NDA/BLA Multi-disciplinary Review and Evaluation

Application Type	Supplemental BLA
Application Number(s)	BLA 103976, Supplement 5231
Priority or Standard	Priority
Submit Date(s)	March 29, 2018
Received Date(s)	March 29, 2018
PDUFA Goal Date	September 29, 2018
Division/Office	DPARP/ODEII
Review Completion Date	September 26, 2018
Established Name	Omalizumab
(Proposed) Trade Name	Xolair
Pharmacologic Class	Anti-IgE
Applicant	Genentech, Inc. and Novartis Pharmaceuticals Corporation
Formulation(s)	Subcutaneous pre-filled syringe for injection
Dosing Regimen	Asthma: 75 to 375 mg subcutaneous every 2-4 weeks, with the dosage determined by baseline serum total IgE level before the start of treatment, and body weight. Chronic Idiopathic Urticaria: 150 or 300 mg subcutaneous every 4 weeks.
Applicant Proposed Indication(s)/Population(s)	1. In adults and children 6 years of age and older with moderate to severe persistent asthma who have a positive skin test or in vitro reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with inhaled corticosteroids 2. In adults and adolescents 12 years of age and older with chronic idiopathic urticaria (CIU) who remain symptomatic despite H1 antihistamine treatment
Recommendation on Regulatory Action	Approval

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OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis

1 Executive Summary

1.1. Product Introduction

This is an efficacy supplement submitted by Genentech, Inc. and Novartis Pharmaceuticals Corporation for BLA 103976 for a new liquid formulation presentation of Xolair in a prefilled syringe (PFS). Xolair is a recombinant DNA-derived humanized IgG1κ monoclonal antibody that selectively binds to the human immunoglobulin E (anti-IgE) epsilon constant region. Xolair is approved for use 1) in adults and children 6 years of age and older with moderate to severe persistent asthma who have a positive skin test or in vitro reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with inhaled corticosteroids, and 2) in adults and adolescents 12 years of age and older with chronic idiopathic urticaria (CIU) who remain symptomatic despite H_1 antihistamine treatment.

The current Xolair product is provided as a sterile, preservative-free, lyophilized powder in a single-use vial containing 150 mg of Xolair for reconstitution with sterile water for injection. Preparation time is about 20 minutes prior to administration and reconstitution must be done carefully to fully reconstitute the powder to avoid the production of foam, bubbles, or particles. Following reconstitution, the solution must be used within 8 hours if stored at 2 to 8° C (36 to 46° F) or within 4 hours if stored at room temperature. Because of the viscosity of the solution, injection can take 5-10 seconds to administer. (b) (4) [redacted].

For asthma, the dosages vary from 75 to 375 mg administered subcutaneously (SC) every 2 or 4 weeks, with the dosage determined by baseline serum total IgE level (range ≥30 to 700 IU/mL) and body weight. For CIU, the dosage is either 150 or 300 mg SC every 4 weeks, independent of serum IgE level or body weight. The applicants are seeking the same dosages, route of administration (SC), and indications for the new presentation.

The new liquid formulation in a PFS has been approved for both indications in over 40 countries, including the EU (2009), Australia (2013), and Canada (2016), whereas the lyophilized formulation of Xolair is registered in over 90 countries, including the US, Japan, Australia, and the EU. The application is all electronic in Common Technical Document format (eCTD) format. The Agency granted the application priority review due to a shortage of sterile water for injection, which is needed to reconstitute the currently approved lyophilized Xolair product, but is not needed for use of the liquid PFS product.

1.2. Conclusions on the Substantial Evidence of Effectiveness

Evidence of efficacy for a new liquid formulation presentation of Xolair in a prefilled syringe (PFS) for the same dosing regimen, route of administration, and indications as the currently approved lyophilized powder relies on the demonstration of bioequivalence of the new liquid formulation compared to the currently approved lyophilized powder and is supported by the similarity of the pharmacodynamic endpoints of free and total IgE (Study C2101).

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

This efficacy supplement for Xolair for a new liquid formulation presentation of Xolair in a prefilled syringe (PFS) is supported by demonstration of bioequivalence and similar pharmacodynamic effects without new safety concerns compared to the approved lyophilized reconstituted powder. The sponsor is seeking approval of the same indications, dosing regimen, and route of administration for the prefilled syringe as the approved lyophilized reconstituted powder. The safety profile of Xolair is well established since its approval in 2003. The new formulation provides improved ease-of-use due to decreased viscosity, decreased preparation time, and removal of post-reconstitution storage limits. Furthermore, in light of the current sterile water for injection shortage, which is necessary for reconstitution of the lyophilized powder, the prefilled syringe provides assurance that patients and providers will continue to have access to Xolair. Therefore, the risk-benefit is favorable for the approval of the new liquid formulation presentation of Xolair in a prefilled syringe (PFS) for the indications currently approved for the lyophilized reconstituted powder (1: in adults and children 6 years of age and older with moderate to severe persistent asthma who have a positive skin test or *in vitro* reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with inhaled corticosteroids, and 2: in adults and adolescents 12 years of age and older with chronic idiopathic urticaria (CIU) who remain symptomatic despite H_1 antihistamine treatment).

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Asthma is characterized by recurring symptoms of wheezing, breathlessness, chest tightness and coughing caused by underlying airway inflammation and airway hyper-responsiveness. Episodic increases in symptoms are referred to as asthma exacerbations. The disease is typically associated with variable and reversible airflow obstruction, but progressive airway remodeling may lead to persistent asthma associated with partially or fully irreversible airway obstruction leading to chronic symptoms despite current standard of care treatment. While many exacerbations may be managed with oral corticosteroids, severe exacerbations may require hospitalization and may even lead to death. Chronic idiopathic urticaria (CIU) is a condition that results in frequent waxing and waning hives that persist for over 6 weeks without an underlying trigger. The exact pathomechanism is unknown, however, it is hypothesized that it is secondary to autoantibodies against the IgE receptor on mast and basophil cells, causing spontaneous degranulation, creating hives. Currently, the only other treatment is oral antihistamines, which frequently does not provide sufficient remission of symptoms.	Asthma is a common condition. While most patients can be treated with existing therapies, a small percentage of the asthma population with severe disease continues to experience significant morbidity and the potential for mortality from this condition. CIU affects 1% of the population. Although some patients respond to oral antihistamines, there are a percentage of patients with persistent symptoms that affect their quality of life.
Current Treatment Options	There are no other anti-IgE therapies. Xolair is available in a lyophilized powder that is reconstituted with sterile water for injection. Preparation time is about 20 minutes prior to administration; reconstitution must be done carefully to fully reconstitute the powder and avoid the production of foam, bubbles, or particles. Further, following reconstitution the solution must be used within 8 hours if stored at 2 to 8° C (36 to 46° F) or within 4 hours if stored at room temperature. Because of the viscosity of the solution, injection can take 5-10 seconds to	The viscosity, prolonged preparation time, required care with mixing, and the limited post-reconstitution storage time introduces several levels of administration complications with the lyophilized powder. The current sterile water for injection storage also poses patient access challenges.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	administer. There is also currently a sterile water for injection shortage.	
Benefit	The new formulation provides decreased viscosity, decreased preparation time, and removal of post-reconstitution storage limits. Furthermore, sterile water for injection is not required for reconstitution for this formulation.	The PFS provides for improved ease of use. The PFS also provides an alternative formulation that does not require reconstitution with sterile water.
Risk and Risk Management	No new safety concerns were identified compared to the lyophilized reconstituted powder. The safety profile of Xolair is well established.	The risk analysis is similar to the approved product.

1.4. Patient Experience Data

Not applicable to this supplement. While this supplement provides for a new PFS formulation, Xolair is administered by a healthcare professional, so patient use data was not obtained.

X Miya Paterniti -S

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DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Miya Paterniti -S, 0.9.2342.19200300.100.1.1=0010923598
Date: 2018.09.26 11:44:12 -04'00'

Cross-Disciplinary Team Leader

2 Therapeutic Context

2.1. Analysis of Conditions

Xolair, in its current lyophilized powder form, is approved 1) for add-on therapy in patients 6 years of age and older with moderate to severe asthma who have a positive skin test or *in vitro* reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with inhaled corticosteroids, and 2) in adults and adolescents 12 years of age and older with chronic idiopathic urticaria (CIU) who remain symptomatic despite H_1 antihistamine treatment.

Asthma is a disease that is the result of chronic inflammation of the lungs that presents as wheezing, shortness of breath, chest tightness, and coughing. Chronic inflammation of the lungs can also lead to airway remodeling, resulting in permanent decrease in lung function [1] [2]. The European Academy of Allergy and Clinical Immunology estimates that asthma affects 300 million people worldwide[3]. Clinical presentations of asthma can vary from mild intermittent to severe persistent. Uncontrolled asthma can make it difficult for patients to partake in daily life activities due to frequent respiratory symptoms that can occur with and without exertion. Patients with poorly controlled asthma are also more prone to exacerbations that may require oral steroids, emergency room visits, and hospitalizations. Given the significant prevalence along with the various phenotypes, there has been an urge to find targeted therapies to treat the underlying pathology.

CIU is a condition that results in frequent waxing and waning hives that persist or over 6 weeks without an underlying trigger[4,5]. The exact pathomechanism is unknown, however, it is hypothesized that it is secondary to autoantibodies against the IgE receptor on mast and basophil cells, causing spontaneous degranulation, creating hives. CIU affects up to 1 percent of the general population and can occur both in children and adults, though it is more common

[1] GINA (Global Initiative for Asthma). Global Strategy for Asthma Management and Prevention, 2018. Available at https://ginasthma.org. Accessed 25 May 2018

[2] NAEPP (National Asthma Education and Prevention Program Expert Panel) Report 3.

[3] Masoli M, Fabian D, Holt S, Beasley R. The global burden of asthma: executive summary of the GINA Dissemination Committee Report. Allergy 2004;59(5):469–78.

[4] Magerl M, Altrichter S, Borzova E, et al. The definition, diagnostic testing, and management of chronic inducible urticarias - The EAACI/GA(2) LEN/EDF/UNEV consensus recommendations 2016 update and revision. Allergy 2016;71(6):780 □802.

[5] Beck LA, Bernstein JA, Maurer M. A Review of International Recommendations for the Diagnosis and Management of Chronic Urticaria. Acta Derm Venereol 2017;97(2):149 □158

in adults[6]. CIU is not only a physical burden to patients due to the inherent pruritic nature of the disease, but it also can cause significant psychiatric morbidity such as depression[7] .

2.2. Analysis of Current Treatment Options

Asthma:
Xolair, in its lyophilized powder form, was the first therapeutic anti-IgE and first biologic approved for the treatment of asthma. There are now three other biologic products (mepolizumab (lyophilized powder, SC injection), reslizumab (intravenous infusion), and benralizumab (prefilled syringe, SC injection)) available for asthma, targeting the anti-IL5 pathways of the allergic inflammation cascade. Other small molecule treatment options for asthma include systemic and inhaled corticosteroids, leukotriene modifiers, long-acting beta-agonist bronchodilators (LABAs), and methylxanthines.

Chronic Idiopathic Urticaria:
Prior to the approval of Xolair for CIU, only second-generation antihistamines (loratadine, fexofenadine, and cetirizine) carried an indication for CIU. Clinical guidelines recommend if patients remain symptomatic on approved antihistamine doses, therapy should be increased to include multiple concomitant antihistamines, H2 blockers, and leukotriene receptor antagonists[8]. If symptoms persist, medications with increased side effects such as dapsone, hydroxychloroquine, or cyclosporine may be attempted. Oral steroids are often used for rescue therapy. Xolair is approved in patients ≥12 year of age with CIU who continues to be symptomatic despite use of second generation antihistamine. Since the approval of Xolair for CIU, initiation of Xolair after failed antihistamine use has become standard of care[8].

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Genentech, Inc. and Novartis Pharmaceuticals Corporation jointly submitted efficacy supplement S-5231 to BLA 103976 for Xolair® for a new liquid formulation presentation of Xolair in a prefilled syringe (PFS). Xolair is currently provided as a sterile, preservative-free lyophilized powder in a vial for reconstitution prior to administration. The PFS presentation is currently

[6] Ferrer, M. Epidemiology, healthcare, resources, use and clinical features of different types of urticaria. J Invesg Allergol Clin Immunol. 2009;19 Suppl 2:21)

[7] Ozkan, M, et al. Psychiatric morbidity and quality of life in patients with chronic idiopathic urticaria. Ann Allergy Asthma Immunol. 2007 July;99(1): 29-33.

[8] Joint Task Force on Practice Parameters. (2014). The diagnosis and management of acute and chronic urticaria: 2014 update. Retrieved from https://www.aaaai.org/Aaaai/media/MediaLibrary/PDF%20Documents/Practice%20and%20Parameters/Urticaria-2014.pdf

approved for both indications in over 40 countries, including the EU (2009), Australia (2013), and Canada (2016), whereas the lyophilized formulation of Xolair is registered in over 90 countries, including the US, Japan, Australia, and the EU.

3.2. Summary of Presubmission/Submission Regulatory Activity

The regulatory history for the development of a PFS for Xolair dates back to 2004. At a meeting with the Center for Biologics Evaluation and Research (CBER) in May 2004, the results of an initial pharmacokinetic (PK) / pharmacodynamic (PD) study (A2204) were presented to the Agency. This study compared the PK (Xolair levels) and PD (i.e., effects on free/total IgE levels) of fresh (non-aged) liquid in a vial versus the approved reconstituted lyophilized product. The results showed consistent Xolair PK and PD between each of the products and dosages (150 and 300 mg). However, a low molecular weight fragment was identified by high-performance liquid chromatography in the aged liquid formulation that was not present in the approved reconstituted lyophilized product [meeting minutes May 20, 2004], that prompted the Agency to recommend that a second study to evaluate PK/PD effects using the liquid product at the end of shelf life. This study was conducted as an extension to the first study (A2204E1), and the results were discussed with the Agency in 2006. In this second study, differences were found in both PK and PD effects between the aged liquid formulation in vials and reconstituted lyophilized Xolair. Furthermore, neither the A2204 nor A2204E1 study used the to-be-marketed formulation in a PFS.

Several interactions with the Agency occurred between 2006 and 2008 to discuss the clinical program to support the PFS. The Agency and the sponsor agreed to use the to-be-marketed PFS liquid formulation in studies that would 1) support bioequivalence between the two formulations (including the aged liquid) on PK (Xolair levels) and PD markers (free and total IgE), 2) assess immunogenicity with chronic administration, and finally 3) demonstrate that the aged liquid has similar effects on a PD endpoint of clinical relevance. To satisfy the last request, four special protocol assessments (SPA) submissions were made before final agreement was reached on the specifics of a clinical bronchoprovocation study (C4160).

