CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

103976Orig1s5231

Trade Name:	XOLAIR
Generic or Proper Name:	omalizumab injection
Sponsor:	Genentech
Approval Date:	September 28, 2018
Indication:	• Moderate to severe persistent asthma in patients 6 years of age and older with a positive skin test or in vitro reactivity to a perennial aeroallergen and symptoms that are inadequately controlled with inhaled corticosteroids. • Chronic idiopathic urticaria in adults and adolescents 12 years of age and older who remain symptomatic despite H1 antihistamine treatment.

CENTER FOR DRUG EVALUATION AND RESEARCH

103976Orig1s5231

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REMS	
Officer/Employee List	
Multidiscipline Review(s) • **Summary Review** • **Office Director** • **Cross Discipline Team Leader** • **Clinical** • **Non-Clinical** • **Statistical** • **Clinical Pharmacology**	**X**
Product Quality Review(s)	
Clinical Microbiology / Virology Review(s)	
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

103976Orig1s5231

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 103976/S-5231

SUPPLEMENT APPROVAL

Genentech
1DNA Way
South San Francisco, CA 94080

Attention: Cheryl Hooi Ming Sim
Regulatory Program Management

Dear Ms. Sim:

Please refer to your Supplemental Biologics License Application (sBLA), dated, March 29, 2018, received March 29, 2018, and your amendments, submitted under section 351(a) of the Public Health Service Act for Xolair (omalizumab) liquid pre-filled syringe in 75 mg and 150 mg.

This Prior Approval supplemental biologics application proposes 75 mg and 150 mg liquid pre-filled syringes to treat patients 6 years and older with moderate to severe asthma and to treat patients 12 years and older with chronic idiopathic urticaria.

APPROVAL & LABELING

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical to the enclosed labeling (text for the prescribing information, Medication Guide) and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements. Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this BLA, including pending "Changes Being Effected" (CBE) supplements, for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 601.12(f)] in MS Word format that includes the changes approved in this supplemental application.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (May 2015, Revision 3). For administrative purposes, designate this submission "Product Correspondence – Final Printed Carton and Container Labels for approved BLA 103976/ S-5231." Approval of this submission by FDA is not required before the labeling is used.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study(ies) requirement for ages less than 6 years of age for moderate to severe persistent asthma and for ages less than 12 years for chronic idiopathic urticaria (CIU) because the product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this age group **and** is not likely to be used in a substantial number of pediatric patients in this group.

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

3501-1 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.

Study Completion	03/19
Final Report Submission:	08/19

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the prescribing information to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

As required under 21 CFR 601.12(f)(4), you must submit final promotional materials, and the prescribing information, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved BLA (in 21 CFR 600.80 and in 21 CFR 600.81).

If you have any questions, call Angela Ramsey, Senior Program Management Officer, at 301-796-2284.

Sincerely,

{See appended electronic signature page}

Sally Seymour, M.D.,
Acting Director
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling
Carton and Container Labeling

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SALLY M SEYMOUR
09/28/2018

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

103976Orig1s5231

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use XOLAIR safely and effectively. See full prescribing information for XOLAIR.

XOLAIR® (omalizumab) injection, for subcutaneous use
XOLAIR® (omalizumab) for injection, for subcutaneous use
Initial U.S. Approval: 2003

WARNING: ANAPHYLAXIS

See full prescribing information for complete boxed warning.

Anaphylaxis, presenting as bronchospasm, hypotension, syncope, urticaria, and/or angioedema of the throat or tongue, has been reported to occur after administration of XOLAIR. Anaphylaxis has occurred after the first dose of XOLAIR but also has occurred beyond 1 year after beginning treatment. Closely observe patients for an appropriate period of time after XOLAIR administration and be prepared to manage anaphylaxis that can be life-threatening. Inform patients of the signs and symptoms of anaphylaxis and have them seek immediate medical care should symptoms occur. (5.1)

----------RECENT MAJOR CHANGES----------

Dosage and Administration (2.1, 2 3, 2.4, 2.5) 09/2018

----------INDICATIONS AND USAGE----------

XOLAIR is an anti-IgE antibody indicated for:

- Moderate to severe persistent asthma in patients 6 years of age and older with a positive skin test or in vitro reactivity to a perennial aeroallergen and symptoms that are inadequately controlled with inhaled corticosteroids (1.1)
- Chronic idiopathic urticaria in adults and adolescents 12 years of age and older who remain symptomatic despite H1 antihistamine treatment (1.2)

Limitations of use:

- Not indicated for other allergic conditions or other forms of urticaria. (1.1, 1.2)
- Not indicated for acute bronchospasm or status asthmaticus. (1.1, 5.3)

----------DOSAGE AND ADMINISTRATION----------

For subcutaneous (SC) administration only. (2.1, 2.2)
Divide doses of more than 150 mg among more than one injection site to limit injections to not more than 150 mg per site. (2.4)

- Asthma: XOLAIR 75 to 375 mg SC every 2 or 4 weeks. Determine dose (mg) and dosing frequency by serum total IgE level (IU/mL), measured before the start of treatment, and body weight (kg). See the dose determination charts. (2.1)
- Chronic Idiopathic Urticaria: XOLAIR 150 or 300 mg SC every 4 weeks. Dosing in CIU is not dependent on serum IgE level or body weight. (2.2)

----------DOSAGE FORMS AND STRENGTHS----------

- Injection: 75 mg/0.5 mL and 150 mg/mL solution in a single-dose prefilled syringe (3)
- For Injection: 150 mg lyophilized powder in a single-dose vial for reconstitution (3)

----------CONTRAINDICATIONS----------

Severe hypersensitivity reaction to XOLAIR or any ingredient of XOLAIR (4, 5.1)

----------WARNINGS AND PRECAUTIONS----------

- Anaphylaxis: Administer only in a healthcare setting prepared to manage anaphylaxis that can be life-threatening and observe patients for an appropriate period of time after administration. (5.1)
- Malignancy: Malignancies have been observed in clinical studies. (5.2)
- Acute Asthma Symptoms: Do not use for the treatment of acute bronchospasm or status asthmaticus. (5.3)
- Corticosteroid Reduction: Do not abruptly discontinue corticosteroids upon initiation of XOLAIR therapy. (5.4)
- Eosinophilic Conditions: Be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy, especially upon reduction of oral corticosteroids. (5.5)
- Fever, Arthralgia, and Rash: Stop XOLAIR if patients develop signs and symptoms similar to serum sickness. (5.6)

----------ADVERSE REACTIONS----------

- Asthma: The most common adverse reactions in clinical studies with adult and adolescent patients ≥12 years of age were arthralgia, pain (general), leg pain, fatigue, dizziness, fracture, arm pain, pruritus, dermatitis, and earache. In clinical studies with pediatric patients 6 to <12 years of age, the most common adverse reactions were nasopharyngitis, headache, pyrexia, upper abdominal pain, pharyngitis streptococcal, otitis media, viral gastroenteritis, arthropod bites, and epistaxis. (6.1)
- Chronic Idiopathic Urticaria: The most common adverse reactions (≥2% XOLAIR-treated patients and more frequent than in placebo) included the following: nausea, nasopharyngitis, sinusitis, upper respiratory tract infection, viral upper respiratory tract infection, arthralgia, headache, and cough. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Genentech at 1-888-835-2555 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

No formal drug interaction studies have been performed. (7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 09/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: ANAPHYLAXIS

Anaphylaxis presenting as bronchospasm, hypotension, syncope, urticaria, and/or angioedema of the throat or tongue, has been reported to occur after administration of XOLAIR. Anaphylaxis has occurred as early as after the first dose of XOLAIR, but also has occurred beyond 1 year after beginning regularly administered treatment. Because of the risk of anaphylaxis, observe patients closely for an appropriate period of time after XOLAIR administration. Health care providers administering XOLAIR should be prepared to manage anaphylaxis that can be life-threatening. Inform patients of the signs and symptoms of anaphylaxis and instruct them to seek immediate medical care should symptoms occur *[see Warnings and Precautions (5.1) and Adverse Reactions (6.1, 6.3)]*.

1 INDICATIONS AND USAGE

1.1 Asthma

XOLAIR is indicated for patients 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.

XOLAIR has been shown to decrease the incidence of asthma exacerbations in these patients.

Limitations of Use:

- XOLAIR is not indicated for the relief of acute bronchospasm or status asthmaticus.
- XOLAIR is not indicated for treatment of other allergic conditions.

1.2 Chronic Idiopathic Urticaria (CIU)

XOLAIR is indicated for the treatment of adults and adolescents 12 years of age and older with chronic idiopathic urticaria who remain symptomatic despite H1 antihistamine treatment.

Limitation of Use:

XOLAIR is not indicated for treatment of other forms of urticaria.

2 DOSAGE AND ADMINISTRATION

2.1 Dosage for Asthma

Administer XOLAIR 75 mg to 375 mg by subcutaneous injection every 2 or 4 weeks. Determine dose (mg) and dosing frequency by serum total IgE level (IU/mL) measured before the start of treatment, and by body weight (kg).

Adjust doses for significant changes in body weight during treatment (see Tables 1 and 2).

Total IgE levels are elevated during treatment and remain elevated for up to one year after the discontinuation of treatment. Therefore, re-testing of IgE levels during XOLAIR treatment cannot be used as a guide for dose determination.

- Interruptions lasting less than one year: Dose based on serum IgE levels obtained at the initial dose determination.

- Interruptions lasting one year or more: Re-test total serum IgE levels for dose determination using Table 1 or 2, based on the patient's age.

Periodically reassess the need for continued therapy based upon the patient's disease severity and level of asthma control.

Adult and adolescent patients 12 years of age and older: Initiate dosing according to Table 1.

Table 1. Subcutaneous XOLAIR Doses Every 2 or 4 Weeks* for Patients 12 Years of Age and Older with Asthma

Pretreatment Serum IgE (IU/mL)	Dosing Freq.	Body Weight			
		30–60 kg	>60–70 kg	>70–90 kg	>90–150 kg
		Dose (mg)			
≥30–100	Every 4 weeks	150	150	150	300
>100–200		300	300	300	225
>200–300		300	225	225	300
>300–400	Every 2 weeks	225	225	300	
>400–500		300	300	375	
>500–600		300	375	**Insufficient Data to Recommend a Dose**	
>600–700		375			

***Dosing frequency:**

- Subcutaneous doses to be administered every 4 weeks
- Subcutaneous doses to be administered every 2 weeks

Pediatric patients 6 to <12 years of age: Initiate dosing according to Table 2.

Table 2. Subcutaneous XOLAIR Doses Every 2 or 4 Weeks* for Pediatric Patients with Asthma Who Begin XOLAIR Between the Ages of 6 to <12 Years

Pre-treatment Serum IgE (IU/mL)	Dosing Freq.	Body Weight									
		20-25 kg	>25-30 kg	>30-40 kg	>40-50 kg	>50-60 kg	>60-70 kg	>70-80 kg	>80-90 kg	>90-125 kg	>125-150 kg
		Dose (mg)									
30-100	Every 4 weeks	75	75	75	150	150	150	150	150	300	300
>100-200		150	150	150	300	300	300	300	300	225	300
>200-300		150	150	225	300	300	225	225	225	300	375
>300-400		225	225	300	225	225	225	300	300		
>400-500		225	300	225	225	300	300	375	375		
>500-600		300	300	225	300	300	375				
>600-700		300	225	225	300	375					
>700-800	Every 2 weeks	225	225	300	375						
>800-900		225	225	300	375						
>900-1000		225	300	375							
>1000-1100		225	300	375							
>1100-1200		300	300								
>1200-1300		300	375								

Insufficient Data to Recommend a Dose

***Dosing frequency:**

- Subcutaneous doses to be administered every 4 weeks
- Subcutaneous doses to be administered every 2 weeks

2.2 Dosage for Chronic Idiopathic Urticaria

Administer XOLAIR 150 mg or 300 mg by subcutaneous injection every 4 weeks.

Dosing of XOLAIR in CIU patients is not dependent on serum IgE (free or total) level or body weight.

The appropriate duration of therapy for CIU has not been evaluated. Periodically reassess the need for continued therapy.

2.3 Administration

XOLAIR is available as a prefilled syringe and as a lyophilized powder in vial for reconstitution. Both XOLAIR prefilled syringe and lyophilized powder should be administered by a healthcare professional. Administer XOLAIR by subcutaneous injection. The injection may take 5-10 seconds to administer. Do not administer more than one injection per site. (Table 3, Table 4).

Table 3. Number of Prefilled Syringes, Injections and Total Injection Volumes

XOLAIR Dose*	75 mg Syringes	150 mg Syringes	Total Volume Injected
75 mg	1	0	0.5 mL
150 mg	0	1	1 mL
225 mg	1	1	1.5 mL
300 mg	0	2	2 mL
375 mg	1	2	2.5 mL

* All doses in the table are approved for use in asthma patients. The 150 mg and 300 mg XOLAIR doses are also approved for use in CIU patients.

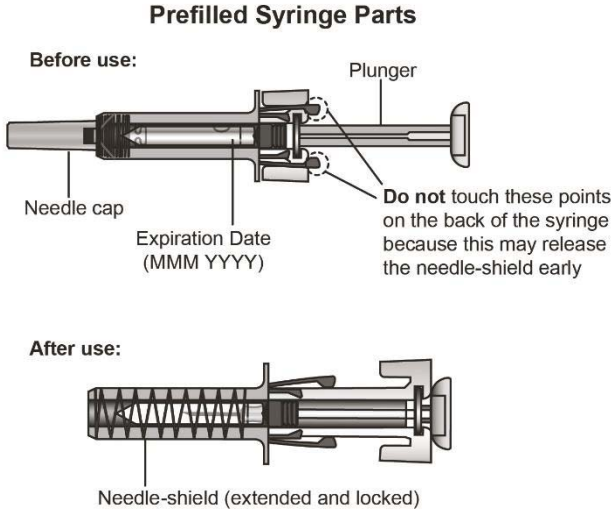
Table 4. Number of Vials, Injections and Total Injection Volumes

XOLAIR Dose*	Number of Vials	Number of Injections	Total Volume Injected
75 mg	1	1	0.6 mL
150 mg	1	1	1.2 mL
225 mg	2	2	1.8 mL
300 mg	2	2	2.4 mL
375 mg	3	3	3.0 mL

* All doses in the table are approved for use in asthma patients. The 150 mg and 300 mg XOLAIR doses are also approved for use in CIU patients.

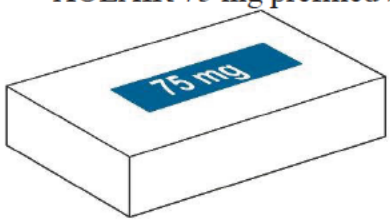
2.4 Preparation for Use and Injection of XOLAIR Prefilled Syringe

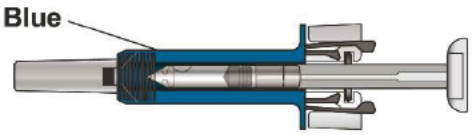
To prepare XOLAIR prefilled syringes for subcutaneous administration, please carefully read and adhere to these instructions for use.



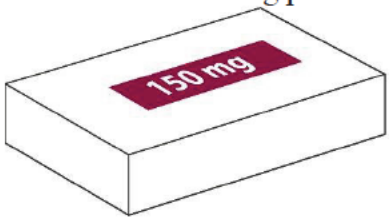
XOLAIR prefilled syringes are available in 2 dose strengths. These instructions are to be used for both dose strengths. You should check the label on the carton that comes with the XOLAIR prefilled syringe to make sure that the dose is correct.

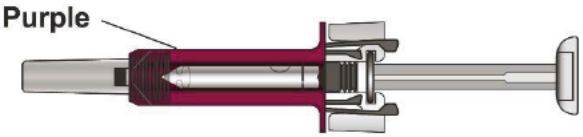
- XOLAIR 75 mg prefilled syringe with a blue needle shield





- XOLAIR 150 mg prefilled syringe with a purple needle shield





Storage Instructions

- Keep the unused syringe in the original carton and store the carton in a refrigerator at 36˚F to 46˚F (2˚C to 8˚C). **Do not** remove the syringe from its original carton during storage.
- Keep the XOLAIR syringe out of direct sunlight.
- **Do not** freeze.
- **Do not** use if the syringe has been frozen.
- Always keep the syringe dry.

Important Information about the Prefilled Syringe

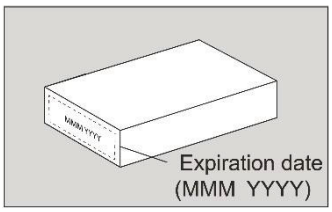
- The removable needle cap of XOLAIR solution for injection in prefilled syringe contains a derivative of natural rubber latex *[see Description (11)]*.
- **Do not** open the sealed outer carton until you are ready to inject XOLAIR.
- **Do not** take the needle cap off until you are ready to inject XOLAIR.
- **Do not** try to take the syringe apart at any time.
- **Do not** reuse the same syringe.
- **Do not** use if the syringe has been dropped or damaged.
- **Do not** use if the packaging is damaged or appears to be tampered with.
- **Do not** leave the syringe unattended.
- Keep the syringe out of the reach of children.

Preparing for the Injection

1 Find a clean, flat, working surface.

- Each XOLAIR carton contains 1 syringe.
- Take the carton containing the syringe out of the refrigerator.

2 Check the expiration date on the XOLAIR carton.

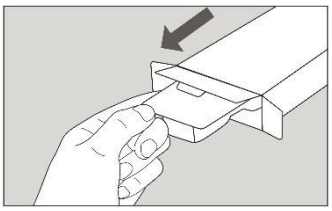


- Do not use it if the expiration date has passed because it may not be safe to use. If the expiration date has passed, safely dispose of the syringe in a sharps container (see step 14 at the end of these instructions for use).

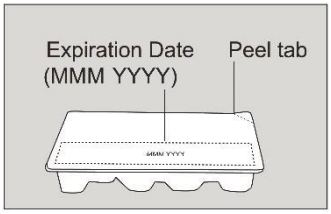
3 Place the carton on a clean flat, surface.

- Set aside the carton for at least 15-30 minutes so the syringe can warm up on its own to room temperature (leave the syringe in the carton to protect it from light).
- If the syringe does not reach room temperature, this could cause the injection to feel uncomfortable and make it hard to push the plunger.
- **Do not** allow the syringe to become hot.
- **Do not** speed up the warming process in any way, and do not put the syringe in a microwave or in warm water.

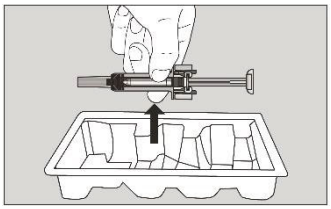
4 Open the carton.



- Wash your hands with soap and water.
- Take the blister pack out of the carton.



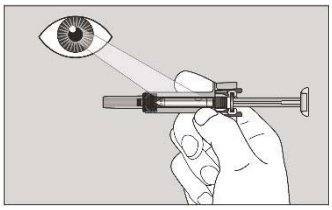
- Check the expiration date on blister pack.
- Do not use it if the expiration date has passed because it may not be safe to use. If the expiration date has passed, safely dispose of the syringe in a sharps container (see step 14 at the end of these instructions for use).



- Be careful when taking out the syringe. **Do not** flip the blister pack upside down to take out the syringe, and **do not** touch the back of the syringe. This may damage the syringe.
- Peel off the blister pack cover. Take the syringe out of the blister pack by holding the middle part of the syringe. When holding the syringe, make sure you always hold the syringe as shown.
- **Do not** handle the syringe by holding the plunger or needle cap.

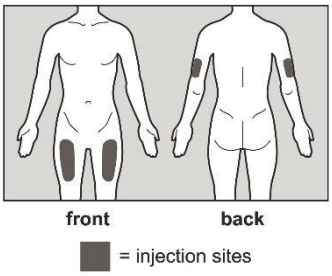
5 Inspect the syringe closely.

- Check the syringe. The liquid in the syringe should be clear to slightly opalescent and colorless to pale brownish-yellow. **Do not** use the syringe if the liquid is cloudy, discolored, or contains foreign particles.
- Check the expiration date on the syringe. **Do not** use the syringe if the expiration date has passed because it may not be safe to use.
- If the medicine does not look as described or if the expiration date has passed, safely dispose of the syringe in a sharps container (see step 14 at the end of these instructions for use).



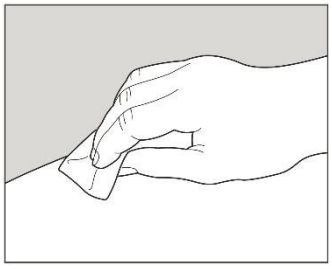
6 Choose an injection site.

- The recommended injection sites are the upper arm and the front and middle of the thighs.
- **Do not** inject into moles, scars, bruises, or areas where the skin is tender, red, hard, or if there are breaks in the skin.
- Choose a different injection site for each new injection at least 1 inch from the area used for the last injection.

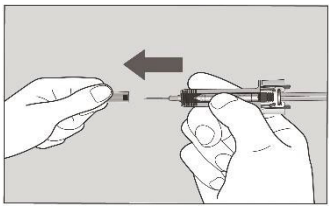


7 Wipe the injection site with an alcohol pad in a circular motion and let it air dry for 10 seconds.

- **Do not** touch the injection site again before giving the injection.
- **Do not** fan or blow on the cleaned area.

