London, 23 August 2018
EMA/622026/2018
Committee for Medicinal Products for Human Use (CHMP)

Preliminary assessment report for paediatric studies submitted in accordance with article 46 of regulation (EC) No 1901/2006, as amended

Fasenra

International non-proprietary name: benralizumab

Procedure no.: EMA/H/C/004433/P46

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1. Introduction

On 8 June 2018, the MAH submitted a completed paediatric study for Fasenra, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

The MAH concludes that the submitted study does not provide adequate data to obtain a paediatric indication or influence the benefit risk profile for Fasenra. Accordingly, it is the MAH opinion that immediate revisions to the SmPC are not warranted. However, the MAH may submit updates to Section 4.5 of the SmPC in a future post-approval variation to provide additional information to healthcare professionals regarding seasonal influenza virus vaccination of patients treated with Fasenra.

2. Scientific discussion

2.1. Information on the development programme

The MAH stated that study D3250C00033, titled “A multicentre, randomised, double-blind, parallel group, placebo controlled, phase 3b study to evaluate the potential effect of benralizumab on the humoral immune response to the seasonal influenza vaccination in adolescent and young adult patients with severe asthma” (ALIZE) is a stand alone study.

This study has been conducted as part of a paediatric programme based on an agreed paediatric investigation plan (PIP) (PIP number: EMEA-001214-PIP01-11) for benralizumab as add-on treatment for uncontrolled asthma with eosinophilic inflammation in children 6 years and older, adolescents (and adults).

2.2. Information on the pharmaceutical formulation used in the study

The same formulation was used as in adult trials and corresponds also to the marketed product, i.e. benralizumab 30 mg/mL solution for injection in a pre-filled syringe with 1 mL fill volume.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for the study described hereafter.

2.3.2. Clinical study

Clinical study number: D3250C00033

Title: A multicentre, randomised, double-blind, parallel group, placebo controlled, phase 3b study to evaluate the potential effect of benralizumab on the humoral immune response to the seasonal influenza vaccination in adolescent and young adult patients with severe asthma” (ALIZE).

Description

Benralizumab is a humanised, afucosylated, monoclonal antibody that binds specifically to the human IL-5 receptor alpha subunit on the target cell. The IL-5 receptor is expressed almost exclusively on the surface of eosinophils and basophils and benralizumab induces direct, rapid, and nearly complete

depletion of eosinophils in the lung tissue, sputum, blood, and bone marrow via a mechanism of enhanced antibody-dependent cell-mediated cytotoxicity.

Benralizumab is indicated as an add-on maintenance treatment in adult patients with severe eosinophilic asthma inadequately controlled despite high-dose inhaled corticosteroids plus long-acting β-agonists. The recommended dose is 30 mg administered by subcutaneous (SC) injection every 4 weeks (Q4W) for the first 3 doses, followed by once every 8 weeks (Q8W) thereafter.

As benralizumab depletes eosinophils, it is important to determine if benralizumab affects functioning of the immune system, especially in adolescents and young adults. In this current Phase IIIb study, a functional response of the immune system has been assessed by measuring antibody responses to the influenza vaccine in adolescent and young adult patients with severe asthma.

Methods

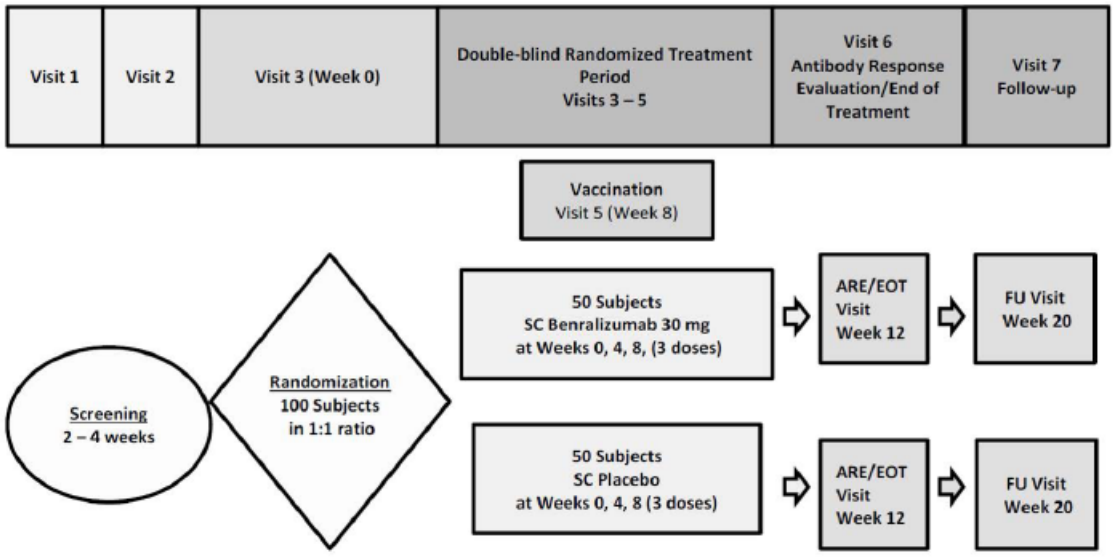
Objectives

Primary: To evaluate the potential effect of benralizumab on the humoral immune response following seasonal influenza virus vaccination in adolescent and young adult patients with severe asthma

Secondary: To assess the potential effect of benralizumab on asthma control and its safety and tolerability

Study design

This was a randomised, double-blind, parallel group, placebo-controlled study conducted at 30 centres in the US. The treatment duration was 12 weeks, with an additional study follow-up of 8 weeks.



ARE Antibody response evaluation; CSP Clinical study protocol; EOT End of treatment; FU Follow-up; SC Subcutaneous.

The study was performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with International Council for Harmonisation/Good Clinical Practice (GCP), applicable regulatory requirements and the AZ policy on Bioethics.

Study population /Sample size

The population consisted of 103 female and male patients aged 12 to 21 years, weighing ≥ 40 kg, with documented evidence of asthma and treatment with inhaled corticosteroids (ICS) and long-acting β2 agonists (LABA). Their asthma was not well controlled: Asthma Control Questionnaire 6 (ACQ-6) ≥ 1.5, or peak flow (PF) of 60-80% predicted, or ≥ 1 exacerbation requiring oral corticosteroids (OCS) in the previous year, or frequent clinical asthma symptoms during the previous 2-4 weeks.

