A multicenter, randomized, double-blind, placebo-controlled 3-period complete cross-over study to assess the bronchodilator effects and safety of glycopyrronium bromide (NVA237) (25 µg and 50 µg o.d.) in asthma patients

Statistical Analysis Plan (SAP)

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**List of abbreviations**

**AE**  Adverse event

**ALT**  Alanine Aminotransferase

**AST**  Aspartate Aminotransferase

**AUC**  Area Under the Curve

**BMI**  Body Mass Index

**BUN**  Blood Urea Nitrogen

**DBP**  Diastolic Blood Pressure

**ECG**  Electrocardiogram

**eCRF**  Electronic Case Report Form

**eDiary**  Electronic Diary

**FAS**  Full Analysis Set

**FEV\(_1\)**  Forced Expiratory Volume in 1 Second

**FVC**  Forced Vital Capacity

**h**  Hour

**ICS**  Inhaled Corticosteroid

**LABA**  Long Acting Beta-2 Agonist

**LFT**  Liver Function Test

**MedDRA**  Medical Dictionary for Drug Regulatory Affairs

**min**  minutes

**µg**  Microgram

**o.d.**  Once Daily

**PEF**  Peak Expiratory Flow

**PK**  Pharmacokinetics

**PPS**  Per-Protocol Set

**PT**  Preferred Term

**QTc**  Corrected QT interval

**RAN**  Randomized Set

**SAE**  Serious Adverse Event

**SAP**  Statistical Analysis Plan

**SAS**  Statistical Analysis System

**SBP**  Systolic Blood Pressure

**SGOT**  Serum Glutamic Oxaloacetic Transaminase

**SGPT**  Serum Glutamic Pyruvic Transaminase

**SOC**  System Organ Class

**TFLs**  Table, Figure, Listing

**ULN**  Upper Limit of Normal
1 Introduction

This document contains details of the statistical methods that will be used in the phase IIb clinical trial CQVM149B2204. This study is designed to evaluate the bronchodilator effects and safety of two doses (25 µg and 50 µg o.d.) of glycopyrronium bromide (NVA237) compared to placebo in asthma patients.

Data will be analyzed according to Section 9 of the study protocol.

Important information is given in the following sections and details are provided, as applicable, in section 5: Appendix.

1.1 Study design

This study uses a randomized, double-blind, placebo controlled, 3-period cross-over clinical trial design to assess the bronchodilator effects and safety of two doses (25 µg and 50 µg o.d.) of glycopyrronium bromide (NVA237) compared to placebo in asthma patients (Figure 1).

Approximately 144 male and female patients will be randomized into one of the following six treatment sequence in a ratio of 1:1:1:1:1:1, expecting 24 patients allocated to each of the treatment sequences. It is intended that approximately 115 patients will complete the study. Each treatment sequence consists of 3 treatment periods during which study drug will be administered in the sequence as laid forth in Table 1. Detailed information regarding sample size calculation is provided in section 3.

This study will enroll patients at multiple centers multi-nationally. Patients will not be stratified to any prognostic or non-prognostic factors.

No interim analysis for efficacy is planned in this study. An independent Data Monitoring Committee (DMC) will not be formed to review any blinded / semi-blinded data.
During a screening epoch, patient eligibility will be assessed. The screening epoch will be followed by a 21-day Run-in epoch during which patients will continue ICS use but be withdrawn from LABA-treatment and switched to short-acting bronchodilator-rescue medication. After the Run-in period, patients will be randomized to one of the 6 treatment sequences and enter the first 7-day study treatment period.

Treatment period one is followed by a 10-day washout period after which patients begin the second 7-day treatment period which is then followed by a second 10-day washout period followed by the third 7-day treatment period. At the end of each treatment period spirometry will be performed to assess the primary endpoint. Procedures in treatment periods two and three mirror-image the procedures of treatment period one.

### 1.2 Study objectives and endpoints

#### 1.2.1 Primary objective

The primary objective of this study is to evaluate the bronchodilator effects of NVA237 delivered by the Concept1 single-dose dry-powder inhaler in patients with asthma in terms of trough FEV₁ (mean of 23 h 15 min and 23 h 45 min post-dose) following 1 week of treatment, by comparing NVA237 at a dose of 25 µg and 50 µg o.d. with placebo.
1.2.2 Secondary objective(s)

Secondary objectives will evaluate the bronchodilator effects of each dose of NVA237 (25 μg and 50 μg o.d.) compared with placebo in terms of:

- Standardized FEV\(_1\) AUC (5 min - 1 h), (5 min - 4 h), and (5 min – 23 h 45 min) after 1 week of treatment in the respective period.
- Peak FEV\(_1\) after 1 week of treatment in the respective period during 5 min to 4 h post-dose.
- FEV\(_1\), Forced Vital Capacity (FVC) and FEV\(_1\)/FVC ratio at all spirometry time-points after 1 week of treatment in the respective period.
- Safety and tolerability of each dose of NVA237 (25 μg and 50 μg o.d.) in the respective period (laboratory tests, vital signs, ECG and adverse events).

To evaluate the bronchodilator effects of each dose of NVA237 (25 μg and 50 μg o.d.) compared with placebo as determined by patient diary data and electronic PEF meter in the respective period in terms of:

- Rescue medication usage over 1 week of treatment.
- Daily morning (pre-medication) and evening peak expiratory flow rate (PEF) over 1 week of treatment.

2 Statistical methods

2.1 Data analysis general information

The final analysis will be performed by [Redacted]. The most recent version of SAS available in the statistical programming environment of [Redacted] will be used for the analysis.

2.1.1 General definitions

Study treatment is the treatment administered in each treatment period (i.e. treatment period 1, treatment period 2, and treatment period 3).

ECG, vital signs and laboratory values which have complete date and time values are assigned to pre or post-dose assessment based on the actual date/time. However, values with missing date/time are assigned to their respective scheduled visit date and time given the visit number and time point are non-missing. If a measurement scheduled as pre-dose is actually performed post-dose, or vice versa, the data will not be used for assessments but will be included in the summaries of the notable values and extreme values.
For efficacy measurements, any measurements scheduled as pre- dose but actually taken post-dose will be set to missing, also any measurements scheduled as post- dose but actually taken pre- dose will be set to missing.

