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CLINICAL INVESTIGATION PLAN (CIP) KCClin01

Clinical Investigation Title:	A first-in-human explorative pilot study in healthy volunteers measuring eye parameters with a new mobile phone application for future monitoring of patients in treatment of substance use disorder
Clinical Investigation Code:	KCClin01
Investigational Device(s):	Previct Drugs
Coordinating/Principal Investigator:	Professor Albert Dahan
Sponsor:	Kontigo Care AB Påvel Snickares Gränd 12 753 20 Uppsala Sweden
Date:	31 March 2023

Revision	Version History
A	First release
B	Second release where the following have been adjusted based on comments from the Ethics Committee: - Clarification on safety checks performed before subject discharge on visit 2. - Clarification on blood sample storage and labeling. Additional changes made: - Addition of two key features for Nystagmus measurement. - Clarification on source data recording and that no medical records will be available instead the subject's General Practitioner will be informed. - Correction of total number of Previct Drugs tests performed on visit 2. - Minor adjustments due to misspellings.
C	Amendment 1 Changes made: - Upper age limit changed from 65 years to 70 years (inclusion criteria 2. amended). - Recruitment period prolonged with 1,5 months (from 5 months to 6,5 months), resulting in a new total study duration of 7 months. - New Clinical Research Manager appointed. Updated Emergency contact details, and contact information in Appendix B.

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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1 SYNOPSIS

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

CLINICAL INVESTIGATION TITLE:
A first-in-human explorative pilot study in healthy volunteers measuring eye parameters with a new mobile phone application for future monitoring of patients in treatment of substance use disorder

CLINICAL INVESTIGATION CODE:

KCClin01

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 on Previct Drugs. The clinical data collected in this early feasibility study is an important step in the product development of Previct Drugs as the data is required for continuing the development of the mathematical models and algorithms for drug detection.

This first study will give valuable information on the feasibility of Previct Drugs function to measure pupils and eye movements and to evaluate if there are any changes in the pupillometric parameters before and after intake of a medicinal product. It will also provide information on the usability of the device. Drug intake will in this first investigation be simulated by a controlled single application of commonly therapeutically used medicinal products from the following classes of drugs: phenethylamines (D1), benzodiazepines (D2), cannabinoids (D3), and opioids (D4).

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, a web-based careportal to be accessed from a computer 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 exemptions 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 adult male and female healthy volunteers, i.e., subjects, for collection of baseline data during one week in the subject's home environment and thereafter performance of a single administration of one of the four medicinal products of interest (D1-D4) at the site in a controlled setting. The investigation population will consist of 48 subjects (12 subjects per arm) fulfilling the eligibility criteria for the clinical investigation. The dropout rate is estimated to 10%. The subjects will be recruited in the Netherlands.

A potential subject will be asked for participation by the site team. The site team will verbally describe the investigation procedures, assessments, benefits, and risks etc. and provide the potential subject with a study specific

subject information sheet. The potential subject will be given at least 72 hours for consideration before signing and date 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 investigation-specific activities are taken place.

At visit 1, once the informed consent has been duly signed, screening and baseline data will be collected, e.g., demographics, relevant medical and surgical history, relevant concomitant medication, history of alcohol and drug usage. All subjects will perform a urine drug screening test to confirm no current drug usage. Fertile woman will perform a urine pregnancy test to confirm no pregnancy. A health examination will be performed including collection of vital signs such as ECG, blood pressure, and pulse for finally confirming that the subject is healthy. A subject fulfilling all inclusion criteria and none of the exclusion criteria will be eligible for further study participation. The subject will perform the first measurements with Previct Drugs in two different ambient light conditions. Three (3) tests with Previct Drugs will first be performed in one light condition, and thereafter the light condition will change to the second condition and the subject will wait approximately 10 minutes before performing three (3) tests with Previct Drugs again. Between visits 1 and 2, the subject will perform measurements with Previct Drugs at home for approximately one week (3 measurements per day). Visit 2 will be performed 1 week after visit 1 (+/- 2 days). Before visit 2, the subject should be fasting from food 6 hours before the visit until 2 hours after the administration of the medicinal product. The subject is free to drink water during the fasting period. Visit 2 will start with subjects being screened for pregnancy (if fertile female) and current drug intake (urine drug screening test). Once these criteria are confirmed, visit 2 will continue with collection of vital signs, i.e., oxygen saturation, pulse, blood pressure, and body temperature. A blood sample will thereafter be taken for LC-MS/MS analysis (specific analysis for the medicinal product). The subject will perform three (3) duplicate measurements with Previct Drugs in two different ambient light conditions ~10 minutes between each test. Three (3) tests with Previct Drugs will first be performed in one light condition, and thereafter the light condition will change to the second condition and the subject will wait approximately 10 minutes before performing three tests with Previct Drugs again. The subject will fill out a study specific device usability questionnaire.

The subject will be administered with the medicinal product the subject has been randomized to. The subject will perform tests with Previct Drugs for up to 5 hours post medicinal product administration. The tests will be performed in two different ambient light conditions:

- Hours 0, 4-5: one test in each light condition with ~ 10 minutes between the tests
- Hours 1-3: two tests in each light condition ~ 10 minutes between the tests in the two different light conditions
- For cannabinoids: an extra test 0.5 hours after administration with one test in each light condition with ~ 10 minutes between the tests

Before start of each test series, a blood sample will be collected for LC-MS/MS analysis. Vital signs will be collected on an hourly basis.

A telephone follow-up call will take place the day after visit 2 (+ 2 days) to confirm the safety of the subject. The subject has thereafter completed the study participation. The total study duration for each subject will be approximately 10 days.

Any relevant concomitant medications used during the study will be recorded. This will be recorded in the eCRF at the visits, but also in the Previct Drugs app during usage by the subject.

Any adverse events (AEs) taken place after signed informed consent will be recorded. Relevant AEs before signed informed consent will be recorded as medical and surgical history. Device deficiencies will also be recorded.

Usability will be recorded at visit 2 through a questionnaire to be answered by the subject.

The duration of the investigation is estimated to approximately 7 months with a recruitment period of 6,5 months.

It is estimated that 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. Male or female healthy volunteers
2. Age 18 to 70 years

3. BMI between 18.5-30 kg/m2
4. Weight between 50-100 kg
5. Healthy as determined by the investigator or designee based on pre-study medical and surgical history and a health examination at enrollment
6. Women 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 and at visit 2 and must agree to use a medically acceptable contraception from enrollment until study completion
7. No current drug usage defined as a negative urine drug test at enrollment and at visit 2
8. Able to use Previct Drugs after initial training (defined as successfully performing a test after trying maximum three times per measurement)
9. Been informed of the nature, the scope, and the relevance of the clinical investigation
10. 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. Abnormal ECG (QTc time>450 ms) at enrollment
6. Current or recent history of alcohol misuse assessed by AUDIT where ≥6 points for women or ≥8 points for men indicates a potential misuse
7. Current or history of psychiatric disorder or drug misuse assessed by M.I.N.I where the outcome will be based on clinical judgement
8. Any disease or condition that may influence pupillary reflexes based on clinical judgement
9. Undergone eye surgery that may influence pupillary reflexes based on clinical judgement
10. Ongoing treatment with medications which may interfere with eye measurements based on clinical judgement
11. Ongoing treatment with medications which may interfere with any of the medicinal products to be used
12. History or presence of allergy or serious reaction to the medicinal products to be used
13. History or presence of cardiovascular disease, e.g., arteriosclerosis, hypertension, or cor pulmonale
14. History or presence of sleep-related breath disorder
15. History or presence of gastrointestinal disease, e.g., paralytic ileus, acute abdomen, delayed gastric emptying, or chronic constipation
16. History or presence of pulmonary disease, e.g., acute pulmonary insufficiency, severe respiratory depression with hypoxia, chronic obstructive lung disease, or bronchial asthma
17. History or presence of autoimmune neuromuscular disease, e.g., myasthenia gravis
18. Not able to read or understand the local language
19. Any other condition that as judged by the investigator may make the follow-up or investigation inappropriate
20. That according to the Declaration of Helsinki is deemed unsuitable for study enrollment

OBJECTIVES:

Primary Objective

- Evaluate if self-administered pupillometry using a mobile phone application can be used to collect pupillograms before and under the influence of phenethylamines, benzodiazepines, cannabinoids, and opioids (D1-D4).

Secondary Objectives

- Evaluate if self-administered pupillometry using a mobile phone application, after refining the method for establishing pupillograms, can be used to collect pupillograms before and under the influence of each medicinal product (D1-D4).
- Evaluate if self-administered pupillometry using a mobile phone application can be used for indicating use of each medicinal product (D1-D4).

- Evaluate the correlation between pupillometric variables and concentration in plasma over time for each medicinal product D1-D4.
- Evaluate the maximum time after medicine intake D1-D4 when pupillometric variables differ from baseline.
- Evaluate if a combination of different pupillometric variables can be used for indicating use of each medicinal product D1-D4.
- Collect usability data to evaluate if the user-interface of Previct Drugs is suitable to be used by users.

Safety objective

- Evaluate the safety of using the mobile phone application Previct Drugs for collecting self-administered pupillometry data.

PERFORMANCE AND SAFETY ENDPOINTS:

Primary Endpoint

- For each medicinal product (D1-D4), the fraction of collected pupillometry data from the mobile phone application at baseline and under the influence of D1-D4, which can be transformed into pre-defined key features using native pupillogram.

