Feasibility study on the use of Redormin® 500 (Ze 91019) on day-time cognition and quality of life in people with occasional sleep problems

Clinical Study Protocol

Study Type	Clinical Trial with Investigational Medicinal Product (IMP)
Study Categorization	Risk category B according to ClinO
Study Registration	NCT05684523
Study ID	Ze 91019-04-2022-01
Sponsor	Zeller Medical AG Seeblickstrasse 1 CH-8590 Romanshorn
Principal Investigator	Christiane Gerhards, MD Research Platform MCN Division of Cognitive Neuroscience University of Basel Birmannsgasse 8 4055 Basel Phone: +41 61 207 0244 Fax: +41 61 207 0241 Email: christiane.gerhards@unibas.ch
Investigational Product	Redormin® 500 (Ze 91019)
Protocol Version and Date	Version 3 (dated 15/02/2023)

SIGNATURE PAGE SPONSOR

Study Title	Feasibility study on the use of Redormin® 500 (Ze 91019) on day-time cognition and quality of life in people with occasional sleep problems
Study number	NCT05684523
Protocol Version	Version 3 (dated 15/02/2023)

Sponsor

The Sponsor has approved this protocol and confirms hereby that this protocol was subject to critical review. The information it contains is consistent with current knowledge of risks and benefits of the investigational product. The Sponsor confirms hereby to conduct the study according to the protocol, current version of the World Medical Association Declaration of Helsinki, and ICH-GCP guidelines as well as the local legally applicable requirements.

Prof. Dr. Veronika Butterweck

Zeller Medical AG, Seeblickstrasse 4, CH–8590 Romanshorn

Medical Director

Place/Date	Signature

SIGNATURE PAGE STUDY SITE

Study Title	Feasibility study on the use of Redormin® 500 (Ze 91019) on day-time cognition and quality of life in people with occasional sleep problems
Study number	NCT05684523
Protocol Version	Version 3 (dated 15/02/2023)
Study Site	University of Basel, Division of Cognitive Neuroscience Birmannsgasse 8, CH-4055 Basel

Trial statistician

I have read and understood this trial protocol and I confirm it was subject to critical review. I agree to conduct the trial as set out in this study protocol, the current version of the World Medical Association Declaration of Helsinki, ICH-GCP guidelines and the local legally applicable requirements.

Nathalie Schicktanz, PhD
Trial statistician

Place/Date _____ Signature _____

Principle Investigator

All documentation for this study that is supplied to me and that has not been previously published will be kept in the strictest confidence.

I have read and understood this trial protocol and agree to conduct the trial as set out in this study protocol, the current version of the World Medical Association Declaration of Helsinki, ICH-GCP guidelines and the local legally applicable requirements.

Christiane Gerhards, MD
Principal Investigator

Place/Date _____ Signature _____

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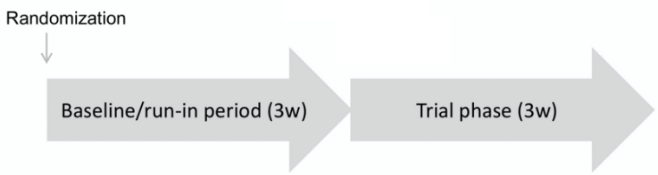
STUDY SYNOPSIS

Sponsor	Zeller Medical AG Seeblickstrasse 1 CH-8590 Romanshorn
Study Title	Feasibility study on the use of Redormin® 500 on day-time cognition and quality of life in people with occasional sleep problems.
Study ID	Ze 91019-04-2022-01
Protocol Version and Date	Version 3 (dated 15/02/2023)
Trial Registration	NCT05684523 / SNCTP
Study Category and Rationale	Risk category B according to ClinO Art. 19. Placebo-controlled study with an approved medicinal product.
Clinical Phase	Phase IV
Background and Rationale	It is well known that cognitive performance and quality of life can be impaired after nights of little or no sleep (Hudson, 2020) (Roth, 2007). Therefore, people with occasional sleep problems, i.e., with 1-2 nights per week with impaired sleep, can suffer from impaired cognition the following day. Moreover, occasional sleep problems may lead to reduced overall quality of life (Buysse, 2007). Many people with insomnia do not wish to use conventional hypnotic drugs because of concerns about adverse effects and the risks of tolerance and dependence, and others do not want to spend the time and efforts required with behavioral therapies (Vincent, 2001). Thus, there is an increasing interest in the use of complementary and alternative medicines, such as herbal and dietary supplements, partly because of their natural properties and perceived relative absence of residual effects. Valerian and hop have both been an integral part of traditional sleep medicine for centuries. Pharmacological and clinical studies are available demonstrating the applicability of Redormin® 500, a 45% methanolic extract from valerian root and from hop strobiles, in sleep disorders (Abourashed, 2004), (Dimpfel, 2006), (Morin, 2005), (Koetter, 2007). Not only could the effect be visualized through EEG measurements, but also new ideas regarding the mechanism of action were brought forth (Koetter, 2007). An agonistic effect on central adenosine receptors, and thus a counteracting effect on caffeine induced sleeplessness through the lignans in hydrophilic valerian root extracts is discussed as a potential mechanism of action for valerian root extract (Schumacher, 2002). The studies available mainly focused on the improvement of sleep quality rather than on improvements of cognitive performance and day performance. Therefore, the aim of this study is to determine the feasibility of investigating the effects of Redormin® 500 on day-time cognition and to assess psychological parameters (subjective cognitive performance, tiredness, mood, stress level, quality of life, motivation), in people with occasional sleep problems.

	Sleep tracking and heart rate variability (HRV) and heart rate (HR) data will be collected using consumer devices of the Charge series by Fitbit. In clinical studies these devices provided reasonable data quality compared to established methods of assessing sleep data while being small, inexpensive, simple to use and unintrusive and therefore ideal to collect nightly sleep data over an extended period of time with minimal impact on the participants.
Objectives	The overall objective of this study is to evaluate the feasibility of the planned study design and to evaluate the effect of Redormin® 500 on cognitive performance (reaction time, working memory) and psychological parameters with daily measures. The primary objective of this study is to evaluate the feasibility of the planned study design. The secondary objectives are to assess the influence of Redormin® 500 on cognitive performance (reaction time, working memory) and psychological parameters (subjective cognitive performance, stress levels, tiredness, mood, quality of life, and motivation; all of these measures with reference to the current day) with daily measures in the evening, and on sleep parameters, HRV and HR as objective measures for the stress level as assessed by the Fitbit tracker. Safety objectives: Safety will be evaluated by obtaining and analysing adverse events during run-in period and treatment period.
Outcomes	Primary outcome measure: Feasibility of the study design will be evaluated considering the following measures: • Recruitment Log: number of interested persons per kind of advertisement, number of persons still interested after having read the participant information, number of participants not eligible during pre-screening • Screening, Identification and Enrolment Log (short: Subject Master List, SML): number of subjects enrolled, screening-failures, drop-outs, reason for screening failure / drop out, withdrawal of IC • Diary (run-in period / treatment period): adherence to the use of the online tool SoSci-Survey, adherence to study medication (treatment period only) • Fitbit: adherence to and use of the Fitbit tracker • Visits 2 and 3 (virtual visits / phone calls): technical problems (Fitbit, SoSci), general feedback (only visit 3) Secondary outcome measures: Online diary with SoSci-Survey *Cognitive parameters:* • Reaction time and lapses (Red Button Task) • Working memory (Digit Span Backwards) *Psychological parameters (Visual Analog Scales, VAS):* • Subjective cognitive performance during the day • Stress level during the day • Tiredness during the day • Mood during the day • Motivation during the day • Quality of life during the day in relation to work/cognitive performance

	• Subjective sleep quality (VAS) Objective sleep parameters and HRV and HR collected by fitness- and sleep tracker (Fitbit) • sleep duration • begin / end of sleep • number of interruptions • other sleep measures assessed by Fitbit (exploratory, see appendix 1) • HRV and HR (indicators for the stress level) <u>Safety outcome measures:</u> • (S)AE-recordings
Study Design	Randomized, double-blind, parallel groups, placebo-controlled, baseline/run-in period of 21 days followed by trial period of 21 days, digital phenotyping (sleep, cognitive/psychological parameters, HRV and HR). 
Inclusion- / Exclusion Criteria	Inclusion criteria: • Healthy • Male or female • Age: 18-65 years old • Occasional sleep problems (in average 1-2 nights per week, PSQI-score >5) with accompanying subjective cognitive problems (in average at least on one day per week) in the last month • Fluent in German • Able and willing to give written informed consent and comply with the requirements of the study protocol Exclusion criteria: • DSM-V diagnosis of insomnia • History of neurologic disorder • Current psychiatric disorder • Presence of moderately severe or severe depressive disorder (PHQ-9 ≥ 15) • Current chronic intake of prescription drugs with psychotropic effects • Current intake of OTC drugs for sleep or mood problems • Presence of pain condition • Diabetes mellitus • Coronary Heart Disease • Chronic obstructive pulmonary disease and other breathing related sleep disorders • Pregnancy, breast feeding • Known hypersensitivity to valerian, hop or nickel (Fitbit) • Tattoos on both wrists (Fitbit, SpO2 measurement) • Inability to read and understand participant's information • Alcohol or other drug abuse (e.g., Cannabis)

	• Positive tox urine test (Barbiturate, Ecstasy (MDMA), Metamphetamin, Oxycodon, THC, Cocain, Morphine, Buprenorphine, Tramadol, Methadon, Benzodiazepine, Amphetamin, Zolpidem, Zopiclon).
Measurements and procedures	<u>Screening visit</u> • medical history and physical examination • mini-DIPS (Margraf) • Pittsburgh sleep quality index (PSQI) • Patient Health Questionnaire for depression (PHQ-9) • Subjective cognitive impairment due to sleep problems • urinalysis (drug screening) <u>Feasibility</u> • Recruitment Log: number of interested persons per kind of advertisement, number of persons still interested after having read the participant information, number of participants not eligible during pre-screening • Screening, Identification and Enrolment Log (short: Subject Master List, SML): number of subjects enrolled, screening-failures, drop-outs, reason for screening failure / drop out, withdrawal of IC • Diary (run-in period / treatment period): adherence to the use of the online tool SoSci-Survey, adherence to study medication (treatment period only) • Fitbit: adherence to and use of Fitbit • Visits 2 and 3 (virtual visits / phone calls): technical problems (Fitbit, SoSci), general feedback (only visit 3) <u>Diary assessed with SoSci-Survey</u> (run-in period and treatment period) Cognitive tasks: • Reaction time and lapses (Red Button Task) • Working memory (Digit Span Backwards) Psychological parameters (Visual Analog Scales, VAS): • Subjective cognitive performance during the day • Stress level during the day • Tiredness during the day • Mood during the day • Motivation during the day • Quality of life during the day • Subjectiv sleep quality (VAS) IMP-intake (during treatment period only) <u>Objective sleep parameters, HRV and HR collected by Fitbit</u> • sleep duration • begin / end of sleep • number of interruptions • other sleep measures assessed by Fitbit (see appendix 1) • HRV and HR (indicators for the stress level) <u>Safety outcome measures</u> (S)AE-recordings
Study Product	Redormin® 500 mg, Filmtabletten (Zeller Medical AG, 8590 Romanshorn, Switzerland) is the Swiss trade name of the co-marketing product of Zeller Schlaf forte, Filmtabletten (Sleeping film

	coated tablets 1000 mg). The herbal medicinal product contains as active substance 500 mg of Valerianae radix (*Valeriana officinalis* L.) dry extract, DER 4-6:1, extraction solvent methanol 45% m/m; 120 mg of Lupuli flos (*Humulus lupulus* L.) dry extract, DER 5-7:1, extraction solvent methanol 45% m/m. Once daily oral administration of 1 film coated tablet Redormin® 500 about 1h before bedtime with some liquid for 21 days.
Control Intervention	Administration of 1 film coated placebo tablet about 1h before bedtime for 21 days. Placebo medication is identical in presentation, shape and color, and similar in scent as Redormin® 500.
Number of Participants with Rationale	Studies that have addressed the specific issue of reasonable sample sizes for feasibility/pilot studies recommend between 20 and 70 study participants. It is planned that 40 subjects will be enclosed in the treatment phase. Approx. 20 volunteers per each treatment group. There will be no replacement of participants after the start of the treatment period. This group size will permit the estimation of a sample size for further trials.
Study Duration	Estimation: approx. 12 months
Study Schedule	First patient in: 02/2023 Last patient out: 01/2024
Principal Investigator	Christiane Gerhards, MD Research Platform MCN Division of Cognitive Neuroscience University of Basel Birmannsgasse 8 4055 Basel Phone: +41 61 207 0244 Fax: +41 61 207 0241 Email: christiane.gerhards@unibas.ch
Study Centre	University of Basel Research Platform MCN Molecular and Cognitive Neurosciences Birmannsgasse 8 4055 Basel
Statistical Considerations	Exploratory, descriptive statistical analyses.
GCP Statement	This study will be conducted in compliance with the protocol, the current version of the Declaration of Helsinki, the ICH-GCP as well as all national legal and regulatory requirements.
Compensation	Participants can keep their fitness and sleep tracker Fitbit after the end of the study participation. Additionally, participants receive 300 CHF study compensation at the end of the treatment phase. In the event of drop-out, the compensation will be paid out according to the effort already put in (pro rata). Travel expenses (the amount exceeding 30 CHF) will be paid based on public transportation fares (2nd class with Half Fare Travelcard) at the end of the screening visit.