Safety measurements (vital signs) and efficacy data measurements (Spirometry, rescue medication and PEF) will be assigned to the treatment starting in the particular treatment period. Safety data (only AEs) will be assigned to treatment if it starts on or after the time of first administration of study drug in a treatment period but not later than the time of first administration of study drug in subsequent treatment period.

Study day will be defined as the number of days since the date of first dose of study medication. The date of first dose of study medication will be defined as Day 1 and the day before the first dose of study medication was defined as Day -1.

Therefore, for a particular date, study day will be calculated as follows:
- for dates on or after the first date of study medication,
  \[ \text{Study day} = \text{Assessment date} - \text{Date of first dose of study medication} + 1; \]
- for dates prior to the first date of study medication,
  \[ \text{Study day} = \text{Assessment date} - \text{Date of first dose of study medication}. \]

Period day will be defined as the number of days since the date of dose given in start of that particular period. The date of dose given in start of that particular period will be defined as period Day 1 and the day before the dose of study medication was defined as period Day -1 for that period.

Therefore, for a particular date, period day will be calculated as follows:
- for dates on or after the date of dose given in start of particular period,
  \[ \text{Period day} = \text{Assessment date} - \text{Date of dose given in start of that particular period} + 1; \]

Period day will be used for calculation of summary statistics.

### 2.1.1.1 Baseline definition

In general, baseline data is defined as the last assessment taken prior to the first dose of study drug on Day 1.

Checks will be performed to ensure the assessments were indeed taken prior to the first dose of study drug on Day 1. If this assessment is missing or not confirmed to be pre-dose, then baseline data will be set to missing without imputation.
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline assessment</th>
<th>Detail</th>
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<tbody>
<tr>
<td><strong>Trough FEV(_1)</strong></td>
<td>45 min and 15 min prior to dosing at Visit 201 (Day 1)</td>
<td>Average of the FEV(_1) values taken in the clinic at 45 and 15 min prior to dosing at Visit 201 (Day 1)</td>
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<tr>
<td><strong>FVC</strong></td>
<td>45 min and 15 min prior to dosing at Visit 201 (Day 1)</td>
<td>Average of the FVC values taken in the clinic at 45 and 15 min prior to dosing at Visit 201 (Day 1)</td>
</tr>
<tr>
<td>Standardized AUC in FEV(_1) across different time intervals (5 min – 1 h, 5 min – 4 h, 5 min – 23 h 45 min)</td>
<td>45 min and 15 min prior to dosing at Visit 201 (Day 1)</td>
<td>Average of the FEV(_1) values taken in the clinic at 45 and 15 min prior to dosing at Visit 201 (Day 1)</td>
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<tr>
<td><strong>Peak FEV(_1)</strong></td>
<td>45 min and 15 min prior to dosing at Visit 201 (Day 1)</td>
<td>Average of the FEV(_1) values taken in the clinic at 45 and 15 min prior to dosing at Visit 201 (Day 1)</td>
</tr>
<tr>
<td>eDiary data (PEF and rescue medication use)</td>
<td>Assessment at run-in visit 101 prior to dosing at Visit 201 (Day 1)</td>
<td>The average from all non-missing records of PEF or rescue medication use</td>
</tr>
<tr>
<td><strong>Vital signs</strong> (pulse rate and systolic and diastolic blood pressures)</td>
<td>Assessment at screening visit 1</td>
<td></td>
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<tr>
<td><strong>Height and weight</strong></td>
<td>Assessment at screening visit 1</td>
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</table>

Detail descriptions for calculating baseline values are provided in the latter sections.

### 2.1.1.2 Post-baseline measurement

Post-baseline measurements are defined as those assessments after the first dose of study drug. When change from baseline is of interest the following formula will be used for each visit and time-point where baseline and post-baseline values are both available:

\[
\text{Change from baseline} = \text{post baseline value} - \text{baseline value.}
\]

Detail descriptions for calculating post baseline value – baseline value. Detail descriptions for calculating post-baseline values are provided in the latter sections.

### 2.2 Analysis sets

The following analysis sets are defined:

- The Randomized Set (RAN) will consist of all patients who were assigned a randomization number; regardless they actually received study medication. The RAN set will be used for a summary of patient disposition, demographics and baseline characteristics.
• The Full Analysis Set (FAS) will consist of all patients in the RAN who received at least one dose of study medication. Following the intent-to-treat principle, patients in the FAS will be analyzed according to the treatment they were randomized to in the assigned treatment sequence. The FAS will be used in the analysis of all efficacy variables.

• The Per Protocol Set (PPS) will include all patients in the FAS who did not have any major protocol deviations that could affect the primary analysis. The list of major protocol deviations is available in Appendix 5.7. Patients in the PPS will be analyzed according to the treatment they actually received. The PPS will be used for supportive and sensitivity analysis to assess robustness of the primary efficacy analysis.

• The Safety Set will consist of all patients who received at least one dose of study medication. Patients in the Safety Set will be analyzed according to treatment received. The Safety Set will be used in the analysis of all safety variables.

2.3 Patient disposition, demographics and other baseline characteristics

2.3.1 Patient disposition

The number of patients will be summarized by treatment sequence for the RAN set. Patients disposition for the screening epoch (Screened patients) and run-in epoch (Patients who entered run-in) will be summarized including the reasons for discontinuation. The overall number of patients who entered, completed, and discontinued in treatment period will be summarized including the reasons for discontinuation by treatment. The overall number of patients who entered, completed, and discontinued in treatment epoch will be summarized including the reasons for discontinuation by treatment sequence.
The overall number of patients with protocol deviations and protocol deviations that lead to exclusion from analysis sets will be tabulated by deviation category (e.g., selection criteria not met, prohibited concomitant medication, key procedures not performed as per protocol) and treatment sequence.

The number of patients with protocol deviations leading to exclusion from each treatment period will be tabulated by deviation category (e.g., selection criteria not met, prohibited concomitant medication, key procedures not performed as per protocol) and treatment. Number of patients with protocol deviations leading to exclusion from the PPS will be tabulated by deviation category, verbatim term and treatment sequence.

The number of patients included in each analysis set will be tabulated, as well as the reasons for exclusions from analysis sets by treatment.

