



# Adrenal function recovery after durable oral corticosteroid sparing with benralizumab in the PONENTE study

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Shareable abstract (@ERSpublications)

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. <https://bit.ly/3PjOEnG>

Cite this article as: Menzies-Gow A, Gurnell M, Heaney LG, *et al.* Adrenal function recovery after durable oral corticosteroid sparing with benralizumab in the PONENTE study. *Eur Respir J* 2022; 60: 2103226 [DOI: 10.1183/13993003.03226-2021].

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Received: 22 Dec 2021  
Accepted: 4 July 2022

## Abstract

**Background** Oral corticosteroid (OCS) dependence among patients with severe eosinophilic asthma can cause adverse outcomes, including adrenal insufficiency. PONENTE's OCS reduction phase showed that, following benralizumab initiation, 91.5% of patients eliminated corticosteroids or achieved a final dosage  $\leq 5$  mg·day<sup>-1</sup> (median (range) 0.0 (0.0–40.0) mg).

**Methods** The maintenance phase assessed the durability of corticosteroid reduction and further adrenal function recovery. For ~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 OCS dosage, Asthma Control Questionnaire (ACQ)-6 and St George's Respiratory Questionnaire (SGRQ), as well as adrenal status, asthma exacerbations and adverse events.

**Results** 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 (range) OCS dosage was unchanged (0.0 (0.0–40.0) mg), 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.



**Conclusions** Most patients successfully maintained maximal OCS reduction while 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, 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 ~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 adrenal insufficiency.

The results of PONENTE's OCS reduction phase 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  $\leq 5$  mg prednisone/prednisolone if adrenal insufficiency was the reason for not further reducing OCS [13]. 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: adrenal insufficiency was detected in 60% of patients at baseline and in 38% at 2–3 months later [13].

After elimination or maximal reduction of OCS, patients entered the maintenance phase. This article details the results of the maintenance phase, which assessed the durability of daily OCS dosage reductions, asthma control and asthma exacerbations over ~6 months after completion of the OCS reduction phase. Adrenal status was re-evaluated for patients with partial or complete adrenal insufficiency 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.

A video abstract of this article is available in the supplementary material.

### Methods

#### Patients

PONENTE (ClinicalTrials.gov: NCT03557307) was an open-label, multicentre, 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 ( $\geq 18$  years old) with SEA who, prior to the start of the study, were using high-dosage inhaled corticosteroids (ICS) plus long-acting  $\beta_2$ -agonists (LABA) for at least 6 months and an OCS dosage equivalent of  $\geq 5$  mg daily for at least 3 months with a stable dosage for at least 4 weeks. Patients were required to have a blood eosinophil count (BEC)  $\geq 150$  cells  $\cdot \mu\text{L}^{-1}$  at study entry or  $\geq 300$  cells  $\cdot \mu\text{L}^{-1}$  in the previous 12 months.

#### Study design

Following enrolment, patients received benralizumab 30 mg every 4 weeks for three doses and then every 8 weeks (supplementary figure S1). 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 S2) [12]. PONENTE's protocol did not allow changes to background medications, including ICS and LABA, during the study [12].

HPA axis function was assessed after patients reached a stable daily OCS dosage of 5 mg for 4 weeks; thereafter, the OCS dosage was titrated downward according to adrenal status and asthma clinical status (supplementary figure S3) [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 adrenal insufficiency more frequently than the supraphysiological 250-µg test in suspected secondary/tertiary adrenal insufficiency. 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 (*e.g.* 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 adrenal insufficiency, including glucocorticoid-induced adrenal insufficiency [16–18], and the assessment protocol utilised in PONENTE mitigated these factors and aligned with clinical practice. The cut-offs chosen to denote normal adrenal function and partial and complete adrenal insufficiency 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 adrenal insufficiency. During the maintenance phase, patients continued benralizumab 30 mg every 8 weeks for three more doses (~24–32 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 (ACQ)-6 on a weekly basis beginning at baseline (week 0, before the first benralizumab dose). The SGRQ was assessed at baseline and at the EOT visit. The validity of the 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 adrenal insufficiency, 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 end-points [12, 13]. Analyses were descriptive only and no p-values were calculated. Continuous variables were summarised using the mean, two-sided 95% confidence interval of the mean, standard deviation, median and range or interquartile range (IQR). Categorical variables were summarised using frequency counts and percentages as well as a two-sided 95% confidence interval for proportions computed using the exact Clopper–Pearson method.