In December 2016, in a written response to a meeting request, the Agency noted that Genentech/Novartis had performed a larger and more definitive PK/PD study (C2101) that now demonstrated bioequivalence between the aged to-be-marketed liquid PFS product and reconstituted lyophilized Xolair. Top line results of the bronchoprovocation study (C4160) were also submitted where differences were noted in the primary outcome of change in log2-transformed allergen PC15 from baseline to Week 16, with the reconstituted lyophilized product outperforming the aged liquid PFS. Based on this new information, the Agency anticipated that the supplement would primarily be supported by the CMC comparability data, the bioequivalence data from study C2101, and immunogenicity data from study C2303.

However, to address the lingering issue of an initial peak seen in the aged liquid in a vial, the Agency specifically requested that the applicants submit the following with the supplement:

1. A discussion of any formulation changes that have occurred since the original stability studies that showed a new peak for aged liquid in a vial.
2. An explanation of why the peak seen with aged liquid in a vial is no longer seen for aged liquid in a PFS.

Those written responses were followed by a teleconference on December 20, 2016, to clarify details of the lingering issues with the development program. At the teleconference, Genentech/Novartis stated that the original peak noted in the aged liquid in vials was characterized as a Fab fragment and was confirmed to also be present in the (non-aged) reconstituted lyophilized material. Characterization of aged liquid in PFS [stated to have been submitted to IND 5369, SN 0342, May 11, 2007, Section 3.2.P.1] identified no new peaks, and was noted to be present at similar levels in both aged vials and aged PFS.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

OSI conducted an audit of the bioanalytical portion of study CIGE025C2101 at Novartis Pharma, AG, East Hanover, NJ. They concluded no objectionable conditions and no action indicated. See Mohsen Rajabi Abhari (DNDBE/OSIS) for the full review.

4.2. Product Quality

The product quality reviewers recommended approval. See Youngmin Liu's (OBP/DBRRII) product quality review.

4.3. Clinical Microbiology

See Anita Khatiwara's (OMPT/CDER/OPQ/OPF/DMA/MABIV) clinical microbiology review. Microbiology recommended a post-marketing commitment to validate the dye leak container closure integrity test using syringes to be implemented prior to March 31, 2019.

4.4. Devices and Companion Diagnostic Issues

The device reviewer recommends approval. See Kathleen Fitzgerald's (CDRH/ODE/DAGRID/GHDB) device review. Human factor studies were determined to not be necessary based upon the sponsor's use related- risk analysis.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

Excipients in the Xolair PFS drug product differ from the reconstituted lyophilized powder as follows:

1. (b) (4)
2. A small increase in the histidine/histidine HCl (b) (4) was made for greater (b) (4)

No safety concerns with respect to systemic or local toxicity were identified with the introduction of arginine to the formulation or the small increase of the histidine/histidine HCl (b) (4)

The BD Hypak Syringe System is used with multiple approved biologic products. The sponsor conducted extractables and leachables studies with the primary container closure system. There were no safety concerns for identified organic and inorganic leachables.

Additional characterization testing will be performed to update the extractable and leachable data with acidic and basic extraction conditions, non-volatile compounds by LC-UV-MS and metal data for the ICH Q3D elemental impurities. The results of this testing will be filed with the Xolair PFS drug product annual reports.

5.2. Referenced NDAs, BLAs, DMFs

IND 5369 (Genentech, Xolair®)
IND 7202 (Genentech, Xolair®)
IND 101,612 (Genentech, Xolair for CIU)
BLA 103976 (Genentech/Novartis, Xolair®)
(b) (4)

(b) (4)

5.3 Drug Formulation

Xolair (b) (4) drug substance is provided as a sterile solution for SC injection in a single-dose prefilled syringe (PFS).

Figure 1. Composition of Xolair Prefilled Syringe

Table P.1-2 Composition of Xolair Prefilled Syringe

Ingredient	Target Amount per PFS (75 mg/0.5 mL)	Target Amount per PFS (150 mg/1 mL)	Function	Reference to Standards
Omalizumab (mg)	75.00	150.00	Active substance	Novartis
L-Arginine Hydrochloride (mg)	21.05	42.10	(b) (4)	USP-NF, Ph. Eur.
L-Histidine Hydrochloride Monohydrate (mg)	1.17	2.34		Ph. Eur.
L-Histidine (mg)	0.68	1.37		USP-NF, Ph. Eur.
Polysorbate 20 (mg)	0.20	0.40		USP-NF, Ph. Eur.
Water for Injection	q.s. 0.50 mL	q.s. 1.00 mL		USP-NF, Ph. Eur.
Total Volume (mL)	0.50	1.00		

Abbreviations: PFS = prefilled syringe; q.s. = quantity sufficient.

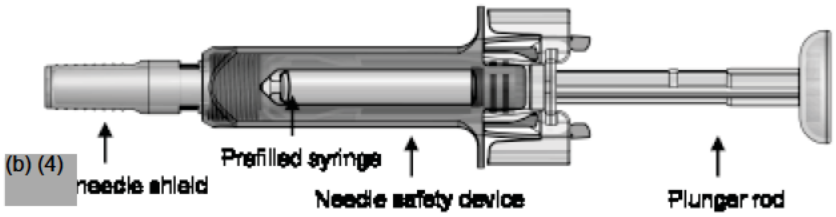
(Excerpted from the sponsor's submission)

The container closure system for the Xolair PFS consists of the following components:

(b) (4)

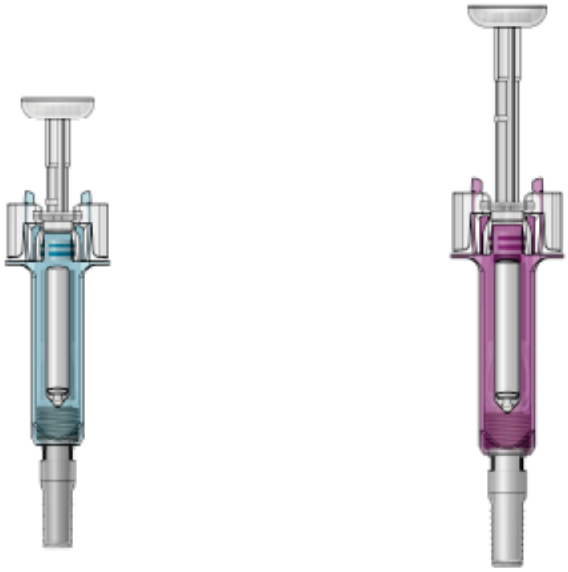
Figure 2. Schematic Drawing of Primary Packaging

Figure 2.3.R-1 Components of the Assembled Xolair PFS-NSD



Abbreviations: PFS-NSD = prefilled syringe with needle safety device.

Figure 2.3.R-2 Schematic Representation of the Xolair 75 mg and 150 mg PFS-NSD



75 mg PFS-NSD (teal NSD) **150 mg PFS-NSD (raspberry NSD)**

Abbreviations: PFS-NSD=prefilled syringe with needle safety device.

(Excerpted from the sponsor's submission)

Figure 3. Primary Packaging: Components of the Assembled, Xolair PFS-NSD and Identity of Materials of Construction

Table 2.3.R-2 Components of the Assembled, Labeled Xolair PFS-NSD

Component	Description	Identity of Materials
Syringe	(b) (4)	
(b) (4) Needle Shield		
Plunger Stopper		
Syringe Labels		
Plunger Rod		
Needle Safety Device		

Abbreviations: PFS-NSD = prefilled syringe with needle safety device.

(Excerpted from the sponsor's submission)

Figure 4. Components of the Xolair PFS-NSD Packaging

Table 2.3.R-3 Components of the Xolair PFS-NSD Packaging

Component	Description	Identity of Materials
Blister Tray	(b) (4)	
(b) (4) Lid		
Carton		
USPI		

Abbreviation: PFS-NSD = prefilled syringe with needle safety device; (b) (4) (b) (4) USPI = US prescribing information.

(Excerpted from the sponsor's submission)

Figure 5. Supplier of Primary Packaging

Table P.7-2 Primary Packaging: Suppliers

Component	Supplier
Syringe with (b) (4) Needle (needle (b) (4) (b) (4)	(b) (4)
Plunger Stopper	
(b) (4) Needle Shield (composed of rubber needle shield and (b) (4) shell)	

(Excerpted from the sponsor's submission)

Secondary Packaging

The secondary packaging is not in contact with the drug product. It consists of two elements:

- Functional passive safety device
- Protective but otherwise nonfunctional outer packaging

Passive Safety Device

Description

The passive safety device is made of two components:

- (b) (4)
-

5.4. Comments on Novel Excipients

Excipients in the Xolair PFS drug product differ from the reconstituted lyophilized powder as follows:

- (b) (4)
- A small increase in the histidine/histidine HCl (b) (4) was made for greater (b) (4)

Figure 6. Composition of Xolair liquid for injection in prefilled syringes and Xolair powder for solution for injection

Table 1-1 Composition of Xolair liquid for injection in prefilled syringes and Xolair powder for solution for injection

Component	Xolair® liquid for injection in pre-filled syringes **Nominal amount per 75 mg omalizumab in mg**	Xolair® liquid for injection in pre-filled syringes **Nominal amount per 150 mg omalizumab in mg**	XOLAIR® powder for solution for injection **Nominal amount per 150 mg omalizumab in mg**
L-Arginine hydrochloride	21.05	42.10	-
L-Histidine hydrochloride monohydrate	1.17	2.34	2.1
L-Histidine	0.68	1.37	1.3
Sucrose	-	-	108
Polysorbate 20	0.20	0.40	0.4
Water for injection	Ad 0.50 mL	Ad 1.00 mL	Ad 1.2 mL

(Excerpted from the sponsor's submission)

L-Arginine is present at a dose of 105 mg in the maximum dose of Xolair at 375 mg. In humans, arginine is classified as a semi-essential or conditionally essential amino acid, depending on the developmental stage and health status of the individual. Preterm infants are unable to synthesize or create arginine internally, making the amino acid nutritionally essential for them. Most healthy people do not need to supplement with arginine, because it is a component of all protein-containing foods and can be synthesized in the body from glutamine via citrulline. L-arginine is generally recognized as safe (GRAS-status) at intakes of up to 20 grams per day[9].There were no concerns related to systemic toxicity with administration of a dose of 105 mg once every 2 to 4 weeks.

To assess potential local toxicity at SC injection sites, the sponsor submitted a published scientific article, the results of a clinical study with human subjects that received SC administration of the excipients in the liquid formulation in PFS including L-arginine, and labels from other products administered by the SC route that contain the excipient, arginine. For long-term parenteral administration, a nonclinical comparative study indicated that a human subject should tolerate L-arginine doses of 6 g/day (Journal of Nutrition 137:1673S-1680S, 2007), which is 57-fold greater than the amount of L-arginine (105 mg) in a single maximum dose of 375 mg Xolair in the liquid formulation. The local tolerability of the excipients in the liquid formulation in PFS including L-arginine was assessed in clinical study [Study Q2569g]. In this excipient-only study, SC injection of formulations containing excipients from the liquid formulation and the lyophilized product were compared and no relevant findings were identified. L-arginine is an excipient in FDA-approved products for parenteral administration, including the SC route, in

[9] Shao-A and Hathcock-JN (2008). Risk assessment for the amino acids taurine, L-glutamine and L-arginine. Regulatory Toxicology Pharmacology 50 (3):376–399.

comparable amounts to that in the Xolair® prefilled syringe (AZACTAM® [IM/IV route; 780 mg arginine per g AZACTAM], CEPTAZ® [IM/IV route; 349 mg arginine per g ceftazidime activity], and PLEGRIDY™ [SC route; 15.8 mg L-arginine HCl per 0.5 mL]).

5.5. Regulatory Background

Under IND 7202, a Type B meeting was held with the sponsor on December 20, 2016. The following nonclinical comment was conveyed to the sponsor.

Nonclinical Comment:

1. *Provide justification for the level of L-arginine hydrochloride in your product. This could include identification of other FDA-approved products administered by the subcutaneous route that contain a comparable dose of this excipient.*

2. *A safety assessment of leachables (and extractables as appropriate) should be conducted with the omalizumab solution in the pre-filled syringe. The study reports should be provided with the sBLA.*

An Information Request was sent on April 30, 2018 to obtain the reports of the extractables and leachables studies. The reports were received by email on May 8, 2018 and submitted to the BLA on May 7, 2018.

5.6. Studies Reviewed

Extractables and Leachables Studies were described in the following documents:

- Module 2.3
- Module 2.4 Nonclinical Summary
- Module 3.2.P.1 Description and Composition of the Drug Product
- Module 3.2.P.2.4 Container Closure System
- Module 3.2.P.7 Container Closure System
- Process Validation Report, Xolair Liquid (Pre-filled Syringe) Extractable/Leachable Summary, Document No. VAL-0131518
- Selection of Rubber Plunger for a Liquid Xolair Drug Product in Pre-Filled Syringe

5.7. Evaluation of Extractables and Leachables Studies

The proposed liquid drug product Xolair is provided as 75 mg/0.5 mL and 150 mg/1 mL solutions intended for SC administration. The primary container closure system for Xolair liquid in the pre-filled syringe configuration consists of a 1 mL long (b) (4) barrel with (b) (4) needle (b) (4), sealed by a (b) (4) needle shield, (b) (4), and a plunger-stopper, (b) (4) product contact surfaces with an (b) (4)

(b) (4)

The extractable and leachable analysis of the primary container closure system was performed by (b) (4)

Extractables Characterization

(b) (4)

Figure 7. Extractables characterized for components used in the Xolair Liquid Drug Product in PFS with water and isopropanol extraction

Extractables Characterized for Components used in the Xolair Liquid Drug Product in Pre-filled Syringes

		Extractables characterized			
Methods		GC/MS (Organic semi-volatiles)	LC/MS (Organic semi volatiles & non-volatiles)	HS GC/MS (Organic volatiles)	ICP-MS (Inorganic metals)
	Extraction solvents				1% nitric acid
Components					
(b) (4)				None observed	Not performed

(Excerpted from the sponsor's submission)

Figure 8. Extractables characterized for components used in the Xolair Liquid Drug Product in PFS with isopropanol (continued) and methylene chloride extraction

Extractables Characterized for Components used in the Xolair Liquid Drug Product in Pre-filled Syringes

		Extractables characterized			
Methods		GC/MS (Organic semi-volatiles)	LC/MS (Organic semi volatiles & non-volatiles)	HS GC/MS (Organic volatiles)	ICP-MS (Inorganic metals)
	Extraction solvents				1% nitric acid
Components					
(b) (4)					

(Excerpted from the sponsor's submission)

Figure 9. Extractables characterized for components used in the Xolair Liquid Drug Product in PFS with methylene chloride (continued) extraction

Extractables Characterized for Components used in the Xolair Liquid Drug Product in Pre-filled Syringes

		Extractables characterized			
Methods		GC/MS (Organic semi-volatiles)	LC/MS (Organic semi volatiles & non-volatiles)	HS GC/MS (Organic volatiles)	ICP-MS (Inorganic metals)
	Extraction solvents				1% nitric acid
Components					
(b) (4)					

(Excerpted from the sponsor's submission)

(b) (4)

Selection of target leachables

The target leachables for the (b) (4) container closure system for Xolair solution in PFS were selected based on the extractable characterization studies.

