CONFIDENTIAL

CLINICAL INVESTIGATION PLAN (CIP)

Clinical Investigation 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
Clinical Investigation Code:	KCClin02
Single identification number:	CIV-22-11-041210
Investigational Device(s):	Previct Drugs
Coordinating/Principal Investigator:	Johan Månflod
Sponsor:	Kontigo Care AB Påvel Snickares Gränd 12 753 20 Uppsala Sweden
Date:	05-Dec-2022

Revision	**Version History**
A	First release

This clinical investigation will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. Furthermore, the clinical investigation will be performed in compliance with ISO 14155:2020, Regulation (EU) 2017/745 and applicable regional or national regulations.

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This Clinical Investigation Plan contains privileged or confidential information, which is the property of the Sponsor. Information may not be disclosed to a third party without written authorization from the Sponsor.

1 SYNOPSIS

NAME OF THE SPONSOR:
Kontigo Care AB
Påvel Snickares Gränd 12
753 20 Uppsala
Sweden

CLINICAL INVESTIGATION 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

CLINICAL INVESTIGATION CODE:

KCClin02

INVESTIGATIONAL DEVICE(S):

Previct Drugs

OVERALL CLINICAL INVESTIGATION DESIGN:
This will be a pre-market, explorative, early feasibility, pilot, controlled clinical investigation designed to collect initial clinical data for the new medical device Previct Drugs. The collected data in this early feasibility study is an important step in the product development of Previct Drugs as the data (together with data from a parallel pilot investigation) is required for continuing the development of the mathematical models and algorithms for drug detection.

The study results will give valuable information on the feasibility of Previct Drugs through measuring the subjects' pupils and eye movements. It will also provide information on the usability of the Previct Drugs.

Previct Drugs is a new non-CE-marked eHealth system intended to be used for future monitoring and treatment of patients with substance use disorder (SUD).Previct Drugs consists of an application (app) to be installed on a smartphone, and a web-based careportal that can be accessed by the healthcare professional for administration and access of registered data, and a database for storage, handling, and analysis of reported data. Previct Drugs is intended to be used by healthcare professionals and patients within treatment of SUD.

In the version of Previct Drugs to be used in this investigation there will be some exceptions compared to the future intended product:

- The careportal will only be used for providing a subject access to the app
- An external computer will be used for the analysis of the collected data from the app
- An R&D cloud will be used for storing the data and results after the study is completed

The investigation will enroll and follow male and female subjects 18 years or older with confirmed SUD, defined as a recurrent visitor at Sprututbytesprogrammet in Uppsala within the last three (3) months, and SUD in accordance with DSM-5 criteria according to investigator/designee judgement. The investigation population will consist of approximately 15-30 subjects (including approximately 20 % dropout rate) fulfilling the eligibility criteria for the clinical investigation. The subjects will be recruited in Sweden.

A potential subject will be asked for participation by the site team. The site team will verbally describe the study procedures, assessments, benefits, and risks and provide the potential subject with a study specific information sheet. The potential subject will be given adequate time to consider participation before signing and dating the informed consent form. The informed consent shall be countersigned and dated by the investigator or designee who provided the information. The informed consent shall be duly signed before any study-specific activities take place.

Before visit 1 the investigator or designee summarizes the information and provides the study subject with written information. At visit 1, once the informed consent has been duly signed, baseline data will be collected e.g., demographics, past and current drug use, and a breath sample for LC-MS/MS analysis and other common baseline data such as relevant medical and surgical history, and relevant concomitant medication. Before the first test with Previct Drugs is performed the site personnel will demonstrate the device whereafter a first test will be done by the subject. The site personnel will observe and assist as required. One test with Previct Drugs contain three different measurements of which the last one will be performed twice in two different light conditions. Through observing the subject during a test, the site personnel will answer questions related to the usability of the device. At visits 2, 3,

and 4, the same clinical measurements and data collection performed at visit 1 will be repeated except for demographics and medical and surgical history. The total study time for a study subject will be 1 day or a maximum of 4 weeks if the study subject chooses to make any or all of the follow-up visits.

Any relevant concomitant medications used during the study will be recorded.

Any adverse events that have taken place after signed informed consent will be recorded. Relevant adverse events before signed informed consent will be recorded as medical and surgical history.

The duration of the investigation is estimated to approximately 5 months, including a 4-month recruitment period.

It is estimated the first subject will be enrolled in Q1 2023.

INCLUSION AND EXCLUSION CRITERIA:

Inclusion Criteria

The subjects have to meet all of the following criteria to be eligible to participate in the clinical investigation:

1. Signed Informed Consent Form
2. Male and female
3. A recurrent visitor at Sprututbytesprogrammet in Uppsala defined as visited the clinic within the last three (3) months
4. SUD in accordanve with DSM-5 criteria according to investigator/designee judgement
5. Age 18 and above
6. Negative urine pregnancy test for all fertile women
7. Been informed of the nature, the scope, and the relevance of the clinical investigation
8. Voluntarily agreed on participation and has duly singed the Informed Consent Form

Exclusion Criteria

Subjects meeting any of the following criteria will not be permitted to participate in the clinical investigation:

1. Participating in another clinical investigation which may affect the study outcome according to clinical judgement
2. Pregnancy or lactating
3. Blind
4. Deaf
5. Any ECG dangerous arrythmia according to the investigator or designee judgement
6. Any disease or condition that may influence pupillary reflexes based on clinical judgement
7. Undergone eye surgery that may influence pupillary reflexes based on clinical judgement
8. Not able to read or understand the local language
9. Any planned travel or treatment which will make it impossible to participate according to the investigator or designee
10. Any other condition that as judged by the investigator may make the follow-up or investigation inappropriate
11. That according to the Declaration of Helsinki is deemed unsuitable for study enrolment

OBJECTIVES:

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.

Secondary Objective(s)

- 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.

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.

PERFORMANCE AND SAFETY ENDPOINTS:

Primary Endpoint

- Observation of a study subject during a test with Previct Drugs through answering the following 18 usability questions:

  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?

Secondary Endpoint(s)

- The fraction of collected pupillometry data from the mobile phone application, which can be transformed into pre-defined key features using native pupillograms.
- The fraction of collected pupillometry data from the mobile phone application, which can be transformed into pre-defined key features using refined pupillograms and and key feature extraction algorithms.

Safety Endpoint

- The incidence and severity of adverse events associated with Previct Drugs.

STATISTICAL METHODS:
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. Two light conditions will also be analyzed separately.

Performance Analysis
Primary analysis: Frequency tables for each of the 18 usability questions in primary endpoint at visit 1 with numbers and percentage for each alternative.

Secondary analysis: Fraction of collected pupillometry data using native/refined pupillogram.
For each of the measurements PLR, NC, and NY the measurements QC control will approve the measurements or not using the native/refined pupillogram. For each subject, the proportion of approved measurements over all measurements during visit 1 will be calculated for each of PLR, NC, and NY. The two light conditions will be analyzed separately. The follow-up analyses will be analyzed separately.

Sample size calculation:
No formal sample size calculation has been performed. Based on available subjects at site.

Safety Analysis:
Safety analyses will only be given descriptively.

2 SPONSOR CIP APPROVAL PAGE

The undersigned, hereby confirms that they have read and understood the content of this Clinical Investigation Plan (CIP) and further approves its content.

_____ _____

Markku Hämäläinen, CSO
Kontigo Care AB

Date (dd-Mmm-yyyy)

_____ _____

Maria Winkvist, Product Manager
Kontigo Care AB

Date (dd-Mmm-yyyy)

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4 ABBREVIATIONS AND ACRONYMS

ADE	Adverse Device Effect
AE	Adverse Event
ASADE	Anticipated Serious Adverse Device Effect
CIP	Clinical Investigation Plan
CIR	Clinical Investigation Report
CRF	Case Report Form
CRO	Contract Research Organization
DMC	Data Monitoring Committee
DMP	Data Management Plan
DMR	Data Management Report
DVP	Data Validation Plan
EEA	European Economic Area
EU	European Union
FDA	Food and Drug Administration
FIM	First in Man
GDPR	General Data Protection Regulation
IB	Investigator Brochure
ICF	Informed Consent Form
IEC	Independent Ethics Committee
ISF	Investigator Site File
ISO	International Organization for Standardization
MDD	Medical Device Directive – Council Directive 93/42/EEC
MDR	Medical Device Regulation – Regulation (EU) 2017/745
PI	Principal Investigator
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SDV	Source Data Verification
SMF	Study Master File
SOP	Standard Operating Procedure
USADE	Unanticipated Serious Adverse Device Effect
WMA	World Medical Association

5 INTRODUCTION

This clinical investigation is an industry-sponsored investigation funded by Kontigo Care AB. A clinical investigation agreement has been established by the sponsor and each participating investigational site, detailing roles, responsibilities, and financial arrangements.

5.1 Background

The rising prevalence of recreational drugs has resulted in addiction becoming a global public health concern, creating financial, emotional, and social burdens for the affected individuals and their surrounding network. In 2014, about 20 million Americans, met the diagnostic criteria of substance use disorder (SUD) in the US. Six million were linked to illicit drug substances, while approximately 16 million were associated with alcohol use disorder (AUD)[1]. In 2015, over 27 million people aged 12 or older were recreational drug users with the highest incidence seen among the age group ranging from 18 to 25. More than 50 000 people were reported to have died from an overdose that year[2]. During the opioid epidemic in 2018, there were 128 deaths per day reported in the US due to an opioid overdose, according to the National Institute of Health. In Europe, the number of adults that used drugs of abuse was estimated to be 96 million in 2019[3].

Despite the high incidence rate of additive disorders, only a small number of patients receive adequate treatment. Major obstacles for treating addiction involve difficulty in diagnosing the disease, detecting patients that are at risk at early stages, as well as the daily monitoring of symptoms and treatments, including self-management[4].

The most common methods for drug detection and analysis of drugs are liquid chromatography (LC), and gas chromatography (GC) coupled with mass-spectrometry (MS) that provide multiple samples with low limit of detection to be quantitatively assayed. However, while these methods have shown to reliably detect the drugs and their metabolites, they suffer from the limitation that they are based in laboratories and are not readily affordable portable detection device for capturing both qualitative and quantitative information with regards to drug use[3].

Recent advances, both in the treatment of substance abuse as well as compliance to medical therapies include mobile technologies that incorporate physiological sensing and computational methods for analysis and serve as a platform for healthcare delivery. Importantly, mobile health (mHealth) applications provide means for remote data collection and patient monitoring, point-of-care diagnostics, as well as promotion of healthy behaviors and health education[5]. Digital behavioral health therapeutics can incorporate mixed media, such as audio, video or text messages, animation, avatars, and virtual reality to allow the content to be tailored to the need of the individual and promote engagement, an essential factor for the intervention to succeed[6].

The drugs associated with SUD are centrally acting drugs, many of which are commonly known to affect the pupil diameter, the ability to track a moving object with saccadic movements, and the light reflex. As drugs are interacting with receptors in the brain and then also interact with nerves and muscles relevant for pupil and eye movement leads to that drug presence can be identified using pupillometric methods [7]. Stimulants (e.g., amphetamine) cause mydriasis (pupil dilation) with variable effects on the light reflex, opiates constrict the pupil (miosis) and in turn reduce the pupillary light reflex (PLR), while smoking cannabis has been shown to obtund the light reflex. Furthermore, while cannabinoids affect saccadic movement, use of benzodiazepines can be manifested with horizontal gaze nystagmus[8]. Previously both qualitative, semi-quantitative, and laboratory based pupillometric data have been used to identify the connections between changes in eyes parameters related to use of different drug classes [9-10]. Nowadays devices, like pupillometers, that can utilize the effect of such drugs on the eye, by capturing the dynamic (light reflex parameters, saccadic and smooth pursuit eye movement) as well as static (pupil size) ocular and pupillary response, may provide meaningful tools for drug detection and monitoring. Remote drug testing is an area where despite progress over the past decades, significant research is needed to provide accurate, sensitive, and feasible devices ~~both~~ for monitoring the compliance of patients in drug rehabilitation programs.

