

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

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STATISTICAL REVIEW(S)



U.S. Department of Health and Human Services
Food and Drug Administration
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Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #: NDA 210-491

Drug Name: SYMDEKO (Tezacaftor/Ivacaftor[TEZ/IVA]) TEZ 100mg/IVA 150 mg once a day in the morning (qAM), IVA 150 mg once a day in the evening (qPM)

Indication(s): Treatment of cystic fibrosis (CF) patients ≥ 12 years homozygous for F508del mutation or with at least one cystic fibrosis transmembrane conductance regulator (CFTR) mutation responsive to TEZ/IVA based on in vitro data and/or clinical evidence

Applicant: Vertex Pharmaceuticals Incorporated

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Keywords: combination therapy, double-blind, mixed models, repeated measures, MMRM, ANCOVA & subgroup analyses

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1 EXECUTIVE SUMMARY

This review considers the combination of daily doses of tezacaftor (TEZ) 100 mg and ivacaftor (IVA) 300 mg (morning dose of 1 fixed-dose combination [FDC] tablet of TEZ 100 mg and IVA 150 mg; evening dose of 1 tablet of IVA 150 mg) for treatment of patients with cystic fibrosis (CF) aged 12 years and older who are homozygous for the F508del mutation or who have at least 1 mutation in the cystic fibrosis transmembrane regulator (CFTR) gene that is responsive to TEZ/IVA based on in vitro data and/or clinical evidence. We focus in this review on three phase 3 studies. The first phase 3 study (Study 106) was a randomized, double-blind, placebo-controlled, parallel-group, multicenter study with a 24-week treatment period in subjects with CF who are homozygous for the F508del-CFTR mutation (F/F genotype). The second phase 3 study (Study 108) was a randomized, double-blind, placebo-controlled, 2-period, 3-treatment, cross-over, multicenter study with an 8-week treatment period and 8-week wash-out period in subjects with CF who are heterozygous for the F508del-CFTR mutation, and have a second allele with a CFTR mutation predicted to have residual function (F/RF genotype). Monotherapy of IVA 300 mg per day was also evaluated in the second study. The third phase 3 study (Study 107) was a phase 3, randomized, double-blind, placebo-controlled, parallel-group, multicenter study in subjects with CF who are heterozygous for the F508del-CFTR mutation and with a second CFTR mutation that is not likely to respond to TEZ and/or IVA therapy (F/MF genotype).

There was statistical evidence of benefit for the combination therapy of TEZ/IVA with respect to the primary endpoint, change from baseline in percent predicted forced expiratory volume in 1 second (ppFEV₁) over the treatment period in Studies 106 and 108. In Study 106, treatment with TEZ/IVA provided 4.0 percentage points (95% confidence interval [CI]: 3.1, 4.8) mean improvement over placebo in absolute change from baseline in ppFEV₁ through week 24. In Study 108, treatment with TEZ/IVA provided 6.8 percentage points (CI: 5.7, 7.8) mean improvement over placebo and 2.1 percentage points (CI: 1.2, 2.9) mean improvement over IVA in absolute change from baseline in ppFEV₁ to the average of week 4 and week 8 measurements. Treatment with IVA provided 4.7 percentage points (CI: 3.7, 5.8) mean improvement over placebo in absolute change from baseline in ppFEV₁ to the average of week 4 and week 8 measurements.

Estimated treatment effects for TEZ/IVA were consistent across subgroups of interest, including sex, age, geographic region, baseline ppFEV₁, use of common CF medications, and *P. aeruginosa* infection status subgroups in both populations of F/F and F/RF. In Study 108, there were consistent treatment effects for both Class II to IV missense mutations and Class V non-canonical splice mutations.

Significant improvements were observed in Study 106 for key secondary endpoints of relative change from baseline in ppFEV₁ through week 24, and rate of pulmonary exacerbations through week 24. In Studies 106 and 108, improvements were also observed for change from baseline in the Cystic Fibrosis Questionnaire-Revised (CFQ-R) respiratory domain score.

Evaluation of the key secondary endpoint of change from baseline in body mass index (BMI) at week 24 compared to placebo in Study 106 did not show a statistically significant improvement.

Efficacy was not demonstrated in Study 107 for CFTR mutations predicted to be non-responsive to the TEZ/IVA combination.

Overall, the results of the phase 3 clinical development programs provide evidence of efficacy of TEZ/IVA in terms of the primary endpoint of ppFEV₁ and key secondary endpoint of CFQ-R respiratory domain score for both the F/F and F/RF populations, and provide evidence of contribution of TEZ to the combination therapy of TEZ/IVA. We recommend approval of this submission.

2 INTRODUCTION

2.1 Overview

2.1.1 Background

CF is a progressive, systemic, life-shortening, genetic disease that is caused by reduced quantity and/or function of the CFTR protein due to mutations in the CFTR gene. In people with CF, loss of chloride transport due to defects in the CFTR protein results in the accumulation of thick, sticky mucus in the bronchi of the lungs, loss of exocrine pancreatic function, impaired intestinal absorption, reproductive dysfunction, and elevated sweat chloride concentration. Currently, there is no cure for CF, and the median predicted age of survival is approximately 40 years of age.

The majority of CF therapies today target symptoms of the disease. CFTR modulators are small molecules that target specific defects caused by mutations in the CFTR gene and thus treat the underlying cause of the disease. Kalydeco (ivacaftor) and Orkambi (lumacaftor/ivacaftor) (LUM/IVA) are the only approved CFTR modulators and are indicated for CF patients with specific mutations.

Both TEZ and IVA are small molecules. TEZ is a modulator; it increases the amount of CFTR protein at the cell surface, resulting in increased chloride transport. The CFTR protein delivered to the cell surface by TEZ then is potentiated by IVA to further increase chloride transport.

This review considers the combination of daily doses of TEZ 100 mg and IVA 300 mg (morning dose of 1 fixed-dose combination tablet of 100 mg TEZ and 150 mg IVA; evening dose of 1 tablet of IVA 150 mg) for treatment of patients with CF 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 TEZ/IVA based on in vitro data and/or clinical evidence.

2.1.2 History of Drug Development

During IND 108105 development, advice regarding the study design and endpoints of the phase 3 trials were given to the applicant. Advice and comments from the Division were delivered through one end-of-phase 2 meeting, a CMC meeting, written responses and a pre-NDA meeting.

Table 1 summarizes these interactions.

Table 1: List of Key Correspondences and Meeting Minutes

Document	Meeting Date/ Document Date	Topic
Type C Meeting Written Response	26 June 2013/ 9 Sept 2013	Toxicology findings and path forward
Type B Meeting Minutes	2 July 2014	Nonclinical and clinical pharmacology assessments
EOP2 Meeting Minutes	5 Nov 2014/	Phase 3 clinical development plan
CMC EOP2 Meeting Minutes	30 July 2015	Discuss VX-661 drug substance control strategy
Type B Meeting Minutes	4 Nov 2015	Discuss proposed assessment of each individual component of the combination regimen
CMC Type B Meeting Minutes	14 Sept 2016	Agency feedback on Continuous Process Verification
Pre-NDA Meeting Minutes	30 May 2017	Discuss clinical data to support a NDA submission
CMC Pre-NDA Meeting Minutes	16 May 2017	Discuss refinements, the resulting control strategies, and implementation of process control and real-time release testing

Source: Reviewer

During the Type B meeting in 2014, phase 3 study endpoints, duration, and demonstration of the efficacy of the components of the combination drug were discussed. The applicant requested guidance regarding how novel endpoints of (b) (4) might be used in their development programs; FDA reiterated that these proposed surrogate endpoints would require qualification to demonstrate they are predictive of a clinically meaningful beneficial effect and that FEV₁ is a well-established surrogate which is commonly used as the basis of full drug approval. In terms of study duration, FDA thought that treatment of 12 weeks may be too short to assess other clinically meaningful endpoints such as exacerbations or weight gain/BMI. FDA suggested that the applicant conduct a randomized, controlled 3-arm trial of the TEZ/IVA combination vs the LUM/IVA combination and vs placebo for a relatively short treatment period to demonstrate efficacy of the TEZ/IVA combination against placebo on FEV₁, followed by randomizing the placebo group to one of the active treatment groups for an extended period of time to obtain additional clinical data, primarily safety, and also efficacy.

In the end-of-phase 2 meeting in 2014, FDA recommended that the applicant include an ivacaftor monotherapy arm in the study, place change in CFQ-R respiratory domain score before absolute change from baseline in BMI in the multiple testing hierarchy, and reiterated the recommendation to include a LUM/IVA arm in the study.

2.1.3 Specific Studies Reviewed

The applicant has submitted the results of two phase 2 studies (Studies 101 and 103) and four phase 3 studies (Studies 106, 107, 108 and an interim analysis of the ongoing open-label extension Study 110). Patients in Study 106 have F/F mutation; patients in Study 107 have F/MF mutation; patients in Study 108 have F/RF mutation; patients in Study 101 have F/F mutation; and patients in Study 103 have F/F mutation.

This review focuses on three placebo-controlled phase 3 clinical trials, Study 106, Study 107 and Study 108. The studies included in the submission are described in Table 2.

Table 2: List of Key Phase 2 and Phase 3 Studies in the Clinical Development Program

Study	Mutations	Study Phase	Treatment Period	# of Randomized Subjects per Arm	Study Objectives
Study 101	F/F and F/G551D	2	28 days	Total 190 subjects with various groups	PK, PD, efficacy and safety of TEZ and TEZ/IVA
Study 103	F/F	2	Part 1: 12 weeks Part 2 (OLE): 40 weeks	Total 39 subjects in part 1; and 27 subjects in part 2.	safety, efficacy and PK
Study 106	F/F	3	24 weeks	TEZ/IVA: 248 Placebo: 256	Efficacy and safety
Study 107	F/MF	3	12 weeks	Total 168 subjects with CF and aged 12 years and older.	Efficacy and safety
Study 108	F/RF	3	Two 8-week	TEZ/IVA period 1: 83; period 2: 78 IVA period 1: 81; period 2: 75; Placebo: period 1: 80; Period 2: 81	Efficacy and safety
Study 109	F/gating	3 (ongoing)			Efficacy and safety
Study 110	Rollover study of studies 106, 107, 108, 109, and 103	3 (ongoing)	96 weeks	459 from study 106; 222 from study 108	Efficacy and safety

Note:

F/F: F508del/F508del;

F/G551D: F508del/G551D;

F/MF: F508del /minimal function non-responsive to TEZ and/or IVA;

F/RF: F508del/residual function;

F/gating: F508del/gating genotype;

OLE: open-label extension

Source: Reviewer

2.1.4 Statistical Issues

There are three potential statistical issues. The first issue is whether there is substantial evidence of efficacy, the second issue is the robustness of efficacy results, and the third issue is whether the overall study program meets the combination rule for fixed dose combination drug development.

I will comment on these issues in section 5.1.

2.2 Data Sources

Data were submitted by the applicant to the CDER electronic data room in SAS transport format. Protocols, correspondence, data listings, and study reports were accessed under the network path <\\CDSESUB1\\evsprod\\NDA210491\\210491.enx>

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The submitted datasets were of acceptable quality and were adequately documented. We are able to reproduce the results of all key primary and secondary analyses.

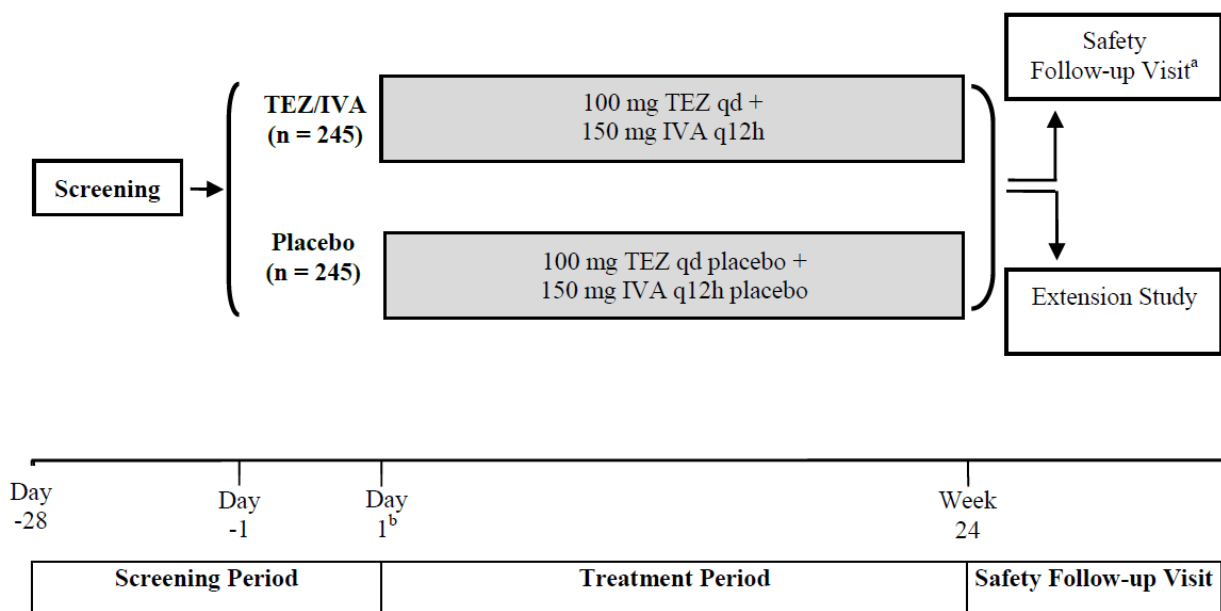
3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

3.2.1.1 Study 106

Study 106 was a phase 3, randomized, double-blind, placebo-controlled, parallel-group, multicenter study in subjects 12 years old and older with CF who are homozygous for the F508del-CFTR mutation. It included a Screening Period, a Treatment Period, and a Safety Follow-up Visit. After completing the 24-week treatment period, the subjects were offered the opportunity to enroll in an extension study of TEZ in combination with IVA, if they met eligibility requirements for the extension study (Study 110). Figure 1 presents the design scheme for Study 106.

Figure 1: Design Scheme for Study 106



FEV₁: forced expiratory volume in 1 second; IVA: ivacaftor; TEZ: tezacaftor; n: number of subjects planned; q12h: every 12 hours; qd: daily

^a The Safety Follow-up Visit was scheduled to occur 28 (± 7) days after the last dose of study drug. A Safety Follow-Up Visit was not required for subjects who completed the Week 24 Visit and enrolled in an extension study of TEZ/IVA within 28 days after the last dose of study drug.

^b Approximately 490 subjects were planned to be stratified by age at the Screening Visit (<18 versus ≥18 years old), sex (male versus female), and FEV₁ severity determined during the Screening Period (<70% versus ≥70% predicted), and then randomized (1:1) before the first dose of study drug on Day 1.

Source: Figure 9-1 in Applicant's Study Report of Study 106.

The patients in Study 106 were male or female aged greater than or equal to 12 years, diagnosed with CF and had F/F genotype, and whose FEV₁ were ≥40% and ≤90% of predicted normal for age, sex, and height during screening.

Subjects who qualified for the study were randomized in a double-blind manner in a 1:1 ratio to the two treatment arms:

- TEZ/IVA BID (morning dose: 1 FDC tablet containing 100 mg TEZ and 150 mg IVA; evening dose: 1 tablet containing 150 mg IVA)
- PBO BID (matching placebo)

Randomization was stratified by three characteristics:

- Age at the Screening Visit (<18 versus ≥18 years old)
- Sex (male versus female)
- FEV₁ severity determined during the Screening Period (<70% versus ≥70% predicted)

Table 3 lists the key endpoints used in Study 106.

Table 3: Primary and Secondary Endpoints of Study 106

	Study 106
Primary Endpoint	Change from baseline in ppFEV ₁ through Week 24
Key Secondary Endpoints	Relative change from baseline in ppFEV ₁ through Week 24
	Number of pulmonary exacerbations (PE _x) through Week 24
	Absolute change from baseline in BMI at Week 24
	Absolute change from baseline in CFQ-R respiratory domain score through Week 24
Secondary 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 time of screening)
	Absolute change in body weight from baseline at Week 24

Source: Reviewer

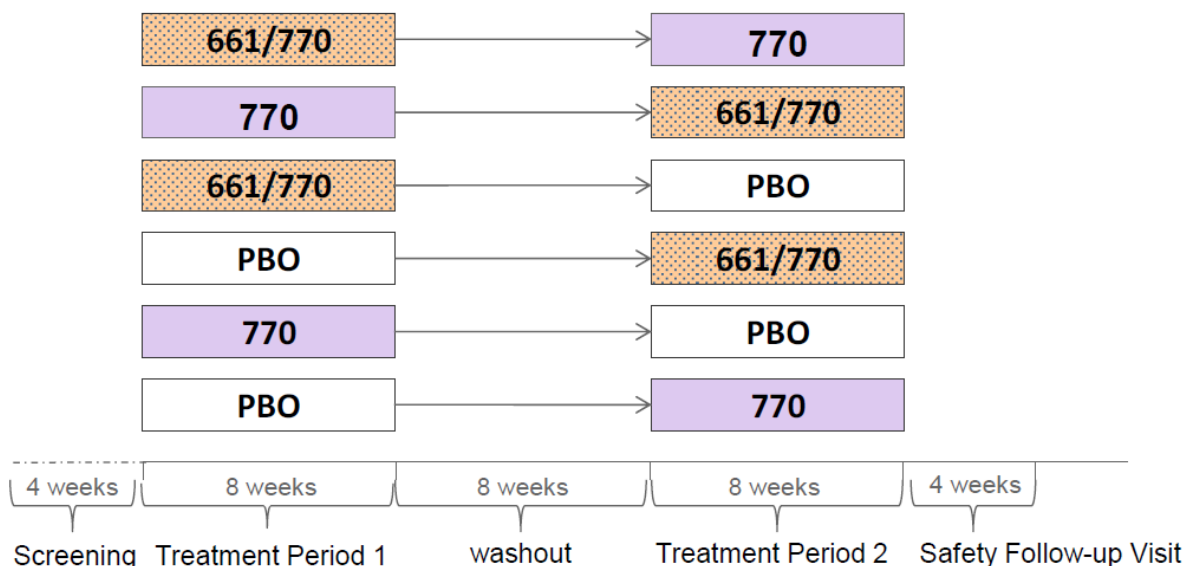
A pulmonary exacerbation was defined as a new event or change in antibiotic therapy (IV, inhaled, or oral) for any 4 or more of the following signs/symptoms:

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

3.2.1.2 Study 108

Study 108 was a phase 3, randomized, double-blind, placebo-controlled, 2-period, 3-treatment, cross-over, multicenter study in subjects aged 12 years and older with CF, heterozygous for the *F508del*-CFTR mutation, and a second allele with a CFTR mutation predicted to have residual function. After completing the 2-period cross-over study, subjects were offered the opportunity to enroll in an extension study of TEZ in combination with IVA, if they met eligibility requirements for the extension study (Study 110). Figure 2 presents the design scheme for Study 108.

Figure 2: Design Scheme for Study 108



661/770: TEZ/IVA; 770: IVA; PBO: placebo.

Source: Figure 6-1 in Applicant's SAP of Study 108.

Subjects qualified for the study were randomized in a double-blind manner in a 1:1:1:1:1:1 ratio to 1 of the 6 treatment sequences, as shown below:

1. Sequence 1: TEZ/IVA in Treatment Period 1→washout→IVA monotherapy in Treatment Period 2
2. Sequence 2: IVA monotherapy in Treatment Period 1→washout→TEZ/IVA in Treatment Period 2
3. Sequence 3: TEZ/IVA in Treatment Period 1→washout→placebo in Treatment Period 2
4. Sequence 4: placebo in Treatment Period 1→washout→TEZ/IVA in Treatment Period 2
5. Sequence 5: IVA monotherapy in Treatment Period 1→washout→ placebo in Treatment Period 2
6. Sequence 6: placebo in Treatment Period 1→washout→IVA monotherapy in Treatment Period 2

The three treatment arms were:

- TEZ/IVA BID (morning dose: 1 FDC tablet containing 100 mg TEZ and 150 mg IVA; evening dose: 1 tablet containing 150 mg IVA)
- IVA BID (morning dose: 1 tablet containing 150 mg IVA; evening dose: 1 tablet containing 150 mg IVA)
- PBO BID (matching placebo)

Randomization was stratified by three characteristics:

- Age at the Screening Visit (<18 versus ≥18 years old)

- FEV₁ severity determined during the Screening Period (<70% versus ≥70% predicted)
- Type of residual function mutation on the second CFTR allele (Class V non-canonical splice mutation versus Classes II to IV residual function mutation)

Table 4 lists the key endpoints used in Study 108.

