14 September 2023
EMA/CHMP/443507/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Xolair

International non-proprietary name: omalizumab

Procedure No. EMEA/H/C/000606/X/0115/G

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Administrative information

Name of the medicinal product:	Xolair
MAH:	Novartis Europharm Limited Vista Building Elm Park Merrion Road Dublin 4 IRELAND
Active substance:	Omalizumab
International Non-proprietary Name/Common Name:	omalizumab
Pharmaco-therapeutic group (ATC Code):	other systemic drugs for obstructive airway diseases (R03DX05)
Therapeutic indication(s):	Allergic asthma Xolair is indicated in adults, adolescents and children (6 to <12 years of age). Xolair treatment should only be considered for patients with convincing IgE (immunoglobulin E) mediated asthma (see section 4.2). *Adults and adolescents (12 years of age and older)* Xolair is indicated as add-on therapy to improve asthma control in patients with severe persistent allergic asthma who have a positive skin test or in vitro reactivity to a perennial aeroallergen and who have reduced lung function (FEV1 <80%) as well as frequent daytime symptoms or night-time awakenings and who have had multiple documented severe asthma exacerbations despite daily high-dose inhaled corticosteroids, plus a long-acting inhaled beta2-agonist. *Children (6 to <12 years of age)* Xolair is indicated as add-on therapy to improve asthma control in patients with severe persistent allergic asthma who have a positive skin test or in vitro reactivity to a perennial aeroallergen and frequent daytime symptoms or night-time awakenings and who

	have had multiple documented severe asthma exacerbations despite daily high-dose inhaled corticosteroids, plus a long-acting inhaled beta2-agonist. <u>Chronic rhinosinusitis with nasal polyps (CRSwNP)</u> Xolair is indicated as an add-on therapy with intranasal corticosteroids (INC) for the treatment of adults (18 years and above) with severe CRSwNP for whom therapy with INC does not provide adequate disease control. <u>Chronic spontaneous urticaria (CSU)</u> Xolair is indicated as add-on therapy for the treatment of chronic spontaneous urticaria in adult and adolescent (12 years and above) patients with inadequate response to H1 antihistamine treatment.
Pharmaceutical form(s):	Solution for injection
Strength(s):	75 mg, 150 mg and 300 mg
Route(s) of administration:	Subcutaneous use
Packaging:	pre-filled syringe (glass), pre-filled syringe (glass) in pre-filled pen, pre-filled syringe (glass) with 27-gauge staked needle and syringe (glass) in pre-filled pen
Package size(s):	*75 mg*: 1 pre-filled syringe, 4 (4 x 1) pre-filled syringes (multipack) 10 (10 x 1) pre-filled syringes (multipack), 1 pre-filled syringe with 27-gauge staked needle, 3 (3 x 1) pre-filled syringes with 27-gauge staked needle (multipack), 6 (6 x 1) pre-filled syringes with 27-gauge staked needle (multipack) 1 pre-filled pen, 3 (3 x 1) pre-filled pens (multipack), 6 (6 x 1) pre-filled pens (multipack) *150 mg:* 1 pre-filled syringe, 4 (4 x 1) pre-filled syringes (multipack) 10 (10 x 1) pre-filled syringes (multipack), 6 (6 x 1) pre-filled syringes (multipack)

	1 pre-filled syringe with 27-gauge staked needle, 3 (3 x 1) pre-filled syringes with 27-gauge staked needle (multipack), 6 (6 x 1) pre-filled syringes with 27-gauge staked needle (multipack) 1 pre-filled pen, 3 (3 x 1) pre-filled pens (multipack), 6 (6 x 1) pre-filled pens (multipack) *300 mg:* 1 pre-filled syringe with 27-gauge staked needle, 3 (3 x 1) pre-filled syringes with 27-gauge staked needle (multipack), 6 (6 x 1) pre-filled syringes with 27-gauge staked needle (multipack) 1 pre-filled pen, 3 (3 x 1) pre-filled pens (multipack), 6 (6 x 1) pre-filled pens (multipack)

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List of abbreviations

AA	Allergic Asthma
ADA	Anti-drug antibody
AE	Adverse event
AI	Autoinjector
AOA	Anti omalizumab antibody
AQL	Acceptable quality limit
AUCinf	Area under the concentration-time curve from time zero to infinity
AUClast	Area under the concentration-time curve from time zero to the last measurable concentration sampling time
BE	Bioequivalence
CCIT	Container closure integrity test
Cmax	Maximum (peak) observed drug concentration after single dose administration
CQA	Critical Quality Attribute
CRSwNP	Chronic rhino sinusitis with nasal polyps
CSU	Chronic spontaneous urticaria
DQA	Device quality attributes
ELISA	Enzyme linked immunosorbent assay
EPR	Essential performance requirements
HIC	Hydrophobic Interaction Chromatography
HLT	High level term
IEC	Ion Exchange Chromatography
IFU	Instructions for use
IgE	Human immunoglobulin E
IPC	In Process Control
MAH	Marketing authorisation holder
MO	Major objection
OC	Other concern
PFP	pre-filled pen
PFS	pre-filled syringe
PFS-AI	Pre-filled syringe assembled into an (autoinjector/pre-filled pen)

PFS-NSD	pre-filled syringe with needle safety device
PK	pharmacokinetic
Ph. Eur.	European Pharmacopeia
QTPP	Quality target product profile
RNS	Rigid needle shield
SAL	Sterility assurance level
SC	Subcutaneous
SEC	Size Exclusion Chromatography
TEAE	Treatment emergent adverse event

1. Background information on the procedure

1.1. Submission of the dossier

Novartis Europharm Limited submitted on 28 July 2022 a group of variation(s) consisting of an extension of the marketing authorisation and the following variation(s):

Variation(s) requested		**Type**
B.II.b.1.c	B.II.b.1.c - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch release/control, and secondary packaging, for biol/immunol medicinal products or pharmaceutical forms manufactured by complex manufacturing processes	II
B.II.b.1.a	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	IAin
B.II.b.2.c.1	B.II.b.2.c.1 - Change to importer, batch release arrangements and quality control testing of the FP - Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing	IAin
B.II.e.1.b.2	B.II.e.1.b.2 - Change in immediate packaging of the finished product - Change in type/addition of a new container - Sterile medicinal products and biological/immunological medicinal products	II
B.II.e.1.b.2	B.II.e.1.b.2 - Change in immediate packaging of the finished product - Change in type/addition of a new container - Sterile medicinal products and biological/immunological medicinal products	II
B.II.e.5.a.1	B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes	IAin
B.II.e.5.a.1	B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes	IAin
B.II.e.5.a.1	B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes	IAin
B.II.e.5.a.1	B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes	IAin
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B.II.e.5.a.1	B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes	IAin
B.II.e.5.a.1	B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change	IAin

Variation(s) requested		Type
	within the range of the currently approved pack sizes	
B.II.e.5.a.1	B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes	IAin
B.IV.z	B.IV.z - Quality change - Change in Medical Devices - Other variation	IB
B.IV.z	B.IV.z - Quality change - Change in Medical Devices - Other variation	IB

Extension application to add a new strength of 300 mg (150 mg/ml) for Xolair solution for injection grouped with quality type II, IB and IAIN variations. The RMP (version 17.0) is updated in accordance.
In addition, the applicant took the opportunity to amend the already authorised pre-filled syringe presentations (005-011) to include an alternative immediate packaging pre-filled syringe (glass) with a 27 gauge staked needle in addition to the existing (pre-filled syringe (glass) with 26 gauge staked needle).

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 7.2 of Commission Regulation (EC) No 1234/2008 – Group of variations

1.3. Information on Paediatric requirements

Not applicable

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.5. Scientific advice

The MAH received Scientific Advice on the development of omalizumab (Xolair) for treatment of allergic asthma and chronic spontaneous urticaria from the CHMP on 28 May 2020 (EMEA/H/SA/45/6/2020/III). The Scientific Advice pertained to the following quality and clinical aspects:

- The proposed bracketing and reduced-testing approach to support registration of the new Xolair combination product configurations. Approach to demonstrate comparability between the current and proposed combination product configurations, and the basis for shelf-life assignment. Adequacy of the process validation program to qualify commercial manufacturing.

- Adequacy of the proposed bioequivalence (BE) study design including sample size and statistical analysis methods. Sufficiency to demonstrate BE for the 300 mg dose to support the approval of the proposed PFS-NSD with 75 and 150 mg doses, and proposed PFS-AI with 75 mg and 150 mg doses.

1.6. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Kristina Dunder Co-Rapporteur: N/A

CHMP Peer reviewer(s): N/A

The Rapporteur appointed by the PRAC was:

PRAC Rapporteur: Mari Thorn

The application was received by the EMA on	28 July 2022
The procedure started on	18 August 2022
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	8 November 2022
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	8 November 2022
The CHMP agreed on the consolidated List of Questions to be sent to the MAH during the meeting on	15 December 2022
The MAH submitted the responses to the CHMP consolidated List of Questions on	20 April 2023
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	23 May 2023
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	8 June 2023
The CHMP agreed on a list of outstanding issues <in writing and/or in an oral explanation> to be sent to the MAH on	22 June 2023
The MAH submitted the responses to the CHMP List of Outstanding Issues on	10 August 2023
The CHMP Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	30 August 2023
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Xolair on	14 September 2023

2. Scientific discussion

2.1. Problem statement

Xolair is currently available in two formulations, powder and solvent for solution for injection and solution for injection in pre-filled syringe with needle safety device (PFS-NSD), each formulation with 75 mg and 150 mg. This line extension application is for the registration of a new strength of 300 mg per 2 ml for Xolair solution for injection grouped with several Type I and Type II quality variations to introduce a pre-filled pen (PFP) and a new pre-filled syringe with a needle safety device (PFS-NSD).

Six new configurations will be registered for Xolair, 75 mg, 150 mg and 300 mg each in a new pre-filled syringe either assembled in a needle safety device (PFD-NSD) or in an autoinjector (PFS-AI)/pre-filled pen. The new PFS-NSD will be registered in addition to the currently approved PFS-NSD for 75 and 150 mg.

The proposed clinical use for the new strength will be for the same indications which are currently approved. The aim of this new strength is to reduce the number of injections for patients.

2.1.1. Disease or condition

Remains unchanged since no new clinical indication is claimed.

2.1.2. Epidemiology

Remains unchanged since no new clinical indication is claimed.

2.1.3. Clinical presentation, diagnosis

Remains unchanged since no new clinical indication is claimed.

2.1.4. Management

Remains unchanged since no new clinical indication is claimed.