The main exclusion criteria were clinically important pulmonary disease other than asthma; known allergy to the product formulation or influenza vaccine or eggs; history of Guillain-Barre syndrome, helminthic parasitic infection, hepatitis, immunodeficiency, cancer; use of immunosuppressive medication; receipt of live attenuated vaccine or influenza vaccine within 30 and 90 days, respectively; alanine aminotransferase (ALT) or aspartate aminotransferase (AST) level ≥ 2.5 times the upper limit of normal (ULN); and at randomisation: severe asthma exacerbation or significant active infection or known influenza infection during the current flu season.

Treatments

Patients received 3 subcutaneous doses of benralizumab or placebo at Weeks 0, 4 and 8 and one dose of seasonal influenza virus vaccine (Flulaval Quadrivalent from GlaxoSmithKline) intramuscularly at Week 8. All treatments were administered at the study centre.

The vaccine is formulated to contain 60 micrograms hemagglutinin (HA) per 0.5 mL dose in the recommended ratio of 15 mcg HA of each of the following 4 viruses (2 A strains and 2 B strains):

- A/California/7/2009 (H1N1),
- A/Hong Kong/4801/2014 (H3N2),
- B/Phuket/3073/2013 (Yamagata lineage), and
- B/Brisbane/60/2008 (Victoria lineage).

Changes to asthma background controller regimen were discouraged during the study. Asthma medications were restricted on the days of scheduled spirometry visits. Short-acting bronchodilators could be used as rescue medication during the study in the event of a worsening in asthma symptoms.

Eligible patients were allocated to treatment arms in a 1:1 ratio using centralised Interactive Voice Response System/Interactive Web Response System. The study was conducted in double-blind fashion with procedures to mitigate unblinding on the basis of blood eosinophil counts.

Outcomes/endpoints

A summary of the efficacy variables is presented hereafter.

The vaccine antibody efficacy variables were hemagglutination-inhibition (HAI) and microneutralisation (MN) antibodies to influenza vaccine. The HAI and MN tests were validated and performed by Focus Diagnostics (USA).

In addition, benralizumab serum concentrations and anti-benralizumab antibodies were measured at Week 0, 8, 12, 20, and after premature discontinuation when applicable (PPD Laboratories- USA).

Efficacy variable summary

Objective			Variable
Priority	Type	Description	Description
Primary	Efficacy	To evaluate the potential effect of benralizumab on the humoral immune response following seasonal influenza virus vaccination in adolescent and young adult patients with severe asthma	- Postdose strain-specific HAI antibody GMFRs from Week 8 - Postdose strain-specific HAI antibody GMTs obtained at Week 12 - Proportion of patients who experience a strain-specific postdose antibody response at Week 12 with antibody response defined as a ≥4-fold rise in HAI antibody titre from Week 8 - Proportion of patients who achieve a strain-specific postdose HAI antibody titre ≥40 at Week 12
Secondary	Efficacy	To further evaluate the potential effect of benralizumab on the humoral immune response following seasonal influenza virus vaccination in adolescent and young adult patients with severe asthma	- Proportion of patients who achieve a strain-specific postdose HAI antibody titre ≥320 at Week 12 - Postdose strain-specific MN GMFRs from Week 8 - Postdose strain-specific serum MN antibody GMTs obtained at Week 12 - Proportion of patients who experience a strain-specific postdose antibody response at Week 12 with antibody response defined as a ≥4-fold rise in MN antibody titre from Week 8
Secondary	Efficacy	To assess the potential effect of benralizumab on asthma control	- Change from baseline in mean ACQ-6 score at Week 12

GMFR Geometric mean fold rise; GMT Geometric mean titre

Statistical Methods

Antibody analyses

The GMFRs for the HAI and MN antibody measurements were defined as:

GMFR = antilogz (mean [logz x])

where “x” is the postdose HAI or MN antibody titre fold rise from Visit 5 (Week 8) and “z” is the natural logarithm. The GMFR value for each patient was calculated as the GMT ratio between Visit 6 (Week 12)/Visit 5 (Week 8), where GMT was calculated for each patient at each visit based on the following definition:

GMT = antilogz (mean [logz y])

where “y” is the HAI or MN antibody titre and “z” is the natural logarithm.

The analysis of the HAI or MN antibody endpoints, strain-specific GMFRs and GMTs, was performed on the vaccine immunogenicity analysis set.

For GMFR and GMT, the geometric least-square mean (LSmean) ratio between treatment (placebo/benralizumab) along with the corresponding 90% CI was calculated via an analysis of covariance (ANCOVA) model on the log transformed variable (antibody titre fold rise from Week 8 or antibody titre at Week 12). The linear model effects were treatment group as a fixed effect and age group (adolescents and young adults) as a fixed categorical covariate.

Antibody response was defined as a ≥ 4-fold rise in HAI or MN antibody from Week 8 to Week 12. The proportion of patients who experienced a postdose antibody response at Week 12 and corresponding 90% Clopper-Pearson exact CI were summarised by treatment. Likewise, the proportions of patients

who achieved at Week 12 a postdose HAI antibody titre ≥ 40 and ≥ 320, respectively, were summarised by treatment and corresponding 90% Clopper-Pearson exact CIs.

A post-hoc sensitivity analysis was performed on the primary efficacy variables excluding one placebo patient that had a serum benralizumab concentration greater than 30 ng/mL.

ACQ-6 score

The analysis of the ACQ-6 score data was performed on the full analysis set (FAS). The ACQ-6 score data actual and change from baseline results were summarised by visit and treatment group using descriptive statistics. The frequency (number and percentage) of ACQ-6 asthma control responder status was summarised at baseline and Week 12 (EOT) by treatment group according to the following limits:

- ACQ-6 (EOT) ≤0.75 → Well controlled
- 0.75< ACQ-6 (EOT) <1.5 → Partly controlled
- ACQ-6 (EOT) ≥1.5 → Not well controlled

Analysis sets

FAS: all patients who were randomised and received any IP. Patients were analysed according to their randomised treatment.

Immunogenicity set: all randomised patients who received at least 1 dose of planned study drugs (ie, 1 dose of influenza vaccine, plus 1 dose of benralizumab or placebo), had pre- (Visit 5/Week 8) and postdose (Visit 6/Week 12) HAI or MN antibody measurements, and had no protocol deviations judged to have the potential to interfere with the generation or interpretation of an antibody response. The analyses were based on the actual treatment received.

Sample size

The study planned a sample size of 50 patients in each treatment group. No formal statistical hypotheses were tested. The sample size justification was based on the precision of the estimate of the GMTs (as GMTvaccine / GMTbenralizumab+vaccine). With 50 patients per arm, the 90% CI for the GMT ratio was 0.67 to 1.48, assuming an observed ratio of 1, and that the log (postdose HAI antibody titre or postdose MN antibody titre) is normally distributed with a standard deviation (SD) of 1.2 on the natural log scale.

