Elimination of Oral Corticosteroids (OCS) with Benralizumab Treatment in OCS-Dependent Asthmatics Using a Rapid, Personalized Algorithm: The PONENTE Trial

Andrew Menzies-Gow[1]; Mark Gurnell[2]; Liam G. Heaney[3]; Jonathan Corren[4]; Elisabeth H. Bel[5]; Jorge Maspero[6]; Timothy Harrison[7,8]; David Jackson[9,10]; David Price[11,12]; Njira Lugogo[13]; James Kreindler[14]; Annie Burden[15]; Alex de Giorgio-Miller[16]; Kelly W. Padilla[17]; Ubaldo J. Martin[18]; Esther Garcia Gil[19]

[1]Royal Brompton & Harefield NHS Foundation Trust, London, UK; [2]Wellcome-MRC Institute of Metabolic Science, Cambridge Biomedical Campus, Cambridge, UK; [3]Centre for Experimental Medicine, Queen's University Belfast, Belfast, UK; [4]David Geffen School of Medicine at UCLA and Allergy Medical Clinic Inc., Los Angeles, CA, USA; [5]Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands; [6]Fundación CIDEA, Buenos Aires, Argentina; [7]Nottingham Respiratory NIHR BRC, University of Nottingham, UK; [8]BioPharmaceuticals R&D Digital, AstraZeneca, Cambridge, UK; [9]Guy's Severe Asthma Center, Guy's & St. Thomas' NHS Trust, London, UK; [10]Asthma UK Centre, School of Immunology & Microbial Sciences, King's College London, London, UK; [11]Observational and Pragmatic Research Institute, Singapore; [12]Centre of Academic Primary Care, Division of Applied Health Sciences, University of Aberdeen, Aberdeen, United Kingdom;[13]University of Michigan Medical Center, Ann Arbor, MI, USA; [14]Global Medical Respiratory, BioPharmaceuticals Medical, AstraZeneca, Wilmington, DE; USA; [15]BioPharmaceuticals R&D, Late Respiratory & Immunology, Biometrics, AstraZeneca, Cambridge, UK; [16]Medical & Scientific Affairs, BioPharmaceuticals Medical, AstraZeneca, Luton, UK; [17]Late Respiratory & Immunology, BioPharmaceuticals R&D, AstraZeneca, Durham, NC, USA; [18]Late Stage Development, Respiratory and Immunology Therapeutic Area, AstraZeneca, Gaithersburg, MD, USA; [19]Global Medical Respiratory, BioPharmaceuticals Medical, AstraZeneca, Barcelona, Spain

Introduction

- According to several studies, 20–60% of patients with severe asthma use oral corticosteroid (OCS) therapy on a regular basis,[1,2] which places them at an increased risk of systemic adverse events (AEs),[2-6] including adrenal insufficiency (AI)[7]
- Several biologics are available for the treatment of severe asthma, and these have led to decreased exacerbation rates, improved symptom control, and decreased use of OCS[8-11]
- Benralizumab is an interleukin-5R alpha-directed cytolytic monoclonal antibody that activates antibody-dependent cell-mediated cytotoxicity, ultimately decreasing eosinophilic inflammation[12]
- In the ZONDA trial, benralizumab led to a 75% median reduction in OCS dosage at Week 28 (compared with a 25% reduction with placebo) for patients with eosinophil levels ≥150 cells/μL,[12] and benralizumab was associated with an exacerbation rate that was 70% lower than placebo[12]
  - ZONDA was a placebo-controlled trial that was not designed to evaluate optimal steroid-reduction schemes
- There is currently a lack of evidence guiding OCS withdrawal following biologic initiation in severe asthma[13]

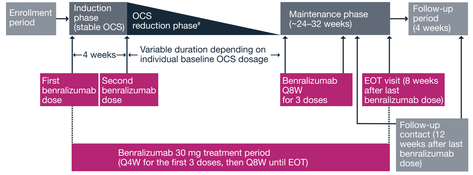
Objective

- We aimed to demonstrate that benralizumab could eliminate or reduce OCS to physiologic dosages following a personalized OCS-reduction scheme while monitoring for and managing AI[14]