2.2. About the product

Omalizumab (Xolair) is a recombinant DNA-derived humanised IgG1 monoclonal antibody that selectively binds to human immunoglobulin E (IgE). Omalizumab inhibits the binding of circulating 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 and results in improved control of symptoms. Omalizumab is approved in the following indications: allergic asthma (AA), chronic spontaneous urticaria (CSU), and chronic rhinosinusitis with nasal polyps (CRSwNP).

With this extension application the MAH applies for the registration of a new strength of 300 mg for Xolair solution for injection (in pre-filled syringe/pre-filled pen) grouped with several Type I and Type II quality variations to introduce a pre-filled pen (PFP) and a new pre-filled syringe with needle safety device (PFS-NSD) and related quality changes. This means that six new presentations for Xolair solution for injection are

introduced; pre-filled syringe assembled in a new needle-safety device (PFS-NSD) or autoinjector (PFS-AI) for all 3 strengths (75mg/0.5mL, 150mg/1.0mL, 300mg/2.0mL).

This line extension does not change the mode of action, pharmacological classification, indication and recommendation for use.

2.3. Type of Application and aspects on development

EMA scientific advice (EMEA/H/SA/45/6/2020/III) was provided on 28 May 2020 (see section 1.5).

2.4. Quality aspects

2.4.1. Introduction

Xolair is currently available in two formulations, both in two strengths:

- Powder and solvent for solution for injection: 75 mg and 150 mg.
- Solution for injection in a pre-filled syringe (PFS) with needle safety device (PFS) 26-gauge staked needle: 75 mg and 150 mg.

In this Line Extension application a new strength of 300 mg presented both as pre-filled syringe and pre-filled pen is introduced. In addition, the introduction of a pre-filled pen and a new additional pre-filled syringe for the strengths 75 and 150 mg is applied for, which altogether results in six new finished product presentations intended to be used in all approved Xolair indications:

- A new PFS-NSD with 27-gauge staked needle for 75 mg, 150 mg and the new strength of 300 mg solution for injection.
- A new prefilled syringe in autoinjector (PFS-AI)/pre-filled pen for 75 mg, 150 mg and the new strength of 300 mg solution for injection

The new PFS-NSD is registered in addition to the currently approved PFS-NSD for the strengths 75 and 150 mg. In the mid-term the new configurations will replace the current PFS-NSD. Until then, both configurations will coexist on the market during a transition period only.

The finished product is presented as solution for injection in pre-filled syringe or pre-filled pen containing 75 mg, 150 mg and 300 mg of omalizumab as active substance.

Other ingredients are; L-Arginine hydrochloride, L-Histidine hydrochloride monohydrate, L-Histidine, Polysorbate 20 and water for injection.

The product is available in pre-filled syringes and pre-filled pens as described in section 6.5 of the SmPC.

This extension application for the registration of a new strength of 300 mg/2 ml for Xolair (omalizumab) solution for injection (in pre-filled syringe/pre-filled pen) is grouped with several Type I and Type II quality variations to introduce a pre-filled pen (PFP) and a new pre-filled syringe with needle safety device (PFS-NSD) and related quality changes. The Type I and Type II quality variations applied for in parallel to the line extension were assessed together with the extension application.

The line extension application together with the grouped variations result in six new drug-device combination product configurations for Xolair Solution for injection. The six new product configurations are a pre-filled syringe assembled in a Needle-safety device or pre-filled pen (autoinjector) for all 3 strengths (75 mg / 0.5 mL, 150 mg/ 1.0mL, 300 mg/ 2.0 mL).

A list of the variations applied for is presented below.

Site additions

Variation 1 - B.II.B.1.c (Type II)

- to add a new site responsible for manufacture and primary packaging of the newly added finished product presentations Xolair solution for injection 75 mg/0.5 mL, 150 mg/1.0 mL and 300 mg/2.0 mL.

The new site will only produce the newly added presentations for Xolair 75mg /0.5mL and 150mg/1.0mL solution for injection as described below and Xolair 300mg/2.0mL solution for injection as per Line Extension/Variation application. The new site is already approved as secondary packaging and quality control site for the current product and is also applicable for the newly developed presentations.

These new alternative presentations of pre-filled syringe as well as the manufacturing process slightly differ to the currently approved presentations as further discussed below in the report.

Also that the manufacture of the currently approved presentations 75 mg/0.5 mL, 150 mg/1.0 mL at remains unchanged. It is also noted that the already approved quality control site for the current product and is also applicable for the newly developed presentations. The manufacturing set-up for the currently approved products remain unchanged.

A new 3.2.P.3.1 module is provided including the sites applicable for the new presentations manufactured at the new site.

This type II variation was assessed together with the extension application of the new strength and taking into account the information provided and discussed further in this report is approvable.

Variation 2 - B.II.b.1.a (Type IA(IN))

- to add an additional alternative secondary packaging site for the newly added finished product presentations Xolair solution for injection 75 mg/0.5 mL, 150 mg/1.0 mL and 300 mg/2.0 mL.

This variation is related to the Line Extension and therefore was assessed together with the extension application and is concluded to be approvable.

Note: The already approved as secondary packaging site and is also applicable for the newly developed presentations.

Variation 3 - B.II.b.2.c.1 (Type IA(IN))

- to add an alternative site responsible for batch release for the newly added finished product presentations Xolair solution for injection 75 mg/0.5 mL, 150 mg/1.0 mL and 300 mg/2.0 mL.

This variation is related to the Line Extension and therefore was assessed together with the extension application and is concluded to be approvable.

Note: Novartis Pharma GmbH, Nürnberg, Germany is already approved as batch release site for the current product and is also applicable for the newly developed presentations.

New 27 gauge staked needle

Variation 4 - B.II.e.1.b.2 (Type II)

- to add an alternative immediate packaging pre-filled syringe (glass) with a 27 gauge staked needle for Xolair solution for injection 75 mg/ 0.5mL

This variation is related to the Line Extension and therefore was assessed together with the extension application. Taking into account the information provided and discussed further in this report it is approvable.

Variation 5 - B.II.e.1.b.2 (Type II)

- to add an alternative immediate packaging pre-filled syringe (glass) with a 27 gauge staked needle for Xolair solution for injection 150 mg/1.0 mL

This variation is related to the Line Extension and therefore was assessed together with the extension application. Taking into account the information provided and discussed further in this report it is approvable.

Packaging configurations

Variation 6 - B.II.e.5.a.1 (Type IA(IN))

- to add a new pack-size of 3 (3 x 1) pre-filled syringes (multipack) in pre-filled syringe (glass) with a 27 gauge staked needle for Xolair solution for injection 75 mg.

This variation is related to the Line Extension and therefore was assessed together with the extension application and is concluded to be approvable.

Variation 7 - B.II.e.5.a.1 (Type IA(IN))

- to add a new pack-size of 6 (6 x 1) pre-filled syringes (multipack) in pre-filled syringe (glass) with a 27 gauge staked needle for Xolair solution for injection 75 mg.

This variation is related to the Line Extension and therefore was assessed together with the extension application and is concluded to be approvable.

Variation 8 - B.II.e.5.a.1 (Type IA(IN))

- to add a new pack-size of 3 (3 x 1) pre-filled syringes (multipack) in syringe (glass) in pre-filled pen for Xolair solution for injection 75 mg.

This variation is related to the Line Extension and therefore was assessed together with the extension application and is concluded to be approvable.

Variation 9 - B.II.e.5.a.1 (Type IA(IN))

- to add a new pack-size of 6 (6 x 1) pre-filled syringes (multipack) in syringe (glass) in pre-filled pen for Xolair solution for injection 75 mg.

This variation is related to the Line Extension and therefore was assessed together with the extension application and is concluded to be approvable.

Variation 10 - B.II.e.5.a.1 (Type IA(IN))

- to add a new pack-size of 3 (3 x 1) pre-filled syringes (multipack) in pre-filled syringe (glass) with a 27 gauge staked needle for Xolair solution for injection 150 mg.

This variation is related to the Line Extension and therefore was assessed together with the extension application and is concluded to be approvable.

Variation 11 - B.II.e.5.a.1 (Type IA(IN))

- to add a new pack-size of 6 (6 x 1) pre-filled syringes (multipack) in pre-filled syringe (glass) with a 27 gauge staked needle for Xolair solution for injection 150 mg.

This variation is related to the Line Extension and therefore was assessed together with the extension application and is concluded to be approvable.

Variation 12 - B.II.e.5.a.1 (Type IA(IN))

- to add a new pack-size of 3 (3 x 1) pre-filled syringes (multipack) in syringe (glass) in pre-filled pen for Xolair solution for injection 150 mg (EU/1/05/319/xxx).

This variation is related to the Line Extension and therefore was assessed together with the extension application and is concluded to be approvable.

Variation 13 - B.II.e.5.a.1 (Type IA(IN))

- to add a new pack-size of 6 (6 x 1) pre-filled syringes (multipack) in syringe (glass) in pre-filled pen for Xolair solution for injection 150 mg (EU/1/05/319/xxx).

This variation is related to the Line Extension and therefore was assessed together with the extension application and is concluded to be approvable.

Devices

Variation 14 - B.IV.1.z (Type IB)

- to add a new needle safety device (not an integrated part of the primary packaging, no CE marking) for Xolair 75mg/0.5mL and 150mg/1.0mL strengths.

The new needle safety device from is the same for both strengths and ensures compatibility with the proposed primary packaging material. The needle safety device for the current product manufactured at the approved site remains unchanged. A notified body opinion is already applied for and has been provided with the D120 questions.

It is also noted that needle safety device for the current product manufactured at the approved site remains unchanged.

This variation is related to the Line Extension and therefore was assessed together with the extension application and is concluded to be approvable.

Variation 15 - B.IV.1.z (Type IB)

- to add a new auto-injector (AI) device (not integrated part of the primary packaging, no CE marking) for Xolair 75mg/0.5mL and 150mg/1.0mL strengths manufactured.

The autoinjector is identical for both strengths, except for the larger viewing window for the 150mg/1.0mL strength. A notified body opinion has been provided with the D120 questions.

This variation is related to the Line Extension and therefore was assessed together with the extension application and is concluded to be approvable.

2.4.2. Active Substance

Omalizumab is a recombinant DNA-derived humanized IgG1 monoclonal antibody that selectively binds to human immunoglobulin E (IgE).

The already approved 3.2.S section for the active substance (AS) omalizumab (15%) remains unchanged and is also applicable for the new finished product strength and presentations.

As there is no change in the active substance and the finished product is based on a fully formulated active substance, there is also no change to the formulation and its excipients.

The active substance omalizumab is already approved for the currently approved Xolair presentations. No changes to the information related to omalizumab are proposed.

2.4.3. Finished Medicinal Product

2.4.3.1. Description of the product and pharmaceutical development

Xolair solution for injection is a sterile, single use, preservative-free, clear to slightly opalescent, colourless to pale brownish-yellow solution for injection.

