

Biostatistics & Statistical Programming /
Novartis Institutes for BioMedical Research

AIN457/Secukinumab

CAIN457X2201

A randomized, double-blind, placebo-controlled parallel group, Phase II, 24-week study investigating the efficacy, safety and tolerability of AIN457 in patients with active overuse tendinopathy refractory to oral NSAIDs/acetaminophen, physiotherapy or corticosteroid injections

Statistical Analysis Plan (SAP)

Author(s): Personal Protected Data

Document type: SAP Documentation – NIBR

Document status: Final amendment 3

Release date: 14 Apr 2020

Number of pages: 74

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1 Introduction

1.1 Scope of document

The RAP documents contain detailed information to aid the production of Statistics & Programming input into the Clinical Study Report (CSR) for trial “CAIN457X2201”.

The Statistical analysis plan (SAP) describes the implementation of the statistical analysis planned in the protocol.

1.2 Study reference documentation

This Statistical Analysis Plan is based on the protocol version 02 incorporating Amendment 02 dated 13Mar2018.

1.3 Study objectives

1.3.1 Primary Objective

- To assess the efficacy of secukinumab 300 mg subcutaneous (s.c.) vs. placebo in patients with overuse rotator cuff tendinopathy in relieving clinical symptoms at week 14.

1.3.2 Secondary Objectives

- To assess the efficacy of secukinumab 300 mg s.c. vs. placebo in patients with overuse rotator cuff tendinopathy in relieving symptoms over time.
- To assess the structural changes in the rotator cuff tendinopathy over time.
- To assess PK/immunogenicity in secukinumab treated patients.
- To confirm the safety and tolerability of secukinumab in patients with overuse rotator cuff tendinopathy over time.

1.3.3 Exploratory Objectives

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1.4 Study design and treatment

This is a randomized, double-blind, placebo-controlled, multi-center, Phase II study of s.c. secukinumab 300 mg in approximately 100 randomized patients with overuse rotator-cuff tendinopathy without systemic inflammatory disease and refractory to SAIDs/acetaminophen, physiotherapy or corticosteroids. The patient and investigator will be blinded throughout the study, while the sponsor will be blinded until after the analysis of the primary endpoint. The study consists of a 4-week screening period, a 2-week run-in period, a 12-week treatment period and a 12-week follow-up period after last treatment (Figure 1-1).

The population will consist of patients with MRI-positive unilateral overuse (non-systemic inflammatory) shoulder tendinopathy, 18 - 65 years of age. Symptoms should have been present for at least 6 weeks but not more than 12 months. The tendinopathy must have been refractory to NSAIDs/acetaminophen as defined in the inclusion criteria. On MRI, patients may have no tendon tear or a partial tendon tear (up to 50% thickness, in max. 50% of patients). The patients should also have had at least 2 weeks of a standardized physiotherapy treatment.

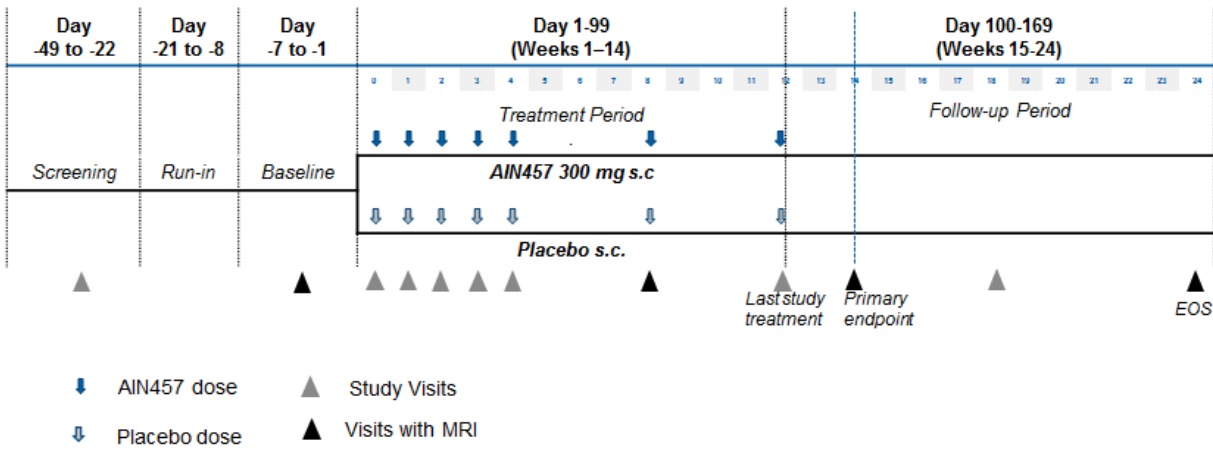
The screening period will be used to assess eligibility and to start/continue patients on physiotherapy. In the run-in period the patient should have 2 weeks of stable NSAID/acetaminophen intake and standardized physiotherapy (defined in the SOM). Patients who meet the eligibility criteria at screening after the run-in period will go through baseline evaluations.