Time to dosage event data were analysed using Kaplan–Meier methods. Time (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 was calculated using a time-based approach:  $365.25 \times \text{total number of exacerbations} / \text{total duration of follow-up (days)}$ .

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

## Results

### Patients

Of 598 patients who entered the OCS reduction phase (supplementary figure S4) [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 (range) OCS dosage was 10.0 (5.0–60.0) mg daily and the median (IQR) ICS dosage was 1000.0 (500.0–1000.0) µg fluticasone propionate-equivalent daily (supplementary table S1) [13]. 62 patients (10.4%) withdrew from the study, including two 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 (range) OCS dosage was 0.0 (0.0–40.0) mg, for both. 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 S2).

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 seven (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 0–32 among the entire population (figure 1), and across patient subgroups stratified by baseline BEC, baseline OCS dosage and duration of OCS use (supplementary table S3).

### 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  $\leq 0.75$ ). Changes in ACQ-6 scores were consistent across patient subgroups stratified by baseline BEC, baseline OCS dosage and duration of OCS use (supplementary figure S5). More than half of patients achieved a clinically meaningful improvement in asthma control (defined as a decrease of at least 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

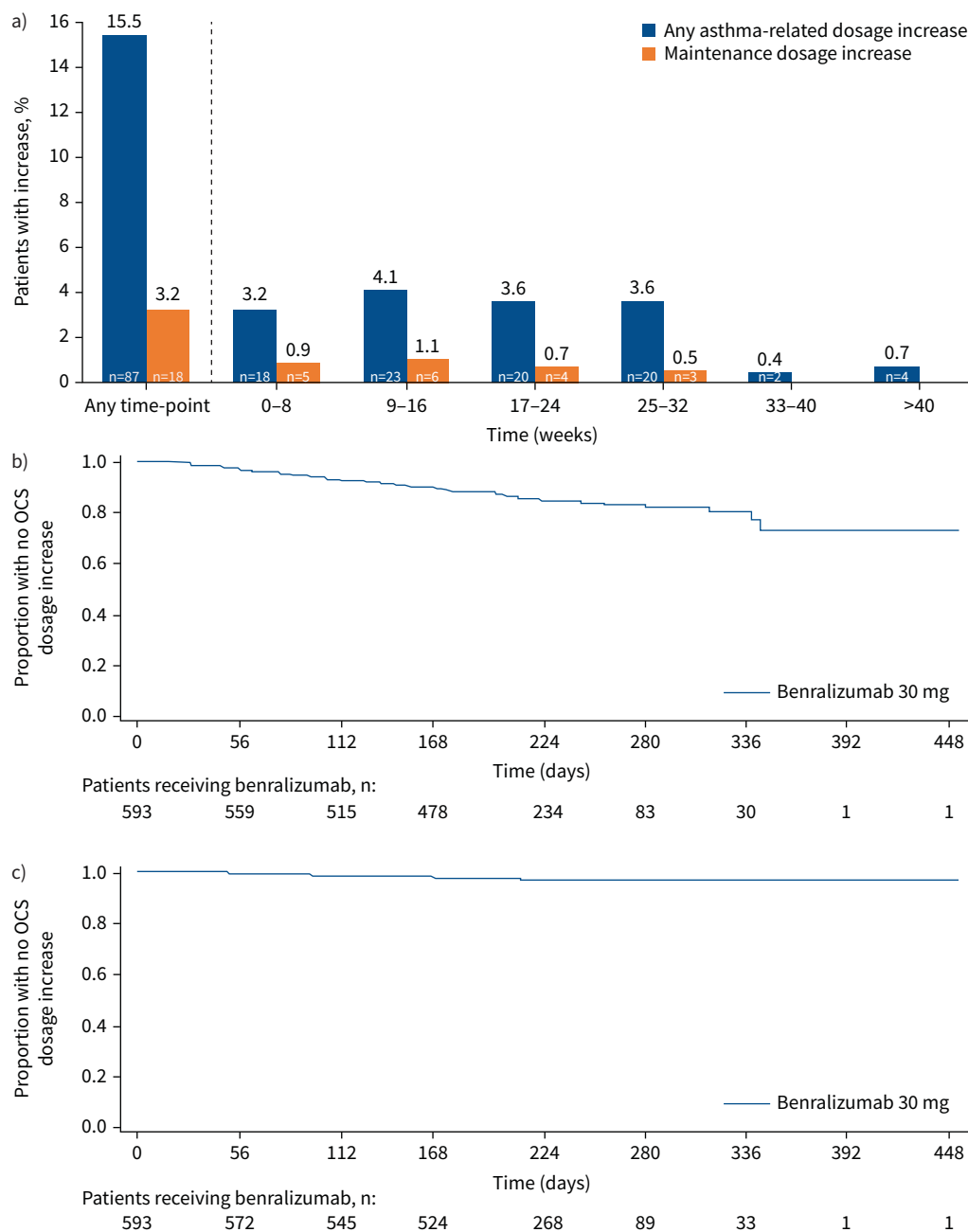
The majority of patients were exacerbation free during the maintenance phase (n=476 (84.5%)) (table 2). 25 patients (4.4%) experienced a total of 29 exacerbations leading to hospitalisation or an emergency room visit during the maintenance phase.