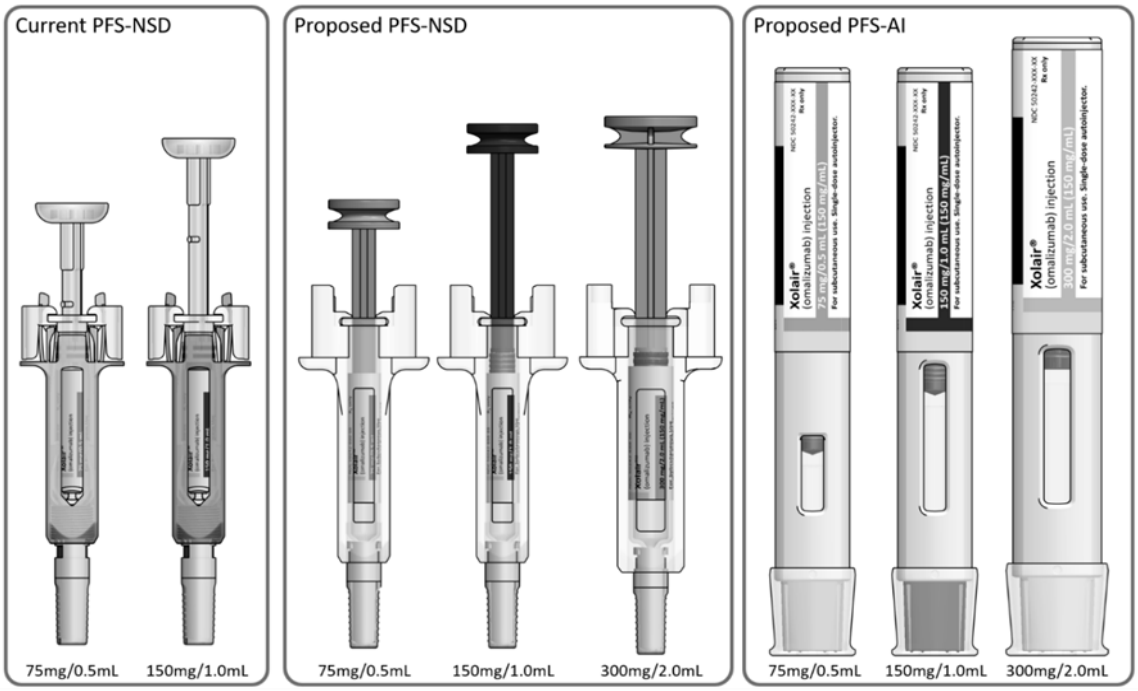
Prefilled Pen (PFP)

The composition of the solution in the bulk pre-filled syringe assembled in the Xolair pre-filled pen is the same as for the pre-filled syringe as presented in **Error! Reference source not found.** above. The primary packaging used for the pre-filled pen is the same as the one used for the new presentations of pre-filled syringe.

The development of the new products is based on the currently marketed Xolair solution for injection products and therefore the composition, manufacturing process and specifications are equivalent for all 3 strengths and are based on the current products. Additionally, the new packaging materials (syringe, stopper) and the new needle safety device for the 75 mg/ 0.5 mL and 150 mg/ 1.0 mL strength are comparable to the currently registered finished products. The new presentations will be manufactured at the new manufacturing site and will use the same fully formulated active substance bulk as the currently registered Xolair solution for injection in pre-filled syringe. As the finished product is a fully formulated active substance (omalizumab 15%), the main difference of 300 mg/ 2.0mL strength is only the fill volume into the respective 2 mL syringe.

The development activities, including changes in the primary packaging and the needle safety device, a change in the manufacturing site and the introduction of autoinjector presentations, were performed for the solution for injection presentations leading to three prefilled syringe and three autoinjector presentations at doses of 75 mg/0.5 mL, 150 mg/1.0 mL and 300 mg/2.0 mL.

Figure 1 Initially commercialized and newly developed Xolair solution for injection presentations.



The six new presentations for Xolair Solution for injection introduced with this application are depicted in Figure 1. The six new product presentations are a pre-filled syringe assembled in a Needle-safety device or autoinjector/pre-filled pen for all 3 strengths (75 mg/0.5 mL, 150 mg/1.0 mL, 300 mg/2.0 mL). The container closure system used for primary packaging of these new presentations is the same for the pre-filled syringe and pre-filled pen. Furthermore, the currently approved finished products are not changed.

The two syringe types for 75 and 150 mg, will coexist on the market during a transition period of approximately 12 months. To ensure that the old and new syringes (75 and 150 mg) can be differentiated by the prescriber and patient, the SmPC and PL has been updated during the procedure by adding additional identifier (colour of the syringe guard and plunger respectively). This is found an acceptable approach to avoid a mix up.

The active substance as well as the formulation of the finished product is the same as is already approved for the original Xolair formulations. No changes to the active substance omalizumab or the formulation are proposed.

The composition is acceptably presented, and the strengths differ only based on the filled volume.

All excipients are of compendial quality and comply with the corresponding Ph. Eur. Monographs. For the compatibility of the active substance with its excipients reference was made to the studies performed with the current product as well as stability studies for these new presentations. The impact of silicone and tungsten (a tungsten pin is used in the manufacture of syringe glass barrel) on the product quality of Xolair solution for injection in pre-filled syringe products has been assessed and found satisfactorily described. The data demonstrate no impact on the physico-chemical stability of the products.

A new needle safety device (NSD) is used for the new strength 300 mg as well as introduced for the strengths 75 mg and 150 mg.

The development related to the changes in the primary packaging, needle safety device, change in the manufacturing site and the introduction of the pre-filled pen (autoinjector) presentations, have been acceptably addressed. The control strategy and the quality target product profile (QTPP) are based on the currently approved solution for injection in pre-filled syringe and in general found adequately described. Quality attributes were assessed following ICH Q9 and relevant quality attributes were defined as critical quality attributes (CQA). The chosen device performance attributes, divided in EPR and DQA, are found relevant and satisfactorily justified.

Manufacturing process development
The development covers the introduction of the new presentation of 300 mg/2 mL and also the transfer of the process to the new manufacturer and the slight change of the primary packaging. In contrast to the initially commercialised Xolair solution for injection products, the primary packaging materials for the newly developed products are obtained ready to use (i.e. washed, siliconized, sterilised and depyrogenated). An adequate comparison of the current and new process has been provided.

The manufacture of primary packaged product is a standard sterile processing method using sterile filtration and aseptic filling of the syringe. The manufacture starts with thawing of the formulated active substance omalizumab.

A risk assessment was performed to evaluate risks associated with the transfer of the process to the new manufacturer. Minor process adaptions have been introduced and confirmed by technical batches manufactured at all three dosage strengths.

The development of the assembly process was adequately addressed.

In conclusion, the development of the manufacturing process is found adequately described.

Comparability
Two *in vitro* comparability studies have been performed to support the introduction of the new presentations and the new manufacture;

a) between the authorised Xolair 75 mg/0.5 mL and 150 mg/1.0 mL solution for injection in pre-filled syringe and the newly developed Xolair 75 mg/0.5 mL, 150 mg/1.0 mL and 300 mg/2.0 mL solution for injection bulk pre-filled syringe (bulk PFS).

b) to evaluate the impact of the assembly process of the bulk primary packed syringes (i.e. bulk PFS) with the needle safety (i.e. NSD) and the autoinjector device (i.e. AI). Also the impact of the devices on bulk finished product quality was addressed.

The comparability exercises were performed by extensively comparing release and stability data as well as data from additional characterization studies

All acceptance criteria were fulfilled, and the results showed comparable stability profiles. Also, comparable levels of sub-visible particles were observed for the tested batches by the extended characterization tests although slightly higher number of subvisible particles was observed for the assembled products, especially higher dosage strengths, when compared in particles per syringe (still within acceptance criteria), which could be explained by the different fill volumes per container. The results are in line with the other study discussed above.

With regard to break-loose and gliding force minor differences were observed between bulk-PFS and PFS-NSD batches. It was clarified that this difference relates to the setup of test procedure. Therefore, the products can be considered comparable.

It is agreed that the assembly and packaging processes for the manufacture of Xolair solution for injection in PFS-NSD and PFS-AI and the respective devices had no impact on physicochemical and biological product quality attributes and that bulk PFS, PFS-NSD and PFS-AI are considered comparable regarding the studied aspects.

In conclusion, it has been adequately demonstrated that the new presentations are comparable to the currently approved product in pre-filled syringe and that the assembly process does not impact the quality of the final products.

Container closure system

Pre-filled syringe
The container closure system of the newly developed Xolair 300 mg/2.0 mL, 150 mg/1.0 mL, 75 mg/0.5 mL solution for injection consists of a sterile, single use, pre-fillable syringe that includes a glass syringe barrel, equipped with a staked stainless-steel needle fixed to the syringe barrel with an adhesive, a rubber plunger stopper, and a rigid needle shield. Syringe barrels and needles are siliconized.

As already commented above the primary packaging materials for the newly developed products are obtained ready to use which is not the case for the currently approved presentations. Also the size of the staked needle differ (27-gauge staked needle to be compared with 26-gauge staked needle used for the currently approved syringes).

The primary packaging has been acceptably described and includes specifications and drawings. The materials in contact with the product (syringe barrel, staked needle, plunger stopper, rubber needle shield) vials and rubber stoppers are in compliance with the Ph. Eur. requirements or ISO standard. The syringe and plunger stopper are controlled for endotoxins and sterility.

Also, information on the suppliers of primary container materials as well as the sterilisation sites and sterilisation procedures are acceptably presented. The sterilisation processes are in compliance with relevant ISO standard. Ethylene oxide residues in syringe glass barrels are evaluated by the syringe suppliers according to the limits established for container closure systems in EMA/CHMP/CVMP/QWP/850374/2015. The limits for ethylene oxide with 1 µg/mL and ethylene chlorohydrin and bromohydrin with 50 µg/mL each are complied with.

The suitability of the container closure system is acceptably addressed covering information on material safety, sorption to container, extractables and leachables, elemental impurities and safety of additional device components. The syringe unit is delivered pre-assembled by the manufacturer. The design of the components is maintained by the supplier although Novartis has developed a design plan covering the components and their combination to confirm existing requirements or establish additional requirements.

Pre-filled pen (autoinjector)
The container closure system used for primary packaging of Xolair 300 mg Solution for injection in pre-filled pen consists of the same primary packaging of Xolair 300 mg Solution for injection in pre-filled syringe.

Xolair 150 mg/1.0 mL and 75 mg/0.5 mL solution for injection in autoinjector use the Xolair AI device, and Xolair 300 mg/2.0 mL solution for injection in autoinjector uses the Xolair AI device. The autoinjector (AI) devices are based on the disposable autoinjector platforms. The materials and components of the device have

been described as well as specifications and test procedures for the device. Detailed drawings are provided also including information on key dimensions.

