# Oral Corticosteroid Tapering During Benralizumab Treatment of Severe, Uncontrolled Eosinophilic Asthma: PONENTE Phase IIIb Clinical Trial

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## Abstract

**Rationale:** In the Phase III ZONDA trial (NCT02075255), benralizumab produced a median 75% reduction from baseline in oral corticosteroid (OCS) dosage (vs. 25% for placebo) while maintaining asthma control for patients with OCS-dependent severe asthma. The OCS tapering speed in ZONDA with its relatively short trial duration (28 weeks) perhaps did not provide enough time for patients receiving baseline prednisone >12.5 mg/day to eliminate OCS use. The PONENTE (NCT03557307) trial builds on ZONDA and other OCS-sparing studies. PONENTE has a more aggressive steroid reduction schedule for prednisone doses ≥7.5 mg/day than previous studies, and it includes an evaluation of adrenal insufficiency (AI) and an algorithm to specifically taper OCS dosage when prednisone is ≤5 mg/day. It also has a longer maintenance phase to assess OCS reduction up to 6 months after completing OCS tapering.

**Methods:** PONENTE is an open-label study divided into three phases. Patients will receive benralizumab 30 mg subcutaneously (first three doses every 4 weeks, then every 8 weeks [Q8W]). OCS reduction is initiated after the second benralizumab dose and will be dependent on baseline OCS use/loss of asthma control until reaching ≤5 mg/day OCS. Following 4 weeks at ≤5 mg/day, further OCS reduction will also be dependent on cortisol concentration and AI status (evaluated by hypothalamic-pituitary-adrenal axis integrity) assessed by ACTH stimulation testing. Adult patients with asthma receiving high-dosage inhaled corticosteroids/long-acting $\beta_2$-agonists (≥6 months before enrollment) and OCS (≥5 mg/day prednisone stable dosage for ≥4 weeks before enrollment), and with blood eosinophil counts of ≥150 cells/μL or ≥300 cells/μL at enrollment and 12 months before, respectively.

**Results:** PONENTE aims to enroll ~600 patients in ~180 clinical centers worldwide. The trial started on August 1, 2018, and planned completion is October 2020. The two primary endpoints are 1) the number of patients achieving 100% reduction in daily OCS, and 2) the number of patients achieving 100% reduction in daily OCS or achieving ≤5 mg/day dosage, if AI prevented further reduction. Safety and change from baseline in health-related quality of life will also be assessed.

**Conclusions:** PONENTE will provide valuable guidance for clinicians on tapering OCS dosage following benralizumab introduction for the treatment of OCS-dependent patients with severe, uncontrolled eosinophilic asthma, including management of AI. These results aim to direct future clinical practice on OCS tapering following introduction of biologics, and potentially drive guideline changes.

## Rationale

- Oral corticosteroids (OCS) are used to treat asthma exacerbations and as maintenance treatment for patients with severe, uncontrolled asthma at risk of exacerbations[1,2]
- An estimated 32–45% of patients with severe asthma rely on recurrent or maintenance OCS use,[3,4] which is associated with adverse events (AEs)[2,5]
- Long-term OCS use can also suppress the hypothalamic-pituitary-adrenal (HPA) axis, potentially resulting in adrenal insufficiency (AI)[6,7]
- Studies have demonstrated that biologic treatment for patients with severe asthma can enable successful reduction or elimination of OCS use without loss of asthma control (benralizumab [ZONDA],[8] mepolizumab [SIRIUS],[9] dupilumab [LIBERTY ASTHMA VENTURE][10])
- However, established methodology for the safe tapering of OCS dosage following biologic initiation has yet to be confirmed
- In the Phase III ZONDA trial, while maintaining asthma control, OCS dosage was reduced with benralizumab treatment from baseline to Week 28 by a median of 75% compared with a 25% reduction with placebo[8]
- The potential for down-titration for patients receiving benralizumab and baseline prednisone >12.5 mg/day was not fully studied in ZONDA because of the relatively short OCS tapering timeline (28 weeks)

## Aim

PONENTE (NCT03557307) is a Phase IIIb trial designed to evaluate additional parameters not investigated in ZONDA on the efficacy and safety of tapering OCS use after initiating benralizumab treatment for adult patients with severe, uncontrolled asthma with eosinophilic inflammation. Evaluated parameters will include safe OCS tapering speed, AI monitoring, and symptom control maintainance following OCS reduction.

