CONFIDENTIAL

Statistical Analysis Plan (SAP)

Sponsor:	Kontigo Care AB Påvel Snickares Gränd 12 753 20 Uppsala Sweden
Study code:	KCClin02
Study title:	A second explorative pilot study evaluating usability and functionality of a new mobile phone application measuring eye parameters of eyes in patients with confirmed SUD
Date:	Version 1.0 15 August 2023

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1 LIST OF ABBREVIATIONS

ADE – Adverse Device Effect
AE – Adverse Event
ASADE – Anticipated Serious Adverse Device Effect
BMI – Body Mass Index
CIP – Clinical Investigational Plan
DSM-5 – The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
ECG – Electrocardiography
eCRF – Electronic Case Report Form
FAS – Full Analysis Set
IMD – Investigational Medical Device
NC – Non-convergence
NY – Horizontal nystagmus
PLR – Pupillary light reflex
PPS – Per Protocol Set
QC – Quality Control
SADE – Serious Adverse Device Effect
SAE – Serious Adverse Event
SAP – Statistical Analysis Plan
SD – Standard Deviation

2 INTRODUCTION

This Statistical Analysis Plan (SAP) gives details regarding the statistical analyses and data presentation outlined in the final Clinical Investigation Plan (CIP) dated [05-Dec-2022]. Any changes from the final CIP are given in Section 8.

The statistical methods described in this document yields when different from the statistical methods presented in the CIP as it should be clear what should be done.

3 CLINICAL INVESTIGATION DETAILS

3.1 Clinical Investigation Objectives

3.1.1 Primary objective

- Evaluate if the user-interface of the mobile phone application Previct Drugs is suitable to be used by patients with substance use disorder.

3.1.2 Secondary objectives

- Evaluate if self-administered pupillometry using a mobile phone application can be used to collect pupillograms for patients with substance use disorder.
- Evaluate if self-administered pupillometry using a mobile phone application, after refining the method for establishing pupillograms and key feature extraction algorithms, can be used to collect pupillograms from patients with substance use disorder.

3.1.3 Safety objective

Evaluate the safety of using the mobile phone application Previct Drugs for collecting self-administered pupillometry data in a substance use disorder population.

3.2 Clinical Investigation Design

KCClin02 is the second clinical investigation of Previct Drugs. The investigational design is a prospective, pilot, explorative, early feasibility, pre-market clinical investigation designed to collect initial clinical data to finalize the development of the first version of Previct Drugs intended to be CE-marked. The aim of the investigation is to evaluate the usability of Previct Drugs when being used by patients with confirmed Substance Use Disorder (SUD). The clinical data that will be collected is an important step in the product development of Previct Drugs as the data is required for continuing the development of the design of the eHealth system.

In this investigation, the investigational population will consist of patients with confirmed SUD in accordance with the CIP. SUD will be defined as a subject who in the last three months has visited the study site and has also been assessed by investigators or designee in accordance with the DSM-5 criteria.

Each subject will participate in the investigation for at least one day and maximum four weeks after the baseline visit. And the duration of the investigation is estimated to approximately 5 months with a recruitment period of 4 months.

3.3 Number of Subjects

The investigation aims to enroll up to 30 SUD subjects.
As this is an early feasibility and explorative investigation, the sample size is not derived from a sample size calculation as no hypothesis is pre-defined. It is based on available subjects from the clinic.

3.4 Methods of Assigning Subject to Device Groups

Once a subject has consented for study participation, the subject will be given a unique subject identification (subject ID) number. If the subject fulfills all inclusion criteria and none of the exclusion criteria, the subject will be seen as eligible.

3.5 Blinding

This in not applicable in this clinical investigation as there is only one treatment arm.

4 STATISTICAL AND ANALYTICAL PLANS

4.1 Sample Size Justification

As this is an early feasibility and explorative investigation, the sample size is not derived from a sample size calculation as no hypothesis is pre-defined. It is based on available subjects from the clinic. The aim is to enroll 30 SUD subjects.

4.2 Definition of Analysis Sets

4.2.1 Safety Analysis Set (SAF)

It is stated in the Clinical Investigational Plan (CIP) that all analyses will be performed on the Full Analyses Set (FAS). Full Analyses Set is defined as all subjects included in the clinical investigation with at least one pupillometric measurement. Hence, the SAF and the FAS will be identical.

4.2.2 Full Analysis Set (FAS)

Full Analyses Set is defined as all subjects included in the clinical investigation with at least one pupillometric measurement.

4.2.3 Use of Analysis Sets

All analyses will be performed on the Full Analyses Set (FAS).