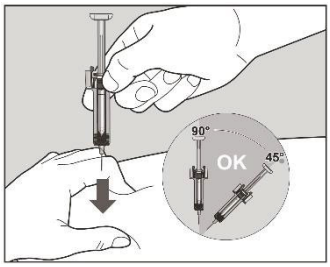


Administering the Injection

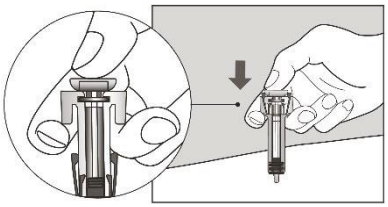


8 Hold the syringe firmly with 1 hand and pull the needle cap straight off with your other hand.
- **Do not** hold the plunger while you remove the needle cap.
- **Do not** touch the needle after removing the needle cap.
- Throw away the needle cap in a sharps container right away.
- There may be a small air bubble in the syringe. This is normal and you should not try to remove the air bubble.
- You may also see a drop of liquid at the end of the needle. This is also normal and will not affect the dose.

9 Use your other hand and gently pinch the area of skin that was cleaned. Hold the pinched skin tight.
- Pinching the skin is important to make sure that you inject under the skin (into the fatty area) but not any deeper (into muscle).



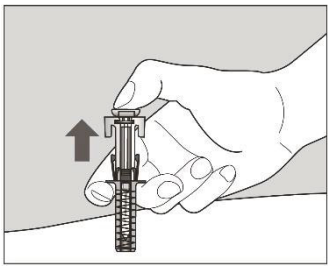
10 Continue holding the syringe by the center and use a quick, dart-like motion to insert the needle all the way into the pinched skin at an angle between 45° to 90°. It is important to use the correct angle to make sure the medicine is delivered under the skin (into the fatty area), or the injection could be uncomfortable and the medicine may not work.
- **Do not** touch the plunger while inserting the needle into the skin.
- **Do not** insert the needle through clothing. Once the needle is inserted, hold the syringe tightly in place and **do not** change the angle of injection or insert the needle again. The patient should not move and should avoid sudden movements throughout the injection.



11 Slowly inject all of the medicine by gently pushing the plunger all the way down.
- You must press the plunger all the way down to make sure that the full dose of medicine gets injected. If the plunger is not fully pressed, the needle shield will not extend to cover the needle when it is removed.

12 Gently release the plunger and allow the needle to be covered by the needle-shield.

- If the needle is not covered, proceed carefully to dispose of the syringe (see step 14 at the end of these instructions for use).



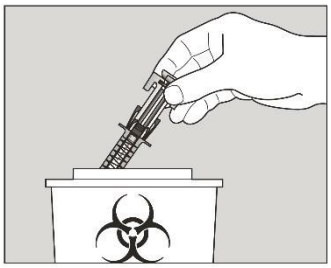
After the Injection

13 There may be a little bleeding at the injection site. You can press a cotton ball or gauze over the injection site.

- **Do not** rub the injection site.
- If needed, you may cover the injection site with a small bandage.
- In case of skin contact with medicine, wash the area that touched the medicine with water.

14 The XOLAIR prefilled syringe is a single-dose syringe and should not be used again.

- Put the used XOLAIR prefilled syringe in a FDA-cleared sharps disposal container right away after use. **Do not** throw away (dispose of) the prefilled syringe in the trash.
- **Do not** put the needle cap back on the needle.



2.5 Preparation for Use and Injection of XOLAIR Lyophilized Powder

The supplied XOLAIR lyophilized powder must be reconstituted with Sterile Water for Injection (SWFI) USP, using the following instructions:

1) Before reconstitution, determine the number of vials that will need to be reconstituted (each vial delivers 150 mg of XOLAIR in 1.2 mL) (see Table 4).
2) Draw 1.4 mL of SWFI, USP, into a 3 mL syringe equipped with a 1-inch, 18-gauge needle.
3) Place the vial upright on a flat surface and using standard aseptic technique, insert the needle and inject the SWFI, USP, directly onto the product.
4) Keeping the vial upright, gently swirl the upright vial for approximately 1 minute to evenly wet the powder. Do not shake.
5) Gently swirl the vial for 5 to 10 seconds approximately every 5 minutes in order to dissolve any remaining solids. **The lyophilized product takes 15 to 20 minutes to dissolve**. If it takes longer than 20 minutes to dissolve completely, gently swirl the vial for 5 to 10 seconds approximately every 5 minutes until there are no visible gel-like particles in the solution. Do not use if the contents of the vial do not dissolve completely by 40 minutes.
6) After reconstitution, XOLAIR solution is somewhat viscous and will appear clear or slightly opalescent. It is acceptable if there are a few small bubbles or foam around the edge of the vial; there should be no visible gel-like particles in the reconstituted solution. Do not use if foreign particles are present.

7) Invert the vial for 15 seconds in order to allow the solution to drain toward the stopper.

8) **Use the XOLAIR solution within 8 hours following reconstitution when stored in the vial at 2ºC to 8ºC (36ºF to 46ºF), or within 4 hours of reconstitution when stored at room temperature.** Reconstituted XOLAIR vials should be protected from sunlight.

9) Using a new 3 mL syringe equipped with a 1-inch, 18-gauge needle, insert the needle into the inverted vial. Position the needle tip at the very bottom of the solution in the vial stopper when drawing the solution into the syringe. The reconstituted product is somewhat viscous. **Withdraw all of the product** from the vial before expelling any air or excess solution from the syringe. Before removing the needle from the vial, pull the plunger all the way back to the end of the syringe barrel in order to remove all of the solution from the inverted vial.

10) Replace the 18-gauge needle with a 25-gauge needle for subcutaneous injection.

11) Expel air, large bubbles, and any excess solution in order to obtain a volume of 1.2 mL corresponding to a dose of 150 mg of XOLAIR. To obtain a volume of 0.6 mL corresponding to a dose of 75 mg of XOLAIR, expel air, large bubbles and discard 0.6 mL from the syringe. A thin layer of small bubbles may remain at the top of the solution in the syringe

12) Administer XOLAIR by subcutaneous injection. The injection may take 5-10 seconds to administer because the solution is slightly viscous. Do not administer more than 150 mg (contents of one vial) per injection site. Divide doses of more than 150 mg among two or more injection sites.

3 DOSAGE FORMS AND STRENGTHS

Injection:
XOLAIR injection is a clear to slightly opalescent and colorless to pale brownish-yellow solution available as:

- 75 mg/0.5 mL in a single-dose prefilled syringe with blue needle shield
- 150 mg/mL in a single-dose prefilled syringe with purple needle shield

For injection: 150 mg white lyophilized powder in a single-dose vial for reconstitution.

4 CONTRAINDICATIONS

The use of XOLAIR is contraindicated in the following:

Severe hypersensitivity reaction to XOLAIR or any ingredient of XOLAIR *[see Warnings and Precautions (5.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Anaphylaxis

Anaphylaxis has been reported to occur after administration of XOLAIR in premarketing clinical trials and in postmarketing spontaneous reports *[see Boxed Warning and Adverse Reactions (6.3)]*. Signs and symptoms in these reported cases have included bronchospasm, hypotension, syncope, urticaria, and/or angioedema of the throat or tongue. Some of these events have been life-threatening. In premarketing clinical trials in patients with asthma, anaphylaxis was reported in 3 of 3507 (0.1%) patients. Anaphylaxis occurred with the first

dose of XOLAIR in two patients and with the fourth dose in one patient. The time to onset of anaphylaxis was 90 minutes after administration in two patients and 2 hours after administration in one patient.

A case-control study showed that, among XOLAIR users, patients with a history of anaphylaxis to foods, medications, or other causes were at increased risk of anaphylaxis associated with XOLAIR, compared to those with no prior history of anaphylaxis *[see Adverse Reactions (6.1)]*.

In postmarketing spontaneous reports, the frequency of anaphylaxis attributed to XOLAIR use was estimated to be at least 0.2% of patients based on an estimated exposure of about 57,300 patients from June 2003 through December 2006. Anaphylaxis has occurred as early as after the first dose of XOLAIR, but also has occurred beyond one year after beginning regularly scheduled treatment.

Administer XOLAIR only in a healthcare setting by healthcare providers prepared to manage anaphylaxis that can be life-threatening. Observe patients closely for an appropriate period of time after administration of XOLAIR, taking into account the time to onset of anaphylaxis seen in premarketing clinical trials and postmarketing spontaneous reports *[see Adverse Reactions (6)]*. Inform patients of the signs and symptoms of anaphylaxis, and instruct them to seek immediate medical care should signs or symptoms occur.

Discontinue XOLAIR in patients who experience a severe hypersensitivity reaction *[see Contraindications (4)]*.

5.2 Malignancy

Malignant neoplasms were observed in 20 of 4127 (0.5%) XOLAIR-treated patients compared with 5 of 2236 (0.2%) control patients in clinical studies of adults and adolescents ≥12 years of age with asthma and other allergic disorders. The observed malignancies in XOLAIR-treated patients were a variety of types, with breast, non-melanoma skin, prostate, melanoma, and parotid occurring more than once, and five other types occurring once each. The majority of patients were observed for less than 1 year. The impact of longer exposure to XOLAIR or use in patients at higher risk for malignancy (e.g., elderly, current smokers) is not known.

In a subsequent observational study of 5007 XOLAIR-treated and 2829 non-XOLAIR-treated adolescent and adult patients with moderate to severe persistent asthma and a positive skin test reaction or in vitro reactivity to a perennial aeroallergen, patients were followed for up to 5 years. In this study, the incidence rates of primary malignancies (per 1000 patient years) were similar among XOLAIR-treated (12.3) and non-XOLAIR-treated patients (13.0) *[see Adverse Reactions (6)]*. However, study limitations preclude definitively ruling out a malignancy risk with XOLAIR. Study limitations include: the observational study design, the bias introduced by allowing enrollment of patients previously exposed to XOLAIR (88%), enrollment of patients (56%) while a history of cancer or a premalignant condition were study exclusion criteria, and the high study discontinuation rate (44%).

5.3 Acute Asthma Symptoms

XOLAIR has not been shown to alleviate asthma exacerbations acutely. Do not use XOLAIR to treat acute bronchospasm or status asthmaticus.

5.4 Corticosteroid Reduction

Do not discontinue systemic or inhaled corticosteroids abruptly upon initiation of XOLAIR therapy for asthma. Decrease corticosteroids gradually under the direct supervision of a physician. In CIU patients, the use of XOLAIR in combination with corticosteroids has not been evaluated.

5.5 Eosinophilic Conditions

In rare cases, patients with asthma on therapy with XOLAIR may present with serious systemic eosinophilia sometimes presenting with clinical features of vasculitis consistent with Churg-Strauss syndrome, a condition which is often treated with systemic corticosteroid therapy. These events usually, but not always, have been associated with the reduction of oral corticosteroid therapy. Physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients. A causal association between XOLAIR and these underlying conditions has not been established.

5.6 Fever, Arthralgia, and Rash

In post-approval use, some patients have experienced a constellation of signs and symptoms including arthritis/arthralgia, rash, fever and lymphadenopathy with an onset 1 to 5 days after the first or subsequent injections of XOLAIR. These signs and symptoms have recurred after additional doses in some patients. Although circulating immune complexes or a skin biopsy consistent with a Type III reaction were not seen with these cases, these signs and symptoms are similar to those seen in patients with serum sickness. Physicians should stop XOLAIR if a patient develops this constellation of signs and symptoms *[see Adverse Reactions (6.3)]*.

5.7 Parasitic (Helminth) Infection

Monitor patients at high risk of geohelminth infection while on XOLAIR therapy. Insufficient data are available to determine the length of monitoring required for geohelminth infections after stopping XOLAIR treatment.

In a one-year clinical trial conducted in Brazil in adult and adolescent patients at high risk for geohelminthic infections (roundworm, hookworm, whipworm, threadworm), 53% (36/68) of XOLAIR-treated patients experienced an infection, as diagnosed by standard stool examination, compared to 42% (29/69) of placebo controls. The point estimate of the odds ratio for infection was 1.96, with a 95% confidence interval (0.88, 4.36) indicating that in this study a patient who had an infection was anywhere from 0.88 to 4.36 times as likely to have received XOLAIR than a patient who did not have an infection. Response to appropriate anti-geohelminth treatment of infection as measured by stool egg counts was not different between treatment groups.

5.8 Laboratory Tests

Serum total IgE levels increase following administration of XOLAIR due to formation of XOLAIR:IgE complexes *[see Clinical Pharmacology (12.2)]*. Elevated serum total IgE levels may persist for up to 1 year following discontinuation of XOLAIR. Do not use serum total IgE levels obtained less than 1 year following discontinuation to reassess the dosing regimen for asthma patients, because these levels may not reflect steady state free IgE levels *[see Dosage and Administration (2.1)]*.

6 ADVERSE REACTIONS

Use of XOLAIR has been associated with:

- Anaphylaxis *[see Boxed Warning and Warnings and Precautions (5.1)]*
- Malignancies *[see Warnings and Precautions (5.2)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Adverse Reactions from Clinical Studies in Adult and Adolescent Patients 12 Years of Age and Older with Asthma

The data described below reflect XOLAIR exposure for 2076 adult and adolescent patients ages 12 and older, including 1687 patients exposed for six months and 555 exposed for one year or more, in either placebo-controlled or other controlled asthma studies. The mean age of patients receiving XOLAIR was 42 years, with 134 patients 65 years of age or older; 60% were women, and 85% Caucasian. Patients received XOLAIR 150 mg to 375 mg every 2 or 4 weeks or, for patients assigned to control groups, standard therapy with or without a placebo.

The adverse events most frequently resulting in clinical intervention (e.g., discontinuation of XOLAIR, or the need for concomitant medication to treat an adverse event) were injection site reaction (45%), viral infections (23%), upper respiratory tract infection (20%), sinusitis (16%), headache (15%), and pharyngitis (11%). These events were observed at similar rates in XOLAIR-treated patients and control patients.

Table 5 shows adverse reactions from four placebo-controlled asthma trials that occurred ≥1% and more frequently in adult and adolescent patients 12 years of age and older receiving XOLAIR than in those receiving placebo. Adverse events were classified using preferred terms from the International Medical Nomenclature (IMN) dictionary. Injection site reactions were recorded separately from the reporting of other adverse events.

Table 5. Adverse Reactions ≥1% More Frequent in XOLAIR-Treated Adult or Adolescent Patients 12 years of Age and Older in Four Placebo-controlled Asthma Trials

Adverse reaction	XOLAIR n=738	Placebo n=717
Body as a whole		
Pain	7%	5%
Fatigue	3%	2%
Musculoskeletal system		
Arthralgia	8%	6%
Fracture	2%	1%
Leg pain	4%	2%
Arm pain	2%	1%
Nervous system		
Dizziness	3%	2%
Skin and appendages		
Pruritus	2%	1%
Dermatitis	2%	1%
Special senses		
Earache	2%	1%

There were no differences in the incidence of adverse reactions based on age (among patients under 65), gender or race.

Anaphylaxis Case Control Study

A retrospective case-control study investigated risk factors for anaphylaxis to XOLAIR among patients treated with XOLAIR for asthma. Cases with an adjudicated history of anaphylaxis to XOLAIR were compared to controls with no such history. The study found that a self-reported history of anaphylaxis to foods, medications or other causes was more common among patients with XOLAIR anaphylaxis (57% of 30 cases) compared to controls (23% of 88 controls) [OR 8.1, 95% CI 2.7 to 24.3]. Because this is a case-control study, the study cannot provide the incidence of anaphylaxis among XOLAIR users. From other sources, anaphylaxis to XOLAIR was observed in 0.1% of patients in clinical trials and at least 0.2% of patients based upon postmarketing reports *[see Warnings and Precautions (5.1), Adverse Reactions (6.3)]*.

Injection Site Reactions

In adults and adolescents, injection site reactions of any severity occurred at a rate of 45% in XOLAIR-treated patients compared with 43% in placebo-treated patients. The types of injection site reactions included: bruising, redness, warmth, burning, stinging, itching, hive formation, pain, indurations, mass, and inflammation.

Severe injection site reactions occurred more frequently in XOLAIR-treated patients compared with patients in the placebo group (12% versus 9%).

The majority of injection site reactions occurred within 1 hour post injection, lasted less than 8 days, and generally decreased in frequency at subsequent dosing visits.

Adverse Reactions from Clinical Studies in Pediatric Patients 6 to <12 Years of Age with Asthma

The data described below reflect XOLAIR exposure for 926 patients 6 to <12 years of age, including 583 patients exposed for six months and 292 exposed for one year or more, in either placebo-controlled or other controlled asthma studies. The mean age of pediatric patients receiving XOLAIR was 8.8 years; 69% were male, and 64% were Caucasian. Pediatric patients received XOLAIR 75 mg to 375 mg every 2 or 4 weeks or, for patients assigned to control groups, standard therapy with or without a placebo. No cases of malignancy were reported in patients treated with XOLAIR in these trials.

The most common adverse reactions occurring at ≥3% in the pediatric patients receiving XOLAIR and more frequently than in patients treated with placebo were nasopharyngitis, headache, pyrexia, upper abdominal pain, pharyngitis streptococcal, otitis media, viral gastroenteritis, arthropod bite, and epistaxis.

The adverse events most frequently resulting in clinical intervention (e.g., discontinuation of XOLAIR, or the need for concomitant medication to treat an adverse event) were bronchitis (0.2%), headache (0.2%) and urticaria (0.2%). These events were observed at similar rates in XOLAIR-treated patients and control patients.

Adverse Reactions from Clinical Studies in Patients with Chronic Idiopathic Urticaria (CIU)

The safety of XOLAIR for the treatment of CIU was assessed in three placebo-controlled, multiple-dose clinical trials of 12 weeks' (CIU Trial 2) and 24 weeks' duration (CIU Trials 1 and 3). In CIU Trials 1 and 2, patients received XOLAIR 75 mg, 150 mg, or 300 mg or placebo every 4 weeks in addition to their baseline level of H1 antihistamine therapy throughout the treatment period. In CIU Trial 3 patients were randomized to XOLAIR 300 mg or placebo every 4 weeks in addition to their baseline level of H1 antihistamine therapy. The data described below reflect XOLAIR exposure for 733 patients enrolled and receiving at least one dose of XOLAIR in the three clinical trials, including 684 patients exposed for 12 weeks and 427 exposed for 24 weeks. The mean age of patients receiving XOLAIR 300 mg was 43 years, 75% were women, and 89% were white. The demographic profiles for patients receiving XOLAIR 150 mg and 75 mg were similar.

Table 6 shows adverse reactions that occurred in ≥2% of patients receiving XOLAIR (150 or 300 mg) and more frequently than those receiving placebo. Adverse reactions are pooled from Trial 2 and the first 12 weeks of Trials 1 and 3.

Table 6. Adverse Reactions Occurring in ≥2% in XOLAIR-Treated Patients and More Frequently than in Patients Treated with Placebo (Day 1 to Week 12) in CIU Trials

Adverse Reactions*	CIU Trials 1, 2 and 3 Pooled		
	150mg (n=175)	300mg (n=412)	Placebo (n=242)
Gastrointestinal disorders			
Nausea	2 (1.1%)	11 (2.7%)	6 (2.5%)
Infections and infestations			
Nasopharyngitis	16 (9.1%)	27 (6.6%)	17 (7.0%)
Sinusitis	2 (1.1%)	20 (4.9%)	5 (2.1%)
Upper respiratory tract infection	2 (1.1%)	14 (3.4%)	5 (2.1%)
Viral upper respiratory tract infection	4 (2.3%)	2 (0.5%)	(0.0%)
Musculoskeletal and connective tissue disorders			
Arthralgia	5 (2.9%)	12 (2.9%)	1 (0.4%)
Nervous system disorders			
Headache	21 (12.0%)	25 (6.1%)	7 (2.9%)
Respiratory, thoracic, and mediastinal disorders			
Cough	2 (1.1%)	9 (2.2%)	3 (1.2%)

* by MedDRA (15.1) System Organ Class and Preferred Term

Additional reactions reported during the 24-week treatment period in Trials 1 and 3 [≥2% of patients receiving XOLAIR (150 mg or 300 mg) and more frequently than those receiving placebo] included: toothache, fungal infection, urinary tract infection, myalgia, pain in extremity, musculoskeletal pain, peripheral edema, pyrexia, migraine, sinus headache, anxiety, oropharyngeal pain, asthma, urticaria, and alopecia.

Injection Site Reactions

Injection site reactions of any severity occurred during the studies in more XOLAIR-treated patients [11 patients (2.7%) at 300 mg, 1 patient (0.6%) at 150 mg] compared with 2 placebo-treated patients (0.8%). The types of injection site reactions included: swelling, erythema, pain, bruising, itching, bleeding and urticaria. None of the events resulted in study discontinuation or treatment interruption.