## Methods

- PONENTE is an ongoing multicenter, open-label, Phase IIIb study that aims to enroll approximately 600 patients in approximately 180 clinical centers worldwide
- Participating countries include Argentina, Belgium, Brazil, Canada, Colombia, Denmark, France, Germany, Italy, Mexico, Poland, Russian Federation, Spain, Sweden, Taiwan, United Kingdom, and the United States
- The trial began enrolling on August 1, 2018, with planned study completion in October 2020

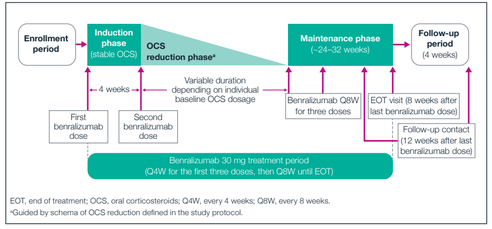
### Study Participants

- Eligibility requirements include:
  - Physician-diagnosed asthma
  - ≥18 years of age
  - High-dosage inhaled corticosteroid (ICS; fluticasone propionate or equivalent >500 μg/day) plus long-acting $\beta_2$-agonist (LABA) use for ≥6 months before enrollment
  - Long-term OCS therapy (prednisone ≥5 mg/day) for ≥3 continuous months (alternate OCS dosing, dosing frequency, and therapy will be allowed if the average daily dosage is equivalent to prednisone ≥5 mg and the patient is switched to daily prednisone/prednisolone at Visit 1)
  - Stable OCS dosage for ≥4 weeks before enrollment
  - Blood eosinophil count ≥150 cells/μL at enrollment or ≥300 cells/μL in the 12 months before enrollment

### Study Design

- From Week 0, patients will receive benralizumab 30 mg by subcutaneous injection every 4 weeks (Q4W) for the first three doses, then every 8 weeks
- Patients will receive benralizumab at the first induction phase visit and throughout the induction phase, OCS tapering phase, and maintenance phase, and will continue their baseline ICS plus LABA maintenance therapy during the study (**Figure 1**)
- During the enrollment period, patients receiving OCS other than prednisone/prednisolone will be switched to this treatment

**Figure 1. PONENTE Study Design**




EOT, end of treatment; OCS, oral corticosteroids; Q4W, every 4 weeks; Q8W, every 8 weeks.
*Guided by schema of OCS reduction defined in the study protocol.

### Oral Corticosteroid Tapering Protocol

- OCS tapering will begin at Week 4. OCS dosage will be reduced according to a schedule depending on baseline OCS dosage, until a dosage of 5 mg/day is achieved (**Figure 2**).

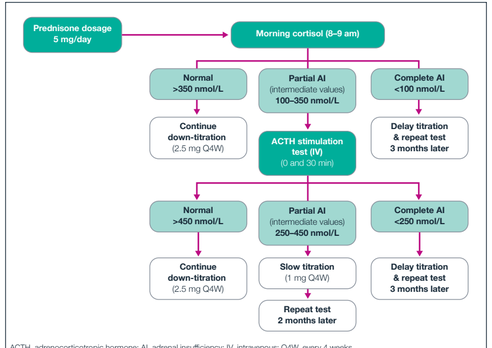
**Figure 2. OCS Down-Titration Schema**

| Baseline prednisone dosage | OCS down-titration schema, until reaching 5 mg/day without asthma deterioration<br>OCS reduction until reaching a prednisone dosage of… | | | | Rescue down-titration after recovering from asthma exacerbation or deterioration<br>OCS reduction until reaching a prednisone dosage of… | |
|---|---|---|---|---|---|---|
| | 20 mg/day | 10 mg/day | 7.5 mg/day | 5 mg/day | 10 mg/day | 5 mg/day |
| >20 mg/day | 5 mg/day Q1W | 5 mg/day Q2W | 2.5 mg/day Q2W | 2.5 mg/day Q4W | 5 mg/day Q4W | 2.5 mg/day Q4W |
| >10–≤20 mg/day | | 5 mg/day Q2W | 2.5 mg/day Q2W | 2.5 mg/day Q4W | 5 mg/day Q4W | 2.5 mg/day Q4W |
| >7.5–≤10 mg/day | | | 2.5 mg/day Q2W | 2.5 mg/day Q4W | | |
| >5–≤10 mg/day | | | | | | 2.5 mg/day Q4W |
| >5–≤7.5 mg/day | | | | 2.5 mg/day Q4W | | |

OCS, oral corticosteroids; Q1W, every week; Q2W, every 2 weeks; Q4W, every 4 weeks.

- The speed of OCS tapering will also depend on the patient's degree of asthma control (investigator assessed, based on patient-reported information, Asthma Control Questionnaire 6 [ACQ-6] scores, compliance with maintenance asthma therapy, and asthma exacerbations)
- An HPA axis integrity evaluation for AI will be performed for patients who reduce their OCS dosages to 5 mg/day and maintain this dosage for 4 weeks (**Figure 3**). Further tapering will depend on AI status.