Kontigo Care AB has developed the new medical device Previct Drugs to be used for measuring pupillometric parameters of eyes for future monitoring of patients in treatment of SUD. Previct Drugs is a standalone medical device software classified as a class I medical device according to the Medical Device Regulation (EU) (MDR) 2017/745 [11]. Previct Drugs pupillometry function is implemented in a smartphone application (app), which uses the smartphone's camera to record videos of the pupil and eye movement, and the resulting data is processed to identify drug. Previct Drugs is thereby a portable device easily used by the user in the home environment.

Previct Drugs is one of the devices developed by Kontigo Care that belongs to the Previct Platform. Today the Previct Alcohol is a CE-marked medical device to be used within treatment and monitoring of alcohol use disorder.

This second clinical investigation of Previct Drugs will be 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 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 study 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. The population will consist of approximately 20-30 subjects fulfilling the eligibility criteria for the clinical investigation. The subjects will be recruited at in Sweden. Each subject will participate in the investigation for at least one day and maximum four weeks after the baseline visit.

The clinical investigation must be reviewed, and approval obtained, by an Independent Ethics Committee (IEC) and the Competent Authority (CA) in each participating country prior to start. The clinical investigation is designed and will be performed in accordance with the MDR, ISO 14155:2020, Declaration of Helsinki, and applicable regional or national regulations

6 IDENTIFICATION AND DESCRIPTION OF THE INVESTIGATIONAL DEVICE

The below is a summary of the investigational device, Previct Drugs, to be used in this clinical investigation [12-14].

Kontigo Care AB has developed the new eHealth system Previct Drugs that uses a smartphone camera-based eye measurement, i.e., pupillometry, to be used in future monitoring and treatment of patients with SUD. Through using Previct Drugs, the healthcare professional will be able to administrate and monitor the patient's treatment of SUD. Previct Drugs contains an app, to be installed on a compatible smartphone and used for eye measurements, a web-based careportal to be accessed from a computer by the healthcare professional for administration and access of registered data, a database for storage, handling, and analysis of reported data, and an admin portal for customer settings, device registrations, and invoicing.

Compared to other versions of Previct that are available on the market today, Previct Drugs rely on the same back-end (web-based careportal, database, and admin portal) whereas the app is amended to conduct a different measurement than what the other versions of Previct currently do. Hence, most portions of the Predict Drugs infrastructure are identical to other existing products.

In the version of Previct Drugs to be used in this investigation there will be some exceptions compared to the future intended version:

- The careportal will only be used for providing a subject access to the app.
- An external computer will be used for the analysis of the collected data from the app.
- An R&D cloud will be used for storing the data and results after the study is completed.
- If it is required to use the admin portal during the investigation it will only be used for tasks such as providing access to the careportal and registration of the study specific smartphones.

Figure 1 below summarize the different parts of Previct Drugs to be used in this investigation.

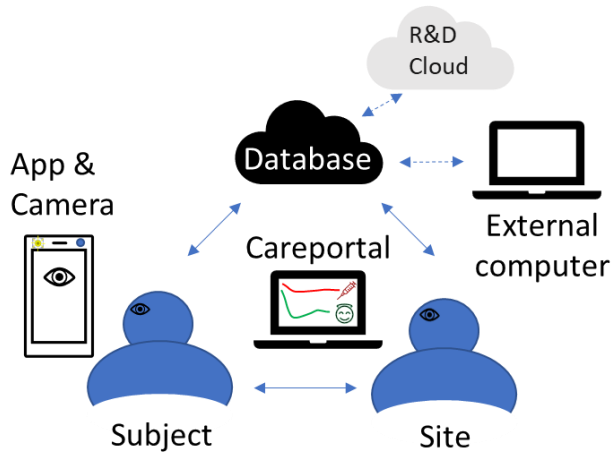

Figure 1. Summary of the different parts of Previct Drugs to be used in this investigation. The subject will perform self-administered eye measurements through the app using the smartphone camera. The results from the eye measurements will be stored in the database and further analysis will be performed in the external computer whereafter these results will also be stored in the database. Once the investigation is completed, the data results will be transferred to the R&D cloud. The careportal will in this investigation be used only for providing a subject access to the app.

The eye measurements with Previct Drugs will in this investigation be performed by the participating subjects. The site personnel will assist as required. A measurement is started in the app by the subject where a video of the face area is recorded through the camera of the study specific smartphone. Before the video recording is started, it will be confirmed that the ambient light is acceptable for the intended imaging. If required, the app will guide the subject to a location where the light condition is suitable. During a test with

Previct Drugs app, three different videos, i.e., measurements, are recorded whereafter the videos are automatically processed. The three different measurements that will be performed during one test are:

1) Pupillary light reflex (PLR)
2) Non-convergence (NC)
3) Horizontal nystagmus (NY)

For the PLR-measurement, the subject will be filmed while the led-lamp on the smartphone is turned on. For the NC-measurement, the subject will be filmed while receiving instructions to cross the eyes. For NY-measurement, the subject will be filmed while looking to the far side.

The three different measurements rely on pupil size (PLR) and iris position (NC and NY). The size and position indicators are extracted using an algorithm implementing artificial intelligence (AI). In parallel with the three pupillometry measurements, the color of the white of the eye is estimated in the PLR measurement (because the led lamp of the mobile phone evens out some of the effects of ambient light) and user motion patterns (tremor) is evaluated in the NY measurement.

Once completed, each video is automatically quality controlled. The evaluation of PLR, NC, and NY measurements rely on data where almost all videos need to be successfully converted to pupil size or iris position. The evaluation of motion patterns (tremor) relies on the position of the eye in collected images, and if too many consecutive images are missing the measurement is unusable. The color of the whites of the eye can be measured in any successful video during the PLR measurement if the led lamp is turned on, meaning it will always succeed if the PLR measurement succeeds. The subject will receive a notification if the measurement was performed successfully or not. The videos and the pupillometric variables will be transferred to the database for storage and to the external computer for further analysis.

In the external computer, key features (parameters that summarize different aspects of the collected raw data/pupillometric variables) will automatically be calculated from the pupillometric variables. As this is an early feasibility study, it is assumed that pupillometric variables will not be able to be processed for all videos with the current pre-defined mathematical models in Previct Drugs. [redacted] During the update of the current mathematical and algorithm models, the data scientists at the software department at the sponsor will have access to the full videos that needs to be annotated. No other personnel at the sponsor will have access to this material.

Once the investigation is completed, the videos will be deleted and only a cut-out of the eye area from the videos will be transferred together with the pupillometric variables and key features to the R&D cloud where it will be stored. It is the stored data and results in the R&D cloud that will be used for continued product development after this clinical investigation.

The web-based careportal will in this investigation be used by the investigator or designee at a participating site for giving a subject access to the app. No other modules in the careportal will be used.

In future version of Previct Drugs, it is assumed that the analysis of the eye measurements will be performed in the app and the results will thereafter be presented in the app to the patient and in the careportal for efficient monitoring and follow-up of the patient's sobriety, mode, feelings, and cravings. Previct Drugs will also be able to be used for follow-up on therapy compliance through that the patient reports on performed tasks, attendance to narcotics anonymous (NA) meetings, and answering questionnaires and assignments as appropriate. For compliance and to encourage the patient to perform the measurements with the app, the patient will in future versions receive personalized messages and trophies when measurements and additional tasks have been successfully completed.

6.1 Manufacturer

Kontigo Care AB is the manufacturer of Previct Drugs with headquarter in Uppsala, Sweden.

6.2 Identification of Investigational Medical Device

The following version of Previct Drugs (Table 1) will be used the investigation.

Table *1*. Description of the versions of the different Previct Drugs parts to be used in the clinical investigation.

Previct Drugs parts	Version
App	2.18
Web-based careportal	2
Database	N/A
R&D cloud	N/A
External computer	N/A
Admin portal	N/A

Previct Drugs app will be accompanied by an electronic study specific Instructions For Use (IFU). Previct Drugs will also be labeled electronically in the app. The IFU and label will clearly describe that Previct Drugs is to be used for clinical investigation only. Below in Figure 2, is an example of the electronic label that will be available in the app.

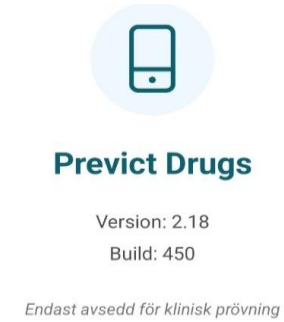

Figure *2***.** Example of the electronic label to be available in the app.

There are no accessories for Previct Drugs.

6.3 Device Traceability

The sponsor and site personnel will keep records documenting traceability of the Previct Drugs app version used in the investigation. The device accountability log at site will include the following information:

- Date and Previct Drugs app version provided to site
- Date, Previct Drugs app version, and subject ID once provided access to subject
- Date withdrawn access for subject
- Date withdrawn access for site

The sponsor will also provide the site with smartphones to be used by the participating subjects during the clinical investigation. All measurements will be performed at the clinic with the study team present. The equipment accountability log on the site will include the following information:

- Date and a smartphone identification provided to site
- Date used by subject
- Date returned from site

The device and equipment accountability may be recorded in the same log.

6.4 Intended Purpose

For the future version of Previct Drugs intended to be CE-marked, the following will be the intended purpose [15]:

Previct Drugs is an eHealth (electronic health) system intended to, in complement with other sources of information*, be used to aid individualized treatment and follow-up of patients undergoing treatment for SUD **. The patient performs regular self-tests for drug sobriety, reporting of mood and executed tasks. The healthcare professional can access the results displayed in the careportal. The results from Previct Drugs intends to aid the healthcare professional to monitor the estimated drug sobriety, therapy adherence and mood of the patient for the purpose to assess the need for follow-up care visits or other actions.
**Such as blood/saliva/urine tests, patient drug use history, behavioral and cognitive findings, patient motivation.*

***Substances of opioids, benzodiazepines, cannabinoids, and central stimulants (e.g., amphetamine and other phenethylamines).*

For the clinical investigation, the following is the intended purpose:
Previct Drugs is an eHealth system intended to be used in the clinical investigation by the investigational site for administration of eye-measurements. It will be used by patients for performing location independent self-administered eye-measurements.

6.5 Indication and Population

For the future version of Previct Drugs intended to be CE-marked, the following will be the indication, intended users, and target population:

- **Indication:** Diagnosed SUD where drug use may occur during the treatment for recovery [15].
- **Intended users:** Healthcare professionals working with treatment for SUD, and patients diagnosed with and in treatment program for SUD. It is the healthcare professional responsibility to assess and decide if Previct Drugs is suitable for use for the individual patient [15].
- **Target population:** Men and women, 18 years and older or younger men and women if healthcare professionals find it suitable [15].

For the clinical investigation, the following is the indication, intended use enviroment, intended users, and target population:

- **Indication:** Not applicable. The indication for being included in the investigation is to be a patient defined as SUD determined by the investigator or designee.
- **Intended use environment:** Previct Drugs is intended to be used at the clinic by patients who participate in the clinical investigation, and by the study team at the study site.
- **Intended users:** Site personnel and patients participating in this clinical investigation for eye-measurements [13].
- **Target population:** men and woman, 18-65 years [13].

6.6 Technical and Functional Features

Previct Drugs contains the functionalities described in Table 2 below. The table describes which functionalities that will be available in the version of Previct Drugs to be used in this investigation.

Table 2. Previct Drugs contains the following functionalities whereof the ones in italic font will be available in the version of Previct Drugs to be used in this investigation.

Technical Functionality	Where	Who	Data generated Task fulfilled
Pupillary light reflex (PLR)	App	Subject	Pupillogram: PLR pupillometric variables, eye-color
Nystagmus (NY)	App	Subject	Pupillogram: NY pupillometric variables, tremor
Non-Convergence (NC)	App	Subject	Pupillogram: NC pupillometric variables
Key-features calculations	External computer	Data scientist (if required)	
Web-based careportal	Web-application	Site	Registration of subject
Database	Database	N/A	Storage of data
Mood (questionnaire)	App	Patient answer	Caregivers define and select questions, monitor mood

Technical Functionality	Where	Who	Data generated Task fulfilled
Feelings	App	Patient answer	Caregivers can monitor feelings
Cravings	App	User defines when they get. Gets a plan to handle cravings.	Caregivers define actions for relapse prevention
Web-based careportal	Web-application	Caregiver	Data display in calendars and graphs
Scheduling of tests	Careportal	Caregiver	Time when test will be done in the app

6.7 Manufacturing and Materials

Previct Drugs is a medical device software. Manufacturing and materials are therefore not applicable. For further information on the development and validation, please see Investigators Brochure [16].

