Supplementary appendix

Corticosteroid Tapering with Benralizumab Treatment for Eosinophilic Asthma: PONENTE Trial

Andrew Menzies-Gow, Jonathan Corren, Elisabeth H. Bel, Jorge Maspero, Liam G. Heaney, Mark Gurnell, Peter Wessman, Ubaldo J. Martin, Shahid Siddiqui, Esther Garcia Gil

Contents

APPENDIX 1: INCLUSION AND EXCLUSION CRITERIA

Inclusion Criteria

Patients must meet all of the following criteria:

- Provision of informed consent prior to any study-specific procedures.
- Female or male aged ≥18 years at the time of Visit 1.

  Women of childbearing potential must agree to use highly effective methods of birth control from enrolment to within 16 weeks after last dose of study drug and must have a negative serum pregnancy test result at Visit 1.
- Women not of childbearing potential are defined as women who are either permanently sterilised (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy) or who are postmenopausal. Weight of ≥40 kg.
- Non-smokers, current smokers, or former smokers with a smoking history of <20 pack-years at Visit 1.
- Peripheral blood eosinophil count ≥150 cells/μL assessed by central laboratory at Visit 1 or documented eosinophil count ≥300 cells/μL in the past 12 months.
- History of physician-diagnosed asthma that requires continuous treatment with high-dosage inhaled corticosteroids (ICS) (high-dosage ICS is the greatest approved dosage in a country) plus a long-acting β_2-agonist (LABA) for at least 6 months before Visit 1. The ICS and LABA can be contained within a combination product or by separate inhalers. Additional maintenance asthma controller medications (e.g., leukotriene receptor antagonists, tiotropium, cromone, theophylline) are allowed.
- Long-term oral corticosteroid (OCS) therapy equivalent to a daily prednisone dosage of at least 5 mg for at least 3 continuous months directly preceding Visit 1 (documented in medical records). Alternate intake of OCS (i.e., every other day) or other frequency is

allowed if the average daily prednisone dosage is equivalent to at least 5 mg and the patient is switched to a daily intake of prednisone/prednisolone at Visit 1. Systemic corticosteroid dosages administered by any route other than oral cannot be used to determine the average daily dosage preceding Visit 1.

- Patients must receive a stable OCS dosage for at least 4 weeks before Visit 1. Patients must agree to switch to study-required prednisone/prednisolone as their OCS for the duration of the study.

Exclusion Criteria

Any of the following excludes patients from participation in the study:

- Clinically important pulmonary disease other than asthma (e.g., active lung infection, chronic obstructive pulmonary disease, bronchiectasis, pulmonary fibrosis, cystic fibrosis, hypoventilation syndrome associated with obesity, lung cancer, alpha-1 antitrypsin deficiency, primary ciliary dyskinesia) or any diagnosis of pulmonary or systemic diseases, other than asthma, that are associated with elevated peripheral eosinophil counts (e.g., allergic bronchopulmonary aspergillosis/mycosis, eosinophilic granulomatous polyangiitis, hypereosinophilic syndrome).
- Known history of allergy or reaction to the study drug formulation.
- History of anaphylaxis to any biologic therapy.
- Helminth parasitic infection diagnosed within 24 weeks before informed consent is obtained that has not been treated with, or has failed to respond to, standard of care therapy.
- Asthma exacerbation that requires the use of systemic corticosteroids, increase in maintenance OCS dosage, or acute upper/lower respiratory infection that requires antibiotics or antiviral medication within 30 days before Visit 2 (first benralizumab dose).

  - An extension of the screening period up to 3 months is allowed to ensure that a patient recovers from any asthma exacerbation or acute upper/lower respiratory infection.
- Intention to use any concomitant medication that is not permitted by the protocol or failure to undergo the required washout period for a prohibited medication.
- History of alcohol or drug abuse within 12 months before informed consent is obtained.
- History of known immunodeficiency disorder, including a positive human immunodeficiency virus test.
- Alanine aminotransferase or aspartate aminotransferase concentration ≥3 times the upper limit of normal confirmed at Visit 1.
- Receipt of immunoglobulin or blood products within 30 days before informed consent is obtained.
- Concurrent enrolment in another clinical trial.
- AstraZeneca staff involved in the planning and/or conduct of the study.
- Employees of the study site or any other individuals involved with the conduct of the study, or immediate family members of such individuals.
- Currently pregnant, breastfeeding, or lactating.
- Received previous treatment with benralizumab.
- Coincidental primary adrenal failure (Addison's disease) or irreversible secondary hypoadrenalism related to another independent cause (e.g., pituitary tumour or its treatment).
- Coexistent inflammatory conditions for which long-term OCS dosages are part of the maintenance treatment, such as, but not limited to, giant cell arteritis or polymyalgia rheumatica.
- Exclusion from genetic research may be for any of the exclusion criteria specified in the main study or any of the following:

- Previous allogeneic bone marrow transplant.
- Non-leukocyte–depleted whole blood transfusion within 120 days of genetic sample collection.

