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
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

Statistical Review and Evaluation

CLINICAL STUDIES (ADDENDUM)

NDA/Serial Number:	202-450/S000 (Cross references: IND 68653)
Drug Name:	Tudorza Pressair® (Aclidinium Bromide, Inhalation Powder 400 µg BID)
Indication(s):	Long-term maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema.
Applicant:	Forest Laboratories, Inc.
Date(s):	Received 3/15/12; User Fee is extended to 7/23/12
Review Priority:	3 months extension
Biometrics Division:	Division of Biometrics 2/Office of Biostatistics
Statistical Reviewer:	Feng Zhou, M.S.
Concurring Reviewers:	Joan Buenconsejo, Ph.D., Team Leader Thomas Permutt, Ph.D., Division Director
Medical Division:	Division of Pulmonary, Allergy, and Rheumatology Products
Clinical Team:	Jennifer Pippins, M.D. (Medical Reviewer) Susan Limb, M.D. (Medical Team Leader) Badrul Chowdhury, M.D., Ph.D. (Medical Division Director)
Project Manager:	Sadaf Nabavian

Keywords: Clinical Studies, NDA review, baseline score

This is the second addendum for NDA 202450 to reflect changes in Table 6 from the original review (Final Statistical Review of NDA 202450 Aclidinium Bromide, in DARRTS dated 05-29-2012).

The results of the primary efficacy analysis are presented in Table 6 of the original review. Baseline scores were reported as least-square means (and standard error) based on analysis of covariance model with baseline score as dependent variable. Modeling the baseline scores is not necessary given patients are randomly assigned to the treatment arms and we are not making inferences on the baseline scores. We are in agreement with the sponsor that mean baseline scores calculated using observed data should be reported instead. The revised table with the corrected baseline scores is presented in Table 6A.

Table 6: Summary of the change from baseline in trough FEV_1 at week 12/24 (LOCF)

			Baseline	**Change from Baseline**	**Treatment Comparison AB – Placebo**		
Study	**Treatment**	**N**	**LS Mean (SE)**	**LS Mean (SE)**	**LS Mean (SE)**	**95%CI**	**P value**
M33	Placebo	185	1.383 (0.033)	-0.025 (0.015)	--	--	--
Wk12	AB200	184	1.308 (0.033)	0.061 (0.015)	0.086 (0.021)	(0.04, 0.13)	<0.001
	AB400	190	1.328 (0.032)	0.099 (0.014)	0.124 (0.021)	(0.08, 0.16)	<0.001
M38a	Placebo	182	1.418 (0.035)	-0.008 (0.015)	--	--	--
Wk12	AB200	182	1.387 (0.035)	0.043 (0.015)	0.051 (0.022)	(0.01, 0.09)	0.019
	AB400	177	1.255 (0.036)	0.064 (0.016)	0.072 (0.022)	(0.03, 0.12)	0.001
M34	Placebo	273	1.419 (0.028)	-0.047 (0.015)	--	--	--
Wk12	AB200	277	1.453 (0.028)	0.030 (0.014)	0.077 (0.020)	(0.04, 0.12)	<0.001
	AB400	269	1.447 (0.029)	0.058 (0.015)	0.105 (0.020)	(0.07, 0.14)	<0.001
M34	Placebo	273	1.419 (0.028)	-0.073 (0.016)	--	--	--
Wk24	AB200	277	1.453 (0.028)	0.026 (0.016)	0.099 (0.022)	(0.06, 0.14)	<0.001
	AB400	269	1.447 (0.029)	0.055 (0.016)	0.128 (0.022)	(0.08, 0.17)	<0.001

SE=standard error. P-value, LS mean, and LSMD obtained from an ANCOVA model with change from baseline in trough FEV_1 as response, with treatment group and sex as factors and baseline trough FEV_1 and age as covariates.

Table 6A: Summary of the change from baseline in trough FEV_1 at week 12/24 (LOCF) - Revised

			Baseline	**Change from Baseline**	**Treatment Comparison AB – Placebo**		
Study	**Treatment**	**N**	**Mean (SD)**	**LS Mean (SE)**	**LS Mean (SE)**	**95%CI**	**P value**
M33	Placebo	185	1.38 (0.57)	-0.025 (0.015)	--	--	--
Wk12	AB200	184	1.36 (0.56)	0.061 (0.015)	0.086 (0.021)	(0.04, 0.13)	<0.001
	AB400	190	1.33 (0.49)	0.099 (0.014)	0.124 (0.021)	(0.08, 0.16)	<0.001
M38a	Placebo	182	1.46 (0.52)	-0.008 (0.015)	--	--	--
Wk12	AB200	182	1.40 (0.58)	0.043 (0.015)	0.051 (0.022)	(0.01, 0.09)	0.019
	AB400	177	1.25 (0.52)	0.064 (0.016)	0.072 (0.022)	(0.03, 0.12)	0.001
M34	Placebo	273	1.50 (0.49)	-0.047 (0.015)	--	--	--
Wk12	AB200	277	1.51 (0.50)	0.030 (0.014)	0.077 (0.020)	(0.04, 0.12)	<0.001
	AB400	269	1.51 (0.53)	0.058 (0.015)	0.105 (0.020)	(0.07, 0.14)	<0.001
M34	Placebo	273	1.50 (0.49)	-0.073 (0.016)	--	--	--
Wk24	AB200	277	1.51 (0.50)	0.026 (0.016)	0.099 (0.022)	(0.06, 0.14)	<0.001
	AB400	269	1.51 (0.53)	0.055 (0.016)	0.128 (0.022)	(0.08, 0.17)	<0.001

SE=standard error. P-value, LS mean, and LSMD obtained from an ANCOVA model with change from baseline in trough FEV_1 as response, with treatment group and sex as factors and baseline trough FEV_1 and age as covariates.

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/s/

FENG ZHOU
07/11/2012

JOAN K BUENCONSEJO
07/11/2012
I concur.

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CLINICAL STUDIES (ADDENDUM)

NDA/Serial Number:	202-450/S000 (Cross references: IND 68653)
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Clinical Team:	Jennifer Pippins, M.D. (Medical Reviewer) Susan Limb, M.D. (Medical Team Leader) Badrul Chowdhury, M.D., Ph.D. (Medical Division Director)
Project Manager:	Sadaf Nabavian

Keywords: Clinical Studies, NDA review, programming error

This is the addendum for NDA 202450. Please refer to the Final Statistical Review of NDA 202450 Aclidinium Bromide for information regarding the efficacy review of the drug.

On March 14, 2012, Forest Laboratories informed the Division that a discrepancy between the source data of the St. George's Respiratory Questionnaire (SGRQ) and the applicant's database was recently identified for Study M34. The applicant submitted the corrected SGRQ data including the updated SGRQ tables, figures, listings, and analysis datasets for the Clinical Study Report (CSR) for Study M34, as well as the Integrated Summary of Effectiveness (ISE).

The sponsor stated that:

> This finding relates to a systematic error in the programming of the data transfer from the CRO (Parexel) to the Sponsor's clinical database. Specifically, in the process of converting the data to the Sponsor's database structure, the code list for the response choices of item 5 of the SGRQ was inverted (i.e., the possible response to item 5 of each SGRQ assessment documented in Parexel's database as 1, 2, 3, 4, or 5 was inverted during the conversion to the Sponsor's database to 5, 4, 3, 2, or 1, respectively).
>
> Forest has evaluated the impact of these changes on the overall interpretation of the SGRQ results for aclidinium bromide. The magnitude of the treatment effect on SGRQ is slightly better for aclidinium as a result of this correction, but not of a magnitude large enough to alter the conclusions. Therefore, the original conclusions are still correct.

I verified the results for the SGRQ using the new data for Study 34 and confirmed that the magnitude of effect was slightly better but did not change the overall conclusion. The results based on ANCOVA model using corrected SGRQ datasets are presented in Table 1, and for comparison purpose, the results using the original datasets are presented in Table 2. Like in the original analyses, only AB400 in Study M34 showed significant difference in SGRQ total scores compared to placebo that exceeds the MCID of -4 at weeks 12 and 24 [-4.1 with 95% CI of (-6.1, -2.1) after 12 weeks treatment and -4.6 with 95%CI of (-6.8, -2.4) after 24 weeks treatment].

Table 1: Summary of the change from baseline in SGRQ Total Score at week 12/24 (Corrected)

			Baseline	**Change from Baseline**	**Treatment Comparison AB - Placebo**		
Study	**Treatment**	**N**	**LS Mean (SE)**	**LS Mean (SE)**	**LS Mean (SE)**	**95%CI**	**P value**
M33	Placebo	181	45.32 (1.25)	-2.04 (0.77)	--	--	--
Wk12	AB200	180	45.60 (1.26)	-4.77 (0.77)	-2.73 (1.09)	(-4.87, -0.59)	0.013
	AB400	189	48.48 (1.23)	-4.58 (0.75)	-2.54 (1.08)	(-4.66, -0.43)	0.019
M38a	Placebo	178	48.76 (1.29)	-4.32 (0.96)	--	--	--
Wk12	AB200	178	47.93 (1.29)	-5.98 (0.96)	-1.66 (1.36)	(-4.32, 1.00)	0.222
	AB400	172	50.55 (1.31)	-5.40 (0.97)	-1.08 (1.37)	(-3.78, 1.61)	0.429
M34	Placebo	271	45.13 (1.09)	-2.36 (0.72)	--	--	--
Wk12	AB200	275	46.42 (1.07)	-5.52 (0.71)	-3.17 (0.99)	(-5.12, -1.21)	0.002
	AB400	269	47.88 (1.09)	-6.45 (0.72)	-4.10 (1.00)	(-6.06, -2.13)	<0.001
M34	Placebo	271	45.13 (1.09)	-2.29 (0.82)	--	--	--
Wk24	AB200	275	46.42 (1.07)	-6.61 (0.80)	-3.82 (1.12)	(-6.01, -1.62)	<0.001
	AB400	269	47.88 (1.09)	-7.41 (0.82)	-4.63 (1.13)	(-6.84, -2.42)	<0.001

SE=standard error. P-value, LS mean, and LSMD obtained from an ANCOVA model with change from baseline in SGRQ score as response, with treatment group and sex as factors and baseline SGRQ score and age as covariates.

Table 2: Summary of the change from baseline in SGRQ Total Score at week 12/24 (Original)

			Baseline	Change from Baseline	Treatment Comparison AB - Placebo		
Study	**Treatment**	**N**	**LS Mean (SE)**	**LS Mean (SE)**	**LS Mean (SE)**	**95%CI**	**P value**
M33	Placebo	181	45.32 (1.25)	-2.04 (0.77)	--	--	--
Wk12	AB200	180	45.60 (1.26)	-4.77 (0.77)	-2.73 (1.09)	(-4.87, -0.59)	0.013
	AB400	189	48.48 (1.23)	-4.58 (0.75)	-2.54 (1.08)	(-4.66, -0.43)	0.019
M38a	Placebo	178	48.76 (1.29)	-4.32 (0.96)	--	--	--
Wk12	AB200	178	47.93 (1.29)	-5.98 (0.96)	-1.66 (1.36)	(-4.32, 1.00)	0.222
	AB400	172	50.55 (1.31)	-5.40 (0.97)	-1.08 (1.37)	(-3.78, 1.61)	0.429
M34	Placebo	271	45.39 (1.04)	-2.06 (0.70)	--	--	--
Wk12	AB200	275	46.58 (1.02)	-5.12 (0.69)	-3.06 (0.96)	(-4.94, -1.18)	0.002
	AB400	269	48.02 (1.04)	-6.03 (0.70)	-3.97 (0.96)	(-5.86, -2.08)	<0.001
M34	Placebo	271	45.39 (1.04)	-2.63 (0.79)	--	--	--
Wk24	AB200	275	46.58 (1.02)	-6.20 (0.77)	-3.57 (1.08)	(-5.69, -1.46)	<0.001
	AB400	269	48.02 (1.04)	-6.92 (0.78)	-4.29 (1.08)	(-6.42, -2.16)	<0.001

SE=standard error. P-value, LS mean, and LSMD obtained from an ANCOVA model with change from baseline in SGRQ score as response, with treatment group and sex as factors and baseline SGRQ score and age as covariates.

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/s/

FENG ZHOU
05/29/2012

JOAN K BUENCONSEJO
05/29/2012
I concur with Ms. Feng Zhou's (addendum) review.

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CLINICAL STUDIES

NDA/Serial Number:	202-450/S000 (Cross references: IND 68653)
Drug Name:	Tudorza Pressair® (Aclidinium Bromide, Inhalation Powder 400 µg BID)
Indication(s):	Long-term maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema.
Applicant:	Forest Laboratories, Inc.
Date(s):	Received 6/23/11; User Fee 4/23/12
Review Priority:	Standard
Biometrics Division:	Division of Biometrics II/Office of Biostatistics
Statistical Reviewer:	Feng Zhou, M.S.
Concurring Reviewers:	Joan Buenconsejo, Ph.D., Team Leader Thomas Permutt, Ph.D., Division Director
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Clinical Team:	Jennifer Pippins, M.D. (Medical Reviewer) Susan Limb, M.D. (Medical Team Leader) Badrul Chowdhury, M.D., Ph.D. (Medical Division Director)
Project Manager:	Sadaf Nabavian

Keywords: Clinical Studies, NDA review, Dropouts, missing data

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

Forest Laboratories, Inc., proposes aclidinium bromide inhalation powder 400 μg twice daily, an orally inhaled anticholinergic (muscarinic receptor antagonist), for long term, maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema. Based on evaluation of 24-hour post-dose trough FEV1 after 12 weeks treatment, the applicant claims aclidinium bromide is effective in relieving bronchoconstriction in COPD patients.

Based on my review, in all three trials, both Aclidinium Bromide 200 and 400 μg twice daily provided statistically significant improvements in trough FEV1 compared to placebo. This was supported by other lung function measurements like peak FEV1 and serial FEV1. Improvement in trough FEV1 is numerically larger in Aclidinium Bromide 400 μg twice daily compared to Aclidinium Bromide 200 μg twice daily. Only Aclidinium Bromide 400 μg twice daily in Trial 34 showed a significant difference in SGRQ total scores compared to placebo that met the MCID of 4 points. This finding was not replicated in the other two trials. Because the overall exacerbation rate was low, it is difficult to make a definitive assessment regarding exacerbation from these three trials.

1.2 Brief Overview of Clinical Studies

Aclidinium bromide is an orally inhaled anticholinergic (muscarinic receptor antagonist), for long-term, maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema. Currently, three long-acting bronchodilators are available to patients with COPD: a long-acting once daily anticholinergic, tiotropium; and two long-acting twice daily β_2-agonists, formoterol and salmeterol. They are often used as monotherapy or in combination with other classes of medication, such as inhaled corticosteroids. In this application, aclidinium bromide provides a new treatment option for patients with COPD.

The clinical efficacy program for aclidinium bromide 200 μg and 400 μg, administered BID was conducted in North America, Europe, Russia, South Africa, and Latin America. The program comprised 3 Phase 3 efficacy studies with 1933 randomized patients (M/34273/34, LAS-MD-33, and LAS-MD-38 [Part A], hereafter, refer to studies M34, M33, and M38a) and 5 supportive studies, 2 Phase 2 dose-range finding studies with 109 randomized patients (M/34273/23 and M/34273/29, hereafter, refer to studies M23 and M29), and 3 long-term safety studies with 1344 randomized patients (LAS-MD-35, LAS-MD-36, and LAS-MD-38 [Part B]).

Study M23 was a phase 2, randomized double-blinds, double-dummy, placebo- and active-comparator controlled, 3-period crossover dose range study and conducted at 2 centers in Germany. This was the first clinical study that investigated the 24-hour bronchodilator profile of multiple doses of inhaled aclidinium bromide BID administered to the same patient population as that included in the phase 3 studies of BID administration. Total of 30 patients were randomized

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into study and it had three arms: aclidinium bromide 400 µg BID, tiotropium 18 µg QD and placebo. Study M29 was a phase 2, randomized, double-blind, double-dummy, placebo- and active-comparator controlled, 5-period crossover dose ranging study and conducted at 11 centers in Germany and Belgium. It had five arms: aclidinium bromide 100 µg BID, 200 µg BID, 100 µg BID, formoterol 12 µg, and placebo. About 79 patients were randomized to the study.

Study M34 had three arms: aclidinium bromide 200 µg BID, 400 µg BID, and placebo. About 280 patients were randomized to each arm. The study was 24 weeks long and was conducted in Europe, South Africa. Studies M33 and M38a were identical in design. They both had three arms: aclidinium bromide 400 µg BID, 200 µg BID, and placebo. About 180 patients were randomized to each arm. Both studies were 12 weeks long and conducted in Canada and USA.

1.3 Statistical Issues and Findings

During my review of the clinical studies, I found no issues that could not be resolved by re-analyzing the data. Multiplicity adjustments were applied to the primary and key secondary endpoints. When different analytical methods and imputation strategies were applied to the primary endpoint, the results were consistent and highly significant. Furthermore, the results generated by the applicant and by me are similar and do not change the overall conclusion.

The major efficacy findings are as follows:

- The treatment effect of aclidinium bromide was measured by the change from baseline at week 12 in trough FEV_1. Both aclidinium bromide 400 µg BID and aclidinium bromide 200 µg BID demonstrated statistically significant improvements compared to placebo in trough FEV_1 after 12 weeks treatment in all three phase 3 studies. The treatment difference between aclidinium bromide 400 µg and placebo ranged from 72 to 124 mL. The magnitude of treatment difference between aclidinium bromide 200 µg and placebo is smaller than that observed between the 400 µg dose and placebo with a treatment effect ranging from 51 to 86 mL.

- Both aclidinium bromide 400 µg BID and aclidinium bromide 200 µg BID demonstrated statistically significant improvements (from baseline FEV_1 which was defined as pre-dose FEV_1 at Day 1) compared to placebo in peak FEV_1 after 12 weeks of treatment in all three phase 3 studies. The treatment effects between aclidinium bromide 400 and placebo ranged from 125 to 192 mL. The magnitude of treatment difference between aclidinium bromide 200 µg and placebo is smaller than that observed between aclidinium bromide 400 µg and placebo with a treatment effect ranging from 115 to 182 mL.

- The percentage of patients achieving an improvement (or at least a 4-point reduction from baseline) in SGRQ Total Score at week 24 was a key secondary efficacy endpoint in Study M34 only. There were significantly higher proportions of patients treated with aclidinium bromide 400 µg or aclidinium bromide 200 µg achieving an improvement in SGRQ total score compared to patients treated with placebo at weeks 12 and 24. This endpoint was also explored in the studies M33 and M38a. A significant difference was only observed between

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the aclidinium bromide 200 µg group and placebo for Study M33. When SGRQ total score was evaluated as a continuous endpoint, only aclidinium bromide 400 µg in Study M34 showed a significant difference in SGRQ total scores compared to placebo that exceeds MCID of -4 at weeks 12 and 24 [-4.0 with 95% CI of (-5.9, -2.1) after 12 weeks treatment and -4.3 with 95% CI of (-6.4, -2.2) after 24 weeks treatment]. Treatment difference between aclidinium bromide 400 µg and placebo in SGRQ total scores in the other two studies ranged from -1.1 to -2.5, while treatment difference between aclidinium bromide 200 µg and placebo ranged from -1.7 to -3.6 in all three studies.

2. INTRODUCTION

2.1 Overview

2.1.1 Class and Indication

Forest Laboratories, Inc., proposes aclidinium bromide inhalation powder 400 µg twice daily (BID), an orally inhaled anticholinergic (muscarinic receptor antagonist), for long-term, maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema. Currently, three long-acting bronchodilators are available to patients with COPD: a long-acting once daily anticholinergic, tiotropium; and two long-acting twice daily β_2-agonists, formoterol and salmeterol. They are often used as monotherapy or in combination with other classes of medication, such as inhaled corticosteroids. In this application, aclidinium bromide provides a new treatment option for patients with COPD.

2.1.2 History of Drug Development

The clinical development program for aclidinium bromide was introduced to the Division of Pulmonary, Allergy, and Rheumatology Products in 2003 and originally focused on the development of aclidinium bromide as a once daily (QD) treatment regimen for patients with COPD. In anticipation of submitting an NDA in 2009 for the QD regimen, Forest Laboratories obtained feedback from the Division on the completeness of the application at a pre-NDA meeting on 03 March 2009. At the meeting, the Division responded that while the results of the two Phase 3 studies, (M/34273/30 and M/34273/31) demonstrated statistical significance for aclidinium bromide 200 µg QD vs. placebo for the primary endpoint of trough FEV_1, the treatment difference of 0.061 L was of "uncertain clinical significance," and the Division recommended "exploration of higher doses and more frequent dosing regimens to ensure the selection of the most appropriate and efficacious dose of aclidinium bromide for marketing."

Based on the Division's feedback at the 03 March 2009 pre-NDA meeting, Forest evaluated a higher and more frequent dosing regimen and generated new data focusing on the evaluation of aclidinium bromide at doses ranging from 100 µg to 400 µg BID.

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On 25 February 2011, Forest received responses from the Division to questions provided in a 31 January 2011 pre-NDA meeting package in support of the aclidinium bromide 400 µg BID dose in COPD: *"The data provided from LAS-MD-33 and M/342723/34 support the proposal of a 400 µg BID dose of aclidinium bromide for COPD patients. The decision regarding filing and potential approval will be based upon our review at the time of NDA submission."*

2.1.3 Specific Studies Reviewed

The clinical efficacy program for aclidinium bromide 200 and 400 µg, administered BID was conducted in North America, Europe, Russia, South Africa, and Latin America. The program comprised three Phase 3 efficacy studies in 1933 randomized patients (M/34273/34, LAS-MD-33, and LAS-MD-38 [Part A]) and five supportive studies, two Phase 2 dose-range finding studies in 109 randomized patients (M/34273/23 and M/34273/29), and three long-term safety studies in 1344 randomized patients (LAS-MD-35, LAS-MD-36, and LAS-MD-38 [Part B]). Study LAS-MD-38 consisted of two parts: part A was a double-blind, placebo-controlled period, and part B, which was an open-label, one treatment arm (aclidinium bromide 400 µg BID), 40-week safety extension.

In this original NDA submission, the focus of my review will be on the two dose-range finding studies, M/34273/23 and M/34273/29 (hereafter referred to as studies M23 and M29) and on the three efficacy studies M/34273/34, LAS-MD-33, LAS-MD-38A (hereafter referred to as studies M34, M33, and M38a) in COPD patients. The dose-ranging trials were conducted to support the selection of dose and nominal dosing frequency and the three Phase 3 studies were conducted to support the efficacy of aclidinium bromide.

Throughout the review, aclidinium bromide will be written as AB and corticosteroid as CS.

2.2 Data Sources

All data was supplied by the applicant to the CDER electronic data room in SAS transport format. The information needed for this review was contained in modules 1, 2.7, and 5.3.5.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy Studies

3.1.1 Study Design

The design of two dose selection studies is summarized in Table 1, Figure 1, and Figure 2. Study M23 was the first clinical study that investigated the 24-hour bronchodilator profile of multiple doses of inhaled aclidinium bromide BID administered to the same patient population as that included in the phase 3 studies of BID administration. The objective of this study was to evaluate

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the efficacy of AB 400 µg BID in moderate to severe COPD patients. A total of 30 patients were randomized into the three arms of the study: AB 400 µg BID, tiotropium 18µg QD, and placebo. Study M29 was designed to assess the efficacy and safety of three doses (100 µg, 200 µg, or 400 µg) BID of AB with placebo and formoterol 12 µg BID in patients with stable moderate to severe COPD. Seventy-nine patients were randomized to the study. During the run-in period and throughout the study, salbutamol/ albuterol were allowed as rescue medication.

Table 1: Design of Dose Selection Studies

Study ID (Period)	**Location**	**Design and treatment duration**	**Number of Patients randomized**	**Treatment arms**	**Primary /Secondary Endpoint(s)**
M23 (M/34273/23) (Mar. 2009 – Jul. 2009)	2 centers in Germany	2 weeks, 3 way cross-over, Double-blind, Parallel-arm, Placebo-controlled Active-controlled	30	AB 400 µg BID Tiotropium 18 µg QD Placebo	Change from baseline in normalized FEV_1 AUC_{0-12} [L] at Day 15
M29 (M/34273/29) (Apr. 2010 – Aug. 2010)	11 centers in Germany and Belgium	1 weeks, 5 way cross-over Double-blind, Parallel-arm, Placebo-controlled Muti-doses	79	AB 400 µg BID AB 200 µg BID AB 100 µg BID Formoterol 12µg BID Placebo	Change from baseline in normalized FEV_1 AUC_{0-12} [L] at Day 7

Figure 1: Study Design for Study M23

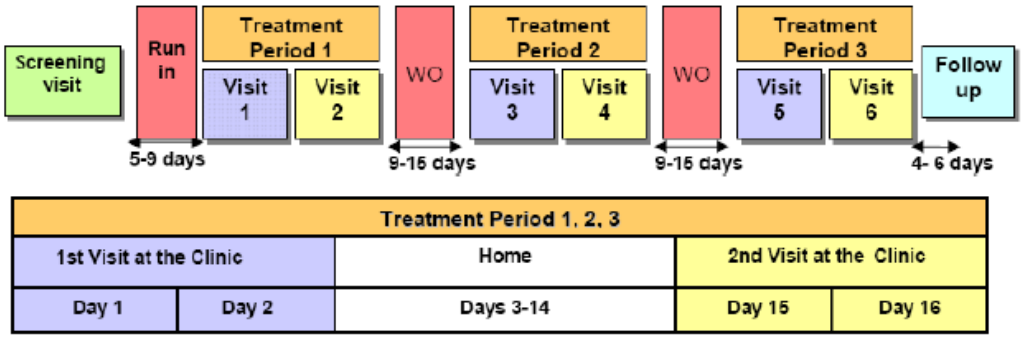
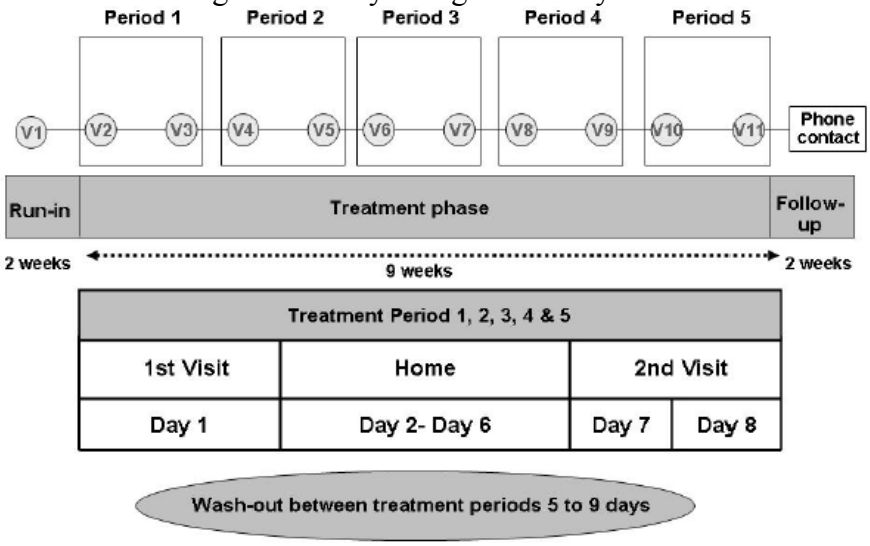


Figure 2: Study Design for Study M29



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The objective of the three Phase 3 studies was to assess the long-term bronchodilator efficacy of AB 200 µg BID and 400 µg BID, as compared with placebo in patients with moderate to severe COPD. The design of the three phase 3 efficacy studies is summarized in Table 2.

Studies M33 and M38a were identical in study design. About 540 patients were randomized to AB 400 µg BID, 200 µg BID, and placebo with a 1:1:1 ratio in each study. Both studies were 12 weeks long and conducted in Canada and USA. Study M34 was almost of similar in design to studies M33 and M38 with the following exceptions: (1) 24 weeks long, (2) conducted in Europe and South Africa, (3) about 840 patients were randomized to AB 400 µg BID, 200 BID, and placebo with a 1:1:1 ratio, and (4) had additional key secondary endpoints not found in the other two studies.

All three studies had two weeks follow-up period. Rescue medication (albuterol hydrofluoroalkane 108 µg/puff or salbutamol sulfate 100 µg/puff) was permitted as needed throughout the study for all participants. In addition, several background medications for the treatment of COPD (e.g., ICSs, oral or parenteral corticosteroids up to a maximum of 10 mg/day of prednisone or 20 mg every other day, long-acting theophylline) were permitted if the patient had been stable for at least 4 weeks before entering the study.

Table 2: Design of Key Controlled Efficacy Studies

Study ID (Period)	**Location**	**Design**	**# of Patients randomized**	**Treatment arms**	**Primary /Secondary Endpoint(s)**
M34 (M/34273/34) (Oct. 2009 – Nov. 2010)	100 sites in 11 countries (Czech Republic, France, Germany, Hungary, Italy, Peru, Poland, Russian, Spain, South Africa, Ukraine)	24 weeks, Double-blind, Parallel-arm, Placebo-controlled	272 280 276	AB 400 µg BID AB 200 µg BID Placebo	Trough FEV_1/ Peak FEV_1, TDI, SGRQ
M33 (LAS-MD-33) (Apr. 2009 – Nov. 2010)	99 sites in USA, Canada	12 weeks, Double-blind, Parallel-arm, Placebo-controlled	190 185 186	AB 400 µg BID AB 200 µg BID Placebo	Trough FEV_1/ Peak FEV_1
M38a (LAS-MD-38A) (Dec. 2009 – Sep. 2010)	103 sites in USA and Canada	12 weeks, Double-blind, Parallel-arm, Placebo-controlled	178 184 182	AB 400 µg BID AB 200 µg BID Placebo	Trough FEV_1/ Peak FEV_1

3.1.2 Efficacy Endpoints and Assessment Schedule

Serial spirometry over 24 hours post-dose was collected in two dose-range finding studies. The primary efficacy endpoint was change from baseline in normalized $AUC_{0\text{-}12h}$ ($AUC_{0\text{-}12h/12}$) of FEV_1 at day 15 and 7 for studies M23 and M29, respectively. Other endpoints analyzed were changes from baseline in $AUC_{0\text{-}12h}$, and $AUC_{0\text{-}12h}$ of FEV_1 and FVC, morning and evening FEV_1 and FVC at pre-dose, peak and by time point, changes from baseline in daily COPD symptom scores, as well as the average of the day and night use of rescue medication.

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In Study M23, the spirometry assessments were taken at the following time points:

- On day 1 at: 60 and 0 min pre-dose, 30 mins, 1, 2, 3, 4, 6, 8, 10, 11, 12 hrs, 12hrs 30mins, 13, 14, and 15 hrs post dose.
- On day 2 at: 16, 19, 22, 23,and 24 hrs post-dose
- On day 15 at: 60* and 0 min* pre-dose, 30 mins, 1, 2, 3, 4, 6, 8, 10, 11, 12 hrs, 12hrs 30mins, 13, 14, and 15 hrs post dose.
- On day 16 at: 16, 19, 22, 23,and 24 hrs post-dose

* PFTs had to be performed a 23 and 24 hrs after the morning dose administration on Day 14.

In Study M29, the spirometry assessments were taken at the following time points:

- On day 1 at: 60 and 0 min pre-dose, 30 mins, 1, 2, 3, 4, 6 hrs post dose.
- On day 7 at: 60* and 0 min* pre-dose, 30 mins, 1, 2, 3, 4, 6, 8, 10, 11, 12, 13, 14, 15, 16, 22, 23, 24 hrs post dose.
- On day 16 at: 16, 19, 22, 23,and 24 hrs post-dose

* PFTs had to be performed a 23 and 24 hrs after the morning dose administration on Day 14.

The primary efficacy endpoint in the three phase 3 efficacy studies was 24-hour post-dose trough FEV_1 (defined as the average of the two values measured at two time points -45 min and -15 min prior to the administration of the morning dose) after 12 weeks treatment.

In Study M33 and M38a, the key secondary efficacy endpoint was peak FEV_1 (defined as the highest FEV_1 value observed in the 3-hour period immediately after morning dosing) at week 12 only. Other endpoints, like FVC (forced vital capacity), PEF (peak expiratory flow), SGRQ (St. George's respiratory questionnaire) score, TDI (transitional dyspnea index) focal score, COPD exacerbation, rescue medication use, etc., were considered exploratory. This review only includes details on trough FEV_1, serial spirometry profiling, SGRQ score, and rescue medication use, as well as COPD exacerbations. These are endpoints commonly evaluated in the COPD development program and are often the basis of showing evidence of efficacy. While the Applicant is not seeking specific claims based on SGRQ, rescue medication use, and exacerbation endpoints, these endpoints were of particular interest because they are alternate, non-spirometric assessments of efficacy that are commonly evaluated in other COPD development programs. The results are considered exploratory and are presented in this review primarily to provide additional context for the efficacy data based on FEV1.

In Study M34, the key secondary efficacy variables include:

- Change from baseline in peak FEV_1 (defined as the highest FEV_1 value observed in the 3-hour period immediately after morning dosing) at week 12
- Percentage of patients achieving an improvement (defined as at least 1 unit change from baseline) in TDI focal score at week 24.
- Percentage of patients achieving an improvement (defined as at least a 4-point reduction from baseline)) in the SGRQ total score at Week 24.

The 12-hour spirometry profiling (at 4, 6, 8, 10, and 12 hours post-dose) was assessed in a subset of patients (20 to 30% of all patients of the study) at clinical visit at week 0, 12, and 24 (Study M34 only). Pre-dose spirometry was assessed at clinical visit at week 0, 1, 4, 8, 12, 18, and 24; post-dose spirometry (up to 3h) was assessed at clinical visit at week 0, 1, 4, 12, and 24 (Study M34 only). Baseline for all the spirometric variables (FEV_1, FEV, and IC) was defined as the

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average of the two values measured at two time point -45 min and -15 min prior to the administration of the first dose at visit 2.

In all three phase 3 efficacy studies, a patient diary to record daily clinical symptoms, rescue medication use, and any adverse events was provided to all patients. SGRQ scores were derived from the diary information. At each study visit, all COPD exacerbations, regardless of treatment, were evaluated based on the definition and recorded on the COPD exacerbation episode electronic Case Report Form (eCRF). Definition for COPD exacerbation was based on the Health Resource Utilization, and was defined as an increase in COPD symptoms (eg, dyspnea, cough, sputum volume, sputum purulence) during at least 2 consecutive days with severity characterized as follows:

- Mild: self-managed by the patient at home by increasing short-acting bronchodilator and/or ICS use
- Moderate: did not lead to hospitalization but was treated with antibiotics and/or systemic corticosteroids
- Severe: led to hospitalization (overnight stay at hospital or emergency room [ER])

For Study M34, COPD exacerbation was also evaluated using the EXACT-PRO questionnaire. The COPD exacerbation counts based on the two methods were summarized and reported.

3.1.3 Patient Disposition, Demographic and Baseline Characteristics

Since the study duration was short in the two dose-range finding studies, majority of patients (90% to 86%) in those studies completed the trial. Detailed information on patient disposition, demographics and baseline characteristics for dose and regimen selection trials is available in the appendix (Table 12 and Table 13).

A total of 1919 patients were included in the ITT populations of the three phase 3 efficacy studies, 643 treated with AB 200 µg BID, 636 treated with AB 400 µg BID, and 640 treated with placebo (Table 3). About 80% to 93% enrolled patients completed the study. The discontinuation occurred more frequently in placebo group than in other treatment groups in all three studies. The primary reasons for premature discontinuation were adverse events (including exacerbation), withdrawal of consent, and lack of efficacy. The number of patients who discontinued prematurely due to lack of efficacy was significantly higher in placebo arm (5%) than in other arms (3% in AB200 and <1% in AB400) in Study M33. There were 14 (<1%) patients (2 in M33, 3 in M38a, and 9 in M34) excluded from the ITT population due to either miss (or unacceptable) baseline or post-baseline FEV_1 assessment or did not receive investigational product. The primary analysis for the primary and key secondary efficacy endpoints was based on the ITT population. The Kaplan- Meier plots on time to the discontinuation are included in the appendix for reference (Figure 18).

Table 3: Patient disposition of three efficacy studies, N (%) Randomized Population

Study	**M34**			**M33**			**M38a**		
Treatment	AB400	AB200	Placebo	AB400	AB200	Placebo	AB400	AB200	Placebo
Screen failed	--	--	22%	--	--	47%	--	--	56%
Randomized	272	280	276	190	185	186	178	184	182
Completed	253 (93)	254 (91)	235 (85)	166 (87)	152 (82)	149 (80)	148 (83)	155 (84)	151 (83)

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Discontinued	19 (7)	26 (9)	41 (15)	24 (13)	33 (18)	37 (20)	30 (17)	29 (16)	31 (17)
Before wk 12	11 (4)	15 (5)	34 (12)	--	--	--	--	--	--
ITT	269	277	273	190	184	185	177	182	182
Subset*	65 (24)	64 (23)	62 (23)	73 (38)	74 (40)	73 (40)	53 (30)	58 (32)	54 (30)
Safety	269	277	273	190	184	185	177	182	182
PP	250 (92)	261 (93)	248 (90)	184 (97)	171 (92)	175 (94)	164 (92)	165 (90)	167 (92)
Primary reason for premature discontinuation									
AE	4 (1)	8 (3)	6 (2)	7 (4)	8 (4)	7 (4)	8 (4)	3 (2)	4 (2)
COPD exacer.	4 (1)	3 (1)	5 (2)	1 (<1)	4 (2)	7 (4)	6 (3)	1 (<1)	4 (2)
Withdrew con.	9 (3)	10 (4)	17 (6)	7 (4)	6 (3)	9 (5)	6 (3)	12 (7)	8 (4)
Protocol viola.	1 (<1)	0	1 (<1)	3 (2)	1 (<1)	2 (1)	3 (2)	4 (2)	3 (2)
Lost follow-up	0	2 (<1)	1 (<1)	0	2 (1)	0	2 (1)	3 (2)	3 (2)
Lack of efficacy	0	3 (1)	8 (3)	1 (<1)	5 (3)	10 (5)	2 (1)	3 (2)	6 (3)
Failed I/E	0	0	0	2 (1)	2 (1)	0	0	0	0
Death*	1 (<1)	2 (<1)	1 (<1)	1 (<1)	0	0	1 (<1)	0	1 (<1)
Other reasons	1 (<1)	0	3 (1)	3 (2)	5 (3)	2 (1)	3 (2)	3 (2)	3 (2)

* Death count is not included in discontinued count. Subset=Serial spriometry sub-study population.

Note: the Screened Population included all patients who signed a written informed consent form and received a patient identification number. The Safety Population included all patients in the Randomized Population who took at least 1 dose of double-blind treatment. The ITT - Efficacy Population included all patients in the Safety Population who had a baseline and at least 1 post-baseline FEV_1 assessment.

The Per-Protocol Population included all patients who met the main inclusion and exclusion criteria, attained a sufficient compliance to the treatment received, and did not present with relevant protocol deviations that could interfere with the efficacy assessments.

The study population in all three efficacy studies consisted of male and female patients who were 40 years of age or older with moderate to severe COPD (post-bronchodilator FEV_1 < 80% and ≥30% of the predicted normal value; post-bronchodilator FEV_1/FVC < 70%) and a smoking history of at least 10 pack years. Most patients were Caucasians. In all three studies, treatment groups were evenly matched in terms of baseline demographics (Table 4). The information about disease severity and rescue medication use at baseline is displayed in Table 5. The disease severity and rescue medication use was different across the three studies.

In study M38a, the mean trough FEV_1 was largest in the placebo group, followed by the AB200 group, and then the AB400 group (1.5 L, 1.4 L, and 1.2 L, respectively). The AB400 treated patients had higher percentage with severe Stage III COPD at baseline (54% in AB400 group, 47% in the AB200, and 37% in the placebo group).

