

SAP REScUE

The SAP was developed prior to data cut-off, in July 2024.

1. Intro

This statistical analysis plan was written for the REScUE-study, set up by Birdgroup. Guidelines ICH E3 Structure and Content of Clinical Study Reports and ICH E9 Statistical Principles for Clinical Trials were consulted for writing this plan.

A complete overview of the study is provided in Protocol Version 1.7 – 2022-02-09

2. Study Design and Objectives

This study compares two dose-escalation regimen of Stelara (Ustekinumab) to treat patients with Crohn's disease who showed a secondary loss of response while on Ustekinumab.

- The first regimen consists of re-induction by ≈ 6 mg/kg IV followed by a maintenance dose of 90 mg SC Q8W.
- The second regimen consists of re-induction by ≈ 6 mg/kg IV followed by a maintenance dose of 90 mg SC Q4W.

2.1 Study Objectives

This study compares the clinical impact of re-induction plus 8 weekly maintenance dose (Q8W) with re-induction plus 4 weekly maintenance dose (Q4W).

The trial is designed to show the superiority of Q4W over Q8W (the latter is currently reimbursed, the former is not).

Primary Objective: (for exact definitions, see [Section 3](#))

- to assess the clinical superiority of ustekinumab re-induction ≈ 6 mg/kg IV followed by 90 mg SC Q4W over ustekinumab re-induction ≈ 6 mg/kg IV followed by 90 mg SC Q8W in patients with CD who show a secondary loss of response over time

Secondary Objectives: (for exact definitions, see [Section 3](#))

- to assess the endoscopic effect of ustekinumab re-induction ≈ 6 mg/kg IV followed by either 90 mg SC Q8W or Q4W in patients with CD who show a secondary loss of response over time.
- to assess the biochemical effect of ustekinumab re-induction ≈ 6 mg/kg IV followed by either 90 mg SC Q8W or Q4W in patients with CD who show a secondary loss of response over time.

- to assess the pharmacodynamic and pharmacokinetic aspects of ustekinumab re-induction $\approx 6\text{mg/kg}$ IV followed by either 90 mg SC Q8W or Q4W in patients with CD who show a secondary loss of response over time
- to assess the quality of life of patient treated with ustekinumab re-induction $\approx 6\text{mg/kg}$ IV followed by either 90 mg SC Q8W or Q4W in patients with CD after experiencing a secondary loss of response over time.
- to assess the safety of ustekinumab re-induction $\approx 6\text{mg/kg}$ IV followed by either 90 mg SC Q8W or Q4W in patients with CD who show a secondary loss of response over time
- to assess socio-economic impact of ustekinumab re-induction $\approx 6\text{mg/kg}$ IV followed by either 90 mg SC Q8W or Q4W in patients with CD who show a secondary loss of response over time.

2.2 Endpoints

Primary Endpoint: (for exact definitions, see [Section 3](#))

- Proportion of patients with steroid free clinical remission (PRO-2 remission: $\text{AP} \leq 1$ AND $\text{SF} \leq 3$) and $\text{FCP} < 250 \mu\text{g/g}$ at week 48.

Secondary Endpoints: (for exact definitions, see [Section 3](#))

- Proportion of patients with complete endoscopic remission ($\text{SES-CD} < 3$) at week 48
- Proportion of patients with endoscopic remission ($\text{SES-CD} < 5$) at week 48
- Proportion of patients with endoscopic response ($\geq 50\%$ decrease in SES-CD) at week 48.
- Proportion of patients with clinical remission (PRO-2 remission: $\text{AP} \leq 1$ AND $\text{SF} \leq 3$) at week 48.
- Proportion of patients with clinical remission (PRO-2 remission: $\text{AP} \leq 1$ AND $\text{SF} \leq 3$) at week 8 after IV re-induction.
- Proportion of patients with biomarker remission ($\text{CRP} < 5 \text{ mg/L}$ and $\text{FCP} < 250 \mu\text{g/g}$) at week 48.
- Proportion of patients with $\text{UST TC} > 1.4 \mu\text{g/mL}$ at all time points (w4-8-16-24-32-40-48) after baseline in the different treatment arms.
- Proportion of patients with SAE in the different treatment arms.

Exploratory Endpoints:

- Pharmacodynamic and pharmacokinetic evaluation.
- Time to clinical response
- Time till clinical relapse (based on physicians discretion) after week 8.
- IBD related hospitalization.
- Need for surgery.
- Improvements in quality of life.
- Pharmacoeconomic evaluation (drug cost, hospitalization, work absenteeism, surgery).
- SUSAR

- SAE.
- Extra intestinal manifestation (joint).