2.3.2 Patient demographics and baseline characteristics

Demographic and baseline characteristics measured before randomization including age, gender, race, ethnicity, height, weight, body mass index (BMI), relevant medical history, screening spirometry parameters (FEV₁, FVC, FEV₁/FVC), FEV₁ reversibility, predicted and percentage of predicted FEV₁, duration of asthma, history of asthma exacerbations, smoking history, prior concurrent medications (non-asthma and asthma-related), vital signs (systolic and diastolic blood pressure, pulse rate) and QTc using Fridericia’s correction will be summarized by treatment sequence using RAN set. Prior asthma treatment, will be summarized by ICS dose level category (ICS/LABA low, medium and high, No ICS/LABA).

Continuous variables will be summarized using descriptive statistics (number of non-missing data, mean, standard deviation, median, first and third quartiles, minimum, and maximum) and categorical variables will be summarized in terms of the number and percentage of patients in each category including a category for missing data if any.

Medical history will be coded with the Medical Dictionary for Regulatory Activities terminology (MedDRA) using the most recent version at the time of database lock. History/conditions will be summarized for the RAN set by primary system organ class and preferred term and treatment sequence. Verbatim recorded history/conditions will be listed together with the coded terms, date of diagnosis/surgery and whether the problem was ongoing at start of the study.

In addition, medical histories/current medical conditions will be summarized by their status at baseline (current medical conditions, past medical conditions) and primary system organ class. Current medical conditions are defined as those which were reported as "Ongoing" at screening.
2.4 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

2.4.1 Study treatment / compliance

2.4.1.1 Duration of exposure

Duration of exposure for the randomized patients will be calculated as the number of days between the first dose date and the last dose date exposed to particular study treatment for a given period (expressed as: Duration of exposure = Date of last known dose of study treatment – Date of first dose of study treatment + 1).

The duration of exposure (in days) and the number of patients exposed will be summarized by treatment for the safety set as a continuous variable with the standard descriptive statistics.

The number of patients who completed the 3-period crossover study and discontinued prematurely will be shown including the reasons for discontinuation of study treatment.

2.4.2 Prior, concomitant and post therapies

Each medication, either an asthma or non-asthma medication, will have the start and end dates recorded on the eCRF. Separate tables will be provided for medications which were started and stopped prior to the first dose of study drug and medications which were taken after the first dose of the study drug (regardless of whether continued or started after the first dose of study drug).

Asthma medications will be summarized by the route of administration, the recorded prespecified drug subcategories (including types of combination) and the coded preferred terms. The summary will be repeated by showing ingredients instead of preferred terms. Non-asthma medications will be summarized by route of administration and preferred term.

Surgical and medical procedures (non-drug therapies) will be coded using MedDRA and presentations will be done by MedDRA primary system organ class and preferred term, separately for prior procedures and those after start of study drug.

Short acting beta2 agonist (SABA) rescue medication usage (mean number of puffs) during the screening/run-in epoch will be summarized.

2.5 Analysis of the primary objective

2.5.1 Primary endpoint

The primary endpoint is the trough FEV$_1$ (mL) after 1 week of treatment.

The trough FEV$_1$ is defined as the mean of the two FEV$_1$ values measured at 23 h 15 min and 23 h 45 min post-dose of the last study treatment in a given period. For trough FEV$_1$, the mean
baseline measurement is defined as the average of the FEV₁ values taken in the clinic at 45 and 15 min prior to dosing at Visit 201 (Day 1).

2.5.2 Statistical hypothesis, model, and method of analysis

The comparison of NVA237 50 µg and 25 µg o.d. versus placebo will be evaluated by testing the following null hypotheses (H₁₀, H₂₀) versus the alternative hypotheses (H₁ₐ, H₂ₐ):

H₁₀: There is no difference between NVA237 50 µg and placebo treatment groups in term of the trough FEV₁ after 1 week of treatment

H₁ₐ: There is a difference between NVA237 50 µg and placebo treatment groups in term of the trough FEV₁ after 1 week of treatment

H₂₀: There is no difference between NVA237 25 µg and placebo treatment groups in term of the trough FEV₁ after 1 week of treatment

H₂ₐ: There is a difference between NVA237 25 µg and placebo treatment groups in term of the trough FEV₁ after 1 week of treatment

The primary endpoint will be analyzed using a linear mixed-effect model on FAS. The model will include period, treatment, and sequence as fixed effect factors and baseline trough FEV₁ as a covariate and patient within sequence as random factor. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom (Kenward and Roger, 1997). The within-patient correlation will be modeled using the unstructured covariance matrix. If the model does not converge, then the compound symmetric covariance structure will be used in the model. Restricted maximum likelihood method will be used for estimation of variance components in mixed model.

The estimated treatment difference of (NVA237 50 µg – Placebo) and (NVA237 25 µg – Placebo) will be displayed along with the standard error, 2-sided 95% confidence interval (CI), and p-value

2.5.3 Handling of missing values/censoring/discontinuations

If any of the 23 h 15 min and 23 h 45 min values contributing to the trough FEV₁ are collected within 7 days of systemic corticosteroid use, 6 h of rescue medication, or actual measurement times are outside the 22 - 25 hour post-dose time window then the individual FEV₁ value will be set to missing.

If one of the two values is missing (or set to missing) then the remaining non-missing value will be taken as trough FEV₁. If both values are missing, or if the patient withdrew from the study (regardless of the reason for discontinuation) then trough FEV₁ will be regarded as missing in which case the missing value(s) of the patient at the particular visit(s) would not directly contribute to the primary analysis.

The model used for the primary variable is based on missing at random mechanism for the missing values and assesses the treatment effects of trough FEV₁ without explicit imputation.
2.5.4 Supportive analyses

As a sensitivity analysis, a model adding a factor for carry-over will be run to investigate whether relevant carry-over effects were observed.

The estimated treatment difference of (NVA237 50 µg – Placebo) and (NVA237 25 µg – Placebo) will be displayed along with the standard error, 2-sided 95% confidence interval (CI), and p-value.

Also as a supportive analysis, the same model used in the primary analysis will also be performed on the PPS to assess the robustness of the results from the primary analysis.

As a supportive analysis, the same model used in the primary analysis will also be performed on the PPS excluding in addition patients with protocol deviation TRT08 (Patient treated with IMP more than 10 days), to assess the robustness of the results from the primary analysis.

