Adrenal function recovery after durable OCS-sparing with benralizumab in the PONENTE study

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Take-home message

In the ~6-month PONENTE maintenance phase, benralizumab-treated patients sustained long-term oral corticosteroid elimination or reduction without loss of asthma control. Improved adrenal function was observed in many patients following steroid reduction.

Abstract (249/250 words)

Oral corticosteroid dependence among patients with severe eosinophilic asthma can cause adverse outcomes, including adrenal insufficiency. PONENTE's oral corticosteroid-reduction phase showed that, following benralizumab initiation, 91.5% of patients eliminated corticosteroids or achieved a final dosage ≤5 mg/day (median, 0.0 mg [range, 0.0-40.0]).

The maintenance phase assessed the durability of corticosteroid reduction and further adrenal function recovery. For approximately 6 months, patients continued benralizumab 30 mg every 8 weeks without corticosteroids or with the final dosage achieved during the reduction phase. Investigators could prescribe corticosteroids for asthma exacerbations or increase daily dosages for asthma control deteriorations.

Outcomes included changes in daily oral corticosteroid dosage, Asthma Control Questionnaire 6 (ACQ-6), and St. George's Respiratory Questionnaire (SGRQ), as well as adrenal status, asthma exacerbations, and adverse events.

598 patients entered PONENTE; 563 (94.1%) completed the reduction phase and entered the maintenance phase. From the end of reduction to the end of maintenance, the median oral corticosteroid dosage was unchanged (0.0 mg; [range, 0.0-40.0]), 3.2% (n=18/563) of patients experienced daily dosage increases, the mean ACQ-6 score decreased from 1.26 to 1.18, and 84.5% (n=476/563) of patients were exacerbation free. The mean SGRQ improvement (–19.65 points) from baseline to the end of maintenance indicated substantial quality-of-life improvements. Of patients entering the maintenance phase with adrenal insufficiency, 32.4% (n=104/321) demonstrated an improvement in adrenal function. Adverse events were consistent with previous reports.

Most patients successfully maintained maximal oral corticosteroid reduction whilst achieving improved asthma control with few exacerbations and maintaining or recovering adrenal function.

Introduction

Patients with severe eosinophilic asthma (SEA) are often oral corticosteroid (OCS) dependent [1–3], which can lead to significant health consequences [4–6]. Exogenous corticosteroid exposure can cause suppression of the hypothalamic-pituitary-adrenal (HPA) axis and adrenal insufficiency (AI), a common but rarely measured consequence of OCS use [7–9].

Biologic therapies for severe asthma can improve asthma symptoms and reduce OCS dependence. In the ZONDA study, benralizumab-treated patients reduced their median OCS dosage from baseline by 75% compared with a 25% reduction in placebo-treated individuals [10]. OCS reductions were maintained for up to 4 weeks in ZONDA [10] and for up to 68 weeks in the follow-up BORA study [11].

PONENTE assessed the ability of patients with SEA to eliminate or reduce long-term, daily OCS use while maintaining asthma control after starting benralizumab [12]. PONENTE included a 4-week induction phase; a variable-duration, personalised OCS-reduction phase; and an approximately 6-month maintenance phase. Adrenal status was first assessed via cortisol levels when patients achieved a stable dosage of 5 mg of prednisone/prednisolone during the OCS-reduction phase and was reassessed at predetermined intervals during both the reduction and maintenance phases for those with partial or complete AI.

The results of PONENTE's OCS-reduction phase [13] demonstrated that 62.9% of patients eliminated daily OCS use while improving asthma control, and 81.9% either eliminated OCS use or achieved a daily dosage ≤5 mg prednisone/prednisolone if AI was the reason for not further reducing OCS. This was achieved with an apparent reduction in asthma exacerbations from a mean of 3.0 (median [range], 2 [0–48]) in the 12 months preceding the study to an overall annualised rate of 0.63 during the study. The OCS dosage reductions were also associated with improved adrenal function: AI was detected in 60% of patients at baseline and in 38% 2 to 3 months later [13].

After elimination or maximal reduction of OCS, patients entered the maintenance phase. This manuscript details the results of the maintenance phase, which assessed the durability of daily OCS dosage reductions, asthma control, and asthma exacerbations over approximately 6 months after completion of the OCS-reduction phase. Adrenal status was re-evaluated for patients with partial or complete AI at the end of the OCS-reduction phase. Changes in quality of life (QOL) using the St. George's Respiratory Questionnaire (SGRQ) were assessed as comparisons to baseline.

Methods

Patients

PONENTE (ClinicalTrials.gov identifier: NCT03557307) was an open-label, multi-centre, OCS-sparing study in OCS-dependent patients with severe asthma. The details of the study design and results of the OCS-reduction phase have been described previously [12,13]. The study included adults (≥18 years old) with SEA who, prior to the start of the study, were using high-dosage inhaled corticosteroids (ICS) plus long-acting β_2-agonists for at least 6 months and an OCS-dosage equivalent of ≥5 mg daily for at least 3 months with a stable dosage for at least 4 weeks. Patients were required to have blood eosinophil counts (BEC) ≥150 cells/μL at study entry or ≥300 cells/μL in the previous 12 months.

Study design

Following enrolment, patients received benralizumab 30 mg every 4 weeks for 3 doses and then every 8 weeks (**Supplementary Figure 1**). During the induction phase (Weeks 0–4), patients remained stable on their baseline OCS dosage but were switched to daily oral prednisone/prednisolone if this was not the OCS they were receiving. During the OCS-reduction phase (Week 4 and onward), patients reduced their OCS according to a schema that depended on starting OCS dosage and asthma control until a daily dosage of 5 mg was achieved (**Supplementary Figure 2**) [12]. PONENTE's protocol did not allow changes to background medications, including ICS and long-acting β_2-agonists, during the study [12].

HPA axis function was assessed after patients reached a stable daily OCS dosage of 5 mg for 4 weeks and, thereafter, the OCS dosage was titrated downward according to adrenal status and asthma clinical status (**Supplementary Figure 3**) [12]. High-dose ICS can contribute to suppression of the HPA axis, which supports the case for optimal sensitivity testing of the HPA axis using both basal and adrenocorticotropic hormone (ACTH)-stimulated cortisol measurements, as was done in the PONENTE study. Cross-reactivity of both endogenous and exogenous corticosteroids has been formally assessed at high concentrations with the Beckman Access cortisol immunoassay (Beckman Coulter, Brea, CA, USA),

and clinically relevant cross-reactivity has not been observed with this or other clinical immunoassays [14]. Any potential for cross-reactivity in PONENTE was mitigated by the careful timing of the testing relative to the most recent dose of steroids [12,13]. Some studies have suggested that the low-dose (0.5–1 µg) synthetic ACTH stimulation test might reveal partial AI more frequently than the supraphysiologic 250-µg test in suspected secondary/tertiary AI. However, a 2016 systematic review reported no differences between the two protocols [15]. Concerns about the use of ACTH stimulation testing for the detection of HPA axis dysfunction have also centred on its susceptibility to false negative results when used in the context of an acute insult to the HPA axis (for example, following pituitary gland surgery or apoplexy). However, despite these recognised limitations, the standard 250-µg test in combination with an unstimulated early morning cortisol test remains the preferred dynamic assessment when screening for secondary/tertiary AI, including glucocorticoid-induced AI [16,17,18], and the assessment protocol utilized in PONENTE mitigated these factors and aligned with clinical practice. The cut-offs chosen to denote normal adrenal function and partial and complete AI were based on the specific assay used and may vary with other clinical immunoassays; a single cut-off value should always be interpreted in the context of the clinical setting.

The maintenance phase was initiated once a patient eliminated OCS without worsening of asthma control or when the dosage of OCS could no longer be reduced due to clinical status or AI. During the maintenance phase, patients continued benralizumab 30 mg every 8 weeks for three more doses (approximately 24 to 32 weeks) either without OCS or with the final OCS dosage achieved during the OCS-reduction phase. If patients experienced an asthma exacerbation, investigators could prescribe a temporary increase in OCS dosage (bolus/burst) and then return to the previous stable OCS dosage. If patients experienced a deterioration in overall asthma control, investigators could increase the long-term, daily dosage.

The maintenance phase ended with an end-of-treatment (EOT) visit conducted 8 weeks after the last dose of benralizumab. A follow-up visit was conducted 12 weeks after the last dose of benralizumab.

Patients were instructed to complete the Asthma Control Questionnaire 6 (ACQ-6) on a weekly basis beginning at baseline (Week 0, before the first benralizumab dose). SGRQ was assessed at baseline and at the EOT visit. The validity of SGRQ in asthma has been established in several studies, with a decrease of 4 points noted as the threshold of meaningful difference [19–22].

The independent ethics committees of the trial centres or the central institutional review boards approved the trial protocol. The trial was conducted in accordance with the principles of the Declaration of Helsinki, and all patients provided written informed consent.

Outcomes

The main outcome measures of the maintenance phase were the change in daily OCS dosage from the end of the OCS-reduction phase to the end of the maintenance phase, the time to first increase in OCS dosage during the maintenance phase, the change in ACQ-6 score from the end of the OCS-reduction phase to the end of the maintenance phase, and the change in SGRQ score from baseline to the end of the maintenance phase.

Safety assessments included the measurement of adrenal status according to serum cortisol levels for patients who entered the maintenance phase with partial or complete AI; the exacerbation rate; and the percentages of patients experiencing adverse events (AEs) and serious adverse events (SAEs).

