09 November 2017
EMA/780390/2017
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Fasenra

International non-proprietary name: benralizumab

Procedure No. EMEA/H/C/004433/0000

Note

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

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List of abbreviations

ACQ-6	Asthma Control Questionnaire-6
ADA	Anti-drug antibodies
ADCC	Antibody-dependent cell-mediated cytotoxicity
ADR	Adverse drug reaction
AE	Adverse event
AER	Asthma exacerbation rate
APFS	Accessorised pre-filled syringe
AQLQ(S)+12	Standardised Asthma Quality of Life Questionnaire for 12 Years and Older
BIW	Biowa
BMI	Body mass index
CI	Confidence interval
CL	Clearance
CLCR	Creatinine clearance
CSR	Clinical study report
Ctrough,ss	Steady-state serum trough concentration
DRMI	Dropout Reason-based Multiple Imputation
DSMB	Data Safety Monitoring Board
EAC	Endpoint Adjudication Committee
EC50	50% of the maximal effective concentration
ED90	Estimated effective dose that gave 90% inhibition
ECL	Electro-chemiluminescent
ECP	Eosinophil cationic protein
ED90	Dose associated with 90% maximum drug treatment effect
EDN	Eosinophilic-derived neurotoxin
EOT	End of Treatment
Epro	Electronic patient-reported outcome
ER	Emergency room
FAS	Full analysis set
FEV1	Forced expiratory volume in 1 second
FU	Follow-up (visit)
FVC	Forced vital capacity
GD	Gestation day
GINA	Global Initiative for Asthma
ICS	Inhaled corticosteroids
Ig	Immunoglobulin
IgG1κ	Immunoglobulin G 1 kappa
IL-5	Interleukin-5
IL-5R	Interleukin-5 receptor
IL-5Rα	Interleukin-5 receptor alpha subunit
IP	Investigational product
ISE	Integrated Summary of Effectiveness
ISI	Integrated Summary of Immunogenicity
ISS	Integrated Summary of Safety
ITT	Intent-to-Treat
KHK	Kyowa Hakko Kirin
LABA	Long-acting β2 agonists
LAMA	Long-acting muscarinic agonists
LBA	Ligand-binding neutralising antibody assay
LS	Least squares
LTRA	Leukotriene receptor antagonists
MAA	Marketing Authorisation Application
mAb	Monoclonal antibody
MACE	Major Adverse Cardiac Event
MAR	Missing at Random
MCID	Minimally clinically important difference
MMRM	Mixed model for repeated measures
MOA	Mechanism of action
MRHD	Maximum recommended human dose

MSD	Meso-Scale discovery
NAb	Neutralising antibody
NAEPP	National Asthma Education and Prevention Program Expert Panel
NK	Natural killer (cell)
OCS	Oral corticosteroids
PD	Pharmacodynamics
PDCO	Paediatric Committee at the European Medicines Agency
PEF	Peak expiratory flow
PIP	Paediatric investigation plan
PK	Pharmacokinetic(s)
PPK	Population pharmacokinetics
PSP	Paediatric study plan
PT	Preferred term
Q4W	Every 4 weeks
Q8W	Every 4 weeks for the first 3 doses followed by every 8 weeks thereafter
RoW	Rest of the World (countries outside the European Union)
SABA	Short-acting β2 agonists
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard deviation
SEAC	Safety Endpoint Adjudication Committee
SOC	System Organ Class
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
Vc	Central volume of distribution
Vp	Peripheral volume of distribution

1. Background information on the procedure

1.1. Submission of the dossier

The applicant AstraZeneca AB submitted on 24 November 2016 an application for marketing authorisation to the European Medicines Agency (EMA) for Fasenra, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 1 April 2016.

The applicant applied for the following indication:

Fasenra is indicated as an add-on maintenance treatment for severe asthma with an eosinophilic phenotype in adult patients.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0213/2016 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0213/2016 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant 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.

New active Substance status

The applicant requested the active substance benralizumab contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

Scientific Advice

The applicant received Scientific Advice from the CHMP on 23 July 2009, 30 May 2013 and 23 January

2014. The Scientific Advices pertained to quality, non-clinical and clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Nithyanandan Nagercoil Co-Rapporteur: Bruno Sepodes

- The application was received by the EMA on 24 November 2016.
- The procedure started on 23 December 2016.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 10 March 2017. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 13 March 2017. The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 24 March 2017.
- During the meeting on 21 April 2017, the CHMP agreed on the consolidated List of Questions to be sent to the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 13 July 2017.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 21 August 2017.
- During the PRAC meeting on 01 September 2017, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP.
- During the CHMP meeting on 14 September 2017, the CHMP agreed on a list of outstanding issues to be sent to the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 09 October 2017.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 25 October 2017.
- During the meeting on 9 November 2017, 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 Fasenra on 9 November 2017.

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The claimed indication is for add-on maintenance treatment for severe asthma with an eosinophilic phenotype in adult patients.

2.1.2. Epidemiology and risk factors, screening tools/prevention

Asthma is a chronic inflammatory disorder of the airways caused by the interaction of genetic and environmental factors. It is characterised by widespread, variable, and reversible airflow obstruction; airway inflammation; excessive mucus production; and airway hyperresponsiveness that lead to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing. Progressive pathologic airway remodelling and scarring may occur in persistent asthma resulting in partially reversible or irreversible airway obstruction.

Asthma affects children and adults of all ages. It is one of the most common chronic diseases worldwide, imposing a substantial social and economic burden. Globally, an estimated 300 million individuals are affected by asthma and this is projected to reach more than 400 million by 2020 (Peters et al 2006). Asthma is also responsible for 346,000 deaths annually. Asthma occurs in all countries regardless of the level of development. In the European Union (EU), reported prevalence varies between 1.5% in Romania to 18.4% within Scotland (GINA 2016).

Asthma presents with varying degrees of severity, ranging from mild, intermittent disease to severe presentations with debilitating, even life-threatening symptoms. Severe asthma is defined as asthma that requires treatment with medium- to high-dose inhaled corticosteroids (ICS) plus a second controller (and/or systemic corticosteroids) to prevent it from becoming uncontrolled, or that remains uncontrolled despite this therapy (Chung et al 2014). Patients who remain uncontrolled continue to suffer symptoms, frequent exacerbations, and compromised quality of life. Exacerbations typically require treatment with high doses of systemic corticosteroids and may also require hospitalisation. Uncontrolled asthma can lead to a dependence on oral corticosteroids, which has a significant impact on patients; systemic corticosteroid exposure leads to serious and irreversible adverse effects, including osteoporosis, anxiety, depression, weight gain, glaucoma, and diabetes.

While the prevalence of uncontrolled severe asthma is estimated to be only 5% to 10% of the total asthmatic population (Barnes and Woolcock 1998, Busse et al 2000, O'Byrne et al 2012), these patients experience considerable morbidity (Polosa and Morjaria 2008) and account for approximately 50% of the total health care costs associated with asthma (Cisternas et al 2003).

2.1.3. Biologic features, aetiology and pathogenesis

Asthma comprises a number of distinct phenotypes, most notably eosinophilic and non-eosinophilic asthma, based on the cell profile of induced sputum samples (Simpson et al 2006, Hancox et al 2012).

Eosinophils are bone marrow-derived granulocytes that have long been recognised as the major inflammatory cells involved in the pathobiology of both childhood-onset, allergic asthma and adult-onset, nonallergic asthma (De Groot at al 2015).

- In childhood-onset, allergic asthma, T-helper (Th)2 cells are believed to drive the immune response, as greater expression of Th2 cytokines including IL-4, IL-5 and IL-13 is seen in allergen-challenged individuals, along with downregulation of Th1 cytokines (IL-2 and interferon-γ).
- Adult-onset eosinophilic asthma frequently develops in the absence of allergen-dependent activation of Th2 lymphocytes, which suggests a distinct underlying mechanism of eosinophilic inflammation apart from allergy. Recent evidence suggests that innate lymphoid cells (ILCs) have a central role in driving this type of eosinophilic asthma.

Thus, in asthma, two different pathways driven by either allergen-specific Th2 cells or allergen-independent ILC2s may lead to production of IL-5, which induces eosinophilic airway inflammation as it plays an important role in the migration, maturation and survival of eosinophils.

2.1.4. Clinical presentation, diagnosis and stage/prognosis

The term "eosinophilic asthma" describes a subphenotype of asthma that is characterised by elevated levels of eosinophils in bronchial biopsies or sputum despite chronic and correct use of adequate doses of ICS. Apart from eosinophilic airway inflammation that is relatively steroid resistant, the eosinophilic asthma phenotype is characterised by specific clinical, functional and inflammatory characteristics and comorbidities: few or no allergies to common allergens, elevated eosinophils in peripheral blood, at risk of severe exacerbations, low FEV1 and often persistent airflow limitation, chronic rhinosinusitis with nasal polyposis, good response to systemic corticosteroids and anti-IL-5 treatment.

Patients with eosinophilic asthma should ideally be diagnosed by analysing sputum samples. However, blood eosinophilia seems to be the most feasible surrogate marker to detect airway eosinophilia in patients with adult-onset airway disease in routine practice. A cut-off value of eosinophils of $<0.09 \times 109$/L has been associated with absence of airway eosinophilia in 92% of patients, whereas a value of $\geq 0.41 \times 109$/L has been associated with sputum eosinophils $\geq$ 3% in 95% of patients (Westerhof 2015).

2.1.5. Management

The current approach to anti-inflammatory controller therapy in asthma is based on a step-wise intensification of a daily maintenance regimen primarily centred around ICS and leukotriene receptor antagonists (LTRAs), with the addition of long-acting β_2 agonists (LABAs) in patients with more severe asthma (GINA 2017). While the majority of asthma patients can be adequately controlled based on these guidelines, a subset of patients with severe asthma is often uncontrolled with the current standard of care (Steps 4 and 5), and their treatment remains a significant unmet need.

There are three mAbs currently available for use as add-on treatment for severe asthma (GINA Step 5): omalizumab, mepolizumab, and reslizumab

- **Omalizumab** is a mAb that binds to immunoglobulin E (IgE) and prevents binding of IgE to FcεRI (high-affinity IgE receptor), thereby reducing the amount of free IgE that is available to trigger the allergic cascade, decreasing multiple markers of airway inflammation, including eosinophils. Omalizumab is marketed for the treatment of *moderate to severe persistent asthma in patients 12 years of age and older based on specific body weight and a positive skin test or in vitro reactivity to a perennial aeroallergen and symptoms that are inadequately controlled with ICS*.
- **Mepolizumab** is an interleukin-5 (IL-5) antagonist mAb. It inhibits the bioactivity of IL-5 by blocking the binding of IL-5 to the alpha chain of the IL-5R complex expressed on the eosinophil cell surface, thereby inhibiting IL-5 signalling and leading to reduced production and survival of eosinophils. Mepolizumab is currently marketed as an *add-on treatment for severe refractory eosinophilic asthma in adult patients*.
- **Reslizumab** is also an IL-5 antagonist mAb, which binds specifically to IL-5 and interferes with IL-5 binding to its cell-surface receptor. It binds human IL-5 blocking its biological function resulting in reduction of the survival and activity of eosinophils. Reslizumab is currently marketed as an *add-on*

therapy in adult patients with severe eosinophilic asthma inadequately controlled despite high-dose inhaled corticosteroids plus another medicinal product for maintenance treatment.

Since two anti-IL-5 mAbs with similar indication to that claimed by the Applicant are already authorised, the unmet medical need is not obvious. Mepolizumab is administered subcutaneously every 4 weeks and reslizumab intravenously every 4 weeks.

2.2. About the product

Benralizumab is a humanised, afucosylated, interleukin-5 receptor alpha (IL-5Rα)-directed cytolytic IgG1κ monoclonal antibody. It binds to the alpha subunit of IL-5R with high affinity and specificity. This receptor is specifically expressed on the surface of eosinophils and basophils. The absence of fucose in the Fc domain of benralizumab results in high affinity for FcγRIII receptors on immune effectors cells such as natural killer (NK) cells leading to apoptosis of eosinophils and basophils through enhanced antibody-dependent cell-mediated cytotoxicity (ADCC). Therefore, benralizumab has been developed in the treatment of eosinophilic asthma.

The recommended posology is 30 mg of benralizumab by subcutaneous injection every 4 weeks for the first 3 doses, and then every 8 weeks thereafter, to be administered by a healthcare professional.

2.3. The development programme/compliance with CHMP guidance/scientific advice

Scientific advice has not been sought from the Committee for Medicinal Products for Human Use (CHMP) on the quality development aspects. Scientific advice on the clinical development programme supporting the use of benralizumab was received from the EMA CHMP through Scientific Advice Procedures (March 2013, EMA/CHMP/SAWP/290939/2013).

The decision to study benralizumab in a severe patient population is consistent with feedback from the CHMP to focus on a severe patient population for the initial development programme. The primary and secondary endpoints and exacerbation definition are in line with CHMP feedback and European CHMP Guideline on the clinical investigation of medicinal products for the treatment of asthma (draft version CHMP/EWP/2922/01 Rev.1 issued in July 2013).

This advice regarding the design of the Phase III studies SIROCCO and CALIMA has been followed (e.g., endpoints, duration, patient population). Additional points were raised.

- The Applicant was advised to ensure eosinophils reached normal levels after termination of treatment. These data were not collected in SIROCCO and CALIMA as, given the unmet need for therapy for these patients, they were allowed to rollover into BORA, an extension study. However, there are data on eosinophil recovery available from earlier studies.
- Drug-drug interaction studies were not conducted. The justification for this approach has been provided and the input data from sparse sampling is considered acceptable.
- Criteria for discontinuation and reinstitution of therapy and potential risks associated with discontinuation and or reinstitution of therapy were not investigated in the Phase III clinical programme because benralizumab is intended to be a chronically administered treatment and discontinuation would lead to the return of eosinophils and symptoms. There are no data available on patients restarting treatment.

2.4. Quality aspects

2.4.1. Introduction

The Fasenra active substance is a humanized, afucosylated, immunoglobulin (IgG) G1 k monoclonal antibody (mAb). It is manufactured in Chinese Hamster Ovary (CHO) cells using animal protein free cell culture medium. It is purified through three chromatographic steps, a low pH virus inactivation step, and a nanofiltration virus removal step. It is manufactured through a validated manufacturing process, referred as the Process 3 throughout the documentation.

The Fasenra finished product is formulated as a 30 mg/mL protein solution in histidine /histidine hydrochloride, α,α-trehalose dehydrate, polysorbate 20 buffer and water for injections. It is manufactured through a validated manufacturing process.

The Fasenra solution for injection is presented as a preservative-free sterile liquid in an accessorized single-dose pre-filled syringe (APFS) for subcutaneous administration containing a nominal label claim of 30 mg in 1.0 mL. The syringe is an integral drug delivery device which follows the relevant requirements of Annex I of the Medical Devices Directive (93/42/EEC) and has been developed as per the ISO 13485:2012 and other international consensus standards. The final finished product is to be commercialized in 1 pack with 1 pre-filled syringe.

2.4.2. Active Substance

General information

Benralizumab is a humanised, afucosylated IgG1 κ monoclonal antibody targeting the alpha subunit of the human interleukin-5 receptor expressed on eosinophils and basophils. It has a high affinity for FcγRIIIA receptors expressed by natural killer cells and macrophages via which the antibody-dependent cell-mediated cytotoxicity (ADCC) effector function of benralizumab causes apoptosis of eosinophils and basophils. Afucosylation enhances affinity for FcγRIIIA receptors and the cell line used has been engineered to eliminate fucosylation competency.

The antibody is composed of two identical heavy chains of approximately 49,400 Da each, and two identical light chains of approximately 23,500 Da each. N-linked biantennary complex type oligosaccharides are attached to each heavy chain at Asn-301.

Manufacture, characterisation and process controls

Manufacture

Manufacture is initiated from the thawing of a single WCB vial. The manufacture, control, characterisation and stability of the producing cell line (CHO) have been adequately addressed. The periodicity of the cell culture process is satisfactorily qualified. The host CHO cell strain is a FUT8 knockout strain rendering the cell line incompetent in the fucosylation of post translational carbohydrates. From the point of establishing the master cell bank (MCB) onwards no directly animal derived material enters the process.

The manufacturing process and controls for the active substance have been defined to an appropriate level of detail. The process description includes details of the proven acceptable ranges (PAR) for critical

process parameters (CPP), non-critical process parameters (NCPP), in-process controls (IPC), process performance attributes (PA) and intermediate hold times.

The definitions of process inputs as critical and non-critical process parameters (CPP and NCPP) and process outputs as in-process controls (IPC), microbial controls and performance attributes are accepted. For the purposes of lifecycle management, it is accepted that should changes to the control criteria and parameter classification be required that this will be managed via the Quality Management System (QMS) acknowledging that any proposal to modify any of the process parameter or process output classifications or control criteria as registered in Section S.2.2.3 and Section S.2.2.4 of the dossier will be made via the appropriate post approval submission for approval. It is also accepted that excursions from the registered limits / ranges, including those for CPP and IPC, would initiate a deviation report with conclusions on quality, safety and efficacy supported by an appropriate investigation via the Applicant's own QMS. By reference to section 3.2.S of the dossier the same commitment to the lifecycle of the control strategy is accepted for the finished product.

Process validation

Process validation has been framed in the context of a three-stage approach that starts with process development as the first stage followed by process performance and qualification (PPQ) as the second stage and the final stage as ongoing process verification. A systematic risk-based approach to process characterisation and validation have been adopted. For manufacturing process characterisation, critical quality attribute designation is described which is then considered further in the process characterisation / quality risk management (QRM) exercise. An enhanced style approach has been established from which process and material understanding is enhanced by leveraging both tacit and explicit knowledge, of which some is derived from further product specific experimentation e.g. via design of experiments (DoE), to derive a comprehensive manufacturing control strategy that is considered compatible with anticipated regulatory oversight over the product lifecycle. The risk assessment has been made in relation to an 'assessed range' of proposed operation i.e. already incorporates risk mitigation by means of establishing the risk within a predefined range of operation and is not a true representation of all potential risk that may be associated with any one parameter when run outside of a proposed window of operability. Although this is technically building into the risk mitigation an element of parameter controllability this can be accepted since this 'pre-assessed range' is expected to represent an operating envelope based on extensive historical technology platform knowledge and capability accepted as tacit process knowledge. The tools employed during the QRM have been satisfactorily described. Data from design of experiments has been presented as computer modelled data in the form of a dashboard of prediction profiles incorporating model qualification and a summary of effect test of the modelled profiles. It has been confirmed that the summary of effect tests account for regions of the prediction profiles where the interaction between parameters concerned are most significant or, in the case of non-linear responses, the region where the highest effect is observed. The design of experiment matrices is not elucidated in the dossier nor is the resultant raw data but given the presented analysis of the data this is not a concern. It is the process characterisation studies that have qualified the proven accepted ranges (PAR) for process parameters described for each unit operation. The analyses of the data and knowledge sufficiently support the rationale to the decision-making process with regards the manufacturing process and its controls. The development activity also describes the evaluation of the overall commercial control strategy after consideration of the process characterisation. This effectively identified the specification parameters that are to be routinely monitored at release and during stability on top of the other process controls already identified. This is presented as a mitigation of risks associated with critical quality attributes by the overall control strategy, as devised, such that residual risk is considered acceptable

according to predetermined thresholds. Part of this risk mitigation does have an element of the controllability of the process within the predetermined and qualified PAR and this is acceptable.

Potential concerns for leachables from the active substance manufacturing process have been sufficiently and adequately addressed.

The process validation or PPQ has been considered an extension of the process development activity. The process is demonstrated to be consistent in its performance, robust and under control. Post validation facility modifications are accepted as having no impact on the validation status of the process. Validation of intermediate hold periods has been adequately performed as has that for reprocessing steps, column lifetime and shipping.

Manufacturing process development

Three manufacturing processes were used during the development of benralizumab. For the purposes of this submission the comparability studies and the data provided are considered satisfactory evidence of the extent of substance comparability between the different clinical phases, particularly between the pivotal clinical studies and the final commercial process.

Characterisation

Physico-chemical characterisation was performed with a testing approach appropriate to monoclonal antibodies. Orthogonal methods allowed confirming the primary structure and composition of benralizumab. The results from these analyses confirm that the molecular weight and primary sequence observed were consistent with the theoretical amino acid sequence of benralizumab.

Charge variants are characterized by orthogonal methods. Their relevance is sufficiently discussed according to impact on biological activity.

Secondary and tertiary structural analysis confirmed the folded state of benralizumab. The proposed potency assay is a cell-based assay. The cell-based bioassay is considered sufficient to control biological activity of benralizumab.

Specification

The specifications set for the release of benralizumab active substance have been set taking ICH Q6B guideline into account. The established acceptance criteria are adequate.

The validation of non-compendial methods has been conducted as per the ICH Q2(R1) guideline. The validation reports on the methods applied on the control of active substance are also applicable to the same tests used for the control of the finished product and have been provided. For compendial methods for endotoxin and bioburden, the relevant pharmacopoeia references have been provided and the suitability of the methods for the control of benralizumab active substance and finished product has been adequately summarised. The validation results demonstrate that the methods selected for the control of active substance at release and stability are suitable for their intended purpose.

The comparability between the different versions of benralizumab has been adequately discussed. The batch analyses provided indicate that all batches complied with the acceptance criteria.

The acceptance criteria for batch release and stability of the active substance benralizumab were established based on a combination of approaches in line with ICH Q6B guideline: published limits

approach (compendial limits/guidance or literature); stability limits approach (clinical risk assessment and evaluated for process capability and adequate active substance and finished product shelf-life) and non-stability limits approach (pre-determined target based on manufacturing capability and product/formulation characterization). The decision tree for determination of acceptance criteria approach was presented.

Container closure system

The safety of the material in contact with the active substance is ensured by compliance with the relevant monographs. Leachables and extractables were adequately assessed. The leachables data support the safety of the container closure system and storage recommendations proposed for the active substance.

Compatibility between active substance and the components of the proposed container closure system has been demonstrated by ongoing stability studies with maintenance of the quality attributes of the active substance during long-term study, with no protein precipitation or adsorption observed. Performance of the container was tested and found to be reproducible.

The container closure system for benralizumab active substance storage and transport has been adequately addressed.

Stability

Long term stability data for benralizumab active substance have been provided for primary batches and for commitment/validation batches. These data together with data from studies at accelerated and stress conditions support the claimed shelf-life. The stability data obtained indicate that the active substance is stable in the proposed commercial container closure system at least up to the period and under conditions tested and that batches obtained from the two manufacturing processes are comparable in respect to stability features.

The proposed active substance shelf life is considered acceptable.

An acceptable Post-Approval stability protocol has been presented. The ongoing long-term stability studies of benralizumab active substance primary and commitment batches will be completed according to the stability protocol. The annual post-approval stability commitment is adequate

2.4.3. Finished Medicinal Product

Description of the product and pharmaceutical development

Description of the product

Fasenra is a sterile clear and colourless aqueous solution for subcutaneous administration with 1ml of the 30mg/ml solution presented in a pre-filled syringe, termed as an accessorised pre-filled syringe (AFPS), which consists of a prefilled syringe (PFS) with a staked 29 gauge ½ inch stainless steel needle, needle

shield and elastomeric plunger stopper fitted with a needle safety shield, extended finger flange and plunger rod.

The finished product contains 30 mg/mL benralizumab in histidine/histidine-HCl, trehalose dihydrate, polysorbate 20 and water for injections.

Fasenra is to be administered by healthcare practitioners (HCP) only in accordance with the Instructions For Use (IFU). The device forms a single integral product with the medicinal product, is not reusable and is discarded immediately after use. The Applicant confirms that the APFS conforms to applicable essential requirements on safety, performance and labelling as outlined in Annex I of the Medical Device Directive 93/42/EEC (MDD). A fully annotated essential requirements checklist is provided to demonstrate compliance with relevant standards and the directive which is supported with further appropriately detailed information.

Pharmaceutical development

Adequate details of the development of the finished product through the clinical and commercial development have been provided. Much of the development information provided also reflects and supports the approach to finished product development, manufacture and control. Manufacturing process characterisation also evaluated potential environmental impacts to product quality such as room temperature, light exposure and exposure to vaporised hydrogen peroxide (VHP) used to decontaminate the filling isolator. A risk assessment with respect leachable substances during product manufacture from formulation of final bulk to fill finish is accepted.

Manufacture of the product and process controls

The manufacturing process of the finished product intended for commercial supply begins with thawing the active substance followed by final formulation, mixing, filtration and filling into ready to fill primary containers. The primary containers are accessorized, labelled and packaged as the finished product.

A process flow diagram summarizing the manufacturing process, as well as the material inputs, critical and non-critical process parameters, and process outputs (in-process controls, microbial controls, and performance attributes) has been provided. The process control strategy has been adequately described and accepted.

Process validation

The full scale manufacturing process is considered to have been validated by process performance and qualification batches (PPQ) to demonstrate process control and repeatability.

Validated reprocessing is described for the final bulk filtration for cases of technical failure only. It is proposed that reprocessing will also be validated at commercial scale in future studies according to the validation protocol provided and this is accepted**.**

The validation of the sterilising filters is accepted. The shipping validation included a report for shipping formulated bulk and shipping of finished assembled product.

Product specification

The specifications set for the release and stability of benralizumab finished product have been set taking ICH Q6B guideline into account: published limits, stability limits approach and non-stability limits

approach. Specifications for historical finished product batches were also provided. The specifications for Farensa finished product was developed using the same control strategy as that used for active substance, based on a product quality attribute risk assessment.

Fasenra finished product is tested using a combination of compendial and non-compendial methods. The analytical procedures applied for the control of final bulk and finished product are the ones used for the control of active substance complemented with some additional analytical procedures.

For compendial test methods, relevant pharmacopoeial references are given and for non-compendial test methods, descriptions of the assay procedures are provided. Verification of the suitability of the compendial methods for benralizumab active substance/ finished product have been provided.

Validation of non-compendial methods has been conducted using pre-approved validation protocols designed in accordance with the principle of ICH Q2(R1) Validation of Analytical Procedures. The validation reports on the methods applied on the control of active substance are also applicable to the same tests used for the control of the finished product. The validation/qualification results for both compendial and non-compendial assays are provided indicating that the assays are suitable for the intended use. The validation of non-compendial methods was adequately performed.

Batch analysis

The batch analyses provided indicate that all batches complied with the specifications in place at the time of their release. The acceptance criteria for release and stability of the finished product are in general acceptable. The product and process-related impurities identified in Farensa finished product include the same species as those identified in the active substance.

Container closure system

The Farensa finished product is commercialized in an accessorized prefilled syringe intended for subcutaneous administration. The various components of the APFS have been sufficiently described: syringe barrel and plunger stopper.

Stability of the product

The proposed finished product shelf life when packaged in the proposed container closure system and stored at the long-term storage condition of 2-8°C of 36 months is supported.

Photostability testing established the protective nature of the secondary packaging. The device functionality over the proposed shelf life has been satisfactorily established.

Comparability exercise for Finished Medicinal Drug Product

Changes between products manufactured by process 2 and process 3 have been sufficiently described and have been supported with comparability data. There were no changes between pivotal phase product and proposed commercial product, including the APFS presentation. Comparability between process 3 clinical and process 3 commercial products has been established.

Adventitious agents

The control of mycoplasma and microbial contamination has been adequately addressed.

The control of entry of adventitious virus into the process has been adequately addressed throughout the dossier. Cumulative viral clearance is achieved through viral inactivation (low pH treatment), physical removal of virus by nanofiltration and three chromatographic steps. The low pH inactivation and virus removal filtration are two dedicated viral clearance steps. Individual reports for each evaluation have been provided. The conduct and evaluation of the studies are agreed as being valid. The performance of chromatography models used during development and viral validation have been additionally qualified based on chromatogram characteristics and step yield when running process stream spiked with model virus. The conclusion that the proposed resin re-use cycles have no impact on viral clearance is supported. Virus carryover experiments were also performed to determine the effectiveness of column sanitization which were found to be supportive of the sanitisation process of each column. The viral safety factor of benralizumab was adequately assessed.

TSE infectivity control has been managed by excluding animal derived raw materials from the production process and the cell bank (MCB and WCB) preparation. A risk assessment in accordance with EMEA/410/01, current revision has been adequately summarized. The conclusions that the bovine sourced materials used during establishment of the MCB pose a low potential risk of BSE are accepted.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

The information provided by the Applicant is a comprehensive and coherent data package supporting this marketing authorisation application (MAA). Relevant guidelines and monographs have been taken into account. The results indicate that benralizumab as well as the finished product can be reproducibly manufactured.

The stability program is in general considered satisfactory. The results generated during the stability studies support the proposed shelf life and storage conditions as defined in the SmPC.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The systematic development of the active substance and the finished product has been well presented and effectively communicated in the quality dossier. The active substance manufacturing process has been well defined. The same applies for the finished product and the information in the dossier adequately supports the finished product development.

2.4.6. Recommendation for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommended an additional point for further investigation.

2.5. Non-clinical aspects

2.5.1. Pharmacokinetics

Primary pharmacodynamic studies

IL-5 is a cytokine that drives growth, differentiation, recruitment and activation of eosinophils and in patients with eosinophilic asthma, eosinophils in lung tissue are an important part of the immune response: this cell population may have a specific role in combating respiratory viral infections. Inhibiting IL-5 could reduce the occurrence of asthma exacerbations.

In vitro pharmacology studies showed that benralizumab, a humanised monoclonal antibody, bound with high affinity to human and cynomolgus monkey IL-5Rα receptors, but not to murine IL-5Rα receptors. Benralizumab blocked activation through the IL-5 receptor, located on eosinophils, resulting in a reduction of the signal to drive eosinophil growth and differentiation, recruitment and activation. Testing for activity at rat IL- 5Rα receptors was not conducted but the rat IL-5Rα receptor gene has ~90% nucleotide identity with the mouse sequence and ~85% identify at the protein level: benralizumab is concluded not to be active at mouse or rat IL-5 receptors. Despite an apparent 2.6-fold difference in binding affinity (42 and 16 pM KD for monkey and human receptors, respectively), there was essentially no quantitative difference in the EC50s for binding to monkey and human eosinophils (40 and 36 pM).

The murine progenitor of benralizumab, KM1259, shares the epitope specificity for hIL-5α receptors with benralizumab and was shown to inhibit binding of IL-5 to IL-5α receptors; benralizumab inhibited IL-5-dependent cell proliferation. The Applicant was asked to provide more information on the physicochemical characteristics of benralizumab and its derivatives used in the pharmacology studies. The Applicant provided some additional details including results of testing for appearance, monomer content (by size exclusion chromatography), pH, osmolarity and oligosaccharide profiling. However, no information was present for fucosylated parent anti-IL-5Rα mAb (KM8400) and physicochemical characterisation was either not done or was not archived. This was accepted.

