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A three-year, open-label extension study of subcutaneous secukinumab to evaluate the long-term efficacy, safety and tolerability in patients with active lupus nephritis

Statistical Analysis Plan (SAP) Amendment 1

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Document History – Changes compared to previous final version of SAP

Date			Time point	Reason for update	Outcome for update	Section and title impacted (Current)
2-Oct-2023	Prior to the final DBL of the study	The purpose of this amendment is to update the analysis plan due to the early termination of the study	Various changes to reflect the updated analysis due to early termination.			Entire Document

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AE	Adverse Event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Classification
CKD	chronic kidney disease
CM	Concomitant Medication
CRF	Case Report Form
CRR	Complete Renal Response
CSR	Clinical Study Re port
CTCAE	Common Criteria for Adverse Events
ECG	Electrocardiogram
eGFR	estimated glomerular filtration rate
ESRD	end-stage renal disease
FAS	Full Analysis Set
GGT	gamma glutamyl transferase
ISN/RPS	International Society of Nephrology / Renal Pathology Society
HDL	high density lipoprotein
LB	laboratory
LDL	low Density Lipoprotein
LFT	liver function test
LLN	lower limit of normal
LN	Lupus Nephritis
MedDRA	Medical Dictionary for Drug Regulatory Affairs
mg	milligram(s)
mL	millilitre(s)
MMF	Mycophenolate mofetil
MPA	Mycophenolic Acid
PD	Protocol deviation
PRR	Partial renal response
PSOC	Primary System Organ Class
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
s.c.	subcutaneous
SD	standard deviation
SMQ	Standardize MedDRA Queries
SoC	Standard of Care
SPP	Safety Profiling Plan
TBL	total bilirubin
TEAE	Treatment Emergent Adverse Event
TG	triglycerides
UACR	Urine Albumin-to-Creatinine Ratio
ULN	upper limit of normal

UPCR	Urine Protein-to-Creatinine Ratio
VS	vital signs

1 Introduction

This Statistical Analysis Plan (SAP) is for study CAIN457Q12301E1, "A three-year, open-label extension study of subcutaneous secukinumab to evaluate the long-term efficacy, safety and tolerability in patients with active lupus nephritis", which is the extension study for CAIN457Q12301.

Data was originally planned to be analyzed by Novartis according to the data analysis section 12 of study protocol CAIN457Q12301E1 version 00, dated 10-Dec-2021. However, this study (CAIN457Q12301E1) along with the core study (CAIN457Q12301) have been terminated early by Novartis due to futile results from interim analysis 1 of the core study. There have been no safety related reasons for early termination or concerns for the participants in this study. The purpose of this version of SAP (SAP amendment 1) is to provide details on the implementation of analyses to be reported in the synoptic Clinical Study Report (synoptic CSR).

Analyses based on this SAP will be executed after all patients complete their planned visits based on the early termination plan.

The statistical methodology is described below and any deviations from the protocol are documented. Additional detailed information regarding the analysis methodology is contained in the Appendix section.

Data analysis will be performed by [redacted] according to this SAP.

1.1 Study design

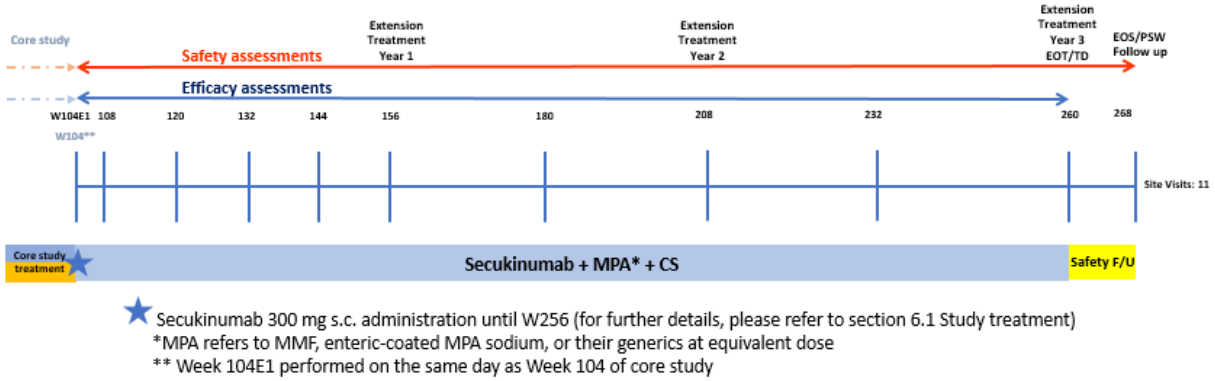
This is a multicenter, optional, open-label, extension study of s.c. secukinumab to evaluate the long-term efficacy, safety and tolerability up to three years in patients with lupus nephritis also receiving Standard of Care (SoC) regimen.