Results

Recruitment / Number analysed

The first patient was enrolled into the study on 01 July 2016, and the last patient last visit was 24 January 2017.

A total of 133 patients were screened and 103 patients were randomised. Out of 30 patients that were not randomised, 18 were screen failure, 4 did not meet randomisation criteria, 3 withdrew from study, 3 had a protocol deviation and 2 were lost to follow-up.

Of the 103 patients randomised, 51 patients were randomised to benralizumab 30 mg and 52 patients to placebo; a total of 100 patients (97%; 50 patients from each treatment group) completed the treatment. A total of 3 patients discontinued treatment and did not complete the study: 1 patient was lost to follow-up and 2 patients withdrew (1 patient in the benralizumab group discontinued due to inability to continue to come to visits, and 1 patient in the placebo group moved out of state). 50 patients in each treatment group were vaccinated.

A total of 99 patients (96%; 50 patients from benralizumab and 49 patients from placebo group) completed the study; 1 patient from placebo group withdrew from the study on Day 58 after receiving all 3 doses of benralizumab due to moving out of state and withdrawal of consent (no immune response evaluation at Week 12).

Analysis sets

	Number (%) of patients	
	Benralizumab 30 mg (N=51)	Placebo (N=52)
Patients randomised	51	52
Patients included in safety analysis set	51 (100.0)	52 (100.0)
Patients excluded from safety analysis set	0 (0.0)	0 (0.0)
Patients included in full analysis set	51 (100.0)	52 (100.0)
Patients excluded from full analysis set	0 (0.0)	0 (0.0)
Patients included in vaccine immunogenicity analysis set	50 (98.0)	49 (94.2)
Patients excluded from vaccine immunogenicity analysis set	1 (2.0)	3 (5.8)
Did not receive both treatment and vaccine	1 (2.0)	2 (3.8)
Missing antibody results	0 (0.0)	1 (1.9)
Patients included in pharmacokinetic analysis set	50 (98.0)	51 (98.1)
Patients excluded from pharmacokinetic analysis set	1 (2.0)	1 (1.9)
No quantifiable postdose concentrations	1 (2.0)	1 (1.9)

Baseline data

In general, baseline demographic data were balanced between treatment groups and the study population was representative of the intended target population.

The majority of patients in the FAS were White (72%) and male (59%). The mean age was 15.9 years (range: 12 to 21 years); 72 (70%) patients were 12 to 17 years (ie, adolescents), and 31 (30%) patients were 18 to 21 years of age (ie, young adults).

The population demographics are summarised in the following table.

Statistics or Category		Benralizumab 30 mg (N=51)	Placebo (N=52)	Total (N=103)
Age (years)[a]	n	51	52	103
	Mean	16.0	15.7	15.9
	SD	2.65	2.99	2.82
	Minimum	12	12	12
	Median	16.0	15.0	16.0
	Maximum	21	21	21
Age group (years) n (%)	≥12 to ≤ 17	36 (70.6)	36 (69.2)	72 (69.9)
	≥18 to ≤ 21	15 (29.4)	16 (30.8)	31 (30.1)
	Total	51 (100.0)	52 (100.0)	103 (100.0)
Sex n (%)	Male	30 (58.8)	31 (59.6)	61 (59.2)
	Female	21 (41.2)	21 (40.4)	42 (40.8)
	Total	51 (100.0)	52 (100.0)	103 (100.0)
Race n (%)	White	38 (74.5)	36 (69.2)	74 (71.8)

Statistics or Category		Benralizumab 30 mg (N=51)	Placebo (N=52)	Total (N=103)
Weight (kg)	n	51	52	103
	Mean	72.41	66.98	69.67
	SD	21.476	17.417	19.626
	Minimum	40.5	40.1	40.1
	Median	65.40	65.50	65.40
	Maximum	122.7	133.3	133.3
Height (cm)	n	51	52	103
	Mean	168.6	166.9	167.8
	SD	10.73	11.10	10.89
	Minimum	149	143	143
	Median	168.0	167.5	168.0
	Maximum	190	200	200
BMI (kg/m^2)[a]	n	51	52	103
	Mean	25.40	23.90	24.64
	SD	7.025	5.091	6.141
	Minimum	15.9	17.2	15.9
	Median	22.70	22.95	22.70
	Maximum	42.4	35.4	42.4
BMI group (kg/m^2) n (%)	n	51	52	103
	Underweight (<18.5)	5 (9.8)	7 (13.5)	12 (11.7)
	Normal (<25)	23 (45.1)	26 (50.0)	49 (47.6)
	Overweight (25-30)	10 (19.6)	12 (23.1)	22 (21.4)
	Obese (>30)	13 (25.5)	7 (13.5)	20 (19.4)

The disease characteristics at baseline were similar between treatment groups. The median time since asthma diagnosis was 12 years. In the last 12 months, the majority of patients (63%) had no exacerbations and 22% had only one exacerbation; 34% of patients had at least one exacerbation requiring systemic corticosteroids treatment and 1 patient had an exacerbation resulting in hospitalisation.

Lung function at baseline was similar between treatment groups. Average baseline pre-BD FEV1 was 2.7 L; percent predicted normal FEV1 was 78.3%, FEV1/forced vital capacity (FVC) ratio was 75.4%, and percent FEV1 reversibility was 19% for all randomised patients.

The most commonly reported background concomitant medications were selective β2-adrenoreceptor agonists (including LABAs and SABAs) (102 patients [99%]), adrenergics in combination with corticosteroids or other drugs, excluding anticholinergics (100 patients [97%]), piperazine derivatives (32 patients [31%]), LTRAs (25 patients [24%]), and corticosteroids (22 patients [21%]).

Vaccine immunogenicity results

Influenza strain antibody response for hemagglutination-inhibition

A summary of the influenza antibody responses for HAI GMFRs and GMTs at Week 12 is presented in the following tables.

The estimated geometric LSMeans between benralizumab and placebo for influenza A H3N2 strain GMFR at Week 12 were slightly different from other strains (ie, ratio >1 in favour of placebo), but the trend was not consistently observed across the other HAI analyses.

The proportion of patients who experienced influenza strain-specific antibody responses with a ≥4-fold rise from Week 8 to Week 12 for HAI were similar across strains and between treatment groups: between 44% to 56% in the benralizumab treatment group and between 31%% and 49% in the placebo group.