Table 4: Demographic and Baseline Characteristics of ITT Patients

Study	**M34**			**M33**			**M38a**		
Treatment	**AB400 (n=269)**	**AB200 (n=277)**	**Placebo (n=273)**	**AB400 (n=190)**	**AB200 (n=184)**	**Placebo (n=185)**	**AB400 (n=177)**	**AB200 (n=182)**	**Placebo (n=182)**
Age (years)									
Mean (SD)	63 (8.4)	62 (7.8)	62 (8.0)	65 (9.5)	63 (9.5)	65 (9.2)	63 (9.0)	63 (8.5)	62 (9.3)
Range	41 – 82	41 – 84	41 – 84	40 – 89	40 – 83	40 - 89	41 – 82	40 - 80	41 – 84
Age group (%)									
<60 yrs	96 (36)	99 (36)	102 (38)	44 (23)	64 (35)	46 (25)	57 (32)	57 (31)	72 (40)
60 to <70 yrs	108 (40)	125 (45)	121 (44)	87 (46)	72 (39)	84 (45)	77 (44)	78 (43)	72 (40)
70+ yrs	65 (24)	53 (19)	50 (18)	59 (31)	48 (26)	55 (30)	43 (24)	47 (26)	38 (20)
Race group (%)									
White	257 (96)	263 (95)	260 (95)	181 (95)	169 (92)	174 (94)	160 (90)	162 (89)	168 (92)
Non-white	12 (4)	14 (5)	13 (5)	9 (5)	15 (8)	11 (6)	17 (10)	20 (11)	14 (8)
Sex (%)									
Female	87 (32)	96 (35)	84 (31)	90 (47)	83 (45)	90 (48)	88 (50)	83 (46)	82 (45)
Male	182 (68)	181 (66)	189 (69)	100 (53)	101 (55)	95 (52)	89 (50)	99 (54)	100 (55)
Region (%)									

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USA	0	0	0	176 (93)	170 (92)	175 (95)	175 (99)	180 (99)	180 (99)
Europe	222 (83)	231 (83)	225 (82)	0	0	0	0	0	0
ROW	47 (17)	46 (17)	48 (18)	14 (7)	14 (8)	10 (5)	2 (1)	2 (1)	2 (1)
BMI Group (%)									
BMI<25	97 (36)	113 (41)	113 (41)	56 (29)	61 (33)	69 (37)	70 (40)	58 (32)	67 (37)
25≤BMI<30	99 (37)	99 (36)	92 (34)	79 (42)	74 (40)	64 (35)	54 (30)	60 (33)	58 (32)
BMI≥30	73 (27)	65 (23)	68 (25)	55 (29)	49 (27)	52 (28)	53 (30)	64 (35)	56 (31)

Table 5: Disease Severity and Rescue Medication for ITT Patients

Study		**M34**			**M33**			**M38a**	
Treatment	**AB400 (n=269)**	**AB200 (n=277)**	**Placebo (n=273)**	**AB400 (n=190)**	**AB200 (n=184)**	**Placebo (n=185)**	**AB400 (n=177)**	**AB200 (n=182)**	**Placebo (n=182)**
Patient is known to have, n (%)									
Chronic Bronchitis	106 (39)	108 (39)	96 (35)	108 (57)	111 (60)	107 (58)	94 (53)	89 (49)	101 (56)
Emphysema	62 (23)	56 (20)	65 (24)	121 (64)	115 (63)	117 (63)	105 (59)	112 (61)	110 (60)
Exacerbations in the previous 12 months, n (%)									
No	172 (64)	180 (65)	185 (68)	147 (77)	138 (75)	133 (72)	128 (72)	137 (75)	145 (80)
1	78 (29)	79 (28)	72 (26)	36 (19)	32 (17)	41 (22)	29 (16)	28 (15)	28 (15)
>1	19 (7)	18 (7)	16 (6)	7 (4)	14 (8)	11 (6)	20 (11)	17 (9)	9 (5)
COPD severity (%)									
Stage I	0	0	0	0	0	0	0	0	2 (1)
Stage II	184 (68)	192 (69)	178 (65)	118 (62)	98 (53)	111 (60)	79 (45)	95 (52)	113 (62)
Stage III	84 (31)	84 (30)	92 (34)	68 (36)	80 (43)	72 (39)	96 (54)	85 (47)	67 (37)
Stage IV	0	0	0	1 (<1)	3 (2)	1 (<1)	0	1 (<1)	0
Missing	1 (<1)	1(<1)	3 (1)	3 (2)	3 (2)	1 (<1)	2 (1)	1 (<1)	0
COPD duration (years)									
Mean (SD)	7.2 (6.7)	7.0 (6.5)	6.4 (5.4)	8.9 (6.4)	8.3 (6.1)	8.5 (6.5)	8.5 (6.2)	7.9 6.2)	7.7 (6.0)
Range	0 - 50	0 - 38	0 - 32	1 – 36	1 – 34	1 – 37	1 – 40	1 – 37	1 - 36
Smoker (%)									
Ex-smoker	121 (45)	137 (49)	129 (47)	110 (58)	100 (54)	98 (53)	88 (50)	85 (47)	80 (44)
Current	148 (55)	140 (51)	144 (53)	80 (42)	84 (46)	87 (47)	89 (50)	97 (53)	102 (56)
Total number of pack per year									
Mean (SD)	42 (21)	40 (20)	39 (18)	57 (29)	53 (23)	53 (28)	54 (28)	54 (31)	53 (28)
Range	12 –153	10 –114	10 –132	10 – 84	10 –125	10 –188	10 –165	10 –290	10 – 168
Baseline FEV_1 [L]									
Mean (SD)	1.5 (0.5)	1.5 (0.5)	1.5 (0.5)	1.3 (0.5)	1.4 (0.6)	1.4 (0.6)	1.2 (0.5)	1.4 (0.6)	1.5 (0.5)
Range	0.6 –3.6	0.5 –3.0	0.5 –2.8	0.6 –2.9	0.5 –2.9	0.5 –3.5	0.5 –3.1	0.5 –3.4	0.5 – 2.9
Baseline percent predicted FEV_1 [%]									
Mean (SD)	51 (13)	52 (13)	52 (14)	48 (13)	46 (14)	48 (15)	44 (13)	46 (14)	49 (14)
Range	25 – 81	24 – 84	20 – 88	22 – 76	19 – 73	19 - 79	21 – 78	22 – 84	18 - 80
Patients using prior medication for COPD before screening									
Any Medication	237 (88)	248 (90)	251 (92)	161 (85)	145 (79)	149 (80)	144 (81)	143 (78)	132 (73)
SABAs	141 (52)	135 (49)	137 (50)	127 (67)	118 (64)	114 (61)	97 (55)	92 (50)	95 (52)
LABA+ICS	38 (14)	37 (13)	42 (15)	73 (38)	73 (40)	64 (34)	54 (31)	57 (31)	55 (30)
LAMAs	77 (29)	86 (31)	58 (21)	53 (28)	60 (33)	56 (30)	51 (29)	49 (27)	43 (24)
ICSs	100 (37)	97 (35)	115 (42)	16 (6)	12 (7)	19 (10)	21 (12)	26 (14)	16 (9)
Oxygen	2 (<1)	2 (<1)	3 (1)	11 (6)	10 (5)	12 (7)	0	0	0
SAMAs	41 (15)	45 (16)	45 (17)	16 (8)	7 (4)	5 (3)	2 (1)	8(4)	3 (2)
LABAs	81 (30)	77 (28)	90 (33)	6 (3)	9 (5)	12 (7)	11 (6)	10 (6)	4 (2)
Xanthines	50 (19)	62 (22)	59 (22)	5 (3)	1 (<1)	2 (1)	6 (3)	6 (3)	6 (3)
SABA+SAMA	30 (11)	32 (12)	26 (10)	2 (1)	0	0	25 (14)	24 (13)	16 (9)

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3.1.4 Statistical Methodologies

The following describes the analysis methods pre-specified in the protocol.

Analysis model

Continuous endpoints such as the primary (i.e. 24-hour post-dose trough FEV_1 after 12 weeks treatment), and secondary endpoints (i.e. peak FEV_1 and SGRQ scores included in this review were analyzed using a analysis of covariance (ANCOVA) model with treatment and sex as factors and baseline and age as covariates. In addition to the primary analysis, a sensitivity analysis for the primary efficacy parameter was conducted using a mixed model for repeated measures (MMRM) with age and baseline value of FEV_1 as covariates, and treatment group, sex, week, and treatment group-by-week interaction as fixed effect factors. The within-patient correlation was modeled using the unstructured covariance matrix in the mixed model, for this analysis observed case was used.

Binary endpoints such as the proportion of patients achieving a clinically relevant improvement in TDI or SGRQ at week 24 were analyzed using a logistic regression model with treatment group, sex, age, and base score as explanatory variables.

Adjustments for Multiplicity

In all Phase 3 efficacy studies, adjustment for multiplicity for the two primary treatment comparisons (AB200 or AB400 versus placebo) of the primary efficacy endpoint was performed using the Hochberg method. If the largest of the p-values for the two primary comparisons was less than or equal to 0.05, then both primary comparisons were declared statistically significant at the 0.05 level of significance. If the largest of the p-values for the two primary comparisons was greater than alpha (0.05), then the remaining hypothesis was to be tested at a 0.025 level of significance.

The following adjustment for multiplicity procedure was applied across the primary and 3 secondary variables:

- Secondary efficacy variables were tested if the primary variable was significant in both treatment comparison (AB200 or AB400 versus placebo), otherwise p-value would be calculated to be reported and interpreted descriptively.
- Testing procedure for secondary variables was performed in a sequential manner as follows:
    - Change from baseline in peak FEV_1 at week 12
    - Percentage of patients achieving an improvement (≥1 unit) in TDI focal score at week 24. (Study M34 only)
    - Percentage of patients achieving an improvement (at least a 4-point reduction from baseline) in the SGRQ total score at Week 24. (Study M34 only)

The change from baseline in peak FEV_1 was examined first by applying the Hochberg procedure at the 5% level of significance. The process for moving in the sequential procedure was the following: testing continued with the next variable if at least one null hypothesis of the two treatment comparisons was rejected, otherwise the sequential testing procedures stopped for inferential purposes but the p-values for the remaining hypotheses were reported and interpreted descriptively. If both doses (treatment comparisons) were significant then Hochberg's procedure was used to correct for multiple treatment comparisons; otherwise no correction was applied because only one dose was tested at 0.05 significance level and the discarded dose could not be inferentially tested anymore in any of the remaining secondary variables in the sequence.

Handling of Missing Data

The data imputation method specified by the applicant was the last observation carried forward (LOCF) method. Any of the 23 hour 10 minute and the 23 hour 45 minute values contributing to the trough FEV_1 that were taken within 6 hours of rescue medication use or that were outside the

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22 hour to 25 hour post-dose time window were considered missing values. If both values were missing, or if the patient withdrew from the study, then trough FEV_1 was regarded as missing. A missing trough FEV_1 value at week 12 was replaced by carrying forward trough FEV_1 from the last evaluable visit as long as the visit was not prior to Day 29. The primary analysis on trough FEV_1 at week 12 was based on LOCF imputed data. Sensitivity analysis was also conducted applying mixed model repeated measures approach (MMRM). On February 15, 2011, Forest responded to the Agency's comments regarding their Statistical Analysis Plan. Specifically, the agency noted that the pre-specified imputation strategy (i.e. LOCF) is not acceptable. In their response, Forest informed that the data from all three studies were already unblinded prior to receiving this comment. They also stated that the actual discontinuation rates were approximately 17% for both studies 33 and 38, and 10% for study 34. Furthermore, they referred to the feedback received from the Agency on the SAP for an earlier Phase 3 study (dated November 13, 2007 and received comments on February 15, 2008). The Agency, at that time, noted that while LOCF is a reasonable imputation method; it may not be a conservative method if more patients discontinue the study due to COPD exacerbation in the placebo group than in the aclidinium group, and recommended that the sponsor conduct sensitivity analyses like BOCF.

While our response in 2008 may be reasonable at that time, this is not the case now, given our understanding about issues surrounding applying a single imputation method or applying mixed model repeated measures approach to missing data. Nonetheless, for this application, the efficacy results were consistent (Table 6 and Table 14) and highly significant regardless of the analytical methods and imputation strategies, that missing data may not be a big issue.

Missing SGRQ scores were imputed by LOCF as well. A missing SGRQ score at week 12 was replaced by carrying forward SGRQ score from the last evaluable visit as long as the visit was not prior to week 4. The primary analysis was based on imputed data. Since SGRQ is a patient reported outcome, for patients who withdrew from the study due to lack of efficacy or adverse event, imputing data based on LOCF may introduce bias. To avoid the problem, I also did an analysis on both SGRQ data without imputation (i.e. patients who had missing SGRQ score at week 12 were excluded from the analysis) and data imputed by baseline observation carried forward method (BOCF, i.e. patients who had missing SGRQ score at week 12 were included in the analysis and their SGRQ score at week 12 was replaced by carrying forward SGRQ score from baseline). All three sets of results were reported in section 3.1.6.

In addition to the mixed effect model mentioned above, responder analysis was applied to SGRQ scores. Patients with a clinically important improvement of 4 units or greater in SGRQ total score was defined as responders. The responder analysis was based on logistic regression with the same covariates as those in the mixed effect model.

A brief summary of COPD exacerbation is included in this review. The exacerbations were defined as mild if they required an increase in the use of rescue medication, as moderate if they required the use of antibiotics or systemic corticosteroids or as severe if they resulted in hospitalization (Cazzola et al, 2008). A new exacerbation was counted if the patient was off (or not required to take) systemic corticosteroids and/or antibiotics for ≥14 days since the prior exacerbation. The number of COPD exacerbations was the total number of exacerbations for a patient during the double-blind treatment period. The number of COPD exacerbations per

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patient/year was analyzed by means of a Poisson regression with over dispersion for rates and with treatment, sex, and baseline COPD severity as factors and age as covariate, adjusting for the log of the corresponding total exposure time in years for a patient (as an offset variable in the model).

Change in the conduct of the study or planned analyses for Study M34

The first version of the protocol dated 23rd April 2001 was amended twice. The applicant claimed that the first patient was enrolled on the final clinical study protocol incorporating Amendment 1 (dated 26th June 2009). The changes were not related to the statistical analysis. An amendment specific to France dated 28th July 2010 was also made and not related to the statistical analysis. As specified in the final SAP (dated 12th December 2010), no major changes were made to the analysis strategy and specific methods in the SAP compared to those defined in the protocol.

3.1.5 Dose Regimen and Interval Selection

One of the major concerns in the original pre-NDA meeting (03 March 2009) was dose and dosing interval selection for patients with COPD. The Division of Pulmonary, Allergy, and Rheumatology Products recommended that the applicant conduct a dose ranging study which included comparison of the same nominal dose as a once-daily regimen with more frequent dosing regimens. In response, the applicant conducted two dose-range finding studies with aclidinium bromide BID doses only. Therefore, there was no direct comparison of BID and QD dosing.

> *FDA stated: Although both pivotal studies demonstrated statistically significant results for the primary endpoint of trough FEV_1, a treatment difference of approximately 60 cc is of uncertain clinical significance. You have not adequately evaluated the appropriate dose and dosing interval of aclidinium bromide. We recommend exploration of higher doses and more frequent dosing regimens. Additional dose ranging should include a comparison of the same nominal dose as a once-daily regimen with more frequent dosing regimens. These dose explorations should be completed prior to NDA submission to ensure the selection of the most appropriate and efficacious dose of aclidinium bromide for marketing.*

In Study M23, out of 30 randomized patients, 27 (90%) patients completed the 2-week study. It had three arms: aclidinium bromide 400 µg BID and placebo via the device proposed for marketing and tiotropium 18 µg QD (AM) and placebo via the Handihaler® device. In Study M29, out of 79 randomized patients, 68 (86%) patients completed the 1-week study. It had five arms: AB100 µg BID, AB200 µg BID, AB400 µg BID, and placebo via the proposed device, as well as formoterol 12 µg BID and placebo via Aerolizer®.

Figure 3 shows the treatment comparisons in change from baseline in normalized FEV_1 AUC0-12h [L] at day 15 (Study M23) and day 7 (Study M29). At day 7, all aclidinium bromide doses showed statistically significantly improvement compared to placebo; there appears to be a dose response, the higher the dose was, the greater the FEV_1 $AUC_{0\text{-}12h}$. AB 400 µg BID appeared to achieve bronchodilation similar to formoterol and tiotropium; adjusted treatment differences among three active drugs and placebo in the change from baseline in FEV_1 $AUC_{0\text{-}12h/12}$ at day 7

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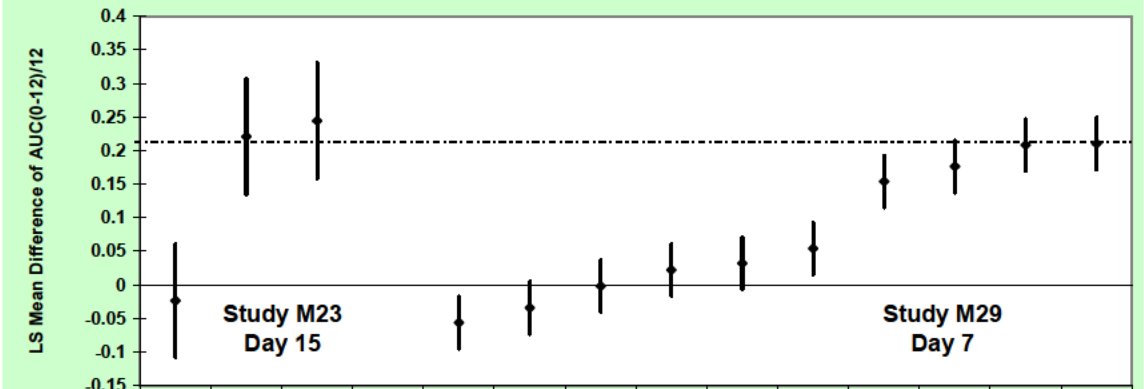
or 15 were comparable and above 0.200 L and reached statistical significant. Although AB 200 µg BID showed statistically significantly improvement compared to placebo, this advantage did not appear to be comparable to formoterol.

Figure 3: Change from Baseline in Normalized FEV_1 AUC0-12h [L]

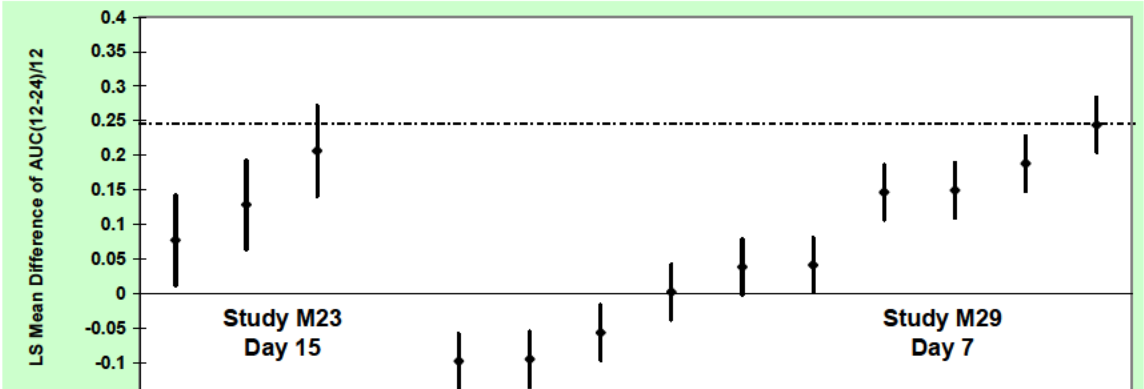


	AB400-T	AB400-P	T-P		AB100-F	AB200-F	AB400-F	AB200-AB100	AB400-AB200	AB400-AB100	AB100-P	AB200-P	AB400-P	F-P
LL-95%CI	-0.11	0.14	0.16		-0.09	-0.07	-0.04	-0.02	-0.01	0.02	0.12	0.14	0.17	0.17
UL-95%CI	0.06	0.31	0.33		-0.02	0.01	0.04	0.06	0.07	0.09	0.19	0.22	0.25	0.25
◆ LS Mean Diff	-0.02	0.22	0.24		-0.06	-0.03	0.00	0.02	0.03	0.05	0.15	0.18	0.21	0.21

Note: AB=Aclidinium Bromide, P=Placebo, T=Tiotropium 18 µg QD, F=Formoterol 12 µg BID

As shown in Figure 4, the treatment difference versus placebo for all aclidinium bromide doses in normalized FEV_1 $AUC_{12\text{-}24}$ was smaller than in normalized FEV_1 $AUC_{0\text{-}12h}$, but reached the statistical significant. The formoterol treatment arm showed statistically significant greater improvement in the change from baseline in normalized FEV_1 $AUC_{12\text{-}24h}$ compared to placebo and all aclidinium bromide doses.

Figure 4: Change from Baseline in Normalized FEV_1 $AUC_{12\text{-}24h}$ [L]



	AB400-T	T-P	AB400-P		AB100-F	AB200-F	AB400-F	AB200-AB100	AB400-AB200	AB400-AB100	AB100-P	AB200-P	AB400-P	F-P
LL-95%CI	0.01	0.06	0.14		-0.14	-0.13	-0.10	-0.04	0.00	0.00	0.11	0.11	0.15	0.20
UL-95%CI	0.14	0.19	0.27		-0.06	-0.05	-0.02	0.04	0.08	0.08	0.19	0.19	0.23	0.28
◆ LS Mean Diff	0.08	0.13	0.21		-0.10	-0.09	-0.06	0.00	0.04	0.04	0.15	0.15	0.19	0.24

Note: AB=Aclidinium Bromide, P=Placebo, T=Tiotropium 18 µg QD, F=Formoterol 12 µg BID

Looking at the FEV_1 time serial profile for Study M23 (Figure 5), in day 1 and day 15, there is a clear separation in FEV1 between AB400 and placebo at Day 1 and at Day 15, at all time points,

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in favor of AB400. Although some differences were observed in the second 12-hour interval, aclidinium bromide 400 mcg generally performed in a similar range to tiotropium.

In study M29, there appears to be a slight dose response at Day 1 with the highest dose AB400 having the greatest FEV1 improvement at hours 3 and 4 (Figure 6). This advantage appears to persist after one week of treatment with AB400 still numerically better than AB200 and AB100 at all time-points suggesting that AB400 has the greatest bronchodilator effect. All AB doses have similar effect as formoterol at all time-points.

Figure 5: 24-hour FEV_1 Profile at Day 1 and Day 15 for Study M23

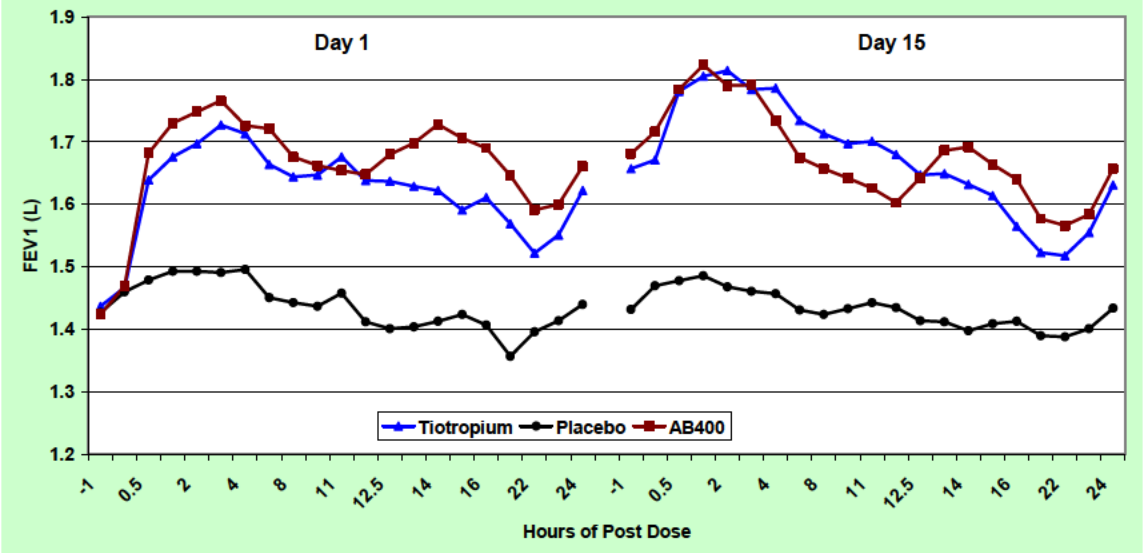
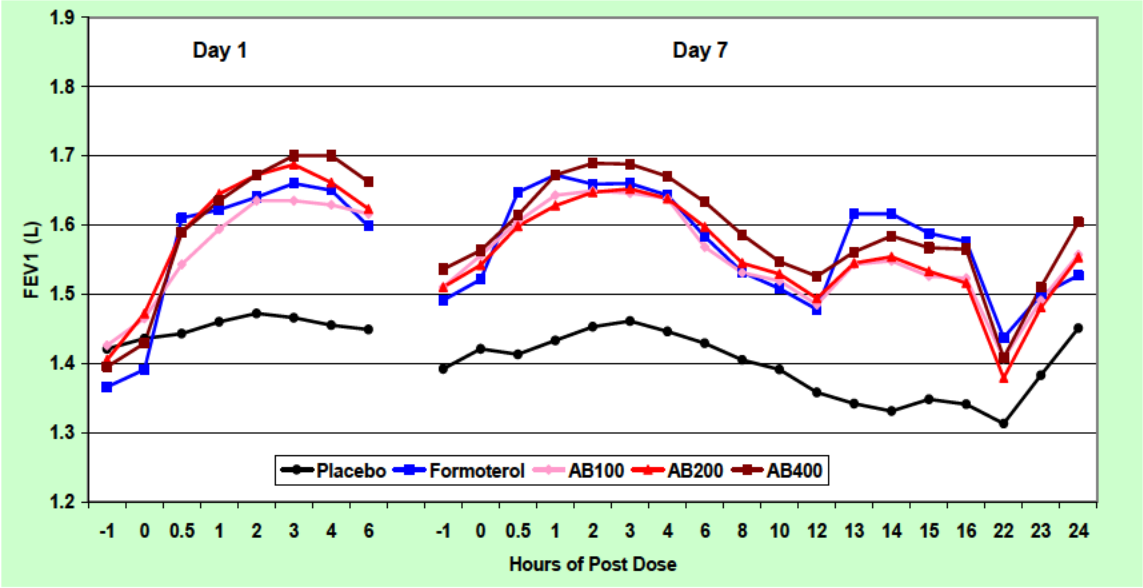


Figure 6: 24-hour FEV_1 Profile at Day 1 and Day 7 for Study M29



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In summary, aclidinium bromide 400 µg administered twice daily demonstrated a greater change in trough FEV1 and serial FEV1 measurements compared to lower nominal doses of 100 and 200 mcg. Also, although some differences were observed in the second 12-hour interval, aclidinium bromide 400 µg administered twice daily generally performed in a similar range as the active comparators, tiotropium and formoterol. While a direct comparison of once-daily to twice-daily aclidinium bromide at the same nominal dose would have been a preferred approach for evaluating the dosing frequency, these results help support the proposed twice-daily dosing.

For more information regarding the dose selection, the reader is referred to the clinical pharmacology summary and the clinical briefing document.

3.1.6 Efficacy Results and Conclusions

Primary efficacy variable – change from baseline at week 12 in trough FEV_1

A summary of the results from the analyses of the primary efficacy endpoint in all three efficacy studies is given in Table 6, Figure 7, and Figure 8. Table 6 shows that the patients treated with AB400 and AB200 had significant greater improvement in trough FEV_1 than the placebo group after 12 weeks' treatment. The treatment difference between AB400 and placebo ranged from 72 to 124 ml at week 12 and was about 128 ml at week 24 (Study M34). AB200 had a smaller effect size compared to AB400.

The treatment comparisons among two doses of AB and placebo are shown in Figure 7. The x-axis represents the treatment comparisons. The horizontal dash line represents the applicant-defined minimum clinically important differences (MCID- 0.10 L). The AB400 treatment groups were superior to placebo group with the treatment difference between AB400 and placebo above the MCID in two out of three studies (M33 and M34). The AB200 treatment group was superior to the placebo but fell short of the MCID in all three studies. The bronchodilatory effect provided by AB400 was numerically greater than that of the AB200 at week 12 or week 24 (M34) in the ITT population. Similar findings were observed using the MMRM analysis (see Table 14 in appendix). Refer to Section 3.1.4 (page 14) for a discussion of the handling of missing data. Figure 8 shows that the trends of the three treatment groups during 12/24 weeks are similar between three studies except placebo group in Study M38a.

Table 6: Summary of the change from baseline in trough FEV_1 at week 12/24 (LOCF)

			Baseline	Change from Baseline	Treatment Comparison AB – Placebo		
Study	**Treatment**	**N**	**LS Mean (SE)**	**LS Mean (SE)**	**LS Mean (SE)**	**95%CI**	**P value**
M33	Placebo	185	1.383 (0.033)	-0.025 (0.015)	--	--	--
Wk12	AB200	184	1.308 (0.033)	0.061 (0.015)	0.086 (0.021)	(0.04, 0.13)	<0.001
	AB400	190	1.328 (0.032)	0.099 (0.014)	0.124 (0.021)	(0.08, 0.16)	<0.001
M38a	Placebo	182	1.418 (0.035)	-0.008 (0.015)	--	--	--
Wk12	AB200	182	1.387 (0.035)	0.043 (0.015)	0.051 (0.022)	(0.01, 0.09)	0.019
	AB400	177	1.255 (0.036)	0.064 (0.016)	0.072 (0.022)	(0.03, 0.12)	0.001
M34	Placebo	273	1.419 (0.028)	-0.047 (0.015)	--	--	--
Wk12	AB200	277	1.453 (0.028)	0.030 (0.014)	0.077 (0.020)	(0.04, 0.12)	<0.001

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	AB400	269	1.447 (0.029)	0.058 (0.015)	0.105 (0.020)	(0.07, 0.14)	<0.001
M34	Placebo	273	1.419 (0.028)	-0.073 (0.016)	--	--	--
Wk24	AB200	277	1.453 (0.028)	0.026 (0.016)	0.099 (0.022)	(0.06, 0.14)	<0.001
	AB400	269	1.447 (0.029)	0.055 (0.016)	0.128 (0.022)	(0.08, 0.17)	<0.001

SE=standard error. P-value, LS mean, and LSMD obtained from an ANCOVA model with change from baseline in trough FEV_1 as response, with treatment group and sex as factors and baseline trough FEV_1 and age as covariates.

Figure 7: Treatment Comparison of the change from baseline in trough FEV_1 at week 12/24

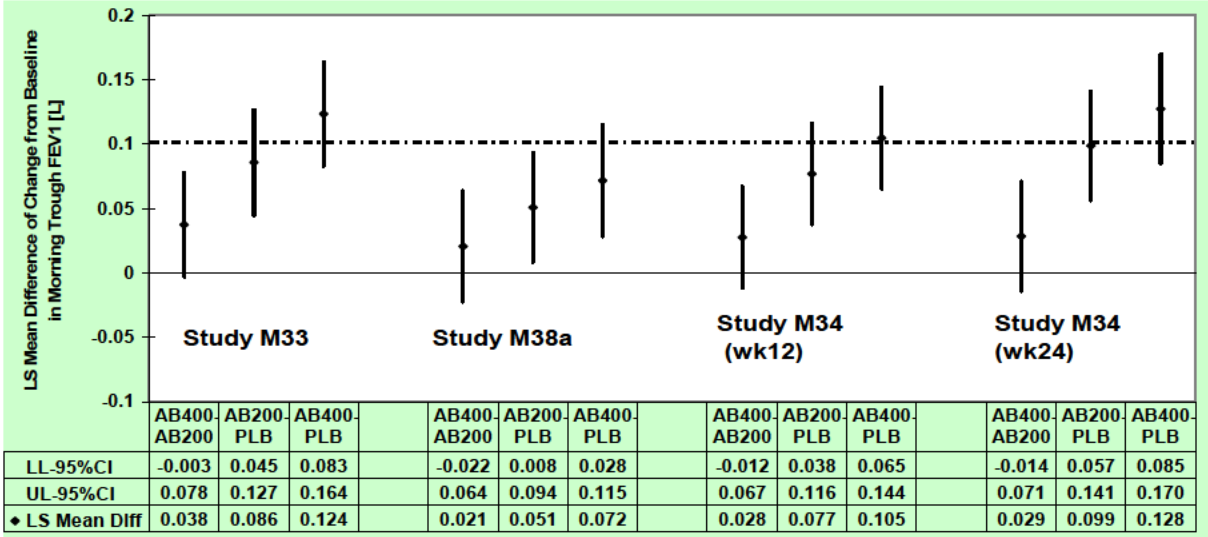
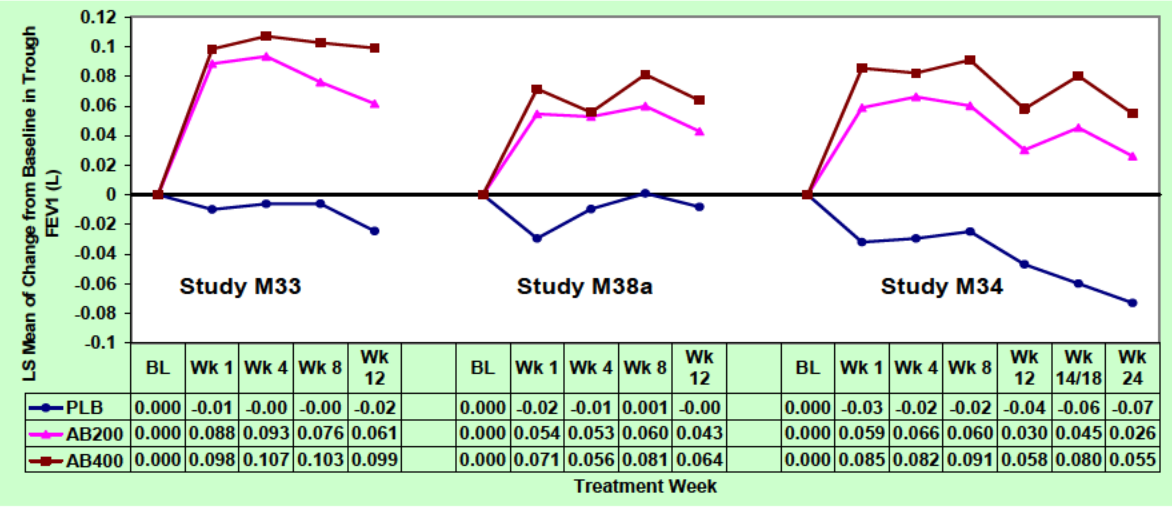


Figure 8: LS mean of change from baseline in trough FEV_1 (L) by visit (LOCF)



Key secondary efficacy variable – Change from baseline at week 12 in peak FEV_1

Patients treated with AB400 and AB200 had higher peak FEV_1 than the placebo group after 12 weeks treatment (Table 7). Of note, the baseline value used in this analysis was the trough FEV_1 baseline value at Day 1. The treatment difference between AB400 and placebo was statistically

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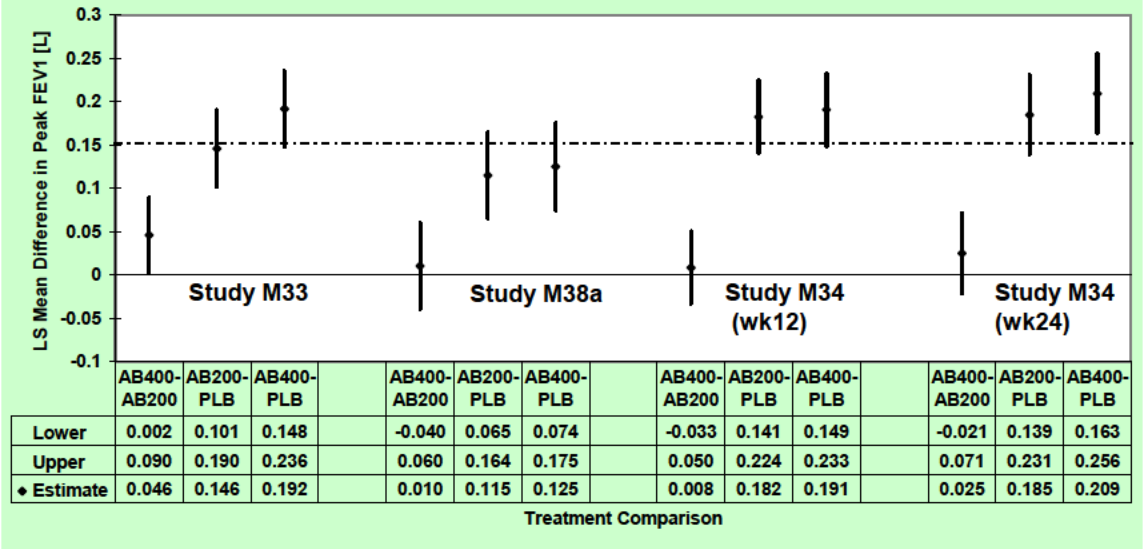
significant and above the applicant-defined MCID (0.15 L - the horizontal dash line) in two studies (M33 and M34), which supports the primary efficacy endpoint (Figure 9). The AB200 treatment group was also superior to the placebo but only one study (M34) was above the MCID (Figure 9). Peak FEV_1 decreased slightly after day 1 and AB400 and AB200 had the same trend by visits (Figure 10).

Table 7: Summary of the change from baseline in peak FEV_1 at week 12/24 (LOCF)

			Baseline*	Change from Baseline	Treatment Comparison AB - Placebo		
Study	**Treatment**	**N**	**LS Mean (SE)**	**LS Mean (SE)**	**LS Mean (SE)**	**95%CI**	**P value**
M33	Placebo	185	1.383 (0.033)	0.071 (0.016)	--	--	--
Wk12	AB200	184	1.308 (0.033)	0.217 (0.017)	0.146 (0.023)	(0.10, 0.19)	<0.001
	AB400	190	1.328 (0.032)	0.263 (0.016)	0.192 (0.022)	(0.15, 0.24)	<0.001
M38a	Placebo	182	1.418 (0.035)	0.087 (0.018)	--	--	--
Wk12	AB200	182	1.387 (0.035)	0.202 (0.018)	0.115 (0.025)	(0.07, 0.16)	<0.001
	AB400	177	1.255 (0.037)	0.212 (0.018)	0.125 (0.026)	(0.07, 0.18)	<0.001
M34	Placebo	273	1.419 (0.028)	0.037 (0.016)	--	--	--
Wk12	AB200	277	1.453 (0.028)	0.219 (0.015)	0.182 (0.021)	(0.14, 0.22)	<0.001
	AB400	269	1.447 (0.029)	0.227 (0.015)	0.191 (0.021)	(0.15, 0.23)	<0.001
M34	Placebo	273	1.419 (0.028)	0.022 (0.017)	--	--	--
Wk24	AB200	277	1.453 (0.028)	0.207 (0.017)	0.185 (0.023)	(0.14, 0.23)	<0.001
	AB400	269	1.447 (0.029)	0.231 (0.017)	0.209 (0.024)	(0.16, 0.26)	<0.001

SE=standard error. P-value, LS mean, and LSMD obtained from an ANCOVA model with change from baseline in peak FEV_1 as response, with treatment group and sex as factors and baseline FEV_1 value and age as covariates.
* The baseline FEV_1 value was the pre-dose FEV_1 at Day 1.

Figure 9: Treatment Comparison of the change from baseline in peak FEV_1 at week 12/24



	AB400-AB200	AB200-PLB	AB400-PLB		AB400-AB200	AB200-PLB	AB400-PLB		AB400-AB200	AB200-PLB	AB400-PLB		AB400-AB200	AB200-PLB	AB400-PLB
Lower	0.002	0.101	0.148		-0.040	0.065	0.074		-0.033	0.141	0.149		-0.021	0.139	0.163
Upper	0.090	0.190	0.236		0.060	0.164	0.175		0.050	0.224	0.233		0.071	0.231	0.256
◆ Estimate	0.046	0.146	0.192		0.010	0.115	0.125		0.008	0.182	0.191		0.025	0.185	0.209

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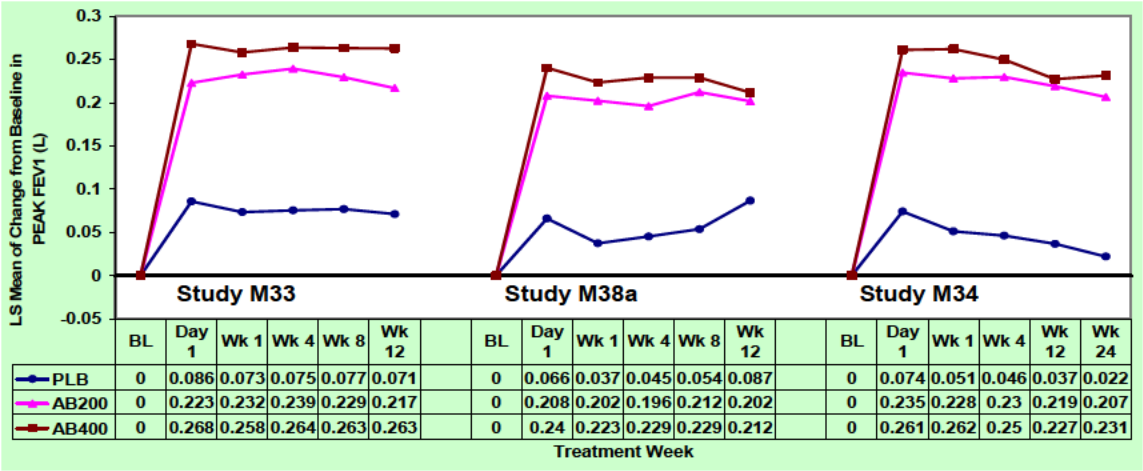
Figure 10: LS Mean of Change from Baseline in Morning Peak FEV_1 (L) by visit (LOCF)



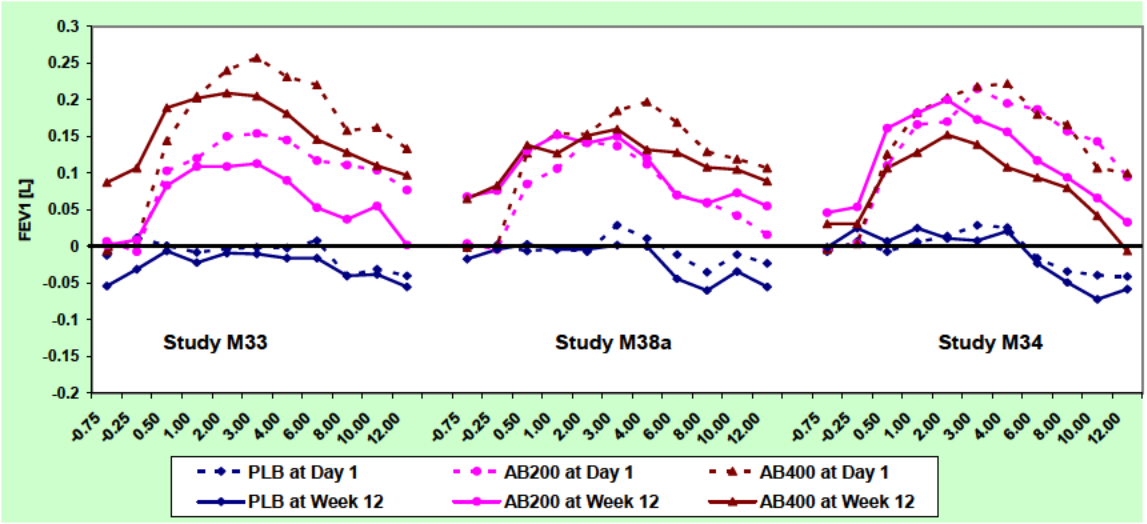
	Study M33						Study M38a						Study M34					
	BL	Day 1	Wk 1	Wk 4	Wk 8	Wk 12	BL	Day 1	Wk 1	Wk 4	Wk 8	Wk 12	BL	Day 1	Wk 1	Wk 4	Wk 12	Wk 24
PLB	0	0.086	0.073	0.075	0.077	0.071	0	0.066	0.037	0.045	0.054	0.087	0	0.074	0.051	0.046	0.037	0.022
AB200	0	0.223	0.232	0.239	0.229	0.217	0	0.208	0.202	0.196	0.212	0.202	0	0.235	0.228	0.23	0.219	0.207
AB400	0	0.268	0.258	0.264	0.263	0.263	0	0.24	0.223	0.229	0.229	0.212	0	0.261	0.262	0.25	0.227	0.231

BL=pre-dose FEV_1 at Day 1

Exploratory efficacy variable – Pulmonary function over time

The FEV_1 measured over time (pre-dose and 12 hour post-dose) on day 1 and week 12 was evaluated in subset of patients (20%) in all three studies. The result of the 12 hours serial spirometry sub-study is presented in Figure 11. The dash lines represent the FEV_1 value at day 1 and solid lines represent the FEV_1 value at week 12. In studies M33 and M38a, separation between the AB400 and placebo curves throughout the 12 hour time period is reflected on both Day 1 and at week 12, which support the persistence of effect over the 12-hour period both after one day of treatment and after three months of treatment. In Study M34, the evidence is not as convincing. In particular, at week 12, change in FEV_1 in the AB400 group appears to deteriorate at a much faster rate compared to the other two studies, and the treatment effect appears to be smaller at the 12-hour time point.