By HS-GC-MS, volatile compounds were observed at trace levels in extraction studies. The sponsor elected to not select volatile compounds as target leachables. From the results of extractable characterization studies, the following target leachables for the (b) (4) container closure system for Xolair solution in PFS were selected:

1. Organic leachables
   - (b) (4)
   -

- (b) (4)
-
-

2. Tracking compounds that also served as surrogates for the presence of other possible (b) (4)

- (b) (4)
-

(b) (4)

Leachables Assessed during Stability Studies

A study to assess leaching of organic and inorganic compounds from the administration device during stability studies was carried out for Process Validation Batches 609002/1 (75 mg/0.5 mL) and 609001/1 (150 mg/1 mL) as well as Clinical Lots L14456 and L14457. GC-MS and ICP-MS methods were used to quantify the target leachables; methods were the same as those used for the extractables studies. Analysis for volatile organic compounds by a HS GC-MS method was not done as no volatile target compounds were identified from the extractables characterization.

Figure 10. 24-Month Leachables Stability Protocol for Xolair Liquid Drug Product in PFS

24-Month Leachables Stability Protocol for Xolair Liquid Drug Product in Pre-filled Syringes

Storage Condition	Interval (months)							
	0*	0.25	1	3	6	12	18	24
Initial	x							
5°C/ambient RH			x	x	x	x	x	x
25°C/60% RH			x	x	x			
30°C/65% RH		x	x					

* T=0 is 24 March, 2006 for the 1.0 mL configuration and 15 March, 2006 for the 0.5 mL configuration
RH= Relative Humidity
Drug Products are stored in a horizontal position.
Samples were pulled at the specific intervals and frozen at -20°C until analysis.

(Excerpted from the sponsor's submission)

(b) (4) [redacted] was found in two samples at levels below the LOQ. No organic leachables were detected in Clinical Lots. No (b) (4) or (b) (4) -containing compounds were detected in any sample.

Figure 11. Organic Leachable Analysis (GC-MS) of Xolair Liquid Drug Product in Pre-Filled Syringes, Process Validation Batch # 609002/1, 0.5 mL, 75 mg

Organic Leachable Analysis (GC-MS) of Xolair Liquid Drug Product in Pre-filled Syringes
Qual lot # 609002/1, 0.5 mL, 75 mg

Target		(b) (4)						
LOQ (µg/mL)								
LOD [a] (µg/mL)								
Condition (°C/%RH)	Time (month)							
	0	ND	BLOQ	ND	ND	ND	ND	ND
5°C/ambient RH	1	ND	BLOQ	ND	ND	ND	ND	ND
	3	ND	BLOQ	ND	ND	ND	ND	ND
	6	ND	BLOQ	ND	ND	ND	ND	ND
	12	ND	BLOQ	ND	ND	ND	ND	ND
	18	BLOQ	BLOQ	BLOQ	BLOQ	BLOQ	ND	ND
	24	ND	BLOQ	BLOQ	ND	ND	ND	ND
25°C/60% RH	1	ND	BLOQ	ND	ND	ND	ND	ND
	2.5	ND	BLOQ	10.0 [b]	ND	ND	ND	ND
	6	ND	BLOQ	10.3	ND	ND	ND	ND
30°C/65% RH	0.25	ND	BLOQ	ND	ND	ND	ND	ND
	1	ND	BLOQ	ND	ND	ND	ND	ND

(b) (4)

ND = Not Detected BLOQ = Below Limit of Quantitation

[a] The limit of detection (LOD) was estimated by dividing the LOQ concentration for a given target compound by 3.3 based on the Method Development/Method Validation that the appropriate LOQ target concentration was estimated to have a signal-to-noise (S/N) of approximately 10 and that of LOD was 3. Therefore, the LOD was estimated by dividing the LOQ concentration for a given target compound by 3.3 (10 divided by 3).

No (b) (4) containing compounds were detected in any sample.

All samples were prepared in singlet and analyzed in duplicate injections.
The numerical results reported here are the average values of duplicate injections of the same sample preparation.

[b] This value was a single determination because the second value was ND.

(Excerpted from the sponsor's submission)

Figure 12. Organic Leachable Analysis (GC-MS) of Xolair Liquid Drug Product in Pre-Filled Syringes, Process Validation Batch # 609001/1, 1.0 mL, 150 mg

Organic Leachable Analysis (GC-MS) of Xolair Liquid Drug Product in Pre-filled Syringes
Qual lot # 609001/1, 1.0 mL, 150 mg

Target		(b) (4)						
LOQ (µg/mL)								
LOD[a](µg/mL)								
Condition (°C/%RH)	Time (month)							
	0	ND	BLOQ	ND	ND	ND	BLOQ	ND
5°C/ambient RH	1	ND	BLOQ	ND	ND	ND	BLOQ	ND
	3	ND	BLOQ	ND	ND	ND	ND	ND
	6	ND	BLOQ	ND	ND	ND	ND	ND
	12	ND	BLOQ	ND	ND	ND	ND	ND
	18	BLOQ	BLOQ	BLOQ	BLOQ	BLOQ	ND	ND
	24	ND	BLOQ	BLOQ	ND	ND	ND	ND
25°C/60% RH	1	ND	BLOQ	ND	ND	ND	ND	ND
	3.5[b]	ND	BLOQ	8.9	ND	ND	ND	ND
	6[b]	ND	BLOQ	9.9	ND	ND	ND	ND
30°C/65% RH	0.25	ND	BLOQ	ND	ND	ND	ND	ND
	1	ND	BLOQ	ND	ND	ND	ND	ND

(b) (4)

ND = Not Detected BLOQ = Below Limit of Quantitation

[a] The limit of detection (LOD) was estimated by dividing the LOQ concentration for a given target compound by 3.3 based on the Method Development/Method Validation that the appropriate LOQ target concentration was estimated to have a signal-to-noise (S/N) of approximately 10 and that of LOD was 3. Therefore, the LOD was estimated by dividing the LOQ concentration for a given target compound by 3.3 (10 divided by 3).

[b] (b) (4) observed at BLOQ

No (b) (4) containing compounds were detected in any sample.

All samples were prepared in singlet and analyzed in duplicate injections.

The numerical results reported here are the average values of duplicate injections of the same sample preparation.

(Excerpted from the sponsor's submission)

Figure 13. Organic Leachable Analysis (GC-MS) of Xolair Liquid Drug Product in Pre-Filled Syringes, Clinical lots L14456 (1.0 mL) and L14457 (0.5 mL)

Organic Leachable Analysis (GC-MS) of Xolair Liquid Drug Product in Pre-filled Syringes
Clinical lots L14456 (1.0 mL) and L14457 (0.5 mL)

Target	(b) (4)							
LOQ (µg/mL)								
Condition (°C/%RH)	Time (month)							
		Lot L14456 (1.0 mL)						
5°C/ambient RH	18	ND	BLOQ	ND	ND	ND	ND	ND
	24	ND	BLOQ	ND	ND	ND	ND	ND
		Lot L14457 (0.5 mL)						
5°C/ambient RH	18	ND	BLOQ	ND	ND	ND	ND	ND
	24	ND	BLOQ	ND	ND	ND	ND	ND

(b) (4)

ND = Not Detected BLOQ = Below Limit of Quantitation

No (b) (4) containing compounds were detected in any sample.

All samples were prepared in singlet and analyzed in duplicate injections.

(Excerpted from the sponsor's submission)

(b) (4)

Figure 14. Metal Analysis (ICP-MS) of Xolair Liquid Drug Product in Pre-Filled Syringes, Process Validation Batch # 609002/1, 0.5 mL, 75 mg

Metal Analysis (ICP-MS) of Xolair Liquid Drug Product in Pre-filled Syringes
Qual lot # 609002/1, 0.5 mL, 75 mg

Element	MLOQ (mg/L)		5°C/ambient RH						25°C/60% RH			30°C/65% RH	
		Time	Months						Months			Months	
		0	1	3	6	12	18	24	1	2.5	6	0.25	1
(b) (4)		0.028	0.025	<MLOQ	<MLOQ	<MLOQ	<MLOQ	<MLOQ	0.024	0.033	0.045	<MLOQ	0.035
		0.024	0.020	0.018	0.017	0.0197	0.025	0.021	0.016	0.020	0.049	0.017	0.018
		0.097	<MLOQ	0.037	0.036	<MLOQ	<MLOQ	<MLOQ	0.043	0.065	0.068	<MLOQ	0.038
		0.35	<MLOQ	0.30	<MLOQ	<MLOQ	<MLOQ	<MLOQ	<MLOQ	0.28	0.26	<MLOQ	<MLOQ
		0.0068	0.0062	0.0065	0.0083	0.0101	0.003	0.006	0.0056	0.0058	0.0059	0.0059	0.0065
		0.0072	0.0054	0.0051	0.0055	0.00719	0.005	<MLOQ	0.0061	0.0059	0.0059	0.0054	0.0054
		0.047	0.038	0.033	0.036	0.0296	0.025	0.029	<MLOQ	0.037	0.031	0.029	0.039
		0.025	0.012	0.042	0.016	0.0098	0.010	0.010	0.013	0.018	0.030	0.037	0.034
		0.0059	0.037	0.0034	0.0035	<MLOQ	<MLOQ	<MLOQ	0.0044	0.0036	0.0047	0.043	0.0037
		0.041	0.026	0.035	0.024	0.0203	0.018	<MLOQ	0.021	0.031	0.025	0.024	0.028
		<MLOQ	<MLOQ	<MLOQ	<MLOQ	<MLOQ	<MLOQ	<MLOQ	<MLOQ	<MLOQ	<MLOQ	<MLOQ	<MLOQ
		0.17	0.10	0.30	0.23	0.232	0.089	0.135	0.015	0.20	0.12	0.31	0.25

MLOQ = Method Limit of Quantitation < MLOQ = Below Method Limit of Quantitation

(Excerpted from the sponsor's submission)

Figure 15. Metal Analysis (ICP-MS) of Xolair Liquid Drug Product in Pre-Filled Syringes, Process Validation Batch # 609001/1, 1.0 mL, 150 mg

Metal Analysis (ICP-MS) of Xolair Liquid Drug Product in Pre-filled Syringes
Qual lot # 609001/1, 1.0 mL, 150 mg

Element	MLOQ (mg/L)		5°C/ambient RH						25°C/60% RH			30°C/65% RH	
		Time	Months						Months			Months	
		0	1	3	6	12	18	24	1	3.5	6	0.25	1
(b) (4)		<MLOQ	<MLOQ	<MLOQ	<MLOQ	<MLOQ	0.025	0.026	0.024	0.033	0.045	<MLOQ	0.035
		0.024	0.022	0.024	0.032	0.0667	0.029	0.080	0.016	0.020	0.049	0.017	0.018
		<MLOQ	<MLOQ	<MLOQ	0.037	<MLOQ	0.052	<MLOQ	0.043	0.065	0.068	<MLOQ	0.038
		0.26	0.25	<MLOQ	<MLOQ	0.262	0.451	<MLOQ	<MLOQ	0.28	0.26	<MLOQ	<MLOQ
		0.011	0.011	0.011	0.011	0.00943	0.005	0.007	0.0056	0.0058	0.0059	0.0059	0.0065
		0.0064	0.0080	0.0071	0.0066	0.00712	0.006	<MLOQ	0.0061	0.0059	0.0059	0.0054	0.0054
		0.064	0.050	0.040	0.042	0.0418	0.041	<MLOQ	<MLOQ	0.037	0.031	0.029	0.039
		0.015	0.025	0.024	0.023	0.0207	0.024	0.021	0.013	0.018	0.030	0.037	0.034
		<MLOQ	0.0056	0.0048	0.0044	<MLOQ	<MLOQ	<MLOQ	0.0044	0.0036	0.0047	0.043	0.0037
		0.035	0.032	0.033	0.031	0.0294	0.037	0.014	0.021	0.031	0.025	0.024	0.028
		<MLOQ	<MLOQ	<MLOQ	<MLOQ	<MLOQ	<MLOQ	<MLOQ	<MLOQ	<MLOQ	<MLOQ	<MLOQ	<MLOQ
		<MLOQ	0.25	0.17	0.16	0.0933	0.053	0.202	0.015	0.20	0.12	0.31	0.25

MLOQ = Method Limit of Quantitation < MLOQ = Below Method Limit of Quantitation

(Excerpted from the sponsor's submission)

Figure 16. Metal Analysis (ICP-MS) of Xolair Liquid Drug Product in Pre-Filled Syringes Clinical Lot L14456 (1.0 mL, 150 mg) and Lot L14457 (0.5 mL, 75 mg)

Metal Analysis (ICP-MS) of Xolair Liquid Drug Product in Pre-filled Syringes Clinical Lot L14456 (1.0 mL, 150 mg) and Lot L14457 (0.5 mL, 75 mg)

Element	MLOQ (mg/L)	Lot L14456		Lot L14457	
		5°C/ambient RH		5°C/ambient RH	
		18 Months	24 Months	18 Months	24 Months
(b) (4)		0.076	0.068	0.074	0.063
		0.026	0.12	0.030	0.053
		0.051	0.043	0.063	0.054
		< MLOQ	< MLOQ	< MLOQ	0.27
		0.0091	0.0086	0.0096	0.0094
		0.0045	0.0048	0.0062	0.0056
		0.046	0.035	0.043	0.046
		0.083	0.077	0.090	0.11
		0.010	0.0095	0.0097	0.012
		0.068	0.059	0.059	0.069
		< MLOQ	< MLOQ	< MLOQ	< MLOQ
		0.16	0.088	0.11	0.13