In testing of binding of benralizumab to eosinophils, some variability in response was seen: testing of samples from 3 humans and 3 monkeys, binding to eosinophils could not be shown in 1 monkey. This variability was not explained and the Applicant was requested to clarify this result and discuss possible clinical implications. The Applicant's response noted that the reasons for not binding to eosinophils in one cynomolgus monkey blood sample of the 3 donors evaluated are not known: in humans, polymorphisms of IL-5Rα are known but these do not affect binding of IL-5 to IL5Rα but comparable data about polymorphisms in monkey IL-5Rα are not available. Other explanations could be assay variability, low IL-5Rα numbers on the eosinophils in this monkey or some technical failure in the assay: none of these are known to be true.

IL-5 receptors are also notably present on basophils, which are also are likely to be targeted by benralizumab. However, benralizumab did not bind to lymphocytes, monocytes or neutrophils.

Benralizumab acts to deplete eosinophils by antibody-dependent cell-mediated cytotoxicity (ADCC). With this action, sufficiently high doses of benralizumab should cause detectable decreases in eosinophil count and even lead to elimination of eosinophils. However, induction of eosinophil apoptosis by ADCC in *in vitro* testing did not result in eosinophil degranulation. In terms of Fc-mediated functions, the Applicant presented data from a publication (Kolbeck et al 2010) in which the afucosylation step was shown to increase potency for binding to FcγRIIIa from both humans and monkeys, supporting the decision to develop the defucosylated antibody, as this *in vitro* testing suggests it should be more effective at

inducing eosinophil depletion *in vivo*. The Applicant was requested to provide the study report relating to this work but responded that there was no such report and all information that was available on methodology applied to Fcγ receptor binding, ADCC and CDC was contained in the publication.

In *in vivo* pharmacology studies, benralizumab, when given to naive or allergen-challenged cynomolgus monkeys, demonstrated rapid and pronounced reduction of eosinophils in blood, bone marrow and bronchoalveolar lavage fluid, demonstrating its pharmacological activity in vivo in this species. However, like results with eosinophil binding, there were some indications that some individuals did not show this profile. The reasons for these instances of difference are not understood. However, the results suggest that the hypothesis, that reducing eosinophilic cell infiltration in the lungs could improve lung function in an asthma challenge, was supported sufficiently to support clinical testing in patients with asthma.

Secondary pharmacodynamics and pharmacodynamic drug interaction studies were not conducted. Safety pharmacology endpoints were included in GLP toxicology studies in cynomolgus monkeys, so minimising use of non-human primates. These studies included assessment of potential effect of benralizumab on cardiovascular, respiratory and central nervous systems, following single and repeated subcutaneous and intravenous doses, up to 30 mg/kg. There was no indication of toxicity in these evaluations.

2.5.2. Pharmacokinetics

Validation studies showed that assays to quantify benralizumab and antibody to benralizumab in cynomolgus monkey serum were suitable for use. Reporting of the stability samples for antibody to benralizumab was incomplete but results suggested that immunogenic reactions occurred only in a minority of monkeys: no objection was raised in respect of these results.

The Applicant assessed kinetics of benralizumab in five toxicity studies of up to 9 months' dosing duration in cynomolgus monkeys dosed either by intravenous or subcutaneous injection at doses up to 30 mg/kg and in pregnant monkeys and offspring in a developmental toxicity study. The product is intended for subcutaneous use by patients and in monkeys bioavailability by this route was ~60% with Tmax seeming to be longer at higher doses but within 3 days at lower doses, i.e. doses closer to the intended human dose. Across studies, exposure was dose-proportional over the range 1-30 mg/kg with no gender difference noted; kinetic results were typical of an IgG1 antibody without an antigen sink. Mean clearance values ranged from 3.6 to 8.4 mL/kg/day and mean terminal elimination half-lives ranged from 7.8 to 20.4 days. In pregnant monkeys, there was evidence of placental and/or milk transfer as infants showed detectable benralizumab concentrations despite not being dosed directly. Excretion of benralizumab in the maternal milk was not investigated directly, however, although it may be assumed that benralizumab will behave similarly to other IgG1 antibodies; the lack of such data is accepted. Immunogenic reactions were seen in a minority of monkeys and correlated with accelerated clearance of, and reduced exposure to, benralizumab.

These studies suffice to show that there was systemic exposure to benralizumab in the nonclinical safety studies.

2.5.3. Toxicology

Single and repeated dose general toxicity studies were completed in cynomolgus monkeys with dosing for up to 9 months, every 2 weeks, with use of subcutaneous and intravenous routes. A pre- and post-natal developmental toxicity study was also completed in pregnant and neonatal cynomolgus monkeys. No genotoxicity or carcinogenicity studies were done. Tissue cross-reactivity studies were completed.

Single dose toxicity

In the *in vivo* toxicity studies, the Applicant selected doses progressively i.e. doses for later studies were selected based on results from earlier studies and the doses selected are accepted as suitable. In the pharmacology file, plasma concentrations up to ~10 µg/ml were considered appropriate for the primary activity of the drug to impede infiltration of eosinophils into the airways following an antigenic challenge, and in the toxicity studies, the typical Cmax plasma concentrations were up to ~850 µg/ml at the top doses used.

Single dose toxicity studies were limited to a non-GLP study in three monkeys only with no control group or terminal necropsy: the primary objective was to evaluate toxicokinetics and immunogenicity of benralizumab. The study has some insufficiencies which hinder interpretation of observed findings of haematuria and proteinuria, in addition to reduction of eosinophil counts, but as there are data from repeat dose GLP compliant studies, this is accepted.

Repeat dose toxicity

Three repeat dose general toxicity studies were completed, all with inclusion of a recovery period. In the first, benralizumab was given by bolus intravenous injection every 3 weeks at doses of 0.1, 1.0, 10, and 30 mg/kg over 9 weeks; in the second, it was given by subcutaneous injection every 2 weeks at 1, 10 and 30 mg/kg over 15 weeks and in the third, every 2 weeks at 10 or 25 mg/kg intravenously or subcutaneous over 39 weeks. These studies included specific safety pharmacology, immunotoxicity (lymphocyte immunophenotyping) and fertility endpoints (including hormone analyses). Testing for development of anti-benralizumab antibodies was also completed and this was seen in 2 of 24 (8.3%), 9 of 36 (25%) and 2 of 36 (5.5%) of monkeys given benralizumab in the 9-, 15- and 39-week studies, respectively.

Benralizumab was not associated with major toxicity. Reduction or depletion of eosinophils was noted and is the intended therapeutic action of the drug. The magnitude of this effect varied across the three studies: nearly full depletion of peripheral and bone marrow eosinophils was still observed after the recovery period (18 days), in the 9-week study; partially reversibility of the reduction in eosinophils was noted in the 39-week study (the recovery period was 12 weeks); but there was apparently, little or no reduction in the 15-week study. The Applicant was asked to detail the time course of eosinophil counts in order to determine if there was a rebound effect on eosinophil counts on withdrawal of benralizumab, noting the period of time needed to elapse for total clearance of the drug after its last dose. Data are only available from a small number of monkeys However, were this effect to happen in patients, it might pose a real risk of asthma exacerbation with potentially severe, including fatal, events; as these relate to loss of the drug in plasma occurring weeks, or months, after the last dose, it may not be recognised as a drug-related event in clinical use. In its analysis, the Applicant presented a summary of the results on recovery eosinophil counts in monkeys in toxicity studies where such data are available and to evaluate whether these data substantiate the concern raised. The Applicant argued that considering results from all available monkeys, there did not appear to be a rebound effect for blood absolute eosinophil values and the majority of monkeys had absolute blood eosinophil values comparable to or lower than baseline at the last timepoint assessed after benralizumab dosing was stopped. In some monkeys with antibodies to benralizumab, blood eosinophils increased later in the study compared to baseline, but it was also the case that some monkeys without detectable anti-benralizumab antibodies showed an increasing trend for blood eosinophils throughout the study during the dosing and recovery phases. It is also relevant to consider the normal range of eosinophils in cynomolgus monkeys: historical control values from one of the testing facilities showed absolute blood eosinophils in Chinese cynomolgus monkeys in the range

20-390 /µl, with a median of 40/µl and this is generally consistent with other published data. Thus, there is a 20-fold range of what might considered normal. This issue was considered resolved.

Other noteworthy findings in the toxicity studies included transient reduction in neutrophil counts (9-week study, 2 females in the 30 mg/kg dose group), gastrointestinal acute inflammation and/or haemorrhage (15-week study, 1 female at 10 mg/kg and 1 male and 2 females at 1 mg/kg), right wrist anomaly (dislocated radial-carpal joint with associated torn ligaments) (39-week study, 1 male at 25 mg/kg intravenously), transient signs of bruising / reddened areas around the eyes, on the face, chest and lower abdomen (petechiae and ecchymosis), decreased platelet count and indicators of circulating erythrocyte mass (39-week study, 1 female at 25 mg/kg intravenously) and minimal-to-mild necrosis of papillary muscle (39-week study, 1 male in each group given benralizumab), with 1 of the 3 males (25 mg/kg, intravenously) also with mild interstitial fibrosis. The Applicant judged that except for the reduction in neutrophils counts, all these were considered to be not related or unlikely related to benralizumab and, therefore, set the NOAEL at the highest tested doses for the 15- and 39-week studies and at equal or lower than the highest tested dose for the 9-week study. Reductions in the neutrophil counts were transient, and only observed in the group with the highest systemic exposure to benralizumab, across the three studies, and benralizumab was not found to bind to neutrophils. Therefore, based on non-clinical data, reductions in neutrophil counts would seem to be of limited clinical concern as this can also be monitored clinically in patients if needed.

The gastrointestinal findings were not related to benralizumab by the Applicant due to the acute nature of the finding and as it was not seen in prior toxicity studies and was not apparently dose-related. Its occurrence in the 15-week study could be viewed as following an inverse dose/effect relationship (3, 1 and 0 monkeys at 1, 10 and 30 mg/kg, respectively); systemic exposure at the low dose was the closest to the systemic exposure expected in humans, although was still somewhat higher. The Applicant was asked to provide further interpretation of the gastrointestinal acute inflammation / haemorrhage. The Applicant's opinion is that the findings are considered as not related to benralizumab based on their low incidence, acute nature, lack of evidence of such finding in other studies, lack of clear dose response and results of tissue cross-reactivity studies, which, in what concerns gastrointestinal tissues, have only revealed staining of intravascular proteins. There is also no clinical signal for specific concern. This was accepted by CHMP concluding that the weight of evidence does not indicate a risk of gastrointestinal inflammation/haemorrhage

Although there was no evidence of cardiotoxicity in the in-life stages of the general toxicity studies, in tissue cross reactivity studies, binding to cardiac myocytes was noted in monkeys but not in humans; however, this binding was cytoplasmic and thus judged not likely to be of *in vivo* relevance. In study AA00095 but not in the other general toxicity studies, there were instances of papillary muscle necrosis seen at post mortem in monkeys. The Applicant considered these were unrelated to benralizumab but was asked to justify this view further as there was little support from the literature that papillary muscle necrosis is a common background finding. The Applicant argues that papillary muscle necrosis showed limited incidence, did not occur in females, and showed no dose-response, and fibrosis was present in a control animal at recovery. Furthermore, the published evidence could support these changes as being regarded as spontaneous background lesions in this species. The Applicant's arguments were accepted by CHMP leading to the conclusion that no corroboration of a causal role for benralizumab can be identified at present..

Repro-toxicity studies

Potential adverse effects on fertility were assessed through inclusion of specific fertility endpoints (menstrual cycle lengths, testicular volume/size, sperm analysis for sperm count, morphology and motility and analysis of reproductive hormones), in addition to the reproductive organ weights and

histopathology analysis at necropsy, in the 39-week repeat dose toxicity study, in which all monkeys were sexually mature. In these assessments, fertility was not affected by benralizumab. This approach to evaluation of effects on fertility, embryofetal and pre- and post-natal development is accepted and supported by the recommendations in the ICH S6 (R1) guideline. However the SmPC, clearly mentions that no animal studies dedicated to investigating effects on fertility have been conducted.

In pregnant monkeys, there was no effect of benralizumab on pregnancy viability or on infant development: in the study, it was given by intravenous injection at doses up to 30 mg/kg every other week from gestation day 20/22 to one month post-partum. Embryofetal development was monitored by ultrasound examinations and gestational length; neonates/infants were evaluated up to reaching 6.5 months of age and, among other aspects, were also examined for effects of benralizumab on T-cell dependent antibody responses. Benralizumab-related findings were limited to a reduction / depletion of eosinophils in the maternal animals and neonates / infants and the occurrence of anti-benralizumab antibodies in some dams (1 out of 14 (7%) and 2 out of 19 (11%) at 10 and 30 mg/kg, respectively); as such, the NOAEL was set at the highest tested dose (corresponding to maternal systemic exposures over 200-times higher than the human exposure, and also to neonate / infant mean plasma concentrations higher than the human plasma Cmax). Considering that depletion of eosinophils in neonates/infants is not an intended effect and may be considered as adverse for the progeny, this is to be included in the SmPC section 5.3, Preclinical safety data, under the heading 'as follows : In the offspring of monkeys dosed while pregnant, there was a reduction in eosinophils'. There was also an apparent increased incidence of third trimester fetal losses in the benrazilumab-treated groups. This was attributed by the Applicant to 3 cases (1 and 2 at 10 and 30 mg/kg, respectively) of complications associated with parturition (breech presentation) and, also considering the lack of developmental abnormalities in any fetuses and no known pharmacological effect of benralizumab capable of explaining a specific causality of third trimester fetal loss, considered as not related to benralizumab treatment. The Applicant's explanation and conclusion are accepted by CHMP, also considering the lack of effects on parturition for approved medicinal products which target IL-5.

The lack of studies with dosing of juvenile animals is also accepted, considering that the medicine is intended for adults, the lack of non-clinical studies in the agreed paediatric investigation plan, and the results from the enhanced pre- and post-natal development study.

Genotoxicity

Genotoxicity studies are not required for this product.

Carcinogenicity

The Applicant's approach to assessing the risk of carcinogenicity with benralizumab was to consider the options for experimentation that might be open to the Applicant: these were not considered suitable or were judged likely to be misleading. The Applicant noted that available evidence with benralizumab from studies in monkeys indicated no specific concern for induction of cancer and considered that further experimental studies with benralizumab would not be useful indicators of clinical risk. The Applicant's arguments to justify limitations on testing methodology are generally agreed. They are detailed below :

Blockade of the cytokine IL-5Rα, as opposed to the receptor, by other antibodies does not lead to total loss of eosinophils indicating that other factors, possibly IL-3 and/or GMCSF, can suffice to perpetuate the cell population, despite that IL-5 is a growth factor for these cells. In this regard, the additional action of benralizumab to deplete eosinophils by ADCC may pose additional risks than a purely IL-5 blocking

antibody. As a consequence, negative results from studies addressing the risk of carcinogenicity with IL-5 blockade might not reflect the profile of benralizumab. A reduction of eosinophils is anticipated with use of benralizumab and in experimental work in mice, elimination of eosinophils was suggested to increase risk of cancer (Simson et al 2007). In brief, this work suggested eosinophils could play a role in limiting risk of developing cancer following injection of a known carcinogen (methylchloroanthrene). This may not be of direct relevance to assessing human risk with benralizumab as the method used injection of a potent carcinogen and the mode of action of eosinophils may be related to the ability to contribute to formation of a capsule round the tumour; nevertheless, the absence of a mention of this by the Applicant suggests it has not shown sufficient consideration of the literature describing some association of IL-5 inhibition / eosinophil depletion with a reduction in tumour risk.

In CHMP scientific advice in 2009, the Applicant's position supporting its lack of experimental studies was endorsed but the Applicant was advised to 'pay some attention, not only to the outcome of the chronic study in monkeys, but also to a thorough evaluation of the available information regarding the role of IL-5 in processes that may impact on cellular (in)stability, e.g. cellular division processes, cellular communication, apoptosis, as well as any impact on the immune function.' The Applicant was asked to provide further consideration of whether any experimental work could be done that could shed more light on the risk of cancer, particularly in relation to depletion of eosinophils. There are published data to the effect that eosinophils can have protective effects against tumours, but there are much conflicting data. The matter is not entirely resolved, but the experimental data are difficult to extrapolate to predicting a relevant clinical risk and the conclusion was made that there is insufficient evidence that benralizumab, by depleting eosinophils, poses a risk of cancer: considering this, its risk/benefit balance was judged favourable.

Local Tolerance

When given as a single subcutaneous injection, benralizumab caused no adverse findings and no histological lesions of toxicological significance were noted at the injection sites for up to 14 days after dosing. There are no local tolerance concerns. In the general toxicity studies, there was no evidence of toxicity to the immune system.

2.5.4. Ecotoxicity/environmental risk assessment

Benralizumab is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Reference is made to guidance on the environmental risk assessment of medicinal products for human use (CHMP/SWP/4447/00) which specifically exempts proteins from the need for an assessment of potential risk to the environment. Therefore, benralizumab is not expected to pose a risk to the environment.

2.5.5. Discussion on non-clinical aspects

The non-clinical development of benralizumab is -overall acceptable. Benralizumab presented pharmacological properties suggesting the potential to deplete tissue eosinophils so leading to a beneficial effect in patients with eosinophilic asthma. In the pharmacology studies, the Applicant responded adequately to a question to the effect that some monkeys did not show binding of benralizumab to eosinophils. The Applicant was unable to provide much further data than was published or supplied in the initial dossier into physicochemical characteristics of test materials used, and Fcγ recreptor binding, ADCC and CDC methods but the dossier was finally accepted with these limitations.

After review of the kinetic section of this dossier, there were no concerns raised.

The Applicant conducted safety studies that should suffice to characterise toxicity of benralizumab: studies were in a suitable species, cynomolgus monkeys, of sufficient duration, and used sufficient doses and were of suitable designs. No major toxicity occurred. The Applicant was asked to provide further comments on a number of issues. In relation to an apparent lack of depletion of eosinophils in a 15-week general toxicity study, the Applicant showed that mean eosinophil values were skewed by large values in individual monkeys and consideration of the mean value could fail to show the full picture. There was high baseline variability - this (i.e. mean baseline eosinophil counts) varied by up to 28-fold. Given this variability, the Applicant's explanation was considered acceptable. There was however insufficient evidence to associate benralizumab with certain findings in the toxicity studies: the Applicant was asked to provide further comment on whether gastrointestinal haemorrhage / inflammation was a suggested toxicity. On consideration, the evidence was judged not to support a causal role for benralizumab and the issue considered solved. The Applicant was also asked to comment on whether there was evidence that longer exposure to benralizumab could have caused papillary muscle necrosis. Its occurrence in 3 males in the longer term general toxicity study in monkeys may be a potential signal but one for which no corroboration of a causal role for benralizumab can be identified at present..

No dedicated fertility studies have been conducted however assessment of specific fertility endpoints (menstrual cycle lengths, testicular volume/size, sperm analysis for sperm count, morphology and motility and analysis of reproductive hormones), in addition to the reproductive organ weights and histopathology analysis at necropsy, were carried out in the 39-week repeat dose toxicity study, in which all monkeys were sexually mature. A statement related to the reduction of eosinophils in the offspring of monkeys dosed while pregnant, is introduced on the SmPC section 5.3.

The Applicant was also asked to comment on the risk of rebound eosinophilia on stopping benralizumab. The majority of animals had absolute blood eosinophil values comparable to or lower than baseline at the last timepoint assessed after benralizumab dosing was stopped and the evidence available did not substantiate the concern raised. There was no relevant signal in the clinical data and this point was considered resolved.

The Applicant was also asked to address whether this drug could, by depleting eosinophils, pose an undue risk of cancer. The response was considered acceptable and the conclusion was that there is no evidence that use of benralizumab would pose an increased risk of cancer in patients and that the product's risk/benefit profile was positive.

2.5.6. Conclusion on non-clinical aspects

No major objections were identified and the concerns raised by CHMP have either been addressed or the limited information acknowledged and accepted by the CHMP following applicant justification. Therefore, there are no remaining objections to grant of a marketing authorisation can be granted and there are no further issues to be resolved were approval to be granted.

2.6. Clinical aspects

2.6.1. Introduction

GCP

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

The applicant 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.

A GCP inspection was conducted in May-June 2017 for the following clinical study D3250C00018 (CALIMA) centre study numbers: 206 (in Argentina) and 5501 (in Philippines) as well as the Sponsor in the US. At the clinical sites, there were a few major and minor findings. At the Sponsor's site, there were one critical finding and three major findings.

Regarding the quality of the data, ethical conduct and GCP compliance, the inspectors considered that in general most of the findings detected can be considered process related, mainly as a consequence of the suboptimal trial management and oversight by the Sponsor on the delegated tasks. Data collected at sites inspected are considered of an acceptable quality and inspectors considered that the trial had been conducted following ethical standards and GCP and that the deficiencies detected have no impact on the inspected trials' data reliability and validity.

- Tabular overview of clinical studies

Pharmacokinetic studies

Type of study	Study identifier	Location of study report in Module 5	Objective(s) of the study	Study design and type of control	Test product(s), Dosage regimen, Route of administration	No. of subjects rand/treated	Healthy subjects or diagnosis of patients	Duration of treatment	Study status; type of report
Healthy subject pharmacokinetic (PK) and initial tolerability studies									
Safety	4563-001 (KHK-sponsored)	NA[a]	Safety	SB/PC	IV Single-dose 0.03 mg/kg 0.1 mg/kg 0.3 mg/kg 1.0 mg/kg 3.0 mg/kg Placebo	40/40	Healthy adult Japanese males	Single IV infusion	Complete; Full
Safety	4562-002 (KHK-sponsored)	NA[a]	Safety	SB/PC	SC Single-dose 25 mg 100 mg 200 mg Placebo	24/24	Healthy adult Japanese males	Single SC dose	Complete; Full
Patient PK and initial tolerability studies									
Safety PK/PD	MI-CP158 (D3250C00001)	5.3.3.2	Safety Steady-state PK PD	OL, DE Multicentre	Benralizumab IV infusion Single-dose 0.0003 mg/kg 0.003 mg/kg: 0.03 mg/kg: 0.1 mg/kg 0.3 mg/kg	44/39 0.0003 mg/kg: 5/3 0.003 mg/kg 6/6 0.03 mg/kg: 6/6 0.1 mg/kg:	Adult subjects with mild asthma	Single IV infusion	Complete; Full
					1.0 mg/kg 3.0 mg/kg	6/5 0.3 mg/kg: 6/6 1.0 mg/kg: 9/8 3.0 mg/kg: 6/5			

Pharmacodynamic studies

Type of study	Study identifier	Location of study report in Module 5	Objective(s) of the study	Study design and type of control	Test products, Dosage regimen, Route of administration	No. of subjects rand/treated	Healthy subjects or diagnosis of patients	Duration of treatment	Study status; type of report
Patient pharmacodynamic (PD) and PK/PD Studies									
PD	MI-CP166 (D3250C00002)	5.3.4.2	PD Safety and tolerability PK Immunogenicity	RD/DB/PC/DE Multicentre	Cohort 1 Single-IV dose Benra 1.0 mg/kg IV Placebo IV Cohort 2 Multiple SC (3) doses (Q4W for 8W) Benra 100 mg SC 200 mg SC Placebo SC	Total: 27/26 Cohort 1 1.0 mg/kg: 8/7 Placebo: 5/5 Cohort 2 100 mg: 4/4 200 mg: 5/5 Placebo: 5/5	Adult patients with asthma who have ≥2.5% eosinophils in sputum	Cohort 1: Single IV infusion Cohort 2: 8 weeks	Complete; Full

Efficacy and safety studies

Type of study	Study identifier	Location of study report in Module 5	Objective(s) of the study	Study design and type of control	Test products, Dosage regimen, Route of administration	No. of subjects rand/treated	Healthy subjects or diagnosis of patients	Duration of treatment	Study status; type of report
Controlled Clinical Studies									
Efficacy and Safety	MI-CP186 (D3250C00004)	5.3.5.1	Efficacy Safety PK Immunogenicity	RD/DB/PC Multicentre	Single IV dose Benra 0.3 mg/kg 1.0 mg/kg Placebo	Total: 110/103 0.3 mg/kg: 36/35 1.0 mg/kg: 36/32 Placebo: 38/36	Adult patients who required an urgent healthcare visit for treatment of an acute asthma exacerbation	Single IV infusion	Complete; Full
Safety	MI-CP197 (D3250C00005)	5.3.5.1	Safety PK Immunogenicity	RD/DB/PC /DE Multicentre	Multiple SC (3) doses (Q4W for 8W) Benra 25 mg 100 mg 200 mg Placebo	Total: 25/24 25 mg: 7/6 100 mg: 6/6 200 mg: 6/6 Placebo: 6/6	Adults aged 18-80 years with asthma	8 weeks	Complete; Full
Efficacy and Safety	4563-003 (KHK-sponsored)	NA[a]	Efficacy Safety PK Immunogenicity	RD/DB/PC /DR Multicentre	Multiple SC doses (Q4W for 3 doses; Q8W for next 4 doses) Benralizumab 100 mg 20 mg 2 mg Placebo	106/103	Suspected eosinophilic adult subjects with uncontrolled, asthma requiring medium- to high-dose ICS + LABA and having a history of ≥2 but ≤6 asthma exacerbations	52 weeks	Complete; Full
Efficacy and Safety	MI-CP220 (D3250C00006)	5.3.5.1	Efficacy Safety and Tolerability Immunogenicity PK QoL	RD/DB/PC /DR	Multiple SC doses (Q4W for 3 doses; Q8W for next 4 doses) Benra 100 mg 20 mg 2 mg Placebo	N=609/606	Eosinophilic + and Eosinophilic-adult patients with uncontrolled asthma requiring medium- to high-dose ICS + LABA	52 weeks	Complete; Full
Efficacy and Safety	D3250C00016 (PAMPERO)	5.3.5.1	Efficacy Safety and Tolerability PK Immunogenicity	RD/DB/PC Multicentre	Multiple SC doses Benra 30 mg Placebo SC 2 dosing regimens: Q4W throughout the treatment period, Q4W for the first 3 doses and then Q8W thereafter	N=13/13	Patients with uncontrolled asthma receiving medium-dose ICS-LABA with/without additional asthma controller(s) and having a history of asthma exacerbation	48 weeks	Prematurely terminated; Abbreviated

Efficacy and safety studies (cont'd)

Type of study	Study identifier	Location of study report in Module 5	Objective(s) of the study	Study design and type of control	Test products, Dosage regimen, Route of administration	No. of subjects rand/treated	Healthy subjects or diagnosis of patients	Duration of treatment	Study status; type of report
Efficacy and Safety	D3250C00017 (SIROCCO)	5.3.5.1	Efficacy Safety PK Immunogenicity	RD/DB/PC Multicentre	Multiple SC doses Benra 30 mg Placebo SC 2 dosing regimens: Q4W throughout the treatment period, Q4W for the first 3 doses and then Q8W thereafter Adolescents in the EU were randomized to benralizumab 30 mg Q8W or placebo only	N=1205/1204	Patients with uncontrolled asthma receiving high-dose ICS-LABA with/without additional asthma controller(s) and having a history of asthma exacerbation	48 weeks	Complete; Full
Efficacy and Safety	D3250C00018 (CALIMA)	5.3.5.1	Efficacy Safety PK Immunogenicity	RD/DB/PC Multicentre	Multiple SC doses Benra 30 mg Placebo SC 2 dosing regimens: Q4W throughout the treatment period, Q4W for the first 3 doses and then Q8W thereafter Adolescents in the EU were randomized to benralizumab 30 mg Q8W or placebo only	N=1306/1306	Patients with uncontrolled asthma receiving medium- or high-dose ICS-LABA with/without additional asthma controller(s) and having a history of asthma exacerbation	56 weeks	Complete; Full
Efficacy and Safety	D3250C00020 (ZONDA)	5.3.5.1	OCS reduction Efficacy Safety	RD/DB/PC Multicentre	Multiple SC doses Benra 30 mg Placebo 2 dosing regimens: Q4W throughout the treatment period, Q4W for the first 3 doses and then Q8W thereafter	220/220	Adult patients with uncontrolled asthma requiring high-dose ICS/LABA and chronic oral corticosteroid therapy	28 weeks	Complete; Full
Safety and Efficacy	D3250C00021 (BORA)	NA[c]	Long-term safety Efficacy	RD/DB Multicentre	Multiple SC doses Benra 30 mg 2 dosing regimens: Q4W throughout the treatment period, Q4W for the first 3 doses and then Q8W thereafter.	2133/2133[b]	Patients who complete SIROCCO, CALIMA, or ZONDA, on IP	56 weeks for adults/108 weeks for adolescents	Ongoing; NA[c]

Efficacy and safety studies (cont'd)

Type of study	Study identifier	Location of study report in Module 5	Objective(s) of the study	Study design and type of control	Test products, Dosage regimen, Route of administration	No. of subjects rand/treated	Healthy subjects or diagnosis of patients	Duration of treatment	Study status; type of report
Efficacy and Safety	D3250C00032 (BISE)	5.3.5.1	Efficacy Safety	RD/DB/PC Multicentre	Multiple SC doses Benra 30 mg Placebo SC Q4W throughout the treatment period Influenza vaccine at Week 8	211/211	Patients with mild to moderate persistent asthma	12 weeks	Complete; Full
Efficacy and Safety	D3250C00029 (GREGALE)	5.3.5.1	Functionality, reliability, and performance of APFS in at-home setting	OL Multicentre	Multiple SC doses Benra 30 mg SC Q4W, 3 doses at study center, 2 doses at home	116/116	Adult patients with severe asthma	20 weeks	Complete; Full
Safety	D3250C00033 (ALIZE)	NA[c]	Anti-influenza antibody response Safety	RD/DB/PC Multicentre	Multiple SC doses Benra 30 mg Placebo Q4W throughout the treatment period Influenza vaccine at Week 8	103/103	Adolescent and young adult patients, 12 to 21 years of age, with severe asthma	12 weeks	Ongoing; NA[c]
Safety	D3250C00037 (MELTEMI)	NA[c]	Long-term safety Limited efficacy	OL Multicentre	Multiple SC doses Benra 30 mg 2 dosing regimens: Q4W or Q8W throughout the treatment period.	345[d]/NA[c]	Patients who have completed SIROCCO, CALIMA, or ZONDA, on IP and have completed at least 16 weeks in BORA	Until benralizumab is commercially available to patient	Ongoing; NA[c]

[a] KHK-sponsored studies are not included in this dossier.
[b] Approximately 1200 patients will remain in BORA through EOT and FU. The remaining patients will rollover into MELTEMI.
[c] Not applicable (or not available) as study is ongoing.
[d] As of 25 October 2016. Approximately 900 patients are expected to rollover into MELTEMI from BORA.

APFS Accessorized pre-filled syringe; Benra Benralizumab; DB Double blind; DE Dose escalation; DR Dose ranging; EU European Union; ICS Inhaled corticosteroids; IP Investigational product; IV Intravenous; LABA Long-acting β2 agonist; NA Not applicable; OCS Oral corticosteroid; OL Open label; PC Placebo controlled; PD Pharmacodynamic; PK Pharmacokinetic; Q4W Every 4 weeks; Q8W Every 8 weeks; SC Subcutaneous.