Figure 11: Mean Change from Baseline of FEV_1 over 0-12 hours in Subsamples (20% of ITT)



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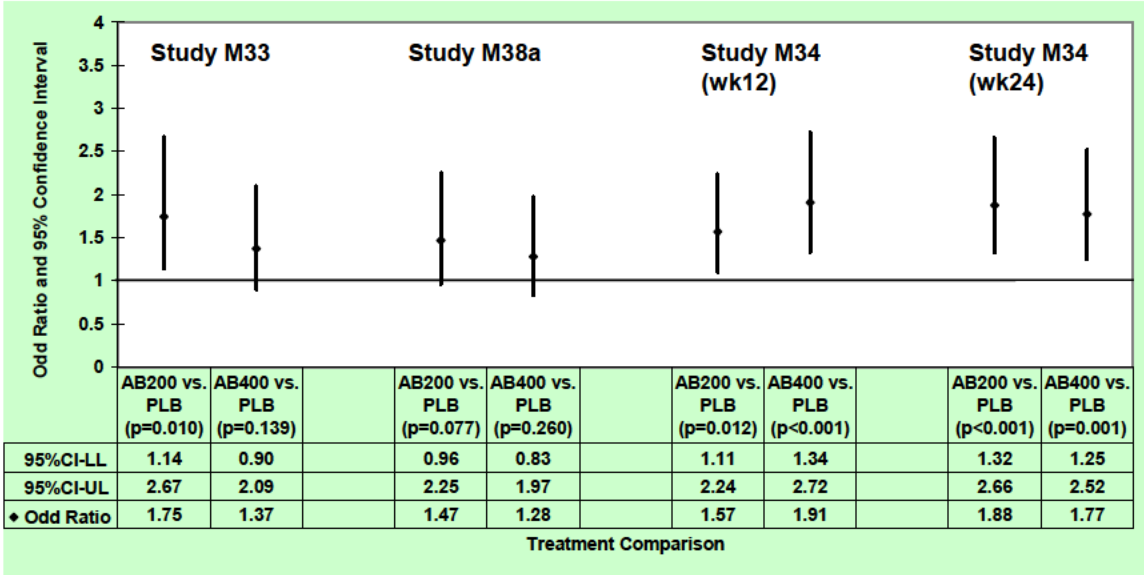
Secondary/Exploratory efficacy variable – Percentage of patients achieving a clinically relevant improvement (≥4 units) in SGRQ total score

Percentage of patients achieving an improvement (or at least a 4-point reduction from baseline) in SGRQ Total Score at week 24 was a key secondary efficacy endpoint in Study M34 only. There were significantly higher proportions of patients treated with AB400 or AB200 achieving an improvement in SGRQ total score compared to patients treated with placebo.

This endpoint was also explored in the studies (M33 and M38a). A significant difference was only observed between the AB200 group and placebo for Study M33 (Figure 12).

Figure 12: Treatment Comparison in Proportion of Patients Who Achieved At Least a 4-point Reduction from Baseline in SGRQ Total Score at week 12/24



The applicant also evaluated SGRQ total score as a continuous endpoint. The ANCOVA model with treatment group and sex as factors as well as age and baseline SGRQ total score as covariates was a protocol pre-specified method to compare the treatment difference for the change from baseline to week 12 (based on the LOCF approach) in SGRQ. A summary of the results from the analyses of SGRQ scores in all three efficacy studies is presented in Table 8. Adjusted mean treatment differences between AB and placebo in the change from baseline to week 12 and 24 using LOCF imputation in SGRQ total score were statistically significant compared with placebo for both doses in Study M34 and M33. AB400 did not show a greater improvement in SGRQ compared with AB200 in Study M33 and M34.

Figure 13 displays the ANCOVA analysis results based on three sets [LOCF imputed, completer (COMP), and BOCF imputed] of SGRQ data. There were little differences among the three sets of analysis results. Since the completion rate was high (80% to 90%) in three studies, imputation of missing data does not play an important role in the analysis. The dash line indicates the MCID (-4) of SGRQ total score. Of note, the interpretation of this cut-off is different from the responder analysis above. In this continuous endpoint analysis, the MCID of -4 is the difference in mean change from baseline between AB and placebo; while the MCID of -4 in the responder

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analysis is the absolute change from baseline in each treatment group. Also the MCID of -4 for this continuous endpoint is often used in other clinical programs.

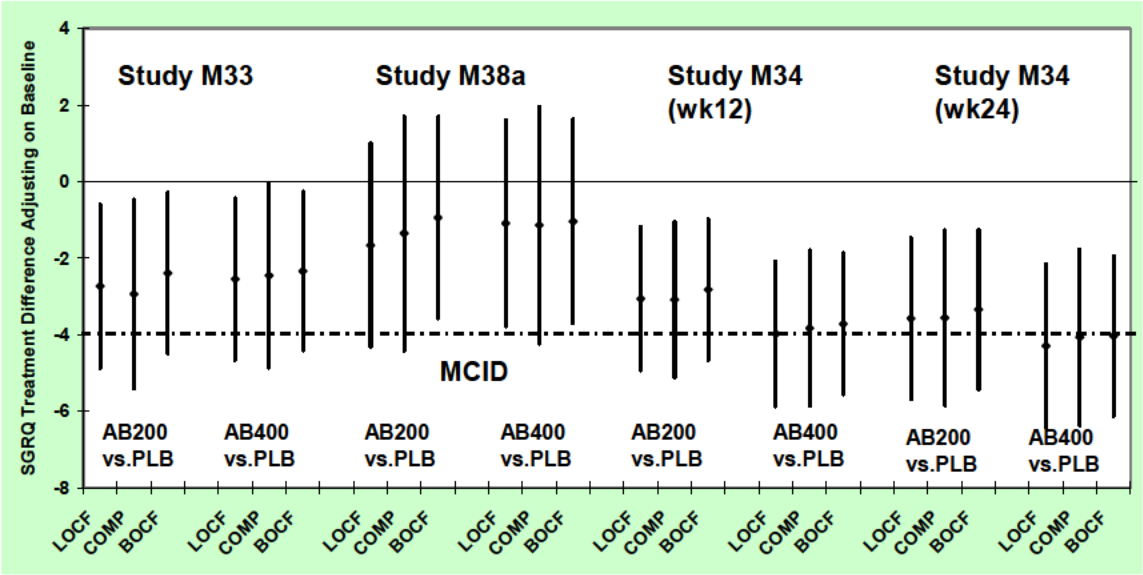
Only AB400 in Study M34 showed significant difference in SGRQ total scores compared to placebo that exceeds the MCID of -4 at weeks 12 and 24 [-4.0 with 95% CI of (-5.9, -2.1) after 12 weeks treatment and -4.3 with 95%CI of (-6.4, -2.2) after 24 weeks treatment]. Treatment difference between AB400 and placebo in SGRQ total scores in the other two studies ranged from -1.1 to -2.54, while the treatment difference between AB200 and placebo ranged from -1.7 to -3.6 in all three studies (Table 8 and Figure 13).

Table 8: Summary of the change from baseline in SGRQ Total Score at week 12/24

			Baseline	Change from Baseline	Treatment Comparison AB - Placebo		
Study	**Treatment**	**N**	**LS Mean (SE)**	**LS Mean (SE)**	**LS Mean (SE)**	**95%CI**	**P value**
M33	Placebo	181	45.32 (1.25)	-2.04 (0.77)	--	--	--
Wk12	AB200	180	45.60 (1.26)	-4.77 (0.77)	-2.73 (1.09)	(-4.87, -0.59)	0.013
	AB400	189	48.48 (1.23)	-4.58 (0.75)	-2.54 (1.08)	(-4.66, -0.43)	0.019
M38a	Placebo	178	48.76 (1.29)	-4.32 (0.96)	--	--	--
Wk12	AB200	178	47.93 (1.29)	-5.98 (0.96)	-1.66 (1.36)	(-4.32, 1.00)	0.222
	AB400	172	50.55 (1.31)	-5.40 (0.97)	-1.08 (1.37)	(-3.78, 1.61)	0.429
M34	Placebo	271	45.39 (1.04)	-2.06 (0.70)	--	--	--
Wk12	AB200	275	46.58 (1.02)	-5.12 (0.69)	-3.06 (0.96)	(-4.94, -1.18)	0.002
	AB400	269	48.02 (1.04)	-6.03 (0.70)	-3.97 (0.96)	(-5.86, -2.08)	<0.001
M34	Placebo	271	45.39 (1.04)	-2.63 (0.79)	--	--	--
Wk24	AB200	275	46.58 (1.02)	-6.20 (0.77)	-3.57 (1.08)	(-5.69, -1.46)	<0.001
	AB400	269	48.02 (1.04)	-6.92 (0.78)	-4.29 (1.08)	(-6.42, -2.16)	<0.001

SE=standard error. P-value, LS mean, and LSMD obtained from an ANCOVA model with change from baseline in SGRQ score as response, with treatment group and sex as factors and baseline SGRQ score and age as covariates.

Figure 13: SGRQ Total Score at Week 12/24



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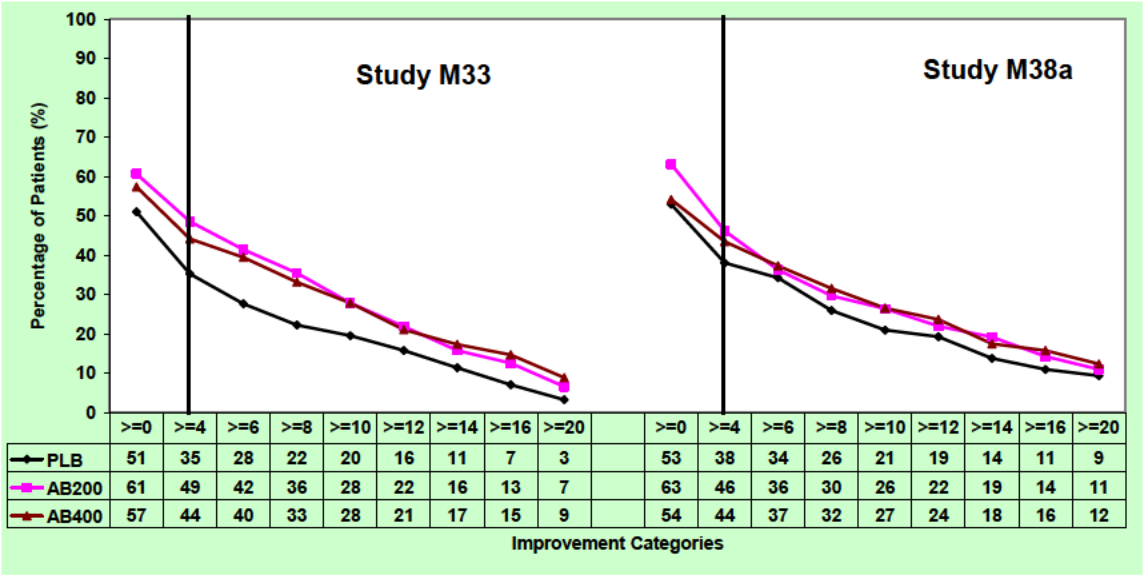
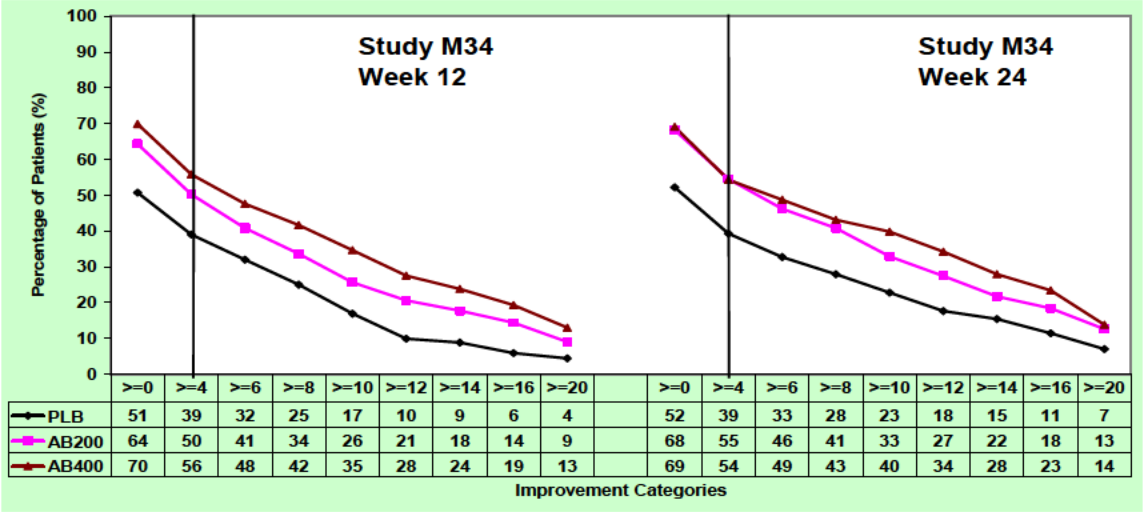
In this review, I have also explored applying multiple cut-offs in the change from baseline in SGRQ total scores and the results (responder profile) are displayed in Figure 14 and Figure 15. The x-axis represents the improvement categories, for example, ≥4 category indicates the patients had at least 4 units improvement compared to the baseline SGRQ total score, and the y-axis represents the percent of patients improved. There is a clear separation between AB400 (maroon) and placebo (black) in Study M34 only; this result supports the protocol pre-specified analysis result. In conclusion, only AB400 showed a significant improvement in SGRQ (≥4 units) total score in one study (M34), there is no other study replicates this result.

Figure 14: The Responder Profile of Change from Baseline in SGRQ at week 12



	>=0	>=4	>=6	>=8	>=10	>=12	>=14	>=16	>=20	>=0	>=4	>=6	>=8	>=10	>=12	>=14	>=16	>=20
PLB	51	35	28	22	20	16	11	7	3	53	38	34	26	21	19	14	11	9
AB200	61	49	42	36	28	22	16	13	7	63	46	36	30	26	22	19	14	11
AB400	57	44	40	33	28	21	17	15	9	54	44	37	32	27	24	18	16	12

Figure 15: The Responder Profile of Change from Baseline in SGRQ



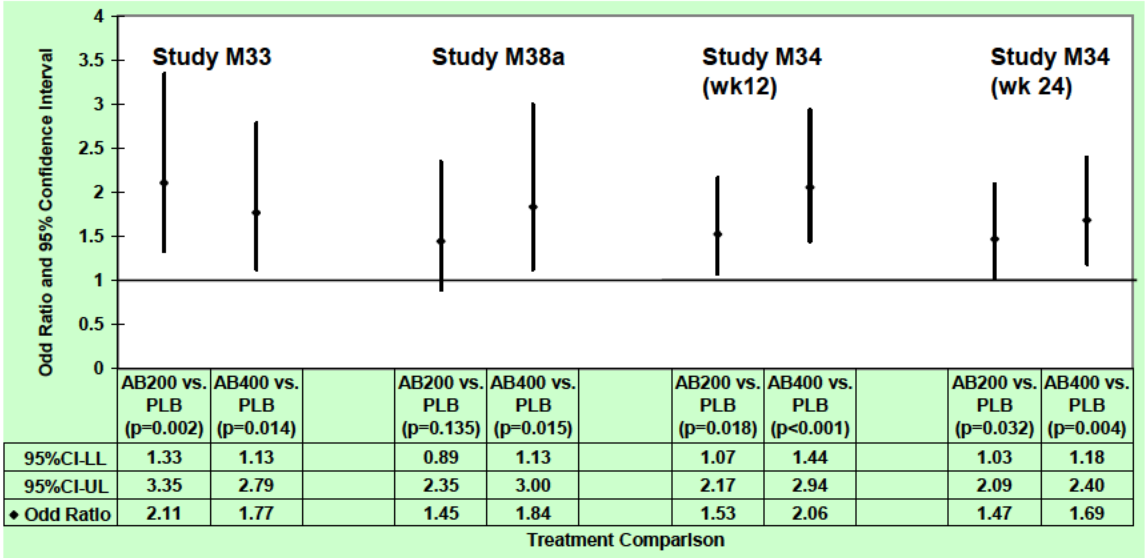
	>=0	>=4	>=6	>=8	>=10	>=12	>=14	>=16	>=20	>=0	>=4	>=6	>=8	>=10	>=12	>=14	>=16	>=20
PLB	51	39	32	25	17	10	9	6	4	52	39	33	28	23	18	15	11	7
AB200	64	50	41	34	26	21	18	14	9	68	55	46	41	33	27	22	18	13
AB400	70	56	48	42	35	28	24	19	13	69	54	49	43	40	34	28	23	14

Reference ID: 3100561

The key secondary efficacy variable for European Submission - Percentage of patients achieving a clinically relevant improvement (≥1-unit) in TDI focal

Percentage of patients achieving an improvement (at least 1 unit change from baseline) in TDI focal score at week 24 is the key secondary efficacy endpoint in Study M34 only. This endpoint was also explored in the studies (M33 and M38a). The results are displayed in Figure 16. Treatment differences were observed between the AB400 group and placebo at week 12 and 24 in all three studies. In Study M38a, only AB200 failed to show significant improvement compared to placebo.

Figure 16: Odds Ratio and 95% Confidence Interval of Treatment Comparison in proportion of patients who achieved a clinically relevant difference as defined by the Applicant in TDI (improvement ≥1 unit) at wk 12/24



The applicant conducted additional analysis on TDI focal score as a continuous endpoint. The ANCOVA model with treatment group and sex as factors as well as age and baseline TDI focal score as covariates was a protocol pre-specified method to compare the treatment difference for change from baseline to week 12 (based on the LOCF approach) in TDI. Treatment differences between AB and placebo in the change from baseline to week 12 using LOCF imputation in TDI focal score were statistically significant compared to placebo for both doses in Study M33 and M38a, and only on AB400 in Study M34. AB200 did not show a significant difference from placebo in Study M34 at week 12. (Table 9)

Table 9: Summary of the Change from Baseline in TDI Focal Score at Week 12/24 (LOCF)

			Baseline	Change from Baseline	Treatment Comparison AB - Placebo		
Study	**Treatment**	**N**	**LS Mean (SE)**	**LS Mean (SE)**	**LS Mean (SE)**	**95%CI**	**P value**
M33	Placebo	181	6.64 (0.17)	-5.94 (0.23)	--	--	--
Wk12	AB200	180	6.43 (0.17)	-5.02 (0.23)	0.93 (0.33)	(0.28, 1.58)	0.005
	AB400	189	6.27 (0.17)	-4.94 (0.23)	1.01 (0.33)	(0.37, 1.64)	0.002
M38a	Placebo	178	6.29 (0.18)	-5.93 (0.25)	--	--	--

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Wk12	AB200	178	6.39 (0.18)	-5.22 (0.24)	0.71 (0.35)	(0.03, 1.39)	0.042
	AB400	172	6.06 (0.18)	-4.94 (0.25)	0.99 (0.35)	(0.29, 1.68)	0.005
M34	Placebo	271	6.72 (0.14)	-5.94 (0.20)	--	--	--
Wk12	AB200	275	6.91 (0.13)	-5.57 (0.19)	0.36 (0.27)	(-0.17, 0.90)	0.181
	AB400	269	6.71 (0.13)	-5.06 (0.19)	0.88 (0.27)	(0.35, 1.42)	0.001
M34	Placebo	271	6.72 (0.14)	-5.83 (0.21)	--	--	--
Wk24	AB200	275	6.91 (0.13)	-5.25 (0.21)	0.58 (0.29)	(0.01, 1.15)	0.048
	AB400	269	6.71 (0.13)	-4.85 (0.21)	0.98 (0.29)	(0.40, 1.55)	0.001

SE=standard error. P-value, LS mean, and LSMD obtained from an ANCOVA model with change from baseline in TDI focal score as response, with treatment group and sex as factors and baseline TDI focal score and age as covariates.

Exploratory efficacy variable – Exacerbation

Results from the analyses of exacerbation are summarized in Table 10.

In Study M34, two approaches were used to evaluate exacerbation (EXACT-PRO and Health Resource Utilization (eCRF)). The annual exacerbation rates based on EXACT-PRO were higher than those based on eCRF: 1.38, 1.00 and 0.98 for placebo, AB200 and AB400 respectively compared to 0.60, 0.43, and 0.40. However, the rate ratios of AB doses over placebo were generally similar between the EXACT-PRO and the eCRF.

The estimated reductions in all exacerbation were approximately 30% compared with placebo for AB400 in studies M33 and M34 (Table 10). A similar reduction in the rate of moderate or severe COPD exacerbation is observed in these two studies. Since these were short-term studies (i.e. 3 or 6 month), and they were not powered to detect a treatment difference in exacerbation, it is not unexpected that the numbers of exacerbation reported are low. Therefore caution is warranted in the interpretation of the results, and the findings are merely for generating hypotheses.

Table 10: Summary of COPD exacerbations in three efficacy studies

	Observed Data				**Estimate Rate***		**Treatment Comparison***		
Treatment	N (%) of Subject with ≥1 exac.	Total Number of exac.	Total Exposure (years)	Rate per year	Rate	95%CI	Rate Ratio	95%CI	Nominal p-value
Study M33 (week 12) - All Exacerbations (eCRF)									
Placebo (185)	22 (12)	22	38.4	0.57	0.79	(0.46, 1.33)	--	--	--
AB200 (184)	16 (9)	17	38.7	0.44	0.55	(0.32, 0.94)	0.70	(0.44, 1.10)	0.118
AB400 (190)	12 (6)	12	40.6	0.30	0.41	(0.23, 0.74)	0.52	(0.32, 0.85)	0.009
Study M38a (week 12)- All Exacerbations (eCRF)									
Placebo (182)	19 (10)	19	38.7	0.49	0.50	(0.36, 0.69)	--	--	--
AB200 (182)	14 (8)	14	38.8	0.36	0.36	(0.25, 0.52)	0.72	(0.44, 1.16)	0.179
AB400 (177)	19 (11)	19	37.6	0.51	0.48	(0.35, 0.66)	0.96	(0.61, 1.50)	0.853
Study M34 (week 24) - All Exacerbations (eCRF)									
Placebo (273)	56 (21)	62	113.5	0.55	0.60	(0.48, 0.75)	--	--	--
AB200 (277)	44 (16)	48	121.7	0.39	0.43	(0.33, 0.55)	0.72	(0.52, 0.99)	0.043

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AB400 (269)	38 (14)	45	120.1	0.37	0.40	(0.31, 0.52)	0.67	(0.48, 0.94)	0.020
Study M34 (week 24) - All Exacerbation (EXACT-PRO)									
Placebo (273)	100 (37)	148	113.5	1.30	1.39	(1.16, 1.67)	--	--	--
AB200 (277)	83 (30)	115	121.7	0.94	1.00	(0.82, 1.23)	0.72	(0.55, 0.94)	0.017
AB400 (269)	78 (29)	111	120.1	0.92	0.98	(0.80, 1.21)	0.71	(0.54, 0.93)	0.012
Study M33 - Moderate or Severe Exacerbation (eCRF)									
Placebo (185)	16 (9)	16	38.4	0.42	0.63	(0.38, 1.03)	--	--	--
AB200 (184)	12 (7)	12	38.7	0.31	0.42	(0.25, 0.71)	0.67	(0.41, 1.08)	0.103
AB400 (190)	11 (6)	11	40.6	0.27	0.42	(0.24, 0.71)	0.66	(0.41, 1.07)	0.091
Study M38a - Moderate or Severe Exacerbation (eCRF)									
Placebo (182)	19 (10)	19	38.7	0.49	0.50	(0.37, 0.68)	--	--	--
AB200 (182)	11 (6)	11	38.8	0.28	0.29	(0.19, 0.42)	0.57	(0.34, 0.94)	0.028
AB400 (177)	16 (9)	16	37.6	0.43	0.41	(0.29, 0.58)	0.82	(0.52, 1.29)	0.397
Study M34 (week 24) - Moderate or Severe Exacerbation (eCRF)									
Placebo (273)	44 (16)	48	113.5	0.42	0.47	(0.38, 0.60)	--	--	--
AB200 (277)	36 (13)	39	121.7	0.32	0.35	(0.27, 0.45)	0.74	(0.53, 1.04)	0.085
AB400 (269)	33 (12)	38	120.1	0.32	0.34	(0.26, 0.44)	0.72	(0.51, 1.02)	0.063

*Analysis is based on Poisson regression model with dispersion adjustment and with the total number of COPD exacerbation during the study as response and with sex, and baseline COPD severity as factors along with age as covariate, adjusting for the log of the corresponding total exposure time in years for a patient (as a offset variable in the model).

Exploratory efficacy variable – Change from Baseline in Overall Use of Rescue Medication

There was some evidence of a reduction in the total daily use of rescue medication in both AB400 and AB200 in Study M33 (Table 11). As shown in Table 11, the overall adjusted mean reduction was 0.7 in the AB200 group and 0.9 in the AB400. This reduction was supported by Study M34 for AB400 group; the overall adjusted mean reduction was 0.9. For AB200 group, the reduction was smaller (0.6) than what was seen in Study M33. Like the exacerbation endpoint, the use of rescue is an exploratory variable. Therefore caution is warranted in the interpretation of the results, and the findings are merely for generating hypotheses.

Table 11: Summary of the change from baseline in Total Daily Use of Rescue Medication (puffs/day) over 12 weeks (LOCF) – Exploratory Analysis

			Baseline	**Change from Baseline**	**Treatment Comparison AB – Placebo**		
Study	**Treatment**	**N**	**LS Mean (SE)**	**LS Mean (SE)**	**LS Mean (SE)**	**95%CI**	**Nominal P value**
M33	Placebo	181	3.89 (0.29)	-0.68 (0.15)	--	--	--
Wk12	AB200	182	3.74 (0.29)	-1.40 (0.15)	-0.72 (0.21)	(-1.13, -0.31)	<0.001
	AB400	186	4.42 (0.28)	-1.55 (0.15)	-0.87 (0.21)	(-1.28, -0.46)	<0.001
M38a	Placebo	173	4.10 (0.38)	-1.14 (0.19)	--	--	--
Wk12	AB200	175	4.81 (0.38)	-1.32 (0.19)	-0.17 (0.27)	(-0.70, 0.35)	0.519
	AB400	171	4.96 (0.38)	-1.45 (0.19)	-0.30 (0.27)	(-0.83, 0.23)	0.262
M34	Placebo	271	3.78 (0.22)	-0.25 (0.24)	--	--	--
Wk12	AB200	277	3.29 (0.22)	-0.86 (0.24)	-0.61 (0.33)	(-1.26, 0.04)	0.066
	AB400	269	3.55 (0.22)	-1.20 (0.24)	-0.95 (0.33)	(-1.60, -0.30)	0.005

SE=standard error. P-value, LS mean, obtained from an ANCOVA model with change from baseline in daily use of rescue medication as response, with treatment group and sex as factors and baseline daily use of rescue medication and age as covariates.

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3.2 Evaluation of Safety

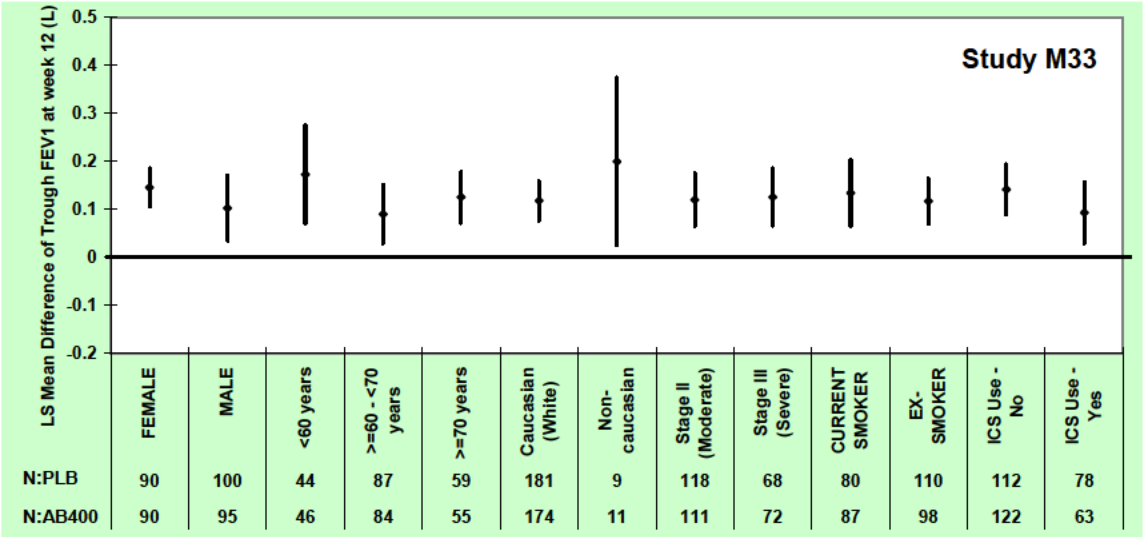
Dr. Jennifer Pippins, the Medical Reviewer, conducted the evaluation of the safety data separately. The reader is referred to the Clinical Briefing Document for information regarding the safety profile of the drug.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

The summary of subgroup analysis on the primary efficacy endpoint in the three phase 3 efficacy studies is given in Figure 17. The subgroups are categorized by age group, gender, COPD severity, smoking status, and ICS use at baseline, based on the categories summarized in Table 4. The results presented in the plots are from the mixed model, similar to the one used for the primary efficacy analysis, with the additional covariate on the subgroups being analyzed. In general, the subgroup analysis results are consistent with the results of overall population.

Interaction between treatment and subgroups were tested. There were statistically significant ($p<0.1$) interactions between treatment and race in Studies M38a and M34, as well as between treatment and ICS use at baseline in Study M33. Because there were only less than 10% of non-Caucasian in the studies, any claims of disparity in terms of patient's race are essentially unsupported. In Study M33, the improvement by AB400 µg over placebo was smaller in patients with ICS use at baseline (0.09L with a 95% CI (0.03L, 0.16L)) than that in patients without ICS use at baseline (0.14L with a 95% CI (0.09L, 0.19L)). No significant interaction was detected in other studies. All studies had the similar trends in subgroup analysis results.

Figure 17: LS Mean Change from Baseline in Trough FEV_1 at Week 12 by Subgroup (ITT)



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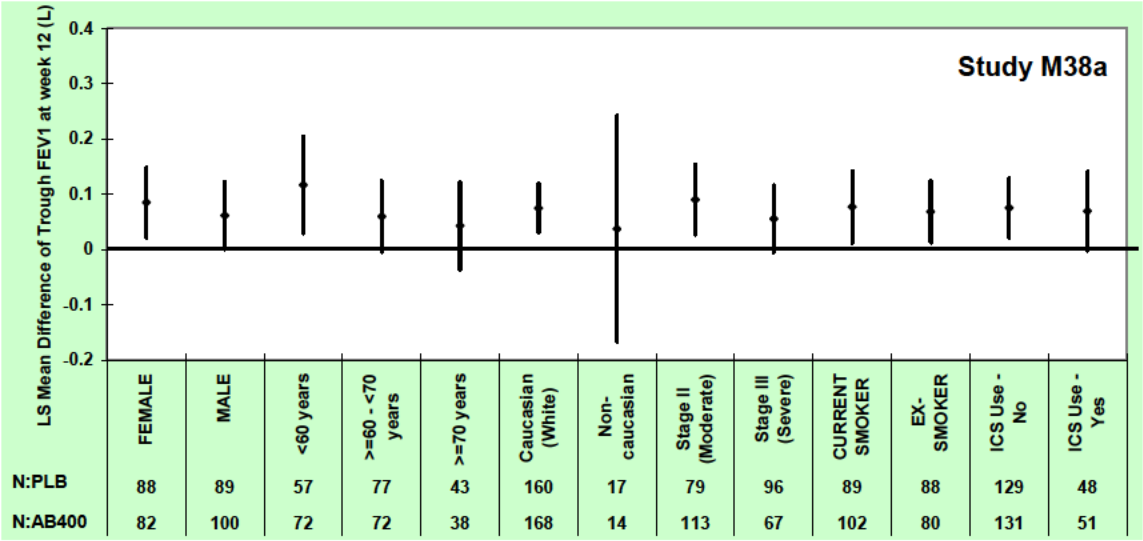

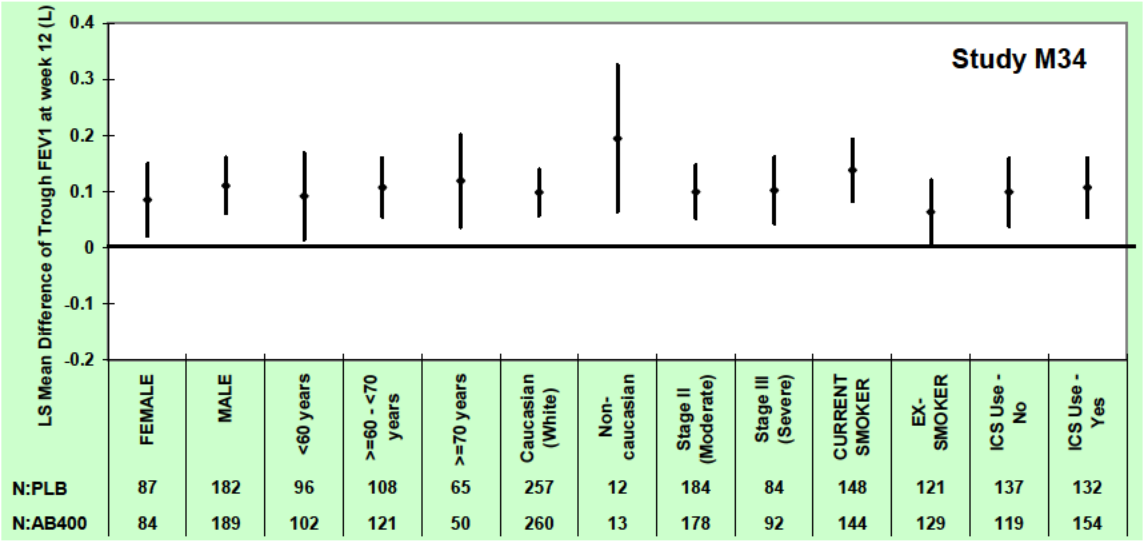

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

During my review of the clinical studies, I found no issues that could not be resolved by re-analyzing the data. Multiplicity adjustments were applied to the primary and key secondary endpoints. When different analytical methods and imputation strategies were applied to the primary endpoint, the results were consistent and highly significant. Furthermore, the results generated by the applicant and by me are similar and do not change the overall conclusion.

The major efficacy findings are as follows:

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• The treatment effect of aclidinium bromide was measured by the change from baseline at week 12 in trough FEV_1. Both aclidinium bromide 400 µg BID and aclidinium bromide 200 µg BID demonstrated statistically significant improvements compared to placebo in trough FEV_1 after 12 weeks treatment in all three phase 3 studies. The treatment difference between aclidinium bromide 400 µg and placebo ranged from 72 to 124 mL. The magnitude of treatment difference between aclidinium bromide 200 µg and placebo is smaller than that observed between the 400 µg dose and placebo with a treatment effect ranging from 51 to 86 mL.

• Both aclidinium bromide 400 µg BID and aclidinium bromide 200 µg BID demonstrated statistically significant improvements (from baseline FEV_1 which was defined as pre-dose FEV_1 at Day 1) compared to placebo in peak FEV_1 after 12 weeks of treatment in all three phase 3 studies. The treatment effects between aclidinium bromide 400 and placebo ranged from 125 to 192 mL. The magnitude of treatment difference between aclidinium bromide 200 µg and placebo is smaller than that observed between aclidinium bromide 400 µg and placebo with a treatment effect ranging from 115 to 182 mL.

• The percentage of patients achieving an improvement (or at least a 4-point reduction from baseline) in SGRQ Total Score at week 24 was a key secondary efficacy endpoint in Study M34 only. There were significantly higher proportions of patients treated with aclidinium bromide 400 µg or aclidinium bromide 200 µg achieving an improvement in SGRQ total score compared to patients treated with placebo at weeks 12 and 24. This endpoint was also explored in the studies M33 and M38a. A significant difference was only observed between the aclidinium bromide 200 µg group and placebo for Study M33. When SGRQ total score was evaluated as a continuous endpoint, only aclidinium bromide 400 µg in Study M34 showed a significant difference in SGRQ total scores compared to placebo that exceeds MCID of -4 at weeks 12 and 24 [-4.0 with 95% CI of (-5.9, -2.1) after 12 weeks treatment and -4.3 with 95% CI of (-6.4, -2.2) after 24 weeks treatment]. Treatment difference between aclidinium bromide 400 µg and placebo in SGRQ total scores in the other two studies ranged from -1.1 to -2.5, while treatment difference between aclidinium bromide 200 µg and placebo ranged from -1.7 to -3.6 in all three studies.

5.2 Conclusions and Recommendations

Forest Laboratories, Inc., proposes aclidinium bromide inhalation powder 400 µg twice daily, an orally inhaled anticholinergic (muscarinic receptor antagonist), for long term, maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema. Based on evaluation of 24-hour post-dose trough FEV1 after 12 weeks treatment, the applicant claims aclidinium bromide is effective in relieving bronchoconstriction in COPD patients.

Based on my review, in all three trials, both Aclidinium Bromide 200 and 400 µg twice daily provided statistically significant improvements in trough FEV1 compared to placebo. This was supported by other lung function measurements like peak FEV1 and serial FEV1. Improvement in trough FEV1 is numerically larger in Aclidinium Bromide 400 µg twice daily compared to

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Aclidinium Bromide 200 µg twice daily. Only Aclidinium Bromide 400 µg twice daily in Trial 34 showed a significant difference in SGRQ total scores compared to placebo that met the MCID of 4 points. This finding was not replicated in the other two trials. Because the overall exacerbation rate was low, it is difficult to make a definitive assessment regarding exacerbation from these three trials.

6. LABEL

The following are suggested edits to the Clinical Studies Section of the Label by the Clinical and Statistical team.

14 CLINICAL STUDIES

The following are suggested edits from the clinical and statistics team.

(b) (4)

[redacted]

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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7. APPENDIX

Figure 18: Kaplan-Meier Curve of Discontinuation for Study M33, M38a, and M34 (in order)

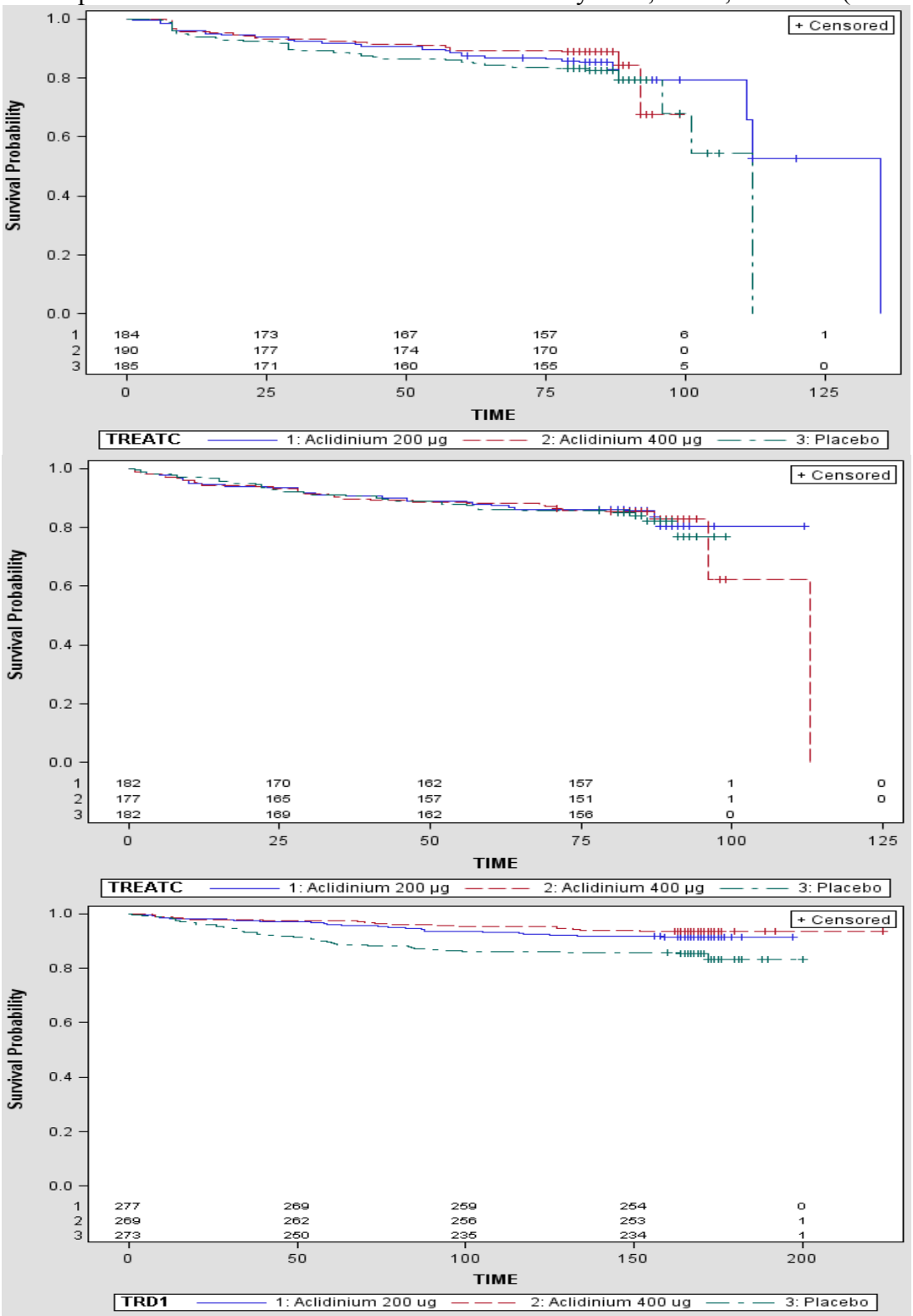

Table 12: Patients' Demographic and Baseline Characteristics, Study M23 (safety population)

		Overall N=30		
		n	Mean (±SD)	Range
Age	[years]	30	58.37 (±7.87)	43.0 – 73.0
Weight	[kg]	30	77.47 (±12.82)	46.20 – 100.40
Height	[m]	30	1.72 (±0.08)	1.58 – 1.88
BMI	[kg/m^2]	30	26.11 (±4.38)	18.50 – 38.50
Smoking duration	[years]	30	39.41 (±9.02)	23.0 – 55.2
Smoking consumption	[pack-years]	30	41.14 (±15.86)	18.2 – 80.0
		n (%)		
Sex	Female	11 (36.67%)		
	Male	19 (63.33%)		
Race	Caucasian	30 (100.00%)		
Smoking status	Current smoker	19 (63.33%)		
	Ex-smoker	11 (36.67%)		

		Pre-bronchodilator test Overall, N=30			Post-bronchodilator test Overall, N=30		
		n	Mean (±SD)	Range	n	Mean (±SD)	Range
FEV_1	(L)	30	1.467 (0.467)	0.72 – 2.43	30	1.707 (0.476)	0.96 – 2.61
FEV_1 of predicted	(%)	30	47.867 (13.372)	26.0 – 74.0	30	55.772 (13.657)	29.6 – 79.6
FVC	(L)	30	3.340 (0.834)	1.76 – 4.76	30	3.748 (0.872)	1.88 – 4.97
FVC of predicted	(%)	30	88.067 (17.663)	61.0 – 125.0	30	98.633 (17.129)	69.0 – 145.0
FEV_1 / FVC	(%)	—	—	—	30	46.233 (10.261)	28.0 – 66.0

		Bronchodilator reversibility Overall, N=30		
		n	Mean (±SD)	Range
FEV_1 absolute reversibility	(L)	30	0.240 (0.131)	0.06 – 0.51
Bronchial reversibility	(%)	30	18.249 (11.906)	4.00 – 47.22
		n (%)		
Reversible	No	14 (46.67%)		
	Yes	16 (53.33%)		

		Overall N=30		
		n	Mean (±SD)	Range
Duration of COPD	[years]	30	9.21 (±6.90)	0.9 – 29.8
		n (%)		
COPD severity (GOLD stage)	Stage II (Moderate)	19 (63.33%)		
	Stage III (Severe)	10 (33.33%)		
	Stage IV (Very severe)	1 (3.33%)		

Prior medication category	Total (N=30) n (%)	Prior medication category	Total (N=30) n (%)
ICS	14 (46.67)	LAMA	10 (33.33)
LABA	1 (3.33)	SABA	30 (100.00)
LABA + ICS	7 (23.33)	SAMA	1 (3.33)

Reversible was defined as: bronchial reversibility ≥ 12% and change from pre-test ≥ 200mL in FEV_1.

