one of the 2 treatment groups: 248 to TEZ/IVA and 256 to placebo. Patients were also stratified by age (<18 versus ≥18 years of age), sex, and FEV1 severity (<70% versus ≥70% predicted). Patients who complete the Week 24 Visit will be offered the opportunity to enroll in an extension study, if they meet the eligibility criteria for the extension study.

Figure 1. Study 106 Design Schematic



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.

Pertinent inclusion criteria included screening FEV1 ≥ 40% and ≤ 90% of predicted normal for age, sex, and height and a sweat chloride value ≥ 60 mmol/L. Patients with major comorbidities, abnormal liver function as determined by LFT's,, an acute pulmonary infection, history of cataracts or lens opacities, abnormal QTc on ECG, and those whose respiratory system was colonized with Burkholderia cenocepacia, Burkholderia dolosa, or Mycobacterium abscessus were excluded. Use of medications and foods metabolized by CYP3A4 were prohibited.

The primary efficacy endpoint was the absolute change in percent predicted FEV1 from study baseline through week 24.

Key secondary endpoints included relative change in ppFEV1 from baseline through week 24, number of pulmonary exacerbations through week 24, absolute change in BMI at week 24, and absolute change in CFQ-R respiratory domain score from baseline through week 24.

Absolute change in sweat chloride through week 24 was also a secondary endpoint.

Results

For the patients randomized, the mean age was 26.3 years (range 12-64 years), 49% were female, and 99% Caucasian. The mean ppFEV1 at baseline was 60% (range 28-96%).

For the primary endpoint, treatment with TEZ 100 mg qd/IVA 150 mg q12h compared to placebo resulted in significant improvement in % predicted FEV1 [treatment difference of 4.0%; 95% CI (3.1, 4.8)] from study baseline through week-24 (Table 3). Results were consistent regardless of age, sex, baseline ppFEV1, or colonization with Pseudomonas.

Table 3: Effect of TEZ/IVA for Efficacy Variables in *F508del/F508del* CF Patients (Study 106)

Absolute Δ in % Predicted FE V_1 (Primary endpoint)	Relative Δ in % Predicted FEV_1	Number of Pulmonary exacerbations through week 24 (rate ratio)	Absolute Δ in BMI at week 24 (kg/m^2)	Absolute Δ in CFQ-R Respiratory Domain Score through week 24 (Points)*
(n=248 for TEZ/IVA and n=256 for PBO) Results shown as difference in mean (95% CI) change from baseline for TEZ/IVA vs. placebo-treated patients:				
4.0 (3.1, 4.8)	6.8 (5.3, 8.3)	0.65 (0.48, 0.88)	0.06 (-0.08, 0.19)	5.1 (3.2, 7.0)

*not statistically significant based on statistical analysis hierarchy

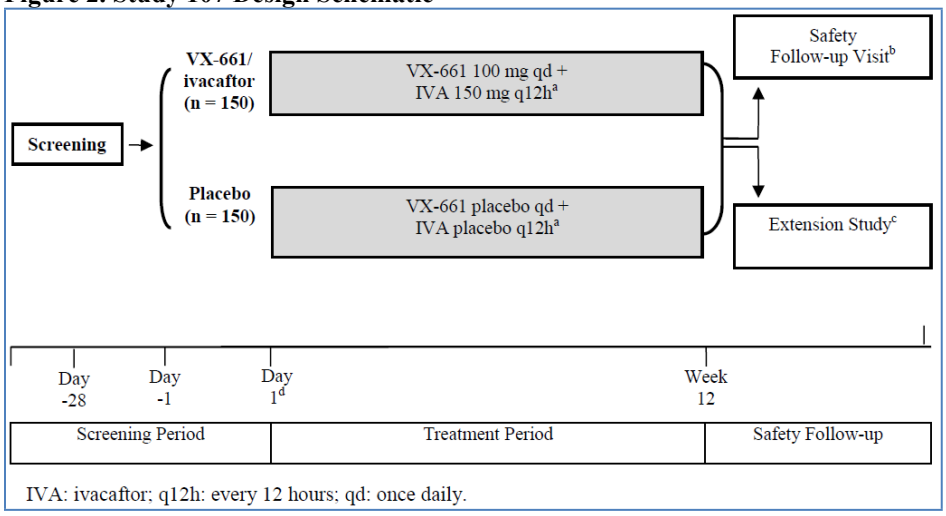
Changes for key secondary endpoints relative change in ppFEV1 from baseline through week 24 and number of pulmonary exacerbations through week 24 were also significant while change in BMI at week 24 was not significant. While the change in CFQ-R respiratory domain score was nominally positive, it was not statistically significant based on earlier failure for the BMI endpoint earlier 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).