Statistical analysis

There was no predefined study hypothesis, and sample size requirements were based on the ability to provide sufficient precision in point estimates for the primary endpoints [12,13]. Analyses were descriptive only, and no *p*-values were calculated. Continuous variables were summarised using the mean, the 2-sided 95% confidence interval (CI) of the mean, the standard deviation (SD), median, and range or interquartile range. Categorical variables were summarised using frequency counts and percentages as well as a 2-sided 95% CI for proportions computed using the exact Clopper-Pearson method.

Time to dosage-event data were analysed using Kaplan-Meier methods. Time (in days) to OCS dosage increase was defined as: date of first day of OCS increase in maintenance phase – date of first day of final OCS dosage in reduction phase + 1. Patients not achieving a dosage event were censored at either the end of the maintenance phase or the end of study participation. The annualised asthma exacerbation rate (AAER) was calculated using a time-based approach: 365.25 × total number of exacerbations/total duration of follow-up (days).

Safety and efficacy analyses included all patients who received at least 1 benralizumab dose during the entire study period. Statistical analyses were completed using SAS software (Cary, NC, USA), version 9.4.

Results

Patients

Of 598 patients who entered the OCS-reduction phase (**Supplementary Figure 4**) [13], 563 (94.1%) completed that phase and entered the maintenance phase, and 538 (90.0%) completed the maintenance phase (defined as having attended the EOT visit). At baseline, the median OCS dosage was 10.0 (range, 5.0–60.0) mg daily and the median ICS dosage was 1000.0 (interquartile range, 500.0–1000.0) µg fluticasone propionate equivalent daily (**Supplementary Table 1)** [13]. Sixty-two patients (10.4%) withdrew from the study, including 2 who withdrew after completing the maintenance phase EOT visit but before the follow-up visit. The most common reasons for withdrawal were protocol deviation (n=17 [2.8%]), patient decision (n=12 [2.0%]), and AE (n=11 [1.8%]).

Change in OCS dosage and time to dosage increase

At the ends of both the OCS-reduction and maintenance phases, the median OCS dosage was 0.0 mg (range for both, 0.0–40.0). The stability in OCS dosage between the ends of the reduction and maintenance phases was consistent across subgroups of patients stratified by baseline BEC, baseline OCS dosage, and duration of OCS use (**Supplementary Table 2**).

Of patients who entered the maintenance phase (n=563), 87 (15.5%) had any asthma-related OCS dosage increase, including 18 (3.2%) who had an increase in long-term OCS dosage during the maintenance phase. Of those who eliminated OCS use during the OCS-reduction phase (n=376), 37 (9.8%) had any asthma-related dosage increase and 7 (1.9%) had an increase in long-term OCS dosage.

Most asthma-related dosage increases (n=80 [92.0%]) were due to exacerbations. All patients who had an increase in long-term OCS dosage during the study experienced an exacerbation or worsening of symptoms. Times to both types of dosage increases were evenly distributed over Weeks 0 to 32 among the entire population (**Figure 1**) and across patient subgroups stratified by baseline BEC, baseline OCS dosage, and duration of OCS use (**Supplementary Table 3**).

Asthma control

Overall, asthma control improved during the maintenance phase (**Table 1**). The mean ACQ-6 score decreased from 1.26 at the end of the reduction phase to 1.18 at the end of the maintenance phase. Additionally, at the end of the maintenance phase, 33.6% (n=201) of patients had well-controlled disease (defined as ACQ-6 ≤0.75). Changes in ACQ-6 scores were consistent across patient subgroups stratified by baseline BEC, baseline OCS dosage, and duration of OCS use (**Supplementary Figure 5**). More than half of patients achieved a clinically meaningful improvement in asthma control (defined as a change of ≤–0.5 points on the ACQ-6 compared with baseline) at all time points tested during the reduction and maintenance phases (**Table 1**).

Asthma exacerbations

The majority of patients were exacerbation free during the maintenance phase (n=476 [84.5%]) (**Table 2**). Twenty-five patients (4.4%) experienced a total of 29 exacerbations leading to hospitalisation or emergency room visit during the maintenance phase.

Quality of life

The mean SGRQ score decreased from 54.3 at baseline to 33.4 at the end of the maintenance phase (mean change, –19.7 [95% CI, –21.7 to –17.6]) (**Table 3**). Changes in SGRQ were consistent across patient subgroups stratified by baseline BEC, baseline OCS dosage, and duration of OCS use (**Supplementary Figure 6**). At the EOT visit, 284 (47.5%) patients achieved a clinically meaningful improvement in QOL (defined as a decrease of ≥4 points on the SGRQ compared with baseline); 240 (40.1%) patients had missing SGRQ data (**Table 3**).

Adrenal status

In all, 533 patients had complete adrenal function data available at the initial testing. Adrenal status changes during the reduction phase have been previously reported [13]. Overall, 96 (18.0%) patients

entered the maintenance phase with partial AI and 109 (20.5%) entered with complete AI; 274 (51.4%) had normal adrenal function; and 54 patients had missing or incomplete data (10.13%). By the end of the maintenance phase, another 22 patients had achieved normal adrenal status. The number of patients with partial AI decreased, and there was a net increase of 13 with complete AI (**Figure 2**).

Of 175 patients with partial AI at initial HPA axis testing, 63 (36.0%) maintained partial AI and 68 (38.9%) recovered to normal function by the final assessment at the end of the maintenance phase; 22 (12.6%) patients with partial AI at initial HPA axis testing had complete AI at the final assessment. Of 146 patients with complete AI initially, nearly one-quarter recovered some degree of adrenal function: 16 (11.0%) recovered to normal function and 20 (13.7%) recovered to partial AI (**Figure 3**).

Adverse events

Fewer than half of patients experienced AEs during the maintenance phase (n=252 [44.8%]) (**Supplementary Table 4**). Nasopharyngitis was the only AE that occurred in more than 3% of patients (n=34 [6.0%]). Forty-three (7.6%) patients experienced SAEs, the most common being asthma (n=9 [1.6%]).

There were no reports of AI or adrenal crisis, but AEs were analysed for potential AI-related events. (Symptoms that could indicate AI were adapted from the Society for Endocrinology [23].) Forty-seven (7.9%) patients during the entire study had evidence of any AE that was potentially indicative of AI, with pyrexia (n=12 [2.0%]) being the most common (**Supplementary Table 4**).

Three (0.5%) participants died during the maintenance phase. One death was attributed to sudden cardiac death, 1 to cardiac arrest, and 1 to acute myocardial infarction. No deaths were attributed to the study drug or to AI.

Discussion

The PONENTE study maintenance phase demonstrated the durable effect of benralizumab on OCS reductions in OCS-dependent patients with SEA. OCS reductions were associated with improved asthma control and improved quality-of-life scores from baseline. Adrenal function further improved in the 6 months after the end of the OCS-reduction phase for some patients, even returning to normal in some who initially had complete AI.

The durable benefits were achieved regardless of baseline BEC. For patients receiving long-term OCS, which can reduce BEC, the use of a single BEC to define or diagnose an eosinophilic phenotype or as a prescribing criterion may inappropriately exclude benralizumab from consideration for therapy and suggests that a single BEC <150 cells/μL in patients receiving OCS cannot exclude a diagnosis of eosinophilic asthma [24,25].

Asthma control was assessed in multiple ways—mean ACQ-6 score, asthma control status, and response—and by all measures asthma control improved during the OCS-reduction phase and was stable over the maintenance phase of the PONENTE study. It should be noted that the ACQ-6 score was expected to decrease since stable or improved asthma control was used to guide the OCS-reduction phase. Exacerbations also decreased, with most patients being exacerbation free, not just during the maintenance phase but during the entire study. A significant improvement in SGRQ score was also evident from baseline to the end of the maintenance phase, signifying meaningful changes in QOL. While this finding is limited by the large portion of patients with missing data, the improvement was consistent with other measures. Our findings confirm those of other studies of biologics that demonstrate QOL benefit in severe asthma populations [26–32]: overall, decreased exacerbations and increased asthma control allow patients to improve health status and feel better, especially those who had been receiving OCS. The substantial improvements in multiple asthma-related outcomes observed in PONENTE (asthma control, exacerbations, and QOL) highlight benralizumab's benefits, even after maximal reduction or elimination of OCS.

PONENTE also demonstrated that OCS reduction and elimination can be achieved safely and for most patients without worsening of adrenal function: the number of patients with normal adrenal function improved from baseline through the reduction phase and to the end of the maintenance phase, with more than half of patients having normal adrenal function by the final assessment. There were no reports of adrenal crisis during the study. Patients were allowed multiple assessment opportunities and the full duration of the reduction and maintenances phases to recover adrenal function. Most individuals with partial AI remained with partial AI or improved to normal adrenal function, although a small number had function that worsened to complete AI from partial AI over the course of the reduction and maintenance phases. There are several possible explanations for apparent worsening adrenal function. First, because categorisation of adrenal function in PONENTE was made using firm cortisol cut off values, small changes in cortisol levels may have resulted in a shift in AI classification without this representing a true physiologic or clinically relevant change. Second, some patients may have experienced an increase in cumulative corticosteroid exposure due to increased adherence to inhaled corticosteroids upon entering the study or owing to intercurrent illness or exacerbations requiring bolus steroid dosing. This complexity reinforces the importance of evaluating adrenal function whilst tapering long-term corticosteroids, especially in patients with evidence of partial AI. In PONENTE, patients with evidence of AI at the end of the maintenance phase were recommended for referral to an endocrinologist for continued care.

The prevalence of AI in patients with severe asthma who receive treatment with OCS is difficult to assess, but one study found that 43.7% of patients taking OCS for asthma had AI. The risk of AI likely increases with higher OCS dosages and longer durations of use [7]. PONENTE further elucidates the extent of AI in this population and provides context for expected changes in adrenal function over time, which is variable and may take weeks to months, or even years, to recover [5,33]. PONENTE also provides an algorithm for monitoring adrenal function whilst reducing OCS dosages.