The Xolair autoinjector devices are push-click devices. When the autoinjector is pressed against the skin, the device will activate. The needle is inserted into the patient's skin and following the needle insertion the injection process starts automatically. The injection process can be monitored through an inspection window on the autoinjector devices. The devices provide visual and auditory feedback throughout the injection process.

MDR compliance pre-filled syringe & pre-filled pen
The notified body opinion report has been provided, in response to a Major Objection raised by the CHMP, for the pre-filled syringe, including the needle safety device, and the autoinjector/pre-filled pen respectively. Compliance with the relevant General Safety and Performance Requirements (GSPRs) in Annex I of Regulation (EU) 2017/745 has been acceptably verified.

Xolair solution for injection in pre-filled syringe products include a functional passive needle safety device (NSD). The needle safety devices are provided to the end user assembled (integrated) with the bulk pre-filled syringes and without modifications.

Suitability for shipping
Shipping verification to demonstrate that the shipping configuration protects the primary packed material and the devices in worst-case transport conditions has been performed. In addition, a transport validation study was performed at worst-case condition. The suitability of the transport conditions has been acceptably demonstrated and the impact on stopper movement at reduced pressure in the cargo compartment of aircrafts was also acceptably addressed.

Suitability for use
The proposed presentations in pre-filled syringe and pre-filled pen are intended for administration by healthcare professionals, lay caregivers and for self-administration for patients 12 years and above. The functionality and safety features with the devices have been acceptably described. The design verification is found extensive and acceptably described in the dossier. The applicant identified user requirements pertaining to the user population and use environments that were evaluated under a human factors engineering process. Furthermore, the notified body opinion has been provided for pre-filled syringe, including the needle safety device, and the autoinjector/pre-filled pen respectively. This support compliance with the General Safety and Performance Requirements of the MDR.

Microbiological attributes
A microbiological challenge test has been performed to verify the container closure integrity for the proposed primary packaging. The results confirm the suitability of the selected container closure system. The testing strategy proposed for the verification of acceptable container closure integrity is found adequate.

2.4.3.2. Manufacture of the product and process controls

Prefilled Syringe (PFS)

With this application a new site is added as a new finished product manufacturing site and primary packaging site. The new site will only produce Xolair 75mg, 150mg and 300 mg in the new PFS. The manufacturing sites for the currently approved PFS remain unchanged.

A new site is added as additional alternative secondary packaging site and an additional batch release site is added for the newly added finished product presentations.

The manufacturing process for the bulk PFS is described in a flow chart (**Error! Reference source not found.**) and detailed in a written narrative description. The manufacturing process is limited to active substance thawing, homogenization, bioburden reduction filtration, sterile filtration and aseptic filling.

The manufacturing process for the assembly of the bulk PFS with the (NSD) and the plunger rod and the process controls are acceptably described and summarised in a flow chart. The manufacturing process at the new site was adapted compared to the registered process at the approved site for the currently approved Xolair pre-filled syringes. These adaptation have been clearly set out in the dossier and are acceptable. The in-process controls are deemed suitable for controlling and monitoring the manufacturing process.

Process validation / verification
Process validation studies were based on a traditional approach. Nine commercial scale consecutive bulk PFS batches of Xolair 300 mg, 150 mg and 75 mg with three batches per strength, were manufactured. A portion of each of the nine bulk PFS batches was subsequently assembled with the needle safety devices (NSD).

All analytical data, for bulk PFS as well as for assembly with NSD complied with IPCs and all process parameters were within the defined proven acceptable ranges. There was one deviation observed for the assembly process of Xolair 150 mg bulk PFS with the needle safety devices which led to a slight process improvement. An acceptable summary of the respective deviation, its root cause analysis, a risk assessment, and the implemented process changes are described in the dossier.

Acceptable results from media fill validations are presented in the dossier.

Results from transport validation studies have been presented. Data from shipping verification studies demonstrated that the proposed commercial packaging configurations adequately protect the finished products and the integrity of the container, as well as functionality of the needle safety device. The transport validation studies have shown that mechanical stress associated with the transport of the products has no impact on finished product quality.

Pre filled pen (PFP)

The first part of the manufacture i.e. the manufacture of the bulk pre-filled syringes is the same as the one described above for the manufacture of the product supplied in pre-filled syringe. Specific for the PFP is the assembly process of the drive unit and syringe unit briefly described and summarised in a flow chart. The description of the manufacturing (assembly) process and the associated control strategy of the pen-injectors have been elaborated during the procedure and are considered acceptable. The manufacturing process at the new site was adapted compared to the registered process at the approved site for the currently approved Xolair pre-filled syringes. These adaptations have been clearly set out in the dossier and are acceptable. The in-process controls are deemed suitable for controlling and monitoring the manufacturing process.

Process validation / verification
For the manufacture of the pre-filled pen adequate information in relation to the validation of the assembly process as well as the transport validation have been provided. The results from the transport validation demonstrate that the pre-filled syringe assembled into a pre-filled pen was not affected by mechanical stress. The validation of the transport is found acceptable and supports the transport conditions chosen.

2.4.3.3. Product specification

The specifications for the pre-filled syringe and the pre-filled pen were presented respectively.

The currently approved specification limits and methods, as approved for currently approved presentations in pre-filled syringes, remain unchanged and are applicable for the newly added products. The proposed additional functionality testing is found in adequate. Updates of the final product specifications in relation to the control of appearance of the final assembled products, PFS-NSD and PFS-AI, have been provided as requested. This is found acceptable.

The evaluation in respect to elemental impurities as per ICH Q3D and N-nitrosamines have been acceptably addressed. The potential sources of elemental impurities in the finished product resulting from the contribution of each factor discussed above have been identified as low or negligible for Xolair.

The risk evaluation for N-nitrosamines follows the guidance in place and cover all potential sources of N-nitrosamines or each of the components in Xolair. It was concluded that none of the finished product components nor process steps pose any potential risk of N-nitrosamines.

Analytical procedures and reference standards
All methods used for the control of the finished products including also functional testing of the pre-filled syringe and pre-filled pen respectively, are included in the dossier. The methods are found acceptably described. The new functionality test methods introduced for the pre-filled pen have been satisfactorily validated and the method transfer to the current test site was demonstrated.

Also a summary of the test methods that have been replaced, added, or removed in the final testing compared to the testing of the initially commercialized Xolair 150 mg/1.0 mL, 75 mg/0.5 mL solution for injection in pre-filled syringe and the testing during development is adequately presented.

There were no changes to the reference standard materials.

Batch analysis
Batch results from the three different strengths of both bulk and assembled pre-filled syringe and pre-filled pen have been provided. Three process validation batches of each strength are provided. In addition, results from one pre-validation batch not assembled is provided for 75 and 150 mg strengths. For the 300 mg strength results from one clinical batch was added as well.

Following the outcome of the comparability exercise demonstrating that the device and the assembly process do not compromise product quality it can be agreed that testing of the bulk pre-filled syringes, except for device specific attributes, is equivalent to that of the assembled products.

The batch results presented are well within the specification criteria and demonstrate a satisfactory reproducibility.

2.4.3.4. Stability of the product

Pre-filled syringe

In line with the current approved PFS product a shelf life of 18 months when stored at 2 – 8 °C is proposed. In addition, an optional short-term storage at room temperature of not more than 48 hours (at 25°C) is proposed.

Stability studies results for pre-filled syringes manufactured according to commercial process have been provided under long term (2 – 8 °C) and accelerated (25 °C/60% RH) storage conditions and under special conditions for Xolair 300 mg, 150 mg, 75 mg solution for injection and include:

- Primary stability studies, conducted on process validation batches produced at the intended commercial manufacturing site using a bracketing and reduced testing approach.
- The primary stability studies also include a photostability study to demonstrate adequate light protection of the product in the commercially representative secondary packaging.
- The primary stability studies furthermore include in-use stability studies at 28 – 32 °C to investigate the stability of the finished product at room temperature at point of care, after refrigerated storage, and before opening and administration to the patient (i.e. in-use/out-of-refrigerator period).
- Supportive stability studies, conducted on technical and clinical batches (representative scale and process as the intended commercial manufacturing process at the new site to support the primary stability.

Supportive data from corresponding bulk PFS as well as technical, characterisation and clinical batches for bulk PFS, have been presented.

The stability studies are designed in accordance with the principles detailed in the ICH guidelines Q5C and Q1A (R2). Long-term studies at 2-8 °C as well as at accelerated conditions at 25°C/60% RH are performed. The study at accelerated conditions is finalised.

The corresponding bulk PFS batches of each strength were placed on stability at long term (2 - 8°C) and accelerated (25°C/60% relative humidity) storage conditions with a full testing scope for up to 18 months. Results from full time storage are provided. At end of the study (18 months) full testing has been performed.

The bracketing and reduced testing approach used is found acceptably justified and is also in line with the recommendation in the EMA scientific advice EMEA/H/SA/45/6/2020/III. This taken into account the results from the comparability exercise discussed elsewhere in this report demonstrating no impact of the assembly process and similar stability profiles for the bulk PFS and assembled product. Also the comparability to the currently approved product in pre-filled syringes, manufactured by the approved site, has been verified, which further supports this approach.

Results from full testing up to 18 months presented as pre-filled syringe with NSD were provided.

All results for the long-term study (bulk PFS and assembled PFS) are well within the requirements set and no significant changes are observed except a slight change in purity. The stability profiles for assembled product are comparable to the respective bulk PFS batches except slightly higher number of subvisible particles. All functional testing complies.

The primary stability studies for the assembled product also included a photostability study. The results demonstrate a slight change in impurity profile justifying the proposed storage condition.

The in-use stability for all three strengths were studied to confirm the applicability of the in-use time of 48h at 25 °C registered for the current commercial Xolair solution for injection in PFS product. The results support the proposed in-use time of 48h at 25 °C.

In conclusion, the stability study approach is found acceptable and relevant test attributes are included in the protocols, also covering functionality testing. The chosen bracketing approach including also reduced testing is found acceptably justified. The proposed shelf life is based on the approved shelf life for the currently approved product in pre-filled syringe manufactured by the approved site.

Stability data for the Xolair 300 mg/2.0 mL, 150 mg/1.0 mL and 75 mg/0.5 mL solution for injection bulk pre-filled syringe (bulk PFS) up to 18 months and stability data for Xolair 300 mg/2.0 mL, 150 mg/1.0 mL and 75 mg/0.5 mL solution for injection in pre-filled syringe (PFS-NSD) up to 18 months has been provided. The results are in accordance with the acceptance criteria. Based on these data as well as supporting 18 months data from technical batches the proposed shelf life of 18 months at 2-8°C is found acceptably justified.