MLOQ = Method Limit of Quantitation
< MLOQ = Below Method Limit of Quantitation

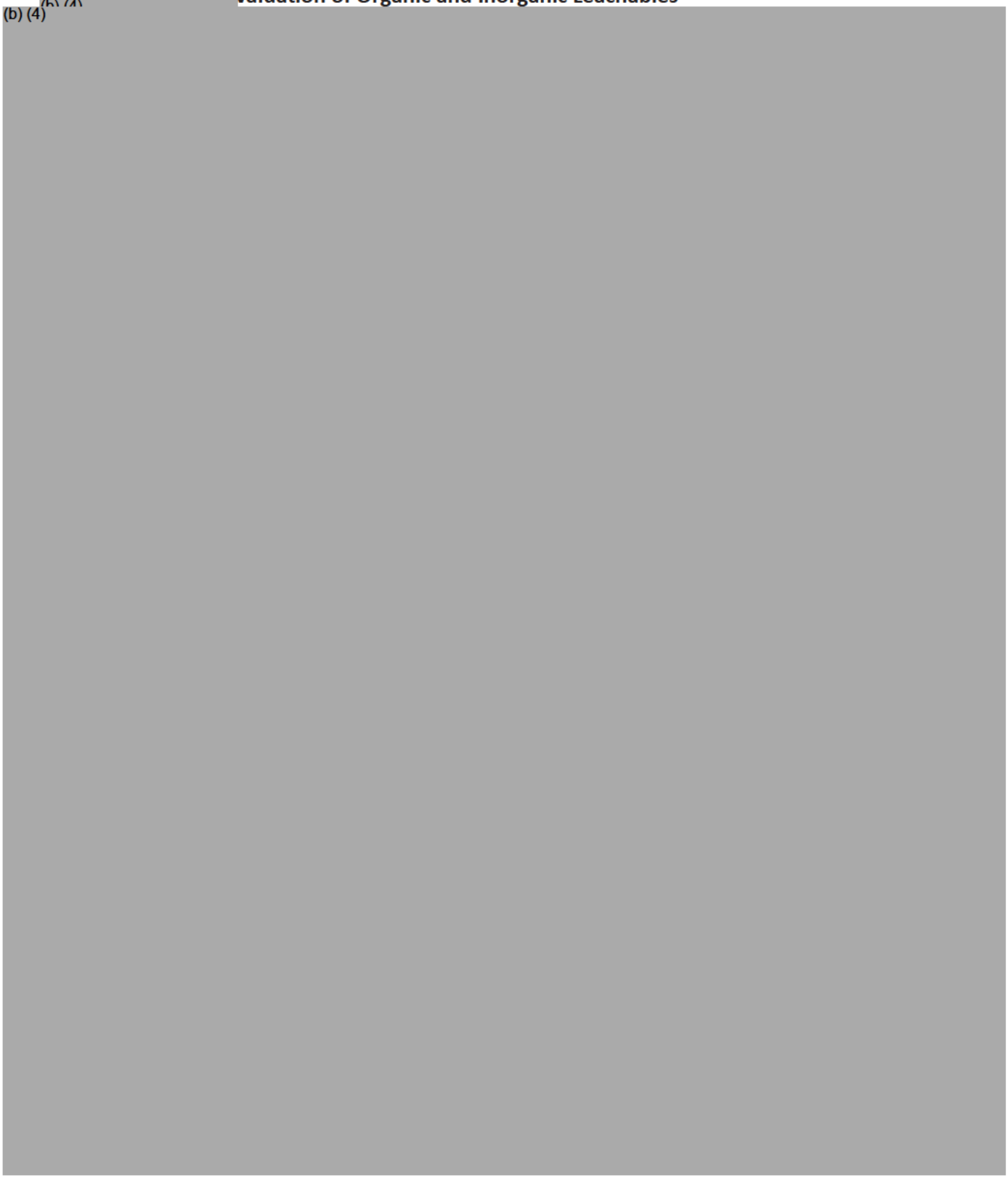
(Excerpted from the sponsor's submission)

Additional Container Closure Characterization Testing

Additional characterization testing will be performed to update the extractable and leachable data with acidic and basic extraction conditions, non-volatile compounds by LC-UV-MS and metal data for the ICH Q3D elemental impurities. The results of this testing will be filed with the Xolair PFS drug product annual reports.

valuation of Organic and Inorganic Leachables

(b) (4)



(b) (4)

[redacted]

X Timothy W. Robison -S

Digitally signed by Timothy W. Robison -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300110610, cn=Timothy W. Robison -S
Date: 2018.09.26 16:13:43 -04'00'

Nonclinical Primary Reviewer and Team Leader

[10] (b) (4)

6 Clinical Pharmacology

6.1. Executive Summary

This is an efficacy supplement (S-5231) submitted by Genentech, Inc. and Novartis Pharmaceuticals Corporation (joint development) to BLA 103976 for Xolair (Omalizumab) for a new liquid formulation presentation of Xolair in a prefilled syringe (PFS). Xolair is currently provided as a sterile, preservative-free lyophilized powder in a vial for reconstitution prior to administration. The clinical development program for the PFS presentation included a pivotal PK comparability study (Study C2101). Other supportive clinical studies included a 6-month immunogenicity and safety study (Study C2303). Study C2101 was an open label, single-dose pharmacokinetic (PK) comparability study that compared the approved lyophilized product with aged and non-aged liquid PFS product in patients with elevated serum IgE levels. A single dose of 150 mg or 300 mg of omalizumab was given depending on screening IgE levels and body weight (as per the dosing in the label). Study C2303 was a 6-month open-label, single-arm study that evaluated the immunogenicity of aged liquid PFS in patients with moderate to severe persistent allergic asthma, to assess the safety and immunogenicity of omalizumab PFS. For details of other supportive studies, see section 8.1.2.

In Study C2101, the 90% confidence interval (CI) for the geometric mean ratios of the dose-normalized PK parameters ($AUC_{0-\infty}$, AUC_{0-last}, C_{max}) for the non- aged liquid formulation in the PFS vs. the marketed lyophilized product and aged liquid formulation in PFS vs. the marketed lyophilized product were all within the 80-125%.

From a Clinical Pharmacology perspective, this supplement is acceptable and supports approval.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Omalizumab is a recombinant DNA derived humanized IgG1k monoclonal antibody that has a molecular weight of approximately 149 kD. Omalizumab inhibits the binding of IgE to IgE receptor (FcεRI) on the surface of mast cells and basophils, limiting release of mediators of the allergic response from the FcεRI bearing cells. Omalizumab pharmacokinetics and pharmacodynamics using reconstituted lyophilized powder has been well characterized with doses up to 600 mg in the original BLA submission

Comparability of the pre-filled syringe (PFS) presentation and the marketed lyophilized product is demonstrated by one pivotal PK comparability study (C2101). Study C2101 was an open label, single-dose pharmacokinetic (PK) comparability study that compared the approved lyophilized product with aged and non-aged liquid PFS product in patients with elevated serum

IgE levels. A single dose of 150 mg or 300 mg of omalizumab was given depending on screening IgE levels and body weight (as per the dosing in the label).

In Study C2101, the 90% confidence interval (CI) for the geometric mean ratios of the dose-normalized PK parameters (AUC0-∞, AUC0-last, Cmax) for the non- aged liquid formulation in the PFS vs. the marketed lyophilized product and aged liquid formulation in PFS vs. the marketed lyophilized product were all within the 80-125% (Figure 18 and Figure 19). See section 6.3.1 for details.

Figure 18. Statistical Analysis for PK parameters of Non-aged Liquid formulation in PFS Vs Lyophyilized product

	Adjusted geometric mean		Ratio of geometric means		
PK parameter (unit)	Test	Reference	Estimate	Lower 90% CL	Upper 90% CL
AUClast/dose (day.ng/mL/mg)	4985 (n=60)	5344 (n=58)	0.93	0.87	1.00
AUCinf/dose (day.ng/mL/mg)	5416 (n=57)	5742 (n=55)	0.94	0.87	1.02
Cmax/dose (ng/mL/mg)	137 (n=60)	143 (n=58)	0.95	0.88	1.03

Source: csr-2101.pdf, table 11-7

Figure 19. Statistical Analysis for PK parameters of Aged Liquid formulation in PFS Vs Lyophyilized product

	Adjusted geometric mean		Ratio of geometric means		
PK parameter (unit)	Test	Reference	Estimate	Lower 90% CL	Upper 90% CL
AUClast/dose (day.ng/mL/mg)	5116 (n=56)	5344 (n=58)	0.96	0.89	1.03
AUCinf/dose (day.ng/mL/mg)	5545 (n=56)	5742 (n=55)	0.97	0.89	1.05
Cmax/dose (ng/mL/mg)	143 (n=56)	143 (n=58)	1.00	0.92	1.08

Source: csr-2101.pdf, table 11-8

Overall, PK comparability has been demonstrated between the liquid formulation in the PFS and the marketed lyophilized product.

6.2.2. General Dosing and Therapeutic Individualization

The sponsor has proposed the same dosing regimen for PFS as the approved lyophilized vial.

Outstanding Issues

None

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

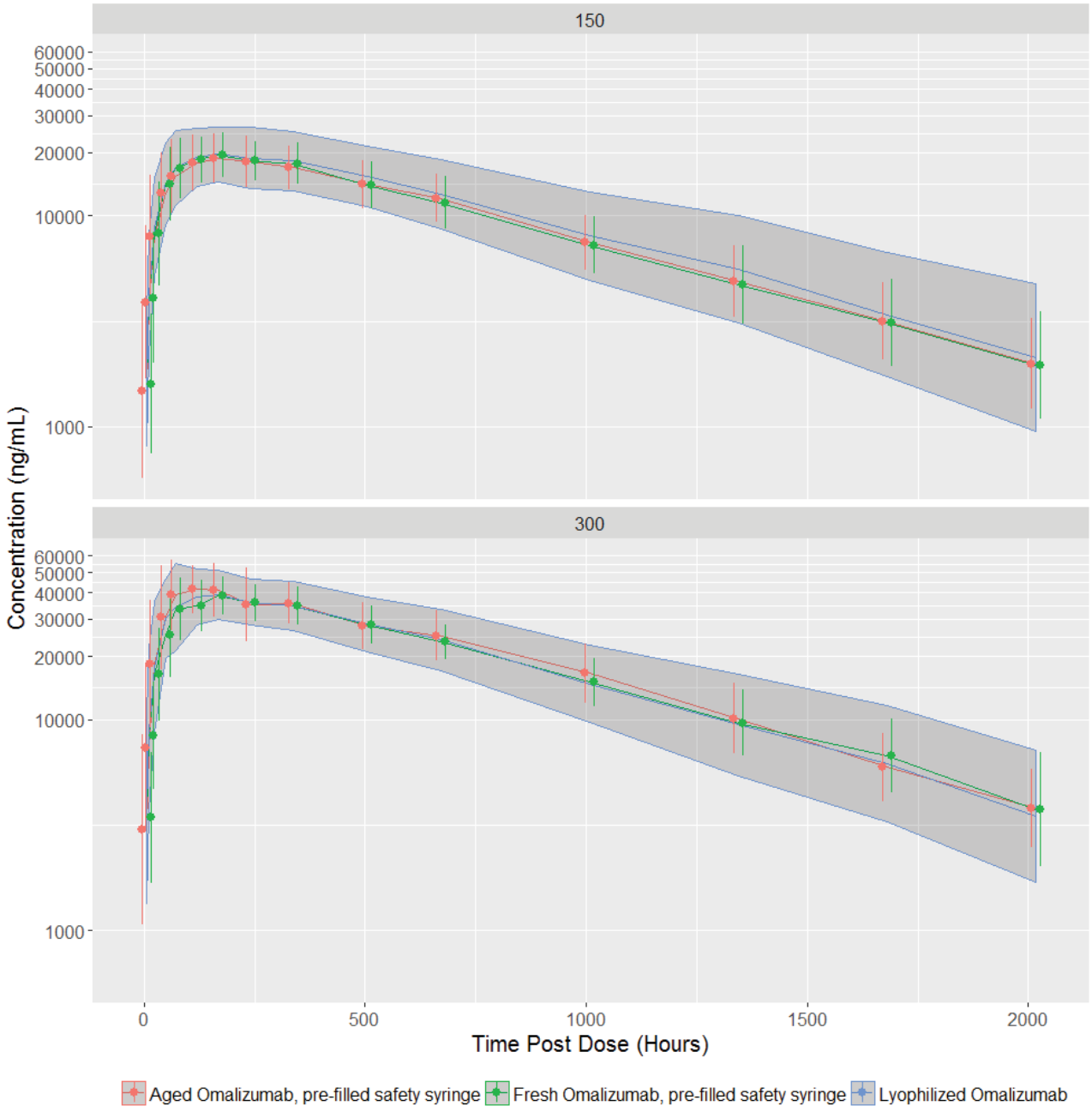
Clinical pharmacology assessment for Pivotal BE Study (C2101)

C2101 was an open-label, randomized, parallel-group three arm study to demonstrate the PK comparability of both non-aged and aged liquid omalizumab in the pre-filled syringe (PFS) with the marketed lyophilized material in patients with elevated serum IgE levels (30-300 IU/mL), including stable atopic individuals with intermittent, mild persistent or moderate persistent asthma and/or allergic or perennial rhinitis. The secondary objective was to explore the pharmacodynamics of the lyophilized product and the liquid in PFS. Currently approved lyophilized powder was compared to a non -aged (6 to 12.7 months old at the time of administration) and an aged liquid formulation. The aged liquid formulations were forced-aged by exposing it to a temperature of 23°C-27°C for several days, mimicking liquid products with specifications at or slightly beyond those proposed for a shelf -life of 18 months. A total of 180 subjects were randomized 1:1:1 to receive a single SC dose of the following: non-aged liquid in PFS, aged liquid PFS and lyophilized product.

A single dose of 150 mg or 300 mg was given depending on screening IgE levels and body weight (as per the dosing in the label). Doses were administered as two 75 mg injections for the 150 mg dose or two 150 mg injections for the 300 mg dose. All doses were administered to the right or left upper arm.

The concentration of omalizumab versus time profiles of the lyophilized product, aged and non-aged liquid formulation in PFS stratified by dose is shown in Figure 20 : Mean (+/- SD) Concentration Versus Time Profiles for the Lyophilized Product, Aged and Non-aged Liquid Formulation in PFS Stratified by DoseFigure 20.

Figure 20. Mean (+/- SD) Concentration Versus Time Profiles for the Lyophilized Product, Aged and Non-aged Liquid Formulation in PFS Stratified by Dose



Source: Reviewer's Analysis

Figure 21. Mean Dose-Normalized Pharmacokinetic Parameters from Study C2101

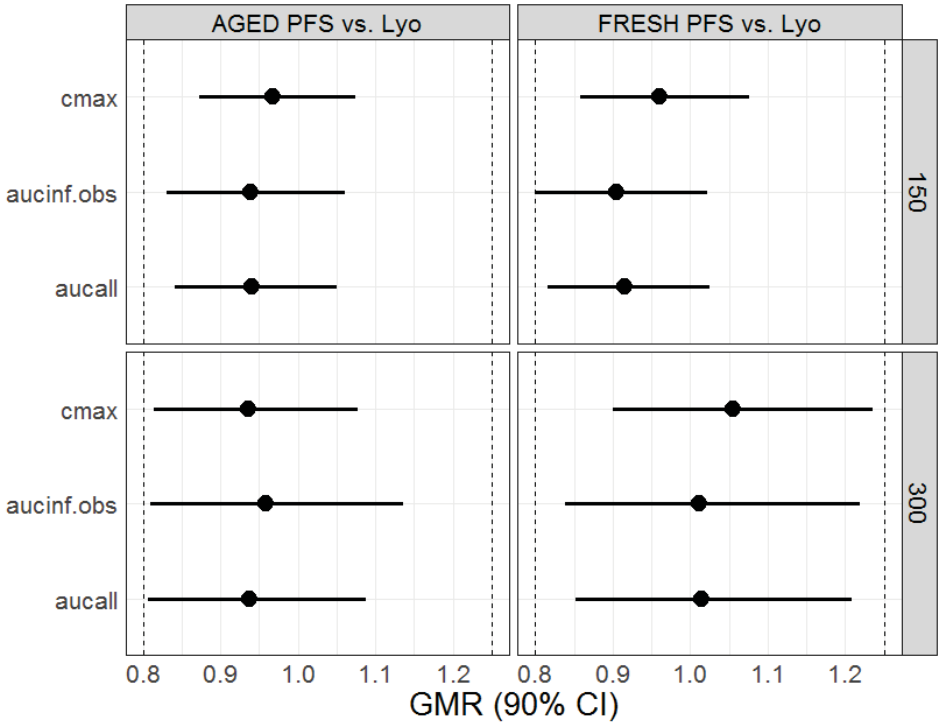
		Omalizumab		
Parameter	**Statistic**	**Lyophilized**	**Non-aged liquid**	**Aged liquid**
Cmax/dose (ng/mL/mg)	N	58*	60*	56*
	Mean (SD)	151 (51.2)	141 (28.1)	147 (39.8)
	CV%	33.9	20.0	27.1
	Median	150	141	149
	Range	74.8 - 344	75.0 - 204	73.1 - 283
AUClast/dose (day.ng/mL/mg)	N	58	60	56
	Mean (SD)	5657 (2036.4)	5148 (2120.3)	5228 (1317.4)
	CV%	33.3	21.7	25.2
	Median	5438	5121	5108
	Range	2240 - 12100	2480 - 7510	2710 - 8280
AUCinf/dose (day.ng/mL/mg)	N	55	57	56
	Mean (SD)	6091 (2036.4)	5624 (1409.1)	5704 (1509.5)
	CV%	33.4	25.1	26.5
	Median	5924	5522	5604
	Range	2260 - 12700	2450 - 8860	2850 - 9110

Source: csr-2101.pdf, table 11-6

The sponsor conducted a formal statistical analysis on dose-normalized PK parameters ($AUC_{0-\infty}$, AUC_{0-last}, C_{max}) using a linear fixed effect model with formulation as factor and body weight as a continuous covariate. The 90% confidence interval (CI) for the geometric mean ratios of the dose-normalized PK parameters ($AUC_{0-\infty}$, AUC_{0-last}, C_{max}) for the non- aged liquid formulation in the PFS vs. the marketed lyophilized product comparison and aged liquid formulation in PFS vs. the marketed lyophilized product comparison were all within 80-125% (Table 1 and Table 2).

