STATISTICS REVIEW MEMORADUM

BLA Number: 103976 **Supplement #: 5225**	**Applicant: Genentech Inc. and Novartis Pharmaceuticals Corporation**	**Stamp Date: December 22, 2015**
Drug Name: Xolair® (omalizumab)	**BLA Type: 351(a) Efficacy Supplement**	**Indications: Moderate to severe persistent asthma (6 to less than 12 years)**

This submission is to support extension of the indication for Xolair (omalizumab) to use in children aged 6 to less than 12 years old. The initial marketing submission of Xolair for moderate to severe persistent asthma in adults and adolescents patients of no less than 12 years age was approved by the FDA on June 20th, 2003. On March 21st, 2014, Xolair was approved for chronic idiopathic urticaria (CIU) in adults and adolescents patients of no less than 12 years age. In December 2008, the applicant submitted a supplemental BLA (STN 103976/5149) for the use of omalizumab in children, aged 6 to less than 12 years, with moderate to severe persistent asthma. An Advisory Committee meeting was convened on November 18th, 2009 and recommended against approval based on inadequate evidence for overall positive benefit-risk, (b) (4)

After completing the long-term safety study in asthma patients (Q2948g, EXCELS), the applicant requested FDA's feedback on seeking to expand the use of Xolair in pediatric patients with severe asthma. Per FDA's feedback through written response to Type C meeting in July, 2015 and clarification letter in September, 2015, the applicant is submitting this supplemental BLA to expand the indication to patients 6 to less than 12 years of age with moderate to severe persistent asthma. The purpose of this application is to seek approval for omalizumab in moderate to severe persistent asthma in patients (6 to less than 12 years of age) with a positive skin test or *in vitro* reactivity to a perennial aeroallergen and symptoms that are inadequately controlled with inhaled corticosteroids (ICS).

This supplemental BLA contains primarily clinical efficacy and safety data. The pivotal clinical efficacy trial, Study IA05, and supporting Study 010 were submitted in 2008, demonstrating that Xolair decreased the incidence of asthma exacerbation rates in pediatric patients 6 to less than 12 years with moderate to severe asthma. There are no additional efficacy or safety data submitted for this supplemental BLA. The statistical review for the submission in 2008 was finalized in 2009 and attached as appendix. Additional statistical review is not needed and filing checklists on the next page are not applicable.

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On **initial** overview of the Supplemental NDA application for RTF:

	Content Parameter for RTF	Yes	No	NA	Comments
1	Electronic Submission: Indexing and reference links within the electronic submission are sufficient to permit navigation through the submission, including access to reports, tables, data, etc.				
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)				
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated.				
4	Data sets in EDR are accessible and conform to applicable guidances (e.g., existence of define.pdf file for data sets).				

THE STATISTICAL SECTION OF THE APPLICATION IS _____.

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

Appendix

Statistical Review for BLA 103976
S5149 by Ms. Feng Zhou

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:	STN103976/0216
Drug Name:	XOLAIR 150mg
Indication(s):	Maintenance treatment of airflow obstruction and reducing exacerbations in moderate to severe allergic asthma in children 6 to <12 years of age
Applicant:	Genentech, Inc.
Date(s):	Received 12/5/08; User Fee 06/6/09
Review Priority:	6-months
Biometrics Division:	Division of Biometrics II/Office of Biostatistics
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Keywords: Clinical Studies, NDA review, Dropouts

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

Xolair® [omalizumab], approved on June 20, 2003, is indicated as maintenance therapy for the prophylaxis of asthma exacerbations and control of symptoms in adults and adolescents (12 years and above) with moderate to severe allergic asthma that is inadequately controlled despite the use of inhaled corticosteroids. The sponsor, Genentech, Inc. and Novartis Pharmaceuticals Corp., submitted this efficacy supplement to extend the current indication of Xolair to patients 6 to 11 years of age. The information for the proposed use of Xolair in pediatric patients consists of the efficacy and safety data collected from Study IA05, and the core part of safety study CIGE025A010, referred to as Study 010 (core).

Study IA05 was a phase 3, double-blind, placebo controlled efficacy and safety study to collect one year efficacy and safety data of Xolair in patients 6-<12 years of age with moderate to severe persistent asthma who were uncontrolled despite treatment according to NHLBI step 3 or 4 (at least medium dose inhaled corticosteroids with or without other controller asthma medications). Study 010 (core) was a phase 3, 7-months, double-blinded, and placebo-controlled safety study in children (6 – 12 years) with allergic asthma requiring daily treatment with inhaled corticosteroids (ICS). Study 010 also consists of a 5-month open label extension period to assess safety and tolerability of Xolair.

The two studies differ primarily in patient populations with respect to baseline asthma control. The sponsor performed *post hoc* efficacy analyses on a subpopulation of Study 010 (core) (298, after excluding 36 subjects who were above 11 years old) based on the methods used in Study IA05.

Both studies show that treatment with Xolair significantly reduced the rate of asthma exacerbations compared with placebo in children 6-11 years of age with allergic asthma. The primary results in IA05 were supported by the secondary endpoint of clinically significant asthma exacerbations carried out to 52 weeks of treatment. Neither study showed that noticeable effect on pulmonary function, asthma symptom scores, rescue medication use or PAQLQ scores.

1.2 Statistical Issues and Findings

Table 1. Annualized Asthma Exacerbation Rates

	Annualized Rate			
Study IA05	***Xolair (n=384) Rate (SE)***	***Placebo (n=192) Rate (SE)***	***Rate Ratio[1] (95% CI)***	***Rate Difference (95% CI)***
Asthma exacerbation rate				
24-week fixed ICS period	0.97 (0.11)	1.39 (0.13)	0.69 (0.53, 0.90)	0.43 (0.09, 0.77)
52-week double-blind period	0.78 (0.09)	1.36 (0.12)	0.57 (0.45, 0.72)	0.58 (0.29, 0.87)

1. The primary analysis model was used for asthma exacerbations (imputed): Poisson regression including terms for treatment, schedule of dosing, exacerbation history, and country.

2. INTRODUCTION

2.1 Overview

Xolair® [omalizumab or rhuMAb-E25], approved on June 20, 2003, is indicated as maintenance therapy for the prophylaxis of asthma exacerbations and control of symptoms in adults and adolescents (12 years and above) with moderate to severe allergic asthma that is inadequately controlled despite the use of inhaled corticosteroids. Xolair's label carries a Boxed Warning and targeted Medication Guide for the risk of anaphylaxis and malignancy.

The submission included the efficacy and safety data collected from Study IA05 and Study 010. Table 2 presents the study design of the two studies. Study 010 was submitted and reviewed previously in the original biologic application (BLA) submission (June 2000). Study 010 (core) was resubmitted as a supportive study on December 2008. In the label, the sponsor used Study IA05 to support the exacerbation benefit of Xolair and Study 010 to support the beclomethasone dipropionate (BDP) dose reduction.

Table 2. Clinical Trials

Study/Center /Study Period	***Study Design***	***Key Inclusion Criteria***	***Patient entered/ completed***	***Primary Endpoint***
IA05 Phase 3 87 centers in 7 countries: Argentina 8, Brazil 3, Canada 6, Colombia 5, Poland 6, US 58, and South Africa 1 4/4/04-1/7/08 52 wks DB period with 16-weeks follow up	Randomized Multi-center Double-blind Parallel-group International	Age 6 - <12 yrs with a diagnosis of allergic asthma ≥1 year with clinical features consistent with moderate to severe persistent asthma, positive prick skin test to at least 1 perennial allergen, tot serum IgE 30-1300 IU, body weight between 20-150kg, and a ≥12% increase in FEV1 after 4 puffs or up to 5 mg of albuterol/salbutamol. Patients were required to have been on fluticasone propionate ≥200 mcg/day or an equivalent dose of another ICS, during which they had to have a documented history of exacerbations. Patients also demonstrated inadequate symptom control during the last 4 weeks of run-in period after the optimized ICS dose.	Xolair: 421/352; Placebo: 207/175;	Rate of clinically significant asthma exacerbation
010 – Safety Study Phase 3 27 centers in US 2/12/98-19/4/99 7-months DB period with 5-month open-label extension	Randomized Multi-center Double-blind Parallel-group Open-label extension	Similar as Study IA05 except body weight ≤90kg and a ≥12% increase in FEV1 after 1 or 2 puffs of albuterol/salbutamol (90mcg/puff); Baseline FEV1≥ 60%; Inadequate symptom control and exacerbation history were not criterions for entry	Xolair: 203/190; Placebo: 95/86	Reduction of ICS use

2.2 Data Sources

Documents reviewed were accessed from the CBER document room at:
\\...\eCTD Submissions\STN103976\103976.enx

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

This efficacy evaluation conducts a comprehensive review of Study IA05 in detail and briefly presents the efficacy results of the core subpopulation of Study 010.

3.1.1 Study IA05

Study Design, Efficacy Endpoints, and Statistical Methodologies

During the year of 2004 and 2008, the sponsor conducted the Study IA05 in 87 centers in 7 countries (Argentina 8, Brazil 3, Canada 6, Colombia 5, Poland 6, United States 58, and South Africa 1). The primary objectives of this study were to 1) confirm the safety of Xolair during the 52 week double-blind treatment period and 16-week follow-up period; 2) demonstrate the effect of Xolair on the clinically significant asthma exacerbation rate during the 24-week double-blind fixed steroid treatment.

Study IA05 was a phase 3, double-blind, placebo controlled, multi-center international trial with 52 weeks of treatment. As shown in Table 3, following a one-week screening period and a 8-week pre-treatment run-in period, eligible patients were randomized to Xolair or placebo in 2:1 ratio. The double-blind treatment period included a 24-week fixed dose steroid phase followed by a 28-week adjustable steroid phase. All patients were followed additional 16 weeks for safety.

Table 3.Study Schema

Phase	**Pre-randomization**		**Study drug treatment**		**No study drug treatment**
Period	**Screen (1 week)**	**Run-in (8 weeks)**	**Double-blind treatment (52 weeks)**		**Follow-up (16 weeks)**
			Fixed Steroid	**Adjustable Steroid**	
Visit (s)	1	2 to 5	6 to 12	13 to 19	20 to 23
Week (s)	-9	-8 to -2	1 to 25	26 to 53	54 to 69
Asthma treatment					
Trial Medication	None	None	Omalizumab or placebo 2:1 randomization ratio		None
ICS	Minimum NHLBI step 3 therapy according to best clinical practice	Monitor NHLBI best clinical practice. Adjust if necessary during first 4 weeks.	No adjustment to ICS dose	Review ICS. Adjust, if necessary, from start of phase and then no more than once every 8 weeks.	NHLBI best clinical practice

Eligible patients were male or female, 6–<12 years old, with moderate to severe allergic asthma who required daily treatment with inhaled corticosteroids (ICS). Enrollment criteria included: a

diagnosis of allergic asthma ≥1 year, positive prick skin test to at least 1 perennial allergen, total serum IgE 30-1300 IU (inclusive), body weight between 20-150 kg, ≥12% increase in FEV1 after 4 puffs or up to 5 mg of albuterol/salbutamol, clinical features consistent with NHLBI NAEPP (1997, update 2002) Steps 3 or 4 (medium ICS dose: FP ≥200 mcg/day or equivalent), documented history of exacerbations, and inadequate symptom control during the last 4 weeks of the run-in period.

Xolair dosing and dosing frequencies are displayed in Table 4 and Table 5 based on body weight and baseline IgE level.

Table 4. Xolair Dosing Table (Ages 6 - < 12 years) (mg/dose)

DOSING INTERVAL	BASELINE IGE (IU/ML)	BODY WEIGHT (KG)									
		20-25	>25-30	>30-40	>40-50	>50-60	>60-70	>70-80	>80-90	>90-125	>125-150
Q4wks	≥30–100	75	75	75	150	150	150	150	150	300	300
	>100–200	150	150	150	300	300	300	300	300	225	300
	>200–300	150	150	225	300	300	225	225	225	300	375
	>300–400	225	225	300	225	225	225	300	300		
	>400–500	225	300	225	225	300	300	375	375		
	>500–600	300	300	225	300	300	375				
	>600–700	300	225	225	300	375					
Q2wks	>700–800	225	225	300	375						
	>800–900	225	225	300	375						
	>900–1000	225	300	375							
	>1000–1100	225	300	375							
	>1100–1200	300	300								
	>1200–1300	300	375								

Do not dose in this area

Table 5. Dosing Schedule (Number of Injections and Total Injection Volumes)

Dose (mg)	Number of Injections	Total Volume Injected (ml)*
75	1	0.6
150	1	1.2
225	2	1.8
300	2	2.4
375	3	3.0

* 1.2 ml maximum delivered volume per vial.

