MEDICAL OFFICER REVIEW

Division Of Pulmonary and Allergy Drug Products (HFD-570)

APPLICATION:	BB IND 05369, SDN 459	**TRADE NAME:**	Xolair
APPLICANT/SPONSOR:	Genentech, Inc. and Novartis Pharmaceuticals Corp.	**USAN NAME:**	Omalizumab (rhuMAb-E25)
MEDICAL OFFICER:	Peter Starke, M.D.	**CATEGORY:**	Recombinant humanized IgG1κ monoclonal antibody
TEAM LEADER:	Lydia Gilbert-McClain, M.D.		
DATE:	April 16, 2009	**ROUTE:**	Subcutaneous injection

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date	CDER Stamp Date	Submission	Comments
February 27, 2009	February 27, 2009	SDN 459	Study Q2948g (EXCELS) interim study report through 11/30/08
March 17, 2009	March 17, 2009	BLA 103976/5149, SDN 0226	Pediatric supplement 120 day safety update

RELATED APPLICATIONS

Document Date	Application Type	Comments

REVIEW SUMMARY:

This is a review of the 4th interim report for PMC #3 Xolair. PMC #3 was for an observational cohort study, Q2948g (EXCELS), to assess the incidence of malignancy and other serious adverse events (SAEs) among approximately 5000 Xolair-treated and 2500 non-Xolair-treated control patients who are followed for 5 years. The interim report is submitted to both the BB-IND and the BLA pediatric supplement currently under review.

The study design has been identified by DPAP to have 3 major design flaws that may inhibit the ability to interpret the results. These flaws have previously been communicated to the sponsors.

The interim study report does not show an imbalance in malignancies, although several imbalances in SAEs are reported when the SAE data are presented by SOC. The meaning of these imbalances is unclear in an ongoing observational study.

OUTSTANDING ISSUES:

In the 120-day safety update to BLA 103976/5149, SDN 0226, the applicants ask whether submission of an addendum containing an in-depth assessment and cumulative review of cardiac disorders to the EXCELS interim study report #4 by July 3, 2009, on or before 90 days of the BLA action date, would be acceptable. This assessment is being made at the request of the EMEA, the EMEA having reviewed the EXCELS interim study report #3 from last year and requested this analysis. This is acceptable. Acceptability will be communicated to the sponsors.

RECOMMENDED REGULATORY ACTION

IND/NEW STUDIES: ___ **SAFE TO PROCEED** ___ **CLINICAL HOLD**

OTHER ACTION(S): X **NAI, COMMENT TO SPONSORS**

SIGNATURES

MEDICAL OFFICER: [signature] **DATE:** 4/16/2009

MEDICAL TEAM LEADER: [signature] **DATE:** 4/17/2009

Regulatory Background

This is a review of the 4th interim report, submitted February 27, 2009 to BB IND 05369, SDN 459, for postmarketing commitment (PMC) #3 for Xolair. PMC #3 was

> "To conduct a prospective, observational cohort study of 5,000 Omalizumab-treated and 2,500 untreated patients that assess the clinical safety of Omalizumab by determining the incidence of malignancy and other serious adverse events (SAEs) in Omalizumab treated patients with moderate to severe persistent asthma and skin test or in vitro reactivity to an aeroallergen compared with patients not treated with Omalizumab. Study subjects will be followed for at least 5 years, and Omalizumab-treated patients will be matched at enrollment to untreated patients by age, gender and race/ethnicity. Interim reports will be filed yearly."

The study to fulfill this commitment is study Q2948g, "An Epidemiologic Study of Xolair® (Omalizumab) Evaluating Clinical Effectiveness and Long-Term Safety in Patients with Moderate to Severe Asthma (EXCELS)". Milestones for the commitment are shown in Table 1. The current PMC status is "Ongoing."

Note that this same information was also submitted in the 120-day safety update to BLA 103976/5149, the pediatric efficacy supplement to extend the current indication for Xolair from 12 years of age and above to 6 through 11 years of age. With the 120-day safety update, the applicants ask whether submission of an addendum containing an in-depth assessment and cumulative review of cardiac disorders to the EXCELS interim study report #4 by July 3, 2009, on or before 90 days of the BLA action date, would be acceptable. This assessment is being made at the request of the EMEA, the EMEA having reviewed the EXCELS interim study report #3 from last year and requested this analysis. This request is acceptable.