The reviewer analyzed subject level concentration-time data from this study and confirmed results of non-compartmental analysis (Figure 21) and statistical analysis (Figure 18 and Figure 19). The reviewer analyzed each dose group (300 mg and 150 mg) separately, without using dose-normalized parameters. The results in each dose group confirmed that PK was comparable between the PFS presentation and the lyophilized product and was consistent with the overall conclusion of comparability (Figure 22).

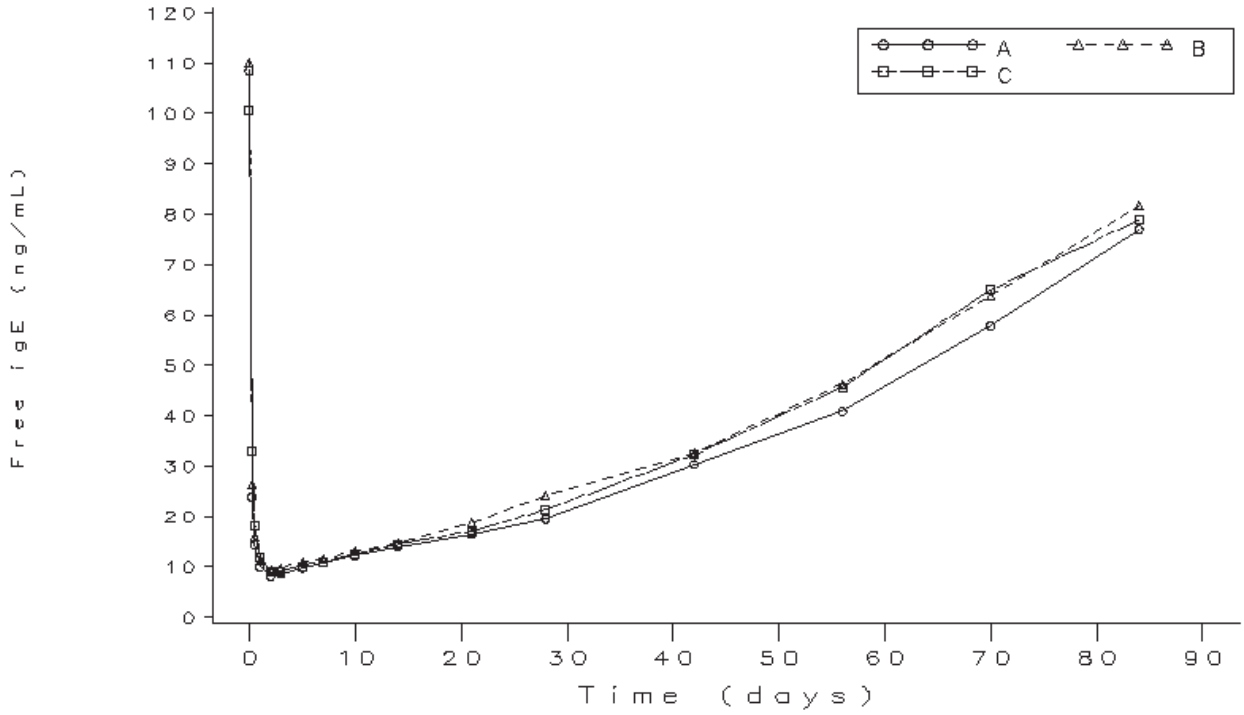
Figure 22. Point estimate and 90% Confidence intervals of Pharmacokinetic Parameters for Aged and Non-aged PFS vs. Lyophilized powder



Source: Reviewer's Analysis

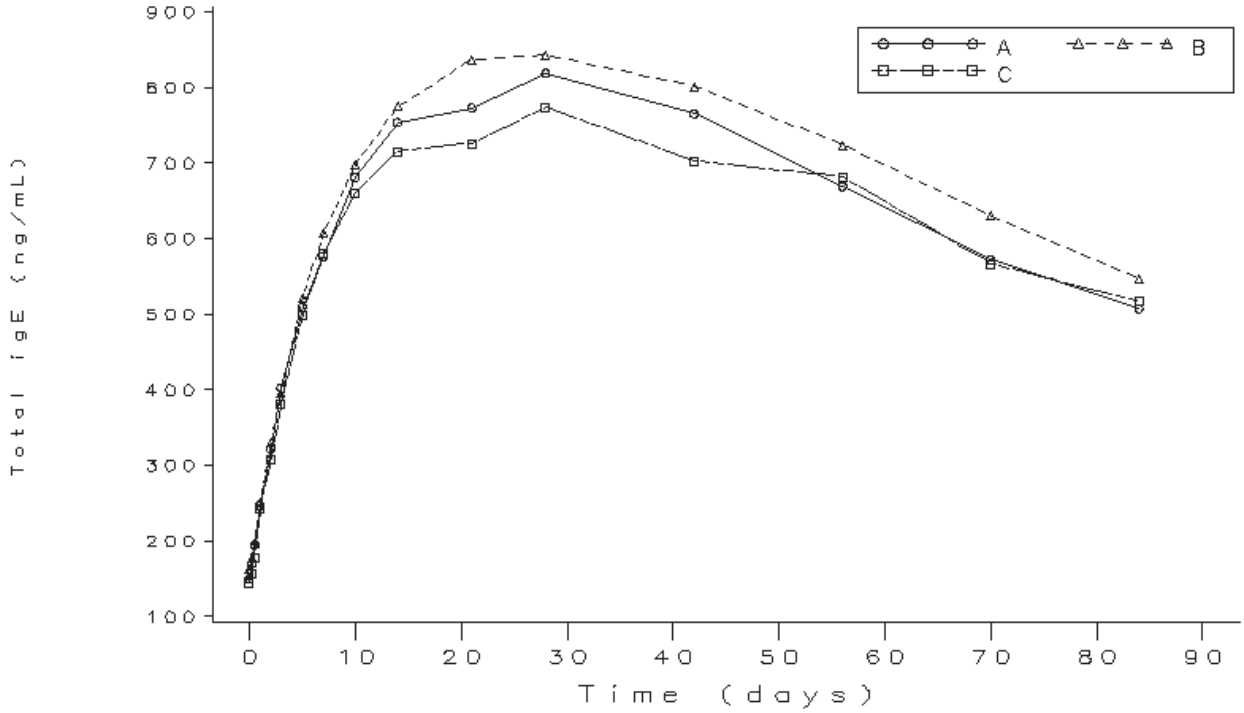
Two key pharmacodynamic endpoints of omalizumab treatment (free IgE, total IgE) display substantial overlap (Figure 23and Figure 24).

Figure 23. Arithmetic mean of Free IgE (ng/mL) Versus Time After Dose



Source: csr-2101.pdf table 14.2-2.1

Figure 24. Arithmetic mean of Total IgE (ng/mL) Versus Time After Dose



Source: csr-2101.pdf table 14.2-2.2

Bioanalytical Assay

Total omalizumab (i.e., the sum of free and IgE bound omalizumab) was determined in serum using ELISA (Enzyme-linked immunosorbent assay). In this assay, human myeloma-derived IgE (monoclonal antibody U266) was coated onto polystyrene microtiter plates by passive adsorption. A monoclonal antibody (AME2) directed against the complementarity-determining regions of omalizumab was conjugated with horseradish peroxidase (HRP) and used as the detection molecule. Omalizumab was captured from the sample matrix onto the plate via its binding interaction with IgE during an overnight incubation step. Following a washout step, the AME2-HRP conjugate was added to the plate, and the plate was incubated a second time. Omalizumab that was captured by IgE was then colorimetrically detected using an O-phenylenediamine (OPD) substrate in a hydrogen peroxide substrate diluent. The initial overnight incubation of diluted samples minimizes IgE:omalizumab immune complex interference in this assay. The lower limit of quantification (LLOQ) was 16 ng/ml.

The calibration curve was generated using 0.156, 0.313, 0.625, 1.25, 2.5, 5, and 10 ng/mL standards. A 4-parameter logistic function was used to fit the data. The assay qualification summary is attached in Figure 25, below.

Based on the bioanalytical inspection report, the analytical data from study C2101) are reliable for Agency review (reviews by Drs. Abhari and Yeh, dated 4 September 2018).

Overall, the analytical methods conducted for Study C2101 was found to be acceptable.

Figure 25. Assay Qualification Summary

TYPE OF ASSAY	Human IgE immobilized as antigen:anti-E25 CDR-HRP MAb for detection
STANDARD	rhuMAb-E25 reference material
SPECIES QUALIFIED	Human
BIOLOGICAL MEDIUM	Human serum, rat serum, human serum treated to remove IgE:rhuMAb-E25 complexes
RANGE OF ASSAY	0.16 - 10 ng/mL
EFFECTIVE RANGE IN BIOLOGICAL MEDIUM	Lower limit: 16 ng/mL rhuMAb-E25 in human serum, 80 ng/mL rhuMAb-E25 in rat serum, 20 ng/mL in human serum treated to remove IgE:rhuMAb-E25 complexes. No upper limit
INTRA-ASSAY PRECISION in 1% human serum	n = 13 for each control Control / Mean / Std dev / %CV Low 0.23 ng/mL 0.01 4.5% Mid 0.90 ng/mL 0.04 4.0% High 4.61 ng/mL 0.18 3.9%
INTER ASSAY PRECISION in 1% human serum	For 13 assays: Control / Mean / Std dev / %CV Low 0.23 ng/mL 0.01 4.5% Mid 0.90 ng/mL 0.04 4.0% High 4.61 ng/mL 0.21 4.6%
ACCURACY	Mean percent recovery of rhuMAb-E25 from 4 individual human serum samples (relative to buffer control): Spike level / Mean / % Recovery Low 0.48 ng/mL 96% Mid 2.30 ng/mL 102% High 5.40 ng/mL 99%
SAMPLE DILUTION BUFFER	PBS/0.5% BSA/0.05% polysorbate 20/0.01% thimerosal for initial 1/100 dilution; subsequent dilutions use 1/100 human serum in PBS/0.5% BSA/0.05% polysorbate 20/0.01% thimerosal
SAMPLE STABILITY	1/100 dilution of serum in sample dilution buffer is stable for 2 weeks at 2-8°C. Neat samples are stable for 2 weeks at 2-8°C, and are stable through 3 freeze-thaw cycles.
NOTEBOOK REFERENCES	Notebooks 18815, 18816, 17774, 19083, 21474 Human serum treated to remove IgE:rhuMAb-E25 complexes: Assay Qualification Summary S95-14-1560.

SPECIFICITY	No crossreaction with serum spiked with 10 µg/mL rhuMAb HER2, DNase, TPA, anti-CD18, or TNF-α
LIMITATIONS	Minimum sample dilution: 1/100 for human serum. 1/500 for rat serum (dilution of rat serum done with 1/100 human serum in PBS/0.5% BSA/0.05% polysorbate 20/0.01% Thimerosal) 1/100 for human serum treated to remove IgE:rhuMAb-E25 complexes (final dilution 1/125)
QUALIFICATION REPORT	In progress
SPECIAL COMMENTS	Overnight incubation of diluted sample in well allows >95% recovery of total rhuMAb-E25 from human serum containing up to 685 IU/mL IgE.

Clinical pharmacology Assessment for Safety Study C2303

Immunogenicity of Omalizumab PFS

C2303 was an open label, single arm, 24-week treatment of patients with moderate to severe persistent allergic asthma, to assess the safety and immunogenicity of omalizumab PFS. The treatment phase was followed by a 16-week follow-up period, during which omalizumab was not administered to the patient. Pharmacokinetic and pharmacodynamic plasma samples were drawn at 25 weeks. Immunogenicity samples were drawn at baseline and at the end of the follow up period (week 41).

No patient had detectable anti-omalizumab antibodies at the end of the follow up period. However, the sensitivity of the anti-omalizumab antibody assays is affected by the presence of omalizumab in the sample. Drug tolerance experiments had shown the Fab and Fc antibody assays can tolerate up to 10 µg/mL of omalizumab before antibodies were no longer detectable. Therefore, the presence of more than 10 µg/mL of omalizumab in serum may cause a false-negative result. The mean trough concentrations at week 25 in study C2303 was 99.2 µg/mL and 35.0 µg/mL for the every 2 weeks and every 4 weeks regimen respectively which are higher than the drug tolerance limit. Refer to section 8.2.4 for the safety findings from study C2303.

6.3.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

Not applicable

Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Not applicable

Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

Not applicable

Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

Not applicable

Question on clinically relevant specifications (TBD)?

