

Biostatistics & Statistical Programming /
Novartis Institutes for BioMedical Research

QVM149

CQVM149B2208

A randomized, double-blind, double dummy, active-controlled, 3-period complete cross-over study to assess the bronchodilator effect and safety of two doses of QVM149 compared to a fixed dose combination of salmeterol/fluticasone in patients with asthma

Statistical Analysis Plan (SAP)

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1 Introduction

1.1 Scope of document

The Statistical analysis plan (SAP) documents contain detailed information to aid the production of Statistics & Programming input into the Clinical Study Report (CSR) for trial “*CQVM149B2208*”.

SAP describes the implementation of the statistical analysis planned in the protocol.

1.2 Study reference documentation

This SAP is based on the final version of the following study documents:

- the study protocol, v00, 20 March 2017
- the SOM, v00, 30 January 2017

1.3 Study objectives

1.3.1 Primary objective(s)

Objective	Endpoint
<ul style="list-style-type: none"> • To demonstrate superiority in peak bronchodilator effect of QVM149 at a dose of 150/50/160 µg o.d. and 150/50/80 µg o.d. compared to a FDC of salmeterol/fluticasone at a dose of 50/500 µg b.i.d. after 3 weeks of treatment in patients with asthma 	<ul style="list-style-type: none"> • Peak FEV1 (mL) defined as the highest bronchodilatory effect on FEV1 during a period of 5 min to 4 h after the last evening dose of each treatment period.

1.3.2 Secondary objective(s)

Objective	Endpoint
<ul style="list-style-type: none"> • To evaluate the bronchodilator effect of each dose of QVM149 compared to salmeterol/fluticasone FDC after 3 weeks of treatment. 	<ul style="list-style-type: none"> • FEV1, Forced Vital Capacity (FVC), and FEV1/FVC ratio at the following timepoints in relation to evening dose : - 45 min, -15 min, 5 min, 15 min, 30 min, 1 h, 2 h, 3h, 4 h, 8 h, 10 h, 11 h 55 min, 14 h, 18 h, 21 h, 23 h 15 min, 23 h 45 min.
<ul style="list-style-type: none"> • To evaluate the bronchodilator effect of each dose of QVM149 compared to salmeterol/ fluticasone FDC by measuring standardized FEV1 AUCs after 3 weeks of treatment respective period. 	<ul style="list-style-type: none"> • FEV1AUC 5 min - 1 h (Day 21) • FEV1AUC 5 min - 4 h (Day 21) • FEV1AUC 5 min (Day 21) - 23 h 45 min (Day 22)
<ul style="list-style-type: none"> • To evaluate post-dose trough bronchodilator effect of each dose of 	<ul style="list-style-type: none"> • Trough FEV1 (mL; mean of FEV1 at 23 h 15 min and 23 h 45 min post-dose)

Objective	Endpoint
<p>QVM149 compared to salmeterol/fluticasone FDC after 3 weeks of treatment in the respective treatment period.</p>	
<ul style="list-style-type: none"> • To evaluate safety and tolerability of each dose of QVM149 and salmeterol/fluticasone FDC when administered for 3 weeks. 	<ul style="list-style-type: none"> • Hematology • Blood chemistry • Urine analysis • Vital signs • ECG • Adverse events

1.4 Study design and treatment

This is a confirmatory, randomized, double-blind, double-dummy, active-controlled, 3-period complete cross-over study. During the 2-week screening period, patients will be required to abstain from using any asthma medication before screening lung function assessments in line with cessation periods. Patients are allowed to use their previous asthma medication between screening spirometry and randomization but need to stop at randomization when study drug administration commences.

Short-acting beta-2-agonist bronchodilators will be provided to each patient to be used as rescue medication throughout the trial. Rescue medication use will be recorded in the patient diary.

The 2-week screening period may be divided into more than one visit for operational reasons with the informed consent being obtained prior to any study related activities.