### 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  $-21.7$ – $-17.6$ )) (table 3). Changes in the SGRQ were consistent across patient subgroups stratified by baseline BEC, baseline OCS dosage and duration of OCS use (supplementary figure S6). At the EOT visit, 284 (47.5%) patients achieved a clinically meaningful improvement in QoL (defined as a decrease of at least 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



**FIGURE 1** Time to oral corticosteroid (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 adrenal insufficiency. 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.

entered the maintenance phase with partial adrenal insufficiency and 109 (20.5%) entered with complete adrenal insufficiency; 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 adrenal insufficiency decreased and there was a net increase of 13 with complete adrenal insufficiency (figure 2).

TABLE 1 Asthma control throughout the study period

	Baseline (n=598)	Initial HPA axis assessment <sup>#</sup> (n=598)	End of OCS reduction phase (n=598)	End of maintenance phase (n=598)
Mean (95% CI) ACQ-6 score	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 (range) ACQ-6 score	2.33 (0.0–6.0)	1.17 (0.0–5.5)	1.00 (0.0–5.3)	0.83 (0.0–5.2)
<b>Asthma control status<sup>¶</sup>, n (%)</b>				
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)
<b>Patients achieving a clinically meaningful improvement in asthma control<sup>*</sup>, n (%)</b>		313 (52.3)	367 (61.4)	358 (59.9)

HPA: hypothalamic–pituitary–adrenal; OCS: oral corticosteroid; ACQ: Asthma Control Questionnaire. <sup>#</sup>: the initial HPA axis assessment was completed when patients reached a stable daily dosage of 5 mg for 4 weeks during the reduction phase; <sup>¶</sup>: uncontrolled disease ACQ  $\geq$ 1.5, partially controlled disease ACQ  $>$ 0.75– $<$ 1.5 and well-controlled disease ACQ  $\leq$ 0.75; <sup>\*</sup>: a clinically meaningful improvement was defined as a decrease of at least 0.5 points on the ACQ-6 compared with baseline. 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).

Of 175 patients with partial adrenal insufficiency at initial HPA axis testing, 63 (36.0%) maintained partial adrenal insufficiency 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 adrenal insufficiency at initial HPA axis testing had complete adrenal insufficiency at the final assessment. Of 146 patients with complete adrenal insufficiency initially, nearly one-quarter recovered some degree of adrenal function: 16 (11.0%) recovered to normal function and 20 (13.7%) recovered to partial adrenal insufficiency (figure 3).

### Adverse events

Fewer than half of patients experienced AEs during the maintenance phase (n=252 (44.8%)) (supplementary table S4). Nasopharyngitis was the only AE that occurred in  $>$ 3% of patients (n=34 (6.0%)). 43 (7.6%) patients experienced SAEs, the most common being asthma (n=9 (1.6%)).

TABLE 2 Exacerbations during the maintenance phase and the entire study period

	Maintenance phase (n=563)	Entire study period (n=598)
<b>Patients experiencing exacerbations, n (%)</b>		
0	476 (84.5)	405 (67.7)
1	64 (11.4)	111 (18.6)
2	17 (3.0)	49 (8.2)
$\geq$ 3	6 (1.1)	33 (5.5)
<b>Total exacerbations, n</b>	116	323
<b>AAER</b>		
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)
<b>Patients experiencing exacerbations leading to hospitalisation or ER visit, n (%)</b>	25 (4.4)	59 (9.9)
<b>Total exacerbations leading to hospitalisation or ER visit, n</b>	29	75
<b>AAER leading to hospitalisation or ER visit</b>		
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; ER: emergency room.