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Table 13: Patients' Demographic and Baseline Characteristics, Study M29 (safety population)

		Overall N=79		
		n	Mean (SD)	Min, Max
Age	[years]	79	61.1 (8.5)	41.0, 81.0
Weight	[kg]	79	81.6 (17.0)	43.0, 122.0
Height	[cm]	79	173.2 (7.5)	158.0, 189.0
BMI	[kg/m^2]	79	27.1 (5.1)	14.7, 38.9
Smoking duration	[years]	79	40.5 (8.4)	16.0, 58.0
Smoking consumption	[pack-years]	79	50.7 (26.8)	10.0, 142.5
		n (%)		
Sex	Female	20 (25.3%)		
	Male	59 (74.7%)		
Race	Caucasian	79 (100.0%)		
Smoking status	Current smoker	45 (57.0%)		
	Ex-smoker	34 (43.0%)		

		Pre-bronchodilator test Overall, N=79			Post-bronchodilator test Overall, N=79		
		n	Mean (SD)	Min, Max	n	Mean (SD)	Min, Max
FEV_1	(L)	79	1.475 (0.456)	0.68, 2.74	78	1.643 (0.459)	0.85, 2.76
FEV_1 of predicted	(%)	79	48.2 (12.5)	24.0, 78.3	78	53.7 (11.8)	30.0, 77.6
FVC	(L)	79	3.398 (0.834)	1.79, 5.84	78	3.698 (0.918)	1.81, 6.59
FVC of predicted	(%)	79	88.2 (13.8)	47.1, 119.2	78	96.1 (14.2)	54.7, 127.5
FEV_1 / FVC	(%)	—	—	—	78	45.1 (9.7)	23.5, 65.7

		Bronchodilator reversibility Overall, N=79		
		n	Mean (SD)	Min, Max
FEV_1 absolute reversibility	(L)	78	0.183 (0.160)	-0.16, 0.53
Bronchial reversibility	(%)	78	13.7 (11.9)	-11.6, 51.8
		n (%)		
Reversible	No	45 (57.7%)		
	Yes	33 (42.3%)		
	Missing	1		

		Overall N=79		
		n	Mean (SD)	Min, Max
Duration of COPD	[years]	79	10.4 (7.9)	0.0, 30.9
		n (%)		
COPD severity (GOLD stage)	Stage II (Moderate)	46 (59.0%)		
	Stage III (Severe)	32 (41.0%)		
	Missing	1		

Prior medication category	Total (N=79) n (%)
Any category	63 (79.8%)
ICS	8 (10.1%)
LABA	14 (17.7%)
LABA + ICS	24 (30.4%)
LAMA	24 (30.4%)

Prior medication category	Total (N=79) n (%)
SABA	46 (58.2%)
SABA + SAMA	4 (5.1%)
SAMA	3 (3.8%)
Xanthines	4 (5.1%)

Note: patient was counted separately in each of the medication category taken

Reversible was defined as: bronchial reversibility ≥ 12% and change from pre-test ≥ 200mL in FEV_1.

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Table 14: Summary of the change from baseline in trough FEV_1 at week 12/24 (MMRM)

			Baseline	Change from Baseline	Treatment Comparison AB - Placebo		
Study	**Treatment**	**N**	**LS Mean (SE)**	**LS Mean (SE)**	**LS Mean (SE)**	**95%CI**	**P value**
M33	Placebo	185	1.383 (0.033)	-0.026 (0.017)	--	--	--
Wk12	AB200	184	1.308 (0.033)	0.064 (0.017)	0.091 (0.023)	(0.04, 0.14)	<0.001
	AB400	190	1.328 (0.032)	0.106 (0.016)	0.132 (0.023)	(0.09, 0.18)	<0.001
M38a	Placebo	182	1.418 (0.035)	-0.009 (0.017)	--	--	--
Wk12	AB200	182	1.387 (0.035)	0.045 (0.017)	0.054 (0.024)	(0.01, 0.10)	0.024
	AB400	177	1.255 (0.037)	0.071 (0.017)	0.080 (0.024)	(0.03, 0.13)	0.001
M34	Placebo	273	1.419 (0.028)	-0.048 (0.015)	--	--	--
Wk12	AB200	277	1.453 (0.028)	0.030 (0.015)	0.078 (0.021)	(0.04, 0.12)	<0.001
	AB400	269	1.447 (0.029)	0.058 (0.015)	0.106 (0.021)	(0.06, 0.15)	<0.001
M34	Placebo	273	1.419 (0.028)	-0.074 (0.017)	--	--	--
Wk24	AB200	277	1.453 (0.028)	0.029 (0.016)	0.103 (0.023)	(0.06, 0.15)	<0.001
	AB400	269	1.447 (0.029)	0.059 (0.016)	0.133 (0.023)	(0.09, 0.18)	<0.001

SE=standard error. P-value, LS mean, and LSMD obtained from an MMRM analysis, which based on all post-baseline observed data using a mixed model with the response variable of change from baseline in morning trough FEV_1, and age as well as baseline FEV_1 value as covariates, and treatment group, sex, visit, and treatment group-by-visit interaction as fixed effect factors. Unstructured covariance matrix is used to model the within subject correlations.

-EOF-.

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/s/

FENG ZHOU
03/12/2012

JOAN K BUENCONSEJO
03/13/2012
I have read and concur with Ms. Zhou's statistical review and conclusion.

THOMAS J PERMUTT
03/13/2012
concur

Statistical Review and Evaluation
CARCINOGENICITY STUDIES

IND/NDA Number:	NDA 202450
Drug name:	LAS 34273
Indication(s):	
Applicant:	
Documents Reviewed:	Electronic submission Electronically submitted dataset Dated
Review Priority:	
Biometrics Division:	Division of Biometrics 6
Statistical Reviewer:	Matthew Jackson, PhD
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Medical Division:	
Reviewing Pharmacologist:	Grace Lee, PhD
Project Manager:	
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Background

In this submission the sponsor included reports of two animal carcinogenicity studies, in mice and rats. These studies were intended to assess the carcinogenic potential of LAS 34273 when administered by inhalation, once daily at appropriate drug levels for about 104 weeks. Results of this review have been discussed with the reviewing pharmacologist, Grace Lee, PhD .

In this review, the phrase "dose response relationship" 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.

Chapter 1

Mouse Study

1.1 Experimental design

Two separate experiments were conducted, one in female and one in male mice. The mice used were B6C3F1/Crl mice. In each experiment, the study consisted of five groups of sixty animals. All animals underwent nose-only flow-past inhalation for one hour a day. One group (a negative control group) inhaled only air, and a second inhaled the lactose vehicle. The other three groups inhaled LAS 34273 in a 10% lactose formulation, for target doses of 0.3, 0.8, and 2.5mg per kilogram of body weight.

The sponsor reports that various quantities, including mortality, clinical signs (including palpable masses), and the results of micro- and macroscopic examinations were recorded, but does not mention the frequency of the examinations which generated this data.

1.2 Sponsor's analysis

1.2.1 Survival analysis

The sponsor does not appear to have conducted statistical analyses of survival. However, based on a count of numbers of premature deaths, the sponsor has nonetheless drawn some conclusions. Among the female mice, the sponsor claims that there was no indication of any group experiencing significantly poorer survival than either the air or vehicle control groups. Among male mice, a significantly increased mortality rate, relative to both control groups, was noted in the low and mid dose groups, but not in the high dose group.

No p-values or estimates for the size of any possible effects have been included in the submission.

1.2.2 Tumor analysis

Incidence rates for all individual tumor types were investigated using the Peto [6] log rank method. No tumor types were found to be positively associated with dose levels.

1.3 Data analysis

1.3.1 Survival analysis

The Kaplan-Meier survival plots are shown as figures 1.1 and 1.2. The numbers and proportions of animals surviving to various times are presented in table 1.1. The results of log-rank tests of heterogeneity of survival and of dose response across the groups are presented in table 1.2, and the results of log-rank survival tests comparing the treated groups with the vehicle control group are presented in table 1.3.

Figure 1.1: Survival curves for female mice

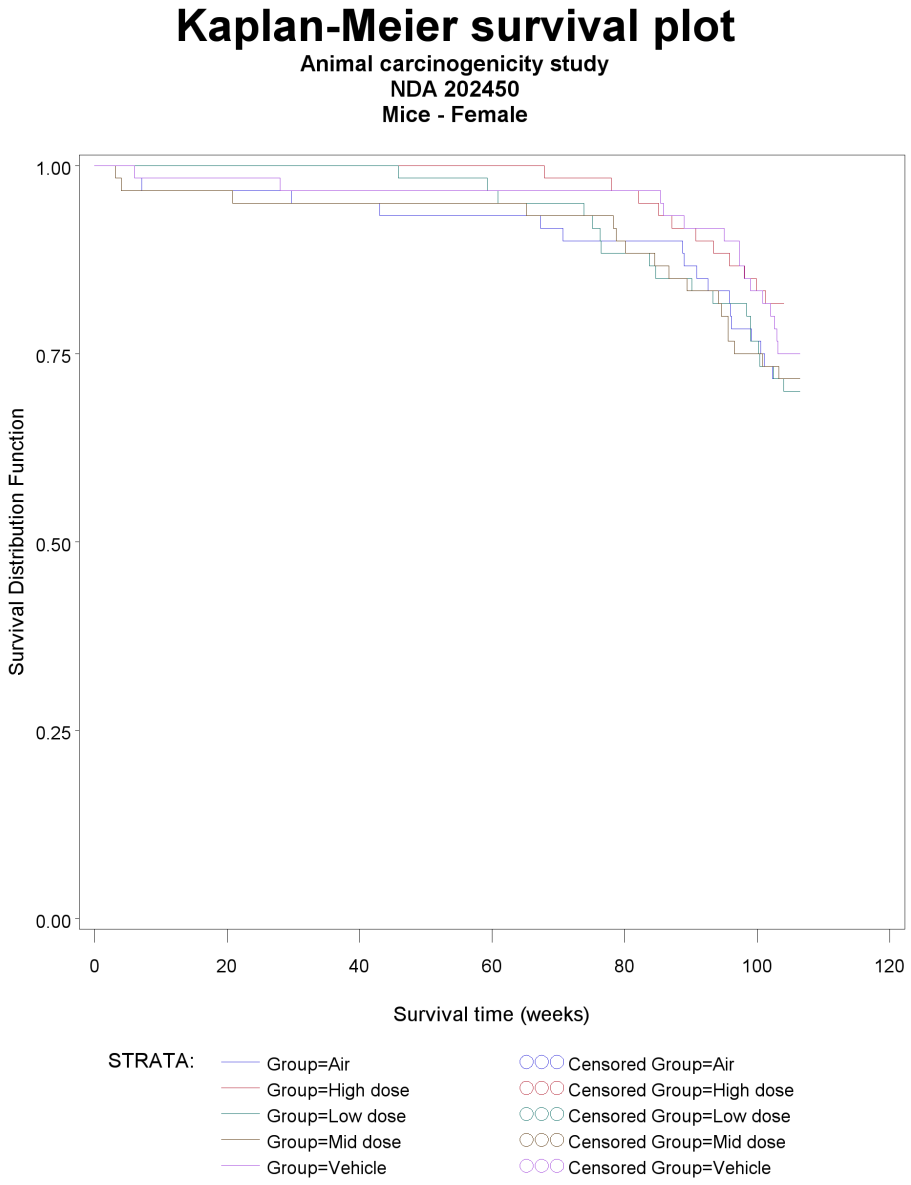

Figure 1.2: Survival curves for male mice

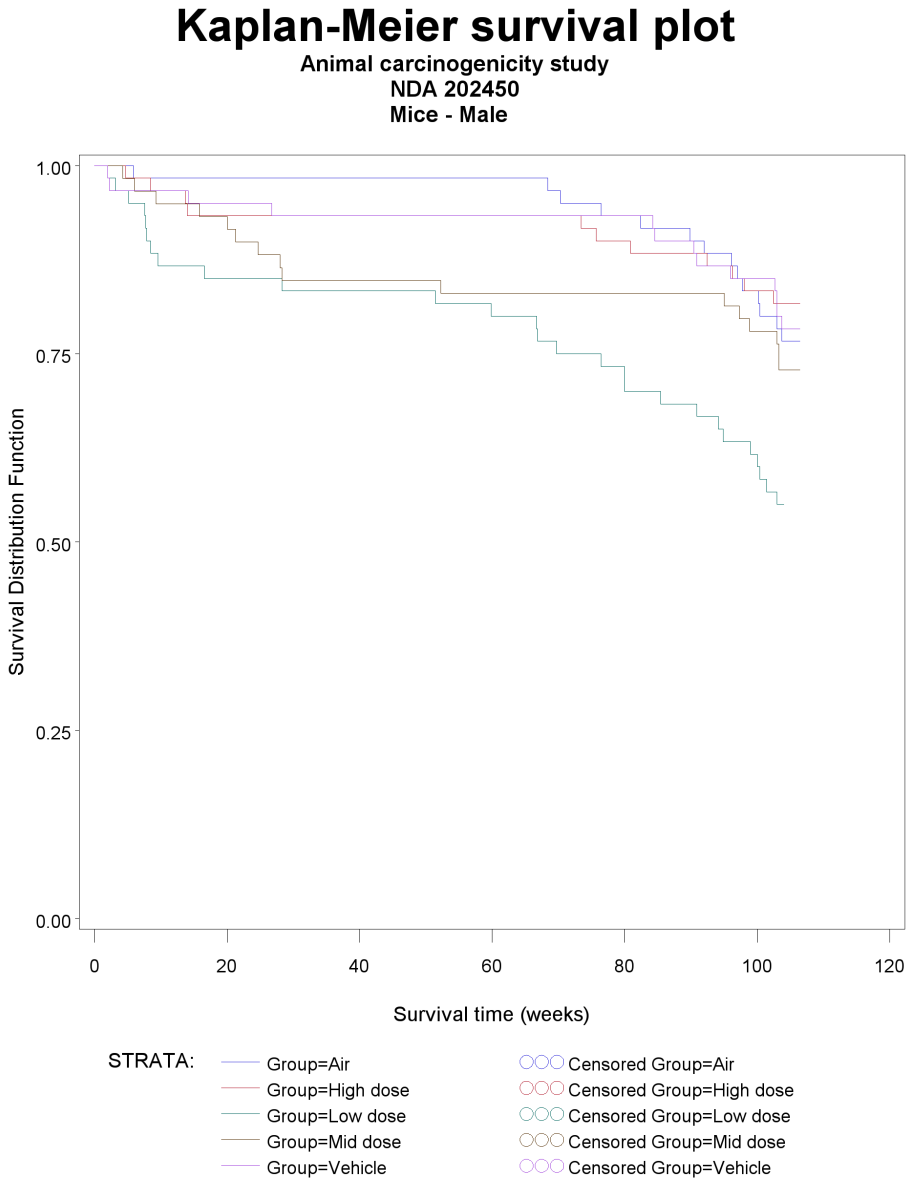

Table 1.1: Numbers of animals alive at certain timepoints (mouse study)

Survival rates at key times
NDA 202450
Animal carcinogenicity study
Mice

Species and Sex	*Dose Group*	*Dose (mg kg)*	*Number at start*	*Number alive after 52 weeks*	*Proportion alive after 52 weeks*	*Number alive after 78 weeks*	*Proportion alive after 78 weeks*	*Number alive after 90 weeks*	*Proportion alive after 90 weeks*	*Number alive at termination*	*Proportion alive at termination*
Mice - Female	Air	0	60	56	93%	54	90%	52	87%	43	72%
	Vehicle	0	60	58	97%	58	97%	55	92%	45	75%
	Low dose	0.3	60	59	98%	53	88%	51	85%	43	72%
	Mid dose	0.8	60	57	95%	56	93%	50	83%	43	72%
	High dose	2.5	60	60	100%	59	98%	55	92%	49	82%
Mice - Male	Air	0	60	59	98%	56	93%	54	90%	46	77%
	Vehicle	0	60	56	93%	56	93%	54	90%	47	78%
	Low dose	0.3	60	49	82%	44	73%	41	68%	33	55%
	Mid dose	0.8	60	50	83%	49	82%	49	82%	43	72%
	High dose	2.5	60	56	93%	54	90%	53	88%	49	82%

Commentry Among the female mice, there is no evidence of a dose related impact on survival (the p-value of the test of homogeneity is 0.6956). Among male mice, there is evidence of heterogeneity of survival ($p = 0.0013$), but this is driven by high mortality in the low dose group (the p-value of the comparison between the low dose group and the control is 0.0015). The other groups experienced comparable survival rates to the control groups.

It is possible that the result indicates a real effect, but in such a case, it would be necessary to explain why mortality was diminished in the low dose group, but not at the higher levels. Absent such an explanation, this result is most likely a false positive, and it should be concluded that there is no evidence of a dose related effect on survival.

Comparison of control groups Kaplan-Meier plots of the control groups are shown as figures 1.3 and 1.4. The results of log-rank tests of survival between the control groups are presented in table 1.4.

Although figure 1.3 suggests that the air control group exerienced higher mortality than the vehicle group, this difference is not statistically significant ($p = 0.5849$). Among the male mice, there is no suggestion of better performance in one group compared with another.

Table 1.2: Results of log-rank tests of survival across all groups

Log-rank tests of survival
NDA 202450
Animal carcinogenicity study

Species and Sex	*Test of homogeneity: chi squared statistic*	*Test of homogeneity: degrees of freedom*	*Number of groups*	*Test of homogeneity: p-value*	*Test of trend (two tailed): p-value*	*Test of trend (one tailed): p-value*
Mice - Female	2.2188	4	5	0.6956	0.2811	0.8594
Mice - Male	17.8462	4	5	0.0013	0.1911	0.9044
Rats - Female	2.6752	4	5	0.6136	0.5775	0.7113
Rats - Male	2.4124	4	5	0.6604	0.2219	0.8891

Table 1.3: Results of log-rank tests of survival between individual treated groups and control

Pairwise comparisons (log-rank) of survival between treated groups and controls
NDA 202450
Animal carcinogenicity study

Species and Sex	*Quantity*	*Low dose*	*Mid dose*	*High dose*
Mice - Female	Chi squared test statistic	0.5502	0.3479	0.2928
	p-value of comparison with control	0.4583	0.5553	0.5884
Mice - Male	Chi squared test statistic	10.0781	0.5166	0.1015
	p-value of comparison with control	0.0015	0.4723	0.7501
Rats - Female	Chi squared test statistic	0.8108	0.0229	0.2485
	p-value of comparison with control	0.3679	0.8798	0.6181
Rats - Male	Chi squared test statistic	0.3450	0.0472	1.0039
	p-value of comparison with control	0.5570	0.8280	0.3164

Figure 1.3: Survival curves for control groups (female mice experiment)

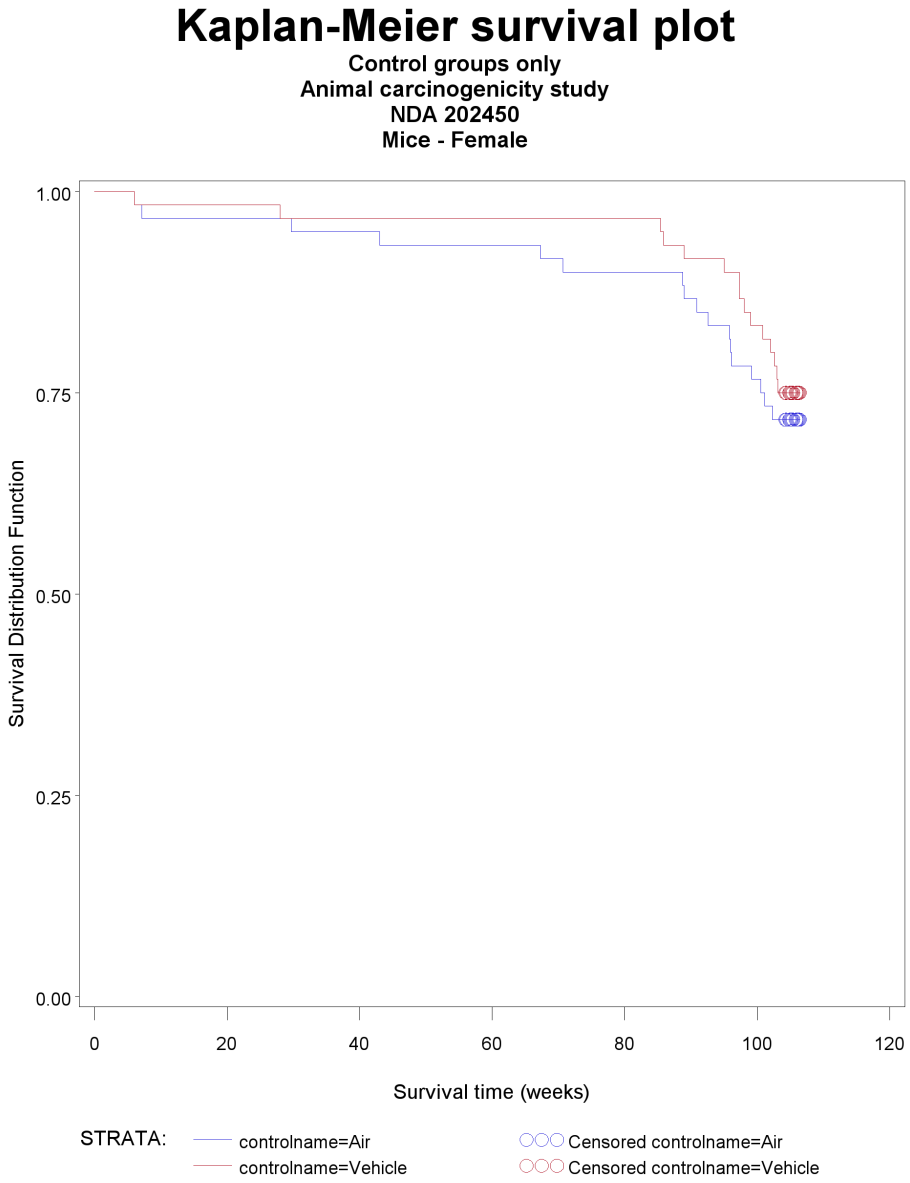

Figure 1.4: Survival curves for male mice

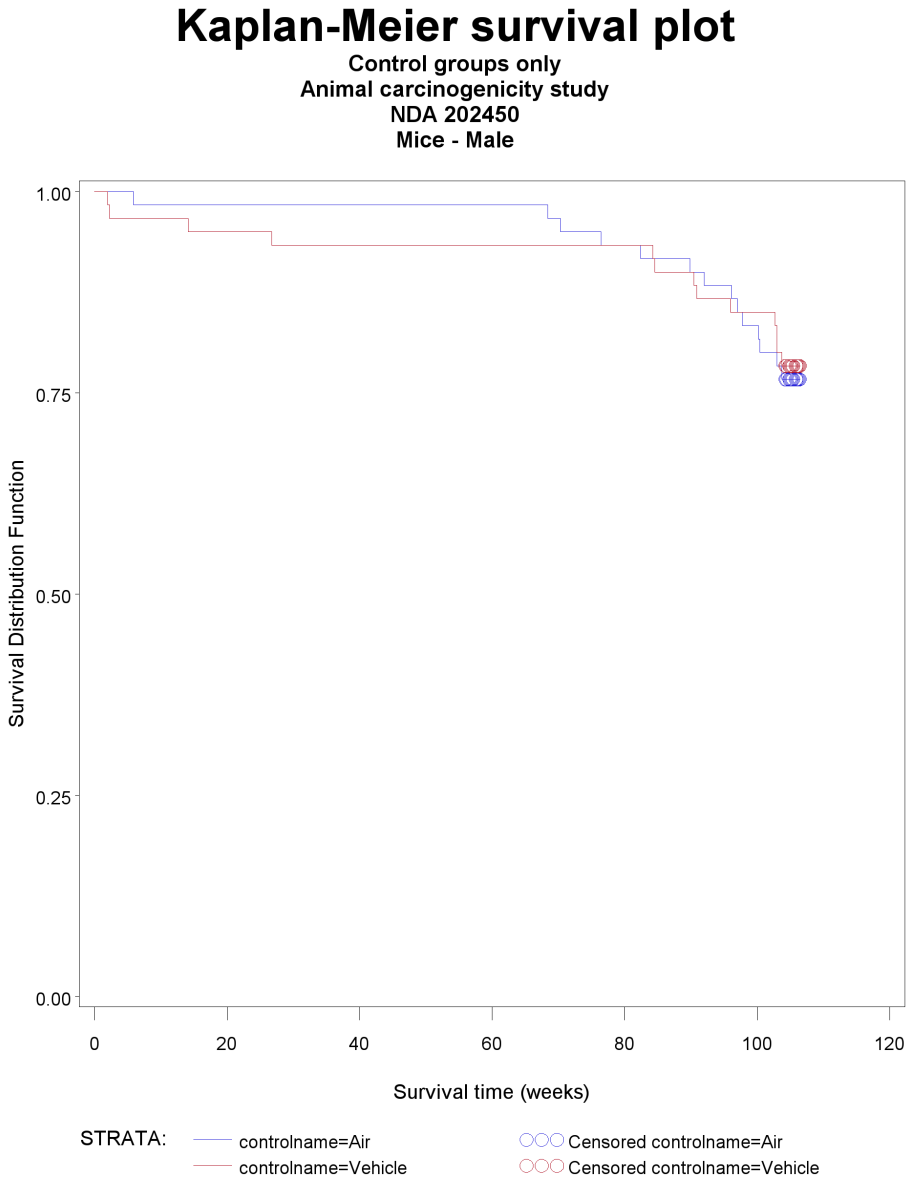

Table 1.4

Log-rank tests of heterogeneity of survival between control groups
NDA 202450
Animal carcinogenicity study

Species and Sex	*Chi^2*	*DF*	*P-value*
Mice - Female	0.2983	1	0.5849
Mice - Male	0.0351	1	0.8514
Rats - Female	0.3254	1	0.5684
Rats - Male	0.1881	1	0.6645

1.3.2 Tumor analysis — Main study

Endpoints

Analyses have been conducted using the sponsor's submitted dataset, and the sponsor's chosen nomenclature. In this dataset, organs or tissue types are described as being either tumorous, examined but found unusable due to autolysis, or unexamined. An organ that has been examined but was not found to be tumorous is not mentioned in the dataset.

From the submitted data, we can infer the numbers of animals for which each organ or tissue type was examined, but only in those cases where at least one anomalous finding (i.e., a tumor was found, or a sample that was planned to be analyzed, could not be, either becasue no sample was taken, or becasue the sample was unusable due to autolosys) was reported. Organs which can thus be deduced to have been successfully analyzed in the majority of animals are, for the purposes of this review, considered *primary*. The lists of primary organs in the experiments on female and male mice respectively are presented in tables 1.5 and 1.6. Organ or tissue types which were examined in only a few organ types are denoted secondary. In the mouse study, there are no secondary organs.

Each tumor type found in a primary organ of at least one animal is considered a co-primary endpoint. In addition, in consultation with Grace Lee, PhD , a list of combination endpoints has been drawn up. This list is presented in table 1.7.

Table 1.5: Primary organs in female mouse experiment

Primary organs in study of female mice NDA 202450 Animal carcinogenicity study
Organ or tissue name
ADRENAL CORTEX
ADRENAL MEDULLA
AORTA
BONE
BRAIN
BRONCHI (MAINSTEM)
CAECUM
CARINA (TRACHEAL B FURCATION)
CLITORAL GLAND
COLON
DUODENUM
EXTRAORBITAL LACR MAL GLANDS
EYES
FEMUR INCLUDING JOINT
GALL BLADDER
HAEMOPOIETIC TISSUE
HARDERIAN GLANDS
ILEUM
JEJUNUM
KIDNEYS
LARYNX
LIVER
LUNGS
LYMPH NODE, MANDIBULAR
LYMPH NODE, MESENTERIC
LYMPH NODE, TRACHEO-BRONCHIAL
MAMMARY GLAND AREA
NASAL CAVITIES (LEVEL 1)
NASAL CAVITIES (LEVEL II)
NASOPHARYNGEAL DUCT & PHARYNX
OESOPHAGUS
OPTIC NERVES
OVARIES
OVIDUCTS
PANCREAS
PARATHYROID GLANDS
PITUITARY GLAND
SALIVARY GLAND, MANDIBULAR

Primary organs in study of female mice NDA 202450 Animal carcinogenicity study
Organ or tissue name
SALIVARY GLAND, SUBLINGUAL
SCIATIC NERVE
SKELETAL MUSCLE (THIGH REGION)
SKIN
SPINAL CORD, LUMBAR
SPINAL CORD, MIDTHORACIC
SPLEEN
STERNUM WITH BONE MARROW
STOMACH, GLANDULAR
STOMACH, NON-GLANDULAR
THYMUS
THYRO D GLANDS
TONGUE
TRACHEA
URINARY BLADDER
UTERUS
VAGINA

Reference ID: 3087610

Table 1.6: Primary organs in male mouse experiment

Primary organs in study of male mice
NDA 202450
Animal carcinogenicity study

Organ or tissue name
ADRENAL CORTEX
ADRENAL MEDULLA
AORTA
BRONCHI (MAINSTEM)
CAECUM
CARINA (TRACHEAL B FURCATION)
COLON
DUODENUM
EPIDIDYMIDES
EXTRAORBITAL LACR MAL GLANDS
EYES
FEMUR INCLUDING JOINT
GALL BLADDER
HAEMOPOIETIC TISSUE
HARDERIAN GLANDS
ILEUM
JEJUNUM
KIDNEYS
LARYNX
LIVER
LUNGS
LYMPH NODE, MANDIBULAR
LYMPH NODE, MESENTERIC
LYMPH NODE, TRACHEO-BRONCHIAL
NASAL CAVITIES (LEVEL II)
NASAL CAVITIES (LEVEL III)
NASOPHARYNGEAL DUCT & PHARYNX
OESOPHAGUS
OPTIC NERVES
PANCREAS
PARATHYROID GLANDS
PITUITARY GLAND
PREPUTIAL GLAND
PROSTATE GLAND
SALIVARY GLAND, MANDIBULAR
SALIVARY GLAND, SUBLINGUAL
SEMINAL VESICLES
SKIN

Primary organs in study of male mice
NDA 202450
Animal carcinogenicity study

Organ or tissue name
SPINAL CORD, LUMBAR
SPINAL CORD, MIDTHORACIC
SPLEEN
STERNUM WITH BONE MARROW
STOMACH, GLANDULAR
STOMACH, NON-GLANDULAR
THYMUS
THYRO D GLANDS
TRACHEA
URINARY BLADDER

Reference ID: 3087610

Table 1.7: Customized endpoints analyzed

Customized and combination endpoints analyzed
NDA 202450
Animal carcinogenicity study

Composite endpoint
All hemangiomas
All hemangiomas and hemangiosarcomas
All hemangiosarcomas
Cholangioma and cholangiocarcinomas
Hepatocellular tumors
Mesenteric hemangiomas and hemangiosarcomas
Ovarian Sertolli cell tumors
Uterine stromal polys and ovarian tubulostromal carcinoma

Reference ID: 3087610

Statistical procedure

The tumor data were analyzed for dose response relationships and pairwise comparisons of tumor incidence in each of the treated groups versus the vehicle control group. Both the dose response relationship tests and pairwise comparisons were performed using the poly-k method described in the paper of Bailer and Portier [1] and developed in the paper of Bieler and Williams [2]. In this method, given a tumor type T, an animal h that lives the full study period (w_m) or dies before the terminal sacrifice with at least one tumor of type T gets a score of $s_h = 1$. An animal that dies at week w_h before the end of the study without such a tumor gets a score of

$$s_h = \left(\frac{w_h}{w_m}\right)^k < 1.$$

The adjusted group size is defined as $\sum_h s_h$. 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 $\sum s_h$ is equal to N (the original group size) if all animals live up to the end of the study or if each animal develops at least one tumor of type T, otherwise the adjusted group size is less than N. These adjusted group sizes are then used for the dose response relationship (or the pairwise) tests using the Cochran-Armitage test. The test is repeated for each tumor type T.

One critical point to consider in the application of the poly-k test is the choice of the appropriate value of k, which depends on the relationship between tumor onset time and increased dose. For long term 104 week standard rat and mouse studies, a value of $k = 3$ is suggested in the literature, and so has been used in this review. For the calculation of p-values, the exact permutation method was used.

For the adjustment of multiple testing of dose response relationship, the FDA guidance for the carcinogenicity study design and data analysis suggests the use of significance levels $\alpha = 0.005$ for common tumors and $\alpha = 0.025$ for rare tumors for a submission with two species, and a significance level $\alpha = 0.01$ for common tumors and $\alpha = 0.05$ for rare tumors for a submission with one species study in order to keep the false-positive rate at the nominal level of approximately 10%. A rare tumor is defined as one in which the published spontaneous tumor rate is less than 1%. For multiple pairwise comparisons of treated group with control, the FDA guidance suggests the use of test levels $\alpha = 0.01$ for common tumors and $\alpha = 0.05$ for rare tumors, for both submissions with one or two species, in order to keep the false-positive rate at the nominal level of approximately 10%.

It should be noted that the FDA guidance for multiple testing for dose response relationship is based on a publication by Lin and Rahman [5]. In this work the authors investigated the use of this rule for Peto analysis. However, in a later work Rahman and Lin [7] showed that this rule for multiple testing for dose response relationship is also suitable for poly-k tests.

Since this is a study involving two species, it follows that for the comparisons of LAS 34273 with vehicle control we use the thresholds for significance presented in table 1.8.

Noteworthy results

The results of the statistical analyses of tumor incidence in primary endpoints are presented in tables 1.9 (female mice) and 1.10 (male mice). The results of analyses of customized endpoints (see table 1.7) are presented in tables 1.11 and 1.12.

Tables 1.13, and 1.14 are excerpted from tables 1.9 and 1.11, and list only those tumor types or customized endpoints for which at least one test of comparison or trend yielded a p-value below 0.05. No significant results were reported in the male mouse experiment.

Hepatocellular carcinomas in female mice Analysis (see table 1.13) of the incidence of hepatocellular carcinomas in female mice yields p-values below 0.05 for the test of trend ($p = 0.0401$), the comparison between the low dose group and the vehicle control ($p = 0.0257$), and the comparison between the high dose group and conntrol ($p = 0.0143$). While it is striking that three of the four tests conducted for this tumor type yielded p-values below 0.05, it must be remembered that these

Table 1.8: Critical p-values used to determine statistical significance

Type of test	Rare tumor	Common tumor
Trend	0.025	0.005
Pairwise test between placebo and high dose	0.05	0.01

tests are not indpendent, and could all be the result of a single unusually low rate in the vehicle control group.

Evidence for this explanation is found in the fact that while none of the female vehicle control mice developed hepatocellular carcinomas, eight of the male vehicle control mice did, as well as two female mice from the air control group and thirteen animals from the male mice air control group.

If hepatocellular carcinomas are considered common, then none of these results remain significant after making an adjustment for multiplicity. If they are considered rare (which according to the most rigid definition of rareness, based on the observed incidence rate in the vehicle control group, they are), then the comparisons between the vehicle control group and both the high and low dose groups remain significant, but the test of trend does not.

However, given the observed incidence rate in the air control group, it seems inappropriate to consider this to be a rare tumor type. Therefore the result should be considered a negative finding.

Hemangiomas in female mice The analysis (see table 1.14) of hemangiomas in female mice yields a p-value of 0.0416 for the test of trend. However, none of the pairwise comparisons with control yield a p-value below 0.05, and the result for the test of trend does not remain significant after making a multiplicity adjustment. This should therefore be considered a negative finding.

1.3.3 Tumor analysis — Vehicle study

Reason for study

The sponsor has included two control groups, treated with air and the vehicle respectively. This provides the opportunity to compare the two groups for signs of increaced tumor incidence as a result of the vehicle. (Note that in both female and male animals, there was no indication of a vehicle related increase in mortality; see table 1.4).

Results

The results of the statistical analyses of tumor incidence in primary endpoints are presented in tables 1.15 (female mice) and 1.16 (male mice). The results of analyses of customized endpoints (see table 1.7) are presented in tables 1.17 and 1.18.

No statistical tests were conducted in either sex for which a p-value below 0.05 was reported.

1.3.4 Analysis of unexamined and autolytic organs

Unexamined animals

No animals have been reported as completely unexamined.

Organs reported autolytic

The numbers of animals with organs reported as being autolytic to the extent that no usable sample was obtainable are presented in tables 1.19 and 1.20.

Among female mice, the organ most frequently reported as autolyzed is the gall bladder. However, even this organ is only autolytic in 7.5% of animals, and in no more than 10% of animals in any one dose group. There does not seem to be any reason to consider the reported levels of autolysis to be problematic.

Among the male mice, the levels of reported autolysis are somewhat higher. This is of less concern than usual, since reports of autolysis are strongly concentrated in the low dose group, the members of which provide the least information for the study. These elevated rates are most likely caused by the fact that the low dose group experienced significantly higher premature death than the other groups. As a result, caution should be used when making inferences concerning the gall bladder or jejunum in low dose animals, but otherwise the reported levels of autolysis are no cause for concern.

Organs reported as unexamined

The numbers of animals with organs reported as being unexamined are presented in tables 1.21 and 1.22.

Among female mice, large numbers did not have their parathyroid (37%) or carina (24%) examined. The levels are high enough that it is probably not reasonable to make inferences concerning these organs. Rates of unexamined organs are otherwise acceptable.

The situation with male mice is similar, except that in addition to inferences concerning the carina and parathyroid, inferences concerning the thymus, which was reported as being unexamined in 17% of animals should also be treated circumspectly.