Eligible subjects may be re-screened once if they are not included in the study within the allowed 2 week screening period. Subjects may also be re-screened at the discretion of the Investigator, and following discussion with the Medical Monitor and/or Sponsor, if the reason for screen failure was considered temporary in nature. All screening data must be obtained within 2 weeks prior to administration of study medication, as stipulated above. Subjects who are re-screened will re-consented and will be allocated a new screening number.

At the end of the screening period, patients will be randomized to one of 6 possible treatment sequences), each consisting of 3 double-blind, double-dummy treatment periods of 21 days (cross-over design). There is no washout period between treatments periods since drug effects from the previous period are not expected to be present after 3 weeks with current treatment in each period.

The treatments are:

1. QVM149 150/50/160 µg o.d. (indacaterol acetate 150 µg/ glycopyrronium bromide 50 µg/ MF 160 µg once daily) – QVM149 high dose
2. QVM149 150/50/80 µg o.d. (150 µg/ 50 µg/ 80 µg once daily) - QVM149 mid dose
3. salmeterol/fluticasone FDC 50/500 µg b.i.d.
- 4.

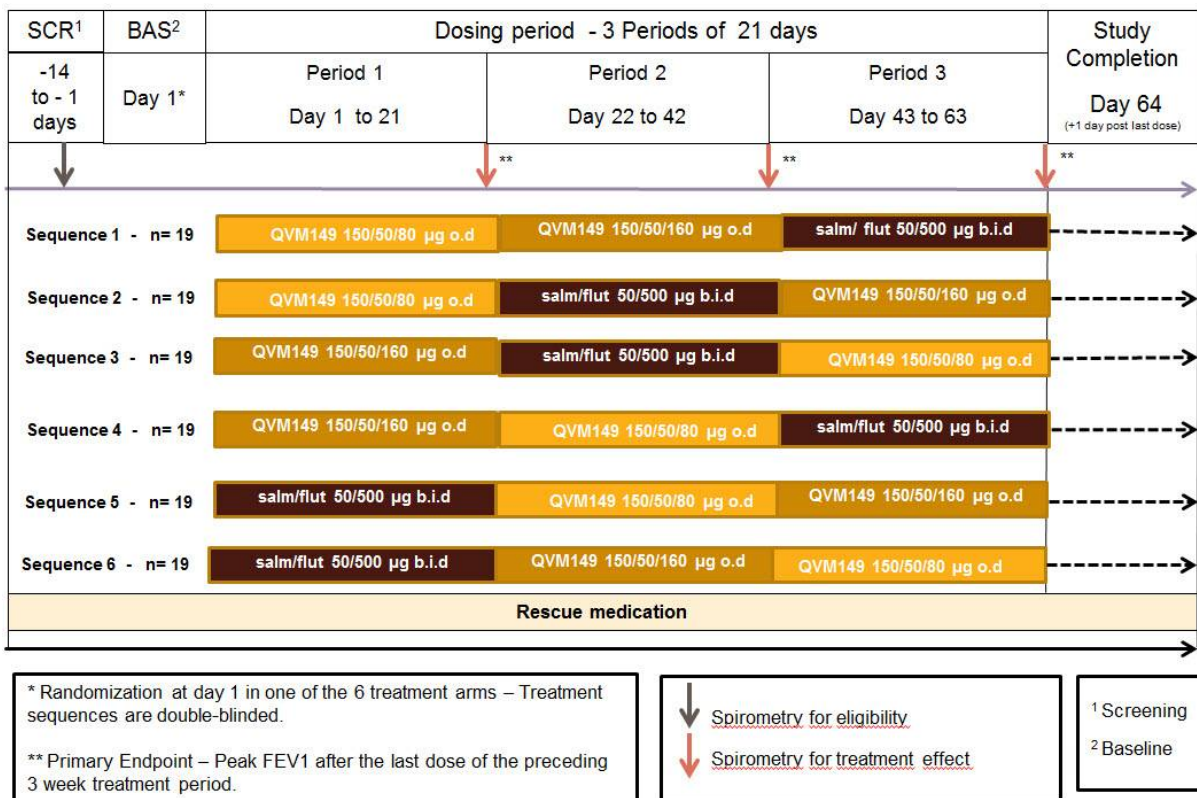
Double blind and double dummy study drug administration schedule