Secondary Endpoints

- For each medicinal product (D1-D4), the fraction of collected pupillometry data from the mobile phone application at baseline and under the influence of D1-D4, which can be transformed into pre-defined key features using refined pupillogram.
- For each medicinal product (D1-D4), change in key features from baseline to the LC-MS/MS verified peak concentration in plasma after administration of medicinal product at visit 2 using native or refined pupillograms.
- For each medicinal product (D1-D4), analysis and plot the correlation between key features and plasma concentration over time using native or refined pupillograms.
- For each medicinal product (D1-D4), change in key features from baseline to 5 hours after administration of medicinal product at visit 2 using native or refined pupillograms.
- For each medicinal product (D1-D4), test known combinations of key features that changes from baseline to the LC-MS/MS verified peak concentration in plasma after administration of medicinal product at visit 2 using native or refined pupillograms.
- User-friendliness of Previct Drugs evaluated by the subject at visit 2.

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). FAS is defined as all subjects included in the clinical investigation with at least one pupillometric test under influence of one of the medicinal products. All analyses will be performed separately for each medicinal product. No comparisons will be performed between the medicinal product groups. The two ambient light conditions will also be analyzed separately.

Primary analysis:

Fraction of collected pupillometry data using native pupillogram. For each of the measurements PLR, NC, and NY, each measurements quality control (QC) will approve the measurements or not using the native pupillogram. For each subject, the proportion of approved measurements over all measurements during day 2 will be calculated for each of PLR, NC, and NY. The distribution over subjects for each medicinal product will be given with mean, SD, median, minimum, and maximum. The two ambient light conditions will be analyzed separately.

Secondary analyses:

Changes within subjects from baseline, without medicinal product, to time points under influence of medicinal product in key features will be analyzed with Fisher's non-parametric permutation test for paired observation for continuous variables and with Sign test for ordinal and dichotomous variables.

Correlation analyses will be performed between change from baseline to verified peak plasma concentration between pupillometry data and plasma concentrations using Spearman correlation and scatter plots. Each individual Spearman correlation coefficient will be calculated between plasma concentration and pupillometry key features for all measurements during visit 2. These spearman correlation coefficients will be analyzed over subjects with Fisher's one sample non-parametric permutation test.

Sample size calculation:
No formal sample size calculation has been performed.

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)

3 TABLE OF CONTENTS

4 ABBREVIATIONS AND ACRONYMS

ADE	Adverse Device Effect
AE	Adverse Event
AI	Artificial Intelligence
App	Application
ASADE	Anticipated Serious Adverse Device Effect
AUD	Alcohol Use Disorder
BMI	Body Mass Index
CDP	Clinical Development Plan
CEP	Clinical Evaluation Plan
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
ECG	Electrocardiogram
eCRF	Electronic case report form
EEA	European Economic Area
eHealth	Electronic Health
EU	European Union
Fft	Fast fourier transform
FAS	Full analysis set
FDA	Food and Drug Administration
GC	Gas Chromatography
GDPR	General Data Protection Regulation
IB	Investigator Brochure
ICF	Informed Consent Form
IEC	Independent Ethics Committee
IFU	Instructions For Use
ISF	Investigator Site File
ISO	International Organization for Standardization
kPa	Kilopascal
LC	Liquid Chromatography
LC-MS/MS	Liquid Chromatography Tandem Mass-Spectroscopy
MCA	Maximum contraction velocity
MCV	Maximum contraction amplitude
MDD	Medical Device Directive – Council Directive 93/42/EEC
MDR	Medical Device Regulation – Regulation (EU) 2017/745
mHealth	Mobile Health
mmHg	Millimeters of mercury

MmX	Maximum distance in window
MS	Mass-Spectrometry
NA	Narcotics Anonymous
NC	Non-Convergence
NCnf	Noise factor
NY	Horizontal Nystagmus
PD	Pharmacodynamic
Pesc	Pupil escape
PK	Pharmacokinetic
PI	Principal Investigator
PLR	Pupillary Light Reflex
PCO2	Partial pressure of carbon dioxide
QC	Quality control
QMS	Quality Management System
RMCA	Relative maximum contraction amplitude
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDV	Source Data Verification
SMF	Study Master File
SOP	Standard Operating Procedure
SpO2	Oxygen saturation
Subject ID	Subject Identification
SUD	Substance Use Disorder
THC	Tetrahydrocannabinol
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 usage. 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.

This first clinical investigation of Previct Drugs will be a prospective, first-in-human, pilot, explorative, early-feasibility, pre-market clinical investigation to collect clinical data required for finalize the development of the first version of Previct Drugs intended to be CE-marked. [redacted]

In this first investigation, drug intake will be simulated through collecting pupillometric data with Previct Drugs before and after a controlled single administration of commonly used medicinal products from the following classes of drugs: phenethylamines (D1), benzodiazepines (D2), cannabinoids (D3), and opioids (D4). For making this possible, a healthy volunteer population has been suggested as the most appropriate study population to use for being able to collect clinical data before and after the single application of the medicinal product. The study population will consist of 48 healthy volunteers (12 per medicinal product) recruited in the Netherlands. Each subject will participate in the investigation for approximately 10 days after the baseline and screening 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 summarizes the different parts of Previct Drugs to be used in this investigation.

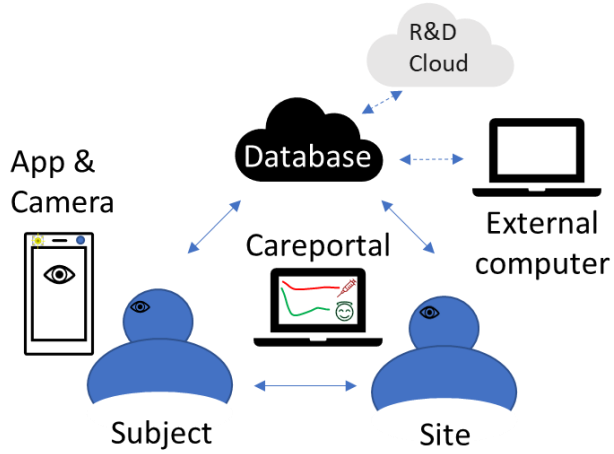

Figure 1. Summary of the different parts of Previct Drugs to be used in this investigation. The subject will perform self-administered eye measurements through the app using the smartphone camera. The results from the eye measurements will be stored in the database and further analysis will be performed in the external computer whereafter these results will also be stored in the database. Once the investigation is completed, the data and 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 subjects (i.e., healthy volunteers). If required, the site personnel will assist. Notification will be sent to the subject to remind when the eye-measurements with Previct Drugs should be performed. 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. The videos that cannot be processed will be transferred to the external computer for manual annotation whereafter the current mathematical models will be refined. All videos will thereafter the processed a second time and new pupillometric variables and key features will be received. 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's 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 this investigation.

In future version of Previct Drugs, [redacted]

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 in the investigation.

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

Previct Drugs module	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) [13] and labeled electronically. 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 Previct Drugs app (in Dutch).

The information available on the electronic label represents the following:

- Version number (connected to documentation that describes the content in that version of the app release).
- Build number representing when built.
- Information that device is to only to be used in a clinical investigation.

The web-based careportal used by the site personnel in the investigations will be labeled as following:

- Version number (connected to documentation that describes the content in that version of the web-based careportal release).
- Date and time when built.
- Link to license information.
- Symbol for copyrights, year, and company name.

Note that the web-based careportal is already an approved platform used for the Previct Alcohol. In the investigation, the careportal will be used for registering subject ID and provide access to the app. No other information about the subjects or the investigation will be added into the careportal.

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 each site with smartphones to be used by the participating subjects during the clinical investigation. The equipment accountability log at site will include the following information:

- Date and smartphone identification provided to site
- Date, smartphone identification, and subject ID once provided to subject
- Date returned from 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 [13]:

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 healthy volunteers 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 users, and target population:

- **Indication:** Not applicable. The indication for being included in the investigation is to be a healthy volunteer defined as healthy determined by the investigator or designee based on pre-study medical and surgical history and health examination performed during screening.
- **Intended users:** Site personnel and healthy volunteers participating in this clinical investigation for eye-measurements [13].
- **Target population:** men and woman, 18-70 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
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

Technical Functionality	Where	Who	Data generated Task fulfilled
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 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 healthy volunteer, 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 used and handed out to the participating subjects.
- The app will be pre-installed on the smartphone once handed out to the subject. The installation of the app on the smartphone will be performed by the sponsor before providing the smartphones to the participating site.

- The subject will receive an activation code from the site personal. The activation code is received through the careportal. Once the app has been activated, the subject will choose a personal pin code to be used for login to the app.
- 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 subject will thereafter report any concomitant medication that have been used since last test. The subject should select "Yes" if the subject wants to report usage of medications or substances. If no usage, the subject should select "No, take me to the test". During the study visits at the site, it is not mandatory to record any medication in the app as it will be recorded in the eCRF as well.
- 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 (PLR NC, and NY), 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.

The app will contain preset notifications to remind the subject when a test should be performed during the investigation. 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. If the videos cannot be automatically processed to pupillometric variables in the app, the external computer will be used for manually annotating the videos. The videos that are manually annotated will be used for refining the current mathematical and algorithms models in Previct Drugs. All collected videos will thereafter be processed in the updated mathematical and algorithm models and new pupillometric variables and key features will be calculated. The results will be transferred to the database.

Direct access to the videos is limited to the data scientists at the sponsor 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

7.1 General

Before this first-in-human 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].