2.6.2. Pharmacokinetics

All studies presented have been performed in patient populations; there are no studies in healthy subjects.

The bioanalytical methods for benralizumab are adequately validated and are suitable for their purposes. Assay performance, in terms of inter-assay precision and inter-assay relative error was considered acceptable. An ELISA assay has been used for study MI-CP158 (LLOQ of 10 ng/mL) and an ECL immunoassay on the Meso Scale Discovery platform has been used for the other studies (LLOQ of 3.86 ng/mL).

A 3-tiered testing approach including screening, confirmation and titre assay was used for the assessment of anti-drug antibody (ADA) responses to benralizumab in clinical studies. Confirmed ADA-positive samples were subsequently tested for in vitro neutralising activity. Two neutralisation assays were developed, a ligand-binding assay and a cell-based assay. The LBA was showed to be more sensitive than the CBA and was selected for the Phase III studies. In general, the bioanalytical methods have been adequately validated and selectivity was evaluated in individual serum samples from asthma and COPD patients. Assay performance, in terms of accuracy and precision are considered acceptable.

A population PK model was developed using FOCE with interaction estimation method using NONMEM software. The model was assessed using GOF plots, VPCs and validated using an external validation dataset. The population PK objectives were clear with appropriate description of the nature of the data to be analysed. The general modelling aspects including software, estimation methods and diagnostics were properly reported. Also, data from the ZONDA clinical trial were used as an external validation dataset. Details for data simulations based on the model were also given.

The statistical methods used are appropriate for summarising the PK data.

Absorption

The slow absorption of benralizumab (3.59 days) is consistent with the reported slow absorption of other monoclonal antibodies (2-8 days). The population PK estimation of benralizumab bioavailability of 57.9% was associated with moderate degree of inter-individual variability (29.1 CV%). However, the anatomical site effects (upper abdomen and thigh vs upper arm) were not included in the population PK model as the fractional effect estimates for anatomical injection site on bioavailability relative to administration to the upper arm (~1.09) were considered not clinically relevant.

For the IV route, benralizumab was administered in a dose range from 0.03 to 3 mg/kg leading to a plasma Cmax range of 0.983 to 82.2 µg/mL. For the SC route, benralizumab was administered in a dose range of 25-200 mg/injection leading to a plasma Cmax range of 1.152 to 15.637 µg/mL.

Clinical studies were not conducted to evaluate the bioequivalence of benralizumab formulations. *In vitro* comparability studies were conducted to evaluate formulation changes.

Distribution

Binding of monoclonal antibodies is generally low, so protein binding studies are not required. Immunoglobulins are expected to partition in plasma, so blood to plasma partitioning studies are not required.

The combined central and peripheral volumes of distribution for benralizumab is 5.68 L (3.23 L Vc + 2.45 L Vp), indicating limited extracellular distribution which is expected for all therapeutic IgG due to their large size and hydrophilic nature.

Elimination

Population PK for benralizumab estimated clearance to be at 0.29 L/day. Clearance was shown to increase with body weight, which is expected for an antibody. Also, the presence of ADAs increased benralizumab clearance by 121%.

No clinical studies have been performed to characterise benralizumab excretion. Benralizumab is an antibody which is broken down by proteolytic enzymes to amino acid and peptides which either excreted by kidney or re-used in protein synthesis.

No studies have been performed to characterise benralizumab metabolism. IgGs are in general metabolised by proteolytic enzymes expressed in various tissues and in plasma, target-mediated elimination and nonspecific endocytosis.

No data are provided by the Applicant on possible active or inactive metabolites. Main IgG metabolites are expected to be amino acids and peptides. The function of these peptides has not been studied.

No data have been provided by the Applicant on the possible genetic polymorphisms which can affect benralizumab metabolism. Investigation is not considered necessary.

Dose proportionality and time dependency

The dose proportionality was investigated after IV single dose benralizumab therapy in patients with asthma. The AUC and Cmax increase appeared to be proportional or less than proportional over an IV dose range of 0.03 to 3.0 mg/kg; however no statistical test has been used to assess dose proportionality. Clearance of benralizumab appeared independent of the administered dose. Linear PKs and absence of target saturation or target-mediated clearance were confirmed using a population PK modelling approach.

Data suggest that consistent benralizumab plasma concentrations are attained following multiple dosing, indicative of no time-dependency in the absence of ADA. However, the Applicant did not provide any information on accumulation ratio for benralizumab.

Intra- and inter-individual variability

Moderate inter-individual variability in clearance and bioavailability was observed using population PK model (21.3 and 29.1% CV, respectively). Minimal inter-occasion variability of 5.1% CV was estimated upon addition of SIROCCO clinical trial to the base population PK model.

Moderate degree of inter-individual variability was also observed in the estimated volumes of distribution (26.9% for Vc and 47.1% for Vp).

Pharmacokinetics in target population

A population PK model based on 9 clinical studies (4 phase III clinical studies and 5 early stage clinical studies) was developed for benralizumab, which was best described with a 2-compartment model with first-order absorption from the SC dosing site and first-order elimination from the central compartment.

Special populations

Impaired renal function

Using the population pharmacokinetic model, the Applicant has shown that renal impairment (primarily mild and moderate) is not a significant covariate on benralizumab clearance compared with asthmatic patients with normal renal function. However, benralizumab pharmacokinetics was not studied in patients with end stage renal disease except for one patient only with severe renal impairment.

Impaired hepatic function

Using base population pharmacokinetic model, hepatic function (as assessed by ALT, AST and TBL) did not impact benralizumab clearance. Separate ad hoc models confirmed no observable clinically significant impact of hepatic function on benralizumab clearance.

Gender and race

Population pharmacokinetic showed that neither gender nor race had a clinically significant impact on benralizumab clearance.

Weight

Using population pharmacokinetic model, body weight had exponential effect on benralizumab clearance (a power parameter estimate of 0.831) and on benralizumab central volume of distribution (a power parameter estimate of 0.815 for V2 and 0.563 for V3). A simulation for the effect of body weight on benralizumab serum concentrations based on 5000 patients randomly sampled showed that the median steady-state exposure in patients within the ≥95th percentile was lower (44%) compared with that in patients within the ≤5th percentile. Thus, it was considered unnecessary to adjust dose based on body weight. However, the data are limited by the body weight range of the subjects recruited in the clinical trials.

Age

Benralizumab average concentrations and terminal half-life showed small difference between age groups (adolescents, adults and old age groups). Yet, due to high standard deviations, these differences are unlikely to be statistically significant.

No pharmacokinetic data are available for paediatric patients below the age of 12 years.

Interactions

Benralizumab clearance is independent of hepatic metabolism and is not subject to protein transporters. Therefore, pharmacokinetic interaction studies are not required.

Using the population pharmacokinetic model, co-administration of oral corticosteroid, montelukast, paracetamol, proton pump inhibitors (PPI), macrolides and theophylline/aminophylline did not have an impact of benralizumab clearance. Therapeutic antibodies typically do not undergo metabolism or transport as clearance pathway. Therefore, they are unlikely to interact with small drug molecules. The median of the deviations of the individual estimates from population mean for benralizumab clearance (eta clearance) did not appear to differ in presence and absence of co-administered drugs such as theophylline and PPIs indicating lack of significant effect on the clearance of benralizumab.

2.6.3. Pharmacodynamics

Mechanism of action

Benralizumab binds to IL-5Rα with high affinity on the surface of human eosinophils and basophils. It induces eosinophil and basophil apoptosis in the presence of NK cells with no associated increase in the concentrations of eosinophil cationic protein (ECP) and eosinophilic-derived neurotoxin (EDN), which provides evidence that benralizumab does not induce eosinophil activation or necrosis. Absence of the monosaccharide fucose on the oligosaccharide core of human IgG1 has previously been shown to result in enhanced binding affinity to FcγRIIIa and subsequently enhanced ADCC activity. Benralizumab depletes eosinophils by inducing apoptosis via enhanced ADCC.

Primary pharmacology

Treatment with benralizumab resulted in the rapid, near complete depletion (typically ≥95%) of blood eosinophils within 24 hours post-dosing and depletion of eosinophils in other key tissue compartments where eosinophils contribute to the pathogenesis of asthma (sputum, lung tissue, and the bone marrow). The depletion of eosinophils was accompanied by a reduction in the eosinophilic granule proteins EDN and ECP, which supports the notion that benralizumab depletes eosinophils via apoptosis and also suggests that benralizumab reduces eosinophilic inflammation. The depletion was reversible, and the majority of

eosinophil counts returned to approximately baseline levels within 6 months after cessation of repeated SC benralizumab dosing.

Additionally, benralizumab depleted peripheral blood basophils to a lesser extent than eosinophils.

Consistent with the mechanism of action, dosing with benralizumab resulted in reduced NK cells following the first dose, after which NK cells trended towards baseline levels. No clinically meaningful trends were associated with NK cell effects.

Dosing with benralizumab also resulted in sustained, increased serum levels of IL 5 and eotaxin 1, which is consistent with the reduction of eosinophils as these cells are primary targets of IL 5 and eotaxin-1.

Benralizumab did not, however, influence other asthma associated biomarkers such as exhaled nitric oxide or total serum IgE levels, which suggests that these biomarkers are not regulated by eosinophils.

Pharmacodynamic interactions

No formal drug-drug interaction studies have been performed. There are no data to suggest that IL-5Rα is expressed on hepatocytes and treatment with benralizumab has no identified effect on other circulating cytokines except for IL 5 and the eosinophil chemokines eotaxin-1 and eotaxin-2. From population PK analysis, commonly used small molecule drugs (montelukast, paracetamol, proton pump inhibitors, macrolides, and theophylline/aminophylline) had no effect on benralizumab clearance. Together, these data indicate that the potential risk of interactions between benralizumab and other drugs is low.

Genetic differences in PD response

The impact of genetic polymorphisms in IL 5Rα or FcγRIIIa on the PD response to benralizumab was not specifically studied. However, based on literature data, it can be argued that genetic differences in PD responses are unlikely to occur with benralizumab.

Relationship between plasma concentration and effect

The Applicant appropriately described the nature of the data to be analysed. The general modelling aspects including software, handling of missing data and covariates are documented.

The Applicant developed a population approach to characterize the exposure-response relationship in phase IIB clinical study. The analysis showed that maximum effect (as judged by asthma exacerbation rate (AER) fractional reduction) was achieved at benralizumab plasma trough concentrations > 690 ng/ml. 90% of the maximum effect was achieved at trough concentrations ~200 ng/ml (corresponding to 30mg Q8W dose). The 30 mg dose maintained interquartile range above ED80. This PK/PD approach for dose selection is endorsed as good way for exposure-response analysis.

The Applicant used empirical PK Quartile correlation method to assess the exposure-response analysis for the primary efficacy endpoint (asthma exacerbation rate). Exposure response analysis for the secondary efficacy endpoint FEV1 was carried out using an Emax model and empirical assessment.

The trough PK quartiles showed no apparent relationship with AER in SIROCCO study indicating that an efficacy plateau was achieved. The results from CALIMA were inconsistent and higher exposures (Q3 and Q4 for of Q4W arm) apparently resulted in a better efficacy. However, pooled data from SIROCCO and CALIMA clinical studies are indicative of no exposure-response relationship and that both Q4W and Q8W have the same efficacy profile. The proposed dose frequency, i.e. Q4W for the first three doses and Q8W thereafter, was selected to achieve rapid airway eosinophil depletion, and thus, hasten the onset of treatment benefit, to maintain eosinophil depletion in more patients within the first 8 weeks, and to induce high zone tolerance and suppress affinity maturation of ADA, which could lower the incidence and affinity of ADA against benralizumab.

Immunogenicity

ADA rates were much lower in the Phase III studies than in earlier studies, including at baseline and in the placebo arms. The same assay was used and, although not performed in the same laboratory, their overall performance specifications were highly comparable. No obvious explanation for this finding was provided. Minor modification to the reagents and the test drug would be consistent with the observed trend but it remains unclear whether these could explain the magnitude of the reported differences.

Only the results of the Phase III studies (two exacerbation studies and one OCS reduction study) are presented hereafter. Two dosing frequencies were investigated in these studies: 30 mg of benralizumab by subcutaneous injection every 4 weeks vs. every 4 weeks for the first 3 doses, then every 8 weeks thereafter.

Baseline ADA rates were approximately 2%. The ADA incidence, defined as the proportion of the study population that became newly ADA-positive (seroconverted) or boosted their pre-existing ADA titre (increase in titre by greater than 4-fold), ranged from 10 to 14% in the exacerbation studies and was slightly lower in the OCS study (7-8%), probably due to OCS immunosuppressant effects. Generally, seroconversion occurred early, between 8 and 16 weeks of treatment, and the likelihood of seroconversion after long-term exposure (>40 weeks) was low.

The median titre peaked at 400 at week 24-32 and then remained constant throughout the study. It is noteworthy that ADAs were also detected in the placebo arm (incidence of up to 4%) but median titres were low (50 to 75). About 30% of the patients had a decrease >75% from their maximum titre (which corresponds to a decrease in titre greater than what would be expected from assay variance), suggesting that benralizumab may generate a tolerogenic immune response. Very high ADA titres (≥25,600) were measured in 8 patients out of more than 1600 patients.

Most of these ADAs (68-80%) were neutralising and most ADA responses (about 70%) were persistent defined as ≥ 2 post-baseline positive samples being separated by a period of ≥16 weeks irrespective of any negative samples in between, or being positive at the last post-baseline assessment**.** Patients with a persistent ADA-positive response and patients with nAbs tended to have higher median ADA titres.

With the lower frequency regimen, the ADA incidence appeared slightly higher with a greater proportion of neutralising ADAs compared to the 4-weekly regimen.

The development of an ADA response during the course of treatment induced lower benralizumab Ctrough,ss; their median was below LLOQ with the lower frequency regimen. In parallel, blood eosinophils tended to increase, especially with the lower frequency regimen and in the subgroup of patients with high ADA titres. Out of the 8 patients with very high ADA titres (≥25,600), which were all neutralising, 7 patients had undetectable drug levels in 4 or more of the post-dose measurements and 7 patients had blood eosinophils returning to approximately equal to or greater than the baseline values at one or several assessments.

Despite clear impact on PK and PD, there was no indication of an effect of ADAs on the efficacy of benralizumab (annual asthma exacerbation rate, FEV1, or total asthma symptom score) and on its safety, including the occurrence of hypersensitivity reactions. In particular, the 8 patients previously mentioned reported 0 or 1 asthma exacerbation over a two-year follow-up. However, complete data on the impact of persistent neutralising ADAs is unknown in the long-term and further data will be provided from the extension trials.

Several findings support that the immunogenic region of benralizumab is its idiotype although the afucosylated Fc region might also represent a novel structure to the immune system. There was a good correlation between the results of the two different nAb assay formats (LBA and CBA). ADAs were shown

to inhibit detection of benralizumab in the PK assay (which requires binding of two anti-neutralising anti-idiotypic mAbs of different specificities). ADA titres and nAb titres by the LBA were directly associated.

2.6.4. Discussion on clinical pharmacology

The pharmacokinetics of benralizumab in patients with asthma have been described using a population PK model. The pharmacokinetics of benralizumab and related covariates have been reasonably well described.

The mechanism of action of benralizumab is well established. By binding to IL-5Rα with high affinity on the surface of human eosinophils and basophils, it induces their apoptosis in the presence of NK cells via enhanced ADCC. Treatment with benralizumab resulted in the rapid, near complete depletion of blood eosinophils within 24 hours post-dosing and depletion of eosinophils in other key tissue compartments (sputum, lung tissue, and bone marrow). Additionally, benralizumab depleted peripheral blood basophils to a lesser extent than eosinophils. Dosing with benralizumab also resulted in sustained, increased serum levels of IL 5 and eotaxin 1, which is consistent with the reduction of eosinophils as these cells are primary targets of IL 5 and eotaxin-1.

The pharmacokinetic/pharmacodynamics relationships for benralizumab were studied using steady state concentrations and efficacy endpoints (AER and FEV1 as primary and secondary efficacy endpoints, respectively). The exposure response could not be established with the two studied endpoints suggesting a plateau of drug effect has been reached.

Overall, in the Phase III studies, 7 to 14% of patients developed ADA to benralizumab, which appeared in the majority of patients to be neutralising and persistent. These ADAs increased the clearance of benralizumab and tended to allow for earlier eosinophil recovery. In rare cases, blood eosinophil counts returned to pre-treatment levels. Although these ADAs did not have any apparent impact on efficacy during the follow-up period and were not associated with hypersensitivity reactions, further data on the long-term impact of persistent neutralising ADAs will be provided from the extension trials as part of the RMP. Nevertheless, pursuing the administration of benralizumab should be reconsidered in individual patients where blood eosinophil counts return to pre-treatment levels.

2.6.5. Conclusions on clinical pharmacology

Extensive PK and PD data have been submitted, and in general, the PK and PD profile of benralizumab have been well characterised. There is no need for dose adjustment in patients with liver or renal impairment but the SmPC mentions the limited data available in patients with creatinine clearance values less than 30 mL/min.

There is no need for dose adjustment in the elderly; however, there are no data in patients over 75 years of age and this should be specified in the SmPC.

There are no data for paediatric patients below the age of 12 years but the current indication is only claimed in adults and this is specified in the SmPC.

The immunogenicity of benralizumab has been well characterised. It is surprising that ADAs have no apparent impact on efficacy despite a clear effect on drug concentration and blood eosinophil level. However, further data on the impact of persistent neutralising ADAs in the long-term will be provided from the extension trials as part of the RMP.

2.7. Clinical efficacy

2.7.1. Dose-response studies and main clinical studies

Study MI-CP220

A Phase IIb dose-ranging study to evaluate the efficacy and safety of MEDI-563 in adults with uncontrolled asthma

This was a randomised, double-blind, placebo-controlled, dose-ranging study evaluating the efficacy and safety of multiple-dose SC administration of benralizumab (2, 20, or 100 mg) in adult patients with uncontrolled asthma. Investigational product was administered as SC injections Q4W for the first 3 doses then Q8W thereafter for the last 4 doses on Weeks 16, 24, 32, and 40. After Week 40, patients were followed for an additional 12 weeks (through Week 52) for assessment of acute exacerbations.

Eligible patients were classified and stratified during the 3-week screening/run-in period as being either eosinophil positive (EOS+) or eosinophil negative (EOS-), using the ELEN Index together with elevated baseline FeNO. The ELEN Index was developed as a surrogate marker of sputum eosinophils ≥2% using multivariate statistical modelling of baseline sputum and blood data from a Phase IIa clinical study

The primary objective was to evaluate the effect of SC benralizumab on the annual asthma exacerbation rate in EOS+ adult subjects with inadequately controlled asthma. An asthma exacerbation was defined as a progressive increase of asthma symptoms (cough, wheeze, chest tightness, and/or shortness of breath) that did not resolve after the initiation of rescue medications and remained troublesome for the subject resulting in the use of systemic corticosteroids (tablets, suspension or injection) or increase of a stable systemic maintenance dose for a duration of at least 3 days.

The primary endpoint of the study was met as there was a statistically significant 41% reduction in the annual asthma exacerbation rate (AER) in the EOS+ 100 mg benralizumab arm versus the EOS+ placebo arm ($p=0.096$- note that $p < 0.169$ was considered statistically significant). A 36% reduction (NS) in the AER was also seen in the EOS+ 20 mg benralizumab arm versus the EOS+ placebo arm and a 22% reduction (NS) in the AER in the EOS- 100 mg benralizumab arm versus the EOS- placebo arm. Greater improvement was evident in subjects with higher baseline peripheral blood eosinophil counts suggesting that peripheral blood eosinophil count may be a useful marker to predict the efficacy of benralizumab in uncontrolled asthma.

Exacerbation studies

The two exacerbation studies of a replicate design were conducted in parallel and are presented together: Study D3250C00017 (SIROCCO) and Study D3250C00018 (CALIMA).

Study D3250C00017 (SIROCCO)

Study title: *A Multicentre, Randomized, Double-blind, Parallel Group, Placebo-controlled, Phase 3 Efficacy and Safety Study of Benralizumab (MEDI-563) Added to High-dose Inhaled Corticosteroid Plus Long-acting β2 Agonist in Patients with Uncontrolled Asthma*

Study D3250C00018 (CALIMA)

Study title: *A Multicentre, Randomized, Double-blind, Parallel Group, Placebo-controlled, Phase 3 Study to Evaluate the Efficacy and Safety of Benralizumab in Asthmatic Adults and Adolescents Inadequately Controlled on Inhaled Corticosteroid Plus Long-acting β2 Agonist*

- **Overall study design**

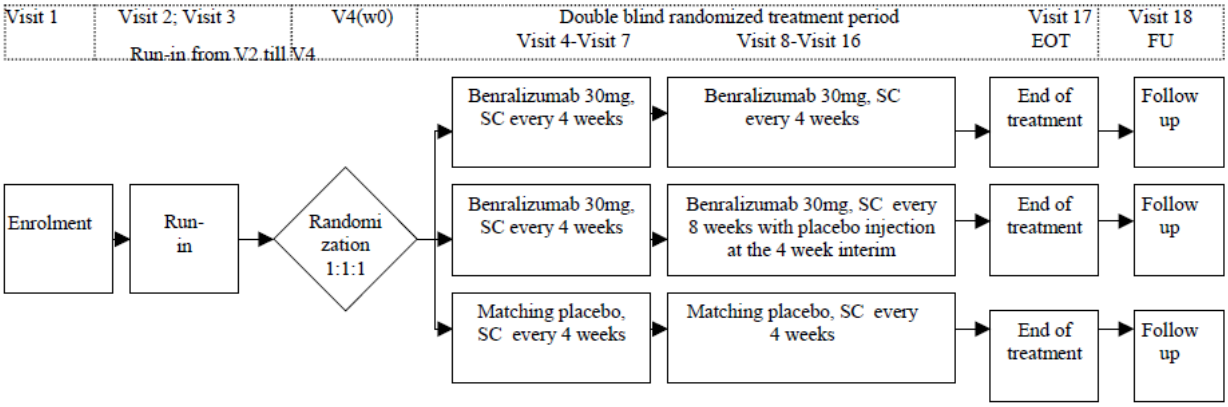
The design was the same except for the treatment duration: 48 weeks in SIROCCO and 56 weeks for CALIMA. There were three treatment arms:

- Benralizumab Q4W: one SC injection of 30 mg every 4 weeks
- Benralizumab Q8W: one SC injection of 30 mg every 4 weeks for the first 3 doses, thereafter every 8 weeks
- Placebo

In the EU, following PDCO request, only the Q8W regimen was administered to adolescents after the first 3 doses; therefore, the randomisation was 1:1 to benralizumab or placebo every 8 weeks.

SIROCCO study

Overall study design (SIROCCO)



- **Main objectives**

Primary: To evaluate the effect of 2 dosing regimens of benralizumab on asthma exacerbations in patients on high-dose ICS-LABA with uncontrolled asthma

Secondary: To assess the effect of 2 dosing regimens of benralizumab on pulmonary function, asthma symptoms and other asthma control metrics, asthma-related and general health-related quality of life, ER/urgent care visits and hospitalisations due to asthma

- **Study participants**

The main inclusion criteria were:

- male or female subjects aged 12 to 75 years and weighing ≥ 40 kg
- with history of asthma requiring treatment with medium-to-high dose ICS (i.e., > 250 µg/day fluticasone dry powder formulation equivalent) and a LABA, for at least 12 months
- with documented treatment with ICS and LABA for at least 3 months:
- with or without OCS and additional maintenance controllers (eg, LTRAs, tiotropium, cromone, theophylline) for at least 30 days

- with evidence of asthma documented by airway reversibility (post-bronchodilator reversibility in FEV1 ≥12% and 200 mL)
- with persistent airflow obstruction as indicated by a pre-bronchodilator forced expiratory volume in 1 second (FEV1) <80% predicted (<90% predicted for patients 12 to 17 years of age)
- uncontrolled asthma as evidenced by an ACQ-6 score ≥1.5 and, during the 7 days prior to randomisation, at least one of these criteria: >2 days with a daytime or nighttime symptoms score ≥1; rescue short-acting β2 agonist (SABA) use on >2 days; ≥1 nocturnal awakening due to asthma
- with at least 2 documented asthma exacerbations requiring use of systemic CS (or temporary increase from usual maintenance OCS dose) in the 12 previous months.

- **Outcomes/endpoints**

Primary endpoint

Annual asthma exacerbation rate, where an asthma exacerbation was defined by a worsening of asthma requiring:

- use of systemic corticosteroids (or a temporary increase in a stable OCS background dose) for at least 3 days; a single depo-injectable dose of corticosteroids was considered equivalent to a 3-day course of systemic corticosteroids
- an ER/urgent care visit (defined as evaluation and treatment for <24 hours in an emergency department or urgent care centre) due to asthma that required systemic corticosteroids (as per above)
- an inpatient hospitalisation due to asthma (defined as an admission to an inpatient facility and/or evaluation and treatment in a healthcare facility for ≥ 24 hours)

Secondary efficacy endpoints

- Pulmonary function: pre-bronchodilator FEV1 at the study centre
- Asthma symptoms and other asthma control metrics as per an ePRO device provided to the patient: asthma symptom score (total, daytime, and night time), rescue medication use, morning and evening peak expiratory flow (PEF), nights with awakening due to asthma, ACQ-6 score (Asthma Control Questionnaire)
- Other parameters associated with exacerbations: time to first asthma exacerbation, annual rate of asthma exacerbations that are associated with an ER/urgent care visit or a hospitalisation
- Health-related QoL outcome: AQLQ(S)+12 (Asthma Quality of Life Questionnaire for 12 Years and Older)

- **Randomisation**

Patients were allocated to the three treatment arms in a 1:1:1 ratio. The randomisation was stratified by age (adults/adolescents), country/region and eosinophil count at screening (≥300/µL or <300/µL) and ICS dose (medium/high) for Study 018.

- **Statistical methods**

The primary analysis set included only patients receiving high ICS dose and with baseline blood eosinophil count ≥300/µL.

To account for multiplicity to test the primary (annual asthma exacerbation rate) and 2 key secondary endpoints (the change in FEV1 and asthma symptom score from baseline to Week 48, respectively) for each of the 2 dosing regimens (for patients with baseline blood eosinophils ≥300/µL) a gate-keeping procedure was followed to control the overall type I error rate.

The primary efficacy variable was the annual asthma exacerbation rate (annualised exacerbation rate) and the primary analysis was to compare the unadjudicated annual asthma exacerbation rate (based on data reported by the investigator in the eCRF) of each benralizumab dosing regimen with placebo. The test used a binomial model with the response variable being the number of asthma exacerbations experienced by a patient over the double-blind treatment period; the model included covariates of treatment group, region, number of exacerbations in the previous year, and the use of maintenance OCS (yes/no). The logarithm of the patient's corresponding follow-up time was used as an offset variable in the model to adjust for patients having different exposure times during which the events occur.

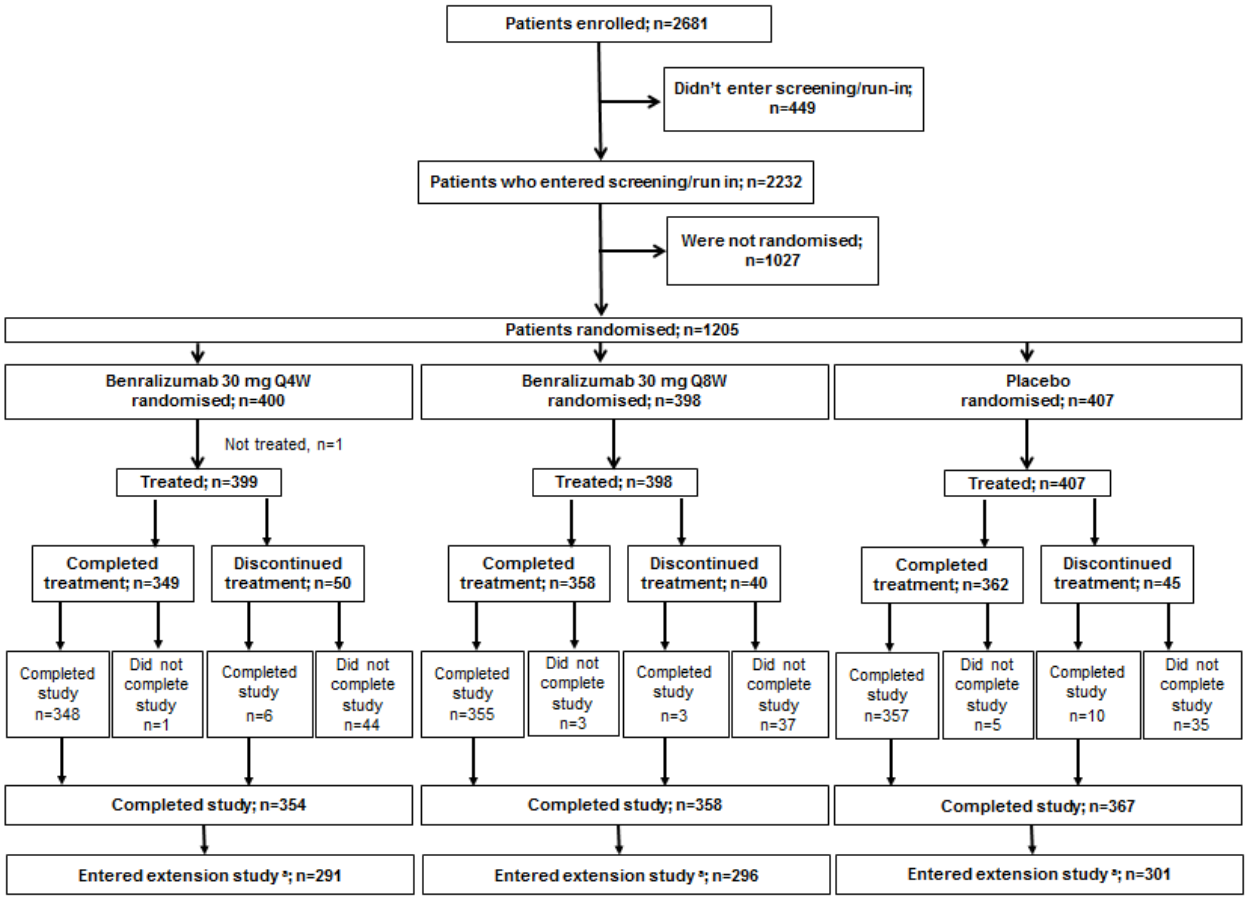
Sensitivity analyses for the primary endpoint and the key secondary endpoints based on different missing data mechanism assumptions: Missing at Random (MAR), Partial Dropout Reason-based Multiple Imputation (Partial-DRMI), Dropout Reason-based Multiple Imputation (DRMI). Missing counts were imputed differently depending on the reason for dropout in the last two cases.