The aim of this three-year extension study is to provide treatment with secukinumab for participants who complete core study treatment in CAIN457Q12301 and to obtain further long-term efficacy, safety and tolerability information.

Due to the futile outcomes from the first interim analysis of the core study, this extension study was terminated early and its final analysis will be performed with all available patients by the time of study termination. Recruitment in this study was stopped on 26-May-2023 with 31 participants randomized. Last patient last visit (LPLV) was on 24-Aug-2023. Moreover, because of the early termination of the study, [redacted] analyses will not be performed. A synoptic CSR will be generated after the final database lock.

An outline of study design in present in Figure 1-1.

Figure 1-1 Study design



EOT: End Of treatment
TD: Treatment Discontinuation
EOS: End Of Study
PSW: Premature Participant/Subject Withdrawal
F/U: Follow up

1.2 Study objectives, endpoints and estimands

Table 1-1 shows the objectives and related endpoints as defined in Protocol-V00. Due to the early termination of the study: the primary objective will be summarized descriptively [redacted] There was no secondary objective defined in the protocol.

Table 1-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
● To assess the long-term efficacy of secukinumab with respect to CRR over time up to Week 260 in adults with Lupus Nephritis (ISN/RPS class III or IV, with or without co-existing class V features) participant on background of SoC therapy	● Proportion of participants achieving CRR CRR is a composite endpoint defined as: ● Estimated Glomerular Filtration Rate (eGFR) ≥ 60 mL/min/1.73 m^2 or no less than 85% of core Baseline values and ● 24-hour Urine-to-Protein Creatinine Ratio (UPCR) ≤ 0.5mg/mg
[redacted]	

1.2.1 Primary estimand(s)

The estimand is the precise description of the treatment effect and reflects strategies to address events occurring during trial conduct which could impact the interpretation of the trial results (e.g., premature discontinuation of treatment).

The attributes of the estimand are:

- Population: All participants who completed treatment (secukinumab 300 mg or placebo) up to Week 104 in the core study and satisfy the inclusion/exclusion criteria to reflect the targeted LN population
- Variable: Complete renal response while on treatment regardless of rescue medication use up to Week 260
- Treatment of interest: secukinumab 300 mg every four weeks
- Remaining intercurrent events: None. Intercurrent events are included in the variable definition.

- Population level summary: Proportion of responders summarized over time.

2 Statistical methods

2.1 Data analysis general information

Data will be summarized descriptively for all available participants by treatment regimen unless otherwise specified.

Summary statistics for continuous variables will generally include the number of subjects (N), mean, standard deviation (SD), median, minimum and maximum.

For categorical or binary variables, the frequency and percent of subjects in each category will be presented.

2.1.1 Treatment groups

Efficacy data will be presented by the following two treatment groups:

1. AIN457 300 mg
2. Placebo-AIN457 300 mg

Safety data will be presented by the following three treatment groups:

1. AIN457 300 mg
2. Placebo-AIN457 300 mg
3. Any AIN457 300 mg

2.2 Analysis sets

The Full Analysis Set (FAS) will be comprised of all subjects who came from the FAS of the core study and enrolled in the extension trial. According to the intent to treat principle, subjects will be analyzed according to the treatment they have been assigned to during the core study.

The Safety Set (SAF) includes all subjects who received at least one dose of study treatment in the extension trial. Subjects will be analyzed according to the treatment received during the core study.

2.3 Patient disposition, demographics and other baseline characteristics

2.3.1 Patient disposition

The number of subjects enrolled in the extension study will be presented. The number and percentage of subjects in the FAS who completed the period up to week 260 and/or the follow up visit and who discontinued the study prematurely (including the reason for discontinuation) will be presented for each core study treatment group.

For each protocol deviation (PD) (including COVID-19 PDs, if any), the number and percentage of subjects for whom the PD applies will be tabulated.

2.3.2 Demographics and other baseline characteristics

As this is an extension study, baseline always refers to the core study CAIN457Q12301 baseline. Patient demographics and baseline disease characteristic will be derived from the core study data, and will be summarized descriptively for FAS by core study treatment groups.