The primary efficacy variable was the rate of clinically significant asthma exacerbations in the 24-week double-blind fixed steroid period. The exacerbation data was collected separately from adverse event data on asthma exacerbation and exacerbation concomitant medication eCRFs. For each treatment group, the rate is defined as the number of exacerbations over the treatment period. The clinically significant asthma exacerbation was defined as worsening of asthma symptoms as judged clinically by the investigators and requiring doubling of the baseline inhaled corticosteroid dose and/or treatment with rescue systemic (oral or IV) corticosteroids for at least

3 days. Patients who discontinued prematurely were included in the analysis using an imputed number of clinically significant asthma exacerbation episodes. One asthma exacerbation was added to the total number for those patients and 9 days were added to the treatment period unless the patients had a clinically significant asthma exacerbation within seven days prior to the premature discontinuation. The duration of the imputed asthma exacerbation was imputed as the median duration of all clinically significant exacerbations observed in the 52-week study.

Four secondary efficacy parameters were defined for analysis:

- change in nocturnal clinical symptom score from baseline to the end (last four weeks) of the 24 week double-blind fixed steroid treatment period (time adjusted)
- rate of asthma exacerbations during the 52 week double-blind treatment period
- change in beta-agonist rescue medication use from baseline to the end (last four weeks) of the 24 week double-blind fixed steroid treatment period
- change in quality of life (PAQLQ(S)) in overall score from baseline to the end (last visit) of the 24 week double-blind fixed steroid treatment period

The primary efficacy analysis was performed using a two-sided test at $\alpha = 0.05$, to compare the rates of clinically significant exacerbations of the two treatment groups over the 24- week double-blind fixed steroid period. Poisson regression model including terms for treatment, country, dosing schedule, and exacerbation history was used for the analysis.

Three sites (008 Argentina, 585 US, and 512 US) were identified during standard trial monitoring procedures having GCP non-compliance issues. Two of those sites, 008 and 585, were closed, and all patients were discontinued. Site 512 was closed to further enrollment but all randomized patients were allowed to continue to the end of the study. There were 68 randomized patients affected, 41 patients at Site 008, 10 at Site 585 and 17 at Site 512. Analysis results including or excluding the three sites do not alter the study conclusion.

All efficacy analyses including the primary analysis were performed on the modified intent-to-treat (MITT) population, which is defined as all randomized patients excluding those from Sites 008 and 585. The sponsor performed the sensitivity analysis on the full ITT, which includes all randomized patients, and per protocol population. All patients who received study medication are included in safety analysis.

Patient Disposition, Demographic and Baseline Characteristics

As shown in Table 6, a total of 627 patients (421 Xolair and 206 placebo patients) were randomized. Note that a total of 628 patients received the study medication because 1 patient (ID: 0555_00009) was not randomized but received placebo. The majority (84%) of patients completed the 52 weeks of active treatment. The main reasons for discontinuations were administrative problems and patient withdrawals of consent.

Table 6. Patients' Accountability N (%)

Study IA05	***Xolair***	***Placebo***	***Total***
Received Treatment	421	207	628
Completed treatment period	352 (83.6)	175 (84.5)	527 (83.9)
Discontinued	69 (16.4)	32 (15.5)	101 (16.1)
Reason of early discontinuation			
Adverse event	2 (0.5)	1 (0.5)	3 (0.5)
Lack of efficacy	1 (0.2)	2 (1.0)	3 (0.5)
Patient's condition no longer requires study drug	3 (0.7)	0 (0.0)	3 (0.5)
Protocol violation	8 (1.9)	6 (2.9)	14 (2.2)
Patient withdrew consent	21 (5.0)	7 (3.4)	28 (4.5)
Lost to follow-up	12 (2.9)	5 (2.4)	17 (2.7)
Administrative problems	22 (5.2)	11 (5.3)	33 (5.2)
Full ITT population	421 (100.0)	206 (99.5)	627 (99.8)
Modified ITT (MITT) population	384 (91.2)	192 (92.8)	576 (91.7)
Per protocol (PP) population	364 (86.5)	180 (97.0)	544 (86.6)
Safety population	421 (100.0)	207 (100.0)	628 (100.0)

Figure 1 presents the survival curves for premature study drug discontinuations. The dropout rates were similar between the two treatment groups.

Figure 1. Time to Study Drug Discontinuation

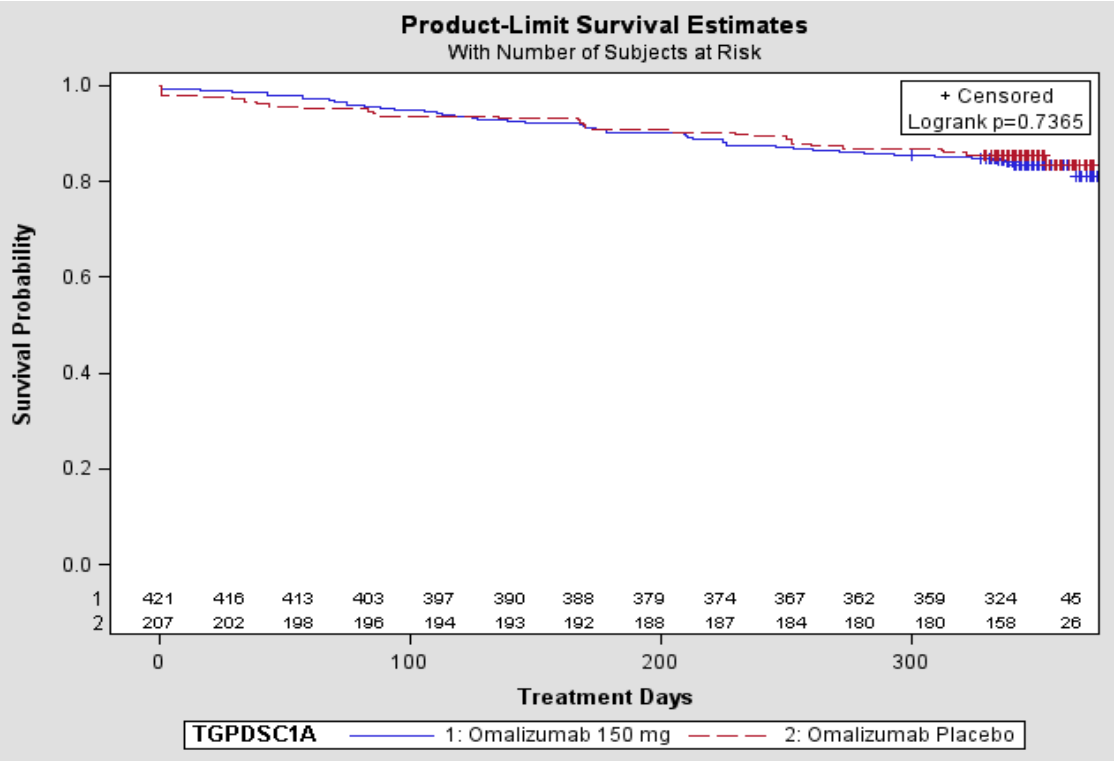


Table 7 shows that the demographic and baseline disease characteristics were generally well balanced between the treatment groups. Overall the mean age was 8.6 years. A higher proportion of patients in the Xolair group fell into the 10 to 11 years age range compared to placebo. Approximately two-thirds of patients were male and the majority of patients were Caucasian. The overall mean FEV1 (% of predicted) for the population was 86.4%.

Table 7. Patients' Demographic and Baseline Characteristics N (%)

Study IA05	***Xolair (n=421)***	***Placebo (n=207)***	***Total (n=628)***
Age (yrs)			
6-8 years old, N (%)	184 (43.7)	107 (51.7)	291 (46.3)
9-11 years old, N (%)	237 (56.3)	100 (48.3)	337 (53.7)
Mean (SD)	8.7 (1.7)	8.4 (1.7)	8.6 (1.7)
Range	6 – 11	6 – 11	6 – 11
Sex			
Female	134 (31.8)	69 (33.3)	203 (32.3)
Male	287 (68.2)	138 (66.7)	425 (67.7)
Race			
Caucasian	249 (59.1)	128 (61.8)	377 (60.0)
Black	69 (16.4)	30 (14.5)	99 (15.8)
Oriental	0 (0.0)	2 (1.0)	2 (0.3)
Other	103 (24.5)	47 (22.7)	150 (23.9)
FEV_1 (% of predicted) (visit 1, pre-bronchodilator)			
Mean (SD)	86.0 (17.8)	87.2 (18.4)	86.4 (18.0)
Median	86.1	88.3	86.9
Range	25 – 148	28 – 142	25 – 148
Increase (%) in FEV1 over baseline within 30 minutes of rescue medication			
N (%)	208 (49.4)	100 (48.3)	308 (49.0)
Mean (SD)	25.8 (17.3)	23.8 (14.9)	25.1 (16.5)
Median	20.3	18.7	19.4
Range	0 – 124	-16 – 77	-16 – 124
Serum total IgE (IU/mL)			
Mean (SD)	476.0 (339.3)	456.9 (335.8)	469.7 (338.0)
Median	404.0	388.0	403.0
Range	27 – 1371	29 – 1376	27 – 1376
Weight (Kg)			
Mean (SD)	33.9 (11.4)	33.9 (12.3)	33.9 (11.7)
Median	31	30.2	30.9
Range	19.3 – 92.3	20.0 – 78.4	19.3 – 92.3
Height (cm)			
Mean (SD)	134.2 (11.5)	132.8 (11.7)	133.7 (11.6)
Median	134	133	134
Range	107 – 165	104 - 168	104 – 168

* Results from reviewer's analysis.

Table 8 shows that asthma medication use at baseline showed small differences between treatment groups: the mean inhaled corticosteroid dose and the proportion of patients taking oral corticosteroids at baseline was slightly higher for the Xolair group. The proportion of patients who took long-acting beta-2 agonists at baseline was slightly higher for the placebo group, while the proportion who took short-acting beta-2 agonists was similar for both groups. The mean duration of asthma was similar for both treatment groups and approximately half of patients had a positive skin prick or RAST test for mold allergen. Xolair patients at baseline reported slightly more seasonal allergies and placebo patients slightly more drug or food allergies, but differences were small.

Table 8. Allergen and Asthma History and Asthma Medication at Baseline

Study IA05	***Xolair (n=421)***	***Placebo (n=207)***	***Total (n=628)***
Inhaled Corticosteroid Dose [a] (mcg/day)			
Mean (SD)	517.8 (285.9)	509.5 (285.0)	515.1 (285.4)
Median	500.0	454.5	454.5
Range	119 – 1705	200 – 1880	119 - 1880
Patients Using at Baseline N (%)			
Inhaled long acting beta-2 agonist	277 (65.8)	146 (70.5)	423 (67.4)
Maintenance oral steroid	8 (1.9)	0 (0.0)	8 (1.3)
Anti-leukotriene therapy	163 (38.7)	67 (32.4)	230 (36.6)
Short acting beta-2 agonist	367 (87.2)	182 (87.9)	549 (87.4)
Normal * number of daily puffs of short acting beta-2 agonist at baseline			
N	367	182	549
Mean (SD)	2.8 (2.7)	2.6 (2.4)	2.8 (2.6)
Median	2.0	2.0	2.0
Range	0 – 18	0 – 8	0 – 18
Duration of allergic asthma (years)			
Mean (SD)	5.7 (2.7)	5.6 (2.6)	5.7 (2.6)
Median	6.0	6.0	6.0
Range	1 – 11	1 – 11	1 – 11
Number of Seasonal Allergies, N (%)			
None	186 (44.2)	101 (48.8)	287 (45.7)
1	34 (8.1)	23 (11.1)	57 (9.1)
2	54 (12.8)	19 (9.2)	73 (11.6)
3	75 (17.8)	41 (19.8)	116 (18.5)
≥4	72 (17.1)	23 (11.1)	95 (15.1)
Number of Food or Drug Allergies, N (%)			
None	326 (77.4)	147 (71.0)	473 (75.3)
1	44 (10.5)	19 (9.2)	63 (10.0)
2	20 (4.8)	18 (8.7)	38 (6.1)
3	12 (2.9)	11 (5.3)	23 (3.7)
≥4	19 (4.5)	12 (5.8)	31 (4.9)
Positive Skin Prick/RAST Test to Mold, N (%)			
Yes	226 (53.7)	103 (49.8)	329 (52.4)
No	190 (45.1)	101 (48.8)	291 (46.3)
Missing	5 (1.2)	2 (1.0)	7 (1.1)
Qualifying exacerbations, N (%)			
One severe exacerbation in the past 12 months	77 (18.3)	40 (19.3)	117 (18.6)
Two independent exacerbation in the previous 12 months	267 (63.4)	128 (61.8)	395 (62.9)
Three independent exacerbations in previous 24 months one of which occur in the past 12 months	77 (18.3)	39 (18.8)	116 (18.5)
Number of clinically significant exacerbations (including qualifying) within past year, N (%)			
Mean (SD)	2.6 (1.4)	2.5 (1.2)	2.6 (1.4)
Median	2.0	2.0	2.0
Range	1 – 12	0 – 7	0 – 12

a: Fluticasone equivalent dose. * Normal number of daily puffs" as recorded on the eCRF.