Methods

- PONENTE was a multicenter, open-label, single-arm Phase IIIb study that assessed the efficacy and safety of daily OCS dosage reduction after initiation of benralizumab[14]
- Patients with asthma requiring high-dosage inhaled corticosteroids (ICS) and long-acting β_2-agonists (LABA) for ≥6 months plus OCS (≥5 mg prednisone or equivalent) for ≥3 months and blood eosinophil counts ≥150 cells/μL at baseline or ≥300 cells/μL in the previous 12 months were enrolled
- Benralizumab was administered throughout the induction and OCS-reduction phases at a dosage of 30 mg by subcutaneous injection every 4 weeks for 3 dosages and then every 8 weeks thereafter (**Figure 1**)

Figure 1. PONENTE Study Design



*Guided by schema of OCS reduction defined in the study protocol.
EOT=end of treatment; OCS=oral corticosteroids; Q4W=every 4 weeks; Q8W=every 8 weeks.
Figure adapted from Menzies-Gow A, et al. *ERJ Open Res*. 2019;5(3):00009–2019.

- The OCS-reduction phase, which began at Week 4 (after the second benralizumab injection), was variable and personalized (**Figure 2**)

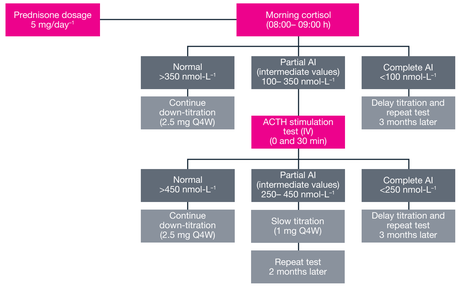
Figure 2. OCS Dosage-reduction Scheme

Baseline OCS dosage	OCS reduction until reaching a prednisone dosage of			
	20 mg/day^{-1}	10 mg/day^{-1}	7.5 mg/day^{-1}	5 mg/day^{-1}
>20 mg/day^{-1}	5 mg/day^{-1} Q1W	5 mg/day^{-1} Q2W	2.5 mg/day^{-1} Q2W	2.5 mg/day^{-1} Q4W
>10– ≤20 mg/day^{-1}		5 mg/day^{-1} Q2W	2.5 mg/day^{-1} Q2W	2.5 mg/day^{-1} Q4W
>7.5– ≤10 mg/day^{-1}			2.5 mg/day^{-1} Q2W	2.5 mg/day^{-1} Q4W

OCS=oral corticosteroids; Q1W=every week; Q2W=every 2 weeks; Q4W=every 4 weeks.
Figure adapted from Menzies-Gow A, et al. *ERJ Open Res*. 2019;5(3):00009–2019.

- When patients achieved a daily OCS dosage of 5 mg for 4 weeks, hypothalamic-pituitary-adrenal (HPA) axis integrity was assessed by measurement of a morning cortisol level and, if necessary, ACTH stimulation test (**Figure 3**)[14]
- OCS reduction continued according to whether patient had normal adrenal function or partial or complete AI; in cases of partial and complete AI, repeat cortisol levels (±ACTH stimulation tests) were repeated 2–3 months later to assess adrenal function recovery and guide further OCS reduction

Figure 3. HPA Axis Assessment and OCS-reduction Scheme from a Daily Prednisone Dosage of 5 mg



ACTH=adrenocorticotropic hormone; AI=adrenal insufficiency; Q4W=every 4 weeks.
Figure adapted from Menzies-Gow A, et al. *ERJ Open Res*. 2019;5(3):00009–2019.
"Partial AI (intermediate values)" as noted in the second row of the figure (immediately following measurement of 08:00 to 09:00 h cortisol) indicates an "indeterminate" result because such values may be associated with a subsequent post-ACTH stimulation level that is either normal, consistent with partial AI, or consistent with complete AI. Language was changed after the publication of the original study protocol to more accurately describe results and adrenal function categorizations.
Note: cortisol concentration thresholds were defined in the absence of any confounders of total cortisol measurement (e.g., women receiving oral estrogen therapy). For females using oral estrogen-containing contraceptives or oral estrogen-containing hormone replacement therapy, the threshold for normal values was 2 times the normal morning cortisol levels and 1.5 times the normal ACTH stimulation test cortisol levels.