Change from baseline in pre-bronchodilator FEV1 and in asthma symptom score was compared between each of the 2 benralizumab treatment groups and the placebo group using a mixed-effect model for repeated measures (MMRM) analysis on patients with a baseline value assessment and at least 1 post-randomisation assessment. Treatment group was fitted as the explanatory variable, region, the use of maintenance OCS (yes/no), visit, and treatment*visit interaction as fixed effects and baseline value as a covariate.

- **Participant flow**

Study 017 (SIROCCO)

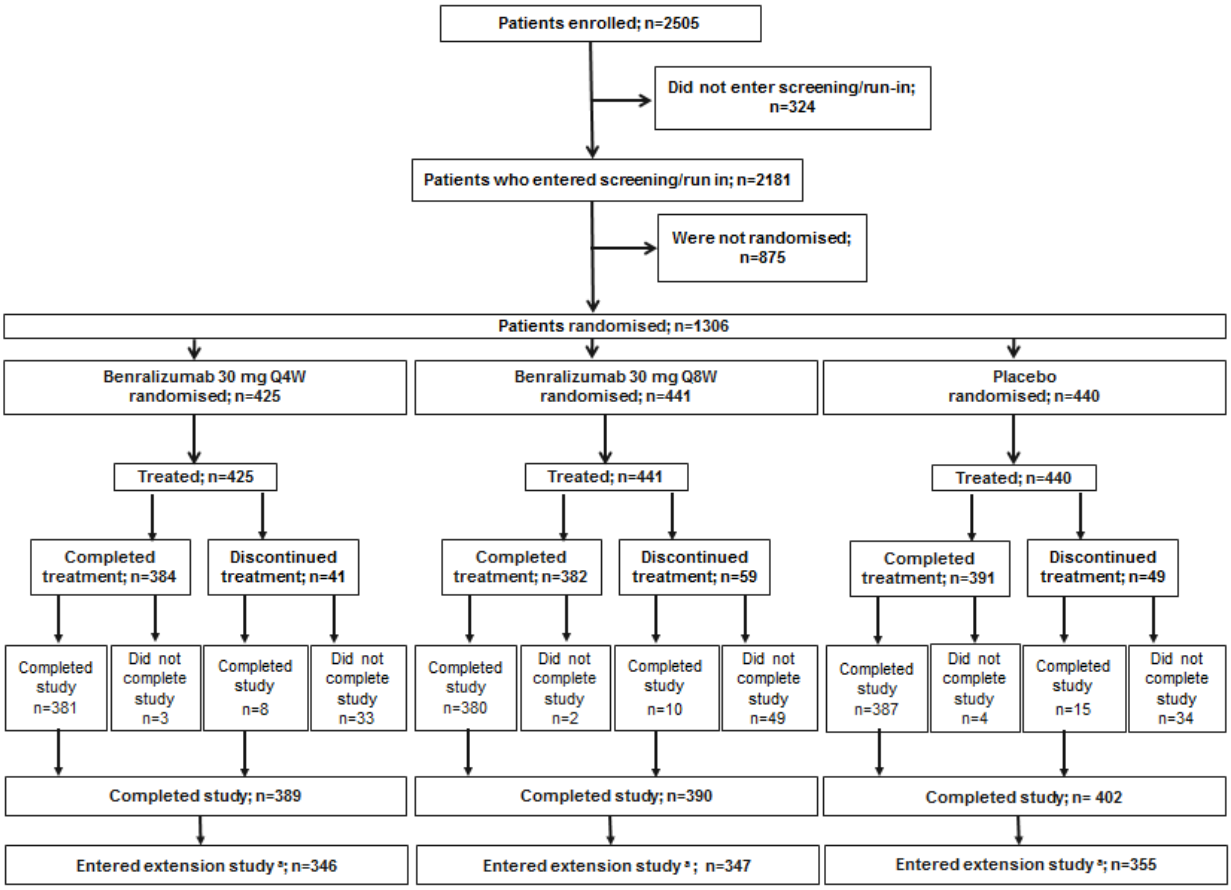
Of the 2232 patients who entered screening/run-in, **1205 patients** were randomised and 1204 patients received treatment with study drug (1 patient lost to follow-up): 399 received benralizumab 30 mg Q4W, 398 patients received benralizumab 30 mg Q8W, and 407 patients received placebo.



A total of 1069 (88.7%) patients completed treatment with study drug and 135 (11.2%) patients discontinued treatment. The proportions of patients who discontinued treatment were similar across treatment arms. The most frequent reasons for discontinuation of study treatment overall were subject decision (4.6%), other (2.2%), and AE (1.8%).

Study 018 (CALIMA)

Of the 2181 patients who entered screening/run-in, **1306 patients** were randomised and all received treatment: 425, 441, and 440 patients received benralizumab 30 mg Q4W, Q8W, and placebo, respectively.



A total of 1157 (88.6%) patients completed treatment with study drug and 149 (11.4%) patients discontinued treatment. The proportions of patients who discontinued treatment were similar across treatment arms. The most frequent reasons for discontinuation of study treatment overall were subject decision (4.8%), other (2.5%), and AE (1.7%).

- **Baseline data**

The baseline data are summarised below for the patient population used in the primary efficacy analyses, i.e. those on high ICS dose and with baseline EBC ≥300/µL.

Demographic and patient characteristics - Full analysis set, baseline blood eosinophils ≥300/µL, high-dose ICS

		SIROCCO				CALIMA			
Demographic characteristic	Statistics or category	Benra 30 mg Q4W (N=275)	Benra 30 mg Q8W (N=267)	Placebo (N=267)	Total (N=809)	Benra 30 mg Q4W (N=241)	Benra 30 mg Q8W (N=239)	Placebo (N=248)	Total (N=728)
Age (years)	n	275	267	267	809	241	239	248	728
	Mean (SD)	49.2 (13.1)	47.6 (14.6)	48.6 (14.7)	48.5 (14.2)	50.1 (13.1)	49.6 (13.0)	48.5 (14.1)	49.4 (13.4)
	Median	51.0	50.0	51.0	51.0	52.0	51.0	50.0	51.0
	Min, Max	12, 74	12, 74	12, 75	12, 75	15, 75	12, 74	12, 75	12, 75
Age group (years), n (%)	≥12 - <18	8 (2.9)	10 (3.7)	12 (4.5)	30 (3.7)	3 (1.2)	6 (2.5)	7 (2.8)	16 (2.2)
	≥18 - <50	117 (42.5)	123 (46.1)	114 (42.7)	354 (43.8)	101 (41.9)	100 (41.8)	114 (46.0)	315 (43.3)
	≥50 - <65	124 (45.1)	105 (39.3)	109 (40.8)	338 (41.8)	108 (44.8)	106 (44.4)	96 (38.7)	310 (42.6)
	≥65 - 75	26 (9.5)	29 (10.9)	32 (12.0)	87 (10.8)	29 (12.0)	27 (11.3)	31 (12.5)	87 (12.0)
	Total	275 (100.0)	267 (100.0)	267 (100.0)	809 (100.0)	241 (100.0)	239 (100.0)	248 (100.0)	728 (100.0)
Sex, n (%)	Male	102 (37.1)	93 (34.8)	87 (32.6)	282 (34.9)	82 (34.0)	101 (42.3)	103 (41.5)	286 (39.3)
	Female	173 (62.9)	174 (65.2)	180 (67.4)	527 (65.1)	159 (66.0)	138 (57.7)	145 (58.5)	442 (60.7)
	Total	275 (100.0)	267 (100.0)	267 (100.0)	809 (100.0)	241 (100.0)	239 (100.0)	248 (100.0)	728 (100.0)
Race, n (%)	White	191 (69.5)	192 (71.9)	191 (71.5)	574 (71.0)	209 (86.7)	203 (84.9)	213 (85.9)	625 (85.9)
	Black or African American	11 (4.0)	10 (3.7)	10 (3.7)	31 (3.8)	5 (2.1)	8 (3.3)	8 (3.2)	21 (2.9)
	Asian	39 (14.2)	35 (13.1)	36 (13.5)	110 (13.6)	27 (11.2)	28 (11.7)	27 (10.9)	82 (11.3)
	Other [a]	34 (12.4)	30 (11.2)	30 (11.2)	94 (11.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Total	275 (100.0)	267 (100.0)	267 (100.0)	809 (100.0)	241 (100.0)	239 (100.0)	248 (100.0)	728 (100.0)
Ethnic group, n (%)	Hispanic or Latino	52 (18.9)	52 (19.5)	57 (21.3)	161 (19.9)	56 (23.2)	52 (21.8)	52 (21.0)	160 (22.0)
	Not Hispanic or Latino	223 (81.1)	215 (80.5)	210 (78.7)	648 (80.1)	185 (76.8)	187 (78.2)	196 (79.0)	568 (78.0)
	Total	275 (100.0)	267 (100.0)	267 (100.0)	809 (100.0)	241 (100.0)	239 (100.0)	248 (100.0)	728 (100.0)
Weight (kg)	n	274	267	267	808	241	239	248	728
	Mean (SD)	78.76 (21.382)	75.35 (18.022)	77.96 (21.872)	77.37 (20.531)	79.08 (20.145)	79.47 (18.526)	80.63 (18.406)	79.74 (19.023)
	Median	76.00	73.00	75.00	75.00	76.00	77.50	79.05	78.00
	Min, Max	41.5, 194.5	41.0, 155.0	41.0, 186.3	41.0, 194.5	42.6, 185.9	41.0, 147.0	41.8, 154.6	41.0, 185.9
BMI (kg/m^2)	n	273	267	267	807	241	239	248	728
	Mean (SD)	28.87 (6.905)	27.70 (6.099)	28.72 (7.041)	28.43 (6.708)	29.08 (7.295)	28.57 (6.060)	29.04 (6.087)	28.90 (6.499)
	Median	28.08	26.44	27.44	27.27	27.65	27.78	28.23	27.78
	Min, Max	15.4, 58.0	15.8, 53.0	16.1, 61.7	15.4, 61.7	15.9, 79.9	16.9, 53.4	16.6, 56.7	15.9, 79.9
BMI group (kg/m^2), n (%)	n	273 (100.0)	267 (100.0)	267 (100.0)	807 (100.0)	241 (100.0)	239 (100.0)	248 (100.0)	728 (100.0)
	Normal (≤25)	79 (28.9)	102 (38.2)	90 (33.7)	271 (33.6)	68 (28.2)	62 (25.9)	68 (27.4)	198 (27.2)
	Overweight (>25-30)	99 (36.3)	83 (31.1)	88 (33.0)	270 (33.5)	90 (37.3)	93 (38.9)	86 (34.7)	269 (37.0)
	Obese (>30)	51 (18.7)	50 (18.7)	48 (18.0)	149 (18.5)	44 (18.3)	55 (23.0)	56 (22.6)	155 (21.3)
	Morbidly obese (>35)	44 (16.1)	32 (12.0)	41 (15.4)	117 (14.5)	39 (16.2)	29 (12.1)	38 (15.3)	106 (14.6)
Local baseline blood eosinophil count (cells/µL)	n	274	263	264	801	237	236	247	720
	Mean (SD)	638 (417.4)	620 (397.6)	621 (351.4)	627 (389.7)	615 (352.6)	621 (336.7)	642 (485.5)	626 (398.3)
	Median	500	500	500	500	500	500	510	500
	Min, Max	300, 3440	300, 3100	300, 2690	300, 3440	300, 2420	300, 2600	300, 4494	300, 4494

Local baseline blood eosinophil count was defined as the result from Visit 1 or 3 used to stratify the patient at randomisation.

[a] Included eCRF race categories "Native Hawaiian or other Pacific Islander", "American Indian or Alaska Native", and "Other".

Lung function at baseline - Full analysis set, baseline blood eosinophils ≥300/µL, high-dose ICS

		SIROCCO				CALIMA			
Lung function variable	**Statistics**	**Benra 30 mg Q4W (N=275)**	**Benra 30 mg Q8W (N=267)**	**Placebo (N=267)**	**Total (N=809)**	**Benra 30 mg Q4W (N=241)**	**Benra 30 mg Q8W (N=239)**	**Placebo (N=248)**	**Total (N=728)**
FEV_1 pre-BD (L)	n	273	266	262	801	239	239	245	723
	Mean (SD)	1.673 (0.577)	1.660 (0.574)	1.654 (0.580)	1.662 (0.576)	1.750 (0.570)	1.758 (0.622)	1.815 (0.648)	1.775 (0.614)
	Median	1.580	1.690	1.630	1.630	1.670	1.690	1.720	1.690
	Min, Max	0.54, 3.72	0.48, 3.54	0.46, 3.48	0.46, 3.72	0.52, 3.45	0.56, 3.79	0.60, 3.80	0.52, 3.80
FEV_1 pre-BD (% PN)	n	273	266	262	801	239	239	245	723
	Mean (SD)	56.5 (14.4)	55.5 (14.6)	56.4 (14.6)	56.1 (14.5)	59.1 (13.7)	57.0 (14.2)	58.2 (13.9)	58.1 (13.9)
	Median	55.6	56.5	58.0	56.8	61.1	58.2	58.7	59.3
	Min, Max	16.8, 87.2	16.8, 85.5	17.7, 93.3	16.8, 93.3	15.7, 88.3	23.2, 89.0	23.2, 93.7	15.7, 93.7
FEV_1/FVC pre-BD	n	273	266	262	801	239	239	245	723
	Mean (SD)	62 (12)	60 (13)	61 (13)	61 (13)	61 (12)	60 (13)	60 (12)	60 (12)
	Median	61	60	62	61	62	59	60	60
	Min, Max	30, 92	26, 98	1, 98	1, 98	25, 88	28, 93	27, 93	25, 93
Reversibility (%)	n	262	253	251	766	235	236	243	714
	Mean (SD)	25.4 (23.5)	27.4 (25.0)	25.5 (22.8)	26.1 (23.8)	26.2 (25.4)	24.9 (22.3)	25.6 (22.5)	25.5 (23.4)
	Median	18.3	21.3	20.4	19.3	19.9	20.0	19.8	19.8
	Min, Max	-6.7, 136.3	-10.2, 156.8	-26.4, 154.2	-26.4, 156.8	-24.3, 124.4	-12.8, 170.5	-9.4, 133.4	-24.3, 170.5

Key respiratory disease characteristics - Full analysis set, baseline blood eosinophils ≥300/µL, high-dose ICS

	SIROCCO				CALIMA			
Patient characteristic Statistics or Category	Benra 30 mg Q4W (N=275)	Benra 30 mg Q8W (N=267)	Placebo (N=267)	Total (N=809)	Benra 30 mg Q4W (N=241)	Benra 30 mg Q8W (N=239)	Placebo (N=248)	Total (N=728)
Number patients with a diagnosis of asthma (n [%])	275 (100.0)	267 (100.0)	267 (100.0)	809 (100.0)	241 (100.0)	239 (100.0)	248 (100.0)	728 (100.0)
Time since asthma diagnosis (years)								
Median	14.85	14.55	13.43	14.36	15.64	16.06	17.02	16.06
Range	1.1, 62.6	1.1, 66.9	1.1, 65.2	1.1, 66.9	1.3, 66.2	1.2, 58.2	1.3, 69.9	1.2, 69.9
Number of exacerbations in the last 12 months (n[%])								
1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4) [a]	0 (0.0)	0 (0.0)	1 (0.1) [a]
2	173 (62.9)	164 (61.4)	149 (55.8)	486 (60.1)	148 (61.4)	144 (60.3)	151 (60.9)	443 (60.9)
3	44 (16.0)	53 (19.9)	53 (19.9)	150 (18.5)	54 (22.4)	59 (24.7)	56 (22.6)	169 (23.2)
≥4	58 (21.1)	50 (18.7)	65 (24.3)	173 (21.4)	38 (15.8)	36 (15.1)	41 (16.5)	115 (15.8)
n	275	267	267	809	241	239	248	728
Mean (SD)	3.0 (1.97)	2.8 (1.52)	3.1 (1.95)	3.0 (1.83)	2.8 (1.70)	2.7 (1.32)	2.8 (1.66)	2.8 (1.57)
Median	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0
Min, Max	2, 17	2, 11	2, 15	2, 17	1, 22	2, 11	2, 18	1, 22
Number of exacerbations in the last 12 months resulting in hospitalisation (n [%])								
0	209 (76.0)	196 (73.4)	200 (74.9)	605 (74.8)	199 (82.6)	196 (82.0)	204 (82.3)	599 (82.3)
1	45 (16.4)	43 (16.1)	41 (15.4)	129 (15.9)	30 (12.4)	24 (10.0)	23 (9.3)	77 (10.6)
2	19 (6.9)	23 (8.6)	20 (7.5)	62 (7.7)	11 (4.6)	18 (7.5)	17 (6.9)	46 (6.3)
3	0 (0.0)	1 (0.4)	5 (1.9)	6 (0.7)	1 (0.4)	1 (0.4)	2 (0.8)	4 (0.5)
≥4	2 (0.7)	4 (1.5)	1 (0.4)	7 (0.9)	0 (0.0)	0 (0.0)	2 (0.8)	2 (0.3)
n	275	267	267	809	241	239	248	728
Mean (SD)	0.3 (0.67)	0.4 (0.85)	0.4 (0.81)	0.4 (0.78)	0.2 (0.54)	0.3 (0.61)	0.3 (0.70)	0.3 (0.62)
Median	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Min, Max	0, 4	0, 6	0, 7	0, 7	0, 3	0, 3	0, 4	0, 4
Nicotine use at study entry (n [%])								
Never smoked	214 (77.8)	220 (82.4)	219 (82.0)	653 (80.7)	175 (72.6)	185 (77.4)	203 (81.9)	563 (77.3)
Current smoker	0 (0.0)	1 (0.4)	1 (0.4)	2 (0.2)	0 (0.0)	1 (0.4)	1 (0.4)	2 (0.3)
Former smoker	61 (22.2)	46 (17.2)	47 (17.6)	154 (19.0)	66 (27.4)	53 (22.2)	44 (17.7)	163 (22.4)
Total	275 (100.0)	267 (100.0)	267 (100.0)	809 (100.0)	241 (100.0)	239 (100.0)	248 (100.0)	728 (100.0)
Nicotine consumption prior to study entry								
Nicotine pack-years, n	61	47	48	156	66	54	45	165
Mean (SD)	5.4 (2.9)	4.8 (2.5)	4.8 (2.7)	5.0 (2.8)	4.5 (3.0)	4.9 (6.1)	4.3 (2.9)	4.6 (4.3)
Median	6.0	5.0	5.0	5.0	5.0	4.5	4.0	4.0
Min, Max	0, 9	0, 9	0, 9	0, 9	0, 9	0, 45	0, 9	0, 45
ACQ-6 score at baseline, n	275	267	267	809	241	239	248	728
Mean (SD)	2.77 (0.95)	2.81 (0.89)	2.90 (0.95)	2.82 (0.93)	2.70 (0.91)	2.80 (0.95)	2.75 (0.94)	2.75 (0.93)
Median	2.67	2.83	2.83	2.83	2.67	2.83	2.67	2.67
Min, Max	0.00, 5.50	0.17, 5.67	0.50, 5.50	0.00, 5.67	0.00, 5.67	0.17, 5.67	0.17, 5.83	0.00, 5.83

ACQ-6 score was defined as the average of the first 6 items of the ACQ questionnaire on symptoms, activity limitations, and rescue medication. Scores ranged from 0 (totally controlled) to 6 (severely uncontrolled). Baseline was defined as the last non-missing value before randomisation.

Nicotine consumption of less than 1 pack-year was recorded as 0 in the case report form.

ACQ-6 Asthma Control Questionnaire-6; Benra Benralizumab; ICS Inhaled corticosteroids; Max Maximum; Min Minimum; N Number of patients in treatment group; n Number of patients in analysis; SD Standard deviation.

[a] After a review of the exacerbation histories, it was found that 1 event for this patient did not meet protocol criteria and was considered an important protocol deviation.

Maintenance asthma medications at baseline - Full analysis set, baseline blood eosinophils ≥300/µL, high-dose ICS

		SIROCCO				CALIMA			
Medication	Statistics or category	Benra 30 mg Q4W (N=275)	Benra 30 mg Q8W (N=267)	Placebo (N=267)	Total (N=809)	Benra 30 mg Q4W (N=241)	Benra 30 mg Q8W (N=239)	Placebo (N=248)	Total (N=728)
ICS	n (%)	275 (100.0)	267 (100.0)	267 (100.0)	809 (100.0)	241 (100.0)	237 (99.2)	248 (100.0)	726 (99.7)
ICS total daily dose (µg) [a]	Mean	894.359	913.424	901.633	903.052	895.390	1002.293	929.469	941.929
	Min, Max	416.67, 3000.00	500.00, 2500.00	125.00, 3000.00	125.00, 3000.00	184.00, 4125.00	250.00, 4750.00	250.00, 3000.00	184.00, 4750.00
LABA	n (%)	275 (100.0)	267 (100.0)	267 (100.0)	809 (100.0)	241 (100.0)	235 (98.3)	248 (100.0)	724 (99.5)
ICS/LABA	n (%)	261 (94.9)	251 (94.0)	250 (93.6)	762 (94.2)	214 (88.8)	213 (89.1)	214 (86.3)	641 (88.0)
OCS	n (%)	38 (13.8)	52 (19.5)	37 (13.9)	127 (15.7)	27 (11.2)	25 (10.5)	28 (11.3)	80 (11.0)
OCS total daily dose (mg) [b]	n	36	52	36	124	27	25	27	79
	Mean	15.347	15.505	13.889	14.990	12.396	8.340	14.370	11.787
	Min, Max	5.00, 60.00	2.50, 60.00	5.00, 30.00	2.50, 60.00	4.00, 66.70	2.00, 25.00	2.50, 50.00	2.00, 66.70
LAMA	n (%)	23 (8.4)	25 (9.4)	22 (8.2)	70 (8.7)	20 (8.3)	28 (11.7)	24 (9.7)	72 (9.9)
LTRA	n (%)	92 (33.5)	103 (38.6)	102 (38.2)	297 (36.7)	70 (29.0)	68 (28.5)	68 (27.4)	206 (28.3)
Xanthine derivatives	n (%)	30 (10.9)	46 (17.2)	41 (15.4)	117 (14.5)	30 (12.4)	35 (14.6)	32 (12.9)	97 (13.3)
Other asthma medications	n (%)	3 (1.1)	3 (1.1)	4 (1.5)	10 (1.2)	6 (2.5)	6 (2.5)	3 (1.2)	15 (2.1)

Baseline was defined as starting on or prior to randomisation and ongoing after randomisation. ICS may have been taken in a separate inhaler or as part of fixed-dose ICS/LABA combination device. ICS and LABA taken as part of a fixed-dose ICS/LABA combination device were included in both the individual and ICS/LABA therapy summaries. ICS total daily dose was the sum of doses across multiple inhalers.

[a] ICS doses were converted to their fluticasone propionate dry powder equivalent for this summary.

[b] OCS doses were converted to their prednisolone equivalent for this summary.

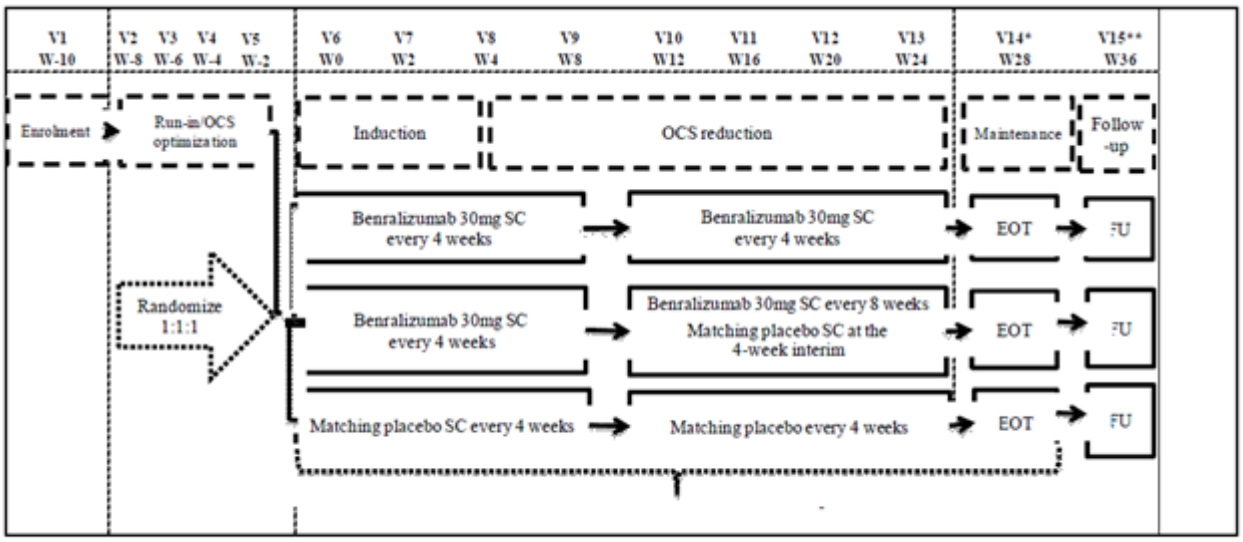
OCS reduction study (ZONDA)

- **Overall study design**

The same randomisation within three treatment arms as in the exacerbation studies was used. The treatment period was divided into 3 phases:

- Induction (from Week 0 to Week 4; patients remained on the optimised OCS dose)
- Reduction (from Week 4 to Week 24, inclusive; OCS dose reduction was initiated at Week 4 with dose reduction following at 4-week intervals)
- Maintenance (after Week 24 to Week 28; the dose of OCS reached at Week 24 or complete elimination of OCS was maintained).

There was a run in/OCS optimisation of up to 10 weeks preceding the randomisation. The dose of OCS was titrated during the optimisation and reduction phases of the study according to specific algorithms in the protocol. Patients who met some pre-specified criteria were eligible for OCS dose reduction during the run-in/OCS optimisation phase and during the reduction phase. Failed attempts at OCS dose reduction were those which resulted in documented clinical deterioration or reduced lung function attributed to asthma.



*Patients entering the extension study (D3250C00021) received their first dose of benralizumab at Visit 1 (Week -10) in that study, which must have occurred on the same day as Visit 14 (EOT; Week 28) for this study (D3250C00020).
**Only those patients who did not enter the extension study completed this Follow-up Visit.

- **Main objectives**

Primary: To compare the effect of 2 dosing regimens of benralizumab on percentage reduction of oral corticosteroid (OCS) dose in adult patients with uncontrolled asthma

Secondary: To assess the effect of 2 dosing regimens of benralizumab on other parameters related to OCS dose, asthma exacerbations, pulmonary function, asthma symptoms and other asthma control metrics, asthma-related quality of life

- **Study participants**

The main inclusion criteria were:

- male or female subjects aged 18 to 75 years and weighing ≥ 40 kg
- with history of asthma requiring treatment with medium-to-high dose ICS (i.e., > 250 µg/day fluticasone dry powder formulation equivalent) and a LABA, for at least 12 months
- with documented treatment with ICS (>500µg fluticasone propionate) and LABA for at least 6 months
- with chronic OCS therapy for at least 6 continuous months and on doses equivalent to 7.5 to 40 mg/day of prednisolone/prednisone at Visit 1 (Week -10) and with a stable dose for at least 2 weeks prior to randomisation (at least 70% compliance from week -10 to 0)
- with/without additional asthma controller (at least 70% compliance from week -10 to 0)
- with evidence of asthma documented by airway reversibility: post-bronchodilator reversibility in FEV1≥12% and 200 mL or airway hyperresponsiveness (PC_{20} FEV1 methacholine concentration ≤8mg/mL) or airflow variability in clinic (FEV1 ≥20% between 2 consecutive clinic visits)
- with persistent airflow obstruction as indicated by a pre-bronchodilator forced expiratory volume in 1 second (FEV1) <80% predicted
- with at least 1 documented asthma exacerbation in the 12 previous months

- with peripheral blood eosinophil count of ≥150 cells/μL assessed by local lab.

- **Outcomes/endpoints**

Primary endpoint

Percentage reduction in final OCS dose compared with baseline (Visit 6), while maintaining asthma control

Secondary efficacy endpoints

- OCS dose reduction while maintaining asthma control:
    - Proportion of patients with 100%, ≥ 50% and ≥ 25% reduction in average daily OCS dose at Visit 14 compared with baseline dose at Visit 6
    - Proportion of patients with average final OCS dose ≤ 5.0 mg daily at Visit 14
    - Proportion of patients with ≥ 25% reduction in the final OCS dose at Visit 14 compared with baseline dose at Visit 6, and with final OCS dose of ≤ 5.0 mg daily at Visit 14
- Asthma exacerbations after randomisation:
    - Proportion of patients with ≥1 asthma exacerbation
    - Annual rate of asthma exacerbations and those associated with an ER visit/hospitalisation
    - Time to the first asthma exacerbation, to first exacerbation requiring hospitalisation, to first exacerbation requiring hospitalisation or ER visit
    - Number of days in hospital due to asthma
    - Mean number of days with OCS taken for exacerbations
- Change from baseline in FEV1, asthma symptom score, rescue medications, home lung function (PEF, nocturnal awakenings), ACQ-6, Asthma Quality of Life Questionnaire (AQLQ[S]+12)

- **Randomisation**

Patients were allocated to the three treatment arms in a 1:1:1 ratio. The randomisation was stratified by country/region and baseline blood eosinophils count (≥150 to <300 cells/μL and ≥300 cells/μL)

- **Statistical methods**

To account for multiplicity in testing the primary endpoint for the 2 dosing regimens, a testing strategy was followed to control the overall type I error rate using the Hochberg procedure.

The primary efficacy variable was the percentage reduction from baseline in the final OCS dose while maintaining asthma control. The baseline OCS dose was defined as the dose upon which the patient was stabilised at randomisation (Week 0). Unless otherwise stated below, the final dose was generally defined as the dose at Week 28. For each of the 2 benralizumab dose regimen arms, the percentage reduction was compared to the placebo arm using a Wilcoxon rank-sum test.