Results and Conclusions

Primary Efficacy Endpoint – Rate of clinically significant asthma exacerbation

As shown in Table 9, the counts of patient with clinically significant asthma exacerbation event with or without imputation for full ITT and MITT populations were similar. Also as shown in Table 10, the results of the primary analysis of rate of clinically significant asthma exacerbation were similar in the two populations with or without the imputation did not affect study conclusions. Analysis results including or excluding the three sites do not alter the study conclusion. The rest of review will be based on the MITT population.

Table 9. Summary of Clinically Significant Asthma Exacerbation Events (AEEs) during 24-wk Fixed Steroid Treatment Period

	MITT (n=576)		***Full ITT (n=627)***	
	Xolair (n=384)	***Placebo (n=192)***	***Xolair (n=421)***	***Placebo (n=206)***
Number of Patients with 1+ Exacerbation	137 (36%)	80 (42%)	149 (35%)	83 (40%)
Total Number of Exacerbations	208	142	221	145
Patient with Clinically Significant AEE (imputed), n (%)				
0	247 (64.3)	112 (58.3)	272 (64.6)	123 (59.7)
1	86 (22.4)	41 (21.3)	97 (23.0)	44 (21.4)
2	38 (9.9)	23 (12.0)	39 (9.3)	23 (11.2)
3	9 (2.3)	12 (6.2)	9 (2.1)	12 (5.8)
≥4	4 (1.0)	4 (2.1)	4 (1.0)	4 (1.9)
Patient with Clinically Significant AEE (observed), n (%)				
0	265 (69.0)	119 (62.0)	298 (70.8)	132 (64.1)
1	74 (19.3)	36 (18.7)	77 (18.3)	37 (18.0)
2	32 (8.3)	22 (11.5)	33 (7.8)	22 (10.7)
3	10 (2.6)	11 (5.7)	10 (2.4)	11 (5.3)
≥4	3 (0.8)	4 (2.1)	3 (0.7)	4 (1.9)

Source: Poisson_IA05.sas;

Table 10. Analyses of the Rates of Clinically Significant Asthma Exacerbations

	MITT (n=576)		***ITT (n=627)***	
	Xolair	***Placebo***	***Xolair***	***Placebo***
	384	192	421	206
Imputed rate of clinically significant Exacerbation per 24-week treatment period	0.45	0.64	0.45	0.63
Ratio (Xolair vs. Placebo)		0.69		0.72
95% CI		(0.53, 0.90)		(0.56, 0.93)
p-value		0.007		0.013
Observed rate of clinically significant Exacerbation per 24-week treatment period	0.40	0.61	0.38	0.58
Ratio (Xolair vs. Placebo)		0.65		0.66
95% CI		(0.49, 0.87)		(0.50, 0.79)
p-value		0.003		0.004

Source: poisson_IA05.sas; Poisson regression model adjusted for treatment, country, dosing schedule, and exacerbation history.

This reviewer confirmed the sponsor's primary and supportive analysis results for the primary and key secondary efficacy variables. Table 11 summarizes the analysis results of asthma exacerbations during the fixed ICS dose, adjust ICS dose, and double-blind periods. During the fixed ICS dose period, the ratio of the exacerbation rate for Xolair to placebo was 0.69 (95% CI: [0.53, 0.90]) which represented a 31% decrease in annual rate compared with placebo (p=0.007).

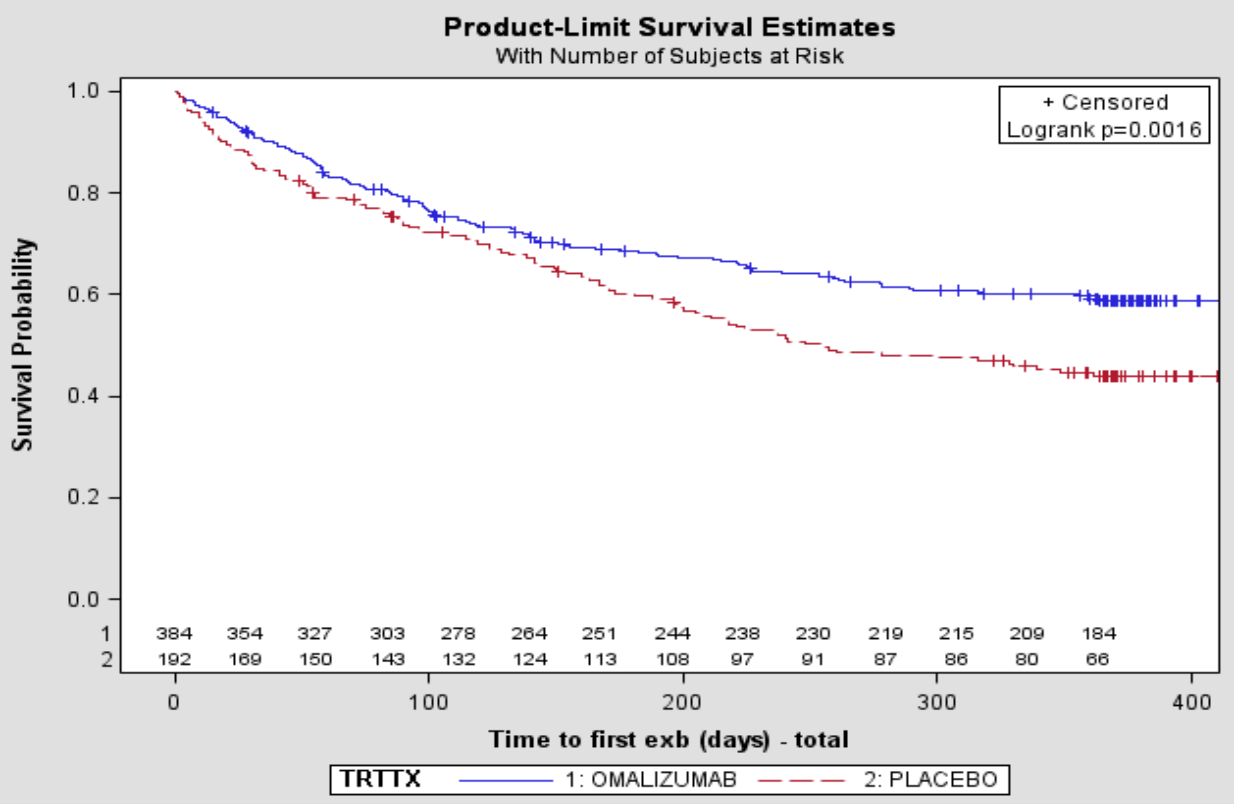
Patients treated with Xolair had a statistically significantly lower rate of clinically significant asthma exacerbations than placebo-treated patients during the 28-weeks adjusted ICS period and 52-weeks entire treatment period. Note that, the estimated annual exacerbation rates during the two treatment periods were similar in the placebo group (1.39 vs. 1.32) but different in the Xolair group (0.97 versus 0.60). Figure 2 displays the Kaplan-Meier curves for the first exacerbation event. Xolair-treated patients delayed the risk of exacerbation compared with the placebo-treated patients (p=0.002). The log-rank test was not statistically significant during the 24-week fixed ICS dosing period (p=0.080).

Table 11. Summary of Analyses of Asthma Exacerbations during the DB Treatment Period

Phase	Annualized Rate			
	Xolair (n=384) Rate (SE)	Placebo (n=192) Rate (SE)	Rate Ratio[1] (95% CI)	Rate Difference (95% CI)
Asthma exacerbation rate (primary and secondary endpoints)				
24-week fixed ICS period	0.97 (0.11)	1.39 (0.13)	0.69 (0.53, 0.90)	0.43 (0.09, 0.77)
28-week adjusted ICS period	0.60 (0.11)	1.32 (0.13)	0.46 (0.34, 0.61)	0.71 (0.37, 1.06)
52-week double-blind period	0.78 (0.09)	1.36 (0.12)	0.57 (0.45, 0.72)	0.58 (0.29, 0.87)

1. The primary analysis model was used for asthma exacerbations (imputed): Poisson regression including terms for treatment, schedule of dosing, exacerbation history, and country.

Figure 2. Time to First Exacerbation during 52-week DB Period

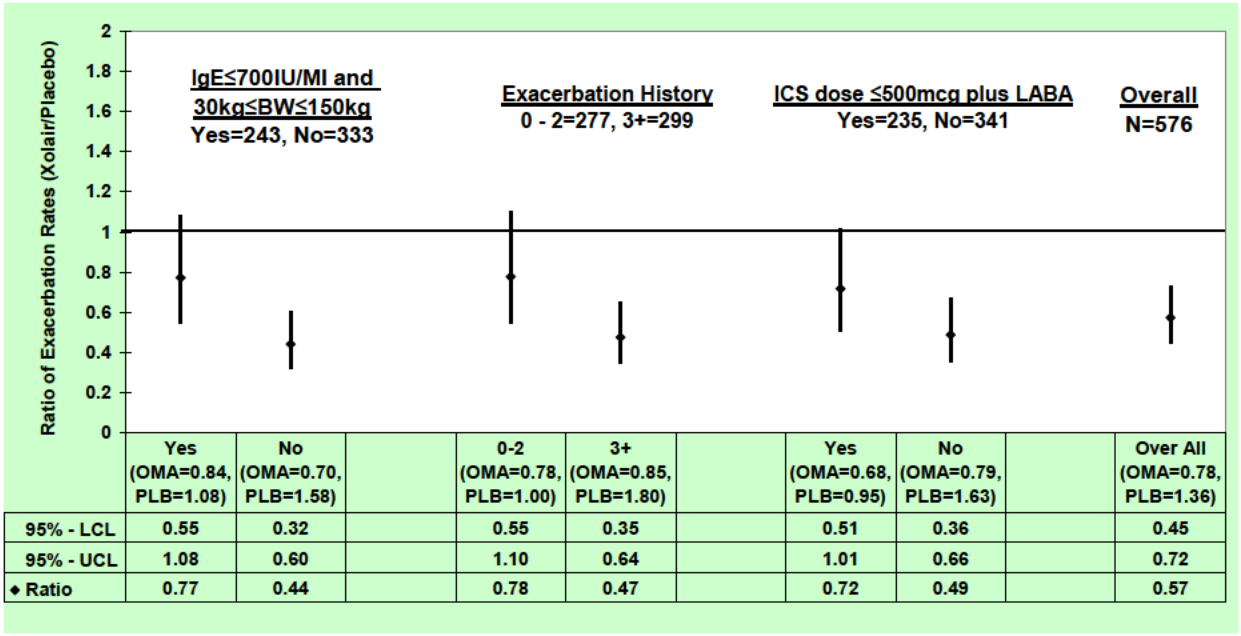


Source: poisson_IA05.sas

This reviewer did the subgroup analyses of rate of clinically significant asthma exacerbation. As shown in Figure 3, Xolair has more benefit in the patient with higher IgE level, with more

than 2 exacerbations during the previous year, or used high dose of ICS during the run-in period compared to placebo. Other subgroup analysis results were displayed in Table 12.