Pre-filled pen

The applicant has provided stability results from batches of pre-filled pen manufactured according to commercial process. Supportive data from corresponding bulk PFS as well as technical, characterization and clinical batches for bulk PFS, and also one clinical batch assembled as pre-filled pen (AI), have been presented.

The batches used in the primary stability studies for bulk PFS were assembled into pre-filled pens.

A shelf life of 18 months at 2-8 °C is proposed as well as an in-use time of 48h at 25°C, in line with currently approved presentations in pre-filled syringe

The same approach for stability studies as for the pre-filled syringe commented above has been used.

In line with the pre-filled syringe, the bracketing and reduced testing approach used is found acceptably justified and is also in line with the recommendation in the EMA scientific advice EMEA/H/SA/45/6/2020/III.

All results for the long-term study are well within the requirements set and no significant changes are observed except a slight change in purity, which are consistent with trends observed for bulk PFS. It is noted that purity as well as the activity are affected when stored at accelerated conditions. These changes are found to be in the range expected for this condition. The stability profiles for assembled product are comparable to the respective bulk PFS batches except slightly higher number off subvisible particles. All functional testing complies.

In conclusion, the stability study approach is found acceptable and relevant test attributes are included in the protocols, also covering functionality testing. The chosen bracketing approach including also reduced testing is found acceptably justified. The proposed shelf life is based on the approved shelf life for the currently approved product in pre-filled syringe manufactured by the approved site.

Results from 18 months stability studies are available for the bulk PFS and the assembled finished product respectively. The same applies for all strengths also including the new strength/ fill volume of 300 mg. The results from the pre-filled syringe and pen applied for shows similar stability profile as for the currently approved presentations in pre-filled syringe. The proposed shelf life of 18 months at 2-8 ºC is found acceptably justified.

2.4.3.5. Adventitious agents

A full adventitious agents safety evaluation of Omalizumab 15% active substance including an evaluation of raw materials, consumables, excipients, cell banks, non-viral and viral adventitious agents, and viral clearance is available in the registered dossier of the originally commercialized products Xolair 75 mg and 150 mg solution for injection in pre-filled syringe.

Since this application does not cover any changes of the active substance, the formulation of the finished product is unchanged and no excipients is of human or animal origin, no assessment of A.2. is provided in this report; this is acceptable.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

This line extension application is for the registration of a new strength of 300 mg per 2 ml for Xolair solution for injection grouped with several Type I and Type II quality variations to introduce a pre-filled pen (PFP) and a new pre-filled syringe with needle safety device (PFS-NSD).

One Major Objection raised during the procedure regarding the Notified Body opinion for the devices used in the medicinal product and all other concerns have been acceptably addressed. In addition all the variations applied for in parallel and grouped to the extension application have been assessed together with the extension application and are approvable.

Information on development, manufacture and control of the finished products has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.4.6. Recommendations for future quality development

Not applicable.

2.5. Non-clinical aspects

2.5.1. Introduction

No new non-clinical studies have been submitted for this extension and no non-clinically changes in the SmPC have been proposed. As such, only a brief overview from previously approved EPARs is provided below.

2.5.2. Pharmacology

Omalizumab is a recombinant humanised IgG1 monoclonal anti-IgE antibody which binds to IgE at the same epitope as FcεRI-receptor. The pool of IgE available to interact with mast cells and basophils via FcεRI-receptor is thereby reduced and allergic responses attenuated. For proof-of-concept studies, the Cynomolgus monkey was chosen as model to predict human pharmacology and toxicology since omalizumab binds Cynomolgus and human IgE with similar affinity but does not bind non-primate IgE.

2.5.3. Pharmacokinetics

The bioavailability of omalizumab after SC administration was 90% in mice and ranged from 64% to 104% in monkeys (this can be compared to a mean bioavailability of omalizumab in humans of 53% to 71%). Pharmacokinetic studies in non-human primates revealed an elimination half-life of approximately 7 days with a maximal concentration after SC application after approximately 5 days. Distribution studies show that >90% of the test material was in the circulation of Cynomolgus monkeys. The uptake of omalizumab ^{125}I-IgE-complexes was greatest in the liver and spleen. Sinusoidal endothelial cells and cells of the reticuloendothelial system were involved in the clearance of the complexes. Staining of cryo-sections of tissues of human or Cynomolgus monkey origin did not result in binding with the exception of lymphoid cells synthesising IgE.

2.5.4. Toxicology

No evidence of toxicity was observed following single iv administration of up to 100 mg/kg in mice and following single IV and SC administration of up to 50 mg/kg in monkeys (corresponding to a maximum that could be delivered as a single IV bolus of a 5 mg/ml formulation).

The repeat-dose characterisation was based on two pivotal cynomolgus studies: one 4-week IV/SC study with a 4-week recovery period (dosing three times weekly in the range 0.1-5.0 mg/kg) and one 6-month IV/SC study with an 8-week recovery period (dosing three times weekly in the range 0.1-5.0mg/kg). Omalizumab had no effect on standard toxicological parameters after repeated administration to Cynomolgus monkeys. Despite the presence of omalizumab-IgE complexes in the cynomolgus studies, there were no indications of immune complex-mediated disease.

Juvenile (8- to 10-month-old) Cynomolgus monkeys received SC doses of 50 or 250 mg/kg omalizumab weekly for 26 weeks. No omalizumab-related effects were observed with the exception of thrombocytopenia and changes secondary to thrombocytopenia. Thrombocytopenia appeared at serum concentrations of omalizumab, which were 1.7x to 16.7x higher than the concentrations detected in Phase III trial patients. Histopathological evaluation revealed haemorrhage in the subcutaneous tissue at the injection site, in seminal vesicles, in the stomach fundus mucosa, or in the duodenal mucosa of a few animals, in the low and/or high dose groups.

A standard Ames test was negative. A full genotoxicity test battery and carcinogenicity evaluation have not been conducted for omalizumab. No carcinogenicity study with omalizumab was performed since omalizumab does not bind rodent IgE.

Male and female fertility, embryotoxicity/teratology, and late gestational/placental transfer were studied in Cynomolgus monkeys. SC administration of omalizumab, at doses of 0, 3, 15 and 75mg/kg once weekly for 6 weeks (to cover the period of spermatogenesis) did not elicit reproductive toxicity in males. The same doses were administered to females for 13 weeks (three menstrual cycles) before mating, during the mating period (maximum of two menstrual cycles) and during early pregnancy (up to Day 25 of gestation). Omalizumab did not elicit reproductive toxicity in female Cynomolgus monkeys. Administration of omalizumab to pregnant monkeys during organogenesis (gestational Days 20 to 50) at doses of 0, 3, 15 and 75mg/kg once daily on Days 20-22, and then once weekly through Day 50 did not elicit maternal toxicity, embryotoxicity or teratogenicity. To assess the effect of omalizumab on late gestation, and to evaluate the placental transfer and milk secretion of omalizumab, doses of 75mg/kg were administered SC to two groups of monkeys (Caesarean section group and natural delivery group). Omalizumab was given once daily on Days 120, 121

and 122 of gestation as a loading dose, and once weekly through Day 150 of gestation for the Cesarean section group, or through Day 28 postpartum for the natural delivery group. There was no evidence of late gestational maternal or offspring toxicity.

Measurable levels of omalizumab were observed in amniotic fluid (~3.3% of maternal serum levels), milk (~0.154%), and fetal (~33%) and neonatal (~33%) serum. Since there was an increased risk of thrombocytopenia in juvenile non-human primates, a restrictive wording in 4.6 Pregnancy and lactation section of the SmPC is considered appropriate.

Studies of local tolerance in rabbits did not indicate local toxicity.

2.5.5. Ecotoxicity/environmental risk assessment

As the active substance in Xolair is an antibody, and therefore considered a natural substance, it is not considered to constitute an environmental risk.

2.5.6. Discussion and conclusion on non-clinical aspects

No novel non-clinical studies or aspects were introduced or discussed by the MAH for this procedure. The new proposed dose formulation of 300mg is acceptable on this context as the previously accepted maximum or total dose is 600mg.

With regard to the environmental risk assessment, the active substance is a natural substance (i.e., a protein), the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, omalizumab is not expected to pose a risk to the environment.

Overall, no new non-clinical concerns have been identified by the CHMP and there are therefore no non-clinical issues in this procedure.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- **Tabular overview of clinical studies**

Study Number	Study design, treatment duration and population	Treatment dose and regimen	Status
Study K12101 Protocol: IGE025K12101 Countries: USA	Open-label, randomised, single-dose, parallel group, three treatments, immunogenicity, safety and tolerability BE study 193 healthy volunteers aged 18-60 years (1:1:1 randomisation, 66/64/63 subjects)	A: single omalizumab dose 300 mg (1 x 300 mg/2 mL) in proposed PFS-AI device B: single omalizumab dose 300 mg (1 x 300 mg/2 mL) in proposed PFS-NSD device C: single omalizumab dose 300 mg (2 x 150 mg/1 mL) in current PFS-NSD device	Complete Start: 09 November 2020 End: 16 July 2021

The terms autoinjector (PFSAI) and pre-filled pen (PFP) have been used interchangeably in this report.

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

The bioequivalence study K12101 was an open-label, randomised, single dose, 3 treatment group, parallel study in healthy volunteers to evaluate the pharmacokinetics (PK), immunogenicity, safety and tolerability of omalizumab. It was conducted in healthy subjects to demonstrate bioequivalence of a single omalizumab dose administered by subcutaneous injection through the 300 mg PFS-AI or the 300 mg PFS-NSD, both in comparison with the currently approved 2 x (150 mg) PFS assembled with a NSD. The primary endpoints were omalizumab serum PK parameters: Cmax, AUClast, and AUCinf.

The study consisted of a 28-day screening period (Day -29 to Day -2), a baseline evaluation on Day -1, and a 12-week PK, immunogenicity, and safety evaluation period, starting with administration of the study treatment on Day 1, and ending with the completion of Day 85 (± 2 days) assessments.

Eligible healthy volunteers (with total IgE ≤150 IU/mL to avoid IgE interferences) were randomised to 1 of the below 3 treatment groups (proposed PFS-AI, proposed PFS-NSD, and current PFS-NSD):

Treatment A	Omalizumab 300 mg (1 x 300 mg/2 mL) as the proposed PFS-AI on Day 1 (Test, lot number 2040464)
Treatment B	Omalizumab 300 mg (1 x 300 mg/2 mL) as the proposed PFS-NSD on Day 1 (Test, lot number 2040465)
Treatment C	Omalizumab 300 mg (2 x 150 mg/1 mL) as the current PFS-NSD on Day 1 (Reference, lot number 3352758)

There were three options on the areas of injection to be used (abdomen, front and middle thigh, or upper arm, cohorts 2-4) as of the protocol amendment v01. Patients enrolled prior to protocol amendment v01 (n=48) were restricted to cohort 1 and were not assigned to a particular area of injection.