6.8 Training and Experience

Investigator and site personnel training will take place by sponsor and Contract Research Organization (CRO) representatives prior to subject recruitment to ensure that Previct Drugs will be used in accordance with the study specific IFU, that complete, accurate and timely data are submitted, that protocol requirements are followed, and that complications, adverse events (AEs) and adverse device effects (ADEs) are correctly reported and investigated, as appropriate. The Principal Investigator (PI) will ensure that appropriate training relevant to the clinical investigation is given to any other site personnel involved in the investigation and that new information of relevance to the performance of the investigation is forwarded to all personnel involved.

It is the responsibility of the sponsor to ensure that involved personnel is appropriately trained on Previct Drugs.

The site personnel are responsible for ensuring that appropriate training is provided to each participating subject according to the CIP and the IFU [13].

6.9 Installation and Use

The installation and use of the different parts of Previct Drugs that will be involved in this investigation is summarized below.

The web-based careportal:

- Kontigo Care will send an email to the investigator or designee that will be responsible for the careportal at the participating site.
- The email will contain information on how to set up an account for the careportal including a link to be used for the investigator or designee to choose a password to be used.
- Once a password has been selected, the investigator or designee will login to the careportal using the selected email address and password. A login code will be sent to the investigators or designees email address. The login code is to be used for login to the careportal.
- The careportal will in this investigation be used for setting up a new user, i.e., participating subject, where the study specific subject ID number will be added only. No other information will be added about the subject in the careportal.

The app:

- Study specific smartphones and chargers will be handed to the site and at each visit out to the participating subjects.

- During the test at the study site, the subject will receive a phone with a pre-installed and activated instance of Previct Drugs. The subject will return the phone after completing the test.
- For performing a test with Previct Drugs, the subject will go to "My tools" and thereafter select "Previct Drugs".
- A quality control will automatically be performed on the smartphone. If the smartphone is not fulfilling the requirements, the subject till receive a notification in the app. The subject should then contact the site personnel for assistance.
- The app will then show instructions regarding how to perform a measurement.
- The subject should thereafter select "Start test".
- The smartphone should be held by the user with approximately 20 cm from the face. The app will verify that the surroundings fulfil the requirements for perform a measurement when a video is recorded of the subject's face and eye area. If this cannot be confirmed, the app will guide the subject how to change the surroundings for performing a measurement.
- A measurement starts with a notification sound whereafter the app will guide the subject how the measurement should be performed.
- After a measurement is completed, an analysis will start to verify if the measurement was performed successfully or not. The subject will be notified accordingly in the app. If the measurement is not performed successfully, the subject should try to perform the measurement one more time.
- In total three different measurements, i.e., video recordings (NC, NY and PLR), will be performed after each other. Thereafter the test is completed for the subject.
- The measurements will be automatically processed to the pupillometric variables and thereafter the videos and the pupillometric variables will be transferred to the database. The videos and variables will not be available in the app/smartphone any longer.

For further guidance, please see the study specific IFU [13].

The database:
The database will be used in the investigation for storage of the videos, pupillometric variables, and key features during the investigation.

The external computer:
The external computer will be used for processing pre-defined key features from the pupillometric variables.

[redacted]

Direct access to the videos is limited to the data scientists at the sponsor's software department. Most videos will not be inspected by anyone as they can be processed automatically by the pre-defined mathematical and algorithms model.

The R&D cloud:
Once the investigation is complete, the pupillometric variables, key features, and cut-out eye areas of the videos will be transferred to a separate and secure R&D cloud for storage. The other parts of the videos will be destroyed. The data in the R&D cloud will be used for the continued development of Previct Drugs after the investigation. Once transferred to R&D cloud, data is permanently deleted from the database. All storage is encrypted and entirely hosted within the European Union/Sweden.

7 JUSTIFICATION OF CLINICAL INVESTIGATION DESIGN

Before this clinical investigation, Previct Drugs has been evaluated in relevant pre-clinical testing and assessments. For a summary on the pre-clinical testing, please see the Investigators Brochure [16].

In parallel to this second clinical investigation a first-in-human early feasibility investigation in healthy volunteers is planned to be performed in the Netherlands.

This second pilot, explorative, early feasibility, pre-market clinical investigation aims to collect usability clinical data of Previct Drugs once used in the intended population (patients with SUD). In addition, it will also give valuable information on the feasibility of Previct Drugs function to measure pupils and eye movement and that it is safe to be used in the intended patient population. The clinical data collected is an important step in the product development of Previct Drugs as the data is required for continuing the development of the mathematical models for signal processing and algorithms for drug detection. The outcome will serve as a basis for finalizing the design of Previct Drugs after this investigation, and continuous studies in clinically significant settings prior to CE marking. For further details on the clinical research program, please see the Clinical Development Plan (CDP) available in the Clinical Evaluation Plan (CEP) [17].

An explorative design has been selected as it is a common approach when there is little or no experience of using a medical device in humans. This investigation is also an early feasibility study where the design of the medical device is not finalized, and the data collected as part of the investigation is required to complete the design.

The endpoints selected to be evaluated in this investigation, have been identified as proper ones to receive preliminary information on the usability of Previct Drugs.

In this study, patients with a known addiction will be studied from a usability perspective. It is important to collect eye data on patients with a substance use disorder. This population is also similar to the group of patients for which the product is intended to be used in the future.

It has been decided that at least one test with Previct Drugs is acceptable given the selected study population. The investigation is designed for three follow-up visits. The follow-up visits are optional for the study subject to complete within a time frame of four weeks after the baseline visit.

This study population was selected to obtain data on usability for a similar population for which the product will be used in the future, as well as to collect eye data on patients with a current addiction.

Applicable inclusion and exclusion criteria have been decided based on the subject population to have a homogenic group, minimize aspects that may interfere with the results of the study, and making sure that any potential risks and safety concerns have been addressed during the screening period before confirming a subject is eligible for participation.

8 BENEFITS AND RISKS OF THE INVESTIGATIONAL DEVICE, CLINICAL PROCEDURE, AND CLINICAL INVESTIGATION

When discussing benefits and risks of a new medical device, there are different aspects that have to be considered, including the potential benefits and risks for the subjects participating in the clinical investigation and for future patients with clinical use of the new device.

The risk management related to Previct Drugs has been conducted in accordance with ISO 14971:2020 and included risk analysis, risk evaluation, and risk control.

The below will summarize potential risks and benefits related to the product, Previct Drugs, and the ones for the clinical investigation related to the study design, assessments, and study population. For detailed information on the performed risks analyses, see respective report/analysis [18-19].

8.1 Anticipated Clinical Benefits

There are no direct clinical benefits for the participating subjects. This is a patient population that usually does not participate in clinical trials, which will probably be appreciated. Although, through participating the subject will assist the sponsor to collect the data required for finalizing the design and evaluate the usability of Previct Drugs after this investigation. It is assumed that the benefit to patients with confirmed SUD will eventually be high once CE-marked and launched on the market.

8.2 Residual Risks and Anticipated Adverse Device Effects

During the risk analysis, hazards and hazardous situations associated with Previct Drugs when used as intended, use errors and reasonably foreseeable misuse have been considered. Risks associated with body contact (mobile phone and computer keyboard) as related to biocompatibility and risks related to information security have also been considered and included.

In total, 47 risks were identified of which 40 are insignificant risks after mitigation and 7 risks that need to be further investigated during the product development of Previct Drugs. No remaining risks are unacceptable after mitigation.

Risk controls have been implemented for all identified risks. There are no remaining risks which needs to be further investigated for risk reducing measures. The risks that were identified as unacceptable before risk mitigation measures were controlled to a satisfactory level and no additional risk control measures were deemed to be necessary. All defined risk control measures have been adequately implemented and verified as part of the testing activities during the product development phase.

The risks can be summarized into 18 different types of hazards, primarily relating to user error and function that could result in an incorrect measurement, erroneous value or false positive and in turn lead to a wrong or missed necessary patient treatment.

The different types of hazards are:

- Use error: knowledge-based failure (5)
- Use error: routine violation (8)
- Use error: rule based (4)
- Use error: related to IFU (2)
- Normal use patient shaking (1)
- Function (1)
- Function: incorrect input (2)
- Function: data transfer (5)
- Function: data loss (7)
- Function: incorrect input (2)
- Function: design (5)
- Information security (1)

- Leads to false security (1)
- Labeling loss (1)
- Biocompatibility: Chemical residues (1)
- Cyber security (1)

The identified hazards may lead to the following adverse events:

- Wrong or missed necessary treatment
- Eyes get irritated

The first listed adverse event related to Previct Drugs is not relevant for this investigation as not action related to treatment will be taken based on the results from Previct Drugs. The second listed adverse event related to irritation in eyes after measurement with Previct Drugs is assumed to be low or non-existing based on the time the flashlight will be used and the distance between the smart phone's camera and the eye area during a measurement.

8.3 Risks Associated with Participating in the Clinical Investigation

Hazards and hazardous situations specifically associated with the study design, assessments, and population have been considered and evaluated. In total, 18 risks were identified of which 17 are insignificant risks after mitigation and 1 risk that need to be further investigated. No remaining risks are unacceptable after mitigation.

The risks can be summarized into 13 different types of hazards, primarily relating to function and usability in the investigation.

- Function: design (2)
- Function: incorrect input (1)
- Function: data loss (1)
- Function: data transfer (4)
- Pilot study not performed as planned (1)
- Pilot study not successful: (1)
- Use error: routine violation (2)
- Use error: rule based (1)
- Use error: knowledge-based failure (1)
- Study assessments: (1)
- Normal use subject shaking (1)
- Non-CE marked product available on the market (2)

During the clinical investigation there is a very small possibility that the identified hazards may lead to the following adverse events:

- Dizziness and/or nausea during test as eyes must be moved from one side to the other side.
- Dizziness and/or nausea during sampling with Breath Explore as several deep breaths for a few minutes is done.

8.4 Possible interactions with concomitant medical treatments

The potential interaction with any ongoing medication during the investigation deems to be low. Study subject enrolled to this investigation is not excluded due to any medication. The use of therapeutic medication, in addition to drug abuse, will be monitored during the study.

8.5 Risk Control

The potential risk for the subject during usage of Previct Drugs is assumed to be low or non-existing based on the identified potential adverse events listed above. Before the subjects will use Previct Drugs themselves, they will receive demonstration and training and will be under

observation during usage of Previct Drugs as all measurements will be at the site. The site personnel will also assist as required during a measurement.

It should also be mentioned that as part of an investigation, the subjects will be well taken care of and monitored closely.

The reporting of adverse events related or unrelated to the device or procedure, and monitoring described in sections 13 and 19, respectively, will assure early detection of any increased risk or unanticipated subject safety concerns.

8.6 Benefit-to-Risk Rationale

In this investigation, there is no specific benefit for the participating subjects. The potential risk of adverse events is seen as low based on the mitigating activities described above. The future benefit of Previct Drugs once being used as intended will eventually be high. Hence, we believe that the benefit-to-risk rationale is in favor of benefit to patients and to society for future usage.

9 OBJECTIVES AND HYPOTHESES OF THE CLINICAL INVESTIGATION

9.1 Primary Objective

The primary objective is to:

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

9.2 Secondary Objectives

The secondary objectives are to:

- 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.

9.3 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.

9.4 Hypothesis

As this is an early feasibility clinical investigation, no hypothesis has been pre-specified since the data collected in this investigation is required for continued product development of Previct Drugs whereafter further investigation(s) will be performed in relevant settings before CE-marking.

In early feasibility investigations, it is also common that no hypothesis can be pre-specified based on the design of the investigation.