The following common background and demographic variables will be summarized:

Continuous variables:

- Age
- Height
- Weight
- Body mass index (BMI) = (body weight in kilograms) / (height in meters)^2

Categorical variables:

- Age categories (< 30 yr, ≥30 yr)
- Gender
- Race
- Ethnicity
- Smoking status at baseline

Baseline disease characteristics will also be summarized for the following variables:

- Patient's global assessment of disease activity, UPCR, eGFR, Serum creatinine(mg/dl), C3(mg/dl), C4(mg/dl), Anti-dsDNA (geometric mean IU/ml), Standard of care induction therapy, corticosteroids (mg/day) at screening, time since first diagnosis of SLE and LN (years), and renal biopsy LN classification

Unless otherwise specified, summary statistics will be presented for continuous variables for each treatment group and for all subjects (total) in the FAS. The number and percentage of subjects in each category will be presented for categorical variables for each treatment group and all subjects (total) in the FAS.

2.3.3 Medical History

Medical history will be presented in a listing.

2.4 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

2.4.1 Study treatment / compliance

The analysis of study treatment data will be based on the safety set. The number of active injections received will be presented by core study treatment group. The duration of exposure to study treatment will also be summarized by core study treatment group. In addition, the number and percentage of patients with cumulative exposure levels (e.g., any exposure, ≥ 108 week, ≥ 112 weeks, ≥ 116 weeks, ≥ 120 weeks, ≥ 124 weeks, etc.) will be presented.

Duration of exposure will be calculated as time from first dose of the treatment in extension to the minimum of (last dose of the treatment+ 84 days) and (last visit date). For subjects who discontinue treatment, this will be the subject's last visit.

Duration of exposure (years) = duration of exposure (days)/ 365.25

Duration of exposure (100 subject years) = duration of exposure (years)/ 100

2.4.2 Concomitant medications

Concomitant medication will be presented in a listing.

2.5 Analysis supporting primary objective(s)

2.5.1 Primary endpoint(s)

Primary endpoint for this study is CRR over time up to Week 260 with the consideration of intercurrent events, which is defined in detail at Section 1.2.1.

2.5.2 Statistical hypothesis, model, and method of analysis

No formal statistical testing will be applied for the primary variable. The proportion of responders over time will be summarized by treatment group in FAS, using descriptive statistics and 95% confidence interval.

2.5.3 Handling of missing values not related to intercurrent event

Not applicable.

2.5.4 Sensitivity analyses

Not applicable.

2.6 Analysis supporting secondary objectives

Not applicable.

2.7 Safety analyses

For all safety analyses, the safety set will be used. All listings and tables will be presented by the treatment that patients received in the core study.

2.7.1 Adverse events (AEs)

On-treatment period is defined as from the first dose in core study to the last dose in extension +84 days. Treatment emergent adverse events (TEAE) (i.e., events started or worsened during the on-treatment period) will be summarized.

The following AE topics will not be provided in summary but will be flagged in the AE listing:

- All reported AEs that started or worsened before first dose in core study

- All reported AEs that started or worsened after last dose in extension + 84 days.

Confidence intervals for the crude rate will be derived.

[redacted]

Safety topics of interest, such as risks defined in the Risk Management Plan (RMP) or topics of interest regarding signal detection or routine analysis are defined in the Program Case Retrieval Sheet.

The crude incidence rates for the safety topics of interest AEs will be summarized. In addition, separate listings will be provided for SAEs.

Algorithms for date imputations will be provided in Programming Datasets Specifications.

2.7.2 Laboratory data

[redacted]

The following laboratory parameters will be analyzed with respect to numerical Common Terminology Criteria for Adverse Events (CTCAE) grades, given in Table 2-2: hemoglobin, platelets, white blood cell count, neutrophils, lymphocytes, creatinine, total bilirubin (TBL), gamma-glutamyl transferase (GGT), alanine aminotransferase (ALT), aspartate, aminotransferase (AST), alkaline phosphatase (ALP), glucose, cholesterol, triglycerides (TG).

These summaries will be split into hematology and chemistry.