This first-in-human, explorative, early feasibility, pilot, clinical investigation aims to collect initial clinical data for usage of the essential parts of Previct Drugs at an early stage of product development. 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 proof of concept of Previct Drugs, its safety, and the usability of the device.

7.2 Study population

A measurement with Previct Drugs relies on that the user can perform a self-administered testing of eye parameters, that a normalization for variation in ambient light conditions can be made, and that drug naïve reference measurements are available from the user. The following must therefore be taken into consideration when designing the first investigation:

- To be performed in an environment where light can be controlled and varied systematically.
- To collect pharmacokinetic/pharmacodynamic (PK/PD) effect in a controlled way for approximately 5 hours after administration of the medicinal product to define the detection window of Previct Drugs.
- To collect baseline data from a naïve population.

The targeted drug substances of interest (phenethylamines, benzodiazepines, cannabis, and opioids) are four therapeutically used medicinal products belonging to the families of drugs of abuse (also illicit drugs). It is well known from the literature [8] that these drug substances can be identified using pupillometric methods. Compared to ordinary pupillometric methods that are often required to be performed using eyes adapted to darkness, Previct Drugs will make it easier for the user to perform a measurement as it is performed in ambient light conditions.

At first, the study population considered to be used in this investigation was patients who use the drug substances of interest as part of their current treatment regime, e.g., oxycodone for pain and benzodiazepines for anxiety. Although, if to use this population the following hurdles were noted: a) the initial therapeutic dosing used to treat a condition is often considerably lower than what is used by drug abusers which may lead to that the dosing is under Previct Drugs detection window, b) it may be unethical to collect a drug naïve baseline from patients as this may extend the start of

treatment, and c) the patient's condition may strongly influence the possibility to perform a controlled PK/PD-study.

Another alternative of study population was to collect data from patients in treatment for SUD as this is the intended target population once Previct Drugs will be placed on the market. Also here we identified issues leading to that it was not optimal to include this population since: a) patients in treatment for SUD will be a non-naïve population which may bias the results and also makes it difficult to collect baseline data, b) it is highly unethical to perform a PK/PD-study by dosing a medicinal product in subjects with a history of addiction, and c) these patients may also be seen as vulnerable population depending on study design where the ISO standard 14155:2020 clearly states that investigations should be avoided in a vulnerable population if possible and should not be conducted when there is no potential for therapeutic benefit.

Based on the above, healthy volunteers have been selected as the most appropriate study population for the first clinical investigation of Previct Drugs. Using a healthy volunteer population will make it possible to:

- Collect drug naïve baseline data where the healthy volunteer will be able to act as his/her own reference.
- Perform a PK/PD-study in a controlled way with up to 5 hours of measurement after administration of medicinal product to evaluate if Previct Drugs can detect the drug substances of interest.

The study population will contain of different ages between 18 to 70 and different eye types to make sure that there is a diversity in the clinical data collected as these factors may impact the eye parameters.

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.

A 10-day study participation period has been decided to be appropriate as it will provide extensive baseline data in a naïve population and the possibility to observe the PK and PD after a single administration of a medicinal product in a controlled setting.

7.3 Medicinal products

The selected medicinal products to be used in this study are all known to affect different eye parameters and movement (tremor) [9-10, 18]. Phenethylamines belong to the group of central stimulants and during usage it gives larger pupils and no or only small light reflex. It may also give the user tremor. Benzodiazepines belong to the group of central depressive substances and under influence the ability to converge the eyes is reduced. Some of the central depressive substances may also give tremor and red eyes. The nystagmus test is also often positive and the reaction to light change is slowed down. During usage of cannabinoids, it also affects the ability to converge the eyes. The sclera (the outer white coating of the eye) may also turn to red, and the pupil may enlarge. Opioids instead gives small pupils that do not react, and no or only minor reaction to light. In Table 3 below, it is summarized the eye parameters and movements (tremor) thar are affected per medicinal product/drug class.

Table 3. Summary eye parameters and movements (tremor) affected per medicinal product/drug class.

	Central stimulants (Phenethylamines)	Central depressive substances (Benzodiazepines)	Cannabinoids	Opioids
Pupil size	Enlarged	Normal	Enlarged (or Normal)	Reduced
Pupillary light reflex (PLR)	Slower	Slower	Normal	No/minor reaction
Non-Convergence (NC)	Normal	Yes	Yes	Normal
Horizontal nystagmus (NY)	Normal	Yes	Normal	Normal
Sclera (the white outer coating of the eye) turns red	Normal	Yes	Yes	Normal
Tremor	Yes	Yes	Normal	Normal

The selected doses to be used for the medicinal products in this investigation have been decided based possibility to affect the eye parameters and making sure that the doses are as low as possible with limited risks as they will be used in a healthy volunteer population without a condition to be treated. The doses have been decided based on current scientific knowledge and prescription range [19]. The administration of the medicinal products will take place in a controlled setting at the site at visit 2, where the healthy volunteer will be under observation by the site personnel during and after the administration. Table 4 below summarizes the dose to be used per medicinal product and the sections thereafter explain the background and doses selected further.

Table 4. The selected doses of the of the medicinal products to be administered in healthy volunteers. Tmax is the time to reach Cmax which is the peak plasma concentration of the drug. WHO-DDD is the by WHO recommended daily defined dose.

Group	Medicinal product	Trade name	T_{max}	Cmax ng/ml of the intended single dose	WHO-ATC/DDD Index (WHO-DDD 2022)	Dose to be used in this investigation
Phenethylamines (D1)	Lisdexamphetamine ATC-code: N06BA12	Elvanse	3-4h 1-1.5h*	~60 ng/ml*2	30 mg oral Lisdexamphetamine 15 mg oral Dexamphetamine	70 mg oral Lisdexamphetamine Corresponding to 19,3 mg Dexamphetamine
Benzodiazepines (D2)	Lorazepam ATC-code: N05BA06	Lorazepam Aurobindo	1-2h	25-37 ng/ml*3	2.5 mg oral	2.5 mg oral Lorazepam
Cannabinoids (D3)	Tetrahydrocannabinol (THC) ATC-code not available	Bedrocan (22%THC) medical cannabis floss The inhalator Volcano will be used for administration	5 min	~52 ng/ml*4	No WHO-DDD available NIH-NIDA recommends equivalents of 5 mg THC as a standard dose for research studies	65 mg Bedrocan (22%, 14.3 mg THC), giving 5 mg THC*5 bioavailable administered using the Volcano inhalator
Opioids (D4)	Oxycodone ATC-code: N02AA05	Oxycodone HCl Teva	1h	41.6 ng/ml	75 mg (this daily dose refers to controlled-release formulation)	20 mg immediate release oral Oxycodone

* Lisdexamphetamine reaches Tmax in ~1 h and is hydrolyzed to the active substance d-amphetamine reaching Tmax in 3-4h (Ermer et al. 2010) [20].
*2 Interpolated Cmax of amphetamine from Ermer 2010 (Table 1, Ermer et al. 2010) [20].

*[3] Based on calculation of 2.5 times the 10-15 ng/ml achieved using 1 mg dosing.
*[4] Calculated as 0.65 fraction from the 82 ng/ml of 100 mg Bedrocan [21].
*[5] The 5 mg is the calculated dose after losses due to incomplete evaporation, losses in the storage balloon, and partial absorption to lungs of the 14.3 mg of THC available in 65 mg medicinal cannabis floss.

7.3.1 Phenethylamines

Central stimulants from the family of phenethylamines (e.g., Lisdexamphetamine and Dexamphetamine) are commonly used to treat attention deficit/hyperactivity disorder (ADHD). The phenethylamine Lisdexamphetamine is a prodrug which is hydrolysed to the active component Dexamphetamine in the body. Lisdexamphetamine (100 mg, counterion dimesylate) and Dexamphetamine (40 mg, counterion sulphate) giving equimolar doses of 29.6 mg of Dexamphetamine have been used in clinical studies on healthy volunteers [22-23]. This concentration has been shown to give measurable effects on pupil size measured using a desktop pupillometer. Lisdexamphetamine is available as prescription medicine (Elvanse) in doses from 20 to 70 mg commonly used for treating ADHD in adults. The WHO-DDD of Dexamphetamine is 15 mg and of Lisdexamphetamine 30 mg. For the KCClin01 investigation, it is decided to use a single dose of 70 mg orally administered Lisdexamphetamine which corresponds to 19.3 mg Dexamphetamine. The selected dose is slightly higher than the WHO-DDD of Dexamphetamine (19.3 vs 15 mg), but lower than what have been previously safely used in clinical studies (29.6 mg) [22-23] and it also falls within the current prescribed range of Lisdexamphetamine (20-70 mg).

7.3.2 Benzodiazepines

Benzodiazepines are commonly used for treatment of anxiety, neurosis, and insomnia. Lorazepam is a short-acting and rapidly cleared benzodiazepine. Lorazepam has previously been studied in healthy volunteers' studies, e.g., Huron et al. (2002) [24] studied doses of 0.026-0.038 mg/kg (i.e., 1.8-2.7 mg at 70 kg) and Haas et al. (2008) [25] at doses of 2 mg. As the WHO-DDD is 2.5 mg Lorazepam we have decided that this will be the single dose to be administered orally in the KCClin01 investigation.