9.5 Claims and Intended Performance of the Investigational Device

The following claims are suggested for Previct Drugs to collect preliminary evidence:

- Previct Drugs enables self-administered pupillometry using a commercially available smartphone.

The primary endpoint relates to the evaluation of specific usability questions about the usefulness of Previct Drugs through observation by the site personnel.

9.6 Risks and Anticipated Adverse Device Effects

No specific risks and anticipated device effects to be evaluated in the investigation. See section 19 for details on how AEs will be recorded and reported during the investigation.

10 DESIGN OF THE CLINICAL INVESTIGATION

10.1 General

This will be a pre-market, explorative, early feasibility, pilot, controlled clinical investigation designed to collect initial clinical data for Previct Drugs. The clinical data collected in this early feasibility study together with the data from the KCClin01 investigation, is an important step in the product development of Previct Drugs as the data is required for evaluating the usability and continuing the development of the mathematical models and algorithms for drug detection.

This investigation will give valuable information on the usability of Previct Drugs once being used in patients with confirmed SUD according to the definition in the CIP. In addition, it will also give valuable information on the feasibility of Previct drugs function to measure pupils and eye movements.

Potential study subjects interested to participate in this investigation will be provided with verbally and written information about the investigation. Each potential subject will be provided with the subject information sheet that explains the investigation, procedures, risks, and benefits. If a subject thereafter consents to participate, the informed consent will be signed and dated by the subject and the investigator who provided the information. The investigation will continue with screening and baseline collection to confirm eligibility. Relevant baseline data will be collected including first measurements with Previct Drugs at the site. The follow-up visits are optional but up to three visits can be scheduled within a period of four weeks after the baseline visit. Four weeks after the baseline visit, the subject will be terminated from the study, even if no follow-up visit was made. It is also possible that all clinic visits are completed faster than the study timeline of four weeks.

The clinical investigation procedures are further explained in section 10.8.

The overall duration of the clinical investigation is anticipated to be approximately 3 months, including two months enrolment period.

No comparator will be used in this investigation as it is an early feasibility study to collect initial data on Previct Drugs.

10.2 Primary Endpoint

- Observation of a study subject during a test with Previct Drugs through answering the following 18 usability questions:

  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?

10.3 Secondary Endpoint(s)

- The fraction of collected pupillometry data from the mobile phone application, which can be transformed into pre-defined key features using native pupillograms.

- The fraction of collected pupillometry data from the mobile phone application, which can be transformed into pre-defined key features using refined pupillograms and key feature extraction algorithms.

10.4 Safety Endpoint

The incidence and severity of adverse events associated with Previct Drugs.

10.5 Investigational Device

The subject will perform two sets of eye measurement tests with Previct Drugs at the first and follow-up visits (if follow-up visits are performed). Each eye measurement set consists of four tests:

- 1 Cross-eyes test
- 1 Nystagmus test
- 2 Contraction tests at 2 different light conditions

10.6 Subjects

10.6.1 Inclusion Criteria

The subjects have to meet all of the following criteria to be eligible to participate the investigation:

1. Signed Informed Consent Form
2. Male and female
3. A recurrent visitor at Sprututbytesprogrammet in Uppsala defined as visited the clinic within the last 3 months
4. SUD in accordance with DSM-5 criteria according to investigator/designee judgement
5. Age 18 years and older
6. Negative urine pregnancy test for all fertile women
7 Been informed of the nature, the scope, and the relevance of the clinical investigation
8 Voluntarily agreed to participation and has duly singed the Informed Consent Form

10.6.2 Exclusion Criteria

Subjects meeting any of the following criteria will not be permitted to participate in the investigation:

1. Participating in another clinical investigation which may affect the study outcome according to clinical judgement
2. Pregnancy or lactating
3. Blind
4. Deaf
5. Any ECG dangerous arrythmia according to the investigator or designee judgment
6. Any disease or condition that may influence pupillary reflexes based on clinical judgement
7. Undergone eye surgery that may influence pupillary reflexes based on clinical judgement
8. Not able to read or understand the local language
9. Any planned travel or treatment which will make it impossible to participate according to the investigator or designee
10. Any other condition that as judged by the investigator may make the follow-up or investigation appropriate
11. That according to the Declaration of Helsinki is deemed unsuitable for study enrolment

10.6.3 Relationship of Investigation Population to Target Population

In this early feasibility investigation of Previct Drugs, it has been decided to use patients with SUD according to the definition in the CIP to collect usability data. The assumed intended population for Previct Drugs that will be CE-marked is patients diagnosed with SUD where Previct Drugs will be used to aid individualized treatment and follow-up of patients undergoing treatment for SUD. The data collected in this investigation will thereby be collected from a very similar population Previct Drugs is intended to be used for.

Data from Previct Drugs measurements will also be collected from this population, which will provide valuable input for continued development of the mathematical models and algorithms for drug detection with Previct Drugs after the investigation is completed.

10.6.4 Number of Subjects

The investigation population will be comprised of 15-30 SUD patients between 18 to 65 years eligible for study participation according to the inclusion and exclusion criteria. If a subject is a screening failure, it will be replaced with another subject.

10.6.5 Methods of Assigning Subjects to Different Treatment Arms

This investigation will contain up to 30 eligible subjects and there will only be one treatment arm.

10.6.6 Subject Withdrawal, Discontinuation, or Lost to Follow-up

Subjects are free to discontinue participation in the clinical investigation at any time and are not required to give a reason for their decision. However, subjects who discontinue the investigation should, if possible, be asked about the reason(s) for their discontinuation and about the presence of any AE/ADE and, if possible,

be assessed by an investigator. Discontinuation from the clinical investigation will not affect the future treatment/care of the subject.

If the subject will withdraw his/her consent no further data will thereafter be recorded. Data collected up to the date of withdrawal of informed consent will be used in the data analysis and for the Clinical investigation Report (CIR).

Subjects may be withdrawn from the clinical investigation and assessments at any time, if deemed necessary by the PI.

Specific reasons for withdrawal of subjects from this clinical investigation are:

- The decision of a subject to withdraw from the investigation (including if the subject withdraws informed consent);
- The Principal Investigator deems the subject unfit for the investigation or suspects poor CIP compliance;
- Subject lost to follow-up;

Incorrectly enrolled subjects will be withdrawn from further investigation and assessments. A subject may, however, continue the clinical investigation under exceptional circumstances (i.e. if continuation of investigation or follow-up are necessary for the subject's safety and wellbeing, or if only a follow-up period remain, and the continuation of the investigation is not expected to be associated with any risk or discomfort for the subject).

10.6.7 Subject Follow-up and Care

Each subject will participate for a minimum of 1 day and a maximum of four (4) weeks after the baseline visit. This investigation period has been decided to be appropriate as it will provide usability data in a population Previct Drugs is intended for. The flexible follow-up period has been decided based on that it is difficult to schedule follow-up visits for this population and that data collection from one visit is enough even though that it would be valuable from a usability perspective to collect data from several visits.

If the clinical investigation is prematurely terminated, the sponsor and the PI(s) will assure that adequate consideration is given to the protection of subjects' interest, including subject follow-up.

10.7 Clinical Investigation Duration

Point of enrolment:	Q1 2023
Point of randomization:	Not applicable
Enrolment period:	4 months
Expected duration of each subject's participation:	1 month
Total expected duration of the clinical investigation:	5 months

10.8 Clinical Investigation Procedures

10.8.1 Schedule of Clinical Investigation Procedures /Assessments

The assessments and procedures that will be performed during the clinical investigation is illustrated in Table 3 below. Further information is provided in the sections below.

Table 3. Clinical Investigation schedule for assessments and procedures.

Assessment	Before visit 1	Visit 1 Day 0	Follow-up visit(s)	Termination
Study information (written and oral)	X			
Signing Informed Consent		X		
Inclusion/Exclusion criteria		X		
Pregnancy test for fertile women (urine)		X	X	

Assessment	Before visit 1	Visit 1 Day 0	Follow-up visit(s)	Termination
ECG (if older than 2 years)		X		
Relevant concomitant medication		X		
Medical and surgical history		X		
Breath test (sample collection for LC/MS-MS analysis)		X	X	
Subjects Demographics[1]		X		
Timeline follow-back drugs and medicines last 24 hours		X	X	
Demonstration of Previct Drugs		X	X	
Measurements with Previct Drugs		X	X	
PI/designee questionnaire /observation (usability)		X	X	
Questions to PI/designee on Previct Drugs		X	X	
Adverse event and/or device deficiency		X	X	X
PI/designee inform subject about follow-up visits(s)[2]		X	X	
End of investigation				X

Notes:
[1]Age, gender
[2]Maximum four (4) follow-up visits, incl visit 1.

10.8.1.1 Subject information (Before visit 1)

Prior to the baseline and visit at Day 0, potential subjects that are interested to participate will contact the site. A poster at the investigational site will inform about the study. The site personnel will give information about the study and perform a brief check towards the eligibility criteria. The investigator or designee will introduce the clinical investigation and explain the objectives of the investigation and assessments and procedures to be performed to a potential subject. The investigator will verbally inform the patient about the study in an understandable manner. The oral information will be an important part before the consenting process. It will be given at the study site, and then the patient can ask questions and return at later occasion before consenting and enrolment in the study. Any queries that a potential subject may have regarding the investigation will be addressed appropriately by the investigator. Potential subjects will be instructed that they are free to obtain further information from the investigator at any time and that they are free to withdraw their consent and to discontinue their participation in the investigation at any time without prejudice.

10.8.1.2 Visit 1 (Baseline Visit)

Before any investigation-related procedures are initiated, the informed consent form (ICF) must be signed and dated by the subject and by the investigator who gave the subject the verbal and written information. The original ICF document will be retained in the Investigator Site File (ISF) and a copy provided to the subject. The investigator must obtain written informed consent from the subject before any clinical investigation-related procedures are performed, for further details on the informed consent process please see section 18.

After written informed consent has been obtained the subject is considered as enrolled. The subject will be allocated to the next available subject ID number, used for the identification of the subject in the investigation.

An enrolled subject will go through the screening parameters, e.g., relevant medical/surgical history, review of relevant current medication, and information on the subjects' demographics. ECG examination will be performed if the existing measurement is older than 2 years. The investigation also requires that a pregnancy test in fertile female subjects is analyzed. A breath test ~~urine~~ test will be performed for determine the drug

content through LC/MS-MS analysis. Information on a subject's drug intake will be collected in the timeline follow-back of drugs and medicines last 24 hours.

After confirmation of the inclusion and exclusion criteria, the subject will be assessed as eligible. If the subject is not eligible, i.e., not fulfilling one of the inclusion criteria or fulfilling one of the exclusion criteria, the subject is to be seen as a screening failure and should be terminated from continuing in the investigation.

Previct Drugs measurement
The first test with Previct Drugs will take place once the subject has been assessed as eligible. The site personnel will demonstrate for the subject how Previct Drugs shall be used according to the IFU, and the procedures described in this CIP. The site personnel will assist as required during a test with Previct Drugs. 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.

At Visit 1, the following assessments/procedures will be performed:

- Informed consent
- Demographics:
  - Age
  - Gender
- Registration of relevant medication
- Relevant medical and surgical history
- ECG (if existing < 2 years)
- Urine pregnancy test for fertile females
- Breath test for measuring drug content with LC/MS-MS analysis
- Time line follow-back on drugs and medicines the last 24 hours information
- Demonstration of Previct Drugs
- First test with Previct drugs
- Investigator/designee observation during measurement and reply on usability questions
- Questions to study subject
- Questions to PI/designee on Previct Drugs
- Recording of adverse events or device deficiencies
- Investigator/designee to inform subject about follow-up visit(s) and /or termination

10.8.1.3 Follow-up visit (maximum three (3) visits)

Follow-up visits are voluntary and the number of follow-up visits per study subject will be based on the study timeline. There is no specific number of follow-up visits, or time between, that need to be followed.