Period 1, Period 2 and Period 3 Study drug administration / Arm	Morning dose	Evening dose
QVM149 150/50/160 µg o.d	Device Concept1 inhalation Placebo QVM149 + Device inhalation Placebo s/f	Device Concept 1 inhalation Active QVM149 + Device inhalation Placebo s/f
QVM149 150/50/80 µg o.d	Device Concept1 inhalation Placebo QVM149 + Device inhalation Placebo s/f	Device Concept1 inhalation Active QVM149 + Device inhalation Placebo s/f
salmeterol / fluticasone 50/500 µg b.i.d (s/f)	Device Concept1 inhalation Placebo QVM149 + Device inhalation Active s/f	Device Concept1 inhalation Placebo QVM149 + Device inhalation Active s/f

Each treatment sequence will have approximately 19 subjects.

Procedures in treatment periods two and three are identical to the procedures of treatment period one. At the end of the last treatment period, subjects will then undergo Study Completion evaluations and will be discharged from the study site.

Safety assessments will include physical examinations, ECGs, vital signs, standard clinical laboratory evaluations (hematology, blood chemistry and urinalysis), adverse event and serious adverse event monitoring.



The study population will consist of male and female patients aged between 18 and 75 years with asthma and who have been treated with ICS and LABA for at least 12 months prior to screening.

A total of approximately 114 patients will be enrolled and randomized with the intention that at least 95 patients complete the study. Patients dropped out may be replaced if the drop-out rate reaches 10%.

Spirometry – Assessments

For each treatment period	Spirometry (timing in relation to study drug administration)
Day 21 (Visit 103) (Visit 203) (Visit 303)	Timing prior to study drug administration -45 min -15 min
	Study drug - evening dose Day 21
	Timing post evening dose + 5 min, + 15 min, + 30 min, + 1 h, + 2 h, + 3 h, + 4 h
Day 22	Day 22
(Visit 104) (Visit 204) (Visit 304)	Timing post evening dose day 21 + 8 h, + 10 h, + 11 h 55 min
	Study drug morning dose
	+ 14 h, + 18 h, + 21 h, + 23 h 15 min, + 23 h 45 min
Day 22 <i>Day 22 = Day 1 of the subsequent treatment period</i>	First evening dose of the next study period

2 First interpretable results (FIR)

First interpretable results (FIR) will be provided for this trial.
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4 Statistical methods: Analysis sets

For all analysis sets, subjects will be analyzed according to the study treatment received.

All subjects that received study drug will be included in the safety analysis set.

The PD analysis set will include all subjects with any available PD data, who received any study drug and experienced no protocol deviations with relevant impact on PD data.

Anyone who did not complete an informed consent will not have their data reported. For subjects for which the actual sequence of treatments received does not match the randomized sequence of treatments, the actual sequence will be used for analysis involving a sequence component (in the linear mixed model with a sequence effect) if the actual sequence is one of the sequences planned in the study design. If the actual sequence is not one of the sequences planned in the study design, the randomized sequence will be used for analysis involving a sequence component but data points from periods in which the subject has not received the randomized treatment will be excluded from the analysis.

The analysis sets and protocol deviation codes are related as follows:

Table 4-1 Protocol deviation codes and analysis sets

Category Deviation code	Text description of deviation	Data exclusion
Subjects are excluded from PD analysis in case of these PDs:		Exclude subject from PD analysis set
<i>INCL01</i>	Written informed consent was not obtained prior to performing study assessment	Exclude from PD set

If updates to this table are needed, an amendment to the SAP needs to be implemented prior to DBL.

5 Statistical methods for Pharmacokinetic (PK) parameters

Not applicable.

6 Statistical methods for Pharmacodynamic (PD) parameters

6.1 Primary objective

The primary objective is to demonstrate superiority in peak bronchodilator effect of QVM149 at a dose of 150/50/160 µg o.d. and 150/50/80 µg o.d. compared to a FDC of salmeterol/fluticasone at a dose of 50/500 µg b.i.d. in patients with asthma.