The AEs observed in PONENTE were consistent with previous reports and no additional safety issues were noted.

One limitation of PONENTE is that patients with normal adrenal function at the initial test were not required to undergo further HPA axis testing; the expectation that adrenal function would remain normal once established cannot be confirmed. Additionally, while the approximate 6-month length of the maintenance phase was longer than previous assessments of corticosteroid-sparing biologics after OCS reduction, an extended study would confirm the durability of the changes and assess the possibility of further adrenal function recovery.

Conclusion

The PONENTE maintenance phase demonstrated that most patients with SEA receiving benralizumab successfully maintained maximal OCS reduction for 6 months after completion of a structured, personalised OCS-reduction plan, whilst achieving improved asthma control and QOL, experiencing no or few exacerbations, and maintaining or recovering adrenal function.

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Taiwan: National Taiwan University Hospital Yunlin Branch, Yunlin County: Chung-Yu Chen; Kaohsiung Chang Gung Memorial Hospital, Kaohsiung: Wen-Feng Fang; China Medical University Hospital, Taichung: Liang-Wen Hang; Chung-Shan Medical University, Taichung: Jeng-Yuan Hsu; Taipei Medical University, Taipei: Han-Pin Kuo and Kang-Yun Lee; MacKay Memorial Hospital, Taipei: Sheng-Yeh Shen; Kaohsiung Medical University, Kaohsiung: Chau-Chyun Sheu; United Kingdom: Cambridge University Hospital NHS Foundation Trust, Cambridge: Robin Gore; University of Bradford, Bradford: Dinesh Saralaya; United States of America: Clinical Research Trials of Florida, Inc., Tampa, FL: Sady A. Alpizar; Penn highlands Healthcare, Dubois, PA: Sandeep Bansal; White Clay Medical Center, Newark, DE: Hummayun Ismail; Lowcountry Lung and Critical Care, Charleston, SC: Thomas D. Kaelin; Kentucky Lung Clinic, Hazard, KY: Firas Koura; Wilmington Health, Wilmington, NC: Mitchell Douglas Lee; East Carolina University, Greenville, NC: Veeranna Maddipati and Anagha Malur; HealthPartners Institute, Bloomington, MN: Charlene E. McEvoy; Clinical Research Institute, Minneapolis, MN: Hemalini Mehta; Virginia Commonwealth University, Richmond, VA: Arjun Mohan; Wake Forest School of Medicine, Winston Salem, NC: Wendy C. Moore, Jeffery Krings, Anna Pippins, Isaac Deaton, Bob Hmieleski, and Paige Field; New York University School of Medicine, New York, NY: Joan Reibman; Sneeze Wheeze & Itch Associates, LLC, Normal, IL: Dareen D. Siri; Washington University School of Medicine, St. Louis, MO: Kaharu Sumino; Emory University, Atlanta, GA: Colin Swenson; University of North Carolina at Chapel Hill, Chapel Hill, NC: Stephen Lloyd Tilley; Abraham Research, PLLC, Fort Mitchell, KY: Manuel Villareal.

Conflict of interest: A. Menzies-Gow has attended advisory boards for AstraZeneca, GlaxoSmithKline, Novartis, Sanofi, and Teva, and is a steering committee member for the AstraZeneca PONENTE study; received speakers' fees from AstraZeneca, Novartis, Sanofi, and Teva; participated in research with AstraZeneca, for which his institution has been remunerated; attended international conferences with Teva; and made consultancy agreements with AstraZeneca and Sanofi.

M. Gurnell is a steering committee member for the AstraZeneca PONENTE study; received travel support from AstraZeneca; and has received speakers' fees from AstraZeneca, Novartis, and Teva.

L.G. Heaney is Academic Lead for the UK MRC Consortium for Stratified Medicine in Severe Asthma; he is industrial partner with Amgen, AstraZeneca, MedImmune, Janssen, Novartis, Roche/Genentech, GlaxoSmithKline, and Boehringer Ingelheim; has prior project grant funding from MedImmune, Novartis UK, Roche/Genentech, and GlaxoSmithKline; has taken part in advisory boards/lectures supported by AstraZeneca, Chiesi, Novartis, Roche/Genentech, GlaxoSmithKline, Teva, Theravance, and Vectura; received travel funding support to international respiratory meetings from AstraZeneca, Chiesi, Novartis, Boehringer Ingelheim, Teva, and GlaxoSmithKline; and has taken part in asthma clinical trials for GlaxoSmithKline, Schering-Plough, Synairgen, Novartis, and Roche/Genentech for which his institution was remunerated.

J. Corren has received grants from AstraZeneca in addition to grants and personal fees from Genentech, Novartis, Regeneron Pharmaceuticals, and Sanofi.

E.H. Bel reports grants from GlaxoSmithKline and Teva, which were paid to her institution; serves on the AstraZeneca Data Safety Monitoring Board for benralizumab; is a steering committee member for the AstraZeneca PONENTE and NOVELTY studies; serves on the GlaxoSmithKline Nucala Global Steering Committee; and received personal fees from GlaxoSmithKline, AstraZeneca, Chiesi, Sanofi/Regeneron, and Teva.

J. Maspero has consulted for AstraZeneca, Sanofi, and Teva; was a speaker for GlaxoSmithKline, Menarini, Novartis, and Uriach; and received research grants from Novartis.

T. Harrison reports grants from AstraZeneca and the National Institute for Health Research, UK; and personal fees and non-financial support from AstraZeneca and is a steering committee member for the AstraZeneca PONENTE study, GlaxoSmithKline, Vectura, Boehringer Ingelheim, Chiesi, and Synairgen. During the study's completion, he also became an employee of AstraZeneca.

D.J. Jackson has received speakers' honoraria from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Novartis, and Teva, and honoraria for attending advisory panels with AstraZeneca, GlaxoSmithKline, Novartis, Chiesi, Sanofi/Regeneron, and Teva.

D. Price has advisory board membership with AstraZeneca, Boehringer Ingelheim, Chiesi, Mylan, Novartis, Regeneron Pharmaceuticals, Sanofi Genzyme, Thermofisher; consultancy agreements with Airway Vista Secretariat, AstraZeneca, Boehringer Ingelheim, Chiesi, EPG Communication Holdings Ltd, FIECON Ltd, Fieldwork International, GlaxoSmithKline, Mylan, Mundipharma, Novartis, OM Pharma SA, PeerVoice, Phadia AB, Spirosure Inc, Strategic North Limited, Synapse Research Management Partners S.L., Talos Health Solutions, Theravance, and WebMD Global LLC; grants and unrestricted funding for investigator-initiated studies (conducted through Observational and Pragmatic Research Institute Pte Ltd) from AstraZeneca, Boehringer Ingelheim, Chiesi, Mylan, Novartis, Regeneron Pharmaceuticals, Respiratory Effectiveness Group, Sanofi Genzyme, Theravance, and UK National Health Service; received payment for lectures/speaking engagements from AstraZeneca, Boehringer Ingelheim, Chiesi, Cipla, GlaxoSmithKline, Kyorin, Mylan, Mundipharma, Novartis, Regeneron Pharmaceuticals, and Sanofi Genzyme; received payment for travel/accommodation/meeting expenses from AstraZeneca, Boehringer Ingelheim, Mundipharma, Mylan, Novartis, and Thermofisher; has stock/stock options from AKL Research and Development Ltd, which produces phytopharmaceuticals; owns 74% of the social enterprise Optimum Patient Care Ltd (Australia and UK) and 92.61% of Observational and Pragmatic Research Institute Pte Ltd (Singapore); has 5% shareholding in Timestamp,

which develops adherence monitoring technology; is peer reviewer for grant committees of the UK Efficacy and Mechanism Evaluation programme, and Health Technology Assessment; and was an expert witness for GlaxoSmithKline.

N. Lugogo received consulting fees for advisory board participation from Amgen, AstraZeneca, Genentech, GlaxoSmithKline, Novartis, Regeneron, Sanofi, and Teva; honoraria for non-speakers' bureau presentations from GlaxoSmithKline and AstraZeneca; and travel support from AstraZeneca; her institution received research support from Amgen, AstraZeneca, Avillion, Evidera, Gossamer Bio, Genentech, GlaxoSmithKline, Regeneron, Sanofi, Novartis, and Teva.

J. Kreindler, A. de Giorgio-Miller, S. Faison, K. Padilla, and U.J. Martin are full-time employees of and stockholders in AstraZeneca. K. Padilla is also a member of the board of advisors for TruLab, Inc. Durham, NC.

A. Burden was a contract employee of AstraZeneca at the time of the study.

E. Garcia Gil was an employee and stockholder of AstraZeneca at the time of the study.

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Data sharing: Data underlying the findings described in this manuscript may be requested in accordance with AstraZeneca's data-sharing policy described at https://astrazenecagroup-dt.pharmacm.com/DT/Home.

Tables

Table 1. Asthma control throughout the study period

	Baseline (n=598)	Initial HPA axis assessment* (n=598)	End of OCS-reduction phase (n=598)	End of maintenance phase (n=598)
Mean ACQ-6 score (95% CI)	2.22 (2.12–2.32)	1.35 (1.26–1.44)	1.26 (1.17–1.36)	1.18 (1.09–1.28)
Median ACQ-6 score (range)	2.33 (0.0–6.0)	1.17 (0.0–5.5)	1.00 (0.0–5.3)	0.83 (0.0–5.2)
Asthma control status, n (%)				
Well-controlled	80 (13.4)	182 (30.4)	182 (30.4)	201 (33.6)
Partially controlled	64 (10.7)	125 (20.9)	131 (21.9)	115 (19.2)
Uncontrolled	404 (67.6)	221 (37.0)	182 (30.4)	155 (25.9)
Missing or incomplete data	50 (8.4)	70 (11.7)	103 (17.2)	127 (21.2)
Patients achieving a clinically meaningful improvement in asthma control**, n (%)		313 (52.3)	367 (61.4)	358 (59.9)

*The initial HPA axis assessment was completed when patients reached a stable daily dosage of 5 mg for 4 weeks during the reduction phase.