4.3 Definition of Baseline

The baseline is defined as the first visit when the first test with Previct Drugs will be performed.

4.4 Summary Statistics

In general, all data collected will be presented with summary statistics and given in subject data listings (an overview of subject data listings are given in Section 9). Summary statistics will include number of subjects with data, number of subjects with missing data, mean, standard deviation, median, minimum and maximum for continuous data and frequency and percentage for categorical data.

4.5 Significance Level

Only descriptive statistics will be used and hence no p-values is planned to be presented. However, if p-values will be calculated these will be two-sided and p-values less than 5% considered statistically significant. If confidence intervals are constructed these will be 95% and two-aided.

4.6 Multiple Comparisons/Multiplicity

No adjustment for multiplicity of testing can be done as there are no tests.

4.7 Handling of Drop-outs, Missing Data and Outliers

Available data from prematurely withdrawn subjects will be included in the analysis as far as possible. Missing data will not be imputed.

4.8 Adjustment for Covariates

No adjustment for covariates is planned.

4.9 Multicenter Studies

This is a single center study.

4.10 Examination of Subgroups

No examination of subgroups is planned. However, the two light conditions will also be analyzed separately and may be considered as sub-groups analyses.

4.11 Blind Review

Not applicable as this is an uncontrolled study.

5 SUBJECTS

5.1 Subject Disposition

The number of subjects that entered the study, withdrawn subjects, completed subjects and the number of subjects at each visit will be summarized.

5.2 Baseline Characteristics and Demographics

Demographics (e.g., age, gender,) and baseline characteristics (e.g., ECG, relevant medical and surgical history, relevant concomitant medication, timeline follow-back drugs and medicine last 24-hours) will be presented using descriptive statistics.

6 TREATMENT INFORMATION AND EXTENT OF EXPOSURE

6.1 Active Treatment

There is no active treatment involved, the device usability will be tested.

6.2 Placebo Treatment

Not applicable

6.3 Extent of Exposure

At Visit 1, the subject will perform an eye measurement series which consists of four performed measurements:

- 1 Cross-eyes test
- 1 Nystagmus test
- 2 Contraction tests

The contraction tests must be performed under two different light conditions. The subject must begin by performing a cross-eye-test, followed by a nystagmus test, and then a contraction test. Adjust the lighting conditions, wait 1 minute, and then perform the second contraction test.

Additional measurements with Previct Drugs during follow-up visits are optional for the study subjects. Up to four (4) follow-up visits within one month after completed Visit 1 is allowed.

6.4 Compliance of Investigational Medical Device (IMD)

During each measurement the Previct Drugs app will inform if the conducted test was approved. If not approved, the subject will be asked to re-do the measurement. If the test cannot be conducted, the subject continues to the next test, or completes the test set, as applicable.

Performed and successful tests are documented in the eCRF for Visit 1 and if applicable for the follow-up visits. The number of attempts per test is not documented in the eCRF. During the on-site visits, compliance is overseen by site personnel. Sponsor is the only part receiving the Previct Drugs data output. Non-compliance related to Previct drugs measurements will be documented by the Sponsor, and where applicable be reported as Protocol Deviations.

6.5 Concomitant Medications

Subjects are allowed to continue their regular medication during the clinical investigation. Relevant concomitant medication data will be listed only.

7 STATISTICAL METHODOLOGY

All efficacy parameters will be presented by treatment and visit using summary statistics.

7.1 Primary efficacy endpoint

7.1.1 Definition

The analysis of the following 18 usability questions from the observation of a study subject during a test with Previct Drugs.

1. Please evaluate the study subject's ability to use the mobile phone?

2. How did you perceive the study subject's ability to follow the instructions given by Previct Drugs?

3. If you experienced that the study subject had difficulties, please select the suitable choice/choices below.

4. How did the study subject experience to put him/herself in the right position to be able to start a test?

5. If you experienced that the study subject had any difficulty, please select the suitable choice/choices below.

6. How would you evaluate the study subject's ability to perform a Cross-eyes test?

7. If you experienced that the study subject had difficulties, please describe:

8. How would you evaluate the study subject's ability to perform a Nystagmus test?

9. If you experienced that the study subject had difficulties, please describe:

10. How would you evaluate the study subject's ability to perform a Contraction Test?

11. If you experienced that the study subject had difficulties, please describe:

12. How did the study subject experience keeping the phone still during the test?

13. If the study subject had difficulties, please select the suitable choice/choices below.

14. In addition to the basic instructions, did the study subject need additional support performing tests with Previct Drugs?