Cardiovascular and Cerebrovascular Events from Clinical Studies in Patients with Asthma

A 5-year observational cohort study was conducted in patients ≥12 years of age with moderate to severe persistent asthma and a positive skin test reaction to a perennial aeroallergen to evaluate the long term safety of XOLAIR, including the risk of malignancy *[see Warnings and Precautions (5.2)]*. A total of 5007 XOLAIR-treated and 2829 non-XOLAIR-treated patients enrolled in the study. Similar percentages of patients in both cohorts were current (5%) or former smokers (29%). Patients had a mean age of 45 years and were followed for a mean of 3.7 years. More XOLAIR-treated patients were diagnosed with severe asthma (50%) compared to the non-XOLAIR-treated patients (23%) and 44% of

patients prematurely discontinued the study. Additionally, 88% of patients in the XOLAIR-treated cohort had been previously exposed to XOLAIR for a mean of 8 months.

A higher incidence rate (per 1000 patient-years) of overall cardiovascular and cerebrovascular serious adverse events (SAEs) was observed in XOLAIR-treated patients (13.4) compared to non-XOLAIR-treated patients (8.1). Increases in rates were observed for transient ischemic attack (0.7 versus 0.1), myocardial infarction (2.1 versus 0.8), pulmonary hypertension (0.5 versus 0), pulmonary embolism/venous thrombosis (3.2 versus 1.5), and unstable angina (2.2 versus 1.4), while the rates observed for ischemic stroke and cardiovascular death were similar among both study cohorts. The results suggest a potential increased risk of serious cardiovascular and cerebrovascular events in patients treated with XOLAIR. However, the observational study design, the inclusion of patients previously exposed to XOLAIR (88%), baseline imbalances in cardiovascular risk factors between the treatment groups, an inability to adjust for unmeasured risk factors, and the high study discontinuation rate limit the ability to quantify the magnitude of the risk.

A pooled analysis of 25 randomized double-blind, placebo-controlled clinical trials of 8 to 52 weeks in duration was conducted to further evaluate the imbalance in cardiovascular and cerebrovascular SAEs noted in the above observational cohort study. A total of 3342 XOLAIR-treated patients and 2895 placebo-treated patients were included in the pooled analysis. The patients had a mean age of 38 years, and were followed for a mean duration of 6.8 months. No notable imbalances were observed in the rates of cardiovascular and cerebrovascular SAEs listed above. However, the results of the pooled analysis were based on a low number of events, slightly younger patients, and shorter duration of follow-up than the observational cohort study; therefore, the results are insufficient to confirm or reject the findings noted in the observational cohort study.

6.2 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to omalizumab in the studies described below with the incidence of antibodies in other studies or to other products may be misleading

Antibodies to XOLAIR were detected in approximately 1/1723 (<0.1%) of patients treated with XOLAIR in the clinical studies evaluated for approval of asthma in patients 12 years of age and older. In three pediatric studies, antibodies to XOLAIR were detected in one patient out of 581 patients 6 to <12 years of age treated with XOLAIR and evaluated for antibodies. There were no detectable antibodies in the patients treated in the phase 3 CIU clinical trials, but due to levels of XOLAIR at the time of anti-therapeutic antibody sampling and missing samples for some patients, antibodies to XOLAIR could only have been determined in 88% of the 733 patients treated in these clinical studies. The data reflect the percentage of patients whose test results were considered positive for antibodies to XOLAIR in ELISA assays and are highly dependent on the sensitivity and specificity of the assays.

6.3 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of XOLAIR in adult and adolescent patients 12 years of age and older. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Anaphylaxis: Based on spontaneous reports and an estimated exposure of about 57,300 patients from June 2003 through December 2006, the frequency of anaphylaxis attributed to XOLAIR use was estimated to be at least 0.2% of patients. Diagnostic criteria of anaphylaxis were skin or mucosal tissue involvement, and, either airway compromise, and/or reduced blood pressure with or without associated symptoms, and a temporal relationship to XOLAIR administration with no other identifiable cause. Signs and symptoms in these reported cases included bronchospasm, hypotension, syncope, urticaria, angioedema of the throat or tongue, dyspnea, cough, chest tightness, and/or cutaneous angioedema. Pulmonary involvement was reported in 89% of the cases. Hypotension or syncope was reported in 14% of cases. Fifteen percent of the reported cases resulted in hospitalization. A previous history of anaphylaxis unrelated to XOLAIR was reported in 24% of the cases.

Of the reported cases of anaphylaxis attributed to XOLAIR, 39% occurred with the first dose, 19% occurred with the second dose, 10% occurred with the third dose, and the rest after subsequent doses. One case occurred after 39 doses (after 19 months of continuous therapy, anaphylaxis occurred when treatment was restarted following a 3-month gap). The time to onset of anaphylaxis in these cases was up to 30 minutes in 35%, greater than 30 and up to 60 minutes in 16%, greater than 60 and up to 90 minutes in 2%, greater than 90 and up to 120 minutes in 6%, greater than 2 hours and up to 6 hours in 5%, greater than 6 hours and up to 12 hours in 14%, greater than 12 hours and up to 24 hours in 8%, and greater than 24 hours and up to 4 days in 5%. In 9% of cases the times to onset were unknown.

Twenty-three patients who experienced anaphylaxis were rechallenged with XOLAIR and 18 patients had a recurrence of similar symptoms of anaphylaxis. In addition, anaphylaxis occurred upon rechallenge with XOLAIR in 4 patients who previously experienced urticaria only.

Eosinophilic Conditions: Eosinophilic conditions have been reported *[see Warnings and Precautions (5.5)]*.

Fever, Arthralgia, and Rash: A constellation of signs and symptoms including arthritis/arthralgia, rash (urticaria or other forms), fever and lymphadenopathy similar to serum sickness have been reported in post-approval use of XOLAIR *[see Warnings and Precautions (5.6)]*.

Hematologic: Severe thrombocytopenia has been reported.

Skin: Hair loss has been reported.

7 DRUG INTERACTIONS

No formal drug interaction studies have been performed with XOLAIR.

In patients with asthma the concomitant use of XOLAIR and allergen immunotherapy has not been evaluated.

In patients with CIU the use of XOLAIR in combination with immunosuppressive therapies has not been studied.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

The data with XOLAIR use in pregnant women are insufficient to inform on drug associated risk. Monoclonal antibodies, such as omalizumab, are transported across the placenta in a linear fashion as pregnancy progresses; therefore, potential effects on a fetus are likely to be greater during the second and third trimesters of pregnancy.

In animal reproduction studies, no evidence of fetal harm was observed in Cynomolgus monkeys with subcutaneous doses of omalizumab up to approximately 10 times the maximum recommended human dose (MRHD) *[see Animal Data]*.

In the US general population the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

In women with poorly or moderately controlled asthma, evidence demonstrates that there is an increased risk of preeclampsia in the mother and prematurity, low birth weight, and small for gestational age in the neonate. The level of asthma control should be closely monitored in pregnant women and treatment adjusted as necessary to maintain optimal control.

Data

Animal Data

Reproductive studies have been performed in Cynomolgus monkeys. There was no evidence of maternal toxicity, embryotoxicity, or teratogenicity when omalizumab was administered throughout the period of organogenesis at doses that produced exposures approximately 10 times the MHRD (on a mg/kg basis with maternal subcutaneous doses up to 75 mg/kg/week). Omalizumab did not elicit adverse effects on fetal or neonatal growth when administered throughout late gestation, delivery, and nursing.

8.2 Lactation

Risk Summary

There is no information regarding the presence of omalizumab in human milk, the effects on the breastfed infant, or the effects on milk production. However, omalizumab is a human monoclonal antibody (IgG1 kappa), and immunoglobulin (IgG) is present in human milk in small amounts. In Cynomolgus monkeys, neonatal serum levels of omalizumab after in utero exposure and 28 days of nursing were between 11% and 94% of the maternal serum level. Levels of omalizumab in milk were 0.15% of maternal serum concentration.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for XOLAIR and any potential adverse effects on the breastfed child from omalizumab or from the underlying maternal condition.

8.4 Pediatric Use

Asthma

Safety and efficacy of XOLAIR for asthma were evaluated in 2 trials in 926 (XOLAIR 624; placebo 302) pediatric patients 6 to <12 years of age with moderate to severe persistent asthma who had a positive skin test or in vitro reactivity to a perennial aeroallergen. One trial was a pivotal trial of similar design and conduct to that of adult and adolescent Asthma Trials 1 and 2. The other trial was primarily a safety study and included evaluation of efficacy as a secondary outcome. In the pivotal trial, XOLAIR-treated patients had a statistically significant reduction in the rate of exacerbations (exacerbation was defined as worsening of asthma that required treatment with systemic corticosteroids or a doubling of the baseline ICS dose) *[see Clinical Studies (14.1)]*.

Safety and efficacy in pediatric patients with asthma below 6 years of age have not been established.

Chronic Idiopathic Urticaria

The safety and effectiveness of XOLAIR for adolescent patients with CIU were evaluated in 39 patients 12 to 17 years of age (XOLAIR 29, placebo 10) included in three randomized, placebo-controlled CIU trials. A numerical decrease in weekly itch score was observed, and adverse reactions were similar to those reported in patients 18 years and older.

Safety and efficacy in pediatric patients with CIU below 12 years of age have not been established.

8.5 Geriatric Use

In clinical studies 134 asthma patients and 37 CIU phase 3 study patients 65 years of age or older were treated with XOLAIR. Although there were no apparent age-related differences observed in these studies, the number of patients aged 65 and over is not sufficient to determine whether they respond differently from younger patients.

10 OVERDOSAGE

The maximum tolerated dose of XOLAIR has not been determined. Single intravenous doses of up to 4,000 mg have been administered to patients without evidence of dose limiting toxicities. The highest cumulative dose administered to patients was 44,000 mg over a 20-week period, which was not associated with toxicities.

11 DESCRIPTION

Omalizumab is a recombinant DNA-derived humanized IgG1κ monoclonal antibody that selectively binds to human immunoglobulin E (IgE). The antibody has a molecular weight of approximately 149 kiloDaltons. XOLAIR is produced by a Chinese hamster ovary cell suspension culture in a nutrient medium that may contain the antibiotic gentamicin. Gentamicin is not detectable in the final product.

XOLAIR (omalizumab) is administered as a subcutaneous (SC) injection and is available in prefilled syringes and in vials.

Prefilled Syringe

XOLAIR (omalizumab) injection is supplied as a sterile, preservative-free, clear to slightly opalescent and colorless to pale brownish-yellow solution for subcutaneous injection. XOLAIR (omalizumab) injection is available as a single-dose prefilled syringe.

Each 75 mg prefilled syringe delivers 75 mg omalizumab in 0.5 mL and contains L-arginine hydrochloride (21.05 mg), L-histidine (0.68 mg), L-histidine hydrochloride monohydrate (1.17 mg), and polysorbate 20 (0.2 mg) in Sterile Water for Injection (SWFI), USP.

Each 150 mg prefilled syringe delivers 150 mg omalizumab in 1 mL and contains L-arginine hydrochloride (42.1 mg), L-histidine (1.37 mg), L-histidine hydrochloride monohydrate (2.34 mg), and polysorbate 20 (0.4 mg) in SWFI, USP.

The needle cap contains a derivative of natural rubber latex which may cause allergic reactions in latex sensitive individuals.

Vial

XOLAIR (omalizumab) for injection is a sterile, white, preservative free, lyophilized powder in a single-dose vial. After reconstitution with 1.4 mL of Sterile Water for Injection, USP, the vial contains 150 mg of omalizumab per 1.2 mL of reconstituted solution for subcutaneous injection. Each 1.2 mL of reconstituted solution also contains L-histidine (1.3 mg), L-histidine hydrochloride monohydrate (2.1 mg), polysorbate 20 (0.4 mg) and sucrose (108 mg).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Asthma

Omalizumab inhibits the binding of IgE to the high-affinity IgE receptor (FcεRI) on the surface of mast cells and basophils. Reduction in surface-bound IgE on FcεRI-bearing cells limits the degree of release of mediators of the allergic response. Treatment with XOLAIR also reduces the number of FcεRI receptors on basophils in atopic patients.

Chronic Idiopathic Urticaria

Omalizumab binds to IgE and lowers free IgE levels. Subsequently, IgE receptors (FcεRI) on cells down-regulate. The mechanism by which these effects of omalizumab result in an improvement of CIU symptoms is unknown.

12.2 Pharmacodynamics

Asthma

In clinical studies, serum free IgE levels were reduced in a dose dependent manner within 1 hour following the first dose and maintained between doses. Mean serum free IgE decrease was greater than 96% using recommended doses. Serum total IgE levels (i.e., bound and unbound) increased after the first dose due to the formation of omalizumab:IgE complexes, which have a slower elimination rate compared with free IgE. At 16 weeks after the first dose, average serum total IgE levels were five-fold higher compared with pre-treatment when using standard assays. After discontinuation of XOLAIR dosing, the XOLAIR-induced increase in total IgE and decrease in free IgE were reversible, with no observed rebound in IgE levels after drug washout. Total IgE levels did not return to pre-treatment levels for up to one year after discontinuation of XOLAIR.

Chronic Idiopathic Urticaria

In clinical studies in CIU patients, XOLAIR treatment led to a dose-dependent reduction of serum free IgE and an increase of serum total IgE levels, similar to the observations in asthma patients. Maximum suppression of free IgE was observed 3 days following the first subcutaneous dose. After repeat dosing once every 4 weeks, predose serum free IgE levels remained stable between 12 and 24 weeks of treatment. Total IgE levels in serum increased after the first dose due to the formation of omalizumab-IgE complexes which have a slower elimination rate compared with free IgE. After repeat dosing once every 4 weeks at 75 mg up to 300 mg, average predose serum total IgE levels at Week 12 were two- to three-fold higher compared with pre-treatment levels, and remained stable between 12 and 24 weeks of treatment. After discontinuation of XOLAIR dosing, free IgE levels increased and total IgE levels decreased towards pre-treatment levels over a 16-week follow-up period.

12.3 Pharmacokinetics

After SC administration, omalizumab was absorbed with an average absolute bioavailability of 62%. Following a single SC dose in adult and adolescent patients with asthma, omalizumab was absorbed slowly, reaching peak serum concentrations after an average of 7–8 days. In patients with CIU, the peak serum concentration was reached at a similar time after a single SC dose. The pharmacokinetics of omalizumab was linear at doses greater than 0.5 mg/kg. In patients with asthma, following multiple doses of XOLAIR, areas under the serum concentration-time curve from Day 0 to Day 14 at steady state were up to 6-fold of those after the first dose. In patients with CIU, omalizumab exhibited linear pharmacokinetics across the dose range of 75 mg to 600 mg given as single subcutaneous dose. Following repeat dosing from 75 to 300 mg every 4 weeks, trough serum concentrations of omalizumab increased proportionally with the dose levels.

In vitro, omalizumab formed complexes of limited size with IgE. Precipitating complexes and complexes larger than 1 million daltons in molecular weight were not observed in vitro or in vivo. Tissue distribution studies in Cynomolgus monkeys showed no specific uptake of ^{125}I-omalizumab by any organ or tissue. The apparent volume of distribution of omalizumab in patients with asthma following SC administration was 78 ± 32 mL/kg. In patients with CIU, based on population pharmacokinetics, distribution of omalizumab was similar to that in patients with asthma.

Clearance of omalizumab involved IgG clearance processes as well as clearance via specific binding and complex formation with its target ligand, IgE. Liver elimination of IgG included degradation in the liver reticuloendothelial system (RES) and endothelial cells. Intact IgG was also excreted in bile. In studies with mice and monkeys, omalizumab:IgE complexes were eliminated by interactions with Fcγ receptors within the RES at rates that were generally faster than IgG clearance. In asthma patients omalizumab serum elimination half-life averaged 26 days, with apparent clearance averaging 2.4 ± 1.1 mL/kg/day. Doubling body weight approximately doubled apparent clearance. In CIU patients, at steady state, based on population pharmacokinetics, omalizumab serum elimination half-life averaged 24 days and apparent clearance averaged 240 mL/day (corresponding to 3.0 mL/kg/day for an 80 kg patient).

Special Populations

Asthma

The population pharmacokinetics of omalizumab was analyzed to evaluate the effects of demographic characteristics in patients with asthma. Analyses of these data suggested that no dose adjustments are necessary for age (6–76 years), race, ethnicity, or gender.

Chronic Idiopathic Urticaria

The population pharmacokinetics of omalizumab was analyzed to evaluate the effects of demographic characteristics and other factors on omalizumab exposure in patients with CIU. Covariate effects were evaluated by analyzing the relationship between omalizumab concentrations and clinical responses. These analyses demonstrate that no dose adjustments are necessary for age (12 to 75 years), race/ethnicity, gender, body weight, body mass index or baseline IgE level.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No long-term studies have been performed in animals to evaluate the carcinogenic potential of XOLAIR.

There were no effects on fertility and reproductive performance in male and female Cynomolgus monkeys that received XOLAIR at subcutaneous doses up to 75 mg/kg/week (approximately 10 times the maximum recommended human dose on a mg/kg basis).

14 CLINICAL STUDIES

14.1 Asthma

Adult and Adolescent Patients 12 Years of Age and Older

The safety and efficacy of XOLAIR were evaluated in three randomized, double-blind, placebo-controlled, multicenter trials.

The trials enrolled patients 12 to 76 years old, with moderate to severe persistent (NHLBI criteria) asthma for at least one year, and a positive skin test reaction to a perennial aeroallergen. In all trials, XOLAIR dosing was based on body weight and baseline serum total IgE concentration. All patients were required to have a baseline IgE between 30 and 700 IU/mL and body weight not more than 150 kg. Patients were treated according to a dosing table to administer at least 0.016 mg/kg/IU (IgE/mL) of XOLAIR or a matching volume of placebo over each 4-week period. The maximum XOLAIR dose per 4 weeks was 750 mg.

In all three trials an exacerbation was defined as a worsening of asthma that required treatment with systemic corticosteroids or a doubling of the baseline ICS dose. Most exacerbations were managed in the outpatient setting and the majority were treated with systemic steroids. Hospitalization rates were not significantly different between XOLAIR and placebo-treated patients; however, the overall hospitalization rate was small. Among those patients who experienced an exacerbation, the distribution of exacerbation severity was similar between treatment groups.

Asthma Trials 1 and 2

At screening, patients in Asthma Trials 1 and 2 had a forced expiratory volume in one second (FEV_1) between 40% and 80% predicted. All patients had a FEV_1 improvement of at least

12% following beta$_2$-agonist administration. All patients were symptomatic and were being treated with inhaled corticosteroids (ICS) and short acting beta$_2$-agonists. Patients receiving other concomitant controller medications were excluded, and initiation of additional controller medications while on study was prohibited. Patients currently smoking were excluded.

Each trial was comprised of a run-in period to achieve a stable conversion to a common ICS (beclomethasone dipropionate), followed by randomization to XOLAIR or placebo. Patients received XOLAIR for 16 weeks with an unchanged corticosteroid dose unless an acute exacerbation necessitated an increase. Patients then entered an ICS reduction phase of 12 weeks during which ICS dose reduction was attempted in a step-wise manner.

The distribution of the number of asthma exacerbations per patient in each group during a study was analyzed separately for the stable steroid and steroid-reduction periods.

In both Asthma Trials 1 and 2 the number of exacerbations per patient was reduced in patients treated with XOLAIR compared with placebo (Table 7).

Measures of airflow (FEV_1) and asthma symptoms were also evaluated in these trials. The clinical relevance of the treatment-associated differences is unknown. Results from the stable steroid phase Asthma Trial 1 are shown in Table 8. Results from the stable steroid phase of Asthma Trial 2 and the steroid reduction phases of both Asthma Trials 1 and 2 were similar to those presented in Table 8.

Table 7. Frequency of Asthma Exacerbations per Patient by Phase in Trials 1 and 2

	Stable Steroid Phase (16 wks)			
	Asthma Trial 1		Asthma Trial 2	
Exacerbations per patient	XOLAIR N=268	Placebo N=257	XOLAIR N=274	Placebo N=272
0	85.8%	76.7%	87.6%	69.9%
1	11.9%	16.7%	11.3%	25.0%
≥2	2.2%	6.6%	1.1%	5.1%
p-Value	0.005		<0.001	
Mean number exacerbations/patient	0.2	0.3	0.1	0.4
	Steroid Reduction Phase (12 wks)			
Exacerbations per patient	XOLAIR N=268	Placebo N=257	XOLAIR N=274	Placebo N=272
0	78.7%	67.7%	83.9%	70.2%
1	19.0%	28.4%	14.2%	26.1%
≥2	2.2%	3.9%	1.8%	3.7%
p-Value	0.004		<0.001	
Mean number exacerbations/patient	0.2	0.4	0.2	0.3

Table 8. Asthma Symptoms and Pulmonary Function During Stable Steroid Phase of Trial 1

	XOLAIR N=268*		Placebo N=257*	
Endpoint	Mean Baseline	Median Change (Baseline to Wk 16)	Mean Baseline	Median Change (Baseline to Wk 16)
Total asthma symptom score	4.3	–1.5†	4.2	–1.1†
Nocturnal asthma score	1.2	–0.4†	1.1	–0.2†
Daytime asthma score	2.3	–0.9†	2.3	–0.6†
FEV_1 % predicted	68	3†	68	0†

Asthma symptom scale: total score from 0 (least) to 9 (most); nocturnal and daytime scores from 0 (least) to 4 (most symptoms).

* Number of patients available for analysis ranges 255-258 in the XOLAIR group and 238-239 in the placebo group.