- If patients experienced an asthma exacerbation (defined as worsening of asthma symptoms leading to the temporary need for systemic corticosteroids, emergency department or urgent care visit because of asthma that required a systemic corticosteroid bolus, or inpatient hospitalization related to asthma), further OCS reductions were allowed after recovery, but at a slower pace
- OCS reduction stopped if patients experienced 2 exacerbations or 2 HPA axis assessments at least 2 months apart indicating AI (i.e., complete AI at both assessments or partial AI at first test and complete AI at second test)
- Primary endpoints were the percentage of patients who achieved a 100% reduction in daily OCS dosage and the percentage of patients who achieved a 100% dosage reduction or a reduction to a daily OCS dosage ≤5 mg if the reason for stopping the reduction was AI
  - The percentage of patients achieving a daily OCS dosage ≤5 mg regardless of the cause for stopping the reduction and the percentage of patients reaching different thresholds of OCS reduction (i.e., >0%, ≥50%, ≥75%, and ≥90%) were also calculated
- Secondary endpoints allowing assessment of asthma symptoms during the OCS-reduction phase, including the percentage of patients who did not experience exacerbations, and safety outcomes, including the percentage of patients with partial and complete AI, were calculated
- Statistical analyses of safety and efficacy included all patients who received at least 1 dose of benralizumab
  - Subgroup analyses were completed according to baseline eosinophil level (<150 cells/μL, ≥150 cells/μL to <300 cells/μL, ≥300 cells/μL)
  - Analyses were descriptive only; no formal hypotheses were tested. Continuous variables were summarized using the mean, two-sided 95% confidence interval (CI) of the mean, the standard deviation, median, and range or interquartile range. Categorical variables were summarized using frequency counts and percentages, as well as a two-sided 95% CI for proportions computed using the exact Clopper-Pearson method. The annualized exacerbation rate was calculated using the time-based approach as 365.25×total number of exacerbations/total duration of follow-up (days).

Results

Patient and baseline characteristics

- 598 patients received at least 1 dose of benralizumab
- The median baseline daily OCS dosage was 10.0 mg (range, 5.0–60.0) and 24.9% of patients were taking daily OCS dosages >10 mg (**Table 1**)

Table 1. Baseline Characteristics

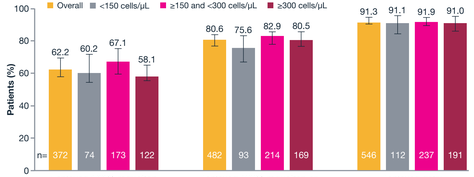
	Total (N=598)
Age, mean (SD), year	53.3 (13.59)
Female, %	64
White, %	80.6
BMI, mean (SD), kg/m^2	28.95 (27.97)
OCS dosage, median (range), mg/day	10.00 (5.0–60.0)
Number of patients taking OCS dosages, n (%)	
5 mg/day	193 (32.3)
>5 to ≤10 mg/day	256 (42.8)
>10 mg/day	149 (24.9)
ACQ-6, mean (SD)	2.2 (1.20)
EOS level, median (IQR), cells/μL	230.0 (150–380)
Number of patients with baseline EOS levels, n (%)	
<150 cells/μL	123 (20.8)
≥150 to <300 cells/μL	258 (43.7)
≥300 cells/μL	210 (35.5)
Exacerbations prior 12 months	
% patients with exacerbations	84.4
Number of exacerbations, median (range)	2.0 (0–48)
Total IgE, median (range)	130.7 (1.5–17840.7)
Phadiatop positive, %	47.2
Relevant medical history, %	
Any allergy	63.7
Allergic rhinitis	47.7
CRSwNP	29.8
Past polypectomy	20.9

[1]The most common comorbidity reported by patients was "any allergy."
ACQ-6=Asthma Control Questionnaire 6; BMI=body mass index; CRSwNP=chronic rhinosinusitis with nasal polyposis; EOS=eosinophils; ICS=inhaled corticosteroids; IgE=immunoglobulin E; IQR=interquartile range; N=number in analysis set; SD=standard deviation.