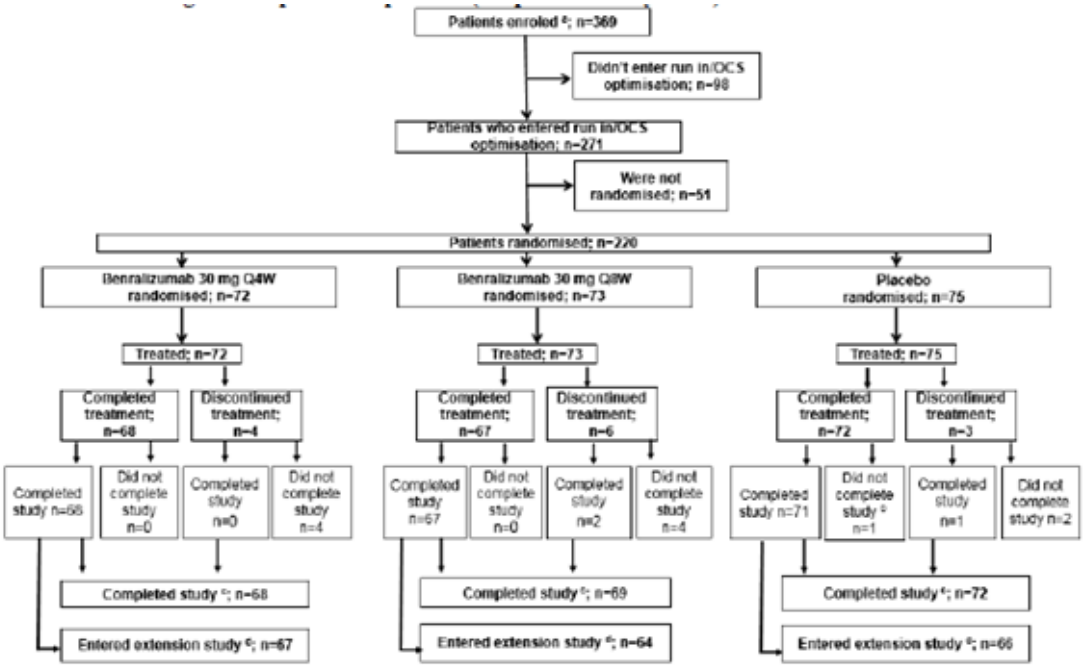
If a patient discontinued from the study during a given dose reduction interval prior to Visit 14 (Week 28), then the patient's final OCS dose was defined as 1 dose level higher than the dose at which the discontinuation occurred. If a patient's asthma deteriorated or an exacerbation occurred during the maintenance phase, the final dose was deemed as 1 dose level higher than the dose at which the asthma exacerbation or deterioration started.

Following review of blinded preliminary data from the study database, instances were identified of patients who recorded an exacerbation following randomisation, but for whom, contrary to the process outlined in the protocol, the site appeared to continue down-titration of the OCS dose following the exacerbation. As a sensitivity analysis, assessment of the primary endpoint was conducted where, for patients who recorded an exacerbation, the final OCS dose used in the percent reduction from baseline calculation was the OCS dose 1 step higher than the dose at which their first exacerbation started.

For the secondary OCS categorical endpoints, a Cochran-Mantel-Haenszel test was used controlling for region. Annual rate of asthma exacerbations were analysed using a negative binomial model as for the two previous studies.

- **Participant flow**

Of 369 patients enrolled, 271 patients entered run-in/OCS optimisation. Of these, 220 patients were randomised to receive treatment with benralizumab 30 mg Q4W (72), Q8W (73), or placebo (75) and a total of 51 patients were not randomised. The most frequent reasons for exclusion from randomisation were eligibility criteria not fulfilled (35 patients) and development of study-specific withdrawal criteria (14 patients).



[a] Informed consent received.
[b] One patient (E7809001), in the placebo group, completed the treatment with IP but did not complete the study due to the patient being lost to follow-up (Appendix 12.2.1.1.1).
[c] Includes patients who discontinued treatment with IP but attended all study visits.
[d] Only patients who completed treatment and the study could roll into the BORA extension study. The number of patients entering BORA is available as data on file.

A total of 207 (94.1%) patients completed treatment with study drug. The proportions of patients who discontinued treatment were similar across the arms.

A total of 54 patients (24.5%) had at least one important protocol deviation, with a greater percentage in the placebo arm (27 [36.0%] patients) compared with the benralizumab 30 mg Q4W (15 [20.8%] patients) and Q8W arms (12 [16.4%] patients). The important protocol deviations were those affecting the assessment of the primary efficacy endpoint.

- **Baseline data**

Patient characteristics

Demographic characteristic	Statistics or category	Benra 30 mg Q4W (N=72)	Benra 30 mg Q8W (N=73)	Placebo (N=75)	Total (N=220)
Age (years)	n	72	73	75	220
	Mean (SD)	50.2 (12.0)	52.9 (10.1)	49.9 (11.7)	51.0 (11.3)
	Median	50.5	53.0	50.0	52.0
	Min, Max	20, 75	27, 75	21, 74	20, 75
Age group (years), n (%)	≥18 - <50	33 (45.8)	29 (39.7)	36 (48.0)	98 (44.5)
	≥50 - <65	31 (43.1)	32 (43.8)	31 (41.3)	94 (42.7)
	≥65 - 75	8 (11.1)	12 (16.4)	8 (10.7)	28 (12.7)
	Total	72 (100.0)	73 (100.0)	75 (100.0)	220 (100.0)
Sex, n (%)	Male	32 (44.4)	26 (35.6)	27 (36.0)	85 (38.6)
	Female	40 (55.6)	47 (64.4)	48 (64.0)	135 (61.4)
Weight (kg)	n	72	73	75	220
	Mean (SD)	84.54 (19.680)	83.91 (21.206)	81.00 (18.364)	83.12 (19.743)
	Median	79.75	79.00	77.80	78.60
	Min, Max	47.0, 139.7	50.0, 155.2	51.5, 136.0	47.0, 155.2
BMI (kg/m^2)	n	72	73	75	220
	Mean (SD)	29.79 (6.790)	30.24 (6.534)	28.73 (5.244)	29.58 (6.219)
	Median	28.54	29.05	28.53	28.69
	Min, Max	19.5, 55.2	18.6, 53.5	19.8, 46.7	18.6, 55.2
Local baseline eosinophil count (cells/µL)	n	71	73	74	218
	Mean (SD)	558 (345.7)	509 (320.2)	656 (589.0)	575 (439.4)
	Median	462	437	535	475
	Min, Max	160, 1740	154, 2140	160, 4550 [b]	154, 4550 [b]

b The 4550 value was queried and confirmed, and the patient had no eosinophilic-driven disease identified other than asthma.

Lung function characteristics

		All patients			
Lung function variable	Statistics	Benra 30 mg Q4W (N=72)	Benra 30 mg Q8W (N=73)	Placebo (N=75)	Total (N=220)
FEV_1 pre-BD (L)	n	72	73	75	220
	Mean (SD)	1.850 (0.741)	1.754 (0.635)	1.931 (0.662)	1.846 (0.681)
	Median	1.675	1.770	1.840	1.780
	Min, Max	0.55, 4.14	0.55, 3.60	0.74, 3.81	0.55, 4.14
FEV_1 pre-BD (% PN)	n	72	73	75	220
	Mean (SD)	57.4 (18.0)	59.0 (17.9)	62.0 (16.5)	59.5 (17.5)
	Median	56.5	62.3	62.5	60.0
	Min, Max	19.0, 106.5	22.7, 100.8	27.0, 99.7	19.0, 106.5
FEV_1/FVC pre-BD (%)	n	72	73	75	220
	Mean (SD)	59 (13)	59 (12)	62 (13)	60 (13)
	Median	56	60	62	60
	Min, Max	25, 92	30, 82	28, 93	25, 93
Reversibility (%)	n	66	68	73	207
	Mean (SD)	24.1 (21.7)	25.1 (19.0)	23.2 (18.0)	24.1 (19.5)
	Median	18.2	22.6	16.4	19.0
	Min, Max	-3.0, 126.0	-3.4, 88.0	-5.4, 93.4	-5.4, 126.0

Baseline was defined as the last non-missing value prior to the first dose of study treatment. Reversibility was calculated based on pre- and post-bronchodilator FEV_1 values at baseline.

Median	2.67	2.67	2.67	2.67
Min, Max	0.33, 5.17	0.00, 5.17	0.83, 5.00	0.00, 5.17

Maintenance asthma medications at baseline

Medication	Statistics	Benra 30 mg Q4W (N=72)	Benra 30 mg Q8W (N=73)	Placebo (N=75)	Total (N=220)
ICS	n (%)	72 (100.0)	73 (100.0)	75 (100.0)	220 (100.0)
ICS total daily dose (µg)[a]	Mean	1032.797	1191.598	1232.256	1153.487
	Min, Max	250.00, 3750.00	100.00, 3250.00	250.00, 5000.00	100.00, 5000.00
LABA	n (%)	72 (100.0)	73 (100.0)	75 (100.0)	220 (100.0)
ICS/LABA	n (%)	66 (91.7)	63 (86.3)	68 (90.7)	197 (89.5)
LAMA	n (%)	21 (29.2)	21 (28.8)	21 (28.0)	63 (28.6)
LTRA	n (%)	28 (38.9)	29 (39.7)	25 (33.3)	82 (37.3)
Xanthine derivatives	n (%)	10 (13.9)	13 (17.8)	10 (13.3)	33 (15.0)
Other asthma medications	n (%)	2 (2.8)	1 (1.4)	3 (4.0)	6 (2.7)

Baseline was defined as starting on or prior to randomisation and ongoing after randomisation. ICS may have been taken in a separate inhaler or as part of fixed-dose combination device. ICS and LABA taken as part of fixed-dose ICS/LABA combination device were included in both the individual and ICS/LABA summaries. ICS total daily dose was the sum of doses across multiple inhalers.

[a] ICS doses were converted to their fluticasone propionate dry powder equivalent for this summary.

OCS at study entry and before randomisation (baseline) – total daily dose

Medication	Statistics	Benra 30 mg Q4W (N=72)	Benra 30 mg Q8W (N=73)	Placebo (N=75)	Total (N=220)
OCS dose at study entry [a]	n	72	73	75	220
	Mean (SD)	16.201 (8.8081)	14.589 (7.8397)	15.080 (6.7314)	15.284 (7.8180)
	Median	10.000	10.000	10.000	10.000
	Q1, Q3	10.00, 20.00	10.00, 20.00	10.00, 20.00	10.00, 20.00
	Min, Max	7.50, 40.00	7.50, 40.00	7.50, 40.00	7.50, 40.00
Optimised (baseline) OCS dose [b]	n	72	73	75	220
	Mean (SD)	15.785 (8.8257)	14.281 (7.7558)	14.147 (6.3527)	14.727 (7.6951)
	Median	10.000	10.000	10.000	10.000
	Q1, Q3	10.00, 20.00	10.00, 20.00	10.00, 20.00	10.00, 20.00
	Min, Max	7.50, 40.00	7.50, 40.00	7.50, 40.00	7.50, 40.00

[a] Patients were transitioned at study entry to equivalent dose of prednisone/prednisolone.
[b] Optimised dose at Visit 6 (randomisation).

Summary of main efficacy results

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Summary of efficacy for trial D3250C00017

Title: *A Multicentre, Randomized, Double-blind, Parallel Group, Placebo-controlled, Phase 3 Efficacy and Safety Study of Benralizumab (MEDI-563) Added to High-dose Inhaled Corticosteroid Plus Long-acting β2 Agonist in Patients with Uncontrolled Asthma*			
Study identifier	SIROCCO		
Design	Randomized, double-blind, double-dummy, parallel group, placebo-controlled		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		48 weeks 2-5 weeks Study BORA
Hypothesis	Superiority		
Treatments groups	BENRA 30 Q4W		Benralizumab 30 mg SC every 4 weeks; 48 weeks; N=400
	BENRA 30 Q8W		Benralizumab 30 mg SC every 4 weeks (3 inj) then every 8 weeks; 48 weeks; N=398
	PLA		Placebo SC every 4 weeks; 48 weeks; N=407
Endpoints and definitions	Primary endpoint	AER	Annualised rate of asthma exacerbations defined as requiring systemic CS
	Secondary endpoint	FEV1	Pre-bronchodilator FEV1 – Change from BL
	Secondary endpoint	TASS	Total asthma symptom score – Change from BL
	Secondary endpoint	ACQ-6	Asthma Control Questionnaire ACQ-6 – Change from BL

	Secondary endpoint	AQLQ(S)	Asthma QoL AQLQ(S)+12 – Change from BL
Database lock	11-05-2016 / 13-06-2016		

Results and Analysis

Analysis description	**Primary Analysis in patients with high ICS dose and BL blood eosinophil count ≥ 300 cells/µL**			
Analysis population and time point description	Intent to treat – End of treatment (EOT)			
Descriptive statistics and estimate variability	Treatment group	**BENRA Q4W**	**BENRA Q8W**	**PLA**
	Number of subject	275	267	267
	Marginal AER (rate/year) 95%CI	0.83 0.68, 1.02	0.74 0.59, 0.92	1.52 1.27, 1.81
	FEV1 (L) LS mean change	0.345	0.398	0.239
	TASS LS mean change	-1.12	-1.30	-1.04
	ACQ-6 LS mean change	-1.32	-1.46	-1.17
	AQLQ(S) LS mean change	1.44	1.56	1.26

Effect estimate per comparison	AER	Comparison groups	BENRA Q4W vs PLA
		Rate ratio (BEN/PLA)	0.55
		95%CI	0.42, 0.71
		P-value	**< 0.001**
		Comparison groups	BENRA Q8W vs PLA
		Rate ratio (BEN/PLA)	0.49
		95%CI	0.37, 0.64
		P-value	**< 0.001**
	FEV1	Comparison groups	BENRA Q4W vs PLA
		LS mean difference	0.106
		95%CI	0.016, 0.196
		P-value	**0.022**
		Comparison groups	BENRA Q8W vs PLA
		LS mean difference	0.159
		95%CI	0.068, 0.249
		P-value	**0.001**
	TASS	Comparison groups	BENRA Q4W vs PLA
		LS mean difference	-0.08
		95%CI	-0.27, +0.12
		P-value	0.442
		Comparison groups	BENRA Q8W vs PLA
		LS mean difference	-0.25
		95%CI	-0.45, -0.06
		P-value	**0.012**

	ACQ-6	Comparison groups	BENRA Q4W vs PLA
		LS mean difference	-0.15
		95%CI	-0.34, +0.04
		P-value	0.111
		Comparison groups	BENRA Q8W vs PLA
		LS mean difference	-0.29
		95%CI	-0.48, -0.10
		P-value	**0.003**
	AQLQ(S)	Comparison groups	BENRA Q4W vs PLA
		LS mean difference	0.18
		95%CI	-0.02, 0.37
		P-value	0.081
		Comparison groups	BENRA Q8W vs PLA
		LS mean difference	0.30
		95%CI	0.10, 0.50
		P-value	**0.004**

Summary of efficacy for trial D3250C00018

Title: *A Multicentre, Randomized, Double-blind, Parallel Group, Placebo-controlled, Phase 3 Study to Evaluate the Efficacy and Safety of Benralizumab in Asthmatic Adults and Adolescents Inadequately Controlled on Inhaled Corticosteroid Plus Long-acting β2 Agonist*			
Study identifier	CALIMA		
Design	Randomized, double-blind, double-dummy, parallel group, placebo-controlled		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		56 weeks 2-5 weeks Study BORA
Hypothesis	Superiority		
Treatments groups	BENRA 30 Q4W		Benralizumab 30 mg SC every 4 weeks; 56 weeks; N=425
	BENRA 30 Q8W		Benralizumab 30 mg SC every 4 weeks (3 inj) then every 8 weeks; 48 weeks; N=441
	PLA		Placebo SC every 4 weeks; 48 weeks; N=440
Endpoints and definitions	Primary endpoint	AER	Annualised rate of asthma exacerbations defined as requiring systemic CS
	Secondary endpoint	FEV1	Pre-bronchodilator FEV1 – Change from BL
	Secondary endpoint	TASS	Total asthma symptom score – Change from BL
	Secondary endpoint	ACQ-6	Asthma Control Questionnaire ACQ-6 – Change from BL
	Secondary endpoint	AQLQ(S)	Asthma QoL AQLQ(S)+12 – Change from BL
Database lock	04-05-2016		
Results and Analysis			
Analysis description	**Primary Analysis in patients with high ICS dose and BL blood eosinophil count ≥ 300 cells/µL**		

Analysis population and time point description	Intent to treat – End of treatment (EOT)			
Descriptive statistics and estimate variability	Treatment group	**BENRA Q4W**	**BENRA Q8W**	**PLA**
	Number of subject	241	239	248
	Marginal AER (rate/year) 95%CI	0.65 0.52, 0.81	0.73 0.58, 0.90	1.01 0.84, 1.22
	FEV1 (L) LS mean change	0.340	0.330	0.215
	TASS LS mean change	-1.28	-1.40	-1.16
	ACQ-6 LS mean change	-1.38	-1.44	-1.19
	AQLQ(S) LS mean change	1.47	1.56	1.31

Effect estimate per comparison	AER	Comparison groups	BENRA Q4W vs PLA
		Rate ratio (BEN/PLA)	0.64
		95%CI	0.49, 0.85
		P-value	**0.002**
		Comparison groups	BENRA Q8W vs PLA
		Rate ratio (BEN/PLA)	0.72
		95%CI	0.54, 0.95
		P-value	**0.019**
	FEV1	Comparison groups	BENRA Q4W vs PLA
		LS mean difference	0.125
		95%CI	0.037, 0.213
		P-value	**0.005**
		Comparison groups	BENRA Q8W vs PLA
		LS mean difference	0.116
		95%CI	0.028, 0.204
		P-value	**0.010**
	TASS	Comparison groups	BENRA Q4W vs PLA
		LS mean difference	-0.12
		95%CI	-0.32, +0.07
		P-value	0.224
		Comparison groups	BENRA Q8W vs PLA
		LS mean difference	-0.23
		95%CI	-0.43, -0.04
		P-value	**0.019**
	ACQ-6	Comparison groups	BENRA Q4W vs PLA
		LS mean difference	-0.19
		95%CI	-0.38, -0.01
		P-value	**0.143**
		Comparison groups	BENRA Q8W vs PLA

		LS mean difference	-0.25
		95%CI	-0.44, -0.07
		P-value	**0.008**
	AQLQ(S)	Comparison groups	BENRA Q4W vs PLA
		LS mean difference	0.16
		95%CI	-0.04, 0.37
		P-value	0.119
		Comparison groups	BENRA Q8W vs PLA
		LS mean difference	0.24
		95%CI	0.04, 0.45
		P-value	**0.019**

Summary of efficacy for trial D3250C00020

Title: *A Multicentre, Randomized, Double-blind, Parallel Group, Placebo-controlled, Phase 3 Efficacy and Safety Study of Benralizumab (MEDI-563) to Reduce Oral Corticosteroid Use in Patients with Uncontrolled Asthma on High Dose Inhaled Corticosteroid plus Long-acting β2 Agonist and Chronic Oral Corticosteroid Therapy*			
Study identifier	ZONDA		
Design	Randomized, double-blind, double-dummy, parallel group, placebo-controlled		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		28 weeks Up to 8 weeks Study BORA
Hypothesis	Superiority		
Treatments groups	BENRA 30 Q4W		Benralizumab 30 mg SC every 4 weeks; 56 weeks; N=72
	BENRA 30 Q8W		Benralizumab 30 mg SC every 4 weeks (3 inj) then every 8 weeks; 48 weeks; N=73
	PLA		Placebo SC every 4 weeks; 48 weeks; N=75
Endpoints and definitions	Primary endpoint	% RED OCS	% reduction in OCS dose from BL
	Secondary endpoint	≥ 50%	% patients with ≥50% reduction in OCS dose from BL
	Secondary endpoint	≤ 5 mg	% patients with final dose ≤ 5 mg
	Secondary endpoint	AER	Annualised rate of asthma exacerbations defined as requiring systemic CS
	Secondary endpoint	FEV1	Pre-bronchodilator FEV1 – Change from BL
Database lock	23-08-2016 / 29-09-2019		

Results and Analysis

Analysis description	**Primary Analysis in Full Analysis set**			
Analysis population and time point description	Intent to treat – The study comprises an induction phase (4 weeks), a reduction phase (20 weeks), a maintenance phase (4 weeks) – The final OCS dose during week 28 is compared to the BL dose while asthma control must be maintained			
Descriptive statistics and estimate variability	Treatment group	**BENRA Q4W**	**BENRA Q8W**	**PLA**
	Number of subject	72	73	75

	% RED OCS Median Q1, Q3	75 19, 100	75 25, 100	25 0, 50
	≥ 50% N (%)	48 (66.7%)	48 (65.8%)	28 (37.3%)
	≤ 5 mg N (%)	44 (61.1%)	43 (58.9%)	25 (33.3%)
	AER (rate/year) 95%CI	0.82 0.54, 1.24	0.54 0.33, 0.87	1.80 1.32, 2.46
	FEV1 LS mean change	0.232	0.239	0.126

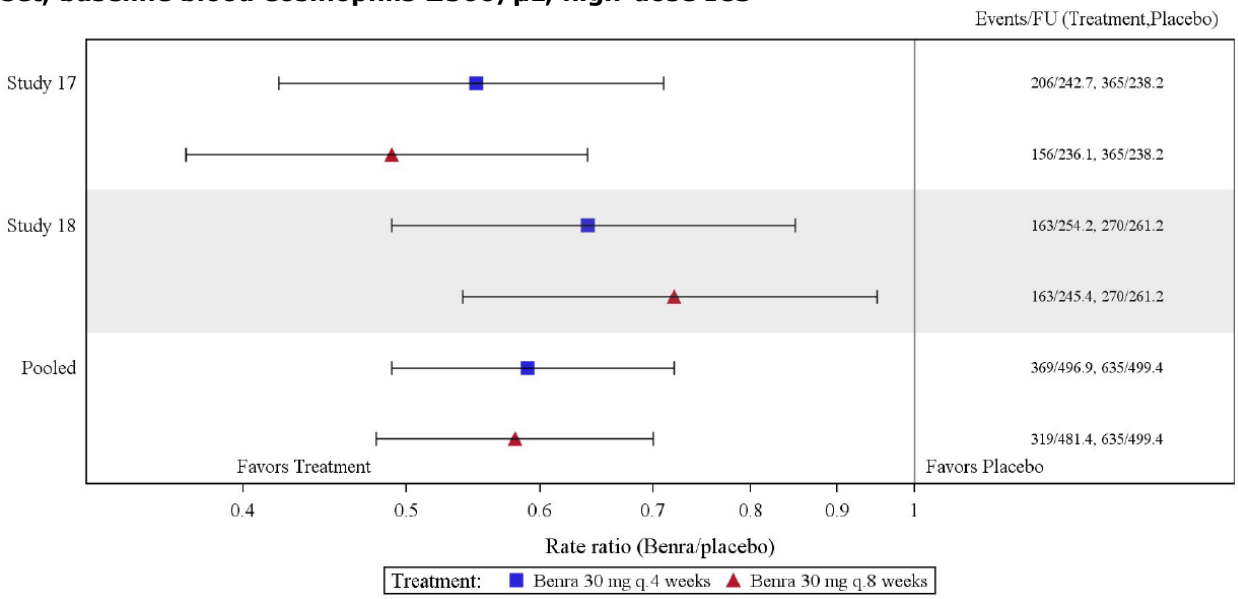
Effect estimate per comparison	% RED OCS	Comparison groups	BENRA Q4W vs PLA
		Difference	33.3
		95%CI	16.7, 50.0
		P-value	**< 0.001**
		Comparison groups	BENRA Q8W vs PLA
		Difference	37.5
		95%CI	20.8, 50.0
		P-value	**< 0.001**
	≥ 50%	Comparison groups	BENRA Q4W vs PLA
		Odds ratio	3.59
		95%CI	1.79, 7.22
		P-value	**< 0.001**
		Comparison groups	BENRA Q8W vs PLA
		Odds ratio	3.03
		95%CI	1.57, 5.86
		P-value	**< 0.001**
	≤ 5mg	Comparison groups	BENRA Q4W vs PLA
		Odds ratio	3.16
		95%CI	1.60, 6.23
		P-value	**< 0.001**
		Comparison groups	BENRA Q8W vs PLA
		Odds ratio	2.74
		95%CI	1.41, 5.31
		P-value	**0.002**
	AER	Comparison groups	BENRA Q4W vs PLA
		Rate ratio (BEN/PLA)	0.45
		95%CI	0.27, 0.76
		P-value	**0.003**
		Comparison groups	BENRA Q8W vs PLA
		Rate ratio (BEN/PLA)	0.30
		95%CI	0.17, 0.53
		P-value	**< 0.001**
	FEV1	Comparison groups	BENRA Q4W vs PLA
		LS mean difference	0.105

		95%CI	-0.040, 0.251
		P-value	0.153
		Comparison groups	BENRA Q8W vs PLA
		LS mean difference	0.112
		95%CI	-0.033, 0.258
		P-value	0.129

Analysis performed across trials (pooled analyses)

Given the replicate design of the two exacerbation studies, an integrated analysis was pre-specified for the key endpoints. Forest plots are presented below.

Annual asthma exacerbation rate ratio comparisons, negative binomial model - Full analysis set, baseline blood eosinophils ≥300/µL, high-dose ICS

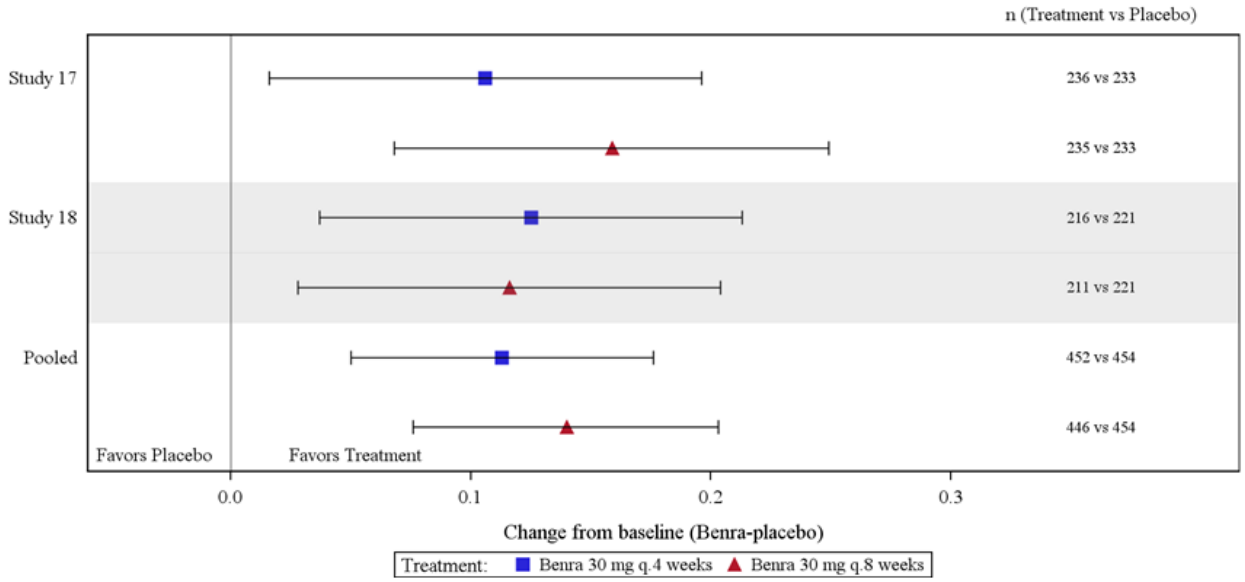


Integrated analysis (negative binomial model)

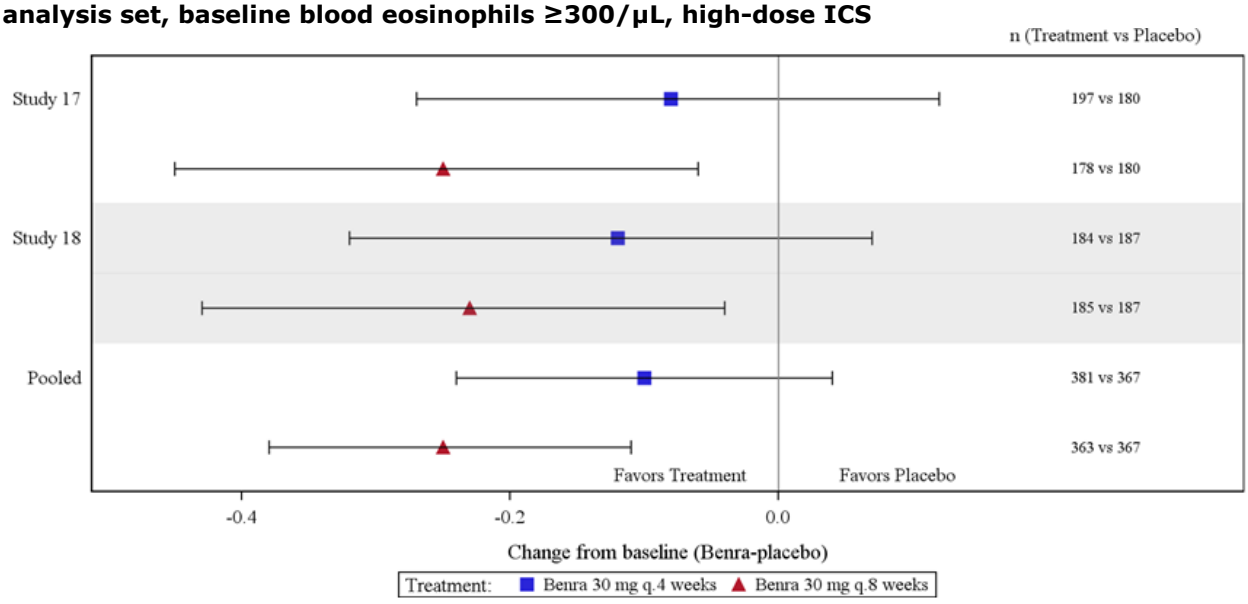
				Annual exacerbation rate	Absolute difference	Rate ratio	
Treatment group	N	Number of events	Total follow-up time (years)	Crude rate	Estimate (95% CI)	Estimate (95% CI)	Estimate (95% CI)	p-value
Benra 30 mg q.4 weeks	516	369	496.9	0.74	0.67 (0.58, 0.78)	-0.47 (-0.64, -0.29)	0.59 (0.49, 0.72)	<0.001
Benra 30 mg q.8 weeks	506	319	481.4	0.66	0.66 (0.57, 0.77)	-0.48 (-0.65, -0.30)	0.58 (0.48, 0.70)	<0.001
Placebo	515	635	499.4	1.27	1.14 (1.00, 1.29)			

Study by treatment interaction test p-value=0.097

Change from baseline in pre-bronchodilator FEV1at EOT treatment comparisons - Full analysis set, baseline blood eosinophils ≥300/µL, high-dose ICS



Change from baseline in total asthma symptom score at EOT treatment comparisons - Full analysis set, baseline blood eosinophils ≥300/µL, high-dose ICS



Subgroup analyses

Integrated efficacy data were analysed by pre-defined subgroups of age at randomisation, gender, BMI, OCS use at baseline, number of asthma exacerbations in previous year, race, geographic region, and country.

Reductions in annual asthma exacerbation rate were similar or favoured benralizumab 30 mg Q4W and Q8W over placebo for all subgroups with the exception of adolescents (ages 12 to <18 years) and Black or African Americans, each of which had a small number of patients/events.