Table 4: Primary and Secondary Endpoints of Study 108

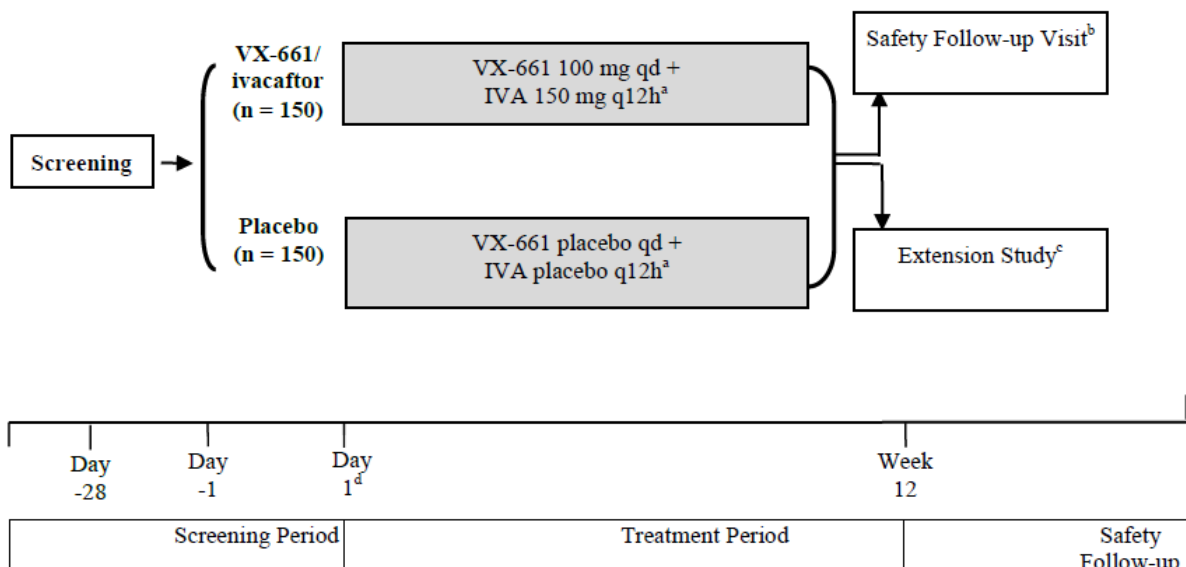
	Study 108
Primary Endpoint	Change in ppFEV1 from study baseline to the average of the Week 4 and Week 8 measurements in each Treatment Period.
Key Secondary Endpoints	Absolute change in CFQ-R respiratory domain score from baseline to the average of the Week 4 and Week 8 measurements in each Treatment Period
Secondary Endpoints	Relative change in ppFEV1 from study baseline to the average of the Week 4 and Week 8 measurements in each Treatment Period
	Change in sweat chloride from study baseline to the average of the Week 4 and Week 8 measurements in each Treatment Period

Source: Reviewer

3.2.1.3 Study 107

Study 107 was a phase 3, randomized, double-blind, placebo-controlled, parallel-group, multicenter study in subjects with CF who are heterozygous for the F508del-CFTR mutation and with a second CFTR mutation that is not likely to respond to TEZ and/or IVA therapy. It has a Screening Period, a Treatment Period and a Safety Follow-up Visit. Figure 3 presents the design scheme for Study 107.

Figure 3: Design Scheme for Study 107



IVA: ivacaftor; q12h: every 12 hours; qd: once daily.

^a During the Treatment Period, subjects in the VX-661/ivacaftor arm will receive 100 mg VX-661 + 150 mg ivacaftor (fixed-dose combination tablet) for the morning dose and 150 mg ivacaftor for the evening dose. Subjects in the Placebo arm will receive matched placebo control tablets.

^b The Safety Follow-up Visit is scheduled to occur 28 (± 7) days after the last dose of study drug. The Safety Follow-up Visit is not required for subjects who complete the Week 12 Visit, and are eligible and enroll in an extension study of VX-661 in combination with ivacaftor.

^c Subjects who complete the Week 12 Visit will be offered the opportunity to enroll into an extension study, if they meet the eligibility criteria for the extension study.

^d Approximately 300 subjects will be stratified by age at the Screening Visit (<18 versus ≥18 years of age), sex (male versus female), and FEV₁ 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: Figure 7-1 in Applicant's SAP of Study 107.

Subjects who qualified for the study were randomized in a double-blind manner in a 1:1 ratio to one of the following two arms:

- TEZ/IVA BID (morning dose: 1 FDC tablet containing 100 mg TEZ and 150 mg IVA; evening dose: 1 tablet containing 150 mg IVA)
- PBO BID (matching placebo)

Randomization was stratified by three characteristics:

- Age at the Screening Visit (<18 versus ≥18 years old)
- Sex (male versus female)
- FEV₁ severity determined during the Screening Period (<70% versus ≥70% predicted)

Table 5 lists the key endpoints used in Study 107.

Table 5: Primary and Secondary Endpoints of Study 107

	Study 107
Primary Endpoint	Change from baseline in ppFEV ₁ through Week 12
Key Secondary Endpoints	Absolute change from baseline in CFQ-R respiratory domain score through Week 12
	Number of pulmonary exacerbations (PE _x) through Week 12
	Absolute change from baseline in BMI at Week 12
Secondary Endpoints	Relative change from baseline in ppFEV ₁ through Week 12
	Absolute change in sweat chloride from baseline through Week 12
	Time to first pulmonary exacerbations through Week 12
	Absolute change in BMI z-score from baseline at Week 12 (in subjects <20 years of age at time of screening)
	Absolute change in body weight from baseline at Week 12

3.2.2 Statistical Methodologies

3.2.2.1 Study 106

The efficacy analyses were conducted on the Full Analysis Set (FAS) population, which was defined as all randomized subjects who carried the intended CFTR allele mutation and had received at least 1 dose of study drug.

The primary efficacy endpoint was change from baseline in percent predicted FEV₁ through Week 24; it was analyzed using a mixed model for repeated measures (MMRM). Least Square Mean (LSMean) changes over 24 weeks from the model were reported. The response variable in the model was change from baseline in ppFEV₁, the model included factors of treatment, visit, treatment-by-visit interaction, sex, age group (<18 versus ≥18 years old) at screening, baseline ppFEV₁, and baseline ppFEV₁-by-visit interaction. For tests of fixed effects, an unstructured (UN) covariance matrix and the Kenward and Roger correction to the degrees of freedom were used.

The primary interest of the study was the comparisons of the changes from baseline in ppFEV₁ through Week 24 between the TEZ/IVA treated group and placebo group. Statistical significance was evaluated using a two-sided hypothesis test at the 5% significance level.

Analyses of key secondary efficacy endpoints of relative change from baseline in ppFEV₁ through Week 24, absolute change from baseline in BMI at Week 24, and absolute change from baseline in CFQ-R respiratory domain score through Week 24 used the same analysis methods as for the primary endpoint.

Analysis of the key secondary endpoint of number of pulmonary exacerbations through Week 24 was based on the FAS population and was carried out by a generalized linear model with negative binomial distribution to compare the rates of pulmonary exacerbations over the 24-week

treatment period between the two treatment groups. The response variable was number of pulmonary exacerbations through Week 24 and the model included terms for treatment, sex, age group at screening (<18 vs. ≥ 18 years old), and baseline ppFEV₁ as covariates. The log of time spent in the study was treated as the offset in the model. A log link function was used in the model.

To control the family-wise Type I error rate, a hierarchical testing procedure was used for comparisons of the primary efficacy endpoint and the key secondary efficacy endpoints. The testing hierarchy was as follows:

1. Absolute change from baseline in ppFEV₁ through Week 24
2. Relative change from baseline in ppFEV₁ through Week 24
3. Number of pulmonary exacerbations through Week 24
4. Absolute change in BMI from baseline at Week 24
5. Absolute change in CFQ-R respiratory domain score from baseline through Week 24

3.2.2.2 Study 108

The primary efficacy endpoint was change in ppFEV₁ from study baseline to the average of the Week 4 and Week 8 measurements in each treatment period, and it was analyzed using an MMRM, with treatment, period, ppFEV₁ at study baseline as fixed effects, and subject as a random effect.

Analysis for the absolute change from study baseline in CFQ-R respiratory domain score to the average of Week 4 and Week 8 in each treatment period was similar to the primary analysis of the primary efficacy endpoint.

3.2.2.3 Study 107

The efficacy analyses were conducted on the FAS population, which was defined as all randomized subjects who carried the intended CFTR allele mutation and had received at least 1 dose of study drug.

The primary efficacy endpoint was change from baseline in percent predicted FEV₁ through Week 12; it was analyzed using an MMRM. The model included absolute change from baseline in percent predicted FEV₁ at each visit as the dependent variable; treatment, visit, and treatment-by-visit interaction as fixed effects; and subject as a random effect with adjustment for sex (male versus female), age group at the screen period (<18 versus ≥ 18 years old), and percent predicted FEV₁ severity determined during screening period (<70 versus ≥ 70). The LS Mean treatment difference obtained from the model was reported, along with a 95% confidence interval, a 1-sided 80% upper confidence interval bound and a 2-sided p-value for the treatment difference between placebo and TEZ/IVA.

Analyses of key secondary efficacy endpoints of absolute change from baseline in CFQ-R respiratory domain score through Week 12 and absolute change from baseline in BMI at Week 24 used the same analysis methods as for the primary endpoint.

Analysis of the key secondary endpoint of number of pulmonary exacerbations through Week 12 was carried out by a generalized linear model with negative binomial distribution to compare the rates of pulmonary exacerbations over the 12-week treatment period between the two treatment groups. The response variable was annualized number of pulmonary exacerbations through Week 12.

The total number of patients planned for this study was 300. There was a futility interim analysis planned when approximately 50% of the planned number of subjects completed 12 weeks of treatment. The futility rule for the interim efficacy analysis was based on a 1-sided 80% upper confidence bound (80% UCB) for: (1) the treatment difference in the absolute change from baseline for ppFEV1 through Week 12; and (2) the within-treatment change from baseline through Week 12 for the TEZ/IVA arm. The pre-determined futility criteria were:

- 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

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

3.2.3.1 Patient Disposition

In this application, among the two phase 3 studies, the main reasons for study discontinuation were adverse event (AE) and subjects' withdrawal of consent. The placebo arm had the larger study discontinuation rate than the study drug treated arm. The patient dispositions for these studies are summarized in Table 6 to Table 8.

Rates for missing data in Study 106 were 6.6% and 6% for the placebo arm and TEZ/IVA arm, respectively.

Missing data rates in Study 108 for the first period were 2.5%, 0% and 1.2% for the placebo arm, IVA arm and TEZ/IVA arm, respectively; for the second period the missing data rates were 0%, 1.3% and 0%, respectively.

Missing data rates in Study 107 were 0% and 2.4% for the placebo arm and TEZ/IVA arm, respectively.

Table 6: Patient Disposition - Study 106

Disposition/Reason	Placebo N = 259 n (%)	TEZ/IVA N = 251 n (%)	Total N = 510 n (%)
All Subjects Set	259	251	510
Randomized Set	259	251	510
FAS	256	248	504
Safety Set	258	251	509
Completed treatment regimen	240 (93.0)	235 (93.6)	475 (93.3)
Completed study participation	241 (93.4)	236 (94.0)	477 (93.7)
Did not complete study participation			
AE	8 (3.1)	4 (1.6)	12 (2.4)
Withdrawal of consent (not due to AE)	6 (2.3)	7 (2.8)	13 (2.6)
Physician decision	0	1 (0.4)	1 (0.2)
Other	3 (1.2)	3 (1.2)	6 (1.2)
Rollover to Study 110	233 (90.3)	231 (92.0)	464 (91.2)

Source: Reviewer

Table 7: Patient Disposition – Study 108

	Placebo n (%)	IVA n (%)	TEZ/IVA n (%)	Total n (%)
All Subjects Set	165	164	167	248
FAS	161	156	161	244
Randomized Set	165	164	167	248
Safety Set	162	157	162	246
Period 1 FAS	81	81	84	244
Period 1 completed treatment regimen	79 (97.5)	81 (100.0)	83 (98.8)	243 (98.8)
Period 1 prematurely discontinued study	6 (7.4)	2 (2.5)	2 (2.4)	10 (4.1)
AE	2 (2.5)	1 (1.2)	0	3 (1.2)
Withdrawal of consent	2 (2.5)	0	0	2 (0.8)
Lost to Follow-up	1 (1.2)	0	0	1 (0.4)
Other noncompliance	1 (1.2)	1 (1.2)	1 (1.2)	3 (1.2)
Other	0	0	1 (1.2)	1 (0.4)
Period 2 FAS	81	76	78	234
Period 2 completed treatment regimen	81 (100.0)	75 (98.7)	78 (100.0)	234 (99.6)
Period 2 prematurely discontinued study	0	1 (1.3)	0	1 (0.4)
AE	0	1 (1.3)	0	1 (0.4)
Completed treatment in both periods	156 (96.3)	154 (98.1)	158 (97.5)	234 (95.1)
Rollover to Extension Study 110	149 (92.0)	149 (94.9)	155 (95.7)	235 (95.5)

Source: Reviewer

Table 8: Patient Disposition – Study 107

Disposition/Reason	Placebo N = 85 n (%)	TEZ/IVA N = 83 n (%)	Total N = 168 n (%)
FAS	85	83	168
Safety Set	85	83	168
Completed treatment regimen	84 (98.8)	81 (97.6)	165 (98.2)
Completed study participation	85 (100)	81 (97.6)	166 (98.8)
AE	0	1 (1.2)	1 (0.6)
Withdrawal of consent (not due to AE)	0	1 (1.2)	1 (0.6)
Rollover to Study 110	81 (95.3)	79 (95.2)	160 (95.2)

Source: Reviewer

3.2.3.2 Patient Demographic and Baseline Characteristics

Demographics and baseline characteristics data for the FAS population are summarized in Table 9 to Table 11. As expected, due to the random treatment assignment, the treatment arms were fairly balanced with respect to each factor considered.

Table 9: Patient Demographic and Baseline Characteristics – Study 106

		Placebo N = 256	TEZ/IVA N = 248	Total N = 504
Sex				
	M	131 (51.2)	127 (51.2)	258 (51.2)
	F	125 (48.8)	121 (48.8)	246 (48.8)
Age (yrs)				
	12 to <18	58 (22.7)	58 (23.4)	116 (23.0)
	≥18	198 (77.3)	190 (76.6)	388 (77.0)
	Mean (SD)	25.7 (9.5)	26.9 (11.2)	26.3 (10.4)
Race				
	White	254 (99.2)	245 (98.8)	499 (99.0)
	Black or African American	0	1 (0.4)	1 (0.2)
	Asian	2 (0.8)	0	2 (0.4)
	Other	0	2 (0.8)	2 (0.4)
Ethnic Group				
	Hispanic or Latino	3 (1.2)	9 (3.6)	12 (2.4)
	Not Hispanic or Latino	250 (97.7)	234 (94.4)	484 (96.0)
	Not collected per local regulations	3 (1.2)	5 (2.0)	8 (1.6)
Geographic region				
	North America	68 (26.6)	59 (23.8)	127 (25.2)
	Europe	188 (73.4)	189 (76.2)	377 (74.8)
Weight (kg)				
	Mean (SD)	58.9 (12.0)	58.1 (12.1)	58.5 (12.0)
Height (cm)				
	Mean (SD)	166.2 (9.7)	165.9 (10.4)	166.1 (10.0)
BMI (kg/m²)				

	Mean (SD)	21.12 (2.88)	20.96 (2.95)	21.04 (2.92)
ppFEV1 (%)				
	Mean (SD)	60.4 (15.7)	59.6 (14.7)	60.0 (15.2)
Sweat chloride (mmol/L)				
	Mean (SD)	100.5 (10.2)	101.3 (10.9)	100.9 (10.6)
CFQ-R respiratory domain score				
	Mean (SD)	69.9 (16.6)	70.1 (16.8)	70.0 (16.7)

Source: Reviewer

Table 10: Patient Demographic and Baseline Characteristics - Study 108

		Placebo N = 80	IVA N =81	TEZ/IVA N = 83	Total N = 244
Sex					
	M	34 (42.5)	41 (50.6)	35 (42.2)	110 (45.1)
	F	46 (57.5)	40 (49.4)	48 (57.8)	134 (54.9)
Age (years)					
	≥12 and <18	11 (13.8)	12 (14.8)	11 (13.3)	34 (13.9)
	≥18	69 (86.3)	69 (85.2)	72 (86.7)	210 (86.1)
	Mean (SD)	32.6 (13.9)	36.3 (15.2)	35.6 (13.5)	34.8 (14.2)
Race					
	White	77 (96.3)	81 (100.0)	80 (96.4)	238 (97.6)
	Black or African American	1 (1.3)	0	2 (2.4)	3 (1.2)
	American Indian or Alaska Native	1 (1.3)	0	0	1 (0.4)
	Not collected per local regulations	1 (1.3)	0	0	1 (0.4)
	Other	0	0	1 (1.2)	1 (0.4)
Ethnic Group					
	Hispanic or Latino	4 (5.0)	4 (4.9)	1 (1.2)	9 (3.7)
	Not Hispanic or Latino	75 (93.8)	77 (95.1)	82 (98.8)	234 (95.9)
	Not collected per local regulations	1 (1.3)	0	0	1 (0.4)
Geographic region					
	North America	39 (48.8)	36 (44.4)	45 (54.2)	120 (49.2)
	Europe	41 (51.3)	45 (55.6)	38 (45.8)	124 (50.8)
Weight (kg)					
	Mean (SD)	69.7 (16.7)	71.1 (18.9)	67.7 (16.5)	69.5 (17.4)
Height (cm)					
	Mean (SD)	168.0 (9.0)	169.7 (9.8)	168.8 (9.6)	168.8 (9.5)
BMI (kg/m²)					
	Mean (SD)	24.56 (5.04)	24.51 (5.50)	23.61 (4.63)	24.22 (5.06)
ppFEV1 (%)					
	Mean (SD)	62.1 (14.0)	62.8 (14.6)	61.8 (14.9)	62.3 (14.5)
Sweat chloride					

(mmol/L)					
	Mean (SD)	70.7 (24.0)	74.9 (24.3)	64.1 (28.9)	69.9 (26.1)
CFQ-R Respiratory					
	Mean (SD)	67.8 (17.5)	70.0 (17.7)	66.5 (17.9)	68.1 (17.7)

Source: Reviewer

Table 11: Patient Demographic and Baseline Characteristics - Study 107

		Placebo N = 85	TEZ/IVA N = 83	Total N = 168
Sex				
	M	43 (50.6)	44 (53.0)	87 (51.8)
	F	42 (49.4)	39 (47.0)	81 (48.2)
Age (yrs)				
	12 to <18	18 (21.2)	19 (22.9)	37 (22.0)
	≥18	67 (78.8)	64 (77.1)	131 (78.0)
	Mean (SD)	26.0 (8.8)	26.2 (9.6)	26.1 (9.2)
Race				
	White	76 (89.4)	78 (94.0)	154 (91.7)
	Black or African American	2 (2.4)	1 (1.2)	3 (1.8)
	Not collected per local regulations	4 (4.7)	4 (4.8)	8 (4.8)
	Other	3 (3.5)	0	3 (1.8)
Ethnic Group				
	Hispanic or Latino	5 (5.9)	1 (1.2)	6 (3.6)
	Not Hispanic or Latino	76 (89.4)	78 (94.0)	154 (91.7)
	Not collected per local regulations	4 (4.7)	4 (4.8)	8 (4.8)
Geographic region				
	North America	51 (60.0)	42 (50.6)	93 (55.4)
	Europe	13 (15.3)	21 (25.3)	34 (20.2)
	Australia	7 (8.2)	10 (12.0)	17 (10.1)
	Israel	14 (16.5)	10 (12.0)	24 (14.3)
Weight (kg)				
	Mean (SD)	57.2 (10.5)	59.9 (12.6)	58.6 (11.7)
Height (cm)				
	Mean (SD)	165.6 (9.1)	166.7 (10.5)	166.1 (9.8)
BMI (kg/m²)				
	Mean (SD)	20.72 (2.53)	21.41 (3.21)	21.06 (2.90)
ppFEV1 (%)				
	Mean (SD)	57.7 (12.7)	57.3 (15.3)	57.5 (14.0)
Sweat chloride (mmol/L)				
	Mean (SD)	102.7 (9.6)	100.6 (13.0)	101.6 (11.4)
CFQ-R respiratory domain score				
	Mean (SD)	64.2 (20.8)	67.7 (16.0)	65.9 (18.6)

Source: Reviewer

3.2.4 Results and Conclusions

3.2.4.1 Study 106

Table 12 summarizes the analysis results of the primary endpoint of Study 106. Tables 13 to Table 16 summarize the analysis results of the key secondary endpoints of Study 106.

The efficacy results indicated that the TEZ/IVA treated group had statistically significant improvements over placebo in absolute change in ppFEV₁, relative change in ppFEV₁, and pulmonary exacerbation rate through Week 24. The estimated absolute mean improvement in ppFEV₁ on TEZ/IVA as compared to placebo was 4.0 percentage points (95% CI: 3.1, 4.8). The estimated exacerbation rate was 0.64 events per year on TEZ/IVA, as compared to 0.99 events per year on placebo, for a rate ratio of 0.65 (95% CI: 0.48, 0.88). However, there was not a statistically significant improvement over placebo in BMI through Week 24. For the endpoint of CFQ-R respiratory domain score, there was great improvement in TEZ/IVA treated group. Compare to placebo which decreased 0.1 points, the mean treatment difference between the TEZ/IVA group and the placebo group was 5.1 points with 95% confidence interval of (3.2, 7.0). We consider this result as the strong evidence of efficacy of TEZ/IVA although these results are nominally significant according to the hierarchical testing procedure.