GLOSSARY OF ABBREVIATIONS

AE	Adverse Event
ASR	Annual Safety Repot
BASEC	Business Administration System for Ethical Committees
BMI	Body Mass Index
BP	Blood Pressure
Bpm	Beats per minute
CA	Competent Authority
CEC	Competent Ethics Committee
CTCAE	Common Terminology Criteria for Adverse Events
ClinO	Ordinance on Clinical Trials in Human Research
eCRF	electronic Case Report Form
CTU	Clinical Trial Unit
DIPS	Diagnostisches Interview bei psychischen Störungen
DKF	Departement klinische Forschung
DS	Digit Span Task
DSMV	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
eCRF	Electronic Case Report Form
EEG	Electroencephalography
EKNZ	Ethikkommission Nordwest- und Zentralschweiz
FADP	Federal Act on Data Protection
Fitbit	Fitness and sleep tracker device
FOPH	Federal Office of Public Health
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
h	hour
H0	Null hypothesis
H1	Alternative hypothesis
hCG	Human choriogonadotropin
HR	Heart Rate
HRA	Federal Act on Research involving Human Beings
HRV	Heart Rate Variability
IC	Informed Consent
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IR	Immediate Release
ISF	Investigator Site File
LabKey	Data management software provided by Labkey®, https://www.labkey.com
LDH	Lactatdehydrogenase
LPLV	Last participant last visit
Studiendatenbank-MCN	is a local database for study data and is implemented using Labkey®.
MNI	Montreal Neurological Institute

OCT 2	Organic Cation Transporter 2
orca	Orchestrate your clinical research activities (QM-System)
PHQ	Patient Health Questionnaire
PI	Principal Investigator
QoL	Quality of Life
SADRS	Serious Adverse Drug Reaction
SAE	Serious Adverse Event
sciCORE	Center for Scientific Computing at the University of Basel
secuTrial®	eCRF system
SD	Source Data
SDV	Source Data Verification
SML	Subject Master List (short for Subject Identification and Enrolment Log)
SNCTP	Swiss National Clinical Trials Portal
SOP	Standard Operating Procedure
SoSci	Online questionnaire tool by SoSci Survey GmbH, http://www.soscisurvey.de
SpO2	Oxygen saturation
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
V/P	Verum/Placebo
VAS	Visual Analog Scale
WI	Working Instruction
WIE	Wechsler Intelligenztest für Erwachsene

STUDY SCHEDULE

Study periods		Screening	Run-in / baseline period (NO treatment)	Visit 2	Treatment period[1]	Follow-up
Visit		1		2		3
Day[1]		1	2-22[1]	23[1]	24-44[1]	45[1]
duration		ca.1.5- 2 h (incl. instructions)	21 days 5 min per day	15-30 min	21 days (5 min per day)	15-30 min
place		Study center	diary at home	virtual visit / phone call	diary at home	virtual visit / phone call
Patient information and obtaining informed consent (IC)	IC	X				
Assignment of the study participant number		X				
Demographics	Screening	X				
Medical History, Physical Examination, Vital Signs		X				
mini-DIPS, PSQI, PHQ-9		X				
Drug screening / tox urine		X				
Check in-/exclusion criteria		X				
Randomization and dispensing of the IMP.	IMP	X				
Instructions for IMP-intake: about 1h before bedtime		X		X		
Intake				X[2]	X	
intake documentation					X	
Return of the IMP			X[3]	X[3]	X[3]	X
Dispensing of the study material: pregnancy test and the Fitbit	Material and instructions	X				
Instructions: • Fitbit (HRV, HR and sleep tracker) handling • SoSci-Survey (diary)		X		(X)		
Pregnancy test		(X) instructions		X (before phone call / virtual visit)		
Daily online assessments during the study (after work): • cognitive tasks (reation time, working memory) • Psychological parameters: subjective cognitive performance, stress level, tiredness, mood, QoL, and motivation; all of these measures with reference to the current day)	Diary during period 1 an 2		X		X	
Daily sleep parameters (sleep duration, begin / end of sleep, number of interruptions) and HRV and HR collected with Fitbit			X		X	
AE/SAE-recording		X[4]	X	X	X	X

[1] Default schedule. The start of study phase I and II must begin no later than day 7 after visit 1 resp. Visit 2. Visits 2 and 3 (follow-up) must each occur no later than day 7 after the last day of the run-in period and treatment phase, respectively.
[2] First intake in the evening of visit 2 and for further 20 days.
[3] In case of withdrawal of IC / drop-out.
[4] AE recording starting after IC.

1 STUDY ADMINISTRATIVE STRUCTURE

Function	**Address**
Sponsor	Zeller Medical AG Seeblickstrasse 1 CH-8590 Romanshorn
CRO	GeneGuide AG Birmannsgasse 8 CH-4055 Basel Switzerland Prof. Dominique de Quervain, MD, E-Mail: dominique.dequervain@unibas.ch Phone: +41 61 207 0237 Prof. Andreas Papassotiropoulos, MD E-Mail: andreas.papas@unibas.ch Phone: +41 61 207 0599
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Trial statistician	Nathalie Schicktanz, PhD Research Platform Division of Cognitive Neuroscience University of Basel Birmannsgasse 8, 4055 Basel E-Mail: nathalie.schicktanz@unibas.ch Phone:+41 61 207 0228
Data Management (Studiendatenbank MCN)	Thomas Schlitt, PhD Research Platform Division of Cognitive Neuroscience University of Basel Birmannsgasse 8, 4055 Basel E-Mail: thomas.schlitt@unibas.ch Phone:+41 61 207 0267

Departement klinische Forschung (DKF)	Universität Basel Departement Klinische Forschung c/o Universitätsspital Basel Schanzenstrasse 55, 4031 Basel
Database	Patrick Simon Phone: +41 61 556 52 91 E-Mail: patrick.simon@usb.ch
Monitoring	Klaus Ehrlich Phone: +41 61 556 56 26 E-Mail: klaus.ehrlich@usb.ch

Data Safety Monitoring Committee

Not applicable

2 ETHICAL AND REGULATORY ASPECTS

The decision of the competent ethics committee (CEC) and the competent authority (CA) concerning the conduct of the study will be made in writing to the Principal Investigator respectively the Sponsor before commencement of this study. The clinical study can only begin once approval from all required authorities has been received. Any additional requirements imposed by the authorities shall be implemented.

2.1 Study registration

The study will be registered in the WHO-listed clinicaltrials.gov registry and in the Swiss National Clinical Trials Portal (SNCTP) before the start of recruitment.

2.2 Categorization of study

This clinical trial comes under category B according to ClinO as Redormin® 500 is authorized in Switzerland and it is used in the approved indication in a placebo controlled study.

2.3 Competent Ethics Committee (CEC)

The Principal Investigator will obtain approval from CEC (EKNZ) before the start of the clinical trial.

No changes are made to the protocol without prior Sponsor and CEC approval, except where necessary to eliminate apparent immediate hazards to study participants.

Serious Adverse Events (SAE) and Suspected Unexpected Serious Adverse Reactions (SUSAR) are reported according to chapter 10.4.

Amendments are reported according to chapter 2.10

2.3.1 Notification and reporting upon completion, discontinuation or interruption of the clinical trial (ClinO, Art. 38)

The following notifications have to be made by the Principal Investigator to the CEC (EKNZ):

- The completion of the study within 90 days. Completion of a clinical trial is marked by the last participant's final visit.
- The discontinuation or interruption of the clinical trial within 15 days. In the notification, the reasons for the discontinuation or interruption shall be stated.
- The final report shall be submitted within one year after completion or discontinuation of the clinical trial.

2.3.2 Notification and reporting of safety and protective measures (ClinO, Art. 37 and 43)

The following notifications and reporting have to be made by the Principal Investigator to the CEC (EKNZ):

- If immediate safety and protective measures have to be taken during the conduct of the clinical trial, a notification shall be submitted within 7 days. In the notification, these measures and the circumstances necessitating them shall be stated.
- Annual safety report (ASR) once a year.

2.4 Competent Authority (CA)

The Sponsor will obtain approval from the CA (Swissmedic) before the start of the clinical study.

No changes are made to the protocol without prior Sponsor and CA approval, except where necessary to eliminate apparent immediate hazards to study participants.

Serious Adverse Events (SAE) and Suspected Unexpected Serious Adverse Reactions (SUSAR) are reported according to chapter 10.4.

Amendments are reported according to chapter 2.11.

2.4.1 Notification and reporting upon completion, discontinuation or interruption of the clinical trial (ClinO, Art. 38)

The following notifications have to be made by the Sponsor to the CA (Swissmedic):

- The completion of the study within 90 days. Completion of a clinical trial is marked by the last participant's final visit.
- The discontinuation or interruption of the clinical trial within 15 days. In the notification, the reasons for the discontinuation or interruption shall be stated.
- The final report shall be submitted within one year after completion or discontinuation of the clinical trial.

2.4.2 Notification and reporting of safety and protective measures (ClinO, Art. 37 and 43)

The following notifications and reporting have to be made by the Sponsor to the CA (Swissmedic):

- if immediate safety and protective measures have to be taken during the conduct of the clinical trial, a notification shall be submitted within 7 days. In the notification, these measures and the circumstances necessitating them shall be stated.
- Annual Safety Report (ASR).

2.5 Ethical Conduct of the Study

The study will be carried out in accordance to the protocol and with principles enunciated in the current version of the Declaration of Helsinki, the guidelines of Good Clinical Practice (GCP) issued by ICH, the Swiss Law and Swiss regulatory authority's requirements. The CEC and the CA will receive annual safety (ASR) and interim reports and they will be informed about study stop/end.

2.6 Declaration of interest

The financial compensation of the trial site will be documented in separate investigator agreements between Sponsor and the site. The compensation covers the additional cost of clinical trial-specific examinations and procedures and the extra administrative workload of the site staff related to the clinical trial. The cost aspects of treatment of clinical trial subjects in the event of clinical trial-related injuries are covered by a separate Insurance.