7.3.3 Cannabinoids

Medicinal cannabinoids is commonly used for treatment of symptoms of e.g., chronic pain, multiple sclerosis, and nausea. Tetrahydrocannabinol (THC) is the most potent psychoactive chemical substance of cannabinoids. The effect of cannabinoids on pupils has been verified in studies on subjects who were weekly users of cannabinoids. THC was administered in form of cigarettes with estimated dosages of 40-90 mg [26]. In the Netherlands, safe use of THC concentrations of 9.75-13.75 mg THC is used for the management of neurological pain and recent results show that high precision dosing of lower doses (0.5-1 mg) relieves neuropathic pain [27]. For research studies, NIH-NIDA recommends a standardized unit of 5 mg THC as a dose measure for research purposes [28]. The research has shown that 5 mg will minimize side effects and still give the "high" effect. According to NIH-NIDA [29], the suggested dose to be used in research should be seen as a help to select dose to be used but does not place a limit on how much can be used. THC can be administered both orally, pulmonary, and intravenous. Evaporation of THC by heating cannabis floss has been found to be a reproducible way to administer THC to the body [30]. At the temperature of 210°C, THC-acid is converted into THC, evaporated, and captured in a balloon and inhaled within a few minutes. Hazekamp et al. (2006) [30] found, using Volcano vaporizing device, that in average of 54% of the total amount of THC is released in vapor, whereof 65% is absorbed by the lungs and 35% is exhaled. Similar results have been published from a clinical study performed by Zuurman et al. (2008) [31]. An available THC product is Bedrocan (22% THC) developed by the supplier Bedrocan. Based on the above assumptions, 65 mg Bedrocan (22% THC) would be required to get a bioavailable dose of 5 mg THC administered with the Volcano vaporizing device, due to losses caused by administration and exhalation. The

research group at Leiden University Medical Center (LUMC) have previously dosed 100 mg Bedrocan (22% THC, 22 mg) and got an average peak THC concentration of Cmax 82 +/- 20 ng/ml concentration in the plasma [21].

For the KCClin01 investigation, it is thereby decided to provide a single dose of an effective bioavailable dose of 5 mg THC [28], by pulmonary administration using Volcano vaporizing device, of 65 mg Bedrocan (22% THC). The effective dose will be 1 THC standard unit by dosing 2.9 standard units of THC available in the cannabis floss.

7.3.4 Opioids

Oxycodone is a prescription opioid commonly used for pain management. It is available in a wide range of single concentration instant release pills of 5-20 mg and oral depot/controlled release formulations of 5-70 mg. The WHO-DDD of Oxycodone is 75 mg. However, the DDD refers to a controlled release formulation and to long-term treatment of chronic pain. Doses of 20 mg oxycodone have been used as a median dose for severe pain relief. Also, doses of 20 mg have been used in PK/PD studies on healthy volunteers and the side effects have been mild [32]. For the KCClin01 investigation, it is decided to administer a single oral dose of 20 mg Oxycodone.

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

When discussing risks and benefits of a new medical device, there are different aspects that have to be considered, including the potential benefits 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 [33-34].

8.1 Anticipated Clinical Benefits

There are no direct clinical benefits for the participating subjects as the study population consists of healthy volunteers. Although, through participating the subject will assist the sponsor to collect the data required for finalizing the design 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 considered to be 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 the study population will contain of healthy volunteers. 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, 31 risks were identified of which 18 are considered to be insignificant risks after mitigation and 13 risks that need to be further investigated. No remaining risks are unacceptable after mitigation.

The risks can be summarized into 12 different types of hazards, primarily relating to function, usability, and side effects of the medicinal products used in the investigation.

- Investigation not performed as planned (4)
- Investigator no successful (2)
- Function: design (1)
- Function: incorrect input (3)
- Function: data loss (1)
- Function: data transfer (4)
- Use error: routine violation (2)
- Use error: rule based (1)
- Use error: knowledge-based failure (1)
- Side effects of medicinal products (9)
- Normal use subject shaking (1)
- Non-CE marked product available on the market (2)

The identified hazards may lead to the following adverse events:

- Infection after blood sampling (for both subject and site personnel)
- Minor pain during/directly after blood sampling
- Feeling light-headed during/directly after blood sampling
- Common side effects of medicinal products:
    - Opiates (Oxycodone):
        - Severe: respiratory depression

- Very common: somnolence, dizziness, headache, constipation, nausea, vomiting, pruritus
- Common: decreased appetite, anxiety, confusional state, depression, insomnia, nervousness, abnormal thinking, abnormal dreams, tremor, lethargy, sedation, dyspnea, bronchospasm, cough decreased, abdominal pain, diarrhea, dry mouth, dyspepsia, rash, hyperhidrosis, asthenia, fatigue

- Benzodiazepines (Lorazepam):
  - Very common: daytime drowsiness, dizziness, muscle weakness, ataxia
  - Other: asthenia, fatigue
- Lisdexamphetamine:
  - Severe: increase in pulse, blood pressure, body temperature, chest pain, tachycardia
  - Very common: decreased appetite, insomnia, dry mouth, headache
  - Other common: agitation, anxiety, libido decreased, affect lability, psychomotor hyperactivity, bruxism, dizziness, restlessness, tremor, palpitation, dyspnea, diarrhea, constipation, upper abdominal pain, nausea, hyperhidrosis, erectile dysfunction, irritability, fatigue, feeling jittery, weight decrease
- Cannabinoids (THC):
  - Main ones for low doses: mild euphoria, sedation, somnolence
  - Other potential ones: mild impairment of short-term memory, dry mouth, redness of the eyes, heightened apatite, increase in heart rate, uncontrolled laughter, changes in the awareness of surroundings (colors, sounds)

The medicinal products to be used in this investigation are all seen as addictive medicines, and thereof it is a risk of that the subject get addictive after study participation. This risk is seen as low or non-existing based on the design and study population.

For complete list of potential side effects also including the more uncommon ones, please see latest available information for each medicinal product.

8.4 Possible interactions with concomitant medical treatments

Possible interactions with any ongoing medication during study participations deems to be low as the study population consists of healthy volunteers which will be confirmed during the screening procedure. Individuals on current treatment with medicines with known interactions to any of the medicinal products to be used will not be included in this investigation.

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 at the first visit and only subjects that successfully can use the device will be identified as eligible.

Based on the study design, population, and especially the medicinal products to be used there are potential adverse events that may occur. The ones listed above, are the common ones which of almost all may be seen as transient. As this is an investigation on healthy volunteers where the medicinal product is to be administered in a single dose, the probability of events which are not transient is low or non-existing. It should also be noted that the medicinal products used are common medicines used within the healthcare today.

The administration of the medicinal products and follow-up of the participating subjects will be performed at sites familiar with these types of medicines and performing investigations of healthy volunteers. The screening criteria that have been added in this investigation will exclude any individuals with medical, neurologic, or psychiatric conditions. Any contraindications to the medicinal products have been considered. Any individual with current or previous alcohol and/or drug abuse will also be screened for exclusion, i.e., through relevant questionnaires and a urine test. Pregnant or lactating females will not be included. A health examining including relevant vital signs, i.e., ECG, blood pressure, and pulse, will also be performed during the screening. To summarize, these checks will be performed to make sure that only healthy individuals are included for further study participation, and that the risk of any potential adverse events of more severe characteristics are avoided as far as possible including the potential risk for addiction.

Before and after the administration of the medicinal product at visit 2, it will again be confirmed that the subject is not pregnant and/or under influence of any drug substance. The subject will also before and after being monitored with relevant vital signs, i.e., oxygen saturation, pulse, blood pressure, and body temperature. Site personnel will be available to take any actions if the status of the subject is changed based on their current routines and general procedures at the site. The subject will not be discharged from the site after visit 2 until it is confirmed that the subject is safe. The subject will not be allowed to drive back home the same day. Alternative transports will be arranged instead. The subject will be followed-up the days after visit 2 to confirm everything is well before the subject has completed the investigation.

One of the more severe potential events are respiratory depression during usage of oxycodone. The probability of a significant respiratory effect at the dose to be used in this investigation is low. In case of any of the following, the site will administer 0.4 mg Naloxone in accordance with their standard procedures: (i) loss of respiratory activity lasting 3 minutes or longer despite active stimulation of the subject; (ii) an increase in end-tidal PCO_2 to 9 kPa (67.5 mmHg) or greater lasting 3 minutes or longer; or (iii) $SpO_2 < 85\%$ lasting 3 minutes or longer despite administration of supplemental oxygen.

It should also be mentioned that as being 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 self-administered pupillometry using a mobile phone application can be used to collect pupillograms before and under the influence of phenethylamines, benzodiazepines, cannabinoids, and opioids (D1-D4).

9.2 Secondary Objectives

The secondary objectives are to:

- Evaluate if self-administered pupillometry using a mobile phone application, after refining the method for establishing pupillograms, can be used to collect pupillograms before and under the influence of each medicinal product (D1-D4).
- Evaluate if self-administered pupillometry using a mobile phone application can be used for indicating use of each medicinal product (D1-D4).
- Evaluate the correlation between pupillometric variables and concentration in plasma over time for each medicinal product D1-D4.
- Evaluate the maximum time after medicine intake D1-D4 when pupillometric variables differ from baseline.
- Evaluate if a combination of different pupillometric variables can be used for indicating use of each medicinal product D1-D4.
- Collect usability data to evaluate if the user-interface of Previct Drugs is suitable to be used by users.

9.3 Safety Objective

To evaluate the safety of using the mobile phone application Previct Drugs for collecting self-administered pupillometry data.

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.
- Previct Drugs enables self-administered monitoring if a person under the influence of selected drugs deviates from its own drug naïve baseline.