Table 12: Absolute Change From Baseline in Percent Predicted FEV₁ Through Week 24 (Study 106, FAS)

	Placebo N = 256	TEZ/IVA N = 248
Mean change from baseline through Week 24	-0.6 (0.3)	3.4 (0.3)
Difference from PBO (95% CI)	N/A	4.0 (3.1, 4.8)
p-value compare to PBO	N/A	<0.0001

Source: Reviewer

Table 13: Relative Change From Baseline in ppFEV₁ Through Week 24 (Study 106, FAS)

	Placebo N = 256	TEZ/IVA N = 248
Mean change from baseline through Week 24	-0.5 (0.6)	6.3 (0.6)
Difference from PBO (95% CI)	N/A	6.8 (5.3, 8.3)
p-value compare to PBO	N/A	<0.0001

Source: Reviewer

Table 14: Negative Binomial Analysis for the Number of Pulmonary Exacerbations Through Week 24 (Study 106, FAS)

	Placebo N = 256	TEZ/IVA N = 248
Number of subjects with events, n %)	88 (34.4)	62 (25.0)
Total number of days (years) on study	42452 (126.35)	41069 (122.23)
Number of events (observed event rate per year)	122 (0.97)	78 (0.64)
Estimated event rate per year	0.99	0.64
Rate ratio, 95% CI	N/A	0.65 (0.48, 0.88)
p value compare to placebo	N/A	0.0054

Source: Reviewer

Table 15: MMRM Analysis of Change From Baseline in BMI at Week 24 (Study 106, FAS)

	Placebo N = 256	TEZ/IVA N = 248
Mean change from baseline at Week 24 kg/m ²)	0.12 (0.05)	0.18 (0.05)
Difference from PBO (95% CI)	N/A	0.06 (-0.08, 0.19)
p-value compare to PBO	N/A	0.4127

Source: Reviewer

Table 16: MMRM Analysis of Change From Baseline in CFQ-R Respiratory Domain Score Through Week 24 (Study 106, FAS)

	Placebo N = 256	TEZ/IVA N = 248
Mean change through Week 24	-0.1 (0.8)	5.0 (0.8)
Difference from PBO (95% CI)	N/A	5.1 (3.2, 7.0)
p-value compare to PBO	N/A	<0.0001

Source: Reviewer

3.2.4.2 Study 108

Table 17 and Table 18 summarize the efficacy results of the primary endpoint and key secondary endpoints. Both the TEZ/IVA treated group and IVA treated group were compared to placebo; the TEZ/IVA treated group was also compared to the IVA treated group. The results indicated that both the TEA/IVA treated group and IVA treated group had statistically significant improvements over placebo in ppFEV1 through treatment period. The estimated absolute mean improvement in ppFEV1 on TEZ/IVA as compared to placebo was 6.8 percentage points (95% CI: 5.7, 7.8); improvement in ppFEV1 on IVA as compared to placebo was 4.7 percentage points (95% CI: 3.7, 5.8).

The results also indicated that the TEA/IVA treated group had a statistically significant improvement over IVA treated group in ppFEV₁. The estimated absolute mean improvement in ppFEV₁ on TEZ/IVA as compared to IVA was 2.1 percentage points (95% CI: 1.2, 2.9). The results indicated that both the TEA/IVA treated group and IVA treated group had statistically significant improvements over placebo in CFQ-R score through treatment period. The estimated absolute mean improvement in CFQ-R score on TEZ/IVA as compared to placebo was 11.1 points (95% CI: 8.7, 13.6); improvement in CFQ-R on IVA as compared to placebo was 9.7 points (95% CI: 7.2, 12.2).

Therefore, strong efficacy of TEZ/IVA compared to placebo in ppFEV₁ and CFQ-R score were demonstrated in this study, and contribution of TEZ to the efficacy of the combination therapy of TEZ/IVA was established in terms of the primary endpoint ppFEV₁.

Table 17: Absolute Change From Study Baseline in ppFEV₁ to the Average of Week 4 and Week 8 Measurements (Study 108, FAS)

	Placebo N = 161	IVA N = 156	TEZ/IVA N = 161
Average change at Week 4 and Week 8	-0.3 (0.5)	4.4 (0.5)	6.5 (0.4)
Mean treatment difference versus placebo, (95% CI)	N/A	4.7 (3.7, 5.8)	6.8 (5.7, 7.8)
P value versus PBO	N/A	<0.0001	<0.0001
Mean treatment difference versus IVA, (95% CI)	N/A	N/A	2.1 (1.2, 2.9)
P value versus IVA	N/A	N/A	P<0.0001

Source: Reviewer

Table 18: Absolute Change from Study Baseline in CFQ-R Respiratory Domain to the Average of Week 4 and Week 8 (Study 108, FAS)

	Placebo N = 161	IVA N = 156	TEZ/IVA N = 161
Mean change to the average at Week 4 and Week 8	-1.0 (1.0)	8.7 (1.0)	10.1 (1.0)
Mean difference versus placebo, 95% CI	N/A	9.7 (7.2, 12.2)	11.1 (8.7, 13.6)
P value versus placebo	N/A	<0.0001	<0.0001
Mean difference versus IVA, 95% CI	N/A	N/A	1.4 (-1.0, 3.9)
P value versus IVA	N/A	N/A	0.2578

Source: Reviewer

3.2.4.3 Study 107

Tables 19 to Table 22 summarize the interim analysis results of the primary endpoint and key secondary endpoints. The results indicated that for the primary endpoint ppFEV1, the 1-sided 80% upper confidence bound for the mean difference between the TEZ/IVA treated group and the placebo group was 1.79, which is smaller than pre-specified threshold of 2.50. The study met the pre-specified futility criteria and was terminated prematurely.

Table 19: Absolute Change From Baseline in Percent Predicted FEV1 Through Week 12 (Study 107, FAS)

	Placebo N = 85	TEZ/IVA N = 83
Mean change from baseline through Week 12	0.4 (5.0)	1.4 (4.9)
Difference from PBO (95% CI)	N/A	1.2 (-0.3, 2.6)
p-value compare to PBO	N/A	0.1176
1-sided 80% UCB for LS mean treatment difference	N/A	1.79

Source: Reviewer

Table 20: MMRM Analysis of Change From Baseline in CFQ-R Respiratory Domain Score Through Week 12 (Study 107, FAS)

	Placebo N = 85	TEZ/IVA N = 83
Mean change from baseline through Week 12	2.4 (13.1)	3.0 (14.2)
Difference from PBO (95% CI)	N/A	2.1 (-1.2, 5.4)
p-value compare to PBO	N/A	0.2056

Source: Reviewer

Table 21: Negative Binomial Analysis for the Number of Pulmonary Exacerbations Through Week 12 (Study 107, FAS)

	Placebo N = 85	TEZ/IVA N = 83
Number of subjects with events, n (%)	21 (24.7)	19 (22.9)
Total number of days (years) on study	7258 (21.60)	7067 (21.03)
Number of events (observed event rate per year)	23 (0.98)	22 (0.97)
Rate ratio, 95% CI	N/A	0.98 (0.55, 1.76)
p value compare to placebo	N/A	0.9533

Source: Reviewer

Table 22: MMRM Analysis of Change From Baseline in BMI at Week 12 (Study 107, FAS)

	Placebo N = 85	TEZ/IVA N = 83
Mean change from baseline through Week 12	0.22 (0.62)	0.17 (0.56)
Difference from PBO (95% CI)	N/A	-0.08 (-0.27, 0.11)
p-value compare to PBO	N/A	0.3828

Source: Reviewer

3.3 Evaluation of Safety

Please refer to the evaluation of safety in the clinical review by Dr. Stacy Chin.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

In this review, subgroup analyses were conducted for the primary endpoint for both Study 106 and Study 108.

For both studies, subgroup analyses were performed for the following factors:

1. Three demographic factors:
 - age (< 18, >=18)
 - sex (F, M)
 - geographic region (North America, Europe).
2. Seven baseline disease/concomitant medication characteristics:
 - baseline ppFEV₁ (< 40, >=40 to <70, >=70)
 - use of common CF medications: inhaled antibiotic (Inh. AB), inhaled bronchodilator (Inh. BD), inhaled hypertonic saline (Inh. HTS), inhaled corticosteroids (Inh. CST) and Azithromycin
 - *P. aeruginosa* infection (positive, negative)

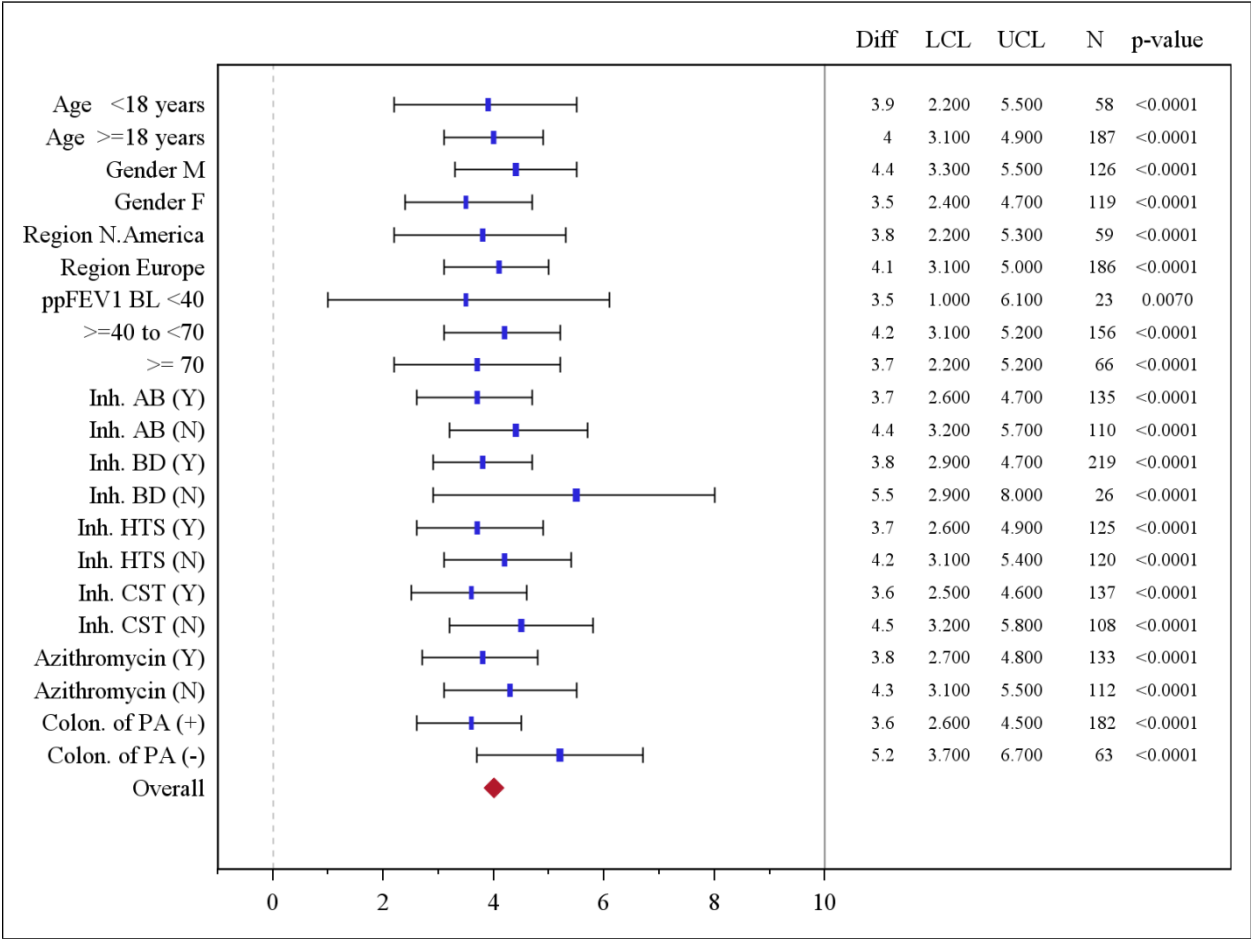
For Study 108, subgroup analyses on the factor of residual function mutation type (Class V non-canonical splice mutation versus Classes II to IV missense mutation) were also conducted.

The majority of the subjects in Studies 106 and 108 are white; there were no subgroup analyses on race.

Figure 4 to Figure 6 illustrate the subgroup analysis results for the primary endpoint for Studies 106 and 108.

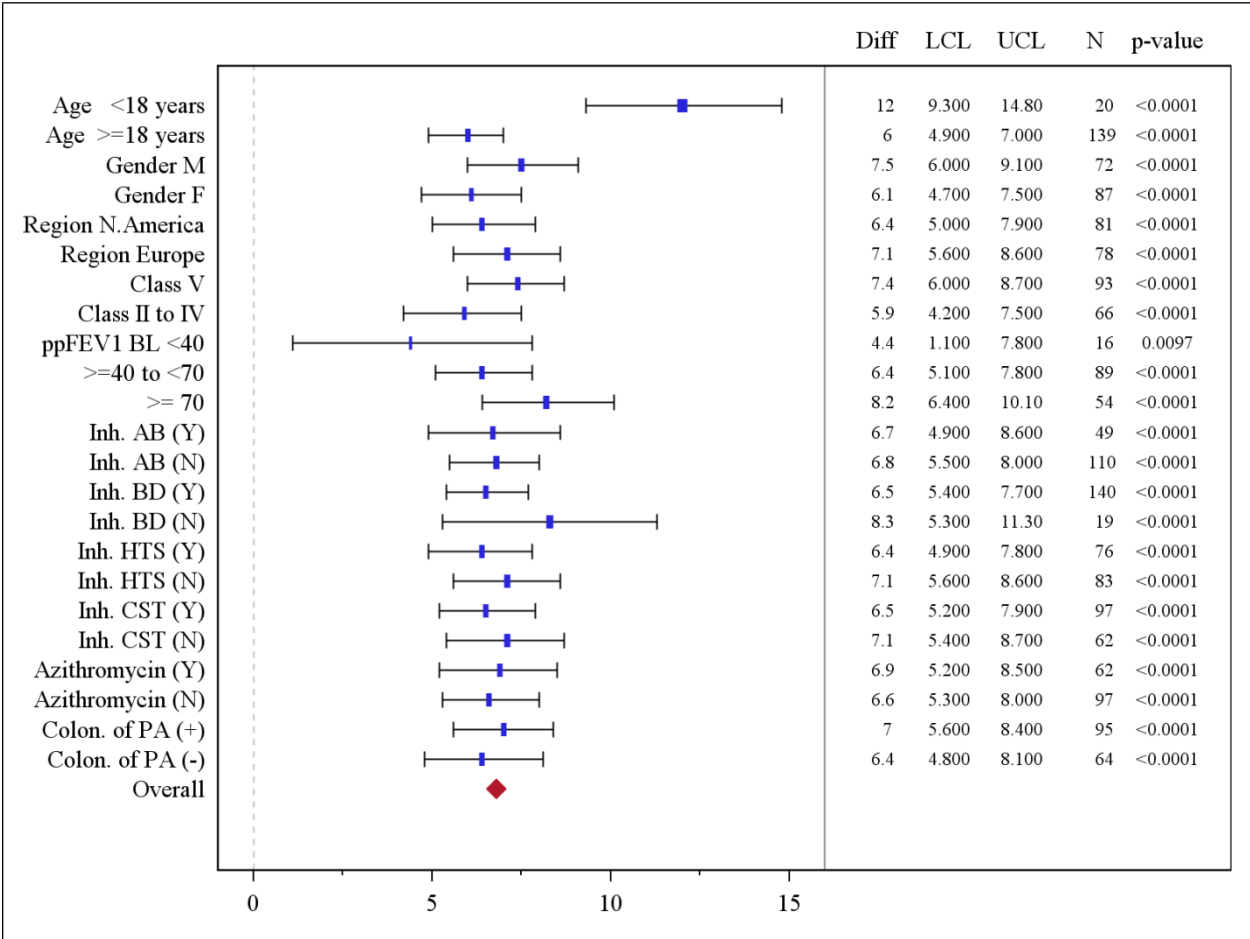
Interpretation of the key results will be given in section 4.1 and 4.2.

Figure 4: Subgroup Analyses on Primary Endpoint of Change from Baseline of ppFEV₁ Through Week 24 (Study 106)



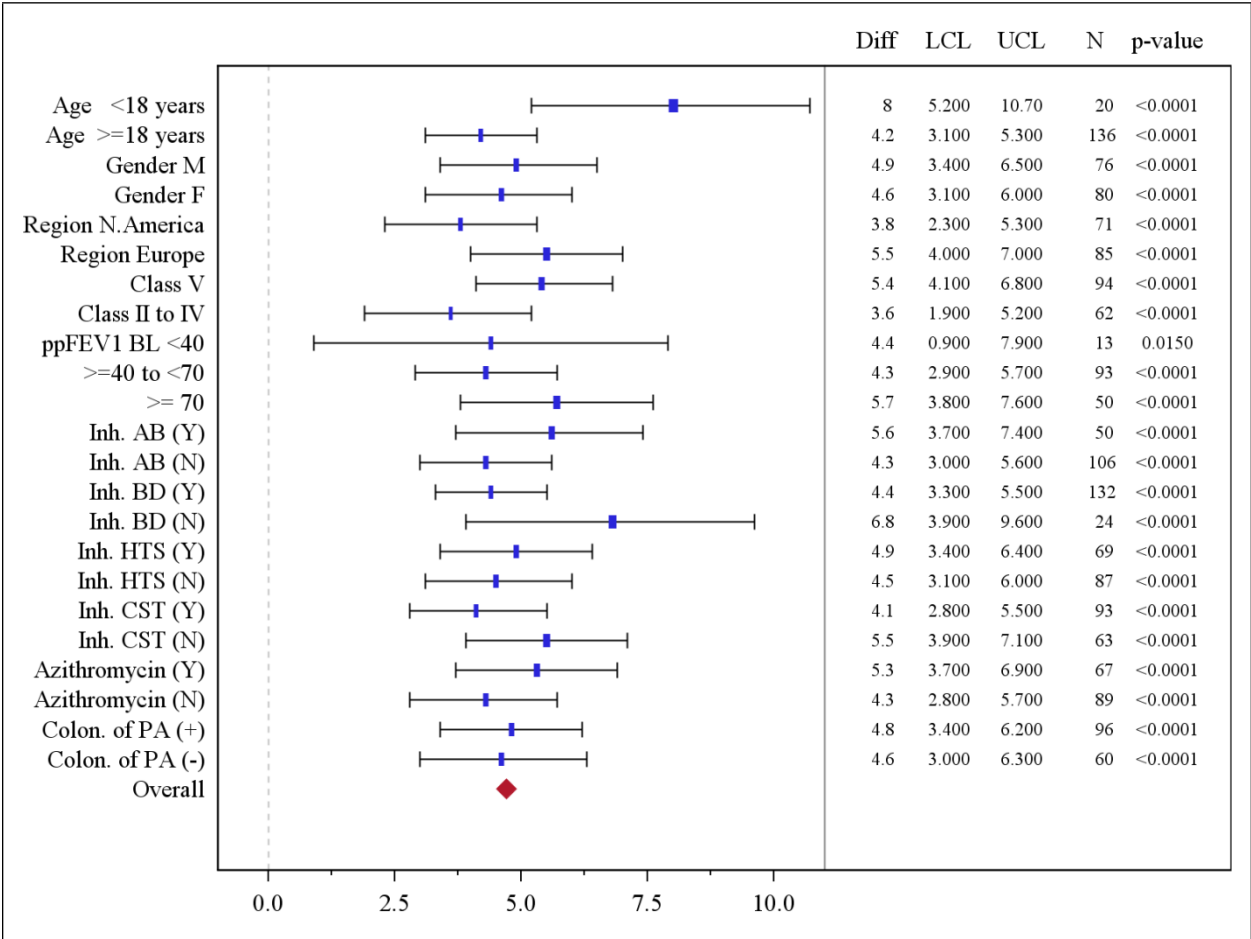
Note: Units for x-axis is percentage points; error bar is 95% confidence interval.
Source: Review

Figure 5: Subgroup Analyses on Primary Endpoint of Absolute Change From Study Baseline in ppFEV₁ to the Average of Week 4 and Week 8 Measurements (Study 108 TEZ/IVA vs PBO)



Note: Units for x-axis is percentage points; error bar is 95% confidence interval.
Source: Reviewer

Figure 6: Subgroup Analyses on Primary Endpoint of Absolute Change From Study Baseline in ppFEV₁ to the Average of Week 4 and Week 8 Measurements (Study 108 IVA vs PBO)



Note: Units for x-axis is percentage points; error bar is 95% confidence interval.
Source: Reviewer

4.1 Sex, Race, Age, and Geographic Region

Subgroup analyses were performed on age (< 18, >=18), sex (M, F) and geographic region (North America, Europe).
Results showed that for both populations of F/F and F/RF, treatment with TEZ/IVA and IVA both produced consistent statistically significant improvements over placebo in ppFEV₁, regardless of age, sex and geographic region.