2.7 Patient Information and Informed Consent

The investigators explain to each participant the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits and any discomfort it may entail. Each participant is informed that the participation in the study is voluntary and that he/she may withdraw from the study at any time. The subjects are informed that they can ask any question, and consult with family member, friends, their treating physiscians or other experts before deciding about their participation in the study. Enough time is given to the subjects between written study information and signing the informed consent form.

All interested persons will be provided with sufficient information to make an informed decision about their participation in the study. The "study information and informed consent form" will be sent by e-mail to interested persons before telephone screening. For details of the recruiting procedures see chapter 7.2.

The formal consent of a participant, using the approved consent form, must be obtained before the participant is submitted to any study procedure.

The participant should read and consider the statement before signing and dating the informed consent form, and should be given a copy of the signed document. The consent form must also be signed and dated by the investigator at the same time as the participant sign, and it will be retained as part of the study records.

2.8 Compensation

Participants can keep their Fitbit after the end of the study participation. Additionally, participants receive 300 CHF study compensation at the end of the treatment phase. In the event of drop-out, the compensation will be paid out according to the effort already put in (pro rata). Travel expenses (the amount exceeding 30 CHF) will be paid based on public transportation fares (2nd class with Half Fare Travelcard) at the end of the screening visit.

2.9 Participant privacy and confidentiality

The investigators affirm and uphold the principle of the participant's right to privacy and that they shall comply with applicable privacy laws. Especially, anonymity of the participants shall be guaranteed when presenting the data at scientific meetings or publishing them in scientific journals.

Individual subject medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited. Subject confidentiality will be further ensured by utilizing subject identification code numbers to correspond to treatment data in the computer files. For a description of the structure of the code, see chapter 12.3.1.

For data verification purposes, authorized representatives of the Sponsor, the Principal Investigator, a competent authority (e.g. Swissmedic), or the ethics committee may require direct access to parts of the medical records relevant to the study, including participants' medical history.

2.10 Early termination of the study

The Sponsor or the Principal Investigator may terminate the study prematurely according to certain circumstances, for example:

- ethical concerns;
- insufficient participant recruitment;
- when the safety of the participants is doubtful or at risk, respectively;
- alterations in accepted clinical practice that make the continuation of a clinical trial unwise.

2.11 Protocol amendments

Substantial amendments are only implemented after approval of the CEC and the CA respectively.

Under emergency circumstances, deviations from the protocol to protect the rights, safety and well-being of participants may proceed without prior approval of the Sponsor, the CEC and the CA. Such deviations shall be documented and reported to the Sponsor, the CEC and the CA as soon as possible.

Other reporting commitments are reported according to the chapters 2.3 and 2.4 and safety issues according to chapter 10.

2.11.1 Reporting to the Competent Ethics Committee (CEC)

Substantial amendments: The following changes are considered to be significant and have to be reported to the CEC by the Principal Investigator (ClinO, Art. 29):

- amendments with effect on the safety and health of the human participants as well as on their rights and obligations;
- deviations from the protocol due to new scientific findings regarding the experimental design, methods, target criteria or statistical evaluation concepts;
- changes of locations or use of additional locations for the implementation of the clinical trial;
- changes of Sponsor or Principal Investigators.

The Principal Investigator shall submit to the CEC any application documents specified in Annex 3 of the ClinO, which are affected by the change. At the same time, the Principal

Investigator shall provide information on the reasons for the change. The ethics committee shall reach a decision within 30 days.

Non-substantial changes must be notified to the CEC in the Annual Safety Report (ASR).

2.11.2 Reporting to the Competent Authority (CA)

Substantial amendments: The following changes are considered to be significant and have to be reported to the CA by the Sponsor (ClinO, Art. 34):

- changes of the study medication, its application or administration;
- changes based on new preclinical or clinical data which may affect product safety; or
- changes concerning the production of the IMP, which may affect product safety.

The Sponsor shall submit to the CA any application documents specified in Annex 4 of the ClinO, which are affected by the change. At the same time, the Sponsor shall provide information on the reasons for the change. The CA shall reach a decision within 30 days after receipt of the complete application documents affected by the change.

Non-substantial changes, which affect the documents submitted to CA, must be communicated to CA as soon as possible.

3 BACKGROUND AND RATIONALE

3.1 Background and Rationale

Insomnia is the most common sleep problem, affecting between 30% and 50% in the general adult population (Brownlow, 2020). Complaints increase with age and are twice as prevalent in women as in men (Morin, 2006).

It is characterized by difficulty initiating and maintaining sleep, along with dissatisfaction with sleep quality or quantity (American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSMV)).

Although prevalence rates are high, only about 6-10% of adults have insomnia meeting full diagnostic criteria for insomnia disorder (Morin, 2012). Insomnia complaints are linked to clinically significant distress or impairment in key areas of functioning, especially daytime cognitive performance (Fortier-Brochu, 2014). Despite significant progress made in the pharmacologic and behavioral treatment of insomnia in the last few years, only a small proportion of those who suffer from insomnia actually seek professional treatment. Many people with insomnia do not wish to use conventional hypnotic drugs because of concerns about adverse effects and the risks of tolerance and dependence, and others do not want to spend the time and efforts required with behavioral therapies. (Vincent, 2001) In turn, there is an increasing interest in the use of complementary and alternative medicines, such as herbal and dietary supplements, partly because of their natural properties and perceived relative absence of residual effects. (Morin, 2012)

In Switzerland, the herbal medicinal product Redormin® 500 has been registered since 2004. It is a fixed combination of a 45% methanolic extract from valerian root and from hop strobiles.

Redormin® 500 is indicated for the relief of sleep disorders such as difficulties in falling asleep, staying asleep, as well as restless sleep. Pharmacological and clinical studies are available demonstrating the applicability of Redormin® 500 in sleep disorders (Abourashed, 2004), (Dimpfel, 2006), (Morin, 2005), (Koetter, 2007).

The studies available mainly focused on the improvement of sleep quality rather than on improvements of cognitive performance during day-time. Therefore, the aim of this study is to determine the feasibility of investigating the effects of Redormin® 500 on cognitive performance (reaction time, working memory) and psychological parameters (subjective cognitive performance, stress levels, tiredness, mood, quality of life, and motivation; all in reference to the current day) with daily measures in the evening.

3.2 Investigational Product (treatment) and Indication

Active study medication consists of 21 film coated tablets of Redormin® 500 formulated for oral administration, manufactured by

Max Zeller Söhne AG,
8590 Romanshorn,
Switzerland

Redormin® 500 mg, Filmtabletten is the Swiss trade name of the co-marketing product of Zeller Schlaf forte, Filmtabletten (Sleeping film coated tablets 1000 mg).
Redormin® 500 is used for the treatment of sleep disorders such as difficulties in falling asleep, staying asleep, as well as restless sleep.
The herbal medicinal product contains as active substance 500 mg of Valerianae radix (*Valeriana officinalis* L.) dry extract, DER 4-6:1, extraction solvent methanol 45% m/m; 120 mg of Lupuli flos (*Humulus lupulus* L.) dry extract, DER 5-7:1, extraction solvent methanol 45% m/m. The preparation contains additional excipients, including indigotine (E 132).

Once daily oral administration of 1 film coated tablet Redormin® 500 about 1h before bedtime for 21 days taken with some liquid.

Further information is provided in the patient information leaflet.

3.3 Preclinical Evidence

In vitro binding experiments with a valerian, hops and their fixed combination extract to selected central nervous system receptors was tested on 14 subtypes of five classes of central receptors (dopamine, serotonin, melatonin, MCH and neuropeptide-Y). Binding affinities could be demonstrated at some of the screened melatonin (ML1 and ML2) and serotonin (5-HT4e, 5-HT6 and 5-HT7) receptor subtypes (Abourashed, E.A., 2004).

A modulation of postsynaptic potentials in rat cortical neurons by valerian extracts macerated with different alcohols suggested that activation of adenosine A(1) and GABA(A) receptors contribute to the sleep-inducing effect of valerian (Sichardt, 2007) .

Hypothermic activity: Hops extract significantly decreased body temperature in male mice. The effects of the plant extract were comparable with melatonin. The hypothermic effects of melatonin and hops extract were antagonized with the competitive melatonin receptor antagonist luzindole. Thus, the hypothermic--and therefore the sleep-inducing effects of hops extract are possibly mediated through activation of melatonin receptors. (Butterweck et al., 2007).

Currently, an agonistic effect on central adenosine receptors, and thus a counteracting effect on caffeine induced sleeplessness through the lignans in hydrophilic valerian root extracts is discussed as a potential mechanism of action for valerian root extract (Schumacher, 2002).

3.4 Clinical Evidence to Date

A pilot study with a fixed extract combination Ze 91019 of valerian and hop was conducted in 30 patients suffering from mild-moderate, non-organic insomnia. Patients were treated with 500 mg valerian extract and 120 mg hop extract. A polysomnographic re-examination after 2 weeks of treatment revealed declines in the sleep latency and the wake time. As a consequence, the sleep efficiency increased (Füssel, 2000).

In a study comparing the above-described valerian-hops combination with diphenhydramine and placebo modest improvements of subjective sleep parameters with both the valerian-hops combination and diphenhydramine were obtained as compared to placebo (Morin, 2005). A clinical study aimed to demonstrate superiority of the fixed extract combination in comparison with placebo and single valerian extract in patients suffering from non-organic insomnia. Objective sleep parameters were registered by means of a transportable home recorder system (QUISI) The fixed extract combination was significantly superior to the placebo in reducing the sleep latency whilst the single valerian extract failed to show superiority to the placebo (Koetter, 2007).

The studies available mainly focused on the improvement of sleep quality rather than on improvements of day-time cognitive performance and psychological parameters like for instance subjective cognitive performance, stress level, mood, quality of life, and motivation.

Therefore, the aim of this study is to determine the feasibility of investigating the effects of Redormin® 500 on day-time cognition and psychological parameters in reference to the current day (subjective cognitive performance, stress level, tiredness, mood, motivation, quality of life related to work/cognitive performance), in people with occasional sleep problems. During the run-in period and the treatment period we will use a daily questionnaire and a fitness and sleep tracking device to collect objective and subjective data. The sleep tracking, the HRV- and the HR -data will be collected using Fitbit devices. The Fitbit company was taken over by Google in 2021. The devices include an xyz accelerometer, optical heart frequency meter and sensors for blood oxygen saturation measurements (these are used for sleep tracking) and also have a GPS tracker. The devices of the Fitbit Charge series (Charge 1-5) are technically similar to each other, while with each generation improvements of the devices have been introduced. The Fitbit Charge 5 is a consumer device, 10 million devices were sold in 2020. Although the Fitbit Charge devices are not medical devices, they have been used in clinical studies and have been compared to other methods of assessing sleep

data. For instance, Stucky et al compared the Fitbit Charge 2 with polysomnographic measures in shift workers and found that «reasonably accurate mean values of sleep and HR [heart rate] estimates» could be obtained, but also suggested improvements such as providing open source data analysis algorithms rather than depending on proprietary black box approaches. Since the Fitbit Charge devices are small, inexpensive, simple to use and unintrusive, they seem optimally suited to collect nightly sleep data in a reasonable quality over an extended period of time with minimal impact on the participants wellbeing while little or no maintenance is needed for using the device.

3.5 Dose Rationale

The recommended dose of Redormin® 500 is one film coated tablet daily according to Swissmedicinfo.ch. (Prescribing information Swissmedic Redormin® 500). The onset of the action was described using an EEG response 60 min after ingestion of a valerian / hop extract. (Schellenberg, 2004). A polysomnographic re-examination after 2 weeks of treatment revealed declines in the sleep latency and the wake time. As a consequence the sleep efficiency increased. (Füssel, 2000).

We will therefore administer 1 film coated tablet Redormin® 500 1 hour before bedtime for 21 days.