The primary endpoint relates to Previct Drugs function to convert pupillometry to key features will collect preliminary evidence for the first claim.

Several of the secondary endpoints relate to Previct Drugs ability to detect a change once under influence of drugs and will collect preliminary evidence for the second claim. Further evidence will eventually be required in future investigations for confirming this claim.

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 on Previct Drugs. 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 and algorithms for drug detection.

This first study will give valuable information on the feasibility of Previct Drugs function to measure pupils and eye movements and to evaluate if there are any changes in the pupillometric parameters before and after intake of a medicinal product. It will also provide information on the usability of the device. Drug intake will in this first investigation be simulated by a controlled single application of commonly therapeutically used medicinal products from the following classes of drugs: phenethylamines (D1), benzodiazepines (D2), cannabinoids (D3), and opioids (D4).

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

Healthy volunteers 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. Each potential subject will be given at least 72 hours to carefully consider participation and to ask any questions related to the investigation after being given the study information. 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 whereafter the subject will use Previct Drugs in his/her home environment for 1 week (+/- 2 days). A second visit will thereafter be performed where the subject will receive a single administration of one of the four medicinal products of interest (D1-D4) according to the randomization list at the site in a controlled setting under observation. Once administered, the subject will be observed for approximately 5 hours where Previct Drugs will be used hourly. The day after visit 2 (+ 2 days), the subject will be telephoned to confirm the safety of the subject. The subject has thereafter completed the investigation.

The clinical investigation procedures are further explained in section 10.8.

The overall duration of the clinical investigation is anticipated to be approximately 7 months, including a 6,5-month enrolment period.

10.2 Primary Endpoint

- For each medicinal product (D1-D4), the fraction of collected pupillometry data from the mobile phone application at baseline and under the influence of D1-D4, which can be transformed into pre-defined key features using native pupillogram.

10.3 Secondary Endpoints

- For each medicinal product (D1-D4), the fraction of collected pupillometry data from the mobile phone application at baseline and under the influence of D1-D4, which can be transformed into pre-defined key features using refined pupillogram.
- For each medicinal product (D1-D4), change in key features from baseline to the LC-MS/MS verified peak concentration in plasma after administration of medicinal product at visit 2 using native or refined pupillograms.

- For each medicinal product (D1-D4), analysis and plot the correlation between key features and plasma concentration over time using native or refined pupillograms.
- For each medicinal product (D1-D4), change in key features from baseline to 5 hours after administration of medicinal product at visit 2 using native or refined pupillograms.
- For each medicinal product (D1-D4), test known combinations of key features that changes from baseline to the LC-MS/MS verified peak concentration in plasma after administration of medicinal product at visit 2 using native or refined pupillograms.
- User-friendliness of Previct Drugs evaluated by the subject at visit 2.

10.4 Safety Endpoint

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

10.5 Investigational Device

Previct Drugs will be used by the subject 6 times at the first visit and thereafter 3 times a day (morning, lunch, evening) for 1 week (+/- 2 days) and finally 24 times at the second visit. The subjects that administer cannabinoids on visit 2 will also perform 2 additional tests with Previct Drugs. A test with Previct Drugs takes approximately 5-15 minutes. Table 5 below summarizes the times Previct Drugs will be used.

Table 5. Summary of the number of tests to be performed with Previct Drugs during the investigation.

Visit	Number of tests	Maximum number of tests
Visit 1	3 duplicate tests in two different ambient light conditions	6 tests
Home period between visits 1 and 2	3 tests per day	27 tests
Visit 2	3 duplicate tests in two different ambient light conditions before single administration of a medicinal product 1 duplicate test hourly for 5 hours in two different ambient light conditions after a single administration of a medicinal product - At hour 1, 2 and 3 an extra test will be performed in each ambient light condition - If administered with cannabinoids, a duplicate test will also be performed 0.5 h after administration	24 tests (26 tests if administered with cannabinoids)

The medicinal products described in section 7 will be used as a single administration at visit 2.

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. Male or female healthy volunteers
2. Age 18 to 70 years
3. BMI between 18.5-30 kg/m2
4. Weight between 50-100 kg
5. Healthy as determined by the investigator or designee based on pre-study medical and surgical history and a health examination at enrolment
6. Women 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 and at visit 2 and must agree to use a medically acceptable contraception from enrollment until study completion
7. No current drug usage defined as a negative urine drug test at enrollment and at visit 2
8. Able to use Previct Drugs after initial training (defined as successfully performing a test after trying maximum three times per measurement)
9. Been informed of the nature, the scope, and the relevance of the clinical investigation
10. Voluntarily agreed on 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. Abnormal ECG (QTc time>450 ms) at enrollment
6. Current or recent history of alcohol misuse assessed by AUDIT where ≥6 points for women or ≥8 points for men indicates a potential misuse
7. Current or history of psychiatric disorder or drug misuse assessed by M.I.N.I where the outcome will be based on clinical judgement
8. Any disease or condition that may influence pupillary reflexes based on clinical judgement
9. Undergone eye surgery that may influence pupillary reflexes based on clinical judgement
10. Ongoing treatment with medications which may interfere with eye measurements based on clinical judgement
11. Ongoing treatment with medications which may interfere with any of the medicinal products to be used
12. History or presence of allergy or serious reaction to the medicinal products to be used
13. History or presence of cardiovascular disease, e.g., arteriosclerosis, hypertension, or cor pulmonale
14. History or presence of sleep-related breath disorder
15. History or presence of gastrointestinal disease, e.g., paralytic ileus, acute abdomen, delayed gastric emptying, or chronic constipation
16. History or presence of pulmonary disease, e.g., acute pulmonary insufficiency, severe respiratory depression with hypoxia, chronic obstructive lung disease, or bronchial asthma
17. History or presence of autoimmune neuromuscular disease, e.g., myasthenia gravis
18. Not able to read or understand the local language
19. Any other condition that as judged by the investigator may make the follow-up or investigation inappropriate
20. That according to the Declaration of Helsinki is deemed unsuitable for study enrollment

10.6.3 Relationship of Investigation Population to Target Population

In this first early feasibility and pilot investigation of Previct Drugs it has been decided to use a healthy volunteer population to be able to collect clinical data before and after a single administration of a medicinal product in a controlled way. The collection of this data is a requirement for continued development of the mathematical models and algorithms for drug detection with Previct Drugs after the investigation has been completed.

10.6.4 Number of Subjects
The investigation population will be comprised of 48 eligible adult healthy volunteers between 18 to 70 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 48 eligible subjects. The subjects will be randomly assigned to one of the four medicinal product groups indicating which medicinal product that the subject will administer at visit 2. Each group will have 12 subjects per group, i.e., 12 subjects per medicinal product.

Once a subject has consented for study participation, the subject will be given a unique subject identification (subject ID) number. If the subject fulfills all inclusion criteria and none of the exclusion criteria, the subject will be seen as eligible. Randomization to one of the four medicinal products will take place at visit 1. Randomization will be based on which criteria the subject fulfils as for each medicinal product there should be at least 3 subjects with bright eyes (defined as blue, green, or grey) and at least 3 subjects with dark eyes (defined as brown), at least 2 subjects between 18-25 years old and at least 2 subjects between 50-70 years old. A subject can fulfill several of these criteria.

The subject will be allocated to the next available randomization number according to the randomization list and the associated medicinal product will thereafter be administered at visit 2 according to this CIP.

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 always 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 PI or designee deems the subject unfit for the investigation or suspects poor CIP compliance;
- Subject lost to follow-up: the site needs to try to reach a subject at least three times before it can be argued that the subject is lost to follow-up. The attempts need to be documented;
- Positive drug urine test at visit 2;
- Positive pregnancy test at visit 2.

Incorrectly enrolled subject 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 be participating approximately 10 days in the clinical investigation. A 10-day study participation period has been decided to be appropriate as it will provide extensive baseline data in a naïve population and to follow a single administration of a medicinal product in a controlled setting.

At visit 2, after the single administration of the medicinal product the subjects will be under observation until its safe for the subject to leave the site. The day after the visit (+ 2 days), the site will telephone the subject to confirm from a safety perspective that no AEs/ADEs have occurred. The subject has thereafter completed the investigation. It is not deemed necessary to have additional follow-up after the completion of this visit as the population consists of healthy volunteers and that a telephone call will be scheduled the days after visit 2 before the subject has completed the participation.

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/Q2/Q3 2023
Point of randomization:	Q1/Q2/Q3 2023
Enrolment period:	6,5 months
Expected duration of each subject's participation:	10 days
Total expected duration of the clinical investigation:	7 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 6 below. Further information is provided in the sections below.

Table 6. Clinical Investigation schedule for assessments and procedures.