2.6 Analysis of the key secondary objective

There is no key secondary efficacy endpoint in this study.
2.7 Analysis of secondary efficacy objective(s)

2.7.1 Spirometry data other than the primary endpoint

2.7.1.1 Standardized AUC in FEV1 across different time intervals (5 min – 1 h, 5 min – 4 h, 5 min – 23 h 45 min)

AUC: The trapezoidal rule will be used to calculate Standardized AUC in FEV1 for 0-1h, 0-4h, and 0-24 h.

AUC 0-1h will be calculated from 5 min to 1h post dose values.
AUC 0-4h will be calculated from 5 min to 4h post dose values.
AUC 0-24h will be calculated from 5 min to 23h 45min post dose values.

For those patients who have more than one FEV1 assessment, their standardized AUC will be approximated by $\Sigma^{m}_{k=2}(t_k - t_{k-1})*0.5*(y_k + y_{k-1}) / (t_m - t_1)$ where m is the number of assessments, k is an index from 1 to m, $t_k$ denotes the $k^{th}$ out of the m time-points $t_1 < \ldots < t_m$, and $y_k$ denotes the FEV1 value measured at time-point $t_k$. Note that if intermediate assessments are missing then the calculation corresponds to a linear interpolation of the missing assessments.

The same model used in the primary analysis will be used for the Standardized AUC in FEV1 across different time intervals (5 min – 1 h, 5 min – 4 h, 5 min – 23 h 45 min) with FEV1 value taken at 45 and 15 min prior to dosing at Visit 201 (Day 1) as baseline covariate.

2.7.1.2 Peak FEV1 during 5 min – 4 h

Peak FEV1 value during 4 h post dose is defined as the maximum value achieved during 4 hours after the morning post dose, i.e. the values between 5 min and 4 h post dose. If any measurements are missing from 5 min onwards then the peak value will not be calculated.

The same model used in the primary analysis will be used for the Peak FEV1 endpoint with FEV1 value taken at 45 and 15 min prior to dosing at Visit 201 (Day 1) as baseline covariate.

2.7.1.3 FVC at day 7

The missing values will be handled similarly as mentioned for trough FEV1 (See Section 2.5.3). The same model used in the primary analysis will be used for the FVC endpoint at day 7 with FVC value taken at 45 and 15 min prior to dosing at Visit 201 (Day 1) as baseline covariate.

2.7.1.4 FEV1 / FVC

For FEV1 / FVC, baseline value is defined as baseline FEV1 (See Section 2.1.1.1) divided by baseline FVC value taken at 45 and 15 min prior to dosing at Visit 201 (Day 1).

The FEV1 / FVC will be summarized descriptively by time point.
2.7.2 Rescue medication

The number of puffs of the rescue medication use in the last 12-hour is recorded twice daily (morning/evening) by the patient in his/her e-Diary. For rescue medication use, the baseline values are defined in section 2.1.1.1. When calculating the baseline value there is no limitation to the 21 days immediately prior to Day 1 (Visit 201). Missing diary data will not be imputed.

If for the value over the whole day (24 hours) the number of puffs is missing for part of the day (either day-time or night-time) then a half day will be used in the denominator to calculate the average value. Any values > 30 for the number of puffs of rescue medication in a 12 hour period will be set to missing. These high numbers are not realistic and could impact the analyses. If a patient has less than 7 days with non-missing data, then the baseline value will be set to missing.

Post-baseline measurements start with the evening recordings at Day 1 (Visit 201) and end with the morning recordings one day after the last morning dose of treatment period 3. Summary data (i.e., mean values and percentage of days with) will be calculated for one week interval for all period. Summary values will only be calculated if a patient has at least 50% of their diary days with evaluable data for that variable in the period of interest. Similar calculations as for baseline diary data will be done.

The mean daily number of puffs of rescue medication use over one week of treatment for particular treatment period will be summarized by treatment.

The same model used in the primary analysis will be used for the analysis except that baseline trough FEV₁ will be replaced with baseline rescue medication as the covariate.

Rescue medication use during the run-in period (for randomized patients) and the wash-out periods will be listed.

2.7.3 Peak Expiratory Flow Rate (PEF)

An electronic Peak Flow Meter will be given to each patient at visit 101 for the measurement of the morning and the evening PEF during the screening, run-in and treatment periods.

PEF will be measured at consistent times for a patient: in the morning prior to taking study medication and in the evening. Patients should be encouraged to perform the measurements before the use of any rescue medication. At each timepoint the patient should be instructed to perform 3 consecutive maneuvers within 10 minutes. These PEF values are captured in the e-Diary. The best of 3 values will be used for analysis.

PEF (liters/min) will be averaged separately for morning and evening values with means over one week of treatment for each period and the baseline run-in phase.

Baseline values are defined similarly as rescue medication and given in section 2.1.1.1
For post-baseline measurements, similar procedure will be followed, as mentioned for rescue medication use.

The same model used in the primary analysis will be used for the analysis except that baseline trough FEV₁ will be replaced with baseline morning/evening PEF as the covariate.

2.8 Safety analyses

All safety evaluation will be based on the safety set.

2.8.1 Adverse events (AEs)

All adverse events including asthma exacerbations, coded with MedDRA using the most actual version at the time of database lock, will be listed. In general, summaries will include treatment-emergent adverse events (TEAEs) only.

TEAEs are those adverse events starting on or after the time of first administration of study drug in a treatment period but not later than the time of first administration of study drug in subsequent treatment period. AEs are considered as treatment emergent up to 14 days after last dose of study drug of the last period.

Any adverse events that started during a washout period will be assigned to a treatment just prior to that washout period.

Any AEs that started during the study before the time of the first inhalation of study drug will be classified as a prior AE.

The number and percentage of patients who reported treatment-emergent adverse events will be summarized by primary system organ class (SOC), preferred term (PT), and treatment for

- all adverse events
- all adverse events by maximum severity
- adverse events suspected to be related to study drug
- serious adverse events
- adverse events leading to permanent study drug discontinuation

Unless otherwise specified, primary system organ classes will be sorted alphabetically and, within each primary system organ class, the preferred terms will be sorted in descending order of frequency in the NVA237 50 μg treatment. If a patient reported more than one adverse event with the same preferred term, the adverse event will be counted only once. If a patient reported more than one adverse event within the same primary system organ class, the patient will be counted only once at the system organ class level.