† Comparison of XOLAIR versus placebo ($p < 0.05$).

Asthma Trial 3

In Asthma Trial 3, there was no restriction on screening FEV_1, and unlike Asthma Trials 1 and 2, long-acting $beta_2$-agonists were allowed. Patients were receiving at least 1000 μg/day fluticasone propionate and a subset was also receiving oral corticosteroids. Patients receiving other concomitant controller medications were excluded, and initiation of additional controller medications while on study was prohibited. Patients currently smoking were excluded.

The trial was comprised of a run-in period to achieve a stable conversion to a common ICS (fluticasone propionate), followed by randomization to XOLAIR or placebo. Patients were stratified by use of ICS-only or ICS with concomitant use of oral steroids. Patients received XOLAIR for 16 weeks with an unchanged corticosteroid dose unless an acute exacerbation necessitated an increase. Patients then entered an ICS reduction phase of 16 weeks during which ICS or oral steroid dose reduction was attempted in a step-wise manner.

The number of exacerbations in patients treated with XOLAIR was similar to that in placebo-treated patients (Table 9). The absence of an observed treatment effect may be related to differences in the patient population compared with Asthma Trials 1 and 2, study sample size, or other factors.

Table 9. Percentage of Patients with Asthma Exacerbations by Subgroup and Phase in Trial 3

	Stable Steroid Phase (16 wks)			
	Inhaled Only		Oral + Inhaled	
	XOLAIR N=126	Placebo N=120	XOLAIR N=50	Placebo N=45
% Patients with ≥1 exacerbations	15.9%	15.0%	32.0%	22.2%
Difference (95% CI)	0.9 (–9.7, 13.7)		9.8 (–10.5, 31.4)	
	Steroid Reduction Phase (16 wks)			
	XOLAIR N=126	Placebo N=120	XOLAIR N=50	Placebo N=45
% Patients with ≥1 exacerbations	22.2%	26.7%	42.0%	42.2%
Difference (95% CI)	–4.4 (–17.6, 7.4)		–0.2 (–22.4, 20.1)	

In all three of the trials, a reduction of asthma exacerbations was not observed in the XOLAIR-treated patients who had FEV_1>80% at the time of randomization. Reductions in exacerbations were not seen in patients who required oral steroids as maintenance therapy.

Pediatric Patients 6 to <12 Years of Age

The safety and efficacy of XOLAIR in pediatric patients 6 to <12 years of age with moderate to severe asthma is based on one randomized, double-blind, placebo controlled, multi-center trial (Trial 4) and an additional supportive study (Trial 5).

Trial 4 was a 52-week study that evaluated the safety and efficacy of XOLAIR as add-on therapy in 628 pediatric patients ages 6 to <12 years with moderate to severe asthma inadequately controlled despite the use of inhaled corticosteroids (fluticasone propionate DPI ≥200 mcg/day or equivalent) with or without other controller asthma medications. Eligible patients were those with a diagnosis of asthma >1 year, a positive skin prick test to at least one perennial aeroallergen, and a history of clinical features such as daytime and/or night-time symptoms and exacerbations within the year prior to study entry. During the first 24 weeks of treatment, steroid doses remained constant from baseline. This was followed by a 28-week period during which inhaled corticosteroid adjustment was allowed.

The primary efficacy variable was the rate of asthma exacerbations during the 24-week, fixed steroid treatment phase. An asthma exacerbation was defined as a worsening of asthma symptoms as judged clinically by the investigator, requiring doubling of the baseline inhaled corticosteroid dose for at least 3 days and/or treatment with rescue systemic (oral or IV) corticosteroids for at least 3 days. At 24 weeks, the XOLAIR group had a statistically significantly lower rate of asthma exacerbations (0.45 vs. 0.64) with an estimated rate ratio of 0.69 (95% CI: 0.53, 0.90).

The XOLAIR group also had a lower rate of asthma exacerbations compared to placebo over the full 52-week double-blind treatment period (0.78 vs. 1.36; rate ratio: 0.57; 95% CI: 0.45, 0.72). Other efficacy variables such as nocturnal symptom scores, beta-agonist use, and measures of airflow (FEV1) were not significantly different in XOLAIR-treated patients compared to placebo.

Trial 5 was a 28-week randomized, double blind, placebo-controlled study that primarily evaluated safety in 334 pediatric patients, 298 of whom were 6 to <12 years of age, with moderate to severe asthma who were well-controlled with inhaled corticosteroids (beclomethasone dipropionate 168-420 mcg/day). A 16-week steroid treatment period was followed by a 12-week steroid dose reduction period. Patients treated with XOLAIR had fewer asthma exacerbations compared to placebo during both the 16-week fixed steroid treatment period (0.18 vs. 0.32; rate ratio: 0.58; 95% CI: 0.35, 0.96) and the 28-week treatment period (0.38 vs. 0.76; rate ratio: 0.50; 95% CI: 0.36, 0.71).

14.2 Chronic Idiopathic Urticaria

Adult and Adolescent Patients 12 Years of Age and Older

The safety and efficacy of XOLAIR for the treatment of CIU was assessed in two placebo-controlled, multiple-dose clinical trials of 24 weeks' duration (CIU Trial 1; n= 319) and 12 weeks' duration (CIU Trial 2; n=322). Patients received XOLAIR 75 mg, 150 mg, or 300 mg or placebo by SC injection every 4 weeks in addition to their baseline level of H1 antihistamine therapy for 24 or 12 weeks, followed by a 16-week washout observation period. A total of 640 patients (165 males, 475 females) were included for the efficacy analyses. Most patients were white (84%) and the median age was 42 years (range 12–72).

Disease severity was measured by a weekly urticaria activity score (UAS7, range 0–42), which is a composite of the weekly itch severity score (range 0–21) and the weekly hive count score (range 0–21). All patients were required to have a UAS7 of ≥16, and a weekly itch severity score of ≥8 for the 7 days prior to randomization, despite having used an H1 antihistamine for at least 2 weeks.

The mean weekly itch severity scores at baseline were fairly balanced across treatment groups and ranged between 13.7 and 14.5 despite use of an H1 antihistamine at an approved dose. The reported median durations of CIU at enrollment across treatment groups were between 2.5 and 3.9 years (with an overall subject-level range of 0.5 to 66.4 years).

In both CIU Trials 1 and 2, patients who received XOLAIR 150 mg or 300 mg had greater decreases from baseline in weekly itch severity scores and weekly hive count scores than placebo at Week 12. Representative results from CIU Trial 1 are shown (Table 10); similar results were observed in CIU Trial 2. The 75-mg dose did not demonstrate consistent evidence of efficacy and is not approved for use.

Table 10. Change from Baseline to Week 12 in Weekly Itch Severity Score and Weekly Hive Count Score in CIU Trial 1 [*]

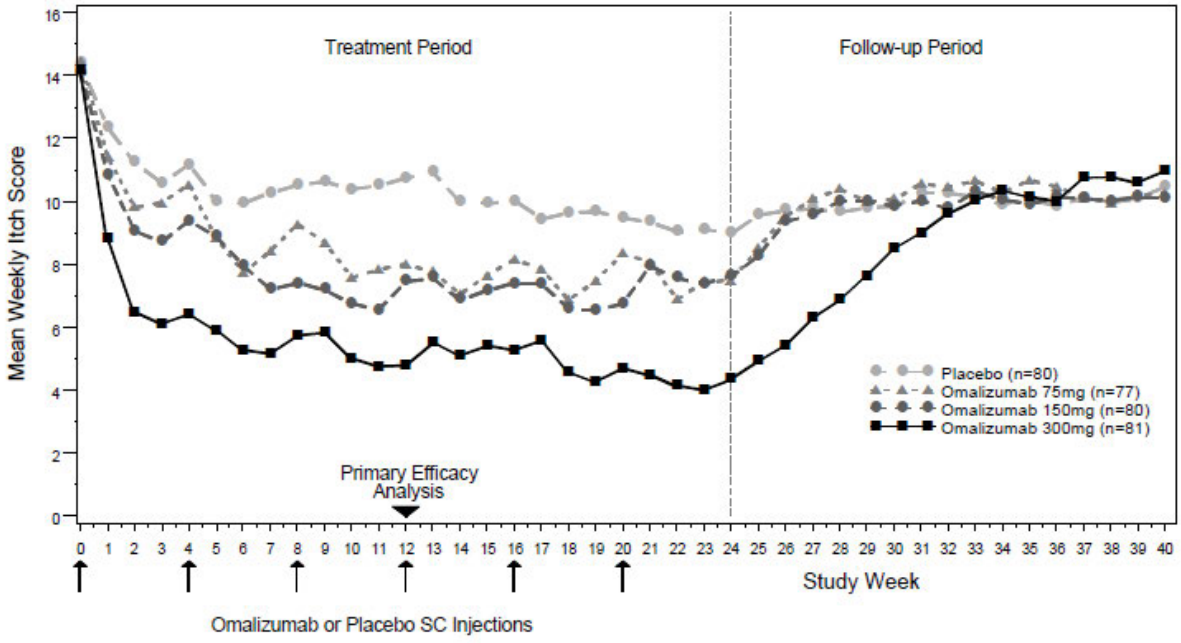
	XOLAIR 75mg	XOLAIR 150mg	XOLAIR 300mg	Placebo
n	77	80	81	80
Weekly Itch Severity Score				
Mean Baseline Score (SD)	14.5 (3.6)	14.1 (3.8)	14.2 (3.3)	14.4 (3.5)
Mean Change Week 12 (SD)	−6.46 (6.14)	−6.66 (6.28)	−9.40 (5.73)	−3.63 (5.22)
Difference in LS means vs. placebo	−2.96	−2.95	−5.80	
95% CI for difference	−4.71, −1.21	−4.72, −1.18	−7.49, −4.10	-
Weekly Hive Count Score [†]				
Mean Baseline Score (SD)	17.2 (4.2)	16.2 (4.6)	17.1 (3.8)	16.7 (4.4)
Mean Change Week 12 (SD)	−7.36 (7.52)	−7.78 (7.08)	−11.35 (7.25)	−4.37 (6.60)
Difference in LS means vs. placebo	−2.75	−3.44	−6.93	
95% CI for difference	−4.95, −0.54	−5.57, −1.32	−9.10, −4.76	-

[*] Modified intent-to-treat (mITT) population: all patients who were randomized and received at least one dose of study medication.

[†] Score measured on a range of 0–21

The mean weekly itch severity score at each study week by treatment groups is shown in Figure 1. Representative results from CIU Trial 1 are shown; similar results were observed in CIU Trial 2. The appropriate duration of therapy for CIU with XOLAIR has not been determined.

Figure 1. Mean Weekly Itch Severity Score by Treatment Group Modified Intent to Treat Patients in CIU Trial 1



In CIU Trial 1, a larger proportion of patients treated with XOLAIR 300 mg (36%) reported no itch and no hives (UAS7=0) at Week 12 compared to patients treated with XOLAIR 150 mg (15%), XOLAIR 75 mg (12%), and placebo group (9%). Similar results were observed in CIU Trial 2.

16 HOW SUPPLIED/STORAGE AND HANDLING

Prefilled Syringe

XOLAIR (omalizumab) injection is a clear to slightly opalescent and colorless to pale brownish-yellow solution in a single-dose prefilled glass syringe with a 26 gauge staked needle, rigid needle cap, and needle shield. Each carton contains one prefilled syringe.

Each XOLAIR 75 mg carton contains one single-dose 75 mg prefilled syringe with a blue needle shield (NDC 50242-214-01).

Each XOLAIR 150 mg carton contains one single-dose 150 mg prefilled syringe with a purple needle shield (NDC 50242-215-01).

XOLAIR prefilled syringe should be shipped and stored under refrigerated conditions 2°C to 8°C (36°F to 46°F) in the original carton. Protect from direct sunlight.

Do not freeze. Do not use if the syringe has been frozen.

Vial

XOLAIR is supplied as a lyophilized, white, sterile powder in a single-dose vial without preservatives. Each carton contains one 150 mg single-dose vial of XOLAIR® (omalizumab) for injection NDC 50242-040-62.

XOLAIR should be shipped at controlled ambient temperature (≤30°C [≤86°F]). Store XOLAIR under refrigerated conditions 2°C to 8°C (36°F to 46°F) in the original carton. Do not use beyond the expiration date stamped on carton.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide).

Information for Patients

Provide and instruct patients to read the accompanying Medication Guide before starting treatment and before each subsequent treatment. The complete text of the Medication Guide is reprinted at the end of this document.

Inform patients of the risk of life-threatening anaphylaxis with XOLAIR including the following points *[see Boxed Warning and Warnings and Precautions (5.1)]*:

- There have been reports of anaphylaxis occurring up to 4 days after administration of XOLAIR
- XOLAIR should only be administered in a healthcare setting by healthcare providers
- Patients should be closely observed following administration
- Patients should be informed of the signs and symptoms of anaphylaxis
- Patients should be instructed to seek immediate medical care should such signs or symptoms occur

Instruct patients receiving XOLAIR not to decrease the dose of, or stop taking any other asthma or CIU medications unless otherwise instructed by their physician. Inform patients

that they may not see immediate improvement in their asthma or CIU symptoms after beginning XOLAIR therapy.

Inform patients the needle cover on the prefilled syringe contains dry natural rubber (a derivative of latex), which may cause allergic reactions in individuals sensitive to latex

Manufactured by:
Genentech, Inc.
A Member of the Roche Group
1 DNA Way
South San Francisco, CA 94080-4990
U.S. License No.:1048

MEDICATION GUIDE

XOLAIR® (ZOHL-air) (omalizumab) injection, for subcutaneous use	**XOLAIR® (ZOHL-air)** (omalizumab) for injection, for subcutaneous use

What is the most important information I should know about XOLAIR?

XOLAIR may cause serious side effects, including:

Severe allergic reaction. A severe allergic reaction called anaphylaxis can happen when you receive XOLAIR. The reaction can occur after the first dose, or after many doses. It may also occur right after a XOLAIR injection or days later. Anaphylaxis is a life-threatening condition and can lead to death. Go to the nearest emergency room right away if you have any of these symptoms of an allergic reaction:

- wheezing, shortness of breath, cough, chest tightness, or trouble breathing
- low blood pressure, dizziness, fainting, rapid or weak heartbeat, anxiety, or feeling of "impending doom"
- flushing, itching, hives, or feeling warm
- swelling of the throat or tongue, throat tightness, hoarse voice, or trouble swallowing

Your healthcare provider will monitor you closely for symptoms of an allergic reaction while you are receiving XOLAIR and for a period of time after your injection. Your healthcare provider should talk to you about getting medical treatment if you have symptoms of an allergic reaction after leaving the healthcare provider's office or treatment center.

What is XOLAIR?

XOLAIR is an injectable prescription medicine used to treat:

- moderate to severe persistent asthma in patients 6 years of age and older whose asthma symptoms are not controlled by asthma medicines called inhaled corticosteroids. A skin or blood test is performed to see if you have allergies to year-round allergens.
- chronic idiopathic urticaria (CIU; chronic hives without a known cause) in patients 12 years of age and older who continue to have hives that are not controlled by H1 antihistamine treatment.

XOLAIR is not used to treat other allergic conditions, other forms of urticaria, acute bronchospasm or status asthmaticus.

Who should not receive XOLAIR?

Do not receive XOLAIR if you:

- are allergic to omalizumab or any of the ingredients. See the end of this Medication Guide for a complete list of ingredients in XOLAIR.

What should I tell my healthcare provider before receiving XOLAIR?

Before receiving XOLAIR, tell your healthcare provider about all of your medical conditions, including if you:

- have a latex allergy or any other allergies (such as food allergy or seasonal allergies). The needle cap on the XOLAIR prefilled syringe may contain latex.
- have sudden breathing problems (bronchospasm)
- have ever had a severe allergic reaction called anaphylaxis
- have or have had a parasitic infection
- have or have had cancer
- are pregnant or plan to become pregnant. It is not known if XOLAIR may harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if XOLAIR passes into your breast milk. Talk with your healthcare provider about the best way to feed your baby while you receive XOLAIR.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, or herbal supplements.

How should I receive XOLAIR?

- XOLAIR should be given by your healthcare provider in a healthcare setting.
- XOLAIR is given in 1 or more injections under the skin (subcutaneous), 1 time every 2 or 4 weeks.

- In asthma patients, a blood test for a substance called IgE must be performed prior to starting XOLAIR to determine the appropriate dose and dosing frequency.
- In patients with chronic hives, a blood test is not necessary to determine the dose or dosing frequency.
- Do not decrease or stop taking any of your other asthma or hive medicine unless your healthcare providers tell you to.
- You may not see improvement in your symptoms right away after XOLAIR treatment.

What are the possible side effects of XOLAIR?

XOLAIR may cause serious side effects, including:

- See "**What is the most important information I should know about XOLAIR?**"
- **Cancer**. Cases of cancer were observed in some people who received XOLAIR.
- **Inflammation of your blood vessels**. Rarely, this can happen in people with asthma who receive XOLAIR. This usually, but not always, happens in people who also take a steroid medicine by mouth that is being stopped or the dose is being lowered. It is not known whether this is caused by XOLAIR. Tell your healthcare provider right away if you have:
  - o rash
  - o shortness of breath
  - o chest pain
  - o a feeling of pins and needles or numbness of your arms or legs
- **Fever, muscle aches, and rash**. Some people who take XOLAIR get these symptoms 1 to 5 days after receiving a XOLAIR injection. If you have any of these symptoms, tell your healthcare provider.
- **Parasitic infection**. Some people who are at a high risk for parasite (worm) infections, get a parasite infection after receiving XOLAIR. Your healthcare provider can test your stool to check if you have a parasite infection.
- **Heart and circulation problems**. Some people who receive XOLAIR have had chest pain, heart attack, blood clots in the lungs or legs, or temporary symptoms of weakness on one side of the body, slurred speech, or altered vision. It is not known whether these are caused by XOLAIR.

The most common side effects of XOLAIR:

- **In adults and children 12 years of age and older with asthma**: pain especially in your arms and legs, dizziness, feeling tired, skin rash, bone fractures, and pain or discomfort of your ears.
- **In children 6 to less than 12 years of age with asthma**: common cold symptoms, headache, fever, sore throat, pain or discomfort of your ear, abdominal pain, nausea, vomiting and nose bleeds.
- **In people with chronic idiopathic urticaria**: nausea, headaches, swelling of the inside of your nose, throat or sinuses, cough, joint pain, and upper respiratory tract infection.

These are not all the possible side effects of XOLAIR. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of XOLAIR.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. If you would like more information, talk to your healthcare provider or pharmacist. You can ask your pharmacist or healthcare provider for information about XOLAIR that is written for health professionals. Do not use XOLAIR for a condition for which it was not prescribed.

For more information, go to www.xolair.com or call 1-866-4XOLAIR (1-866-496-5247).

What are the ingredients in XOLAIR?

Active ingredient: omalizumab

Inactive ingredients:

Prefilled syringe: L-arginine hydrochloride, L-histidine, L-histidine hydrochloride monohydrate, and polysorbate 20

Vial: L-histidine, L-histidine hydrochloride monohydrate, polysorbate 20 and sucrose

Manufactured by: **Genentech, Inc.**, A Member of the Roche Group, 1 DNA Way, South San Francisco, CA 94080-4990. U.S. License No.: 1048

Jointly marketed by:

Genentech USA, Inc., A Member of the Roche Group, 1 DNA Way, South San Francisco, CA 94080-4990

Novartis Pharmaceuticals Corporation, One Health Plaza, East Hanover, NJ 07936-1080

This Medication Guide has been approved by the U.S. Food and Drug Administration Revised:9/2018

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

103976Orig1s5231

MULTI-DISCIPLINE REVIEW

Summary Review
Office Director
Cross Discipline Team Leader Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

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) .

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

Digitally signed by Miya Paterniti -S
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. [redacted] (b) (4)
2. A small increase in the [redacted] (b) (4) was made for greater [redacted]

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 [redacted] (b) (4) [redacted] (b) (4).

The [redacted] (b) (4) 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®)

[redacted] (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	(b) (4)
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	(b) (4) mL	(b) (4) mL		USP-NF, Ph. Eur.
Total Volume (mL)	0.50	1.00		

Abbreviations: PFS = prefilled syringe (b) (4)

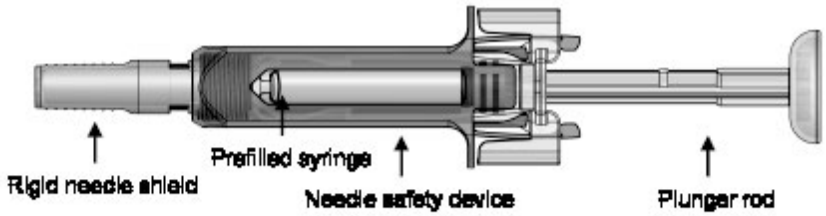
(Excerpted from the sponsor's submission)

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

- a 1 mL long barrel made from colorless (b) (4) glass (Ph. Eur., USP) (b) (4) (b) (4) and with a staked 26G (b) (4) needle.
- a gray plunger stopper (Ph. Eur, USP), made of (b) (4) (b) (4)
- a rigid needle shield consisting of a gray (b) (4) rubber needle shield (Ph. Eur, USP) and a (b) (4) rigid shell.