Assessment	Pre-Day 0 At least 72 h before Visit 1	Visit 1 Day 0	Home period 1	Visit 2 Day 7 (+/- 2 days)	Telephone follow-up call 1 (+ 2 days)
Study information (written and oral)	X				
Informed consent		X			
Demographics (e.g., age, gender, weight, length, BMI, eye color)		X			
Inclusion/Exclusion criteria		X			
Health examination (e.g., ECG, pulse, blood pressure)		X			
Pregnancy test		X		X	
Confirmation contraceptives		X			
Urine test – drug screening		X		X	
Previct Drugs training		X			
Questionnaire AUDIT		X			
Questionnaire M.I.N.I.		X			
Relevant medical and surgical history		X			
Relevant medication review/concomitant medication		X	X	X	X
Hand-out of smartphone and setting up Previct Drugs		X			

Assessment	Pre-Day 0 At least 72 h before Visit 1	Visit 1 Day 0	Home period 1	Visit 2 Day 7 (+/- 2 days)	Telephone follow-up call 1 (+ 2 days)
Previct Drugs measurements		X	X	X	
Blood sample				X	
LC-MS/MS analysis				X	
Vital signs (e.g., oxygen saturation, pulse, blood pressure, body temperature)				X	
Randomization		X			
Administration of medicinal product				X	
Usability questionnaire				X	
Clinical impression by investigator/designee before discharged at visit 2				X	
Adverse event and device deficiency		X		X	X
Study exit					X

10.8.2 Subject information (at least 72 hours prior to Day 0)
Prior to the baseline and screening visit at Day 0, potential subjects that are interested to participate will contact the site. The site personnel will give information about the study and perform a brief check towards the eligibility criteria. The investigator will introduce the clinical investigation and explain the objectives of the investigation and assessments and procedures to be performed to a potential subject. The subject information sheet that has been provided to the subject further describes the clinical investigation, potential discomforts, risks, and benefits of participation. The investigator will also describe this information verbally. Potential subjects will be given time for asking questions and adequate time, at least 72 hours, to think through the decision. 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.

10.8.3 Visit 1 (Day 0)
Informed consent and screening procedure
This visit will be scheduled at least 72 hours from the time the potential subject was provide with the study information. If the subject is willing to participate in the investigation, he/she needs to sign and date the Informed Consent Form (ICF) together with the investigator that provided the information. The original ICF will be retained in the Investigator Site File (ISF) and copy provided to the subject. The investigator must obtain written informed consent before any clinical investigation-related procedures are performed, for further details on the informed consent procedure 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. A health examination will be performed where ECG, heart rate, and blood pressure are measured. Pregnancy test will be performed on fertile female subjects, i.e., all women who are not surgically sterile or postmenopausal for at least 1 year prior to informed consent, to confirm that no pregnancy is ongoing. The investigation also requires that fertile female subjects use contraceptives throughout the investigation. If a subject is not using contraceptives, the investigator or designee will inform the subject to use contraceptives during the investigation. A urine test will be performed

for drug screening. The subject will also fill in two different questionnaires (AUDIT and M.I.N.I) relating to psychiatric disorders, substance and alcohol usage. Training for using Previct Drugs will also take place where the site personnel will demonstrate how Previct Drugs shall be used according to the IFU, and the procedures described in this CIP.

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
At visit 1, the first measurements of Previct Drugs will take place once the subject has been assessed as eligible. The subject will perform three (3) duplicate measurements with Previct Drugs in two different ambient light conditions. Three (3) tests with Previct Drugs will first be performed in one light condition, and thereafter the light condition will change to the second condition and the subject will wait approximately 10 minutes before performing three tests with Previct Drugs again.

The subject has thereafter completed the procedures and assessments for visit 1. The site personnel will provide information to the subject on how the measurements of Previct Drugs shall be performed in the home environment until the next visit. The site personnel will also schedule the date of the next visit. Lastly, the subject will be randomized to the medicinal product to be administered at visit 2.

During Screening/Baseline the following assessments/procedures will be performed:

- Informed consent
- Demographics
- Relevant medical and surgical history
- Registration of relevant medication
- Health examination: ECG, pulse, blood pressure
- Urine pregnancy test for fertile female subjects
- Confirmation of contraceptives for fertile female subjects
- Urine test for drug screening
- Questionnaires to be answered by subject (AUDIT and M.I.N.I)
- Training of Previct Drugs
- Verification of subject eligibility (check inclusion/exclusion criteria)
- Hand-out of study specific smartphone, charger and setting up Previct Drugs for the subject
- First measurements with Previct Drugs
- Registration of any AEs or DDs
- Information on performing Previct Drugs measurement in the home environment
- Schedule of next visit
- Randomization

10.8.4 Home period 1
Between visit 1 and visit 2 the subject will perform measurements with Previct Drugs in the home environment. Three (3) measurements will be performed per day, once in the morning, once in the mid of the day, and once in the evening. Each time Previct Drugs is to be used the subject will also fill in if any medications have been used. The subject will receive a notification when its time to perform a measurement.

10.8.5 Visit 2 (+/- 2 days)

Visit 2 will be performed 1 week after visit 1 (+/- 2 days). Before visit 2, the subject should be fasting 6 hours before the scheduled time. The subject can eat again 2 hours after the administration of the medicinal product. The subject is free to drink water during the fasting period.

Visit 2 will start with a pregnancy test for fertile women and urine test for drug screening for all subjects. If any of these criteria is not fulfilled, the subject will be withdrawn from the clinical investigation and no further investigation-related activities will be performed.

Visit 2 will continue with collection of vital signs, i.e., oxygen saturation, pulse, blood pressure, and body temperature. A blood sample will thereafter be taken for LC-MS/MS analysis (specific analysis for the medicinal product). The subject will perform three (3) duplicate measurements with Previct Drugs in two different ambient light conditions. Three (3) tests with Previct Drugs will first be performed in one light condition, and thereafter the light condition will change to the second condition and the subject will wait approximately 10 minutes before performing three tests with Previct Drugs again. The subject will fill out a study specific usability questionnaire.

The subject will be administered with the medicinal product according to the randomization scheme. Measurements with Previct Drugs, blood sampling for LC-MS/MS analysis (specific analysis for the medicinal product), and collection of vital signs (oxygen saturation, pulse, blood pressure, and body temperature) will thereafter be performed according to the following schedule (Table 7):

Table 7. Schedule over Previct Drugs measurements and blood sampling at visit 2.

Hour (approx.)	**Activity**
0	• Administration of medicine • Collection of vital signs • 1 test with Previct Drugs in light condition 1 • Wait ~10 minutes • 1 test with Previct Drugs in light condition 2
0.5	**For subject administered with cannabinoids only:** • Blood sampling for LC-MS/MS • 1 test with Previct Drugs in light condition 1 • Wait ~10 minutes • 1 test with Previct Drugs in light condition 2
1	• Blood sampling for LC-MS/MS • Collection of vital signs • **2 tests** with Previct Drugs in light condition 1 • Wait ~10 minutes • **2 tests** with Previct Drugs in light condition 2
2	• Blood sampling for LC-MS/MS • Collection of vital signs • **2 tests** with Previct Drugs in light condition 1 • Wait ~10 minutes • **2 tests** with Previct Drugs in light condition 2
3	• Blood sampling for LC-MS/MS • Collection of vital signs • **2 tests** with Previct Drugs in light condition 1 • Wait ~10 minutes

Hour (approx.)	Activity
	• **2 tests** with Previct Drugs in light condition 2
4	• Blood sampling for LC-MS/MS • Collection of vital signs • 1 test with Previct Drugs in light condition 1 • Wait ~10 minutes • 1 test with Previct Drugs in light condition 2
5	• Blood sampling for LC-MS/MS • Collection of vital signs • 1 test with Previct Drugs in light condition 1 • Wait ~10 minutes • 1 test with Previct Drugs in light condition 2

During and after the administration of the medicinal product, the subjects will be observed by the site personnel. If the status of the subject would change, additional observations through e.g., measurements of vital signs will take place and additional steps will be taken based on the general procedures at the participating site.

The subject will be assessed/asked for any AEs that may have occurred, and a review of the concomitant medication.

The subject has thereafter completed the procedures and assessments for visit 2. The subject shall return the study specific smartphone with the app installed and the charger to the site personnel. The site personnel will also schedule the date of the telephone follow-up call. The subject will leave the site after visit 2, once its been confirmed by the site personnel that the subject is safe after been administered with the medicinal product the same day. This safety check will include a clinical impression by the investigator/designee to confirm the subject's health status, e.g., physical appearance and communication. Final collection of vital signs (oxygen saturation, pulse, blood pressure, and body temperature) will also be performed to confirm within normal range or if changed during the day that the value is back to baseline. If the values are not within normal range or back to baseline, the subject may require staying longer/overnight if he/she cannot be discharged based on the safety check.

During visit 2 (+/- 2 days) the following assessments and procedures will be performed:

- Urine pregnancy test for fertile female subjects
- Urine test for drug screening
- Vital signs: oxygen saturation in blood, pulse, blood pressure, temperature
- Previct Drugs measurements
- Collection of blood samples for LC-MS/MS analysis
- Usability questionnaire
- Registration of any AEs or DDs
- Concomitant medication review
- Return of study specific smartphone with the app installed and charger
- Clinical impression by investigator/designee before discharged
- Schedule for telephone follow-up call

10.8.6 Telephone follow-up call 1 (+ 2 days)
A telephone follow-up call will be performed the day after visit 2 (+ 2 days) for confirm safety where the subject will be asked for any AEs that may have occurred. Any changes in concomitant medication will also be recorded. After the call, the subject has completed the investigation.

10.8.7 Screening and Baseline Measurements
The data collected at visit 1 during screening and baseline will describe the study population and confirm eligibility. Age, gender, and eye color will be recorded. Weight and length will also be recorded to calculate Body Mass Index (BMI). 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.

Health examination
A health examination will be performed to confirm that the subject is healthy. During the examination, ECG, pulse, and blood pressure will be measured.

Pregnancy test and confirmation usage of contraceptives
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 and at visit 2 and agree to use contraception from enrollment until study completion.

Urine test drug screening
To confirm no current drug use, a rapid one step screening test will be used for qualitative detection of multiple drugs and drug metabolites in human urine. It measures amphetamine, cocaine, marijuana, morphine, phencyclidine, benzodiazepines, methadone, opiate, barbiturate, methamphetamine, methylenedioxy-methamphetamine, and tricyclic antidepressants.