Table 2-2 CTCAE grades for laboratory parameters to be analyzed

CTCAE v4.0 Term	Grade 1	Grade 2	Grade 3	Grade 4
HGB decreased (Anemia)	<LLN – 100 g/L	<100 – 80 g/L	<80 g/L	See note below
Platelet count decreased	<LLN – 75.0 x10e9 /L	<75.0 - 50.0 x10e9 /L	<50.0 – 25.0 x10e9 /L	<25.0 x 10e9 /L
White blood cell decreased	<LLN - 3.0 x 10e9 /L	<3.0 - 2.0 x 10e9 /L	<2.0 - 1.0 x 10e9 /L	<1.0 x 10e9 /L
Neutrophil count decreased	<LLN - 1.5 x 10e9 /L	<1.5 - 1.0 x 10e9 /L	<1.0 - 0.5 x 10e9 /L	<0.5 x 10e9 /L
Lymphocyte count decreased	<LLN - 0.8 x 10e9/L	<0.8 - 0.5 x 10e9 /L	<0.5 - 0.2 x 10e9 /L	<0.2 x 10e9 /L
Creatinine increased*	>1 - 1.5 x baseline; >ULN - 1.5 x ULN	>1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN	>3.0 baseline; >3.0 - 6.0 x ULN	>6.0 x ULN
TBL increased	>ULN - 1.5 x ULN	>1.5 - 3.0 x ULN	>3.0 - 10.0 x ULN	>10.0 x ULN
GGT increased	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
ALT increased	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
AST increased	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
ALP increased	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
Glucose increased (Hyperglycemia)	; >ULN - 8.9 mmol/L	>8.9 - 13.9 mmol/L	>13.9 - 27.8 mmol/L	>27.8 mmol/L
Glucose decreased (Hypoglycemia)	<LLN - 3.0 mmol/L	<3.0 - 2.2 mmol/L	<2.2 - 1.7 mmol/L	<1.7 mmol/L
Cholesterol high	>ULN - 7.75 mmol/L	>7.75 - 10.34 mmol/L	>10.34 - 12.92 mmol/L	>12.92 mmol/L
Hypertriglyceridemia	1.71 - 3.42 mmol/L	>3.42 - 5.7mmol/L	>5.7 - 11.4 mmol/L	>11.4 mmol/L

Note: Grade 4 Hemoglobin events are defined as life-threatening anemia events and will not be displayed in the table, as a numerical range is not provided in the CTCAE.

*Note: for “creatinine increased” the baseline criteria do not apply.

Summaries for newly occurring or worsening clinically notable lipid abnormalities will also be provided cumulatively for each of the following parameters and categories:

- HDL:
  - <=LLN
  - <0.8 x LLN
- LDL, cholesterol, triglycerides:
  - >=ULN
  - >1.5 x ULN

- >2.5 x ULN

Newly occurring or worsening liver enzyme abnormalities will also be summarized based on the event criteria given in Table 2-3:

Table 2-3 Liver-related events

Parameter	Criterion
ALT	>3xULN; >5xULN; >8xULN;>10xULN, >20xULN
AST	>3xULN; >5xULN; >8xULN >10xULN; >20xULN
ALT or AST	>3xULN; >5xULN; >8xULN >10xULN; >20xULN
TBL	>1.5xULN, >2xULN, >3xULN,
ALP	>2xULN, >3xULN. >5xULN
ALT or AST & TBL	ALT or AST>3xULN & TBL >2xULN; ALT or AST >5xULN & TBL >2xULN; ALT or AST >8xULN & TBL >2xULN; ALT or AST >10xULN & TBL >2xULN
ALP & TBL	ALP >3xULN & TBL >2xULN ALP >5xULN & TBL >2xULN
ALT or AST & TBL & ALP	ALT or AST>3xULN & TBL >2xULN & ALP <2xULN **(Hy's Law**) Note: elevated ALP may suggest obstruction as a consequence of gall bladder or bile duct disease; ALP may also be increased in malignancy. FDA therefore terms Hy's Law cases as indicators of *pure hepatocellular injury*. This does not mean that cases of ALT or AST >3xULN & TBL >2xULN & ALP ≥2xULN may not result in severe DILI.
Notes: In studies which enrolled subjects with pre-existing liver disease, baseline LFT may be increased above ULN; in such a case it is meaningful to add the condition "and worse than baseline" to the abnormality criteria	

For a combined criterion to be fulfilled, all conditions have to be fulfilled on the same visit. The criteria are not mutually exclusive, e.g. a subject with ALT = 6.42xULN is counted for ALT >3xULN and ALT>5x ULN.

2.7.3 Other safety data

2.7.3.1 ECG data

A listing of ECG collected in the extension trial will be provided by treatment and by subject.

2.7.3.2 Vital signs

The summary of vital signs will only include treatment emergent data, which are defined as those vital sign measurements after the first dose of core study treatment and on or before last dose + 84 days in extension.