Eligible patients as per inclusion/exclusion criteria will be randomized to one of the two treatment arms: 7 s.c. injections of secukinumab 300 mg or placebo in a 12-week treatment period, followed by a 12-week follow-up period. Randomization will be stratified by the following 2 factors: Partial tear/no tear and previous steroid injection (yes/no), in order to achieve approximate balance between these factors in the treatment groups. The assessments to address the primary endpoint will be performed at 14 weeks (2 weeks after the last injection).

Patients will come to the out-patient clinic approximately 2-4 hours prior to dosing for the evaluations. Dosing will be on-site, except for injections at 1 and 3 weeks, that can be done either on site or by a nurse at the patient's home.

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.

Figure 1-1 Study design



2 First interpretable results (FIR)

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3 Interim analyses

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4 Statistical methods: Analysis sets

For patients for which the actual treatment received does not match the randomized treatment the treatment actually received will be used for the analysis.

The safety analysis set will include all patients that received any study drug.

The PK analysis set will include all patients with at least one available valid (i.e. not flagged for exclusion) PK concentration measurement, who received any study drug and experienced no protocol deviations with relevant impact on PK data.

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

For efficacy data summaries and statistical analyses for the Day 127 visit, only patients who have completed the treatment Epoch will be included. For Day 169, only patients who have completed the treatment Epoch and have completed the Follow-up Epoch will be included.

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
Patients are excluded from PK analysis in case of these PDs:		
INCL01	<i>Written informed consent was not obtained before any study assessment was performed</i>	Exclude patient from PK analysis set Yes
Patients are excluded from PD analysis in case of these PDs:		
INCL01	<i>Written informed consent was not obtained before any study assessment was performed</i>	Exclude patient from PD analysis set Yes
INCL3B	<i>Patient did not fulfil the following: Tendinopathy with no more than a 50% tear as established by ultrasound at screening (historic data acceptable if not older than 3 months) and MRI at baseline: Sein MRI tendinopathy scoring system grade I-III; with no tear or partial tear [maximum 50% tendon thickness (Bauer tendon thickness score maximum 2); AP length maximum 10 mm (Bauer tendon length score max 2)]. Maximum 50% of patients with partial tear</i>	Exclude patient from PD analysis set
INCL3C	<i>Patient did not fulfil the following: Pain in the affected shoulder (at rest or on movement) on at least 3 days out of 7 days in the past week prior to baseline and a score of ≥ 4 out of 10 on a VAS pain scale</i>	Exclude patient from PD analysis set
COMD02	<i>Patient received prohibited concomitant medication</i>	Exclude patient from PD analysis set
Patients are excluded from PK and PD analysis in case of these PDs:		
INCL01	<i>Written informed consent was not obtained before any study assessment was performed</i>	Exclude patient from PK and PD analysis sets Yes

5 Statistical methods for Pharmacokinetic (PK) parameters

5.1 Variables

The following pharmacokinetic parameter will be determined using the actual recorded sampling times with Phoenix WinNonlin (Version 6.4 or higher): C_{min}. PK samples will be collected on Days 1, 29, 85, and at EOS.

5.2 Descriptive analyses

AIN457 serum concentration data will be listed by treatment, patient, and visit/sampling time point. Descriptive summary statistics will be provided by treatment and visit/sampling time point, including the frequency (n, %) of concentrations below the LLOQ and reported as zero.