Regulatory interactions with Genentech, as summarized by Dr. Jim Kaiser in his last review of this PMC in February 2008, have been as follows: "FDA communicated with Genentech by telephone regarding trial Q2948g in June 2004. Genentech sent responses to FDA on November 8, 2004, and FDA sent a letter to Genentech regarding the trial on June 21, 2005. Significant concerns were raised about the ability of the trial to address the safety concerns from the PMC. The chief point of FDA concern was the exclusion from the trial of subjects with possible predisposition to cancer, an exclusion that was removed in a protocol amendment dated September 23, 2005. Genentech submitted a second protocol amendment in March 2007 about which FDA did not send comments. Genentech submitted a 2nd mandated annual report of the results of trial Q2948g on February 28, 2007. Subsequent to review of the report, on October 3, 2007 FDA told Genentech that the protocol has three potentially significant design flaws, and requested further information from Genentech to address the significance of these flaws." The three major flaws identified by DPAP include:

1) Patients could be enrolled who had previous exposure to Xolair,
2) The protocol (subsequently amended) excluded patients with a history of cancer, and
3) No minimal duration of exposure to Xolair was required.

Genentech responded with comments to the IND.

Table 1. PMC #3, Milestones

Milestone	Commitment	Proposed Revised Date	Completion Date / Study Status
Submission of Final Protocol	December 31, 2003	NA	December 24, 2003
Study Start Date	NA	NA	NA
Completion of Accrual	March 31, 2006	NA	November 17, 2006
Completion of Trial	March 31, 2011	June 30, 2011	Ongoing
Submission of Final Study Report to FDA	September 30, 2011	December 31, 2011	Ongoing

Summary of the Study Plan

This is a 5-year, multicenter, prospective, observational cohort study in patients ≥12 years of age with moderate to severe persistent asthma and a positive skin test or in vitro reactivity to an aeroallergen, with the intent to assess the long-term safety of Xolair for risks of malignancy and other serious adverse events. The study plan calls for enrollment of approximately 5000 Xolair-treated and 2500 non-Xolair-treated patients, and follow them for 5 years with no treatment assignment. The primary objective is to compare the long-term clinical safety profile of Xolair compared to placebo, with the secondary objectives to assess the benefit of Xolair as determined by measures of asthma control, work productivity and activity impairment, and healthcare use over time. Study visits are scheduled every 6 months, and study data is captured electronically (b) (4) .

Interim Results

The interim report is dated February 26, 2009, covering the period from initiation of the study on June 4, 2004, through the cutoff date of November 30, 2008.

Patients were recruited from 489 sites in the United States that span a variety of practice settings, including managed care organizations, community physicians, and academic centers. As of the cutoff date, 7951 patients ≥12 years of age had been enrolled, 5041 in the Xolair cohort, 2886 in the non-Xolair cohort, and 24 of uncertain cohort designation. Note that of the 2886 patients in the non-Xolair cohort, 255 initiated treatment with Xolair at some time after enrollment. Of the 7951 enrolled patients, 7948 patients (>99.9%) had completed the baseline visit, 6956 (87.5%) had completed the 12-month visit, 5625 (70.7%) had completed the 24-month visit, 2784 (35.0%) had completed the 36-month visit, and 428 (5.4%) had completed the 48-month visit. Of the 7951 enrolled patients, 4468 (56.2%) were enrolled prior to the first protocol amendment (23 September 2005) and 3483 (43.8%) were enrolled after this amendment. This amendment removed the exclusion criterion for patients with a history of cancer or a history of a pre-malignant condition and patients who are being assessed for possible cancer diagnosis.

The study report notes that the majority of patients in the Xolair cohort were receiving Xolair prior to their enrollment in the study. Specifically, 1212 patients (24.0%) had received more than 12 months of prior Xolair treatment, 1094 (21.7%) more than 6 months and up to 12 months of prior treatment, 1176 (23.3%) from 2 months to 6 months of prior treatment, 983 (19.5%) more than 7 days and up to 2 months of prior Xolair treatment, and

569 received their first Xolair dose no more than 7 days prior to enrollment. The median duration of Xolair on-study treatment is stated to be 25.1 months.

Table 2 shows total SAEs, deaths, pregnancies, and malignancies. Patients in the non-Xolair cohort who initiated treatment with Xolair are listed separately under the non-Xolair cohort. A total of 217 patients (141 Xolair, 76 non-Xolair) were reported to have experienced 277 malignancy events thus far in the study. Of these, 209 narratives were reviewed by an oncologist to assess whether the event was a true malignancy, whether the malignancy was study emergent and whether it was a primary malignancy, resulting in 106 patients in the Xolair cohort with 120 confirmed study-emergent primary malignancies, 57 patients in the non-Xolair cohort with 63 confirmed study-emergent primary malignancies, none in the "unsure" cohort, and 4 in patients in the non-Xolair cohort after initiating Xolair treatment. Excluding non-melanoma skin cancers, there were 91 primary malignancies, 55 in the Xolair cohort, 33 in the non-Xolair cohort who did not receive Xolair, and 3 in the non-Xolair cohort after initiating Xolair treatment [T19, p 100-101]. Review of the table revealed no clear pattern to the malignancies.