At Visit 2, 3 and 4 the following assessments will be performed:

- Registration of relevant medication
- Urine pregnancy test for fertile females
- Breath test for measuring drug content with LC/MS-MS analysis
- Time line follow-back on drugs and medicines the last 24 hours information
- Demonstration of Previct Drugs
- Measurement with Previct drugs
- Investigator/designee observation during measurement and reply to usability questions
- Questions to study subject
- Questions to PI/designee on Previct Drugs

- Recording of adverse events or device deficiencies
- Investigator/designee to inform subject about follow-up visit(s) and /or termination

10.8.2 Screening/Baseline Measurements

The data collected at visit 1 during screening and baseline will describe the study population and confirm eligibility. Age and gender will be recorded. ECG, if older than 2 years, relevant medical and surgical history and relevant current medication will be recorded. Relevant medical and surgical history is defined as any previous or existing condition that may potentially affect the outcome of the study according to the best judgment of the investigator or designee.

Pregnancy test and confirmation

Woman of childbearing potential (defined as all women who are not surgically sterile or postmenopausal for at least 1 year prior to enrollment) must have a negative urine pregnancy test at enrollment. If the pregnancy test is positive the subject is not eligible and cannot be enrolled in the investigation.

Exhaled breath test drug testing (Breath Explor®)

To measure the actual content of drugs a breath test will be performed. The breath test is not mandatory and will be carried out on a voluntary basis. This test will be used for a qualitative detection of thirty-six (36) most common drugs using LC-MS/MS analysis method.

3_CMC, 4-flouro amphetamine, 4-FMA, 4-MMC, 6-MAM, alprazolam, amphetamine, buprenorphine, BZE, CBD, clonazepam, codeine, diazepam, EDDP, ephedrine, flunitrazepam, gabapentinin, hydromorphone, ketamine, cocaine, lorazepam, LSD, MDMA, methadone, methylamphetamine, methylfenidat, morphine, oxazepam, ocycodon, pentedrone, pregabalin, temazepam, THC, tramadol zolpidem, zopiclone.

10.8.3 Performance Variables and Measurements

10.8.3.1 Previct Drugs - pupillometric variables and key features

Previct Drugs will be used for collecting data on eye parameters and tremor during each visit. From each test, data on pupillometric variables and key features will be extracted. Drug intake, if any, will in this second investigation only be monitored, if feasible , using breath tests combined with timeline follow-back interview where drugs use the last 24 hours is recorded.

:

The aim of the eHealth system is to detect the use of phenethylamines (D1), benzodiazepines (D2), cannabinoids (D3), and opioids (D4). They all affect different eye parameters and movements (tremor) as summarized in section 7. Thereby, it is assumed that the following parameters (alone or in combination) will be affected once under influence of each drug class:

- Phenethylamines (D1): pupil size, light reflex, and tremor
- Benzodiazepines (D2): light reflex, non-convergence, nystagmus, color of sclera, and tremor
- Cannabinoids (D3): pupil size, non-convergence, and color of the sclera
- Opioids (D4): pupil size and light reflex

During a test with Previct Drugs, three measurements will be performed (NC, NY and PLR,). From the measurements five pupillograms (pupillometric variables) are extracted, and from which 23 key features will be calculated. The pupillograms are time series measuring the variation in the size of the pupil, position of the iris, x/y variation in the position of the eye (tremor), and the color of the sclera (redness over time). Quantitative pupillometry transform the pupillograms into key features. The first set of key features extracted and used in this investigation is further explained in the sections below. The number of pre-defined key features are for:

- PLR: 6 basic and 3 combined (for both left and right eye)
- NC: 1 combined (calculated from 3 basic)
- NY: 4 basic (for both left and right eye)

For tremor, 8 key features will be calculated. For color of sclera, 1 key feature will be calculated.

For the key features where values are received for both left and right eye, an average value will be calculated. It should also be noted that the algorithms used to extract both pupillograms from videos and calculation of the key features are proprietary.

See Table 4 below for a summary of measurements, pupillograms, and key features extracted after a test with Previct Drugs.

Table 4. Summary of the measurements, pupillograms, and key features extracted after a test with Previct Drugs.

Measurement	Pupillometric variable	Key feature
PLR (for both left and right eye, mean values will be calculated)	Variation in size of pupil	1. Dbase 2. Latency 3. MCV 4. Dcon 5. Ctime 6. Dend 7. MCA 8. RMCA 9. Pesc
NC	Position of iris	1. NCdiff: NCdiff for NCnf>5, NCdiff = 0 for NCnf<=5
NY	Position of iris	1. NYmass 2. NYnumber 3. NYmaxAMP 4.NYaverageAmp
Tremor*	x/y variation in the position of the eye	1. Mm5 2. Mm10 3. Mm30 4. D1m 5. D2m 6. Pa 7. Pb 8. Pc
Color of sclera**	Redness of the eye	1. Redness

*Measured in the NY measurement.
**Measured in the PLR measurement.

Pupillary light reflex (PLR) measurement

The PLR will measure the contraction pattern of the pupil upon stimulating the eye with light. The ambient light level will be calculated through the smartphone's camera. The contraction pattern is clearly affected when influenced with certain type of drugs and is a common measurement in emergency medical care and by law enforcement in traffic controls. During the PLR measurement, the app will record the eyes during the time the flashlight of the smartphone camera is illuminating the eyes for approximately 4.5 seconds. Shortly after the light is turned off the video recording is stopped. The ambient light level will be calculated through the smartphone's camera. From the PLR measurement, the following pre-defined key-features will be extracted based on current knowledge [7, 20]:

- Dbase: baseline pupil diameter, before light reaction
- Latency: time from start of illumination to start of pupil contraction
- MCV (maximum contraction velocity): maximum slope of the contraction curve during the acute contraction phase
- Dcon: pupil diameter at the time when the acute pupil contraction has ended
- Ctime: contraction time, i.e., the time from start of pupil contraction until the acute pupil contraction has ended
- Dend: pupil diameter at the end of the illumination (i.e., after about 4.5 seconds of illumination)

Through combining the above key features, the following derived key features will also be extracted:

- MCA (maximum contraction amplitude): Dbase - Dcon
- RMCA (relative MCA): MCA/Dbase *100
- Pesc (Pupil escape): Dend – Dcon

Figure 3 below shows an example of a pupillogram for the PLR measurement and the pre-defined key features that will be extracted.

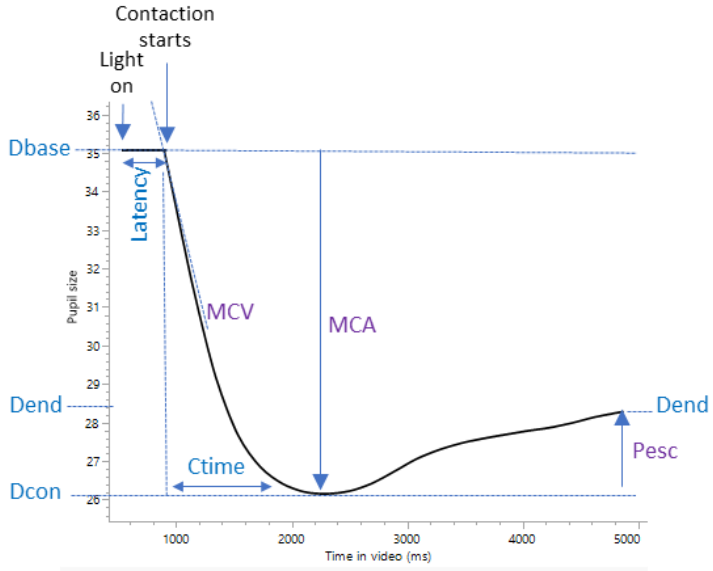

Figure 3. An example of the pupillogram for the PLR measurement with the pre-defined key features that will be extracted. The example is from Hall et al. 2018 [7].

Non-convergence (NC) measurement

The NC will measure the lack of ability to cross the eyes as this is an important parameter for identification of drug usage. A majority (>92%) of the human population can cross the eyes (convergence) in a normal condition. During this measurement, the position of the eye in relation to a fix point and the distance between the irises of the eyes are measured. The subject will use a finger to cross the eyes towards. Through the recorded film it will be possible to estimate the distance between the irises over time. From the NC measurement, the following pre-defined key-features will be calculated based on current knowledge [21]:

- NCbase: distance between irises near the start of the measurement while focusing on an object far away
- NCcon: distance between irises while focusing on an object located close to the face
- NCnf (noise factor): a number representing the typical noise level of the NCbase measurements

Through combining the above key features, the following derived key feature is the one to be evaluated for the NC measurement in the investigation:

- NCdiff: NCdiff = NCbase – NCcon for NCnf>5, NCdiff = 0 for NCnf<=5

Figure 4 below shows an example of a pupillogram for the NC measurement and the pre-defined key features that will be extracted.

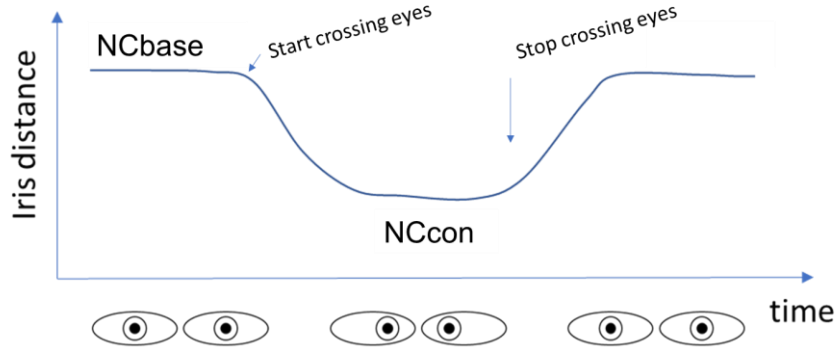

Figure 4. Non-convergence, the inability to cross eyes is measured as distance between the center of the irises.

Nystagmus (NY) measurement

Nystagmus is an involuntary repetitive rhythmic slide-to-slide, up and down, or circular motion of the eyes that occurs due to a variety of conditions. The horizontal and vertical repetitive movements also often occur under the influence of central depressive agents e.g., benzodiazepines.

Nystagmus tends to be more common and visible when the eyes are turned towards end-location (i.e., looking sideways while keeping head pointing forward). In Previct Drugs, the NY will measure the motion of the irises during a time when the subject receive instructions to look in a certain direction. The ambient light level will be calculated through the smartphone's camera. Using the collected video, the location of the irises can be estimated over time.

From the NY measurement, the following pre-defined key-features will be extracted based on current knowledge [22]:

- NYmass: NmassL, NmassR: average of the approximate integral (mass) of nystagmus-like events for both eyes
- NYnumbers: the number of nystagmus-like events
- NYmaxAmp: the maximum gaze amplitude from baseline direction to maximum edge direction
- NYaverageAmp: the average gaze amplitude from baseline direction of the eye for all analyzed frames

Figure 5 below shows an example of a pupillogram for the NY measurement and the pre-defined key features that will be extracted.

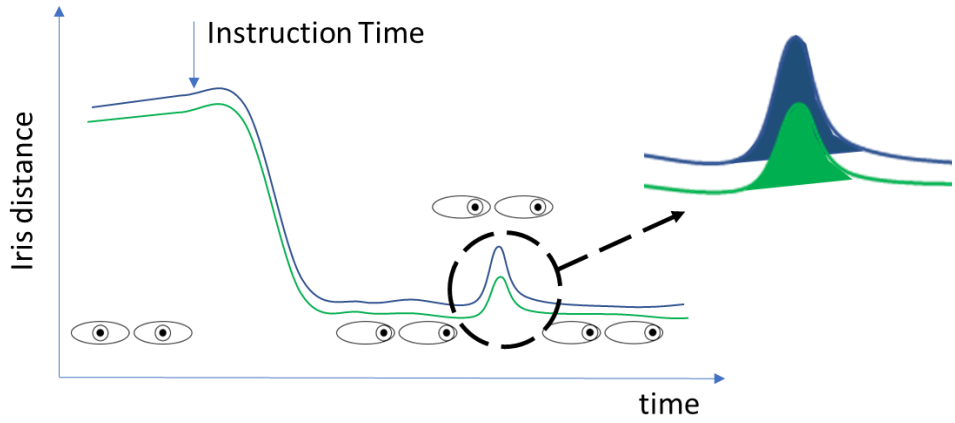

Figure 5. An example of the NY measurement, where the subject will start looking straight, then receives an instruction to look to the far side. Nystagmus is an involuntary, rapid, and transient motion of the eyes while looking at the far side. The key feature of nystagmus is approximately the integral of peaks with nystagmus-like

peak-width in the region of the person looking to the far side, as illustrated in the enlarged section. For each eye, the number of and the sum of the integrals of all nystagmus like peaks are reported as key features. Also the average amplitude and the maximum gaze movement of the eyes are recorded.