Study 107

Study 107 was a Phase 3, 12-week randomized, double-blind, placebo-controlled study parallel-group study conducted to assess the efficacy and safety of TEZ 100 mg qd/IVA 150 mg q12h in CF patients ≥12 years of age heterozygous for the *F508del* mutation with a second mutation predicted to be non-responsive to TEZ/IVA therapy (*F508del/NR*). Three factors were taken 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 in the FRT cell Ussing Chamber assay).

With the exception of a 12-week rather than 24-week treatment period, the design of Study 107 was the same as Study 106. The study schematic is shown below.

Figure 2. Study 107 Design Schematic



The primary endpoint was absolute change in ppFEV1 from baseline through week 12. 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.

Results

A total of 168 patients were randomized 1:1 to receive either TEZ/IVA (83 patients) or placebo (85 patients). For the patients randomized, the mean age was 26 years (range 13-52 years), 92% Caucasian, and 48% female. The mean ppFEV1 at baseline was 58% (range 31-97%).

The study was terminated prematurely based on an interim futility analysis (Table 4).

Table 4. Effect of TEZ/IVA for Efficacy Variables in CF Patients Predicted to be Non-responsive to TEZ/IVA Therapy (Study 107)

Absolute Δ in ppFEV1 through week 12 (Primary endpoint)	Absolute Δ in CFQ-R Respiratory Domain Score through week 12 (points)	Number of Pulmonary exacerbations through week 12 (rate ratio)	Absolute Δ in BMI at week 12 (kg/m^2)
(n=83 for TEZ/IVA and n=85 for PBO) Results shown as difference in mean (95% CI) change from baseline for TEZ/IVA vs. placebo-treated patients:			
1.2 (-0.3, 2.6)	2.1 (-1.2, 5.4)	0.98 (0.55, 1.76)	-0.08 (-0.27, 0.11)

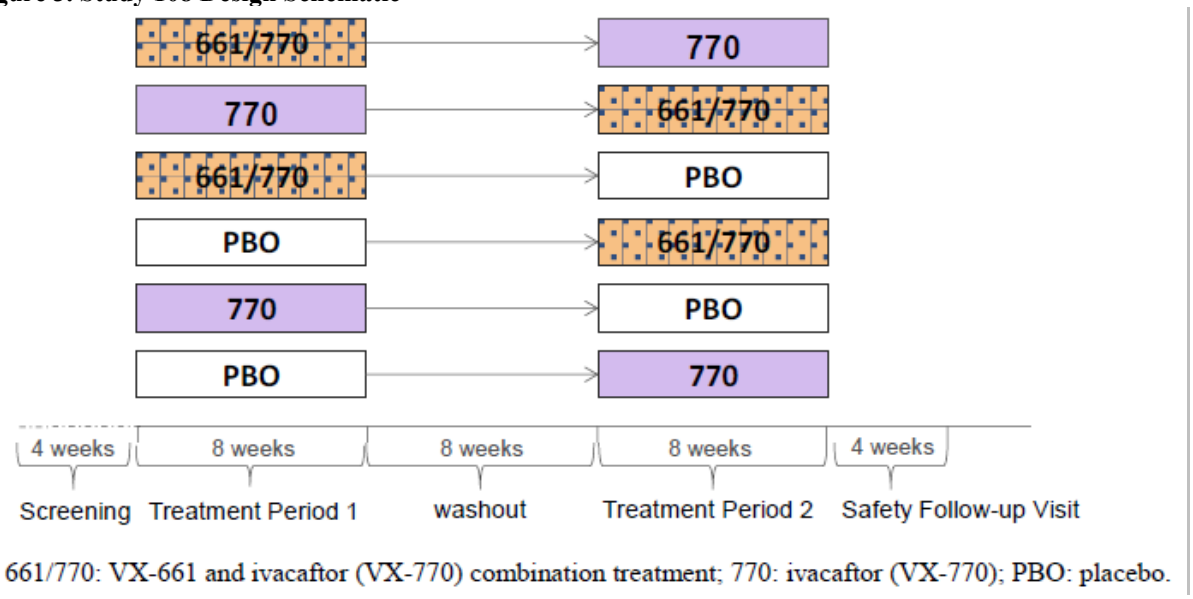
Change in sweat chloride was -3.5 mmol/L compared to placebo.

Study 108

Study 108 was a phase 3, randomized, double-blind, placebo-controlled, 2-period, 3-treatment, incomplete block, crossover, multicenter study. The study enrolled 246 CF patients 12 years of age and older who were heterozygous for the *F508del* mutation who also had a second allele with a *CFTR* mutation predicted to be responsive to TEZ/IVA based on clinical phenotype (population based incidence of pancreatic sufficiency > 50%), biomarker data (average sweat chloride <86 mmol/L, or in vitro responsiveness to IVA.