APPENDIX 2: SAFETY ASSESSMENTS

Hypothalamic-Pituitary-Adrenal Axis Evaluation

For patients who reach OCS dosages of 5 mg/day, hypothalamic-pituitary-adrenal (HPA) axis integrity will be assessed at the end of a 4-week period with 5 mg/day by evaluation of morning cortisol concentrations (8–9 am). For patients who have baseline OCS dosages of 5 mg/day, HPA axis integrity will be assessed 4 weeks after first dose of benralizumab administration and before initiation of the OCS-tapering phase. For females using oral estrogen-containing contraceptives or oral estrogen-containing hormone replacement therapy, the threshold for normal values is 2 times the normal morning cortisol concentrations and 1.5 times the normal adrenocorticotropic hormone (ACTH) stimulation test cortisol concentrations.

The last OCS dose will be received 24 hours before the morning cortisol test. Additionally, patients will not receive ICS/LABA treatment on the morning of cortisol testing. If a patient requires a short course of macrolides, antivirals, or azoles, there will be a window of ≥1 week before testing cortisol concentrations. Serum samples for cortisol will be collected between 8–9 am and sent to a central laboratory for evaluation. Depending on the results, the subsequent actions are the following:

- If cortisol concentrations are within normal range and the patient does not exhibit any signs and/or symptoms of adrenal insufficiency (AI), the patient will continue OCS down-titration by 2.5 mg every 4 weeks (Q4W).
- If cortisol concentrations are within normal range but the patient exhibits signs and/or symptoms of AI, OCS down-titration will continue at a slower pace (1 mg Q4W).

- If cortisol concentrations are less than the normal range and more than the complete AI range (partial AI), the patient will be instructed to maintain the current OCS dosage and return for an additional visit within 1 week for an ACTH stimulation test.
- If complete AI is confirmed, the respective site will inform the patient that the OCS dosage will remain the same without further reduction until there is evidence of recovery from the complete AI without worsening of asthma control. The test will be repeated 3 months later, and the patient will be educated for symptom awareness of adrenal suppression and use of steroid emergency cards. If morning cortisol tests again indicate complete AI at 3 months, the OCS dosage will not be modified. If morning cortisol tests at 3 months indicate risk of AI, reductions will be 1 mg Q4W. If results indicate normal values, reductions will be 2.5 mg Q4W.

The ACTH stimulation test (Synacthen®, Cortrosyn™) will be performed when morning cortisol concentrations are less than the normal range but more than complete AI concentrations (i.e., intermediate values). Patients will be scheduled within 1 week after the morning cortisol results for the ACTH stimulation test. Patients will be required to withhold OCS use for ≥24 hours before the morning of testing and withhold ICS/LABA use on the morning of testing. An intravenous injection of tetracosactide 250 μg will be given. A blood sample for serum cortisol will be collected before and 30 minutes after injection. Peak cortisol response at 30 minutes will be selected to assess AI, and the OCS taper will follow the applicable scenario below:

- If a normal peak cortisol concentration is demonstrated at 30 minutes, the patient will continue OCS dosage titration by 2.5 mg Q4W.
- If the peak cortisol concentration at 30 minutes is less than the normal range but more than the concentration of complete AI (partial AI), or there are some signs/symptoms of

AI or corticosteroid withdrawal syndrome, the patient will continue OCS down-titration at a slower speed (1 mg Q4W) until the next site visit. The morning cortisol test will be repeated 2 months later.

- If complete AI is confirmed, OCS dosage will remain the same without further reduction until there is evidence of recovery from complete AI without worsening of asthma control. The test will be repeated 3 months later, and patients will be educated for symptom awareness of adrenal suppression and use of steroid emergency cards.

Assessment of Asthma Exacerbations

An asthma exacerbation is defined as a worsening of asthma symptoms that leads to any of the following:

- A temporary bolus/burst of systemic corticosteroids (at a dosage more than one step greater than the current titration step) for at least 3 consecutive days to treat symptoms of asthma worsening or a single depo-injectable dose of corticosteroids. A per-protocol up-titration of OCS dosage to one step greater is not necessarily considered to be an exacerbation event.
    - Patients who experience an exacerbation during the screening period (between Visits 1 and 2) can be granted an extension of the screening period to ensure recovery from an asthma exacerbation and stabilisation of the OCS dosage.
- An emergency department or urgent care visit (defined as evaluation and treatment for <24 hours in an emergency department or urgent care centre) related to asthma that requires systemic corticosteroids (as per the above).
- Inpatient hospitalisation (defined as admission to an inpatient facility and/or evaluation and treatment in a health care facility for ≥24 hours) related to asthma.

Patients who experience an exacerbation during the treatment period can remain on the study drug at the investigator's discretion. Asthma exacerbations will be treated with oral or other systemic corticosteroids according to standard practice.