In addition, the most frequent adverse events will be presented by preferred term in descending order of frequency in the NVA237 50 μg treatment.
2.8.1.1 Adverse events of special interest / grouping of AEs

2.8.1.2 AE reporting for CT.gov and EudraCT

For the legal requirements of clinicaltrials.gov and EudraCT, two required tables on treatment emergent adverse events which are not serious adverse events with an incidence greater than 2% and on treatment emergent serious adverse events and SAE suspected to be related to study treatment will be provided by system organ class and preferred term on the safety set population.

If for a same patient, several consecutive AEs (irrespective of study treatment causality, seriousness and severity) occurred with the same SOC and PT:

- a single occurrence will be counted if there is ≤ 1 day gap between the end date of the preceding AE and the start date of the consecutive AE
- more than one occurrence will be counted if there is > 1 day gap between the end date of the preceding AE and the start date of the consecutive AE

For occurrence, the presence of at least one SAE / SAE suspected to be related to study treatment / non SAE has to be checked in a block e.g., among AE's in a ≤ 1 day gap block, if at least one SAE is occurring, then one occurrence is calculated for that SAE.

The number of deaths resulting from SAEs suspected to be related to study treatment and SAEs irrespective of study treatment relationship will be provided by SOC and PT.

2.8.2 Deaths

A summary of deaths will be presented by primary system organ class, preferred term, and treatment regardless of study drug relationship.

All the deaths in the clinical database will be listed with the investigator-reported principal cause, presented side by side, but only those between the first treatment up to 30 days after last dose of study drug of the last period will be included in summary tables.

2.8.3 Laboratory data

All laboratory samples will be processed through the central laboratory. Laboratory data consist of hematology, clinical chemistry and urinalysis measurements. All data will be listed with abnormal values flagged.

All data will be summarized by period. As laboratory samples are scheduled pre-dose at Day 1 of the respective period, measurements cannot be assigned to any treatment.

A listing of all patients with notable laboratory and a listings of patients with clinically notable LFT values will be provided.
2.8.4 Other safety data

2.8.4.1 ECG

ECG measurements include ventricular rate, QT interval, RR interval, PR interval, QRS duration, and Fridericia’s QTc (calculated as \(QTcF = QT / 3\sqrt{RR}\) (in seconds), where \(3\sqrt{\text{ denotes the cube root}}\). Furthermore, an overall interpretation of the central cardiologist will be provided as well as a specification of abnormal findings. All data will be listed.

All data will be summarized by period. As ECG is scheduled pre-dose at Day 1 of the respective period, measurements cannot be assigned to any treatment. A listing of all patients with notable QTc values will be provided.

2.8.4.2 Vital signs

Vital signs measurements include systolic and diastolic blood pressure (SBP and DBP), pulse rate, height and body weight (at selected visits only).

Baseline vital signs (systolic and diastolic blood pressure (SBP and DBP), pulse rate) and baseline height and weight are defined in section 2.1.1.1.

Vital signs data measured more than 7 days after last inhalation of study drug are regarded as post-treatment data and will not be summarized, only listed. All data will be included in the analyses regardless of rescue medication use.

The following analyses will be performed by treatment:
- absolute values and change from baseline summarized by parameter, and visit
- the number and percentage of patients by parameter, and visit with
  - pulse rate < 40 bpm, 40 – 90 bpm, and > 90 bpm
  - SBP < 90 mm Hg, 90 – 140 mm Hg, and > 140 mm Hg
  - DBP < 50 mm Hg, 50 – 90 mm Hg, and > 90 mm Hg
- the number and percentage of patients with newly occurring or worsening notable vital signs values (see Section 5.5 for definition of notable values) summarized by parameter (except height and weight), scheduled post-baseline visit and additionally at any time on treatment considering all post-baseline data from scheduled, unscheduled and premature discontinuation visits

The by-visit summaries will include the post-baseline SBP, DBP, and pulse rate values (even if from post-baseline unscheduled and premature discontinuation visits, if not measured more than 7 days after last dose).

For a patient to meet the criterion of a newly occurring clinically notable value, the patient needs to have a baseline value that is not clinically notable for that parameter. For a patient to
meet the criterion of a worsening clinically notable value, the patient needs to have a baseline value that is clinically notable and also have a worse post-baseline value. For patients with missing baseline value, any post-baseline notable value will be considered as newly occurring. A listing of all patients with notable vital sign values and changes will be provided.

2.9 Pharmacokinetic endpoints
Not Applicable

2.10 PD and PK/PD analyses
Not Applicable

2.11 Patient-reported outcomes
Not Applicable

2.12 Biomarkers
Not Applicable

2.14 Interim analysis
No interim analysis will be performed in this study.

3 Sample size calculation
The assumptions to support the sample size calculations were based on 7 historical cross-over studies: NVA237A2205, NVA237A2208, QVA149A2210, QMF149A2202, GSK study HZA113310 (clinicaltrials.gov nr. NCT00980200) and the dose ranging studies with Tiotropium (Beeh et al., 2014) and Umeclidinium (Lee et al., 2015).

The two doses of interest were investigated in studies NVA237A2205 and NVA237A2208. The mean treatment estimates observed in these studies suggest that a treatment difference to Placebo of at least 100 mL in trough FEV₁ could be expected after treatment with glycopyrronium bromide 50 µg o.d. and a treatment difference to Placebo of around 70 mL and up to 90 mL could be expected after treatment with glycopyrronium bromide 25 µg o.d. This is considered conservative estimates as both studies were conducted in COPD patients and asthma patients may be expected to show larger treatment effects.

The within subject standard deviations observed in the above mentioned 7 studies varied substantially between 102 mL and 237 mL. Only those historical studies with a similar patient population were considered (i.e. excluding the Umeclidinium study which enrolled mild
asthmatics). This resulted in a standard deviation of 209 mL being used for powering the current study.

Randomizing 144 subjects and assuming a drop-out rate of up to 20% (i.e. 115 subjects completing the study) the power for the comparison of glycopyrronium bromide 50 µg o.d. with Placebo on a 2-sided 5% level would be 95%. For the comparison of glycopyrronium bromide 25 µg o.d. with Placebo the power would be 71% assuming a true underlying treatment difference of 70mL and 90% for an underlying difference of 90 mL. The sample size was calculated via simulation in a program written in R3.2.2.