After a 4-week screening period patients enter an 8-week treatment period (Period 1) followed by an 8-week washout period then another 8-week treatment period (Period 2). Approximately 34 patients were randomized (1:1:1:1:1:1) to one of the 6 treatment sequences (Figure 3). Patients were also stratified by age (<18 versus ≥18 years of age), FEV1 severity (<70% versus ≥70% predicted), and type of mutation on the second *CFTR* allele (non-canonical splice mutation versus missense mutation. Patients who complete the Week 24 Visit were offered the opportunity to enroll in an extension study, if they met the eligibility criteria.

Figure 3. Study 108 Design Schematic*



661/770: VX-661 and ivacaftor (VX-770) combination treatment; 770: ivacaftor (VX-770); PBO: placebo.

*661=Tezacaftor, 770=Ivacaftor, 661/770=TEZ/IVA combination, PBO=Placebo

Pertinent inclusion criteria included screening FEV1 ≥ 40% and ≤ 90% of predicted normal for age, sex, and height and either a sweat chloride value ≥ 60 mmol/L or, if the sweat chloride value is < 60 mmol/L, there must be documented evidence of chronic sinopulmonary disease. Patients with major comorbidities, abnormal liver or kidney function, an acute pulmonary infection, history of cataracts or lens opacities, abnormal QTc on ECG, and those whose respiratory system was colonized with Burkholderia cenocepacia, Burkholderia dolosa, or Mycobacterium abscessus were excluded.

For subjects who are on a stable regimen of inhaled cycling antibiotics, the Treatment Period 1 Day 1 Visit was timed to occur at the end of an off-cycle. The first dose of study drug (TEZ 100 mg once daily/IVA 150 mg twice daily, IVA 150 mg twice daily alone, or matching placebos, was administered on Treatment Period 1 Day 1.

The use of medications or foods known to be CYP 3A4 inducers and inhibitors was prohibited.

The primary efficacy endpoint was the absolute change in percent predicted FEV1 from study baseline to the average of the Week 4 and Week 8 measurements in each treatment period.

Absolute change in the CFQ-R respiratory domain score from study baseline to the average of the Week 4 and Week 8 measurements in each treatment period was a key secondary endpoint.

Results

Of the 244 patients included in the study who were randomized and received a dose of study medication, 146 patients had a splice mutation and 98 patients had a missense mutation, as the second allele. One hundred fifty-six patients received IVA, 161 patients received TEZ/IVA, and 161 patients received placebo. Patients' mean age was 35 years (range 12-72 years), 55% were female, and 98% Caucasian. The mean FEV1 at study baseline was 62% predicted (range 35 to 94).

For the overall population, treatment with TEZ/IVA compared to placebo resulted in significant improvement in % predicted FEV_1 [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)] (Table 5).

Table 5. Primary and Key Secondary Efficacy Analyses (Study 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)
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.

For the purpose of this supplement, evaluating the efficacy for the splice and missense subpopulations was also relevant. Statistically significant improvements compared to placebo were observed in the subgroups of patients with splice and missense mutations (Table 6).

Given the small size of the subgroups, statistical significance within individual mutations would not be expected but for transparency and to help corroborate in vitro findings for individual mutations, efficacy data, for the most part positive, with minimum and maximum values are also included in Table 6. Both Table 6 and the individual mutation results for in vitro findings should be presented in labelling.

Table 6. Effect of TEZ/IVA for Efficacy Variables in Splice and Missense *CFTR* Mutation Subgroups (Study 108)			
Mutation (n)	**Absolute Change in percent predicted FEV_1 [*†]**	**Absolute Change in CFQ-R Respiratory Domain Score (Points) [*‡]**	**Absolute Change in Sweat Chloride (mmol/L) [*‡]**
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 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 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.

Summary of Efficacy

In this application, the TEZ/IVA combination has demonstrated efficacy for both CF patients homozygous for the *F508del* mutation (study 106), those who have missense mutations predicted to be responsive to CFTR modulators (study 108), and those with certain non-canonical splice mutations for which clinical data were available (study 108). TEZ/IVA did not establish efficacy for mutations predicted to be non-responsive to CFTR modulators (study 107).