Summary statistics will include mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum and maximum. Concentrations below LLOQ will be treated as

zero in summary statistics and for PK parameter calculations. A geometric mean will not be reported if the dataset includes zero values. Pharmacokinetic parameters will be calculated and will be listed by treatment and patient.

6 Statistical methods for efficacy parameters

Baseline is defined as day 1 or if data is missing at day 1 then the last non-missing pre-dose value will be used as the baseline.

6.1 Primary objective

The primary aim of this study is to assess the efficacy of secukinumab 300 mg s.c. vs. placebo in patients with overuse rotator cuff tendinopathy in relieving clinical symptoms at week 14.

6.1.1 Variable

The primary variable, the WORC score, will be available at pre-dose, day 1 and weeks 2, 4, 8, 12, 14, 18 and 24. The total score and the subscores will be included in the summaries and statistical analyses detailed in the following sections and will take the form of percentage of normal scores derived as:

- Physical symptoms score = $(600 - \text{sum of Physical symptoms answers})/6$
- Sports and Recreation score = $(400 - \text{sum of Sports and Recreation answers})/4$
- Work score = $(400 - \text{sum of Work answers})/4$
- Lifestyle score = $(400 - \text{sum of Lifestyle answers})/4$
- Emotions score = $(300 - \text{sum of Emotions answers})/3$
- Total score = $(2100 - \text{sum of all answers})/21$

If there are ≤ 2 missing values in a domain, the domain score can be calculated using the average of the other items in the domain. If there are more than 2 missing items in a domain, the concerning WORC questionnaire is considered incomplete and is excluded from the analyses.

6.1.2 Descriptive analyses

Descriptive statistics for actual results, changes from baseline and percentage change from baseline will be presented by treatment and timepoint and will be repeated for the subsets of patients with tear or no tear, as well as for the subsets of patients with steroid or non-steroid use prior to treatment.

6.1.3 Statistical model, assumptions and hypotheses

The primary end-point (change from baseline in WORC score at Week 14) will be analyzed by repeated measures analysis of covariance including all WORC scores available. The change at Week 14 will be compared between treatments to address the primary objective.

The baseline WORC score will be included as a covariate. The stratification factors partial tear/no tear and previous steroid injection (yes/no) will be included in the model as fixed effects along with fixed effects for treatment, timepoint and the treatment by timepoint interaction. An unstructured within-patient covariance will be considered.

The number of covariance and mean parameters may be reduced by model comparison tools such as the BIC criterion for model fit. Missing variables will be considered missing at random.

The adjusted mean of treatment effect at Week 14 as well as the difference between treatment arms will be reported along with a 95% one-sided (90% two-sided) confidence interval.

The primary analysis will also be repeated for patients where the affected arm is the dominant arm.

6.1.3.1 Model checking procedures

Residual plots will be produced to assess the adequacy of the models.

6.1.3.2 Graphical presentation of results

Data will be presented graphically using mean (SE) plots and repeated for the subsets of patients with tear or no tear, as well as for the subsets of patients with steroid or non-steroid use prior to treatment.

6.2 Secondary Objectives

6.2.1 Variables

Secondary variables include:

- Change from baseline in WORC score at weeks 2, 4, 8, 12, 18 and 24.
- Disability of Arm, Shoulder and Hand Questionnaire (QuickDASH) score at weeks 2, 4, 8, 12, 14, 18 and 24 (where available in local language/dialect).
- American Shoulder and Elbow Surgeons Shoulder Evaluation Form (ASES) score at weeks 2, 4, 8, 12, 14, 18 and 24
- EQ5D-5L your health today and index scores (see Appendix 1 for SAS code) at weeks 2, 4, 8, 12, 14, 18 and 24
- Pain score using a VAS scale (considering the last 24 hours) at weeks 2, 4, 8, 12, 14, 18 and 24
- Patient global assessment (PGA) score of disease activity, using a VAS scale (considering the last 24 hours), at weeks 2, 4, 8, 12, 14, 18 and 24
- Physician global assessment (PhGA) score of disease activity, using a VAS scale (considering the last 24 hours), at weeks 2, 4, 8, 12, 14, 18 and 24
- MRI Sein score at weeks 8, 14 and 24

6.2.2 Derivations and analysis considerations for secondary variables

Baseline is defined as day 1 or if data is missing at day 1 then the last non-missing predose value will be used as the baseline.