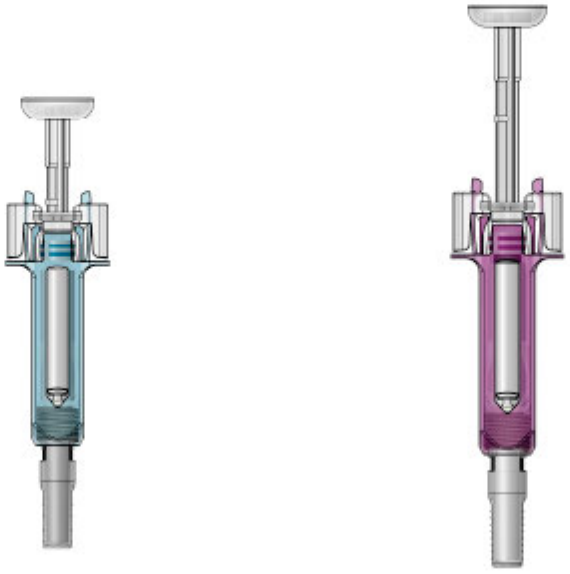
Figure 2. Schematic Drawing of Primary Packaging

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	1 mL long glass syringe with 26G (b) (4) staked-in needle	(b) (4)
Rigid Needle Shield	Rubber needle shield with rigid shell	
Plunger Stopper	(b) (4)	
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	(b) (4)
Blister Tray	
(b) (4) Lid	
Carton	
USPI	

Abbreviation: PFS-NSD = prefilled syringe with needle safety device; (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 Staked Needle (needle already fixed with adhesive)	(b) (4)
Plunger Stopper	
Rigid Needle Shield (composed of rubber needle shield and rigid 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 (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	(b) (4) mL	(b) (4) mL	(b) (4) 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) glass barrel with staked needle 26G (b) (4), sealed by a rigid needle shield, (b) (4), and a plunger-stopper, (b) (4)

In earlier studies, the extractable profiles of Xolair liquid in pre-filled syringes with (b) (4) (b) (4) rubber plungers were evaluated using a combination of analytical methods, including LC-UV, GC-MS and ICP-MS. The results of the extractable study demonstrated that the (b) (4) (b) (4) The stability study of Xolair in prefilled syringes with both plungers showed comparable stability with vials. Based on these results, (b) (4) were selected for use with the liquid Xolair prefilled syringe.

(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				(b) (4)
Components					
					(b) (4)

(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				(b) (4)
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				(b) (4)
Components					
					(b) (4)

(Excerpted from the sponsor's submission)

(b) (4)

Selection of target leachables

The target leachables for the elastomeric 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 elastomeric 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)

(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)

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
(b) (4) lot # 609002/1, 0.5 mL, 75 mg

ND = Not Detected BLOQ = Below Limit of Quantitation

No (b) (4) 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
(b) (4) lot # 609001/1, 1.0 mL, 150 mg

(b) (4)

(b) (4)

ND = Not Detected BLOQ = Below Limit of Quantitation

(b) (4)

b (b) (4) observed at BLOQ

No (b) (4) 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

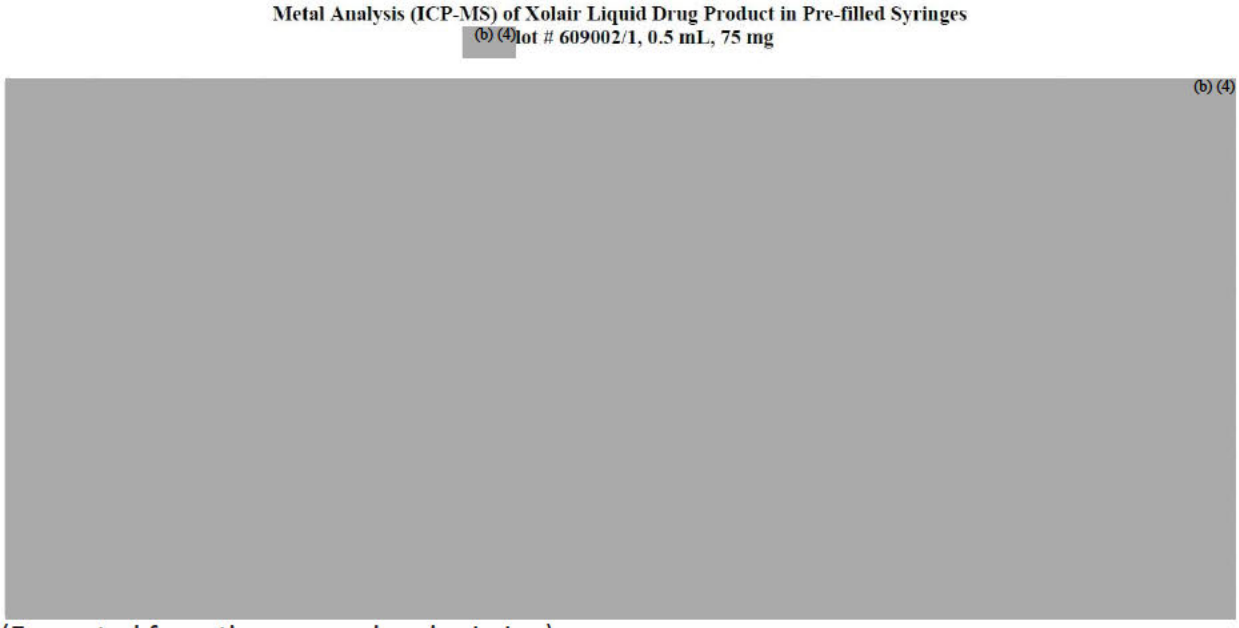
No (b) (4) compounds were detected in any sample.

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

(Excerpted from the sponsor's submission)

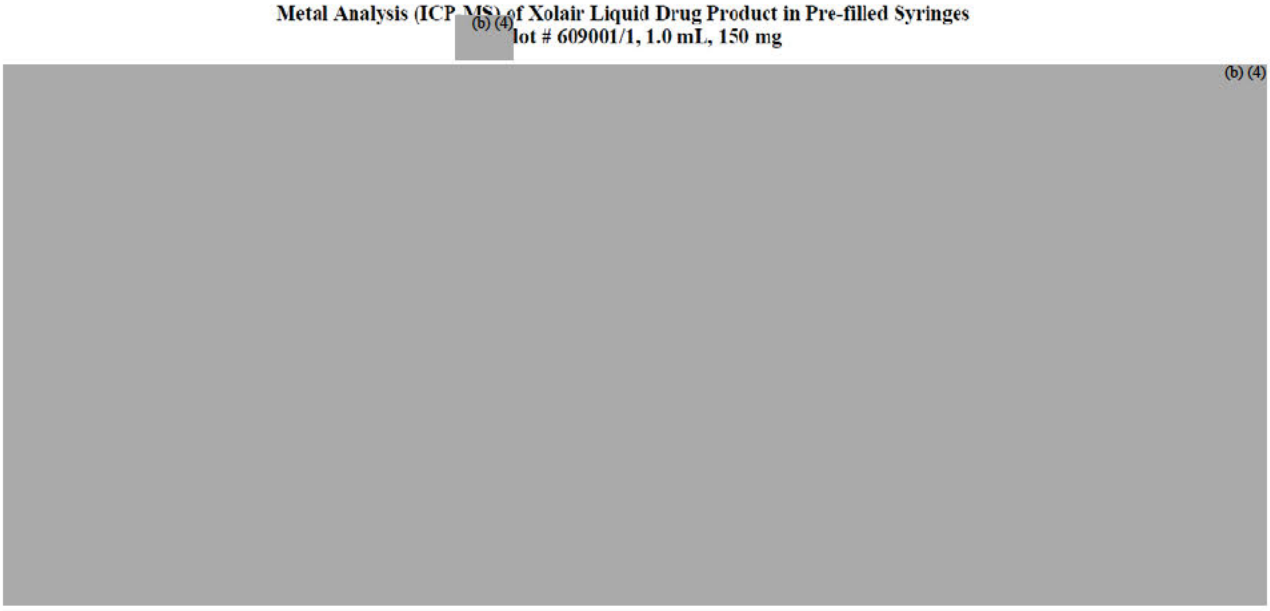
(b) (4)

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



(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



(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)

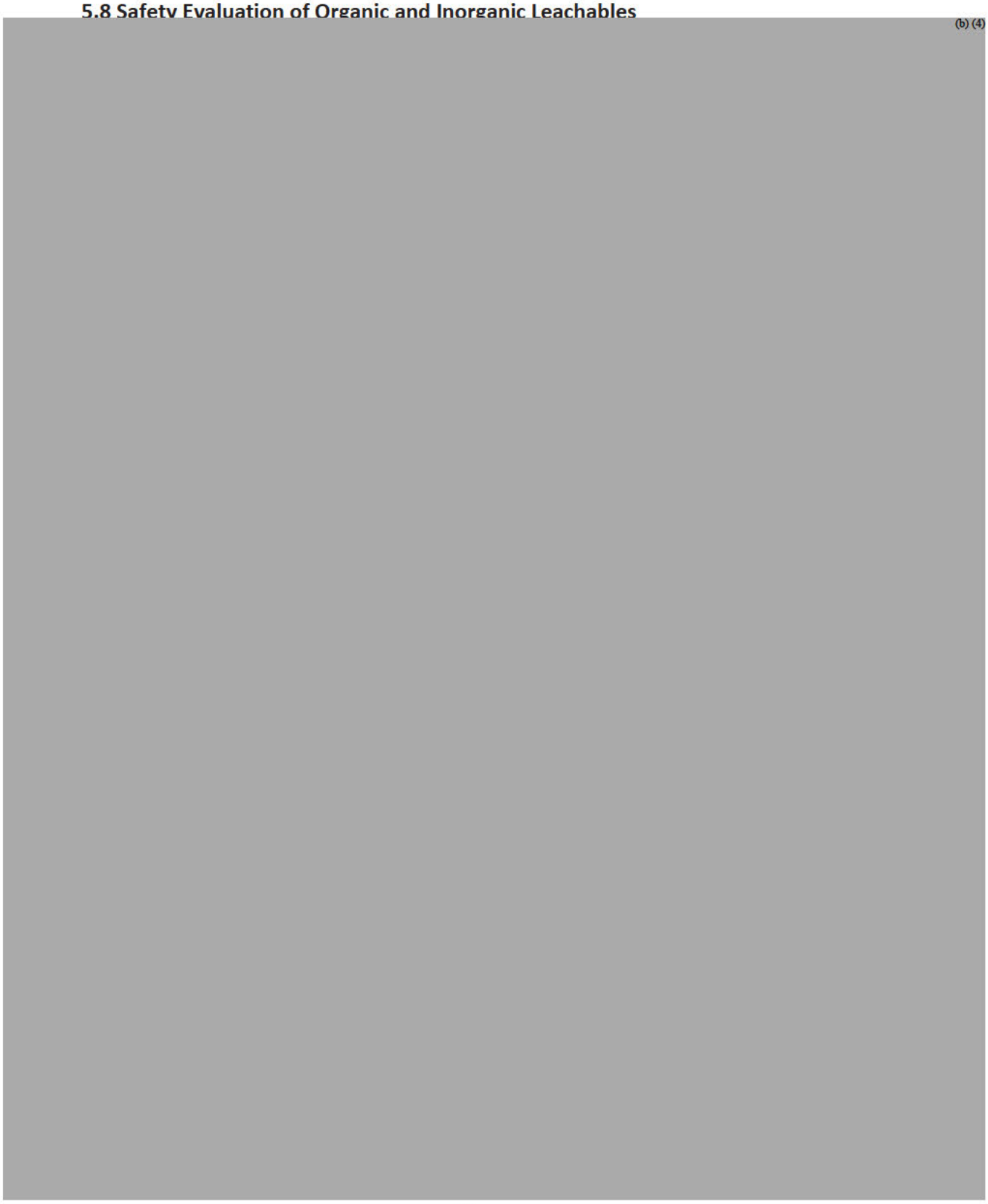
(Excerpted from the sponsor's submission)

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.

5.8 Safety Evaluation of Organic and Inorganic Leachables

(b) (4)



(b) (4)

X Timothy W. Robison -S

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Nonclinical Primary Reviewer and Team Leader

10 (b) (4)

(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

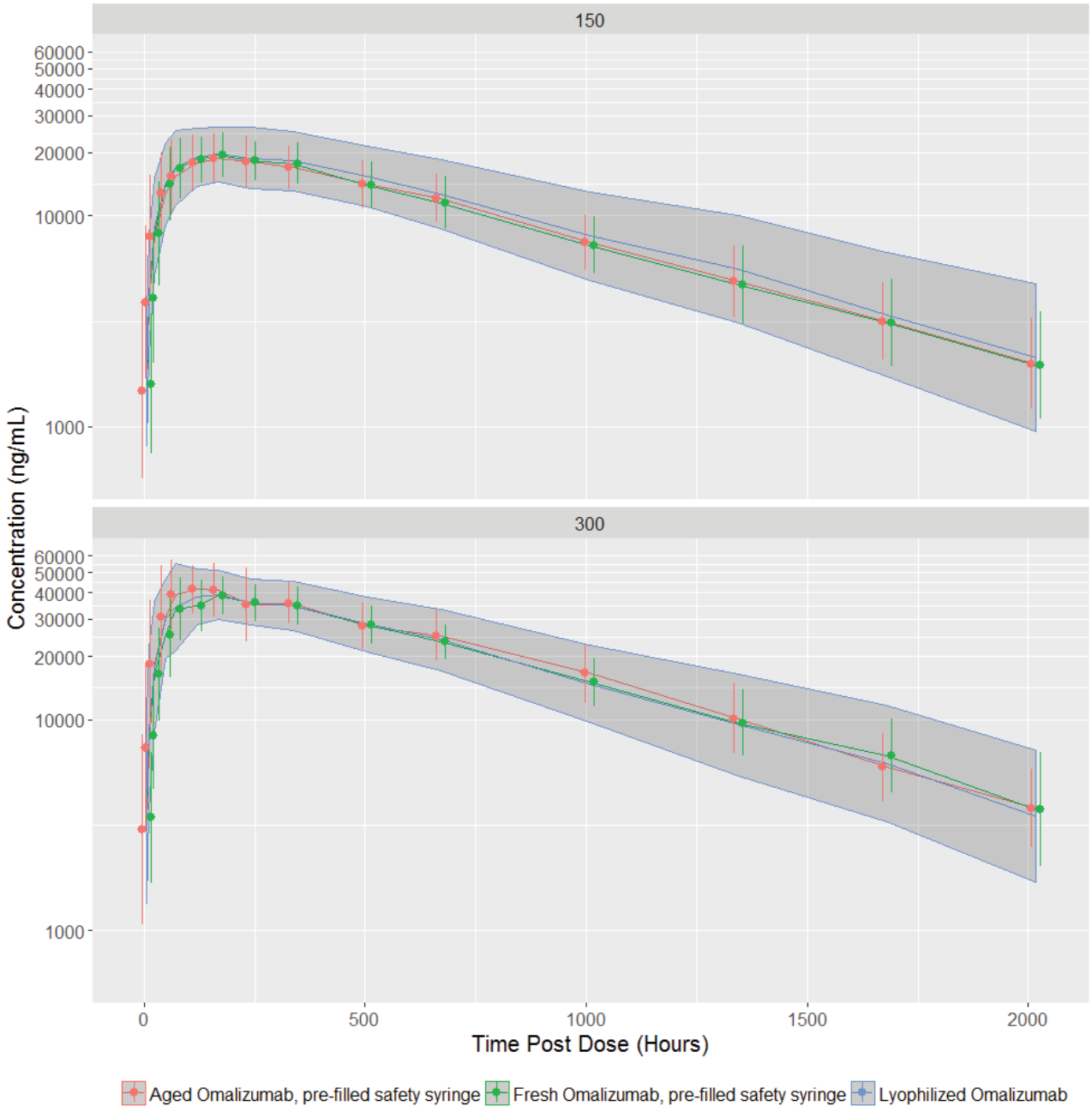
Clinical pharmacology assessment for Pivotal BE Study (C2101)

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

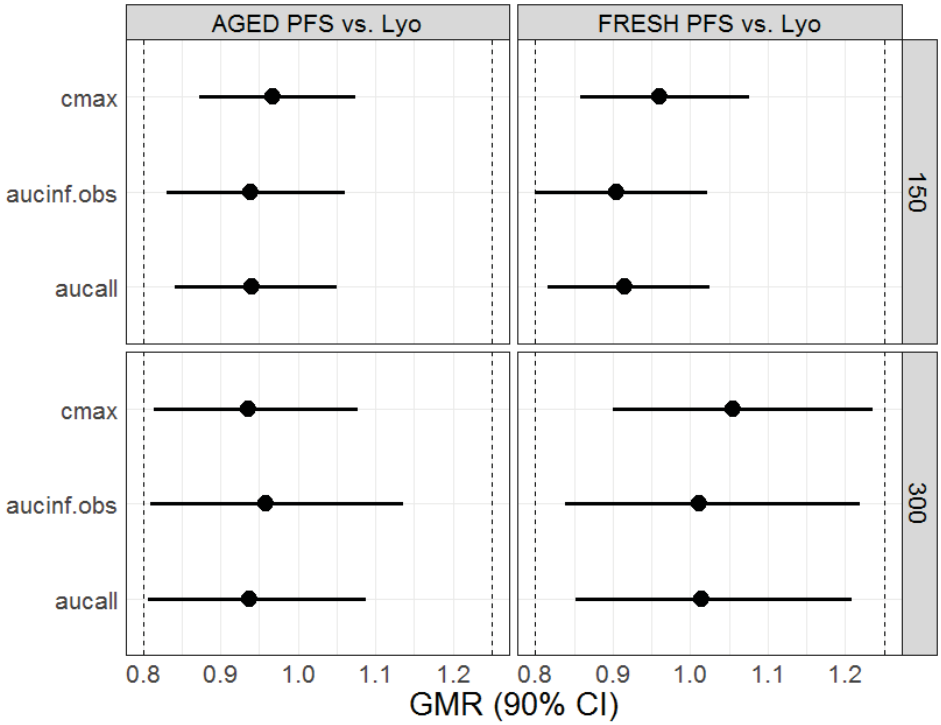
		Omalizumab		
Parameter	**Statistic**	**Lyophilized**	**Non-aged liquid**	**Aged liquid**
Cmax/dose (ng/mL/mg)	N	58*	60*	56*
	Mean (SD)	151 (51.2)	141 (28.1)	147 (39.8)
	CV%	33.9	20.0	27.1
	Median	150	141	149
	Range	74.8 - 344	75.0 - 204	73.1 - 283
AUClast/dose (day.ng/mL/mg)	N	58	60	56
	Mean (SD)	5657 (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).