6.1.1 Variables

The primary endpoint is the peak FEV₁ (mL) defined as the highest bronchodilatory effect on FEV₁ during a period of 5 min to 4 h after the last dose of the preceding 3 week treatment period.

6.1.2 Descriptive analyses

The primary variable will be determined after the last dose of the preceding 3 week treatment. FEV₁ measurements to consider defining peak FEV₁ are on day 21 +5 min, +15 min, +30 min, +1h, +2h, +3h and +4h (timing from the post-evening dose). Peak FEV₁ will be listed by treatment sequence and subject, and summarized by treatment.

6.1.3 Statistical model, assumptions and hypotheses

The following hypothesis will be tested for each of QVM149 doses versus salmeterol/fluticasone separately:

H₀: There is no difference in terms of the peak FEV₁ after 21 days of treatment between:

the QVM149 high dose and salmeterol/fluticasone

OR

the QVM149 mid dose and salmeterol/fluticasone

H₁: There is a difference in terms of the peak FEV₁ after 21 days of treatment between:

the QVM149 high dose and salmeterol/fluticasone

AND

the QVM149 mid dose and salmeterol/fluticasone

Each test will be conducted at a one-sided 2.5% level.

The primary variable will be analyzed using a linear mixed model. The model will include period, treatment, and sequence as fixed effect factors and patient as a random effect. Restricted maximum likelihood method will be used. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom.

The pairwise treatment differences of each QVM149 dose versus salmeterol/fluticasone along with the corresponding 2-sided 95% confidence intervals will be presented. In addition, difference between adjusted means and the corresponding two-sided 95% confidence interval for QVM high versus mid doses will be estimated.

No adjustment for multiplicity is planned because both tests are required to be positive.

6.1.3.1 Model checking procedures

Missing values

If a patient takes rescue medication within 6h prior to the spirometry assessments and the visit is not rescheduled to the next day then all spirometry assessment data from this visit and the following visits in this treatment period will be set to missing. If rescue medication is taken during the 24-hour spirometry assessment then from the time of the rescue medication intake, all post-timepoint spirometry assessments will be considered as missing in this treatment period.

Sensitivity analyses

A sensitivity analysis will be conducted to evaluate the presence of any potential carry-over effects by applying the same model as described above and adding a factor modeling the first order carry-over effects.

Note: In a 3-treatments×3-periods crossover, carry-over is not confounded with sequence. Calculate carry-over term: the value of the treatment for the preceding period. It should be done at the dataset level before running the model with this additional “carryover” term. SAS LAG() function should be used.

```
Proc sort data=a;
```

```
by subject period;
```

```
Data cross3;
```

```
set a;
```

```
carryover = lag (trt);
```

```
if (period=1) then carryover = 1; # one of the treatment levels
```

LAG() gives the preceding value of the argument variable, so the data must be sorted in the correct order. The first period has no carry-over.

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Subgroup analysis

The primary analysis will be performed by subgroup of patients based on their compliance of study medication within the 7 days before the spirometry assessment within the treatment period: if spirometry assessment is done on the evening of day 21 of the treatment period, then compliance will be calculated between day 15 and day 21 on a total number of 14 doses.

This analysis will be provided per compliance of study medication within the 7 days before spirometry assessment defined as follows:

- <80% Compliance of study medication within the 7 days before spirometry assessment (less than a total number of 12 doses)

80-100% Compliance of study medication within the 7 days before spirometry assessment (more or equal a total number of 12 doses)

6.1.3.2 Graphical presentation of results

Plot of the pairwise treatment differences of each QVM149 dose versus salmeterol/fluticasone and QVM149 high versus mid dose along with the corresponding 2-sided 95% confidence intervals at day 21 will be displayed.