2.3 Design

This is a Prospective Randomized, double blind multicenter interventional study. Patients are randomized to Q4W or Q8W, with randomization stratified by previous exposure to anti-TNF and baseline use of steroids using variable length permuted block randomization with equal allocation proportions (1:1). Patients are treated as shown in the schedule below and followed for 48 weeks (measurement times indicated in the schedule. For a complete overview of the in- and exclusion criteria: see protocol.

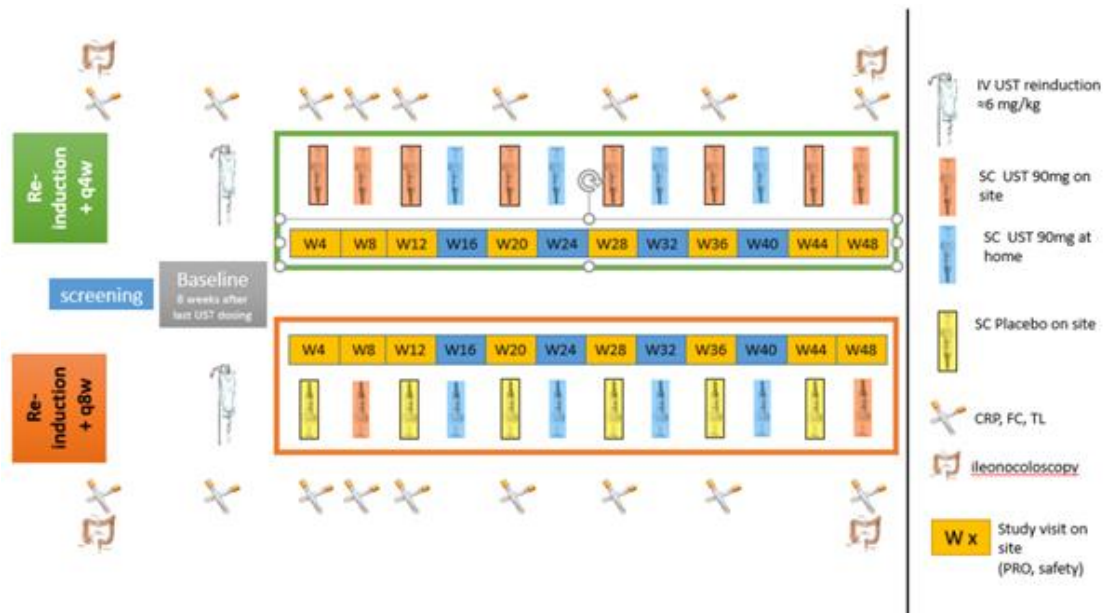


Figure 1: Overview of study-design

2.3.1 Concomittant medication

- 5-aminosalicylate: any dosing, need to be stable during the study
- Steroids: prednisolone equivalent ≤ 20 mg at baseline, from week 16 tapering with 5 mg per week prednisolone equivalent is obligatory (for beclomethasone dipropionate, taper via EOD or magistral preparation). If tapering is applied, restart or increasing of the dose is allowed during the study. Initiation of steroids during the study is allowed as of week 24 .
- Azathioprine/6-mercaptopurine/methotrexate: stable dosing during study, except stop for side-effects, initiation not allowed during study, switch from azathioprine to 6-mercaptopurine (and vice versa) allowed at equivalent dose.
- Biologics: not allowed
- Jak inhibitors: not allowed
- Non registered investigational product: not allowed

- Antibiotics: allowed if not started for luminal CD

2.4 Sample size justification

To achieve 80% power to detect an expected 30% difference in proportions of treatment response between the two study arms using a chi-square test with a two-sided alpha of 5%, between 64 to 86 patients in total are necessary depending on the rate in the reference group ranging from 10% to 60%. The maximum sample size of 86 patients corresponds with about a 35% vs 65% response rate and has 90% power for a reference rate of 10% or 60%. To account further for an expected attrition rate of 20%, the study therefore requires 108 patients (54 patients in each treatment arm) to achieve at least 80% power regardless of the response rate in the reference group.

3. General Analysis Definitions

3.1 Populations

- Safety Population: all patients that received at least one dose of study medication.
- ITT-population: all randomized patients.

Safety analyses will be conducted on the Safety Population. Other analyses will be conducted on the ITT-population unless specified otherwise.