OCS reduction

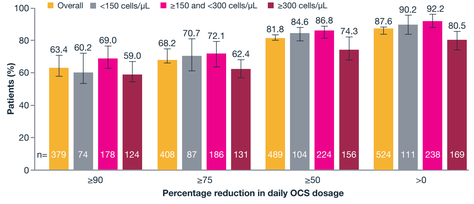
- 62.2% (95% CI, 58.18–66.11) of patients eliminated OCS use and 80.6% (95% CI, 77.20–83.70) eliminated use or reduced the daily dosage to ≤5 mg if AI prevented further reduction
  - 91.3% (95% CI, 88.75–93.44) of patients achieved a daily OCS dosage ≤5 mg, regardless of the cause for stopping the reduction
- The percentages of patients who reduced or eliminated OCS were similar across baseline eosinophil level subgroups (**Figures 4 and 5**)

Figure 4. OCS Down-titration Results: Overall and by Baseline Eosinophil Subgroups



AI=adrenal insufficiency; OCS=oral corticosteroids.
Overall N=598; EOS ≥300, n=210; EOS <300, n=381.
Confidence interval calculated using the Clopper-Pearson exact method. *Sustained over at least 4 weeks without worsening of asthma.

Figure 5. OCS Reductions by Pre-specified Threshold: Overall and by Baseline Blood Eosinophil

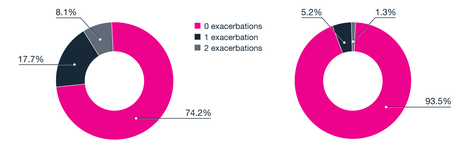


EOS=eosinophils; OCS=oral corticosteroids.

Asthma control and exacerbations

- Nearly three-quarters of patients were exacerbation-free during the OCS-reduction phase (**Figure 6**)
- 39 patients required an emergency department or urgent care visit or hospitalization due to asthma exacerbations (**Figure 6**)

Figure 6. Exacerbations During OCS-reduction Phase

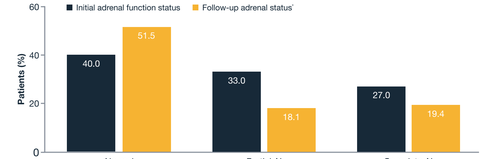


AER=annualized asthma exacerbation rate; ER=emergency room; OCS=oral corticosteroids.
Hospitalization was defined as admission to an inpatient facility and/or evaluation and treatment in a health care facility for ≥24 hours.

Adrenal function status

- Initially, 60% of patients tested had partial or complete AI which decreased to 37.5% 2–3 months later (**Figure 7**)

Figure 7. Adrenal Function Status During OCS-reduction Phase



Complete AI=morning cortisol <100 nmol/L or ACTH stimulation test <250 nmol/L; normal=morning cortisol >350 nmol/L or ACTH stimulation test >450 nmol/L; partial AI=ACTH stimulation test 250–450 nmol/L.
68 patients with incomplete or missing adrenal function status information: 48 did not reach a stable daily OCS dosage of 5 mg and, therefore, did not undergo testing and 20 had indeterminate cortisol, but not ACTH evaluation to complete full adrenal function status. Therefore, percentages are based on N=530.
58 patients with partial or complete AI (34 and 24 patients, respectively) at initial testing did not have adrenal function status completed at final HPA testing, leading to 141 patients with partial AI and 119 with complete AI being tested for adrenal function status at final HPA axis testing.
ACTH=adrenocorticotropic hormone; AI=adrenal insufficiency; OCS=oral corticosteroid.

Safety

- The AE profile was consistent with what is known from clinical trials and previous experience

Conclusions

- Irrespective of baseline eosinophil count, most OCS-dependent asthma patients treated with benralizumab achieved OCS elimination or maximal possible reduction in those in whom AI was detected
- The findings from PONENTE can inform physician decisions and clinical practice by supporting the use of a personalized OCS-reduction algorithm

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