If No, please forward to question no. 17.

15. What type of additional support did the study subject need? Please select the suitable choice/choices below.

16. Was the study subject able to perform the test after receiving additional support?

17. How many efforts did it take the study subject to perform test with Previct Drugs?

18. How likely do you think it is that the study subject will be able to perform tests with Previct Drugs without assistance in a home environment?

7.1.2 Analysis

1.Frequency table for each of the 18 questions with numbers and percentage for each alternative.

2. For answers "very easy" and "easy" and answers, "very good" and "good" favoring Kontigo product will be added together and given with numbers, percentages and 95% confidence intervals.

7.1.3 Presentation

All data collected from patients included in the FAS will be presented with summary statistics, i.e. number of observations, number of missing observations, minimum value, median value, maximum value and standard deviation for continuous data and frequency and percentage for categorical data. Summary statistics will include number of subjects with data, number of subjects with missing data, mean, standard deviation, median, minimum and maximum for continuous data and frequency and percentage for categorical data.
Table with summary statistics will be divided by treatment group, visit and relevant stratification factors such as the light conditions.
An example in the tables below.

Table 1 Example of a table presenting data for continuous variable.

Statistica	Group 1	Group 2	Group 3	Group 4
N	X	X	X	X
Missing	X	X	X	X
Min	X.XX	X.XX	X.XX	X.XX
Median	X.XX	X.XX	X.XX	X.XX
Mean	X.XX	X.XX	X.XX	X.XX
Standard deviation	X.XX	X.XX	X.XX	X.XX

Table 2 Example of a table presenting data for a categorial variable.

Statistica	Group 1	Group 2	Group 3	Group 4
Missing	X (%)	X (%)	X (%)	X (%)
Category 1	X (%)	X (%)	X (%)	X (%)
Category 2	X (%)	X (%)	X (%)	X (%)
:	:	:	:	:
:	:	:	:	:
Category n	X (%)	X (%)	X (%)	X (%)

7.2 Secondary Efficacy Endpoints

7.2.1 Definitions

Secondary 1

Fraction of collected pupillometry data using native pupillogram.
For each of the measurements PLR, NC, and NY the measurements QC control will approve the measurements or not using the native pupillogram.

Secondary 2

Fraction of collected pupillometry data using refined pupillogram.
For each of the measurements PLR, NC, and NY the measurements QC control will approve the measurements or not using the refined pupillogram.

7.2.2 Analyses

Secondary 1

For each subject, the proportion of approved measurements over all measurements during visit 1 will be calculated for each of PLR, NC, NY, TR and Redness. The two light conditions will be analyzed separately for for PLR. The follow-up analyses will be analyzed separately and compared with the success rate at visit 1.

Secondary 2

For each subject, the proportion of approved refined measurements over all measurements during visit 1 will be calculated for each of PLR, NC, NY, TR and Redness.. The distribution over subjects in each drug class will be given with Mean, SD, median, minimum and maximum. The two light conditions will be analyzed separately. The follow-up analyses will be analyzed separately.
and compared with the success rate at visit 1.

7.2.3 Presentation

All data collected from patients included in the FAS will be presented with summary statistics, i.e. number of observations, number of missing observations, minimum value, median value, maximum value and standard deviation for continous data and frequency and percentage for categorical data. Summary statistics will include number of subjects with data, number of subjects with missing data, mean, standard deviation, median, minimum and maximum for continuous data and frequency and percentage for categorical data.
Table with summary statistics will be divided by treatment group, visit and relevant stratification factors such as the light conditions.
An example in the tables below.

Table 3: Example of a table presenting data for a continuous variable.

Statistica	Group 1	Group 2	Group 3	Group 4
N	X	X	X	X
Missing	X	X	X	X
Min	X.XX	X.XX	X.XX	X.XX
Median	X.XX	X.XX	X.XX	X.XX
Mean	X.XX	X.XX	X.XX	X.XX
Standard deviation	X.XX	X.XX	X.XX	X.XX

Table 4: Example of a table presenting data for a categorial variable.

Statistica	Group 1	Group 2	Group 3	Group 4
Missing	X (%)	X (%)	X (%)	X (%)
Category 1	X (%)	X (%)	X (%)	X (%)
Category 2	X (%)	X (%)	X (%)	X (%)
:	:	:	:	:
:	:	:	:	:
Category n	X (%)	X (%)	X (%)	X (%)

7.3 Safety Endpoints

For full details on Adverse Events (AEs), Adverse Device Effects (ADEs), Serious Adverse Events (SAEs), Serious Adverse Device Effects (SADEs) and Unanticipated Serious Adverse Device Effect (USADE) please see KC09-104 Clinical Investigation Plan_KCClin01_RevC_31Mar2023.