An enzyme-linked immunosorbent assay (ELISA) method was used to measure total omalizumab concentration in human serum.

A multitiered strategy was applied for the detection of anti-omalizumab antibodies (AOA or antidrug antibodies ADA). Anti-omalizumab-Fab and -Fc antibodies were quantified in human serum using validated ELISA methods.

Total IgE was quantified in human serum using a fluorimetric sandwich-immunoassay on the Phadia ImmunoCAP platform.

Non-compartmental analysis with Phoenix WinNonlin (Version 8.1) was used for the bioequivalence study K1201. For the statistical analysis, log-transformed PK parameters (Cmax, AUClast, and AUCinf) were analysed by a fixed effects model, with treatment, body area of injection, body weight strata as fixed effects and IgE levels at Baseline as covariate.

Results

A total of 193 subjects were enrolled and randomised. PK parameters are available for all 193 subjects. Overall, the majority of subjects were female (70.5%) and White (85.5%). The three treatment groups were balance with regards to sex, weight and age.

For all three parameters Cmax, AUClast and AUCinf and both comparisons proposed PFS-AI vs current PFS-NSD and proposed PFS-NSD versus current PFS-NSD, the ratios of geometric least square means, 95% CIs and the 90% CIs were all contained within the pre-defined limits of 80-125%, indicating similarity of exposure between the proposed 300 mg/2 mL PFS-AI vs current 2 x 150 mg/1 mL PFS-NSD (Table 1) and proposed 300 mg/2 mL PFS-NSD (Table 2) vs current 2 x 150 mg/1 mL PFS-NSD.

Table 1: Statistical Comparisons of Omalizumab Serum PK Parameter Values for Proposed PFS-AI Versus Current PFS-NSD

	Treatment A (Test)		**Treatment C (Reference)**					
Parameter	**Geometric LSMs**	**n**	**Geometric LSMs**	**n**	**GMR (%)**	**95% CI**	**90% CI**	**Inter-subject CV%**
Cmax (ng/mL)	41900	66	38600	63	108.45	99.62 - 118.06	101.00 - 116.45	24.57
AUClast (ng*h/mL)	35900000	66	32800000	63	109.31	99.67 - 119.89	101.17 - 118.11	26.80
AUCinf (ng*h/mL)	40100000	60	36500000	57	110.01	100.09 - 120.91	101.63 - 119.07	26.02

Treatment A (Test): Omalizumab 300 mg (1 x 300 mg/2 mL) as the proposed PFS-AI on Day 1
Treatment C (Reference): Omalizumab 300 mg (2 x 150 mg/1 mL) as the current PFS-NSD on Day 1
Source: [Study K12101-Table 14.2-1.3]

Table 2: Statistical Comparisons of Omalizumab Serum PK Parameter Values for Proposed PFS-NSD Versus Current PFS-NSD

	Treatment B (Test)		Treatment C (Reference)					
Parameter	**Geometric LSMs**	**n**	**Geometric LSMs**	**n**	**GMR (%)**	**95% CI**	**90% CI**	**Inter-subject CV%**
Cmax (ng/mL)	38800	64	38600	63	100.59	92.29 - 109.63	93.59 - 108.11	24.57
AUClast (ng*hr/mL)	33400000	64	32800000	63	101.58	92.50 - 111.55	93.92 - 109.87	26.80
AUCinf (ng*hr/mL)	37400000	58	36500000	57	102.66	93.26 - 113.02	94.73 - 111.27	26.02

Treatment B (Test): Omalizumab 300 mg (1 x 300 mg/2 mL) as the proposed PFS-NSD on Day 1
Treatment C (Reference): Omalizumab 300 mg (2 x 150 mg/1 mL) as the current PFS-NSD on Day 1.
Source: [Study K12101-Table 14.2-1.4]

In addition to the above primary objective, the ratio of geometric least square means and 90% CIs for Cmax, AUClast and AUCinf were within 80-125% between proposed PFS-AI (Treatment A) and proposed PFS-NSD (Treatment B) (Table 3).

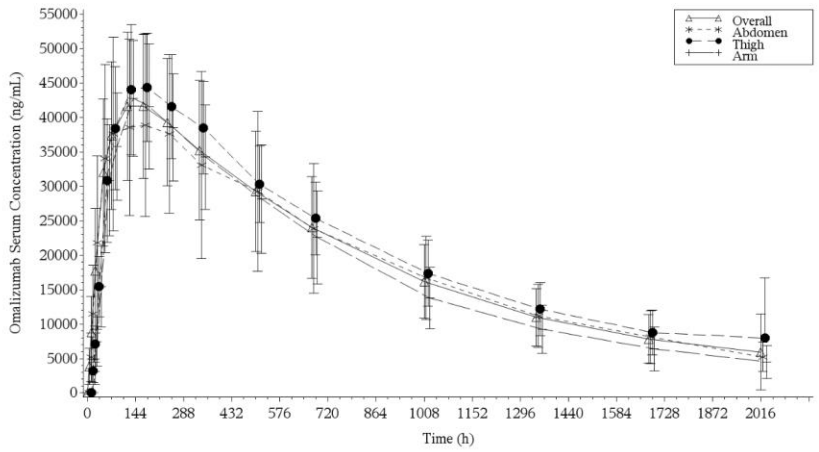
Table 3: Statistical comparisons of omalizumab serum PK parameter values for proposed PFS-AI versus proposed PFS-NSD

	Treatment A (Test)		Treatment B (Reference)				
Parameter	**Geometric LSMs**	**n**	**Geometric LSMs**	**n**	**GMR (%)**	**90% CI**	**Inter-subject CV%**
Cmax (ng/mL)	41900	66	38800	64	107.81	100.37 - 115.81	24.57
AUClast (ng*hr/mL)	35900000	66	33400000	64	107.61	99.56 - 116.32	26.80
AUCinf (ng*hr/mL)	40100000	60	37400000	58	107.15	98.98 - 116.00	26.02

Treatment A (Test): Omalizumab 300 mg (1 x 300 mg/2 mL) as the proposed PFS-AI on Day 1
Treatment B (Test): Omalizumab 300 mg (1 x 300 mg/2 mL) as the proposed PFS-NSD on Day 1
Source: [Study K12101-Table 14.2-1.5]

Within each treatment group, the profiles and PK parameter are comparable across the sites of injection (abdomen, thigh and arm, see for example Figure 1 for the PFS-AI). Median Tmax by treatment was reached between 5 and 7 days. The terminal elimination half-life of omalizumab was similar across the treatments and independent of site of injection. The mean (±SD) terminal elimination half-life ranged between 24.2 (±5.22) and 25.3 (±4.98) days across the treatments. The overall coefficients of variation for the Cmax, AUClast and AUCinf values were found to be around 30% indicating low variability.

Figure 2 Arithmetic Mean (SD) Omalizumab Serum Concentration-Time Profiles for Proposed PFS-AI by Body Area of Injection.



Source: [Study K12101-Figure 14.2-1.14]

Across all subjects, treatments, and time points, ADAs were observed in 3 subjects (Table 4). In the subjects with ADAs, the omalizumab exposure was not altered and was consistent with the exposure in other subjects receiving the same dose. One of the subjects with positive ADA on Day 85 experienced a moderate AE of generalised pruritus considered related to study drug on Day 82. No other drug-related AEs were reported by these subjects at the time they tested positive for ADA.

Table 4: Summary of overall anti omalizumab antibody (AOA = ADA) status

		Treatment A (N=66)			Treatment B (N=64)			Treatment C (N=63)			Overall (N=193)		
	Body Area of Injection	Abdomen	Thigh	Arm	Abdomen	Thigh	Arm	Abdomen	Thigh	Arm	Abdomen	Thigh	Arm
Visit	AOA* Status												
Day 1 (Predose)	AOA Negative (%)	23 (34.8%)	23 (34.8%)	19 (28.8%)	17 (26.6%)	22 (34.4%)	23 (35.9%)	22 (34.9%)	20 (31.7%)	20 (31.7%)	62 (32.1%)	65 (33.7%)	62 (32.1%)
Day 71	AOA Negative (%)	24 (36.4%)	22 (33.3%)	16 (24.2%)	16 (25.0%)	22 (34.4%)	25 (39.1%)	23 (36.5%)	20 (31.7%)	19 (30.2%)	63 (32.6%)	64 (33.2%)	60 (31.1%)
	AOA Positive (%)	0 (0.0%)	0 (0.0%)	1 (1.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)
Day 85 (EOS)	AOA Negative (%)	23 (34.8%)	22 (33.3%)	18 (27.3%)	15 (23.4%)	20 (31.3%)	25 (39.1%)	23 (36.5%)	20 (31.7%)	19 (30.2%)	61 (31.6%)	62 (32.1%)	62 (32.1%)
	AOA Positive (%)	0 (0.0%)	0 (0.0%)	1 (1.5%)	0 (0.0%)	1 (1.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	1 (0.5%)
Overall	AOA Negative (%)	24 (36.4%)	23 (34.8%)	17 (25.8%)	17 (26.6%)	21 (32.8%)	25 (39.1%)	23 (36.5%)	20 (31.7%)	20 (31.7%)	64 (33.2%)	64 (33.2%)	62 (32.1%)
	AOA Positive (%)	0 (0.0%)	0 (0.0%)	2 (3.0%)	0 (0.0%)	1 (1.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	2 (1.0%)

Treatment A (Test): Omalizumab 300 mg (1 x 300 mg/2 mL) as the proposed PFS-AI on Day 1
Treatment B (Test): Omalizumab 300 mg (1 x 300 mg/2 mL) as the proposed PFS-NSD on Day 1
Treatment C (Reference): Omalizumab 300 mg (2 x 150 mg/1 mL) as the current PFS-NSD on Day 1
*Anti-omalizumab antibody

Baseline total IgE levels reached up to 155 ng/mL, with two subjects exceeding 150 ng/mL.

2.6.2.2. Pharmacodynamics

No new pharmacodynamics studies were submitted as part of this application.

2.6.3. Discussion on clinical pharmacology

The design of study K12101 was generally in line with the given advice (EMEA/H/SA/45/6/2020/III) and is acceptable.

The analytical methods were previously validated and found acceptable. Where available, new partial validations fulfilled all required acceptance criteria. Regarding the drug tolerance of the ADA methods, it was first after 1296h (54 days) that mean concentrations reached levels below 10000 ng/mL, thus any sample prior to that timepoint is likely to have an interference leading to a false negative readout. In consequence, ADA analysis was conducted from day 71. It is unclear why the MAH has not developed an improved assay. The immunogenicity remains in the same range as previously studied; thus the issue was not further pursued within this procedure. The MAH is however advised to develop a better method with higher drug tolerance for future applications.