The proportion of patients who experienced HAI antibody responses ≥40 at Week 12 were similar across strains and between treatment groups: between 78% and 100% in the benralizumab treatment group and between 80% and 100% in the placebo group.

The proportion of patients who experienced HAI antibody responses ≥320 at Week 12 was much higher for influenza A strains (H1N1 and H3N2) than for influenza B strains (Yamagata and Victoria) in both treatment groups.

Comparable results were seen in the sensitivity analyses excluding the patient with PK anomalies.

Influenza strain antibody response geometric mean ratios by antibody for hemagglutination-inhibition, ANCOVA model (Vaccine Immunogenicity Set)

				Within-group estimates		Treatment comparison	
Influenza Strain	Timepoint/ Parameter	Treatment Group	n	Geometric LSMean estimate	SE	Estimated geometric LSMean ratio	90% CI
Influenza A H1N1	Week 12/ GMT	Benralizumab 30mg (N=50)	50	521.06	1.13	1.00	(0.76, 1.31)
		Placebo (N=49)	49	518.60	1.13		
	Week 12/ GMFR	Benralizumab 30mg (N=50)	50	3.60	1.22	0.87	(0.56, 1.35)
		Placebo (N=49)	49	3.13	1.22		
Influenza A H3N2	Week 12/ GMT	Benralizumab 30mg (N=50)	50	170.73	1.15	1.28	(0.93, 1.77)
		Placebo (N=49)	49	219.35	1.15		
	Week 12/ GMFR	Benralizumab 30mg (N=50)	50	3.25	1.18	1.19	(0.82, 1.71)
		Placebo (N=49)	49	3.85	1.18		
Influenza B Yamagata lineage	Week 12/ GMT	Benralizumab 30mg (N=50)	50	61.47	1.13	1.03	(0.79, 1.34)
		Placebo (N=49)	49	63.15	1.13		
	Week 12/ GMFR	Benralizumab 30mg (N=50)	50	3.42	1.16	0.93	(0.67, 1.29)
		Placebo (N=49)	49	3.17	1.16		
Influenza B Victoria lineage	Week 12/ GMT	Benralizumab 30mg (N=50)	50	53.10	1.14	1.26	(0.93, 1.70)
		Placebo (N=49)	49	66.85	1.14		
	Week 12/ GMFR	Benralizumab 30mg (N=50)	50	4.08	1.19	0.80	(0.54, 1.19)
		Placebo (N=49)	49	3.27	1.19		

ANCOVA Analysis of covariance; CI Confidence interval; CV% Geometric coefficient of variation; GMFR Geometric mean fold rise; GMT Geometric mean titre; GM Geometric mean; GSD Geometric standard deviation; HAI Hemagglutination-inhibition; LSMean Least-square means; N Number of patients within each treatment; n Number of patients in analysis; SE Standard error.

Influenza strain antibody response ≥4-fold rise from Week 8 to 12 for hemagglutination-inhibition (Vaccine immunogenicity set)

Influenza Strain	Treatment Group	Category	n (%)	90% Clopper-Pearson CI[a]
Influenza A H1N1	Benralizumab 30mg (N=50)	≥ 4-fold rise	22 (44.0)	(0.32, 0.57)
	Placebo (N=49)	≥ 4-fold rise	15 (30.6)	(0.20, 0.43)
Influenza A H3N2	Benralizumab 30mg (N=50)	≥ 4-fold rise	25 (50.0)	(0.38, 0.62)
	Placebo (N=49)	≥ 4-fold rise	24 (49.0)	(0.37, 0.62)
Influenza B Yamagata lineage	Benralizumab 30mg (N=50)	≥ 4-fold rise	24 (48.0)	(0.36, 0.60)
	Placebo (N=49)	≥ 4-fold rise	24 (49.0)	(0.37, 0.62)
Influenza B Victoria lineage	Benralizumab 30mg (N=50)	≥ 4-fold rise	28 (56.0)	(0.43, 0.68)
	Placebo (N=49)	≥ 4-fold rise	20 (40.8)	(0.29, 0.54)

CI Confidence interval; HAI Hemagglutination-inhibition; N Number of patients within each treatment; n Number of patients in analysis.
[a] Results from the Clopper-Pearson method.

Influenza strain antibody response of antibody titre ≥40 at Week 12 for hemagglutination-inhibition (Vaccine immunogenicity set)

Influenza Strain	Treatment Group	Category	n (%)	90% Clopper-Pearson CI[a]
Influenza A H1N1	Benralizumab 30mg (N=50)	Antibody titre ≥ 40	50 (100.0)	(0.94, 1.00)
		Antibody titre < 40	0 (0.0)	
	Placebo (N=49)	Antibody titre ≥ 40	49 (100.0)	(0.94, 1.00)
		Antibody titre < 40	0 (0.0)	
Influenza A H3N2	Benralizumab 30mg (N=50)	Antibody titre ≥ 40	49 (98.0)	(0.91, 1.00)
		Antibody titre < 40	1 (2.0)	
	Placebo (N=49)	Antibody titre ≥ 40	48 (98.0)	(0.91, 1.00)
		Antibody titre < 40	1 (2.0)	
Influenza B Yamagata lineage	Benralizumab 30mg (N=50)	Antibody titre ≥ 40	43 (86.0)	(0.75, 0.93)
		Antibody titre < 40	7 (14.0)	
	Placebo (N=49)	Antibody titre ≥ 40	39 (79.6)	(0.68, 0.88)
		Antibody titre < 40	10 (20.4)	
Influenza B Victoria lineage	Benralizumab 30mg (N=50)	Antibody titre ≥ 40	39 (78.0)	(0.66, 0.87)
		Antibody titre < 40	11 (22.0)	
	Placebo (N=49)	Antibody titre ≥ 40	43 (87.8)	(0.77, 0.95)
		Antibody titre < 40	6 (12.2)	

CI Confidence interval; HAI Hemagglutination-inhibition; N Number of patients within each treatment; n Number of patients in analysis.
[a] Results from the Clopper-Pearson method.