No adjustment for multiple comparisons is made.

4 Change to protocol specified analyses

FEV1/FVC ratio will be summarized descriptively only. The same model as for the primary endpoint will not be applied.

Vital signs: Protocol states vital signs will be listed. In addition the following analysis will be performed

- absolute values and change from baseline summarized by parameter, and visit
- the number and percentage of patients by parameter, and visit with
  - pulse rate < 40 bpm, 40 – 90 bpm, and > 90 bpm
  - SBP < 90 mm Hg, 90 – 140 mm Hg, and > 140 mm Hg
  - DBP < 50 mm Hg, 50 – 90 mm Hg, and > 90 mm Hg
- the number and percentage of patients with newly occurring or worsening notable vital signs values (see Section 5.5 for definition of notable values) summarized by parameter (except height and weight), scheduled post-baseline visit and additionally at any time on treatment considering all post-baseline data from scheduled, unscheduled and premature discontinuation visits

Laboratory and ECG data: Protocol states ECG and laboratory data will be listed. In addition descriptive summaries by period will be presented.

5 Appendix

This appendix gives details about statistical methods in addition to the report text. All analyses will be performed by using SAS Version 9.4.

5.1 Imputation rules

5.1.1 Study drug

Missing/partial start date or end date of study treatment will not be imputed.

5.1.2 AE date imputation
Rules for imputing AE end date or start date will be provided in Programming Dataset Specification (PDS) document in details.

5.1.3 Concomitant medication date imputation
Rules for imputing the CM end date or start date will be provided in Programming Dataset Specification (PDS) document in details.

5.1.3.1 Prior therapies date imputation
Missing/partial start date or end date of prior therapies will not be imputed.

5.1.3.2 Post therapies date imputation
Rules for imputing the post therapies end date or start date will be provided in Programming Dataset Specification (PDS) document in details.

5.2 AEs and Concomitant medications coding/grading
The MedDRA version which will be available at the time of database lock, will be used for the coding purpose of the adverse events. For coding purpose of the concomitant medications, the available WHO-DD (World Health Organization- Drug Dictionary) version at the time of database lock, will be used.

5.3 Data pooling and assessment windows
Data from unplanned or unscheduled visits or the early treatment/study discontinuation visits will be listed. For patients who do not complete the study treatment, the treatment discontinuation visit will be an unscheduled visit.

Clinical laboratory measurements, vital signs and ECG data from unplanned or unscheduled visits will only be included in the summaries of the notable values and extreme values. All efficacy data (including spirometry data) from these visits will not be used for missing data imputation unless specified otherwise.

Laboratory, vital signs, and ECG values that have complete data and time values will be slotted into pre- or post-dose assessment based on the actual date/time. For values with missing date/time, scheduled visit date and time will be used. This rule will be applied to data from scheduled visits only. If a measurement scheduled as pre-dose is actually performed post-dose, or vice versa, the data will not be used for by time point assessments.

5.4 Laboratory parameters derivations
The following table shows the criteria for clinically notable laboratory values. Not all parameters have notable criteria defined.
<table>
<thead>
<tr>
<th>Laboratory parameter (unit)</th>
<th>Lower bound of clinically notable range</th>
<th>Upper bound of clinically notable range</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hematology</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematocrit (v/v)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>0.37</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>0.32</td>
<td></td>
</tr>
<tr>
<td>Hemoglobin (g/L)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>115</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>95</td>
<td></td>
</tr>
<tr>
<td>Platelets (x10^9/L)</td>
<td>75</td>
<td>700</td>
</tr>
<tr>
<td>WBC (x10^9/L)</td>
<td>2.8</td>
<td>16.0</td>
</tr>
<tr>
<td><strong>Chemistry</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albumin (g/L)</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Alkaline Phosphatase (U/L)</td>
<td>-</td>
<td>3xULN</td>
</tr>
<tr>
<td>ALT/SGPT (U/L)</td>
<td>-</td>
<td>3xULN</td>
</tr>
<tr>
<td>AST/SGOT (U/L)</td>
<td>-</td>
<td>3xULN</td>
</tr>
<tr>
<td>Bilirubin Total (mcmol/L)</td>
<td>-</td>
<td>34.2</td>
</tr>
<tr>
<td>BUN (mmol/L)</td>
<td>-</td>
<td>9.99</td>
</tr>
<tr>
<td>Creatinine (mcmol/L)</td>
<td>-</td>
<td>176.8</td>
</tr>
<tr>
<td>Glucose (mmol/L)</td>
<td>2.78</td>
<td>9.99</td>
</tr>
<tr>
<td>Gamma GT (U/L)</td>
<td>-</td>
<td>3 x ULN</td>
</tr>
<tr>
<td>Potassium (mmol/L)</td>
<td>3</td>
<td>6</td>
</tr>
</tbody>
</table>

_v = volume, ULN = upper limit of normal_

**Notable liver function test values**

<table>
<thead>
<tr>
<th>Criterion</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT &gt; 3 x the upper limit of normal range (ULN)</td>
</tr>
<tr>
<td>ALT &gt; 5 x ULN</td>
</tr>
<tr>
<td>ALT &gt; 8 x ULN</td>
</tr>
<tr>
<td>ALT &gt; 10 x ULN</td>
</tr>
<tr>
<td>ALT &gt; 20 x ULN</td>
</tr>
<tr>
<td>ALT or AST &gt; 3 x ULN</td>
</tr>
<tr>
<td>ALT or AST &gt; 5 x ULN</td>
</tr>
<tr>
<td>ALT or AST &gt; 8 x ULN</td>
</tr>
<tr>
<td>ALT or AST &gt; 10 x ULN</td>
</tr>
<tr>
<td>ALT or AST &gt; 20 x ULN</td>
</tr>
<tr>
<td>Total bilirubin &gt; 1 x ULN</td>
</tr>
<tr>
<td>Total bilirubin &gt; 1.5 x ULN</td>
</tr>
<tr>
<td>Total bilirubin &gt; 2 x ULN</td>
</tr>
<tr>
<td>Total bilirubin &gt; 3 x ULN</td>
</tr>
<tr>
<td>ALP &gt; 1.5 x ULN</td>
</tr>
<tr>
<td>ALP &gt; 2 x ULN</td>
</tr>
<tr>
<td>ALP &gt; 3 x ULN</td>
</tr>
<tr>
<td>ALP &gt; 5 x ULN</td>
</tr>
<tr>
<td>ALT or AST &gt; 3 x ULN and total bilirubin &gt; 1.5 x ULN</td>
</tr>
</tbody>
</table>
ALT or AST > 3 x ULN and total bilirubin > 2 x ULN
ALT or AST > 5 x ULN and total bilirubin > 2 x ULN
ALT or AST > 8 x ULN and total bilirubin > 2 x ULN
ALT or AST > 10 x ULN and total bilirubin > 2 x ULN
ALT or AST > 20 x ULN and total bilirubin > 2 x ULN
ALP > 3 x ULN and total bilirubin > 2 x ULN
ALP > 5 x ULN and total bilirubin > 2 x ULN
ALT or AST > 3 x ULN and (nausea or vomiting or fatigue or general malaise or abdominal pain or (rash and eosinophilia))*