[redacted]

[redacted]

The number and percentage of subjects with newly occurring notable vital signs will be presented. Criteria for notable vital sign abnormalities are provided in Table 2-4:

Table 2-4 Criteria for notable vital sign abnormalities

Vital sign (unit)	Notable abnormalities
Systolic blood pressure (mmHg)	>= 140 mmHg or < 90 mmHg
Diastolic blood pressure (mmHg)	>=90 mmHg or <60 mmHg
Pulse (bpm)	> 100 bpm or <60 bpm

2.7.3.3 Immunogenicity

Not applicable.

2.8 Pharmacokinetic endpoints

Not applicable.

2.9 PD and PK/PD analyses

Not applicable.

2.10 Patient-reported outcomes

Not applicable.

2.11 Biomarkers

Not applicable.

[redacted]

2.13 Interim analysis

Not applicable.

3 Sample size calculation

Sample size is based on participants continuing from core study to extension study.

4 Change to protocol specified analyses

The following significant changes due to early termination of the study are implemented SAP:

1. In section 5.2, the target day corresponding to visit W104E1 has been updated to "Day 729" to reflect the analyses of this extension study will use the baseline from the core study. The protocol keeps the target day of visit W104E1 to "Day 0" to avoid changes in operation.
2. Terminate the study early due to the futile outcomes from the first interim analysis in the core study.
3. Change the Clinical Study Report type from full to abbreviated.
4. Indicate the CRO [redacted] will carry out the final analysis.
5. Exclude intercurrent events for the primary objective.
6. [redacted]
7. Removal of some safety analyses.
8. Add safety topics of interest AEs safety analyses.

5 Appendix

5.1 Description of efficacy variables

Complete Renal Response (CRR)

The CRR will be used to determine efficacy. CRR is a composite endpoint defined as:

- eGFR $\geq$ 60 mL/min/1.73m^2 or no less than 85% of Baseline

and

- 24-hour UPCR $\leq$ 0.5 mg/mg

Estimated glomerular filtration rate (eGFR)

The glomerular filtration rate will be estimated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (Martínez Martínez et al 2013) based on subject gender, age (years) and serum creatinine (mg/dL).

Central laboratory serum creatinine values will be used for all renal function data analysis.

Urine Protein-to-Creatinine Ratio (UPCR)

Urine Protein-to-Creatinine Ratio (UPCR), expressed in mg/mg, will be determined by a central laboratory by dividing the protein concentration by the creatinine concentration as measured in the urine collected.

Depending on the objective to be assessed, the UPCR will be determined using one of the following two types of urine collection, 24-hour urine collection or first morning void urinary sample.

Both the 24-hour urine collection and the first morning void will be collected in the subjects' home.

5.2 Visit windows, baseline and post-baseline definitions, missing data handling

Baseline and post-baseline definitions

In general, a baseline value refers to the core study and is the last measurement made prior to administration of the first dose of study treatment in core. Baseline information will be presented appropriately in the “by visit” summaries in both safety and efficacy tables.

A post-baseline value refers to a measurement taken after the first dose of study treatment in extension study.

For early discontinuation visit mapping in different assessments, the early discontinuation week will be the next visit of corresponding assessment based on the patients’ last scheduled visit.

Analysis visit windows

Analysis visit windows will be used for the data that is summarized by visit; they are based on the study visit and evaluation schedule and comprise a set of days around the nominal visit day. For any assessment, there are protocol defined scheduled visits around which analysis visit windows were created to cover the complete range of days within the study.

When visit windows are used, all visits will be re-aligned, i.e., they will be mapped into one of the visit windows, as in Table 5-1. E.g., if the Week 108 visit of a subject is delayed and occurs on Day 802 instead of on Day 760, it will be re-aligned to visit window Week 120. In the case of major deviations from the visit schedule, or due to unscheduled visits, several assessments of a subject may fall in a particular visit window (either scheduled or unscheduled). Statistical approaches to handle multiple assessments in a given visit window are specified below.

For lab/vital signs, follow-up (F/U) visit is excluded from analysis visit mapping window. Only assessments that come as F/U nominal visit will be directly assigned as analysis F/U visit. Other assessments that are beyond the last on-treatment visit window (W260) or after nominal F/U visit date won't be mapped to any analysis visit. F/U visit will not be included in the summary tables by visit.

Of note, subjects are allowed to have gaps in visits. All data collected will be displayed in listings.