Questionnaires (AUDIT and M.I.N.I)
To confirm that there is no current or recent history of alcohol misuse, the questionnaire AUDIT will be used at enrollment where ≥6 points for women or ≥8 points for men indicates a potential misuse.

To confirm that there is no history or current drug misuse or psychiatric disorder, the questionnaire M.I.N.I will be used at enrollment where based on the outcome the investigator or designee will evaluate if it indicates a potential misuse or psychiatric condition.

10.8.8 Performance Variables and Measurements

10.8.8.1 Previct Drugs - pupillometric variables and key features
Previct Drugs will be used for collecting data on eye parameters and tremor during baseline and under influence of medicinal products. From each test, data on pupillometric variables and key features will be extracted. Drug intake will in this first investigation be simulated by a controlled single application of commonly therapeutically used medicinal products form the following classes of drugs: 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 medicinal product:

- 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 (PLR, NC, and NY). From the measurements five pupillograms (pupillometric variables) are extracted, and from which 21 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: 2 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 8 below for a summary of measurements, pupillograms, and key features extracted after a test with Previct Drugs.

Table 8. 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 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, 35]:

- 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 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.

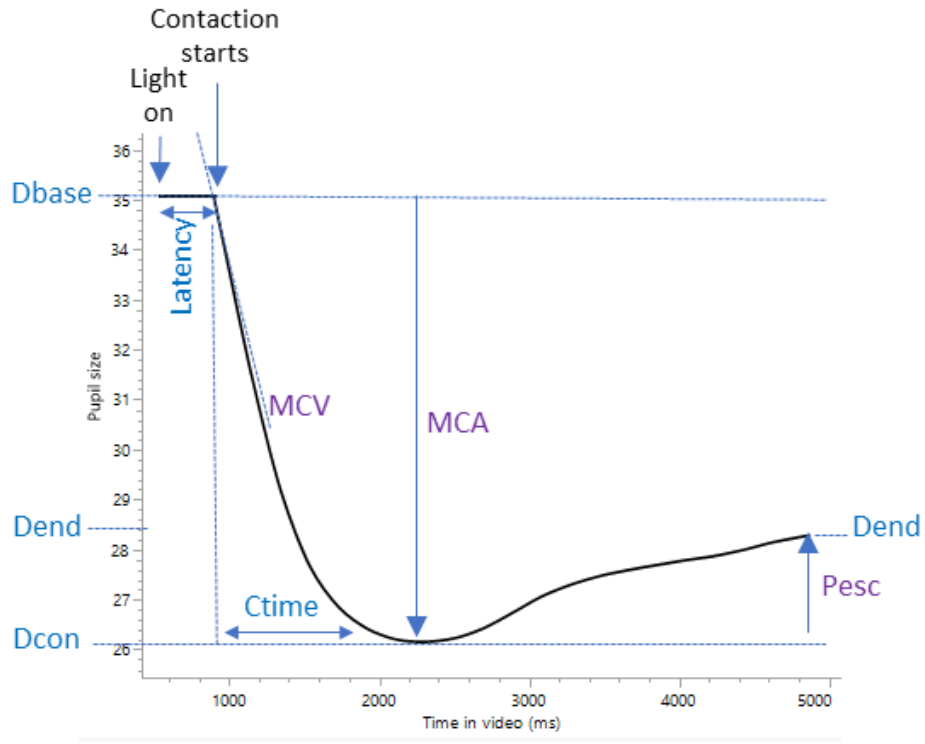

Figure 3. An example of the pupillogram for the PLR measurement with the pre-defined key features that will be extracted. The example is from Hall et al. 2018 [7].

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. The ambient light level will be calculated through the smartphone's camera. 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 [36]:

- 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: Cdiff 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.

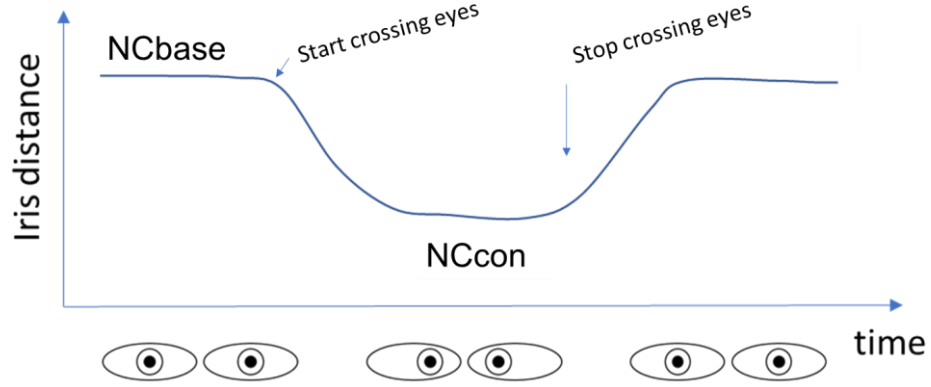

Figure 4. Non-convergence, the inability to cross eyes is measured as distance between the center of the irises.

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 [37]:

- 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.

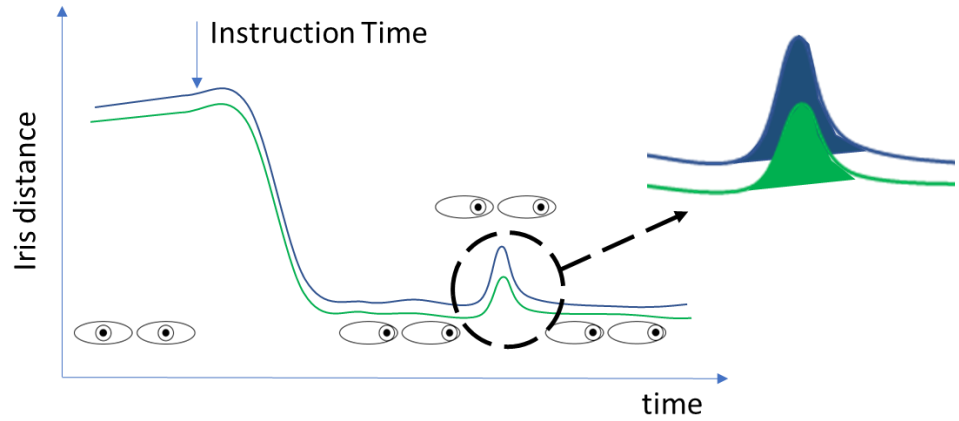

Figure 5. An example of the NY measurement, where the subject will start looking straight, then receives an instruction to look to the far side. Nystagmus is an involuntary, rapid, and transient motion of the eyes while looking at the far side. The key feature of nystagmus is approximately the integral 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 [38]:

- 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 [39].

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 [40]:

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

10.8.8.2 LC-MS/MS analysis

LC-MS/MS analysis will be used as a reference analysis in this investigation for analyzing the concentrations in plasma of the four different medicinal products used in this investigation.

Before administration of the medicinal product at visit 2, a blood sample will be taken for LC-MS/MS analysis (specific analysis for the medicinal product). The subject will thereafter be administered the medicinal product according to the randomization list, and a blood sample will be taken from the subject hourly up to 5 hours for LC-MS/MS analysis (specific analysis for the medicinal product). In total, 6 blood samples will be taken at visit 2 per subject except for the subjects administered with cannabinoids where also a 7th blood sample will be taken about 30 minutes post medicine administration. Each blood sample will be collected and thereafter prepared at the site according to instructions from the laboratory. Each sample will be stored in a -70°C freezer until time for shipment to the laboratory for analysis. There will be limited access to the freezer. Each blood sample will be labeled with relevant study information, e.g., investigation code, date and time of sample collection, subject ID and for which analyte the sample should be analyzed for. Only the site personnel have access to the subject ID key which will kept in a safe place at the site. No subject identification, e.g., subject name, will be available at the blood sample. The samples will be sent for LC-MS/MS analysis to a selected laboratory which have established and validated analysis methods in place for the different medicinal products used.

The peak concentration in plasma is estimated to be the following for each medicinal product after a single administration (see further information under section 7):

- Phenethylamines (D1): 3-4 hours (Lisdexamphetamine reaches Tmax in ~1 h and is hydrolyzed to the active substance d-amphetamine reaching Tmax in 3-4h)
- Benzodiazepine (D2): 1-2 hours

- Cannabinoids (D3): 5 minutes
- Opioid (D4): 1 hour

10.8.8.3 Subject usability

Subject usability for Previct Drugs will be captured on visit 2. It will be captured through a questionnaire to be filled out by the subject. The questionnaire will contain questions regarding user friendliness, e.g., understanding the instructions for using Previct Drugs, the easiness of performing a complete test including the different measurements that are part of a test. Each question in the questionnaire will be answered by the subject through choosing the most correct answer on a 4- or 5-point Likert scale, replying on a yes/no question, or writing an answer in a free text field.

10.8.9 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.

10.8.10 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.

During the study, the videos from Previct Drugs app which could not be automatically processed will be labelled and manually annotated. This will be performed by data scientists at the sponsor's software department. It is only these data scientists that will have access to the complete videos.

10.8.11 Potential Confounding Factors

This is an explorative and early feasibility investigation aiming to collect data on Previct Drugs when it comes to usage, safety, and the possibility to detect difference in pupillometric key parameters before and after a single administration of a medicinal product.