Influenza strain antibody response of antibody titre ≥320 at Week 12 for hemagglutination-inhibition (Vaccine immunogenicity set)

Influenza Strain	Treatment Group	Category	n (%)	90% Clopper-Pearson CI[a]
Influenza A	Benralizumab 30mg	Antibody titre ≥ 320	42 (84.0)	(0.73, 0.92)
H1N1	(N=50)	Antibody titre < 320	8 (16.0)	
	Placebo	Antibody titre ≥ 320	42 (85.7)	(0.75, 0.93)
	(N=49)	Antibody titre < 320	7 (14.3)	
Influenza A	Benralizumab 30mg	Antibody titre ≥ 320	25 (50.0)	(0.38, 0.62)
H3N2	(N=50)	Antibody titre < 320	25 (50.0)	
	Placebo	Antibody titre ≥ 320	30 (61.2)	(0.48, 0.73)
	(N=49)	Antibody titre < 320	19 (38.8)	
Influenza B	Benralizumab 30mg	Antibody titre ≥ 320	1 (2.0)	(0.00, 0.09)
Yamagata lineage	(N=50)	Antibody titre < 320	49 (98.0)	
	Placebo	Antibody titre ≥ 320	1 (2.0)	(0.00, 0.09)
	(N=49)	Antibody titre < 320	48 (98.0)	
Influenza B	Benralizumab 30mg	Antibody titre ≥ 320	4 (8.0)	(0.03, 0.17)
Victoria lineage	(N=50)	Antibody titre < 320	46 (92.0)	
	Placebo	Antibody titre ≥ 320	2 (4.1)	(0.01, 0.12)
	(N=49)	Antibody titre < 320	47 (95.9)	

CI Confidence interval; HAI Hemagglutination-inhibition; MN Microneutralization antibodies to influenza vaccine; N Number of patients within each treatment; n Number of patients in analysis.
[a] Results from the Clopper-Pearson method.

Influenza strain antibody response for microneutralisation

A summary of the influenza antibody responses for MN GMFRs and GMTs at Week 12 is presented in the following tables.

The ratio of the geometric LSMeans GMFR between benralizumab and placebo for the A/H3N2 strain and the B-Yamagata strain at Week 12 was >1 in favour of placebo, but the trend was opposite for the 2 other strains.

The proportion of patients who experienced influenza strain-specific antibody responses with a ≥4-fold rise from Week 8 to Week 12 for MN were similar across strains and between treatment groups: between 28% and 44% in the benralizumab group and between 39% and 43% ibn the placebo group.

Influenza strain antibody response geometric mean ratios by antibody for microneutralisation, ANCOVA model (Vaccine Immunogenicity Set)

				Within-group estimates		Treatment comparison	
Influenza Strain	Timepoint/ Parameter	Treatment Group	n	Geometric LSMean estimate	SE	Estimated geometric LSMean ratio	90% CI
Influenza A H1N1	Week 12/ GMT	Benralizumab 30mg (N=50)	50	3324.65	1.18	1.06	(0.72, 1.54)
		Placebo (N=49)	49	3507.92	1.19		
	Week 12/ GMFR	Benralizumab 30mg (N=50)	50	4.53	1.29	0.86	(0.49, 1.52)
		Placebo (N=49)	49	3.91	1.29		
Influenza A H3N2	Week 12/ GMT	Benralizumab 30mg (N=50)	50	3653.38	1.18	1.01	(0.70, 1.47)
		Placebo (N=49)	49	3706.34	1.18		
	Week 12/ GMFR	Benralizumab 30mg (N=50)	50	2.97	1.20	1.12	(0.75, 1.67)
		Placebo (N=49)	49	3.34	1.20		
Influenza B Yamagata lineage	Week 12/ GMT	Benralizumab 30mg (N=50)	50	361.46	1.14	0.96	(0.71, 1.29)
		Placebo (N=49)	49	346.79	1.14		
	Week 12/ GMFR	Benralizumab 30mg (N=50)	50	2.73	1.17	1.11	(0.78, 1.59)
		Placebo (N=49)	49	3.04	1.17		
Influenza B Victoria lineage	Week 12/ GMT	Benralizumab 30mg (N=50)	50	148.70	1.18	1.43	(0.99, 2.06)
		Placebo (N=49)	49	212.47	1.18		
	Week 12/ GMFR	Benralizumab 30mg (N=50)	50	3.76	1.22	0.93	(0.60, 1.44)
		Placebo (N=49)	49	3.50	1.22		

H1N1 strain=A/California/07/2009. H3N2 strain=A/Hong Kong/4801/2014. Yamagata lineage strain= B/Phuket/3073/2013. Victoria lineage strain=B/Brisbane/60/2008
N=Number of patients within each treatment. n=Number of patients in analysis.
GMFR=Geometric mean fold rise. GMT=Geometric mean titer. LSMean=Least-square means. SE=Standard error. CI=Confidence Interval

Influenza strain antibody response ≥4-fold rise from Week 8 to 12 for microneutralisation (Vaccine immunogenicity set)

Influenza Strain	Treatment Group	Category	n (%)	90% Clopper-Pearson CI[a]
Influenza A H1N1	Benralizumab 30mg (N=50)	≥ 4-fold rise	21 (42.0)	(0.30, 0.55)
	Placebo (N=49)	≥ 4-fold rise	20 (40.8)	(0.29, 0.54)
Influenza A H3N2	Benralizumab 30mg (N=50)	≥ 4-fold rise	22 (44.0)	(0.32, 0.57)
	Placebo (N=49)	≥ 4-fold rise	21 (42.9)	(0.31, 0.56)
Influenza B Yamagata lineage	Benralizumab 30mg (N=50)	≥ 4-fold rise	14 (28.0)	(0.18, 0.40)
	Placebo (N=49)	≥ 4-fold rise	19 (38.8)	(0.27, 0.52)
Influenza B Victoria lineage	Benralizumab 30mg (N=50)	≥ 4-fold rise	20 (40.0)	(0.28, 0.53)
	Placebo (N=49)	≥ 4-fold rise	19 (38.8)	(0.27, 0.52)

CI Confidence interval; MN Microneutralization antibodies; N Number of patients within each treatment; n Number of patients in analysis.
[a] Results from the Clopper-Pearson method.

Efficacy results

Change from baseline in Asthma Control Questionnaire score at Week 12

Improvement in ACQ-6 scores was noted at Week 4 and maintained through Week 12 for the benralizumab and placebo groups. The mean ACQ-6 score change from baseline for the benralizumab group was slightly larger than was observed for placebo at Week 12. There was no clear difference between benralizumab and placebo in the proportion of patients not well controlled at Week 12.