**A clinically meaningful improvement was defined as a decrease of at least 0.5 points on the ACQ-6 compared with baseline.

Uncontrolled disease: ACQ ≥1.5; partially controlled disease: >0.75 to <1.5; well-controlled disease: ≤0.75.

At baseline, 548 patients had ACQ-6 data available to calculate the mean and median scores; at initial HPA axis assessment, 528 patients had available data; at the end of the OCS-reduction phase, 495 patients had available data; and at the end of the maintenance phase, 471 patients had available data. The total number of patients reported at each time point includes the last observation carried forward. All percentages are calculated as a proportion of the entire patient population (N=598).

ACQ-6, Asthma Control Questionnaire 6; CI, confidence interval; HPA, hypothalamic-pituitary-adrenal; OCS, oral corticosteroid.

Table 2. Exacerbations during the maintenance phase and the entire study period

	Maintenance phase (n=563)	Entire study period (n=598)
Patients experiencing exacerbations, n (%)		
0	476 (84.5)	405 (67.7)
1	64 (11.4)	111 (18.6)
2	17 (3.0)	49 (8.2)
3 or more	6 (1.1)	33 (5.5)
Total exacerbations, n	116	323
AAER		
Mean (95% CI)	0.36 (0.28–0.43)	0.49 (0.42–0.57)
Median (range)	0.00 (0.0–7.0)	0.00 (0.0–8.9)
Patients experiencing exacerbations leading to hospitalisation or emergency room visit, n (%)	25 (4.4)	59 (9.9)
Total number of exacerbations leading to hospitalisation or emergency room visit, n	29	75
AAER leading to hospitalisation or emergency room visit		
Mean (95% CI)	0.09 (0.05–0.14)	0.13 (0.09–0.17)
Median (range)	0.00 (0.0–7.0)	0.00 (0.0-8.9)

AAER, annualised asthma exacerbation rate; CI, confidence interval.

Table 3. Quality of life throughout study period

	Baseline (n=598)	End of maintenance phase (n=598)
Mean SGRQ score (95% CI)	54.27 (52.60–55.95)	33.40 (31.22–35.58)
Median SGRQ score (range)	56.59 (5.06–98.55)	31.75 (1.55–87.62)
QOL change, n (%)		
Improvement*		284 (47.5)
No change		39 (6.5)
Worsening*		35 (5.9)
Missing or incomplete data		240 (40.1)

*A clinically meaningful improvement was defined as a decrease of at least 4 points on the SGRQ score compared with baseline; a worsening was defined as an increase of at least 4 points.

At baseline, 570 patients had SGRQ data available to calculate the mean and median scores; at the end of the maintenance phase, 370 had available data. All percentages are calculated as a proportion of the entire patient population (N=598).

CI, confidence interval; QOL, quality of life; SGRQ, St. George's Respiratory Questionnaire.

Figure Legends

Figure 1. Time to OCS dosage increases

An asthma-related OCS dosage increase was defined as any increase associated with asthma maintenance or treatment of asthma exacerbations, asthma-related adverse events, or signs/symptoms of AI. A long-term OCS dosage increase was defined as a change that resulted in an increase in long-term dosage: if patients received an OCS burst to treat an exacerbation but then returned to the original long-term dosage, this was not counted as a long-term dosage increase.

(a) Bar graph of time to first asthma-related OCS dosage increase and time to first maintenance OCS dosage increase according to week during the maintenance phase.
(b) Kaplan-Meier curve of time to first asthma-related OCS dosage increase during the maintenance phase.
(c) Kaplan-Meier curve of time to first maintenance OCS dosage increase during the maintenance phase.

AI, adrenal insufficiency; OCS, oral corticosteroid.

Figure 2. Adrenal status throughout the study period

533 patients had complete test results at the initial testing: 51 patients did not reach a stable daily OCS dosage of 5 mg and, per protocol, did not undergo assessment of adrenal function and 14 patients had incomplete or missing assessments.

Complete AI=morning cortisol <100 nmol/L or ACTH stimulation test <250 nmol/L; partial AI=ACTH stimulation test 250–450 nmol/L; normal=morning cortisol >350 nmol/L or ACTH stimulation test >450 nmol/L.

ACTH, adrenocorticotropic hormone; AI, adrenal insufficiency; OCS, oral corticosteroid.

Figure 3. Changes in adrenal status during the study period

Complete AI=morning cortisol <100 nmol/L or ACTH stimulation test <250 nmol/L; partial AI=ACTH stimulation test 250–450 nmol/L; normal=morning cortisol >350 nmol/L or ACTH stimulation test >450 nmol/L.

ACTH, adrenocorticotropic hormone; AI, adrenal insufficiency.

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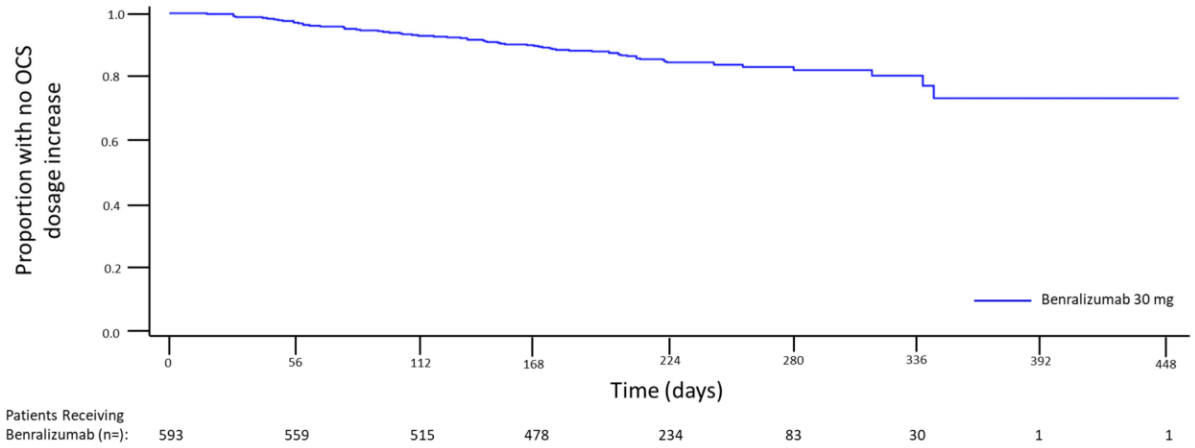
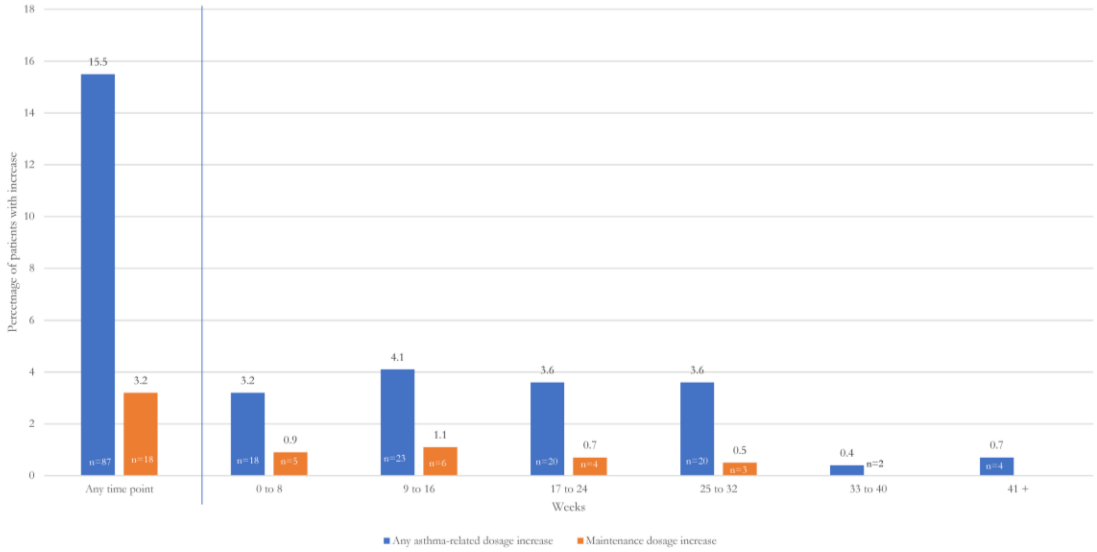
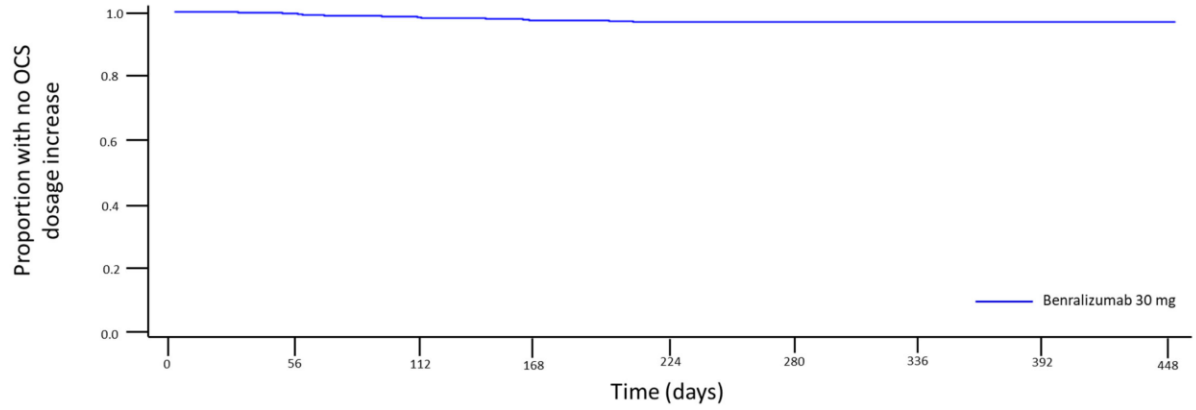
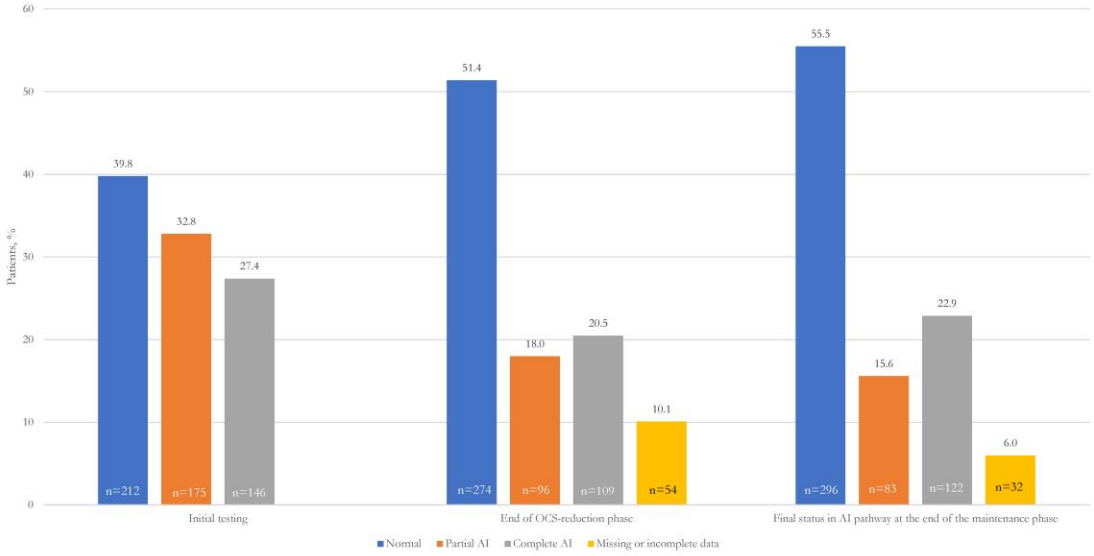