Table 5-1 Analysis visit windows

Analysis Visit	Target Day	Analysis Visit Window	Group 1	Group 2	Group 3
W104E1	729	716-743	716-743	709-743	709-876
W108	757	744-799	744-799	744-799	
W120	841	800-883	800-883	800-876	
W132	925	884-967	884-967	877-974	877-1044
W144	1009	968-1051	968-1051	975-1044	
W156	1093	1052-1177	1052-1177	1045-1177	1045-1177
W180	1261	1178-1359	1178-1359	1178-1359	1178-1359
W208	1457	1360-1541	1360-1541	1360-1541	1360-1541
W232	1625	1542-1723	1542-1723	1542-1723	1542-1723
W260	1821	≥1724	≥1724	≥1724	≥1724
		Group 1: Vital Signs, Body Weight, Hematology, Clinical Chemistry (exclude eGFR), Coagulation Panel, Fasting lipid panel, FMV urine collection Group 2: eGFR Group 3: 24-hr urine collection			

5.3 Statistical models

5.3.1 Summary statistics for binary and categorical data

Summary statistics for discrete variables will be presented in contingency tables and will include count and frequency in each category.

For n subjects, each at risk to experience a certain event with probablity π, the crude incidence is estimated as x/n, where x is the number of subjects with the event.

Absolute and relative frequencies will be displayed as well as 95% confidence interval for the relative frequency based on the score method including continuity correction [Newcombe (1998)]:

With z as $(1-\alpha/2)$-quantile of the standard normal distribution (SAS: z= PROBIT (1- α/2)), n as total number of subjects (i.e., number of subjects in the denominator), and p as estimated crude incidence (number of subjects with event $/n$) and $q = 1-p$.

Then the lower limit is

$$L = 100 \times \max\left(0, \frac{2np + z^2 - 1 - z\sqrt{z^2 - 2 - 1/n + 4p(nq+1)}}{2(n+z^2)}\right)$$

and the upper limit is

$$U = 100 \times \min\left(1, \frac{2np + z^2 + 1 + z\sqrt{z^2 + 2 - 1/n + 4p(nq - 1)}}{2(n + z^2)}\right).$$

Note: if $L > p$ then $L = p$ and if $U < p$ then $U = p$.

5.3.2 Crude incidence and related risk estimates

For n subjects, each at risk to experience a certain event with probability π, the crude incidence is estimated as $p=x/n$, where x is the number of subjects with the event.

Absolute and relative frequencies will be displayed as well as 95% confidence interval for the relative frequency based on the score method including continuity correction (Newcombe 1998).

With z as (1-α/2)-quantile of the standard normal distribution (SAS: z = PROBIT(1-α/2), n as total number of subjects (i.e. number of subjects in the denominator), and p as estimated crude incidence (number of subjects with event / n) it is q=1-p.

Then the lower limit is

$$L = \max\left(0, \frac{2np + z^2 - 1 - z\sqrt{z^2 - 2 - 1/n + 4p(nq + 1)}}{2(n + z^2)}\right)$$

and the upper limit is

$$U = \min\left(1, \frac{2np + z^2 + 1 + z\sqrt{z^2 + 2 - 1/n + 4p(nq - 1)}}{2(n + z^2)}\right).$$

In addition, if L > p then L = p and if U < p then U = p.

If appropriate, an exact 100*(1-α)% confidence interval (Clopper-Pearson, 1934) will be obtained by using the SAS procedure PROC FREQ with the EXACT BINOMIAL statement. However, the confidence interval derived via the score method including continuity correction will be the default in safety analyses.

6 Reference

ICH E9(R1) Harmonized Guideline: addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials. Final version on 20 November 2019.

Clopper CJ, Pearson ES (1934). The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika, 26; 404–413.

Garwood F (1936). Fiducial limits for the Poisson distribution. Biometrika, 46; 441–453.

Levin A, Stevens PE, Bilous RW, et al (2013) 'Kidney disease: Improving global outcomes (KDIGO) CKD work group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease' Kidney International Supplements; 3(1):1-150.

Martínez-Martínez MU, Martínez-Martínez MU, Mandeville P, et al (2013) CKD-EPI is the most reliable equation to estimate renal function in patients with systemic lupus erythematosus. Nefrologia; 33(1):99-106.

Newcombe, RG. (1998) Two-sided confidence intervals for the single proportion: comparison of seven methods. Statistics in Medicine; 17: 857-872.

Sahai H, Khurshid Anwer (1993). Confidence intervals for the mean of a poisson distribution: a review. Biom J, 35 (7); 857-867

Ulm K (1990). A simple method to calculate the confidence interval of a standard mortality ratio. American Journal of Epidemiology, 131(2); 373-375