Not applicable

Justin A. Penzenstadler -S

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DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2002109069, cn=Justin A. Penzenstadler -S
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Anshu Marathe -S

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Clinical Pharmacology Primary Reviewer Clinical Pharmacology Team Leader

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

Figure 26. Liquid PFS Clinical Development Program

Study	Design	N	Treatments	Endpoints
Local excipient tolerability				
Q2569g (2002)	SB, 3-way crossover excipient safety study in healthy adults	36	Lyophilized excipient Liquid excipient Placebo	Injection-site tolerance: 1 – pain-time curve 2 – severity of injection-site reactions
Early formulation development (liquid product in vials)				
A2204 (2004)	OL, SD bioequivalence in atopic subjects with elevated serum IgE (30-300 IU/mL)	155	Lyophilized Liquid in vial, non-aged	PK and PD (free/total IgE)
A2204E1 (2006)	OL, SD PK and PD in atopic subjects with elevated serum IgE (30-300 IU/mL)	40	Lyophilized Liquid in vial, force aged (6-12.7 months)	PK and PD (free/total IgE)
Pivotal studies with the to-be-marketed product				
C2101 (2008)	OL, SD bioequivalence in atopic subjects with elevated serum IgE (30-300 IU/mL)	180	Lyophilized PFS, aged PFS, non-aged	Bioequivalence and PD
Other studies				
C2303 (2008)	6-month, OL, single-arm immunogenicity safety study in adolescents and adults with mod to severe persistent “allergic” asthma	155	PFS, forced & naturally aged	Immunogenicity Safety and tolerability
Q4160g (2009)	16-week, R, DB, PC inhaled aeroallergen broncho-provocation study in adults with mild “allergic” asthma with allergen challenge at 8 and 16 weeks.	61	Lyophilized (N=16) PFS, aged (N=23) Placebo (N=14)	Change of allergen PC_{15} concentration from baseline to Week 16
Studies are shown in chronological order with the year of completion shown in parenthesis.				

7.2. Review Strategy

The two pivotal studies (C2101 and C2303) are reviewed in more detail in Sections 8.1.1 and 8.1.2. Both studies used the to-be-marketed liquid PFS product. C2101 was an open label, single-dose bioequivalence study that compared the approved lyophilized product with aged and non-aged liquid PFS product, and C2303 was a 6-month open-label, single-arm study that evaluated the immunogenicity of aged liquid PFS.

In addition, summaries of Study Q4160 and Study Q2569g are provided in Section 8.1.2. Study Q4160 was a failed bronchoprovocation study the Agency initially asked for due to concerns of differences noted between the aged liquid Xolair material and reconstituted lyophilized Xolair in earlier studies (Figure 1, Study A2204E1). The bronchoprovocation study failed on the primary and secondary endpoints. This may be due to an improper inclusion criterion and small sample size. However, the Agency is not considering this as either a meaningful or as a pivotal study given that bioequivalence was demonstrated in C2101 and immunogenicity was evaluated in C2303. Study Q2569g was a randomized, single-blind, three-way crossover study designed to evaluate pain and local irritation related to SC injection of the excipient in the liquid formulation of Xolair compared to the excipients of the reconstituted lyophilized Xolair. Study Q2569g provides supplemental safety information.

8 Clinical Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Pivotal Study: C2101

Administrative Information:
Study title: An open-label, randomized, single-dose, three parallel group study of SC dosed lyophilized, aged and non-aged liquid Xolair (final market formulation in pre-filled safety syringes) to determine bioequivalence and pharmacodynamics in subjects with elevated IgE.
Study dates: July 31, 2007- June 13, 2008
Study sites: United States
Study report date: March 18, 2009

Objectives:
Primary objective: To demonstrate bioequivalence of a single SC dose of both aged and non-aged liquid Xolair packaged as a PFS with the marketed lyophilized material.
Secondary objective: To explore the single SC dose PD of aged and non-aged liquid Xolair packaged as a PFS and the marketed lyophilized material.

Study Design and Conduct:
Procedures

This was an open-label, randomized, parallel group, single-dose bioequivalence study that compared serum Xolair PK and the effects on PD (free and total IgE) of non-aged and aged liquid Xolair in the PFS with reconstituted lyophilized Xolair.

Patient Population
The study enrolled adults with intermittent, mild persistent or moderate persistent asthma and/or allergic or perennial rhinitis with an elevated serum IgE level (30-300 IU/mL).

Treatment
A total of 180 subjects received either a dose of 150 mg or 300 mg, depending on screening IgE levels and body weight. Both the 75 mg/0.5 mL and 150 mg/mL dosage strengths of non-aged and aged PFS were evaluated, administered as two 75 mg injections for the 150 mg dose or two 150 mg injections for the 300 mg dose.

Endpoints
PK of Xolair was measured by total Xolair in serum. PD was measured by free and total IgE in serum by 84 days after administration

Statistical Analysis Plan
All subjects randomized that received at least part of the study drug were included in the data analysis. All subjects with evaluable PK and PD data were included in the PK and PD data analysis. Regarding the safety population, all subjects who received at least one dose of the study drug was included. All subjects were analyzed according to treatment received.

During the course of the study, a decision was made to identify protocol deviations and to define an additional per protocol population not planned in the protocol to study the impact of the protocol deviations on study results. There were 14 protocol deviations (see below).

The statistical analysis was based on the PK full analysis data set which consisted of all subjects with evaluable PK data. These analyses were repeated on the per protocol population which excluded subjects with major deviations.

Compliance with Good Clinical Practice
A statement of compliance with Good Clinical Practice is in the CSR.

Study Results:
Financial Disclosure
The financial disclosure information from this trial does not impact the interpretation of the efficacy or safety results. See Appendix 19.2 of this review for additional details.

Data Quality and Review
This submission was appropriately indexed and complete to permit review.

Patient Disposition
Originally, a total of 165 patients were to be enrolled. However, due to a number of patients with protocol deviations, 180 patients were recruited to ensure 52 patients/group in the per protocol population. One hundred seventy seven subjects (98%) completed the study. Three patients withdrew, two withdrew consent and one was lost to follow up.

Protocol Amendments
Three minor administrative amendments were made before database lock and were determined to not affect the interpretation of the study results.

Protocol Violations/Deviations
The randomization list was not available when one center wanted to start dosing patients. The decision was made to allocate patients to treatment on a systemic (non-randomized) basis which led to 14 protocol deviations requiring exclusion from the per protocol (PP) populations.

Two subjects were randomized, but given the wrong medication in error. One other patient was excluded from the PP population due to having duplicate randomization numbers. There were 15 other patients with minor protocol deviations (i.e. missed visits, lack of documentation of the time syringes were removed from fridge, etc.) during the conduct of the study that were not considered to impact study results and did not lead to exclusion.

Demographic Characteristics
Demographic and baseline characteristics of the treatment groups were similar. About half the subjects were male, 101 (56.1%). The majority (71%) were Caucasian with an average age of 38 years (range: 18 – 65 years), and a mean weight of 71.1 kg, SD = 10.44 kg (range: 45.8 – 90.0 kg). Mean baseline IgE at screening was 199.1, 214.8, and 198.8 ng/mL for the Xolair (lyophilized), non-aged liquid PFS, and aged liquid PFS groups, respectively.

PK/PD
PK results are summarized in Figure 27. The confidence limits (CL) for the PK analysis for AUC_{last}, AUC_{inf} and C_{max} were within 0.8 to 1.25, the criteria set for bioequivalence. For the PD assessment, free and total IgE concentration time profiles were similar for all three formulations.

Figure 27. C2101 PK results and ratios

PK Parameter	Adjusted geometric Mean (n)			Ratio of Geometric Mean (Upper, Lower 90% CL)	
	Non-aged Liquid PFS	Aged Liquid PFS	Xolair	Non-aged vs Xolair	Aged vs Xolair
AUClast/dose (day.ng/mL/mg)	4985 (n=60)	5116 (n=56)	5344 (n=58)	0.93 (0.87, 1.00)	0.96 (0.89, 1.03)
AUCinf/dose (day.ng/mL/mg)	5416 (n=57)	5545 (n=56)	5742 (n=55)	0.94 (0.87, 1.02)	0.97 (0.89, 1.05)

Cmax/dose (ng/mL/mg)	137 (n=60)	143 (n=56)	143 (n=58)	0.95 (0.88, 1.03)	1.00 (0.92, 1.08)

Source: M5, csr-c2101.pdf, T2, p6, T3, p7

The free and total IgE results are shown in Figure 28 and Figure 29 respectively. The PD results were similar across treatment groups. Mean minimum free IgE levels were 7.7, 8.9, and 8.3 ng/mL for the Xolair (lyophilized), non-aged liquid, and aged liquid formulations, respectively. The maximum percent reductions in free IgE were 95.2, 95.1, and 94.9% for the Xolair, non-aged liquid, and aged liquid formulations, respectively.

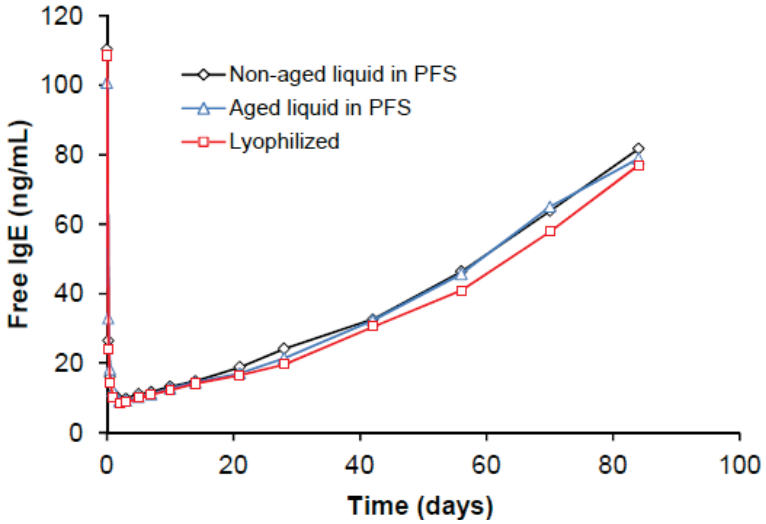

Figure 28. C2101. Arithmetic mean free IgE serum concentrations by formulation

Source: M2, summary-clin-pharm.pdf, F3.1, p28

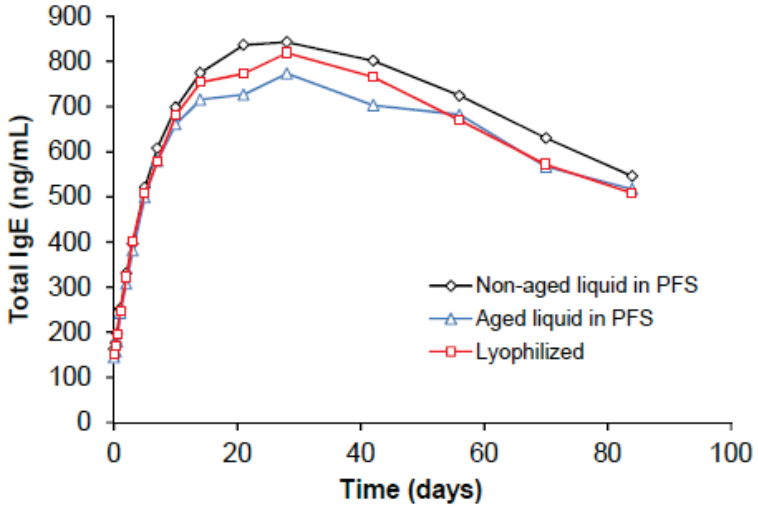

Figure 29. C2101. Arithmetic mean total IgE serum concentrations by formulation

Source: M2, summary-clin-pharm.pdf, F3.3, p29

Additional review of the PK and PD results can be found in Section 6. Clinical Pharmacology.

Safety:
No deaths, serious adverse events, or adverse events leading to withdrawal were reported. Eight-five (47%) subjects reported at least one mild to moderate adverse event. Headache was the most frequently reported adverse event (17% of subjects) and was evenly balanced over the treatment groups. Other commonly reported events include infections.

Reviewer comments: Although limited safety conclusions can be made on this single-dose study for a drug intended to be used chronically, no concerning safety issues were identified.

8.1.2. Pivotal Study: C2303

Administrative Information:
Study title: An open-label, single arm study to assess the safety and immunogenicity of Xolair liquid administered SC in a pre-filled safety syringe (75 mg or 150 mg) over a period of 6 months to male and female adolescents and adults with moderate to severe persistent allergic asthma.
Study dates: July 5, 2007-September 22, 2008
Study sites: Germany, Spain, United States
Study report date: February 13, 2009

Objectives:
Primary objective: To assess the immunogenic potential of Xolair liquid when administered over a period of 6 months to Xolair naïve, moderate to severe persistent allergic asthma patients age 12 years or older.

Secondary objective: To assess the safety and tolerability of Xolair liquid when administered over a period of 6 months to Xolair naïve, moderate to severe persistent allergic asthma patients age 12 years or older.

Study Design and Conduct:

Procedures
Study C2303 was a 6-month, open-label, single-arm study that assessed the immunogenic potential of thermally forced and naturally aged liquid Xolair PFS.

Patient Population
The population consisted of adolescents and adults ≥12 years of age and older with stable, moderate to severe persistent allergic asthma, a body weight ≥30 kg and ≤150 kg, and a total serum IgE level ≥30 to ≤700 IU/ml. Enrollment was restricted to individuals who had not previously been exposed to Xolair.

Treatment
The patients were treated with the liquid formulation of omalizumab as add-on therapy and were dosed every 2 or 4 weeks. The treatment dose was selected based on body weight and serum IgE level.
The patients were treated with the liquid formulation of Xolair in a PFS as add-on therapy and were dosed ever 2 or 4 weeks based on IgE and body weight dosing parameters previously approved for the lyophilized formulation for asthma. The treatment phase was then followed by a 16 week follow up period. Study visits were at -1 week (baseline) and at weeks 1 (treatment start), 5, 17, 25 (treatment end), 29, 33, 37, and 41 (end of study).

Endpoints
Immunogenic potential was assessed by human anti-human antibody (HAHA – Fab and Fc) assays performed at baseline and at the end of the follow-up period (week 41). Safety was assessed based on pre- and post-treatment physical examinations; adverse event reports solicited at each visit; and periodic hematology, blood chemistries, and urinalyses. Total serum Xolair (trough levels), free IgE, and total IgE were collected at the end of the treatment period just prior to administration of the last dose.

Statistical Analysis Plan
There were two patient populations: the safety population and the intent-to-treat population. Both populations consisted of all patients that received any part of a dose of the study drug and had any post-baseline assessment. The intent-to-treat population was not used in any analysis.

Compliance with Good Clinical Practice
A statement of compliance with Good Clinical Practice is located in the CSR.

Study Results:

Financial Disclosure
The financial disclosure information from this trial does not impact the interpretation of the efficacy or safety results. See Appendix 19.2 of this review for additional details.

Data Quality and Review
This submission was appropriately indexed and complete to permit review.

Disposition
Out of the 155 treated patients, 140 (90.3%) completed the 24-week treatment period. The most common cause of premature discontinuation during this period was protocol deviation (3.2%) and adverse events (2.6%). After database lock, one subject was not discontinued in error due to a protocol deviation (has history of chronic hives). The patient withdrew consent and discontinued from the study on Day 4/7 treatment period.

Of the 148 patients who entered the follow-up period, 136 (91.9%) completed the follow-up period. The most common reason for discontinuing during this period was lost to follow-up (2.0%). There were three patients who were not formally entered into the follow up, but

provided safety data during the follow up period. These three subjects were included in the total 148. Protocol deviations were reported for these three subjects.

Protocol Amendments
Minor amendments were made before database lock and were determined to not affect the interpretation of the study results.