Figure 3. Ratio of Asthma Exacerbations Rate during the 52-week DB Period by Subgroup



	Yes (OMA=0.84, PLB=1.08)	No (OMA=0.70, PLB=1.58)		0-2 (OMA=0.78, PLB=1.00)	3+ (OMA=0.85, PLB=1.80)		Yes (OMA=0.68, PLB=0.95)	No (OMA=0.79, PLB=1.63)		Over All (OMA=0.78, PLB=1.36)
95% - LCL	0.55	0.32		0.55	0.35		0.51	0.36		0.45
95% - UCL	1.08	0.60		1.10	0.64		1.01	0.66		0.72
◆ Ratio	0.77	0.44		0.78	0.47		0.72	0.49		0.57

Poisson regression including terms for treatment and schedule of dosing, exacerbation history, and country

Table 12. Annualized Rate of Asthma Exacerbation during DB Period by Subgroup

Subgroup	*Omalizumab n=384*			*Placebo B=192*			*Ratio of Xolair/Placebo (95%CI)*
	N	Rate-24[1]	Rate-52[2]	N	Rate-24	Rate-52	Ratio-24, Ratio-52
*SEX (SEX: p>=0.006, TRT*SEX: p>=0.349)*							
Male	259	0.94	0.80	129	1.18	1.24	0.79 (0.56, 1.11), 0.64 (0.48, 0.86)
Female	125	0.99	0.68	63	1.60	1.35	0.62 (0.41, 0.93), 0.51 (0.34, 0.75)
*AGE Group (AGE: p>=0.034, TRT*AGE: p>=0.196)*							
6 – 8	168	1.00	0.85	97	1.72	1.71	0.58 (0.40, 0.84), 0.50 (0.35, 0.70)
9 – 11	216	0.69	0.64	95	0.82	0.97	0.84 (0.58, 1.22), 0.66 (0.48, 0.92)
*Race (White vs. Non-white) (Race: p=0.242, Trt*Race: p=0.482)*							
White	212	1.04	0.69	113	1.18	1.09	0.88 (0.60, 1.29), 0.64 (0.47, 0.86)
Non-white	172	1.22	0.81	79	2.13	1.53	0.57 (0.40, 0.82), 0.53 (0.38, 0.75)
*Country (US vs. Non-US) (Country: p<.001, Trt*Country: p=0.091)*							
US	189	1.47	1.29	90	1.94	1.88	0.76 (0.54, 1.08), 0.68 (0.50, 0.94)
Non-US	195	0.80	0.58	102	1.29	1.29	0.62 (0.41, 0.94), 0.45 (0.31, 0.64)
*IgE≤700IU/mL and Body Weight ≥30kg and ≤150kg (IgE_WGT: p=0.454, TRT*IgE_WGT: p=0.014)*							
Yes	163	0.88	0.84	80	0.95	1.08	0.93 (0.61, 1.40), 0.77 (0.55, 1.08)
No	221	0.87	0.70	112	1.62	1.58	0.54 (0.38, 0.75), 0.44 (0.32, 0.60)
*IgE≤700IU/Ml (IgE: p=0.806, Trt*IgE: p=0.167)*							
Yes	281	1.03	1.44	141	1.36	2.34	0.75 (0.55, 1.03), 0.61 (0.46, 0.81)
No	103	0.68	0.93	51	1.26	2.26	0.54 (0.33, 0.90), 0.41 (0.25, 0.68)
*Exacerbation History (Exhis: p=0.096, Trt*Exhis: p=0.041)*							
0 – 2	181	0.98	0.78	96	1.05	1.00	0.93 (0.62, 1.40), 0.78 (0.55, 1.10)
3+	203	1.01	0.85	96	1.76	1.80	0.57 (0.41, 0.79), 0.47 (0.35, 0.64)
*Baseline %Predicted FEV1 (BFEV: p=0.027, TRT*BFEV: p=0.984)*							

FEV1 ≤ 80%	146	1.42	0.83	67	2.11	1.50	0.67 (0.46, 0.98), 0.55 (0.39, 0.78)
FEV1 > 80%	238	0.94	0.69	125	1.28	1.22	0.74 (0.51, 1.07), 0.56 (0.41, 0.78)
*Baseline ICS dose (BICS: p=0.003, TRT*BICS: p=0.235)*							
ICS ≤ 500mcg	242	0.97	0.77	127	1.18	1.21	0.82 (0.59, 1.15), 0.64 (0.48, 0.85)
ICS > 500mcg	142	1.08	0.83	65	2.04	1.76	0.53 (0.35, 0.81), 0.47 (0.32, 0.70)
*Baseline LABA USER (LABA p=0.147, TRT*LABA: p=0.848)*							
YES	247	0.80	0.68	134	1.08	0.50	0.75 (0.54, 1.03), 0.55 (0.42, 0.74)
NO	137	1.00	0.79	58	1.74	0.81	0.57 (0.37, 0.89), 0.59 (0.39, 0.90)
*Baseline ICS dose and LABA (BICS_LABA: p=0.002, TRT*BICS_LABA: p>=0.014)*							
ICS ≤ 500mcg + LABA	149	0.80	0.68	86	0.77	0.59	1.04 (0.68, 1.60), 0.72 (0.51, 1.01)
ICS > 500mcg + LABA	235	1.00	0.79	106	1.84	0.47	0.54 (0.39, 0.76), 0.49 (0.36, 0.66)
*Baseline ICS dose and %Predicted FEV1 (FEV_ICS: p=0.002, TRT*FEV_ICS: p=0.476)*							
FEV1<=80% + ICS>500	62	1.52	0.97	20	3.77	2.51	0.40 (0.22, 0.73), 0.39 (0.22, 0.69)
FEV1<=80% + ICS≤500	84	1.32	0.80	47	1.45	1.23	0.91 (0.56, 1.47), 0.65 (0.42, 1.01)
FEV1>80% + ICS>500	80	1.09	0.81	45	1.68	1.56	0.65 (0.35, 1.21), 0.52 (0.28, 0.95)
FEV1>80% + ICS≤500	158	0.84	0.67	80	1.06	1.12	0.78 (0.50, 1.27), 0.60 (0.41, 0.88)

Source: poisson_IA05.sas;
Poisson regression model adjusted for treatment, country, dosing schedule, and exacerbation history.

1. Rate-24 = exacerbation rate at end of 24-week fixed steroid period
2. Rate-52 = exacerbation rate at end of 52-week treatment period

Other Exacerbation related Endpoints

The rate of clinically severe asthma exacerbation was analyzed at the end of the 24- and 52-week treatment period for the MITT population (without imputation). A severe asthma exacerbation was defined as an exacerbation where the PEF or FEV1 was < 60% personal best. As shown in Table 13, the rate of clinically severe asthma exacerbations decreased by 50% for Xolair compared to placebo during the 52-weeks treatment period. Similar results were shown in the exacerbation due to the systemic CSD and ICS dosing doubling. The number of patients who had hospital admissions, ER visits, unscheduled doctors visits was analyzed at the end of the 24- and 52-Week treatment periods for the MITT population. At the end of the 52-Week treatment period, there was a trend favoring Xolair treatment, but no statistically significant difference between treatments was achieved.

Table 13. Annualized Rates of Other Asthma Exacerbation Endpoints during the DB Period

	24-week Fixed Steroid Period		***52-week BD Treatment period***	
	Xolair (n=384) Rate (SE)	***Placebo (n=192) Rate (SE)***	***Xolair (n=384) Rate (SE)***	***Placebo (n=192) Rate (SE)***
Severe exacerbation	0.22 (0.18)	0.40 (0.21)	0.19 (0.18)	0.38 (0.17)
Xolair/Placebo (95%CI)	--	0.55 (0.32, 0.95)	--	0.49 (0.30, 0.81)
Exac. Due to systemic CSD	0.90 (0.09)	1.27 (0.13)	0.72 (0.09)	1.26 (0.12)
Xolair/Placebo (95%CI)	--	0.71 (0.52, 0.97)	--	0.57 (0.42, 0.77)
Exac. Due to ICS doubling	0.09 (0.38)	0.16 (0.37)	0.10 (0.31)	0.18 (0.33)
Xolair/Placebo (95%CI)	--	0.54 (0.19, 1.50)	--	0.52 (0.22, 1.24)
Hospital Admission	0.08 (0.28)	0.07 (0.45)	0.07 (0.27)	0.13 (0.28)
Xolair/Placebo (95%CI)	--	1.10 (0.43, 2.83)	--	0.53 (0.26, 1.09)
ER visits	0.14 (0.32)	0.16 (0.28)	0.11 (0.30)	0.14 (0.34)
Xolair/Placebo (95%CI)	--	0.87 (0.37, 2.07)	--	0.81 (0.33, 2.01)
Doctor visits	0.70 (0.14)	0.66 (0.17)	0.58 (0.13)	0.65 (0.12)
Xolair/Placebo (95%CI)	--	1.07 (0.70, 1.64)	--	0.89 (0.63, 1.26)

1. The primary analysis model was used for asthma exacerbations (without imputation): Poisson regression including terms for treatment, and schedule of dosing.

Other Secondary Endpoints

As shown in Table 14 and Table 15, Xolair appears to have small benefit on average in improving the pulmonary function, PEF, and asthma symptoms compared to the placebo group. The treatment differences did not reach the statistical significance except in FVC and nocturnal asthma symptom score at 24-week fixed ICS dose period. (See Figure 7, Figure 8, Figure 9, Figure 10, and Figure 11 in Appendix for the average profiles over time in %predicted FEV1, nocturnal and daytime asthma symptom score, and number of puffs per day of asthma rescue medication used.)

Table 14. Analyses of Pulmonary Function Data over DB Treatment Period

			Double-blind treatment period			
		Baseline value	Observed value at 24-week	Observed value at 52-week	From ANCOVA On change from baseline LS Mean (SE), 95% CI	
Treatment	N	Mean (SE)	Mean (SE)	Mean (SE)	LOCF to 24-week	LOCF to 52-week
FEV1 (L)						
Xolair	384	1.615 (0.02)	1.770 (0.04)	1.852 (0.02)	0.038 (0.024)	0.035 (0.024)
Placebo	192	1.599 (0.03)	1.712 (0.03)	1.799 (0.04)	(-0.009, 0.085)	(-0.013, 0.082)
FVC (L)						
Xolair	384	1.982 (0.03)	2.163 (0.03)	2.267 (0.03)	0.061 (0.025)	0.051 (0.025)
Placebo	192	1.975 (0.04)	2.097 (0.04)	2.209 (0.04)	(0.011, 0.110)	(0.002, 0.101)
FEF 25-75% (L/sec)						
Xolair	384	1.673 (0.04)	1.861 (0.04)	1.914 (0.04)	0.043 (0.046)	0.047 (0.046)
Placebo	192	1.653 (0.05)	1.801 (0.06)	1.852 (0.06)	(-0.048, 0.134)	(-0.043, 0.138)
Percent predicted FEV1 (%)						
Xolair	384	84.99 (0.90)	86.80 (0.87)	85.69 (0.86)	1.17 (1.15)	1.22 (1.19)
Placebo	192	86.37 (1.34)	86.41 (1.21)	85.49 (1.36)	(-1.08, 3.42)	(-1.11, 3.55)

a: LS Means are obtained from the ANCOVA model with treatment, baseline value, sex, dosing schedule, and country effects.