**Figure 3. Hypothalamic-Pituitary-Adrenal Axis Evaluation**




ACTH, adrenocorticotropic hormone; AI, adrenal insufficiency; IV, intravenous; Q4W, every 4 weeks.
If there are some signs/symptoms of AI, regardless of cortisol concentrations, physicians are allowed to reduce OCS more slowly (1 mg/Q4W).

- Patients experiencing their first asthma exacerbation or deterioration may continue OCS reduction after recovery on a slower schedule, based on investigators' judgment (**Figure 2**)
- OCS tapering will cease for patients experiencing their second asthma exacerbation or deterioration (patients will continue their same dosages or return to a dosage one step greater than the one prescribed before the exacerbation)

### Adrenal Insufficiency Analysis

- For patients with cortisol concentrations less than the normal range but more than the complete AI range (partial AI), an adrenocorticotropic hormone (ACTH) stimulation test (Synacthen®, Cortrosyn™) will be performed within 1 week of cortisol test results
- For patients without evidence of AI, as assessed by morning cortisol or ACTH stimulation test, OCS dosage will be reduced by 2.5 mg Q4W
- For patients with partial AI or symptoms suggestive of AI in the absence of abnormal AI tests, OCS tapering will follow a speed of 1 mg Q4W, and the test will be repeated 2 months later
  - If test results are normal, OCS dosage is potentially reduced directly to 0 mg/day (if the patient is receiving ≤3 mg/day)
  - If the patient is still at risk, OCS dosage of 1 mg Q4W will be continued
- No further OCS tapering will be allowed for patients experiencing complete AI based on two tests performed 3 months apart
  - If morning cortisol test results after 3 months indicate risk of AI, reduction will be 1 mg Q4W
  - If test results are normal, reduction will be 2.5 mg Q4W

### Maintenance Phase

- Patients who completely cease OCS use or are maintained on the lowest OCS dosage possible without occurrence of AI or loss of asthma control will enter the 6-month maintenance phase
- OCS dosage increase is allowed if asthma worsens during this phase

### Safety Assessments

- Safety will be monitored at each study center visit from enrollment to the follow-up visit at the end of the study
- Glucocorticoid toxicity index (GTI) will be measured at the induction phase, when patients achieve an OCS dosage ≤5 mg/day, and at the end of treatment or discontinuation

### Outcome Measures

- PONENTE has two primary efficacy endpoints:
  - Whether patients achieve 100% reduction in daily OCS dosage that is maintained for ≥4 weeks without asthma worsening
  - Whether patients achieve 100% reduction in daily OCS dosage or a daily OCS dosage ≤5 mg, if the reason for no further OCS reduction is AI, that is maintained for ≥4 weeks without asthma worsening
- Key supportive variables for primary efficacy endpoints include:
  - Patients who achieve daily OCS dosage ≤5 mg that is sustained over ≥4 weeks without worsening of asthma
  - Patients who achieve ≥90%, ≥75%, and ≥50% reduction in daily OCS dosage that is sustained over ≥4 weeks without worsening of asthma
  - Change from baseline in daily OCS dosage (mg) from start to end of the OCS reduction phase
- Secondary efficacy endpoints include:
  - Sustained reduction of daily OCS dosage with benralizumab while maintaining asthma control for approximately 6 months after the end of OCS tapering (maintenance phase)
  - Effect of this treatment schedule on patients' asthma control and health-related quality of life (measured by ACQ-6 and St. George's Respiratory Questionnaire)
  - Daily OCS dosage reduction during both the OCS tapering and maintenance phases
- Safety outcomes include the incidence of complete AI, annualized severe asthma exacerbation rate/rate leading to hospitalizations/emergency department visits, AEs, severe AEs, GTI, laboratory parameters, and vital signs

## Conclusions

- PONENTE will evaluate a protocol for OCS tapering, including reduction to less than the physiological dosage of prednisone or equivalent 5 mg/day, following benralizumab initiation for OCS-dependent patients with severe eosinophilic asthma
- PONENTE will be the largest OCS-sparing trial for patients with severe asthma conducted to date and the first to directly address AI management
- Several other advantages of PONENTE over previous studies on OCS reduction following the initiation of biologic therapy include:
  - Personalized and more rapid OCS tapering schedule that depends on baseline OCS dosage and degree of asthma control
  - Detailed safety methodology for AI monitoring during OCS reduction to <5 mg/day
  - Significantly longer maintenance phase (approximately 24–34 weeks vs. 4 weeks for published studies of other biologics)
- PONENTE results will provide valuable guidance for clinicians on tapering OCS dosage for patients being treated with benralizumab

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