Following database lock, one patient was found to have failed screening (total IgE outside protocol), but completed screening assessments. This case raised no safety issues, nor did it affect the outcome of the study. The patient's data is not included in the study database.

Protocol Violations/Deviations
The most common protocol deviation were study medication errors (5.2%) such as incorrect dosing and Xolair taken during follow up period. Most deviations (inclusion/exclusion criteria, excluded concomitant treatment received) were minor and not expected to impact the study results.

Demographics
Demographic and baseline disease characteristics were balanced between groups. The majority of subjects were female (61.3%) and Caucasian (83.9%) with a mean age of 43 years, a median duration of asthma of 14 years (range 1-70 years). The study enrolled 13 (8%) subjects 12 to 17 years of age and 7 (5%) subjects ≥65 years. A total of 10% were current smokers. Mean baseline serum IgE was 216.5 (SD 146.9, range 32 – 665) IU/mL.

Immunogenicity
A total of 155 subjects were enrolled at 37 sites, of whom 140 (90%) completed 24 weeks of treatment. Of the 148 subjects who entered the follow-up period, 136 (92%) completed follow-up and received anti-drug-antibody (ADA)testing.

Per the clinical pharmacology review, drug tolerance experiments had shown the Fab and Fc antibody assays can tolerate up to 10 µg/mL of omalizumab before antibodies were no longer detectable. Therefore, the presence of more than 10 µg/mL of omalizumab in serum may cause a false-negative result. The mean trough concentrations at week 25 in study C2303 was 99.2 µg/mL and 35.0 µg/mL for the every 2 weeks and every 4 weeks regimen respectively which are higher than the drug tolerance limit. Therefore, immunogenicity may be under reported.

See Section 6.3.1 regarding discussion regarding the immunogenicity analysis.

Safety:
Refer to section 8.2.4 for safety discussion.

8.1.3. Summaries of Other Studies

Study Q4160

This study was performed in response to the Agency's concerns with the initial low molecular weight fragment identified by HPLC in the aged liquid formulation that was not present in the reconstituted lyophilized Xolair (Study A2204E1). Due to this peak, the Agency requested the sponsor to evaluate the aged to-be-marketed liquid Xolair PFS on a clinically relevant pharmacodynamic measure. The sponsor chose assessment of bronchoprovocation. This measure was chosen prior to the approval of Xolair for CIU, which would now be a relevant clinical model.

The study was conducted in North America between November 2007 and June 2009. It was a multi-center, randomized, double-blind parallel group, 3 arm, placebo-controlled study that compared the effectiveness of reconstituted lyophilized Xolair with aged liquid PFS. The study consisted of a 16-week treatment period and a 16-week follow-up period. A total of 61 subjects were enrolled and randomized 2:2:1 to receive Xolair (reconstituted lyophilized, n=24), aged liquid Xolair in a PFS (n=23), or placebo (n=14), of whom 58 (95%) completed the full 16 weeks of study treatment. Study drug was administered every 2 or 4 weeks based on IgE and body weight dosing parameters previously approved for the lyophilized formulation for asthma.

An allergen challenge was conducted to determine the allergen concentration required to evoke a 15% drop (PC_{15}) in FEV_1 at baseline, and repeated at 8 and 16 weeks. The primary outcome measure (as proposed by the applicants and agreed to by the Agency in the SPA) was the change in log-transformed allergen PC_{15} from baseline to Week 16. The secondary outcome measure was the ratio of the allergen FEV_1 two-point slope at the Week 16 allergen challenge to the allergen FEV_1 two-point slope at the baseline allergen challenge.

Evaluation of the demographic and baseline characteristics of the study population revealed that the groups were reasonably similar, except that the aged liquid Xolair group had lower median screening total IgE levels (115 IU/mL) compared with either the Xolair (132.5 IU/mL) or placebo groups (171 IU/mL). In addition, a total of 9 (16%) of the 58 subjects had pre-dose total IgE levels <30 IU/mL and therefore would not have qualified (as patients) for Xolair treatment based on the approved dosing table, and these subjects were disproportionally represented in the aged liquid PFS arm.

There were no deaths and two SAEs, both in the lyophilized Xolair treatment groups. In one event, a 22-year-old man developed severe pyrexia during the treatment period and was hospitalized. It was concluded that it was secondary to a viral illness. In the other event, a 30-year-old woman experienced a spontaneous abortion during the follow up period.

Median increases in log 2-transformed allergen PC_{15} at Week 16 (primary endpoint) in subjects receiving Xolair, aged Xolair in PFS, and placebo were 1.85, 1.15, and 0.36, respectively, the difference between Xolair and the aged liquid PFS being 0.58 (95% CI: -0.41, 1.63). The median

ratio of the allergen FEV_1 two-point slope at Week 16 compared to baseline (secondary endpoints) in subjects receiving Xolair, aged liquid PFS, and placebo were 0.29, 0.52, and 0.95, respectively. When tested for superiority compared with placebo, the lyophilized Xolair group achieved a statistically significant increase in allergen PC15 while the aged liquid Xolair group did not. Both lyophilized and aged liquid Xolair demonstrated an increase in PC15 at Week 16, but only the lyophilized formulation demonstrated a statistically significant difference compared with placebo.

Based on the primary and secondary results, this study was a failed study. A relatively small sample size, variability in results, and lack of sensitivity of PC_{15} as a PD measure likely contributed to the failed study. Moreover, the allergen challenge may also not be a sufficiently sensitive PD clinical measure to detect meaningful differences between formulations.

In retrospect, the utility of this bronchoprovocation study to evaluate the clinical impact of the differences in the two formulations is questionable. At this time, we have a better understanding of the two formulations and a bioanalytical assessment of the extra peak in the aged formulation. With this supplement, we have data demonstrating bioequivalence between the two formulations and we have some immunogenicity data with the new formulation. Additional clinical data are no longer considered necessary.

If clinical data were necessary, knowing the relatively robust results of the clinical trials conducted for the CIU clinical program, which had not been conducted at the time that this study was conceived and conducted, it is possible that a study conducted in CIU patients might have yielded more satisfactory answers. Further, ruling out any clinically meaningful differences between two formulations is now understood to require a non-inferiority design, which in turn would require a far larger trial size than this study employed. Therefore, the Agency is not considering this bronchoprovocation study as either a meaningful or pivotal study.

Study Q2569g

This was a randomized, single-blind, three-way crossover study designed to evaluate pain and local irritation related to SC injection of the excipients in the liquid formulation of Xolair compared with that of the excipients in the reconstituted lyophilized Xolair. It was performed in 2002 in 26 healthy adults. The primary outcome measure was the AUC0–60min for the VAS pain–time curve. The secondary outcome measure was the severity of burning, itching, warmth, redness, rate of hive formation, and size of injection-site reaction as assessed by the Local Injection-Site Symptom Assessment (LISSA). No meaningful differences in local reactions to the excipients in either formulation were noted.

Of note, the sponsor reports that study investigators were unable to be reached after multiple attempts to obtain financial disclosure.

8.1.4. Assessment of Efficacy Across Trials

Assessment of efficacy relied on demonstration of bioequivalence between the new liquid formulation in the PFS compared to the approved lyophilized powder. The bioequivalence results are discussed under Study C2101 in both the clinical and clinical pharmacology sections.

8.2. Review of Safety

8.2.1. Safety Review Approach

Xolair has been on the market since 2003. The safety profile for Xolair is well established and described in the current prescription label. This new formulation differs from the current formulation (b) (4) The changes to the drug substance manufacturing process involve changes to only (b) (4) in the manufacturing process.

The safety review relies on Study C2303, the 6-month, open-label, single arm immunogenicity safety study. The safety data of all the studies (Figure 26) were not pooled together due to the difference in types of study designs, the different endpoints, and different patient populations. Interpretation of the C2303 safety assessment is limited as it is a single arm, open-label study. Therefore, our safety review focused on the findings of C2303 as well as a summary of the post-marketing safety data from the lyophilized Xolair currently on market. After the supplemental submission, a 120-day safety update was submitted on June 29, 2018. Review of the 120-safety update included no new safety data, studies, or literature.

8.2.2. Review of the Safety Database- Study C2303

Overall Exposure

A total of 155 patients were enrolled in Study C2303, with the mean exposure time of 23 weeks with 90% of patients completing at least 20 weeks. The Xolair dose was individualized for each patient based on the patient's body weight and total serum IgE level at the initial visit.

Relevant characteristics of the safety population:

The study population consisted of adolescent and adults 12 years of age or older with moderate to severe persistent allergic asthma. Patients had not been exposed to Xolair in the past.

Adequacy of the safety database:

As Xolair has been on the market since 2003 and this supplement is for a new formulation without differences in the active drug, the safety database is adequate to characterize the safety of Xolair prefilled syringe in the targeted patient population for use.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

No data integrity or submission quality issues that hinder the safety review of this BLA were identified.

Categorization of Adverse Events

In this program, an adverse event (AE) is defined as the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after starting the study drug even if the event is not considered to be related to study drug. The study drug includes the investigational drug (Xolair) under evaluation given during any phase/period of the study.

Adverse events were collected throughout each study and coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 19.1. Adverse events during the treatment period were defined as AEs that begin between the first treatment dose and 28 days post last treatment dose. The occurrence of adverse events were questioned during Study Visits only. However, if the patient spontaneously volunteered such events, these were recorded. SAEs are monitored continuously and every SAE, regardless of causality, occurring after the patient began the study drug and until the end of 15-week follow-up period needed to be reported to the sponsor within 24 hours of the occurrence.

Routine Clinical Tests

Safety assessments consisted of routine reporting of all adverse events, serious adverse events, relationship to the drug, and pregnancies. Participants also underwent regular monitoring of bloodwork (hematology, chemistry, urine analysis), along with regular vital sign and physical exams. A 12 lead ECG was obtained at Visit 1 if it had not been obtained in the month prior.

8.2.4. Safety Results- Study C2303

The safety results for Study C2303 are summarized in Table 1.

Table 1. Study C2303 Safety Summary: Deaths, SAEs, and AEs Leading to Discontinuation

Category/PT	**Xolair n (%) N=155**
Deaths during the treatment period	1 (<1%)
Asthma exacerbation	1 (<1%)
SAEs	14 (9.0%)
Asthma	4 (3%)
Anemia	1 (<1%)
Angina unstable	1 (<1%)

Bronchiectasis	1 (<1%)
Cardiac arrest	1 (<1%)
Cartilage injury	1 (<1%)
Dehydration	1 (<1%)
Enteritis	1 (<1%)
Epilepsy	1 (<1%)
Gastric ulcer	1 (<1%)
Intervertebral disc protrusion	1 (<1%)
Laryngeal inflammation	1 (<1%)
Pneumonia	1 (<1%)
Post procedural swelling	1 (<1%)
AEs leading to discontinuation	4 (3%)
Anemia	1 (<1%)
Dehydration	1 (<1%)
Injection site pain	1 (<1%)
Pregnancy	1 (<1%)

Deaths

There was one death during the study. A 60-year-old man died of cardiac arrest 26 days after the last treatment dose. The patient had a severe asthma exacerbation and received dexamethasone and nebulized ipratropium bromide- albuterol sulfate at an acute care clinic. He did not respond to the treatment and later died of respiratory and cardiac arrest. No patients died during follow up period.

Serious Adverse Events

Fourteen patients (9.0%) had serious adverse events during the treatment period with two of these patients (1.3%) discontinuing the study due to these events. The serious adverse event included bronchiectasis, epilepsy, intraoperative glottis swelling, asthma exacerbation, pneumonia, unstable angina, gastric ulcer, spontaneous miscarriage, herniated disc, torn knee cartilage, dehydration, anemia, and injection site pain. Asthma was the only serious adverse event occurring during the treatment period that occurred in more than one patient. One patient had a serious adverse event during the follow up period, but did not discontinue.

Dropouts and/or Discontinuations Due to Adverse Effects

Of the 155-total number of patients, 4 patients discontinued during the treatment period due to adverse event (anemia, dehydration, injection site pain, or pregnancy). One patient discontinued during the follow up period due to adverse event (asthma). Both anemia and injection site pain were categorized as SAEs.

Treatment Emergent Adverse Events and Adverse Reactions

Eighty percent of patients enrolled experienced at least one AE with most of these labeled mild to moderate in severity. The most common adverse event was asthma (17.4%), sinusitis (17.4%) and upper respiratory tract infection (11.6%). There were no new or unanticipated AEs reported in this study and the frequency of the AEs were consistent with previous studies.

Reported AEs of clinical interest include hypersensitivity reactions, hemorrhages, malignancies, parasitic infection, thrombocytopenia, serum sickness, and eosinophilic granulomatosis with polyangiitis (previously called Churg-Strauss). These AEs occurred in 3 or fewer patients. The most common reaction was hypersensitivity both including (31.6%) and excluding (19.4%) anaphylaxis, injection site reactions and skin reactions. There were seven cases of hemorrhages, but all mild to moderate and subjects did not discontinue therapy. One case of suspected malignancy occurred (elevated PSA) and unlikely related to the study medication. There were 3 cases of urticaria. Hypersensitivity reaction was the most common reported AEs in the follow up period (12.8%). Using Sampson criteria to identify true anaphylaxis cases, only two partially met Sampson criteria, but lacked temporal relationship to fully meet the definition of anaphylaxis.

Laboratory Findings

Most patients remained within the normal range of hematology and metabolic panel parameters during both the treatment and follow up period. Fourteen patients (9.0%) did experience ≥1 urine protein. Other laboratory changes from baseline had one or fewer patients. One patient had a ≥50% decrease from baseline in platelet count, but recovered by end of follow up period. One patient had a transient ≥20% increase from baseline in creatinine during treatment period. The same patient had ≥20% decrease in hemoglobin and hematocrit that remained lower during the remainder of the study. One other patient had a ≥3x upper limit of normal increase in SGPT from baseline and remained high rest of the study. 121 patients had an absolute reduction in platelet from baseline but majority (74.9%) were $<100 \times 10^9$/L. Severe thrombocytopenia was seen in a previous study and currently addressed in the label, however, in this study, no patient experienced a platelet drop below 75x10^9/L.

Vital Signs

Body temperature, sitting blood pressure and pulse, height and weight were obtained at baseline and regular intervals. Changes in mean and median vital signs were very small or essentially none.

Electrocardiograms (ECGs)

12 lead ECG was done at screening unless a normal ECG was available within the past month. No notable changes in ECG was reported.

Reviewer comment: It should be noted that comparative safety with the currently approved Xolair product is not directly possible in this single arm, open-label study without a comparator

arm. Therefore, interpretation of the safety assessments, including adverse event reports in this study, is limited. That stated, review of the safety profile in the study did not identify new safety issues.