Table 15. Analyses of Diary Data over DB Treatment Period

			Double-blind treatment period			
		Baseline value	Observed value at 24-week	Observed value at 52-week	From ANCOVA On change from baseline LS Mean (SE), 95% CI	
Treatment	N	Mean (SE)	Mean (SE)	Mean (SE)	LOCF to 24-week	LOCF to 52-week
Morning PEF (L/min)						
Xolair	384	225.5 (3.1)	243.9 (3.4)	255.1 (3.6)	4.15 (2.63)	0.39 (3.33)
Placebo	192	217.0 (4.4)	232.3 (5.0)	246.9 (5.3)	(-1.02, 9.32)	(-6.15, 6.94)
Evening PEF (L/min)						
Xolair	384	230.4 (3.1)	247.8 (3.4)	258.4 (3.7)	4.95 (2.52)	-0.47 (3.30)
Placebo	192	222.2 (4.4)	235.9 (5.0)	251.5 (5.4)	(-0.01, 9.91)	(-6.96, 6.01)
Nocturnal Asthma Symptom Score						
Xolair	384	1.179 (0.04)	0.555 (0.03)	0.412 (0.03)	-0.124 (0.05)	-0.077 (0.05)
Placebo	192	1.168 (0.05)	0.663 (0.05)	0.480 (0.05)	(-0.23, -0.02)	(-0.18, 0.02)
Morning Asthma Symptom Score						
Xolair	384	0.551 (0.02)	0.279 (0.02)	0.205 (0.02)	-0.024 (0.03)	-0.035 (0.03)
Placebo	192	0.565 (0.02)	0.307 (0.02)	0.243 (0.02)	(-0.08, 0.03)	(-0.09, 0.01)
Daytime Asthma Symptom Score						
Xolair	384	1.489 (0.04)	0.757 (0.04)	0.586 (0.04)	-0.081 (0.06)	-0.026 (0.06)
Placebo	192	1.490 (0.05)	0.826 (0.05)	0.602 (0.05)	(-0.20, 0.03)	(-0.14, 0.09)
Total Clinical Asthma Symptom Score						
Xolair	384	3.231 (0.07)	1.585 (0.08)	1.192 (0.07)	-0.235 (0.12)	-0.135 (0.12)
Placebo	192	3.234 (0.10)	1.795 (0.12)	1.301 (0.11)	(-0.48, 0.01)	(-0.37, 0.10)
Number of Puffs of Asthma Rescue Medication						
Xolair	384	3.006 (0.13)	1.674 (0.15)	1.265 (0.13)	-0.267 (0.22)	-0.120 (0.19)
Placebo	192	2.866 (0.17)	1.849 (0.19)	1.313 (0.16)	(-0.69, 0.16)	(-0.50, 0.26)
PAQLQ – Overall						

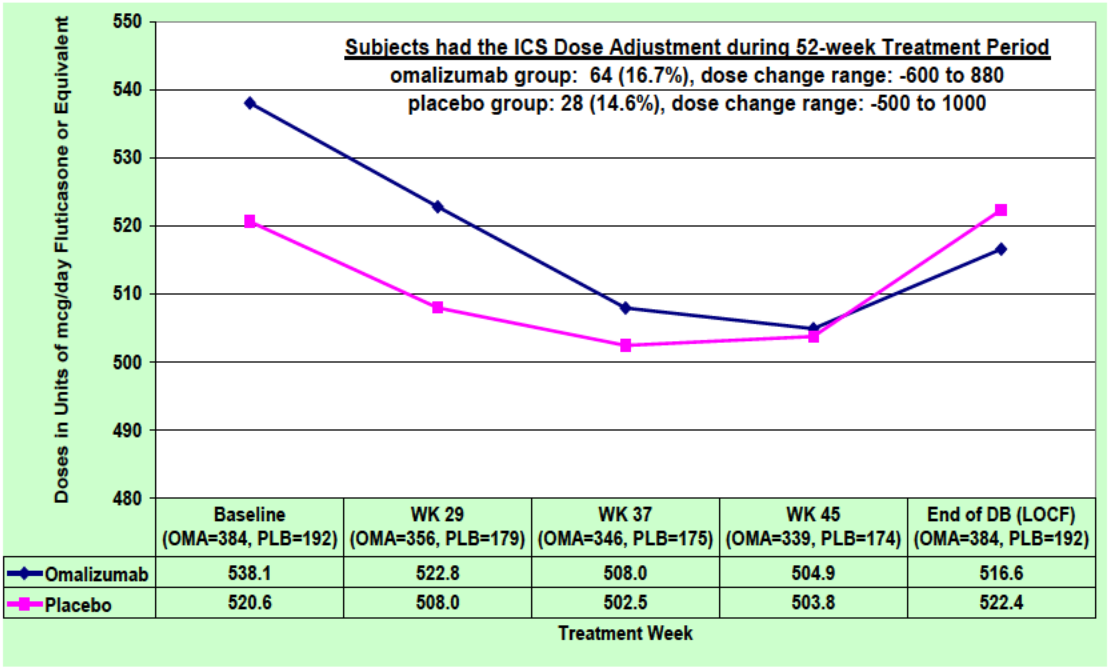
Xolair	384	4.97 (0.06)	5.91 (0.06)	6.20 (0.05)	0.06 (0.09)	0.06 (0.08)
Placebo	192	4.89 (0.09)	5.81 (0.08)	6.12 (0.07)	(-0.11, 0.24)	(-0.10, 0.23)

a: LS Means are obtained from the ANCOVA model with treatment, baseline value, sex, dosing schedule, and country effects.

ICS Dose Reduction

Figure 4 displays the mean over the 52-week treatment period in inhaled corticosteroid dose. At week-52, the ICS dose in the Xolair group was reduced by just 3.6% relative to baseline, compared to a slight increase (1.8%) in the placebo group. The difference between treatment groups approached but did not achieve statistical significance (p=0.054) using van Elteren test stratified by dose schedule.

Figure 4. Mean in ICS Dose during the 52-week DB Period



Doses are in units of mcg/day fluticasone or equivalent

Conclusion -

The primary and supportive analyses support a conclusion that treatment with Xolair significantly reduced the rate of asthma exacerbations compared with placebo in children 6-11 years of age with allergic asthma during the 52-weeks treatment period. No significant differences were seen between the treatment groups for changes in pulmonary function, asthma symptom scores, rescue medication use or PAQLQ scores. Xolair did not significantly reduce the inhaled corticosteroid dose compared to placebo during the 52-weeks treatment period. Subgroup analyses of the primary efficacy endpoint show consistency of results among severity groups, high ICS dose, and LABA use.

3.1.2 Study 010

Study Design and Endpoints

During the year of 1998 and 1999, the sponsor conducted Study 010 in 27 centers in US. The primary objective of the study was to determine the safety of administration of Xolair in 6-12 years old allergic asthma patients who were well-controlled with inhaled corticosteroids. The study was a randomized, double-blind, parallel group, placebo-controlled, and multicenter trial in which safety and efficacy data were collected.

Study 010 had a 7-month double-blind and a 5-month open-label treatment periods. The 7-month, double-blind treatment period included a 16-week stable treatment period followed by a 12-week steroid dose-reduction period. As shown in Table 16, following a 7-week screening period and 6-week pre-treatment run-in period, eligible patients were randomized to Xolair or placebo in 2:1 ratio during a 7-month double-blind core study comprised of 16 weeks stable treatment period followed by 12 weeks steroid dose-reduction period. All patients who completed the 7-month core study were eligible for the 5-month extension.

Table 16.Study Schema

Period	**I** **Screening**	**II** **Run-in**	**III** **Double-blind Core** **IIIA Stabilization** **IIIB Steroid reduction**	**IV** **Open-label Extension**
Visit	1	2	3-13	14-20
Week	-7	-6/-4 to 0	0 to 28	29-52
Asthma treatment / Study treatment	None	None	rhuMAb-E25 or Placebo	rhuMAb-E25
Inhaled Corticosteroids	BDP ≥ 168-420 µg/day or equivalent	BDP 168-420 µg/ day	IIIA: BDP 168-420 µg/ day stable dose (16 weeks) IIIB: tapered BDP dose up to 8 wks, BDP stable dose 4 wks	BDP treatment as appropriate for maintenance (24 weeks)

Eligible patients were male or female, 6–12 years old, with moderate to severe allergic asthma who required daily treatment with inhaled corticosteroids. Enrollment criteria included: diagnosis of allergic asthma ≥1 year, positive prick skin test to at least 1 perennial allergen, total serum IgE 30-1300 IU (inclusive) and body weight ≤90 kg, ≥12% increase in FEV1 after 4 puffs or up to 5 mg of albuterol/salbutamol, baseline FEV1 ≥60% predicted, asthma well-controlled on a minimum effective dose of ICS of 168 to 420 mcg/day of BDP for ≥3 months prior to randomization. Note that, unlike study IA05, inadequate symptom control and documented history of exacerbations prior to randomization were not criterions for entry.

The patients dosing regimen are determined from Table 17 below.

Table 17. Xolair Dosing Table (Ages 6 - < 12 years)

Baseline IgE (IU/mL)	Milligrams (mg) Per Dose Body weight (kg) 20-30	>30-40	>40-50	>50-60	>60-70	>70-90	Frequency of Dosing
>30-100	150	150	150	150	150	150	Q4wk
>100-200	150	150	300	300	300	300	
>200-300	150	300	300	300	225	225	Q2wk
>300-400	300	300	225	225	225	300	
>400-500	300	225	225	300	300	375	
>500-600	300	225	300	300	375		Not Dosed
>600-700	225	225	300	375			
>700-800	225	300	375				
>800-900	225	300	375				
>900-1000	300	375					
>1000-1100	300	375					
>1100-1200	300						
>1200-1300	375						

Using 2:1 randomization (active: placebo), a total of 324 patients were to be randomized. For the purpose of this submission, the sponsor included only the subpopulation 6-11 years of age of the ITT population (defined as all randomized patients) of Study 010 (298) in the post hoc analyses.

Primary endpoints were defined during the steroid reduction phase only:

1. Proportion of patients with ≥50% dose reduction of the dose of BDP
2. Proportion of patients with complete withdrawal of the dose of BDP (100% dose reduction)
3. Percent reduction in the dose of BDP

Exploratory endpoints included measures of asthma exacerbations (was defined as an exacerbation requiring treatment with oral or IV corticosteroids or doubling of patient's baseline BDP), asthma symptoms and medication use, spirometry and peak flow, and overall assessment of treatment

The percent reductions in the dose of BDP and the proportion of patients with reduction in the dose of BDP were analyzed using the generalized Cochran-Mantel-Haenszel (van Elteren) test stratified by treatment schedule. The patients' last recorded BDP dose in the steroid reduction phase was used as their 'final dose'. The BDP reduction was imputed as 0% if patients who did not enter the steroid-reduction period. The post hoc analyses for the clinically significant asthma exacerbation were performed using the same model as in Study IA05.

Patient Disposition, Demographic and Baseline Characteristics

After excluding 36 patients who were above 11 years old, the core consists of 298 patients. As shown in Table 18, a total of 92.6% of patients in ITT population completed the treatment phase (28 weeks). The most common reasons for discontinuation from the study were 'patient withdrew consent' and 'administrative problems'. The rest of analyses will base on the ITT population.

Table 18. Patients' Accountability N (%), (Core Population)

Study 010 core	***Xolair***	***Placebo***	***Total***
6 -11 years of age			
Randomized	203	95	298
Completed treatment period	190 (93.6)	86 (90.5)	276 (92.6)
Discontinued	13 (6.4)	9 (9.5)	22 (7.4)
Reason of early discontinuation			
Adverse event	1 (0.5)	0 (0.0)	1 (0.3)
Lack of efficacy	1 (0.5)	1 (1.1)	2 (0.7)
Patient's condition no longer requires study drug	0 (0.0)	0 (0.0)	0 (0.0)
Protocol violation	1 (0.5)	1 (1.1)	2 (0.7)
Patient withdrew consent	6 (3.0)	4 (4.2)	10 (3.4)
Lost to follow-up	2 (1.0)	0 (0.0)	2 (0.7)
Administrative problems	2 (1.0)	3 (3.2)	5 (1.7)
ITT population	203	95	298
Safety population	203	95	298

Table 19 shows that the demographic and baseline disease characteristics were generally well balanced between the treatment groups. Overall the mean age of the patient population was 8.6 years. A higher proportion of patients in the Xolair group fell into the 10 to 11 years age range compared to placebo. Approximately two-thirds of patients were male and the majority of patients were Caucasian. The overall mean FEV1 (% of predicted) for the population was 86.4%.

Table 19 shows that asthma medication uses at baseline were similar between treatment groups. In the Xolair group, the mean inhaled corticosteroid dose IgE level was slightly higher. The slightly higher proportion of patients in Xolair group was hospitalized and visited doctor due to asthma. The mean duration of asthma was similar for both treatment groups.