Quickdash

At least 10 of the 11 items must be completed for a score to be calculated. The assigned values for all completed responses are summed and averaged, producing a score out of five. This value is then transformed to a score out of 100 by subtracting one and multiplying by 25.

This transformation is done to make the score easier to compare to other measures scaled on a 0-100 scale. A higher score indicates greater disability.

ASES

The shoulder score is derived by the following formula:

$(10 - \text{Visual analog scale pain score}) \times 5 + (5/3) \times \text{Cumulative activities of daily living score}$.

Pain VAS

For Pain VAS the result from the site visit where the assessment date matches the actual visit date will be used in the summaries and analyses. If the result from the site is not available then the result from the diary data where the assessment date matches the actual visit will be used.

Sein Scores

The following rules will be applied for selection of the appropriate result for the descriptive statistics and statistical analyses:

- If an adjudicated result is present then it should be used as the result for that timepoint.
- If there are 2 results present that match then there was no need for an adjudicated result and either result can be used for the analysis, by default the first one will be used.
- If there is only 1 result available then this single result will be used in the analysis.

6.2.3 Descriptive analyses

Descriptive statistics will be presented by treatment and timepoint for actual results, changes from baseline and percentage change from baseline. A frequency table and a shift table will be provided for Sein scores. Summaries will also be presented by affected/unaffected arm/dominant/non-dominant arm as appropriate for selected endpoints.

For Pain VAS the descriptive statistics will be repeated for the subsets of patients with tear or no tear, as well as for the subsets of patients with steroid or non-steroid use prior to treatment.

6.2.4 Statistical model, assumptions and hypotheses

The secondary variables (except for the Sein score) will be summarized descriptively and analyzed similar to the primary analysis.

The secondary variable Sein MRI score at weeks 14 and 24 will be analyzed by ordinal categorical regression. A model with an additive treatment effect on the cumulative logistic scale will be used, and the common treatment effect estimated and reported together with 90% asymptotic two-sided confidence intervals. Baseline SEIN score will be included as a covariate and the stratification factors, partial tear/no tear and previous steroid injection (yes/no) will be included in the model as fixed effects.

All the secondary analyses will also be repeated for patients where the affected arm is the dominant arm.

6.2.4.1 Model checking procedures

Residual plots will be produced to assess the adequacy of the models.

6.2.4.2 Graphical presentation of results

Data will be presented graphically as mean (SE) profiles (apart from Sein scores). Graphical presentation of Sein scores using a barchart will be provided to highlight changes over time.

For Pain VAS the mean (SE) profiles will be repeated for the subsets of patients with tear or no tear, as well as for the subsets of patients with steroid or non-steroid use prior to treatment

6.3 Exploratory objectives

6.3.1 Variables

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6.3.2 Derivations and analysis considerations for exploratory variables

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6.3.3 Descriptive analyses

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7 Statistical methods for safety and tolerability data

7.1 Variables

Adverse events, serious adverse events, vital signs (blood pressure, pulse rate, body temperature), height and body weight, ECG evaluations, laboratory measurements (haematology, clinical chemistry, lipid panel, glucose, urinalysis, immunogenicity), tuberculosis screening, chest X-ray, ultrasound, local tolerability (injection site reactions), pregnancy testing, assessment of fertility, as well as patient demographics, baseline characteristics, patient examination, and treatment information.

7.2 Descriptive analyses

Patient demographics and other baseline characteristics

All data for background and demographic variables will be listed by treatment group and patient. Summary statistics will be provided by treatment group.

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

Treatment

Data for study drug administration and concomitant therapies (including rescue medication) will be listed by treatment group and patient.

Vital signs

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

Serum chemistries will include sodium, potassium, BUN/urea, bicarbonate, calcium, phosphorous, total protein, calcium, albumin, uric acid, creatinine, CK, total bilirubin, AST (SGOT), ALT (SGPT), GGT and alkaline phosphatase, at all timepoints specified in the Assessment schedule.

If the total bilirubin concentration is increased above 1.5 times the upper limit of normal, direct and indirect reacting bilirubin should be differentiated.