8.2.5. Analysis of Submission-Specific Safety Issues

Anaphylaxis

Anaphylaxis has been reported to occur after administration of Xolair in premarketing trials (0.1%) and post marketing spontaneous report. Therefore, this AE was of clinical interest in C2303 study. Using Standard MedDRA (SMQ) algorithm, there were no patients with Category A core anaphylactic components during treatment period. A broader SMQ search for possible anaphylactic reaction (i.e. upper airway/respiratory terms, angioedema/urticaria, or cardiovascular terms) was also performed. Except for asthma (17.4%) and cough (5.8%), the incidence of these possible anaphylaxis components was low (<2%). The cases were also manually adjudicated against Sampson's criteria to identify any true anaphylaxis cases. Only two met partial criteria, but they lacked clinical context/temporal relationship to fully meet Sampson criteria. Urticaria was reported in 3 patients (1.9%), but only one was related to study drug.

8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

See Section 8.1.3 Study Q2569g

8.2.7. Specific Safety Studies/Clinical Trials

See section 8.2.2.

8.2.8. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

The liquid PFS presentation has been marketed in the EU since 2010, and is now approved in over 40 countries, including the EU (2009), Australia (2013), and Canada (2016), and the applicant estimates that approximately (b) (4) patient years of exposure is now available with this presentation. The lyophilized formulation of Xolair is registered in over 90 countries, including the US, Japan, Australia, and the EU, so the safety database with that formulation is much larger.

The applicants performed a post marketing analysis of spontaneous AE reports, literature reports, and surveillance studies from between January 1, 2011 through March 31, 2017. The specific risk categories, which are derived from earlier potential clinical concerns in the Xolair development program, were included in the search and analysis, and are shown in Table 2. As expected, more cases were found with the lyophilized formulation (n=1233) as compared with the liquid PFS formulation (n=156). However, the proportional reporting rate (calculated as the

number of cases for a risk divided by the total number of either lyophilized or liquid cases for a given region) were similar. In summary, the results did not show any safety trends for the new liquid PFS formulation compared with the lyophilized formulation.

Table 2. Postmarketing Safety: Risks considered during the medical analysis and respective search criteria

Risk name	Search criteria (MedDRA term and level)
Anaphylaxis / anaphylactoid reactions	Anaphylactic reaction (SMQ narrow) Anaphylactic/Anaphylactoid shock conditions (SMQ narrow) Anaphylactic reaction (SMQ broad) – Algorithmic search*
Serum Sickness Syndrome / Serum Sickness-Like Disease	Serum sickness (PT) Serum sickness-like reaction (PT)
Antibody formation to Xolair	Drug specific antibody present (PT) Human anti-human antibody test (PT)
Churg Strauss Syndrome / Hypereosinophilic syndrome	Eosinophilic disorders (HLT) Vascular inflammations (HLGT)
Thrombocytopenia	Hematopoietic thrombocytopenia (SMQ broad) Immune thrombocytopenic purpura (PT)
Arterial Thromboembolic Events (ATE)	Ischemic central nervous system vascular conditions (SMQ narrow) Hemiparesis (PT) Hemiplegia (PT) Hemorrhagic central nervous system vascular conditions (SMQ narrow) Myocardial infarction (SMQ broad) Sudden cardiac death (PT) Sudden death (PT) Cardiac death (PT)
Malignant neoplasms	Malignancies (SMQ broad)
Injection site reactions	Injection site reactions (HLT)
MedDRA: Medical Dictionary for Regulatory Activities; SMQ: Standard MedDRA Query; HLGT: High Level Group Term; HLT: High Level Term; PT: Preferred Term	

1. Source: M2, clinical-overview.pdf, T5.1, p33; and summary-clin-safety.pdf, T6-1, p55

Expectations on Safety in the Postmarket Setting

No anticipated differences in how the drug was administered and used in the clinical trial versus its expected use in the post market setting that could lead to increased risk.

8.2.9. Integrated Assessment of Safety

Study C2303 was reviewed and used as the key study in the safety evaluation of the liquid PFS formulation. There were no new safety concerns that altered the risk: benefit profile of the drug. There were no unexpected safety findings in this patient population. The frequency of AEs was consistent with previous studies in the same population. Most of the AEs experienced were mild or moderate in severity. Asthma was the most common AE (3.9%). Study related AEs were mainly injection site irritation, pain, or pruritus.

Local tolerance was also studied in Study Q2569g which included assessment of pain, and injection-site reactions (burning, itching, warmth, redness, rate of hive formation, and size of injection-site reaction). No meaningful differences in local reactions to the excipients in either formulation were noted.

SUMMARY AND CONCLUSIONS

8.3. Conclusions and Recommendations

We recommend approval of the new liquid formulation presentation of Xolair in a prefilled syringe (PFS) for the same indications, dosing regimen, and route of administration as the approved lyophilized reconstituted powder. Evidence of efficacy relies on the demonstration of bioequivalence of the new liquid formulation compared to the currently approved lyophilized powder and is supported by the similarity of the pharmacodynamic endpoints of free and total IgE. The safety profile of Xolair is well established since its original approval in 2003. The new formulation provides improved ease-of-use due to decreased viscosity, decreased preparation time, and removal of post-reconstitution storage limits. Furthermore, in light of the current sterile water for injection shortage which is necessary for reconstitution of the lyophilized powder, the prefilled syringe provides assurance that patients and providers will continue to have access to Xolair. Therefore, the risk-benefit is favorable for the approval of the new liquid formulation presentation of Xolair in a prefilled syringe (PFS).

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Primary Clinical Reviewer

X Miya Paterniti -S
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Clinical Team Leader

9 Advisory Committee Meeting and Other External Consultations

No specific safety or efficacy concerns were identified for this approved therapy in a new formulation and device, therefore an Advisory Committee Meeting or other external consultations was not warranted.

10 Pediatrics

Xolair was approved for the treatment moderate to severe asthma in patients 12 years of age and older in June of 2003. At the time of approval, there was a safety concern for risk of malignancy. Pediatric studies were waived for children 0 through 5 years of age due to safety concerns. In December of 2009, a pediatric supplement for patients 6-11 years of age with moderate to severe asthma was given a Complete Response action after an Advisory Committee recommended that the risk/benefit did not support use in this population, at which time a risk/benefit statement was placed in the Pediatric Use section. A supplement for the indication for chronic idiopathic urticaria (CIU) in patients 12 years of age and older was approved on March 21, 2014. Pediatric studies for children less than 12 years of age were waived because of similar safety concerns. Subsequently, a large post marketing safety study (EXCELS) did not demonstrate a malignancy risk, after which resubmission of the pediatric supplement for asthma in patients 6-11 years of age was approved in July 2016. Studies in asthma patients less than 6 years were not encouraged because this is not a patient population in which moderate to severe asthma that would require treatment with Xolair occurs. The same is true for CIU in patients less than 12 years of age (i.e. CIU is uncommon and cases requiring Xolair are rare).

Novartis submitted an iPSP to IND 07202 for the Xolair PFS presentation on June 9, 2017, and the PSP has been submitted to this supplement. The PSP requests a waiver of pediatric studies for both “asthma” and “CIU” and for all age groups not covered by the current indications for the approved lyophilized product (i.e., <6y for asthma, <12 years for CIU) because the currently approved indications and age ranges are appropriate for both presentations and no additional studies in younger age ranges are necessary. PeRC agreed on a partial waver for asthma less than 6 years of age and chronic idiopathic urticaria less than 12 years of age as the product fails to represent a meaningful therapeutic benefit over existing therapies for pediatric patients and is unlikely to be used in a substantial number of all pediatric age groups or the pediatric age group(s) for which a waiver is being requested.

The Xolair PFS formulation will be labeled for the same indications and age ranges as the current lyophilized presentation and the pediatric assessment for these indications and age ranges will be considered complete.

11 Labeling Recommendations

11.1. Prescription Drug Labeling

The proposed and approved labeling changes are summarized below.

Summary of Significant Labeling Changes		
Section	Proposed Labeling	Approved Labeling
(b) (4)		

12 Postmarketing Requirements and Commitment

Microbiology recommended a postmarketing commitment to validate the dye leak container closure integrity test (CCIT). The sponsor agreed to the PMC language, as follows:

To validate the dye leak container closure integrity test (CCIT) using syringes and to include in the routine test positive control syringes with a breach size close to the validated limit of detection.

Microbiology recommended validation of the dye leak CCIT using syringes to be implemented prior to March 31, 2019 and reported per 21 CRF 601.12 and the sponsor agreed.

13 Division Director (Clinical)

This is an efficacy supplement for a new liquid formulation presentation of Xolair in a prefilled syringe (PFS). Xolair is currently available as a lyophilized powder in a single-use vial. The Division granted a priority review for this application due to a shortage of sterile water for injection, which is necessary to reconstitute the currently approved lyophilized Xolair product.

The liquid formulation in a PFS has been approved in over 40 countries, including the EU, Australia in Canada. In the US, there has been a long regulatory history that is described in Section 3. Typically for a change in formulation from lyophilized powder to a liquid for injection with no change in route of administration, a program is expected to assess CMC comparability, PK/PD comparability, patient use, safety and immunogenicity. Early in this development program an additional peak was detected by high-performance liquid chromatography in the aged liquid formulation. This raised concerns and led to a clinical study to assess whether there were differences between the formulations on a PD endpoint (bronchoprovocation).

The pivotal PK comparability study (Study C2101) compared the approved lyophilized product with aged and non-aged liquid PFS product in patients with elevated serum IgE levels. The results showed that the 90% CI for the geometric mean ratios of the dose-normalized PK parameters (AUC0-∞, AUC0-last, Cmax) for the PFS vs. the marketed lyophilized product were all within 80-125%. PD endpoints of free and total IgE were comparable.

Study C2303 was a 6-month open-label, single-arm study that evaluated the safety and immunogenicity of aged liquid PFS in patients with moderate to severe persistent allergic asthma. No new safety concerns were identified. While immunogenicity was also not identified as an issue, the Sponsor's assay is not sensitive in the presence of drug.

Study Q4160g was the clinical study in patients with asthma comparing the aged liquid PFS and lyophilized formulation using bronchoprovocation as a PD endpoint. The study failed on the primary and secondary endpoints. The study may have failed because of a small sample size, variability in results, and the allergen challenge may also not be a sufficiently sensitive PD clinical measure to detect meaningful differences between formulations. In retrospect, the utility of this bronchoprovocation study to evaluate the clinical impact of the differences in the two formulations is questionable. Currently, we have a better understanding of the two formulations, including bioanalytical assessment of the formulations, which shows comparability. We have data demonstrating PK and PD comparability between the two formulations. Additional clinical data on a PD endpoint, such as bronchoprovocation are no longer considered necessary.

The CMC team has determined that the sponsor has provided comparability studies to demonstrate the PFS omalizumab is analytically comparable to the current approved lyophilized omalizumab in product quality. The original peak noted in the aged liquid in vials were determined to be Fab fragments and was confirmed to also be present in the (non-aged) reconstituted lyophilized material. Characterization of aged liquid in PFS identified no new peaks and was noted to be present at similar levels in both aged vials and aged PFS. The CMC team recommends approval. The microbiology team recommends a PMC to evaluate the container closure integrity.

I recommend approval of this supplement. The submitted data supports approval of the new formulation. The PFS requires less preparation and does not require sterile water, which is important given the current shortage of sterile water for injection. Therefore, the risk-benefit is favorable for the new liquid formulation presentation of Xolair in a PFS for the indications currently approved for the lyophilized reconstituted powder

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Date: 2018.09.26 17:47:25 -04'00'

Division Director

14 Appendices

14.1. References

See footnotes.

14.2. Financial Disclosure

Clinical Investigator Financial Disclosure
Review Template

Application Number: sBLA 103976, S-5231

Submission Date(s): March 18, 2009

Applicant: Novartis Pharmaceuticals Corporation

Product: Xolair pre-filled syringe

Reviewer: Jennifer Lan, M.D.

Date of Review: 06/18/2018

Covered Clinical Study (Name and/or Number): Study No: CIGE025C2101 An open-label, randomized, single-dose, three parallel group study of SC dosed lyophilized, aged, and non-aged liquid Xolair (final market formulation in pre-filled safety syringes) to determine bioequivalence and pharmacodynamics in subjects with elevated IgE.

Was a list of clinical investigators provided?	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 6		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: n/a		

Significant payments of other sorts: n/a Proprietary interest in the product tested held by investigator: n/a Significant equity interest held by investigator in sponsor of covered study: n/a		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant)

Application Number: sBLA 103976, S-5231

Submission Date(s): March 29, 2018

Applicant: Novartis Pharmaceuticals Corporation

Product: Xolair pre-filled syringe

Reviewer: Jennifer Lan, M.D.

Date of Review: 06/25/2018

Covered Clinical Study (Name and/or Number): Study No: CIGE025C2303 An open label, single arm study to assess the safety and immunogenicity of Xolair liquid administered SC in a pre-filled safety syringe (75 mg or 150 mg) over a period of 6 months to male and female adolescents and adults with moderate to severe persistent allergic asthma

Was a list of clinical investigators provided?	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 121 (including sub-investigators)		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):		

Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: n/a Significant payments of other sorts: n/a Proprietary interest in the product tested held by investigator: n/a Significant equity interest held by investigator in sponsor of covered study: n/a		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant)

Application Number: sBLA 103976, S-5231

Submission Date(s): March 29, 2018

Applicant: Genetech, Inc.

Product: Xolair pre-filled syringe

Reviewer: Jennifer Lan, M.D.

Date of Review: 06/25/2018

Covered Clinical Study (Name and/or Number): Study No: Q2569g A Randomized, Single-Center, Single-Blind, Three-Way
Crossover Study to Evaluate the Pain of Two SC Excipient
Formulations

Was a list of clinical investigators provided?	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 3 (including sub-investigators)		
Number of investigators who are sponsor employees (including both full-time and part-time employees): unknown		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): unknown		
If there are investigators with disclosable financial interests/arrangements, identify the		

number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: n/a Significant payments of other sorts: n/a Proprietary interest in the product tested held by investigator: n/a Significant equity interest held by investigator in sponsor of covered study: n/a		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) unknown		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant)

Application Number: sBLA 103976, S-5231

Submission Date(s): March 29, 2018

Applicant: Genetech, Inc.

Product: Xolair pre-filled syringe

Reviewer: Jennifer Lan, M.D.

Date of Review: 06/25/2018

Covered Clinical Study (Name and/or Number): Study No: Q4160g A Phase II, Multicenter, Randomized, Double-Blind, Parallel-
Group, Placebo-Controlled Study to Evaluate the Efficacy and Safety of
Lyophilized and Aged Liquid Xolair in the Prevention of Allergen Induced
Airway Obstruction in Adults with Mild Allergic Asthma

Was a list of clinical investigators provided?	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 23 (including sub-investigators)		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455):		

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Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: n/a

Significant payments of other sorts: n/a

Proprietary interest in the product tested held by investigator: n/a

Significant equity interest held by investigator in sponsor of covered study: n/a</td></tr>
<tr><td>Is an attachment provided with details of the disclosable financial interests/arrangements:</td><td>Yes ☐</td><td>No ☐ (Request details from applicant)</td></tr>
<tr><td>Is a description of the steps taken to minimize potential bias provided:</td><td>Yes ☐</td><td>No ☐ (Request information from applicant)</td></tr>
<tr><td colspan="3">Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0</td></tr>
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