Tremor

Measurement of tremor is used to extract information which can be predictive of drug usage. In Previct Drugs, tremor will be measured based on the video collected during the NY measurement. Tremor will be calculated using the position of a part of the eye, i.e., in an eye box. If the subject is moving the hand or head during the video recording, the eye position will in turn move. Meaning that tremor will be calculated using the continuous estimate of the distance the eyes move frame-by-frame in the recorded video. This creates a time series with high values if there were large moves between two frames, and small values if there were small or no motion between two frames.

Based on the time series of distances, the following pre-defined key features will be extracted [23]:

- Maximum distance in window (mmX): the maximum distance observed within X consecutive frames, seen during a stretch of about 2-4 seconds. To capture motion of different frequencies, several mmX variables will be extracted:
  - Mm5 = window of 5 frames
  - Mm10 = window of 10 frames
  - Mm30 = window of 30 frames
- Maximum derivative values seen during a stretch of about 2-4 seconds. The time series is differentiated (once or twice) and the top 10% of observed differentiated values (irrespective of sign) are averaged. Two differentiation features will be extracted:
  - D1m = first order differentiation
  - D2m = second order differentiation
- Frequency patterns will be derived using a fourier transform. In brief, 64 consecutive data points will be subjected to fast fourier transform (fft) and the resulting coefficients will be combined to produce the following features:
  - Pa = Power / prevalence of about 1 Hz motion patterns
  - Pb = Power / prevalence of about 2 Hz motion patterns
  - Pc = Power / prevalence of about 3-5 Hz motion patterns

Color of sclera

Color of sclera will be measured during the PLR measurement. Change from white to more reddish color may be a symptom once under influence of cannabinoids. CIELAB color coordinates will be used to describe the color of sclera (the white outer coating area of the eye). Several CIELAB color coordinates are available in Previct Drugs, each representing a distinct color [24].

After a measurement, the sclera is extracted, and the color is measured. The redness is expressed in a numerical scale where 1 represents a typical red color and 0 represents instead a typical white color.

The following pre-defined key feature will be extracted [25]:

- Redness: The average of the redness of left and right eye (CIELABredleft and CIELABredright)

10.8.4 Safety Variables and Measurements

The safety measurement will be the onset, severity, duration, and frequency of AEs (anticipated and unanticipated), including determination of causality. Only events, which are new after the consent has been signed or have increased in severity after the consent has been signed, will be recorded. All AEs will be recorded and reported, and all data required both to assess the safety and to comply with the IEC and CA requirements will be collected. All events will be followed up until resolved or judged as clinically stable according to the investigator or designee, if possible.

10.8.5 Activities Performed by Sponsor

The sponsor is responsible for training the site personnel to use Previct Drugs including the study specific smartphones. This will take place during site initiation and thereafter as required, e.g., if new site personnel or any re-training is required. See section 6.8 for further information on training.

For being able to have different light conditions at the site in the room the Previct Drugs measurements will be performed at the visits, the sponsor will install an easy to use and repeatable way to change the ambient light conditions of a room.

The sponsor is also responsible for delivering the study specific smartphones to be used in the investigation where Previct Drugs app will be pre-installed. The study specific smartphones will be collected by the sponsor after the investigation is completed.

The sponsor will also make sure that the site personnel have access to the careportal.

[redacted]

10.8.6 Potential Confounding Factors

This is an explorative and early feasibility investigation aiming to collect data on Previct Drugs when it comes to usage and safety.

The collected data is required for further development of Previct Drugs before CE-marking. Future studies will focus on confirming the possibility of drug detection once the development of Previct Drugs is complete and the design has been frozen.

As this is the second pilot investigation using self-administered testing of eyes with a smartphone camera, we do not know how well the subjects can perform a measurement. This is an important usability question and may hamper the aim to collect information if eye measurements can be used for future detection of drug use.

10.8.7 Samples obtained from subject

Exhaled breath samples for LC-MS/MS analysis will be collected at visit 1 and at follow-up visits. Once the LC-MS/MS analysis has been performed and the result has been provided to the site(s), the sample can be discarded. The sample will not be stored for potential future use.

11 MONITORING PLAN

During the investigation, the monitor will have regular contact with the investigational site. These contacts will include visits to confirm that the facilities remain adequate to specified standards and that the site personnel are carrying out the procedures as stated in the CIP. All data must be accurately recorded in the eCRF. Source Data Verification (SDV), a comparison of data in the eCRF with the subjects' medical records and other records of source data at the investigational site, will also be performed. The eCRF and source documents and records must be made accessible during each visit.

The monitor and other sponsor personnel will be available between visits if the PI or other site personnel needs information and/or advice. As a preparation step prior to a monitoring visit, the monitor will check the eCRF to confirm that data has been recorded. Authorized representatives of the sponsor and/or appropriate regulatory agencies, including IEC, may visit the site to perform audits/inspections, including SDV.

A detailed description of the monitoring activities will be explained in the investigation specific monitoring plan.

11.1 Subject Records and Source Data

Prior to consenting to participating in the investigation, a potential subject will contact the site to inform that he/she is interested to participate. The site personnel will perform a brief check against eligibility criteria and collect contact details for being able to schedule a first visit to provide study information orally and in written format. The subject will be informed that the collected information prior to consent is for research purpose but that none of the information provided to the site prior to informed consent will be recorded in any study documentation.

Subject data recorded directly in the eCRF, and not into the medical record or other records of source data, will be considered as source data. It is the responsibility of the PI to record essential information in the medical records, in accordance with national regulations and requirements. The origin of the source data in this clinical investigation will be further specified in a separate document ("Origin of Source Data").

In general, the following information shall be recorded in the medical records:

- Clinical investigation code
- Subject identification number
- That informed consent for participating in the clinical investigation was obtained
- Reason participating in investigation
- All visits during the investigation period
- All AEs

The PI is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data recorded in the eCRFs. Completed sections of eCRFs will be monitored on regular basis.

11.2 Access to Source Data and Documentation

The Principal Investigator should guarantee access to source documents for the monitor and auditors as well as for inspection by appropriate Regulatory Agencies / Competent Authorities, and Independent Ethics Committees (IECs), if required.

12 STATISTICAL CONSIDERATIONS

12.1 Statistical Design, Method and Analytical Procedures

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. Two light conditions will also be analyzed separately.

Primary analyses: The analysis of the 18 usability questions given in section 10.2 Primary endpoint at visit 1 in the following way:
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.

First secondary analyses: 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. For each subject, the proportion of approved measurements over all measurements during visit 1 will be calculated for each of PLR, NC, and NY. The two light conditions will be analyzed separately. The follow-up analyses will be analyzed separately.

Second secondary analyses: 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. For each subject, the proportion of approved measurements over all measurements during visit 1 will be calculated for each of PLR, NC, and NY. 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.

Analysis of demographics and baseline variables: Age, gender, relevant medical and surgical history and the six questions regarding "Timeline follow-back drugs and medicines last 24 hours will be tabulated in a baseline table for FAS population.

12.2 Sample size

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.

12.3 Drop-out Rates

Drop-out rate is not applicable.

12.4 Level of Significance and Power

Only descriptive statistics will be used. The primary analysis is descriptively, and no power calculation has been conducted.

12.5 Pass / Fail Criteria

Since only descriptive statistics will be used, no pass or fail criteria have been applied.

12.6 Interim Analysis

No interim analysis is planned to be performed.

12.7 Reporting of Deviations from the Original Statistical Analysis Plan (SAP)

Any deviations from the original SAP will be described and justified in a CIP amendment and/or in a revised SAP and/or in the final report, as appropriate.

12.8 Subgroups for Analysis

No pre-specific subgroups analyses will be performed.

12.9 Procedures that Take into Account all the Data

Baseline and safety data which will be analyzed with descriptive statistics.

12.10 Missing, Unused or Spurious Data

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

12.11 Exclusion of Particular Information from the Testing of the Hypothesis

Not applicable.

13 DATA MANAGEMENT

Data management and handling will be conducted according to the investigation specific Data Management Plan (DMP) in accordance with applicable guidelines and CROs Standard Operating Procedures (SOPs). Any deviations, i.e., discrepancies and additions from the process defined in the DMP will be described in an investigation specific Data Management Report (DMR).

Data will be collected using electronic case report forms (eCRFs) specifically designed for this clinical investigation and through the Previct Drugs app. The PI or an authorized person will record subject data in the eCRF in a precise and accurate manner. Abbreviations should not be used. The PI or delegate is responsible for the data entered in the eCRFs and for signing the eCRF at the end of the clinical investigation. The data should be recorded as soon as they are generated.

The person entering data into the database is not allowed to attempt any personal interpretation or to make any decisions on the data other than self-evident corrections as listed in the investigation data entry instructions or data handling report. Single data entry type will be applied. Data for screening failures will be collected in the database.

Data validation /data cleaning procedures are designed to assure validity and accuracy of clinical data. These procedures consist of manual review during data entry and computerized edit checks and queries for identifying data values that are outside the allowed range, incomplete or inconsistent, and CIP deviations. The Data Validation Plan (DVP) specifies the checks that are to be performed on subject data for the clinical investigation. All investigation-specific and standard data validation programming will be tested in a separate testing environment prior to use in the clinical investigation.

When all data from all endpoints have been entered, discrepancies solved and all reconciliation with the SAE database is complete, the database will be locked, and the data will be analyzed.

The sponsor is responsible for that the EU General Data Protection Regulation (GDPR) is followed in this clinical investigation.

Data collected in this investigation will be recorded, collected, processed, and may be transferred to European Economic Area (EEA) countries in relation to CE-marking and regulatory agencies requests. Furthermore, data may be transferred to the competent authority in USA, if the sponsor decides to enter this market in the future. It will be confirmed that the country has an adequate level of data protection according to decision by the EU Commission or through referring to appropriate safeguards.

13.1 Data Retention

The medical records of clinical investigation subjects must be retained in accordance with local legislation and in accordance with the maximum period of time permitted by the hospital, institution or private practice.

The PI shall retain all clinical investigation records during the investigation and for the period required by the applicable regulatory requirements or for at least 10 years after the premature termination or completion of the clinical investigation, whichever ever is the longest. The PI must take measures to prevent accidental or premature destruction of these documents. The PI should contact the Sponsor prior to destruction of any records or reports pertaining to the clinical investigation in order to ensure they no longer need to be retained. In addition, if the PI leaves the hospital, he/she should provide the Sponsor with the name and address of the person who will look after and be responsible for the clinical investigation-related records. If the records will be transferred to another person/party, the transfer will be documented at the investigation site or at the Sponsor.

The Sponsor will retain the Study Master File (SMF) in line with applicable regulations or for at least 10 years after the clinical investigation has ended, or, in the event that the device is subsequently placed on the market, at least 10 years after the last device has been placed on the market.

13.2 Monitoring, Audits and Inspections

During the clinical investigation, the monitor will have regular contacts with the investigation site. These contacts will include visits to confirm that the facilities remain adequate to specified standards and that the investigation team is carrying out the procedure stated in the CIP. All data must be accurately recorded in the eCRF. Source data verification (SDV), a comparison of data in the eCRF with the subject's medical records and other records at the investigation site, will also be performed. The eCRF and source documents and records must be made accessible during the monitoring visit.

The monitor or other Sponsor personnel will be available between visits if the PI or other site personnel at the site needs information and/or advise. Authorized representatives of the Sponsor and/or regulatory agencies may visit the site to perform audits/inspections, including SDV.