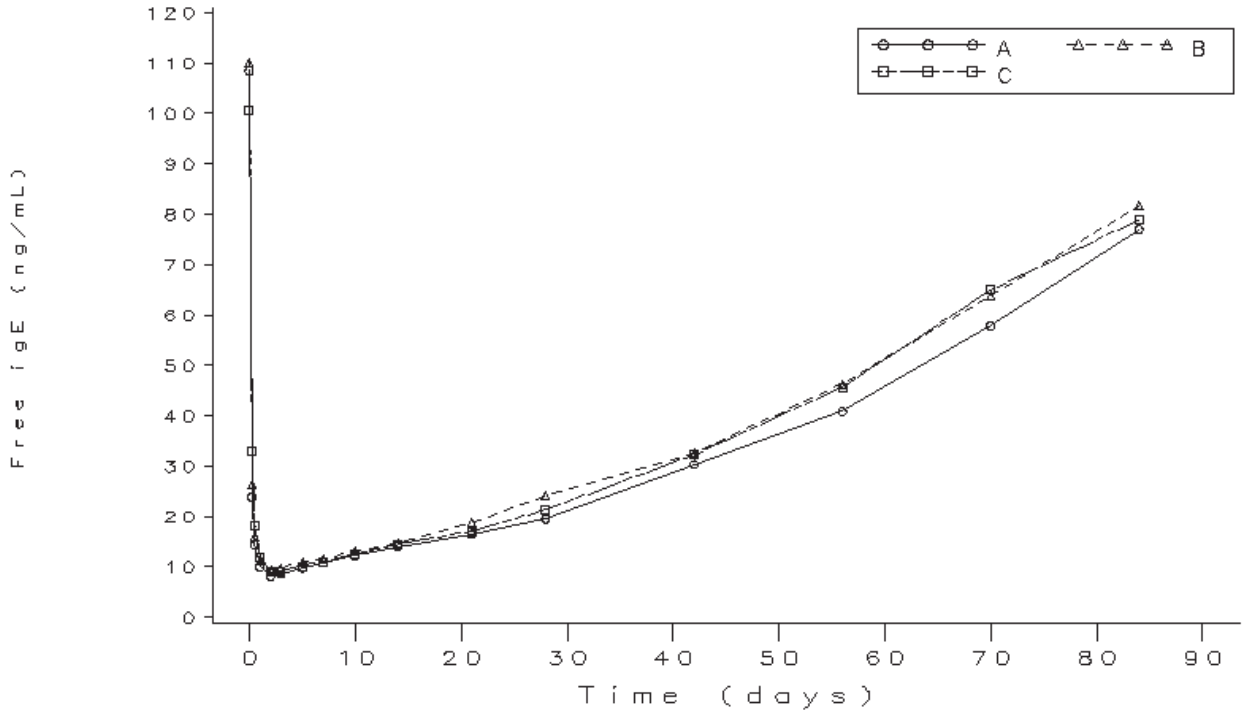
Figure 22. Point estimate and 90% Confidence intervals of Pharmacokinetic Parameters for Aged and Non-aged PFS vs. Lyophilized powder



Source: Reviewer's Analysis

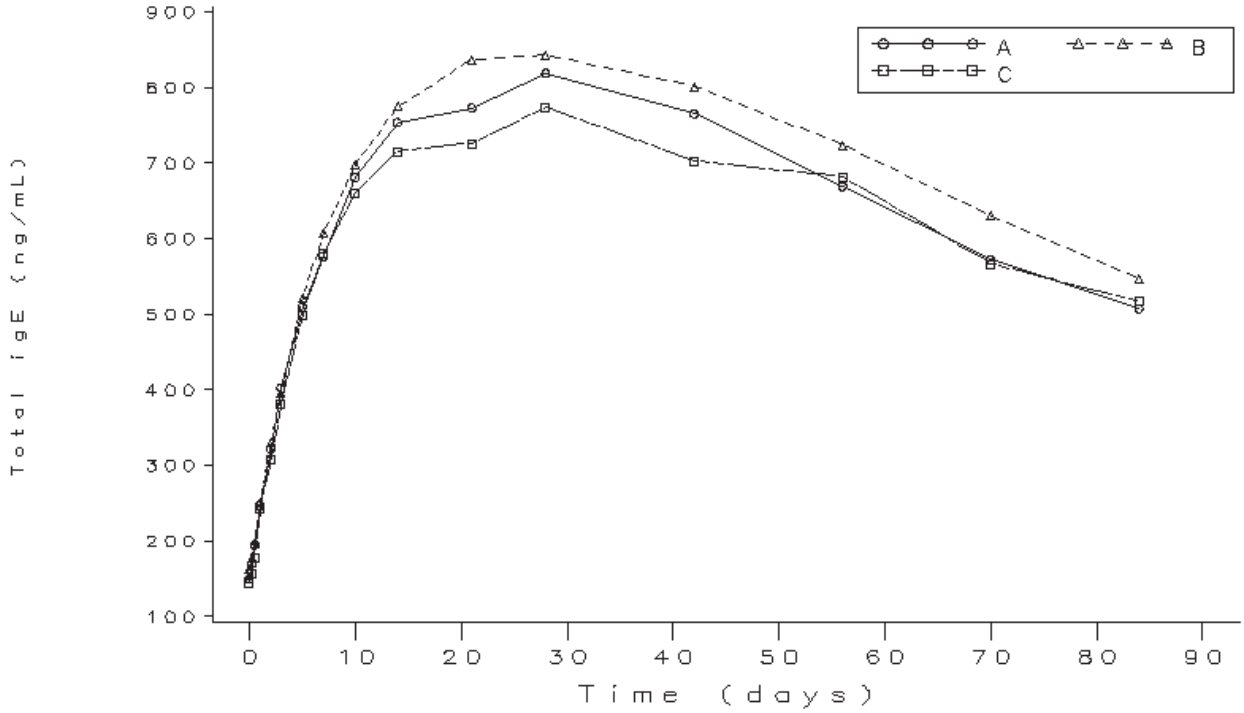
Two key pharmacodynamic endpoints of omalizumab treatment (free IgE, total IgE) display substantial overlap (Figure 23and Figure 24).

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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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.

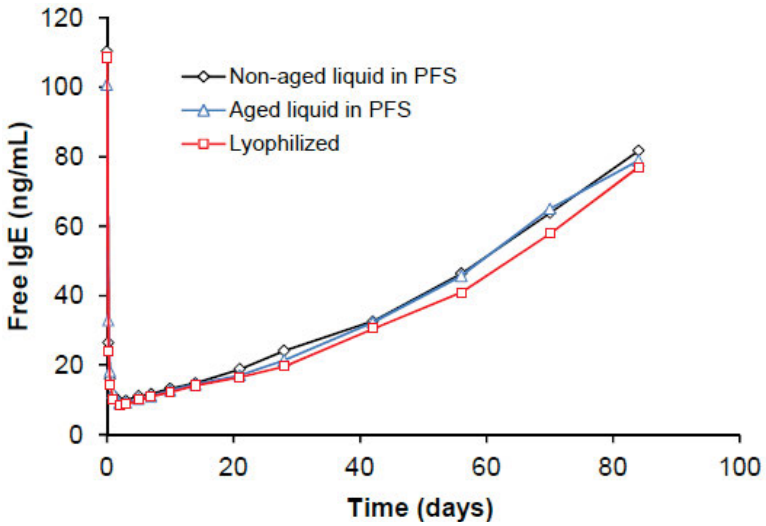

Figure 28. C2101. Arithmetic mean free IgE serum concentrations by formulation

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

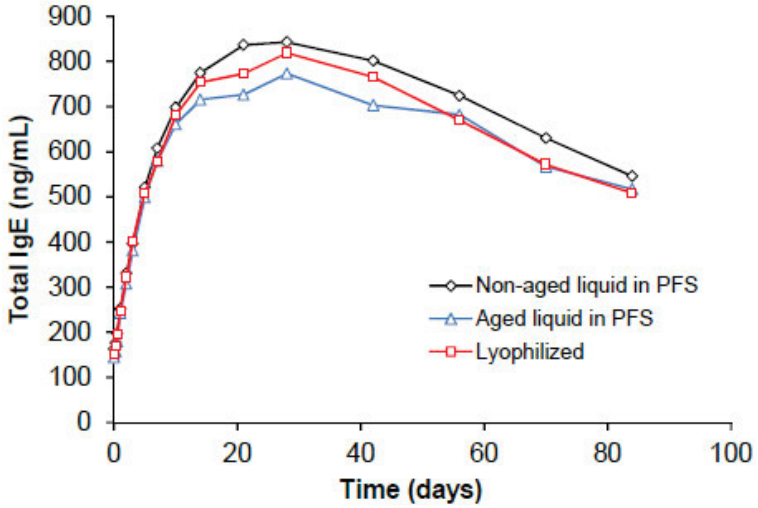

Figure 29. C2101. Arithmetic mean total IgE serum concentrations by formulation

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) (b) (4). The changes to the drug substance manufacturing process involve changes to (b) (4) 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 x 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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Date: 2018.09.26 11:49:15 -04'00'

Primary Clinical Reviewer

X Miya Paterniti -S
Digitally signed by Miya Paterniti -S
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 11:44:48 -04'00'

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. [redacted] (b) (4) 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
[redacted] (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

X Sally M. Seymour -S

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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):		

<table>
<tr><td colspan="3">0</td></tr>
<tr><td colspan="3">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</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>
<tr><td>Is an attachment provided with the reason:</td><td>Yes ☐</td><td>No ☐ (Request explanation from applicant)</td></tr>
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/s/

MIYA O PATERNITI
09/26/2018

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

103976Orig1s5231

OTHER REVIEW(S)

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: August 14, 2018

To: Angela Ramsey
Regulatory Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)

From: Kyle Snyder, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Kathleen Klemm, PharmD
Team Leader (OPDP)

Subject: OPDP Labeling Comments for XOLAIR® (omalizumab) injection and for injection, for subcutaneous use

BLA: 103976/S-5231

In response to DPARP's consult request dated April 11, 2018, OPDP has reviewed the proposed prescribing information (PI), Medication Guide (MG), and carton and container labels for BLA 103976/S-5231, XOLAIR® (omalizumab) injection and for injection, for subcutaneous use. This supplement provides for a new dosage formulation in prefilled syringe.

PI and MG: OPDP's comments on the proposed labeling are based on the draft PI and MG received by electronic mail from DPARP on August 8, 2018. Comments on the proposed PI and MG are provided below.

Carton and Container Labels: OPDP's comments on the proposed labels are based on the draft carton and container labels received by electronic mail from DPARP on August 13, 2018. OPDP offers the following comments:

1. (b) (4)

2. (b) (4)

Thank you for your consult. If you have any questions, please contact Kyle Snyder at (240) 402-8792 or kyle.snyder@fda.hhs.gov.

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

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/s/

KYLE SNYDER
08/14/2018

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs

PATIENT LABELING REVIEW

Date:	August 10, 2018
To:	Sally Seymour, MD Acting Director **Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Marcia Williams, PhD Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Kelly Jackson, PharmD Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
Subject:	DMPP Concurrence with Submitted: Medication Guide (MG)
Drug Name (established name):	XOLAIR (omalizumab)
Dosage Form and Route:	injection, subcutaneous use
Application Type/Number:	BLA 103976
Supplement Number:	S5231
Applicant:	Genentech Inc.

1 INTRODUCTION

On March 29, 2018, Genentech Inc. submitted for the Agency's review a supplemental Biologic License Application (sBLA) to seek marketing approval of omalizumab in liquid formulation in prefilled syringe for XOLAIR (omalizumab) indicated for moderate to severe persistent asthma in patients 6 years of age and older with a positive skin test or in vitro reactivity to a perennial aeroallergen and symptoms that are inadequately controlled with inhaled corticosteroids and chronic idiopathic urticaria in adults and adolescents 12 years of age and older who remain symptomatic despite H1 antihistamine treatment . On April 19, 2018, the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Medication Guide (MG) for XOLAIR (omalizumab) for injection, for subcutaneous use.

This memorandum documents the DMPP review and concurrence with the Applicant's proposed MG for XOLAIR (omalizumab).

2 MATERIAL REVIEWED

- Draft XOLAIR (omalizumab) MG received on March 29, 2018, and received by DMPP on August 8, 2018.
- Draft XOLAIR (omalizumab) Prescribing Information (PI) received on March 29, 2018, revised by the Review Division throughout the review cycle, and received by DMPP on August 8, 2018.

3 CONCLUSIONS

We find the Applicant's proposed MG is acceptable as submitted.

4 RECOMMENDATIONS

- Consult DMPP regarding any additional revisions made to the Prescribing Information (PI) to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

KELLY D JACKSON
08/10/2018

MARCIA B WILLIAMS
08/10/2018

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	July 12, 2018
Requesting Office or Division:	Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Application Type and Number:	BLA 103976/S-5231
Product Name and Strength:	Xolair (omalizumab) Pre-filled Syringe 75 mg/0.5 mL 150 mg/mL
Product Type:	Combination Product
Rx or OTC:	Prescription
Applicant/Sponsor Name:	Genentech Inc.
FDA Received Date:	March 29, 2018
OSE RCM #:	2018-754
DMEPA Safety Evaluator:	Lissa C. Owens, PharmD
DMEPA Team Leader:	Sarah K. Vee, PharmD

1 REASON FOR REVIEW

This review responds to a request from the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) to review the proposed container label, carton labeling, medication guide, and prescribing information submitted on March 29, 2018, in an efficacy supplement (BLA 103976/S-5231) for Xolair. The Division requested that DMEPA review the proposed labeling for any vulnerability from a medication error perspective.

2 REGULATORY HISTORY

On December 20, 2016, the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) had a Type B meeting with the sponsor to provide feedback for a prefilled syringe formulation of omalizumab. Following the Type B meeting, DPARP requested that DMEPA respond to the potential need for a human factors study.

We reviewed the comprehensive use-related risk analysis and justification for why no human factors validation studies are needed that were submitted by the sponsor and determined that a human factors study was not needed[a].

3 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C-N/A
ISMP Newsletters	D-N/A
FDA Adverse Event Reporting System (FAERS)*	E-N/A
Other	F-N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

4 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Xolair (omalizumab) was approved on June 20, 2003 for the treatment of moderate to severe persistent asthma in patients 6 years of age and older with a positive skin test or in vitro reactivity to a perennial aeroallergen and symptoms that are inadequately controlled with

[a] Barlow, M. Comprehensive Use-Related Risk Analysis Memo for Xolair IND 7202. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 FEB 1. RCM No.: 2016-2982

inhaled corticosteroids. And on March 21, 2014, Xolair was approved for chronic idiopathic urticaria in adults and adolescents 12 years of age and older who remain symptomatic despite H1 antihistamine treatment.

Supplement 5231 is an efficacy supplement seeking marketing approval of omalizumab in liquid formulation in a prefilled syringe as a new presentation. In addition, this supplement seeks to add a 75 mg strength presentation in addition to the marketed 150 mg strength presentation. The single-dose prefilled syringe has been added to the dosage and administration section. We note that the dosing table has been modified to include a column for dose frequency which allows the combination of the 4 week dosing schedule with the two week dosing schedule into one table. In addition, the statement 'Do Not Dose' in the table has been replaced with the statement 'Insufficient Data to Recommend a Dose.'

Under the Administration section, a table (table 3) has been added: 'Number of Prefilled Syringes, Injections and Total Injection Volumes' and an additional section (section 2.4): 'Preparation for Use of XOLAIR Prefilled Syringe.' We note that this information is intended for medical or healthcare professionals only since Xolair should be administered by a healthcare provider. We note that the terms 'single-dose' and 'single-use' are both used in the labels and labeling. We make recommendations in section 5.1.

5 CONCLUSION & RECOMMENDATIONS

We reviewed the proposed container label, carton labeling, medication guide, and prescribing information, and determined that the labeling can be improved to increase the clarity of important information.

5.1 RECOMMENDATIONS FOR GENENTECH

We recommend the following be implemented at the time of next printing for the vial presentation.

A. Vial Container Label, Carton Labeling, and Prescribing Information

1. Replace 'single-use vial' with 'single-dose vial' to maintain consistency throughout the labeling.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Xolair received on March 29, 2018 from Genentech Inc.

Table 2. Relevant Product Information for Xolair	
Initial Approval Date	June 20, 2003
Active Ingredient	omalizumab
Indication	• Moderate to severe persistent asthma in patients 6 years of age and older with a positive skin test or in vitro reactivity to a perennial aeroallergen and symptoms that are inadequately controlled with inhaled corticosteroids. • Chronic idiopathic urticaria in adults and adolescents 12 years of age and older who remain symptomatic despite H1 antihistamine treatment.
Route of Administration	Subcutaneous
Dosage Form	**Current:** Single-use vial **Proposed addition:** Single-dose prefilled syringe
Strength	**Current:** 150 mg **Proposed addition:** 75 mg and 150 mg
Dose and Frequency	• Asthma: XOLAIR 75 to 375 mg SC every 2 or 4 weeks. Determine dose (mg) and dosing frequency by serum total IgE level (IU/mL), measured before the start of treatment, and body weight (kg). See the dose determination charts. • Chronic Idiopathic Urticaria: XOLAIR 150 or 300 mg SC every 4 weeks. Dosing in CIU is not dependent on serum IgE level or body weight
How Supplied	**Current:** lyophilized, sterile powder in a single use vial without preservatives. Each vial delivers 150 mg of Xolair upon reconstitution with 1.4 mL SWFI, USP. Each carton contains one single-use vial. **Proposed addition:** solution in a single-dose prefilled glass syringe with a 26 gauge staked needle, rigid needle cap, and needle shield. Each carton contains one prefilled syringe. 75 mg has a blue needle shield and 150 mg has a purple needle shield

Storage	Vial: Ship at controlled ambient temperature (≤30°C [≤86°F]). Store XOLAIR under refrigerated conditions 2°C to 8°C (36°F to 46°F). Pre-filled Syringe: Ship and store under refrigerated conditions 2°C to 8°C (36°F to 46°F). Take the carton containing the prefilled syringe out of the refrigerator and leave it unopened for about 15–30 minutes so that it reaches room temperature.
Container Closure	(b) (4)
	Pre-filled Syringe: Glass syringe barrel with staked needle where the needle is fixed to the syringe barrel with an adhesive, Rubber plunger stopper, Rigid needle shield (RNS) composed of a rubber needle shield covered by a rigid shield. The rubber needle shield (b) (4), whereas the rigid shield (b) (4) (b) (4)

APPENDIX B. PREVIOUS DMEPA REVIEWS

On July 6, 2018, we searched DMEPA's previous reviews using the terms, Xolair. Our search identified three previous reviews[bcd], and we confirmed that our previous recommendations were considered.

[b] Owens, L. Label and Labeling Review for Xolair BLA 103976. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2014 JAN 6. RCM No.: 2013-2097.

[c] Owens, L. Label and Labeling Review for Xolair BLA 103976. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 MAY 31. RCM No.: 2016-302.

[d] Barlow, M. Comprehensive Use-Related Risk Analysis Memo for Xolair IND 7202. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 FEB 1. RCM No.: 2016-2982.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[e] along with postmarket medication error data, we reviewed the following Xolair labels and labeling submitted by Genentech Inc.

- Container label received on March 29, 2018
- Carton labeling received on March 29, 2018
- Medication Guide (Image not shown) received on March 29, 2018
- Prescribing Information (Image not shown) received on March 29, 2018

G.2 Label and Labeling Images

Ring code labels are:

- Color labels that do not contain any graphics or text
- Affixed around the circumference of the syringe barrel as illustrated below
- Used to aid in visual identification of the drug dosage during packaging operations

[e] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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

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/s/

LISSA C OWENS
07/12/2018

SARAH K VEE
07/12/2018

CLINICAL FILING REVIEW AND CHECKLIST

NDA/BLA:	**BLA 103976, Supplement 5231**
Drug Name:	**Xolair (omalizumab)**
Applicant(s):	**Genentech and Novartis**
Stamp Date:	**March 29, 2018**
PDUFA Date:	**September 28, 2018 (Priority review clock)**
Review Date:	**May 7, 2018**

Introduction

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 omalizumab in a prefilled syringe (PFS). Xolair is recombinant DNA-derived humanized IgG1κ monoclonal antibody that selectively binds to human immunoglobulin E (anti-IgE) epsilon constant region. Xolair is currently provided as a sterile, preservative-free lyophilized powder in a vial for reconstitution prior to administration.

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 ("asthma"), 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. 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, with the dosage not dependent on serum IgE level or body weight. The applicants are seeking the same dosages, route of administration (SC), and indications for the new presentation as the approved product.

This new presentation 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 has a stamp date of March 29, 2018, and is all electronic in Common Technical Document format (eCTD) format. The applicants have requested a 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). The PSP and PREA waiver request were submitted to the supplement to the supplement on April 24, 2018.

Regulatory History

There is a very long regulatory history regarding the development of a liquid formulation of Xolair, dating back to 2004. At a meeting with 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 (omalizumab levels) and PD (i.e., effects on free/total IgE levels) of fresh (non-aged) liquid in a vial vs the approved reconstituted lyophilized product. The results showed consistency for omalizumab PK and PD between each of the products and dosages (150 and 300 mg). However, a low molecular weight fragment was identified by HPLC in 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 be

conducted 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 aged liquid formulation in vials and reconstituted lyophilized Xolair. There were two concerns. First, the Agency was concerned that the study did not use the to-be-marketed formulation in a PFS. Second, there was concern regarding the new peak that had been noted with the aged liquid in a vial, which was identified as (b) (4) [meeting minutes July 18, 2006]. This prompted the Agency to recommend additional studies. Several interactions with the Agency occurred between 2006 and 2008 to discuss the nature of the studies. The path that was agreed upon was 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 (omalizumab levels) and PD markers (free and total IgE), 2) assess whether there is any immunogenicity with chronic administration, and finally 3) demonstrate that the aged liquid has similar effects on a pharmacodynamic endpoint of clinical relevance. To satisfy the last request to compare aged liquid PFS vs reconstituted lyophilized product on an endpoint clinical relevance, four SPA protocol submissions were made before final agreement was reached on specifics of a clinical bronchoprovocation study (C4160).

After those discussions, there was a hiatus of interactions with the Agency until July of 2015. At that time, Genentech/Novartis submitted a briefing package discussing a potential resubmission of pediatric studies to support an extension of the asthma indication from ≥12 years to children 6 to 11 years of age. Along with that discussion, the applicants appended questions about the liquid PFS presentation. However, the information regarding the liquid formulation that was provided in the briefing package was not sufficient to allow meaningful responses. As a result, except for responding about whether an iPSP should be submitted to support a PFS supplement, the Agency requested submission of further data prior to responding further. In December of 2016, in a written response to a meeting request, the Agency noted that that Genentech/Novartis had performed a larger and more definitive PK/PD study (C2101) that now appeared to support bioequivalence between aged to-be-marketed liquid PFS product and reconstituted lyophilized Xolair, as well as a 6-month immunogenicity safety study (C2303) that showed that the new formulation was not immunogenic. Top line results of the bronchoprovocation study (C4160) were also submitted, and interestingly, 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 BE 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 [Figure 1b, section 3.2.P.1]. In response, the Division stated that this information was different than our previous understanding of the information that had been presented to and discussed with the Agency in 2006, and asked Novartis to clarify why, if this is so, a clinical development program with the two formulations (and the aged liquid), including a PK/PD, a safety/immunogenicity study, and a bronchoprovocation study, was deemed necessary to be performed. Initially, Novartis noted that these studies were done to support the shelf-life. The Division responded that it is the Agency's understanding that the clinical program was performed because of differences in the formulations, namely due to a peak in the aged liquid vial product that had been identified prior to 2007 and referenced in the responses and in previous meetings with the Agency. The Division stated that we would like to have a clear chronology and understanding of the product characterization studies and CMC data associated with this peak. Specifically, when the peak was originally identified, what subsequently changed, and whether there is a peak in the current to-be-marketed formulation. The Agency stated that this information must be submitted with the supplement. One additional pre-supplement meeting, primarily to discuss the content and format of the supplement, occurred in July 2017.