Triiodothyronine (T3), thyroxine (T4), thyroid-stimulating hormone (TSH), Rheumatoid factor (RF), anti-cyclic citrullinated peptide (anti-CPP) antibodies, and interferon-gamma release test done only at screening. FSH is only done at screening and only in patients who are reported post-menopausal at screening.

Adverse events

All information obtained on adverse events will be displayed by treatment group and patient. The number and percentage of patients with adverse events will be tabulated by body system and preferred term with a breakdown by treatment. A patient with multiple adverse events within a body system is only counted once towards the total of this body system.

Adverse event reporting for Clinical Trial Safety Disclosure (CTSD)

For the legal requirements of ClinicalTrials.gov and EudraCT, two required tables, 1) on treatment emergent adverse events which are not serious adverse events with an incidence greater than 0% and 2) 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. These tables will be produced by Novartis.

The summary will be done by treatment i.e. active (AIN457) or Placebo.

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.

Pregnancy test

All pregnancy test results for pre-menopausal women who are not surgically sterile will be listed by treatment, patient and visit/time.

Tolerability of investigational treatments

Tolerability will be assessed by adverse events, laboratory values, injection site reaction and immunogenicity. The local tolerability at the site of s.c. injection of the study treatment will

be assessed in case of any local reaction, until this has disappeared. The assessment of pain, redness, swelling, induration, haemorrhage and itching will be recorded, capturing AEs, including the severity (mild, moderate, severe) and the duration of the adverse reaction. Data will be listed and summarized by treatment group.

Immunogenicity

All immunogenicity results for AIN patients will be listed by treatment, patient and visit/time.

7.3 Graphical presentation

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

8 Appendices

8.1 Appendix 1

Computing EQ-5D-5L crosswalk index values with SAS using the United States (US) value set

The variables for the 5 dimensions of the EQ-5D-5L descriptive system should be named 'mobility', 'selfcare', 'activity', 'pain', and 'anxiety'. If they are given different names the syntax code below will not work properly. The 5 variables should contain the values for the different dimensions in the EQ-5D health profile (i.e. 1, 2, 3, 4 or 5). The variable 'EQindex' contains the values of the EQ-5D-5L crosswalk index values on the basis of the US set of weights.