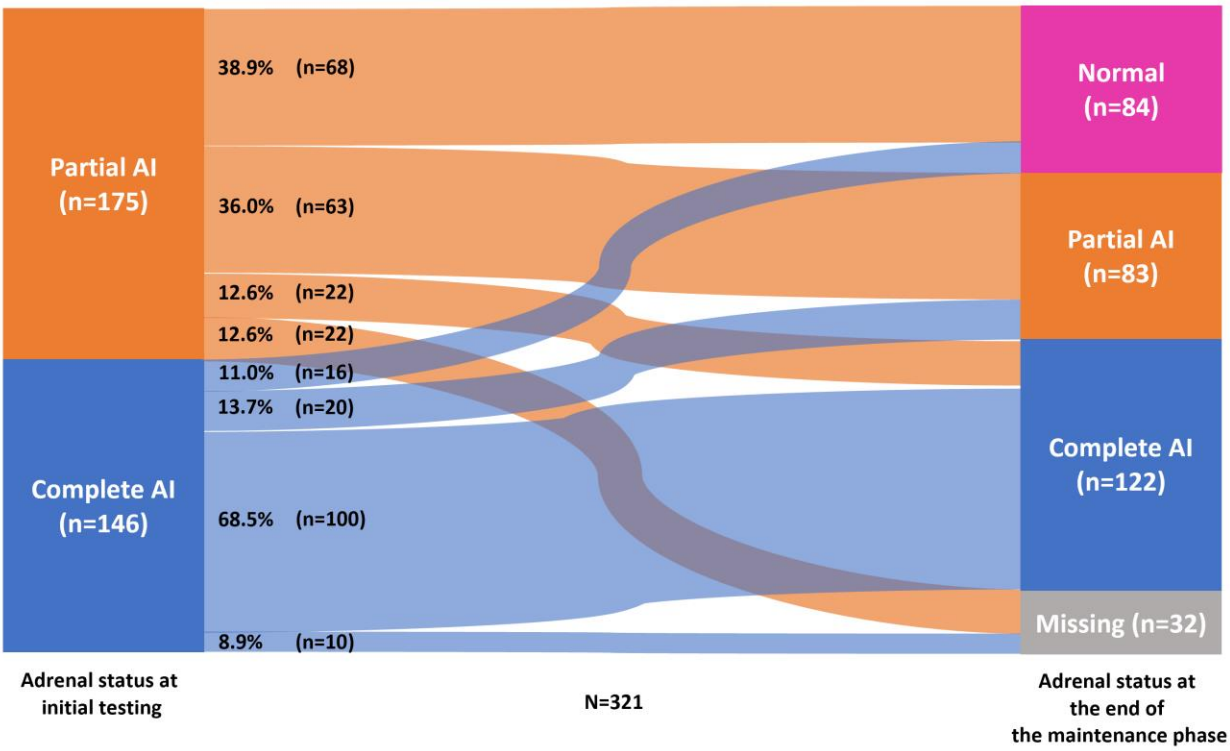
Patients Receiving Benralizumab (n=):	593	559	515	478	234	83	30	1	1





Patients Receiving Benralizumab (n=):	593	572	545	524	268	89	33	1	1


60
50
40
30
20
10
0
Patients, %
39.8
32.8
27.4
51.4
18.0
20.5
10.1
55.5
15.6
22.9
6.0
n=212
n=175
n=146
n=274
n=96
n=109
n=54
n=296
n=83
n=122
n=32
Initial testing
End of OCS-reduction phase
Final status in AI pathway at the end of the maintenance phase
Normal
Partial AI
Complete AI
Missing or incomplete data


Partial AI
(n=175)
Complete AI
(n=146)
38.9% (n=68)
36.0% (n=63)
12.6% (n=22)
12.6% (n=22)
11.0% (n=16)
13.7% (n=20)
68.5% (n=100)
8.9% (n=10)
Normal
(n=84)
Partial AI
(n=83)
Complete AI
(n=122)
Missing (n=32)
Adrenal status at
initial testing
N=321
Adrenal status at
the end of
the maintenance phase

Supplementary Material

Supplementary Table 1. PONENTE study's key demographics and baseline characteristics

Baseline characteristic	Total (N=598)
Age, mean (SD), years	53.3 (13.6)
Age at diagnosis, n (%) <18 years ≥18 years	 151 (25.3) 447 (74.7)
Female, %	64
White, % American Indian or Alaskan Native Asian Black or African American, % Native Hawaiian or other Pacific Islander Other	80.6 7.8 4.9 4.4 0.2 2.0
BMI, mean (SD), kg/m^2	28.95 (27.97)
OCS dosage, median (range)	10.00 (5.0-60.0)
Number of patients taking OCS dosages, n (%) 5 mg/day >5 to ≤10 mg/day >10 mg/day	 193 (32.3) 256 (42.8) 149 (24.9)
Duration of chronic OCS use, n (%) Patients taking OCS <1 year Patients taking OCS ≥1 year	 134 (23.3) 440 (76.7)
EOS count, median (IQR), cells/µL	230.0 (150–380)
Number of patients with baseline EOS counts, n (%) <150 cells/µL ≥150 to <300 cells/µL ≥300 cells/µL	 123 (20.8) 258 (43.7) 210 (35.5)
ACQ-6, mean (SD)*	2.2 (1.20)
Exacerbations in prior 12 months % patients with exacerbations Number of exacerbations, mean (SD) Number of exacerbations, median (range)	 84.4 3 (4.1) 2.0 (0–48)
Total IgE, median, range	130.7 (1.5, 17840.7)
Phadiatop positive, %	47.2
Comorbidities, %	
Any allergy	63.7
Allergic rhinitis	47.7
CRSwNP	29.8
Past polypectomy†	20.9
Smoking status, n (%)	

Current smoker	7 (1.2)
Former smoker	145 (24.2)
Non-smoker	446 (74.6)
Pack-year history, years (n=152)	
Mean (SD)	8.1 (5.67)
Median (range)	8.0 (0–20.0)

*Uncontrolled disease: ACQ ≥1.5; partially controlled disease: >0.75 to <1.5; well-controlled disease: ≤0.75.

ACQ-6, Asthma Control Questionnaire-6; BMI, body mass index; CI, confidence interval; CRSwNP, chronic rhinosinusitis with nasal polyps; EOS, eosinophil; IgE, immunoglobulin E; IQR, interquartile range; OCS, oral corticosteroid; SD, standard deviation.