6.2 Secondary objectives

6.2.1 Variables

The secondary endpoints are:

- FEV₁, Forced Vital Capacity (FVC), and FEV₁/FVC ratio
- Standardized AUC in FEV₁ across different time intervals (5 min – 1 h, 5 min – 4 h, 5 min – 23h 45 min) at Day 21 (FEV₁AUC(5 min - 1 h), FEV₁AUC(5 min - 4 h) FEV₁AUC(5 min-23 h 45 min))
- Trough FEV₁ (mL)

FEV₁, Forced Vital Capacity (FVC), and FEV₁/FVC ratio are collected at the following timepoints in relation to evening dose on day 21: - 45 min, -15 min, 5 min, 15 min, 30 min, 1 h, 2 h, 3h, 4 h, 8 h, 10 h, 11 h 55 min, 14 h, 18 h, 21 h, 23 h 15 min, 23 h 45 min.

Trough FEV₁ (mL) is defined as the mean of FEV₁ at 23 h 15 min and 23 h 45 min post-dose from the last evening dose of each period, i.e. on day 21.

For FEV₁AUC(5 min-23 h 45 min), FEV₁AUC(5 min - 1 h), FEV₁AUC(5 min - 4 h), the standardized AUCs are derived using the linear trapezoidal rule and adjusting for the length of the assessment interval.

It will be calculated as the AUC_{0-24h} divided by the t_f-t_l hours time interval for each subject (t_f=time of the first observation, t_l is the time for the last observation).

$$\frac{1}{2} \sum_{f-1}^{i} \frac{(C_{i+1} + C_i)(t_{i+1} - t_i)}{t_f - t_l}$$

where,

C_i = the highest value at planned relative timepoint i

t_i = the actual time for planned relative timepoint i

i = the planned relative time of assessment

f = the first i

l = the last i .

6.2.2 Descriptive analyses

All secondary endpoints, FEV1, Forced Vital Capacity (FVC), FEV1/FVC, standardized AUC in FEV1 (5 min-23 h 45 min), in FEV1 (5 min - 1 h), in FEV1 (5 min - 4 h) and trough FEV1 will be listed by treatment sequence and subject, and reported using summary statistics by treatment.

6.2.3 Statistical model, assumptions and hypotheses

The secondary endpoints standardized AUC in FEV1 (5 min-23 h 45 min), in FEV1 (5 min - 1 h), in FEV1 (5 min - 4 h) and trough FEV1 will be analyzed by fitting the same model as described for the primary endpoint above.

6.2.3.1 Model checking procedures

Missing values

If an observation is missing between two non-missing observations, the AUC will be linearly interpolated between the two non-missing values i.e. the subject's profile will be assumed to be linear between the two available values. Multiple occurrences of such missing values (an observation missing between adjacent non-missing observations) will be handled in a similar manner. But in case of missing consecutive assessments, then the patient profile will be excluded from analysis. No imputation will be made if either the first or the last observation is missing and AUC (0-24hr) is calculated from the available part of the profile ignoring the first and last time points.

If a patient takes rescue medication within 6h prior to the spirometry assessments and the visit is not rescheduled to the next day then all spirometry assessment data from this visit and the following visits in this treatment period will be set to missing. If rescue medication is taken during the 24-hour spirometry assessment then from the time of the rescue medication intake, all post-time point spirometry assessments will be considered as missing in this treatment period. AUC FEV1 will only be calculated if the last time point in AUC is prior to intake of rescue medication (e.g. if a patient takes rescue medication at 2hrs, then FEV1 AUC(5min-1h) will be computed with FEV1 AUC(5min – 4h) and FEV1 AUC (5min – 23h 45min) set to missing.)

6.2.3.2 Graphical presentation of results

Plot of the pairwise treatment differences of standardized AUC in FEV1 (5 min-23 h 45 min), in FEV1 (5 min - 1 h), in FEV1 (5 min - 4 h) and trough FEV1 of each QVM149 dose versus salmeterol/fluticasone and for QVM149 high versus mid dose along with the corresponding 2-sided 95% confidence intervals at day 21 will be displayed.

Additionally, Plots (Mean (SD) and boxplots) of FEV1, Forced Vital Capacity (FVC), and FEV1/FVC ratio over the 24h after the evening dose given on day 21 will be produced by treatment, in addition plot of mean of FEV1 by period and sequence will be displayed.