Glucocorticoid Toxicity Index

Glucocorticoid toxicity index (GTI) will be assessed as described by Miloslavsky et al [1]. The composite GTI captures common glucocorticoid toxicities that are sensitive to differing cumulative glucocorticoid dosages over the period of a typical clinical trial (6 months to 3 years). Individual items within the GTI are weighted relative to each other for severity. The instrument can measure not only worsening, but also improvement of glucocorticoid toxicity from baseline. The composite GTI measures change in glucocorticoid toxicity rather than absolute glucocorticoid toxicity to account for the effects of prior glucocorticoid therapy. Scoring is performed as per the schedule of assessments, using entry assessment as the baseline. GTI items are ranked in order of severity within each domain. The relative weights for each toxicity item are derived using multicriteria decision analysis, which has been used for the creation of multiple classification criteria sets for a variety of inflammatory diseases, including rheumatoid arthritis [2], systemic sclerosis [3], and systemic lupus erythematosus [4].

The composite GTI will be assessed at the induction phase, when patients achieve OCS dosages of 5 mg/day, and at end of treatment or discontinuation. Items assessed will include body mass index, glucose tolerance (glycosylated haemoglobin), blood pressure, low-density lipoprotein, steroid myopathy, skin toxicity, neuropsychiatric toxicity, and infection.

References

1 Miloslavsky EM, Naden RP, Bijlsma JW, et al. Development of a Glucocorticoid Toxicity Index (GTI) using multicriteria decision analysis. *Ann Rheum Dis* 2017; **76**: 543–546.

2. Neogi T, Aletaha D, Silman AJ, et al. The 2010 American College of Rheumatology/European League Against Rheumatism classification criteria for rheumatoid arthritis: Phase 2 methodological report. *Arthritis Rheum* 2010; **62**: 2582–2591.

3. Johnson SR, Naden RP, Fransen J, et al. Multicriteria decision analysis methods with 1000Minds for developing systemic sclerosis classification criteria. *J Clin Epidemiol* 2014; **67**: 706–714.

4. Tedeschi SK, Johnson SR, Boumpas D, et al. Developing and refining new candidate criteria for systemic lupus erythematosus classification: An international collaboration. *Arthritis Care Res (Hoboken)* 2018; **70**: 571–581.

APPENDIX 3: EFFICACY ASSESSMENTS

Patient-Reported Outcomes

- Patients will be supplied with and trained on an electronic patient-reported outcomes (ePRO) device at Visit 2.
- The study centre staff will be trained on how to use the ePRO device and will be responsible for instructing patients on how to use it.

Asthma Control Questionnaire 6

- The Asthma Control Questionnaire 6 (ACQ-6) is a shortened version of the ACQ that assesses asthma symptoms (night-time awakening, symptoms on awakening, activity limitation, shortness of breath, wheezing) and short-acting β_2-agonist use, omitting the measurement of forced expiratory volume in 1 second from the original ACQ score [1].
- The ACQ-6 will be completed by patients on-site using a paper questionnaire.
- Patients will be asked to recall their experiences with asthma during the previous week and score each question on a 7-point scale ranging from 0 (totally controlled) to 6 (severely uncontrolled).
    - Overall score will be calculated as the mean response to all questions.
- Individual ACQ-6 total score changes of $\geq$0.5 are considered clinically meaningful.
- The questionnaire will be completed every 12 weeks during the treatment period starting at Week 0 through to the end of treatment.

St. George's Respiratory Questionnaire

- St. George's Respiratory Questionnaire (SGRQ) is a 50-item patient-reported outcomes instrument developed to measure the health status of patients with airway obstruction diseases [2]. The questionnaire is divided into two parts:
  - Part 1 consists of eight items that pertain to the severity of respiratory symptoms in the preceding 4 weeks.
  - Part 2 consists of 42 items related to the daily activity and psychosocial impacts of the individual's respiratory condition.
- SGRQ yields a total score and three domain scores (symptoms, activity, and impacts). The total score indicates the impact of disease on overall health status.
- Total score is expressed as a percentage of overall impairment; 100 represents the worst possible health status and 0 indicates the best possible health status.
- Likewise, domain scores range from 0 to 100, with greater scores indicating greater impairment [3].
- A 4-unit decrease in SGRQ total score has been established as the criterion for minimal meaningful improvement [4].
- SGRQ responders are those with ≥4-unit decreases in SGRQ total score.
- SGRQ will be completed on-site at the beginning of Visit 2 and end of treatment/discontinuation visit using the ePRO device.

References

1. Juniper EF, Bousquet J, Abetz L, Bateman ED, Goal Committee. Identifying 'well-controlled' and 'not well-controlled' asthma using the Asthma Control Questionnaire. *Respir Med* 2006; **100**: 616–621

2. Jones PW, Quirk FH, Baveystock CM. The St George’s Respiratory Questionnaire. *Respir Med* 1991; **85(Suppl B)**: 25–31.
3. Jia CE, Zhang HP, Lv Y, Liang R, Jiang YQ, Powell H, Fu JJ, Wang L, Gibson PG, Wang G. The Asthma Control Test and Asthma Control Questionnaire for assessing asthma control: Systematic review and meta-analysis. *J Allergy Clin Immunol* 2013; **131**: 695–703.
4. Jones PW. St. George's Respiratory Questionnaire: MCID. *COPD* 2005; **2**: 75–79.