3.6 Explanation for choice of placebo

The placebo arm is included in this trial to maintain the study blinding, allowing for an unbiased assessment of efficacy and safety. The placebo treatment allows to assess the sensitivity of the test to be maximised in order to distinguish between effective and non-effective treatments. Placebo medication is identical in presentation, shape and color, and similar in scent as Redormin® 500 consisting of additives that are very similar to those used for the verum formulation.

3.7 Risks / Benefits

Risks

Redormin® 500 is well tolerated (Morin, 2005); all participants will be informed about known side-effects of Redormin® 500:

- gastrointestinal discomfort such as nausea, vomiting, diarrhea and belly pain. Frequency of these side-effects is not known.
- Rashes in rare cases due to excipients used in the herbal medicinal product.
- Based on experience in pregnant women to date, there is no known risk to the child when used as directed. However, systematic scientific studies have never been carried out. All female participants of childbearing potential will perform a pregnancy test before administration of the study drug.

Participants will be asked to report side-effects to the study physician.

Rarely, Fitbit can cause a skin rash / eczema when worn over extended periods of time. Participants will be advised to stop wearing the device if they develop itches or skin rash and to report this to the study physician.

Benefits

The benefit of this feasibility study lies in the gain of knowledge regarding the feasibility of performing a study on the effects of Redormin® 500 on cognition and quality of life in people with occasional sleep problems. No benefit for individual participants can be assumed as participants can be randomized to placebo or verum.

3.8 Justification of choice of study population

It is widely accepted that insomnia symptoms increase with advancing age, annual incidence rates for insomnia symptoms have been estimated to be 3-5%. (Miner, 2017). We want to evaluate the impact of occasional sleeping problems on cognitive performance. We therefore

aim to investigate a population working/studying or still working, to see whether they profit from the herbal extract Redormin® 500.

4 STUDY OBJECTIVES

4.1 Overall Objective

The overall objective of this study is to evaluate the feasibility of the planned study design to evaluate the effect of Redormin® on cognitive performance (reaction time, working memory) and psychological parameters with daily measures.

4.2 Primary Objective

The primary objective of this study is to evaluate the feasibility of the planned study design.

4.3 Secondary Objectives

The secondary objectives are to evaluate the impact of Redormin® 500 on cognitive performance (reaction time, working memory) and psychological parameters (subjective cognitive performance, stress level, tiredness, mood, quality of life, and motivation; all parameters in reference to the current day) with daily measures in the evening, and on sleep parameters and heart rate variability (HRV) and heart rate (HR) as indicators for the stress level assessed with the Fitbit tracker.

4.4 Safety Objectives

Safety will be evaluated by obtaining and analysing adverse events during run-in period and treatment period.

5 STUDY OUTCOMES

5.1 Primary Outcome measure

Feasibility of the study deign will be evaluated considering the following measures:

- Recruitment Log: number of interested persons per kind of advertisement, number of persons still interested after having read the participant information, number of participants not eligible during pre-screening
- Screening, Identification and Enrolment Log (short: Subject Master List): number of subjects enrolled, screening-failures, drop-outs, reason for screening failure / drop out, withdrawal of IC)
- Diary (run-in period / treatment period): adherence to the use of the online tool SoSci-Survey, adherence to study medication (treatment period only)
- Fitbit: adherence to and use of Fitbit
- Visits 2 and 3 (virtual visits / phone calls): technical problems (Fitbit, SoSci-Survey); general feedback (visit 3)

5.2 Secondary Outcomes measures

Online diary with SoSci-Survey

We have chosen a smartphone-based assessment of cognitive functions. Such assessments have become increasingly common in clinical research. The advantages over laboratory testing are the ability to easily record cognitive functions on a daily basis, to record these functions in the natural environment, and to reduce the burden on study participants. Clinical trials that have used smartphone-based cognitive assessments have reported good adherence, high reliability and high construct validity (Moore, 2017). Regarding the negative effects of sleep deprivation on cognition, a recent study has shown that smartphone-based testing is suitable for documenting impairments in cognitive performance (including reaction time and working memory) (Holding, 2021). Since we are interested in deficits after nights of disturbed sleep, we need to record cognitive performance on a daily basis. Laboratory testing would not be appropriate for this purpose. Furthermore, in the planned study, we do not intend to test all cognitive functions, but focus on reaction time and working memory functions that are suitable for repeated testing.

Cognitive parameters:

- Reaction time and lapses (Red Button Task)
- Working memory (Digit Span Backwards)

Psychological parameters (Visual Analog Scales, VAS):

- Subjective cognitive performance during the day
- Stress level during the day
- Tiredness during the day
- Mood during the day
- Motivation during the day
- Quality of life in regard to work/cognitive performance during the day
- Subjectiv sleep quality (VAS)

Objective sleep data, HRV and HR collected by fitness- and sleep tracker Fitbit

- sleep duration,
- begin / end of sleep,
- number of interruptions
- other sleep measures assessed by Fitbit (exploratory, see appendix 1)

5.3 Safety Outcome measures

(S)AE-recordings

6 STUDY DESIGN

6.1 General study design

Pharmacological feasibility study of Redormin® 500 with the following design:

- randomized
- double-blind (participant, study team)
- placebo-controlled
- parallel

The duration of the study from first participant in to last participant out is approx. 12 months. Duration for an individual study participant will be at most 9 weeks, depending on the time gaps between screening and beginning of run-in period, run-in period and treatment period, and end of treatment period and follow-up which will be each 6 days at most.

The study participation begins with a screening visit (visit 1). After signing the informed consent form and after successful completion of the screening (definitive inclusion in the study), randomization will be performed. Each participant will be randomized to receive either placebo or Redormin® 500 for 21 days in the treatment period. Participants will then be given the study medicinal product, the fitness- and sleep tracker (Fitbit) and, if applicable, the pregnancy test. A member of the study team instructs participants on the further course of study participation, shows how to use the Fitbit, explains how to keep a diary with SoSci-Survey, and arranges further appointments.

The run-in period starts the day after screening or at the latest 7 days later. The run-in period lasts 21 days and serves the purpose of monitoring the sleep parameters, cognitive parameters and psychological parameters as baseline. Each participant will be provided with daily links to the online-tool SoSci-Survey (web-application for creating online cognitive tests and questionnaires) via SMS to their smartphones.

The run-in period ends with a virtual visit (visit 2; at the latest 7 days later): AE recording, administrative issues during run-in period, feedback. If there are no safety reasons and the participant has not withdrawn from informed consent and there are no other withdrawal criteria according to chapter 7.4, the participant can be accepted into the treatment period. There will be no replacement of participants after the start of the treatment period.

At the end of the treatment period each participant will have a short virtual follow-up visit (visit 3; at the latest 7 days later): AE recording, administrative issues during run-in period, feedback.

After completion of the treatment phase or in case of early discontinuation of study participation, participants will be asked to return the IMP box using the envelope received during screening visit.

6.2 Methods of minimizing bias

To minimize bias, participants will be randomly allocated to treatment groups, approx. 20 in each group, and study will be double-blinded.

6.2.1 Randomization

The randomization list is provided by Ivers-Lee CSM, Burgdorf (CH) (see section 8.1.3) and facilitates a balanced randomization over age groups (18-40 years, 41-65 years) and sex (male, female). Ivers-Lee CSM provides blinded medication sets (one medication set per participant) which are labelled with consecutive medication numbers ("Medikations-Nr."). The randomization list is imported to the eCRF system secuTrial® by a data manager of the DKF who is not involved in the conduct of the study. The original files will be kept under closure until data base lock is performed.

After definitive inclusion in the study, the allocation of the medication number to the participant is performed (visit 1). Each participant will be allocated to one of the two randomization groups, either placebo or Redormin® 500 for 21 days in the treatment period. This allocation will be made through the eCRF system secuTrial® by the study center.

Participants will be randomly allocated to the two groups, while accounting for sex and age as covariates of potential importance.

Drop-outs during the run-in period are replaced until 40 participants have started the treatment phase, approx. 20 to each group. Drop-outs during the treatment phase will not be replaced.

6.2.2 Blinding procedures

Placebo medication is identical in presentation, shape and color, and similar in scent as Redormin® 500 consisting of additives that are very similar to those used for the verum formulation. The number of tablets taken and appearance are the same for this study.

Neither the participants nor the researchers know which participants belong to the control group, nor to the test group.

6.2.3 Other methods of minimizing bias

Study team members involved in handing out the IMP, data acquisition or data analysis are blinded.

6.3 Unblinding Procedures (code break)

In an emergency situation, e.g. adverse events, and up to the decision of the Principal Investigator if medically important, it is allowed to break the blind of the participant and to reveal the codes in secuTrial®.

The Principal Investigator or a representative can perform the unblinding of the participant at any time. To ensure that unblinding is possible at any time, there is a unblinding procedure implemented in secuTrial®. The Principal Investigator or a representative will report to the Sponsor and document the unblinding. Not involved study team members will not be informed about the result.

7 STUDY POPULATION

7.1 Eligibility criteria

Participants fulfilling all of the following inclusion criteria are eligible for the study:

- Healthy
- Male or female
- Age: 18-65 years old
- Occasional sleep problems (in average 1-2 nights per week, PSQI-score >5) with accompanying subjective cognitive problems (in average at least on one day per week) in the last month.
- Fluent in German
- Able and willing to give written informed consent and comply with the requirements of the study protocol

The presence of any one of the following exclusion criteria will lead to exclusion of the participant:

- DSM-V diagnosis of insomnia (mini-DIPS)
- History of neurologic disorder
- Current psychiatric disorder
- Presence of moderately severe or severe depressive disorder (PHQ-9 ≥ 15)
- Current chronic intake of prescription drugs with psychotropic effects
- Current intake of OTC drugs for sleep or mood problems
- Presence of pain condition
- Diabetes mellitus
- Coronary Heart Disease
- Chronic obstructive pulmonary disease and other breathing related sleep disorders
- Pregnancy, breast feeding
- Known hypersensitivity to valerian, hop or nickel (Fitbit)
- Tattoos on both wrists (Fitbit, SpO2 measurement)
- Inability to read and understand participant's information
- Alcohol or other drug abuse (e.g., Cannabis)
- Positive tox urine test (Barbiturate, Ecstasy (MDMA), Metamphetamin, Oxycodon, THC, Cocain, Morphine, Buprenorphine, Tramadol, Methadon, Benzodiazepine, Amphetamin, Zolpidem, Zopiclon)

7.2 Recruitment and screening

We will advertise for German speaking study participants in Switzerland and neighboring countries using the following channels: mcn.unibas.ch, markt.unibas.ch, social media, and flyers in public transport using a QR code to link to our website mcn.unibas.ch for detailed information.

After contacting the study center, the interested person will be sent the "Participant information and informed consent form" together with some administrative information. If the person is still interested in participating, a study team member will contact the interested person by phone to inform him/her about the study and answer his/her questions. Afterwards, a pre-screening with a check of the main in- and exclusion criteria will be performed. If the interested person meets all inclusion criteria and none of the exclusion criteria and is still interested in participating, the screening visit will be definitively and the visits 2 and 3 provisionally arranged.

The telephone screening documents will be filed as part of the Source Data (SD) in the participant's dossier. The telephone screening documents of participants not eligible for a study participation will be anonymized. All recruitment steps will be documented: number of prospective participants (per kind of announcement), number of pre-screenings performed, number of pre-screening failures, etc.

For screening procedures see chapter 9.4.1.

Travel expenses will be paid at the end of the screening visit.

7.3 Assignment to study groups

After informed consent, each participant will be assigned to a participant number. Upon completion of the screening each participant not being a screening-failure will be allocated to one of the two randomization groups as described in section 6.2.1.