4.2 Baseline Disease Characteristics

Subgroup analyses on primary endpoint of ppFEV₁ were performed on baseline disease characteristics of baseline ppFEV₁ (< 40, >=40 to <70, >=70), use of Inhaled Antibiotic (Yes, No), use of Inhaled Bronchodilator (Yes, No), use of Inhaled Hypertonic Saline (Yes, No), use of

Inhaled Corticosteroids (Yes, No), use of Azithromycin (Yes, No) and *P. aeruginosa* infection status (Positive, Negative) for both Study 106 and Study 108. Results showed that TEZ/IVA treatment and IVA treatment had consistent and significant improvements over placebo in ppFEV₁ regardless of all baseline disease characteristics considered in both populations (F/F and F/RF).

Subgroup analyses by residual function mutation indicated that TEZ/IVA treatment and IVA treatment had consistent and significant improvements over placebo in ppFEV₁ in both patients with Class V non-canonical splice mutations and Classes II to IV missense mutations.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

As mentioned in section 2.1.4, the first potential statistical issue was regarding substantial evidence of efficacy. Study 106 and Study 108 were very different in study design and study duration. The primary endpoints of Study 106 and Study 108 were not exactly the same. For Study 108 it was the average of the week 4 and week 8 measurements of ppFEV₁ while for Study 106 it was the ppFEV₁ over 24 weeks. These two studies were independent studies and both demonstrated substantial improvements in ppFEV₁, a well-established surrogate for studying CF. Demonstration of substantial evidence of efficacy was also supported by the key secondary endpoint of CFQ-R respiratory domain score in both studies (testing of CFQ-R score in Study 106 was only nominally significant due to the testing hierarchy, but the strength of evidence was strong: $p < 0.0001$), an endpoint directly measuring how patients feel and function in daily life. During the end-of-phase 2 meeting, FDA had recommended that the applicant place the CFQ-R score higher in the testing order than BMI, given a concern that 24 weeks of treatment might not be long enough to capture a difference in BMI between the treated group and the placebo group. Sweat chloride was an additional secondary endpoint; although it was not placed in the statistical testing hierarchy, it is considered an important endpoint due to the mechanism of action of the treatment; it increases the chloride transportation and thus is expected to decrease the sweat chloride concentration. Sweat chloride results of Study 106 and Study 108 are presented in Table 23 and Table 24, and provide some support for a treatment effect.

Since Study 107 did not provide evidence of a treatment effect, the mutations studied were not part of the labeling claim of the study drug. Overall, I conclude that there is substantial evidence of efficacy on TEZ/IVA in CF patients with F/F or F/RF mutation.

Table 23: MMRM Analysis of Absolute Change From Baseline in Sweat Chloride Concentration (mmol/L) Through Week 24 (Study 106, FAS)

	Placebo N = 256	TEZ/IVA N = 248
Mean change from baseline through Week 24	0.2 (0.5)	-9.9 (0.5)
Difference from PBO (95% CI)	N/A	-10.1 (-11.4, -8.8)
p-value compare to PBO	N/A	<0.0001

Source: Reviewer

Table 24: Linear Mixed Effects Model for Absolute Change From Study Baseline in Sweat Chloride to the Average of Week 4 and Week 8 Measurements (FAS) -Study 108

	Placebo N = 161	IVA N = 156	TEZ/IVA N = 161
Average change at Week 4 and Week 8	-0.4 (1.0)	-4.9 (1.0)	-9.9 (1.0)
LS mean treatment difference versus placebo, (95% CI)	N/A	-4.5 (-6.7, -2.3)	-9.5 (-11.7, -7.3)
P value versus PBO	N/A	<0.0001	<0.0001
LS mean treatment difference versus. IVA, (95% CI)	N/A	N/A	-5.1 (-7.0, -3.1)
P value versus IVA	N/A	N/A	P<0.0001

Source: Reviewer

The second potential statistical issue was the robustness of efficacy results, i.e., the sensitivity of the results to violations in the assumptions underlying the key analyses. The robustness of the results can be affected by a high rate of missing data. But in these two studies, the missing rates were not high. In Study 106, the missing rate was 6~6.6%, with a higher rate in the placebo group. There were no sensitivity analyses conducted in this study. In the primary analyses using the MMRM model, the mechanism of missing at random was assumed. This assumption may not hold, since subjects who discontinue treatment may plausibly tend to have worse outcome than subjects who stay on treatment. To assess the robustness of the results, I conducted a sensitivity analysis using an approach with an alternative missing data assumption by imputing the missing data using the baseline value; the results are presented in Table 25. Compared to Table 12, there was no noticeable difference. This result provides some support for the robustness of the efficacy data in the presence of missing data.

Table 25: Absolute Change From Baseline in Percent Predicted FEV1 Through Week 24 (FAS, impute missing value using baseline value) - Study 106

	Placebo N = 256	TEZ/IVA N = 248
Mean change from baseline through Week 24	-0.7 (0.3)	3.2 (0.3)
Difference from PBO (95% CI)	N/A	3.9 (3.1, 4.7)
p-value compare to PBO	N/A	<0.0001

Source: Reviewer

In Study 108, the missing data rate was very low at 0~2.5%, and there were no sensitivity analyses conducted. I do not expect any differences in conclusions with varying missing data assumptions considering this very low missing rate. Therefore, I consider the efficacy results from Studies 106 and 108 to be convincing despite the missing data.

To study the contribution of each component to the efficacy of a combination therapy based on clinical efficacy data, a factorial design for the study is required. However, neither Study 106 nor Study 108 employed a full factorial design. Only Study 108 included a monotherapy arm of IVA. There was no monotherapy arm of TEZ in any study. There were no clinical data demonstrating the contribution of IVA to the combination therapy. Please refer to clinical pharmacology's review on *in vitro* results. Comparison of TEZ/IVA to IVA demonstrated statistically significant improvements in the primary endpoint of ppFEV₁ but not the key secondary endpoint of CFQ-R score. Contribution of TEZ to TEZ/IVA was demonstrated in only one study. During the drug development, FDA had recommended including an IVA arm in Study 106 but in the final program the IVA arm was not included in this study. However, all things considered, mainly given the strong statistical evidence ($p < 0.0001$) supporting the contribution of TEZ in terms of the primary endpoint that was observed in Study 108, I conclude that contribution of TEZ to the combination therapy was reasonably demonstrated.

5.2 Collective Evidence

As summarized in Table 26, effectiveness of TEZ/IVA was examined in two studies: Study 106 and Study 108. Statistically significant efficacy of TEZ/IVA over placebo was achieved on the change from baseline in ppFEV₁ through Week 24 or to the average of Week 4 and Week 8 measurements in two studies. Statistically significant efficacy of TEZ/IVA over placebo was achieved on the key secondary endpoints of relative change from baseline of ppFEV₁ through Week 24, rate of pulmonary exacerbations through Week 24, and change from baseline of CFQ-R respiratory domain score to the average of Week 4 and Week 8 measurement. There was strong evidence of benefit for TEZ/IVA over placebo on change from baseline in CFQ-R score through Week 24, although this result was considered as nominal according to the hierarchical testing procedure.

Statistically significant demonstration of efficacy of IVA over placebo was achieved on change from baseline of ppFEV₁ to the average of Week 4 and Week 8 measurement and in change

from baseline of CFQ-R Respiratory Domain Score to the average of Week 4 and Week 8 measurement in one study.

Statistically significant demonstration of efficacy of TEZ/IVA over IVA was achieved on change from baseline of ppFEV₁ to the average of Week 4 and Week 8 measurement in one study.

However, there was not a statistically significant benefit of TEZ/IVA over placebo in terms of change from baseline in BMI through Week 24.

Table 26: Summary of the Key Efficacy Test Results

Endpoints	Study 106	Study 108
ppFEV ₁	✓	✓
Relative ppFEV ₁	✓	N/A
# of exacerbation	✓	N/A
BMI	✗	N/A
CFQ-R Score	✓-	✓
Note: ✓: statistically significant; ✗: not statistically significant; ✓-: nominally significant		

Source: Reviewer

5.3 Labeling Recommendations

Testing of CFQ-R score was statistically significant in Study 108 and nominally significant in Study 106 because the test of BMI, which was not statistically significant, was higher in the multiple testing hierarchy than CFQ-R score. Recall that during the end-of-phase 2 meeting, FDA had recommended that the applicant place CFQ-R score higher in the testing order than BMI, given a concern that 24 weeks of treatment might not be long enough to capture a difference in BMI between the treated group and the placebo group. CFQ-R score is an important endpoint which directly measures how patients feel and function in daily life; it is a key secondary endpoint in both studies. Given the large effect size of the results in both studies, we (biostatistics team and clinical review team) think that it is appropriate and important to include CFQ-R in the labeling.

Sweat chloride is another important endpoint in studying CF due to the expected mechanism of how the drug works. It increases chloride transportation, and thus is expected to decrease its concentration. Given the large effect size of the results in both studies, we think it is appropriate to include this endpoint in the labeling.

5.4 Conclusions and Recommendations

Vertex Pharmaceuticals has proposed TEZ/IVA (TEZ 100mg/IVA 150 mg qAM, IVA 150 mg qPM) for treating CF patients of 12 years of age or older who are homozygous for F508del mutation or with at least one CFTR mutation responsive to TEV/IVA based on in vitro data and/or clinical evidence.

Effectiveness and safety of TEZ/IVA combination therapy were examined with this submission. The review focused on three phase 3 studies to investigate the efficacy of TEZ/IVA combination therapy in terms of change from baseline of ppFEV₁ through Week 24 (or to the average of Week 4 and Week 8 measurements).

The benefits of TEZ/IVA combination therapy over placebo for the major endpoints were examined. In support of the efficacy, TEZ/IVA combination therapy, in both patients with F/F or F/RF mutations, showed statistically greater improvement on the pre-defined primary endpoint of change from baseline of ppFEV₁ through Week 24 (or to the average of Week 4 and Week 8 measurement) in two independent studies. Contribution of TEZ in the TEZ/IVA combination therapy was also observed in change from baseline of ppFEV₁ to the average of Week 4 and Week 8 measurement in one study.

Based on two independent studies, strong evidence of benefit in CFQ-R score was demonstrated.

Limited assessments were conducted on the impact of missing data of the efficacy results, due to low rates of missingness in both studies. Robustness of results was supported in a missing data sensitivity analyses.

Subgroup analyses were conducted to investigate the level of consistency or heterogeneity of the treatment effect across subgroups of interest, including demographic factors age, sex, geographic region, and baseline disease characteristics including baseline ppFEV₁, common CF medication use and residual function mutation subgroup (in one study). All the subgroups had results consistent with the overall results.

Study 107 did not demonstrate treatment benefit in the patients who have the mutations which are not part of the labeling claim in this submission.

I conclude that the clinical data contained in this submission support effectiveness of TEZ/IVA (TEZ 100mg/IVA 150 mg qAM, IVA 150 mg qPM) for treating CF patients of 12 years of age or older who have F/F or F/RF mutations.

We recommend approval for this submission.

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

/s/

MINGYU XI
02/02/2018

YONGMAN KIM
02/05/2018
I concur.



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Science
Office of Biostatistics

Statistical Review and Evaluation

CARCINOGENICITY STUDY

IND/NDA Number:	NDA 210491
Drug Name:	Symdeko™ (Ivacaftor and Tezacaftor), VX-661
Indication(s):	Treatment of cystic fibrosis.
Studies	One Two Year Oral Gavage Carcinogenicity Study in Rats and One Six-Month Oral Gavage Carcinogenicity Study in rasH2 Transgenic Mice.
Applicant:	Sponsor: Vertex Pharmaceuticals, Inc. 50 Northern Avenue Boston, Massachusetts 02210
	Test facility for rat study: (b) (4)
	Test facility for mouse study: (b) (4)
Documents Reviewed:	Electronic submission, dated: July 31, 2017 via SN0005 Electronic data submitted on July 31, 2017 via SN0005.
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Biometrics Division:	Division of Biometrics -VI
Statistical Reviewer:	Malick Mbodj, Ph.D.
Secondary Reviewer:	Hepei Chen
Concurring Reviewer:	Karl Lin, Ph.D.
Medical Division:	Division of Pulmonary, Allergy, and Rheumatology Products
Reviewing Pharmacologist:	Eleni Salicru, PhD
Project Manager:	Lee, Jessica K
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1. Background

In this submission, the sponsor included reports of two animal carcinogenicity studies, one in regular rats and one in transgenic mice. These studies were intended to assess the carcinogenic potential of VX-661 in rats and mice when administered orally by gavage at appropriate drug levels for about 104 weeks in rats and 26 weeks in mice. Results of this review have been discussed with the reviewing pharmacologist Dr. Salicru.

In this review, the phrase "dose response relationship" (trend) refers to the linear component of the effect of treatment, and not necessarily to a strictly increasing or decreasing mortality or tumor incidence rate as dose increases.

2. Rat Study

In this study two separate experiments were conducted, one in male rats and one in female rats. In each of these two experiments there were three treated groups and one vehicle control group. Two hundred and eighty Sprague-Dawley rats of each sex were assigned to three treated groups and one vehicle control group by a stratified randomization scheme designed to achieve similar group mean body weights in equal size of 70 animals, as indicated in Table 1. The dose levels for the three treated groups were 5, 15, and 50 mg/kg/day for males and 5, 20, and 75 mg/kg/day for females, for up to 104 weeks. In this review, these dose groups were referred to as the low, medium, and high dose group, respectively. The vehicle control group received the vehicle [0.5% methylcellulose (400 cps) (w/v), 0.5% sodium lauryl sulfate (SLS) (w/v), and 0.01% simethicone (w/v) in deionized water], administered orally by gavage for about 104 weeks in the same manner as the treated groups. Due to early termination threshold of 20 survivors rats in the male and female vehicle control groups, early final scheduled necropsies were conducted (based on FDA recommendations) at Week 103 and at Week 101 for all surviving male and female rats, respectively.

Table 1: Experimental Design in Rat Study

Group Name	Group N0.	Dose Level (mg/kg/day)		Number of Animal	
		Male	Female	Males	Females
Vehicle Control	1	0	0	70	70
Low	2	5	5	70	70
Medium	3	15	20	70	70
High	4	50	75	70	70

All animals were dosed for up to 100 consecutive weeks (females) or 102 consecutive weeks (males)

During the administration period, all animals were checked for morbidity, mortality, injury, twice daily (a.m. and p.m.). The animals were removed from the cage, and detailed observations were conducted for each animal at least once during the pre-dose phase, prior to dosing on Day 1, and weekly throughout the dosing phase. Detailed examinations for palpable masses were done weekly, the time of onset, location, size, appearance, and progression of each grossly visible or palpable mass, observed in carcinogenicity rats, was recorded weekly, particular attention being paid to the animals during and for the four hours after dosing. Any animal showing signs of severe debility or intoxication, and if determined to be moribund or suffering excessively will be euthanized. Observations will include, but will not be limited to, evaluation for reaction to treatment. Histopathological examinations were performed on all animals found dead or killed moribund or sacrificed at the end of the experiment. Body weights for all animals were measured and recorded at receipt, prior to randomization and once weekly for the first 14 weeks, every two weeks until Week 28, every four weeks thereafter for the duration of the study, and on the day of the scheduled terminal necropsy.

2.1. Sponsor's analyses

2.1.1. Survival analysis

The Kaplan-Meier's curves were presented graphically for male and female rats separately. An overall test for survival was used to compare the homogeneity of survival rates across the groups using a log-rank test at the 0.05 significance level. If the survival rates were significantly different ($p < 0.05$), then a follow up analysis was done where each treatment group was compared to the vehicle control group using a log-rank test.

Any animal with accidental injury that causes its death or its unscheduled sacrifice was censored in the estimation. In addition, all animals still alive at the end of the experimental period were censored at the following day. Results of all pair-wise comparisons are reported at the 0.05 and 0.01 significance levels. All endpoints were analyzed using two-tailed tests.

Sponsor's findings:

Sponsor's analysis showed the numbers of rats surviving to their terminal necropsy were 20, 21, 16, and 25 in the vehicle control group, low, medium, and high dose groups, in male rats, respectively, and 19, 17, 23, and 21 in vehicle control, low, medium, and high dose groups, in female rats, respectively. The sponsor's report concluded that, there was no statistically significant increase in mortality across the vehicle control group and the three treated groups in either sex of rats. The pairwise comparisons showed no statistically significant increase in mortality between each of the treated groups, and the vehicle control group in either sex of rats.

2.1.2. Tumor data analysis

Tumor incidence data were analyzed within each sex, using both survival adjusted and unadjusted tests. The unadjusted tests will be based on the incidence and number of sites examined for each tumor type. The Cochran-Armitage trend test will be calculated and Fisher's exact test will be used to compare each treatment group with the vehicle control group. The survival adjusted test will be conducted according to the prevalence/mortality methods described by Peto et al. The incidence of each tumor type was analyzed with a one-sided trend test using the positive dose response relationship in tumor occurrence across vehicle control and treated groups. In addition, one-sided pairwise comparisons of vehicle control and treated groups were conducted. The analysis of tumors was based on the following fixed time intervals: Weeks 1-50, 51-80, 81- end of study, (up to, but not including, scheduled terminal sacrifices), and terminal sacrifice for male and female rats. The actual dose levels were used as the scores. All animals that died or were sacrificed after the first animal of that sex was terminally sacrificed were included in the scheduled terminal sacrifice interval for the incidental finding analyses. All tumors in the scheduled terminal sacrifice interval were considered incidental for the purpose of statistical analysis.

Adjustment for the multiplicity:

For multiplicity adjustment, the sponsor used significance levels of 0.005 and 0.025 for common and rare tumors, respectively in dose response relationship (trend) tests and significance levels of 0.01 and 0.05 for common and rare tumors, respectively in pairwise comparisons. Site-specific background historical control database was used to determine whether the tumors should be designated as rare or common.

Sponsor's findings:

Following the multiple testing adjustment method described above, the sponsor's analysis showed no tumor types with a statistically significant dose response relationship in tumor incidences with increased VX-661 dose. The pairwise comparisons also showed no tumor types with a statistically significant increase in tumor incidences in VX-661 treated groups, when compare to the vehicle control group in either male or female rats.

2.2 Reviewer's analyses

To verify sponsor's analysis and to perform additional analyses suggested by the reviewing pharmacologist, this reviewer independently performed the survival and tumor data analyses. Data used in this reviewer's analyses were provided by the sponsor electronically on June 15, 2017 via SN0151.

It was noticed that male and female rats were dosed for at least up to 102 consecutive weeks or 100 consecutive weeks, respectively. The respective scheduled sacrifice interval was at Week 103 and at Week 101 for all surviving males and females, respectively.

2.2.1 Survival analysis

In the reviewer's analysis, intercurrent mortality data were analyzed using the Kaplan-Meier product limit method. The Kaplan-Meier's curves were presented graphically for male and female rats separately. The dose response relationship and homogeneity of survival distributions were tested for the treatment groups using the Likelihood Ratio test and the Log-Rank test. The intercurrent mortality data are given in Tables 1A and 1B in the appendix for male and female rats, respectively. The Kaplan-Meier curves for survival rate are given in Figures 1A and 1B in the appendix for male and female rats, respectively. Results of the tests for dose response relationship and homogeneity of survivals, are given in Tables 2A and 2B in the appendix for male and female rats, respectively.

Reviewer's findings:

This reviewer's analysis showed the numbers of rats surviving to their terminal necropsy were 20, 21, 16, and 25 in the vehicle control group, low, medium, and high dose groups, in male rats, respectively, and 19, 17, 23, and 21, in female rats, respectively. This reviewer's analysis showed no statistically significant increase in mortality across the vehicle control group and the three treated groups in either sex of rats. The pairwise comparisons showed no statistically significant increase or decrease in mortality between each of the treated groups and the vehicle control group in either sex of rats.

2.2.2. Tumor data analysis

In the reviewer's analysis, the tumor data were analyzed for dose response relationship across vehicle control group and the treated groups, as well as the pairwise comparisons of vehicle control group with each of the treated groups using the Poly-k method described in the paper of Bailer and Portier (1988) and Bieler and Williams (1993). In this method, an animal that lives the full study period ($w_{\max}$) or dies before the terminal sacrifice with development of the tumor type being tested gets a score of $s_h = 1$. An animal that dies at Week w_h without development of the given tumor type before the end of the study gets a

score of $s_h = \left(\frac{w_h}{w_{\max}} \right)^k < 1$. The adjusted group size is defined as Σs_h . As an interpretation, an animal with score $s_h = 1$ can be considered as a whole animal, while an animal with score $s_h < 1$ can be considered as a partial animal. The adjusted group size Σs_h is equal to N (the original group size) if all animals live up to the end of the study or if each animal develops the given tumor being tested, otherwise the adjusted group size is less than N. These adjusted group sizes are then used for the dose response relationship (or the pairwise comparison) tests using the Cochran-Armitage test. One critical point for Poly-k test is the choice of the appropriate value of k. For long term 104-week standard rat and mouse studies, a value of k=3 is suggested in the literature [Gebregziabher and Hoel (2009), Moon et al. (2003), Portier, et al. (1986)]. Hence, this reviewer used k=3 for the analysis of the data. Based on the intent to treat (ITT) principle Wmax was considered as 105 for both male and female rats.