14 AMENDMENTS TO THE CIP

Any change to the approved clinical investigation documents will be documented and include a written justification. Any effects of the implemented changes on other clinical investigation documents shall be evaluated and documented. If deemed necessary, affected documents shall be properly updated and relevant parties notified. The version number and date of amendments shall be documented.

All amendments to the CIP will be documented in an amendment log and communicated to relevant parties.

Proposed amendments to the CIP shall be agreed upon between the Sponsor and PI, or the Coordinating Investigator (if applicable). The amendments to the CIP shall be notified to, or approved by, the IEC and regulatory agencies, if required.

15 DEVIATIONS FROM THE CIP

A CIP deviation is a failure to follow, intentionally or unintentionally, the requirements of the CIP. Every effort should be made to comply with the requirements of the CIP and the investigator is not allowed to deviate from the CIP. Furthermore, waivers from the CIP is prohibited.

As required by national regulations or guidelines, requests for deviations and reports of deviations will be provided to the IEC if the deviation affects subject's rights, safety and well-being, or the scientific integrity of the clinical investigation.

Under emergency circumstances deviations from the CIP may proceed without prior approval by the Sponsor and favorable opinion of the IEC if the rights, safety and well-being of human subjects need to be protected. Such deviations will be documented and reported to the Sponsor and IEC as soon as possible in accordance with national regulations.

When the monitor or Sponsor identifies that the Principal Investigator is out of compliance, this will be notified to the Principal Investigator in writing, with a request to correct the source of the deviation immediately. Corrective action will be implemented to avoid repeated non-compliance, which will usually include re-training and may include terminating the clinical investigation at the site.

The Sponsor is responsible for analyzing deviations and assessing their significance. Corrective action(s) will be implemented to avoid repeated deviations, which may include suspending the clinical investigation at the investigation site or disqualify the Principal Investigator.

16 DEVICE ACCOUNTABILITY

The Sponsor and the PI will keep records documenting the location of all provided study specific smartphones where Previct Drugs app is installed on from shipment to the investigational sites until return. This will be documented by a shipment log stored at the sponsor and in a device/equipment accountability log(s) at the investigational site. The accountability logs at site will include information on: date and version Previct Drugs delivered to site, date when providing access to a specific subject, date access withdrawn for a specific subject, and date access withdrawn for site.

Provided and withdrawn access to the careportal of Previct Drugs to the site personnel will also be documented.

Other equipment, as applicable, provided by the Sponsor to the investigation site as part of the clinical investigation will also be documented.

The monitor will verify the accountability process at each site during the site monitoring visits.

17 STATEMENTS OF COMPLIANCE

This clinical investigation will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki (Appendix C). Furthermore, the clinical investigation will be conducted in compliance with ISO 14155:2020 and applicable regional or national regulations.

17.1 Institutional Ethics Review

The final CIP, including the final version of the ICF, must be approved or given a favorable opinion in writing by an IEC and Regulatory Agency / Competent Authority before enrolment of any subject into the clinical investigation. The Principal Investigator is responsible for informing the IEC of any amendment to the CIP as per local requirements.

Any additional requirements imposed by the IEC or Regulatory Agency shall be followed.

17.2 Insurance

The Sponsor will be responsible for ensuring adequate insurance covering any injuries to the subject caused by the investigational medical device.

18 INFORMED CONSENT PROCESS

All subjects will receive written and verbal information regarding the clinical investigation prior to any investigation-related procedures take place. This information will emphasize that participation in the clinical investigation is voluntary and that the subject may withdraw from the investigation at any time and for any reason. All subjects will be given the opportunity to ask questions about the investigation and will be given at enough time to decide whether to participate in the investigation or not. If any new important information arises during the clinical investigation the subject will be informed both orally and in writing.

Potential subjects will be identified through advertisement. A potential subject that is interested to participate will contact the site and the site will provide with the written subject information sheet and give an oral summary of the investigation over phone. The information provided includes in general information on the study specific procedures and assessments, potential risks, and benefits, where data will be stored, information on subject reimbursement etc. The potential subjects will be informed that they have the right to think about their decision to participate in the investigation properly and that they will be given the opportunity to ask questions and can consider participation before decisions are made. After receiving all available information, sufficient time to ask questions and consider, if the potential subject decides to participate in the study, the ICF will be signed and dated by the subject together with the investigator who gave the verbal and written information.

18.1 Subject reimbursement

The subjects will be reimbursed for participating in the investigation. For completing the first visit, the subjects will be reimbursed with gift card with a value of 500 SEK. After each follow-up visit a gift card with a value of 250 SEK will be given to the study subject. There will be no reimbursement for traveling

19 ADVERSE EVENTS, ADVERSE DEVICE EFFECTS AND DEVICE DEFICIENCIES

The definitions and procedures for reporting Adverse Events (AE), Adverse Device Effects (ADE), Serious Adverse Events (SAE), Serious Adverse Device Effects (SADE) and Unanticipated Serious Adverse Device Effects (USADE) are presented in the subsections below. It is of utmost importance that all staff involved in the investigation is familiar with the definitions and procedures and it is the responsibility of the Principal Investigator to ensure this.

19.1 Definitions

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 uncludes 'comparator' if the comparator is a medical device.

Adverse Event (AE)
ISO 14155:2020
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.

MDR 2017/745
Means any untoward medical occurrence, unintended disease or injury or any untoward clinical signs, including an abnormal laboratory finding, in subjects, users or other persons, in the context of a clinical investigation, whether or not related to the investigational device.

Device Deficiency
ISO 14155:2020
Inadequacy of an investigational medical device related to its identity, quality, durability, reliability, safety or performance. This may include malfunctions, use error, or inadequacy in the information supplied by the manufacturer.

Note 1: Device deficiencies include malfunctions, use errors, and inadequacy in the information supplied by the manufacturer including labelling.

Note 2: This definition includes device deficiencies related to the investigational medical device or the comparator.

MDR 2017/745

Device deficiency means any inadequacy in the identity, quality, durability, reliability, safety or performance of an investigational device, including malfunction, use errors or inadequacy in information supplied by the manufacturer.

Serious Adverse Device Effect (SADE)
ISO 14155:2020
Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

Serious Adverse Event (SAE)
ISO 14155:2020
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.

MDR 2017/745
Serious adverse event means any adverse event that led to any of the following:

a) death
b) serious deterioration in the health of the subject, that resulted in any of the following:
    i. life-threatening illness or injury,
    ii. permanent impairment of a body structure or a body function,
    iii. hospitalisation or prolongation of patient hospitalisation,
    iv. medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
    v. chronic disease,
c) foetal distress, foetal death or a congenital physical or mental impairment or birt defect.

Serious health threat
ISO 14155:2020
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)
ISO 14155:2020
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.

19.2 Non-reportable adverse events

Not applicable as all AEs will be recorded.

19.3 Methods for discovering and documenting AE/ADE

All subjects will be carefully monitored for the occurrence of AEs throughout the clinical investigation, from the first day to the completion of follow up. Events prior to randomization will be considered medical history. The Principal Investigator will collect safety information using non-leading questions such as "have you experienced any new health problems or worsening of existing conditions?". Events directly observed or spontaneously volunteered by subjects will also be recorded throughout the clinical investigation.

Clearly related signs, symptoms and abnormal diagnostic procedure results should be grouped together and reported as a single diagnosis or syndrome whenever possible.

All AEs, including but not limited to events reported by the subject or reported in response to an open question by the Principal Investigator or member of the investigation team, which fall into any of the previously defined definitions must be recorded as an AE in the CRF and should include the following information:

- Brief description of the event (diagnosis)
- Date of event onset (and time, if relevant)
- Date of event resolution (and time, if relevant)
- Severity
- Seriousness
- Causality assessment (i.e. relationship to medical device and/or procedure)
- Event treatment
- Event outcome / resolution

If the AE meets the seriousness criteria it should be subject to expedited reporting as described in 19.4.

19.3.1 Severity

Severity describes the intensity of an AE and will be assessed as:

1) Mild: asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
2) Moderate: minimal, local or non-invasive intervention indicated, limiting age-appropriate instrumental activities of daily living.
3) Severe or medically significant but not immediately life-threatening: hospitalization or prolongation of hospitalization indicated; disabling; limiting self care activities of daily living.
4) Life-threatening consequences; urgent intervention indicated.
5) Death related to AE.

If an AE changes in severity, it should be reported as an AE of new severity but with the same description and identifier.

19.3.2 Causality

Causality is the relationship between the use of the medical device (including the investigational device, the comparator and the medical – surgical procedure) and the occurrence of each AE.

During the causality assessment, clinical judgment shall be used and the relevant documents, such as the IB, the CIP or the risk analysis report shall be consulted, as all the foreseeable SAEs and the potential risks are listed and assessed there. The presence of confounding factors, such as concomitant medication/treatment, the natural history of the underlying disease, other concurrent illness or risk factors shall also be considered.

For the purpose of harmonizing reports, each SAE will be classified according to four different levels of causality. The Sponsor and the Principal Investigator will use the following definitions to assess the

relationship of the SAE to the investigational medical device, the comparator, or the medical – surgical procedures:

- **Not related:** relationship to the device or procedures can be excluded when:
  - The event has no temporal relationship with the use of the investigational device or the procedures related to the investigational device;
  - The serious event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible;
  - The discontinuation of medical device application or the reduction of the levels of activation/exposure – when clinically feasible – and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious event;
  - The event involves a body-site or an organ than cannot be affected by the device or procedure;
  - The serious event can be attributed to another cause (e.g. an underlying or concurrent illness/clinical condition, an effect of another device, drug, treatment or other risk factors);
  - The event does not depend on a false result given by the investigational device used for diagnosis, when applicable;
- In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.
- **Possible:** the relationship with the use of the investigational device or comparator, or the relationship with procedures, is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/clinical condition or/and an effect of another device, drug or treatment). Cases were relatedness cannot be assessed or no information has been obtained should also be classified as possible.
- **Probable:** the relationship with the use of the investigational device or comparator, or the relationship with procedures, seems relevant and/or the event cannot bereasonably be explained by another cause.
- **Causal relationship:** the serious event is associated with the investigational device, comparator or with procedures beyond reasonable doubt when:
  - The event is known side effect of the product category the device belongs to or of similar devices and procedures;
  - The event has a temporal relationship with investigational device use/application or procedures;
  - The event involved a body-site or organ that:
    - The investigational device or procedures are applied to;
    - The investigational device or procedures have an effect on;
  - The serious event follows a known response pattern to the medical device (if the response pattern is previously known);
  - The discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of activation/exposure), impact on the serious event (when clinically feasible);
  - Other possible causes (e.g. an underlying or concurrent illness/clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out;
  - Harm to the subject is due to error in use;
  - The event depends on a false result given by the investigational device used for diagnosis, when applicable;
- In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

The Sponsor and the Principal Investigator will distinguish between AEs related to the investigational device, the comparator and those related to the procedures (any procedure specific to the clinical investigation). An AE can be related to both the procedures and the device. Complications of procedures are considered not related if the said procedures would have been applied to the subjects also in the absence of device use/application.

Particular attention shall be given to the causality evaluation of USADE, since the occurrence of USADE could suggest that the clinical investigation places subjects at increased risk of harm than was expected beforehand.

In case of disagreement between the Sponsor and the Principal Investigator assessments of the AE, both opinions shall be communicated to concerned parties.

19.4 Methods for Discovering and Documenting Device Deficiencies

Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance shall be reported as a device deficiency without unnecessary delay to the Sponsor by using the device deficiency form. It is the Principal Investigator's responsibility to record every observed device deficiency together with an assessment. The Sponsor shall review all device deficiencies and determine and document in writing whether they could have led to a SADE. Device deficiencies that are assessed to or have SADE potential should be subjected to expedited reporting as described in section 19.4.

19.5 Reporting of SAE/SADE and Device Deficiencies with SADE potential

MDR 2017/745

The following events are considered reportable events according to Regulation (EU) 2017/745:

- Any SAE that has a causal relationship with the investigational device, the comarator or the investigation procedure or where such causal relationship is reasonably possible;
- Any device deficiency that might have led to a SAE if:
  - Suitable action had not been taken or
  - Intervention had not been made or
  - If circumstances had been less fortunate
- New findings/updates in relation to already reported events.