ALT = alanine aminotransferase, AST = aspartate aminotransferase, ALP = alkaline phosphatase
* Based on the signs/symptoms information as recorded on the liver events eCRF, not the adverse events eCRF.

5.5 Vital signs and ECG – definition of clinically notable values

The following table shows the clinical notable criteria for vital signs.

<table>
<thead>
<tr>
<th>Vital sign parameter (unit)</th>
<th>Lower bound of clinically notable range</th>
<th>Upper bound of clinically notable range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Notable value considering newly occurring or worsening cases</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>&lt; 75</td>
<td>&gt; 200</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>&lt; 40</td>
<td>&gt; 115</td>
</tr>
<tr>
<td>Pulse rate (bpm)</td>
<td>&lt; 40</td>
<td>&gt; 130</td>
</tr>
<tr>
<td>Notable change from baseline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>≤ 90 and decrease from baseline by ≥ 20</td>
<td>≥ 180 and increase from baseline by ≥ 20</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>≤ 50 and decrease from baseline by ≥ 15</td>
<td>≥ 105 and increase from baseline by ≥ 15</td>
</tr>
<tr>
<td>Pulse rate (bpm)</td>
<td>≤ 50 and decrease from baseline by ≥ 15</td>
<td>≥ 120 and increase from baseline by ≥ 15</td>
</tr>
</tbody>
</table>
The following table shows the clinical notable criteria for QTcF.

### Clinical notable criteria for QTcF (Fridericia's formula)

<table>
<thead>
<tr>
<th>ECG parameter (unit)</th>
<th>Clinically notable range</th>
</tr>
</thead>
<tbody>
<tr>
<td>QTc (msec)</td>
<td>&gt; 450 (male)</td>
</tr>
<tr>
<td>QTc (msec)</td>
<td>&gt; 460 (female)</td>
</tr>
<tr>
<td>QTc (msec)</td>
<td>&gt; 500 (both)</td>
</tr>
</tbody>
</table>

#### 5.6 Statistical models

##### 5.6.1 Primary analysis

The following Linear Mixed Model will be used for trough FEV₁, other spirometry endpoints, PEF and rescue medication use:

The primary endpoint and other secondary endpoints will be analyzed using a linear mixed-effect model. The model will include period, treatment, and sequence as fixed effect factors and patients within sequence as random factor and baseline trough FEV₁ as a covariate. Restricted maximum likelihood method will be used. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. The within-patient correlation will be modeled using the unstructured covariance matrix. In case of the analysis failing to converge, compound symmetric covariance structure will be used.

The following Linear Mixed Model will be used for trough FEV₁, other spirometry endpoints, PEF and rescue medication use:

\[
\text{Dependent variable} = \text{intercept} + \text{period} + \text{treatment} + \text{sequence} + \text{baseline value} + \text{random(patient (sequence))} + \text{error.}
\]

Results will be presented with LSM and SE for treatment effects and LSM, SE, associated two-sided 95% confidence interval, and two-sided p-value for treatment differences of each NVA237 dose versus placebo.

The SAS procedure Proc MIXED will be used.

##### 5.6.2 Sensitivity analysis

The following Linear Mixed Model will be used for sensitivity analysis:

The primary endpoint will be analyzed using a linear mixed-effect model. The model will include period, treatment, sequence and carry-over factor as fixed effect factors and patients within sequence as random factor and baseline trough FEV₁ as a covariate. Restricted maximum
likelihood method will be used. The Kenward-Roger approximation will be used to estimate
denominator degrees of freedom. The within-patient correlation will be modeled using the
unstructured covariance matrix. In case of the analysis failing to converge, compound
symmetric covariance structure will be used.

The following Linear Mixed Model will be used for trough FEV₁, other spirometry endpoints,
PEF and rescue medication use:

Dependent variable = intercept + period + treatment + sequence + carry-over factor + baseline
value + random(patient (sequence)) + error.

Results will be presented with LSM and SE for treatment effects and LSM, SE, associated two-
sided 95% confidence interval, and two-sided p-value for treatment differences of each NVA237 dose versus placebo.

The SAS procedure Proc MIXED will be used.

5.6.3 Key secondary analysis
Not Applicable

5.7 Rule of exclusion criteria of analysis sets

Rule of exclusion criteria from analysis sets due to protocol deviations will be included prior to
database lock.
Protocol deviations leading to exclusion from analysis sets.