Table 19. Patients' Demographic and Baseline Characteristics N (%), (ITT Population)

Study 010 core	***Xolair (n=203)***	***Placebo (n=95)***	***Total (n=298)***
Age (yrs)			
6-8 years old, N (%)	68 (33.5)	30 (31.6)	98 (32.9)
9-11 years old, N (%)	135 (66.5)	65 (68.4)	200 (67.1)
Mean (SD)	9.1 (1.6)	9.1 (1.6)	9.1 (1.6)
Median (Range)	5 – 11	6 – 11	9 (5 – 11)
Sex			
Female	60 (29.6)	32 (33.7)	92 (20.9)
Male	143 (70.4)	63 (66.3)	206 (69.1)
Race			
Caucasian	149 (73.4)	76 (80.0)	225 (75.5)
Black	36 (17.7)	12 (12.6)	48 (16.1)
Oriental	3 (1.5)	0 (0.0)	3 (1.0)

Other	15 (7.4)	7 (7.4)	22 (7.4)
FEV_1 (%predicted) (visit 1, pre-bronchodilator)			
Mean (SD)	83.7 (14.7)	85.4 (13.8)	84.3 (14.4)
Median (Range)	84.0 (49 – 129)	86.0 (43 – 116)	84 (43 – 129)
Mean Qualifying FEV_1 Reversibility (%)			
Mean (SD)	20.6 (10.5)	20.1 (7.9)	20.4 (9.7)
Median (Range)	17.2 (12 – 94)	17.7 (12 – 42)	17.4 (12 – 94)
Serum total IgE (IU/mL)			
Mean (SD)	352.7 (269.4)	322.8 (276.7)	343.2 (271.6)
Median (Range)	259 (20 – 1269)	211 (31 – 1212)	241 (20 – 1269)
Inhaled Corticosteroid Dose [a] (mcg/day)			
Mean (SD)	167.7 (59.0)	159.5 (55.)	165.1 (57.8)
Median (Range)	200 (100 – 400)	150 (100 – 300)	150 (100 – 400)
Patients Medical History at Baseline			
Hospitalized for asthma treatment in past year – n (%)	17 (8.4)	7 (7.4)	24 (8.1)
Man number of ER visits for asthma treatment in the past year	0.6	0.5	0.6
Mean number of doctor's office visits for urgent asthma treatment in the past year	1.9	1.5	1.8
Duration of allergic asthma (years)			
Mean (SD)	6.0 (2.7)	5.7 (2.7)	5.9 (2.7)
Median (Range)	6 (1 – 11)	5 (1 – 12)	6 (1 – 12)

a: Fluticasone equivalent dose.

Results and Conclusions

BDP Dose Reduction

Based on the sponsor analysis shown in Table 20, there was a statistically significant reduction in the mean ICS dose (based on beclomethasone or equivalents) at the end of the 28-week double-blind treatment period for Xolair patients compared with placebo.

Table 20. Percent Change from Baseline to the End of the 28-week DB period in ICS dose (ITT)

	Omalizumab N=203	Placebo N=95
Number of patients	203	94
Mean (SD)	-73.4 (37.22)	-63.4 (40.32)
Median	-100.0	-75.0
Range	-100 - 100	-100 - 100
p-value	0.013	

End of 12-week steroid adjustable period = Visit 13 (week 28) or early discontinuation
Source: SCE-Table 3.2-5

a. copied from the submission because the sponsor did not send the ICS dose usage data set of t_spi_ics.xpt which was used to create this table.

Post Hoc Efficacy Endpoint – Rate of Moderate/Severe Exacerbations

In the protocol of Study 010 (core) the definition of a clinically significant asthma exacerbation was slightly different to that for Study IA05. In the *post hoc* analysis, the definition of clinically

significant asthma exacerbation used for Study IA05 was applied to the subpopulation of Study 010 (core). Analysis of clinically significant asthma exacerbations with imputation during the 16-week fixed steroid dose period and 12-week adjusted steroid dose are presented in Table 21. As shown in Table 22, the ratio of the exacerbation rate for Xolair to the rate on placebo during the both treatment periods were 0.57 (95%CI: [0.35, 0.97]) and 0.45 (95%CI: [0.28, 0.71]) which represented a 43% and 55% decrease in annual rate compared with placebo ($p<0.003$). Figure 5 graphically displays the rate ratio of Xolair and placebo from Poisson model.

Table 21. Summary of Asthma Exacerbations during 16-week Fixed Dose Period

	With imputation		***Without imputation***	
	Xolair (n=203)	***Placebo (n=95)***	***Xolair (n=203)***	***Placebo (n=95)***
Number of Patients with an Exacerbation	33 (16%)	25 (26%)	27 (13%)	19 (20%)
Total Number of Exacerbations	39	29	32	23
Patient with Clinically Significant Asthma Exacerbation Event, n (%)				
0	170 (83.7)	70 (73.7)	176 (86.7)	76 (80.0)
1	28 (13.8)	22 (23.2)	23 (11.3)	16 (16.8)
2	4 (2.0)	2 (2.1)	3 (1.5)	2 (2.1)
3	1 (0.5)	1 (1.1)	1 (0.5)	1 (1.1)
≥4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Rate of clinically significant Exacerbation per treatment period	0.18	0.32	0.14	0.25
Ratio (Xolair vs. Placebo)		0.58		0.58
95% CI		(0.345, 0.96)		(0.32, 1.04)
p-value		0.033		0.068

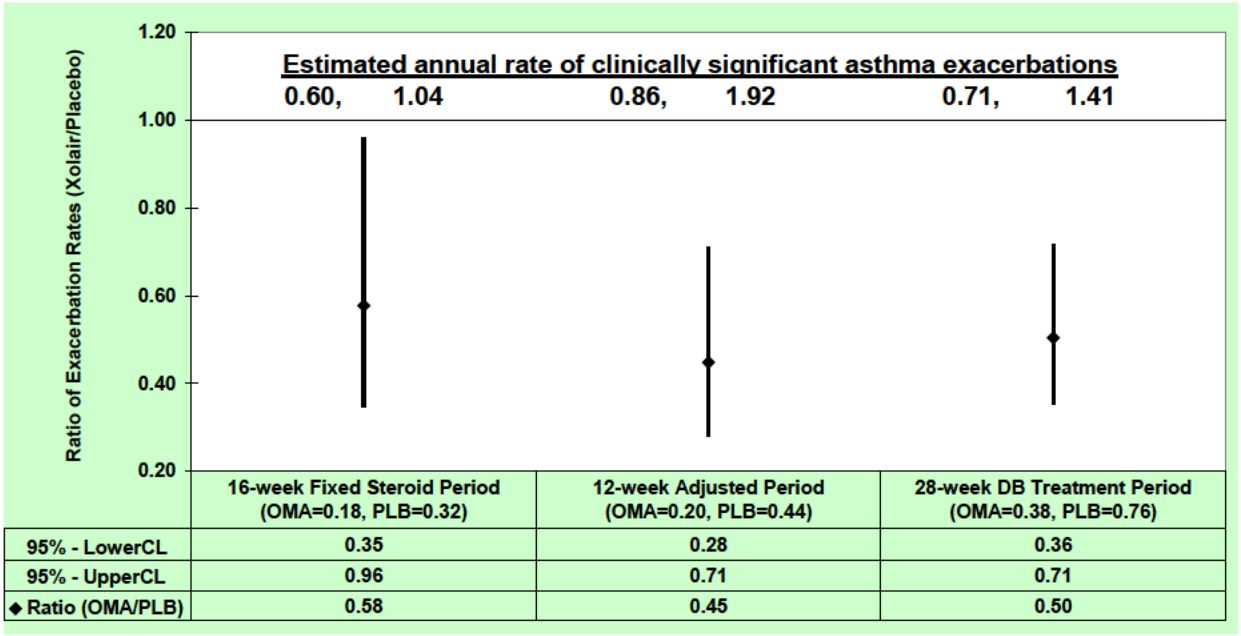
Source: poisson_010.sas;
Poisson regression model adjusted for treatment, country, dosing schedule, and history of total number of ER and doctor's office visits.

Table 22. Summary of Asthma Exacerbation s during 28-week DB Treatment Period

	With imputation		***Without imputation***	
	Xolair (n=203)	***Placebo (n=95)***	***Xolair (n=203)***	***Placebo (n=95)***
Number of Patients with an Exacerbation	27 (13%)	19 (20%)	27 (13%)	19 (20%)
Total Number of Exacerbations	79	69	67	60
Patient with Clinically Significant Asthma Exacerbation Event, n (%)				
0	141 (69.5)	47 (49.5)	150 (73.9)	55 (57.9)
1	48 (23.6)	34 (35.8)	42 (20.7)	27 (28.4)
2	11 (5.4)	10 (10.5)	8 (3.9)	9 (9.5)
3	3 (1.5)	1 (1.1)	3 (1.5)	1 (1.1)
≥4	0 (0.0)	3 (3.2)	0 (0.0)	3 (0.2)
Between treatment comparison, p-value		<.001		0.03
Rate of clinically significant Exacerbation per treatment period	0.38	0.76	0.32	0.66
Ratio (Xolair vs. Placebo)		0.504		0.483
95% CI		(0.355, 0.714)		(0.327, 0.713)
p-value		<.001		<.001

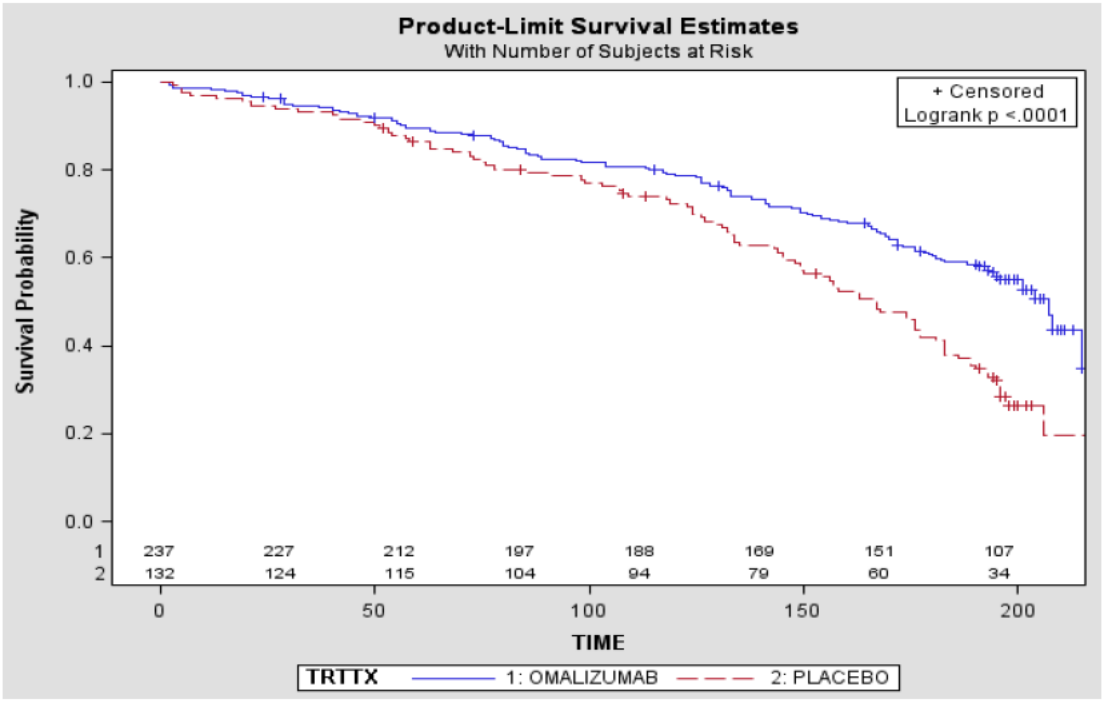
Source: poisson_010.sas;
Poisson regression model adjusted for treatment, country, dosing schedule, and history of total number of ER and doctor's office visits.

Figure 5. Summary of Clinically Significant Asthma Exacerbations during 28-week DB period



	16-week Fixed Steroid Period (OMA=0.18, PLB=0.32)	12-week Adjusted Period (OMA=0.20, PLB=0.44)	28-week DB Treatment Period (OMA=0.38, PLB=0.76)
95% - LowerCL	0.35	0.28	0.36
95% - UpperCL	0.96	0.71	0.71
◆ Ratio (OMA/PLB)	0.58	0.45	0.50

Figure 6. Time to First Exacerbation during 28-week DB Period



Source: poisson_010.sas

Secondary Endpoint

As show in Table 23 and Table 24, there was little change in FEV1, FVC, and FEF 25-75% over time with minimal difference between the two treatment groups. Xolair show some benefit in improving the pulmonary function, PEF, and asthma symptom, but the effect size is very small compared to placebo group and did not reach the statistical significance except FVC and nocturnal asthma symptom score at 24-week fixed ICS dose period.