SAEs/SADEs and device deficiencies with with SADE potential must be reported to the Sponsor immediately, but not later than 3 calendar days after investigational site investigation personnel's awareness of the event, regardless of the time that may have elapsed from the time the event occurred.

The initial report should contain as much information as possible, but as a minimum the following information:

- Subject ID
- SAE ID
- Date of procedure/first use
- Date of event onset
- SAE or DD
- Age (years)
- Patient gender (female, male, other, unknown)
- Classification of event:
  - death,
  - life-threatening illness or injury,
  - permanent impairment/chronic disease,
  - hospitalization,
  - medical or surgical intervention,
  - foetal distress, foetal death or congenital physical or mental or birth defect,
  - not applicable[1]
- Description of event:
  - Nature of the observed symptoms

[1] This option is only to be selected in case of reportable device deficiencies that did not lead to an SAE.

  - Duration and severity of the symptoms
  - Date of onset of first signs of the event (before it became a SAE)
  - Medical background of the patient
  - Medical care of the patient
  - Comments on the event in relation to already known safety data
- Action/treatment/outcome
- Relationship to procedure (not related, possible, probable, causal)
- Relationship to the device (not related, possible, probable, causal)
- Unanticipated SADE (Yes, No)
- Investigation arm (test group, comparison group, blinded, not applicable)
- Event status (resolved, resolved with sequelae, ongoing, death)
- Date of event resolution (if ongoing enter not applicable)

The Sponsor must also promptly receive a completed report. All SAEs have to be reported whether or not they are considered causally related to the investigational medical device, comparator or medical – surgical procedure.

SAE/SADE EMERGENCY CONTACT DETAILS
Name: Christina Schönborg, Clinical Research Manager, Devicia AB
Phone: + 46 (0) 701 090 221
Email: christina.schonborg@devicia.com

In accordance with MDR (EU) 2017/745, the Sponsor shall report, without delay to all Member States in which the clinical investigation is being conducted, all of the following:

(a) Any SAE that has a causal relationship with the investigational device, the comparator or the investigation procedure or where such causal relationship is reasonably possible;
(b) Any device deficiency that might have led to a SAE if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate;
(c) Any new findings in relation to any event referred to above.

The period for reporting shall take account of the severity of the event. Where necessary to ensure timely reporting, the Sponsor may submit an initial report that is incomplete followed by a complete report.

The Sponsor should inform the IEC and Regulatory Agencies / Competent Authorities about reportable events through EUDAMED (once established) or per local requirements.

19.6 Foreseeable adverse events and anticipated adverse device effects

For potential AEs, see section 8.

19.7 Data Monitoring Committee

No Data Monitoring Committee will be established in this investigation since the timeline of recruitment in the investigation is short and no severe AEs related to the investigation is expected.

20 VULNERABLE POPULATION

Not applicable in this clinical investigation.

21 SUSPENSION OR EARLY TERMINATION OF THE CLINICAL INVESTIGATION

If the clinical investigation is terminated early or suspended due to reasons of safety, the Sponsor will promptly inform the Principal Investigator(s) and the investigation site(s) of the termination or suspension and the reason(s) thereof. The IEC will also be informed promptly and provided with the reason(s) for the termination or suspension by the Sponsor or by the Principal Investigator(s) / investigation site(s).

In addition, CIP violations may result in termination of the Clinical Investigation at a site.
CIP violations are deviations made without permission as a result of error or fraud/misconduct. Where the monitor or Sponsor identifies that the Principal Investigator is out of compliance, this will be noted to the Principal Investigator in writing, with a request to correct the source of the deviation immediately. Corrective actions will be implemented to avoid repeated non-compliance, including re-training. However, in case of repeated non-compliance despite implemented corrective actions, the clinical investigation will be terminated at the site.

21.1 Criteria for Breaking the Blinding Code

Not applicable in this clinical investigation.

21.2 Subject Follow-up

If the clinical investigation is prematurely terminated, the Sponsor and the Principal Investigator(s) will assure that adequate consideration is given to the protection of subjects' interest, including subject follow-up.

22 PUBLICATION POLICY

The clinical investigation will be registered in a publicly accessible database before recruitment of the first subject.

A final report of the clinical investigation (CIR) will be completed, even if the investigation is prematurely terminated. The report will be prepared by the Sponsor according to the guideline presented in Annex D of ISO 14155:2020.

All publications and presentations must be based upon the CIR.

All information supplied by the Sponsor in connection with this investigation will remain the sole property of the Sponsor and is to be considered confidential information. No confidential information will be disclosed to others without obtaining prior written consent from the Sponsor and will not be used except in the conduct of this investigation.

The Sponsor may choose to publish or present data from this clinical investigation. If a Principal Investigator is offered first authorship, he/she will be asked to comment and approve the publication. The Sponsor has the right to use the results for registration and internal presentation and for promotion.

23 REFERENCES

Ref	Document	Document ID
01	Carreiro S, Newcomb M, Leach R, Ostrowski S, Boudreaux ED, Amante D. Current reporting of usability and impact of mHealth interventions for substance use disorder: A systematic review. Drug and alcohol dependence. 2020;215:108201.	N/A
02	Mahmud MS, Fang H, Carreiro S, Wang H, Boyer E. Wearables Technology for Drug Abuse Detection: A Survey of Recent Advancement. Smart Health. 2018;13.	N/A
03	Teymourian H, Parrilla M, Sempionatto JR, Montiel NF, Barfidokht A, Van Echelpoel R, et al. Wearable Electrochemical Sensors for the Monitoring and Screening of Drugs. ACS Sensors. 2020;5(9):2679-700.	N/A
04	Ferreri F, Bourla A, Mouchabac S, Karila L. e-Addictology: An Overview of New Technologies for Assessing and Intervening in Addictive Behaviors. Front Psychiatry. 2018;9:51.	N/A
05	Boyer EW, Smelson D, Fletcher R, Ziedonis D, Picard RW. Wireless Technologies, Ubiquitous Computing and Mobile Health: Application to Drug Abuse Treatment and Compliance with HIV Therapies. J Med Toxicol. 2010;6(2):212-6.	N/A
06	Lord SE, Campbell ANC, Brunette MF, Cubillos L, Bartels SM, Torrey WC, et al. Workshop on Implementation Science and Digital Therapeutics for Behavioral Health. JMIR Ment Health. 2021;8(1):e17662.	N/A
07	Hall CA and Chilcott RP. Eyeing up the future of the pupillary light reflex in neurodiagnostics. Diagnostics (Basel). 2018;8(1),19.	N/A
08	Murillo R, Crucilla C, Schmittner J, Hotchkiss E, Pickworth WB. Pupillometry in the detection of concomitant drug use in opioid-maintained patients. Methods Find Exp Clin Pharmacol. 2004;26(4):271-5.	N/A
09	Wallace et al. in March (1997) Drug Abuse Handbook, ISBN 0-8493-2637-0, Chapter 4.3	N/A
10	Drogtecken och symptom. Rikspolisstyrelsens rapport, RPS 1995:7.	N/A
11	Qualification and classification of Previct Drugs	KC005-022 Rev03
12	Device description Previct Drugs	KC005-004 Rev06
13	Instructions For Use Previct Drugs KCClin02	KC003-2022-01- AA, November 2022
14	Previct Drugs system architecture	KC005-061 Rev01
15	Intended purpose Previct Drugs	KC005-003 Rev05
16	Investigator's Brochure Previct Drugs	KC09-107 RevA
17	Clinical Evaluation Plan Previct Drugs	KC09-101 RevB
18	Risk management summary report Previct Drugs	KC005-019 Rev02
19	Risk analysis KCClin01	KC005-014 Rev02
20	Key feature extraction contraction PLR	KC005-047 Rev01
21	Key feature extraction convergence crossing eye	KC005-048 Rev01
22	Key feature extraction nystagmus	KC005-056 Rev01
23	Key feature extraction motion pattern	KC005-058 Rev01
24	Hardeberg YJ. Digital red eye removal. J Imaging Sci Technol. 2000;46:375-9.	N/A
25	Key feature extraction color of eye	KC005-057 Rev01

24 APPENDICES

24.1 Appendix A – Clinical Investigation Plan Agreement Form

Investigation code: KCClin02

CIP version: KC09-108 Rev A

I agree to the terms of this CIP. I will conduct the investigation according to the procedures specified herein.

Site No.: 01
Mottagning för särskild vård, sprutbytet,
Husläkarmottagning för hemlösa
Region Uppsala, Sweden

Coordinating/Principal Investigator

Name: Dr. Johan Månflod

Signature: _____

Date (dd-Mmm-yyyy): _____

24.2 Appendix B – Clinical Investigation Contact List

COORDINATING /PRINCIPAL INVESTIGATOR
Name: Johan Månflod
Professional position: Medical Doctor
Address: Mottagning för särskild vård, Märstagatan 2, 753 23 Uppsala, Sweden
Phone: + 46 (0)18 617 73 04
E-mail: johan.manflod@regionuppsala.se

Clinical investigation
Role: Coordinating /Principal Investigator
Responsibility: Responsible for the conduct of the clinical investigation at site 01.
Qualification: Medical Doctor

CLINICAL INVESTIGATION SITE(S)
Site 01: Mottagning för särskild vård, sprutbytet, Husläkarmottagning för hemlösa
Address: Märstagatan 2, 753 Uppsala, Sweden

SPONSOR REPRESENTATIVE
Name: Markku Hämäläinen, CSO
Address: Kontigo Care AB, Påvel Snickares Gränd 12, 753 20 Uppsala, Sweden
Phone: + 46 (0) 18 410 88 80, + 46 (0) 769 473132
E-mail: markku.hamalainen@kontigocare.com

OTHER SPONSOR REPRESENTATIVE
Name: Maria Winkvist, Product Manager
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Phone: +46 (0) 727 140 277
E-mail: maria.winkvist@kontigocare.com

CONTRACT RESEARCH ORGANIZATION
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PROJECT MANAGER:
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BIOSTATISTICIAN
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Phone: +46 (0) 70 963 36 13
E-mail: info@stat-grp.se

SAFETY OFFICER
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Phone: +46 (0)723 611 968
E-mail: elisabeth.liljensten@devicia.com

CLINICAL DATA MANAGER:
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Address: Argongatan 2C, 431 53, Mölndal, Sweden
Phone: +46 (0) 72-551 57 02
E-mail: matina.starck@devicia.com

CLINICAL INVESTIGATION MONITOR
To be decided

CLINICAL INVESTIGATION PLAN AUTHOR(S)
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Address: Påvel Snickares Gränd 12, 753 20 Uppsala, Sweden
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E-mail: markku.hamalainen@kontigocare.com

24.3 Appendix C – Declaration of Helsinki

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI
Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington, DC, USA, October 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

PREAMBLE

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

   The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

GENERAL PRINCIPLES

3. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."
4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.
5. Medical progress is based on research that ultimately must include studies involving human subjects.
6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.
7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.
8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.
9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.
11. Medical research should be conducted in a manner that minimises possible harm to the environment.
12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.
13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.
14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.
15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

RISKS, BURDENS AND BENEFITS

16. In medical practice and in medical research, most interventions involve risks and burdens.

    Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

    Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

    When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

VULNERABLE GROUPS AND INDIVIDUALS

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

    All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research

SCIENTIFIC REQUIREMENTS AND RESEARCH PROTOCOLS

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

    The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

    In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions

RESEARCH ETHICS COMMITTEES

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

    The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

PRIVACY AND CONFIDENTIALITY

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

INFORMED CONSENT

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.
26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

    After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed

consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.
28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.
29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.
30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.
31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.
32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

USE OF PLACEBO

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

    Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

    Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

    and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

    Extreme care must be taken to avoid abuse of this option

POST-TRIAL PROVISIONS

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

RESEARCH REGISTRATION AND PUBLICATIONS AND DISSEMINATION OF RESULTS

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.
36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

UNPROVEN INTERVENTIONS IN CLINICAL PRACTICE

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.