Supplementary Table 2. Daily OCS dosages at baseline and throughout the study according to patient subgroups

	Baseline dosage, mg		Dosage at end of the reduction phase, mg		Dosage at end of the maintenance phase, mg	
	Mean (95% CI)	Median (range)	Mean (95% CI)	Median (range)	Mean (95% CI)	Median (range)
Entire population	(n=598)		(n=593)		(n=557)	
	10.76 (10.18–11.34)	10.00 (5.0–60.0)	2.26 (1.92–2.59)	0.00 (0.0–40.0)	1.96 (1.66–2.26)	0.00 (0.0–40.0)
Patient subgroups according to baseline BEC						
<150 cells/µL	(n=123)		(n=122)		(n=116)	
	12.39 (10.86–13.93)	10.00 (5.00–50.0)	2.48 (1.67–3.28)	0.00 (0.0–30.0)	2.09 (1.46–2.73)	0.00 (0.0–15.0)
≥150 to <300 cells/µL	(n=258)		(n=256)		(n=242)	
	11.28 (10.33–12.23)	10.00 (5.0–60.0)	2.00 (1.46–2.53)	0.00 (0.0–40.0)	1.68 (1.20–2.16)	0.00 (0.0–40.0)
≥300 cells/µL	(n=210)		(n=208)		(n=193)	
	9.16 (8.45–9.87)	10.00 (5.0–30.0)	2.41 (1.93–2.89)	0.00 (0.0–20.0)	2.22 (1.74–2.70)	0.00 (0.0–20.0)
Patient subgroups according to baseline daily OCS dosage						
5 mg/day	(n=193)		(n=192)		(n=184)	
	5.00 (NC–NC)	5.00 (5.0–5.0)	1.38 (1.07–1.70)	0.00 (0.0–10.0)	1.36 (1.04–1.69)	0.00 (0.0–10.0)
>5 to ≤10 mg/day	(n=258)		(n=256)		(n=243)	
	9.63 (9.52–9.74)	10.00 (6.3–10.0)	2.19 (1.77–2.61)	0.00 (0.0–20.0)	2.07 (1.64–2.50)	0.00 (0.0–20.0)
>10 mg/day	(n=147)		(n=145)		(n=130)	
	20.31 (18.90–21.73)	20.00 (12.5–60.0)	3.53 (2.50–4.56)	0.00 (0.0–40.0)	2.59 (1.71–3.46)	0.00 (0.0–40.0)
Patient subgroups according to duration of long-term OCS use at baseline						
<1 year	(n=134)		(n=130)		(n=120)	
	10.07 (8.97–11.17)	10.00 (5.0–50.0)	1.49 (0.96–2.02)	0.00 (0.0–15.0)	1.22 (0.72–1.72)	0.00 (0.0–15.0)
≥1 year	(n=440)		(n=440)		(n=418)	
	10.95 (10.25–11.65)	10.00 (5.0–60.0)	2.39 (2.00–2.78)	0.00 (0.0–40.0)	2.12 (1.76–2.48)	0.00 (0.0–40.0)

CI, confidence interval; NC, not countable; OCS, oral corticosteroid.

Supplementary Table 3. Times to OCS dosage increases during the maintenance phase according to patient subgroups

	Patients with any asthma-related dosage increase, n (%)							Patients with maintenance dosage increase, n (%)				
	Any time to increase	Weeks						Any time to increase	Weeks			
		0–8	9–16	17–24	25–32	33–40	41 or later		0–8	9–16	17–24	25–32
Patient subgroups according to baseline BEC												
<150 cells/µL (n=122)	21 (17.21)	4 (3.28)	8 (6.56)	4 (3.28)	3 (2.46)	1 (0.82)	1 (0.82)	3 (2.46)	0	2 (1.64)	1 (0.82)	0
≥150 to <300 cells/µL (n=256)	32 (12.50)	9 (3.52)	6 (2.34)	7 (2.73)	8 (3.13)	0	2 (0.78)	9 (3.52)	3 (1.17)	2 (0.78)	2 (0.78)	2 (0.78)
≥300 cells/µL (n=208)	34 (16.35)	5 (2.40)	9 (4.33)	9 (4.33)	9 (4.33)	1 (0.48)	1 (0.48)	6 (2.88)	2 (0.96)	2 (0.96)	1 (0.48)	1 (0.48)
Patient subgroups according to baseline daily OCS dosage												
5 mg/day (n=192)	23 (11.98)	5 (2.60)	4 (2.08)	4 (2.08)	8 (4.17)	1 (0.52)	1 (0.52)	4 (2.08)	2 (1.04)	0	1 (0.52)	1 (0.52)
>5 to ≤10 mg/day (n=256)	38 (14.84)	9 (3.52)	12 (4.69)	6 (2.34)	9 (3.52)	1 (0.39)	1 (0.39)	6 (2.34)	1 (0.39)	2 (0.78)	1 (0.39)	2 (0.78)
>10 mg/day (n=145)	26 (17.93)	4 (2.76)	7 (4.83)	10 (6.90)	3 (2.07)	0	2 (1.38)	8 (5.52)	2 (1.38)	4 (2.76)	2 (1.38)	0
Patient subgroups according to duration of long-term OCS use at baseline												
<1 year (n=130)	12 (9.23)	6 (4.62)	3 (2.31)	1 (0.77)	2 (1.54)	0	0	3 (2.31)	2 (1.54)	1 (0.77)	0	0
≥1 year (n=440)	72 (16.36)	11 (2.50)	19 (4.32)	18 (4.09)	18 (4.09)	2 (0.45)	4 (0.91)	14 (3.18)	2 (0.45)	5 (1.14)	4 (0.91)	3 (0.68)

BEC, blood eosinophil count; OCS, oral corticosteroid.

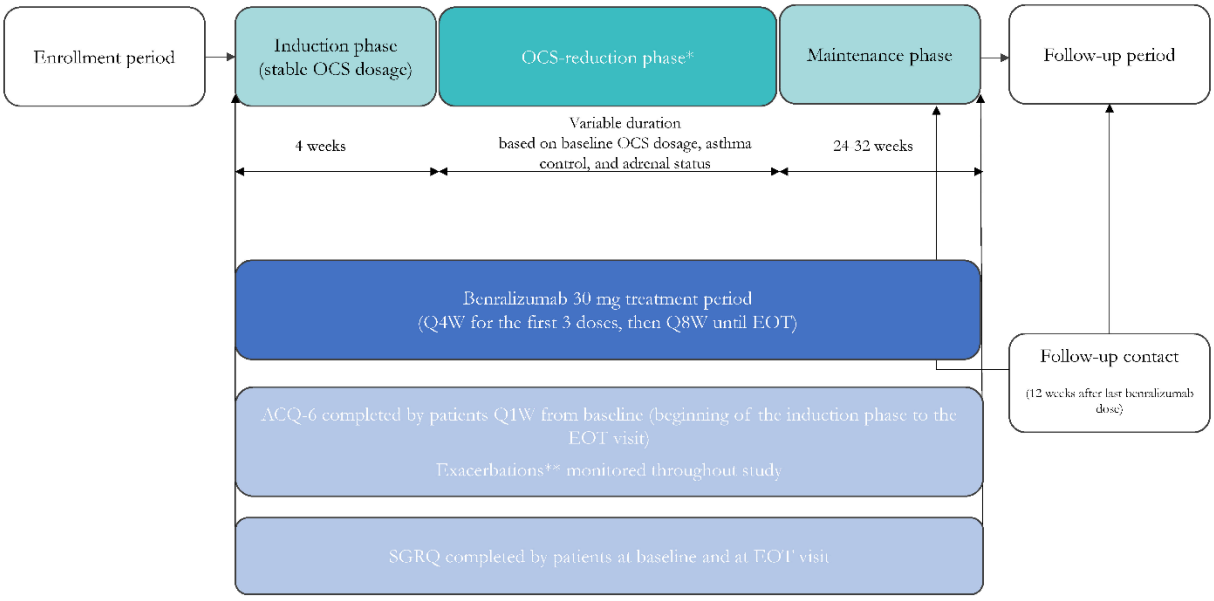
Supplementary Table 4. Adverse events and serious adverse events during the maintenance phase and the entire study period

	Maintenance phase (N=563)	Entire study period (N=598)
Patients experiencing any AE, n (%)	252 (44.8)	424 (70.9)
	AEs occurring in at least 3% of patients, n (%) Nasopharyngitis, 34 (6.0)	AEs occurring in at least 3% of patients, n (%) Nasopharyngitis, 64 (10.7) Influenza-like illness, 33 (5.5) Headache, 29 (4.8) Viral URTI, 28 (4.7) Asthma, 27 (4.5) URTI, 25 (4.2) Hypertension, 21 (3.5) Sinusitis, 19 (3.2)
Patients experiencing any SAE, n (%)	43 (7.6)	89 (14.9)
	SAEs occurring in at least 1% of patients, n (%) Asthma, 9 (1.6)	SAEs occurring in at least 1% of patients, n (%) Asthma, 23 (3.8) Pneumonia, 11 (1.8)
Patients with AE or concomitant medication potentially indicative of AI[*], n (%)		61 (10.2)
Patients with AE potentially indicative of AI, n (%)		47 (7.9)
		AEs potentially indicative of AI, n (%) Pyrexia, 12 (2.0) Nausea, 8 (1.3) Fatigue, 7 (1.2) Dizziness, 5 (0.8) Muscle spasms, 5 (0.8) Abdominal pain, 4 (0.7) Vomiting, 3 (0.5) Asthenia, 2 (0.3) Dizziness postural, 2 (0.3) Hypoglycemia, 1 (0.2) Hypotension, 1 (0.2) Prerenal failure, 1 (0.2)

AE, adverse event; AI, adrenal insufficiency; SAE, serious adverse event; URTI, upper respiratory tract infection.