PFS vs Lyophilized Vial for Reconstitution

The current Xolair product is provided as a sterile, preservative-free, lyophilized powder in a single-use vial containing 150 mg of omalizumab ((b) (4)% concentration) for reconstitution with sterile water for injection (SWFI). 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 administer.

The new presentation is a sterile injection solution formulation of omalizumab in a prefilled syringe (PFS). It will be provided in two dosage strengths, 75 and 150 mg (75 mg per 0.5 mL and 150 mg per 1 mL), both with a concentration of 150 mg/mL (15% concentration). The final to-be-marketed formulation contains histidine (b) (4) L-arginine HCl, and polysorbate 20 (PS20) at a pH of 6.0 (see Table 1). The formulation differs from the current formulation in that it contains L-arginine but no sucrose, (b) (4) (b) (4). After reconstitution, however, the lyophilized presentation is at a concentration of 150 mg in 1.2 mL or 125 mg/mL.

The drug substance manufacturing site for both presentations is Novartis Pharma, in Huningue, France. The application states that this has been one of several commercial batch sites for the (b) (4)% lyophilized Xolair product since 2005, and has been the sole commercial batch site for the commercial batches of the (b) (4)% liquid PFS product since 2005 as well.

The changes to the drug substance manufacturing process involve changes to (b) (4) (b) (4) manufacturing process, other steps being the same. Omalizumab lyophilized powder drug substance is manufactured using the identical cell banks, raw materials, manufacturing process (cell culture and purification), and in-process control tests as omalizumab liquid, with the exception of (b) (4). At this step, the following changes are made (b) (4)

(b) (4)

Two comparability studies testing the chromatographic and electrophoretic profiles, and SE-HPLC, HI-HPLC, and IE-HPLC analyses, are said to have shown no differences in bulk substance batches for both omalizumab (b) (4)% and (b) (4)%, including no new peaks, with all samples showing the same general shape.

Table 1. Comparison of Formulations

Ingredient	Reconstituted Xolair 150 mg Lyophilate	Liquid PFS 75 mg/0.5 mL	Liquid PFS 150 mg/1 mL	Function
Omalizumab	150.0	75.0	150.0	Active
L-Arginine HCl	--	21.05	42.10	(b) (4)
Sucrose	108.0	--	--	
L-Histidine HCl	2.1	1.17	2.34	
L-Histidine	1.3	0.68	1.37	
Polysorbate 20	0.4	0.2	0.4	
SWFI	(b) (4)			
(b) (4)				
Total volume (mL)	1.2	0.5	1.0	

Source: M2, drug-product.pdf, T2.3P-2, p9; M3, P.2.2, pharmaceutical-development-dp.pdf, TP.2.2-1, p1

The liquid PFS presentation will be provided in a prefilled glass syringe with a 26g (b) (4) stainless steel staked needle. The device has a passive needle safety device and a rigid needle shield (which has components made from latex) (Figure 1). The plunger stopper is made from (b) (4) The passive needle safety device and plunger rod are 510k cleared medical devices manufactured by (b) (4) (b) (4)

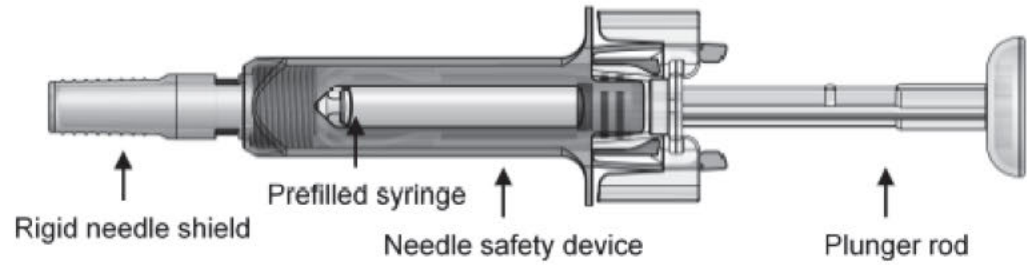


Figure 1.PFS Presentation
Source: M2, drug-product.pdf, F2.3P-1, p8

Physiochemical Characterization

Based on the primary stability data and additional stability studies, the applicants are proposing a shelf life of 18 months when stored at 2°C to 8°C. The main issue with regard shelf life is an increase in degradation products measured by HPLC compared to initial values that is seen at all storage conditions when compared with the approved lyophilized powder presentation. Photostability data also suggest that the drug product should be protected from light.

In response to the Teleconference of December 20, 2016, the applicants submitted an analysis of the physiochemical characterization of the liquid formulation aged in PFSs, evaluating whether the new formulation has any new SE-HPLC peaks when compared to lyophilized formulation. Not unexpectedly for a liquid formulation, the formation of degradation products as measured by hydrophobic-interaction high-performance liquid chromatography (HI-HPLC), ion-exchange HPLC (IE-HPLC), and size-exclusion HPLC (SE-HPLC), occurs faster for omalizumab when in a solution than in the approved Xolair lyophilized powder. The applicants state that the peaks that increased in the aged liquid PFS formulation are "due to sources of heterogeneity known to exist in the lyophilized formulation. Xolair degradation in PFSs proceeded along the same pathways as known in the lyophilized formulation, although there were increased levels of some known forms", including: (b) (4)

(b) (4)

(b) (4)

(b) (4)

Polysorbate 20, one of the excipients in both the new and the lyophilized formulations, can undergo degradation either by (b) (4) mechanism. While (b) (4) primarily forms (b) (4), among other degradation products such

(b) (4)

The reviews will evaluate the significance and extent of these issues.

Table 2. Xolair Drug Product Analytical Methods, Forms Detected, and Assessment of New Forms

Product Attribute Characterized and Method	Forms Detected	Assessment of New Forms
Size Heterogeneity: SE-HPLC (Q12389)	(b) (4)	Side-by-side profiles of four aged liquid formulation in PFS batches, lyophilized formulation batch, and liquid reference standard in full-scale and expanded views do not show any new forms.
Structural Heterogeneity: HI-HPLC (Q12374)		
Charge Heterogeneity: IE-HPLC (Q12435)		
Primary Sequence Confirmation: Peptide Map Using Endoproteinase Asp-N (Q12392)		Side-by-side profiles of four aged liquid formulation in PFS batches, lyophilized formulation batch, and liquid reference standard in full-scale view do not show any new peaks.

Abbreviations: HI = hydrophobic-interaction; HPLC = high-performance liquid chromatography; IE = ion-exchange; PFS = prefilled syringe; SE = size-exclusion.

Source: M3, P.2.2, pharmaceutical-development-dp.pdf, TP.2.2-14, p34

Bioequivalence and Other Studies

No efficacy trials were conducted. However, a number bioequivalence and other studies were performed to support the new liquid PFS presentation, as outlined chronologically by the date the study concluded in Table 3.

Of these studies, two are considered pivotal, studies C2101 and C2303. Both used the to-be-marketed liquid PFS product. The first was an open label, single-dose bioequivalence study, that compared the approved lyophilized product with aged and non-aged liquid PFS product, and the second was a 6-month open-label, single-arm study that evaluated the immunogenicity of aged liquid PFS. Details of the individual studies follow the table.

Table 3. Liquid PFS Clinical Development Program

Study	Design	N	Treatments	Endpoint or Results
Local excipient tolerability				
Q2569g (2002)	SB, 3-way crossover excipient safety study in healthy adults	36	Lyophilized excipient Liquid excipient Placebo	Similar pain and local 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	Bioequivalent 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 mo)	Differences noted in PK and PD effects on 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	Bioequivalent
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	Reliable antibody results in 106 subjects: No immunogenicity noted
Other studies				
Q4160g (2009)	16 week, R, DB, PC inhaled aeroallergen broncho-provocation study in adults with mild "allergic" asthma. Allergen challenge at 8 an 16 weeks.	61	Lyophilized (N=16) PFS, aged (N=23) Placebo (N=14)	1° outcome: Differences noted in change in log2-transformed allergen PC15 from baseline to Week 16
Studies are shown in chronological order with the year of completion shown. *Study numbers shown in **bold** font are considered by the applicants to be "pivotal" studies.				

Source: M2, summary-clin-pharm.pdf, T 2-1; M5, tabular-listing.pdf

Local Excipient Tolerability Study

Study Q2569g

This was a randomized, single-blind, three-way crossover study designed to evaluate pain and local irritation related to subcutaneous injection of the excipients in the liquid formulation of omalizumab compared with that of 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

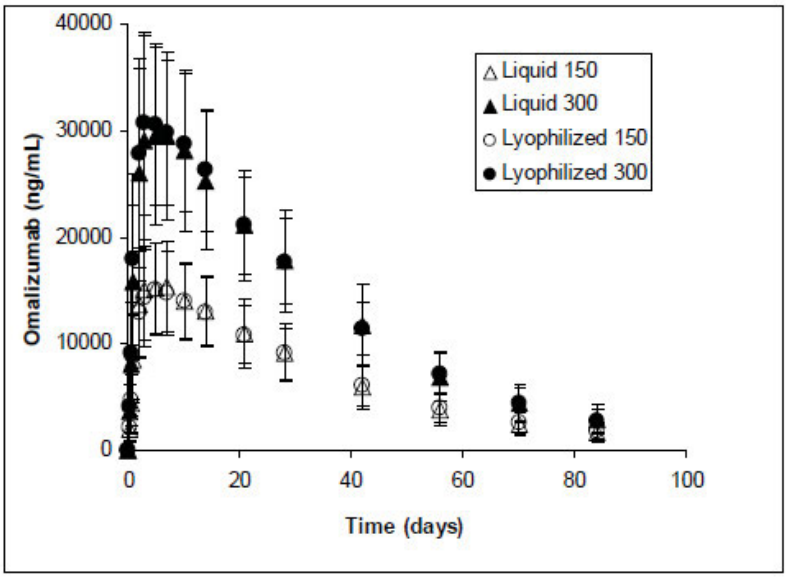
curve. The secondary outcome measure was the severity of burning, itching, warmth, redness, rate of hive formation, and size of injection-site reaction as assessed by the Local Injection-Site Symptom Assessment (LISSA). No meaningful differences in local reactions to the excipients in either formulation were noted.

Studies conducted with liquid omalizumab in a vial

Study A2204

This was an open-label, randomized, parallel group, single-dose bioequivalence study that compared the PK (serum omalizumab) and PD (free and total IgE) of fresh liquid omalizumab in vials with reconstituted lyophilized Xolair in atopic adults (18-65y) with mild to moderate allergic asthma and/or allergic rhinitis and an elevated serum IgE level. A total of 155 subjects were enrolled, and 154 completed the study. There were no SAEs, and no safety issues were noted.

As shown in Figure 2 and Table 4, the serum concentration-time profiles of omalizumab were similar at both dose levels. As shown in Figure 3 and Figure 4, serum free and total IgE levels were similar at both dose levels.



Mean (+/- SD) X-axis is nominal time

Figure 2. A2204. Mean omalizumab serum concentrations by formulation and dose

Source: M5, csr-a2204.pdf, p14

Table 4. A2404. Summary of analysis results for dose-normalized omalizumab PK parameters

Parameter	Treatment	N	Arithmetic mean (± SD)	Estimated Ratio of means	90% CI for ratio of means
AUC_{0-inf}/dose [(ng.d/mL)/mg]	Liquid Lyophilized	73 80	4256 (± 1252) 4303 (± 1127)	0.98	(0.91, 1.05)
$AUC_{0-tlast}$/dose [(ng.d/mL)/mg]	Liquid Lyophilized	73 80	3894 (± 1080) 3915 (± 961)	0.98	(0.92, 1.05)
C_{max}/dose [(ng/mL)/mg]	Liquid Lyophilized	73 80	109 (± 30) 107 (± 28)	1.01	(0.95, 1.08)

Source: M5, csr-a2204.pdf, p14

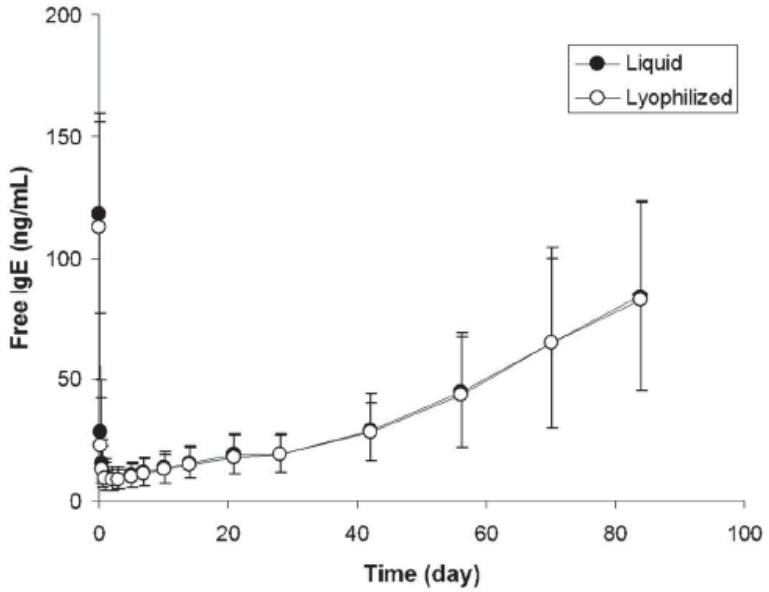


Figure 3. A2204. Arithmetic mean (plus/minus SD) free IgE serum concentrations by formulation
Source: M2, summary-clin-pharm.pdf, F3.2, p28

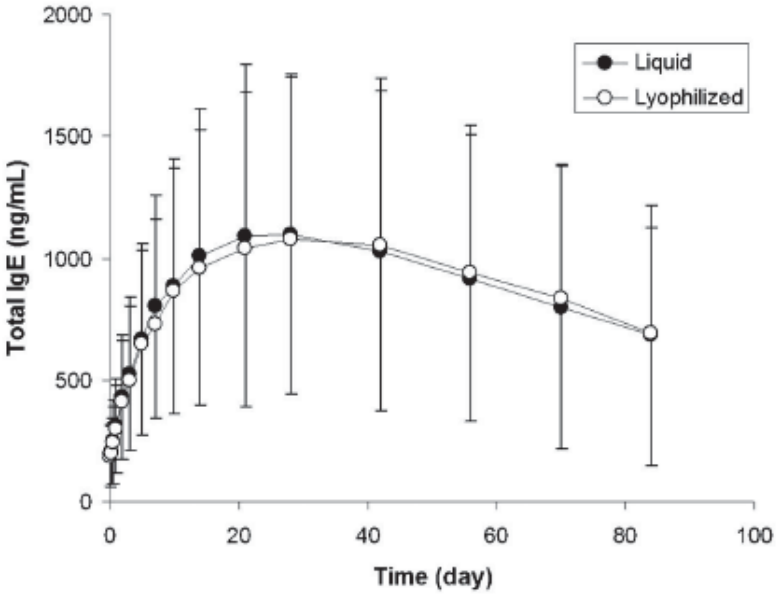


Figure 4. A2204. Arithmetic mean (plus/minus SD) total IgE serum concentrations by formulation
Source: M2, summary-clin-pharm.pdf, F3.4, p30

Study A2204E1

This was an open-label, randomized, parallel group, single-dose extension of bioequivalence study A2204. The study compared single doses of force-aged liquid omalizumab in a vial with reconstituted lyophilized Xolair on PK/PD parameters in atopic adults (18-65y) with mild to moderate allergic asthma and/or allergic rhinitis and an elevated serum IgE level. A total of 40 patients received either a dose of 150 mg or 300 mg depending on screening IgE levels and body

weight. There were no SAEs, and no safety issues were noted. The study was performed at 3 US sites between June 2005 and February 2006. Data from one of the study sites was lost because of Hurricane Katrina, and the site was replaced by a different site in San Diego. Site replacement was accompanied by an increase in the range of the age of the liquid studied from 23-26 months to 23-29 months.

As shown in Figure 5, the serum concentration-time profiles of omalizumab in the lyophilized vs the aged liquid in vials were not similar at either dose level, nor were the profiles similar for the aged liquid in vials when compared with previous results for the fresh liquid in vials from study A2204 (Figure 6). As shown in Figure 7 and Figure 8, comparison of serum free and total IgE levels in the fresh and aged liquid in vials were not similar at either dose level.

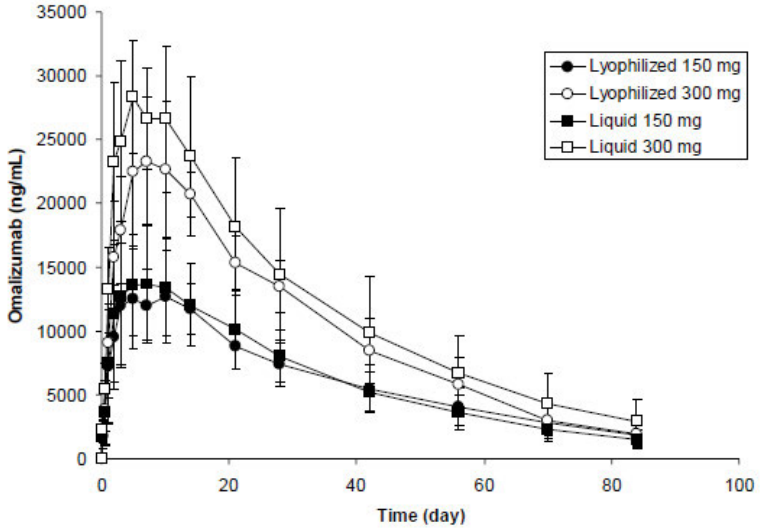


Figure 5. A2204E1. Mean omalizumab serum concentrations by formulation and dose – linear concentration scale

Source: M5, csr-a2204e1.pdf, F7-1, p38

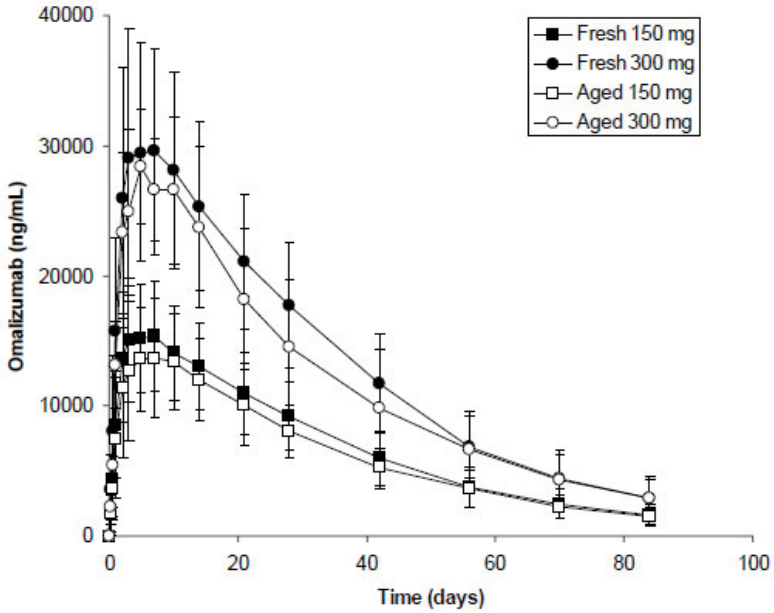


Figure 6. Mean omalizumab serum concentrations - cross-study comparison of fresh (A2204) vs aged (a2204E1) liquid in vials
Source: M5, csr-a2204e1.pdf, F7-4, p41

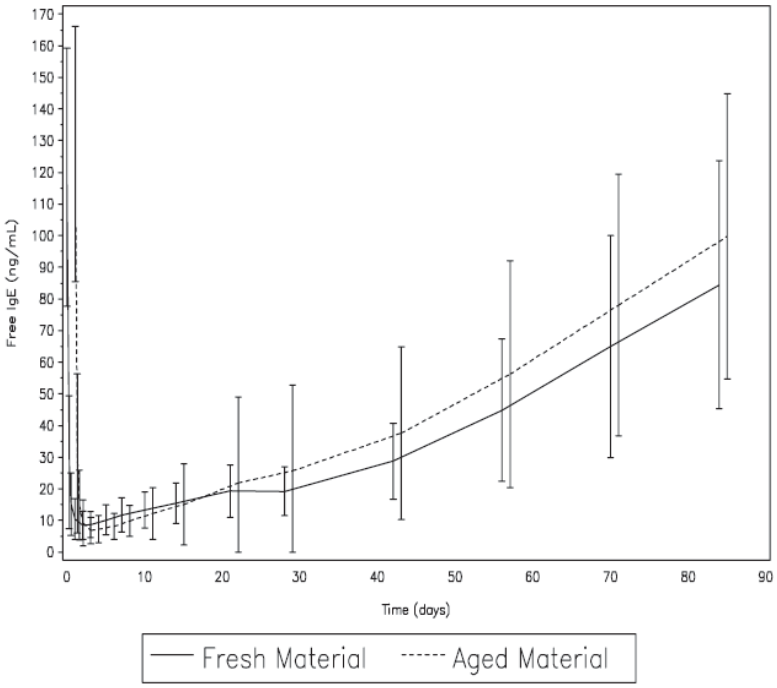


Figure 7. Mean free IgE (ng/mL) - cross-study comparison of fresh (A2204) vs aged (a2204E1) liquid in vials
Source: M5, csr-a2204e1.pdf, F7-7, p47

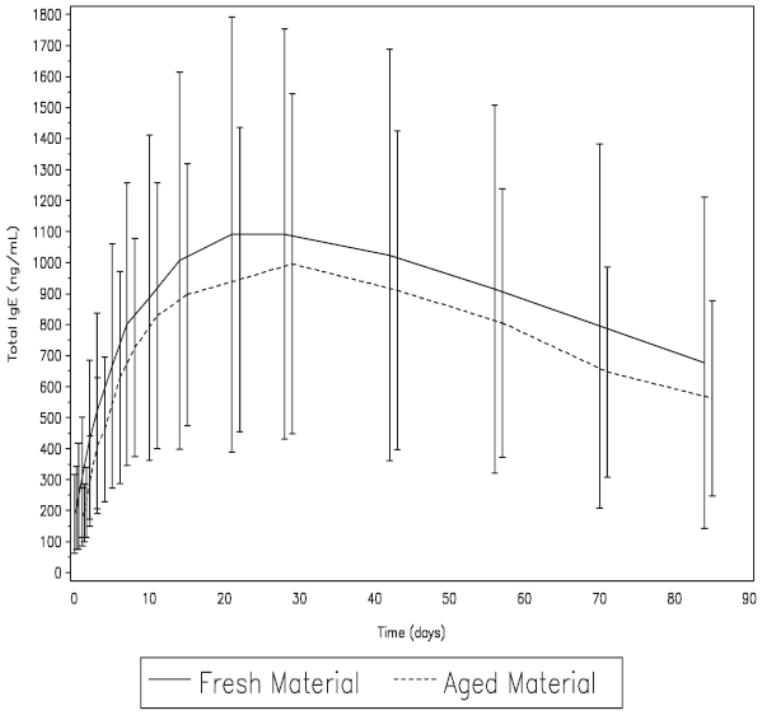


Figure 8. Total IgE (ng/mL) - cross-study comparison of fresh (A2204) vs aged (a2204E1) liquid in vials
Source: M5, csr-a2204e1.pdf, F7-8, p48

Pivotal studies conducted with the to-be-marketed liquid PFS formulation

Study C2101 (Pivotal)

This was an open-label, randomized, parallel group, single-dose bioequivalence study that compared serum omalizumab PK and the effects on PD (free and total IgE) of non-aged and aged liquid omalizumab in the PFS with reconstituted lyophilized Xolair in atopic adults with intermittent, mild persistent or moderate persistent asthma and/or allergic or perennial rhinitis and an elevated serum IgE level (30-300 IU/mL). No efficacy evaluations were performed. The study was conducted in the United States between July 2007 and June 2008.