1.3.5 Tables of results

Table 1.9

Table of reported tumors in Mouse Study
NDA 202450
Animal carcinogenicity study
Female mice

Organ or tissue name	*Tumor name*	*Quantity*	*Vehicle*	*Low dose*	*Mid dose*	*High dose*
ADRENAL CORTEX	CORTICAL ADENOMA	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
		Poly-3 adjusted incidence rate	1.8%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.05,9.9)	(0,6.8)	(0,6.8)	(0,6.4)
		Poly-3 adjusted number of animals at risk	54.6	52.8	52.1	56.2
BONE	OSTEOSARCOMA	P-value of test of trend or comparison	.9360	.7430	1	1
		Number of animals reported with tumor	1	1	0	0
		Poly-3 adjusted incidence rate	1.8%	1.9%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.05,9.7)	(0.05,10.1)	(0,6.8)	(0,6.4)
		Poly-3 adjusted number of animals at risk	55.6	53.4	52.1	56.2
BRAIN	GRANULAR CELL TUMOUR	P-value of test of trend or comparison	.2605			.5045
		Number of animals reported with tumor	0	0	0	1
		Poly-3 adjusted incidence rate	0.0%	0.0%	0.0%	1.8%
		95% CI for poly-3 adjusted incidence rate (%)	(0,6.5)	(0,6.8)	(0,6.8)	(0.04,9.6)
		Poly-3 adjusted number of animals at risk	55.6	52.8	52.1	56.2
DUODENUM	ADENOMATOUS POLYP	P-value of test of trend or comparison	.0660		.4762	.2477
		Number of animals reported with tumor	0	0	1	2
		Poly-3 adjusted incidence rate	0.0%	0.0%	2.0%	3.6%
		95% CI for poly-3 adjusted incidence rate (%)	(0,6.5)	(0,7.1)	(0.05,10.6)	(0.44,12.5)
		Poly-3 adjusted number of animals at risk	55.6	50.3	50.8	55.3
FEMUR INCLUDING JOINT	HAEMANGIOSARCOMA	P-value of test of trend or comparison	.1935		.4860	.5045
		Number of animals reported with tumor	0	0	1	1
		Poly-3 adjusted incidence rate	0.0%	0.0%	1.9%	1.8%
		95% CI for poly-3 adjusted incidence rate (%)	(0,6.5)	(0,6.8)	(0.05,10.3)	(0.04,9.6)
		Poly-3 adjusted number of animals at risk	55.6	52.8	52.1	56.4
HAEMOPOIETIC TISSUE	HISTIOCYTIC SARCOMA	P-value of test of trend or comparison	.8117	.1113	.4860	
		Number of animals reported with tumor	0	3	1	0
		Poly-3 adjusted incidence rate	0.0%	5.7%	1.9%	0.0%

Reference ID: 3087610

Table 1.9

Table of reported tumors in Mouse Study
NDA 202450
Animal carcinogenicity study
Female mice

Organ or tissue name	*Tumor name*	*Quantity*	*Vehicle*	*Low dose*	*Mid dose*	*High dose*
		95% CI for poly-3 adjusted incidence rate (%)	(0,6.5)	(1.18,15.9)	(0.05,10.3)	(0,6.4)
		Poly-3 adjusted number of animals at risk	55.6	52.8	52.6	56.2
	MALIGNANT LYMPHOMA	P-value of test of trend or comparison	.8794	.9145	.1281	.9433
		Number of animals reported with tumor	17	11	23	11
		Poly-3 adjusted incidence rate	30%	21%	42%	19%
		95% CI for poly-3 adjusted incidence rate (%)	(18.4,44.1)	(10.6,34.1)	(28.7,56.8)	(9.87,31.9)
		Poly-3 adjusted number of animals at risk	56.7	53.3	54.1	57.1
HARDERIAN GLANDS	ADENOCARCINOMA	P-value of test of trend or comparison	.3051	.4860	.4860	.5045
		Number of animals reported with tumor	0	1	1	1
		Poly-3 adjusted incidence rate	0.0%	1.9%	1.9%	1.8%
		95% CI for poly-3 adjusted incidence rate (%)	(0,6.5)	(0.05,10.3)	(0.05,10.3)	(0.04,9.6)
		Poly-3 adjusted number of animals at risk	55.6	52.8	52.3	56.6
	ADENOMA	P-value of test of trend or comparison	.3035	.6429	.9339	.5101
		Number of animals reported with tumor	3	3	1	4
		Poly-3 adjusted incidence rate	5.4%	5.6%	1.9%	7.1%
		95% CI for poly-3 adjusted incidence rate (%)	(1.12,15.1)	(1.16,15.7)	(0.05,10.3)	(1.95,17.3)
		Poly-3 adjusted number of animals at risk	55.6	53.4	52.1	56.2
JEJUNUM	ADENOMATOUS POLYP	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
		Poly-3 adjusted incidence rate	1.8%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.05,9.7)	(0,7.1)	(0,7.3)	(0,6.6)
		Poly-3 adjusted number of animals at risk	55.6	50.1	49.4	54.3
KIDNEYS	CARCINOMA	P-value of test of trend or comparison	.5023		.4860	
		Number of animals reported with tumor	0	0	1	0
		Poly-3 adjusted incidence rate	0.0%	0.0%	1.9%	0.0%

Reference ID: 3087610

Table 1.9

Table of reported tumors in Mouse Study
NDA 202450
Animal carcinogenicity study
Female mice

Organ or tissue name	*Tumor name*	*Quantity*	*Vehicle*	*Low dose*	*Mid dose*	*High dose*
		95% CI for poly-3 adjusted incidence rate (%)	(0,6.5)	(0,6.8)	(0.05,10.3)	(0,6.4)
		Poly-3 adjusted number of animals at risk	55.6	52.8	52.1	56.2
LIVER	HAEMANGIOSARCOMA	P-value of test of trend or comparison	.2605			.5045
		Number of animals reported with tumor	0	0	0	1
		Poly-3 adjusted incidence rate	0.0%	0.0%	0.0%	1.8%
		95% CI for poly-3 adjusted incidence rate (%)	(0,6.5)	(0,6.8)	(0,6.8)	(0.04,9.6)
		Poly-3 adjusted number of animals at risk	55.6	52.8	52.1	56.7
	HEPATOCELLULAR ADENOMA	P-value of test of trend or comparison	.8640	.7033	.5792	.9234
		Number of animals reported with tumor	6	5	6	3
		Poly-3 adjusted incidence rate	11%	9.5%	12%	5.3%
		95% CI for poly-3 adjusted incidence rate (%)	(4.03,22.2)	(3.13,21.0)	(4.27,23.4)	(1.1,14.9)
		Poly-3 adjusted number of animals at risk	55.6	52.9	52.1	56.2
	HEPATOCELLULAR CARCINOMA	P-value of test of trend or comparison	.0401	.0257	.2338	.0143
		Number of animals reported with tumor	0	5	2	6
		Poly-3 adjusted incidence rate	0.0%	9.3%	3.8%	11%
		95% CI for poly-3 adjusted incidence rate (%)	(0,6.5)	(3.08,20.7)	(0.46,13.2)	(3.96,21.9)
		Poly-3 adjusted number of animals at risk	55.6	53.7	52.6	56.6
LUNGS	PULMONARY ADENOCARCINOMA	P-value of test of trend or comparison	.8111	.4732	.8678	.8817
		Number of animals reported with tumor	2	3	1	1
		Poly-3 adjusted incidence rate	3.6%	5.7%	1.9%	1.8%
		95% CI for poly-3 adjusted incidence rate (%)	(0.44,12.5)	(1.18,15.9)	(0.05,10.3)	(0.04,9.6)
		Poly-3 adjusted number of animals at risk	55.6	52.8	52.1	56.2
	PULMONARY ADENOMA	P-value of test of trend or comparison	.9316	.7575	.9673	.9729
		Number of animals reported with tumor	4	3	1	1

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Table 1.9

Table of reported tumors in Mouse Study
NDA 202450
Animal carcinogenicity study
Female mice

Organ or tissue name	*Tumor name*	*Quantity*	*Vehicle*	*Low dose*	*Mid dose*	*High dose*
		Poly-3 adjusted incidence rate	7.2%	5.7%	1.9%	1.8%
		95% CI for poly-3 adjusted incidence rate (%)	(1.98,17.6)	(1.18,15.9)	(0.05,10.3)	(0.04,9.6)
		Poly-3 adjusted number of animals at risk	55.6	52.8	52.1	56.2
MAMMARY GLAND AREA	ADENOCARCINOMA	P-value of test of trend or comparison	.9284	.8559	.8678	1
		Number of animals reported with tumor	2	1	1	0
		Poly-3 adjusted incidence rate	3.6%	2.0%	1.9%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.44,12.5)	(0.05,10.9)	(0.05,10.3)	(0,6.5)
		Poly-3 adjusted number of animals at risk	55.6	49.6	52.1	55.2
NASOPHARYNGEAL DUCT & PHARYNX	OSTEOSARCOMA	P-value of test of trend or comparison	.7442	.4860		
		Number of animals reported with tumor	0	1	0	0
		Poly-3 adjusted incidence rate	0.0%	1.9%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,6.5)	(0.05,10.3)	(0,6.8)	(0,6.4)
		Poly-3 adjusted number of animals at risk	55.6	52.6	52.1	56.2
OVARIES	CYSTADENOMA	P-value of test of trend or comparison	.6999	.4860	.1046	
		Number of animals reported with tumor	0	1	3	0
		Poly-3 adjusted incidence rate	0.0%	1.9%	5.9%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,6.5)	(0.05,10.3)	(1.23,16.5)	(0,6.5)
		Poly-3 adjusted number of animals at risk	55.6	52.2	50.6	55.2
	HAEMANGIOMA	P-value of test of trend or comparison	.7393	.4811		
		Number of animals reported with tumor	0	1	0	0
		Poly-3 adjusted incidence rate	0.0%	1.9%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,6.5)	(0.05,10.4)	(0,7.1)	(0,6.5)
		Poly-3 adjusted number of animals at risk	55.6	51.6	50.3	55.2
	LUTEOMA	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
		Poly-3 adjusted incidence rate	1.8%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.05,9.7)	(0,7.0)	(0,7.1)	(0,6.5)

Table 1.9

Table of reported tumors in Mouse Study
NDA 202450
Animal carcinogenicity study
Female mice

Organ or tissue name	*Tumor name*	*Quantity*	*Vehicle*	*Low dose*	*Mid dose*	*High dose*
		Poly-3 adjusted number of animals at risk	55.6	51.6	50.3	55.2
	TUBULOSTROMAL ADENOMA	P-value of test of trend or comparison	.2607			.5000
		Number of animals reported with tumor	0	0	0	1
		Poly-3 adjusted incidence rate	0.0%	0.0%	0.0%	1.8%
		95% CI for poly-3 adjusted incidence rate (%)	(0,6.5)	(0,7.0)	(0,7.1)	(0.05,9.7)
		Poly-3 adjusted number of animals at risk	55.6	51.6	50.3	55.2
PITUITARY GLAND	ADENOCARCINOMA, pars distalis	P-value of test of trend or comparison	.7488	.4952		
		Number of animals reported with tumor	0	1	0	0
		Poly-3 adjusted incidence rate	0.0%	1.9%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,6.7)	(0.05,10.3)	(0,7.0)	(0,6.5)
		Poly-3 adjusted number of animals at risk	53.6	52.4	51.1	55.2
	ADENOMA, pars distalis	P-value of test of trend or comparison	.9942	.6970	.9473	.9975
		Number of animals reported with tumor	7	6	3	1
		Poly-3 adjusted incidence rate	13%	12%	5.8%	1.8%
		95% CI for poly-3 adjusted incidence rate (%)	(5.37,25.3)	(4.35,23.9)	(1.21,16.2)	(0.05,9.7)
		Poly-3 adjusted number of animals at risk	53.8	51.8	51.8	55.2
SKELETAL MUSCLE (THIGH REGION)	SARCOMA, NOS	P-value of test of trend or comparison	.5000		.4811	
		Number of animals reported with tumor	0	0	1	0
		Poly-3 adjusted incidence rate	0.0%	0.0%	1.9%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,6.5)	(0,6.8)	(0.05,10.4)	(0,6.4)
		Poly-3 adjusted number of animals at risk	55.6	52.8	51.4	56.2
SKIN	MALIGNANT SCHWANNOMA	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
		Poly-3 adjusted incidence rate	1.8%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.05,9.7)	(0,6.8)	(0,6.8)	(0,6.4)
		Poly-3 adjusted number of animals at risk	55.7	52.8	52.1	56.2
	OSTEOSARCOMA	P-value of test of trend or comparison	.7454	.4907		

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Table 1.9

Table of reported tumors in Mouse Study
NDA 202450
Animal carcinogenicity study
Female mice

Organ or tissue name	*Tumor name*	*Quantity*	*Vehicle*	*Low dose*	*Mid dose*	*High dose*
		Number of animals reported with tumor	0	1	0	0
		Poly-3 adjusted incidence rate	0.0%	1.9%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,6.5)	(0.05,10.1)	(0,6.8)	(0,6.4)
		Poly-3 adjusted number of animals at risk	55.6	53.6	52.1	56.2
	SEBACEOUS GLAND ADENOMA	P-value of test of trend or comparison	.7442	.4860		
		Number of animals reported with tumor	0	1	0	0
		Poly-3 adjusted incidence rate	0.0%	1.9%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,6.5)	(0.05,10.3)	(0,6.8)	(0,6.4)
		Poly-3 adjusted number of animals at risk	55.6	52.8	52.1	56.2
SPLEEN	HAEMANGIOMA	P-value of test of trend or comparison	.7442	.4860		
		Number of animals reported with tumor	0	1	0	0
		Poly-3 adjusted incidence rate	0.0%	1.9%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,6.5)	(0.05,10.3)	(0,6.8)	(0,6.4)
		Poly-3 adjusted number of animals at risk	55.6	52.8	52.1	56.2
	HAEMANGIOSARCOMA	P-value of test of trend or comparison	.3847	1	.4788	.7568
		Number of animals reported with tumor	1	0	2	1
		Poly-3 adjusted incidence rate	1.8%	0.0%	3.8%	1.8%
		95% CI for poly-3 adjusted incidence rate (%)	(0.05,9.7)	(0,6.8)	(0.46,13.2)	(0.04,9.6)
		Poly-3 adjusted number of animals at risk	55.6	52.8	52.1	56.4
STOMACH, GLANDULAR	ADENOMATOUS POLYP	P-value of test of trend or comparison	.7430	.4860		
		Number of animals reported with tumor	0	1	0	0
		Poly-3 adjusted incidence rate	0.0%	1.9%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,6.5)	(0.05,10.3)	(0,7.0)	(0,6.4)
		Poly-3 adjusted number of animals at risk	55.6	52.1	51.3	56.2
STOMACH, NON-GLANDULAR	SQUAMOUS PAPILLOMA	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
		Poly-3 adjusted incidence rate	1.8%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.05,9.7)	(0,6.8)	(0,6.8)	(0,6.4)

Reference ID: 3087610

Table 1.9

Table of reported tumors in Mouse Study
NDA 202450
Animal carcinogenicity study
Female mice

Organ or tissue name	*Tumor name*	*Quantity*	*Vehicle*	*Low dose*	*Mid dose*	*High dose*
		Poly-3 adjusted number of animals at risk	55.6	52.8	52.1	56.2
THYMUS	THYMOMA	P-value of test of trend or comparison	.6284	.4800	.4747	
		Number of animals reported with tumor	0	1	1	0
		Poly-3 adjusted incidence rate	0.0%	2.1%	2.1%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,6.8)	(0.05,11.1)	(0.05,11.3)	(0,6.7)
		Poly-3 adjusted number of animals at risk	52.6	48.6	47.6	53.2
THYROID GLANDS	C-CELL CARCINOMA	P-value of test of trend or comparison	.9366	.7477	1	1
		Number of animals reported with tumor	1	1	0	0
		Poly-3 adjusted incidence rate	1.8%	1.9%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.05,9.9)	(0.05,10.1)	(0,7.0)	(0,6.5)
		Poly-3 adjusted number of animals at risk	54.6	53.4	51.1	55.2
	FOLLICULAR CELL ADENOMA	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
		Poly-3 adjusted incidence rate	1.8%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.05,9.9)	(0,6.8)	(0,7.0)	(0,6.5)
		Poly-3 adjusted number of animals at risk	54.6	52.8	51.1	55.2
TONGUE	SQUAMOUS PAPILLOMA	P-value of test of trend or comparison	.5047		.4906	
		Number of animals reported with tumor	0	0	1	0
		Poly-3 adjusted incidence rate	0.0%	0.0%	1.9%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,6.6)	(0,6.8)	(0.05,10.3)	(0,6.4)
		Poly-3 adjusted number of animals at risk	54.6	52.8	52.1	56.2
UTERUS	ENDOMETRIAL ADENOCARCINOMA	P-value of test of trend or comparison	.0669			.2523
		Number of animals reported with tumor	0	0	0	2
		Poly-3 adjusted incidence rate	0.0%	0.0%	0.0%	3.6%
		95% CI for poly-3 adjusted incidence rate (%)	(0,6.5)	(0,6.8)	(0,6.8)	(0.43,12.3)
		Poly-3 adjusted number of animals at risk	55.6	52.8	52.1	56.3
	ENDOMETRIAL STROMAL POLYP	P-value of test of trend or comparison	.3289	.7268	.5928	.5128

Reference ID: 3087610

Table 1.9

Table of reported tumors in Mouse Study
NDA 202450
Animal carcinogenicity study
Female mice

Organ or tissue name	*Tumor name*	*Quantity*	*Vehicle*	*Low dose*	*Mid dose*	*High dose*
		Number of animals reported with tumor	5	4	5	6
		Poly-3 adjusted incidence rate	9.0%	7.6%	9.6%	11%
		95% CI for poly-3 adjusted incidence rate (%)	(2.96,20.0)	(2.09,18.5)	(3.13,21.0)	(3.96,21.9)
		Poly-3 adjusted number of animals at risk	55.6	52.8	52.3	56.6
	HAEMANGIOSARCOMA	P-value of test of trend or comparison	.2605			.5045
		Number of animals reported with tumor	0	0	0	1
		Poly-3 adjusted incidence rate	0.0%	0.0%	0.0%	1.8%
		95% CI for poly-3 adjusted incidence rate (%)	(0,6.5)	(0,6.8)	(0,6.8)	(0.04,9.6)
		Poly-3 adjusted number of animals at risk	55.6	52.8	52.1	56.2
	LEIOMYOMA	P-value of test of trend or comparison	.5108	.6696	.8678	.6977
		Number of animals reported with tumor	2	2	1	2
		Poly-3 adjusted incidence rate	3.6%	3.8%	1.9%	3.6%
		95% CI for poly-3 adjusted incidence rate (%)	(0.44,12.5)	(0.46,13.2)	(0.05,10.3)	(0.43,12.3)
		Poly-3 adjusted number of animals at risk	55.6	52.8	52.1	56.2
	LEIOMYOSARCOMA	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
		Poly-3 adjusted incidence rate	1.8%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.04,9.6)	(0,6.8)	(0,6.8)	(0,6.4)
		Poly-3 adjusted number of animals at risk	56.1	52.8	52.1	56.2

Reference ID: 3087610

Table 1.10

Table of reported tumors in Mouse Study
NDA 202450
Animal carcinogenicity study
Male mice

Organ or tissue name	*Tumor name*	*Quantity*	*Vehicle*	*Low dose*	*Mid dose*	*High dose*
ADRENAL CORTEX	CORTICAL ADENOCARCINOMA	P-value of test of trend or comparison	.5152		.4757	
		Number of animals reported with tumor	0	0	1	0
		Poly-3 adjusted incidence rate	0.0%	0.0%	2.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,6.6)	(0,8.4)	(0.05,10.9)	(0,6.7)
		Poly-3 adjusted number of animals at risk	54.1	42.7	49.6	53.5
	SUBCAPSULAR CELL ADENOMA	P-value of test of trend or comparison	.9288	.8264	.8597	1
		Number of animals reported with tumor	2	1	1	0
		Poly-3 adjusted incidence rate	3.7%	2.3%	2.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.44,12.7)	(0.06,12.6)	(0.05,10.9)	(0,6.7)
		Poly-3 adjusted number of animals at risk	54.1	42.7	49.6	53.5
DUODENUM	ADENOMATOUS POLYP	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
		Poly-3 adjusted incidence rate	1.8%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.05,9.9)	(0,8.4)	(0,7.4)	(0,6.8)
		Poly-3 adjusted number of animals at risk	54.1	42.2	48.6	52.4
FEMUR INCLUDING JOINT	HAEMANGIOSARCOMA	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
		Poly-3 adjusted incidence rate	1.8%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.05,9.9)	(0,8.4)	(0,7.3)	(0,6.7)
		Poly-3 adjusted number of animals at risk	54.1	42.7	49.6	53.5
HAEMOPOIETIC TISSUE	HISTIOCYTIC SARCOMA	P-value of test of trend or comparison	.7659	.5912	.8597	.8750
		Number of animals reported with tumor	2	2	1	1
		Poly-3 adjusted incidence rate	3.7%	4.7%	2.0%	1.9%
		95% CI for poly-3 adjusted incidence rate (%)	(0.44,12.7)	(0.57,16.2)	(0.05,10.9)	(0.05,10.1)
		Poly-3 adjusted number of animals at risk	54.6	42.9	49.6	53.5
	MALIGNANT LYMPHOMA	P-value of test of trend or comparison	.4612	.2375	1	.5088
		Number of animals reported with tumor	2	4	0	3
		Poly-3 adjusted incidence rate	3.7%	9.3%	0.0%	5.5%

Reference ID: 3087610

Table 1.10

Table of reported tumors in Mouse Study
NDA 202450
Animal carcinogenicity study
Male mice

Organ or tissue name	*Tumor name*	*Quantity*	*Vehicle*	*Low dose*	*Mid dose*	*High dose*
		95% CI for poly-3 adjusted incidence rate (%)	(0.44,12.7)	(2.53,22.1)	(0,7.3)	(1.12,15.1)
		Poly-3 adjusted number of animals at risk	54.1	43.1	49.6	55.0
	MAST CELL TUMOUR	P-value of test of trend or comparison	.4198	1	.7276	.7477
		Number of animals reported with tumor	1	0	1	1
		Poly-3 adjusted incidence rate	1.8%	0.0%	2.0%	1.9%
		95% CI for poly-3 adjusted incidence rate (%)	(0.05,9.9)	(0,8.4)	(0.05,10.9)	(0.05,10.1)
		Poly-3 adjusted number of animals at risk	54.1	42.7	49.6	53.5
HARDERIAN GLANDS	ADENOMA	P-value of test of trend or comparison	.4851	.6868	.5973	.6422
		Number of animals reported with tumor	4	3	4	4
		Poly-3 adjusted incidence rate	7.5%	6.9%	8.0%	7.5%
		95% CI for poly-3 adjusted incidence rate (%)	(2.06,18.2)	(1.43,19.1)	(2.22,19.6)	(2.06,18.2)
		Poly-3 adjusted number of animals at risk	53.1	43.4	49.8	53.5
LIVER	HAEMANGIOMA	P-value of test of trend or comparison	.2677			.4953
		Number of animals reported with tumor	0	0	0	1
		Poly-3 adjusted incidence rate	0.0%	0.0%	0.0%	1.9%
		95% CI for poly-3 adjusted incidence rate (%)	(0,6.6)	(0,8.4)	(0,7.3)	(0.05,10.1)
		Poly-3 adjusted number of animals at risk	54.1	42.7	49.6	53.5
	HAEMANGIOSARCOMA	P-value of test of trend or comparison	.6094	1	1	.8750
		Number of animals reported with tumor	2	0	0	1
		Poly-3 adjusted incidence rate	3.7%	0.0%	0.0%	1.9%
		95% CI for poly-3 adjusted incidence rate (%)	(0.44,12.7)	(0,8.4)	(0,7.3)	(0.05,10.1)
		Poly-3 adjusted number of animals at risk	54.3	42.7	49.6	53.5
	HEPATOCELLULAR ADENOMA	P-value of test of trend or comparison	.2980	.5968	.3091	.3866
		Number of animals reported with tumor	10	8	12	12
		Poly-3 adjusted incidence rate	18%	18%	24%	22%
		95% CI for poly-3 adjusted incidence rate (%)	(9.08,31.4)	(8.19,33.4)	(13.1,38.9)	(12,36.2)
		Poly-3 adjusted number of animals at risk	54.6	43.5	49.9	53.5
	HEPATOCELLULAR CARCINOMA	P-value of test of trend or comparison	.4127	.7739	.7466	.6063

Reference ID: 3087610

Table 1.10

Table of reported tumors in Mouse Study
NDA 202450
Animal carcinogenicity study
Male mice

Organ or tissue name	*Tumor name*	*Quantity*	*Vehicle*	*Low dose*	*Mid dose*	*High dose*
		Number of animals reported with tumor	8	5	6	8
		Poly-3 adjusted incidence rate	15%	12%	12%	15%
		95% CI for poly-3 adjusted incidence rate (%)	(6.5,27.1)	(3.79,25.1)	(4.53,24.8)	(6.5,27.1)
		Poly-3 adjusted number of animals at risk	54.9	43.5	49.7	54.6
LUNGS	PULMONARY ADENOCARCINOMA	P-value of test of trend or comparison	.9793	.8446	.9911	.9932
		Number of animals reported with tumor	6	3	1	1
		Poly-3 adjusted incidence rate	11%	7.0%	2.0%	1.9%
		95% CI for poly-3 adjusted incidence rate (%)	(4.11,22.6)	(1.46,19.5)	(0.05,10.9)	(0.05,10.1)
		Poly-3 adjusted number of animals at risk	54.4	42.7	49.6	53.5
	PULMONARY ADENOMA	P-value of test of trend or comparison	.5892	1	.9783	.9196
		Number of animals reported with tumor	9	0	3	5
		Poly-3 adjusted incidence rate	16%	0.0%	6.1%	9.3%
		95% CI for poly-3 adjusted incidence rate (%)	(7.77,29.3)	(0,8.4)	(1.25,16.9)	(3.08,20.7)
		Poly-3 adjusted number of animals at risk	54.8	42.7	49.6	53.7
NASAL CAVITIES (LEVEL II)	OSTEOMA	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
		Poly-3 adjusted incidence rate	1.8%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.05,9.9)	(0,8.4)	(0,7.3)	(0,6.7)
		Poly-3 adjusted number of animals at risk	54.1	42.7	49.6	53.5
PANCREAS	ISLET CELL ADENOMA	P-value of test of trend or comparison	.7273	.4375		
		Number of animals reported with tumor	0	1	0	0
		Poly-3 adjusted incidence rate	0.0%	2.3%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,6.6)	(0.06,12.6)	(0,7.3)	(0,6.7)
		Poly-3 adjusted number of animals at risk	54.1	42.7	49.6	53.5
SALIVARY GLAND, MANDIBULAR	ADENOMA	P-value of test of trend or comparison	.2677			.4953
		Number of animals reported with tumor	0	0	0	1
		Poly-3 adjusted incidence rate	0.0%	0.0%	0.0%	1.9%
		95% CI for poly-3 adjusted incidence rate (%)	(0,6.6)	(0,8.4)	(0,7.3)	(0.05,10.1)

Reference ID: 3087610

Table 1.10

Table of reported tumors in Mouse Study
NDA 202450
Animal carcinogenicity study
Male mice

Organ or tissue name	*Tumor name*	*Quantity*	*Vehicle*	*Low dose*	*Mid dose*	*High dose*
		Poly-3 adjusted number of animals at risk	54.1	42.7	49.6	53.5
SKIN	SQUAMOUS CARCINOMA	P-value of test of trend or comparison	.5152		.4757	
		Number of animals reported with tumor	0	0	1	0
		Poly-3 adjusted incidence rate	0.0%	0.0%	2.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,6.6)	(0,8.4)	(0.05,10.9)	(0,6.7)
		Poly-3 adjusted number of animals at risk	54.1	42.7	49.8	53.5
SPLEEN	HAEMANGIOMA	P-value of test of trend or comparison	.5152		.4757	
		Number of animals reported with tumor	0	0	1	0
		Poly-3 adjusted incidence rate	0.0%	0.0%	2.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,6.6)	(0,8.4)	(0.05,10.9)	(0,6.7)
		Poly-3 adjusted number of animals at risk	54.1	42.7	49.6	53.5
	HAEMANGIOSARCOMA	P-value of test of trend or comparison	.8969	1	.8597	1
		Number of animals reported with tumor	2	0	1	0
		Poly-3 adjusted incidence rate	3.7%	0.0%	2.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.44,12.7)	(0,8.4)	(0.05,10.9)	(0,6.7)
		Poly-3 adjusted number of animals at risk	54.5	42.7	49.6	53.5
STOMACH, GLANDULAR	ADENOMATOUS POLYP	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
		Poly-3 adjusted incidence rate	1.8%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.05,9.9)	(0,8.4)	(0,7.5)	(0,6.7)
		Poly-3 adjusted number of animals at risk	54.1	42.7	47.7	53.5
STOMACH, NON-GLANDULAR	SQUAMOUS PAPILLOMA	P-value of test of trend or comparison	.7259	.4375		
		Number of animals reported with tumor	0	1	0	0
		Poly-3 adjusted incidence rate	0.0%	2.3%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,6.6)	(0.06,12.6)	(0,7.4)	(0,6.7)
		Poly-3 adjusted number of animals at risk	54.1	42.7	48.7	53.5

Reference ID: 3087610

Table 1.11

Table of reported tumors in Mouse Study
NDA 202450
Animal carcinogenicity study
Female mice
Composite endpoints

Composite endpoint	*Quantity*	*Vehicle*	*Low dose*	*Mid dose*	*High dose*
All hemangiomas	P-value of test of trend or comparison	.8111	.2338		
	Number of animals reported with tumor	0	2	0	0
	Poly-3 adjusted incidence rate	0.0%	3.8%	0.0%	0.0%
	95% CI for poly-3 adjusted incidence rate (%)	(0,6.5)	(0.46,13.2)	(0,6.8)	(0,6.4)
	Poly-3 adjusted number of animals at risk	55.6	52.8	52.1	56.2
All hemangiomas and hemangiosarcomas	P-value of test of trend or comparison	.1201	.4788	.2880	.1932
	Number of animals reported with tumor	1	2	3	4
	Poly-3 adjusted incidence rate	1.8%	3.8%	5.8%	7.0%
	95% CI for poly-3 adjusted incidence rate (%)	(0.05,9.7)	(0.46,13.2)	(1.18,15.9)	(1.91,17.0)
	Poly-3 adjusted number of animals at risk	55.6	52.8	52.1	57.2
All hemangiosarcomas	P-value of test of trend or comparison	.0416	1	.2880	.1932
	Number of animals reported with tumor	1	0	3	4
	Poly-3 adjusted incidence rate	1.8%	0.0%	5.8%	7.0%
	95% CI for poly-3 adjusted incidence rate (%)	(0.05,9.7)	(0,6.8)	(1.18,15.9)	(1.91,17.0)
	Poly-3 adjusted number of animals at risk	55.6	52.8	52.1	57.2
Hepatocellular tumors	P-value of test of trend or comparison	.4380	.2634	.3448	.4021
	Number of animals reported with tumor	6	9	8	8
	Poly-3 adjusted incidence rate	11%	17%	15%	14%
	95% CI for poly-3 adjusted incidence rate (%)	(4.03,22.2)	(7.92,29.8)	(6.75,28.1)	(6.26,26.2)
	Poly-3 adjusted number of animals at risk	55.6	53.9	52.6	56.6

Reference ID: 3087610

Table 1.12

Table of reported tumors in Mouse Study
NDA 202450
Animal carcinogenicity study
Male mice
Composite endpoints

Composite endpoint	*Quantity*	*Vehicle*	*Low dose*	*Mid dose*	*High dose*
All hemangiomas	P-value of test of trend or comparison	.2038		.4757	.4953
	Number of animals reported with tumor	0	0	1	1
	Poly-3 adjusted incidence rate	0.0%	0.0%	2.0%	1.9%
	95% CI for poly-3 adjusted incidence rate (%)	(0,6.6)	(0,8.4)	(0.05,10.9)	(0.05,10.1)
	Poly-3 adjusted number of animals at risk	54.1	42.7	49.6	53.5
All hemangiomas and hemangiosarcomas	P-value of test of trend or comparison	.6156	1	.8736	.8930
	Number of animals reported with tumor	4	0	2	2
	Poly-3 adjusted incidence rate	7.3%	0.0%	4.0%	3.7%
	95% CI for poly-3 adjusted incidence rate (%)	(2.02,17.9)	(0,8.4)	(0.49,14.0)	(0.45,13.0)
	Poly-3 adjusted number of animals at risk	54.7	42.7	49.6	53.5
All hemangiosarcomas	P-value of test of trend or comparison	.8380	1	.9639	.9703
	Number of animals reported with tumor	4	0	1	1
	Poly-3 adjusted incidence rate	7.3%	0.0%	2.0%	1.9%
	95% CI for poly-3 adjusted incidence rate (%)	(2.02,17.9)	(0,8.4)	(0.05,10.9)	(0.05,10.1)
	Poly-3 adjusted number of animals at risk	54.7	42.7	49.6	53.5
Hepatocellular tumors	P-value of test of trend or comparison	.3714	.6643	.6205	.5000
	Number of animals reported with tumor	17	13	15	18
	Poly-3 adjusted incidence rate	31%	29%	30%	33%
	95% CI for poly-3 adjusted incidence rate (%)	(19.1,45.6)	(16.4,45.2)	(17.9,45.4)	(20.7,47.5)
	Poly-3 adjusted number of animals at risk	55.0	44.3	50.0	54.6

Table 1.13

Table of tumors reported significant in at least one arm - Mouse Study
NDA 202450
Animal carcinogenicity study
Female mice

Organ or tissue name	*Tumor name*	*Quantity*	*Vehicle*	*Low dose*	*Mid dose*	*High dose*
LIVER	HEPATOCELLULAR CARCINOMA	P-value of test of trend or comparison	.0401	.0257	.2338	.0143
		Number of animals reported with tumor	0	5	2	6
		Poly-3 adjusted incidence rate	0.0%	9.3%	3.8%	11%
		95% CI for poly-3 adjusted incidence rate (%)	(0,6.5)	(3.08,20.7)	(0.46,13.2)	(3.96,21.9)
		Poly-3 adjusted number of animals at risk	55.6	53.7	52.6	56.6

Table 1.14

Table of tumors reported significant in at least one arm - Mouse Study
NDA 202450
Animal carcinogenicity study
Female mice
Composite endpoints

Composite endpoint	*Quantity*	*Vehicle*	*Low dose*	*Mid dose*	*High dose*
All hemangiosarcomas	P-value of test of trend or comparison	.0416	1	.2880	.1932
	Number of animals reported with tumor	1	0	3	4
	Poly-3 adjusted incidence rate	1.8%	0.0%	5.8%	7.0%
	95% CI for poly-3 adjusted incidence rate (%)	(0.05,9.7)	(0,6.8)	(1.18,15.9)	(1.91,17.0)
	Poly-3 adjusted number of animals at risk	55.6	52.8	52.1	57.2

Table 1.15

Table of reported tumors in Mouse Study
NDA 202450 (vehicle study)
Animal carcinogenicity study
Female mice

Organ or tissue name	*Tumor name*	*Quantity*	*Air*	*Vehicle*
ADRENAL CORTEX	CORTICAL ADENOMA	P-value of test of comparison		.5094
		Number of animals reported with tumor	0	1
		Poly-3 adjusted incidence rate	0.0%	1.8%
		95% CI for poly-3 adjusted incidence rate (%)	(0,6.8)	(0.05,9.9)
		Poly-3 adjusted number of animals at risk	52.3	54.6
ADRENAL MEDULLA	PHEOCHROMOCYTOMA	P-value of test of comparison		1
		Number of animals reported with tumor	1	0
		Poly-3 adjusted incidence rate	1.9%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.05,10.3)	(0,6.8)
		Poly-3 adjusted number of animals at risk	52.3	52.8
BONE	OSTEOSARCOMA	P-value of test of comparison		.5140
		Number of animals reported with tumor	0	1
		Poly-3 adjusted incidence rate	0.0%	1.8%
		95% CI for poly-3 adjusted incidence rate (%)	(0,6.8)	(0.05,9.7)
		Poly-3 adjusted number of animals at risk	52.3	55.6
HAEMOPOIETIC TISSUE	HISTIOCYTIC SARCOMA	P-value of test of comparison		1
		Number of animals reported with tumor	4	0
		Poly-3 adjusted incidence rate	7.6%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(2.09,18.5)	(0,6.5)
		Poly-3 adjusted number of animals at risk	52.8	55.6
	MALIGNANT LYMPHOMA	P-value of test of comparison		.4042
		Number of animals reported with tumor	14	17
		Poly-3 adjusted incidence rate	26%	30%
		95% CI for poly-3 adjusted incidence rate (%)	(15,40.3)	(18.4,44.1)
		Poly-3 adjusted number of animals at risk	53.6	56.7
HARDERIAN GLANDS	ADENOMA	P-value of test of comparison		.8881
		Number of animals reported with tumor	5	3
		Poly-3 adjusted incidence rate	9.6%	5.4%

Reference ID: 3087610

Table 1.15

Table of reported tumors in Mouse Study
NDA 202450 (vehicle study)
Animal carcinogenicity study
Female mice

Organ or tissue name	*Tumor name*	*Quantity*	*Air*	*Vehicle*
		95% CI for poly-3 adjusted incidence rate (%)	(3.2,21.4)	(1.12,15.1)
		Poly-3 adjusted number of animals at risk	51.9	55.6
JEJUNUM	ADENOMATOUS POLYP	P-value of test of comparison		.5238
		Number of animals reported with tumor	0	1
		Poly-3 adjusted incidence rate	0.0%	1.8%
		95% CI for poly-3 adjusted incidence rate (%)	(0,7.1)	(0.05,9.7)
		Poly-3 adjusted number of animals at risk	50.5	55.6
LIVER	HAEMANGIOSARCOMA	P-value of test of comparison		1
		Number of animals reported with tumor	3	0
		Poly-3 adjusted incidence rate	5.7%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(1.16,15.7)	(0,6.5)
		Poly-3 adjusted number of animals at risk	53.0	55.6
	HEPATOCELLULAR ADENOMA	P-value of test of comparison		.4072
		Number of animals reported with tumor	4	6
		Poly-3 adjusted incidence rate	7.6%	11%
		95% CI for poly-3 adjusted incidence rate (%)	(2.09,18.5)	(4.03,22.2)
		Poly-3 adjusted number of animals at risk	52.3	55.6
	HEPATOCELLULAR CARCINOMA	P-value of test of comparison		1
		Number of animals reported with tumor	2	0
		Poly-3 adjusted incidence rate	3.8%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.46,13.2)	(0,6.5)
		Poly-3 adjusted number of animals at risk	52.6	55.6
LUNGS	PULMONARY ADENOCARCINOMA	P-value of test of comparison		.2619
		Number of animals reported with tumor	0	2
		Poly-3 adjusted incidence rate	0.0%	3.6%
		95% CI for poly-3 adjusted incidence rate (%)	(0,6.8)	(0.44,12.5)
		Poly-3 adjusted number of animals at risk	52.3	55.6
	PULMONARY ADENOMA	P-value of test of comparison		.3664

Reference ID: 3087610

Table 1.15

Table of reported tumors in Mouse Study
NDA 202450 (vehicle study)
Animal carcinogenicity study
Female mice

Organ or tissue name	*Tumor name*	*Quantity*	*Air*	*Vehicle*
		Number of animals reported with tumor	2	4
		Poly-3 adjusted incidence rate	3.8%	7.2%
		95% CI for poly-3 adjusted incidence rate (%)	(0.46,13.2)	(1.98,17.6)
		Poly-3 adjusted number of animals at risk	52.3	55.6
MAMMARY GLAND AREA	ADENOCARCINOMA	P-value of test of comparison		.5212
		Number of animals reported with tumor	1	2
		Poly-3 adjusted incidence rate	1.9%	3.6%
		95% CI for poly-3 adjusted incidence rate (%)	(0.05,10.3)	(0.44,12.5)
		Poly-3 adjusted number of animals at risk	52.3	55.6
OVARIES	LUTEOMA	P-value of test of comparison		.5392
		Number of animals reported with tumor	0	1
		Poly-3 adjusted incidence rate	0.0%	1.8%
		95% CI for poly-3 adjusted incidence rate (%)	(0,7.5)	(0.05,9.7)
		Poly-3 adjusted number of animals at risk	47.7	55.6
PANCREAS	ISLET CELL ADENOMA	P-value of test of comparison		1
		Number of animals reported with tumor	1	0
		Poly-3 adjusted incidence rate	1.9%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.05,10.3)	(0,6.6)
		Poly-3 adjusted number of animals at risk	52.4	54.8
PITUITARY GLAND	ADENOMA, pars distalis	P-value of test of comparison		.7654
		Number of animals reported with tumor	8	7
		Poly-3 adjusted incidence rate	16%	13%
		95% CI for poly-3 adjusted incidence rate (%)	(7.17,29.7)	(5.37,25.3)
		Poly-3 adjusted number of animals at risk	49.4	53.8
SKIN	HAEMANGIOSARCOMA	P-value of test of comparison		1
		Number of animals reported with tumor	1	0
		Poly-3 adjusted incidence rate	1.9%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.05,10.3)	(0,6.5)

Reference ID: 3087610

Table 1.15

Table of reported tumors in Mouse Study
NDA 202450 (vehicle study)
Animal carcinogenicity study
Female mice

Organ or tissue name	*Tumor name*	*Quantity*	*Air*	*Vehicle*
		Poly-3 adjusted number of animals at risk	52.3	55.6
	MALIGNANT SCHWANNOMA	P-value of test of comparison		.5140
		Number of animals reported with tumor	0	1
		Poly-3 adjusted incidence rate	0.0%	1.8%
		95% CI for poly-3 adjusted incidence rate (%)	(0,6.8)	(0.05,9.7)
		Poly-3 adjusted number of animals at risk	52.3	55.7
SPLEEN	HAEMANGIOMA	P-value of test of comparison		1
		Number of animals reported with tumor	1	0
		Poly-3 adjusted incidence rate	1.9%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.05,10.3)	(0,6.5)
		Poly-3 adjusted number of animals at risk	52.3	55.6
	HAEMANGIOSARCOMA	P-value of test of comparison		.7662
		Number of animals reported with tumor	1	1
		Poly-3 adjusted incidence rate	1.9%	1.8%
		95% CI for poly-3 adjusted incidence rate (%)	(0.05,10.3)	(0.05,9.7)
		Poly-3 adjusted number of animals at risk	52.3	55.6
STOMACH, NON-GLANDULAR	SQUAMOUS PAPILLOMA	P-value of test of comparison		.5140
		Number of animals reported with tumor	0	1
		Poly-3 adjusted incidence rate	0.0%	1.8%
		95% CI for poly-3 adjusted incidence rate (%)	(0,6.8)	(0.05,9.7)
		Poly-3 adjusted number of animals at risk	52.3	55.6
THYROID GLANDS	C-CELL CARCINOMA	P-value of test of comparison		.5094
		Number of animals reported with tumor	0	1
		Poly-3 adjusted incidence rate	0.0%	1.8%
		95% CI for poly-3 adjusted incidence rate (%)	(0,6.8)	(0.05,9.9)
		Poly-3 adjusted number of animals at risk	52.3	54.6
	FOLLICULAR CELL ADENOMA	P-value of test of comparison		.7617
		Number of animals reported with tumor	1	1

Table 1.15

Table of reported tumors in Mouse Study
NDA 202450 (vehicle study)
Animal carcinogenicity study
Female mice

Organ or tissue name	*Tumor name*	*Quantity*	*Air*	*Vehicle*
		Poly-3 adjusted incidence rate	1.9%	1.8%
		95% CI for poly-3 adjusted incidence rate (%)	(0.05,10.3)	(0.05,9.9)
		Poly-3 adjusted number of animals at risk	52.4	54.6
UTERUS	ENDOMETRIAL STROMAL POLYP	P-value of test of comparison		.3790
		Number of animals reported with tumor	3	5
		Poly-3 adjusted incidence rate	5.6%	9.0%
		95% CI for poly-3 adjusted incidence rate (%)	(1.16,15.7)	(2.96,20.0)
		Poly-3 adjusted number of animals at risk	53.3	55.6
	LEIOMYOMA	P-value of test of comparison		.2619
		Number of animals reported with tumor	0	2
		Poly-3 adjusted incidence rate	0.0%	3.6%
		95% CI for poly-3 adjusted incidence rate (%)	(0,6.8)	(0.44,12.5)
		Poly-3 adjusted number of animals at risk	52.3	55.6
	LEIOMYOSARCOMA	P-value of test of comparison		.5185
		Number of animals reported with tumor	0	1
		Poly-3 adjusted incidence rate	0.0%	1.8%
		95% CI for poly-3 adjusted incidence rate (%)	(0,6.8)	(0.04,9.6)
		Poly-3 adjusted number of animals at risk	52.3	56.1

Reference ID: 3087610

Table 1.16

Table of reported tumors in Mouse Study
NDA 202450 (vehicle study)
Animal carcinogenicity study
Male mice

Organ or tissue name	*Tumor name*	*Quantity*	*Air*	*Vehicle*
ADRENAL CORTEX	SUBCAPSULAR CELL ADENOMA	P-value of test of comparison		.2431
		Number of animals reported with tumor	0	2
		Poly-3 adjusted incidence rate	0.0%	3.7%
		95% CI for poly-3 adjusted incidence rate (%)	(0,6.5)	(0.44,12.7)
		Poly-3 adjusted number of animals at risk	55.0	54.1
DUODENUM	ADENOMATOUS POLYP	P-value of test of comparison		.4954
		Number of animals reported with tumor	0	1
		Poly-3 adjusted incidence rate	0.0%	1.8%
		95% CI for poly-3 adjusted incidence rate (%)	(0,6.5)	(0.05,9.9)
		Poly-3 adjusted number of animals at risk	55.0	54.1
EPIDIDYMIDES	INTERSTITIAL CELL ADENOMA	P-value of test of comparison		1
		Number of animals reported with tumor	1	0
		Poly-3 adjusted incidence rate	1.8%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.05,9.7)	(0,6.6)
		Poly-3 adjusted number of animals at risk	55.0	54.1
FEMUR INCLUDING JOINT	HAEMANGIOSARCOMA	P-value of test of comparison		.4954
		Number of animals reported with tumor	0	1
		Poly-3 adjusted incidence rate	0.0%	1.8%
		95% CI for poly-3 adjusted incidence rate (%)	(0,6.5)	(0.05,9.9)
		Poly-3 adjusted number of animals at risk	55.0	54.1
HAEMOPOIETIC TISSUE	HISTIOCYTIC SARCOMA	P-value of test of comparison		.2431
		Number of animals reported with tumor	0	2
		Poly-3 adjusted incidence rate	0.0%	3.7%
		95% CI for poly-3 adjusted incidence rate (%)	(0,6.5)	(0.44,12.7)
		Poly-3 adjusted number of animals at risk	55.0	54.6
	MALIGNANT LYMPHOMA	P-value of test of comparison		.9680
		Number of animals reported with tumor	6	2
		Poly-3 adjusted incidence rate	11%	3.7%

Reference ID: 3087610

Table 1.16

Table of reported tumors in Mouse Study
NDA 202450 (vehicle study)
Animal carcinogenicity study
Male mice