Asthma Control Questionnaire (ACQ-6) by timepoint (Full Analysis Set)

		Benralizumab 30mg (N=51)		Placebo (N=52)	
Timepoint	Statistics	Variable Analyzed (Score)	Change from Baseline (Score)	Variable Analyzed (Score)	Change from Baseline (Score)
Baseline	n	51		52	
	Mean	1.95		1.76	
	SD	0.884		0.950	
	Minimum	0.0		0.0	
	Median	1.83		1.75	
	Maximum	3.8		3.3	
Week 4	n	51	51	50	50
	Mean	1.47	-0.48	1.44	-0.30
	SD	0.984	0.980	0.877	0.739
	Minimum	0.0	-2.5	0.0	-2.0
	Median	1.33	-0.50	1.42	-0.17
	Maximum	3.7	2.8	3.3	1.5
Week 8	n	50	50	50	50
	Mean	1.47	-0.47	1.34	-0.39
	SD	0.943	0.890	0.781	0.873
	Minimum	0.0	-2.8	0.0	-2.7
	Median	1.33	-0.50	1.17	-0.50
	Maximum	4.7	1.2	3.0	1.5
Week 12	n	50	50	49	49
	Mean	1.44	-0.50	1.29	-0.42
	SD	1.058	1.114	0.830	0.925
	Minimum	0.0	-2.8	0.0	-2.7
	Median	1.17	-0.42	1.17	-0.33
	Maximum	4.3	4.3	3.8	1.2

Baseline is Week 0.
Patients were asked to recall how their asthma has been during the previous week by responding to 1 bronchodilator use question and 5 symptom questions. Questions were weighted equally and scored from 0 (totally controlled) to 6 (severely uncontrolled). For each individual patient, the mean ACQ-6 score was the mean of the responses to the questions for each visit.
N=Number of patients within each treatment
n=Number of patients in analysis. SD=Standard deviation.

ACQ-6 control response status at end of treatment (Full analysis set)

		Number (%) of patients	
Timepoint	**Category**	**Benralizumab 30 mg (N=51) n (%)**	**Placebo (N=52) n (%)**
Baseline	≤0.75 (Well controlled)	5 (9.8)	8 (15.4)
	>0.75 - <1.5 (Partly controlled)	8 (15.7)	8 (15.4)
	≥1.5 (Not well controlled)	38 (74.5)	36 (69.2)
Week 12	≤0.75 (Well controlled)	12 (23.5)	16 (30.8)
	>0.75 - <1.5 (Partly controlled)	20 (39.2)	14 (26.9)
	≥1.5 (Not well controlled)	18 (35.3)	19 (36.5)
	Missing	1 (2.0)	3 (5.8)

ACQ-6 Asthma Control Questionnaire 6; N Number of patients within each treatment; n Number of patients in analysis.
Baseline is Week 0.
Patients were asked to recall how their asthma has been during the previous week by responding to 1 bronchodilator use question and 5 symptom questions. Questions were weighted equally and scored from 0 (totally controlled) to 6 (severely uncontrolled). For each individual patient, the mean ACQ-6 score was the mean of the responses to the questions for each visit.

Safety results

The majority of patients in each treatment group received 3 administrations of investigational product (100/103 patients [97%]); 2 patients in the placebo group (2%) received 1 dose of IP, and 1 patient in the benralizumab group (1%) received 2 doses of IP.

Overview of adverse events

AE category	Number (%) of patients[a]		
	Benralizumab 30 mg (N=51)	Placebo (N=52)	Total (N=103)
Any AE	22 (43.1)	23 (44.2)	45 (43.7)
Any AE with outcome = death	0 (0.0)	0 (0.0)	0 (0.0)
Any SAE (including events with outcome = death)	0 (0.0)	2 (3.8)	2 (1.9)
Any AE leading to discontinuation of IP	0 (0.0)	0 (0.0)	0 (0.0)
Any AE leading to study discontinuation	0 (0.0)	0 (0.0)	0 (0.0)
Any AE of maximum intensity			
Mild	10 (19.6)	12 (23.1)	22 (21.4)
Moderate	9 (17.6)	10 (19.2)	19 (18.4)
Severe	3 (5.9)	1 (1.9)	4 (3.9)
Any causally related AE	1 (2.0)	2 (3.8)	3 (2.9)

AE Adverse event; IP Investigational product; N Number of patients within each treatment; SAE Serious AE.
[a] Patients with multiple events in the same category are counted only once in that category. Patients with events in more than 1 category are counted once in each of those categories.

The number of patients with any AEs were numerically balanced between the benralizumab group (43%) and the placebo group (44%). The incidence of the most common AEs (ie, those occurring at a frequency of ≥ 3% in any group) regardless of causality, were similar between groups and included asthma, headache, nasopharyngitis, oropharyngeal pain, viral gastroenteritis, and upper respiratory tract infection.

Most common adverse events (frequency of ≥ 3%) by preferred term

Preferred term	Number (%) of patients[a]		
	Benralizumab 30 mg (N=51)	Placebo (N=52)	Total (N=103)
Patients with any AE	22 (43.1)	23 (44.2)	45 (43.7)
Asthma	3 (5.9)	4 (7.7)	7 (6.8)
Headache	2 (3.9)	4 (7.7)	6 (5.8)
Nasopharyngitis	2 (3.9)	4 (7.7)	6 (5.8)
Oropharyngeal pain	3 (5.9)	2 (3.8)	5 (4.9)
Gastroenteritis viral	3 (5.9)	1 (1.9)	4 (3.9)
Upper respiratory tract infection	3 (5.9)	1 (1.9)	4 (3.9)

AE Adverse event; MedDRA Medical Dictionary for Regulatory Activities, N Number of patients within each treatment.
[a] Number (%) of patients with an AE, sorted in decreasing frequency of preferred term (total). Patients with multiple events in the same category (ie, same preferred term) are counted only once in that category.
MedDRA Version 19.1

Overall, AEs were most commonly reported within the SOC of infections and infestations (23%; 24/103) and were numerically imbalanced (difference ≥ 3%) between the treatment groups (25% in the benralizumab group and 21% in the placebo group). The second most commonly reported SOC of

respiratory, thoracic, and mediastinal disorders (14%; 14/103) were numerically balanced between the treatment groups (13.7% in the benralizumab group and 13.5% in the placebo group).

The majority of AEs that occurred were assessed as not related to the IP by the Investigator (41%; 42/103). In the on-study period, 3 patients had AEs assessed as related to IP: injection site pain (1 patient in the benralizumab group), influenza-like illness (1 patient in the placebo group), and skin papilloma (1 patient in the placebo group).

A total of 2 patients had SAEs in this study, both from the placebo group and occurred after the treatment period was complete; these were suicidal ideation and asthma, which were not considered causally related to IP.