For the calculation of p-values, if there were less than 10 tumor bearing animals across all treatment groups for a given tumor type, the exact tests based on the discrete permutation distribution were used, with dose levels (0, 5, 15, and 50 for male rats and 0, 5, 20, and 75 female rats) as scores, and asymptotic tests were used for tumor types with higher incidences. The tumor rates and the p-values of the tested tumor types are listed in Tables 3A and 3B in the appendix for male rats and female rats, respectively.

Multiple testing adjustments:

Following the FDA more recently revised draft guidance for the carcinogenicity study design and data analysis, for the two-year rat study this reviewer used significance levels of 0.005 and 0.025 for common and rare tumors, respectively in dose response relationship (trend) tests and significance levels of 0.01 and 0.05 for common and rare tumors, respectively in pairwise comparisons.

A tumor is defined as a rare tumor if the published spontaneous rate or the spontaneous rate of the vehicle control of the tumor is less than 1%, and a common tumor is defined as one with tumor rate greater than or equal to 1%.

Reviewer's findings:

The tumor types with p-values less than 0.05 for dose response relationship and/or pairwise comparisons of vehicle control and treated groups are reported in Table 2.

Table 2: Tumor Types with P-Values ≤ 0.05 for Dose Response Relationship or the pairwise Comparisons

Treated Groups and Vehicle Control Group in Rats

Sex	Organ Name	Tumor Name	0 mg Cont N=70	5 mg Low N=70	15 mg Med N=70	50 mg High N=70	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
Male	Bone Marrow, Femur	Lymphoma	1	0	1	4	0.0273	1.0000	0.7343	0.2024
	Bone Marrow, Sternum	Lymphoma	1	0	1	4	0.0273	1.0000	0.7343	0.2024
	Epididymides	Lymphoma	0	0	0	3	0.0190*	.	.	0.1339
	Galt	Lymphoma	0	0	1	4	0.0069*	.	0.4815	0.0669
	Harderian Glands	Lymphoma	1	0	1	4	0.0273	1.0000	0.7343	0.2024

Sex	Organ Name	Tumor Name	0 mg Cont N=70	5 mg Low N=70	15 mg Med N=70	50 mg High N=70	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
Male	Kidneys	Lymphoma	1	0	1	4	0.0273	1.0000	0.7343	0.2024
	Liver	Lymphoma	1	0	2	4	0.0323	1.0000	0.4815	0.2024
	Lung	Lymphoma	0	0	2	4	0.0096*	.	0.2349	0.0669
	Lymph Node, Mandibular	Lymphoma	0	0	2	4	0.0096*	.	0.2349	0.0669
	Lymph Node, Mesenteric	Lymphoma	0	0	2	4	0.0096*	.	0.2349	0.0669
	Multicentric Neoplasm	Lymphoma	1	0	3	4	0.0431	1.0000	0.2895	0.2024
	Nose, Level D	Lymphoma	1	0	1	4	0.0273	1.0000	0.7343	0.2024
	Prostate Gland	Lymphoma	1	0	1	4	0.0273	1.0000	0.7343	0.2024
	Salivary Gland, Mandibular	Lymphoma	0	0	0	4	0.0049*	.	.	0.0669
	Salivary Gland, Parotid	Lymphoma	0	0	1	3	0.0225*	.	0.4815	0.1339
	Skin	Lymphoma	0	0	0	3	0.0190*	.	.	0.1339
	Spleen	Lymphoma	1	0	2	4	0.0323	1.0000	0.4815	0.2024
	Stomach, Glandular	Lymphoma	0	0	0	3	0.0190*	.	.	0.1339
	Thyroid Gland	Adenoma/Carcinoma Follicular Cell	1	4	6	3	0.4753	0.1723	0.0405	0.3347
Female	Pituitary Gland	Carcinoma, Pars Distalis	1	2	3	5	0.0366	0.5195	0.3466	0.0938
	Uterus with Cervix	Polyp, Endometrial Stromal	0	2	5	0	0.7734	0.2532	0.0354*	.
		Endometrial Stromal Sarcoma /Polyp	0	3	5	2	0.3727	0.1299	0.0354*	0.2264

*: Statistically significant at 0.005 and 0.025 level in rare tumor or 0.01 and 0.05 level in common tumor for tests of dose response relationship and pairwise comparison, respectively.

Following the multiple testing adjustment method described above, this reviewer's analysis showed statistically significant increasing dose response relationships across the vehicle control and the treated groups of male rats for the incidence of lymphoma in, epididymides, galt, lung, lymph Node, mandibular, lymph node, mesenteric, salivary gland, mandibular, salivary gland, parotid, skin, and stomach, glandular (p-value = 0.0190, 0.0069, 0.0096, 0.0096, 0.0096, 0.0049, 0.0225, 0.0190, , and <0.0190, respectively), since these tumor types was considered as rare tumors. The pairwise comparisons test showed no tumor types with a statistically significant increase in tumor incidences in VX-661 treated groups, when compare to the vehicle control group in male rats.

For female rats, this reviewer's analysis showed significant increases in the incidence of polyp, endometrial stromal and in the combined polyp, endometrial stromal and sarcoma, endometrial stromal in uterus with cervix in the medium dose groups compared with the vehicle control group (p-value = 0.0354 and 0.0354, respectively), since these tumor types were considered as rare tumors. No other significant dose response relationship or pairwise comparisons were noted in either sex.

3. Mouse Study

Two separate experiments were conducted, one in male mice and one in female mice. In each of these two experiments there were three treated groups, one vehicle control group, and one positive control group. One hundred and ten Tg rasH2 transgenic mice of each sex were assigned randomly to one of the five groups by a stratified randomization scheme designed to achieve similar group mean body weights in equal size of 25 animals except the positive control group which had 10 animals. The dose levels for treated groups were 30, 100, or 500 mg/kg/day for both male and female mice, for up to 26 weeks as indicated in Table 3. In this review, these dose groups would be referred to as the low, medium, and high dose group, respectively. The positive control group was administered with a total of three intraperitoneal injections of 1000 mg/kg of urethane formulated in 0.9% sterile saline, one each on Days 1, 3 and 5. This group was included to verify sensitivity of the test system to detect carcinogenicity effect. The vehicle control group received daily oral vehicle control article only [0.5% methylcellulose/0.5% sodium dodecyl sulfate/0.01% simethicone in deionized water], were administered in the same manner as the treated groups. The positive control mice were sacrificed on Day 78 (males) and Day 76 (females).

Table 3: Experimental Design in Mouse Study

Group Name	Group NO.	Dose Level (mg/kg/day)	Number of Animal	
			Males	Females
Vehicle Control	1	0	25	25
Low	2	30	25	25
Medium	3	100	25	25
High	4	500	25	25
Positive control	5	1000(urethane)	10	10

The positive control was administered with 3 intra-peritoneal injections on Days 1, 3 and 5.

The surviving positive control animals were sacrificed on either Day 76 (females) or Day 78

During the study period, all animals were observed for general health/mortality and moribundity twice daily (at least 6 hours apart), abnormal findings were recorded throughout the study. Cage side observations were conducted for each carcinogenicity animal once daily within 2 hours after the last animal was dosed in each group. Detailed observations were conducted for each carcinogenicity animal at least once during the pre-dose phase, prior to dosing on Day 1, and weekly thereafter throughout the dosing phase. Observations will include, but will not be limited to, evaluation for reaction to treatment. The time of onset, location, size, appearance, and progression of each grossly visible or palpable mass, observed in carcinogenicity mice, was recorded at the same intervals as detailed observations, particular attention being paid to the animals during and for the first hour after dosing. Any animal showing signs of severe debility or intoxication, and if determined to be moribund or suffering excessively will be euthanized. Histopathological examinations were performed on all animals found dead, killed moribund, or sacrificed at the end of the experiment. Body weights of individual animals were recorded pre-dose on Day 1, weekly through Week 13, and biweekly thereafter.

3.1. Sponsor's analyses

3.1.1 Survival analysis

The Kaplan-Meier's curves were presented graphically for male and female mice separately. The generalized Wilcoxon test for survival was used to compare the homogeneity of survival rates across the groups at the 0.05 significance level. If the survival rates were significantly different, the generalized Wilcoxon test was used to make pairwise comparisons of each treated group with the vehicle control

group. Additionally, the positive control group was compared to the vehicle control group using the generalized Wilcoxon test.

Survival times in which the status of the animal's death was classified as an accidental death, planned interim sacrifice or terminal sacrifice were considered censored values for the purpose of the Kaplan-Meier estimates and survival rate analyses.

Sponsor's findings:

Sponsor's analysis showed the numbers of mice surviving to their terminal necropsy were 24, 22, 24, and 19, in vehicle control, low, medium, and high dose groups in male mice, respectively, and 23, 23, 25, and 23, in female mice, respectively. Also, the numbers of mice surviving to their interim necropsy for the positive control groups in male and female mice were 10 and 9 respectively. The sponsor's report concluded that there were no statistically significant findings in survival rate in either sex of mice.

3.1.2 Tumor data analysis

Tumor incidence data were analyzed within each sex, via Peto's method, without continuity correction, incorporating the context (incidental or fatal, or mortality-independent) in which tumors were observed. The incidence of each tumor type was analyzed with a one-sided trend test using the positive dose response relationship in tumor occurrence across vehicle control and treated groups. In addition, one-sided pairwise comparisons of vehicle control and treated groups were conducted. The analysis of tumors was based on the following fixed time intervals: weeks 1 - end of study (up to, but not including, scheduled terminal sacrifices), and scheduled terminal sacrifice, for male and female mice. The actual dose levels were used as the scores. Tumors classified as mortality-independent such as, but not limited to, those of the mammary gland and skin, were analyzed with Peto's mortality-independent method incorporating the day of detection. All animals that died or were sacrificed after the first animal of that sex was terminally sacrificed were included in the scheduled terminal sacrifice interval for the incidental finding analyses. All tumors in the scheduled terminal sacrifice interval were considered incidental for the purpose of statistical analysis.

For the calculation of p-values, if there were less than 10 tumor bearing animals across all treatment groups for a given tumor type, the exact tests based on the discrete permutation distribution were used and asymptotic tests were used for tumor types with higher incidences.

Each diagnosed tumor type was analyzed separately. All metastases and invasive tumors will be considered secondary and not statistically analyzed. In addition, tumors were combined for analysis purposes at the discretion of the Study Director.

Tumor incidence in the positive control group will be compared to the vehicle control group with a 1-sided Fisher's exact test at both the 0.01 and 0.05 significance levels. Only the following tumors will be statistically analyzed: alveolar-bronchiolar adenoma, alveolar-bronchiolar carcinoma, and hemangiosarcoma in the spleen.

Multiple testing adjustment:

For multiplicity adjustment testing, no detailed information was provided in the sponsor's report.

Sponsor's findings:

Among males there was a statistically significant increase in hemangiosarcoma in the spleen when comparing the 30 mg/kg/day dose group to control. There were no other statistically significant tumor findings in the test article groups when compared to the vehicle control group among males.

Among females, there were no statistically significant tumor findings in the test article groups when compared to the vehicle control group.

3.2 Reviewer's analyses

Similar to the rat study, this reviewer independently performed the survival and tumor data analyses of the mouse study. For the analysis of the survival data and the tumor data of the mouse study, this reviewer used similar methodologies that were used for the analyses of the survival and tumor data of the rat study. Data used in this reviewer's analyses were provided by the sponsor electronically.

3.2.1 Survival analysis

The intercurrent mortality data are given in Tables 4A and 4B in the appendix for male and female mice, respectively. The Kaplan-Meier curves for death rate are given in Figures 2A and 2B in the appendix for male and female mice, respectively. Results for test of dose response relationship and homogeneity of survivals among treatment groups are given in Tables 5A and 5B in the appendix for male and female mice, respectively.

Reviewer's findings:

This reviewer's analysis showed the numbers of mice surviving to their terminal necropsy were 24, 22, 24, and 19, in vehicle control, low, medium, and high dose groups in male mice, respectively, and 23, 23, 25, and 23, in female mice, respectively. Also, the numbers of mice surviving to their interim necropsy for the positive control groups in male and female mice were 10 and 9 respectively. This reviewer's analysis showed a statistically significant dose response relationship in the mortality of male mice with p-value = 0.0253. The pairwise comparisons in male mice showed a statistically significant increased mortality in high dose groups when compared to the vehicle control group with p-value = 0.0314.

For female mice, the test showed no statistically significant dose response relationship in mortality. The pairwise comparisons showed no statistically significant increase or decrease in mortality between each of the treated groups and the vehicle control group.

3.2.2 Tumor data analysis

The tumor rates and the p-values of the tumor types tested for dose response relationship and the pairwise comparisons of vehicle control and treated groups are given in Table 6A and 6B in the appendix for male and female mice, respectively.

Multiple testing adjustment:

Also following the same FDA 2001 draft guidance for the carcinogenicity study design and data analysis, for mouse study the significance levels were 0.05 for all dose response relationship tests and pairwise comparisons, regardless of common or rare tumors.

Reviewer's findings:

The tumor types with p-values less than 0.05 for dose response relationship and/or pairwise comparisons of vehicle control and treated groups are reported in Table 4.

Table 4: Tumor Types with P-Values ≤ 0.05 for Dose Response Relationship or the pairwise Comparisons

Treated Groups and Vehicle Control Group in Mice

sex	Organ Name	Tumor Name	0 mg Veh. Cont N=25	30 mg Low N=25	100 mg Med N=25	500 mg High N=25	1000 mg pos C N=10	P_Value Dose Resp	P_Value VCvs.L	P_Value VCvs.M	P_Value VCvs.H	P_Value VC vs.Pos C
Male	Spleen	Hemangiosarcoma	0	5	0	2	10	0.4046	0.0197*	.	0.1919	<0.000*

Following the multiple testing adjustment method described above, this reviewer's analyses showed no tumor types with a statistically significant dose response relationship in tumor incidences with increased VX-661 dose in either sex of mice. The pairwise comparisons showed statistically significant increases in the low dose group for the incidences of hemangiosarcoma in the spleen, when compare to the vehicle control group in male mice (p-values =0.0197), since this tumor type was considered as rare tumors.

The pairwise comparisons also showed no tumor types with a statistically significant increase in tumor incidences in VX-661 treated groups, when compare to the vehicle control group in female mice.

The pairwise comparisons showed statistically significant increases in the positive control dose group for the incidences of alveolar-bronchiolar adenoma and in the combined alveolar-bronchiolar adenoma and carcinoma, in lungs with bronchi, hemangiosarcoma in spleen and in the whole body, when compared to the vehicle control group in both male and female mice (p-values =<0.000, <0.000, <0.000, <0.000, and <0.000, <0.0001, <0.000, <0.000, respectively).

4. Summary

In this submission, the sponsor included reports of two animal carcinogenicity studies, one in regular rats and one in transgenic mice. These studies were intended to assess the carcinogenic potential of VX-661 in rats and mice when administered orally by gavage at appropriate drug levels for about 104 weeks in rats and 26 weeks in mice.

Rat Study:

In this study two separate experiments were conducted, one in male rats and one in female rats. In each of these two experiments there were three treated groups and one vehicle control group. Two hundred and eighty Sprague-Dawley rats of each sex were assigned to three treated groups and one vehicle control group by a stratified randomization scheme designed to achieve similar group mean body weights in equal size of 70 animals, as indicated in Table 1. The dose levels for the three treated groups were 5, 15, and 50 mg/kg/day for male rats males and 5, 20, and 75 mg/kg/day for females, for up to 104 weeks. In this review these dose groups were referred to as the low, medium, and high dose group, respectively. The vehicle control group received the vehicle [0.5% methylcellulose (400 cps) (w/v), 0.5% sodium lauryl sulfate (SLS) (w/v), and 0.01% simethicone (w/v) in deionized water], administered orally by gavage for about 104 weeks in the same manner as the treated groups. Due to early termination threshold of 20 survivors rats in the male

and female vehicle control groups, early final scheduled necropsies were conducted (based on FDA recommendations) at Week 103 and at Week 101 for all surviving male and female rats, respectively.

This reviewer's analysis showed the numbers of rats surviving to their terminal necropsy were 20, 21, 16, and 25 in the vehicle control group, low, medium, and high dose groups, in male rats, respectively, and 19, 17, 23, and 21, in female rats, respectively. This reviewer's analysis showed no statistically significant increase in mortality across the vehicle control group and the three treated groups in either sex of rats. The pairwise comparisons showed no statistically significant increase or decrease in mortality between each of the treated groups and the vehicle control group in either sex of rats.

For tumor data, this reviewer's analysis showed statistically significant increasing dose response relationships across the vehicle control and the treated groups of male rats for the incidence of lymphoma in, epididymides, gall, lung, lymph Node, mandibular, lymph node, mesenteric, salivary gland, mandibular, salivary gland, parotid, skin, and stomach, glandular (p-value = 0.0190, 0.0069, 0.0096, 0.0096, 0.0096, 0.0049, 0.0225, 0.0190, and <0.0190, respectively), since these tumor types were considered as rare tumors. The pairwise comparisons test showed no tumor types with a statistically significant increase in tumor incidences in VX-661 treated groups, when compared to the vehicle control group in male rats.

For female rats, this reviewer's analysis showed significant increases in the incidence of polyp, endometrial stromal and in the combined polyp, endometrial stromal and sarcoma, endometrial stromal in uterus with cervix in the medium dose groups compared with the vehicle control group (p-value = 0.0354 and 0.0354, respectively), since this tumor type was considered as rare tumors.

No other significant dose response relationship or pairwise comparisons were noted in either sex.

Mouse Study:

Two separate experiments were conducted, one in male mice and one in female mice. In each of these two experiments there were three treated groups, one vehicle control group, and one positive control group. One hundred and ten Tg rasH2 transgenic mice of each sex were assigned randomly to one of the five groups by a stratified randomization scheme designed to achieve similar group mean body weights in equal size of 25 animals except the positive control group which had 10 animals. The dose levels for treated groups were 30, 100, or 500 mg/kg/day for both male and female mice, for up to 26 weeks as indicated in Table 3. In this review, these dose groups would be referred to as the low, medium, and high dose group, respectively. The positive control group was administered with a total of three intraperitoneal injections of 1000 mg/kg of urethane formulated in 0.9% sterile saline, one each on Days 1, 3 and 5. This group was included to verify sensitivity of the test system to detect carcinogenicity effect. The vehicle control group received daily oral vehicle control article only [0.5% methylcellulose/0.5% sodium dodecyl sulfate/0.01% simethicone in deionized water], were administered in the same manner as the treated groups. The positive control mice were sacrificed on Day 78 (males) and Day 76 (females).

This reviewer's analysis showed the numbers of mice surviving to their terminal necropsy were 24, 22, 24, and 19, in vehicle control, low, medium, and high dose groups in male mice, respectively, and 23, 23, 25, and 23, in female mice, respectively. Also, the numbers of mice surviving to their interim necropsy for the positive control groups in male and female mice were 10 and 9 respectively. This reviewer's analysis showed a statistically significant dose response relationship in the mortality of male mice with p-value = 0.0253. The pairwise comparisons in male mice showed a statistically significant increased mortality in high dose groups when compared to the vehicle control group with p-value = 0.0314.

For female mice, the test showed no statistically significant dose response relationship in mortality. The

pairwise comparisons showed no statistically significant increase or decrease in mortality between each of the treated groups and the vehicle control group.

For tumor data, following the multiple testing adjustment method described above, this reviewer's analyses showed no tumor types with a statistically significant dose response relationship in tumor incidences with increased VX-661 dose in either sex of mice. The pairwise comparisons showed statistically significant increases in the low dose group for the incidences of hemangiosarcoma in the spleen, when compare to the vehicle control group in male mice (p-values =0.0197), since this tumor type was considered as rare tumors.

The pairwise comparisons also showed no tumor types with a statistically significant increase in tumor incidences in VX-661 treated groups, when compare to the vehicle control group in female mice.

The pairwise comparisons showed statistically significant increases in the positive control dose group for the incidences of alveolar-bronchiolar adenoma and in the combined alveolar-bronchiolar adenoma and carcinoma in lungs with bronchi, and hemangiosarcoma in spleen and in the whole body when compared to the vehicle control group in both male and female mice (p-values =<0.000, <0.000, <0.000, <0.000, and <0.000, <0.0001, <0.000, <0.000, respectively).