The medication number will be allocated to the participant number by secuTrial® via a member of the study team after successful screening on appointment 1. The medication number will be listed in addition to the Source Data (SD; secuTrial®), in the Subject Master List (SML), and in the Drug Accountability Logs per site and per participant.

7.4 Criteria for withdrawal / discontinuation of participants

Participants have the right to withdraw from the study at any time for any reason without being obliged to give reason.

The investigators also have the right to withdraw participants from the study if it is in the best interest of the participant.

Participants must be withdrawn from the study under the following circumstances:

- The participant withdraws consent.
- Development of an intolerable AE due to study participation as determined by the Investigator.
- Development of an intercurrent illness or a participant requires treatment or medication that is not allowed, or a condition (e.g., traumatic event) or a procedural complication (e.g., technical or organizational) occurs, which would interfere with the participant's continued participation.
- Pregnancy.
- Occurrence of a significant protocol violation during the study (as judged by the PI).
- Participant entered the study in violation of the protocol (as judged by the PI).
- Non-compliance during the run-in phase (e.g. less than 70% completion of the SoSci-Survey or Fitness and sleep tracker is worn less than 70% of the total time).

There will be no withdrawal in the following non-compliance cases during the treatment phase:

- No regular completion of the SoSci-Survey;
- Fitness and sleep tracker (Fitbit) is not regularly worn and/or only during night.

The reasons for withdrwal / discontinuation will be documented in the Source Data and secuTrial®.

There will be a virtual final visit after withdrawal for safety reasons by zoom or phone call. A final visit should also take place in all other cases, if possible. In all cases, the final visit serves - in addition to the safety issues - to clarify administrative issues (e.g. return of the IMP), to inquire about the reason for termination and for a final feedback.

Withdrawal date and reason will be listed in the SD, in the SML and in the eCRF.

Safety data will be analyzed for all participants, who received at least one dose of study medication. For information about data handling see chapter 12.2.

7.5 Contraception and pregnancy

Based on experience to date, there is no known risk to the child when Redormin® 500 is used as directed. However, systematic scientific studies have not been carried out. To minimize risk of a pregnancy all female participants of childbearing potential are advised to use adequate contraception during the study (e.g. condoms, diaphragm).

All female participants of childbearing potential will perform a pregnancy test before the beginning of the trial period (before visit 2).

If a pregnancy should occur the pregnant participant will be withdrawn immediately from the clinical study. No follow-up of the pregnancy is planned.

8 STUDY INTERVENTION

8.1 Identity of Investigational Products

8.1.1 Experimental Intervention

Active ingredients of one film coated tablet:

500 mg Valerianae office. Rad. Extr. Methan. Sic (Drug extraction Ratio, DER) (4-7 :1)

120 mg Lupuli Strob. Extr. Methan. Sic (DER 7-10:1)

Active study medication consists of 21 film coated tablets of Redormin® 500 formulated for oral administration taken 1 tablet in the evening with some liquid one hour before bedtime.

Extract number:	Ze 91019
Trade name:	*Redormin® 500*
Dosage form:	film coated tablet
Film coated tablet weight:	1 g
Manufacturer:	Max Zeller Söhne AG
Description:	(Excipients of the film coated tablet)
Silica, colloidal anhydrous	granulating aid, antiadherent, disintegrant, flow promotor
Cellulose, microcrystalline	granulating aid, binder, diluent, coating agent
Croscarmellose sodium	disintegrant
Magnesium stearate	lubricant, antiadherent
Stearic acid	moisture barrier
Hypromellose	film forming agent
Titanium dioxide	colouring agent
Macrogol 20 000	film-forming agent
Indigo carmine alumnium (E 132)	colouring agent

8.1.2 Control Intervention

Placebo film coated tablet is identical in presentation, shape and color, and similar in scent to test product Redormin® 500 film coated tablet.

Active ingredient:	n.a.
Extract number:	n.a.
Trade name:	n.a.
Dosage form:	film coated tablet
Film coated tablet weight:	1 g
Manufacturer:	Max Zeller Söhne AG
Description:	(Excipients of the film coated tablet)
Silica, colloidal anhydrous	granulating aid, antiadherent, disintegrant, flow promotor
Cellulose, microcrystalline	granulating aid, binder, diluent, coating agent
Croscarmellose sodium	disintegrant
Magnesium stearate	lubricant, antiadherent

Stearic acid	moisture barrier
Hypromellose	film forming agent
Titanium dioxide	colouring agent
Macrogol 20 000	film-forming agent
Indigo carmine alumnium (E 132)	colouring agent
Valerian oil	Valerian aroma

8.1.3 Packaging, Labelling and Supply (re-supply)

Manufacturing and (unlabeled) primary packaging of the study medication is performed by Max Zeller Söhne AG at CH-8590 Romanshorn.

Generation of the randomization list, blinded labeling and packaging according to the randomization list and according to study specifications will be performed by Ivers-Lee-CSM at CH-3400 Burgdorf.

Packaging: Thermoforming foil: PVC 250 µm/ PE 30 µm/ PVdC 90 g/m2.

Aluminium foil: 20 µm.

Ivers-Lee-CSM will provide the study medication directly to the study site.

8.1.4 Storage Conditions

The IMP will be kept at room temperature (15-25°C) and protected from light and will be stored for the entire study until last participant out in our division. The storage temperature will be controlled with LogTag temperature recorder.

8.2 Administration of experimental and control interventions

8.2.1 Experimental Intervention

Redormin® 500 is already on the market. For the study the same composition and administration will be used: One film coated tablet Redormin® 500 will be taken orally about 1h before bedtime with some liquid. The participant will take the medicinal herbal product over 21 days.

8.2.2 Control Intervention

For reasons of comparison, the intake of the placebo will be similar to that of the verum: One placebo tablet will be taken orally about 1h before bedtime with some liquid. The participant will take the placebo over 21 days.

8.3 Dose modification

Not applicable

8.4 Compliance with study intervention

The IMP kits contain 3 blisters. Each blister contains 10 film coated tablets. All subjects have to return unused medication at the end of the trial period or after withdrawal for drug accountability reasons and for correct disposal of remaining tablets after study end.

To monitor adherence to study medication, participants document tablet intake of the previous night in the SoSci-Survey online tool as part of the daily survey.

Blinding is warranted (see chapter 6.2, Methods of minimizing bias).

8.5 Data Collection and Follow-up for withdrawn participants

Subject withdrawn because of (S)AE will be followed up until resolution or stabilization, see chapter 10.1.2.

8.6 Trial specific preventive measures

In case of headache, pain or fever, non-steroidal anti-inflammatory drugs are allowed and has to be recorded as concomitant medication.

8.7 Concomitant Interventions (treatments)

Treatments with any substances or medications known to affect sleep, including prescription psychotropics, sedatives, hypnotics, nicotine-replacement therapies, over-the-counter sleep aids, or herbal products are prohibited during the course of the study.

All concomitant treatment will be recorded in the eCRF.

8.8 Study Drug Accountability

The supplies from and the returns to the study center for destruction will be documented on the site in the Drug accountability log. This log documents the following:

- IMP-boxes received by the study center from the Sponsor
- IMP-boxes contain three blisters. Each blister contains 10 film coated tablets.
- Individual drug accountability per participant (also in the SD of each participant): boxes returned to the study center by the participants in the event of a drop-out during the run-in period or the treatment period or after completion of study participation (visit 3)
- Boxes sent back by the study center to the Sponsor at the end of the study (after LPLV) by mail.

The IMP kits will be returned by study participants to the study center by mail.

The documentation includes the following information:

- participant number
- medication number
- delivery date,
- date of receipt,
- delivered boxes,
- batch number,
- expiry date,
- number of tablets returned.

Upon return from patients, the study center annotates the respective participant number on the IMP boxes.

The Principal Investigator is responsible for all medication supplies and also for maintaining accurate study medication accountability records throughout the study. Written documentation is mandatory.

Each dispensing of study medication will be documented in the SD.

At the end of the study, one copy of the medication inventory dispensing record should be sent ot the Sponsor and one kept in the Investigator’s study file.

8.9 Return or Destruction of Study Drug

Used and unused medication will be sent back to the Sponsor for destruction/disposal. Upon receiving unused medication, the Sponsor will perform a physical check for identity (verum vs. placebo) of the unused tablets (only for medication which was returned from participants). This check will only occur after unblinding of study data. A certificate of destruction will be filed at the Sponsor and Principal Investigator.

9 STUDY ASSESSMENTS

9.1 Study flow chart(s) / table of study procedures and assessments

See study schedule (Table 1, Duration of study parts, page 15)

9.2 Assessments of outcomes

9.2.1 Assessment of primary outcome

Feasibility measures

Recruitment Log

- number of interested persons per kind of advertisement,
- number of persons still interested after having read the participant information,
- number of pre-screenings,
- number of pre-screening failures (with reason).

SD resp. Screening, Identification and Enrolment Log (short: Subject Master List):

- number of subjects enrolled,
- number of screening-failures,
- number of drop-outs run-in period (investigators),
- number of drop-outs treatment period (investigators),
- reasons for screening failures,
- reasons for drop outs during run-in period (investigator),
- reasons for drop outs during treatment period (investigator),
- number of withdrawals of IC by participant during run-in period,
- number of withdrawals of IC by participant during treatment period,
- reasons for withdrawals during run-in period (participant),
- reasons for withdrawals during treatment period (participant),

Diary (SoSci-Survey)

- Number of complete diary entries during the run-in period (x/21)
- Number of complete diary entries during treatment period (x/21)
- Number of Digit Span tasks completed during the run-in period (x/21)
- Number of Digit Span tasks completed during the treatment period (x/21)
- Number of Red Button tasks completed during the run-in period (x/21)
- Number of Red Button tasks completed during the treatment period (x/21)
- Number of days on which the IMP has been taken during the treatment period (x/21)

Sleep and HRV and HR data (Fitbit)

- Number of days the Fitbit was worn throughout the night during the run-in period (x/21)
- Number of days the Fitbit was worn throughout the day during the run-in period (x/21)
- Number of days the Fitbit was worn throughout the night during the treatment period (x/21)
- Number of days the Fitbit was worn throughout the day during the treatment period (x/21)
- Number of nights for which the Fitbit data are available during the run-in period (x/21)
- Number of days for which the Fitbit data are available during the run-in period (x/21)
- Number of nights for which the Fitbit data are available during the treatment period (x/21)
- Number of nights for which the Fitbit data are available during the treatment period (x/21)

Visits 2 and 3 (virtual visits / phone calls):

- Visit 2 was performed
- Visit 3 was performed
- The participant reports technical problems with Fitbit (Visits 2 and 3)
- The participant reports technical problems with SoSci-Survey (Visits 2 and 3)

- The participant reports technical problems with the Fitbit App (Visits 2 and 3)
- The participant reports organizational problems such as scheduling, lack of availability of information or material (Visits 2 and 3)
- general feedback, incl. the question "What do you guess, did you receive verum or placebo?" with reason for the (forced) choice (Visit 3)

9.2.2 Assessment of secondary outcomes

Diary with SoSci Survey Questionnaire (run-in period and treatment period)

SoSci checks that all questions have been answered before submitting the questionnaire. If not, a reminder appears once.

Cognitive parameters

- *Reaction time test (Red Button Task)*, adapted from (Dinges and Powell, 1985): participant sits in front of a screen showing a gray circle in the middle of the screen. The circle's color turn into red and participant will be instructed to push a button as soon as the color changes. Parallel versions will be used.

  Score: The average of all reaction times. The period between the time of color change and button push is measured in milliseconds and will be considered as reaction time.
- *Working memory* will be assessed with the digit span task backward, a subtest of the "Wechsler Intelligenztest für Erwachsene" (WIE; (von Aster 2006)). Parallel versions will be used.

  Stop rule: both digit spans of a level (same length) were wrongly reproduced;

  Score: number of correct remembered digit spans. Total scores for digit span backward will be calculated as described in the manual of the WIE.