Table 23. Analyses of Pulmonary Function Data over 28-week DB Period

			Double-blind treatment period		
		Baseline value	***Observed value at 16-week***	***Observed value at 28-week***	***From ANCOVA On change from baseline*** LS Mean (SE), 95% CI
Treatment	N	Mean (SE)	Mean (SE)	Mean (SE)	LOCF to Week 28
FEV1 (L)					
Xolair	203	1.734 (0.03)	1.811 (0.03)	1.824 (0.03)	0.046 (0.03), (-0.011, 0.103)
Placebo	95	1.794 (0.05)	1.835 (0.05)	1.832 (0.05)	p=0.114
FVC (L)					
Xolair	203	2.195 (0.04)	2.288 (0.04)	2.321 (0.04)	0.021 (0.03), (-0.042, 0.084)
Placebo	95	2.247 (0.07)	2.323 (0.07)	2.351 (0.07)	P=0.517
FEF 25-75% (L/sec)					
Xolair	203	1.659 (0.05)	1.738 (0.05)	1.719 (0.05)	0.092 (0.06), (-0.022, 0.206)
Placebo	95	1.708 (0.07)	1.712 (0.07)	1.652 (0.07)	p=0.114
Percent predicted FEV1 (%)					
Xolair	203	83.7 (1.03)	87.4 (1.08)	88.4 (1.05)	1.938 (1.25), (-0.72, 4.59)
Placebo	95	85.4 (1.42)	88.2 (1.46)	88.8 (1.70)	p=0.152

a: LS Means are obtained from the two-way ANCOVA model with treatment, baseline value, dosing schedule, and sex effects.

Table 24. Analyses of Diary Data over 28-week DB Period

			Double-blind treatment period			
		Baseline value	***Observed value at >14-16wk***	***Observed value at >24-28wk***	***From ANCOVA On change from baseline*** LS Mean (SE), 95% CI	
Treatment	N	Mean (SE)	Mean (SE)	Mean (SE)	LOCF to week 16	LOCF to week 28
Morning PEF (L/min)						
Xolair	203	252.5 (4.0)	261.7 (4.3)	264.3 (4.4)	4.70 (3.6)	6.59 (4.2)
Placebo	95	252.7 (5.4)	257.0 (6.1)	257.8 (6.5)	(-2.3, 11.8)	(-1.7, 14.9)
Nocturnal Asthma Symptom Score						
Xolair	203	0.24 (0.03)	0.15 (0.02)	0.15 (0.02)	-0.025 (0.03)	-0.126 (0.04)
Placebo	95	0.25 (0.04)	0.19 (0.04)	0.26 (0.05)	(-0.09, 0.04)	(-0.21, -0.04)
Morning Asthma Symptom Score						
Xolair	203	0.19 (0.02)	0.14 (0.02)	0.13 (0.02)	-0.020 (0.03)	-0.061 (0.03)
Placebo	95	0.19 (0.03)	0.18 (0.03)	0.19 (0.03)	(-0.07, 0.03)	(-0.11, -0.01)
Daytime Asthma Symptom Score						
Xolair	203	0.58 (0.04)	0.38 (0.04)	0.35 (0.04)	-0.094 (0.05)	-0.174 (0.06)
Placebo	95	0.62 (0.06)	0.47 (0.06)	0.54 (0.06)	(-0.20, 0.01)	(-0.29, -0.06)
Total Clinical Asthma Symptom Score						
Xolair	203	1.00 (0.07)	0.66 (0.06)	0.62 (0.07)	-0.116 (0.09)	-0.353 (0.11)
Placebo	95	1.07 (0.12)	0.82 (0.11)	0.99 (0.12)	(-0.30, 0.07)	(-0.57, -0.13)
Number of Puffs of Asthma Rescue Medication						
Xolair	203	1.25 (0.11)	0.79 (0.10)	0.80 (0.10)	-0.124 (0.14)	-0.363 (0.17)
Placebo	95	1.31 (0.18)	0.97 (0.14)	0.99 (0.14)	(-0.40, 1.55)	(-0.70, -0.02)

a: LS Means are obtained from the two-way ANCOVA model with treatment, baseline value, dosing schedule ,and sex effects.

Conclusion -
Results from patients 6-<12 years of age in Study 010 (core) support the efficacy of Xolair in terms of reducing exacerbation rates. The reductions were comparable to those obtained in Study IA05. The rate of clinically significant asthma exacerbations during the 16-week fixed steroid treatment period was statistically significantly lower in Xolair patients compared with placebo, representing a 42% relative decrease for Xolair patients. Similarly, the rate of clinically significant asthma exacerbations during the 28-week double-blind treatment period was statistically significantly lower in Xolair patients compared with placebo, representing a relative decrease of 50%. The percentage reduction of ICS dose at the end of the 28-week treatment period was statistically significantly greater for Xolair patients. The proportion of patients with a reduction of ICS dose was also statistically significantly higher in Xolair patients at the end of the 28-week treatment period. No significant differences were seen between the treatment groups for changes in pulmonary function, asthma symptom scores, rescue medication use or QOL scores.

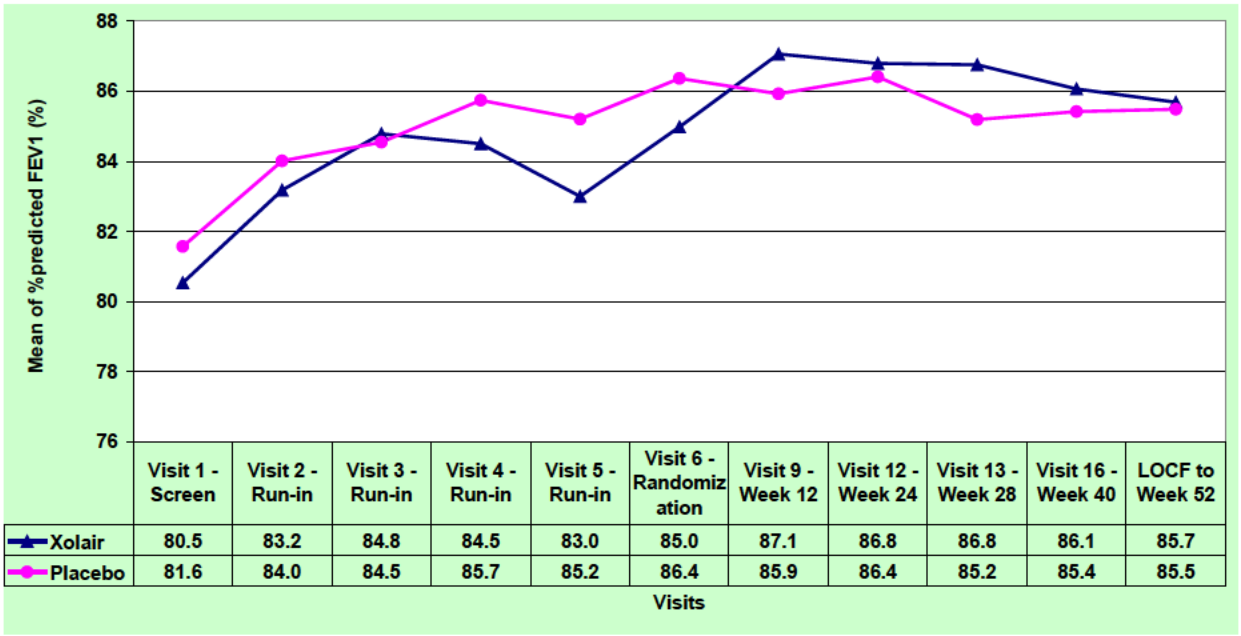
3.3 Evaluation of Safety

Dr. Peter Starke, the Medical Reviewer, conducted the evaluation of the safety data separately. Reader is referred to Dr. Starke's review for information regarding the safety profile of the drug.

4. APPENDIX

Following figures were generated from Diary data (a_diar1.xpt and a_diar2.xpt).

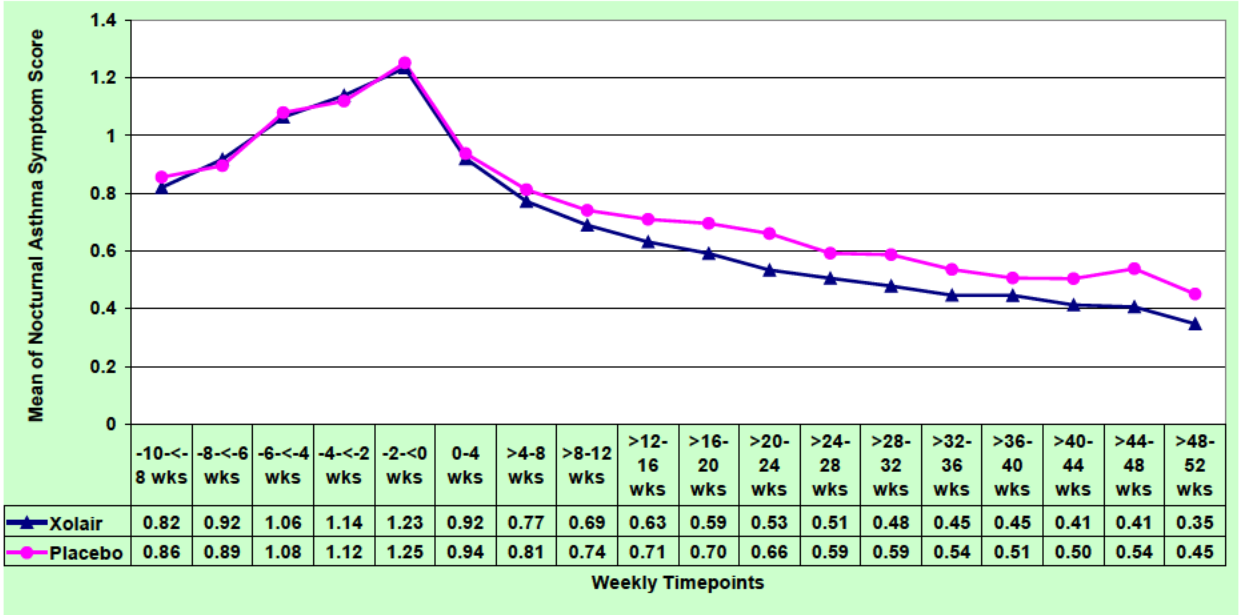
Figure 7. Raw Mean %Predicted FEV1 (%) by Visits (MITT)



	Visit 1 - Screen	Visit 2 - Run-in	Visit 3 - Run-in	Visit 4 - Run-in	Visit 5 - Run-in	Visit 6 - Randomization	Visit 9 - Week 12	Visit 12 - Week 24	Visit 13 - Week 28	Visit 16 - Week 40	LOCF to Week 52
Xolair	80.5	83.2	84.8	84.5	83.0	85.0	87.1	86.8	86.8	86.1	85.7
Placebo	81.6	84.0	84.5	85.7	85.2	86.4	85.9	86.4	85.2	85.4	85.5

Visits

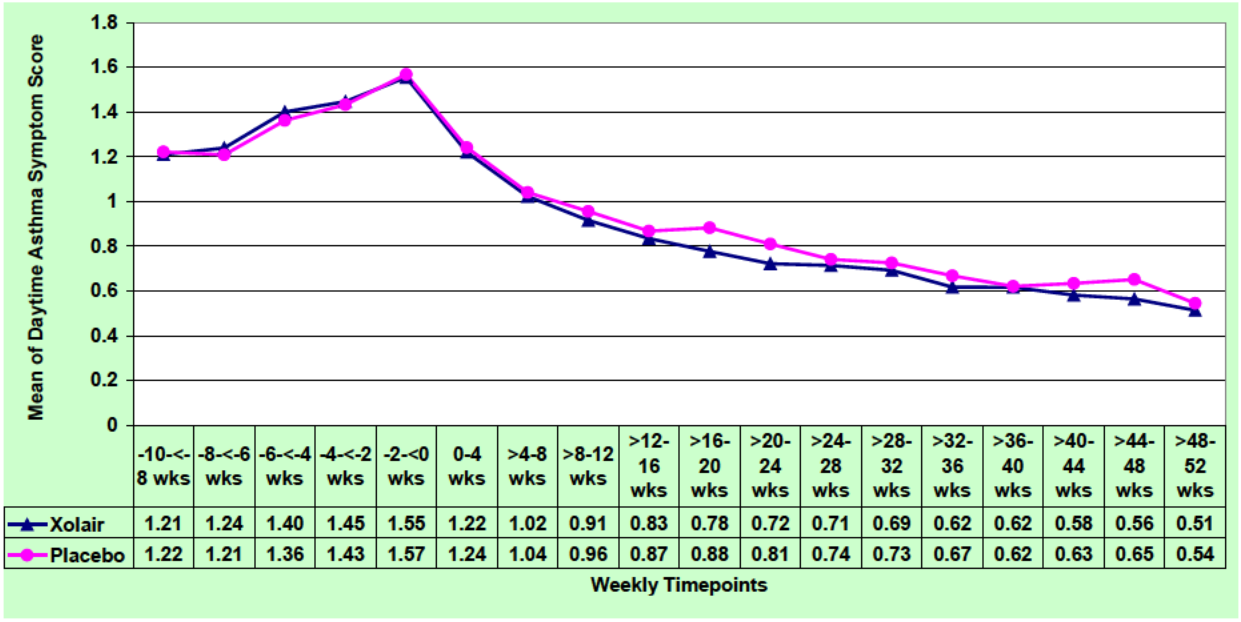
Figure 8. Raw Mean of Nocturnal Asthma Symptoms Score by 2 or 4-weekly (MITT)