The statistical methods for study K12101 are acceptable. The use of a fixed effects model is acceptable given the parallel design of study K12101. Of note, the 95% CI used in the statistical testing of the primary endpoint is more conservative than required (90% CI).

In study K12101, 48 subjects were enrolled prior to the first protocol amendment, i.e. not randomised to a particular injection site and restricted to cohort 1. Upon CHMP's request, the MAH clarified that the 48 subjects were included in the PK analysis, and randomised to treatment and injection site.

For AUCinf, subjects with AUC%extrap exceeding 20% were excluded. This amounted to up to 6 subjects per arm. It is not acceptable to exclude subjects for PK reasons. As noted in the scientific advice, the sampling time was too short, which resulted in a risk for too high extrapolated area. However, as the active substance is the same, the elimination is expected to be similar for all three treatments, and thus AUCinf would not have been needed as primary endpoint. AUClast is considered sufficient to detect difference in absorption, which is the relevant point here. Thus the results of the study can be accepted for AUClast and Cmax, and the issue on the exclusion for AUCinf is not further pursued.

The results indicate that the 300 mg of new PFS-AI or the new PFS-NSD result in comparable exposure as 2x 150 mg of the current PFS-NSD. Similarly, both new presentations were found to result in similar PK parameters. The exposure after injection at the different sites was consistent across the three product presentations. The low variability is in line with earlier data.

Section 4.2 of the SmPC has been updated with the number of syringes/pens and number of injections necessary to achieve the desired dose. The 300 mg pre-filled syringe strength and all dose strengths of the PFS-AI are not intended for children under 12 years due to the pain caused by the higher injection volume in younger patients and the risk of intramuscular injection for the PFS-AI. This is acceptable and adequately reflected in SmPC section 4.2.

2.6.4. Conclusions on clinical pharmacology

The line extension is acceptable from PK perspective. The PK parameters for both new presentations (PFS-AI and PFS-NSD) are similar to those of 2x 150 mg of the current PFS-NSD presentation. Since PK with the new presentations is similar, it is acceptable to use the same SmPC text for PK.

2.6.5. Clinical efficacy

No new efficacy data was generated in support of this application as efficacy is extrapolated from the approved presentations by means of bioequivalence (see clinical pharmacology above). This is acceptable.

2.6.6. Clinical safety

2.6.6.1. Patient exposure

In the single-dose study K12101, a total of 193 healthy subjects received treatment with omalizumab; 66 subjects with the proposed 300 mg PFS-AI, 64 subjects with the proposed 300 mg PFS-NSD and 63 subjects with the currently approved 2 x (150 mg) PFS-NSD. The proportion of subjects who received injections in the abdomen, thigh or arm was comparable across the treatment groups and the majority of subjects completed the study (>93% in each treatment group).

2.6.6.2. Adverse events

In study K12101, the proportion of subjects with at least one treatment-emergent AE (TEAE) was comparable across treatment groups. Overall, a total of 252 TEAEs were reported by 95 subjects (49.2%).

Thirty (15.5%) subjects reported AEs considered to be drug-related by the investigator during the study, and the majority of AEs were of mild to moderate intensity (Table 5).

Table 5 Overview of treatment-emergent AEs (Study K12101)

	Proposed PFS-AI (N=66) n (%)	**Proposed PFS-NSD (N=64) n (%)**	**Current PFS-NSD (N=63) n (%)**	**Overall (N=193) n (%)**
TEAEs	33 (50.0)	27 (42.2)	35 (55.6)	95 (49.2)
Mild	23 (34.8)	22 (34.4)	25 (39.7)	70 (36.3)
Moderate	10 (15.2)	5 (7.8)	9 (14.3)	24 (12.4)
Severe	0 (0.0)	0 (0.0)	1 (1.6)	1 (0.5)
Related TEAEs	12 (18.2)	9 (14.1)	9 (14.3)	30 (15.5)
SAEs	0 (0.0)	0 (0.0)	1 (1.6)	1 (0.5)
Related SAEs	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
TEAEs leading to study discontinuation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
TEAEs leading to death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

TEAEs = Treatment-emergent adverse events. N = Number of subjects dosed. Percentages are based on the number of subjects dosed per treatment. Data are presented for the number (n) and percentage of subjects with events.

	Proposed PFS-AI (N=66) n (%)	Proposed PFS-NSD (N=64) n (%)	Current PFS-NSD (N=63) n (%)	Overall (N=193) n (%)

TEAEs are AEs with a start date during the on-treatment period. The on-treatment period lasted from the date of first administration of study treatment to 84 ± 2 days after the date of the last actual administration of any study treatment.
AEs with Relationship to study drug coded as likely, probably, possible were classed as drug-related.
Source: [Study K12101-Table 12-1]

Most frequently occurring adverse events

Overall, treatment-emergent AEs were most frequently reported in the SOCs of General disorders and administration site conditions (24.4%), followed by Nervous system disorders (17.1%), and were generally balanced between the treatment groups. The most frequently occurring AEs (PTs with an incidence of ≥5% of subjects in any group) are shown in Table 5-3.

Among the PTs reported in ≥5% of subjects in any group, PTs reported were headache, injection site pain, injection site induration, injection site erythema, injection site swelling and nausea (Table 5-3).

When considering local injection site related PTs such as 'injection site pain', 'injection site induration' and 'injection site erythema', the incidence of these PTs was numerically higher in the PFS-AI group compared to the proposed and current PFS-NSD groups. The majority of injection site related AEs were mild in severity, none were severe, and all resolved without treatment:

- For injection site pain, the majority of events occurred within 2 minutes of dosing (9 of 12 events). The majority of events resolved within 12 hours. All events were mild in severity and resolved without treatment.
- For injection site induration, onset of the events ranged from 1 minute to approximately 11 hours after dosing, with the majority of events reported within 15 minutes of dosing (10 of 12 events). Of the 12 events reported, 11 were mild in severity and one event (following 1 x 300 mg/2 mL proposed PFS-AI) was moderate. All events resolved within 1.5 days of onset without treatment.
- For injection site erythema, onset of the events ranged from 1 minute to 15 minutes after dosing. Duration of the events ranged from approximately 1.5 to 22 hours. Of the 10 events reported, eight were mild in severity and two (both following 1 x 300 mg/2 mL proposed PFS-AI) were moderate. All events resolved without treatment.

Table 6 Adverse events by preferred term reported in ≥5% of subjects in any treatment group (Study K12101)

Preferred term	Proposed PFS-AI (N=66)	Proposed PFS-NSD (N=64)	Current PFS-NSD (N=63)	Overall (N=193)
Any TEAE	**33 (50.0%)**	**27 (42.2%)**	**35 (55.6%)**	**95 (49.2%)**
Headache	11 (16.7%)	7 (10.9%)	10 (15.9%)	28 (14.5%)
Injection site pain	5 (7.6%)	4 (6.3%)	3 (4.8%)	12 (6.2%)

Preferred term	Proposed PFS-AI (N=66)	Proposed PFS-NSD (N=64)	Current PFS-NSD (N=63)	Overall (N=193)
Injection site induration	6 (9.1%)	5 (7.8%)	1 (1.6%)	12 (6.2%)
Injection site erythema	6 (9.1%)	2 (3.1%)	2 (3.2%)	10 (5.2%)
Nausea	2 (3.0%)	4 (6.3%)	0 (0.0%)	6 (3.1%)
Injection site swelling	4 (6.1%)	0 (0.0%)	0 (0.0%)	4 (2.1%)

Adverse events are classified according to MedDRA® Version 23.1.
Data are presented for the number (n) and percentage of subjects with events.
Although a subject may have had 2 or more clinical adverse experiences, the subject was counted only once within a category.
AEs are ordered by PT by descending frequency in the current PFS-NSD group.
TEAEs are AEs with a start date during the on-treatment period. The on-treatment period lasted from the date of first administration of study treatment to 84 ± 2 days after the date of the last actual administration of any study treatment.
Source: [Study K12101-Table 12-2]

Post-hoc analysis of injection site AEs

Post-hoc exploratory analyses were performed to gain further insights on the injection site reactions. Treatment group comparisons based on post-hoc analysis did not show statistically significant differences in the incidence of AEs pertaining to high level term (HLT) "injection site reactions" between the PFS-AI group compared to the proposed and current PFS-NSD groups, nor between the proposed PFS-NSD group versus the current PFS-NSD group.

2.6.6.3. Serious adverse event/deaths/other significant events

There were no deaths or subject discontinuation due to AE or AE of special interest reported in the study. Only one subject (who received treatment with the current PFS-NSD) reported an SAE (appendicitis), which was severe and not considered to be related to study treatment by the investigator.

2.6.7. Discussion on clinical safety

Overall omalizumab administered as PFS-AI and PFS-NSD was safe and generally well-tolerated by the healthy adult subjects in study K12101. There were no deaths or subject discontinuation due to AE or AE of special interest reported in the study. One subject experienced an SAE of appendicitis considered unrelated to study drug. This is agreed by the CHMP.

Overall, TEAEs were reported by 95 (49.2%) subjects in the study, including 30 (15.5%) subjects reporting AEs assessed as drug-related by the investigator. The most commonly reported events were headache (14.5%), injection site pain (6.2%) and injection site induration (6.2%). The majority of injection site reactions (47 of 61 events) reported in the four specific categories: injection site pain, injection site erythema/redness, injection site induration/swelling and injection site tenderness, were reported within the first 12 hours after dosing and were mild in severity and resolved without treatment.

There was a numerical imbalance across treatment arms for these specific categories of injection site reactions. Incidence of injection site reaction was lower following 2 x (150 mg/1 mL) current PFS-NSD (Treatment C) than following 1 x 300 mg/2 mL proposed PFS-AI (Treatment A) and 1 x 300 mg/2 mL proposed PFS-NSD (Treatment B). However, as the reactions were generally mild in severity and resolved without treatment, no further actions are warranted due to this finding.

The safety profile for the proposed PFS-AI and PFS-NSD are generally in line with that seen for the current PFS-NSD. No SmPC update was necessary.

2.6.8. Conclusions on the clinical safety

AE observed in study K12101 were consistent with the known safety profile of omalizumab. No new safety concerns have been identified.

Taking into account that bioequivalence has been shown, the safety profile of the proposed 300 mg strength can be assumed to be equivalent to that of the existing 150 mg strength.

2.7. Risk Management Plan

2.7.1. Safety concerns

Summary of safety concerns

Important identified risks	Anaphylaxis/anaphylactoid reactions Churg Strauss Syndrome (CSS) / Hypereosinophilic Syndrome (HES)
Important potential risks	Arterial Thromboembolic Events (ATEs) Malignant neoplasms in adults and adolescents ≥ 12 years of age Malignant neoplasms (children 6 to less than 12 years old)

2.7.2. Pharmacovigilance plan

No additional pharmacovigilance activities.