Organ or tissue name	*Tumor name*	*Quantity*	*Air*	*Vehicle*
		95% CI for poly-3 adjusted incidence rate (%)	(4.03,22.2)	(0.44,12.7)
		Poly-3 adjusted number of animals at risk	55.0	54.1
	MAST CELL TUMOUR	P-value of test of comparison		.4954
		Number of animals reported with tumor	0	1
		Poly-3 adjusted incidence rate	0.0%	1.8%
		95% CI for poly-3 adjusted incidence rate (%)	(0,6.5)	(0.05,9.9)
		Poly-3 adjusted number of animals at risk	55.0	54.1
HARDERIAN GLANDS	ADENOMA	P-value of test of comparison		.6210
		Number of animals reported with tumor	4	4
		Poly-3 adjusted incidence rate	7.3%	7.5%
		95% CI for poly-3 adjusted incidence rate (%)	(1.98,17.6)	(2.06,18.2)
		Poly-3 adjusted number of animals at risk	55.0	53.1
KIDNEYS	LEIOMYOMA	P-value of test of comparison		1
		Number of animals reported with tumor	1	0
		Poly-3 adjusted incidence rate	1.8%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.05,9.7)	(0,6.6)
		Poly-3 adjusted number of animals at risk	55.0	54.1
LIVER	HAEMANGIOSARCOMA	P-value of test of comparison		.6840
		Number of animals reported with tumor	2	2
		Poly-3 adjusted incidence rate	3.6%	3.7%
		95% CI for poly-3 adjusted incidence rate (%)	(0.44,12.5)	(0.44,12.7)
		Poly-3 adjusted number of animals at risk	55.1	54.3
	HEPATOCELLULAR ADENOMA	P-value of test of comparison		.9914
		Number of animals reported with tumor	21	10
		Poly-3 adjusted incidence rate	37%	18%
		95% CI for poly-3 adjusted incidence rate (%)	(24,50.7)	(9.08,31.4)
		Poly-3 adjusted number of animals at risk	57.1	54.6
	HEPATOCELLULAR CARCINOMA	P-value of test of comparison		.9214

Reference ID: 3087610

Table 1.16

Table of reported tumors in Mouse Study
NDA 202450 (vehicle study)
Animal carcinogenicity study
Male mice

Organ or tissue name	*Tumor name*	*Quantity*	*Air*	*Vehicle*
		Number of animals reported with tumor	13	8
		Poly-3 adjusted incidence rate	23%	15%
		95% CI for poly-3 adjusted incidence rate (%)	(13,37.0)	(6.5,27.1)
		Poly-3 adjusted number of animals at risk	55.7	54.9
	MALIGNANT ITO CELL TUMOUR	P-value of test of comparison		1
		Number of animals reported with tumor	1	0
		Poly-3 adjusted incidence rate	1.8%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.05,9.7)	(0,6.6)
		Poly-3 adjusted number of animals at risk	55.0	54.1
LUNGS	PULMONARY ADENOCARCINOMA	P-value of test of comparison		.1293
		Number of animals reported with tumor	2	6
		Poly-3 adjusted incidence rate	3.6%	11%
		95% CI for poly-3 adjusted incidence rate (%)	(0.44,12.5)	(4.11,22.6)
		Poly-3 adjusted number of animals at risk	55.0	54.4
	PULMONARY ADENOMA	P-value of test of comparison		.1114
		Number of animals reported with tumor	4	9
		Poly-3 adjusted incidence rate	7.3%	16%
		95% CI for poly-3 adjusted incidence rate (%)	(1.98,17.6)	(7.77,29.3)
		Poly-3 adjusted number of animals at risk	55.0	54.8
LYMPH NODE, MESENTERIC	HAEMANGIOSARCOMA	P-value of test of comparison		1
		Number of animals reported with tumor	1	0
		Poly-3 adjusted incidence rate	1.9%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.05,10.3)	(0,7.0)
		Poly-3 adjusted number of animals at risk	52.0	51.2
NASAL CAVITIES (LEVEL II)	OSTEOMA	P-value of test of comparison		.5047
		Number of animals reported with tumor	0	1
		Poly-3 adjusted incidence rate	0.0%	1.8%
		95% CI for poly-3 adjusted incidence rate (%)	(0,6.7)	(0.05,9.9)

Table 1.16

Table of reported tumors in Mouse Study
NDA 202450 (vehicle study)
Animal carcinogenicity study
Male mice

Organ or tissue name	*Tumor name*	*Quantity*	*Air*	*Vehicle*
		Poly-3 adjusted number of animals at risk	53.7	54.1
PROSTATE GLAND	ADENOCARCINOMA	P-value of test of comparison		1
		Number of animals reported with tumor	1	0
		Poly-3 adjusted incidence rate	1.8%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.05,9.7)	(0,6.6)
		Poly-3 adjusted number of animals at risk	55.4	54.1
SEMINAL VESICLES	ADENOCARCINOMA	P-value of test of comparison		1
		Number of animals reported with tumor	1	0
		Poly-3 adjusted incidence rate	1.8%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.05,9.7)	(0,6.6)
		Poly-3 adjusted number of animals at risk	55.0	54.1
SKIN	FIBROSARCOMA	P-value of test of comparison		1
		Number of animals reported with tumor	1	0
		Poly-3 adjusted incidence rate	1.8%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.05,9.7)	(0,6.6)
		Poly-3 adjusted number of animals at risk	55.6	54.1
	HAEMANGIOSARCOMA	P-value of test of comparison		1
		Number of animals reported with tumor	1	0
		Poly-3 adjusted incidence rate	1.8%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.05,9.7)	(0,6.6)
		Poly-3 adjusted number of animals at risk	55.0	54.1
SPLEEN	HAEMANGIOSARCOMA	P-value of test of comparison		.2431
		Number of animals reported with tumor	0	2
		Poly-3 adjusted incidence rate	0.0%	3.7%
		95% CI for poly-3 adjusted incidence rate (%)	(0,6.5)	(0.44,12.7)
		Poly-3 adjusted number of animals at risk	55.0	54.5
STOMACH, GLANDULAR	ADENOMATOUS POLYP	P-value of test of comparison		.4954
		Number of animals reported with tumor	0	1

Reference ID: 3087610

Table 1.16

Table of reported tumors in Mouse Study
NDA 202450 (vehicle study)
Animal carcinogenicity study
Male mice

Organ or tissue name	*Tumor name*	*Quantity*	*Air*	*Vehicle*
		Poly-3 adjusted incidence rate	0.0%	1.8%
		95% CI for poly-3 adjusted incidence rate (%)	(0,6.5)	(0.05,9.9)
		Poly-3 adjusted number of animals at risk	55.0	54.1

Reference ID: 3087610

Table 1.17

Table of reported tumors in Mouse Study
NDA 202450 (vehicle study)
Animal carcinogenicity study
Female mice
Composite endpoints

Composite endpoint	*Quantity*	*Air*	*Vehicle*
All hemangiomas	P-value of test of comparison		1
	Number of animals reported with tumor	1	0
	Poly-3 adjusted incidence rate	1.9%	0.0%
	95% CI for poly-3 adjusted incidence rate (%)	(0.05,10.3)	(0,6.5)
	Poly-3 adjusted number of animals at risk	52.3	55.6
All hemangiomas and hemangiosarcomas	P-value of test of comparison		.9880
	Number of animals reported with tumor	5	1
	Poly-3 adjusted incidence rate	9.4%	1.8%
	95% CI for poly-3 adjusted incidence rate (%)	(3.08,20.7)	(0.05,9.7)
	Poly-3 adjusted number of animals at risk	53.0	55.6
All hemangiosarcomas	P-value of test of comparison		.9743
	Number of animals reported with tumor	4	1
	Poly-3 adjusted incidence rate	7.5%	1.8%
	95% CI for poly-3 adjusted incidence rate (%)	(2.06,18.2)	(0.05,9.7)
	Poly-3 adjusted number of animals at risk	53.0	55.6
Hepatocellular tumors	P-value of test of comparison		.6589
	Number of animals reported with tumor	6	6
	Poly-3 adjusted incidence rate	11%	11%
	95% CI for poly-3 adjusted incidence rate (%)	(4.27,23.4)	(4.03,22.2)
	Poly-3 adjusted number of animals at risk	52.6	55.6

Reference ID: 3087610

Table 1.18

Table of reported tumors in Mouse Study
NDA 202450 (vehicle study)
Animal carcinogenicity study
Male mice
Composite endpoints

Composite endpoint	*Quantity*	*Air*	*Vehicle*
All hemangiomas and hemangiosarcomas	P-value of test of comparison		.6316
	Number of animals reported with tumor	4	4
	Poly-3 adjusted incidence rate	7.3%	7.3%
	95% CI for poly-3 adjusted incidence rate (%)	(1.98,17.6)	(2.02,17.9)
	Poly-3 adjusted number of animals at risk	55.1	54.7
All hemangiosarcomas	P-value of test of comparison		.6316
	Number of animals reported with tumor	4	4
	Poly-3 adjusted incidence rate	7.3%	7.3%
	95% CI for poly-3 adjusted incidence rate (%)	(1.98,17.6)	(2.02,17.9)
	Poly-3 adjusted number of animals at risk	55.1	54.7
Hepatocellular tumors	P-value of test of comparison		.9930
	Number of animals reported with tumor	30	17
	Poly-3 adjusted incidence rate	52%	31%
	95% CI for poly-3 adjusted incidence rate (%)	(38.2,66.0)	(19.1,45.6)
	Poly-3 adjusted number of animals at risk	57.8	55.0

Reference ID: 3087610

Table 1.19

Organs reported as autolytic
NDA 202450
Animal carcinogenicity study
Female Mice

Organ or tissue name	*Vehicle(count)*	*Vehicle(%)*	*Low dose(count)*	*Low dose(%)*	*Mid dose(count)*	*Mid dose(%)*	*High dose(count)*	*High dose(%)*	*Total(count)*	*Total(%)*
CAECUM	.	.	3	5.0%	4	6.7%	3	5.0%	10	4.2%
COLON	.	.	.	.	.	.	1	1.7%	1	0.4%
DUODENUM	.	.	3	5.0%	2	3.3%	2	3.3%	7	2.9%
EYES	1	1.7%	3	5.0%	2	3.3%	3	5.0%	9	3.8%
GALL BLADDER	2	3.3%	6	10%	5	8.3%	5	8.3%	18	7.5%
ILEUM	.	.	5	8.3%	3	5.0%	5	8.3%	13	5.4%
JEJUNUM	.	.	5	8.3%	4	6.7%	3	5.0%	12	5.0%
STOMACH, GLANDULAR	.	.	1	1.7%	1	1.7%	.	.	2	0.8%

Reference ID: 3087610

Table 1.20

Organs reported as autolytic
NDA 202450
Animal carcinogenicity study
Male Mice

Organ or tissue name	Vehicle(count)	Vehicle(%)	Low dose(count)	Low dose(%)	Mid dose(count)	Mid dose(%)	High dose(count)	High dose(%)	Total(count)	Total(%)
CAECUM	2	3.3%	5	8.3%	5	8.3%	1	1.7%	13	5.4%
COLON	.	.	1	1.7%	.	.	.	.	1	0.4%
DUODENUM	1	1.7%	6	10%	5	8.3%	2	3.3%	14	5.8%
EYES	1	1.7%	4	6.7%	6	10%	.	.	11	4.6%
GALL BLADDER	5	8.3%	14	23%	4	6.7%	6	10%	29	12%
ILEUM	1	1.7%	8	13%	6	10%	1	1.7%	16	6.7%
JEJUNUM	2	3.3%	9	15%	5	8.3%	3	5.0%	19	7.9%
LYMPH NODE, MESENTERIC	.	.	1	1.7%	.	.	.	.	1	0.4%
PANCREAS	.	.	1	1.7%	.	.	.	.	1	0.4%
SKIN	.	.	.	.	.	.	1	1.7%	1	0.4%
STOMACH, GLANDULAR	.	.	.	.	1	1.7%	.	.	1	0.4%

Table 1.21

Organs reported as unexamined
NDA 202450
Animal carcinogenicity study
Female Mice

Organ or tissue name	Vehicle(count)	Vehicle(%)	Low dose(count)	Low dose(%)	Mid dose(count)	Mid dose(%)	High dose(count)	High dose(%)	Total(count)	Total(%)
ADRENAL CORTEX	1	1.7%	.	.	.	.	.	.	1	0.4%
ADRENAL MEDULLA	3	5.0%	.	.	.	.	3	5.0%	6	2.5%
AORTA	.	.	1	1.7%	1	1.7%	.	.	2	0.8%
BRONCHI (MAINSTEM)	2	3.3%	1	1.7%	1	1.7%	.	.	4	1.7%
CARINA (TRACHEAL BIFURCATION)	13	22%	14	23%	15	25%	15	25%	57	24%
CLITORAL GLAND	2	3.3%	4	6.7%	4	6.7%	2	3.3%	12	5.0%
DUODENUM	.	.	1	1.7%	.	.	.	.	1	0.4%
EXTRAORBITAL LACRIMAL GLANDS	.	.	1	1.7%	.	.	.	.	1	0.4%
GALL BLADDER	.	.	.	.	1	1.7%	1	1.7%	2	0.8%
ILEUM	1	1.7%	.	.	.	.	1	1.7%	2	0.8%
JEJUNUM	.	.	.	.	1	1.7%	.	.	1	0.4%
LARYNX	1	1.7%	.	.	.	.	3	5.0%	4	1.7%
LYMPH NODE, MANDIBULAR	3	5.0%	1	1.7%	1	1.7%	5	8.3%	10	4.2%
LYMPH NODE, MESENTERIC	2	3.3%	3	5.0%	4	6.7%	1	1.7%	10	4.2%
LYMPH NODE, TRACHEO-BRONCHIAL	3	5.0%	5	8.3%	3	5.0%	5	8.3%	16	6.7%
MAMMARY GLAND AREA	1	1.7%	4	6.7%	1	1.7%	1	1.7%	7	2.9%
NASAL CAVITIES (LEVEL 1)	1	1.7%	.	.	.	.	.	.	1	0.4%
NASAL CAVITIES (LEVEL II)	1	1.7%	1	1.7%	2	3.3%	.	.	4	1.7%
NASOPHARYNGEAL DUCT & PHARYNX	.	.	2	3.3%	.	.	.	.	2	0.8%
OESOPHAGUS	1	1.7%	1	1.7%	.	.	.	.	2	0.8%
OPTIC NERVES	4	6.7%	2	3.3%	1	1.7%	4	6.7%	11	4.6%
OVARIES	.	.	2	3.3%	2	3.3%	1	1.7%	5	2.1%
OVIDUCTS	.	.	1	1.7%	.	.	1	1.7%	2	0.8%
PANCREAS	1	1.7%	.	.	.	.	.	.	1	0.4%
PARATHYROID GLANDS	21	35%	23	38%	19	32%	25	42%	88	37%
PITUITARY GLAND	2	3.3%	1	1.7%	1	1.7%	1	1.7%	5	2.1%
SALIVARY GLAND, MANDIBULAR	.	.	1	1.7%	.	.	.	.	1	0.4%

Table 1.21

Organs reported as unexamined
NDA 202450
Animal carcinogenicity study
Female Mice

Organ or tissue name	*Vehicle(count)*	*Vehicle(%)*	*Low dose(count)*	*Low dose(%)*	*Mid dose(count)*	*Mid dose(%)*	*High dose(count)*	*High dose(%)*	*Total(count)*	*Total(%)*
SALIVARY GLAND, SUBLINGUAL	.	.	2	3.3%	2	3.3%	.	.	4	1.7%
SCIATIC NERVE	.	.	1	1.7%	.	.	.	.	1	0.4%
SKELETAL MUSCLE (THIGH REGION)	.	.	.	.	1	1.7%	.	.	1	0.4%
SPINAL CORD, LUMBAR	1	1.7%	.	.	.	.	1	1.7%	2	0.8%
STERNUM WITH BONE MARROW	.	.	.	.	.	.	1	1.7%	1	0.4%
THYMUS	3	5.0%	5	8.3%	6	10%	4	6.7%	18	7.5%
THYROID GLANDS	1	1.7%	.	.	1	1.7%	1	1.7%	3	1.3%
TONGUE	1	1.7%	.	.	.	.	.	.	1	0.4%
TRACHEA	3	5.0%	1	1.7%	.	.	.	.	4	1.7%

Reference ID: 3087610

Table 1.22

Organs reported as unexamined
NDA 202450
Animal carcinogenicity study
Male Mice

Organ or tissue name	Vehicle(count)	Vehicle(%)	Low dose(count)	Low dose(%)	Mid dose(count)	Mid dose(%)	High dose(count)	High dose(%)	Total(count)	Total(%)
ADRENAL MEDULLA	1	1.7%	4	6.7%	4	6.7%	4	6.7%	13	5.4%
AORTA	.	.	.	.	1	1.7%	.	.	1	0.4%
BRONCHI (MAINSTEM)	1	1.7%	2	3.3%	1	1.7%	2	3.3%	6	2.5%
CAECUM	1	1.7%	.	.	.	.	.	.	1	0.4%
CARINA (TRACHEAL BIFURCATION)	22	37%	20	33%	11	18%	18	30%	71	30%
COLON	1	1.7%	1	1.7%	1	1.7%	.	.	3	1.3%
EYES	1	1.7%	.	.	.	.	.	.	1	0.4%
GALL BLADDER	1	1.7%	.	.	2	3.3%	1	1.7%	4	1.7%
HARDERIAN GLANDS	1	1.7%	.	.	.	.	.	.	1	0.4%
ILEUM	1	1.7%	.	.	1	1.7%	.	.	2	0.8%
LARYNX	6	10%	2	3.3%	3	5.0%	1	1.7%	12	5.0%
LYMPH NODE, MANDIBULAR	.	.	1	1.7%	1	1.7%	2	3.3%	4	1.7%
LYMPH NODE, MESENTERIC	3	5.0%	12	20%	9	15%	.	.	24	10%
LYMPH NODE, TRACHEO-BRONCHIAL	9	15%	17	28%	19	32%	9	15%	54	23%
NASAL CAVITIES (LEVEL III)	.	.	.	.	1	1.7%	.	.	1	0.4%
NASOPHARYNGEAL DUCT & PHARYNX	.	.	1	1.7%	.	.	.	.	1	0.4%
OESOPHAGUS	.	.	.	.	.	.	1	1.7%	1	0.4%
OPTIC NERVES	11	18%	8	13%	5	8.3%	11	18%	35	15%
PANCREAS	.	.	.	.	1	1.7%	.	.	1	0.4%
PARATHYROID GLANDS	27	45%	22	37%	21	35%	13	22%	83	35%
PITUITARY GLAND	7	12%	6	10%	3	5.0%	2	3.3%	18	7.5%
PREPUTIAL GLAND	1	1.7%	2	3.3%	1	1.7%	2	3.3%	6	2.5%
PROSTATE GLAND	.	.	1	1.7%	.	.	.	.	1	0.4%
SALIVARY GLAND, SUBLINGUAL	1	1.7%	.	.	1	1.7%	2	3.3%	4	1.7%
SEMINAL VESICLES	.	.	1	1.7%	.	.	.	.	1	0.4%
SPINAL CORD, LUMBAR	.	.	.	.	2	3.3%	.	.	2	0.8%
STOMACH, GLANDULAR	.	.	.	.	1	1.7%	.	.	1	0.4%

Reference ID: 3087610

Table 1.22

Organs reported as unexamined
NDA 202450
Animal carcinogenicity study
Male Mice

Organ or tissue name	Vehicle(count)	Vehicle(%)	Low dose(count)	Low dose(%)	Mid dose(count)	Mid dose(%)	High dose(count)	High dose(%)	Total(count)	Total(%)
STOMACH, NON-GLANDULAR	.	.	.	.	1	1.7%	.	.	1	0.4%
THYMUS	7	12%	20	33%	8	13%	7	12%	42	18%
THYROID GLANDS	2	3.3%	.	.	.	.	2	3.3%	4	1.7%
TRACHEA	.	.	2	3.3%	5	8.3%	.	.	7	2.9%
URINARY BLADDER	.	.	.	.	1	1.7%	1	1.7%	2	0.8%

Reference ID: 3087610

Chapter 2

Rat Study

2.1 Experimental design

Two separate experiments were conducted, one in female and one in male rats. The rats used were HanBrl:WIST rats. In each experiment, the study consisted of five groups of sixty animals. All animals underwent nose-only flow-past inhalation for one hour a day. One group (a negative control group) inhaled only air, and a second inhaled the lactose vehicle. The other three groups inhaled LAS 34273 in a 10% lactose formulation, for target doses of 0.02, 0.07, and 0.2mg per kilogram of body weight.

The sponsor reports that various quantities, including mortality, clinical signs (including palpable masses), and the results of micro- and macroscopic examinations were recorded, but does not mention the frequency of the examinations which generated these data.

2.2 Sponsor's analysis

2.2.1 Survival analysis

The sponsor does not appear to have conducted statistical analyses of survival. However, based on a count of numbers of premature deaths, the sponsor has concluded that in neither sex was there was any indication of a treated group experiencing significantly poorer survival than either the air or vehicle control groups.

No p-values or estimates for the size of any possible effects have been included in the submission.

2.2.2 Tumor analysis

Incidence rates for all individual tumor types were investigated using the Peto [6] log rank method. Although some non-neoplastic findings of note were reported, the sponsor claims that for no tumor type was there any indication of a dose responce in incidence.

2.3 Data analysis

2.3.1 Survival analysis

The Kaplan-Meier survival plots are shown as figures 2.1 and 2.2. The numbers and proportions of animals surviving to various times are presented in table 2.1. The results of log-rank tests of heterogeneity of survival and of dose response across the groups are presented in table 1.2, and the results of log-rank survival tests comparing the treated groups with the vehicle control group are presented in table 1.3.

Figure 2.1: Survival curves for female rats

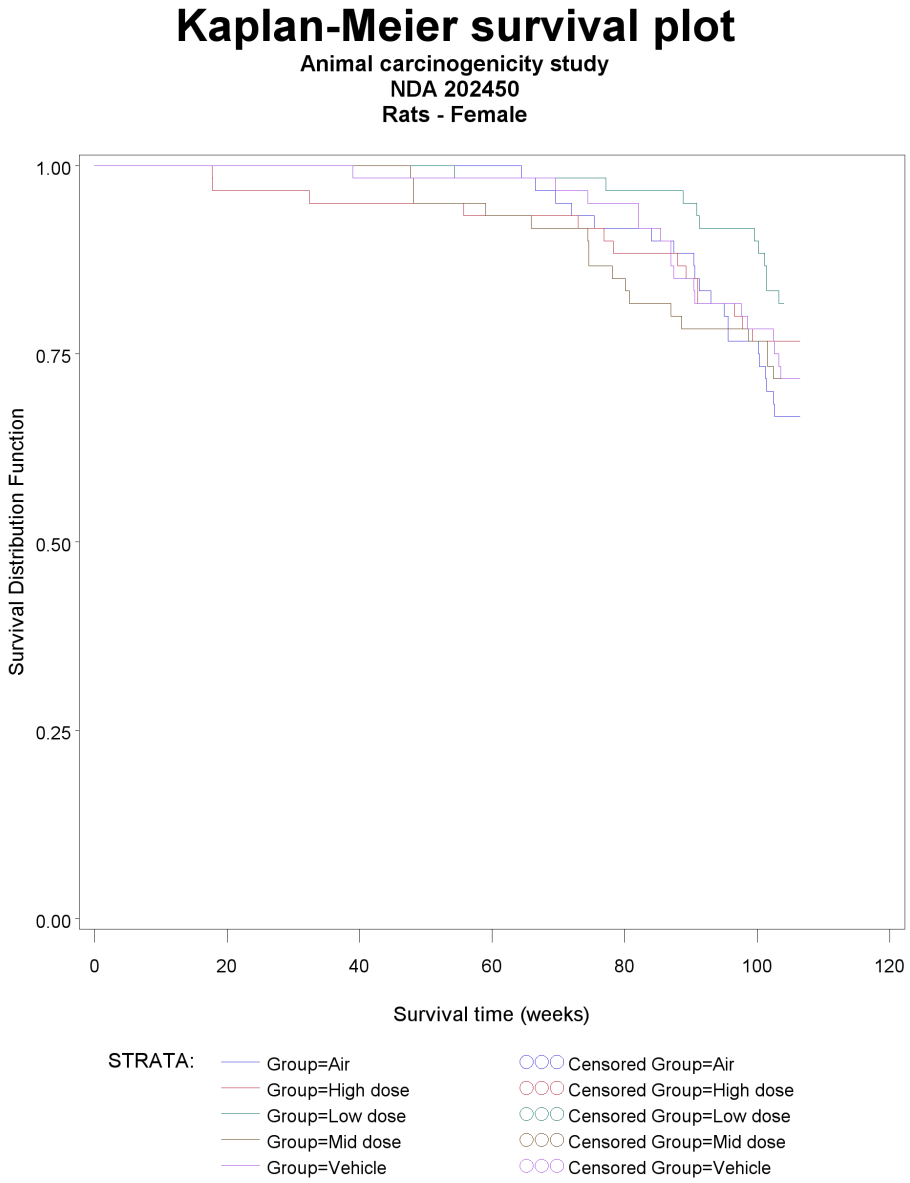

Figure 2.2: Survival curves for male rats

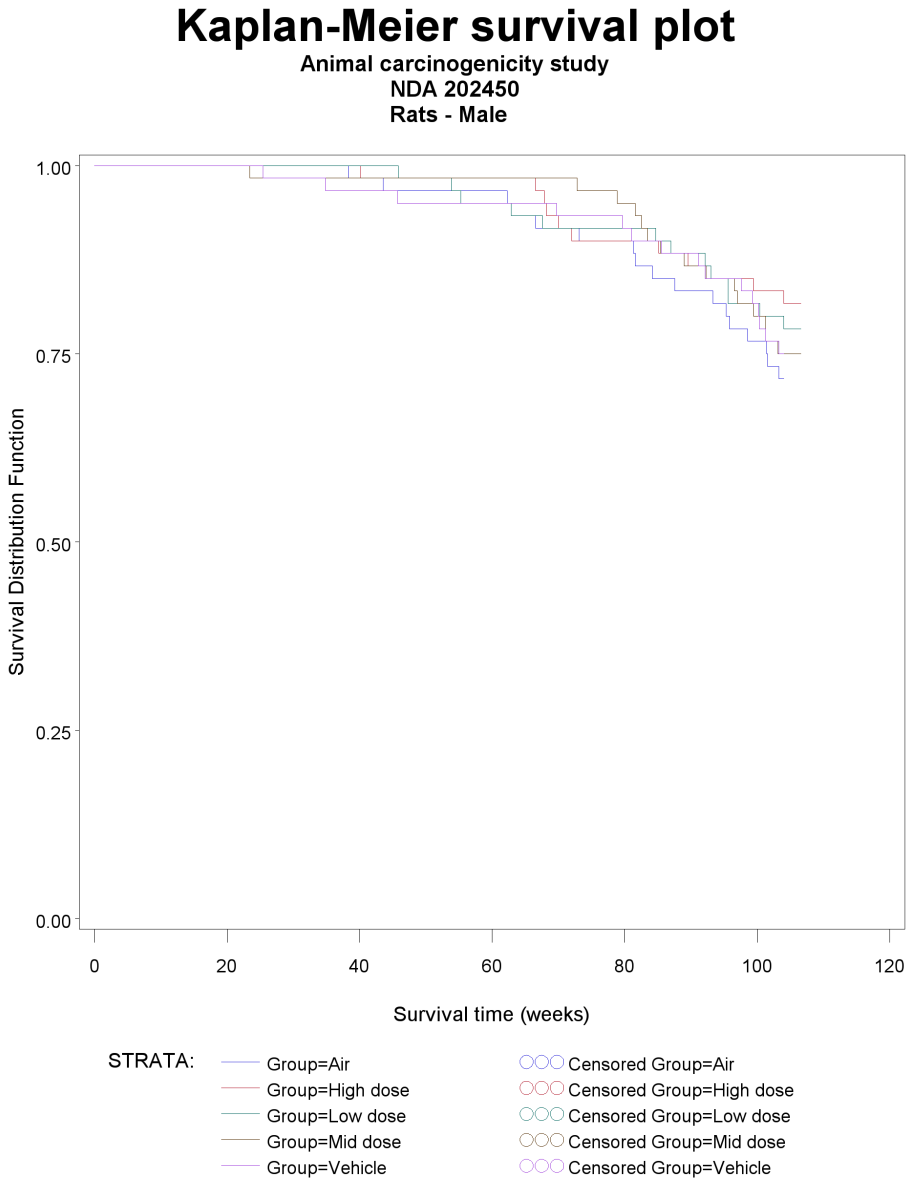

Table 2.1: Numbers of animals alive at certain timepoints (rat study)

Survival rates at key times
NDA 202450
Animal carcinogenicity study
Rats

Species and Sex	*Dose Group*	*Dose (mg kg)*	*Number at start*	*Number alive after 52 weeks*	*Proportion alive after 52 weeks*	*Number alive after 78 weeks*	*Proportion alive after 78 weeks*	*Number alive after 90 weeks*	*Proportion alive after 90 weeks*	*Number alive at termination*	*Proportion alive at termination*
Rats - Female	Air	0	60	60	100%	55	92%	53	88%	40	67%
	Vehicle	0	60	59	98%	57	95%	51	85%	43	72%
	Low dose	0.02	60	60	100%	58	97%	57	95%	49	82%
	Mid dose	0.07	60	57	95%	52	87%	47	78%	43	72%
	High dose	0.2	60	57	95%	54	90%	51	85%	46	77%
Rats - Male	Air	0	60	58	97%	54	90%	50	83%	43	72%
	Vehicle	0	60	57	95%	56	93%	53	88%	45	75%
	Low dose	0.02	60	59	98%	55	92%	53	88%	48	80%
	Mid dose	0.07	60	59	98%	58	97%	52	87%	45	75%
	High dose	0.2	60	59	98%	54	90%	52	87%	50	83%

Commentry There is no evidence, either graphical or as a result of statistical tests, of a dose related survial effect, either among female or male rats.

Comparison of control groups Kaplan-Meier plots of the control groups are shown as figures 2.3 and 2.4. The results of log-rank tests of survival between the control groups are presented in table 1.4.

As with the comparison of the treated groups with the controls, there is no evidence, either graphical or as a result of statistical tests, of a dose related survial effect, either among female or male control rats.

2.3.2 Tumor analysis — Main study

Endpoints

As in the mouse study, organs have been classed as either primary or secondary (see Section 1.3.2). The lists of organs adduced to be primary are presented in tables 2.2 and 2.3. Organs adduced to be secondary are listed in tables 2.4 and 2.5.

It is noteworthy that the mammary glands of the male rats have been reported as unexamined in every single animal.

The same customized endpoints have been analyzed as were considered in the mouse study (see table 1.7).

Figure 2.3: Survival curves for control groups (female rats experiment)

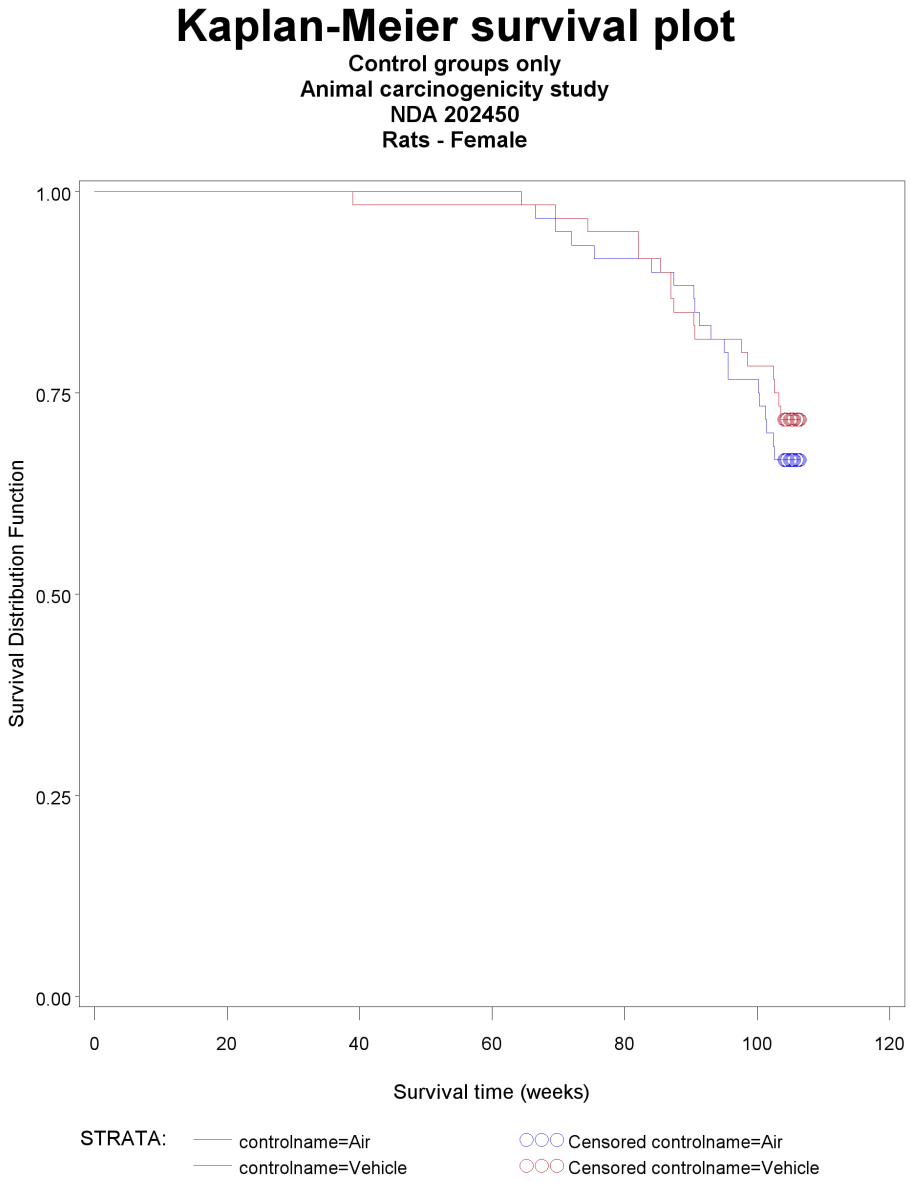

Figure 2.4: Survival curves for male rats

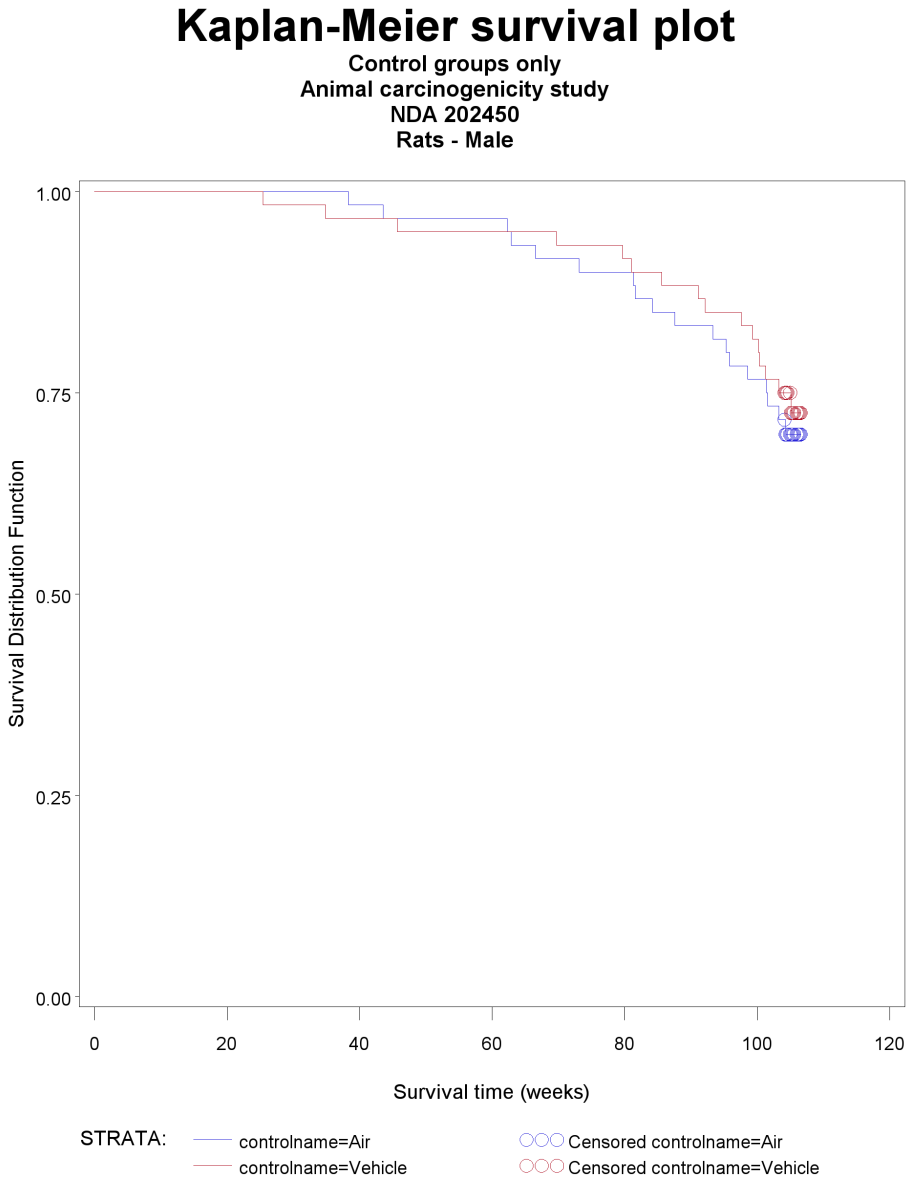

Table 2.2: Primary organs in female rat experiment

Primary organs in study of female rats
NDA 202450
Animal carcinogenicity study

Organ or tissue name
ADRENAL CORTICES
ADRENAL MEDULLAS
BRAIN
CEREBELLUM
CERVIX
CLITORAL GLANDS
HEMOLYMPHORET. SYS
JEJUNUM
KIDNEYS
LIVER
MAMMARY GLAND
MANDIB.LYMPH NODES
MESENT. LYMPH NODE
OVARIES
PANCREAS
PARATHYROID GLANDS
PITUITARY GLAND
SKIN/SUBCUTIS
SPLEEN
SUBLINGUAL GLANDS
THYMUS
THYROID GLAND
TONGUE
UTERUS
VAGINA

Reference ID: 3087610

Table 2.3: Primary organs in male rat experiment

Primary organs in study of male rats
NDA 202450
Animal carcinogenicity study

Organ or tissue name
ADRENAL CORTICES
ADRENAL MEDULLAS
BRAIN
BRAIN STEM
FEMUR
HEMOLYMPHORET. SYS
LIVER
MANDIB.LYMPH NODES
MESENT. LYMPH NODE
NASAL CAVITY-LEVEL
PANCREAS
PARATHYROID GLANDS
PITUITARY GLAND
SKIN/SUBCUTIS
SPLEEN
SUBLINGUAL GLANDS
TESTES
THYMUS
THYROID GLAND
TONGUE

Reference ID: 3087610

Table 2.4: Secondary organs in female rat experiment

Secondary organs in study of female rats
NDA 202450
Animal carcinogenicity study

Organ or tissue name
BODY CAVITIES

Reference ID: 3087610

Table 2.5: Secondary organs in male rat experiment

Secondary organs in study of male rats
NDA 202450
Animal carcinogenicity study

Organ or tissue name
BODY CAVITIES
MAMMARY GLAND

Reference ID: 3087610

Statistical procedure

The same statistical procedures are used to assess tumor incidence in rats are were used in mice (see Section 1.3.2). Note that the critical p-values used to determine significance are presented in table 1.8.

Noteworthy results

The results of the statistical analyses of tumor incidence in primary endpoints are presented in tables 2.6 (female rats) and 2.7 (male rats). The results of analyses of customized endpoints (see table 1.7) are presented in tables 2.8 and 2.9.

Tables 2.10 and 2.11 are excerpted from tables 2.8, and2.9, and list only those tumor types or customized endpoints for which at least one test of comparison or trend yielded a p-value below 0.05. No significant results were reported any individual tumor types in the rat experiment.

Incidence rates for tumors found in secondary organs have not been analyzed statistically. Count data for such tumors are presented in table 2.12.

Ovarian Sertolli cell tumors The p-value of the test of trend for ovarian Sertolli cell tumors (in female rats) is 0.0459 (see table 2.10), driven by three cases in the high dose group, compared with a single case in the vehicle control group, and none in the low or mid dose groups. However, this result does not remain significant after making an adjustment for multiplicity. Furthermore, the comparison between the high dose group and the control group is not significant ($p = 0.3017$). Consequently, there does not seem to be any reason to consider this anything other than a negative result.

Hemangiomas and hemangiosarcomas combined in male rats The significant result for hemangiomas and hemangiosarcomas combined is for the comparison between the low dose group ($p = 0.0283$). However, neither the test of trend nor the comparison between the mid or high dose group and the vehicle control yield p-values below 0.05. This should therefore be considered a negative result.

2.3.3 Tumor analysis — Vehicle study

Reason for study

Noteworthy results

The results of the statistical analyses of tumor incidence in primary endpoints are presented in tables 2.13 (female rats) and 2.14 (male rats). The results of analyses of customized endpoints (see table 1.7) are presented in tables 2.15 and 2.16. Table 2.17 is excerpted from table 2.13, and lists the tumor type (mammary fibroadenomas) for which tests were conducted which yielded p-values below 0.05. No such tests were conducted for any customized endpoints, or of single tumor types in male rats.

Mammary fibroadenomas Fifteen female animals in the vehicle control group developed mammary fibroadenomas, compared with just five in the air control group. The p-value of the test of comparison is 0.0136. Since these are common tumors, this result is not significant after adjusting for multiplicity, regardless of whether it is considered a test of trend, or a pairwise comparison.

After discussions with the reiewing pharmacologist, an additional calculation has been conducted, where the three LAS 34273 groups (who all received the vehicle in addition to various levels of LAS 34273), have been combined with the vehicle control group, and compared with the Air control for the incidence of mammary fibroadenomas in female rats. In this analysis, the combined vehicle group contained 49 tumor bearing animals, from a survival adjusted population of 214, compared with 5 tumor bearing animals in a survival adjusted population of 54 in the air control group. The p-value of this test was 0.0161.

2.3.4 Analysis of unexamined and autolytic organs

Unexamined animals

No animals have been reported as completely unexamined.

Organs reported autolytic

No organ in any rat was found to have been autolyzed to the extent that a usable sample could not be obtained.

Organs reported as unexamined

The numbers of animals with organs reported as being unexamined are presented in tables 2.18 and 2.19.

The parathyroid has been reported as unexamined in 18% of male, and 18% of female animals. This is probably not enough to undermine findings concerning this organ, but is still noteworthy. More worrysome is the fact that the mammary glands have not been examined in any male rats.