TABLE 3 Quality of life (QoL) throughout the study period

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

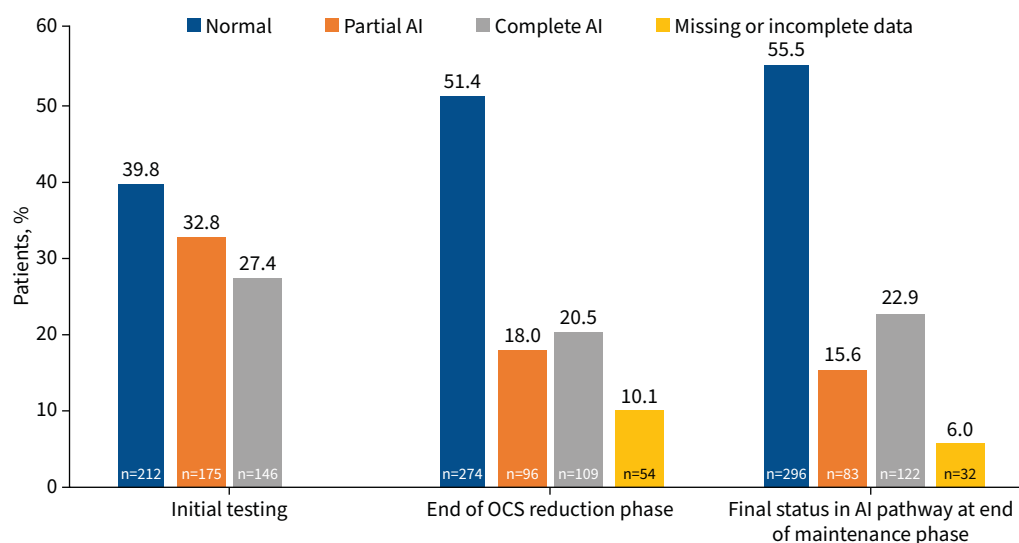
SGRQ: St George's Respiratory Questionnaire. <sup>#</sup>: a clinically meaningful improvement was defined as a decrease of at least 4 points on the SGRQ compared with baseline; a worsening was defined as an increase of at least 4 points. At baseline, 570 patients had SGRQ available data to calculate 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).

There were no reports of adrenal insufficiency or adrenal crisis, but AEs were analysed for potential adrenal insufficiency-related events. (Symptoms that could indicate adrenal insufficiency were adapted from the Society for Endocrinology [23].) 47 (7.9%) patients during the entire study had evidence of any AE that was potentially indicative of adrenal insufficiency, with pyrexia (n=12 (2.0%)) being the most common (supplementary table S4).

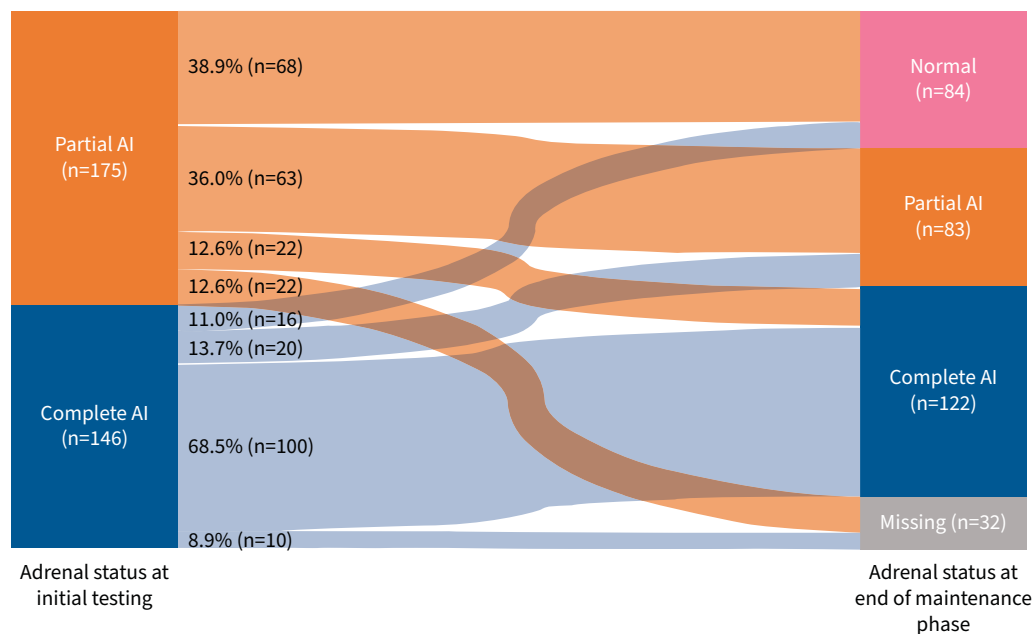
Three (0.5%) participants died during the maintenance phase. One death was attributed to sudden cardiac death, one to cardiac arrest and one to acute myocardial infarction. No deaths were attributed to the study drug or to adrenal insufficiency.