Differences between regions were observed and further studied. Central and Eastern Europe, which showed the lowest treatment effect of any region in the benralizumab 30 mg Q8W arm, included Bulgaria, Czech Republic, Poland, Romania, Russian Federation, and Ukraine. A consistent lack of treatment effect (equivalent to placebo) was observed in most of these countries, with the exception of the Russian Federation, and an effect clearly favouring placebo was observed in the Romania. Romania accounts for

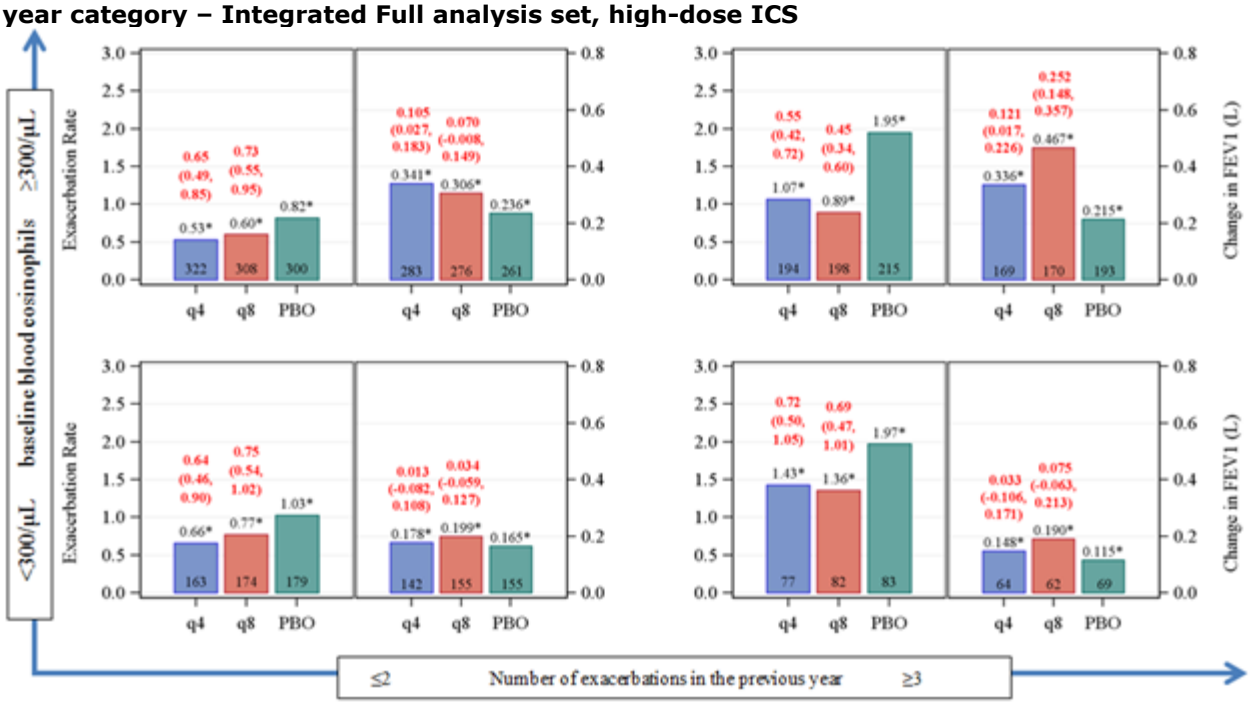
4.2% of patients in CALIMA and the Central and Eastern Europe region accounts for ~35% of patients in CALIMA. The crude placebo rates in the Central and Eastern Europe countries ranged from 0.21 to 1.40 in the integrated data and were some of the lowest across all countries.

The primary efficacy endpoint was analysed post hoc by geographic regions categorised as EU, North America, and RoW; EU was classified in two different ways. The results from these analyses indicated that the reductions in annual asthma exacerbation rate favoured benralizumab 30 mg Q8W over placebo in each of the 3 geographic regions analysed:

- EU: 33% (placebo rate: 1.20) but 54% (placebo rate: 1.96) when restricted to Western EU countries (Germany, Spain, France, United Kingdom, Italy, and Sweden);
- North America: 41% (placebo rate: 1.43);
- RoW: 52% (placebo rate: 1.27) but 40% (placebo rate: 1.08) when including eastern EU countries.

Subgroup analyses from SIROCCO and CALIMA identified patients with higher prior exacerbation history and baseline blood eosinophil count as potential predictors of improved treatment response. When considered alone or in combination, these factors may further identify patients who may achieve a greater response from benralizumab treatment (see figure below).

Annual exacerbation rate ratio and change from baseline in pre-bronchodilator FEV1 to EOT by baseline blood eosinophil count category and by number of exacerbations in the previous year category – Integrated Full analysis set, high-dose ICS



Efficacy in children and adolescents

A total of 108 adolescent patients, aged 12 – 17 years (mean 14.3 years), were evaluated for the primary efficacy endpoint and selected secondary efficacy endpoints, in concordance with the requirements from the PDCO. They were only 68 in the group with baseline blood eosinophils ≥300/µL. The results of the primary endpoint are shown below.

Annual asthma exacerbation rate ratio in adolescent patients (Integrated SIROCCO/CALIMA - FAS)

	Baseline blood eosinophils ≥300/µL			All adolescents combined		
	Benra 30 mg Q4W (N=17)	Benra 30 mg Q8W (N=24)	Placebo (N=27)	Benra 30 mg Q4W (N=22)	Benra 30 mg Q8W (N=40)	Placebo (N=46)
Number of events	16	17	8	16	26	18
Total follow-up time (years)	13.8	21.8	24.7	18.9	37.8	43.2
Crude annual exacerbation rate	1.16	0.78	0.32	0.85	0.69	0.42
Annual exacerbation rate, estimate	1.14	0.81	0.32	0.78	0.70	0.41
(95% CI)	(0.56, 2.32)	(0.43, 1.53)	(0.14, 0.71)	(0.38, 1.62)	(0.42, 1.18)	(0.23, 0.73)
Absolute difference, estimate	0.82	0.49	-	0.37	0.29	-
(95% CI)	(-0.03, 1.67)	(-0.08, 1.07)	-	(-0.25, 0.99)	(-0.15, 0.73)	-
Rate ratio (benra/placebo)	3.56	2.54	-	1.89	1.70	-
(95% CI)	(1.23, 10.32)	(0.91, 7.03)	-	(0.75, 4.80)	(0.78, 3.69)	-
p-value	0.019	0.074	-	0.179	0.181	-

Statistical analysis model: a negative binomial model including covariates study code, treatment group, baseline blood eosinophils (≥300/µL or <300/µL), and treatment group by baseline blood eosinophils interaction. For the combined baseline blood eosinophils group, treatment group by baseline blood eosinophils interaction was excluded in the model.
Total follow-up time was defined as the time from randomisation up to and including the date of Visit 17 or 19 (end of treatment visit at Week 48 or Week 56) or last contact if the patient is lost to follow-up.
The log of each patient's corresponding follow-up time was used as an offset variable in the model to adjust for patients having different exposure times during which the events occurred.
Annual exacerbation rates were model estimated.

In contrast to the results in adults, there was no detectable difference between the benralizumab and placebo arms for each of these endpoints, and the 95% confidence intervals were wide for each of these repeated measures analyses. While eosinophil depletion was observed in adolescent patients treated with benralizumab, there was a lack of any consistent trend favouring benralizumab across efficacy endpoints, and point estimates generally favoured placebo albeit with very wide confidence intervals. Adolescent patients in SIROCCO and CALIMA when compared with the overall population (adults and adolescents combined) at baseline had better FEV1, lower symptoms, and fewer prior exacerbations. These differences along with the low placebo exacerbation rate suggest that the adolescent population differs from the adult population in these studies. The small sample size and the wide confidence intervals around treatment differences do not allow definitive conclusions to be made.

Supportive studies

Lung-function study in patients with mild to moderate asthma (BISE)

The primary objective of the study was to evaluate the effect of benralizumab on pulmonary function in mild to moderate asthmatic patients using FEV1 as the primary endpoint. The key secondary objectives were to assess the effects of benralizumab on asthma symptoms and other asthma control metrics.

Of the 211 patients randomised, all patients received at least one dose of IP; a total of 197 (93.4%) patients completed treatment. In general, demographic characteristics were balanced across the 2 treatment groups with respect to age, gender, race, and ethnicity. The patient population was predominantly White (93.4%). A high percentage of the patient population was in the obese (23.2%) or morbidly obese (17.5%) category. Demographic and patient characteristics of the baseline blood eosinophil count ≥300/µL and <300/µL subgroups were similar to those of the full analysis set.

A statistically significant improvement in change from baseline pre-bronchodilator FEV1 at Week 12 was observed for benralizumab compared with placebo (0.08 L [0.00, 0.15], p=0.040). Modelling of pre-bronchodilator FEV1 change from baseline suggested an increased treatment effect as the baseline

blood eosinophil count increased. In general, positive trends in favour of benralizumab were observed across a number of secondary endpoints, although none of the differences were statistically significant at a nominal 5% significance level.

At-home use study (GREGALE)

This study included 116 male and female patients 18 to 75 years of age with severe asthma (ie, uncontrolled asthma despite receiving medium- or high-dose ICS/LABAs and OCS with or without additional asthma controllers). A total of 109 patients (94.0%) completed treatment with IP; all of whom completed the study. The majority of patients were White (81.0%), and approximately half of the patients were female (55.2%). The mean age was 47.6 years (range: 18 to 75 years).

The primary objective was to assess patient- or caregiver-reported functionality and reliability of the benralizumab accessorised pre-filled syringe (APFS) in an at-home setting and performance of the APFS after use. This aspect of this study pertains to the use of the device, not the efficacy of benralizumab. A secondary objective was to assess the effect of benralizumab on asthma control metrics, specifically the change from baseline in mean ACQ-6 score. Decreases from baseline in the mean ACQ-6 score were observed at all post-baseline time points, and a greater percentage of patients had an ACQ-6 score that indicated their asthma was well controlled at Week 20 (26%) compared with baseline (4%). More than half of patients (57%) reported to be improved based on ACQ-6 score at Week 20.

2.7.2. Discussion on clinical efficacy

Design and conduct of clinical studies

This application is based on three pivotal placebo-controlled trials in severe uncontrolled asthma, for which the Applicant received CHMP scientific advice. Two trials with a replicate design investigated the effect of benralizumab on asthma exacerbations and a third trial investigated its potential corticosteroid sparing effect.

The study population of these three trials had severe uncontrolled asthma defined in accordance with current guidelines (ATS, GINA - 2014). These patients required treatment with medium-to-high dose inhaled corticosteroids (ICS) combined with a long-acting β2 agonist (LABA), with or without additional maintenance controllers including oral corticosteroids (GINA Steps 4 and 5). Despite of this treatment, these patients had persistent airflow obstruction, asthma symptoms, and a history of frequent exacerbations requiring systemic corticosteroid treatment (at least two per year in the exacerbation studies).

The key dose-ranging Phase II trial had evaluated the effect of benralizumab on the annual asthma exacerbation rate in uncontrolled eosinophilic asthma using the ELEN Index (a surrogate marker of sputum eosinophils ≥2%) together with elevated baseline FeNO. While the trial failed to meet its primary objective, it showed that pre-treatment eosinophil blood count was positively correlated with treatment benefit; above the threshold of 400 cells/μL, a clinically relevant response was apparent at doses of 20 and 100 mg. There were no selection criteria of eosinophilic asthma in the Phase III exacerbation studies but the primary analysis was in the population of patients on high ICS dose and with baseline eosinophil blood count ≥300 cells/μL. In the OCS reduction study, only patients with peripheral blood eosinophil count ≥150 cells/μL were enrolled.

All three placebo-controlled pivotal trials tested two dosing regimens using the same benralizumab dose (30 mg) administered at a different frequency after three 4-weekly doses: continuing every 4 weeks or with longer intervals of 8 weeks.

Exacerbation studies

In line with current CHMP guidance, the duration of the exacerbation trials was ~12 months (with a double-blind treatment of 48 months in one trial and 56 months in the other).

The primary endpoint of asthma exacerbations corresponds to 'severe exacerbations' as defined in ATS and CHMP guidelines (need for systemic CS, emergency room visit or hospitalisation due to asthma). It is agreed that this is the most important outcome in this patient population because they constitute the greatest risk to patients, are a cause of anxiety to patients and their families, result in the greatest stress on health care providers, and generate the greatest cost to the health care system. In addition, serious exacerbations requiring ER/urgent care visit or hospitalisation were adjudicated by an independent committee.

The main secondary endpoints were pulmonary function tests (pre-bronchodilator FEV1), asthma symptoms measured by patients at home with a dedicated ePRO device and reflected in the asthma symptom score as well as in the Asthma Control Questionnaire (ACQ-6), quality of life assessed with the standardised Asthma Quality of Life Questionnaire (AQLQ(S)+12). These are all validated questionnaires and the secondary endpoints are considered appropriate.

The randomisation was central and stratified by age (adults/adolescents), country/region and eosinophil count at screening (≥300/µL or <300/µL) and ICS dose (medium/high) for one of the studies). The trials were conducted in a double-blind, double-dummy fashion, with patients and investigators involved in their treatment and clinical evaluation were not aware of the treatment allocation. Specific measures were taken to maintain the blind to blood eosinophil counts, which were performed in a central laboratory.

OCS reduction study

The third trial was designed to investigate the corticosteroid sparing effect of benralizumab in patients requiring at least 7.5 mg/day of oral prednisone or equivalent; this dose is considered to have significant toxicity, especially when combined with the burden of high ICS doses. The trial included before randomisation an OCS optimisation phase (up to 8 weeks) to establish the lowest OCS dose needed to control the patient's symptoms, this dose being stable for the last 2 weeks before randomisation. However, historical dose optimisation (i.e. failed attempt to reduce OCS dose within the preceding 6 months) was also accepted if adequately documented in the source records.

After randomisation, this dose had to be maintained for 4 weeks before the OCS reduction phase was started following a pre-defined algorithm. This phase lasted 20 weeks and was followed by a maintenance phase of 4 weeks without any dose adjustment, during which the evaluation of outcomes was conducted. The maintenance period of 4 weeks, although considered acceptable for short-term evaluation, was confirmed with longer follow-up to evaluate the durability of the response.

The primary endpoint in this trial was the relative reduction in OCS dose compared with the baseline dose while maintaining asthma control (no worsening of asthma symptoms and pulmonary function; no exacerbation). Furthermore, while the CHMP endorsed the study design, it also advised that the absolute decrease in OCS would be a key secondary endpoint and that this should be clinically meaningful and evaluated in relation to the baseline dose. However, this was neither implemented nor discussed by the Applicant.

The secondary endpoints were related to the OCS dose reductions as well as asthma exacerbations, FEV1, asthma symptom score, ACQ-6 and AQLQ(S)+12 scores.

The three trials were multinational and the EU contributed to more than one third to half of the study population, especially Eastern EU countries. A double-blind extension of the three studies is ongoing with some interim results provided upon CHMP request.

Clinical studies in special populations

	Age 65-74 (Older subjects number /total number)	Age 75-84 (Older subjects number /total number)	Age 85+ (Older subjects number /total number)
Controlled Trials	311	9	None
Non Controlled trials	None	None	None

Efficacy data and additional analyses

Exacerbation studies

Population

The pooled population of the full efficacy analysis set (i.e. with baseline blood eosinophils ≥300/µL and high-dose ICS) comprised **1537 patients,** with a median age of 51 years, only 46 adolescents and 174 elderly patients ≥65 years of age (11%). As expected in this adult asthma population, the majority (63%) were female and obesity (a risk factor for poor asthma control) was reported in 35% of the cases. Most patients (about 80%) were Caucasian. Median EBC was 500/µL with a maximum of 4,000; this means that half of the patients had mild/moderate eosinophilia. Moderate hypereosinophilia (EBC ≥1,500/µL) was reported in up to 3% of patients with no other diagnosis than asthma and often allergic manifestations.

The population in Study 017 (SIROCCO) appeared to exhibit slightly more severe disease than in Study 018 (CALIMA): slightly lower median pre-bronchodilator FEV1 (57% vs 59% predicted) at baseline; higher proportion of patients with ≥4 exacerbations in the previous year (21% vs. 16%) and with at least one hospitalisation (25% vs 18%); higher median ACQ-6 score (2.83 vs. 2.67). The demographics and baseline disease characteristics were broadly similar across treatment arms (~ 500 patients each).

All patients were taking ICS and LABA as required by protocol except for 2 subjects that did not take LABA. The median dose of ICS was 1000 µg/d in adults and 500 µg/d in adolescents. The proportion of patients taking at least one additional controller was 51% in SIROCCO and 41% in CALIMA; most patients (63% and 66%, respectively) were taking one additional controller, the most frequent being a leukotriene receptor antagonist (LTRA). Slightly more patients were taking OCS in SIROCCO (16%) than in CALIMA (11%) but overall, this proportion was not very high. Maintenance therapy was broadly comparable between treatment arms. It was stable in most patients since overall, only 7% patients had any dose increase or initiated a new background asthma controller medication during the study, with the number of patients evenly distributed across treatment arms.

In both studies, treatment adherence was good with only 11% of patients discontinuing treatment. The main reason was patient decision (5%), which is unfortunately not very informative. Nevertheless, treatment withdrawals and their reasons were balanced across treatment arms. Likewise, a high proportion of patients (about 90%) completed the studies.

The level of important protocol deviations (about 8%) is considered low; most were related to asthma documentation regarding spirometry results (5%). They were also balanced across treatment arms. This observation does not raise any concern.

Primary endpoint

In both studies, the crude annual exacerbation rate on placebo was below 2/year, especially in CALIMA, where it was ~1/year, which would not correspond to the target population of patients with uncontrolled asthma and frequent (≥ 2) severe exacerbations. Likewise, the proportion of patients with at least one serious exacerbation (requiring ER/hospitalisation) was low on placebo, especially in CALIMA (< 10%), where this proportion was similar in all treatment arms. The differences between the placebo arms of the two studies are consistent with the baseline characteristics of the two study populations suggesting that patients in SIROCCO were more severely affected than in CALIMA.

While the two trials met their primary endpoint, the treatment effect in relative terms (exacerbation rate reduced by approximately 40% for both regimens in the integrated analysis) and absolute terms (an estimated difference of about 0.5/year, from 1.14 to 0.66/year) is considered modest from a clinical perspective. When comparing the two studies, the magnitude of the treatment effect in both relative and absolute terms appeared greater in a population with more frequent exacerbations as reflected in the crude placebo rates. The two regimens appeared equivalent in the integrated analysis. While 2 dosing regimens were studied in the phase III clinical trials, the recommended dosing regimen is an administration every 4 weeks for the first 3 doses, then every 8 weeks thereafter (see section 4.2) as no additional benefit was observed by more frequent dosing (see also section 2.6.3).

Given the low frequency of serious exacerbations in this population, the clinical relevance of the benefit in terms of decrease in ER visits or hospitalisations is questionable. Unexpectedly, only the regimen with less frequent dosing achieved a statistically significant difference, decreasing the annual rate from 0.10 to 0.06/year (38% in relative terms) in the integrated analysis. It is considered that this result is not robust and no relevant benefit on ER visits/hospitalisations can be attributed to benralizumab in these trials.

Secondary endpoints

Pulmonary function

Significant increase in the pre-bronchodilator FEV1 (key secondary endpoint) was reported at the end of treatment with benralizumab compared to placebo. Unexpectedly, the improvement was more important with less frequent dosing in SIROCCO; it is noted that there was already a difference between the two regimens at week 4 and 8, while all patients were receiving the same treatment.

Mean improvements of more than 200 mL were measured in all treatment arms, including placebo. Mean differences between benralizumab and placebo ranged between 100 and 160 mL, which can be considered clinically relevant. The results of other endpoints support some level of improvement in pulmonary function with benralizumab compared to placebo with no obvious differences between the two dosing regimens.

Asthma symptoms

A statistically significant improvement in total asthma symptom score and ACQ-6 score was only observed with the lower frequency regimen compared to placebo while no or borderline significant difference was observed with the higher frequency regimen. It is noted that the placebo effect was important with an absolute decrease in the asthma total score of about 1 and in in the ACQ-6 score >1 both trials. The clinical relevance of a mean difference between placebo and benralizumab of 0.25 for the asthma score is unknown as there is no accepted minimally clinically important difference (MCID) for this endpoint. For the ACQ-6 score, a mean difference between placebo and benralizumab of 0.2 to 0.3 is below the MCID of 0.5. However, according to a literature review (Bateman, 2015), to exceed this MCID is hardly achievable when treatments are added to highly effective medications, such as ICSs or ICS/LABA combinations.

When analysed in terms of ACQ-6 responders (patients achieving a minimally clinically important difference of ≤-0.5), at least half the patients responded to placebo and the difference with benralizumab was very small, at maximum 10% in one study in favour of the Q8W regimen. Furthermore, the proportion of patients that were not well controlled (score ≥ 1.5) at the end of the trial was not very different between the benralizumab and placebo arms: 31-32% vs. 37% in SIROCCO and 33-35% vs 41% in CALIMA, respectively.

Importantly, the small differences in asthma scores did not translate into significant difference in the use of asthma rescue medication between treatment arms (~ -0.5 puffs/day). Likewise, a similar decrease in the proportion of nights with nocturnal awakenings due to asthma was reported across all treatment arms.

Finally, the quality of life analysis (AQLQ(S)+12) showed results in line with the asthma scores. A responder analysis (improvement ≥ 0.5) indicated better results overall in CALIMA than SIROCCO with no significant differences between benralizumab and placebo arms: 55-57% vs 49% in SIROCCO and 60-61% vs 59% in CALIMA.

It is concluded that asthma control improved in all treatment arms throughout the trials and the differences between benralizumab and placebo appear to be small. However, the interpretation of these PRO outcomes is unclear in this clinical setting (patients with severe asthma on a combination of high ICS dose and LABA), as reflected by similar results for previously authorised anti-IL5 products.

Subgroup analyses

Efficacy on the primary endpoint was observed in all subgroups with the exception of adolescents (ages 12 to <18 years) and Black or African Americans, each of which had a small number of patients/events. The Applicant is not proposing to include adolescents in the indicated population at this time. In CALIMA, while the point estimate favoured placebo for the Black/African American subgroup, the placebo event rate was low and the CI was wide given the small number of patients. This trend was not replicated in SIROCCO, and therefore, while the data supporting efficacy in this population are limited, the Applicant considers that there is no reason to conclude that benralizumab would behave differently in this patient population. In addition, given the increased asthma morbidity and mortality reported in Black/African American asthmatic patients, this subgroup has not been excluded from the indicated population.

The Applicant has investigated in depth the differences in the treatment effect between regions and countries. These appeared largely driven by the placebo crude exacerbation rates, the treatment effect tending to be higher when placebo rate was higher. As already highlighted, the overall placebo rates were low in the two studies despite the inclusion criterion of ≥ 2 exacerbations in the previous year. It is unclear how this criterion could be verified based on the patient medical notes and the number of severe exacerbations may well have been overestimated, especially for enrolment purposes. It is noteworthy that the two countries that enrolled the highest numbers of patients in CALIMA were Argentina (placebo crude rate: 0.68) and Poland (placebo crude rate: 0.67).

In Western EU, the annual exacerbation rate was reduced by 54% from a placebo rate of 1.96/year, but the effect was decreased to 33% when Eastern EU countries were added.

Potential predictors of efficacy

Outcomes generally improved as the number of exacerbations in the previous year increased, which logically translated into increasing placebo crude exacerbation rates: 0.59/year in patients with 2

exacerbations in the previous year vs. 1.71/year in patients with ≥ 3 exacerbations in the previous year (CALIMA).

Outcomes also improved as the baseline blood eosinophil count (BEC) increased. In the largest subgroup of patients with ≥ 450 cells/μL, annual exacerbations rates (AER) were reduced by 41% with the Q4W regimen and 50% with the Q8W regimen; at week 48, pre-bronchodilator FEV1 had increased on average by 154 mL with the Q4W regimen and 224 mL with the Q8W regimen (integrated analysis).

An analysis where both factors were combined was conducted with the cut-off of 300/μL for BEC. In the subpopulation of patients with 2 exacerbations in the previous year, where the placebo annual exacerbation rate was ≤1, there was little difference in the outcomes according to BEC and the treatment effect was minimal: AER reduction by 25-35% and marginal increase in mean pre-bronchodilator FEV1 (13-105 mL). In contrast, in the subpopulation of patients with ≥ 3 exacerbations in the previous year, where the placebo annual exacerbation rate was about 2, patients with higher baseline BEC fared better than those with lower baseline BEC: AER reduction by ~50% vs ~30%, respectively, and increase in mean pre-bronchodilator FEV1 of 121 mL (Q4W) and 252 mL (Q8W) vs. 33 mL (Q4W) and 75 mL (Q8W).

It is concluded that the benefit of benralizumab, especially the Q8W regimen, is demonstrated in patients with a high frequency of asthma exacerbations and high BEC. However, in those with a low frequency of exacerbations, the benefit is extremely modest, if not marginal, regardless of their BEC level.

Nevertheless, the Applicant considers that it is unnecessary to single out and include prior history of exacerbations in the indication statement and that there is no single eosinophil level that defines the eosinophilic phenotype. The Applicant argues that efficacy was demonstrated across a range of baseline eosinophil levels, including in the <300/μL population. As such, an eosinophil cut-off is not included in the proposed indication. Of note, however, baseline blood eosinophil level and prior history of exacerbation are both potential predictors of benefit in patients to be prescribed benralizumab, and therefore, this evidence has been added to Section 5.1 of the proposed SmPC. This option is acceptable and is in line with the SmPC of similar products.

OCS reduction study

Population

A total of **220 patients** were randomised to receive treatment with benralizumab 30 mg Q4W (72), Q8W (73), or placebo (75). Treatment adherence was good with only 6% of patients discontinuing treatment. Likewise, a high proportion of patients (about 95%) completed the study.

A high level (25%) of important protocol deviations regarding the determination of the OCS dose (primary endpoint) was reported as investigators and/or patients did not adhere to the titration algorithm. The deviation rate appeared imbalanced, with almost twice as many deviations in the placebo arm than in the benralizumab arms. Some of these imbalances are likely to favour placebo while others are likely to favour benralizumab; however, the biases are expected to be in favour of placebo, and thus, do not raise concern.

Given the small sample size of the study, some differences were observed across treatment arms, e.g. slightly older patients with longer asthma duration, lower BEC at baseline, and higher number of exacerbations in the previous year, in the benralizumab Q8W arm compared to the placebo arm.

More than half the patients (53%) took additional controller(s), mainly an LTRA, and this was well balanced over treatment arms. The ICS dose tended to be higher in the placebo arm but the median was 1000 μg/d of fluticasone propionate equivalent in all arms. A small percentage of patients (2%) deviated

from protocol because they received a dose lower than 500 µg/d but they were equally distributed across the three treatment arms.

For 67/220 patients (30%), historical optimisation occurred; this was roughly balanced across treatment arms (26%, 33% and 32% in the benralizumab Q4W, Q8W and placebo, respectively). At baseline (pre-randomisation), the OCS dose was ≤ 10 mg/d in the majority of patients (114/220 patients; 52%) while it was between 11.5 and 20 mg/d in 83 patients (38%) and > 20 mg/d in 23 patients (11%). Although the OCS dose was in the low-medium range in most patients, the cumulative burden with the ICS dose has to be taken into account. There were few dose modifications during the optimisation phase, with only 20% (31/153) of dose reductions.

It is considered that the study population was representative of the target population. The majority of patients had uncontrolled asthma (based on ACQ-6 score) and two thirds had experienced at least 2 exacerbations in the previous year (although this number may be questionable like in the exacerbation studies).

Primary endpoint

Overall, the proportion of patients that could reduce their OCS dose was 76% and 79% in the benralizumab Q4W and Q8W arms, respectively, compared to 53% in the placebo arm. The median percent reduction was 75% in the benralizumab arms versus 25% in the placebo arms, which was statistically significant (p< 0.001). About one third of the patients (33% and 37% in the benralizumab arms, respectively) had a dose reduction of > 90% compared with 12% of the patients in the placebo arm.

Absolute changes in OCS dose have also been provided. Patients with relatively low baseline doses (≤12.5 mg/d - median 10 mg/d) had a final median dose of 0 and a median decrease of 7.5 mg/d in the benralizumab arms vs a median decrease of 2.5 mg/d in the placebo arm (final dose of 7.5 mg/d). Patients with higher baseline doses (>12.5 mg/d – median 20 mg/d) had a final median dose of 7.5-10 mg/d and a median decrease of 12-14 mg/d in the benralizumab arms vs a median decrease of 5 mg/d in the placebo arm (median dose of 15 mg/d). Given the correlation between systemic CS dose and occurrence of adverse reactions, dose reductions of the magnitude observed in the benralizumab arms (median 7 – 14 mg/d) are considered clinically relevant. Furthermore, the objective of achieving a final dose ≤ 5mg is considered clinically meaningful; this was achieved by 61% and 59% of the patients in the benralizumab arms (Q4W and Q8W, respectively) vs 33% in the placebo arm (p ≤ 0.002).

While it is agreed that a reduction by ≤ 5 mg in OCS dose is not clinically meaningful, a smaller proportion of patients had a meaningless OCS decrease in the benralizumab 30 mg Q4W and Q8W arms compared with the placebo arm (31% and 34% vs 51%, respectively; p=0.012 and 0.053, respectively). However, this result is not considered compelling from a clinical perspective.

In line with the outcomes in the exacerbations studies, results improved as baseline BEC increased and also as the number of previous yearly exacerbations increased, the main reason being that the placebo response decreased while the response to benralizumab was similar; the proportion of patients that could reduce their OCS dose decreased from 67% (1 exacerbation in the previous year) to 38% (≥3 exacerbations in the previous year) while this proportion ranged between 72% and 83% in the benralizumab arms.

The % reduction was roughly the same irrespective of the baseline OCS dose (≤ 10 mg/d or > 10 mg/d). Finally, for this primary variable of OCS dose, there was no clear trend for a difference between the two benralizumab regimens.

Secondary endpoints

Twice as many patients experienced at least one exacerbation during the study in the placebo arm compared to the benralizumab arms. The annualised exacerbation rate was 1.80 on placebo and the decrease with benralizumab was notable considering that the OCS dose was reduced in these patients. The regimen with the lower dosing frequency appeared more effective with an AER decreased by 70% (vs 55% in the benralizumab Q4W arm).

The mean improvement in FEV1 compared to placebo (about 100 mL) was not statistically significant. A significant improvement in ACQ-6 and AQLQ(S)+12 scores, with a decrease in the need for rescue medications, was only reported for the benralizumab Q8W regimen. However, in terms of responder rates for these scores, the difference between this regimen and placebo was small (8%).

The proportion of patients that were still not well controlled at the end of the study was approximately the same in the benralizumab Q4W arm (53%) as in the placebo arm (60%), but it was much lower in the Q8W arm (34%). At the end of the study, the proportion of patients with deterioration of this score was 6%, 1% and 16% in the benralizumab Q4W arm, Q8W and placebo, respectively.