2.3.5 Tables of results

Table 2.6

Table of reported tumors in Rat Study
NDA 202450
Animal carcinogenicity study
Female rats

Organ or tissue name	*Tumor name*	*Quantity*	*Vehicle*	*Low dose*	*Mid dose*	*High dose*
ADRENAL MEDULLAS	COMPLEX PHEOCHROMOCYTOMA	P-value of test of trend or comparison	.4882		.4904	
		Number of animals reported with tumor	0	0	1	0
		Poly-3 adjusted incidence rate	0.0%	0.0%	1.9%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,6.7)	(0,6.5)	(0.05,10.4)	(0,6.8)
		Poly-3 adjusted number of animals at risk	53.2	55.0	51.8	52.4
	PHEOCHROMOCYTOMA: MALIGNANT	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
		Poly-3 adjusted incidence rate	1.9%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.05,10.1)	(0,6.5)	(0,7.0)	(0,6.8)
		Poly-3 adjusted number of animals at risk	53.2	55.0	51.1	52.4
BRAIN	ASTROCYTOMA	P-value of test of trend or comparison	.7512	.5182		
		Number of animals reported with tumor	0	1	0	0
		Poly-3 adjusted incidence rate	0.0%	1.8%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,6.7)	(0.04,9.4)	(0,7.0)	(0,6.8)
		Poly-3 adjusted number of animals at risk	53.9	57.1	51.1	52.4
	GRANULAR CELL TUMOR	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
		Poly-3 adjusted incidence rate	1.9%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.05,10.1)	(0,6.3)	(0,7.0)	(0,6.8)
		Poly-3 adjusted number of animals at risk	53.9	57.0	51.1	52.4
	OLIGODENDROGLIOMA	P-value of test of trend or comparison	.2477			.5000
		Number of animals reported with tumor	0	0	0	1
		Poly-3 adjusted incidence rate	0.0%	0.0%	0.0%	1.9%
		95% CI for poly-3 adjusted incidence rate (%)	(0,6.7)	(0,6.3)	(0,7.0)	(0.05,10.1)
		Poly-3 adjusted number of animals at risk	53.9	57.0	51.1	53.1
CEREBELLUM	GRANULAR CELL TUMOR	P-value of test of trend or comparison	.7345	1	.7427	1
		Number of animals reported with tumor	1	0	1	0
		Poly-3 adjusted incidence rate	1.9%	0.0%	2.0%	0.0%

Reference ID: 3087610

Table 2.6

Table of reported tumors in Rat Study
NDA 202450
Animal carcinogenicity study
Female rats

Organ or tissue name	*Tumor name*	*Quantity*	*Vehicle*	*Low dose*	*Mid dose*	*High dose*
		95% CI for poly-3 adjusted incidence rate (%)	(0.05,10.1)	(0,6.3)	(0.05,10.4)	(0,6.8)
		Poly-3 adjusted number of animals at risk	53.9	57.0	51.1	52.4
CERVIX	LEIOMYOSARCOMA	P-value of test of trend or comparison	.7512	.5182		
		Number of animals reported with tumor	0	1	0	0
		Poly-3 adjusted incidence rate	0.0%	1.8%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,6.7)	(0.04,9.4)	(0,7.0)	(0,6.8)
		Poly-3 adjusted number of animals at risk	53.9	57.0	51.1	52.4
	STROMAL POLYP	P-value of test of trend or comparison	.4836		.4904	
		Number of animals reported with tumor	0	0	1	0
		Poly-3 adjusted incidence rate	0.0%	0.0%	1.9%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,6.7)	(0,6.3)	(0.05,10.4)	(0,6.8)
		Poly-3 adjusted number of animals at risk	53.9	57.0	51.8	52.4
CLITORAL GLANDS	CARCINOMA	P-value of test of trend or comparison	.2429			.4904
		Number of animals reported with tumor	0	0	0	1
		Poly-3 adjusted incidence rate	0.0%	0.0%	0.0%	1.9%
		95% CI for poly-3 adjusted incidence rate (%)	(0,6.7)	(0,6.4)	(0,7.1)	(0.05,10.4)
		Poly-3 adjusted number of animals at risk	53.2	56.1	50.6	51.9
HEMOLYMPHORET. SYS	MALIGNANT LYMPHOMA	P-value of test of trend or comparison	.7512	.5182		
		Number of animals reported with tumor	0	1	0	0
		Poly-3 adjusted incidence rate	0.0%	1.7%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,6.7)	(0.04,9.4)	(0,7.0)	(0,6.8)
		Poly-3 adjusted number of animals at risk	53.9	57.9	51.1	52.4
JEJUNUM	ADENOMA	P-value of test of trend or comparison	.2441			.4952
		Number of animals reported with tumor	0	0	0	1
		Poly-3 adjusted incidence rate	0.0%	0.0%	0.0%	1.9%
		95% CI for poly-3 adjusted incidence rate (%)	(0,6.7)	(0,6.3)	(0,7.0)	(0.05,10.3)
		Poly-3 adjusted number of animals at risk	53.9	57.0	51.1	52.4
KIDNEYS	NEPHROBLASTOMA	P-value of test of trend or comparison	1	1	1	1

Reference ID: 3087610

Table 2.6

Table of reported tumors in Rat Study
NDA 202450
Animal carcinogenicity study
Female rats

Organ or tissue name	*Tumor name*	*Quantity*	*Vehicle*	*Low dose*	*Mid dose*	*High dose*
		Number of animals reported with tumor	1	0	0	0
		Poly-3 adjusted incidence rate	1.8%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.05,9.9)	(0,6.3)	(0,7.0)	(0,6.8)
		Poly-3 adjusted number of animals at risk	54.8	57.0	51.1	52.4
LIVER	CHOLANGIOCARCINOMA	P-value of test of trend or comparison	.7500	.5182		
		Number of animals reported with tumor	0	1	0	0
		Poly-3 adjusted incidence rate	0.0%	1.8%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,6.7)	(0.04,9.4)	(0,7.0)	(0,7.0)
		Poly-3 adjusted number of animals at risk	53.9	57.0	51.1	51.8
	CHOLANGIOMA	P-value of test of trend or comparison	.1733		.4904	.4904
		Number of animals reported with tumor	0	0	1	1
		Poly-3 adjusted incidence rate	0.0%	0.0%	2.0%	1.9%
		95% CI for poly-3 adjusted incidence rate (%)	(0,6.7)	(0,6.3)	(0.05,10.4)	(0.05,10.4)
		Poly-3 adjusted number of animals at risk	53.9	57.0	51.1	51.8
	HEPATOCELLULAR ADENOMA	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
		Poly-3 adjusted incidence rate	1.9%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.05,10.1)	(0,6.3)	(0,7.0)	(0,7.0)
		Poly-3 adjusted number of animals at risk	53.9	57.0	51.1	51.8
MAMMARY GLAND	ADENOCARCINOMA	P-value of test of trend or comparison	.8029	.8538	1	.9055
		Number of animals reported with tumor	6	4	0	3
		Poly-3 adjusted incidence rate	11%	7.0%	0.0%	5.7%
		95% CI for poly-3 adjusted incidence rate (%)	(4.03,22.2)	(1.91,17.0)	(0,7.0)	(1.18,15.9)
		Poly-3 adjusted number of animals at risk	55.1	57.2	51.1	53.0
	ADENOMA	P-value of test of trend or comparison	.6148	.5182	.4904	
		Number of animals reported with tumor	0	1	1	0
		Poly-3 adjusted incidence rate	0.0%	1.8%	2.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,6.7)	(0.04,9.4)	(0.05,10.4)	(0,6.8)

Reference ID: 3087610

Table 2.6

Table of reported tumors in Rat Study
NDA 202450
Animal carcinogenicity study
Female rats

Organ or tissue name	*Tumor name*	*Quantity*	*Vehicle*	*Low dose*	*Mid dose*	*High dose*
		Poly-3 adjusted number of animals at risk	53.9	57.0	51.1	52.4
	FIBROADENOMA	P-value of test of trend or comparison	.3953	.9286	.8322	.6865
		Number of animals reported with tumor	15	10	11	13
		Poly-3 adjusted incidence rate	27%	17%	21%	25%
		95% CI for poly-3 adjusted incidence rate (%)	(15.8,41.0)	(8.59,29.9)	(10.8,34.7)	(13.8,38.9)
		Poly-3 adjusted number of animals at risk	55.5	57.2	52.9	52.9
MANDIB.LYMPH NODES	HEMANGIOMA	P-value of test of trend or comparison	.2453			.5000
		Number of animals reported with tumor	0	0	0	1
		Poly-3 adjusted incidence rate	0.0%	0.0%	0.0%	1.9%
		95% CI for poly-3 adjusted incidence rate (%)	(0,6.8)	(0,6.3)	(0,7.0)	(0.05,10.3)
		Poly-3 adjusted number of animals at risk	52.5	57.0	51.1	52.4
MESENT. LYMPH NODE	HEMANGIOSARCOMA	P-value of test of trend or comparison	.7368	1	.7427	1
		Number of animals reported with tumor	1	0	1	0
		Poly-3 adjusted incidence rate	1.9%	0.0%	2.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.05,10.1)	(0,6.4)	(0.05,10.4)	(0,6.8)
		Poly-3 adjusted number of animals at risk	53.9	56.1	51.1	52.4
OVARIES	CYSTADENOCARCINOMA	P-value of test of trend or comparison	.7512	.5182		
		Number of animals reported with tumor	0	1	0	0
		Poly-3 adjusted incidence rate	0.0%	1.8%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,6.7)	(0.04,9.4)	(0,7.0)	(0,6.8)
		Poly-3 adjusted number of animals at risk	53.9	57.0	51.1	52.4
	GRANULOSA CELL TUMOR	P-value of test of trend or comparison	.4775	.7180	.3209	.6839
		Number of animals reported with tumor	2	2	4	2
		Poly-3 adjusted incidence rate	3.7%	3.5%	7.8%	3.8%
		95% CI for poly-3 adjusted incidence rate (%)	(0.45,13.0)	(0.42,12.1)	(2.14,18.9)	(0.46,13.2)
		Poly-3 adjusted number of animals at risk	53.9	57.1	51.1	52.4
	GRANULOSA CELL TUMOR MALIGNANT	P-value of test of trend or comparison	.5832	1	1	.8750
		Number of animals reported with tumor	2	0	0	1

Reference ID: 3087610

Table 2.6

Table of reported tumors in Rat Study
NDA 202450
Animal carcinogenicity study
Female rats

Organ or tissue name	*Tumor name*	*Quantity*	*Vehicle*	*Low dose*	*Mid dose*	*High dose*
		Poly-3 adjusted incidence rate	3.7%	0.0%	0.0%	1.9%
		95% CI for poly-3 adjusted incidence rate (%)	(0.45,13.0)	(0,6.3)	(0,7.0)	(0.05,10.3)
		Poly-3 adjusted number of animals at risk	53.9	57.0	51.1	52.4
	SERTOLI CELL TUMOR	P-value of test of trend or comparison	.1484	1	1	.4928
		Number of animals reported with tumor	1	0	0	2
		Poly-3 adjusted incidence rate	1.9%	0.0%	0.0%	3.8%
		95% CI for poly-3 adjusted incidence rate (%)	(0.05,10.1)	(0,6.3)	(0,7.0)	(0.46,13.2)
		Poly-3 adjusted number of animals at risk	53.9	57.0	51.1	52.8
	SERTOLI CELL TUMOR MALIGNANT	P-value of test of trend or comparison	.2441			.4952
		Number of animals reported with tumor	0	0	0	1
		Poly-3 adjusted incidence rate	0.0%	0.0%	0.0%	1.9%
		95% CI for poly-3 adjusted incidence rate (%)	(0,6.7)	(0,6.3)	(0,7.0)	(0.05,10.3)
		Poly-3 adjusted number of animals at risk	53.9	57.0	51.1	52.4
	THECOMA	P-value of test of trend or comparison	.2441			.4952
		Number of animals reported with tumor	0	0	0	1
		Poly-3 adjusted incidence rate	0.0%	0.0%	0.0%	1.9%
		95% CI for poly-3 adjusted incidence rate (%)	(0,6.7)	(0,6.3)	(0,7.0)	(0.05,10.3)
		Poly-3 adjusted number of animals at risk	53.9	57.0	51.1	52.4
	TUBULOSTROMAL CARCINOMA	P-value of test of trend or comparison	.4836		.4904	
		Number of animals reported with tumor	0	0	1	0
		Poly-3 adjusted incidence rate	0.0%	0.0%	2.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,6.7)	(0,6.3)	(0.05,10.4)	(0,6.8)
		Poly-3 adjusted number of animals at risk	53.9	57.0	51.1	52.4
PANCREAS	ISLET CELL CARCINOMA	P-value of test of trend or comparison	.7512	.5182		
		Number of animals reported with tumor	0	1	0	0
		Poly-3 adjusted incidence rate	0.0%	1.7%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,6.7)	(0.04,9.4)	(0,7.0)	(0,6.8)

Table 2.6

Table of reported tumors in Rat Study
NDA 202450
Animal carcinogenicity study
Female rats

Organ or tissue name	*Tumor name*	*Quantity*	*Vehicle*	*Low dose*	*Mid dose*	*High dose*
		Poly-3 adjusted number of animals at risk	53.8	57.4	51.1	52.3
PITUITARY GLAND	ADENOMA: PARS ANTERIOR	P-value of test of trend or comparison	1	.9848	.8121	1
		Number of animals reported with tumor	29	19	23	7
		Poly-3 adjusted incidence rate	51%	33%	44%	13%
		95% CI for poly-3 adjusted incidence rate (%)	(36.6,64.4)	(20.6,46.3)	(29.8,58.7)	(5.37,25.3)
		Poly-3 adjusted number of animals at risk	57.1	58.4	52.7	53.0
	ADENOMA: PARS INTERMEDIA	P-value of test of trend or comparison	.4836		.4904	
		Number of animals reported with tumor	0	0	1	0
		Poly-3 adjusted incidence rate	0.0%	0.0%	1.9%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,6.7)	(0,6.3)	(0.05,10.4)	(0,6.8)
		Poly-3 adjusted number of animals at risk	53.9	57.0	51.5	52.4
SKIN/SUBCUTIS	HEMANGIOSARCOMA	P-value of test of trend or comparison	.2441			.4952
		Number of animals reported with tumor	0	0	0	1
		Poly-3 adjusted incidence rate	0.0%	0.0%	0.0%	1.9%
		95% CI for poly-3 adjusted incidence rate (%)	(0,6.7)	(0,6.3)	(0,7.0)	(0.05,10.3)
		Poly-3 adjusted number of animals at risk	53.9	57.0	51.1	52.4
	KERATOACANTHOMA	P-value of test of trend or comparison	.8052	.2662		
		Number of animals reported with tumor	0	2	0	0
		Poly-3 adjusted incidence rate	0.0%	3.5%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,6.7)	(0.42,12.1)	(0,7.0)	(0,6.8)
		Poly-3 adjusted number of animals at risk	53.9	57.0	51.1	52.4
	SQUAMOUS CELL CARCINOMA	P-value of test of trend or comparison	.4836		.4904	
		Number of animals reported with tumor	0	0	1	0
		Poly-3 adjusted incidence rate	0.0%	0.0%	1.9%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,6.7)	(0,6.3)	(0.05,10.4)	(0,6.8)
		Poly-3 adjusted number of animals at risk	53.9	57.0	51.4	52.4
THYMUS	THYMOMA: LYMPHOCYTIC	P-value of test of trend or comparison	.7998	.8351	.8000	.9338

Reference ID: 3087610

Table 2.6

Table of reported tumors in Rat Study
NDA 202450
Animal carcinogenicity study
Female rats

Organ or tissue name	*Tumor name*	*Quantity*	*Vehicle*	*Low dose*	*Mid dose*	*High dose*
		Number of animals reported with tumor	3	2	2	1
		Poly-3 adjusted incidence rate	5.6%	3.5%	4.0%	2.0%
		95% CI for poly-3 adjusted incidence rate (%)	(1.16,15.7)	(0.43,12.3)	(0.48,13.7)	(0.05,10.6)
		Poly-3 adjusted number of animals at risk	53.7	56.4	50.3	50.2
THYROID GLAND	C-CELL ADENOMA	P-value of test of trend or comparison	.3025	.6947	.4783	.4893
		Number of animals reported with tumor	3	3	4	4
		Poly-3 adjusted incidence rate	5.6%	5.3%	7.8%	7.6%
		95% CI for poly-3 adjusted incidence rate (%)	(1.16,15.7)	(1.08,14.6)	(2.14,18.9)	(2.09,18.5)
		Poly-3 adjusted number of animals at risk	53.9	57.0	51.1	52.4
	FOLLICULAR ADENOMA	P-value of test of trend or comparison	.1284	.7111	.8677	.3213
		Number of animals reported with tumor	2	2	1	4
		Poly-3 adjusted incidence rate	3.7%	3.5%	2.0%	7.6%
		95% CI for poly-3 adjusted incidence rate (%)	(0.44,12.7)	(0.42,12.1)	(0.05,10.4)	(2.09,18.5)
		Poly-3 adjusted number of animals at risk	54.3	57.0	51.1	52.8
	FOLLICULAR CARCINOMA	P-value of test of trend or comparison	.8198	.7701	.7427	1
		Number of animals reported with tumor	1	1	1	0
		Poly-3 adjusted incidence rate	1.9%	1.8%	2.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.05,10.1)	(0.04,9.4)	(0.05,10.4)	(0,6.8)
		Poly-3 adjusted number of animals at risk	53.9	57.0	51.1	52.4
UTERUS	ADENOCARCINOMA	P-value of test of trend or comparison	.2656	.7701	.2944	.4928
		Number of animals reported with tumor	1	1	3	2
		Poly-3 adjusted incidence rate	1.9%	1.8%	5.9%	3.8%
		95% CI for poly-3 adjusted incidence rate (%)	(0.05,10.1)	(0.04,9.4)	(1.21,16.2)	(0.46,13.2)
		Poly-3 adjusted number of animals at risk	53.9	57.0	51.1	52.6
	ADENOMA	P-value of test of trend or comparison	.7512	.5182		
		Number of animals reported with tumor	0	1	0	0
		Poly-3 adjusted incidence rate	0.0%	1.8%	0.0%	0.0%

Reference ID: 3087610

Table 2.6

Table of reported tumors in Rat Study
NDA 202450
Animal carcinogenicity study
Female rats

Organ or tissue name	*Tumor name*	*Quantity*	*Vehicle*	*Low dose*	*Mid dose*	*High dose*
		95% CI for poly-3 adjusted incidence rate (%)	(0,6.7)	(0.04,9.4)	(0,7.0)	(0,6.8)
		Poly-3 adjusted number of animals at risk	53.9	57.0	51.1	52.4
	LEIMYOSARCOMA	P-value of test of trend or comparison	.4278	1	1	.7429
		Number of animals reported with tumor	1	0	0	1
		Poly-3 adjusted incidence rate	1.8%	0.0%	0.0%	1.9%
		95% CI for poly-3 adjusted incidence rate (%)	(0.05,9.9)	(0,6.3)	(0,7.0)	(0.05,10.3)
		Poly-3 adjusted number of animals at risk	54.3	57.0	51.1	52.6
	MALIGNANT SCHWANNOMA	P-value of test of trend or comparison	.4836		.4904	
		Number of animals reported with tumor	0	0	1	0
		Poly-3 adjusted incidence rate	0.0%	0.0%	1.9%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,6.7)	(0,6.3)	(0.05,10.4)	(0,6.8)
		Poly-3 adjusted number of animals at risk	53.9	57.0	51.7	52.4
	STROMAL POLYP	P-value of test of trend or comparison	.4949	.5654	.8672	.5904
		Number of animals reported with tumor	8	9	5	8
		Poly-3 adjusted incidence rate	15%	16%	9.7%	15%
		95% CI for poly-3 adjusted incidence rate (%)	(6.62,27.6)	(7.35,27.9)	(3.2,21.4)	(6.75,28.1)
		Poly-3 adjusted number of animals at risk	53.9	57.1	51.5	52.8
	STROMAL SARCOMA	P-value of test of trend or comparison	.2853	.5182	.4904	.4952
		Number of animals reported with tumor	0	1	1	1
		Poly-3 adjusted incidence rate	0.0%	1.7%	1.9%	1.9%
		95% CI for poly-3 adjusted incidence rate (%)	(0,6.7)	(0.04,9.4)	(0.05,10.4)	(0.05,10.3)
		Poly-3 adjusted number of animals at risk	53.9	57.6	51.6	52.8
VAGINA	GRANULAR CELL TUMOR	P-value of test of trend or comparison	.7512	.5182		
		Number of animals reported with tumor	0	1	0	0
		Poly-3 adjusted incidence rate	0.0%	1.8%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,6.7)	(0.04,9.4)	(0,7.0)	(0,6.8)
		Poly-3 adjusted number of animals at risk	53.9	57.0	51.1	52.4

Table 2.6

Table of reported tumors in Rat Study
NDA 202450
Animal carcinogenicity study
Female rats

Organ or tissue name	*Tumor name*	*Quantity*	*Vehicle*	*Low dose*	*Mid dose*	*High dose*
	HEMANGIOMA	P-value of test of trend or comparison	.2477			.5000
		Number of animals reported with tumor	0	0	0	1
		Poly-3 adjusted incidence rate	0.0%	0.0%	0.0%	1.9%
		95% CI for poly-3 adjusted incidence rate (%)	(0,6.7)	(0,6.3)	(0,7.0)	(0.05,10.1)
		Poly-3 adjusted number of animals at risk	53.9	57.0	51.1	53.3

Reference ID: 3087610

Table 2.7

Table of reported tumors in Rat Study
NDA 202450
Animal carcinogenicity study
Male rats

Organ or tissue name	*Tumor name*	*Quantity*	*Vehicle*	*Low dose*	*Mid dose*	*High dose*
ADRENAL CORTICES	CARCINOMA	P-value of test of trend or comparison	.5047		.5047	
		Number of animals reported with tumor	0	0	1	0
		Poly-3 adjusted incidence rate	0.0%	0.0%	1.8%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,6.7)	(0,6.7)	(0.05,9.9)	(0,6.6)
		Poly-3 adjusted number of animals at risk	53.7	53.9	54.5	54.3
ADRENAL MEDULLAS	COMPLEX PHEOCHROMOCYTOMA	P-value of test of trend or comparison	.5023		.5000	
		Number of animals reported with tumor	0	0	1	0
		Poly-3 adjusted incidence rate	0.0%	0.0%	1.9%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,6.7)	(0,6.7)	(0.05,10.1)	(0,6.6)
		Poly-3 adjusted number of animals at risk	53.7	53.9	53.8	54.3
BRAIN	ASTROCYTOMA	P-value of test of trend or comparison	.3063	.5000	.5093	.5093
		Number of animals reported with tumor	0	1	1	1
		Poly-3 adjusted incidence rate	0.0%	1.9%	1.8%	1.8%
		95% CI for poly-3 adjusted incidence rate (%)	(0,6.7)	(0.05,10.1)	(0.05,9.7)	(0.05,9.7)
		Poly-3 adjusted number of animals at risk	53.7	53.9	55.0	55.2
	GRANULAR CELL TUMOR	P-value of test of trend or comparison	.2523			.5047
		Number of animals reported with tumor	0	0	0	1
		Poly-3 adjusted incidence rate	0.0%	0.0%	0.0%	1.8%
		95% CI for poly-3 adjusted incidence rate (%)	(0,6.7)	(0,6.7)	(0,6.6)	(0.05,9.9)
		Poly-3 adjusted number of animals at risk	53.7	53.9	54.5	54.3
BRAIN STEM	ASTROCYTOMA	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
		Poly-3 adjusted incidence rate	1.9%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.05,10.1)	(0,6.7)	(0,6.6)	(0,6.6)
		Poly-3 adjusted number of animals at risk	53.7	53.9	54.5	54.3
FEMUR	OSTEOSARCOMA	P-value of test of trend or comparison	.2523			.5047
		Number of animals reported with tumor	0	0	0	1
		Poly-3 adjusted incidence rate	0.0%	0.0%	0.0%	1.8%

Reference ID: 3087610

Table 2.7

Table of reported tumors in Rat Study
NDA 202450
Animal carcinogenicity study
Male rats

Organ or tissue name	*Tumor name*	*Quantity*	*Vehicle*	*Low dose*	*Mid dose*	*High dose*
		95% CI for poly-3 adjusted incidence rate (%)	(0,6.7)	(0,6.7)	(0,6.6)	(0.05,9.9)
		Poly-3 adjusted number of animals at risk	53.7	53.9	54.5	54.3
HEMOLYMPHORET. SYS	HISTIOCYTIC SARCOMA	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
		Poly-3 adjusted incidence rate	1.9%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.05,10.1)	(0,6.7)	(0,6.6)	(0,6.6)
		Poly-3 adjusted number of animals at risk	53.8	53.9	54.5	54.3
	MALIGNANT LYMPHOMA	P-value of test of trend or comparison	.9962	.9387	1	1
		Number of animals reported with tumor	3	1	0	0
		Poly-3 adjusted incidence rate	5.4%	1.8%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(1.12,15.1)	(0.05,9.9)	(0,6.6)	(0,6.6)
		Poly-3 adjusted number of animals at risk	55.6	54.7	54.5	54.3
LIVER	HEPATOCELLULAR ADENOMA	P-value of test of trend or comparison	.8329	.7570	.7570	1
		Number of animals reported with tumor	1	1	1	0
		Poly-3 adjusted incidence rate	1.9%	1.8%	1.8%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.05,10.1)	(0.05,9.9)	(0.05,9.9)	(0,6.6)
		Poly-3 adjusted number of animals at risk	53.7	54.3	54.5	54.3
	HEPATOCELLULAR CARCINOMA	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
		Poly-3 adjusted incidence rate	1.9%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.05,10.1)	(0,6.7)	(0,6.6)	(0,6.6)
		Poly-3 adjusted number of animals at risk	53.7	53.9	54.5	54.3
MANDIB.LYMPH NODES	LIPOSARCOMA	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
		Poly-3 adjusted incidence rate	1.9%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.05,10.1)	(0,6.8)	(0,6.6)	(0,6.7)
		Poly-3 adjusted number of animals at risk	53.7	52.9	54.5	53.3
MESENT. LYMPH NODE	HEMANGIOMA	P-value of test of trend or comparison	.2969	.5000	.5047	.5000

Reference ID: 3087610

Table 2.7

Table of reported tumors in Rat Study
NDA 202450
Animal carcinogenicity study
Male rats

Organ or tissue name	*Tumor name*	*Quantity*	*Vehicle*	*Low dose*	*Mid dose*	*High dose*
		Number of animals reported with tumor	0	1	1	1
		Poly-3 adjusted incidence rate	0.0%	1.9%	1.8%	1.9%
		95% CI for poly-3 adjusted incidence rate (%)	(0,6.7)	(0.05,10.1)	(0.05,9.9)	(0.05,10.1)
		Poly-3 adjusted number of animals at risk	53.7	53.9	54.5	53.3
	HEMANGIOSARCOMA	P-value of test of trend or comparison	.8146	.2476		
		Number of animals reported with tumor	0	2	0	0
		Poly-3 adjusted incidence rate	0.0%	3.7%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,6.7)	(0.45,13.0)	(0,6.6)	(0,6.7)
		Poly-3 adjusted number of animals at risk	53.7	53.9	54.5	53.3
NASAL CAVITY-LEVEL	COMPOUND ODONTOMA	P-value of test of trend or comparison	.7535	.5047		
		Number of animals reported with tumor	0	1	0	0
		Poly-3 adjusted incidence rate	0.0%	1.8%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,6.7)	(0.05,9.9)	(0,6.6)	(0,6.6)
		Poly-3 adjusted number of animals at risk	53.7	54.6	54.5	54.3
	OSTEOSARCOMA	P-value of test of trend or comparison	.5047		.5047	
		Number of animals reported with tumor	0	0	1	0
		Poly-3 adjusted incidence rate	0.0%	0.0%	1.8%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,6.7)	(0,6.7)	(0.05,9.9)	(0,6.6)
		Poly-3 adjusted number of animals at risk	53.7	53.9	54.7	54.3
PANCREAS	ISLET CELL ADENOMA	P-value of test of trend or comparison	.9592	.3160	1	1
		Number of animals reported with tumor	1	3	0	0
		Poly-3 adjusted incidence rate	1.9%	5.5%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.05,10.1)	(1.14,15.4)	(0,6.6)	(0,6.6)
		Poly-3 adjusted number of animals at risk	53.7	54.3	54.5	54.3
	ISLET CELL CARCINOMA	P-value of test of trend or comparison	.5458	1	.5089	.8820
		Number of animals reported with tumor	2	0	3	1
		Poly-3 adjusted incidence rate	3.7%	0.0%	5.5%	1.8%
		95% CI for poly-3 adjusted incidence rate (%)	(0.45,13.0)	(0,6.7)	(1.14,15.4)	(0.05,9.9)

Reference ID: 3087610

Table 2.7

Table of reported tumors in Rat Study
NDA 202450
Animal carcinogenicity study
Male rats

Organ or tissue name	*Tumor name*	*Quantity*	*Vehicle*	*Low dose*	*Mid dose*	*High dose*
		Poly-3 adjusted number of animals at risk	53.7	53.9	55.0	54.3
PARATHYROID GLANDS	ADENOMA	P-value of test of trend or comparison	.8383	.7168	.7632	1
		Number of animals reported with tumor	1	1	1	0
		Poly-3 adjusted incidence rate	2.2%	2.4%	2.1%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.05,11.5)	(0.06,13.2)	(0.05,11.1)	(0,7.9)
		Poly-3 adjusted number of animals at risk	46.5	40.9	48.1	45.0
PITUITARY GLAND	ADENOMA: PARS ANTERIOR	P-value of test of trend or comparison	.4238	.9480	.9818	.7394
		Number of animals reported with tumor	16	10	8	14
		Poly-3 adjusted incidence rate	29%	18%	14%	25%
		95% CI for poly-3 adjusted incidence rate (%)	(17.3,42.9)	(8.75,30.4)	(6.38,26.7)	(14.4,39.0)
		Poly-3 adjusted number of animals at risk	55.3	56.3	55.6	55.8
	ADENOMA: PARS INTERMEDIA	P-value of test of trend or comparison	.4455	1	1	.7617
		Number of animals reported with tumor	1	0	0	1
		Poly-3 adjusted incidence rate	1.9%	0.0%	0.0%	1.8%
		95% CI for poly-3 adjusted incidence rate (%)	(0.05,10.3)	(0,6.7)	(0,6.7)	(0.05,9.9)
		Poly-3 adjusted number of animals at risk	52.7	53.9	53.7	54.3
SKIN/SUBCUTIS	BASAL CELL CARCINOMA	P-value of test of trend or comparison	.5047		.5047	
		Number of animals reported with tumor	0	0	1	0
		Poly-3 adjusted incidence rate	0.0%	0.0%	1.8%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,6.7)	(0,6.7)	(0.05,9.9)	(0,6.6)
		Poly-3 adjusted number of animals at risk	53.7	53.9	54.7	54.3
	FIBROMA	P-value of test of trend or comparison	.7934	.9411	.9433	.9433
		Number of animals reported with tumor	3	1	1	1
		Poly-3 adjusted incidence rate	5.6%	1.9%	1.8%	1.8%
		95% CI for poly-3 adjusted incidence rate (%)	(1.16,15.7)	(0.05,10.1)	(0.05,9.9)	(0.05,9.9)
		Poly-3 adjusted number of animals at risk	53.8	53.9	54.5	54.3
	FIBROSARCOMA	P-value of test of trend or comparison	.6291	.5047	.5047	
		Number of animals reported with tumor	0	1	1	0

Reference ID: 3087610

Table 2.7

Table of reported tumors in Rat Study
NDA 202450
Animal carcinogenicity study
Male rats

Organ or tissue name	*Tumor name*	*Quantity*	*Vehicle*	*Low dose*	*Mid dose*	*High dose*
		Poly-3 adjusted incidence rate	0.0%	1.8%	1.8%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,6.7)	(0.05,9.9)	(0.05,9.9)	(0,6.6)
		Poly-3 adjusted number of animals at risk	53.7	54.1	54.6	54.3
	HEMANGIOMA	P-value of test of trend or comparison	.7523	.5000		
		Number of animals reported with tumor	0	1	0	0
		Poly-3 adjusted incidence rate	0.0%	1.9%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,6.7)	(0.05,10.1)	(0,6.6)	(0,6.6)
		Poly-3 adjusted number of animals at risk	53.7	53.9	54.5	54.3
	KERATOACANTHOMA	P-value of test of trend or comparison	.9246	.6911	.6981	1
		Number of animals reported with tumor	2	2	2	0
		Poly-3 adjusted incidence rate	3.7%	3.7%	3.7%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.45,13.0)	(0.45,13.0)	(0.44,12.7)	(0,6.6)
		Poly-3 adjusted number of animals at risk	53.7	53.9	54.6	54.3
	LIPOMA	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
		Poly-3 adjusted incidence rate	1.9%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.05,10.1)	(0,6.7)	(0,6.6)	(0,6.6)
		Poly-3 adjusted number of animals at risk	53.7	53.9	54.5	54.3
	MALIGNANT SCHWANNOMA	P-value of test of trend or comparison	.7558	1	.7570	1
		Number of animals reported with tumor	1	0	1	0
		Poly-3 adjusted incidence rate	1.9%	0.0%	1.8%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.05,10.1)	(0,6.7)	(0.05,9.9)	(0,6.6)
		Poly-3 adjusted number of animals at risk	53.7	53.9	55.0	54.3
	SARCOMA	P-value of test of trend or comparison	.7535	.5047		
		Number of animals reported with tumor	0	1	0	0
		Poly-3 adjusted incidence rate	0.0%	1.8%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,6.7)	(0.05,9.9)	(0,6.6)	(0,6.6)

Table 2.7

Table of reported tumors in Rat Study
NDA 202450
Animal carcinogenicity study
Male rats

Organ or tissue name	*Tumor name*	*Quantity*	*Vehicle*	*Low dose*	*Mid dose*	*High dose*
		Poly-3 adjusted number of animals at risk	53.7	54.8	54.5	54.3
	SQUAMOUS CELL CARCINOMA	P-value of test of trend or comparison	.6302	.5000	.5047	
		Number of animals reported with tumor	0	1	1	0
		Poly-3 adjusted incidence rate	0.0%	1.9%	1.8%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,6.7)	(0.05,10.1)	(0.05,9.9)	(0,6.6)
		Poly-3 adjusted number of animals at risk	53.7	53.9	55.0	54.3
SPLEEN	HEMANGIOMA	P-value of test of trend or comparison	.1907		.5047	.5047
		Number of animals reported with tumor	0	0	1	1
		Poly-3 adjusted incidence rate	0.0%	0.0%	1.8%	1.8%
		95% CI for poly-3 adjusted incidence rate (%)	(0,6.7)	(0,6.7)	(0.05,9.9)	(0.05,9.9)
		Poly-3 adjusted number of animals at risk	53.7	53.9	54.8	54.3
TESTES	LEYDIG CELL TUMOR	P-value of test of trend or comparison	.5206	.7524	.7570	.7570
		Number of animals reported with tumor	1	1	1	1
		Poly-3 adjusted incidence rate	1.9%	1.9%	1.8%	1.8%
		95% CI for poly-3 adjusted incidence rate (%)	(0.05,10.1)	(0.05,10.1)	(0.05,9.9)	(0.05,9.9)
		Poly-3 adjusted number of animals at risk	53.7	53.9	54.5	54.3
THYMUS	THYMIC LYMPHOSARCOMA	P-value of test of trend or comparison	.2559			.5094
		Number of animals reported with tumor	0	0	0	1
		Poly-3 adjusted incidence rate	0.0%	0.0%	0.0%	1.8%
		95% CI for poly-3 adjusted incidence rate (%)	(0,6.8)	(0,7.0)	(0,6.6)	(0.05,9.9)
		Poly-3 adjusted number of animals at risk	52.7	51.9	54.5	54.3
	THYMOMA: EPITHELIAL TYPE MALIGNANT	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
		Poly-3 adjusted incidence rate	1.9%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.05,10.1)	(0,7.0)	(0,6.6)	(0,6.6)
		Poly-3 adjusted number of animals at risk	53.2	51.9	54.5	54.3
	THYMOMA: LYMPHOCYTIC	P-value of test of trend or comparison	.3463	.4926	1	.5143

Table 2.7

Table of reported tumors in Rat Study
NDA 202450
Animal carcinogenicity study
Male rats

Organ or tissue name	*Tumor name*	*Quantity*	*Vehicle*	*Low dose*	*Mid dose*	*High dose*
		Number of animals reported with tumor	1	2	0	2
		Poly-3 adjusted incidence rate	1.9%	3.9%	0.0%	3.7%
		95% CI for poly-3 adjusted incidence rate (%)	(0.05,10.3)	(0.47,13.5)	(0,6.6)	(0.44,12.7)
		Poly-3 adjusted number of animals at risk	52.7	51.9	54.5	54.6
THYROID GLAND	C-CELL ADENOMA	P-value of test of trend or comparison	.9236	.9865	.9873	.9873
		Number of animals reported with tumor	5	1	1	1
		Poly-3 adjusted incidence rate	9.3%	1.9%	1.8%	1.8%
		95% CI for poly-3 adjusted incidence rate (%)	(3.08,20.7)	(0.05,10.1)	(0.05,9.9)	(0.05,9.9)
		Poly-3 adjusted number of animals at risk	53.7	53.9	54.5	54.3
	C-CELL CARCINOMA	P-value of test of trend or comparison	.5716	1	.8820	.8820
		Number of animals reported with tumor	2	0	1	1
		Poly-3 adjusted incidence rate	3.7%	0.0%	1.8%	1.8%
		95% CI for poly-3 adjusted incidence rate (%)	(0.45,13.0)	(0,6.7)	(0.05,9.9)	(0.05,9.9)
		Poly-3 adjusted number of animals at risk	54.0	53.9	54.5	54.3
	FOLLICULAR ADENOMA	P-value of test of trend or comparison	.8340	.7524	.7570	1
		Number of animals reported with tumor	1	1	1	0
		Poly-3 adjusted incidence rate	1.9%	1.9%	1.8%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.05,10.1)	(0.05,10.1)	(0.05,9.9)	(0,6.6)
		Poly-3 adjusted number of animals at risk	53.7	53.9	54.5	54.3
TONGUE	HEMANGIOSARCOMA	P-value of test of trend or comparison	.2523			.5047
		Number of animals reported with tumor	0	0	0	1
		Poly-3 adjusted incidence rate	0.0%	0.0%	0.0%	1.8%
		95% CI for poly-3 adjusted incidence rate (%)	(0,6.7)	(0,6.7)	(0,6.6)	(0.05,9.9)
		Poly-3 adjusted number of animals at risk	53.7	53.9	54.5	54.3

Table 2.8

Table of reported tumors in Rat Study
NDA 202450
Animal carcinogenicity study
Female rats
Composite endpoints

Composite endpoint	*Quantity*	*Vehicle*	*Low dose*	*Mid dose*	*High dose*
All hemangiomas	P-value of test of trend or comparison	.0605			.2476
	Number of animals reported with tumor	0	0	0	2
	Poly-3 adjusted incidence rate	0.0%	0.0%	0.0%	3.8%
	95% CI for poly-3 adjusted incidence rate (%)	(0,6.7)	(0,6.3)	(0,7.0)	(0.45,13.0)
	Poly-3 adjusted number of animals at risk	53.9	57.0	51.1	53.3
All hemangiomas and hemangiosarcomas	P-value of test of trend or comparison	.1250	1	.8714	.5000
	Number of animals reported with tumor	2	0	1	3
	Poly-3 adjusted incidence rate	3.7%	0.0%	2.0%	5.6%
	95% CI for poly-3 adjusted incidence rate (%)	(0.45,13.0)	(0,6.3)	(0.05,10.4)	(1.16,15.7)
	Poly-3 adjusted number of animals at risk	53.9	57.0	51.1	53.3
All hemangiosarcomas	P-value of test of trend or comparison	.5450	1	.8714	.8750
	Number of animals reported with tumor	2	0	1	1
	Poly-3 adjusted incidence rate	3.7%	0.0%	2.0%	1.9%
	95% CI for poly-3 adjusted incidence rate (%)	(0.45,13.0)	(0,6.3)	(0.05,10.4)	(0.05,10.3)
	Poly-3 adjusted number of animals at risk	53.9	57.0	51.1	52.4
Cholangioma and cholangiocarcinomas	P-value of test of trend or comparison	.2806	.5182	.4904	.4904
	Number of animals reported with tumor	0	1	1	1
	Poly-3 adjusted incidence rate	0.0%	1.8%	2.0%	1.9%
	95% CI for poly-3 adjusted incidence rate (%)	(0,6.7)	(0.04,9.4)	(0.05,10.4)	(0.05,10.4)
	Poly-3 adjusted number of animals at risk	53.9	57.0	51.1	51.8
Hepatocellular tumors	P-value of test of trend or comparison	1	1	1	1
	Number of animals reported with tumor	1	0	0	0
	Poly-3 adjusted incidence rate	1.9%	0.0%	0.0%	0.0%
	95% CI for poly-3 adjusted incidence rate (%)	(0.05,10.1)	(0,6.3)	(0,7.0)	(0,6.8)
	Poly-3 adjusted number of animals at risk	53.9	57.0	51.1	52.4
Mesenteric hemangiomas and hemangiosarcomas	P-value of test of trend or comparison	.7368	1	.7427	1
	Number of animals reported with tumor	1	0	1	0

Reference ID: 3087610

Table 2.8

Table of reported tumors in Rat Study
NDA 202450
Animal carcinogenicity study
Female rats
Composite endpoints

Composite endpoint	*Quantity*	*Vehicle*	*Low dose*	*Mid dose*	*High dose*
	Poly-3 adjusted incidence rate	1.9%	0.0%	2.0%	0.0%
	95% CI for poly-3 adjusted incidence rate (%)	(0.05,10.1)	(0,6.4)	(0.05,10.4)	(0,6.8)
	Poly-3 adjusted number of animals at risk	53.9	56.1	51.1	52.4
Ovarian Sertolli cell tumors	P-value of test of trend or comparison	.0459	1	1	.3017
	Number of animals reported with tumor	1	0	0	3
	Poly-3 adjusted incidence rate	1.9%	0.0%	0.0%	5.7%
	95% CI for poly-3 adjusted incidence rate (%)	(0.05,10.1)	(0,6.3)	(0,7.0)	(1.18,15.9)
	Poly-3 adjusted number of animals at risk	53.9	57.0	51.1	52.8
Uterine stromal polys and ovarian tubulostromal carcinoma	P-value of test of trend or comparison	.4962	.5654	.7830	.5904
	Number of animals reported with tumor	8	9	6	8
	Poly-3 adjusted incidence rate	15%	16%	12%	15%
	95% CI for poly-3 adjusted incidence rate (%)	(6.62,27.6)	(7.35,27.9)	(4.35,23.9)	(6.75,28.1)
	Poly-3 adjusted number of animals at risk	53.9	57.1	51.5	52.8

Reference ID: 3087610

Table 2.9

Table of reported tumors in Rat Study
NDA 202450
Animal carcinogenicity study
Male rats
Composite endpoints