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. Demographic and baseline characteristics of the treatment groups were similar. Seventy-nine subjects (43.9%) were male, 101 (56.1%) female, the majority (71%) were Caucasian, the average age was 38 (range: 18 – 65 years), and the mean weight was 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. There were no SAEs, and no safety issues were noted.

PK results are summarized in Table 5, and free and total IgE results are shown in Figure 9 and Figure 10, respectively. The confidence limits (CL) for both the dose normalized AUCinf and Cmax were within 0.8 to 1.25, the criteria set for bioequivalence. Free and total IgE concentration time profiles were similar for all three formulations. 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.

Table 5. 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

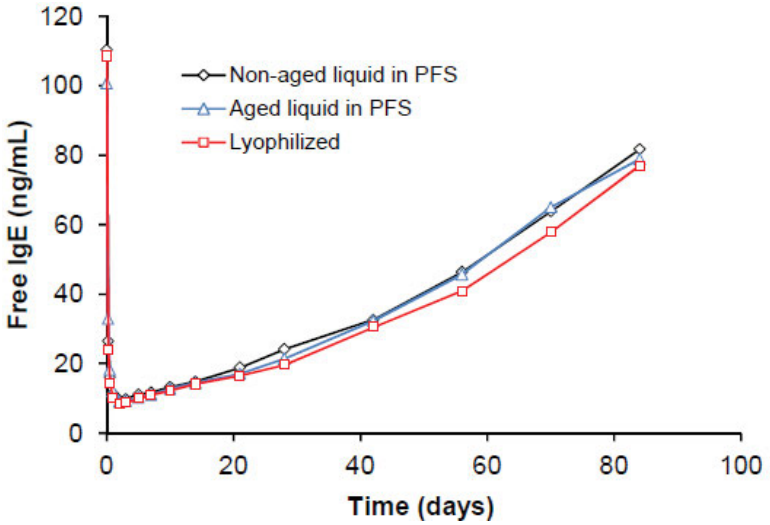


Figure 9. C2101. Arithmetic mean total IgE serum concentrations by formulation

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

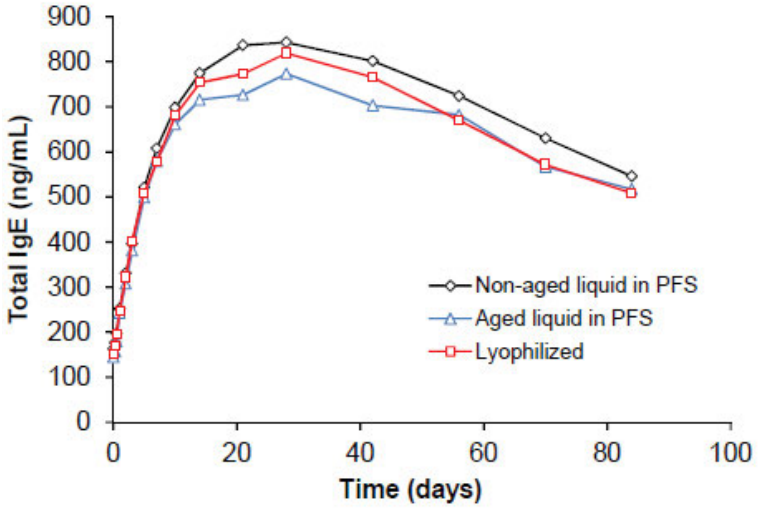


Figure 10. C2101. Arithmetic mean total IgE serum concentrations by formulation

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

Study C2303 (Pivotal)

At a meeting in 2006, because of concerns with differences noted between the aged liquid omalizumab material and reconstituted lyophilized Xolair, the Agency requested that the applicants evaluate the immunogenic potential of the aged to-be-marketed liquid PFS presentation. Study C2303, an immunogenicity safety study, was performed to address the Agency's concerns. The study was conducted in multiple centers in the United States and Europe between July 2007 and September 2008.

It was a six-month, open-label, single-arm study that assessed the immunogenic potential of thermally forced and naturally aged liquid omalizumab PFS. The population was 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 omalizumab. The dosage of omalizumab was selected based on baseline body weight and total IgE, administered every 2 or 4 weeks (same as the approved dosage tables) for 24 weeks, with 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). The study included aged liquid batches from omalizumab manufactured by Novartis in the US, Germany, and Spain, but not from the proposed French manufacturing site.

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 omalizumab (trough levels), free IgE, and total IgE were collected at the end of the treatment period just prior to administration of the last dose.

A total of 155 subjects were enrolled at 37 sites, of whom 140 (90.3%) completed 24 weeks of treatment. Of the 148 subjects who entered the follow-up period, 136 (91.9%) completed follow-up and received HAHA testing. Of these, what were considered to be reliable antibody results (i.e., having PK data and a conclusive antibody result with a corrected predicted omalizumab concentration below 10 μg/mL at the time of antibody assay) were obtained in 106 subjects.

Demographic and baseline disease characteristics include a mean age of 42.7 years, with 13 (8.4%) 12 to 17 years, 108 (69.7%) 18 to 54 years, 27 (17.4%) 55 to 64 years, and 7 (4.5%) ≥65 years. The majority were female (61.3%) and Caucasian (83.9%). The median duration of asthma was 14 years (range 1-70 years), and 10.3% were current smokers. Mean baseline serum IgE was 216.5 (SD 146.9, range 32 – 665) IU/mL.

Of the 136 subjects who completed follow-up and received HAHA testing, none had positive tests, either prior to or after treatment. In other words, no evidence of immunogenicity was found with the aged liquid PFS presentation, which is comparable with the historical results of immunogenicity testing performed during the original clinical trials conducted prior to approval of the lyophilized Xolair product. The PK/PD information confirmed that subjects had received omalizumab and that the active ingredient in the study (i.e., omalizumab) did exert its expected effect on IgE, which is important with regard to interpretation of the immunogenicity results.

During the treatment period, 4 subjects discontinued due to an adverse event, 14 experienced SAEs, there were two pregnancies, and there was one death, which occurred 26 days after the last treatment. The patient was a 60 year old male who died of respiratory and cardiac arrest

after experiencing a severe asthma exacerbation that was unresponsive to dexamethasone and a combination of ipratropium and salbutamol (Duoneb) in an acute care clinic. One additional SAE occurred during the follow-up period.

It should be noted that, while the immunogenicity results for this study are stand-alone and easily interpretable, comparative safety with the currently approved Xolair product is not directly possible because as a single arm, open-label study there was no comparator arm with the approved lyophilized product. Therefore, interpretation of the safety assessments, including adverse event reports in this study, is limited. That stated, review of the SAEs and adverse events in the study did not provide any pointers toward new safety issues.

Other Studies

Study Q4160

Study Q4160 (AQUA) was an allergen bronchoprovocation study that was performed in response to Agency's concerns with differences noted between the aged liquid omalizumab material and reconstituted lyophilized Xolair. At a meeting in 2006, the Agency requested that the applicants evaluate the aged to-be-marketed liquid omalizumab PFS presentation on a pharmacodynamic measure of clinical relevance, and the applicants selected bronchoprovocation testing as that measure. The applicants submitted the study protocol as a Special Protocol Assessment (SPA), and the Agency agreed in 2007 that the design of the study was generally adequate to generate supportive PD data for the liquid PFS presentation. 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 and placebo in reducing the airway reactivity to an inhaled allergen solution. The population was adults with mild allergic asthma. Although mild allergic asthma is not the indicated asthma population for omalizumab, this population was chosen because the study involved performance of bronchoprovocation testing. 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 omalizumab in a PFS (n=23), or placebo (n=14), of whom 58 completed the full 16 weeks of study treatment. Study drug was administered every 2 or 4 weeks depending on the subjects' screening weight and total IgE. 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 omalizumab 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 of the 58 subjects had pre-dose total IgE levels <30 IU/mL and therefore would not have qualified (as patients) for omalizumab treatment based on the approved dosing table, and these subjects were disproportionally represented in the aged liquid PFS arm.

There were no deaths and only two SAEs, one each in the Xolair and liquid PFS treatment groups, neither of which appeared related to treatment. Review showed no clinically meaningful between-group differences in treatment-emergent adverse events.

Results for the primary and secondary endpoint are shown in Table 6. Median increases in log 2-transformed allergen PC_{15} at Week 16 (primary endpoint) in subjects receiving Xolair, aged omalizumab 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.

On the basis of the primary and secondary results, this study was a failed study. The applicants argue that differences in baseline IgE levels adversely affected the results of the study. In a meeting in 2016, they presented data from CIU patients showing that baseline IgE did effect the results of clinical CIU endpoints. However, correcting for this by removing low IgE outliers in a post-hoc analysis did not resolve the issue, as the results still showed differences between the treatment groups. A relatively small sample size, variability in results, and lack of sensitivity of PC_{15} as a PD measure are more likely significant contributory reasons for failure of the study. Not only was the sample size likely too small, allergen challenge may also not be a sufficiently sensitive PD clinical measure to detect meaningful differences between formulations. In retrospect, the Agency's understanding of how to rule out differences between two formulations has progressed in the interim since this study was designed and conducted. For example, 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 as either a meaningful or as a pivotal study.

Table 6. Q4160. Primary and Secondary Endpoints (Modified ITT)

	Xolair (n = 22)	LIQ PFS (n = 23)	PBO (n = 13)	Xolair - PBO	LIQ - PBO	Xolair - LIQ PFS Difference (95% CI)
Primary Endpoint: Change in Allergen PC_{15} from Baseline to Week 16						
Median [a]	1.85	1.15	0.36	1.44	0.71	0.58 (-0.41, 1.63)
Range (min, max)	(-1.10, 3.50)	(-2.30, 4.03)	(-1.09, 3.09)			
p-value [b]				0.0133	0.13	
Secondary Endpoint: Ratio of FEV_1 Two-Point Slope at Week 16 over Baseline						
Median [a]	0.29	0.52	0.95	-0.52	-0.37	-0.15 (-0.43, 0.08)
Range (min, max)	(-0.26, 2.08)	(-0.009, 3.18)	(0.12, 2.20)			
p-value [b]				0.0028	0.09	

LIQ PFS= aged liquid omalizumab in PFS; PBO = placebo.
Note: Numbers transposed from tables in CSR, which show LIQ-LYO. LOCF for missing data.
a Hodges-Lehmann estimate of the median.
b p-value based on the exact Wilcoxon-Mann-Whitney test.

Source: M5, csr-q4160.pdf, T7, p50; T8, p51; T9, p54; T10, p55; T14.2/3.4, p106

Postmarketing Safety

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 applicants estimate that approximately 225,000 patient years of exposure is now available with this presentation. That said, 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 postmarketing 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 7. 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 7. 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 omalizumab	Drug specific antibody present (PT) Human anti-human antibody test (PT)
Churg Strauss Syndrome / Hypereosinophilic syndrome	Eosinophilic disorders (HLT) Vascular inflammations (HLGT)
Thrombocytopenia	Haematopoietic 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	

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

Pediatric Considerations

As submitted, the supplement did not contain a Pediatric Assessment, waiver request, or PSP for the new presentation. In a 2015 meeting package, the applicants noted that they planned to submit an iPSP to address the PREA requirements for the PFS formulation, and in Written Responses dated July 15, 2015, the Agency agreed. Novartis submitted an iPSP to IND 07202 for Xolair on June 9, 2017, requesting a waiver of studies for the liquid PFS presentation for both asthma and CIU and for all age groups not covered by their current indications (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. While the Agency agreed, we noted that we believed that the supplement would not trigger PREA because no changes are proposed to the active ingredients, indications, dosing regimen, or route of administration, and it was not believed that the product would be a considered to be a new dosage form because in both instances what the patient receives is an injection solution. Therefore, we informed Novartis that it would not be necessary to submit an iPSP with the supplement.

However, the liquid PFS presentation does in fact represent a new dosage form that will trigger PREA because the dosage form (as defined in the USP chapter on dosage forms) is defined as that which is approved in the commercial formulation, meaning that the change between a powder for injection and a solution in a PFS represents a new dosage form. Therefore, the previous determination that the supplement will not trigger PREA was not correct. To avoid a filing issue, the applicants were asked to resubmit the PSP to the supplement, and this was done on April 24, 2018. The supplement will be discussed at a Pediatric Review Committee (PeRC) that is scheduled for June 6, 2018.

Proposed Labeling

The proposed labeling includes new text in sections 2 (Dosage and Administration), 3 (Dosage Forms and Strengths), (b) (4), 11 (Description), and 16 (How Supplied). The changes to sections 3, 11, and 16 encompass addition of the new dosage form. In the D&A section (2), (b) (4)

Also, in the D&A section the applicants are proposing to combine the two adult/adolescent asthma dosing tables into one table – the dosing information in the combined table otherwise remaining the same except for one change (b) (4)

Discussion

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 omalizumab in a prefilled syringe (PFS). Xolair is currently provided as a sterile, preservative-free lyophilized powder in a vial for reconstitution prior to administration, which is viscid and takes about 20 minutes to prepare prior to administration.

The regulatory history for this supplement extends over 14 years, with multiple interactions between the companies and the Agency since 2004. In 2006, because a "new" peak was noted in the aged liquid formulation when compared with the approved reconstituted lyophilized product, i.e., a low molecular weight fragment that was identified by HPLC, and because the first bioequivalence study performed with aged liquid in a vial did not show bioequivalence, the Agency recommended that the applicants repeat the bioequivalence testing using the to-be-marketed liquid PFS presentation, as well as to conduct two additional studies: 1) a safety study evaluating the immunogenicity of the aged product, and 3) a pharmacodynamic study evaluating an endpoint of clinical relevance to patients. Those studies were conducted over the subsequent several years, although the companies waited until 2015 to again interact with the Agency about the results.

When the results of these studies were presented to the Agency in 2015, it was clear that study C2101 demonstrated bioequivalence between the to-be-marketed liquid FS product and the currently marketed lyophilized product on both PK (omalizumab) and on PD (free and total IgE) measures, and the immunogenicity study (C2303) demonstrated that the liquid PFS aged to the end of shelf life was not immunogenic. However, results in the pharmacodynamic study (Q4160) did not align between the current and proposed Xolair presentations, with the currently marked Xolair product outperforming the proposed aged liquid PFS product on a test of prevention of bronchospasm (PC_{15}) over a 16-week treatment period. Regardless, the Agency is not considering study Q4160 as either a meaningful or a pivotal study. Rather, the application depends upon the results of the pivotal bioequivalence study (C2101), the immunogenicity study (C2404), and the comparison of the physiochemical differences between the two products.

The applicants now argue that the "new" peak noted originally in 2004 is in fact not new, but rather, is similar to peaks found with the lyophilized product, with the exception that the liquid product develops those peaks earlier in the ageing process than the lyophilized product. However, other physiochemical differences are introduced by use of a liquid prefilled into a syringe, including other degradation products, visible and nonvisible particles, etc., which must be carefully evaluated. Since study C2101 demonstrated bioequivalence between the two products and study C2404 demonstrated that the new presentation is not immunogenic, approval of this application will rely almost entirely on the Agency's assessment of those physiochemical differences.

Fileability Determination

The application is fileable from a clinical perspective. See the checklist below.

Potential review issues and 74-day letter comments

No clinical review issues or 74-day comments.

Clinical Filing Checklist

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic common technical document (eCTD).	X			eCTD
2.	Is the clinical section legible and organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
LABELING					
6.	Has the applicant submitted a draft prescribing information that appears to be consistent with the Physician Labeling Rule (PLR) regulations and guidances (see http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm	X			
SUMMARIES					
7.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
8.	Has the applicant submitted the integrated summary of safety (ISS)?			X	While no ISS was submitted, in a teleconference dated July 13, 2017, the Agency stated

	Content Parameter	Yes	No	NA	Comment
					that the sponsor's proposed Summary of Clinical Safety would be sufficiently comprehensive that it would not be necessary to submit a separate ISE, SCE, and ISS.
9.	Has the applicant submitted the integrated summary of efficacy (ISE)?			X	See 8 above.
10.	Has the applicant submitted a benefit-risk analysis for the product?	X			The Clinical Overview in Module 2 presents a benefit-risk summary.
11.	Indicate if the Application is a 505(b)(1) or a 505(b)(2).			X	351(a)
505(b)(2) Applications					
12.	If appropriate, what is the relied upon listed drug(s)?			X	
13.	Did the applicant provide a scientific bridge demonstrating the relationship between the proposed product and the listed drug(s)/published literature?			X	
14.	Describe the scientific bridge (e.g., BA/BE studies)			X	
DOSAGE					
15.	If needed, has the applicant made an appropriate attempt to determine the correct dosage regimen for this product (e.g., appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Treatment Arms: Location in submission:				The applicants did not explore dose ranging. The dosage regimen proposed for the PFS formulation is the same as that for the reconstituted lyophilized formulation.
EFFICACY					
16.	Do there appear to be the requisite number of adequate and well-controlled studies in the application?			X	No efficacy studies were conducted.
17.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?			X	
18.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.			X	
19.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S.			X	

	Content Parameter	Yes	No	NA	Comment
	population/practice of medicine in the submission?				
SAFETY					
20.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
21.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			X	
22.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
23.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dosage (or dosage range) believed to be efficacious?	X			
24.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
25.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	X			
26.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
27.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
28.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
29.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

	Content Parameter	Yes	No	NA	Comment
PEDIATRIC USE					
30.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			See Pediatric Considerations section
PREGNANCY, LACTATION, AND FEMALES AND MALES OF REPRODUCTIVE POTENTIAL USE					
31.	For applications with labeling required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, has the applicant submitted a review of the available information regarding use in pregnant, lactating women, and females and males of reproductive potential (e.g., published literature, pharmacovigilance database, pregnancy registry) in Module 1 (see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307 htm)?	X			
ABUSE LIABILITY					
32.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
33.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
DATASETS					
34.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
35.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
36.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?			X	Datasets for the completed studies were submitted. There are no pivotal efficacy studies.
37.	Are all datasets to support the critical safety analyses available and complete?	X			
38.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
39.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
40.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			

	Content Parameter	Yes	No	NA	Comment
FINANCIAL DISCLOSURE					
41.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
42.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

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

/s/

PETER R STARKE
05/07/2018

SALLY M SEYMOUR
05/07/2018