The collected data is required for further development of Previct Drugs before CE-marking. [redacted]

A potential confounding factor may be that not all suggested pupillometric key parameters will be affected after administration of some or all of the medicinal products. This is expected as in this

first investigation it is important to study all potential pupillometric key parameters that can be used for future drug detection or not.

Another potential confounding factor is the dose level for each medicinal product which in the study will be significantly lower compared to patients with SUD. The argumentation for the set dose is the population studied in this investigation, i.e., healthy volunteers, where we need to have a low dose as possible from a safety perspective but that still is assumed be detectable through pupillometry based on current scientific evidence.

As this is the first-in-man 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.

10.8.12 Samples obtained from subject

Blood samples will be collected at visit 2 for LC-MS/MS analysis. In total, 6 samples will be collected per subject except for the subjects receiving cannabinoid where also a 7th sample will be collected. See Table 7 above where it is stated timepoints when the blood sampling will be collected. 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' 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 provide with written and oral information and perform a brief check against eligibility criteria and collect contact details for being able to schedule the first study visit. 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 will be considered as source data if not available in other records of source data. It is the responsibility of the PI to record essential information in the medical records, in accordance with national regulations and requirements. As this investigation will enroll healthy volunteers there will not be any medical record available at the site to record any investigation related information in. Therefore, the subject's General Practitioner will be informed in writing that the subject is participating in an investigation and which medicinal product is planned to be administered at visit 2. The origin of the source data in this clinical investigation will be further specified in a separate document ("Origin of Source Data").

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 PI should guarantee access to source documents for the monitor and auditors as well as for inspection by appropriate regulatory agencies, and 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). FAS is defined as all subjects included in the clinical investigation with at least one pupillometric test under influence of one of the medicinal products. All analyses will be performed separately for each medicinal product. No comparisons will be performed between the medicinal product groups. The two ambient light conditions will also be analyzed separately. Baseline will be defined as the three last Previct Drugs tests performed at visit 2 before administration of the medicinal product whereof mean value will be calculated.

Since this clinical investigation is without a control group no adjustment for baseline variables can be performed for confounders. This is also an early feasibility and exploratory investigation, meaning no confirmatory hypotheses will be tested and no adjustment for multiplicity will be done.

Baseline and safety variables will be given descriptively, for each medicinal product group. All significance tests will be two-sided and conducted at the 5% significance level. A detailed Statistical Analysis Plan (SAP) will be finalized prior database lock.

12.2 Primary analysis

Fraction of collected pupillometry data using native pupillogram. For each of the measurements PLR, NC, and NY, each measurements quality control (QC) will approve the measurements or not using the native pupillogram. For each subject, the proportion of approved measurements over all measurements during day 2 will be calculated for each of PLR, NC, and NY. The distribution over subjects for each medicinal product will be given with mean, SD, median, minimum, and maximum. The two ambient light conditions will be analyzed separately.

12.3 Secondary analyses

Analysis of the first secondary endpoint:

Fraction of collected pupillometry data using refined pupillogram. For each of the measurements PLR, NC, and NY, each 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 day 2 will be calculated for each of PLR, NC, and NY. The distribution over subjects for each medicinal product will be given with mean, SD, median, minimum, and maximum. The two ambient light conditions will be analyzed separately.

Analyses for the second and fourth secondary endpoint will be changes in key features within subjects from baseline, without medicinal product, to time points under influence of medicinal product with verified peak concentration in plasma and up to 5 hours. For continuous variables the mean values will be used and for ordered categorical variables the last one will be used. If several time points have the same peak concentration the data from the first one will be selected. If the QC control has not approved a measurement that measurement will not be used in the analyses. These analyses will be performed both for the native and the refined pupillograms. For comparison of change within subjects, Fisher's non-parametric permutation test for paired observation for continuous variables will be used together with Sign test for ordinal and dichotomous variables. For change in continuous variables, mean differences with 95% confidence interval together with effect size and p-value will be the main result. Continuous variables and changes in continuous variables will be described by mean, SD, median, minimum, and maximum.

Categorical variables will be described with numbers and percentages. Change in categorical variables will be given as increase, no change and decrease.

Third secondary endpoint:
The two following correlation analyses will be performed between pupillometry key features and plasma concentrations:

- Correlations between change from baseline to verified peak plasma concentration between pupillometry data and plasma concentrations using Spearman correlation and scatter plots.
- For each subject, calculate Spearman correlation coefficient between plasma concentration and pupillometry key features for all measurements during visit 2. These Spearman correlation coefficients will be analyzed over subjects with Fisher's one sample non-parametric permutation test.

Selected important analyses will be illustrated graphically with individual plots over time, boxplots over time, and scatterplots for correlations.

Fifth secondary endpoint:
The change of known combinations of key features from baseline to verified peak concentration will be analyzed in the same way as described for the second secondary endpoint above.

Sixth secondary endpoint:
User-friendliness of Predict Drugs evaluated by a Subject usability Questionnaire at visit 2 will only be analyzed descriptively with numbers and percentages.

12.4 Sample size

The investigation aims to enroll 11 subjects, i.e., healthy volunteers, per medicinal product group that have completed the clinical investigation until the telephone follow-up call. For four medicinal products, the total will be 44 subjects. In order to take account for a drop-out rate of 10%, 12 subjects will be included per medicinal product group and in total 48 subjects in the clinical investigation.

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.

12.5 Drop-out Rates

A drop-out rate of 10% has been estimated. If the drop-out rate will exceed in an any of the medicinal product groups, additional subjects may be enrolled.

12.6 Level of Significance and Power

This early feasibility and exploratory investigation does not incorporate any historical controls or comparators. Only descriptive statistics will be used. P-values will only be reported descriptively to illustrate differences between time points of measurements. The primary analysis is descriptively, and no power calculation has been conducted.

12.7 Pass / Fail Criteria

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

12.8 Interim Analysis

No interim analysis is planned to be performed.

12.9 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.

12.10 Pre-subgroups for Analysis

No pre-specific subgroups analyses will be performed.

12.11 Procedures that Take into Account all the Data

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

12.12 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.

12.13 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 or designee is not allowed to deviate from the CIP. Furthermore, waivers from the CIP are 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 PI is out of compliance, this will be notified to the PI 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 PI.

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.

If any study specific smartphone with the app installed is not returned by the subject to the site, the site and/or the sponsor will withdraw access in the careportal for this subject thereby making the app non-functional. The app will not be able to start or use by the subject thereafter.

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 subject information sheet and informed consent form, must be approved or given a favorable opinion in writing by an IEC, the regulatory agency in the specific country, and other relevant authorities as applicable before enrolment of any subject into the clinical investigation. The PI 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 least 72 hours 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 opportunity to ask questions and at least 72 hours to consider participation prior to deciding. A pre-screening will be performed by the site personnel during the call.

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 investigation, the subjects will be reimbursed with 125 EUR. Subjects that only complete visit 1 (i.e., screening and baseline) will be reimbursed with 15 EUR. Subjects will also be offered reimbursement for reasonable travel expenses for the visits performed at the site based on current Dutch km-costs (0.19 EUR/km) by car as well as parking expenses, or actual costs for bus, train and/or metro. Taxi may be used and thereby reimbursed if required.

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)

ISO 14155:2020

Adverse event related to the use of an investigational medical device.

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

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

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

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 birth 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 informed consent will be considered medical history. The PI 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 PI or site team, which fall into any of the previously defined definitions must be recorded as an AE in the eCRF 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 AEs 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 PI 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 be reasonably 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 PI 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 PI 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 PI'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 19.5.

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 comparator 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 SADE potential must be reported to the Sponsor immediately, but not later than **3 calendar days** after the site 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
  - 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)

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

- 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: Ada Saltarski, Clinical Research Manager, Devicia AB
Phone: +46 (0) 725 568 088
Email: ada.saltarski@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 about reportable events through EUDAMED (once established) or per local requirements.

In case of a multicenter clinical investigation, the Sponsor shall also inform all PIs in writing of all reportable events at all investigation sites that have been reported to the Sponsor, within a time frame established based on the perceived risk as defined in the risk analysis report.

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 PI(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 PI(s) / investigation site(s).

In addition, CIP violations may result in termination of the Clinical Investigation at an investigation site. CIP violations are deviations made without permission as a result of error or fraud/misconduct. Where the monitor or Sponsor identifies that the PI is out of compliance, this will be noted to the PI 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 PI 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

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12	Device description Previct Drugs	KC005-004 Rev06
13	Instructions For Use Previct Drugs KCClin01	KC003-2022-01-NL AA, September 2022
14	Previct Drugs system architecture	KC005-061 Rev01
15	Intended purpose Previct Drugs	KC005-003 Rev05
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33	Risk management summary report Previct Drugs	KC005-019 Rev02
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24 APPENDICES

24.1 Appendix A – Clinical Investigation Plan Agreement Form

Investigation code: KCClin01

CIP version: KC09-104 Rev B

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

Site No.: 01 Leiden University Medical Center (LUMC)

Coordinating/Principal Investigator

Name: Prof Albert Dahan

Signature: _____

Date (dd-Mmm-yyyy): _____

24.2 Appendix B – Clinical Investigation Contact List

COORDINATING/PRINCIPAL INVESTIGATOR
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Clinical investigation
Role: Coordinating/Principal Investigator
Responsibility: Responsible for the conduct of the study at site 01 LUMC
Qualification: Medical Doctor and Professor of Anesthesiology, Head of the Anesthesia and Pain Research Unit at LUMC

CLINICAL INVESTIGATION SITE(S)
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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.