	-10-<-8 wks	-8-<-6 wks	-6-<-4 wks	-4-<-2 wks	-2-<0 wks	0-4 wks	>4-8 wks	>8-12 wks	>12-16 wks	>16-20 wks	>20-24 wks	>24-28 wks	>28-32 wks	>32-36 wks	>36-40 wks	>40-44 wks	>44-48 wks	>48-52 wks
Xolair	0.82	0.92	1.06	1.14	1.23	0.92	0.77	0.69	0.63	0.59	0.53	0.51	0.48	0.45	0.45	0.41	0.41	0.35
Placebo	0.86	0.89	1.08	1.12	1.25	0.94	0.81	0.74	0.71	0.70	0.66	0.59	0.59	0.54	0.51	0.50	0.54	0.45

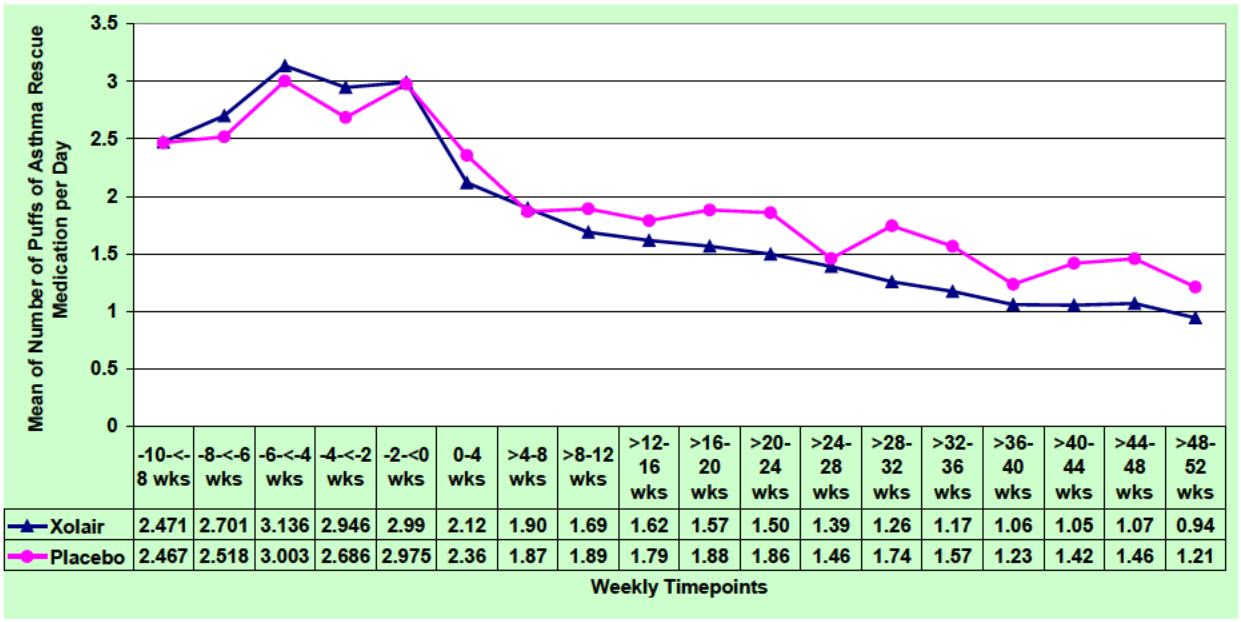
Weekly Timepoints

Figure 9. Raw Mean of Daytime Asthma Symptoms Score by 2 or 4-weekly (MITT)



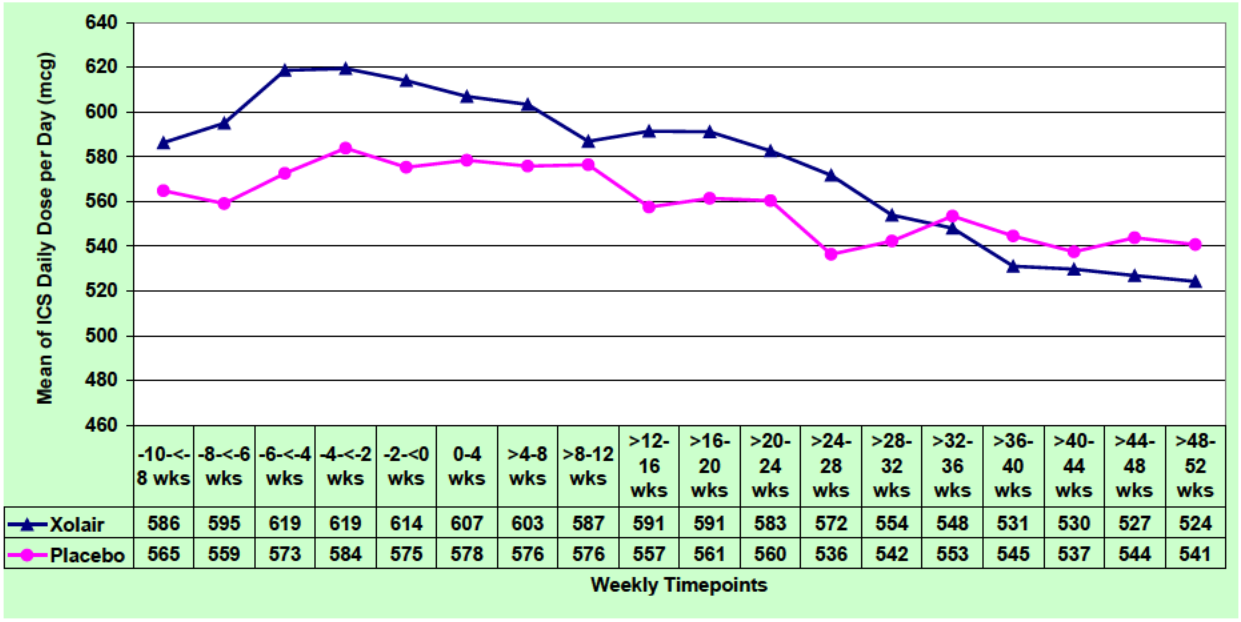
	-10-<-8 wks	-8-<-6 wks	-6-<-4 wks	-4-<-2 wks	-2-<0 wks	0-4 wks	>4-8 wks	>8-12 wks	>12-16 wks	>16-20 wks	>20-24 wks	>24-28 wks	>28-32 wks	>32-36 wks	>36-40 wks	>40-44 wks	>44-48 wks	>48-52 wks
Xolair	1.21	1.24	1.40	1.45	1.55	1.22	1.02	0.91	0.83	0.78	0.72	0.71	0.69	0.62	0.62	0.58	0.56	0.51
Placebo	1.22	1.21	1.36	1.43	1.57	1.24	1.04	0.96	0.87	0.88	0.81	0.74	0.73	0.67	0.62	0.63	0.65	0.54

Figure 10. Raw Mean of Number of Puffs/day of Asthma Rescue Medication by 2 or 4-weekly (MITT)



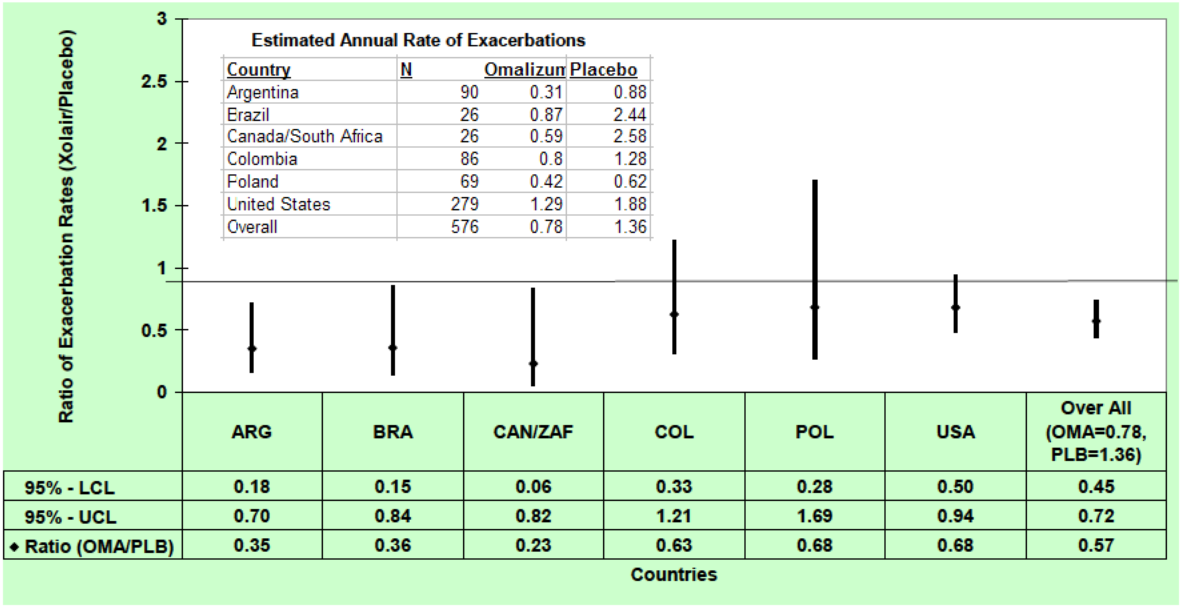
	-10-<-8 wks	-8-<-6 wks	-6-<-4 wks	-4-<-2 wks	-2-<0 wks	0-4 wks	>4-8 wks	>8-12 wks	>12-16 wks	>16-20 wks	>20-24 wks	>24-28 wks	>28-32 wks	>32-36 wks	>36-40 wks	>40-44 wks	>44-48 wks	>48-52 wks
Xolair	2.471	2.701	3.136	2.946	2.99	2.12	1.90	1.69	1.62	1.57	1.50	1.39	1.26	1.17	1.06	1.05	1.07	0.94
Placebo	2.467	2.518	3.003	2.686	2.975	2.36	1.87	1.89	1.79	1.88	1.86	1.46	1.74	1.57	1.23	1.42	1.46	1.21

Figure 11. Raw Mean of Daily ICS Dose Used by 2 or 4-weekly (MITT)



	-10-<-8 wks	-8-<-6 wks	-6-<-4 wks	-4-<-2 wks	-2-<0 wks	0-4 wks	>4-8 wks	>8-12 wks	>12-16 wks	>16-20 wks	>20-24 wks	>24-28 wks	>28-32 wks	>32-36 wks	>36-40 wks	>40-44 wks	>44-48 wks	>48-52 wks
Xolair	586	595	619	619	614	607	603	587	591	591	583	572	554	548	531	530	527	524
Placebo	565	559	573	584	575	578	576	576	557	561	560	536	542	553	545	537	544	541

Figure 12. Asthma Exacerbation During the 52-week DB Treatment Period by Country (MITT)



Estimated Annual Rate of Exacerbations

Country	N	Omalizum	Placebo
Argentina	90	0.31	0.88
Brazil	26	0.87	2.44
Canada/South Africa	26	0.59	2.58
Colombia	86	0.8	1.28
Poland	69	0.42	0.62
United States	279	1.29	1.88
Overall	576	0.78	1.36

	ARG	BRA	CAN/ZAF	COL	POL	USA	Over All (OMA=0.78, PLB=1.36)
95% - LCL	0.18	0.15	0.06	0.33	0.28	0.50	0.45
95% - UCL	0.70	0.84	0.82	1.21	1.69	0.94	0.72
◆ Ratio (OMA/PLB)	0.35	0.36	0.23	0.63	0.68	0.68	0.57

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/s/

FREDA COONER
02/18/2016

THOMAS J PERMUTT
02/19/2016
I concur.