It is concluded that a clinically meaningful decrease in the frequency of asthma exacerbations was observed with benralizumab despite decrease in OCS dose, especially with the low frequency regimen. This was associated for this regimen with some degree of improvement in asthma scores. Nevertheless, at the end of the study, one third of the patients on this regimen were still poorly controlled.

Durability of response

Following CHMP request, OCS dose and exacerbation data for all benralizumab-treated patients in the extension trial (BORA) were analysed up to the data cut-off date of 21 October 2016. All patients had reached 40 weeks of treatment (i.e., 12 additional weeks after the end of ZONDA) and, at that time point, the proportion of patients off OCS (39% in the benralizumab Q8W arm) and those with no change/increase in dose (16%) were similar to those at the end of ZONDA. The median dose was maintained at 5 mg/d while the number of exacerbations appeared to remain stable.

Assessment of paediatric data on clinical efficacy

There were only 68 adolescents in the group of patients with baseline blood eosinophils ≥300/µL. Compared with the whole population, the enrolled adolescents appeared to have less severe disease, which is likely to explain treatment failure in this subgroup despite near complete depletion of eosinophils. The higher AER on benralizumab than on placebo has not been discussed by the Applicant. It is noted that in the adolescent subpopulation, the incidence of nasopharyngitis and bronchitis was higher on benralizumab than on placebo while it was the same in the whole population. This might have contributed to the increased frequency of asthma exacerbations on benralizumab.

In conclusion, no claim can be envisaged in this paediatric population based on the results currently available.

2.7.3. Conclusions on clinical efficacy

Two large well-designed pivotal exacerbations studies demonstrated a statistically significant effect of benralizumab on the annual rate of asthma exacerbations in a population of patients with uncontrolled asthma despite high ICS doses and with a baseline blood eosinophil count ≥300 cells/µL. However, this effect is considered modest from a clinical perspective (a difference of about 0.5 exacerbations/year, from ~1.3 to ~0.8/year). The likely reason for this result is the low exacerbation rate in the study population

despite appropriate inclusion criteria. Moreover, given the low frequency of serious exacerbations in this population, the clinical relevance of the decrease in ER visits and hospitalisations is also questionable. Pooled data from the two trials did not indicate an exposure-response relationship and showed that both Q4W and Q8W dosing frequencies have the same efficacy profile.

A significant effect on the pulmonary function was also observed but the impact of benralizumab on asthma control was small and mostly restricted to the lower frequency regimen; there is no plausible biological explanation for this numerical superiority. It is agreed that the interpretation of these PRO outcomes is unclear in this clinical setting (add-on to the combination of high ICS dose and LABA in patients with severe asthma), as reflected by similar results for previously authorised anti-IL5 products.

In the small OCS sparing trial, a significant and clinically meaningful reduction in OCS dose has been achieved. Improvement in exacerbation rates and asthma control was again more apparent with the lower frequency regimen. Importantly, the effect on OCS dose and exacerbations was maintained during the extension study for at least 3 additional months of treatment.

Based on the results from the three trials, the regimen selected by the Applicant for treatment recommendation is the lower frequency regimen (Q8W), supported and accepted by CHMP. In addition, the objective of the first three doses every 4 weeks is to achieve rapid airway eosinophil depletion, and thus, hasten the onset of treatment benefit, and to lower the incidence and affinity of ADAs against benralizumab.

As reported with other mAbs targeting the same pathway in patients with an eosinophilic asthma phenotype, the primary effects of benralizumab are correlated with baseline eosinophil levels but it is agreed with the Applicant that no threshold needs to be introduced in the indication wording of the SmPC. The wording of the indication in the SmPC adequately reflects the target population of adult patients with severe eosinophilic asthma inadequately controlled despite high-dose inhaled corticosteroids plus long-acting beta-agonists.

2.7.4. Clinical safety

Analyses for the safety assessments were planned using pooled data from the Phase III, placebo-controlled, asthma exacerbation studies, SIROCCO and CALIMA. This is the primary pool upon which Integrated Summary of Safety (ISS) data have been summarised.

The second pool comprises of all completed Phase II or III asthma studies. Nine studies are included: MI-CP186, MI-CP197, MI-CP220, SIROCCO, CALIMA, ZONDA, BISE, GREGALE, plus patients who received treatment in PAMPERO. Safety data have not been pooled due to the substantial differences in study design, duration, and doses studied. None of the Phase II studies evaluated the 30 mg SC fixed dose studied in Phase III or assessed the Q4W versus Q8W dosing regimen (after the first 3 initial 4-week doses). However, any relevant safety findings from these studies are presented under the appropriate sections, including potential risks.

BORA is a long-term extension study for eligible patients who complete the SIROCCO, CALIMA, or ZONDA studies on treatment with investigational product (IP). BORA is evaluating the safety and tolerability of benralizumab treatment for an additional 56 weeks (adult patients) or 108 weeks (adolescent patients). A brief overview of blinded adverse events is presented (29 July 2016).

A Data Safety Monitoring Board (DSMB) and two independent adjudication committees, one for asthma exacerbations (to review all ER visits and/or hospitalisations) and the other to review major adverse cardiovascular events (MACE) and malignancies, were used across the Phase III programme.

Patient exposure

Phase III exacerbation studies

In total, 841 patients received benralizumab 30 mg Q4W, 822 patients received benralizumab 30 mg Q8W, and 847 patients received placebo. Overall, a total of 1556 out of 1663 patients (93.6%) were treated with benralizumab for ≥24 weeks and 1387 out of 1663 patients (83.4%) were treated with benralizumab for ≥48 weeks.

Duration of exposure (Safety analysis set)

	Statistics	Benra 30 mg Q4W (N=841)	Benra 30 mg Q8W (N=822)	Placebo (N=847)
Duration of exposure (days) [a]	n	841	822	847
	Mean (SD)	316.2 (76.2)	310.7 (81.9)	314.0 (76.7)
	Min, Max	1, 447	1, 399	1, 400
Total drug exposure weeks, n (%)				
<8		25 (3.0)	25 (3.0)	20 (2.4)
≥8 to <16		14 (1.7)	23 (2.8)	23 (2.7)
≥16 to <24		20 (2.4)	22 (2.7)	17 (2.0)
≥24 to <36		16 (1.9)	17 (2.1)	22 (2.6)
≥36 to <48		371 (44.1)	369 (44.9)	380 (44.9)
≥48 to <60		394 (46.8)	366 (44.5)	385 (45.5)
≥60		1 (0.1)	0 (0.0)	0 (0.0)

All Phase II and III studies in asthma

Using the subcutaneous route, 2442 patients received benralizumab and 1259 patients received placebo. The median treatment duration was 309 days. Overall, including the intravenous route, 2514 patients received benralizumab and 1297 patients received placebo.

Adverse events

Phase III exacerbation studies

There was a numerical imbalance in the incidence of TEAEs, with lower incidences of these events being reported by patients in the benralizumab 30 mg Q4W and Q8W arms compared with the placebo arm. Treatment-emergent AEs leading to study drug discontinuation were reported at slightly higher incidences by patients in the benralizumab 30 mg Q4W (2.0%) and Q8W (2.2%) arms compared with the placebo arm (0.8%). The incidence of SAEs was similar across arms and the incidence of deaths was low and similar across arms.

Overview of TEAEs – on-study period - (Safety analysis set)

	Number (%) of patients [a]			
AE category	**Benra 30 mg Q4W (N=841)**	**Benra 30 mg Q8W (N=822)**	**Placebo (N=847)**	**Total (N=2510)**
Any AE	621 (73.8)	605 (73.6)	653 (78.0)	1887 (75.2)

Overview of TEAEs – on-study period - (Safety analysis set)

	Number (%) of patients [a]			
AE category	**Benra 30 mg Q4W (N=841)**	**Benra 30 mg Q8W (N=822)**	**Placebo (N=847)**	**Total (N=2510)**
Any AE with outcome=death	5 (0.6)	4 (0.5)	3 (0.4)	12 (0.5)
Any SAE (including events with outcome=death)	97 (11.5)	95 (11.6)	119 (14.0)	311 (12.4)
Any AE leading to discontinuation of IP	18 (2.1)	18 (2.2)	8 (0.9)	44 (1.8)

The most common TEAEs overall were nasopharyngitis (16.0%), asthma (14.3%), upper respiratory tract infection (8.7%), and bronchitis (8.3%). The incidences of the most common TEAEs (those with a frequency of ≥3% in any treatment arm) were similar across arms.

Adverse events related to investigational product

The most common TEAEs considered related to study drug by the investigator (defined as those occurring at a frequency of >1% patients in any treatment arm) were headache, pyrexia, and fatigue reported by 40 (1.6%), 26 (1.0%), and 22 (0.9%) patients. The incidences of all other TEAEs assessed as related to study drug by the investigator were low and similar across arms.

Adverse events by severity

The majority of patients (90%) had events that were assessed as mild or moderate in intensity by the investigator; this includes events considered serious and non-serious.

The incidence of all severe TEAEs was similar across arms: 8.9%, 10.1%, and 10.7% for benralizumab 30 mg Q4W, Q8W, and placebo arms, respectively. Overall, the most frequently reported PTs of severe intensity were asthma (79 patients [3.1%]) and pneumonia (11 patients [0.4%]). The incidences of all other severe PTs were low and similar across arms.

Serious adverse events and deaths

Deaths

Phase III exacerbation studies

A total of 12 patients had TEAEs with outcomes of death: 5 in the benralizumab 30 mg Q4W arm, 4 in the benralizumab 30 mg Q8W arm, and 3 in the placebo arm. Nine of the deaths occurred in the on treatment period and 3 of the deaths occurred during the post treatment period. None of the deaths were considered treatment-related by the investigator. Of note, there were also 3 pre-treatment deaths.

All deaths occurred in adults patients (range: 42 to 75 years of age); 10 patients were overweight and of these, 2 were obese (BMI >30 to 35 kg/m2) and 2 were morbidly obese (BMI >35 kg/m2). The causes of death varied with no consistent pattern across arms: myocardial infarction (2), asthma (1), cerebral haemorrhage (1), opioid overdose (1), sudden death (1), pulmonary embolism (1), colon neoplasm (1), accident/suicide (2), unknown cause (2).

Phase III ZONDA study

Two patients (0.9% of all patients) died in the benralizumab 30 mg Q8W arm: acute cardiac failure (1) and pneumonia with pulmonary insufficiency (1), the latter being considered related to the study drug by

the investigator. This 53-year-old white male, died following a TEAE of pneumonia 20 days after the third dose of benralizumab 30 mg. He was hospitalised and the diagnosis was right-sided community-acquired pneumonia with middle lobe syndrome and severe worsening bronchial asthma. The patient developed atrial fibrillation and although treated with amiodarone, the event persisted. The patient had hypercholesterolemia, hypertension, angina pectoris, and congestive heart failure.

Other studies

One additional patient died in the BISE study received 3 doses of benralizumab 30 mg and died due to an SAE of pancytopenia. Risk factors for the event included a history of asbestos exposure and concomitant use of ramipril and amiodarone. The event was not considered related to study drug by the investigator and Sponsor.

Serious Adverse Events

Phase III exacerbation studies

Overall, 299 patients (11.9%) had SAEs (including those with an outcome of death) during the on-treatment period. A slightly lower incidence of SAEs was reported by patients in the benralizumab 30 mg Q4W (92 patients [10.9%]) and benralizumab Q8W (92 patients [11.2%]) arms compared with the placebo arm (115 patients [13.6%]).

The most common SAEs by PT (defined as those occurring at a frequency of >2 patients in any treatment arm) were asthma, pneumonia, osteoarthritis, hypertension, and nephrolithiasis, reported by 139 (5.5%), 16 (0.6%), 6 (0.2%), 4 (0.2%), and 3 (0.1%) of all patients, respectively. The incidences of the most common SAEs were similar across arms, and with the exception of the PT of asthma, the incidence of SAEs was low (<1% in any treatment arm).

A total of 8 patients (0.3%) had the following SAEs considered related to the study drug by the investigator:

- 4 patients (0.5%) in the benralizumab 30 mg Q4W (1 patient each with SAEs of allergic granulomatous angiitis [synonymous with Churg-Strauss syndrome], panic attack, paraesthesia, and urticaria);
- 2 patients (0.2%) in the benralizumab 30 mg Q8W arm (1 patient each with SAEs of asthma and herpes zoster);
- 2 patients (0.2%) in the placebo arm (1 patient each with SAEs of injection site erythema and non-cardiac chest pain).

Of note, the SAE of paraesthesia was not a demyelinating event (verbatim term: paraesthesia of lower limbs with pain); the event was severe in intensity and was not resolved at the end of the study. The SAE of urticaria in the benralizumab 30 mg Q4W arm was not resolved at the end of the study; all other SAEs that were considered related to study drug by the investigator were resolved.

Phase III ZONDA study

A lower incidence of SAEs was reported by patients in the benralizumab 30 mg Q4W and Q8W arms compared with the placebo arm (7 of 72 patients [9.7%], 7 of 73 patients [9.6%], and 14 of 75 patients [18.7%], respectively). Asthma (7 patients [3.2%]) and pneumonia (5 patients [2.3%]) were among the most commonly reported SAEs, in addition to status asthmaticus (3 patients [1.4%]), and influenza (2 patients [0.9%]). No other SAEs were reported for more than one patient in any treatment arm. A total of 3 patients (1.4%) had the following SAEs considered treatment-related by the investigator: 1 patient

(1.4%) in the benralizumab 30 mg Q4W arm with an SAE of hypersensitivity and 2 patients (2.7%) in the benralizumab 30 mg Q8W arm with SAEs of pneumonia and presyncope (verbatim term: vasovagal reaction after administration of the last dose of study drug).

Laboratory findings

In the Phase III studies, there were no clinically meaningful trends in haematology and clinical chemistry parameters, no clinically meaningful shifts in haematology and clinical chemistry parameters for individual patients, and the incidence of TEAE PTs related to haematology and clinical chemistry were low and similar across arms.

There were non-clinically significant decreases in both studies from baseline in neutrophils and lymphocytes in the benralizumab 30 mg Q4W and Q8W arms; corresponding decreases from baseline were not observed in the placebo arm. However, the mean absolute values remained within their respective reference ranges at all post-baseline time points and there were no apparent clinical manifestations associated with these transient changes.

There were no clinically meaningful trends in urinalysis, immunoglobulins, or T cell, B cell and natural killer cell flow cytometry findings over time and no clinically important findings identified in any treatment arm.

In the ECG sub-study conducted as part of SIROCCO, no clinically meaningful differences between the total benralizumab and placebo arms at Week 4/Day 6 were observed for any of the ECG variables, including the QT interval. At Week 4/Day 6, the incidence of QTcF outliers remained the same in the benralizumab arm compared to baseline; in the placebo arm, 5 patients (7.1%) had QTcF values of >450 ms and no patients had values of >480 ms. No patients in either treatment arm reported increases from baseline of >30 or >60 ms. No treatment-emergent findings were identified and the ECG assessments coincided with the benralizumab time to maximum concentration (Tmax).

Potential risks

Potential risks based on the mechanism of actions and/or potential risks with monoclonal antibodies include serious infections, risk of helminthic infection, hypersensitivity reactions (including immune reactivity), and malignancy.

Serious infections

Phase III asthma exacerbation studies

A total of 49 patients (2.0%) had SAEs under the SOC of Infections and infestations: 12 (1.4%) in the benralizumab 30 mg Q4W arm, 18 (2.2%) in the benralizumab 30 mg Q8W arm, and 19 (2.2%) in the placebo arm.

The most common serious infection PTs were pneumonia and bacterial pneumonia, influenza, appendicitis and bacterial urinary tract infection (see table). Bronchitis, chronic sinusitis, and viral pneumonia were reported by 2 patients overall but not within a single treatment arm. Overall, the pattern of serious infections was expected for a population of high-risk severe asthma patients.

Only one of the infectious SAEs was considered treatment-related by the investigator: herpes zoster (verbatim term: shingles face - no intraorbital involvement), reported by a patient in the benralizumab 30 mg Q8W arm.

Phase III ZONDA study

Twelve (12) of 220 patients (5.5%) had SAEs under the SOC of Infections and infestations during the on-treatment period: 2 of 72 patients [2.8%] and 2 of 73 patients [2.7%] in the benralizumab 30 mg Q4W and Q8W arms, respectively, vs 8 of 75 patients [10.7%] in the placebo arm.

Pneumonia (5 patients [2.3%]) and influenza (2 patients [0.9%]) were the most commonly reported serious infections, with a lower incidence of these events being reported by patients in the benralizumab 30 mg Q4W and Q8W arms compared with the placebo arm. With the exception of an SAE of pneumonia reported by one patient in the benralizumab 30 mg Q8W arm (see SAE section), none of these SAEs was considered treatment-related by the investigator.

Herpes zoster

An analysis of all TEAEs (serious and non-serious) of herpes zoster in the Phase III exacerbation studies was done based on feedback from the FDA. Events included herpes zoster, shingles, herpes infection forehead, and herpetic neuritis. In the on-treatment period, these TEAEs were similar across treatment arms, reported by 3 patients (0.4%) in the benralizumab 30 mg Q4W arm and 6 patients (0.7%) in both the benralizumab 30 mg Q8W and placebo arms. Apart from the case mentioned above, all of the other events were non-serious.

In addition, one patient in MI-CP220 (benralizumab 100 mg arm) had an SAE of herpes zoster that was considered by the investigator to be related to study drug. The patient experienced an SAE of moderate herpes zoster 17 days after receiving the fifth dose of study drug; the patient also had an SAE of moderate asthma. The event resolved with sequelae of paraesthesia and pain; other immunosuppressive risk factors were a prior bout of bronchitis that preceded the asthma exacerbation and a systemic course of corticosteroids used to treat the severe asthma exacerbation during the patient's hospitalisation.

Helminthic infections

A theoretical risk of depleting eosinophils is interference with expulsion of helminthic parasites. Patients at high risk for these infections were monitored for such infections as per local medical practice while on benralizumab. No cases of helminthic infections were reported in the Phase III studies.

Two patients in MI-CP220, one each in the benralizumab 2 mg and 100 mg arms had TEAEs associated with helminthic parasites; both patients had TEAEs of strongyloidiasis based on positive serology (research tool) only and were asymptomatic; one patient was already positive at screening and the other was living in an endemic area. Both patients received anti-strongyloides treatment and completed the study.

Hypersensitivity reactions

Phase III asthma exacerbation studies

A total of 78 patients (3.1%) had hypersensitivity TEAEs during the on-treatment period, with similar incidences across arms: 26 (3.1%) in the benralizumab 30 mg Q4W arm, 24 (2.9%) in the benralizumab Q8W arm and 28 (3.3%) in the placebo arm. The most common hypersensitivity TEAE was urticaria, reported by 46 patients (1.8%) overall, with similar incidence across arms.

Of the 50 patients with hypersensitivity TEAEs receiving benralizumab, 27 had a history of allergy to one or more substances, 14 had nasal polyposis and 11 had atopic dermatitis (eczema). There were 3 SAE events of urticaria, 5 cases of hypersensitivity related to a concomitant medication and 2 TEAEs of anaphylactic reactions in the same patient due to food/peanut allergies.

A total of 14 patients (0.6%) had hypersensitivity TEAEs judged causally related to study drug by the investigator. Seven of these patients continued treatment with the study drug. The majority of related hypersensitivity TEAEs were mild or moderate in intensity and subsequently resolved.

Phase III ZONDA study

A total of 4 of 220 patients (1.8%) had hypersensitivity TEAEs during the on-treatment period, and the incidences of TEAEs of hypersensitivity were low and similar across arms: 1 of 72 patients (1.4%) in the benralizumab 30 mg Q4W arm, 2 of 73 patients (2.7%) in the benralizumab Q8W arm, and 1 of 75 patients (1.3%) in the placebo arm. The most common hypersensitivity TEAE was urticaria. All cases were assessed as causally related to study drug by the investigator and were mild to moderate in intensity, with the exception of one SAE of severe allergic reaction, which led to treatment (benralizumab 30 mg Q4W) discontinuation.

Major adverse cardiovascular events (MACE)

In the Phase III exacerbation studies, 17 patients (0.7%) had 18 TEAEs submitted to the MACE subcommittee for adjudication in the on-treatment period; a total of 11 patients (0.4%) had MACE as determined by the Safety Endpoint Adjudication Committee (SEAC):

- 3 patients (0.4%) in the benralizumab 30 mg Q4W arm
- 4 patients (0.5%) in the benralizumab 30 mg Q8W arm
- 4 patients (0.5%) placebo arm.

Of the 7 patients who received benralizumab, four had a history of, or concurrent heart disease and/or risk factors for heart disease, including hypertension, hypercholesterolemia/hyperlipidaemia, history of coronary artery disease, heart failure, and angina. None of the events were considered treatment-related by the investigator.

In the ZONDA study, 2 patients, both in the benralizumab Q8W arm (2.7%), had 1 TEAE each submitted to the SEAC; these 2 fatal TEAEs (acute cardiac failure and pneumonia) were not determined by the SEAC to be MACE (the death by acute cardiac failure was judged "undetermined death").

Malignancies

In the Phase III exacerbation studies, 5 patients had 5 TEAEs during the on-study period submitted to the malignancy sub-committee for adjudication: 3 in the benralizumab 30 mg Q4W arm (ovarian epithelial cancer, gall bladder cancer, gastric cancer); 1 in the benralizumab 30 mg Q8W arm (colon cancer) and 1 in the placebo arm (breast cancer). All of these malignancies were adjudicated as new malignancies and considered not related to study drug by the investigator.

Three malignancies were reported by investigators in other studies: papillary thyroid cancer (benralizumab 30 mg), cervix carcinoma (placebo), and malignant melanoma (benralizumab 100 mg).

Injection site reactions

In the Phase III asthma exacerbation studies, a total of 61 patients (2.4%) experienced injection site reactions: 27 (3.2%) in the benralizumab 30 mg Q4W arm, 18 (2.2%) in the benralizumab 30 mg Q8W arm and 16 (1.9%) in the placebo arm. The administration site most commonly associated with injection site reactions was the arm (41 events [1.6%]).

Overall, the most frequently reported injection site reactions were injection site pain (20 patients [0.8%]) and injection site erythema (19 patients [0.8%]). With one exception, all injection site reactions were non-serious, transient in nature, and the majority were mild in intensity. One patient in the placebo arm

had an SAE of injection site erythema that was severe in intensity and resulted in the study drug being withdrawn; the SAE appeared to be associated with intramuscular administration rather than SC administration by the site, as indicated by magnetic resonance imaging results.

In the ZONDA study, a total of 4 patients (1.8%) experienced mild injection site reactions: 2 patients (2.8%) in the benralizumab 30 mg Q4W arm, no patients in the benralizumab 30 mg Q8W arm, and 2 patients (2.7%) in the placebo arm.

Adverse drug reactions

Adverse events considered as adverse drug reactions (ADRs) by the Applicant are: pharyngitis, headache, pyrexia, hypersensitivity reactions, and injection site reactions. This is based on incidences in the exacerbation studies and information from outside the benralizumab development programme. For the ADR of hypersensitivity reactions, although the incidence was similar across the benralizumab 30 mg Q4W, Q8W, and placebo arms (3.1%, 3.2%, and 3.2%, respectively), a qualitative review of cases combined with a plausible mechanism of action suggest that there may be a reasonable possibility of a causal relationship between benralizumab and the events to support the inclusion of hypersensitivity reactions (urticaria, papular urticaria and rash) as an ADR.

Safety in special populations

Use in pregnancy

Out of 18 pregnancies on benralizumab, there were 9 deliveries of healthy babies, 3 spontaneous abortions, 3 elective abortions, 2 anomalies (prenatal hydronephrosis, cytogenetic anomaly at a prenatal test), and one lost to follow-up.

Out of 7 pregnancies on placebo, there were 5 deliveries of healthy babies, 1 spontaneous abortion, and 1 elective abortion.

Use in the elderly

In the Phase III exacerbation studies, there was no clear trend for TEAEs in patients aged ≥65 years, who had a lower incidence in the benralizumab 30 mg Q4W arm (70.6%), and a higher incidence in the benralizumab 30 mg Q8W and placebo arms (82.4% and 83.3%, respectively) compared with patients aged 18 to 64 years (74.0%, 72.4%, and 77.1%, respectively).

The incidences of SAEs were slightly higher in patients aged ≥65 years for the benralizumab 30 mg Q4W, Q8W, and placebo arms (13.8%, 15.4%, and 17.5%, respectively) compared with patients aged 18 to 64 years (10.6%, 11.3%, and 13.4%, respectively). Deaths were reported for 8 patients aged 18 to 64 years (4 in the benralizumab 30 mg Q4W arm, 3 in the benralizumab 30 mg Q8W arm, and 1 in the placebo arm) and 1 patient aged ≥65 years (placebo arm).

Incidences of the most common TEAEs were generally similar in patients aged ≥65 years and patients aged 18 to 64 years.

Use in adolescents

Adolescent patients in the EU were not randomised to the benralizumab 30 mg Q4W arm; thus, there were fewer adolescent patients in the benralizumab 30 mg Q4W arm (24 patients) compared with the benralizumab 30 mg Q8W and placebo arms (38 and 46 patients, respectively).

The incidences of TEAEs in adolescent patients in the Phase III exacerbation studies were lower in all arms, including placebo (range: 58.3% to 63.2%) compared with the overall population (range: 73.1% to 77.1%).

Five adolescent patients reported SAEs; 2 (8.3%) in the benralizumab 30 mg Q4W arm and 3 (6.5%) in the placebo arm; no deaths were reported in adolescent patients. The number of TEAEs leading to treatment discontinuation were low, with no notable difference in adolescent patients compared with patients overall.

In general, the incidences of the most common TEAEs were lower in adolescent patients compared with patients overall (adults and adolescents), with the exception of sinusitis, pharyngitis, bronchitis and pyrexia.

Safety related to drug-drug interactions and other interactions

The effect of OCS use on AEs rates has been evaluated in the asthma exacerbation studies.

Patients with OCS use reported higher incidences of TEAEs compared with patients with no OCS use in the benralizumab 30 mg Q4W (87.5% vs 71.3%), benralizumab 30 mg Q8W (85.0% vs 71.2%), and placebo (89.9% vs 75.2%) arms. Patients with OCS use reported also higher incidences of SAEs compared with patients with no OCS use in the benralizumab 30 mg Q4W (21.9% vs 9.5%), benralizumab 30 mg Q8W (15.9% vs 10.4%), and placebo (22.9% vs 12.2%).

The higher incidences of TEAEs and SAEs in patients with OCS use are not unexpected given that the patients with OCS use were those with more severe disease. In addition, a proportion of the TEAEs and SAEs may be attributable to the OCS use itself.

Among the most commonly reported TEAEs, incidences between the benralizumab 30 mg Q4W and Q8W arms were generally similar in patients with and without OCS use. However, nasopharyngitis and headache were reported at higher incidences in patients with OCS use compared with patients with no OCS use in the benralizumab 30 mg Q4W arm (24.0% vs 15.3% and 19.8% vs 5.9%, respectively) and benralizumab 30 mg Q8W arm (23.0% vs 14.0% and 15.0% vs 7.6%, respectively). Importantly, for these two events, the incidences were higher in patients with OCS use when comparing to placebo (13.8% for nasopharyngitis and 7.3% for headache) while they were similar in patients without OCS use (16.8% and 6.1%, respectively).

Discontinuation due to AEs

Phase III exacerbation studies

A total of 44 patients (1.8%) had TEAEs leading to study drug discontinuation: 18 (2.1%) in the benralizumab 30 mg Q4W arm, 18 (2.2%) in the benralizumab 30 mg Q8W arm, and 8 (0.9%) in the placebo arm. The only TEAEs leading to discontinuation that occurred in ≥2 patients in any treatment arm were asthma (4 patients overall [0.2%]), urticaria (3 patients overall [0.1%]), and rash and arthralgia (2 patients overall for each [0.1%]); the incidences of these TEAEs leading to treatment discontinuation were similar across arms. There was no pattern observed or single PT driving differences between arms in patients who discontinued treatment.

Phase III ZONDA study

A total of 5 patients (2.3%) had TEAEs leading to study drug discontinuation. Three patients (4.1%) in the benralizumab 30 mg Q8W arm reported 4 TEAEs leading to discontinuation: allergic dermatitis, acute

cardiac failure (a fatal SAE), pneumonia (a fatal SAE), and atrial fibrillation (also an SAE). In addition, 2 patients (2.7%) in the placebo arm reported 2 TEAEs leading to discontinuation: urticaria and pericarditis (also an SAE).

2.7.5. Discussion on clinical safety

The safety database comprises a total of 2575 patients having received at least 1 dose of benralizumab and 1307 patients having received placebo, which is considered an acceptable population size. Currently, only 1-year data are available and extension studies are ongoing over 2 additional years. The two large exacerbation studies form the basis for the evaluation of the safety profile of benralizumab at its recommended regimen. Following CHMP request, an interim analysis of the SAE reports collected in the extension trials and the KHK trial for registration in Asia has been provided (cut-off date 21 October 2016).

Treatment-emergent AEs, including severe TEAEs, occurred slightly less frequently on benralizumab than on placebo; the difference was mainly driven by asthma events and bronchitis. However, headache, pharyngitis (but not nasopharyngitis), cough and pyrexia were slightly more frequent on benralizumab than on placebo. Their frequency was < 10%. The vast majority of TEAEs (90%) was mild or moderate. Investigators attributed headache, fatigue and pyrexia to the drug but the incidence of fatigue being comparable on placebo, it is unlikely that this was drug-related.

There were 15 deaths during the clinical programme, 12 in benralizumab-treated patients, and most were associated to comorbidities/risk factors in a population severely affected since 3 patients also died during screening. One case of fatal pneumonia complicated with atrial fibrillation in a patient with congestive heart failure was considered drug-related; infection is a known risk for this type of treatment. The high mortality rate in overweight/obese patients did not appear to be related to a lack of treatment benefit in these patients.

SAEs rates were low (about 12% overall) and slightly lower on benralizumab than on placebo. Asthma was the most common SAE (frequency of ~ 5%). The incidences of the other most common SAEs were low and similar across treatment arms. A few SAEs were attributed by the investigator to study drug; this is plausible for asthma, infections, allergic reactions but unlikely for Churg-Strauss syndrome, panic attack and paraesthesia. The interim analysis of the ongoing extension trials did not suggest any increase in the occurrence of SAEs or any new safety signal as treatment duration increased beyond one year.

About 2% of patients discontinued benralizumab treatment, slightly more than placebo. The main reasons were asthma and allergic-type reactions.

Based on mechanism of action and type of molecule potential risks include serious infections, helminthic infection, hypersensitivity reactions, and malignancy. During the clinical programme there was no increase in the incidence of serious infections, of herpes zoster and helminthic infections over a 1-year period. There does not appear to be an increased cardiovascular risk and malignancy risk either. However, this will need to be confirmed with the longer-term data of the extension studies.