Composite endpoint	*Quantity*	*Vehicle*	*Low dose*	*Mid dose*	*High dose*
All hemangiomas	P-value of test of trend or comparison	.2269	.2476	.2523	.2523
	Number of animals reported with tumor	0	2	2	2
	Poly-3 adjusted incidence rate	0.0%	3.7%	3.7%	3.7%
	95% CI for poly-3 adjusted incidence rate (%)	(0,6.7)	(0.45,13.0)	(0.44,12.7)	(0.44,12.7)
	Poly-3 adjusted number of animals at risk	53.7	53.9	54.8	54.3
All hemangiomas and hemangiosarcomas	P-value of test of trend or comparison	.1807	.0283	.2523	.0613
	Number of animals reported with tumor	0	5	2	4
	Poly-3 adjusted incidence rate	0.0%	9.3%	3.7%	7.4%
	95% CI for poly-3 adjusted incidence rate (%)	(0,6.7)	(3.08,20.7)	(0.44,12.7)	(2.02,17.9)
	Poly-3 adjusted number of animals at risk	53.7	53.9	54.8	54.3
All hemangiosarcomas	P-value of test of trend or comparison	.3090	.1214		.2523
	Number of animals reported with tumor	0	3	0	2
	Poly-3 adjusted incidence rate	0.0%	5.6%	0.0%	3.7%
	95% CI for poly-3 adjusted incidence rate (%)	(0,6.7)	(1.16,15.7)	(0,6.6)	(0.44,12.7)
	Poly-3 adjusted number of animals at risk	53.7	53.9	54.5	54.3
Hepatocellular tumors	P-value of test of trend or comparison	.9258	.8820	.8820	1
	Number of animals reported with tumor	2	1	1	0
	Poly-3 adjusted incidence rate	3.7%	1.8%	1.8%	0.0%
	95% CI for poly-3 adjusted incidence rate (%)	(0.45,13.0)	(0.05,9.9)	(0.05,9.9)	(0,6.6)
	Poly-3 adjusted number of animals at risk	53.7	54.3	54.5	54.3
Mesenteric hemangiomas and hemangiosarcomas	P-value of test of trend or comparison	.5507	.1214	.5047	.5000
	Number of animals reported with tumor	0	3	1	1
	Poly-3 adjusted incidence rate	0.0%	5.6%	1.8%	1.9%
	95% CI for poly-3 adjusted incidence rate (%)	(0,6.7)	(1.16,15.7)	(0.05,9.9)	(0.05,10.1)
	Poly-3 adjusted number of animals at risk	53.7	53.9	54.5	53.3

Reference ID: 3087610

Table 2.10

Table of tumors reported significant in at least one arm - Rat Study
NDA 202450
Animal carcinogenicity study
Female rats
Composite endpoints

Composite endpoint	*Quantity*	*Vehicle*	*Low dose*	*Mid dose*	*High dose*
Ovarian Sertolli cell tumors	P-value of test of trend or comparison	.0459	1	1	.3017
	Number of animals reported with tumor	1	0	0	3
	Poly-3 adjusted incidence rate	1.9%	0.0%	0.0%	5.7%
	95% CI for poly-3 adjusted incidence rate (%)	(0.05,10.1)	(0,6.3)	(0,7.0)	(1.18,15.9)
	Poly-3 adjusted number of animals at risk	53.9	57.0	51.1	52.8

Reference ID: 3087610

Table 2.11

Table of tumors reported significant in at least one arm - Rat Study
NDA 202450
Animal carcinogenicity study
Male rats
Composite endpoints

Composite endpoint	*Quantity*	*Vehicle*	*Low dose*	*Mid dose*	*High dose*
All hemangiomas and hemangiosarcomas	P-value of test of trend or comparison	.1807	.0283	.2523	.0613
	Number of animals reported with tumor	0	5	2	4
	Poly-3 adjusted incidence rate	0.0%	9.3%	3.7%	7.4%
	95% CI for poly-3 adjusted incidence rate (%)	(0,6.7)	(3.08,20.7)	(0.44,12.7)	(2.02,17.9)
	Poly-3 adjusted number of animals at risk	53.7	53.9	54.8	54.3

Reference ID: 3087610

Table 2.12

Tumor counts for organs reported widely unanalyzed
NDA 202450
Animal carcinogenicity study

Species and Sex	*Organ or tissue name*	*Tumor name*	*Quantity*	*Vehicle*	*Low dose*	*Mid dose*	*High dose*
Rats - Female	BODY CAVITIES	HEMANGIOSARCOMA	Number of tumors found	1	0	0	1
			Number of animals examined	5	5	11	4
Rats - Male	BODY CAVITIES	HEMANGIOSARCOMA	Number of tumors found	0	1	0	1
			Number of animals examined	5	5	4	8
		LIPOMA	Number of tumors found	0	0	0	1
			Number of animals examined	5	5	4	8
		MALIGNANT NEURINOMA	Number of tumors found	0	0	0	1
			Number of animals examined	5	5	4	8
		MESOTHELIOMA	Number of tumors found	0	1	0	0
			Number of animals examined	5	5	4	8

Reference ID: 3087610

Table 2.13

Table of reported tumors in Rat Study
NDA 202450 (vehicle study)
Animal carcinogenicity study
Female rats

Organ or tissue name	*Tumor name*	*Quantity*	*Air*	*Vehicle*
ADRENAL MEDULLAS	PHEOCHROMOCYTOMA: MALIGNANT	P-value of test of comparison		.5000
		Number of animals reported with tumor	0	1
		Poly-3 adjusted incidence rate	0.0%	1.9%
		95% CI for poly-3 adjusted incidence rate (%)	(0,6.7)	(0.05,10.1)
		Poly-3 adjusted number of animals at risk	53.2	53.2
BRAIN	GRANULAR CELL TUMOR	P-value of test of comparison		.5000
		Number of animals reported with tumor	0	1
		Poly-3 adjusted incidence rate	0.0%	1.9%
		95% CI for poly-3 adjusted incidence rate (%)	(0,6.7)	(0.05,10.1)
		Poly-3 adjusted number of animals at risk	53.2	53.9
CEREBELLUM	GRANULAR CELL TUMOR	P-value of test of comparison		.5000
		Number of animals reported with tumor	0	1
		Poly-3 adjusted incidence rate	0.0%	1.9%
		95% CI for poly-3 adjusted incidence rate (%)	(0,6.7)	(0.05,10.1)
		Poly-3 adjusted number of animals at risk	53.2	53.9
CERVIX	GRANULAR CELL TUMOR	P-value of test of comparison		1
		Number of animals reported with tumor	1	0
		Poly-3 adjusted incidence rate	1.9%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.05,10.1)	(0,6.7)
		Poly-3 adjusted number of animals at risk	53.2	53.9
	LEIOMYOMA	P-value of test of comparison		1
		Number of animals reported with tumor	1	0
		Poly-3 adjusted incidence rate	1.9%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.05,10.1)	(0,6.7)
		Poly-3 adjusted number of animals at risk	53.2	53.9
HEMOLYMPHORET. SYS	MALIGNANT LYMPHOMA	P-value of test of comparison		1
		Number of animals reported with tumor	1	0
		Poly-3 adjusted incidence rate	1.9%	0.0%

Reference ID: 3087610

Table 2.13

Table of reported tumors in Rat Study
NDA 202450 (vehicle study)
Animal carcinogenicity study
Female rats

Organ or tissue name	*Tumor name*	*Quantity*	*Air*	*Vehicle*
		95% CI for poly-3 adjusted incidence rate (%)	(0.05,10.1)	(0,6.7)
		Poly-3 adjusted number of animals at risk	54.0	53.9
KIDNEYS	NEPHROBLASTOMA	P-value of test of comparison		.5047
		Number of animals reported with tumor	0	1
		Poly-3 adjusted incidence rate	0.0%	1.8%
		95% CI for poly-3 adjusted incidence rate (%)	(0,6.7)	(0.05,9.9)
		Poly-3 adjusted number of animals at risk	53.2	54.8
LIVER	HEPATOCELLULAR ADENOMA	P-value of test of comparison		.8786
		Number of animals reported with tumor	2	1
		Poly-3 adjusted incidence rate	3.8%	1.9%
		95% CI for poly-3 adjusted incidence rate (%)	(0.45,13.0)	(0.05,10.1)
		Poly-3 adjusted number of animals at risk	53.2	53.9
MAMMARY GLAND	ADENOCARCINOMA	P-value of test of comparison		.0624
		Number of animals reported with tumor	1	6
		Poly-3 adjusted incidence rate	1.9%	11%
		95% CI for poly-3 adjusted incidence rate (%)	(0.05,10.1)	(4.03,22.2)
		Poly-3 adjusted number of animals at risk	53.6	55.1
	FIBROADENOMA	P-value of test of comparison		.0136
		Number of animals reported with tumor	5	15
		Poly-3 adjusted incidence rate	9.3%	27%
		95% CI for poly-3 adjusted incidence rate (%)	(3.02,20.3)	(15.8,41.0)
		Poly-3 adjusted number of animals at risk	54.0	55.5
MESENT. LYMPH NODE	HEMANGIOSARCOMA	P-value of test of comparison		.5000
		Number of animals reported with tumor	0	1
		Poly-3 adjusted incidence rate	0.0%	1.9%
		95% CI for poly-3 adjusted incidence rate (%)	(0,6.7)	(0.05,10.1)
		Poly-3 adjusted number of animals at risk	53.2	53.9
OVARIES	GRANULOSA CELL TUMOR	P-value of test of comparison		.2476

Reference ID: 3087610

Table 2.13

Table of reported tumors in Rat Study
NDA 202450 (vehicle study)
Animal carcinogenicity study
Female rats

Organ or tissue name	*Tumor name*	*Quantity*	*Air*	*Vehicle*
		Number of animals reported with tumor	0	2
		Poly-3 adjusted incidence rate	0.0%	3.7%
		95% CI for poly-3 adjusted incidence rate (%)	(0,6.7)	(0.45,13.0)
		Poly-3 adjusted number of animals at risk	53.2	53.9
	GRANULOSA CELL TUMOR MALIGNANT	P-value of test of comparison		.2476
		Number of animals reported with tumor	0	2
		Poly-3 adjusted incidence rate	0.0%	3.7%
		95% CI for poly-3 adjusted incidence rate (%)	(0,6.7)	(0.45,13.0)
		Poly-3 adjusted number of animals at risk	53.2	53.9
	SERTOLI CELL TUMOR	P-value of test of comparison		.5000
		Number of animals reported with tumor	0	1
		Poly-3 adjusted incidence rate	0.0%	1.9%
		95% CI for poly-3 adjusted incidence rate (%)	(0,6.7)	(0.05,10.1)
		Poly-3 adjusted number of animals at risk	53.2	53.9
PITUITARY GLAND	ADENOMA: PARS ANTERIOR	P-value of test of comparison		.7131
		Number of animals reported with tumor	31	29
		Poly-3 adjusted incidence rate	54%	51%
		95% CI for poly-3 adjusted incidence rate (%)	(39.9,67.6)	(36.6,64.4)
		Poly-3 adjusted number of animals at risk	57.8	57.1
SKIN/SUBCUTIS	COMPOUND ODONTOMA	P-value of test of comparison		1
		Number of animals reported with tumor	1	0
		Poly-3 adjusted incidence rate	1.9%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.05,10.1)	(0,6.7)
		Poly-3 adjusted number of animals at risk	54.0	53.9
	SQUAMOUS CELL CARCINOMA	P-value of test of comparison		1
		Number of animals reported with tumor	1	0
		Poly-3 adjusted incidence rate	1.9%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.05,10.1)	(0,6.7)

Reference ID: 3087610

Table 2.13

Table of reported tumors in Rat Study
NDA 202450 (vehicle study)
Animal carcinogenicity study
Female rats

Organ or tissue name	*Tumor name*	*Quantity*	*Air*	*Vehicle*
		Poly-3 adjusted number of animals at risk	53.4	53.9
SUBLINGUAL GLANDS	ADENOMA	P-value of test of comparison		1
		Number of animals reported with tumor	1	0
		Poly-3 adjusted incidence rate	2.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.05,10.4)	(0,6.8)
		Poly-3 adjusted number of animals at risk	51.2	52.5
THYMUS	THYMOMA: LYMPHOCYTIC	P-value of test of comparison		.7815
		Number of animals reported with tumor	4	3
		Poly-3 adjusted incidence rate	7.5%	5.6%
		95% CI for poly-3 adjusted incidence rate (%)	(2.06,18.2)	(1.16,15.7)
		Poly-3 adjusted number of animals at risk	53.1	53.7
THYROID GLAND	C-CELL ADENOMA	P-value of test of comparison		.5000
		Number of animals reported with tumor	2	3
		Poly-3 adjusted incidence rate	3.8%	5.6%
		95% CI for poly-3 adjusted incidence rate (%)	(0.45,13.0)	(1.16,15.7)
		Poly-3 adjusted number of animals at risk	53.2	53.9
	FOLLICULAR ADENOMA	P-value of test of comparison		.2523
		Number of animals reported with tumor	0	2
		Poly-3 adjusted incidence rate	0.0%	3.7%
		95% CI for poly-3 adjusted incidence rate (%)	(0,6.7)	(0.44,12.7)
		Poly-3 adjusted number of animals at risk	53.2	54.3
	FOLLICULAR CARCINOMA	P-value of test of comparison		.7524
		Number of animals reported with tumor	1	1
		Poly-3 adjusted incidence rate	1.9%	1.9%
		95% CI for poly-3 adjusted incidence rate (%)	(0.05,10.1)	(0.05,10.1)
		Poly-3 adjusted number of animals at risk	53.2	53.9
UTERUS	ADENOCARCINOMA	P-value of test of comparison		.7524
		Number of animals reported with tumor	1	1

Reference ID: 3087610

Table 2.13

Table of reported tumors in Rat Study
NDA 202450 (vehicle study)
Animal carcinogenicity study
Female rats

Organ or tissue name	*Tumor name*	*Quantity*	*Air*	*Vehicle*
		Poly-3 adjusted incidence rate	1.9%	1.9%
		95% CI for poly-3 adjusted incidence rate (%)	(0.05,10.1)	(0.05,10.1)
		Poly-3 adjusted number of animals at risk	53.2	53.9
	ADENOMA	P-value of test of comparison		1
		Number of animals reported with tumor	2	0
		Poly-3 adjusted incidence rate	3.8%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.45,13.0)	(0,6.7)
		Poly-3 adjusted number of animals at risk	53.2	53.9
	LEIMYOSARCOMA	P-value of test of comparison		.5047
		Number of animals reported with tumor	0	1
		Poly-3 adjusted incidence rate	0.0%	1.8%
		95% CI for poly-3 adjusted incidence rate (%)	(0,6.7)	(0.05,9.9)
		Poly-3 adjusted number of animals at risk	53.2	54.3
	STROMAL POLYP	P-value of test of comparison		.1006
		Number of animals reported with tumor	3	8
		Poly-3 adjusted incidence rate	5.6%	15%
		95% CI for poly-3 adjusted incidence rate (%)	(1.16,15.7)	(6.62,27.6)
		Poly-3 adjusted number of animals at risk	53.2	53.9

Reference ID: 3087610

Table 2.14

Table of reported tumors in Rat Study
NDA 202450 (vehicle study)
Animal carcinogenicity study
Male rats

Organ or tissue name	*Tumor name*	*Quantity*	*Air*	*Vehicle*
ADRENAL CORTICES	ADENOMA	P-value of test of comparison		1
		Number of animals reported with tumor	1	0
		Poly-3 adjusted incidence rate	1.9%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.05,10.3)	(0,6.7)
		Poly-3 adjusted number of animals at risk	52.2	53.7
ADRENAL MEDULLAS	GANGLIONEUROMA	P-value of test of comparison		1
		Number of animals reported with tumor	1	0
		Poly-3 adjusted incidence rate	1.9%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.05,10.3)	(0,6.7)
		Poly-3 adjusted number of animals at risk	52.5	53.7
	PHEOCHROMOCYTOMA: BENIGN	P-value of test of comparison		1
		Number of animals reported with tumor	1	0
		Poly-3 adjusted incidence rate	1.9%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.05,10.3)	(0,6.7)
		Poly-3 adjusted number of animals at risk	52.2	53.7
BRAIN STEM	ASTROCYTOMA	P-value of test of comparison		.5048
		Number of animals reported with tumor	0	1
		Poly-3 adjusted incidence rate	0.0%	1.9%
		95% CI for poly-3 adjusted incidence rate (%)	(0,6.8)	(0.05,10.1)
		Poly-3 adjusted number of animals at risk	52.2	53.7
HEMOLYMPHORET. SYS	HISTIOCYTIC SARCOMA	P-value of test of comparison		.5048
		Number of animals reported with tumor	0	1
		Poly-3 adjusted incidence rate	0.0%	1.9%
		95% CI for poly-3 adjusted incidence rate (%)	(0,6.8)	(0.05,10.1)
		Poly-3 adjusted number of animals at risk	52.2	53.8
	MALIGNANT LYMPHOMA	P-value of test of comparison		.5177
		Number of animals reported with tumor	2	3
		Poly-3 adjusted incidence rate	3.7%	5.4%

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Table 2.14

Table of reported tumors in Rat Study
NDA 202450 (vehicle study)
Animal carcinogenicity study
Male rats

Organ or tissue name	*Tumor name*	*Quantity*	*Air*	*Vehicle*
		95% CI for poly-3 adjusted incidence rate (%)	(0.45,13.0)	(1.12,15.1)
		Poly-3 adjusted number of animals at risk	53.4	55.6
LIVER	HEPATOCELLULAR ADENOMA	P-value of test of comparison		.8821
		Number of animals reported with tumor	2	1
		Poly-3 adjusted incidence rate	3.8%	1.9%
		95% CI for poly-3 adjusted incidence rate (%)	(0.46,13.2)	(0.05,10.1)
		Poly-3 adjusted number of animals at risk	52.5	53.7
	HEPATOCELLULAR CARCINOMA	P-value of test of comparison		.7571
		Number of animals reported with tumor	1	1
		Poly-3 adjusted incidence rate	1.9%	1.9%
		95% CI for poly-3 adjusted incidence rate (%)	(0.05,10.3)	(0.05,10.1)
		Poly-3 adjusted number of animals at risk	52.2	53.7
MANDIB.LYMPH NODES	LIPOSARCOMA	P-value of test of comparison		.5048
		Number of animals reported with tumor	0	1
		Poly-3 adjusted incidence rate	0.0%	1.9%
		95% CI for poly-3 adjusted incidence rate (%)	(0,6.8)	(0.05,10.1)
		Poly-3 adjusted number of animals at risk	52.2	53.7
MESENT. LYMPH NODE	HEMANGIOSARCOMA	P-value of test of comparison		1
		Number of animals reported with tumor	3	0
		Poly-3 adjusted incidence rate	5.7%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(1.18,15.9)	(0,6.7)
		Poly-3 adjusted number of animals at risk	52.5	53.7
PANCREAS	ISLET CELL ADENOMA	P-value of test of comparison		.9434
		Number of animals reported with tumor	3	1
		Poly-3 adjusted incidence rate	5.7%	1.9%
		95% CI for poly-3 adjusted incidence rate (%)	(1.18,15.9)	(0.05,10.1)
		Poly-3 adjusted number of animals at risk	52.3	53.7
	ISLET CELL CARCINOMA	P-value of test of comparison		.6983

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Table 2.14

Table of reported tumors in Rat Study
NDA 202450 (vehicle study)
Animal carcinogenicity study
Male rats

Organ or tissue name	*Tumor name*	*Quantity*	*Air*	*Vehicle*
		Number of animals reported with tumor	2	2
		Poly-3 adjusted incidence rate	3.8%	3.7%
		95% CI for poly-3 adjusted incidence rate (%)	(0.46,13.2)	(0.45,13.0)
		Poly-3 adjusted number of animals at risk	52.3	53.7
PARATHYROID GLANDS	ADENOMA	P-value of test of comparison		.5169
		Number of animals reported with tumor	0	1
		Poly-3 adjusted incidence rate	0.0%	2.2%
		95% CI for poly-3 adjusted incidence rate (%)	(0,8.2)	(0.05,11.5)
		Poly-3 adjusted number of animals at risk	43.2	46.5
PITUITARY GLAND	ADENOMA: PARS ANTERIOR	P-value of test of comparison		.7740
		Number of animals reported with tumor	19	16
		Poly-3 adjusted incidence rate	34%	29%
		95% CI for poly-3 adjusted incidence rate (%)	(21.4,47.8)	(17.3,42.9)
		Poly-3 adjusted number of animals at risk	56.0	55.3
	ADENOMA: PARS INTERMEDIA	P-value of test of comparison		.5000
		Number of animals reported with tumor	0	1
		Poly-3 adjusted incidence rate	0.0%	1.9%
		95% CI for poly-3 adjusted incidence rate (%)	(0,6.8)	(0.05,10.3)
		Poly-3 adjusted number of animals at risk	52.2	52.7
SKIN/SUBCUTIS	BASAL CELL CARCINOMA	P-value of test of comparison		1
		Number of animals reported with tumor	1	0
		Poly-3 adjusted incidence rate	1.9%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.05,10.1)	(0,6.7)
		Poly-3 adjusted number of animals at risk	53.0	53.7
	FIBROMA	P-value of test of comparison		.5091
		Number of animals reported with tumor	2	3
		Poly-3 adjusted incidence rate	3.8%	5.6%
		95% CI for poly-3 adjusted incidence rate (%)	(0.46,13.2)	(1.16,15.7)

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Table 2.14

Table of reported tumors in Rat Study
NDA 202450 (vehicle study)
Animal carcinogenicity study
Male rats

Organ or tissue name	*Tumor name*	*Quantity*	*Air*	*Vehicle*
		Poly-3 adjusted number of animals at risk	52.4	53.8
	KERATOACANTHOMA	P-value of test of comparison		.9018
		Number of animals reported with tumor	4	2
		Poly-3 adjusted incidence rate	7.7%	3.7%
		95% CI for poly-3 adjusted incidence rate (%)	(2.09,18.5)	(0.45,13.0)
		Poly-3 adjusted number of animals at risk	52.2	53.7
	LIPOMA	P-value of test of comparison		.5048
		Number of animals reported with tumor	0	1
		Poly-3 adjusted incidence rate	0.0%	1.9%
		95% CI for poly-3 adjusted incidence rate (%)	(0,6.8)	(0.05,10.1)
		Poly-3 adjusted number of animals at risk	52.2	53.7
	MALIGNANT SCHWANNOMA	P-value of test of comparison		.5048
		Number of animals reported with tumor	0	1
		Poly-3 adjusted incidence rate	0.0%	1.9%
		95% CI for poly-3 adjusted incidence rate (%)	(0,6.8)	(0.05,10.1)
		Poly-3 adjusted number of animals at risk	52.2	53.7
	PAPILLOMA	P-value of test of comparison		1
		Number of animals reported with tumor	1	0
		Poly-3 adjusted incidence rate	1.9%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.05,10.3)	(0,6.7)
		Poly-3 adjusted number of animals at risk	52.2	53.7
	RHABDOMYOSARCOMA	P-value of test of comparison		1
		Number of animals reported with tumor	1	0
		Poly-3 adjusted incidence rate	1.9%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.05,10.1)	(0,6.7)
		Poly-3 adjusted number of animals at risk	53.1	53.7
	SARCOMA	P-value of test of comparison		1

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Table 2.14

Table of reported tumors in Rat Study
NDA 202450 (vehicle study)
Animal carcinogenicity study
Male rats

Organ or tissue name	*Tumor name*	*Quantity*	*Air*	*Vehicle*
		Number of animals reported with tumor	1	0
		Poly-3 adjusted incidence rate	1.9%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.05,10.3)	(0,6.7)
		Poly-3 adjusted number of animals at risk	53.0	53.7
TESTES	LEYDIG CELL TUMOR	P-value of test of comparison		.8821
		Number of animals reported with tumor	2	1
		Poly-3 adjusted incidence rate	3.8%	1.9%
		95% CI for poly-3 adjusted incidence rate (%)	(0.46,13.2)	(0.05,10.1)
		Poly-3 adjusted number of animals at risk	52.2	53.7
THYMUS	THYMOMA: EPITHELIAL TYPE MALIGNANT	P-value of test of comparison		.5096
		Number of animals reported with tumor	0	1
		Poly-3 adjusted incidence rate	0.0%	1.9%
		95% CI for poly-3 adjusted incidence rate (%)	(0,7.0)	(0.05,10.1)
		Poly-3 adjusted number of animals at risk	51.6	53.2
	THYMOMA: LYMPHOCYTIC	P-value of test of comparison		.9435
		Number of animals reported with tumor	3	1
		Poly-3 adjusted incidence rate	5.8%	1.9%
		95% CI for poly-3 adjusted incidence rate (%)	(1.21,16.2)	(0.05,10.3)
		Poly-3 adjusted number of animals at risk	51.9	52.7
THYROID GLAND	C-CELL ADENOMA	P-value of test of comparison		.7480
		Number of animals reported with tumor	6	5
		Poly-3 adjusted incidence rate	11%	9.3%
		95% CI for poly-3 adjusted incidence rate (%)	(4.27,23.4)	(3.08,20.7)
		Poly-3 adjusted number of animals at risk	52.6	53.7
	C-CELL CARCINOMA	P-value of test of comparison		.5072
		Number of animals reported with tumor	1	2
		Poly-3 adjusted incidence rate	1.9%	3.7%

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Table 2.14

Table of reported tumors in Rat Study
NDA 202450 (vehicle study)
Animal carcinogenicity study
Male rats

Organ or tissue name	*Tumor name*	*Quantity*	*Air*	*Vehicle*
		95% CI for poly-3 adjusted incidence rate (%)	(0.05,10.3)	(0.45,13.0)
		Poly-3 adjusted number of animals at risk	52.2	54.0
	FOLLICULAR ADENOMA	P-value of test of comparison		.7571
		Number of animals reported with tumor	1	1
		Poly-3 adjusted incidence rate	1.9%	1.9%
		95% CI for poly-3 adjusted incidence rate (%)	(0.05,10.3)	(0.05,10.1)
		Poly-3 adjusted number of animals at risk	52.2	53.7
TONGUE	SQUAMOUS CARCINOMA	P-value of test of comparison		1
		Number of animals reported with tumor	1	0
		Poly-3 adjusted incidence rate	1.9%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.05,10.3)	(0,6.7)
		Poly-3 adjusted number of animals at risk	52.2	53.7

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Table 2.15

Table of reported tumors in Rat Study
NDA 202450 (vehicle study)
Animal carcinogenicity study
Female rats
Composite endpoints

Composite endpoint	*Quantity*	*Air*	*Vehicle*
All hemangiomas and hemangiosarcomas	P-value of test of comparison		.2476
	Number of animals reported with tumor	0	2
	Poly-3 adjusted incidence rate	0.0%	3.7%
	95% CI for poly-3 adjusted incidence rate (%)	(0,6.7)	(0.45,13.0)
	Poly-3 adjusted number of animals at risk	53.2	53.9
All hemangiosarcomas	P-value of test of comparison		.2476
	Number of animals reported with tumor	0	2
	Poly-3 adjusted incidence rate	0.0%	3.7%
	95% CI for poly-3 adjusted incidence rate (%)	(0,6.7)	(0.45,13.0)
	Poly-3 adjusted number of animals at risk	53.2	53.9
Hepatocellular tumors	P-value of test of comparison		.8786
	Number of animals reported with tumor	2	1
	Poly-3 adjusted incidence rate	3.8%	1.9%
	95% CI for poly-3 adjusted incidence rate (%)	(0.45,13.0)	(0.05,10.1)
	Poly-3 adjusted number of animals at risk	53.2	53.9
Mesenteric hemangiomas and hemangiosarcomas	P-value of test of comparison		.5000
	Number of animals reported with tumor	0	1
	Poly-3 adjusted incidence rate	0.0%	1.9%
	95% CI for poly-3 adjusted incidence rate (%)	(0,6.7)	(0.05,10.1)
	Poly-3 adjusted number of animals at risk	53.2	53.9
Ovarian Sertolli cell tumors	P-value of test of comparison		.5000
	Number of animals reported with tumor	0	1
	Poly-3 adjusted incidence rate	0.0%	1.9%
	95% CI for poly-3 adjusted incidence rate (%)	(0,6.7)	(0.05,10.1)
	Poly-3 adjusted number of animals at risk	53.2	53.9
Uterine stromal polys and ovarian tubulostromal carcinoma	P-value of test of comparison		.1006
	Number of animals reported with tumor	3	8

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Table 2.15

Table of reported tumors in Rat Study
NDA 202450 (vehicle study)
Animal carcinogenicity study
Female rats
Composite endpoints

Composite endpoint	*Quantity*	*Air*	*Vehicle*
	Poly-3 adjusted incidence rate	5.6%	15%
	95% CI for poly-3 adjusted incidence rate (%)	(1.16,15.7)	(6.62,27.6)
	Poly-3 adjusted number of animals at risk	53.2	53.9

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Table 2.16

Table of reported tumors in Rat Study
NDA 202450 (vehicle study)
Animal carcinogenicity study
Male rats
Composite endpoints

Composite endpoint	*Quantity*	*Air*	*Vehicle*
All hemangiomas and hemangiosarcomas	P-value of test of comparison		1
	Number of animals reported with tumor	3	0
	Poly-3 adjusted incidence rate	5.7%	0.0%
	95% CI for poly-3 adjusted incidence rate (%)	(1.18,15.9)	(0,6.7)
	Poly-3 adjusted number of animals at risk	52.5	53.7
All hemangiosarcomas	P-value of test of comparison		1
	Number of animals reported with tumor	3	0
	Poly-3 adjusted incidence rate	5.7%	0.0%
	95% CI for poly-3 adjusted incidence rate (%)	(1.18,15.9)	(0,6.7)
	Poly-3 adjusted number of animals at risk	52.5	53.7
Hepatocellular tumors	P-value of test of comparison		.8245
	Number of animals reported with tumor	3	2
	Poly-3 adjusted incidence rate	5.7%	3.7%
	95% CI for poly-3 adjusted incidence rate (%)	(1.18,15.9)	(0.45,13.0)
	Poly-3 adjusted number of animals at risk	52.5	53.7
Mesenteric hemangiomas and hemangiosarcomas	P-value of test of comparison		1
	Number of animals reported with tumor	3	0
	Poly-3 adjusted incidence rate	5.7%	0.0%
	95% CI for poly-3 adjusted incidence rate (%)	(1.18,15.9)	(0,6.7)
	Poly-3 adjusted number of animals at risk	52.5	53.7

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Table 2.17

Table of tumors reported significant in at least one arm - Rat Study
NDA 202450 (vehicle study)
Animal carcinogenicity study
Female rats

Organ or tissue name	*Tumor name*	*Quantity*	*Air*	*Vehicle*
MAMMARY GLAND	FIBROADENOMA	P-value of test of comparison		.0136
		Number of animals reported with tumor	5	15
		Poly-3 adjusted incidence rate	9.3%	27%
		95% CI for poly-3 adjusted incidence rate (%)	(3.02,20.3)	(15.8,41.0)
		Poly-3 adjusted number of animals at risk	54.0	55.5

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Table 2.18

Organs reported as unexamined
NDA 202450
Animal carcinogenicity study
Female Rats

Organ or tissue name	Vehicle(count)	Vehicle(%)	Low dose(count)	Low dose(%)	Mid dose(count)	Mid dose(%)	High dose(count)	High dose(%)	Total(count)	Total(%)
ADRENAL CORTICES	.	.	.	.	.	.	1	1.7%	1	0.4%
ADRENAL MEDULLAS	1	1.7%	2	3.3%	.	.	1	1.7%	4	1.7%
BODY CAVITIES	55	92%	55	92%	49	82%	56	93%	215	90%
CERVIX	.	.	.	.	.	.	1	1.7%	1	0.4%
CLITORAL GLANDS	2	3.3%	1	1.7%	1	1.7%	2	3.3%	6	2.5%
JEJUNUM	.	.	.	.	.	.	1	1.7%	1	0.4%
KIDNEYS	.	.	.	.	.	.	1	1.7%	1	0.4%
LIVER	.	.	.	.	.	.	1	1.7%	1	0.4%
MANDIB.LYMPH NODES	2	3.3%	.	.	.	.	.	.	2	0.8%
MESENT. LYMPH NODE	.	.	1	1.7%	.	.	1	1.7%	2	0.8%
OVARIES	.	.	.	.	.	.	1	1.7%	1	0.4%
PANCREAS	1	1.7%	.	.	.	.	2	3.3%	3	1.3%
PARATHYROID GLANDS	9	15%	13	22%	10	17%	12	20%	44	18%
SPLEEN	.	.	.	.	.	.	1	1.7%	1	0.4%
SUBLINGUAL GLANDS	2	3.3%	1	1.7%	.	.	.	.	3	1.3%
THYMUS	1	1.7%	1	1.7%	1	1.7%	3	5.0%	6	2.5%
TONGUE	.	.	.	.	.	.	1	1.7%	1	0.4%
UTERUS	.	.	.	.	.	.	1	1.7%	1	0.4%
VAGINA	.	.	.	.	.	.	1	1.7%	1	0.4%

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Table 2.19

Organs reported as unexamined
NDA 202450
Animal carcinogenicity study
Male Rats

Organ or tissue name	Vehicle(count)	Vehicle(%)	Low dose(count)	Low dose(%)	Mid dose(count)	Mid dose(%)	High dose(count)	High dose(%)	Total(count)	Total(%)
ADRENAL MEDULLAS	.	.	.	.	1	1.7%	.	.	1	0.4%
BODY CAVITIES	55	92%	55	92%	56	93%	52	87%	218	91%
MAMMARY GLAND	60	100%	60	100%	60	100%	60	100%	240	100%
MANDIB.LYMPH NODES	1	1.7%	1	1.7%	.	.	1	1.7%	3	1.3%
MESENT. LYMPH NODE	.	.	.	.	.	.	1	1.7%	1	0.4%
PARATHYROID GLANDS	10	17%	15	25%	8	13%	10	17%	43	18%
PITUITARY GLAND	1	1.7%	.	.	1	1.7%	.	.	2	0.8%
SUBLINGUAL GLANDS	3	5.0%	2	3.3%	2	3.3%	.	.	7	2.9%
THYMUS	1	1.7%	2	3.3%	.	.	.	.	3	1.3%

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Chapter 3

Assessment of the validity of a negative study

3.1 Issues of concern when selecting the dose levels

The selection of an appropriate dose level for the high dose group is made difficult by the need to satisfy two competing imperatives: on the one hand, if the dose level is insufficiently high, then genuine carcinogenic effects may not be apparent, but on the other hand, if the dose level is too high, then there is a risk of non-carcinogenic toxic effects killing the animals before they have a chance to demonstrate a carcinogenicity effect.

Haseman [4] suggested that a satisfactory balance between these two imperatives has been found when the following two conditions are both satisfied:

1. Were enough animals exposed, for a sustained amount of time, to the risk of late developing tumors?

2. Were dose levels high enough to pose a reasonable tumor challenge to the animals?

There is no consensus among experts regarding the number of animals and length of time at risk, although most carcinogenicity studies are designed to run for two years with fifty animals per treatment group. The following are some rules of thumb regarding these two issues as suggested by experts in this field:

Haseman [4] has done an investigation on the first issue. He gathered data from 21 studies using Fischer 344 rats and B6C3Fl mice conducted at the National Toxicology Program (NTP). It was found that, on the average, approximately 50% of the animals in the high dose group survived the two year study period. Also, in a personal communication with Dr. Karl Lin of Division of Biometrics-6, Haseman suggested that, as a rule of thumb, a 50% survival of 50 initial animals or 20 to 30 animals still alive in the high dose group, between weeks 80—90, would be considered as a sufficient number and adequate exposure. In addition Chu, Cueto and Ward [3], suggested that "to be considered adequate, an experiment that has not shown a chemical to be carcinogenic should have groups of animals with greater than 50% survival at one year."

It appears, from these three sources that the proportions of survival at 52 weeks, 80–90 weeks, and two years are of interest in determining the adequacy of exposure and number of animals at risk.

Regarding the question of adequate dose levels, it is generally accepted that the high dose should be close to the maximum tolerated dose (MTD). In the paper of Chu, Cueto and Ward [3], the following criteria are mentioned for dose adequacy. A high dose is considered as close to MTD if any of the criteria is met:

1. A dose is considered adequate if there is a detectable loss in weight gain of up to 10% in a dosed group relative to the controls.

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2. The administered dose is also considered an MTD if dosed animals exhibit clinical signs or severe histopathologic toxic effects attributed to the chemical.

3. In addition, doses are considered adequate if the dosed animals show a slight increased mortality compared to the controls.

3.2 Assessment of the validity of the mouse study

3.2.1 LAS 34273 study

Since the mouse study is a negative study, it follows that it is appropriate to consider whether, retrospectively, the study can be viewed as having posed a suitable tumor challenge to the animals, without having caused excessive toxic effects.

With the exception of the low dose male group, each dose group (male and female) had at least 49 (82%) animals still alive after 90 weeks. Therefore, toxicity related mortality was low enough that we can be comfortable that the dose levels were not excessive.

There is no evidence of a dose related reduction in survival in either male or female mice. However, there is clear evidence of a dose related reduction in weight gain (see table 3.1). It follows that the dose levels were sufficiently high that the animals did indeed face an appropriately high tumor challenge.

Table 3.1: Weight changes by group (mice)

Sex	Vehicle control			LAS 34273					
	Δ_{C_A}	Δ_{C_V}	$\frac{\Delta_L}{\Delta_{C_V}} - 1$	Δ_L	$\frac{\Delta_L}{\Delta_{C_V}} - 1$	Δ_M	$\frac{\Delta_M}{\Delta_{C_V}} - 1$	Δ_H	$\frac{\Delta_H}{\Delta_{C_V}} - 1$
Female	15.4	13.8	−10.4%	12.9	−6.5%	12.0	−13.0%	11.3	−15.2%
Male	16.1	16.1	+0.0%	15.2	−5.6%	14.1	−12.4%	13.2	−18.0%

3.3 Assessment of the validity of the rat study

The rat study is also a negative study, so again, it is appropriate to consider whether the dose levels were suitable. Survival rates at 90 weeks (see table 2.1) are 85% or above in both male and female vehicle control groups, and in all treated groups except for the female mid dose group (where it is 78%). There is thus no reason to worry about excsssive mortality.

Again, there is no sign of dose related mortality. However, there is clear evidence of a dose related reduction in weight gain (see table 3.2), so we may once again be comfortable with the dose selection.

Table 3.2: Weight changes by group (rats)

Sex	Vehicle control			LAS 34273					
	Δ_{C_A}	Δ_{C_V}	$\frac{\Delta_L}{\Delta_{C_V}} - 1$	Δ_L	$\frac{\Delta_L}{\Delta_{C_V}} - 1$	Δ_M	$\frac{\Delta_M}{\Delta_{C_V}} - 1$	Δ_H	$\frac{\Delta_H}{\Delta_{C_V}} - 1$
Female	263.1	267.0	+1.5%	239.2	−10.4%	246.3	−7.8%	230.6	−13.6%
Male	507.5	498.3	−1.8%	431.3	−13.4%	405.5	−18.6%	394.6	−20.8%

Chapter 4

Conclusions

4.1 Mouse study

Both the main study of LAS 34273 and the vehicle study are negative studies.

The only result worthy of continued consideration is for hepatocellular carcinomas in female mice (LAS 34273 study). The comparison between the high dose and vehicle control group is significant for rare tumors, although the test of trend is not. No cases of such tumors were reported in the vehicle control group, meaning that these tumors should be considered rare, although the fact that there were two cases in the air control group leads one to the conclusion that hepatocellular carcinomas should instead be considered common. This is therefore not considered a positive finding, but the evidence is nonethelss strongly suggestive.

Dosing seems to have been appropriate: large numbers of animals lived to the ninetieth week, and while there was no sign of a dose related increase in mortality, there was a clear indication of a dose related reduction in weight gain.

The number of animals for which the parathyroid or gall bladder (or thymus, in the case of male mice) were not examined is sufficiently high that negative results for these organs should be treated with less weight than is customary.

4.2 Rat study

Both the main study, of LAS 34273 , and the vehicle study are negative studies.

The only result worthy of further consideration is the result for mammary fibroadenomas in female vehicle control rats, compared with female air control rats. The test is not significant for common tumors, but the p-value (0.0136) is close to the threshold for significance. Furthermore, the fact that fifteen female vehicle control rats developed such tumors, compared with just five female air control rats is hard to disregard. It should also be remembered that unlike the situation with the LAS 34273 study, no attempt has been made to make the vehicle dose as close to the MTD as possibe. This test should therefore be consided to have less power than the LAS 34273 study, which in turn suggests that this near-significant result be given more weight than usual. In light of these observations, the fact that the male rats did not have their mammary glands examined is deeply regretable.

Dosing seems to have been appropriate: large numbers of animals lived to the ninetieth week, and while there was no sign of a dose related increase in mortality, there was a clear indication of a dose related reduction in weight gain.

Reference ID: 3087610

Bibliography

[1] A J Bailer and C J Portier. Effects of treatment-induced mortality and tumor-induced mortality on tests for carcinogenicity in small samples. *Biometrics*, 44(2):417–31, 1988.

[2] G S Bieler and R L Williams. Ratio estimates, the delta method, and quantal response tests for increased carcinogenicity. *Biometrics*, 49(3):793–801, 1993.

[3] KC Chu, C Cueto, and JM Ward. Factors in the evaluation of 200 National Cancer Institute carcinogen bioassays. *Journal of toxicology and environmental health*, 8(1-2):251–280, 1981.

[4] J K Haseman. A reexamination of false-positive rates carcinogenesis studies. *Fundamental and applied toxicology*, 3(4):334–339, 1983.

[5] K K Lin and M A Rahman. Overall false positive rates in tests for linear trend in tumor incidence in animal carcinogenicity studies of new drugs. *J Biopharm Stat*, 8(1):1–15; discussion 17–22, 1998.

[6] R Peto, M C Pike, N E Day, R G Gray, P N Lee, S Parish, J Peto, S Richards, and J Wahrendorf. Guidelines for simple, sensitive significance tests for carcinogenic effects in long-term animal experiments. *IARC Monogr Eval Carcinog Risk Chem Hum Suppl*, NIL(2 Suppl):311–426, 1980.

[7] M A Rahman and K K Lin. A comparison of false positive rates of peto and poly-3 methods for long-term carcinogenicity data analysis using multiple comparison adjustment method suggested by Lin and Rahman. *J Biopharm Stat*, 18(5):949–58, 2008.

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/s/

MATTHEW T JACKSON
02/14/2012

KARL K LIN
02/15/2012
Concur with review

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

Statistical Review and Evaluation

CLINICAL STUDIES

NDA/Serial Number:	202-450/S000 (Cross references: IND 68653)
Drug Name:	Aclidinium Bromide, Inhalation Powder
Indication(s):	Long-term maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema.
Applicant:	Forest Laboratories, Inc.
Date(s):	Received 6/23/11; User Fee 4/23/12
Review Priority:	Standard
Biometrics Division:	Division of Biometrics II/Office of Biostatistics
Statistical Reviewer:	Feng Zhou, M.S.
Concurring Reviewers:	Joan Buenconsejo, Ph.D., Team Leader Thomas Permutt, Ph.D., Division Director
Medical Division:	Division of Pulmonary, Allergy, and Rheumatology Products
Clinical Team:	Jennifer Pippins, M.D. (Medical Reviewer) Susan Limb, M.D. (Medical Team Leader) Badrul Chowdhury, M.D., Ph.D. (Medical Division Director)
Project Manager:	Sadaf Nabavian

Keywords: Clinical Studies, NDA filing review, Dropouts, LOCF

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	X			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	X			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	X			
4	Data sets in EDR are accessible and conform to applicable guidances (e.g., existence of define.pdf file for data sets).	X			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? ___Yes

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	X			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	X			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			X	There is no interim analyses
Appropriate references for novel statistical methodology (if present) are included.	X			
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	X			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	X			

There is no statistical comment are included in the 74-days letter.

Reference ID: 3000658

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/s/

FENG ZHOU
08/15/2011

JOAN K BUENCONSEJO
08/15/2011