Psychological parameters (Visual Analog Scales, VAS):

Visual analog scales (VAS) are used to assess the psychological parameters and the sleep quality during the run-in period and the treatment period. Respondents specify their level of agreement to the statement by indicating a position along a continuous line between two end-points. The score ranges from 1 and 101.

Endpoints of the VAS for

- Subjective cognitive performance during the day: very poor and very good
- Tiredness during the day: not at all and very strong
- Mood during the day: very bad and very good
- Stress level during the day: very low and very high
- Motivation during the day: not at all and very high
- Quality of life (regarding cognitive performance) during the day: very low and very high
- Sleep quality last night: very bad and very good

Objective sleep parameters, heart rate variability (HRV) and heart rate (HR) collected with sleep tracker Fitbit (run-in period and treatment period)

Sleep parameters collected via sleep tracker (Fitbit) are sleep duration, begin / end of sleep and number of interruptions.

We will use Fitbit Charge 5 devices (or alternatively, depending on availability the very similar Charge 4) see https://www.fitbit.com/global/de-ch/products/trackers/charge5.

When the Fitbit Charge 5 device is worn by the participant it tracks sleep data in addition to other activity data automatically. The data is collected via the Fitbit app on the users' smartphone and then collated at the servers of the company when the Fitbit device is connected via bluetooth to the smartphone. The Fitbit Charge devices have up to 7 day battery lifetime and can collect data for up to 7 days, i.e. ideally after 3-4 days the devices are recharged and connected to the Fitbit app to ensure data is uploaded to the Fitbit server and to avoid data loss. We will not use or permanently store the GPS data collected by the Fitbit devices in this study.

9.3 Assessment of safety outcomes

AEs will be recorded throughout the study from visit 1 until the Follow up visit (visit 3) according to chapters 10.2 and 10.3. Adverse Events that begin or that worsen in severity after at least one dose of study medication has been administered will be considered treatment emergent AEs (TEAEs).

Each AE occurring to a participant, either spontaneously revealed by the participant, observed by the Investigator, or elicited by asking a non-leading question such as "How are you feeling?", and whether believed by the Investigator to be related or unrelated to the study medication, must be recorded on the AE information page of the eCRF and on the participant's records.

Following information needs to be collected: time of onset, duration, resolution, action to be taken, assessment of intensity, relationship with study treatment; see Section 10 for AE definition and procedures.

9.4 Procedures at each visit and during treatment periods

9.4.1 Screening visit

During the screening visit the Investigator explains to the participant the aims of the study, the study procedures, the drug under investigation and potential risks (see also chapter 3.7 risks and benefits). Written informed consent will be obtained from all participants. Participants who are candidates for enrolment into the study will be evaluated for eligibility during the screening visits by the Investigator (inclusion, exclusion criteria).

Screening visit consists of

- assessment of personal history (incl. sociodemographic information, incl. sex, age, BMI, job/financial situation, Covid-Q (vaccination yes/no, been ill with Covid yes/no, if yes "did you have sleep problems already before?"))
- assessment of medication history,
- physical examination,
- tox urine (including Barbiturate, Ecstasy (MDMA), Metamphetamin, Oxycodon, THC, Cocain, Morphine, Buprenorphine, Tramadol, Methadon, Benzodiazepine, Amphetamin, Zolpidem, Zopiclon)

  The nal von minden Drug-Screen® rapid multi test consisting of competitive immunoassays for the qualitative determination of various drugs and drug metabolites in human urine will be performed in a urine sample.

The following questionnaires will be used to assess sleep problems and psychiatric disorders:

- The mini-DIPS is a reliable interview with good construct validity Margraf (Suppiger et al., 2008) and is designed to assess the most relevant mental disorders according to DSM-V, text revision (DSM-V-TR). The DIPS will be also used to exclude the presence of other mental disorders than subclinical insomnia and to exclude clinical insomnia.
- The Pittsburgh Sleep Quality Index (PSQI) is a self-rated questionnaire which assesses sleep quality and disturbances over a 1-month time interval. The 19 self-rated questions assess a wide variety of factors relating to sleep quality, including estimates of sleep duration and latency and of the frequency and severity of specific sleep-related problems. These I9 items are grouped into seven component scores, each weighted equally on a 0-3 scale. The seven component scores are then summed to yield a global PSQI score, which has a range of 0-21; higher scores indicate worse sleep quality. A score of greater than 5 is indicative for poor sleep quality (Buysse et al., 2007)
- Question on the frequency of day-time cognitive problems related to poor sleep. "How many times per week do you experience cognitive difficulties that you attribute to poor sleep (considering the last 4 weeks)?"

- *The Patient Health Questionnaire (PHQ)* is a self-administered version of the PRIME-MD diagnostic instrument for common mental disorders. The PHQ-9 is the depression module, which scores each of the 9 DSM-IV criteria as "0" (not at all) to "3" (nearly every day).

  Score ranges from 0 to 27. Higher scores indicating higher degree of depression.

The investigator decides, whether there are contraindications for the administration of study medication.

The medical examination performed covers:

- Vital signs (blood pressure / heart rate) will be taken with the participant having been in a seated position for at least 5 minutes.
- Height / weight (for calculation of BMI)
- Physical examination; findings will be recorded as "normal" or "abnormal".
  Tox urine tests to control for use of Barbiturate, Ecstasy (MDMA), Metamphetamin, Oxycodon, THC, Cocain, Morphine, Buprenorphine, Tramadol, Methadon, Benzodiazepine, Amphetamin, Zolpidem, Zopiclon

Screening failures equal to participants not meeting all inclusion criteria or meeting one or more of the exclusion criteria.

After successful completion of the screening (enrolment in the study), the allocation of the medication number to the participant will be performed. Each participant will be randomized to receive either placebo or Redormin® 500 for 21 days in the treatment period. Participants will then be given the study medicinal product, the fitness- and sleep tracker Fitbit and, if applicable, the pregnancy test. A member of the study team instructs participants on the further course of study participation, shows how to use the fitness- and sleep tracker Fitbit and how to install and use the Fitbit app, explains how to keep a diary with SoSci-Survey, and arranges appointments for the visits 2 and 3. All participants can keep the Fitbit watch for personal use after the end of the study or after exclusion.

9.4.2 Run in period

The run-in period lasts 21 days and serves the purpose of monitoring the sleep parameters, HRV, HR and cognitive parameters as baseline. Each participant will be provided with daily links to the online-tool SoSci-Survey (web-application for creating online cognitive tests and questionnaires) via SMS to their smartphones.

The run-in period begins the day after screening visit. If technical or administrative problems occur, the start can be delayed until maximum the 7th day after visit 1.

Participants will be advised to perform the tests each day after work/studying/homework at around 5 p.m. and record HRV, HR and sleep parameters by wearing a Fitbit during the whole day and night and allowing their Fitbit to connect to their smartphone via Bluetooth.

9.4.3 Visit 2 – start of treatment period

Whenever possible, visit 2 (virtual visit or phone call) will take place the day after the end of the run-in period; but not later than the 7^{t}h day thereafter.

Shortly (max. 1 day) before visit 2, all female participants of childbearing potential will perform a pregnancy test at home. Pregnancy test will be performed in a urine sample according to instructions of Axaclear, Axapharm. Axaclear is a one-step hCG (monoclonal anti-hCG antibodies) urine pregnancy test used for qualitative (visual) determination of hCG in urine specimen for early detection of pregnancy.

Content of visit 2:

- (S)AE recording for run-in period,
- Administrative or technical issues during run-in period,
- Further instructions for treatment period: IMP-intake (once daily one hour before bedtime).

Further, during this visit, it is decided whether the requirements for the start of the treatment phase are met. If continuation of study participation is not possible, this visit is also the final

visit. The participant can be accepted into the treatment period, if there are no safety reasons, the participant hasn't withdrawn from informed consent and if there are no other withdrawal criteria according to chapter 7.4. There will be no replacement of participants after the start of the treatment period.

9.4.4 Treatment period

The treatment period lasts 21 days and begins with the first intake on the evening of the day on which visit 2 took place. During the treatment days, the participants document the intake of the tablets in the daily SoSci-Survey questionnaire.

Participants will be instructed to perform the diary each day after work/studying/homework at around 5 p.m., as they did during the run-in period, and record sleep parameters HRV and HR by wearing Fitbit during the days and nights and allowing their Fitbit to connect to their smartphone via Bluetooth.

9.4.5 Follow up visit (visit 3)

Whenever possible, the follow up visit (virtual visit or phone call) will take place the day after the end of the treatment period; but not later than the 7th day thereafter.

Content of visit 3:

- (S)AE recording for run-in period,
- how to handle remaining study medication,
- Administrative or technical issues during treatment period,
- General feedback (incl. the question "What do you guess, did you receive verum or placebo?" with reason for the (forced) choice).

10 SAFETY

10.1 Definitions

10.1.1 Adverse Event (AE)

An Adverse Event (AE) is any untoward medical occurrence in a patient or a clinical investigation participant administered a pharmaceutical product and which does not necessarily have a causal relationship with the study procedure. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal investigational product, whether or not related to the medicinal investigational product [ICH E6 1.2].

10.1.2 Serious Adverse Event (SAE)

A Serious Adverse Event (SAE) is classified as any untoward medical occurrence that:

- results in death,
- is life-threatening,
- requires in-patient hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity, or
- is a congenital anomaly/birth defect

In addition, important medical events that may not be immediately life-threatening or result in death, or require hospitalization, but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed above should also usually be considered serious. (ICH E2A)

SAEs should be followed until resolution or stabilization. Participants with ongoing SAEs at study termination (including safety visit) will be further followed up until recovery or until stabilization of the disease after termination.

10.1.3 Unexpected Adverse Drug Reaction

An "unexpected" adverse drug reaction is an adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. investigator's brochure for drugs that are not yet approved and prescribing information for approved drugs, respectively). (ICH E2A)

10.1.4 Suspected Unexpected Serious Adverse Reactions (SUSARs)

The Principal-Investigator evaluates any SAE that has been reported regarding seriousness, causality and expectedness. If the event is <u>related</u> to the investigational product and is both <u>serious</u> and <u>unexpected</u>, it is classified as a SUSAR. In order to determine a SUSAR unblinding is needed.

10.2 Assessment of (Serious) Adverse Events and other safety related events

10.2.1 Assessment of causality

Both Investigator and Sponsor-Investigator make a causality assessment of the event to the study drug, based on the criteria listed in the ICH E2A guidelines:

<u>Assessment of Causality</u>

Both Investigator and Sponsor make a causality assessment of the event to the study drug, based on the criteria listed in the ICH E2A guidelines:

Relationship	Description
Definitely	Temporal relationship Improvement after dechallenge* Recurrence after rechallenge (or other proof of drug cause)
Probably	Temporal relationship Improvement after dechallenge

	No other cause evident
Possibly	Temporal relationship Other cause possible
Unlikely	Any assessable reaction that does not fulfil the above conditions
Not related	Causal relationship can be ruled out
*Improvement after dechallenge only taken into consideration, if applicable to reaction	

10.2.2 Assessment of Severity

The severity of each AE must be assessed by the Investigator using one of the following categories, and recorded in the eCRF:

Mild: Causing no limitation of usual activities;
the Participant may experience slight discomfort.

Moderate: Causing some limitation of usual activities;
the Participant may experience annoying discomfort.

Severe: Causing inability to carry out usual activities;
the Participant may experience intolerable discomfort or pain.

10.3 Documentation

10.3.1 Serious Adverse Events (SAE)

During the entire duration of the study all serious adverse events (SAEs) are collected, fully investigated and documented in source documents and electronic case report forms (eCRF). Study duration encompassed the time from when the participant signs the informed consent until the follow-up / final visit.