## 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 QoL scores from baseline. Adrenal function further improved in the 6 months after



**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 oral corticosteroid (OCS) dosage of 5 mg and, per protocol, did not undergo assessment of adrenal function, and 14 patients had incomplete or missing assessments. Normal: morning cortisol >350 nmol·L<sup>-1</sup> or adrenocorticotropic hormone (ACTH) stimulation test >450 nmol·L<sup>-1</sup>; partial adrenal insufficiency (AI): ACTH stimulation test 250–450 nmol·L<sup>-1</sup>; complete AI: morning cortisol <100 nmol·L<sup>-1</sup> or ACTH stimulation test <250 nmol·L<sup>-1</sup>.



**FIGURE 3** Changes in adrenal status during the study period (n=321). Normal: morning cortisol  $>350 \text{ nmol}\cdot\text{L}^{-1}$  or adrenocorticotropic hormone (ACTH) stimulation test  $>450 \text{ nmol}\cdot\text{L}^{-1}$ ; partial adrenal insufficiency (AI): ACTH stimulation test  $250\text{--}450 \text{ nmol}\cdot\text{L}^{-1}$ ; complete AI: morning cortisol  $<100 \text{ nmol}\cdot\text{L}^{-1}$  or ACTH stimulation test  $<250 \text{ nmol}\cdot\text{L}^{-1}$ .

the end of the OCS reduction phase for some patients, even returning to normal in some who initially had complete adrenal insufficiency.

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  $<150 \text{ cells}\cdot\mu\text{L}^{-1}$  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 the 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 [20, 26–31]: 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 adrenal insufficiency remained with partial adrenal insufficiency or improved to normal adrenal



function, although a small number had function that worsened to complete adrenal insufficiency from partial adrenal insufficiency 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 adrenal insufficiency classification without this representing a true physiological or clinically relevant change. Second, some patients may have experienced an increase in cumulative corticosteroid exposure due to increased adherence to ICS upon entering the study or owing to intercurrent illness or exacerbations requiring bolus steroid dosing. This complexity reinforces the importance of evaluating adrenal function while tapering long-term corticosteroids, especially in patients with evidence of partial adrenal insufficiency. In PONENTE, patients with evidence of adrenal insufficiency at the end of the maintenance phase were recommended for referral to an endocrinologist for continued care.

The prevalence of adrenal insufficiency 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 adrenal insufficiency. The risk of adrenal insufficiency likely increases with higher OCS dosages and longer durations of use [7]. PONENTE further elucidates the extent of adrenal insufficiency 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, 32]. PONENTE also provides an algorithm for monitoring adrenal function while 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 ~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.

### Conclusions

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, while achieving improved asthma control and QoL, experiencing no or few exacerbations, and maintaining or recovering adrenal function.

**Acknowledgements:** Writing and editing assistance, including preparation of a draft manuscript under the direction and guidance of the authors, incorporating author feedback and manuscript submission, was provided by Jennifer Gibson (Kay Square Scientific, Newtown Square, PA, USA). This support was funded by AstraZeneca.

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The PONENTE clinical trial was prospectively registered at ClinicalTrials.gov with identifier number NCT03557307. Data underlying the findings described in this article may be requested in accordance with AstraZeneca's data-sharing policy described at <https://astrazenecagroup-dt.pharmacm.com/DT/Home>

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 attend 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. 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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. 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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 and K. Padilla 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. U.J. Martin was an employee of and stockholder in AstraZeneca at the time of the study. A. Burden was a contract employee of AstraZeneca at the time of the study; her current affiliation is Ardnamhor Consulting Limited, Kilcreggan, UK. E. 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Support statement: This study was funded by AstraZeneca. Funding information for this article has been deposited with the Crossref Funder Registry.

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