

## **Supplementary Material S3. Study restrictions**

### **1. Permitted medications, medication withholding and study restrictions**

The use of the following medications was permitted between study visits, provided that they were maintained at a stable dose during the study and were withheld prior to visit 1 (screening 1), visit 2, and visit 4 and for the durations specified:

- Theophylline for at least 24 hours
- Long-acting  $\beta$ 2-agonists (e.g., formoterol, salmeterol) for at least 24 hours
- Short-acting  $\beta$ 2-agonists (e.g., salbutamol) for at least 8 hours. Rescue salbutamol was allowed for as-needed use at any time during the study, however, if rescue salbutamol was used within 8 hours of a study visit the visit was to be rescheduled.
- Short-acting anticholinergics (e.g., ipratropium) for at least 8 hours
- Combination short-acting bronchodilators (e.g., salbutamol/ipratropium) for at least 8 hours
- Long-acting anticholinergics (e.g., tiotropium) for at least 48 hours
- Inhaled steroids (e.g., fluticasone, budesonide) for at least 48 hours
- Combinations of inhaled steroids and long-acting  $\beta$ 2-agonists (e.g., fluticasone/salmeterol, budesonide/formoterol) for at least 48 hours prior to study visits

These medications could be administered after lung function procedures at all visits.

### **2. Permitted medications**

The following medications could be taken during the course of the study. Any medications not listed were subject to approval by the investigator:

- Inhaled steroids (if the dose had been stabilized for at least 6 weeks prior to the screening visit and was stable throughout the study period)
- Topical or ophthalmic corticosteroids
- Contraceptives

### **3. Prohibited medications**

Use of the following medications was prohibited during the course of the study:

- Systemic corticosteroids (for 3 months prior to and for the duration of the study)
- Intranasal corticosteroids (for 3 months prior to and for the duration of the study)

### **4. Study restrictions**

Subjects were required to:

- Abstain from consuming products containing poppy seeds for the 7 days prior to visit 1
- Abstain from drinking alcohol for the 48 hours prior to all visits
- Abstain from strenuous physical activity (defined as anything different from the subject's normal physical routine) for the 3 days prior to all visits
- Attend all study visits after a light breakfast
- Abstain from intake of any food or drink containing caffeine for the 8 hours prior to all lung function testing

- Abstain from eating foods rich in nitrates for the 24 hours prior to visits 2 and 4
- Abstain from blood donation during the study, unless as part of study procedures
- Not use any prohibited medication
- Females were to avoid becoming pregnant for the duration of the study