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Mathematical Statistician

Concur: Karl Lin, Ph.D. Team Leader, DBVI
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cc:

Archival NDA 203756- VX-661

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5. Appendix

Table1A: Intercurrent Mortality Rate
Male Rats

Week	0mg/kg/day Vehicle Control		5mg/kg/day		15mg/kg/day		50mg/kg/day	
	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %
0 - 50	6	8.57	8	11.43	7	10.00	7	10.00
51 - 80	18	34.29	18	37.14	24	44.29	18	35.71
81 - 104	26	71.43	23	70.00	23	77.14	20	64.29
Ter. Sac.	20	28.57	21	30.00	16	22.86	25	35.71
Total	70	100.00	70	100.00	70	100.00	70	100.00

Table1B: Intercurrent Mortality Rate
Female Rats

Week	0mg/kg/day Vehicle Control		5mg/kg/day		20mg/kg/day		75mg/kg/day	
	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %
0 - 50	5	7.14	2	2.86	3	4.29	9	12.86
51 - 80	27	45.71	26	40.00	24	38.57	29	54.29
81 - 104	19	72.86	25	75.71	20	67.14	11	70.00
Ter. Sac.	19	27.14	17	24.29	23	32.86	21	30.00
Total	70	100.00	70	100.00	70	100.00	70	100.00

Table 2A: Intercurrent Mortality Comparison for
Male Rats

Test Statistics	P-value for Vehicle Cont. Low, Med, high	P-value for Vehicle Cont. vs Low	P-value for Vehicle Cont. vs Med	P-value for Vehicle Cont. vs High
Dose-Response (Likelihood Ratio)	0.3022	0.9532	0.3190	0.4152
Homogeneity (Log-Rank)	0.3619	0.9527	0.3127	0.4118

Table 2B: Intercurrent Mortality Comparison for
Female Rats

Test Statistics	P-value for Vehicle Cont. Low, Med, high	P-value for Vehicle Cont. vs Low	P-value for Vehicle Cont. vs Med	P-value for Vehicle Cont. vs High
Dose-Response (Likelihood Ratio)	0.6124	0.7922	0.5303	0.7079
Homogeneity (Log-Rank)	0.7591	0.7894	0.5254	0.7048

**Table3A: Tumor Rates and P-Values for Dose Response Relationship and the pairwise comparisons
Male Rats Using Poly-3 test**

Organ Name	Tumor Name	0 mg Cont N=70	5 mg Low N=70	15 mg Med N=70	50 mg High N=70	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
Adrenal Glands	Adenoma, Cortical	0	1	0	1	0.3268	0.4940	.	0.5116
	Carcinoma, Cortical	1	0	0	0	1.0000	1.0000	1.0000	1.0000
	Adenoma/Carcinoma Cortical	1	1	0	1	0.5567	0.7470	1.0000	0.7644
	Leukemia	0	0	1	0	0.4970	.	0.4750	.
	Lymphoma	1	0	2	3	0.0818	1.0000	0.4815	0.3347
	Pheochromocytoma	8	9	10	12	0.2265	0.4782	0.3077	0.2780
Aorta	Lymphoma	1	0	0	0	1.0000	1.0000	1.0000	1.0000
Bone	Osteochondroma	1	0	0	0	1.0000	1.0000	1.0000	1.0000
Bone Marrow, Femur	Leukemia	0	0	1	0	0.4970	.	0.4750	.
	Lymphoma	1	0	1	4	0.0273	1.0000	0.7343	0.2024
	Sarcoma, Histiocytic	1	0	0	0	1.0000	1.0000	1.0000	1.0000
Bone Marrow, Sternum	Leukemia	0	0	1	0	0.4970	.	0.4750	.
	Lymphoma	1	0	1	4	0.0273	1.0000	0.7343	0.2024
	Sarcoma, Histiocytic	1	0	0	0	1.0000	1.0000	1.0000	1.0000
Bone, Femur	Lymphoma	0	0	1	2	0.0670	.	0.4815	0.2588
	Sarcoma, Histiocytic	1	0	0	0	1.0000	1.0000	1.0000	1.0000
Bone, Sternum	Lymphoma	1	0	1	2	0.1808	1.0000	0.7343	0.5176
Brain	Astrocytoma	1	0	0	2	0.1790	1.0000	1.0000	0.5262
	Granular Cell Tumor	2	0	2	2	0.3339	1.0000	0.6636	0.7176
	Lymphoma	1	0	0	3	0.0612	1.0000	1.0000	0.3347
	Meningioma	0	1	0	0	0.7455	0.4940	.	.
	Oligodendroglioma	0	1	0	0	0.7455	0.4940	.	.
	Schwannoma	1	0	0	0	1.0000	1.0000	1.0000	1.0000
Cavity, Abdominal	Leiomyosarcoma	0	1	0	0	0.7455	0.4940	.	.
	Lymphoma	0	0	1	0	0.5000	.	0.4815	.
Cavity, Thoracic	Hibernoma	1	0	0	0	1.0000	1.0000	1.0000	1.0000
Coagulating Glands	Adenocarcinoma	0	1	0	0	0.7455	0.4940	.	.
	Lymphoma	0	0	0	1	0.2667	.	.	0.5116
	Sarcoma, Histiocytic	1	0	1	0	0.7515	1.0000	0.7343	1.0000
Epididymides	Lymphoma	0	0	0	3	0.0190*	.	.	0.1339
	Mesothelioma	1	0	1	0	0.7485	1.0000	0.7275	1.0000
	Sarcoma, Histiocytic	1	0	1	0	0.7515	1.0000	0.7343	1.0000
Eyes	Lymphoma	1	0	1	2	0.1808	1.0000	0.7343	0.5176

Organ Name	Tumor Name	0 mg Cont N=70	5 mg Low N=70	15 mg Med N=70	50 mg High N=70	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
Galt	Lymphoma	0	0	1	4	0.0069*	.	0.4815	0.0669
Harderian Glands	Lymphoma	1	0	1	4	0.0273	1.0000	0.7343	0.2024
Heart	Leukemia	0	0	1	0	0.4970	.	0.4750	.
	Lymphoma	1	0	1	3	0.0744	1.0000	0.7343	0.3347
	Mesothelioma, Atriocaval	0	1	0	0	0.7455	0.4940	.	.
	Sarcoma, Histiocytic	0	1	0	0	0.7455	0.4940	.	.
	Schwannoma, Endocardial	0	1	0	1	0.3268	0.4940	.	0.5116
	Lymphoma	1	0	1	3	0.0744	1.0000	0.7343	0.3347
Kidneys	Adenocarcinoma	0	1	0	0	0.7455	0.4940	.	.
	Leukemia	0	0	1	0	0.4970	.	0.4750	.
	Lipoma	1	0	0	0	1.0000	1.0000	1.0000	1.0000
	Lymphoma	1	0	1	4	0.0273	1.0000	0.7343	0.2024
	Sarcoma, Histiocytic	0	0	1	0	0.5000	.	0.4815	.
Lacrimal Glands, Exorbita	Lymphoma	1	0	1	3	0.0744	1.0000	0.7343	0.3347
Large Intestine, Cecum	Sarcoma, Histiocytic	0	0	1	0	0.5000	.	0.4815	.
Large Intestine, Colon	Lymphoma	0	0	0	2	0.0723	.	.	0.2646
Large Intestine, Rectum	Lymphoma	0	0	0	1	0.2667	.	.	0.5116
	Sarcoma, Histiocytic	1	0	1	0	0.7515	1.0000	0.7343	1.0000
Larynx	Lymphoma	0	0	0	1	0.2667	.	.	0.5116
Liver	Adenoma, Hepatocellular	3	1	1	3	0.3383	0.9391	0.9292	0.6840
	Carcinoma, Hepatocellular	2	0	1	1	0.5946	1.0000	0.8603	0.8878
	Hepatocellular Adenoma/Carcinoma	4	1	2	4	0.2881	0.9688	0.8754	0.6564
	Leukemia	0	0	1	0	0.4970	.	0.4750	.
	Lymphoma	1	0	2	4	0.0323	1.0000	0.4815	0.2024
	Sarcoma, Histiocytic	1	2	1	0	0.8800	0.4909	0.7343	1.0000
Lung	Adenocarcinoma	0	1	1	0	0.6319	0.4940	0.4815	.
	Carcinoma, Squamous Cell	1	0	0	0	1.0000	1.0000	1.0000	1.0000
	Hemangiosarcoma	0	0	0	1	0.2667	.	.	0.5116
	Leukemia	0	0	1	0	0.4970	.	0.4750	.
	Lymphoma	0	0	2	4	0.0096*	.	0.2349	0.0669
	Pheochromocytoma	0	0	0	1	0.2667	.	.	0.5116
	Sarcoma, Histiocytic	1	2	1	0	0.8800	0.4909	0.7343	1.0000
	Lymphoma	0	0	1	0	0.5000	.	0.4815	.
Lymph Node, Axillary	Lymphoma	0	0	0	1	0.2667	.	.	0.5116
Lymph Node, Mandibular	Carcinoma, Squamous Cell	1	0	0	0	1.0000	1.0000	1.0000	1.0000

Organ Name	Tumor Name	0 mg Cont N=70	5 mg Low N=70	15 mg Med N=70	50 mg High N=70	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
Lymph Node, Mediastinal	Lymphoma	0	0	2	4	0.0096*	.	0.2349	0.0669
	Sarcoma, Histiocytic	1	0	0	0	1.0000	1.0000	1.0000	1.0000
	Sarcoma, Histiocytic	1	0	0	0	1.0000	1.0000	1.0000	1.0000
Lymph Node, Mesenteric	Lymphoma	0	0	2	4	0.0096*	.	0.2349	0.0669
Mammary Gland	Sarcoma, Histiocytic	1	0	1	0	0.7515	1.0000	0.7343	1.0000
	Adenocarcinoma	0	1	0	0	0.7455	0.4940	.	.
	Carcinoma, Undifferentiated	0	0	1	0	0.5000	.	0.4815	.
Multicentric Neoplasm	Fibroadenoma	1	0	1	0	0.7485	1.0000	0.7275	1.0000
	Hemangiosarcoma	1	1	0	1	0.5567	0.7470	1.0000	0.7644
	Leukemia	0	0	1	0	0.4970	.	0.4750	.
	Lymphoma	1	0	3	4	0.0431	1.0000	0.2895	0.2024
	Mesothelioma	1	1	1	0	0.8305	0.7470	0.7275	1.0000
Nerve, Sciatic	Sarcoma, Histiocytic	2	2	1	0	0.9484	0.6830	0.8654	1.0000
	Lymphoma	0	0	0	2	0.0699	.	.	0.2588
	Leukemia	0	0	1	0	0.4970	.	0.4750	.
Nose, Level A	Lymphoma	1	0	1	3	0.0744	1.0000	0.7343	0.3347
	Leukemia	0	0	1	0	0.4970	.	0.4750	.
	Lymphoma	1	0	1	2	0.1808	1.0000	0.7343	0.5176
Nose, Level B	Adenoma	0	0	1	0	0.4970	.	0.4750	.
	Leukemia	0	0	1	0	0.4970	.	0.4750	.
	Lymphoma	1	0	1	3	0.0744	1.0000	0.7343	0.3347
Nose, Level C	Sarcoma, Histiocytic	1	0	0	0	1.0000	1.0000	1.0000	1.0000
	Leukemia	0	0	1	0	0.4970	.	0.4750	.
	Lymphoma	1	0	1	4	0.0273	1.0000	0.7343	0.2024
Nose, Level D	Sarcoma, Histiocytic	1	0	0	0	1.0000	1.0000	1.0000	1.0000
	Schwannoma	1	0	0	0	1.0000	1.0000	1.0000	1.0000
	Adenoma, Acinar Cell	0	0	2	0	0.5152	.	0.2287	.
Pancreas	Adenoma, Islet Cell	4	3	5	1	0.9201	0.7634	0.4204	0.9739
	Carcinoma	0	1	0	0	0.7455	0.4940	.	.
	Carcinoma, Islet Cell	2	3	0	2	0.5982	0.4771	1.0000	0.7089
Parathyroid Glands	Lymphoma	1	0	1	3	0.0744	1.0000	0.7343	0.3347
	Islet Cell Adenoma/Carcinoma	6	6	5	3	0.8972	0.5876	0.6483	0.9267
	Sarcoma, Histiocytic	1	0	1	0	0.7515	1.0000	0.7343	1.0000
Pituitary Gland	Adenoma, Pars Distalis	45	47	41	39	0.8550	0.3378	0.6673	0.8087

Organ Name	Tumor Name	0 mg Cont N=70	5 mg Low N=70	15 mg Med N=70	50 mg High N=70	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
Pituitary Gland	Adenoma, Pars Intermedia	0	0	1	1	0.1972	.	0.4750	0.5172
	Carcinoma, Pars Distalis	1	0	0	0	1.0000	1.0000	1.0000	1.0000
	Pars Distalis Adenoma/Carcinoma	46	47	41	39	0.8619	0.3550	0.6850	0.8224
	Leukemia	0	0	1	0	0.4970	.	0.4750	.
	Lymphoma	1	0	1	3	0.0744	1.0000	0.7343	0.3347
Preputial Glands	Leukemia	0	0	1	0	0.4970	.	0.4750	.
	Lymphoma	0	0	0	1	0.2667	.	.	0.5116
	Sarcoma, Histiocytic	1	0	0	0	1.0000	1.0000	1.0000	1.0000
Prostate Gland	Adenocarcinoma	0	1	1	0	0.6319	0.4940	0.4815	.
	Lymphoma	1	0	1	4	0.0273	1.0000	0.7343	0.2024
	Sarcoma, Histiocytic	1	0	1	0	0.7515	1.0000	0.7343	1.0000
Salivary Gland, Mandibula	Lymphoma	0	0	0	4	0.0049*	.	.	0.0669
Salivary Gland, Parotid	Lymphoma	0	0	1	3	0.0225*	.	0.4815	0.1339
Salivary Gland, Sublingua	Lymphoma	0	0	0	1	0.2667	.	.	0.5116
Seminal Vesicles	Adenocarcinoma	0	1	0	0	0.7455	0.4940	.	.
	Lymphoma	0	0	0	1	0.2667	.	.	0.5116
	Sarcoma, Histiocytic	1	0	1	0	0.7515	1.0000	0.7343	1.0000
Skeletal Muscle, Biceps F	Lymphoma	0	0	0	2	0.0723	.	.	0.2646
Skin	Adenoma, Basal Cell	1	1	0	1	0.5567	0.7470	1.0000	0.7644
	Adenoma, Sebaceous Cell	0	1	0	1	0.3319	0.4940	.	0.5172
	Carcinoma, Basal Cell	0	0	0	1	0.2667	.	.	0.5116
	Basal Cell Adenoma/Carcinoma	1	1	0	2	0.2617	0.7470	1.0000	0.5176
	Carcinoma, Squamous Cell	0	0	2	1	0.2154	.	0.2287	0.5116
	Hair Follicle Tumor	0	0	0	1	0.2667	.	.	0.5116
	Histiocytoma	0	0	0	1	0.2667	.	.	0.5116
	Keratoacanthoma	4	5	3	6	0.2914	0.4848	0.7414	0.3990
	Keratoacanthoma Squamous Cell Adenoma/Carcinoma	8	8	6	9	0.4271	0.5683	0.7518	0.5409
	Lymphoma	0	0	0	3	0.0190*	.	.	0.1339
	Papilloma, Squamous Cell	4	3	1	3	0.6187	0.7634	0.9624	0.8016
Skin, Subcutis	Fibroma	4	2	1	2	0.7388	0.8879	0.9624	0.9041
	Fibrosarcoma	2	2	0	1	0.7691	0.6738	1.0000	0.8836
	Fibroma/Fibrosarcoma	6	4	1	3	0.8196	0.8129	0.9899	0.9217
	Fibrous Histiocytoma	1	0	3	3	0.1033	1.0000	0.2895	0.3347
	Hemangiosarcoma	1	1	0	0	0.9364	0.7470	1.0000	1.0000
	Lipoma	1	0	2	2	0.1905	1.0000	0.4719	0.5262

Organ Name	Tumor Name	0 mg Cont N=70	5 mg Low N=70	15 mg Med N=70	50 mg High N=70	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
Skin, Subcutis	Lymphoma	0	0	0	1	0.2667	.	.	0.5116
	Rhabdomyosarcoma	0	0	0	1	0.2711	.	.	0.5172
	Sarcoma, Histiocytic	0	1	0	0	0.7455	0.4940	.	.
	Schwannoma	1	1	1	1	0.5252	0.7410	0.7213	0.7586
Small Intestine, Duodenum	Lymphoma	0	0	1	0	0.5000	.	0.4815	.
Small Intestine, Ileum	Lymphoma	0	0	1	2	0.0670	.	0.4815	0.2588
	Sarcoma, Histiocytic	0	0	1	0	0.5000	.	0.4815	.
Small Intestine, Jejunum	Lymphoma	0	0	0	1	0.2667	.	.	0.5116
	Sarcoma, Histiocytic	0	0	1	0	0.5000	.	0.4815	.
Spinal Cord, Cervical	Lymphoma	1	0	0	0	1.0000	1.0000	1.0000	1.0000
Spinal Cord, Lumbar	Meningioma	1	0	0	0	1.0000	1.0000	1.0000	1.0000
Spinal Cord, Thoracic	Meningioma	1	0	0	0	1.0000	1.0000	1.0000	1.0000
Spleen	Hemangiosarcoma	0	0	0	1	0.2667	.	.	0.5116
	Leukemia	0	0	1	0	0.4970	.	0.4750	.
	Lymphoma	1	0	2	4	0.0323	1.0000	0.4815	0.2024
	Sarcoma, Histiocytic	1	0	0	0	1.0000	1.0000	1.0000	1.0000
Stomach, Glandular	Lymphoma	0	0	0	3	0.0190*	.	.	0.1339
	Sarcoma, Histiocytic	0	0	1	0	0.5000	.	0.4815	.
Stomach, Nonglandular	Lymphoma	0	0	0	1	0.2667	.	.	0.5116
	Papilloma, Squamous Cell	0	0	1	0	0.4970	.	0.4750	.
Testes	Adenoma, Interstitial Cell	2	1	0	0	0.9844	0.8751	1.0000	1.0000
	Leukemia	0	0	1	0	0.4970	.	0.4750	.
	Lymphoma	0	0	0	2	0.0723	.	.	0.2646
	Mesothelioma	1	0	1	0	0.7485	1.0000	0.7275	1.0000
	Sarcoma, Histiocytic	1	0	1	0	0.7515	1.0000	0.7343	1.0000
Thymus	Lymphoma	1	0	3	3	0.1033	1.0000	0.2895	0.3347
	Sarcoma, Histiocytic	0	1	1	0	0.6319	0.4940	0.4815	.
	Thymoma	1	0	0	0	1.0000	1.0000	1.0000	1.0000
Thyroid Gland	Adenoma, C-Cell	8	8	8	3	0.9667	0.5888	0.5252	0.9754
	Adenoma, Follicular Cell	1	2	4	1	0.6759	0.4909	0.1498	0.7644
	Carcinoma, C-Cell	2	1	1	1	0.6934	0.8751	0.8603	0.8878
	Carcinoma, Follicular Cell	1	2	2	2	0.3856	0.4909	0.4620	0.5176
	Lymphoma	0	0	1	2	0.0693	.	0.4815	0.2646
	Adenoma/Carcinoma C-Cell	10	9	9	4	0.9722	0.6570	0.5897	0.9805
	Adenoma/Carcinoma Follicular Cell	1	4	6	3	0.4753	0.1723	0.0405	0.3347

Organ Name	Tumor Name	0 mg Cont N=70	5 mg Low N=70	15 mg Med N=70	50 mg High N=70	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
Tongue	Carcinoma, Squamous Cell	0	0	0	1	0.2667	.	.	0.5116
	Lymphoma	0	0	0	1	0.2667	.	.	0.5116
Tooth/Teeth	Ameloblastoma	0	1	0	0	0.7455	0.4940	.	.
Trachea	Lymphoma	0	0	0	2	0.0699	.	.	0.2588
Ureters	Sarcoma, Histiocytic	0	0	1	0	0.5000	.	0.4815	.
Urinary Bladder	Lymphoma	0	0	0	1	0.2667	.	.	0.5116
	Sarcoma, Histiocytic	1	0	1	0	0.7515	1.0000	0.7343	1.0000
Zymbal`S Gland	Carcinoma, Pars Distalis	1	0	0	0	1.0000	1.0000	1.0000	1.0000
	Carcinoma, Zymbals Gland	0	0	0	1	0.2667	.	.	0.5116
	Leukemia	0	0	1	0	0.4970	.	0.4750	.
	Lymphoma	1	0	0	2	0.1790	1.0000	1.0000	0.5262
	Sarcoma, Histiocytic	1	0	0	0	1.0000	1.0000	1.0000	1.0000

Table 3B: Tumor Rates and P-Values for Dose Response Relationship and the pairwise comparisons
Female Rats Using Poly-3 test