You can copy and paste the syntax below directly into a SAS syntax window.

```
*****
```

```
*SAS syntax code for the computation of index*
```

```
*values with the US TTO value set*
```

```
*****;
```

```
data Euroqol.US_tto;  
set Euroqol.EQ5D_states;  
EQindex = .;
```

```
if (mobility=1 and selfcare=1 and activity=1 and pain=1 and anxiety=1) then EQindex = 1.000;  
if (mobility=1 and selfcare=1 and activity=1 and pain=1 and anxiety=2) then EQindex = 0.876;  
if (mobility=1 and selfcare=1 and activity=1 and pain=1 and anxiety=3) then EQindex = 0.844;  
if (mobility=1 and selfcare=1 and activity=1 and pain=1 and anxiety=4) then EQindex = 0.700;  
if (mobility=1 and selfcare=1 and activity=1 and pain=1 and anxiety=5) then EQindex = 0.550;  
if (mobility=1 and selfcare=1 and activity=1 and pain=2 and anxiety=1) then EQindex = 0.861;  
if (mobility=1 and selfcare=1 and activity=1 and pain=2 and anxiety=2) then EQindex = 0.820;  
if (mobility=1 and selfcare=1 and activity=1 and pain=2 and anxiety=3) then EQindex = 0.809;  
if (mobility=1 and selfcare=1 and activity=1 and pain=2 and anxiety=4) then EQindex = 0.669;  
if (mobility=1 and selfcare=1 and activity=1 and pain=2 and anxiety=5) then EQindex = 0.524;  
if (mobility=1 and selfcare=1 and activity=1 and pain=3 and anxiety=1) then EQindex = 0.827;  
if (mobility=1 and selfcare=1 and activity=1 and pain=3 and anxiety=2) then EQindex = 0.806;  
if (mobility=1 and selfcare=1 and activity=1 and pain=3 and anxiety=3) then EQindex = 0.800;  
if (mobility=1 and selfcare=1 and activity=1 and pain=3 and anxiety=4) then EQindex = 0.661;  
if (mobility=1 and selfcare=1 and activity=1 and pain=3 and anxiety=5) then EQindex = 0.517;  
if (mobility=1 and selfcare=1 and activity=1 and pain=4 and anxiety=1) then EQindex = 0.682;  
if (mobility=1 and selfcare=1 and activity=1 and pain=4 and anxiety=2) then EQindex = 0.663;  
if (mobility=1 and selfcare=1 and activity=1 and pain=4 and anxiety=3) then EQindex = 0.659;  
if (mobility=1 and selfcare=1 and activity=1 and pain=4 and anxiety=4) then EQindex = 0.544;  
if (mobility=1 and selfcare=1 and activity=1 and pain=4 and anxiety=5) then EQindex = 0.426;  
if (mobility=1 and selfcare=1 and activity=1 and pain=5 and anxiety=1) then EQindex = 0.463;  
if (mobility=1 and selfcare=1 and activity=1 and pain=5 and anxiety=2) then EQindex = 0.450;  
if (mobility=1 and selfcare=1 and activity=1 and pain=5 and anxiety=3) then EQindex = 0.446;  
if (mobility=1 and selfcare=1 and activity=1 and pain=5 and anxiety=4) then EQindex = 0.369;  
if (mobility=1 and selfcare=1 and activity=1 and pain=5 and anxiety=5) then EQindex = 0.289;  
if (mobility=1 and selfcare=1 and activity=2 and pain=1 and anxiety=1) then EQindex = 0.888;  
if (mobility=1 and selfcare=1 and activity=2 and pain=1 and anxiety=2) then EQindex = 0.846;  
if (mobility=1 and selfcare=1 and activity=2 and pain=1 and anxiety=3) then EQindex = 0.835;  
if (mobility=1 and selfcare=1 and activity=2 and pain=1 and anxiety=4) then EQindex = 0.695;  
if (mobility=1 and selfcare=1 and activity=2 and pain=1 and anxiety=5) then EQindex = 0.550;
```


[illegible]

[illegible]

[illegible]

[illegible]

[illegible]

[illegible]

[illegible]

[illegible]

[illegible]

[illegible]

[illegible]

[illegible]

[illegible]

[illegible]

[illegible]

```
if (mobility=5 and selfcare=5 and activity=5 and pain=3 and anxiety=1) then EQindex = 0.145;
if (mobility=5 and selfcare=5 and activity=5 and pain=3 and anxiety=2) then EQindex = 0.124;
if (mobility=5 and selfcare=5 and activity=5 and pain=3 and anxiety=3) then EQindex = 0.118;
if (mobility=5 and selfcare=5 and activity=5 and pain=3 and anxiety=4) then EQindex = 0.075;
if (mobility=5 and selfcare=5 and activity=5 and pain=3 and anxiety=5) then EQindex = 0.030;
if (mobility=5 and selfcare=5 and activity=5 and pain=4 and anxiety=1) then EQindex = 0.078;
if (mobility=5 and selfcare=5 and activity=5 and pain=4 and anxiety=2) then EQindex = 0.060;
if (mobility=5 and selfcare=5 and activity=5 and pain=4 and anxiety=3) then EQindex = 0.055;
if (mobility=5 and selfcare=5 and activity=5 and pain=4 and anxiety=4) then EQindex = 0.015;
if (mobility=5 and selfcare=5 and activity=5 and pain=4 and anxiety=5) then EQindex = -0.026;
if (mobility=5 and selfcare=5 and activity=5 and pain=5 and anxiety=1) then EQindex = -0.024;
if (mobility=5 and selfcare=5 and activity=5 and pain=5 and anxiety=2) then EQindex = -0.037;
if (mobility=5 and selfcare=5 and activity=5 and pain=5 and anxiety=3) then EQindex = -0.040;
if (mobility=5 and selfcare=5 and activity=5 and pain=5 and anxiety=4) then EQindex = -0.074;
if (mobility=5 and selfcare=5 and activity=5 and pain=5 and anxiety=5) then EQindex = -0.109;
```

```
if (mobility = .) or (selfcare = .) or (activity = .) or (pain = .) or (anxiety = .) then EQindex = . ;
```

```
output;
run;
```