2.7.3. Risk minimisation measures

Safety concern	Risk minimization measures	Pharmacovigilance activities
Important Identified risks		
Anaphylaxis/anaphylactoid reactions	Routine risk minimization measures: SmPC sections – 4.2, 4.4 and 4.8. PL sections - 2 and 4 Legal status: Prescription only medicine. Medicinal product subject to restricted medical prescription.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: -Follow-up using a targeted checklist.

Safety concern	Risk minimization measures	Pharmacovigilance activities
	Additional risk minimization measures: None.	-Expedited reporting to the EMA (and to other countries as per local regulations) of all cases of serious anaphylaxis, anaphylactoid reactions, or a combination of individual symptoms meeting accepted diagnostic criteria and assessed as related to omalizumab. Additional pharmacovigilance activities: None.
Churg Strauss Syndrome (CSS) / Hypereosinophilic Syndrome (HES)	Routine risk minimization measures: SmPC sections - 4.4 and 4.8. PL sections - 2 and 4 Legal status: Prescription only medicine. Medicinal product subject to restricted medical prescription. Additional risk minimization measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.
Important potential risks		
Arterial Thromboembolic Events (ATEs)	Routine risk minimization measures: SmPC section - 4.8 (This is not an ADR. The available data from the pooled CT database and observational study has been summarized) PL sections - None Legal status: Prescription only medicine. Medicinal product subject to restricted medical prescription. Additional risk minimization measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: -Follow-up using a targeted checklist. Additional pharmacovigilance activities: None.
Malignant neoplasms in adults and adolescents ≥ 12 years of age	Routine risk minimization measures: SmPC sections – None. PL sections – None. Legal status: Prescription only medicine. Medicinal product subject to restricted medical prescription. Additional risk minimization measures:	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: -Follow-up using a targeted checklist. Additional pharmacovigilance activities: None.

Safety concern	Risk minimization measures	Pharmacovigilance activities
	None.	
Malignant neoplasms (children 6 to less than 12 years old)	Routine risk minimization measures: SmPC sections - None PL sections - None Legal status: Prescription only medicine. Medicinal product subject to restricted medical prescription. Additional risk minimization measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: -Follow-up using a targeted checklist. Additional pharmacovigilance activities: None.

2.7.4. Conclusion

The CHMP considered that the risk management plan version 17 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the MAH fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.9. Product information

2.9.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Xolair 75mg and 150mg solution for injection in pre-filled syringe. The bridging report submitted by the MAH has been found acceptable.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Xolair is approved with three different indications:

- For allergic asthma in adults, adolescents and children (6 to <12 years of age) in patients with convincing IgE (immunoglobulin E) mediated asthma. Xolair is indicated as add-on therapy to improve asthma control in patients with severe persistent allergic asthma who have a positive skin test or in vitro reactivity to a perennial aeroallergen as well as frequent daytime symptoms or night-time awakenings and who have had multiple documented severe asthma exacerbations despite daily high-dose inhaled corticosteroids, plus a long-acting inhaled beta2-agonist. Patients >11 years of age should have reduced lung function (FEV1 <80%).
- As an add-on therapy with intranasal corticosteroids for the treatment of adults (18 years and above) with severe chronic rhinosinusitis with nasal polyps for whom therapy with intranasal corticosteroids does not provide adequate disease control.
- As add-on therapy for the treatment of chronic spontaneous urticaria in adult and adolescent (12 years and above) patients with inadequate response to H1 antihistamine treatment.

3.1.2. Available therapies and unmet medical need

Not applicable.

3.1.3. Main clinical studies

A single PK study has been performed to support this application. The bioequivalence study K12101 was an open-label, randomized, single dose, 3 treatment group, parallel study in healthy volunteers to evaluate the pharmacokinetics (PK), immunogenicity, safety and tolerability of omalizumab.

3.2. Favourable effects

The new presentations were all supported by bioequivalence data. Bioequivalence was confirmed as the results indicate that the 300 mg of new PFS-AI or the new PFS-NSD result in comparable exposure as 2x 150 mg of the current PFS-NSD. Similarly, both new presentations were found to result in similar PK parameters. The exposure after injection at the different sites was consistent across the three product presentations. Efficacy is extrapolated from the approved presentations as supported by the bioequivalence study.

3.3. Uncertainties and limitations about favourable effects

No new uncertainties and limitations about favourable effects have been identified.

3.4. Unfavourable effects

Systemic safety is extrapolated from the approved presentations as supported by the bioequivalence study. Safety data were also collected in this study showing that there was a numerical imbalance across treatment arms for injection site reactions. Incidence of injection site reaction was lower following 2 x (150 mg/1 mL) current PFS-NSD than following 1 x 300 mg/2 mL proposed PFS-AI and 1 x 300 mg/2 mL proposed PFS-NSD.

3.5. Uncertainties and limitations about unfavourable effects

A total of 193 healthy subjects received treatment with omalizumab; 66 subjects with the proposed 300 mg PFS-AI, 64 subjects with the proposed 300 mg PFS-NSD and 63 subjects with the currently approved 2 x (150 mg) PFS-NSD. Thus, the database for local tolerance is limited and more injection site reactions were recorded for the 300 mg strength. However, as the reactions were generally mild in severity and resolved without treatment, no further actions are warranted due to this finding.

3.6. Effects Table

Not applicable.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Efficacy is deemed similar to the approved presentations as confirmed by means of bioequivalence. Systemic safety can also be concluded based on these data. The amount of local tolerance data is limited and a numerical imbalance across treatment arms was recorded. Nevertheless, as the reactions were generally mild in severity and resolved without treatment, no further actions are warranted due to this finding.

3.7.2. Balance of benefits and risks

The benefit/risk balance is deemed similar for the new (new strength of 300 mg per 2 ml for Xolair solution for injection, a pre-filled pen (PFP) and a new pre-filled syringe with needle safety device (PFS-NSD)) and the approved (powder and solvent for solution for injection and solution for injection in PFS-NSD, each formulation with 75 mg and 150 mg) presentations of Xolair.

3.8. Conclusions

The overall benefit/risk balance of Xolair is positive, subject to the conditions stated in section ‘Recommendations’.

4. Recommendations

Outcome

Based on the CHMP review of data on quality and safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Xolair is favourable in the following indication(s):

Allergic asthma

Xolair is indicated in adults, adolescents and children (6 to <12 years of age).

Xolair treatment should only be considered for patients with convincing IgE (immunoglobulin E) mediated asthma (see section 4.2).

Adults and adolescents (12 years of age and older)
Xolair is indicated as add-on therapy to improve asthma control in patients with severe persistent allergic asthma who have a positive skin test or in vitro reactivity to a perennial aeroallergen and who have reduced lung function (FEV1 <80%) as well as frequent daytime symptoms or night-time awakenings and who have had multiple documented severe asthma exacerbations despite daily high-dose inhaled corticosteroids, plus a long-acting inhaled beta2-agonist.

Children (6 to <12 years of age)
Xolair is indicated as add-on therapy to improve asthma control in patients with severe persistent allergic asthma who have a positive skin test or in vitro reactivity to a perennial aeroallergen and frequent daytime symptoms or night-time awakenings and who have had multiple documented severe asthma exacerbations despite daily high-dose inhaled corticosteroids, plus a long-acting inhaled beta2-agonist.

Chronic rhinosinusitis with nasal polyps (CRSwNP)

Xolair is indicated as an add-on therapy with intranasal corticosteroids (INC) for the treatment of adults (18 years and above) with severe CRSwNP for whom therapy with INC does not provide adequate disease control.

Chronic spontaneous urticaria (CSU)

Xolair is indicated as add-on therapy for the treatment of chronic spontaneous urticaria in adult and adolescent (12 years and above) patients with inadequate response to H1 antihistamine treatment.

The CHMP therefore recommends the extension of the marketing authorisation for Xolair subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in

the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The Marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

In addition, CHMP recommends the variations to the terms of the marketing authorisation, concerning the following changes:

Variations requested		**Type**	**Annexes affected**
B.II.e.5.a.1	B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes	Type IAin	I, IIIA, IIIB and A
B.II.e.1.b.2	B.II.e.1.b.2 - Change in immediate packaging of the finished product - Change in type/addition of a new container - Sterile medicinal products and biological/immunological medicinal products	Type II	I, IIIA, IIIB and A
B.II.b.1.c	B.II.b.1.c - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch release/control, and secondary packaging, for biol/immunol medicinal products or pharmaceutical forms manufactured by complex manufacturing processes	Type II	None
B.II.b.2.c.1	B.II.b.2.c.1 - Change to importer, batch release arrangements and quality control testing of the FP - Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing	Type IAin	II and IIIB
B.II.e.5.a.1	B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes	Type IAin	I, IIIA, IIIB and A
X.02.III	Annex I_2.(c) Change or addition of a new strength/potency	Line Extension	I, IIIA, IIIB and A

B.II.e.5.a.1	B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes	Type IAin	I, IIIA, IIIB and A
B.II.e.5.a.1	B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes	Type IAin	I, IIIA, IIIB and A
B.IV.z	B.IV.z - Quality change - Change in Medical Devices - Other variation	Type IB	None
B.II.e.5.a.1	B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes	Type IAin	I, IIIA, IIIB and A
B.II.e.1.b.2	B.II.e.1.b.2 - Change in immediate packaging of the finished product - Change in type/addition of a new container - Sterile medicinal products and biological/immunological medicinal products	Type II	I, IIIA, IIIB and A
B.II.e.5.a.1	B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes	Type IAin	I, IIIA, IIIB and A
B.II.b.1.a	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	Type IAin	None
B.II.e.5.a.1	B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes	Type IAin	I, IIIA, IIIB and A
B.IV.z	B.IV.z - Quality change - Change in Medical Devices - Other variation	Type IB	None
B.II.e.5.a.1	B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes	Type IAin	I, IIIA, IIIB and A

Extension application to add a new strength of 300 mg (150 mg/ml) for Xolair solution for injection grouped with quality type II, IB and IAIN variations to introduce a pre-filled pen (PFP) and a new pre-filled syringe with a needle safety device (PFS-NSD). The RMP (version 17.0) is updated in accordance.
In addition, the applicant took the opportunity to amend the already authorised pre-filled syringe presentations (005-011) to include an alternative immediate packaging pre-filled syringe (glass) with a 27 gauge staked needle in addition to the existing (pre-filled syringe (glass) with 26 gauge staked needle). In addition, changes were introduced in the Product Information in accordance with the latest QRD template.