[*]Glucocorticoids (hydrocortisone) and solutions affecting electrolyte balance

Supplementary Figure 1. PONENTE study design

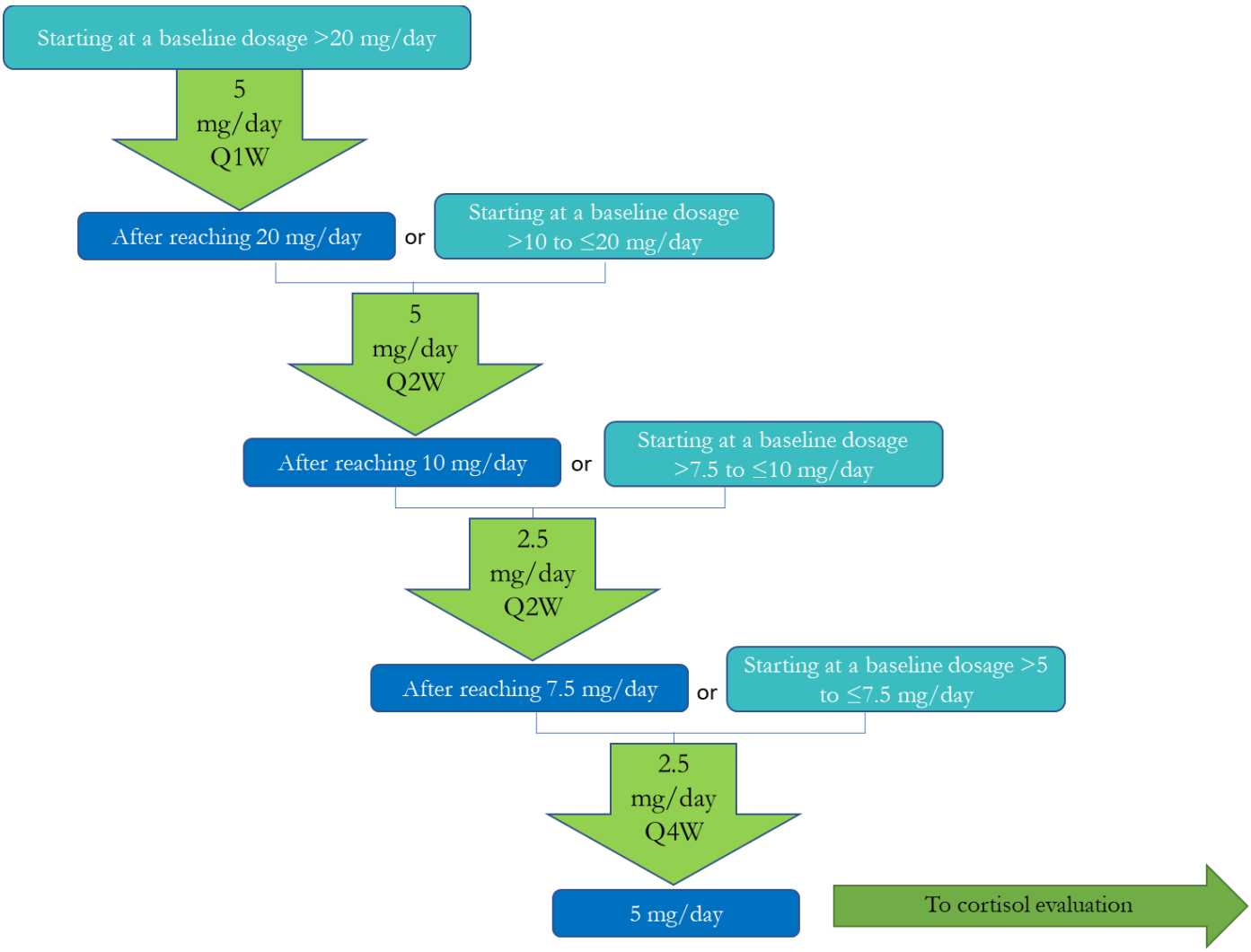


*Guided by the schema of OCS reduction defined in the study protocol.

**Exacerbations were 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 hospitalisation related to asthma.

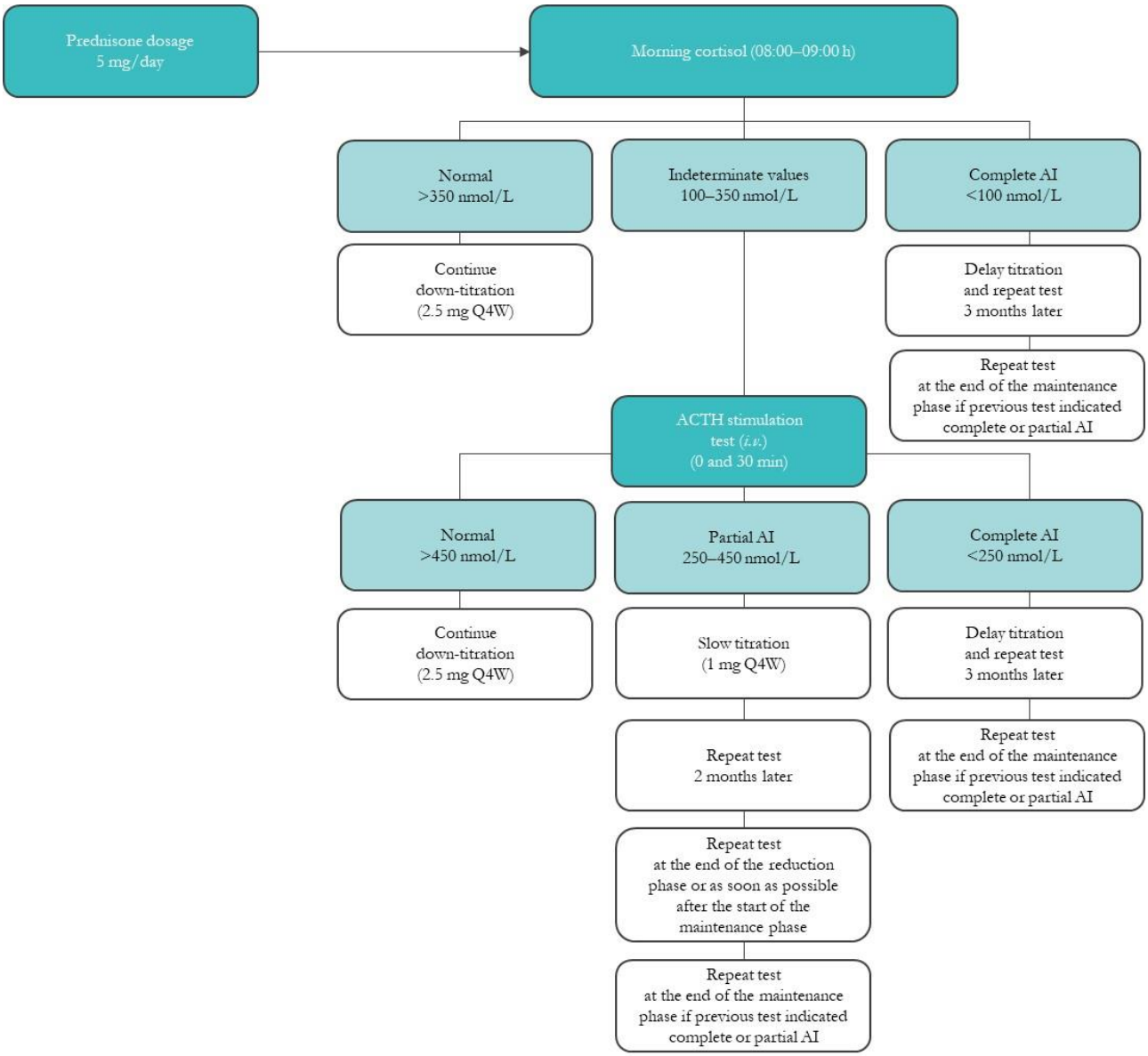
ACQ-6, Asthma Control Questionnaire 6; EOT, end of treatment; OCS, oral corticosteroid; Q1W, every week; Q4W, every 4 weeks; Q8W, every 8 weeks; SGRQ, St. George's Respiratory Questionnaire.