Organ Name	Tumor Name	0 mg Cont N=70	5 mg Low N=70	20 mg Med N=70	75 mg High N=70	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
Adrenal Glands	Adenoma, Cortical	0	0	0	1	0.2252	.	.	0.4722
	Lymphoma	1	0	1	0	0.7417	1.0000	0.7655	1.0000
	Pheochromocytoma	3	2	2	2	0.5623	0.8208	0.8358	0.7855
	Pheochromocytoma, Complex	0	0	0	1	0.2303	.	.	0.4795
	Pheochromocytoma / Pheochromocytoma Complex	3	2	2	3	0.3416	0.8208	0.8358	0.6094
Aorta	Lymphoma	1	0	0	0	1.0000	1.0000	1.0000	1.0000
Bone Marrow, Femur	Lymphoma	2	0	0	0	1.0000	1.0000	1.0000	1.0000
	Sarcoma, Histiocytic	0	0	0	1	0.2252	.	.	0.4722
Bone Marrow, Sternum	Lymphoma	2	0	0	0	1.0000	1.0000	1.0000	1.0000
	Sarcoma, Histiocytic	0	0	0	1	0.2252	.	.	0.4722
Bone, Femur	Lymphoma	1	0	0	0	1.0000	1.0000	1.0000	1.0000
Bone, Sternum	Lymphoma	2	0	0	0	1.0000	1.0000	1.0000	1.0000
Brain	Astrocytoma	2	1	0	1	0.6400	0.8799	1.0000	0.8590
	Carcinoma, Pars Distalis	1	1	2	4	0.0458	0.7597	0.5288	0.1707
	Carcinoma, Renal Tubule, (Av)	0	1	0	0	0.7483	0.5065	.	.
	Lymphoma	1	0	0	0	1.0000	1.0000	1.0000	1.0000
Cavity, Abdominal	Mesothelioma	0	1	0	0	0.7483	0.5065	.	.
Clitoral Glands	Lymphoma	0	0	1	0	0.4934	.	0.5190	.
	Papilloma, Squamous Cell	0	1	0	0	0.7483	0.5065	.	.
	Sarcoma, Histiocytic	1	0	0	0	1.0000	1.0000	1.0000	1.0000
Eyes	Lymphoma	0	0	1	0	0.4934	.	0.5190	.
Eyes, Optic Nerves	Schwannoma	0	0	1	0	0.4934	.	0.5190	.
Galt	Lymphoma	0	0	1	0	0.4934	.	0.5190	.
Harderian Glands	Lymphoma	1	0	1	0	0.7417	1.0000	0.7655	1.0000
	Sarcoma, Histiocytic	0	0	1	0	0.4901	.	0.5128	.
	Schwannoma	0	0	1	0	0.4934	.	0.5190	.
Heart	Hemangiosarcoma	0	0	1	0	0.4901	.	0.5128	.
	Lymphoma	1	0	1	0	0.7417	1.0000	0.7655	1.0000
	Sarcoma, Histiocytic	1	0	0	0	1.0000	1.0000	1.0000	1.0000
Heart	Schwannoma, Endocardial	0	0	1	0	0.4901	.	0.5128	.
Joint, Tibiofemoral	Lymphoma	1	0	0	0	1.0000	1.0000	1.0000	1.0000

Organ Name	Tumor Name	0 mg Cont N=70	5 mg Low N=70	20 mg Med N=70	75 mg High N=70	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
Kidneys	Adenoma, Renal Tubule, (Av) Type	0	0	1	0	0.4901	.	0.5128	.
	Carcinoma, Renal Tubule,	0	1	1	0	0.6074	0.5065	0.5128	.
	Renal Tubule Adenoma/Carcinoma	0	1	1	0	0.6074	0.5065	0.5128	.
	Lymphoma	1	0	1	0	0.7417	1.0000	0.7655	1.0000
	Mesothelioma	0	1	0	0	0.7483	0.5065	.	.
	Pheochromocytoma	0	0	1	0	0.4901	.	0.5128	.
	Sarcoma, Histiocytic	1	0	1	0	0.7416	1.0000	0.7659	1.0000
Lacrimal Glands, Exorbita	Lymphoma	0	0	1	0	0.4934	.	0.5190	.
Large Intestine, Colon	Lymphoma	0	0	1	0	0.4934	.	0.5190	.
Large Intestine, Rectum	Sarcoma, Histiocytic	1	0	0	0	1.0000	1.0000	1.0000	1.0000
Larynx	Lymphoma	0	0	1	0	0.4934	.	0.5190	.
Liver	Adenoma, Hepatocellular	1	0	0	1	0.4087	1.0000	1.0000	0.7325
	Cholangioma	0	0	0	2	0.0518	.	.	0.2264
	Lymphoma	2	0	1	0	0.8675	1.0000	0.8842	1.0000
	Pheochromocytoma	0	1	0	0	0.7483	0.5065	.	.
	Sarcoma, Histiocytic	1	0	1	1	0.3682	1.0000	0.7659	0.7325
Lung	Adenocarcinoma	1	1	0	0	0.9354	0.7532	1.0000	1.0000
	Lymphoma	1	0	1	0	0.7417	1.0000	0.7655	1.0000
	Pheochromocytoma	1	1	1	0	0.8158	0.7532	0.7595	1.0000
	Sarcoma, Histiocytic	1	0	1	1	0.3682	1.0000	0.7659	0.7325
Lymph Node, Hepatic	Sarcoma, Histiocytic	1	0	0	0	1.0000	1.0000	1.0000	1.0000
Lymph Node, Iliac	Lymphoma	1	0	0	0	1.0000	1.0000	1.0000	1.0000
Lymph Node, Mandibular	Lymphoma	1	0	1	0	0.7417	1.0000	0.7655	1.0000
	Sarcoma, Histiocytic	0	0	1	0	0.4901	.	0.5128	.
Lymph Node, Mediastinal	Sarcoma, Histiocytic	0	0	1	0	0.4901	.	0.5128	.
Lymph Node, Mesenteric	Hemangiosarcoma	1	0	1	0	0.7416	1.0000	0.7659	1.0000
	Lymphoma	1	0	1	0	0.7417	1.0000	0.7655	1.0000
	Sarcoma, Histiocytic	1	0	0	0	1.0000	1.0000	1.0000	1.0000
Mammary Gland	Adenocarcinoma	25	17	20	20	0.4542	0.9325	0.8260	0.7411
	Adenoma	3	2	1	0	0.9725	0.8127	0.9422	1.0000
	Fibroadenoma	31	24	22	19	0.8863	0.9215	0.9576	0.9660
	Lymphoma	0	0	1	0	0.4934	.	0.5190	.
	Sarcoma, Endometrial Stromal	0	0	0	1	0.2303	.	.	0.4795
	Sarcoma, Histiocytic	1	0	0	0	1.0000	1.0000	1.0000	1.0000

Organ Name	Tumor Name	0 mg Cont N=70	5 mg Low N=70	20 mg Med N=70	75 mg High N=70	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
Multicentric Neoplasm	Adenocarcinoma/Adenoma	28	18	21	20	0.5808	0.9603	0.8670	0.8471
	Hemangiosarcoma	2	0	2	0	0.7909	1.0000	0.7020	1.0000
	Lymphoma	2	0	1	0	0.8675	1.0000	0.8842	1.0000
	Mesothelioma	0	1	0	0	0.7483	0.5065	.	.
	Sarcoma, Histiocytic	1	0	1	2	0.1457	1.0000	0.7659	0.4688
Nerve, Sciatic	Lymphoma	0	0	1	0	0.4934	.	0.5190	.
	Sarcoma, Histiocytic	1	0	0	0	1.0000	1.0000	1.0000	1.0000
Nose, Level A	Lymphoma	1	0	1	0	0.7417	1.0000	0.7655	1.0000
	Sarcoma, Histiocytic	0	0	1	0	0.4901	.	0.5128	.
Nose, Level B	Lymphoma	1	0	1	0	0.7417	1.0000	0.7655	1.0000
	Sarcoma, Histiocytic	0	0	1	0	0.4901	.	0.5128	.
Nose, Level C	Lymphoma	1	0	1	0	0.7417	1.0000	0.7655	1.0000
	Sarcoma, Histiocytic	0	0	1	0	0.4901	.	0.5128	.
	Schwannoma	0	0	1	0	0.4934	.	0.5190	.
Nose, Level D	Lymphoma	1	0	1	0	0.7417	1.0000	0.7655	1.0000
	Sarcoma, Histiocytic	0	0	1	0	0.4901	.	0.5128	.
Ovaries	Lymphoma	1	0	1	0	0.7417	1.0000	0.7655	1.0000
	Mesothelioma	0	1	0	0	0.7483	0.5065	.	.
	Sex-Cord/Stromal Tumor	1	1	1	0	0.8200	0.7597	0.7659	1.0000
Oviducts	Lymphoma	0	0	1	0	0.4934	.	0.5190	.
	Mesothelioma	0	1	0	0	0.7483	0.5065	.	.
Pancreas	Carcinoma, Islet Cell	2	0	1	0	0.8699	1.0000	0.8891	1.0000
	Lymphoma	0	0	1	0	0.4934	.	0.5190	.
	Mesothelioma	0	1	0	0	0.7483	0.5065	.	.
	Pheochromocytoma	1	0	1	0	0.7383	1.0000	0.7595	1.0000
	Sarcoma, Histiocytic	1	0	0	1	0.4087	1.0000	1.0000	0.7325
Parathyroid Glands	Adenoma	0	0	1	0	0.4901	.	0.5128	.
Pituitary Gland	Adenoma, Pars Distalis	54	57	52	43	0.8560	0.7545	0.8987	0.9209
	Adenoma, Pars Intermedia	0	0	1	0	0.4901	.	0.5128	.
	Carcinoma, Pars Distalis	1	2	3	5	0.0366	0.5195	0.3466	0.0938
Pituitary Gland	Pars Distalis Adenoma/Carcinoma	55	59	55	48	0.7421	0.7684	0.8602	0.8588
	Lymphoma	2	0	0	0	1.0000	1.0000	1.0000	1.0000
Salivary Gland, Mandibular	Lymphoma	0	0	1	0	0.4934	.	0.5190	.
Salivary Gland, Parotid	Lymphoma	0	0	1	0	0.4934	.	0.5190	.
Salivary Gland, Sublingual	Lymphoma	0	0	1	0	0.4934	.	0.5190	.

Organ Name	Tumor Name	0 mg Cont N=70	5 mg Low N=70	20 mg Med N=70	75 mg High N=70	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
Skeletal Muscle	Lymphoma	1	0	0	0	1.0000	1.0000	1.0000	1.0000
Skeletal Muscle, Biceps, Femoris	Lymphoma	0	0	1	0	0.4934	.	0.5190	.
	Sarcoma, Endometrial Stromal	0	0	0	1	0.2303	.	.	0.4795
	Sarcoma, Histiocytic	1	0	0	0	1.0000	1.0000	1.0000	1.0000
Skin	Carcinoma, Basal Cell	0	1	0	0	0.7483	0.5065	.	.
	Carcinoma, Sebaceous Cell	0	1	0	0	0.7483	0.5065	.	.
	Carcinoma, Squamous Cell	0	1	0	0	0.7483	0.5065	.	.
	Carcinoma Basal Cell/ Carcinoma Sebaceous Cell	0	2	0	0	0.8071	0.2532	.	.
	Keratoacanthoma	1	0	0	0	1.0000	1.0000	1.0000	1.0000
	Keratoacanthoma/Carcinoma Squamous Cell	1	1	0	0	0.9354	0.7532	1.0000	1.0000
Skin, Subcutis	Fibroma	1	0	0	0	1.0000	1.0000	1.0000	1.0000
	Fibrosarcoma	2	0	0	1	0.5348	1.0000	1.0000	0.8531
	Fibroma/Fibrosarcoma	3	0	0	1	0.6424	1.0000	1.0000	0.9206
	Fibrous Histiocytoma	2	0	0	0	1.0000	1.0000	1.0000	1.0000
	Hemangiosarcoma	1	0	0	0	1.0000	1.0000	1.0000	1.0000
	Lipoma	1	0	1	0	0.7416	1.0000	0.7659	1.0000
	Melanoma	1	0	0	0	1.0000	1.0000	1.0000	1.0000
	Sarcoma, Histiocytic	0	0	1	1	0.1738	.	0.5128	0.4795
	Schwannoma	0	0	0	1	0.2303	.	.	0.4795
Small Intestine, Duodenum	Lymphoma	0	0	1	0	0.4934	.	0.5190	.
	Mesothelioma	0	1	0	0	0.7483	0.5065	.	.
Small Intestine, Ileum	Lymphoma	0	0	1	0	0.4934	.	0.5190	.
	Mesothelioma	0	1	0	0	0.7483	0.5065	.	.
	Pheochromocytoma	0	0	1	0	0.4901	.	0.5128	.
Small Intestine, Jejunum	Leiomyosarcoma	0	0	0	1	0.2252	.	.	0.4722
	Lymphoma	0	0	1	0	0.4934	.	0.5190	.
Spinal Cord, Lumbar	Astrocytoma	0	0	1	0	0.4901	.	0.5128	.
Spleen	Lymphoma	1	0	1	0	0.7417	1.0000	0.7655	1.0000
Spleen	Mesothelioma	0	1	0	0	0.7483	0.5065	.	.
Spleen	Sarcoma, Histiocytic	1	0	1	0	0.7416	1.0000	0.7659	1.0000
Stomach, Glandular	Lymphoma	1	0	1	0	0.7417	1.0000	0.7655	1.0000
	Sarcoma, Histiocytic	1	0	1	1	0.3682	1.0000	0.7659	0.7325
Stomach, Nonglandular	Leiomyosarcoma	1	0	0	0	1.0000	1.0000	1.0000	1.0000

Organ Name	Tumor Name	0 mg Cont N=70	5 mg Low N=70	20 mg Med N=70	75 mg High N=70	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
Thymus	Lymphoma	0	0	1	0	0.4934	.	0.5190	.
	Lymphoma	1	0	1	0	0.7417	1.0000	0.7655	1.0000
	Pheochromocytoma	1	0	0	0	1.0000	1.0000	1.0000	1.0000
Thyroid Gland	Sarcoma, Histiocytic	1	0	1	0	0.7416	1.0000	0.7659	1.0000
	Adenoma, C-Cell	5	8	3	3	0.8386	0.3066	0.8760	0.8214
	Adenoma, Follicular Cell	0	1	0	0	0.7483	0.5065	.	.
	Carcinoma, C-Cell	1	2	2	0	0.8325	0.5195	0.5288	1.0000
	Carcinoma, Follicular Cell	0	2	1	0	0.7125	0.2597	0.5128	.
	Lymphoma	0	0	1	0	0.4934	.	0.5190	.
	Adenoma/Carcinoma C -Cell	6	10	5	3	0.9245	0.2341	0.7551	0.8881
	Adenoma/Carcinoma Follicular Cell	0	3	1	0	0.8094	0.1299	0.5128	.
Tongue	Carcinoma, Squamous Cell	0	1	0	0	0.7483	0.5065	.	.
Trachea	Lymphoma	0	0	1	0	0.4934	.	0.5190	.
Ureters	Lymphoma	0	0	1	0	0.4934	.	0.5190	.
Urinary Bladder	Lymphoma	0	0	1	0	0.4934	.	0.5190	.
Uterus with Cervix	Sarcoma, Histiocytic	1	0	0	0	1.0000	1.0000	1.0000	1.0000
	Adenocarcinoma	1	0	1	0	0.7416	1.0000	0.7659	1.0000
	Granular Cell Tumor	0	0	1	0	0.4901	.	0.5128	.
	Leiomyoma	0	0	1	0	0.4901	.	0.5128	.
	Lymphoma	0	0	1	0	0.4934	.	0.5190	.
	Polyp, Endometrial Stromal	0	2	5	0	0.7734	0.2532	0.0354*	.
	Sarcoma, Endometrial Stromal	0	1	0	2	0.0933	0.5065	.	0.2264
	Endometrial Stromal Sarcoma /Polyp	0	3	5	2	0.3727	0.1299	0.0354*	0.2264
Vagina	Granular Cell Tumor	9	6	9	7	0.4968	0.8504	0.6045	0.7100
	Lymphoma	0	0	1	0	0.4934	.	0.5190	.
	Sarcoma, Endometrial Stromal	0	1	0	1	0.2928	0.5065	.	0.4795
Zymbal`S Gland	Sarcoma, Histiocytic	1	0	0	0	1.0000	1.0000	1.0000	1.0000
	Carcinoma, Pars Distalis	0	1	1	1	0.2688	0.5065	0.5128	0.4722

Figure 1A: Kaplan-Meier Survival Curves for
Male Rats

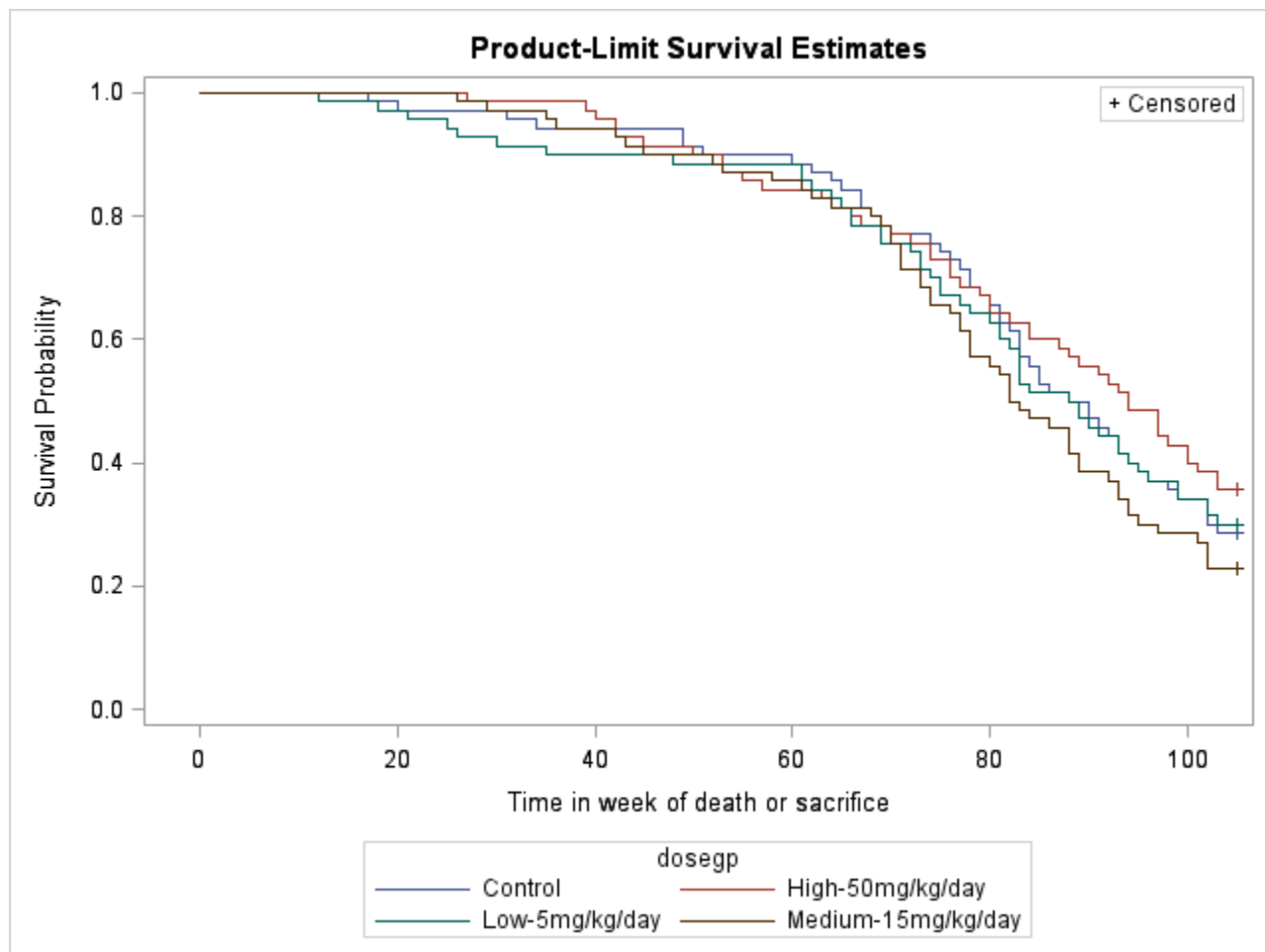


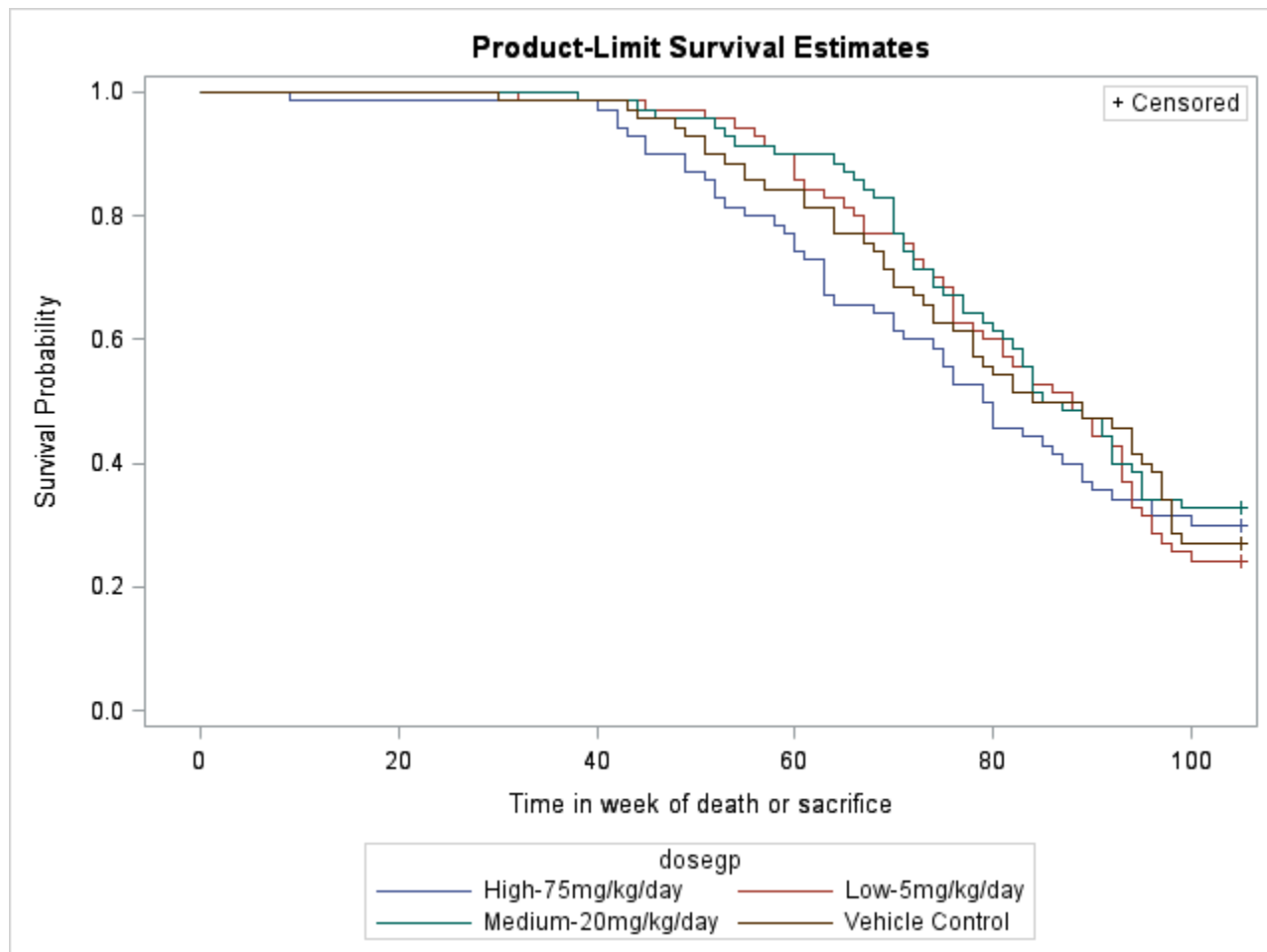
Figure 1B: Kaplan-Meier Survival Curves for
Female Rats