10.3.2 Adverse Events (AE)

The following information needs to be collected for adverse events during the treatment period:

- time of onset,
- duration,
- resolution,
- action to be taken,
- assessment of intensity, and
- relationship with study treatment.

During the run-in period:

- time of onset,
- duration,
- resolution,
- action to be taken,
- assessment of intensity, and
- relationship with study treatment.

For assessment of safety outcomes see chapters 9.3

10.4 Reporting of serious adverse events (SAE) and other safety related events

10.4.1 Reporting of SAEs

All SAEs must be reported immediately and within a maximum of 24 hours to the Sponsor of the study. The Sponsor will re-evaluate the SAE and return the form to the site.

SAEs during the treatment period resulting in death are reported to the EKNZ within 7 days.

10.4.2 Reporting of SUSARs

A SUSAR needs to be reported to the CEC (EKNZ) via Principal Investigator and to the CA (Swissmedic) via Sponsor within 7 days, if the event is fatal, or within 15 days (all other events).

10.4.3 Reporting of immediate safety and protective measures

All suspected new risks and relevant new aspects of known adverse reactions that require safety-related measures, i.e. so called safety signals, must be reported to the Sponsor within 24 hours. The Sponsor must report the safety signals within 7 days to the CEC (EKNZ) via BASEC and to the Swissmedic.

10.4.4 Reporting and handling of pregnancies

Pregnant participants must be withdrawn immediately from the clinical study.

Any pregnancy during the treatment period of the study and within 14 days after discontinuation of study medication will be reported to the Sponsor within 24 hours. No follow-up of the pregnancy is planned.

10.4.5 Periodic reporting of safety (Art. 43 ClinO)

An annual safety report (ASR) is submitted once a year to the local Ethics Committee via BASEC and to the CA via Principal Investigator resp. Sponsor. The start date for the ASR is the Sponsor's first authorization to conduct the clinical trial.

The ASR is submitted to the CEC and to Swissmedic throughout the duration of the clinical trial, and the last ASR / DSUR submission will cover the Last Patient Last Visit.

10.5 Follow-up of (Serious) Adverse Events (AE)

All (Serious) Advese Events are followed up until stabilization or recovery.

If (S)AEs last beyond the regular completion or discontinuation of study participation, the following applies:

Occurrence before start of treatment period and before intake of the first tablet (including run-in period until visit 2):

- Open SAE: final visit as soon as possible. No further follow-up on the outcome of the AE.
- Open AE: final visit as soon as possible. No further follow-up on the outcome of the AE.

Occurrence during treatment period (visit 2 (first intake of the IMP) to visit 3):

- Open SAE: final visit as soon as possible; follow-up of the SAE during three months or until recovery or stabilization via phone, Zoom, or email (at least three documented attempts).
- Open AE: final visit as soon as possible; follow-up of the AE during one month or until recovery or stabilization via phone, Zoom, or email (at least three documented attempts).

In all cases of AE or SAE during treatment period: If the last visit is not possible (for any reason), at least three documented attempts should be made to re-schedule.

11 STATISTICAL METHODS

11.1 Hypothesis

The aim is to explore the feasibility of the study by using descriptive statistics of the variables listed under 9.2.1. e.g., displaying the number of participants in the different phases of recruitment and visits, the percentage of tablet intake, of completed daily online assessment, and wearing Fitbit during sleep periods. No a priori hypothesis is formulated.

11.2 Determination of Sample Size

It is planned to randomize 40 participants (20 participants per group). For replacement of drop outs during run-in phase see 6.2.1.

Studies that have addressed the specific issue of reasonable sample sizes for feasibility/pilot studies recommend between 20 and 70 study participants (see Table 4, Whitehead, 2016).

Table 4. The current flat rules of thumb for overall pilot trial sample size of a two armed trial.

Author	Recommended pilot trial sample size
Julious[16]	24
Kieser and Wassmer[12]	20–40
Browne[10]	30
Sim and Lewis[11]	≥55
Teare et al.[17]	70

With the planned 40 study participants, we are within the range of these recommendations.

Study feasibility and effect sizes to allow estimation of the required sample sizes for later studies are to be estimated with data of this study.

11.3 Statistical criteria of termination of trial

None

11.4 Planned Analyses

All data points of all subjects will be listed in subject data listings. Tables with summary statistics (frequency and percentage for categorial data and n, mean, SD, Q25, Median, Q75, minimum and maximum for continuous data) will be presented for socio-demographic data, primary and secondary outcomes and AEs. The structure of listings and tables follows Guideline ICH E3.

In addition, we plan exploratory statistical analyses with the data acquired.

11.4.1 Unblinding for analysis

Only after formal locking the database including all merged data (Studiendatenbank-MCN including secuTrial® data, SoSci-Survey- and Fitbit-logfiles), the unblinding for analysis is performed by assigning the treatment information (Placebo or Verum) from the randomization list to the participant numbers.

11.4.2 Datasets to be analyzed, analysis populations

We will analyze and describe all primary and secondary outcome measures using data of those participants, who were randomized to one of the study groups (visit 1) and have not been withdrawn or dropped out during the run-in phase (for details see chapter 7.4.) regardless if they completed all tests and investigations during treatment phase. After 40 participants have reached the treatment phase, drop-outs will not be replaced.

Cases of screening failure, drop-out and withdrawal of informed consent will be thoroughly described to assess the reason(s) for dropping out.

11.4.3 Interim analyses

No interim analyses are planned.

11.4.4 Safety analysis

Safety data will be analyzed for all participants, who received at least one dose of study medication.

11.4.5 Deviation(s) from the original statistical plan

Deviations from the original statistical plan will be justified and reported to the ethical committee and regulatory authorities.

If in the meantime other studies find important effects or confounding effects related to our study, we will include these confounders (if we have assessed those) as an additional analysis in our statistical plan in addition to our planned analyses.

11.4.6 Handling of missing data and drop-outs

Missing data will be recorded as NA.

Drop-Outs see chapter 11.4.1.

11.4.7 Software

The software environment «R» will be used for statistical computing.

12 QUALITY ASSURANCE AND CONTROL

12.1 Responsibilities

The Sponsor has an overall responsibility for the implementation and conduct of the study.

The Principal Investigator is responsible for implementing and maintaining quality assurance and quality control systems with written SOPs and Working Instructions in the study center. Adequate information and training of the involved staff is in his charge and should be documented. The web-based quality management system orca (https://orca.dkfbasel.ch/) is used.

12.2 Data handling and record keeping / archiving

12.2.1 Case Report Forms (CRF)

Study data is recorded with electronic Case Report Forms (eCRF). secuTrial® will be used for the eCRF (see contract with CTU). For each enrolled study participant a eCRF will be maintained. The eCRF will be kept current, as it has to reflect participant status at each phase during the course of study. For confidentiality reasons eCRFs must not contain any personal data of study participants. It will be used a coded identification consisting of a participant number (see chapter 12.3.1). Authorized for eCRF entries are the study coordinator, the investigators and other authorized members of the study team. secuTrial® has a detailed audit trail so that every relevant change is traceable and assignable to the person who made it. Data is entered into the eCRF and can be validated for completeness and discrepancies automatically.

We will perform single data entry. Entries in the eCRF must be consistent with information recorded in the source documents. eCRF data should be accurate, consistent, complete and reliable.

12.2.2 SoSci Survey and sleep tracking (Fitbit) data

The diary-logfiles (questionnaire, Red Button Task and the Digit Span Task) and the sleep tracking, HRV and HR data (Fitbit) will not be entered in the eCRF (secuTrial®). These data will be transferred to a secure electronical archive (Studiendatenbank-MCN) to guarantee originality and to prepare the data for data analysis. Studiendatenbank-MCN is a local database for study data and is implemented using LabKey®. LabKey® Server is a software suite for integrating and analyzing biomedical research data. It provides of a secure data repository and access via a webbrowser. Studiendatenbank-MCN extends the LabKey® server platform with scripts and workflows for archiving and tracking study data and related logfiles as well as performing the data transformation to provide data files in the format for statistical analysis as detailed in the statistical methods section.

Questionnaires, Red Button Task and the Digit Span Task will be performed with SoSci-Survey. These data will be transferred to LabKey® after LPLV according to the procedures described in chapter 12.3.3. During the data collection phase, data collected with SoSci-Survey are stored at sciCORE (Center for Scientific Computing at the University of Basel). The data cannot be changed by the study team. The originality is thus ensured.

To obtain the sleep tracking and HRV and HR data (Fitbit) we will use the data report export option that can be requested via the Fitbit website (https://www.fitbit.com). Fitbit provides compressed data files which contain several subfolders. The folders *Physical Activity*, *Sleep* und *Others* contain all data relevant for this study including data files in json format, which allows to extract sleep onset and wake times, sleep duration and number of interruptions as well as heart rate variability data. The data file provided by Fitbit will be downloaded to the project folder on the file server of the University of Basel. We will extract the data folders Physical Activity, Sleep und Others from the compressed data file provided by Fitbit and delete the remaining data from our computers.

We will request data from Fitbit three times per participant. First data request will take place about 1-4 days after the start of the run-in period to check if Fitbit data collection works technically. The second data request will be made shortly before Visit 2 to check whether the participants have worn their Fitbit. The data of the first two data requests will be stored in Studiendatenbank MCN. This data is only used to create short reports. The first export verifies that data has been recorded and that the device is working (technical verification). On the second export, a compliance check is made. Specifically, it is checked if Fitbit has been worn during at least 70% of the run-in period.

At the end of the treatment period the final data export request will be triggered to Fitbit for every participant. This time the extracted data folders will be kept for analysis; files will be stored in a separate folder for each participant and a README file with the participant id and checksums of the data files will be generated by a script in the same folder on the file server of the University of Basel. By storing and using only the data in the Physical Activity, Sleep and Others folders, no GPS data will be collected by us.

The Fitbit data sets and SoSci-Survey logfiles will be imported to Studienbankdatenbank-MCN for archiving and data transformation for statistical analysis using R scripts.

12.2.3 Specification of source documents

Source data are all information in original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (e.g. hospital records, laboratory notes, recorded data from automated instruments, and records kept at the pharmacy and other departments involved in the clinical trial). (GCP 1.51/2)

Source data will consist of the following documents:

Paper documentation:

- Informed Consent Form
- Screening documentation, incl. telephone screening
- AE-log, concomitant medication
- Addictive Behaviors
- Administrative documents: visit documentations, visit plan, etc.
- Feasibility measures
    - Visits 2 and 3 (virtual visits / phone calls): technical problems (Fitbit, SoSci), general feedback (only visit 3)
    - Recruitment Log (number of interested persons per kind of advertisement, number of persons still interested after having read the participant information, number of participants not eligible during pre-screening): certified copy out of the recruitment/organsiation database.
    - Participant Dossier (number of subjects enrolled, screening-failures, drop-outs, reason for screening failure / drop out, withdrawal of IC): certified copy out of the electronic SML

Direct data entry with secuTrial®

- Sociodemographic questionnaire
- Covid-19 questionnaire
- PHQ-9
- Pittsburgh sleep quality index (PSQI)

Direct data entry with SoSci-Survey (diary during run-in-period and treatment period):

- Cognitive tasks:
    - Reaction time and lapses (Red Button Task)
    - Working memory (Digit Span Backwards)
- Psychological parameters (Visual Analog Scales, VAS):
    - Subjective cognitive performance during the day

- Stress level during the day
- Tiredness during the day
- Mood during the day
- Motivation during the day
- Quality of life during the day

- Subjectiv sleep quality (VAS)
- Feasibility measures: adherence to the use of the online tool SoSci-Survey, adherence to study medication (treatment period only)

Sleep, HRV, and HR data (Fitbit)

Sleep, HRV, and HR data (Fitbit) will be downloaded as provided by Fitbit upon data export request. The file provided is compressed (zip), it contains several folders incl. Physical Activity, Sleep and Others. These folders contain the data files we require for analysis in csv and json format (see also 12.2.1); in particular the score.csv file and the daily_sleep-[date].json files (separate files per day). sleep_score.csv file contains scores computed by Fitbit: overall score, composition score, revitalization score, duration score, deep sleep in minutes, resting heart rate, restlessness.

daily sleep-[date].json files contain information on sleep duration, begin / end of sleep, number of interruptions

For more details see appendix 1

Feasibility measures: adherence to and use of fitness and sleep tracker Fitbit.