3.2 Endpoints

- Steroid Free Clinical Remission at week 48:
 - $AP \leq 1$ AND $SF \leq 3$ and $FCP < 250 \mu\text{g/g}$
 - Steroid Free: no steroid use in the 90 days prior to the 48 week-measurement
- Complete Endoscopic remission at week 48
 - $SES\text{-}CD < 3$
- Endoscopic remission at week 48
 - $SES\text{-}CD < 5$
- Endoscopic response at week 48
 - $\geq 50\%$ decrease in $SES\text{-}CD$
- Clinical Remission at week 8 and 48
 - $AP \leq 1$ AND $SF \leq 3$
- Biomarker remission at week 48
 - $CRP < 5 \text{ mg/L}$ and $FCP < 250 \mu\text{g/g}$
- Time to clinical remission:
 - Clinical remission: $AP \leq 1$ AND $SF \leq 3$
- Time till clinical relapse after week 8
 - Time zero: week 8
 - Clinical relapse: definition at physicians discretion
 - Only those in remission at week 8 are included

- Improvement in quality of life

4. Analyses and Summaries

4.1 Study patients

The number of patients in each population will be tabulated by treatment. The number of screen failed patients and the reason for screen failure will be tabulated. Protocol deviations will be summarised by treatment in the ITT-population.

4.2 Demographics and other baseline characteristics

Following baseline information will be summarised by treatment in the ITT-population:

- Demographics
 - Age
 - Sex
 - Ethnic origin
 - Smoking status
 - Other conditions/diseases relevant to CD (incl. extra-intestinal manifestations)
 - IBD surgeries (specified by number resections, length of resections of small intestine, location of colonic resection, perianal surgical interventions)
 - BMI
 - Disease duration
 - Montreal classification
 - Endoscopic score
 - CRP
 - Faecal calprotectin
- Prior treatment
 - Failed advanced therapies
 - Failed advanced classes
 - Concomittant corticosteroids
 - Concomittant immunomodulators

4.3 Efficacy Evaluation

4.3.1 Primary Endpoint

4.3.1.1 Estimand

- Population: ITT trial population
- Outcome measure: Steroid Free Clinical Remission at week 48 as defined in section 3.2
- Intercurrent events:

- Treatment discontinuation: composite endpoint – treatment discontinuation part of ‘failure’
- Start forbidden medication: composite outcome – patients who started forbidden medication are labelled as failing on this endpoint
- Summary statistic
 - Odds ratio from a Chi Squared test stratified by the randomization-stratification factors.

4.3.1.2 Missing data

- For the primary analysis, we will use covariate adjustment as described in Van Lancker, Bretz, and Dukes (2024). Outcomes will be modeled in each arm separately, using a set of baseline predictors. The two models are then used to estimate the treatment-effect on the trial population. This approach assumes MAR given the covariates in the model
 - Covariates included: +The stratification factors +In case of convergency-issues in the analysis, the last factor will be dropped
- Two sensitivity analyses are foreseen:
 - Stratified Chi-Square assuming all those with missing outcome at week 48 have failed on the primary endpoint
 - Assuming missingness depends on outcomes in the previous weeks:
 - Imputation based on stratification factors and clinical remission in week 4-8-12-20-28-36-44
 - Multiple imputation will be performed using MICE using predictive mean matching

4.3.2 Secondary Endpoints

For the secondary endpoints, no sensitivity analyses are foreseen.

For all the secondary endpoints, the same estimand as the primary endpoint is targeted as far as the population (ITT-population) and the handling of intercurrent events go.

4.3.2.1 Time to clinical remission (positive event)

Two analyses are foreseen:

1. KM, stratified logrank and stratified Cox model, censoring patients at last available assessment assuming this drop out is non-informative
2. As the drop out is probably not non-informative (who drops out will probably tend to be in worse condition), a competing risk analysis is performed with drop out of study as competing event. This re-defines the endpoint as ‘in-study-clinical response’

In both cases, it is assumed that the event does not occur at visits prior to the last available visit, unless observed.

4.3.2.2 Time to clinical relapse (negative event)

Two analyses (KM, stratified logrank, stratified Cox) with different event-time definitions are foreseen. Censoring time is set to the last available assessment.

1. Event at time it is first observed
2. If there are missing visits prior to the observed event, the event time is set to the earliest date of consecutive missing visits prior to the event

4.3.2.3 Quality of Life

Descriptive analyses, presenting mean, SD, median and Q1-Q3 at the different timepoints. Number of missing observations will be presented at each timepoint.

In the safety population by treatment, the number of that type of AE, the number of patients with that type of AE and the proportion of patients with that type of AE will be summarised:

- Any AE
- Any Serious AE
- SUSAR For all these categories, the numbers will be tabulated overall and separately according to relationship to study drug.

References

Van Lancker, Kelly, Frank Bretz, and Oliver Dukes. 2024. "Covariate Adjustment in Randomized Controlled Trials: General Concepts and Practical Considerations." *Clinical Trials* 21 (4): 399–411. <https://doi.org/10.1177/17407745241251568>.