Table 3 shows SAEs reported in ≥1% of patients by primary MedDRA SOC. In four SOCs, the percentages of patients with SAEs are higher in Xolair-treated patients than in non-Xolair-treated patients. These include the SOCs of cardiac disorders; infections and infestations; nervous system; and respiratory, thoracic, and mediastinal disorders. Since the study is ongoing, it is premature to come to any conclusions regarding these differences.

As requested by the EMEA, and based on last year's interim report #3, Genentech/Novartis are performing further analyses of cardiac events. The results of these additional analyses are expected in early July 2009 as an amendment to this interim report. It is unclear why the EMEA singled out cardiac events from others with differentials in SAE events.

Conclusions

This observational cohort study has some significant limitations which have already been identified and communicated to the sponsors. The interim study report does not show an imbalance in malignancies, although several imbalances in SAEs are reported when the SAE data are presented by primary SOC. The meaning of these imbalances is unclear in an ongoing observational study.

Comments to Sponsors

1. Your proposal to submit further analyses of cardiac events in study Q2948g (EXCELS) as an amendment to interim report #4 in early July 2009, is acceptable.

Table 2. SAEs: Deaths, Pregnancies, and Malignancies

SAEs, n (%)	Non-Xolair cohort		Xolair cohort n=5041	Cohort unsure n=24
	Prior to Xolair n=2886	After starting Xolair n=255		
Any SAE	362 (12.5)		927 (18.4)	
Deaths	28		53	
Deaths ≤6 months after stopping Xolair[1]	26		45	
Rate (95% CI) per 1000 person-years[1]	4.0 (2.9, 5.4)		4.1 (2.7, 6.1)	
Other Deaths (>6 months after stopping Xolair or in patients in the non-Xolair cohort who died after starting Xolair)		2	8	
Pregnancies[2]				
Pregnant when enrolled	3		11	
New pregnancy	51		83	
Spontaneous AB	1		6	
Malignancies				
Patients with malignancies	76 (2.6%)		141 (2.8%)	
Malignancy events				
No previous CA history	42 (2.0%)		85 (2.6%)	
Previous CA or pre-CA history	21 (7.8%)		31 (7.3%)	
Active CA at baseline	4 (21.1%)		5 (14.3%)	
Unclassified history status	9 (1.7%)		20 (1.5%)	
Confirmed Primary Malignancy events	63	4	120	0
Rate per 1000 person-years	10.01	8.06	9.83	
Confirmed Primary Malignancies excluding non-melanoma skin cancers	33	3	55	0
Rate per 1000 person-years	5.24	4.55	6.04	

1 Deaths and death rate included in the Xolair group include deaths out to 6 months after the last Xolair dose
2 Patients on Xolair are referred to Xolair pregnancy registry for additional pregnancy follow-up

Source: Text p 97-99; T19, p100-101; T21, p197

Table 3. SAEs reported in ≥1% of patients, by MedDRA SOC

SAEs by MedDRA SOC, n (%)	Non-Xolair n=2886	Xolair n=5041	Unsure n=24	All n=7951
Any SAE	362 (12.5)	927 (18.4)	1 (4.2)	1290 (16.2)
Cardiac disorders	24 (0.8)	76 (1.5)	0	100 (1.3)
Gastrointestinal disorders	34 (1.2)	70 (1.4)	0	104 (1.3)
Infections and infestations	73 (2.5)	211 (4.2)	0	284 (3.6)
Injury, poisoning and procedural complications	34 (1.2)	53 (1.1)	0	87 (1.1)
Musculoskeletal and connective tissue disorders	29 (1.0)	61 (1.2)	0	90 (1.1)
Nervous system disorders	13 (0.5)	55 (1.1)	1 (4.2)	69 (0.9)
Respiratory, thoracic and mediastinal disorders	151 (5.2)	456 (9.0)	0	607 (7.6)

Note: SOCs with a disproportionate frequency of events in one group vs another are highlighted. All of the SOCs with a higher disproportionate frequency are in patients treated with Xolair.

Source: T12, p77