12.2.4 Record keeping / Archiving

The Sponsor will keep the Trial Master File (TMF) and the Principal Investigator the Investigator Site File (ISF) archived, for a minimum of 10 years after study termination or premature termination of the clinical trial. The TMF will be archived in the archives of Max Zeller Söhne AG. The ISF wil be archived in the archives of the Division of Cognitive and Molecular Neuroscience and in case of the eCRF in the electronic archive-system of the University Hospital Basel. Data electronically captured with SoSci-Survey as well as sleep tracking and HRV and HR data (Fitbit) will be archived in a read only status in Studiendatenbank-MCN for at least 10 years (for further information on Studiendatenbank-MCN/LabKey® see chapter 12.3.3).

The study team will archive all essential data, such as a printout version of the eCRFs, medical records including logs for concomitant medication, laboratory reports, informed consent documents, IP disposition records including randomization and decryption lists, safety reports, information regarding participants who discontinued, and other pertinent data.

If the Principal Investigator moves, withdraws from the investigation or retires, the responsibility for maintaining the records may be transferred to another person (e.g.: Sponsor, other Investigator) who will accept the responsibility. Notice of this transfer must be made to and agreed upon by the Sponsor.

12.3 Data management

12.3.1 Pseudonymization and Coding

After obtaining informed consent, the participant number will be assigned. Each subject will be assigned to a numeric code (3 digits) starting with 101.

To use Fitbit, an account must be created with a gmail address. We will create a study gmail account for each participant, which will not allow any person-identifying details about the participant. The fitbit and the gmail accounts are managed by us. We obtain Fitbit data via a request for information, which can be triggered in the Fitbit account. As soon as we have the data after completion of the study participation (regular or early termination), we delete the Fitbit account and the gmail account. The deletion of the accounts will be triggered by the

study team. According to Fitbit, it may take up to 90 days for the data to be completely deleted by Fitbit. The fitbit user name and the mail address will also be entered in the SML.

The diary with SoSci-Survey is pseudonymized, i.e. no identifying data such as name, date of birth, etc. is collected. Instead, a code is used. All data is stored on a server at sciCORE (Center for Scientific Computing at the University of Basel), without identifying characteristics of the respective computer (IP address, time stamp). Secure data transmission with SSL. The phone number is used to send the SMS every evening of the two periods (run-in, treatment). There is a list linking the SoSci-code (serial nr) with the phone number. Access to this list is highly protected and will be deleted after LPLV as soon as the data is saved in the Studiendatenbank MCN . The SoSci-code will be entered in the SML.

Telephone screening is performed prior to assignment of the study participant number. The telephone screening document is encrypted with a separate random numeric code generated in the project-specific administration database. The telephone screening form does not contain any other identifying information. For persons signing the informed consent, this code is also entered into the SML. For individuals who do not sign the consent form, the telephone screening will be kept in anonymous form. Some of the questions in the telephone screening relate to the feasibility of the research project.

All codes are listed in the electronic combined Screening, Enrolment and Identification Log. This Subject Master List (SML) will be kept under lock and key. Access to the participant identification list will have only authorized study team members. After the monitoring close out visit the study documentation will be transferred to the archive of the Research Platform MCN as part of the ISF (s. 12.3). As representatives of GeneGuide AG, Prof. Dominique de Quervain and Prof. Andreas Papassotiropoulos can authorize access to the Subject Master List. As the principal investigator for the project and as representative of the University of Basel, Dr. Christiane Gerhards can also authorize access to the Subject Master List. GeneGuide (CRO) has the overall responsibility for the conduct of the study at the study site (University of Basel).

12.3.2 Data Security and Access

Trial and participant data will be handled with uttermost discretion and is only accessible to authorized personnel who require the data to fulfil their duties within the scope of the study. On the eCRFs and in the Studiendatenbank MCN, participants are only identified by a unique participant number, other codes (Fitbit username, serial nr, telephone screening code), and additionally the age can be noted (see chapter 12.3.1).

All Source Data are kept under lock and key. All electronic systems used in this study are password protected, to ensure that only authorized persons can enter the system to view, add or modify data according to their permissions within the scope of the study. Software running on servers of the University of Basel, especially Studiendatenbank-MCN, SoSci-Survey and the electronic SML (encrypted) are additionally protected via the VPN (2-factor authentification) of the university.

The Principal Investigator will permit study related monitoring visits, audits, EC reviews, and regulatory inspections, and provide direct access to all source data.

12.3.3 Data Management Systems, Back-up

SecuTrial® (eCRF) runs on a server maintained by the IT-department of the University Hospital Basel. The data management group at the Clinical Trial Unit (CTU) of the University Hospital Basel implements the eCRF. The user administration and user training is performed by the CTU according to predefined processes. Back-up of eCRF data is performed according to the processes of the IT-department of the University Hospital Basel. SecuTrial® has a detailed audit trail so that every relevant change is traceable and assignable to the person who made it.

Studiendatenbank-MCN and SoSci-Survey run on servers maintained and backed up by sciCORE of the University of Basel. The data manager of the Divisions of Molecular and

Cognitive Neuroscience is responsible for the implementation of the tasks, for the user administration and for providing user training.

Studiendatenbank-MCN has a detailed audit trail, changes of the data or access rights are traceable and assignable to the person who made it. Backups of the Studiendatenbank-MCN database are performed daily by sciCORE. Additional database backups are performed by the data manager at key stages e.g. when the data collection is finished and are stored on the same secure file-system as the logfiles.

The *source data (including SoSci-Survey- and Fitbit-logfiles*) are stored in a read-only folder on a file-system with restricted user access maintained and backed up by the IT department. Metainformation on the source data (SHA-1 hashes (checksums), file id, file modification time, path to the file on the file-system, date and time information logged in the log-file) is stored in the Studiendatenbank-MCN to enable verification of data originality. Source data that is necessary for data analysis is read into Studiendatenbank-MCN data tables ("lists"), transformed as necessary and finally stored as text-files with time-stamps in Studiendatenbank-MCN, where they will be available for download by the trial statistician.

12.3.4 Preparation for data analysis

As a first step, we evaluate for each subject and visit if all expected files or entries are available and stored in the correct sequence (via the time-stamp). Deviations are documented in the Studiendatenbank-MCN. Before relevant content of the source data is read into data tables, we further validate if the file-content corresponds to the expected data format. Within Studiendatenbank-MCN we track for each subject, visit and task information on deviations (such as missing data, data inconsistencies). Deviation information is carried forward into the dataset for statistical analysis. The data relevant for the analysis are extracted and prepared for export for statistical analysis. The principal investigator or his designee reviews data entered or uploaded in the Studiendatenbank-MCN study folder. Once all queries have been clarified, the principal investigator requests the database lock. Only after the database lock, the master randomization list, which is stored in secuTrial for randomization of the participants during data capture, is requested from the DKF data manager. The master randomization list is stored in a separate folder in the Studiendatenbank-MCN and then the file is released to the study statistician for statistical analysis (see 11.4.1).

In the case of the Fitbit data, pseudonymization (removal of personal information and assignment of the participant number) and reduction to the data relevant for the study are performed first. The exact procedure is described in a SOP.

12.3.5 Analysis and Archiving

The eCRF (secuTrial®) will be locked after all data was monitored and all raised queries have been resolved. Data is exported and transferred to the investigator by the CTU according to internally defined processes. The exported data will be archived by the data manger MCN in the Studiendatenbank-MCN (see 12.3.3).

The data collected by direct data entry by the participants during the run-in and the treatment period (SoSci) and the sleep tracking, HRV and HR data (Fitbit) are stored and archived as original data in the Studiendatenbank-MCN in a read-only folder on the university file system.

The data analysis will be performed with R.

12.3.6 Electronic and central data validation

Data is entered into the eCRF and will be validated for completeness and discrepancies automatically. An audit trail system maintains a record of initial entries and changes (reasons for changes, time and date of changes, user identification of entry and changes).

An independent monitor from the CTU Basel will review the data entered into the eCRF. The monitor will raise queries using the query management system implemented. The Principal Investigator or his designee have to respond to the query and confirm or correct the corresponding data. Thereafter the monitor can close the query.

12.4 Monitoring

The aim of monitoring is to evaluate the progress of the study, to verify the accuracy and completeness of CRFs, to ensure that all protocol requirements, applicable local authority regulations and investigator's obligations are being fulfilled, and to resolve any inconsistencies in the study records. The Principal Investigator will allow the Sponsor to periodically monitor at mutually convenient times during and after the study and they will answer questions during monitoring. The database documentation for this project will be disclosed to the Sponsor.

Monitoring will be provided by the CTU Basel (see contract). Monitoring will be performed according to the separate monitoring plan. The SOP for Monitoring will be disclosed to the Sponsor. The certificate of Quality Assurance will be provided to the Sponsor.

12.5 Audits and inspections

Audits by the CEC or the Sponsor or inspections by regulatory authorities during study or after study closure may be performed to ensure proper study conduct and data handling procedures according to ICH-GCP guidelines and regulatory requirements. Audits and inspections may include verification of all source documents, check of CRFs and site files and a visual inspection of the study site. Direct access to all documents and places at study site is mandatory. In case of an announced audit or inspection immediate notification of the respective other party is necessary.

The investigators will permit study related monitoring visits, audits, IEC reviews, and regulatory inspections, and provide direct access to all essential documents including the source data. Essential documents permit individually and collectively an evaluation of the conduct of a study and the quality of the data produced. Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial.

All involved parties must keep the participant data strictly confidential.

12.6 Confidentiality and Data Protection

Participant's confidentiality will be maintained at all times. Personnel from the Sponsor, CTU Basel, from the Department of Clinical Pharmacology and Toxicology (USB), clinical laboratory (USB), from regulatory authorities and members of IEC are obliged to respect medical secrecy and to refrain from divulging the participant's identity or any other personal information they might fortuitously be aware of.

The participants name or other personal identifiable data are not recorded in the eCRF.

Direct access to source documents will be permitted for purposes of monitoring (chapter 12.4), audits and inspections (chapter 12.5). People who will have access to protocol, dataset, statistical code, etc. during and after the study (publication, dissemination) will be declared.

13 PUBLICATION AND DISSEMINATION POLICY

A detailed description of the publication policy is documented in the separate investigators agreement.

14 FUNDING AND SUPPORT

This study is funded by Zeller Medical AG

15 INSURANCE

The Sponsor declares to have taken out an insurance policy for the total study length, covering the participants in respect of the risks involved in this study. In case of injury or disability deriving from participation in the study, the subject is requested to inform without delay the investigator responsible for the study.

The Sponsor will take out reasonable third-party liability insurance cover in accordance with all local legal requirements. Details are covered in the investigator agreement.

The Sponsor will arrange for Participants participating in this study to be insured against financial loss due to personal injury caused by the pharmaceutical products being tested or by medical steps taken in the course of the study.

In the event of a Participant suffering any deterioration in health or well-being or any harmful susceptibility or toxicity caused by participation in the study, the Sponsor will provide adequate compensation without regard to the question of legal liability, based on the policy of the Sponsor. The issue of legal liability will be resolved between the Investigator and the Sponsor after the Sponsor had provided adequate compensation to the subjects.

16 REFERENCES

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16.2 References

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