Supplementary Figure 2. OCS dosage-reduction scheme to a daily dosage of 5 mg



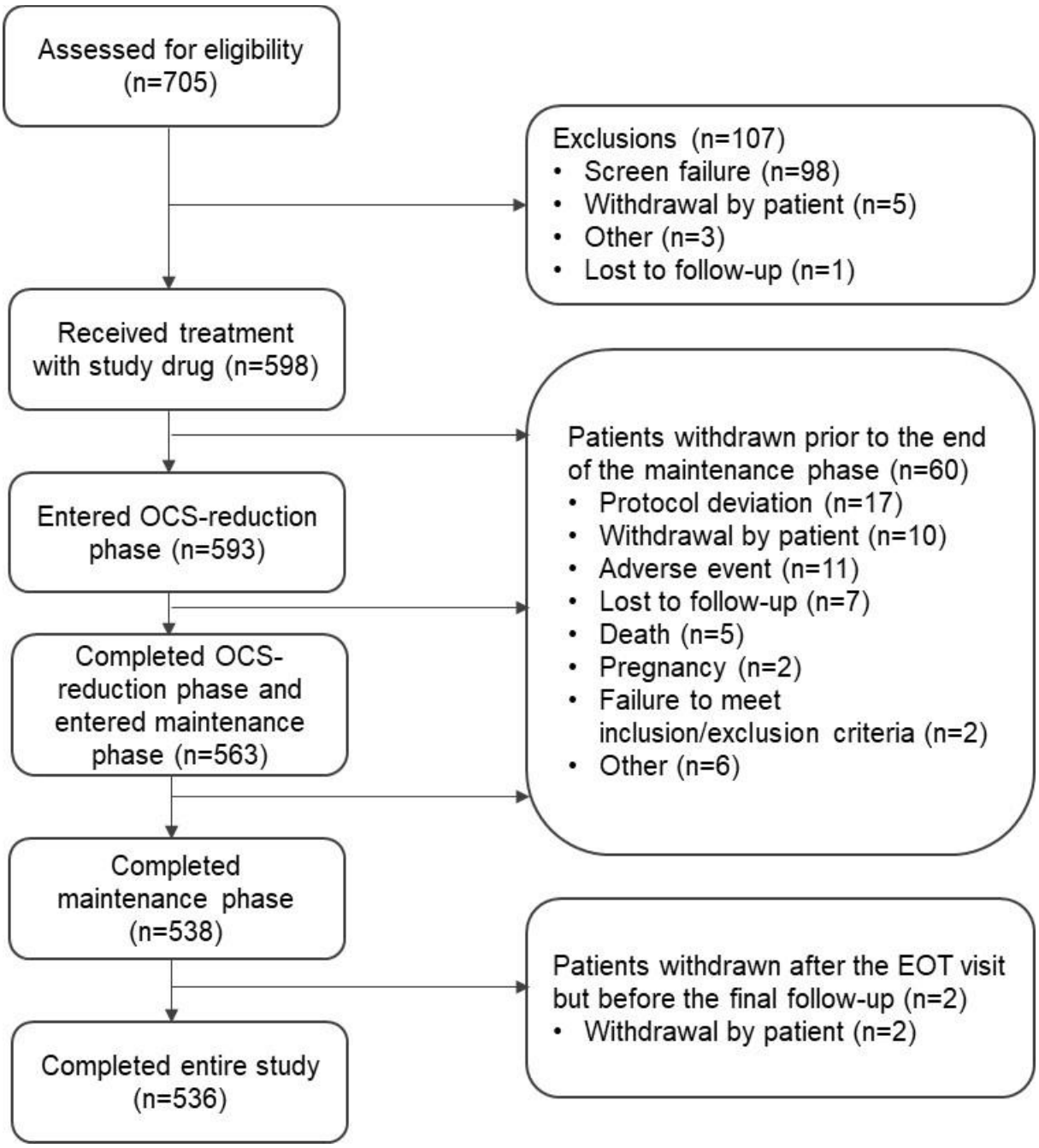
OCS, oral corticosteroid; Q1W, every week; Q2W, every 2 weeks; Q4W, every 4 weeks.
Reproduced from Lancet Respir Med, Menzies-Gow A, et al, Oral corticosteroid elimination via a personalised reduction algorithm in adults with severe, eosinophilic asthma treated with benralizumab (PONENTE): a multicentre, open-label, single-arm study, published online ahead of print October 4, 2021, with permission from Elsevier.

Supplementary Figure 3. HPA axis assessment and OCS-reduction scheme from a daily dosage of 5 mg



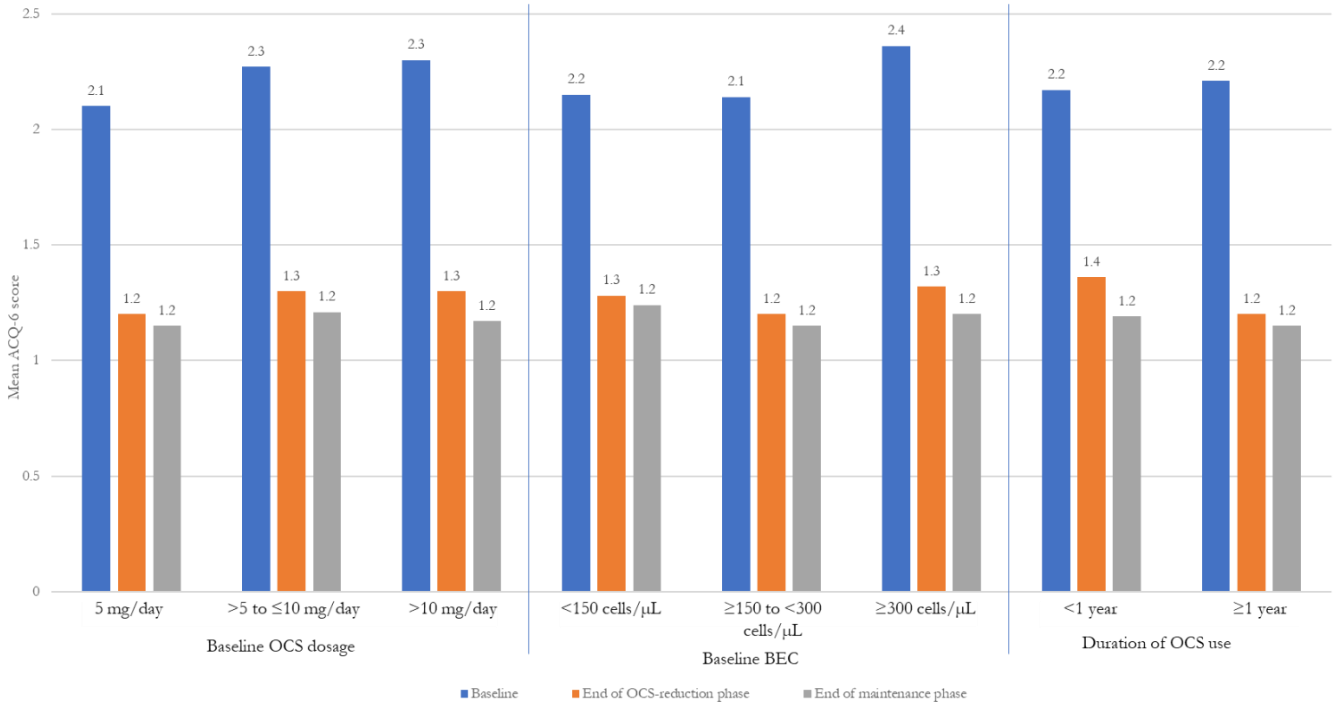
ACTH, adrenocorticotropic hormone; AI, adrenal insufficiency; HPA, hypothalamic-pituitary-adrenal; i.v., intravenous; OCS, oral corticosteroid; Q4W, every 4 weeks.

Supplementary Figure 4. Flow chart of patient inclusion in PONENTE



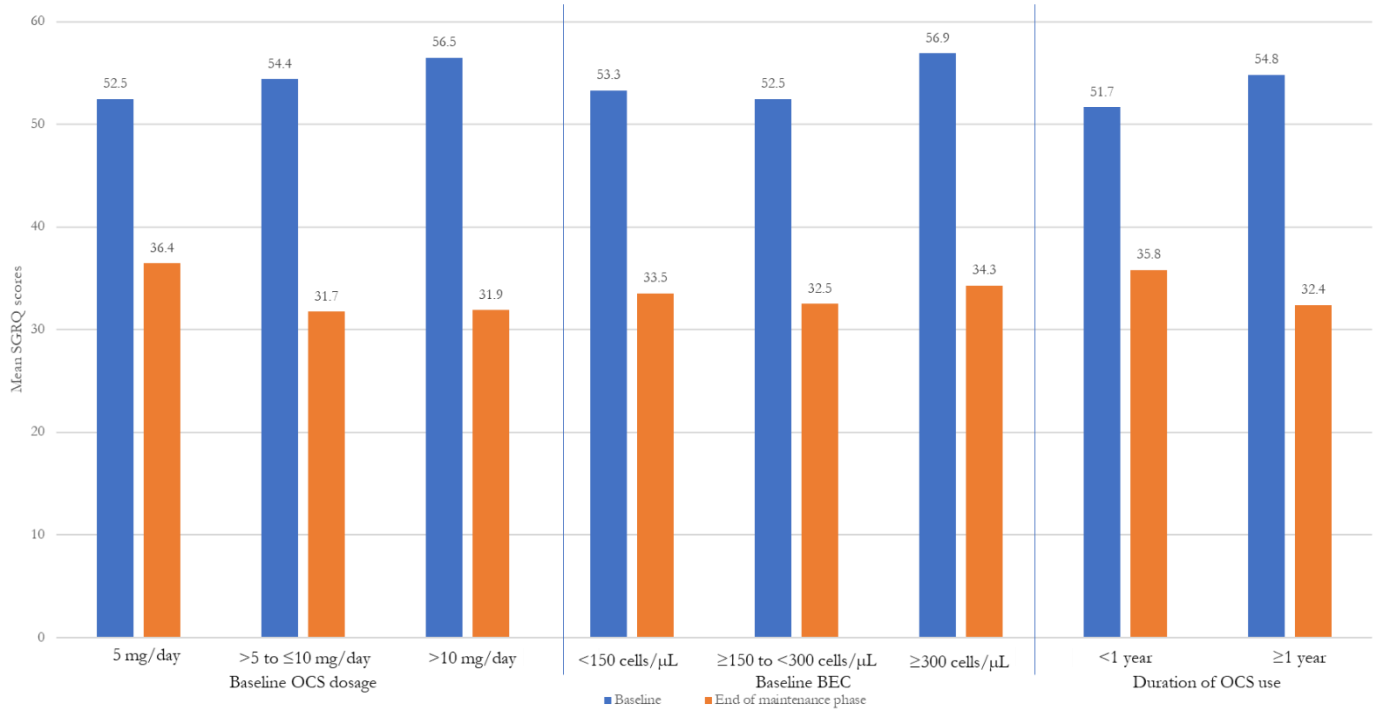
EOT, end of study; OCS, oral corticosteroid.

Supplementary Figure 5. ACQ-6 scores throughout study period according to patient subgroups



ACQ-6, Asthma Control Questionnaire 6; BEC, blood eosinophil count; OCS, oral corticosteroid.

Supplementary Figure 6. SGRQ scores throughout study period according to patient subgroups



BEC, blood eosinophil count; OCS, oral corticosteroid; SGRQ, St. George's Respiratory Questionnaire.