It is not surprising that TEZ/IVA was efficacious for the missense and splice mutations since IVA alone has demonstrated efficacy in those subpopulations, however for these mutation groups, clinical data demonstrated that the TEZ/IVA combination was superior to IVA alone. While there was no IVA monotherapy in study 106, an admittedly not optimal cross-study comparison suggests that the TEZ/IVA combination is no worse, and possibly better than the related, marketed lumacaftor/ivacaftor combination, Orkambi.

As was done in 2017 for Kalydeco, in vitro data were included in the application to support its use in determining whether certain, possibly more rare *CFTR* mutation would likely be responsive to TEZ/IVA. While this information will be included in the Symdeko label, it is important to be aware that the in vitro assay methodology for the TEZ/IVA program is

different than the assay used for the Kalydeco program so cross label (Kalydeco vs Symdeko) comparisons of in vitro findings are invalid. Equally important information that will be spelled out in labelling is that for the TEZ/IVA program, in vitro data alone are unable to determine whether treatment with the TEZ/IVA combination, Symdeko, offers any additional benefit over IVA monotherapy, Kalydeco, alone. Clinical data are required to make this determination.

8. Safety

Safety Database

The overall safety profile of TEZ/IVA is based primarily on pooled data from three double blind, placebo controlled, Phase 3 clinical trials; 2 parallel-group trials of 12 and 24-week duration and one cross-over design trial of 8 weeks duration in which 496 CF patients ≥12 years of age received at least one dose of TEZ 100 mg qd/IVA 150 mg q12h and 505 received placebo. Eligible patients were also able to participate in an open label extension safety study (up to 96 weeks of TEZ/IVA). Demographics and baseline characteristics were very similar between active drug and placebo treatment groups. Approximately 50% of patients were female, mean age was approximately 29 years and, as expected, the patient population was overwhelmingly Caucasian (97%). Pediatric patients (12 to <18 years) accounted for 20% of the study population. Approximately 60% of the population was from Europe and 40% from North America.

Deaths, Serious Adverse Events, and Discontinuations due to Adverse Events

There were no deaths reported in the TEZ/IVA placebo-controlled development program, however, one death due to respiratory failure and influenza infection occurring in the open label extension study was reported in the 120-day safety update.

Consistent with the disease, most serious adverse events (SAEs) were related to pulmonary exacerbations of CF, which occurred in approximately 7% of patients who received TEZ/IVA therapy and 10% of patients who received placebo.

Other SAEs occurred infrequently (≤1% in any group). The only SAE that was greater in the TEZ/IVA group compared to placebo, whether considered drug-related or not by investigators, was distal intestinal obstruction syndrome (1% TEZ/IVA vs 0% placebo; 3 vs 0 patients).

There were 18 CF patients (approximately 2%) who discontinued treatment due to an adverse event during the placebo-controlled studies. The number of patients who had adverse events leading to treatment discontinuation was very similar between the TEZ/IVA and placebo treatment groups (1.6% vs 2.0%, respectively).

Liver and other safety concerns

Given the Warning and Precaution regarding liver-related adverse reactions in the IVA (Kalydeco) monotherapy label, monitoring of liver function was a focus of the TEZ/IVA safety monitoring plan.

<u>Liver-related adverse events</u>

The number of patients with liver-related adverse events was very similar between the placebo (3.6%) and TEZ/IVA (3.4%) groups. The percentage of subjects with other AEs in the hepatobiliary SOC was also similar between the placebo (0.8%) and TEZ/IVA (0.4%) groups. There were no SAEs in the hepatobiliary SOC.

Transaminase elevations

There were no clinically meaningful differences in transaminases or other liver-related laboratory assessments between treatment groups in the pooled Phase 3 placebo-controlled studies. The incidence of maximum transaminase (ALT or AST) >8, >5, or >3 x the upper limit of normal (ULN) between TEZ/IVA treated patients and placebo treated patients was 0.2%, 1.0%, and 3.4%, respectively, in TEZ/IVA treated patients compared to 0.4%, 1.0%, and 3.4%, respectively, in placebo treated patients. One patient (0.2%) on TEZ/IVA and 2 patients (0.4%) on placebo permanently discontinued treatment for elevated transaminases. No TEZ/IVA treated patients experienced a transaminase elevation >3 x ULN associated with elevated total bilirubin >2 x ULN (met Hy's Law criteria). There were no elevated transaminase events that were considered SAEs.

Given the known association of IVA to cataracts demonstrated in a juvenile animal nonclinical study conducted for the Kalydeco program, ophthalmologic assessments were performed on patients enrolled in study 106 (the large, longer, 24-week study) to assess for the development of eye opacities. These patients had ophthalmologic exams at baseline (screening) and at week 24. A total of 435 subjects had ophthalmologic examinations at baseline and during or after the 24 week treatment period. The background incidence of subjects with cataracts by treatment group was 15 (6.0%) in the TEZ/IVA group and 11 (4.3%) in the placebo group. Over the course of the study, the incidences of treatment emergent cataracts were essentially the same (0.4%) for both the TEZ/IVA and placebo treated groups. There were no SAEs of cataracts.