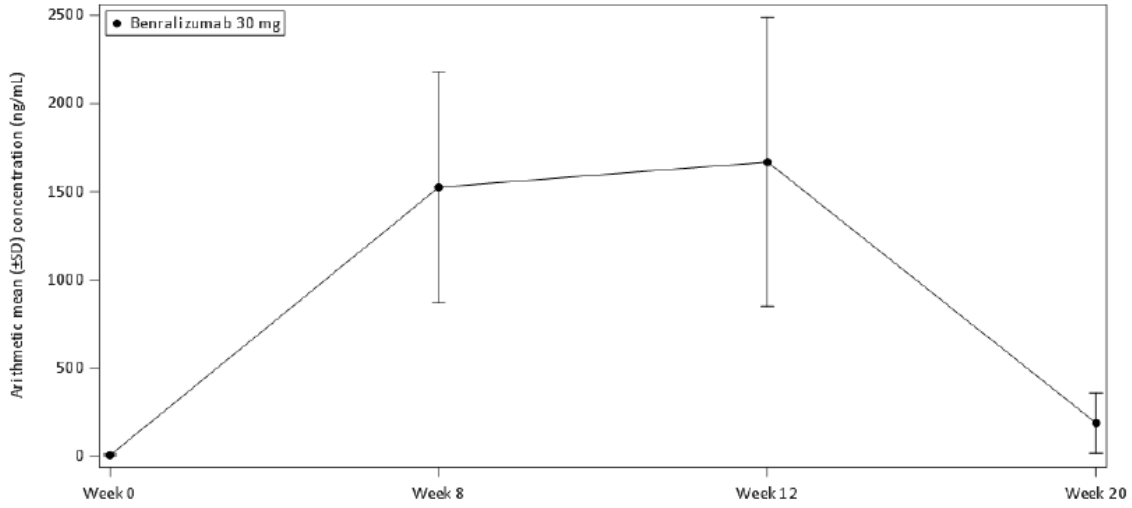
With the exception of the expected depletion of eosinophils observed over time in the benralizumab treatment group, mean values for haematology and clinical chemistry parameters were similar between the 2 treatment groups across the study and no meaningful trends were observed.

Regarding asthma exacerbations over time, 6 patients (12%) in the benralizumab group and 4 patients (8%) in the placebo group experienced an exacerbation requiring systemic corticosteroid therapy; one patient in the benralizumab group had 2 exacerbations during the study.

PK results

Serum concentrations were quantifiable in all benralizumab treated patients at Week 12, with a geometric mean value of 1323.551 ng/mL.

Arithmetic mean (±SD) serum trough concentrations (ng/mL) of benralizumab (PK analysis set)



Immunogenicity results

Overall, the prevalence of ADA was 15.7% (8/51 patients) in the study. Two (3.9%) patients were ADA-positive at baseline. Post-baseline ADA responses first became evident at Week 12, when 4/51 patients (7.8%) were newly ADA-positive, with the remaining 2 patients first becoming ADA-positive at Week 20. One patient maintained a low 1:50 titre throughout the study, and PK and eosinophils were not affected by this low level reactivity. In another patient, Week 12 PK values were well below the geometric mean 90% CI but the eosinophils remained depleted. In all 8 of the ADA-positive patients, blood eosinophil levels were depleted at the time of the vaccine assessment (Week 12), indicating that sufficient benralizumab was present to maintain the PD effect of the drug.

Individual data in patients with positive ADAs to benralizumab

Patient Identifier	Total Number of Doses	Visit	Days from Previous Dose	Days from First Dose	ADA Result	Titre	PK Concentration (ng/mL)	Eosinophils Values (10^9/L)
E7806015 ++	3	Week 0		0	Negative	<50	24.1	0.21
		Week 8	28	57	Negative	<50	1450	
		Week 12	29	85	Positive	400	59.4	0.09
		Week 20	85	141	Positive	1600	17.1	0.19
E7812002 ++	3	Week 0		0	Positive	50	<3.86	0.23
		Week 8	29	57	Positive	50	1730	
		Week 12	29	85	Positive	50	1810	0.02
		Week 20	91	147	Positive	50	205	0.03
E7824007 ++	3	Week 0		0	Positive	1600	<3.86	0.1
		Week 8	29	56	Positive	400	809	
		Week 12	29	84	Positive	1600	7.07	0.01
		Week 20	85	140	Positive	6400	<3.86	0.09
E7826003 ++	3	Week 0		0	Negative	<50	<3.86	0.22
		Week 8	29	56	Negative	<50	925	
		Week 12	29	84	Negative	<50	1100	0.01
		Week 20	86	141	Positive	6400	<3.86	0.39
E7830001 ++	3	Week 0		0	Negative	<50	<3.86	0.7
		Week 8	22	56	Negative	<50	1720	
		Week 12	35	90	Negative	<50	1730	0.01
		Week 20	84	139	Positive	400	<3.86	0.08
E7830002 ++	3	Week 0		0	Negative	<50	<3.86	0.05
		Week 8	27	57	Negative	<50	2680	
		Week 12	31	87	Positive	50	3550	0.06
		Week 20	85	141	Positive	200	82.5	0.02
E7833002 ++	3	Week 0		0	Negative	<50	<3.86	0.35
		Week 8	27	56	Negative	<50	666	
		Week 12	29	84	Positive	<=50	364	0.03
		Week 20	85	140	Positive	400	<3.86	0.48
E7834006 ++	3	Week 0		0	Negative	<50	6.94	0.38
		Week 8	29	56	Negative	<50	1450	
		Week 12	29	84	Positive	100	544	0.01
		Week 20	85	140	Positive	3200	7.83	0.44

ADA Anti-drug antibodies; PK Pharmacokinetics.
Treatment=Benralizumab 30 mg
Only persistent and transient positive patients are presented.
Note: ++ Persistent positive is defined as positive result at ≥2 post-baseline assessments (with ≥16 weeks between first and last positive) or positive at last post-baseline assessment.
Note: + Transient positive is defined as having at least one post-baseline ADA-positive assessment and not fulfilling the conditions of persistent positive.
Eosinophils values were only collected at Week 0, Week 12, and Week 20.

2.3.3. Discussion on clinical aspects

Validation of the immunogenicity assays

The HAI assay is based on the haemagglutination of RBCs when multiple copies of the haemagglutinin protein on the surface of influenza virus bind specifically to sialic acid-containing receptors on the surface of RBCs. Antibody binding to specific antigenic determinants on HA blocks haemagglutination in a concentration dependent manner. The HAI assays were validated appropriately. The estimates of assay precision are within 25% in total, which is better than the 50% threshold specified for each sample per parameter (day, technician, RBC lot and repeatability). The variance within the assays is

almost completely due to the inherent characteristics of the assay with its doubling dilutions rather than the technician or RBC lot or day. The HAI results were the primary endpoints of the trial.