Table4A: Intercurrent Mortality Rate
Male Mice

Week	0mg/kg/day Vehicle Cont.		30mg/kg/day		100mg/kg/day		500mg/kg/day		1000 mg/kg/day Positive Cont.	
	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %
0 - 13	.	.	.	.	1	4.00	3	12.00		
IS									10	100.00
14 - 26	1	4.00	3	12.00	.	.	3	24.00	.	.
Ter. Sac.	24	96.00	22	88.00	24	96.00	19	76.00	.	.
Total	25	100.00	25	100.00	25	100.00	25	100.00	10	100.00

IS: Interim sacrifice on Day 78

Table4B: Intercurrent Mortality Rate
Female Mice

Week	0mg/kg/day Vehicle Cont.		30mg/kg/day		100mg/kg/day		500mg/kg/day		1000 mg/kg/day Positive Cont.	
	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %
0 - 13	2	8.00	.	.	.	.	1	4.00	1	10.00
IS									9	90.00
14 - 26	.	.	2	8.00	.	.	1	8.00	.	.
Ter. Sac.	23	92.00	23	92.00	25	100.00	23	92.00	.	.
Total	25	100.00	25	100.00	25	100.00	25	100.00	10	100.00

IS: Interim sacrifice on Day 76

Table 5A: Intercurrent Mortality Comparison for
Male Mice

Test Statistics	P-value for Vehicle Cont. Low, Med, high	P-value for Vehicle Cont. vs Low	P-value for Vehicle Cont. vs Med	P-value for Vehicle Cont. vs High	P-value for Vehicle Cont. vs Positive Cont.
Dose-Response (Likelihood Ratio)	0.0253*	0.2829	0.9885	0.0314*	.
Homogeneity (Log-Rank)	0.0596	0.2900	0.9885	0.0386*	.

* = statistically significant at the 0.05 significance level.

Table 5B: Intercurrent Mortality Comparison for
Female Mice

Test Statistics	P-value for Vehicle Cont. Low, Med, high	P-value for Vehicle Cont. vs Low	P-value for Vehicle Cont. vs Med	P-value for Vehicle Cont. vs High	P-value for Vehicle Cont. vs Positive Cont.
Dose-Response (Likelihood Ratio)	0.8063	0.9667	0.0935	0.9834	0.5014
Homogeneity (Log-Rank)	0.5573	0.9667	0.1531	0.9834	0.4765

Table 6A: Tumor Rates and P-Values for Dose Response Relationship and The pairwise Comparisons
Male Mice Using Poly-3 test

Organ Name	Tumor Name	0 mg Cont N=25	30 mg Low N=25	100 mg Med N=25	500 mg High N=25	1000 mg pos cont N=10	P_Value Dose Resp	P_Value PCvs.L	P_Value PCvs.M	P_Value PCvs.H	P_Value PCvs.Pos
Bone Marrow, Femur	Hemangiosarcoma	0	0	1	0	0	0.4783	.	0.4898	.	.
Lungs With Bronchi	Alveolar-Bronchiolar Adenoma	2	0	5	1	10	0.5667	1.0000	0.1916	0.8379	<0.000*
	Alveolar-Bronchiolar Carcinoma	3	0	0	0	3	1.0000	1.0000	1.0000	1.0000	0.0200
	Adenoma/Carcinoma Alveolar Bronchiolar	5	0	5	1	10	0.7981	1.0000	0.6099	0.9783	<0.000*
	Hemangiosarcoma	0	0	0	0	1	.	.	.	.	0.0741
Multicentric	Lymphoma	0	0	0	1	0	0.2174	.	.	0.4444	.
Spinal Cord, Lumbar	Hemangiosarcoma	1	0	0	0	0	1.0000	1.0000	1.0000	1.0000	1.0000
Spleen	Hemangiosarcoma	0	5	0	2	10	0.4046	0.0197*	.	0.1919	<0.000*
Whole Body	hemangiosarcoma	1	5	1	3	10	0.3046	0.0768	0.7449	0.2238	<0.000*

Table 6B: Tumor Rates and P-Values for Dose Response Relationship and The pairwise comparisons

Female Mice Using Poly-3 test

Organ Name	Tumor Name	0 mg Cont N=25	30 mg Low N=25	100 mg Med N=25	500 mg High N=25	1000 mg pos cont N=10	P_Value Dose Resp	P_Value PCvs.L	P_Value PCvs.M	P_Value PCvs.H	P_Value PCvs.Pos
Harderian Glands	Carcinoma	1	0	1	1	0	0.3895	1.0000	0.7757	0.7556	1.0000
Lungs with Bronchi	Alveolar-Bronchiolar Adenoma	4	0	2	2	9	0.5356	1.0000	0.9232	0.9066	<0.000*
	Alveolar-Bronchiolar Carcinoma	1	0	0	1	1	0.4275	1.0000	1.0000	0.7556	0.1567
	Adenoma/Carcinoma Alveolar Bronchiolar	5	0	2	3	9	0.4128	1.0000	0.9624	0.8786	0.0001*
Ovaries	Teratoma	0	0	0	1	0	0.2421	.	.	0.5000	.
Salivary Glands	Hemangiosarcoma	0	1	0	0	0	0.7579	0.5106	.	.	.
Spleen	Hemangiosarcoma	0	1	0	1	7	0.3091	0.5106	.	0.5000	<0.000*
Thymus	Thymoma	0	0	1	0	0	0.5053	.	0.5208	.	.
Whole Body	Hemangiosarcoma	0	2	0	1	7	0.4354	0.2553	.	0.5000	<0.000*

Figure 2A: Kaplan-Meier Survival Curves for
Male Mice

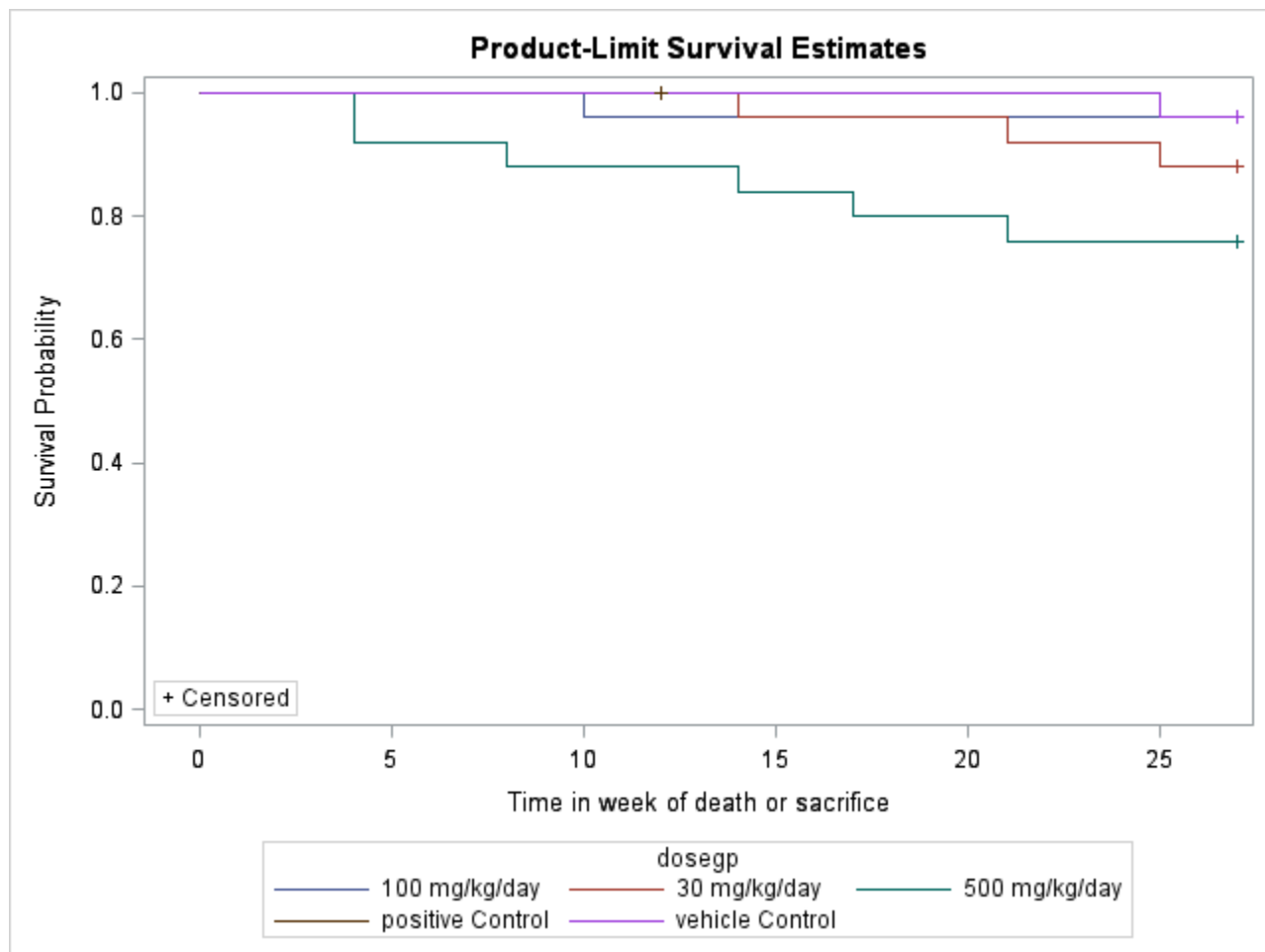
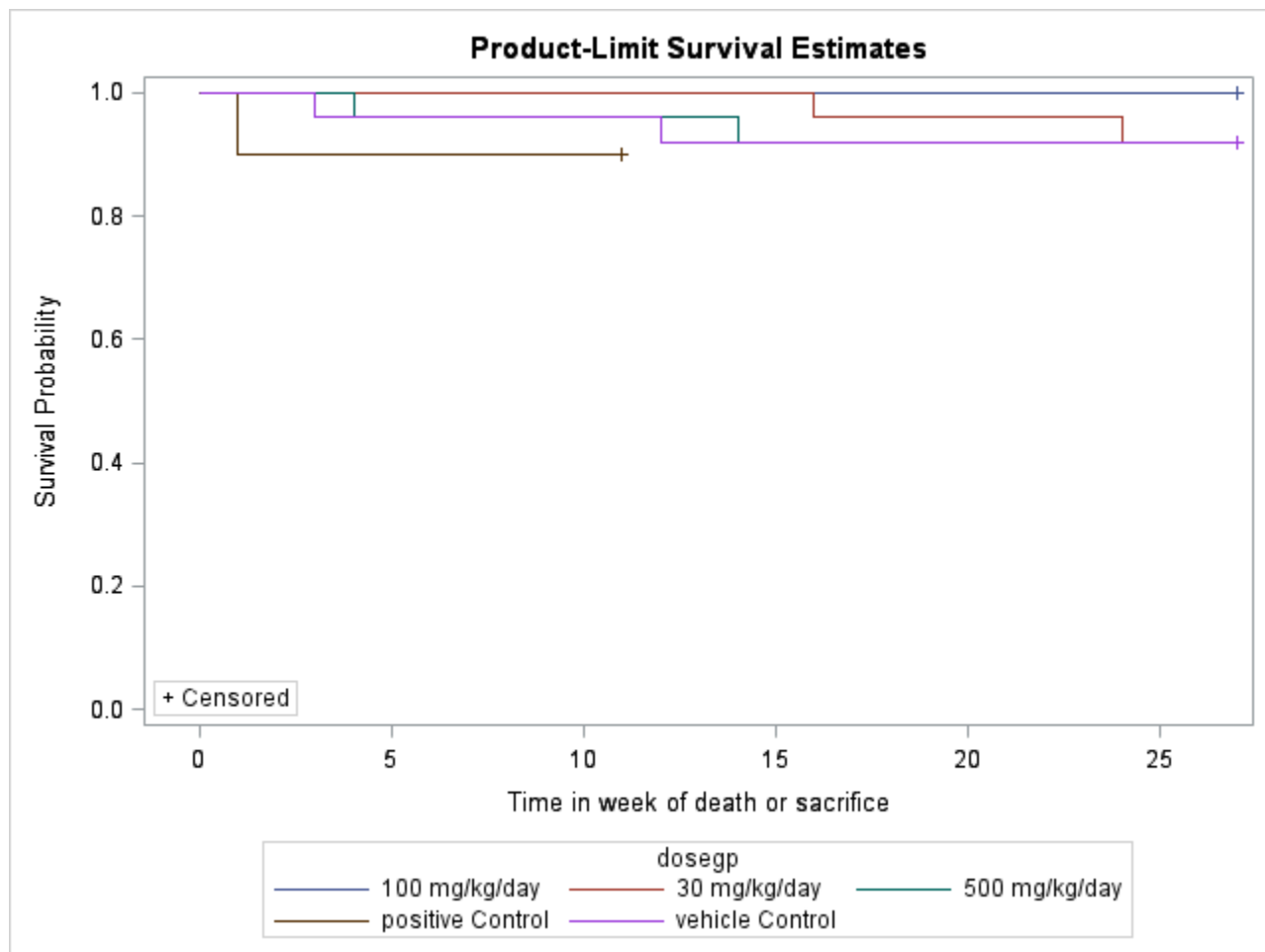


Figure 2B: Kaplan-Meier Survival Curves for
Female Mice

6. References:

1. Bailer AJ, Portier CJ (1988). "Effects of treatment-induced mortality and tumor-induced mortality on tests for carcinogenicity in small samples." *Biometrics*, 44, 417-431.
2. Bieler, G. S. and Williams, R. L. (1993). "Ratio estimates, the delta method, and quantal response tests for increased carcinogenicity". *Biometrics* 49, 793-801.
3. Gebregziabher M, Hoel D (2009) Applications of the poly-k statistical test to life-time cancer bioassay studies. *Hum Ecol Risk Assess* 15(5):858{875.
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9. Tarone RE, "Test for trend in life table analysis", *Biometrika* 1975, 62: 679-82

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/s/

MALICK MBODJ
11/22/2017

KARL K LIN
11/22/2017
Concur with review.

HEPEI CHEN
11/22/2017

STATISTICAL REVIEW AND EVALUATION FILING REVIEW OF AN NDA

NDA #: NDA 210491

Related IND #: IND 108105

Product Name: Symdeko (morning dose: TEZ 100mg/IVA 150 mg, evening dose: IVA 150 mg)

Indication: treatment of patients with CF 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 TEZ/IVA based on in vitro data and/or clinical evidence

Applicant: Vertex Pharmaceuticals Incorporated

Dates: Stamp Date: 6/28/2017

Review Priority: Priority

Biometrics Division: Office of Biostatistics, DB II

Statistical Reviewer: Mingyu Xi Ph.D.

Concurring Reviewers: Yongman Kim, Ph.D. (acting statistical team leader)

Medical Division: Division of Pulmonary, Allergy, and Rheumatology Products

Clinical Team: Stacy Chin, M.D., Anthony Durmowicz, M.D.

Project Manager: Jessica Lee

1. Summary of Efficacy/Safety Clinical Trials to be Reviewed

Table 1: Summary of Trials to be Assessed in the Statistical Review

Trial ID	Design*	Treatment/ Sample Size	Endpoint/Analysis	Preliminary Findings
Study VX14-661- 106 (1/30/2015 – 1/20/2017)	DB, R, PC trial, 12 years of age or older (24 wks) in F/F subjects	TEZ/IVA: N = 248 Placebo: N = 256	Primary: absolute change from baseline in percent predicted FEV1 (ppFEV1 through Week 24, where ppFEV1 is the ratio of FEV1 (L) to the predicted FEV1 (L), expressed as a percentage. Key Secondary: 1. Relative change from baseline in ppFEV1 through Week 24 2. Number of PExs through Week 24 3. Absolute change from baseline in body mass index (BMI) at Week 24 4. Absolute change from baseline in CFQ-R respiratory domain score through Week 24	Primary: 4.0 (3.1, 4.8) P < 0.0001 Key Secondary: 1. 6.8 (5.3, 8.3) p < 0.0001 2. 0.65 (0.48, 0.88) p = 0.0054 3. 0.06 kg/m ² p = 0.4127 4. 5.1 (3.2, 7.0) p < 0.0001
Study VX14-661- 108 (3/27/2015 – 2/16/2017)	DB, R, PC, 2-period, 3- treatment, crossover trial, 12 years of age or older (8 wks)	TEZ/IVA (A): N = 161 IVA (B): N = 156 Placebo (C): N = 161	Primary: absolute change in percent predicted FEV1 (ppFEV1) from study baseline to the average of the Week 4 and Week 8 measurements in each of the 2 Treatment Periods Key Secondary: CFQ-R respiratory domain score Secondary: 1. ppFEV1: relative change 2. Sweat chloride concentration	Primary: A vs C: 6.8 (5.7, 7.8) p < 0.0001 A vs B: 2.1 (1.2, 2.9) p < 0.0001 Key Secondary: 11.1 (8.7, 13.6) p < 0.0001

* MC: multi-center, R: randomized, DB: double-blind, PC: placebo controlled

2. Assessment of Protocols and Study Reports

Table 2: Summary of Information Based Upon Review of the Protocol(s) and the Study Report(s)

Content Parameter	Response/Comments
Designs utilized are appropriate for the indications requested.	Yes
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	Yes
Interim analyses (if present) were pre-specified in the protocol with appropriate adjustments in significance level. DSMB meeting minutes and data are available.	N/A
Appropriate details and/or references for novel statistical methodology (if present) are included (e.g., codes for simulations).	N/A
Investigation of effect of missing data and discontinued follow-up on statistical analyses appears to be adequate.	Yes

3. Electronic Data Assessment

Table 3: Information Regarding the Data

Content Parameter	Response/Comments
Dataset location	\\CDSESUB1\evsprod\NDA210491\0001\m5\datasets
Were analysis datasets provided?	Yes
Dataset structure (e.g., SDTM or ADaM)	ADaM
Are the define files sufficiently detailed?	Yes
List the dataset(s) that contains the primary endpoint(s)	adsp.xpt (study 106), adsp.xpt (study 108)
Are the <i>analysis datasets</i> sufficiently structured and defined to permit analysis of the primary endpoint(s) without excess data manipulation?	Yes
Are there any initial concerns about site(s) that could lead to inspection? If so, list the site(s) that you request to be inspected and the rationale.	No
Safety data are organized to permit analyses across clinical trials in the NDA/BLA.	Yes

4. Filing Issues

Table 4: Initial Overview of the NDA/BLA for Refuse-to-file (RTF):

Content Parameter	Yes	No	NA	Comments
Index is sufficient to locate necessary reports, tables, data, etc.	X			
ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	X			
Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated.	X			
Data sets are accessible, sufficiently documented, and of sufficient quality (e.g., no meaningful data errors).	X			
Application is free from any other deficiency that render the application unreviewable, administratively incomplete, or inconsistent with regulatory requirements	X			

IS THE APPLICATION FILEABLE FROM A STATISTICAL PERSPECTIVE?

Yes

5. Comments to be Conveyed to the Applicant

5.1. Refuse-to-File Issues

N/A

5.2. Information Requests/Review Issues

We do not have any information requests at this time.

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/s/

MINGYU XI
08/11/2017

YONGMAN KIM
08/11/2017