<p>| INCL01 | Informed consent not obtained or incorrect version signed or obtained after first assessment performed | Exclude from PPS, RAN, FAS and SAF |
| INCL02 | Age less than 18 years or greater than 65 years or missing | Exclude from PPS |
| INCL03 | No current diagnosis of persistent Asthma at least 12 months prior to V1 | Exclude from PPS |
| INCL04 | Patient not treated with any dose of daily ICS/LABA combination or not in stable dose 4 weeks prior to Visit 1 | Exclude from PPS |
| INCL05 | Pre-Bronchodilator FEV1 at V101 or V102 less than 50% or greater than 80% of predicted normal value | Exclude from PPS |
| INCL06 | Reversibility value not met (FEV1 less than 12% or greater than 200 ml) at visit 101 | Exclude from PPS |
| EXCL01 | Patient has a contraindication to study drug or hypersensitivity to any study drug or to similar drugs within the class or any component specified in the protocol | Exclude from PPS |
| EXCL09 | Clinical significant condition compromising patient safety or compliance, interfere with evaluation or preclude completion of the study | Exclude from PPS |
| EXCL12 | Patient had an Asthma attack/exacerbation requiring systemic corticosteroids or hospitalization or ER visits within 6 weeks prior to Visit 1 | Exclude from PPS |</p>
<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
<th>Exclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>EXCL14</td>
<td>Patient with a Respiratory Tract Infection 4 weeks prior to Visit 1</td>
<td>Exclude from PPS</td>
</tr>
<tr>
<td>EXCL15</td>
<td>Patient has a smoking history of &gt; 10 pack years or missing</td>
<td>Exclude from PPS</td>
</tr>
<tr>
<td>EXCL16</td>
<td>Patient smoked or inhaled tobacco within the 6 month period prior to Visit 1</td>
<td>Exclude from PPS</td>
</tr>
<tr>
<td>EXCL17</td>
<td>Patient has a chronic condition affecting the upper respiratory tract that interfere with study evaluation or participation in the trial</td>
<td>Exclude from PPS</td>
</tr>
<tr>
<td>EXCL18</td>
<td>Patient has a history of chronic lung diseases other than asthma</td>
<td>Exclude from PPS</td>
</tr>
<tr>
<td>EXCL19</td>
<td>Patient taking prohibited asthma related medication after the minimum cessation period or taken medication not according to instructions specified in Table 5-2 of protocol prior to visit 101 run in period</td>
<td>Exclude from PPS</td>
</tr>
<tr>
<td>EXCL20A</td>
<td>Patient taking Prohibited medication after the minimum cessation period or taken medication not according to instructions specified in Table 5-3 of protocol prior to visit 101 run in period with impact in efficacy analysis (medical lead decision)</td>
<td>Exclude from PPS</td>
</tr>
<tr>
<td>EXCL21</td>
<td>Patient is on maintenance immunotherapy for allergies for at least 3 months prior to Visit 101 who are expected to change therapy</td>
<td>Exclude from PPS</td>
</tr>
<tr>
<td>EXCL22</td>
<td>Patient unable to use dry powder inhaler device</td>
<td>Exclude from PPS</td>
</tr>
<tr>
<td>EXCL24</td>
<td>Patient using other Investigational drugs within 30 days of Visit 101 or 5 half lives whichever is longer.</td>
<td>Exclude from PPS</td>
</tr>
<tr>
<td>EXCL25</td>
<td>Patient shown intolerable to LABA withdrawal during the Run-in period</td>
<td>Exclude from PPS</td>
</tr>
<tr>
<td>EXCL26</td>
<td>Patient with a history of Paradoxical bronchospasm</td>
<td>Exclude from PPS</td>
</tr>
<tr>
<td>EXCL27</td>
<td>Patient who have discontinued LAMA therapy due to intolerance or lack of efficacy</td>
<td>Exclude from PPS</td>
</tr>
<tr>
<td>EXCL28</td>
<td>Patient where variability in FEV1 value between visit 101 and 102 is &gt; 20%</td>
<td>Exclude from PPS</td>
</tr>
<tr>
<td>COMD03A</td>
<td>Patient taking prohibited asthma related medication or taken medication not according to instructions after the Visit 101 (list specified in Table 5-2 of protocol) with potential impact on key efficacy evaluations of period 1</td>
<td>Exclude from PPS in period 1</td>
</tr>
<tr>
<td>COMD03B</td>
<td>Patient taking prohibited asthma related medication or taken medication not according to instructions after the Visit 101 (list specified in Table 5-2 of protocol) with potential impact on key efficacy evaluations of period 2</td>
<td>Exclude from PPS in period 2</td>
</tr>
<tr>
<td>COMD03C</td>
<td>Patient taking prohibited asthma related medication or taken medication not according to instructions after the Visit 101 (list specified in Table 5-2 of protocol) with potential impact on key efficacy evaluations of period 3</td>
<td>Exclude from PPS in period 3</td>
</tr>
<tr>
<td>COMD04A</td>
<td>Patient taking prohibited medication or taken medication not according to instructions after the Visit 101 (list specified in Table 5-3 of protocol) with potential impact on key efficacy evaluations of period 1</td>
<td>Exclude from PPS in period 1</td>
</tr>
<tr>
<td>COMD04B</td>
<td>Patient taking prohibited medication or taken medication not according to instructions after the Visit 101 (list specified in Table 5-3 of protocol) with potential impact on key efficacy evaluations of period 2</td>
<td>Exclude from PPS in period 2</td>
</tr>
</tbody>
</table>
### Table 5-3 of protocol) with potential impact on key efficacyevaluations of period 2

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>COMD04C</td>
<td>Patient taking prohibited medication or taken medication not according to instructions after the Visit 101 (list specified in Table 5-3 of protocol) with potential impact on key efficacy evaluations of period 3</td>
<td>Exclude from PPS in period 3</td>
</tr>
<tr>
<td>WITH02</td>
<td>Unblinding of study treatment and patient still in the study</td>
<td>Exclude from PPS</td>
</tr>
<tr>
<td>TRT02</td>
<td>Patient received expired treatment.</td>
<td>Exclude from PPS</td>
</tr>
<tr>
<td>TRT03</td>
<td>Patient took more than one daily dose of study drug during treatment period</td>
<td>Exclude from PPS</td>
</tr>
<tr>
<td>TRT04A</td>
<td>Patient took study drug during washout period of period 1</td>
<td>Exclude from PPS in period 2</td>
</tr>
<tr>
<td>TRT04B</td>
<td>Patient took study drug during washout period of period 2</td>
<td>Exclude from PPS in period 3</td>
</tr>
<tr>
<td>TRT05</td>
<td>Patient compliance with daily ICS dose is less than 80%</td>
<td>Exclude from PPS</td>
</tr>
<tr>
<td>OTH01</td>
<td>Patient who received study medication before or without randomization</td>
<td>Exclude from PPS, RAN and FAS</td>
</tr>
<tr>
<td>OTH02</td>
<td>Patient was Randomized but no study drug was taken</td>
<td>Exclude from SAF, FAS and PPS</td>
</tr>
<tr>
<td>OTH03</td>
<td>Severe ICH-GCP non compliance of study site in the study (eg: fraud)</td>
<td>Exclude from PPS, RAN, FAS and SAF</td>
</tr>
</tbody>
</table>

### 6 Reference