The MN assay is not as robust as the HAI assay with substantial variation between different runs reflecting for example the difficulties in generating reproducible cell monolayers, virus activity, and cytopathic effect detection. Collectively the factors inherent in the assay account for 52% - 75% of variability in the incurred sample analysis, together with an overlay of variable technical performance. Problems were sufficient to prompt re-evaluation of several of these factors. The MN assay for A/Hong Kong/4801/2014 (H3N2) was particularly susceptible to false positives / cross reaction when sheep reference antisera for H1N1 (titres <360) or B strains (<570) were used and the negative serum sample was weak positive. Thus, any results from the MN assay for A/Hong Kong/4801/2014 need to be treated with caution. The issues with the MN assay are considered acceptable given that these results are supportive of the HAI results.

Immune response after flu revaccination

This study was not designed and powered to show formal equivalence of the immune response after injection of benralizumab or placebo. For HAI antibodies, 90% confidence intervals for the geometric LSMeans ratios for week 12 GMTs and GMFRs all contain 1 and the ratios fluctuate between 0.80 and 1.28, with no consistent trend across the 4 strains, thus suggesting random variations of similar response. Furthermore, in the benralizumab group, the proportion of patients with ≥ 4-fold rise of HAI antibodies from Week 8 to 12 is higher than or comparable to that in the placebo group for the four strains. Close similarity is also observed between the proportion of patients with antibody titre ≥ 40 at week 12, with a maximum 10% difference and no consistent trend across strains.

Likewise, for MN antibodies, 90% confidence intervals for the geometric LSMeans ratios for week 12 GMTs and GMFRs all contain 1 and the ratios fluctuate between 0.86 and 1.43, with no consistent trend across the 4 strains. Close similarity is observed between the proportion of patients with ≥ 4-fold rise of MN antibodies from Week 8 to 12 except for one strain where the difference is 11% in favour of placebo.

In conclusion, the humoral immune response after flu vaccination does not appear to be affected by benralizumab treatment.

Efficacy

At week 8, the median improvement in ACQ-6 score was 0.5 in both treatment arms; this difference corresponds to the minimally clinically important difference. However, this improvement was not sustained with median differences 4 weeks later of -42 and -33 after benralizumab and placebo, respectively. In addition, more patients experienced an exacerbation in the benralizumab group (12%) compared with the placebo group (8%), with one patient treated with benralizumab having 2 exacerbations during the 20-week study period. It is noteworthy that a numerical difference in favour of placebo was previously found in the adolescent subpopulation of the pivotal exacerbation trials.

In conclusion, the trial did not suggest any beneficial effect of benralizumab on asthma control or exacerbations in this adolescent population. This result is consistent with the data submitted in the initial application, which are described in the current SmPC (section 5.1 – Paediatric population).

Safety

Almost half the patients experienced treatment-emergent AEs in both treatment groups, most being mild or moderate. The only ADR reported with benralizumab was injection site pain, which is listed in the SmPC of Fasenra. There is a slight imbalance in the overall infection rate, higher in the

benralizumab group (25%) than in the placebo group (21%), which was also noted in the pivotal exacerbation studies (41% vs 35%, respectively), but without specific pattern of infections. In this trial, there were 7 events of upper respiratory infection and 2 events of sinusitis in each treatment group; the only imbalance is in the number of gastroenteritis events 4 vs 1.

In conclusion, these data are consistent with the benign safety profile of benralizumab.

Immunogenicity of benralizumab

Early development of ADAs is known with benralizumab and the prevalence in adolescents in this trial (about 16%) appears in line with that reported in the pivotal studies mainly conducted in adults (13%). These ADAs have been associated with increased drug clearance and increased blood eosinophil levels in some cases.

As expected, the highest ADA titre was measured at week 20 (i.e., 12 weeks after last IP administration) in 7/8 patients; in the 8th patient, a stable titre of 50 throughout the trial including pre-treatment questions the existence of true ADA (without this case, the ADA prevalence would be 14%).

Four (4) of the patients that developed ADAs had trough levels of benralizumab notably lower at week 12 (after the 3rd injection) than at week 8 (after the 2nd injection) in contrast to the general population, which showed increased or similar drug levels at week 12 compared to week 8.

Furthermore, eosinophil recovery was observed more rapidly in 5 of the patients that developed ADAs in comparison to the general population, which usually showed eosinophil depletion sustained at week 20; in these 5 cases, blood eosinophil levels at week 20 were higher than or close to baseline levels (week 0). However, blood eosinophil levels were still low in all cases at week 12, except for one patient, where it was the same as baseline level.

In conclusion, these data in adolescents and young adults are in line with those obtained in the pivotal trials of benralizumab in adults.

3. Rapporteur's overall conclusion and recommendation

Long-lived (or "memory") plasma cells survive in specialised niches within the bone marrow and depend on signals from their environment, most likely cytokines and ligands for adhesion receptors. Eosinophils have been reported to function as a critical component of the bone marrow survival niche where they are thought to provide pro-survival signals to nearby plasma cells *(Nature Immunology 2011, 12(2): 151-60)*. However, recent findings argue against a role of eosinophils during the maintenance of the plasma cell pool and challenge the hitherto postulated concept of an eosinophil-sustained bone marrow niche *(Eur. J. Immunol. 2018, 48: 815-21 & 822-8)*.

The main objective of this placebo-controlled trial requested by the PDCO was to investigate whether eosinophil depletion by benralizumab could affect the humoral immune response of adolescents to revaccination, as reflected by the anticipated increase in HAI and MN antibodies following one injection of seasonal flu vaccine given with a short treatment (3 injections) of benralizumab.

The study was not designed to formally show equivalent response in the presence of benralizumab or placebo but a descriptive summary of the increase in HAI and MN antibodies 4 weeks after the vaccination of a population of 100 asthmatic adolescents and young adults was presented. Given that the role of eosinophils may be less critical than previously thought, this approach is acceptable and indeed the results suggest that the humoral immune response to flu vaccine is not affected by benralizumab treatment.

This trial also provided further information regarding the efficacy, safety and immunogenicity of benralizumab in adolescents. No evidence of efficacy was shown while the safety and immunogenicity profiles appear similar to those observed in adults. These results are consistent with the data described in the current SmPC of Fasenra, and therefore, there is no need to amend the SmPC.

☒ **Fulfilled**

No regulatory action required.