Common Adverse Events

Common adverse events are listed in Table 10 below. Most AEs were reflective of what would be expected in the general population and showed little difference between placebo and active treatment with TEZ/IVA.

Table 10: Incidence of Adverse Drug Reactions from the 12 and 24-Week Parallel Group Trials (106, 107) that Occurred in ≥3% of TEZ/IVA-Treated Patients and Greater than Placebo

Adverse Reactions (Preferred Term)	TEZ/IVA N=334 N (%)	Placebo N=343 N (%)
Headache	49 (15)	44 (13)
Nausea	29 (9)	24 (7)
Sinus congestion	13 (4)	6 (2)
Dizziness	13 (4)	8 (3)

The safety profile of TEZ/IVA was similar across age, sex, baseline percent predicted FEV1 (ppFEV1), and geographic region subgroups.

Summary of Safety

The safety database for the TEZ/IVA program is based on pooled data from three double blind, placebo controlled, Phase 3 clinical trials; 2 parallel-group trials of 12 and 24-week duration

and one cross-over design trial of 8 weeks duration in which 496 CF patients ≥12 years of age received the proposed dose of TEZ 100 mg qd/IVA 150 mg q12h. Safety data obtained from both the approved IVA (Kalydeco) monotherapy program and post-marketing data are supportive. For the most part, the nature of the adverse events identified for TEZ/IVA are generally consistent with the types of events commonly observed in patients with CF and differed little from those observed for the Kalydeco program. Given the Warning and Precaution on negative effects on liver function included in the IVA (Kalydeco) monotherapy label, while the TEZ/IVA liver safety data are reassuring, the potential for liver toxicity should still be considered real. Additionally, since TEZ/IVA contains IVA, the known association of IVA to cataracts shown in nonclinical studies conducted in the Kalydeco program applies and ophthalmologic monitoring will also be needed for pediatric patients who receive TEZ/IVA. However, given the seriousness of the disease and the demonstrated efficacy, the relatively low incidence of liver-related side effects and the, to date, unproven link of the nonclinical finding of cataracts to humans, the safety profile of TEZ/IVA is acceptable.

9. Advisory Committee Meeting

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. Pediatrics

CF is an orphan disease and not subject to PREA. (b) (4)

11. Other Relevant Regulatory Issues

- Financial Disclosure: Vertex submitted the FDA 3454 financial interest forms, in accordance with 21CFR part 54. From the list of 2198 investigators submitted, for the pivotal studies (106, 107, and 108) , 39 had disclosable financial interests/arrangements; 2 received compensation for conducting the study and 37 received all received “significant payment of other sorts". Given the large number of investigators/study sites spread the 3 studies, it would be highly unlikely that results from these investigators sires would impact the positive results seen in studies 106 and 108 or the negative results in study 107.
- DSI audits information: Audits were conducted at the Claire Keating, M.D., Emily DiMango, M.D., and James Wallace, M.D. clinical sites for this NDA submission as well as the Vertex establishment, Boston, MA. No substantial issues that would negatively impact data integrity were identified.
- Other: There are no outstanding issues with consults received from the OPDP, DMEPA, OSE or other groups in CDER. The CDRH was consulted during previous IVA reviews to help address the adequacy of available tests for identification of

specific CF gene mutation identification. CDRH noted that there are several FDA-cleared diagnostic tests available that can detect the *F508del* mutation, the most common in the *CFTR* gene, and other relevant mutations.

12. Labeling

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 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). Inclusion of a "Limitation of Use" statement in labelling noting that in vitro data alone are unable to determine whether TEZ/IVA (Symdeko) conveys additional clinical benefit over IVA monotherapy (Kalydeco) is being considered. The final labeling, specifically, data presentation and language in the Clinical Pharmacology (section 12.1), particularly the presentation and format of the in vitro data, and Clinical Studies (section 14) are still being discussed at the time of this review.

13. Regulatory Action/Risk Benefit Assessment

- Regulatory Action

The regulatory action for this NDA is for Approval.

- Risk Benefit Assessment

The potential benefits of TEZ/IVA in CF patients for the indicated population of patients with CF are substantial and outweigh any potential safety concerns.

1. Postmarketing Risk Management Activities

None

2. Oher Postmarketing Study Commitments

None

3. Comments to Applicant

None

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

/s/

ANTHONY G DURMOWICZ
01/19/2018