Adverse Event (AE)

Untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users, or other persons, whether or not related to the investigational medical device and whether anticipated or unanticipated.

Note 1: This definition includes events related to the investigational medical device or the comparator.

Note 2: This definition includes events related to the procedures involved.

Note 3: For users or other persons, this definition is restricted to events related to the use of investigational medical devices or comparators.

Adverse Device Effect (ADE)
Adverse event related to the use of an investigational medical device.

Note 1: This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device.

Note 2: This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.

Note 3: This includes 'comparator' if the comparator is a medical device.

Serious Adverse Event (SAE)
Adverse event that led to any of the following:

a) death,
b) serious deterioration in the health of the subject, users, or other persons as defined by one or more of the following:
    i. A life-threatening illness or injury, or
    ii. A permanent impairment of a body structure or a body function including chronic diseases, or
    iii. In-patient or prolonged hospitalization, or
    iv. medical or surgical intervention to prevent life-threatening illness or injury, or permanent impairment to a body structure or a body function,
c) foetal distress, foetal death, a congenital abnormality, or birth defect including physical or mental impairment.

Note: Planned hospitalization for pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event.

Serious Adverse Device Effect (SADE)
Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

Serious safe threat
Signal from any adverse event or device deficiency that indicates an imminent risk of death or a serious deterioration in the health in subjects, users, or other persons, and that requires prompt remedial action for other subjects, users, or other persons.

Note: This would include events that are of significant and unexpected nature such that they become alarming as a potential serious health hazard or possibility of multiple deaths occurring at short intervals.

Unanticipated Serious Adverse Device Effect (USADE)
Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current risk assessment.

Note: Anticipated Serious Adverse Device Effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk assessment.

AEs will be documented as reported in the eCRF, without use of specific coding dictionaries.

7.3.1 Analyses

Safety data will, as all other variables, be presented using summary statistics.

7.3.2 Presentation

AE/ADE:
The following summaries of AEs and SAEs will be given by for each medicinal product group and in total:

- Total number of AEs
- Total number of unique AEs
- Total number of unique, related AEs
- Total number (%) of subjects with at least one AE
- Total number (%) of subjects with at least one related AE
- Total number (%) which had AE as reason for premature discontinuation of IMD

Severity, action taken, concomitant therapy started, and subject outcome of the AEs will be given in data listings only. AEs, which were reason for premature discontinuation of IMD, will be listed separately.

The total number of SAEs and patients with a least one SAE will be given. Further summaries of SAEs depending on the number of SAEs observed.

SAE/SADE:
SAEs/SADEs, if any, will be listed only.

7.4 Interim Analysis

There will be no interim analysis in this clinical investigation.

8 CHANGES FROM THE CIP

No changes from the CIP are presented in this SAP except that missing data is added to the list of summary statistics.

9 STATISTICAL DELIVERABLES

The following documents will be delivered:

- SAP
  - This document and hereby delivered
- Statistical analyses and summary tables
  - This will delivered as the result of the statistical analyses and as well used as background material for the Clinical Investigational Report (CIR)
- Appendices with patient data listings:
  - Discontinued patients
    - This is a part of the clean file documentation but will as well be delivered as a part of the Statistical Report
  - CIP deviations
    - This is a part of the clean file documentation but will as well be delivered as a part of the Statistical Report
  - Patients excluded from the efficacy analysis
    - Assume this means excluded from FAS and these patients will be reported as described above
  - Demographic
    - This will be included in the Statistical Report and in the CIR
  - Exposure to IMD
    - This will be included in the Statistical Report and in the CIR
  - Individual efficacy response (both primary and secondary variables)
    - This is not applicable in this study considering the design. However, all relevant efficacy data will be presented by subject and as summary statistics.
  - Adverse event
    - This will be included in the Statistical Report and in the CIR
  - Listing of individual laboratory measurements
    - This will be included in the Statistical Report and in the CIR
  - Timeline follow-back- drugs and medicine the last 24 hours
    - This will be included in the Statistical Report and in the CIR
  - ECG

- This will be included in the Statistical Report and in the CIR

10 SOFTWARE

The statistical software used will be described in the statistical analysis report but will probably be Excel (latest available version in Office 365), STATA (version 16.0) and StatXact (version 11.1.0).

11 REFERENCES

KC09-108 Clinical Investigation Plan_KCClin02_RevA-5Dec2022

12 APPROVAL

Issued by:

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