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7 Statistical methods for safety and tolerability data

7.1 Variables

Adverse events, vital signs (blood pressure, pulse rate, body temperature), ECG intervals, laboratory measurements, as well as subject demographics, baseline characteristics, and treatment information.

The last daily dose of inhaled corticosteroids (ICS) taken before being enrolled into the study will be categorized into three categories: Low, medium and high defined based on 2017 GINA report.

<http://ginasthma.org/2017-gina-report-global-strategy-for-asthma-management-and-prevention/>

Box 3-6. Low, medium and high daily doses of inhaled corticosteroids

Adults and adolescents (12 years and older)			
Drug	Daily dose (mcg)		
	Low	Medium	High
Beclometasone dipropionate (CFC)*	200–500	>500–1000	>1000
Beclometasone dipropionate (HFA)	100–200	>200–400	>400
Budesonide (DPI)	200–400	>400–800	>800
Ciclesonide (HFA)	80–160	>160–320	>320
Fluticasone furoate (DPI)	100	n.a.	200
Fluticasone propionate(DPI)	100–250	>250–500	>500
Fluticasone propionate (HFA)	100–250	>250–500	>500
Mometasone furoate	110–220	>220–440	>440
Triamcinolone acetonide	400–1000	>1000–2000	>2000

7.2 Descriptive analyses

Subject demographics and other baseline characteristics

All data for background and demographic variables will be listed by treatment sequence and subject. Summary statistics will be provided for all subjects, as well as for each treatment sequence.

Relevant medical history, current medical conditions, results of laboratory screens, drug tests and any other relevant information will be listed by treatment sequence and subject.

Subject disposition

A disposition summary will be presented for all subjects. This table will present the number and percentage of subjects who completed each study epoch and discontinued early for each epoch, along with the reasons for early discontinuation.

The number and percentage of subjects in each analysis set will be summarized for all subjects. All analysis set results will be presented in listings by treatment sequence and subject. A

separate listing of all subjects excluded from any analysis set and the reasons for their exclusion will be provided.

All study epoch completion data will be listed by treatment sequence and subject.

Treatment

Data for study drug administration (rescue medication) and concomitant therapies will be listed by treatment sequence and subject.

Vital signs

All vital signs data will be listed by treatment sequence, subject, and visit/time and if ranges are available abnormalities (and relevant orthostatic changes) will be flagged. Summary statistics will be provided by treatment and visit/time.

ECG evaluations

All ECG data will be listed by treatment sequence, subject and visit/time, abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time.

Clinical laboratory evaluations

All laboratory data will be listed by treatment sequence, subject, and visit/time and if normal ranges are available abnormalities will be flagged. A separate listing is provided presenting all parameters in a subject with any abnormal values. Summary statistics will be provided by treatment and visit/time.

Adverse events

All information obtained on adverse events will be displayed by treatment and subject.

The number and percentage of subjects with treatment emergent adverse events will be tabulated by body system and preferred term with a breakdown by treatment. Adverse events starting on or after the time of the first inhalation of study drug will be classified as a treatment emergent adverse event. An adverse event starting in one period and continuing into the next period is counted only in the onset period. A subject with multiple adverse events within a body system and treatment period is only counted once towards the total of this body system and treatment.

Any adverse event occurring during the washout period is counted under the current treatment epoch. For example, if AE occurs during the washout period just after treatment period 1, it will be counted under treatment epoch 1. 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.

Rescue medication

Rescue medications use collected during the entire treatment duration will be listed by treatment sequence, subject.

The number of patients using rescue medication (salbutamol/albuterol) over the last week of the treatment period and the mean of the number of puffs per subject taken over the last week of treatment will be summarized by treatment.

Protocol Deviations

Protocol deviations will be listed by treatment sequence and subject.

Liver events

Liver event data may be reported in listings and summaries if data is collected during the study.

7.3 Graphical presentation

Boxplots to visualize trends in longitudinal safety data (vitals, ECG, lab parameter) will be created.

9 Reference list

Kieser M, Friede T (2003) Simple procedures for blinded sample size adjustment that do not affect the type I error rate. *Statistics in Medicine*; 22: 35-3581.