A low rate of hypersensitivity reactions (~ 3%) was reported and it was comparable on benralizumab and placebo. Even those attributed by the investigator to the study drug (< 1% in the exacerbation studies) were equally frequent across treatment arms. Therefore, benralizumab appears to have low allergic potential and most of the reported hypersensitivity reactions are likely to be associated to other allergic factors in this asthma population. Out of ~ 1800 patients, only 2 patients (0.1%) developed a serious urticaria that was attributed to benralizumab and led to treatment discontinuation.

The rate of injection site reactions was slightly higher with benralizumab compared to placebo but the majority were mild in intensity.

On the basis of the Phase III exacerbation studies, the proposed list of ADRs is agreed (pharyngitis, headache, pyrexia, hypersensitivity reactions, and injection site reactions).

Data on pregnancy exposure from the clinical studies (18 cases) are insufficient to inform on drug-associated risk but do not raise concern. Therefore, the SmPC recommend to avoid the use of benralizumab during pregnancy.

The safety in the elderly (up to 75 years) does not raise any concern. There are almost no data above 75 years of age (4 patients in the 75-84 years' age range) but there was no trend of increased toxicity with age.

Assessment of paediatric data on clinical safety

In general, the AEs profile appeared better in adolescents than in adults regardless of the treatment but these data are limited and no indication is claimed in this population.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.7.6. Conclusions on clinical safety

Treatment with benralizumab is well tolerated, irrespective of the frequency of administrations, as reflected in the short list of generally mild adverse reactions. Although longer-term data are needed to confirm that there is no risk of serious infections and malignancies, there is currently no major clinical safety concern with the use of this product. A specific clinical study will be implemented in the post marketing setting to monitor the risk of malignancies.

2.8. Risk Management Plan

Safety concerns

Benralizumab	
Important identified risks	None
Important potential risks	• Serious infections • Helminth infections • Serious hypersensitivity reactions including anaphylaxis/anaphylactic reactions • Malignancies • Loss of/reduction in long-term efficacy due to persistent neutralising anti-drug antibodies
Missing information	• Safety profile in pregnant and lactating women • Safety profile of long-term use of benralizumab 30 mg SC

Pharmacovigilance plan

Study/activity Type, title and category (1-3)	**Objectives**	**Safety concerns addressed**	**Status**	**Date for submission of interim or final reports (planned or actual)**
D3250C00021 (BORA) A Multicenter, Double-blind, Randomized, Parallel Group, Phase 3 Safety Extension Study to Evaluate the Safety and Tolerability of Benralizumab (MEDI-563) in Asthmatic Adults and Adolescents on Inhaled Corticosteroid Plus Long-acting β2 Agonist (Category 3)	To assess the safety and tolerability of 2 dosing regimens of benralizumab for (1) adult patients during the 56 week treatment period and through the follow-up period (16 weeks from day of last dose) and (2) adolescent patients during the 108-week treatment period and through the follow-up period (16 weeks from day of last dose)	Important Potential Risks: Serious infections, Malignancies, Helminth infections, Serious hypersensitivity reactions including anaphylaxis/anaphylactic reactions Loss of/reduction in long-term efficacy due to persistent neutralising anti-drug antibodies Missing information: Safety profile in pregnancy/lactation, Long term safety	Ongoing	Final study report completion planned Q4 2018
D3250C00037 (MELTEMI) A Multicentre, Open-label, Safety Extension Study with Benralizumab (MEDI 563) for Asthmatic Adults on Inhaled Corticosteroid Plus Long acting β2 Agonist (Category 3)	To assess the safety and tolerability of 2 dosing regimens of benralizumab for adult patients	Important Potential Risks: Serious infections, Malignancies, Helminth infections, Serious hypersensitivity reactions including anaphylaxis/anaphylactic reactions Loss of/reduction in long-term efficacy due to persistent neutralising anti-drug antibodies Missing information: Safety profile in pregnancy/lactation, Long term safety	Ongoing	Final study report completion planned Q4 2019
The Benralizumab Pregnancy Exposure Study: A VAMPSS Post-Marketing Surveillance Study	To monitor planned and unplanned pregnancies exposed to benralizumab and	Missing information: Safety profile in Pregnancy/lactation	Planned	Protocol will be provided within 4 months after EC decision

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status	Date for submission of interim or final reports (planned or actual)
(Category 3)	to evaluate the possible teratogenic effect of this medication relative to the primary pregnancy outcome of major birth defects and the secondary pregnancy outcomes of preterm delivery, small for gestational age infants, spontaneous abortion, and stillbirth.			
A post approval measure to adequately characterise the potential risk of malignancy of benralizumab in a real-world setting The Applicant is exploring potential methodologies for data collection and analysis, and how we may be able to study the potential risk of malignancies of benralizumab in a real-world setting.- (Category 3)	To study potential risk of malignancy	Important potential risk of malignancy	Planned	A study synopsis together with feasibility assessment will be forthcoming with the aim of delivering a protocol by 30-06-2018-for PRAC/CHMP agreement.

Risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important identified risks		
None		
Important potential risks		
Serious infections	None proposed.	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Helminth infections	SmPC Section 4.4 (Special warnings and precautions for use) states the following: Parasitic (Helminth) Infection Eosinophils may be involved in the immunological response to some helminth infections. Patients with known helminth infections were excluded from participation in clinical trials. It is unknown if Fasenra may influence a patient's response against helminth infections. Patients with pre-existing helminth infections should be treated before initiating therapy with Fasenra. If patients become infected, while receiving treatment with Fasenra and do not respond to anti-helminth treatment, treatment with Fasenra should be discontinued until infection resolves.	None
Serious hypersensitivity reactions including anaphylaxis/anaphylactic reactions	Benralizumab SmPC Section 4.3 (Contraindications) states that Fasenra is contraindicated in patients with hypersensitivity to the active substance or to any of the excipients listed in SmPC Section 6.1 (List of excipients). Benralizumab SmPC Section 4.4 (Special warnings and precautions for use) states the following: Hypersensitivity reactions (eg, urticaria, papular urticaria, rash) have occurred following administration of Fasenra. These reactions generally occur within hours of administration, but in some instances have a delayed onset (i.e. days). In the event of a hypersensitivity reaction, Fasenra should be discontinued. SmPC Section 4.8 (Undesirable effects) lists Hypersensitivity reactions as a common (≥1/100 to <1/10) adverse reaction.	None
Malignancy	None proposed.	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Loss of/reduction in long-term efficacy due to persistent neutralising anti-drug antibodies	SmPC section 5.1 (Pharmacodynamic properties) states: Immunogenicity Overall, treatment -emergent anti- drug antibody response developed in 107 out of 809 (13%) patients treated with Fasenra at the recommended dosing regimen during the 48 to 56 week treatment period of the exacerbation trials. Most antibodies were neutralising and persistent. Anti -benralizumab antibodies were associated with increased clearance of benralizumab and increased blood eosinophil levels in patients with high anti-drug antibody titres compared to antibody negative patients; in rare cases, blood eosinophil levels returned to baseline levels. Based on current patient follow-up, no evidence of an association of anti- drug antibodies with efficacy or safety was observed In addition SmPC section 4.2 (Posology and method of administration) includes the following instruction: Fasenra is intended for long-term treatment. A decision to continue the therapy should be made at least annually based on disease severity, level of exacerbation control and blood eosinophil counts.	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Missing information		
Safety profile during pregnancy/lactation	SmPC Section 4.6 (Fertility, pregnancy and lactation) states: <u>Pregnancy</u> There is a limited amount of data (less than 300 pregnancy outcomes) from the use of benralizumab in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. See Section 5.3 (Preclinical safety data). Monoclonal antibodies, such as benralizumab, are transported across the placenta linearly as pregnancy progresses; therefore, potential exposure to a fetus is likely to be greater during the second and third trimester of pregnancy. It is preferable to avoid the use of Fasenra during pregnancy. Its administration to pregnant women should only be considered if the expected benefit to the mother is greater than any possible risk to the fetus.	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	Breast-Feeding It is unknown whether benralizumab or its metabolites are excreted in human or animal milk. Risk to the breast-fed child cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from using Fasenra taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman. Fertility There are no fertility data in humans. Animal studies showed no adverse effects of benralizumab treatment on fertility. See SmPC Section 5.3 (Preclinical safety data).	
Safety profile of the long-term use of benralizumab 30 mg SC	SmPC Section 4.8 (Undesirable effects) states: A total of 2,514 patients, out of whom 1,663 patients had severe uncontrolled eosinophilic asthma received benralizumab during clinical studies of 48 to 56 weeks duration.	None

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.0 edition 4 is acceptable.

2.9. Pharmacovigilance

Pharmacovigilance system

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

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant request alignment of the PSUR cycle with the international birth date (IBD). The IBD will be in line with the pending FDA approval date which will be available within November 2017. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.10. New Active Substance

The applicant declared that benralizumab has not been previously authorised in a medicinal product in the European Union.

The CHMP, based on the available data, considers benralizumab to be a new active substance as it is not a constituent of a medicinal product previously authorised within the Union.

2.11. Product information

2.11.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.11.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Fasenra (benralizumab) is included in the additional monitoring list as

- It contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU;
- It is a biological product that is not covered by the previous category and authorised after 1 January 2011;

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic context

3.1.1. Disease or condition

The term "eosinophilic asthma" describes a subphenotype of asthma characterised by elevated levels of eosinophils in bronchial biopsies or sputum despite chronic and correct use of adequate doses of inhaled corticosteroids (ICS). The target population remains uncontrolled with the current standard of care, i.e. treatment with the combination of high-dose ICS and long-acting β2 agonist (LABA) plus possibly a third controller or OCS (Steps 4 and 5 of the GINA classification). Patients who remain uncontrolled continue to suffer symptoms, frequent exacerbations, and compromised quality of life. Exacerbations typically require treatment with high doses of systemic corticosteroids and may also require hospitalisation. Uncontrolled asthma can lead to a dependence on oral corticosteroids, which has significant morbidity.

The aim of therapy is to improve asthma control by reducing the frequency of asthma exacerbations, improving lung function and decreasing asthma symptoms.

3.1.2. Available therapies and unmet medical need

As shown in GINA step 5, the add-on maintenance therapies currently available for these patients are tiotropium for inhalation and three targeted therapies with injectable monoclonal antibodies: omalizumab (anti-IgE), mepolizumab and reslizumab (anti-IL-5). The last two molecules target the same pathway as benralizumab, and therefore, the unmet medical need claimed by the Applicant is not endorsed by CHMP. However, the frequency of administrations is lower than for the two other anti-IL-5 products, and therefore, benralizumab administration could be more convenient for the patient.

3.1.3. Clinical studies

The application is supported by two large randomised double-blind placebo-controlled trials (SIROCCO and CALIMA) of a replicate design (exacerbation studies) in patients with uncontrolled asthma despite inhaled corticosteroid plus long-acting β2-agonist and one small randomised double-blind placebo-controlled trial (ZONDA) (OCS reduction study). Two dosing frequencies were tested (30 mg subcutaneously every 4 or 8 weeks) over 12 months in the exacerbation studies and 6 months in the OCS reduction study. Together, about 1500 patients (500/treatment arm) with severe uncontrolled asthma receiving high doses of ICS+ LABA (± third controller) and with baseline blood eosinophil count ≥300 cells/μL were randomised in the exacerbation studies. Eligible patients should also have experienced at least 2 asthma exacerbations requiring systemic CS during the 12 months preceding study entry.

In the third trial (OCS sparing effect), 220 patients (~75/treatment arm) with severe asthma receiving high doses of ICS+ LABA + OCS and with baseline blood eosinophil count ≥150 cells/μL were randomised.

3.2. Favourable effects

Exacerbation studies

With the two dosing regimens, a similar 40% reduction in the annual asthma exacerbation rate was observed compared to placebo in the integrated analysis:

- benralizumab Q4W RR = 0.59 [0.49, 0.72]; p < 0.001
- benralizumab Q8W RR = 0.58 [0.48, 0.70]; p < 0.001

An improvement in pre-bronchodilator FEV1 was observed at the end of treatment in comparison with placebo:

- benralizumab Q4W LS mean difference =+ 0.106 L [0.016, 0.196]; p = 0.022 (SIROCCO)
  LS mean difference =+ 0.125 L [0.037, 0.213]; p = 0.005 (CALIMA)
- benralizumab Q8W LS mean difference =+ 0.159 L [0.068, 0.249]; p = 0.001 (SIROCCO)
  LS mean difference =+ 0.116 L [0.028, 0.204]; p = 0.010 (CALIMA)

A decrease in total asthma symptom score was observed at the end of treatment in comparison with placebo (statistically significant with the Q8W regimen only):

- benralizumab Q4W LS mean difference =- 0.08 [-0.27, 0.12]; p = 0.442 (SIROCCO)
  LS mean difference =- 0.12 [-0.32, 0.07]; p = 0.224 (CALIMA)
- benralizumab Q8W LS mean difference =- 0.25 [-0.45, -0.06]; p = 0.012 (SIROCCO)
  LS mean difference =- 0.23 [-0.43, -0.04]; p = 0.019 (CALIMA)

A decrease in the ACQ-6 score was observed at the end of treatment in comparison with placebo (mostly statistically significant with the Q8W regimen):

- benralizumab Q4W LS mean difference =- 0.15 [-0.34, 0.04]; p = 0.111 (SIROCCO)
  LS mean difference =- 0.19 [-0.38, 0.01]; p = 0.043 (CALIMA)
- benralizumab Q8W LS mean difference =- 0.29 [-0.48, -0.10]; p = 0.003 (SIROCCO)
  LS mean difference =- 0.25 [-0.44, -0.07]; p = 0.008 (CALIMA)

An increase in the AQLQ(S) score was observed at the end of treatment in comparison with placebo (statistically significant with the Q8W regimen only):

- benralizumab Q4W LS mean difference =+ 0.18 [-0.02, 0.37]; p = 0.081 (SIROCCO)
  LS mean difference =+ 0.16 [-0.04, 0.37]; p = 0.119 (CALIMA)
- benralizumab Q8W LS mean difference =+ 0.30 [0.10, 0.50]; p = 0.004 (SIROCCO)
  LS mean difference =+ 0.24 [0.04, 0.45]; p = 0.019 (CALIMA)

OCS reduction study

With the two dosing regimens, a %reduction from baseline in OCS dose was observed compared to placebo:

- benralizumab Q4W Difference = 33.3 [16.7, 50.0]; p < 0.001
- benralizumab Q8W Difference = 37.5 [20.8, 50.0]; p < 0.001

The proportion of patients with a ≥50% reduction from baseline in final OCS dose was greater at week 28 than with placebo:

- benralizumab Q4W 66.7% vs 37.3% - OR = 3.59 [1.79, 7.22]; p < 0.001
- benralizumab Q8W 65.8% vs 37.3% - OR = 3.03 [1.57, 5.86]; p < 0.001

The median absolute reduction from baseline (BL) in final OCS dose was greater at week 28 than with placebo and clinically meaningful:

- in patients with BL OCS dose ≤12.5 mg/d: 7.5 mg/d vs 2.5 mg/d

- in patients with BL OCS dose >12.5 mg/d: 12-14 mg/d vs 5 mg/d

The proportion of patients with an average final OCS dose ≤ 5mg/d was greater at week 28 than with placebo:

- benralizumab Q4W 61.1% vs 33.3% - OR = 3.16 [1.60, 6.23]; p < 0.001
- benralizumab Q8W 58.9% vs 33.3% - OR = 2.74 [1.41, 5.31]; p = 0.002

A reduction in the annual asthma exacerbation rate over 28 weeks was observed compared to placebo:

- benralizumab Q4W RR = 0.45 [0.27, 0.76]; p = 0.003
- benralizumab Q8W RR = 0.30 [0.17, 0.53]; p < 0.001

The durability of the effects of benralizumab on the OCS dose and exacerbations has been shown for at least 3 additional months of treatment in the extension trials.

Subgroup analyses identified prior exacerbation history and baseline blood eosinophil count as potential predictors of improved treatment response. When considered alone or in combination, these factors may further identify patients who may achieve a greater response from benralizumab treatment.

3.3. Uncertainties and limitations about favourable effects

In both exacerbation studies, the crude annual exacerbation rate on placebo was below 2/year, especially in CALIMA, where it was ~1/year, which would not correspond to the target population of patients with uncontrolled asthma and frequent (≥ 2) severe exacerbations.

Likewise, the proportion of patients with at least one serious exacerbation (requiring ER/hospitalisation) was low on placebo, especially in CALIMA (< 10%), where this proportion was similar in all treatment arms. A significant reduction in the rate of serious exacerbations was only found for benralizumab Q8W in SIROCCO (RR = 0.37; p < 0.001). Therefore, this result is not robust.

In both studies, the treatment effects on asthma symptoms and asthma control as well as quality of life did not appear consistent across the two dosing regimens in contrast with the effect on exacerbations and FEV1. Unexpectedly, the lower frequency regimen appeared the most efficacious. Likewise, in the OCS reduction study, the treatment effects on asthma symptoms, asthma control as well as quality of life did not appear consistent across the two dosing regimens. Again, the lower frequency regimen appeared the most efficacious. While no plausible biological explanation for this observation could be found, the Q8W regimen is considered the most appropriate.

There were notable differences in the treatment effect between regions and countries. These appear largely driven by the placebo crude exacerbation rates, the treatment effect tending to be higher when placebo rate is higher. It is noteworthy that the two countries that enrolled the highest numbers of patients in CALIMA were Argentina (placebo crude rate: 0.68) and Poland (placebo crude rate: 0.67). In Western EU, the annual exacerbation rate was reduced by 54% from a placebo rate of 1.96/year, but the effect was decreased to 33% when Eastern EU countries were added.

No treatment effect was observed in the subgroup of adolescents that were enrolled in the exacerbation trials. Therefore, benralizumab is only proposed as add on therapy in adults patients with severe eosinophilic asthma inadequately controlled despite high dose corticosteroid plus long-acting β-agonist.

3.4. Unfavourable effects

Treatment-emergent AEs, including severe TEAEs, occurred slightly less frequently on benralizumab than on placebo; the difference was mainly driven by asthma events and bronchitis.

SAEs rates were low (about 12% overall) and slightly lower on benralizumab than on placebo. Asthma was the most common SAE (frequency of ~ 5%). The incidences of the other most common SAEs were low and similar across treatment arms.

About 2% of patients discontinued benralizumab treatment, slightly more than placebo. The main reasons were asthma and allergic-type reactions.

A low rate of hypersensitivity reactions (~ 3%) was reported and it was comparable on benralizumab and placebo. Even those attributed by the investigator to the study drug (< 1% in the exacerbation studies) were equally frequent across treatment arms.

The rate of injection site reactions was slightly higher with benralizumab compared to placebo but the majority were mild in intensity.

On the basis of the Phase III exacerbation studies, the proposed list of ADRs to be specified in the SmPC includes few adverse drug reactions: pharyngitis, headache, pyrexia, hypersensitivity reactions, and injection site reactions.

In the Phase III exacerbation studies, there was no clear trend for TEAEs in patients aged ≥65 years compared with patients aged 18 to 64 years. The incidences of SAEs were slightly higher in patients aged ≥65 years for the benralizumab 30 mg Q4W, Q8W, and placebo arms (13.8%, 15.4%, and 17.5%, respectively) compared with patients aged 18 to 64 years (10.6%, 11.3%, and 13.4%, respectively). Incidences of the most common TEAEs were generally similar in patients aged ≥65 years and patients aged 18 to 64 years.

Overall, in the Phase III studies, 7 to 14% of patients developed ADA to benralizumab, which appeared in the majority of patients to be neutralising and persistent. These ADAs increased the clearance of benralizumab and tended to allow for earlier eosinophil recovery. However, these ADAs did not have any apparent impact on short-term efficacy and were not associated with hypersensitivity reactions.

3.5. Uncertainties and limitations about unfavourable effects

There are almost no data in patients above the age of 75 years as this is not a substantial subgroup in the target population. Furthermore, the safety profile of benralizumab did not appear to worsen with age and the potential for drug-drug interaction is very low.

Direct blockade of IL-5 by other antibodies does not lead to complete loss of eosinophils due to redundant signalling by IL-3 and granulocyte macrophage colony-stimulating factor. The additional action of benralizumab to deplete eosinophils through ADCC may pose additional risks than a purely blocking antibody. Currently, the data submitted do not show any evidence that use of benralizumab would pose an increased risk of cancer in patients.

Data are limited data beyond one year of treatment and therefore the potential risk of serious infections and malignancies cannot be adequately evaluated. However, the interim analysis of the ongoing extension trials did not suggest any increase in the occurrence of SAEs or any new safety signal as treatment duration increased beyond one year. Likewise, the long-term impact of persistent neutralising ADAs will be further characterised based on information from the extension trials. Submission of the full reports of the ongoing studies, when completed, is included in the RMP.

3.6. Effects table

Effects Table for benralizumab for treatment for severe asthma with an eosinophilic phenotype in adult patients

Effect	Short Description	Unit	BEN Q4W	BEN Q8W	PLA	Uncertainties/ Strength of evidence	References
	Favourable Effects in patients with baseline blood eosinophils ≥300/µL and high-dose ICS						
AER	Annual asthma exacerbation rate	Per year 95% CI	0.67 (0.58, 0.78)	0.66 (0.57, 0.77)	1.14 (1.00, 1.29)	Low placebo rate; modest % reduction (~40%) Lower reduction in patients with BL eosinophils <300/µL (~30%) Higher effect in patients with > 2 prior exacerbations/year	Pooled 1+2
			0.82 (0.54, 1.24)	0.54 (0.33, 0.87)	1.80 (1.32, 2.46)	Notable %reduction especially with BEN Q8W (70%)	3
RED OCS	Median % reduction in OCS dose from BL	%	75	75	25	The difference in %patients with a meaningless reduction (≤ 5mg) was 31% (BEN Q4W), 34% (BEN Q8W) vs 51% (PLA) (NS)	3
	Median absolute reduction in OCS dose from BL	mg/d	8.1	7.5	2.5		
	% patients with ≥50% decrease	%	67	66	37		
FEV1	LS mean change from BL in pre-broncho dilator FEV1	L	0.345 0.340	0.398 0.330	0.239 0.215	Clinical improvement in all arms including placebo; clinically relevant difference between BEN and PLA	1 2
			0.232	0.239	0.126	No statistical difference	3
TASS	LS mean change from BL in total asthma symptom score		-1.12 -1.28	-1.30 -1.40	-1.04 -1.16	Clinical improvement in all arms including placebo; significant difference only between BEN Q8W and PLA, but of questionable clinical relevance	1 2
			-0.54	-0.71	-0.53	No statistical difference	3
ACQ-6	LS mean change from BL in ACQ-6		-1.32 -1.38	-1.46 -1.44	-1.17 -1.19	Clinical improvement in all arms including placebo; significant difference mostly between BEN Q8W and PLA, but of questionable clinical relevance	1 2
			-0.81	-1.12	-0.57	Significant and clinically relevant difference for BEN Q8W only	3
	Unfavourable Effects						
HEAD	Incidence of headache	%	7.5	8.6	6.3	Most adverse drug reactions were mild	Pooled 1+2
PHAR	Incidence of pharyngitis	%	4.4	5.0	3.4	Similar incidence irrespective of age category (18-65 or 65-75)	

Effect	Short Description	Unit	BEN Q4W	BEN Q8W	PLA	Uncertainties/ Strength of evidence	References
HYS	Incidence of hypersensitivity reactions	%	3.1	3.2	3.2	Anti-drug antibodies (7-14% of the patients) were not associated with hypersensitivity reactions.	
PYR	Incidence of pyrexia	%	3.8	2.9	1.7		
ISR	Incidence of injection site reactions	%	3.2	2.2	1.9		

Abbreviations: BEN= benralizumab; PLA=placebo; CI=confidence interval; BL=baseline
Notes: 1=SIROCCO; 2=CALIMA; 3=ZONDA

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Effect on asthma exacerbations

While the two exacerbation trials met their primary endpoint, the treatment effect in relative terms (exacerbation rate reduced by approximately 40% for both regimens in the integrated analysis) and absolute terms (an estimated difference of about 0.5/year, from 1.14 to 0.66/year) is considered modest from a clinical perspective. The magnitude of the treatment effect in both relative and absolute terms appeared greater in patients with more frequent exacerbations as reflected in the crude placebo rates. Therefore, a likely explanation for the failure to achieve better results is related to the selection of patients that did not have a prior history of sufficiently frequent and/or documented severe asthma exacerbations.

Likewise, given the low frequency of serious exacerbations in this population, the clinical relevance of the benefit in terms of decrease in ER visits or hospitalisations is questionable. Unexpectedly, only the regimen with less frequent dosing achieved a statistically significant difference, decreasing the annual rate from 0.10 to 0.06/year (38% in relative terms) in the integrated analysis.

Mean improvements of more than 200 mL were measured in all treatment arms, including placebo. Mean differences between benralizumab and placebo ranged between 100 and 160 mL, which can be considered clinically relevant.

It is noted that for the outcomes of total asthma symptom score and ACQ-6 score, the placebo effect was important with an absolute decrease in the asthma total score of about 1 and in the ACQ-6 score >1 in both trials. The clinical relevance of a mean difference between placebo and benralizumab of 0.25 for the asthma score is unknown as there is no accepted minimally clinically important difference (MCID) for this endpoint. Likewise, the clinical relevance of a difference of 0.2 to 0.3 for the ACQ-6 score may be questioned as this is below the MCID of 0.5. However, according to a literature review (Bateman, 2015), to exceed this MCID is hardly achievable when treatments are added to highly effective medications, such as ICSs or ICS/LABA combinations.

Importantly, the small differences (asthma symptom and ACQ-6) between benralizumab and placebo in asthma scores did not translate into significant difference in the use of asthma rescue medication between benralizumab and placebo (~ -0.5 puffs/day). Likewise, a similar decrease in the proportion of nights with nocturnal awakenings due to asthma was reported across benralizumab and placebo arms.

Finally, a responder analysis of the quality of life questionnaire AQLQ(S)+12 (improvement ≥ 0.5) indicated better results overall in CALIMA than SIROCCO with no significant differences between benralizumab and placebo arms: 55-57% vs 49% in SIROCCO and 60-61% vs 59% in CALIMA.

OCS sparing effect

The available analysis in terms of % reduction in OCS dose is difficult to interpret (median reduction of 75% for benralizumab vs 25% for placebo) but a median absolute decrease of 8 mg/d is clinically relevant compared to 2.5 mg/d for placebo. Furthermore, a final dose ≤ 5mg/d (considered a clinically meaningful objective) was achieved by 61% and 59% of the patients in the benralizumab arms (Q4W and Q8W, respectively) vs 33% in the placebo arm ($p \leq 0.002$). Finally, the sparing effect was maintained for at least 3 additional months of treatment in the extension trial.

In contrast to the results of the exacerbation studies, the reduction in the frequency of exacerbations by 70% with benralizumab Q8W and 55% with benralizumab Q4W (from an annualised rate of 1.80/year) is considered important especially since the OCS dose was reduced in parallel.

Safety profile

The toxicity of benralizumab is very low with few ADRs identified at present. Despite its observed immunogenicity, hypersensitivity reactions did not occur more frequently than on placebo.

3.7.2. Balance of benefits and risks

Despite its dramatic effect on blood eosinophils benralizumab has demonstrated a modest effect on the frequency of exacerbations as reflected in relative terms by a ~40% reduction in the annual exacerbation rate and in absolute terms by a difference of about 0.5/year from 1.14 to 0.66/year. It is noteworthy that in similar patient populations, the two other anti-IL-5 agents (mepolizumab and reslizumab) achieved reductions in asthma exacerbations rates greater than 50% from a level of ~1.80/year.

Regarding the other benefits of benralizumab, a clinically relevant improvement in lung function was demonstrated by an increase in FEV1 ≥ 100 mL compared to placebo. While the benefits in terms of asthma symptoms, asthma control and quality of life are considered small or marginal, the interpretation of the PRO outcomes is difficult in this clinical setting (patients with severe asthma treated with a combination of high ICS dose and LABA), as reflected by similar results for previously authorised anti-IL5 products.

In more severe patients receiving chronic OCS therapy, benralizumab has shown a clinically meaningful OCS sparing effect associated with an important reduction (> 50%) in the frequency of asthma exacerbation despite reduction in OCS dose.

Overall, the extent of the effect of benralizumab is considered moderate but the benefit outweigh the risks of this treatment given its low toxicity as shown in the clinical trials. Therefore, the benefit/risk balance is considered positive in the studied population.

3.7.3. Additional considerations on the benefit-risk balance

Like with the other authorised anti-IL-5 agents, the benefits of therapy have been shown to increase with increasing frequency of exacerbations and baseline blood eosinophil count. In the subpopulation of patients with 2 exacerbations in the previous year, where the placebo annual exacerbation rate was ≤1, there was little difference in the outcomes according to baseline blood eosinophil count and the treatment

effect was minimal: AER reduction by 25-35% and marginal increase in mean pre-bronchodilator FEV1 (13-105 mL).

In contrast, in the subpopulation of patients with ≥ 3 exacerbations in the previous year, where the placebo annual exacerbation rate was about 2, patients with higher baseline blood eosinophil count (≥300/µL) fared better than those with lower baseline count: AER reduction by ~50% vs ~30%, respectively, and increase in mean pre-bronchodilator FEV1 of 121 mL (Q4W) and 252 mL (Q8W) vs. 33 mL (Q4W) and 75 mL (Q8W), respectively.

In conclusion, the benefit of benralizumab, especially with the Q8W regimen, is demonstrated in patients with a high frequency of asthma exacerbations and high baseline blood eosinophil count. However, in those with a low frequency of exacerbations, the benefit is extremely modest, if not marginal, regardless of their baseline blood eosinophil count.

Notwithstanding, it is not considered appropriate to restrict the indication based on the above risk factors (baseline blood eosinophil count, frequency of exacerbations). This information is described in Section 5.1 of the SmPC in line with the SmPC of the two other anti-IL-5 products.

Despite a certain degree of correlation between benralizumab effects and blood eosinophil levels at baseline, their levels during treatment appear to be poorly correlated with the frequency of exacerbations and the pulmonary function. This is especially striking in a very limited number of patients with high titre neutralising ADAs, who exhibited undetectable drug concentrations and blood eosinophil levels in the range of their pre-treatment levels but reported 0 or 1 asthma exacerbation over a two-year follow-up. Further long-term data will be provided from the extension trials as part of the RMP. Nevertheless, pursuing the administration of benralizumab should be reconsidered in individual patients where blood eosinophil counts return to pre-treatment levels.

3.8. Conclusion

The overall B/R of benralizumab is positive as add on maintenance therapy in adult patients with severe eosinophilic asthma inadequately controlled despite high dose of corticosteroid plus long-acting β-agonist.

4. Recommendations

Outcome

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

Fasenra 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 CHMP therefore recommends the granting of the marketing authorisation 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).

Other 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.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

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

Risk Management Plan (RMP)

The 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.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that benralizumab is a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.