Clinical Study Protocol

Randomized placebo-controlled phase II cross-over study on the influence of fampridine on working memory in mild to moderate depression

Study-ID: FamD_2025

Study Type	Clinical Trial with Investigational Medicinal Product (IMP)
Study Categorization	Risk category B according to ClinO
Study Registration	NCT0675178 HumRes66269
Study ID	FamD_2025
Sponsor	Research Cluster Molecular and Cognitive Neurosciences UNIVERSITY OF BASEL Birmannsgasse 8, 4055 Basel Contact persons: Prof. Dominique de Quervain, MD Co-Director Research Cluster Molecular and Cognitive Neurosciences Director Division of Cognitive Neuroscience E-Mail: dominique.dequervain@unibas.ch Phone: +41 61 207 02 37 Prof. Andreas Papassotiropoulos, MD Co-Director Research Cluster Molecular and Cognitive Neurosciences Director Division of Molecular Neuroscience E-Mail: andreas.papas@unibas.ch Phone: +41 61 207 05 99 Prof. Annette Brühl, MD Chief physician Zentrum für Affektive -, Stress- und Schlafstörungen & Zentrum für Alterspsychiatrie, Universitäre Psychiatrische Kliniken (UPK) Basel E-Mail: annette.bruehl@upk.ch Phone: +41 61 325 50 97
Principal Investigators	Dr. Christiane Gerhards, MD 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	Fampridine (Fampyra®)
Protocol Version and Date	Version 7 (dated 17/11/2025)

SIGNATURE PAGE

Study Title	Randomized placebo-controlled phase II cross-over study on the influence of fampridine on working memory in mild to moderate depression
Study number	NCT06751784 HumRes66269
Protocol Version	Version 7 (dated 17/11/2025)

The sponsors, the principal investigator, the trial statistician and the psychologist have approved the protocol and confirm hereby to conduct the study according to the protocol, current version of the World Medical Association Declaration of Helsinki, the ICH-GCP guidelines and the local legally applicable requirements.

The principal investigator has received the ICF and consider it appropriate for use.

Prof. Dominique de Quervain, MD
Sponsor

Basel 1.12.25
Place/Date

Signature

Prof. Andreas Papassotiropoulos, MD
Sponsor

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TABLE OF CONTENTS

STUDY SYNOPSIS

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Study Title	Randomized placebo-controlled phase II cross-over study on the influence of fampridine on working memory in mild to moderate depression
Study ID	FamD_2025
Protocol Version and Date	Version 6 (dated 06/10/25)
Trial Registration	The trial will be registered on clinicaltrials.gov and on HumRes.
Study Category and Rationale	Risk category B according to ClinO Art. 19 Fampridine is approved in Switzerland for treatment of gait problems in patients with MS. We will use fampridine for a different indication.
Clinical Phase	Phase II, proof of concept
Background and Rationale	Cognitive deficits, including working memory deficits, are often present in depression and there are currently no effective pharmacological treatments targeting working memory deficits. We have recently demonstrated that fampridine, a potassium channel blocker, can enhance working memory in healthy individuals with lower baseline performance, suggesting it may hold potential for addressing cognitive deficits in clinical populations. The primary aim of this study is to evaluate whether fampridine improves working memory performance in mild to moderate depression.
Objectives	The primary objective of this study is to evaluate if fampridine improves working memory in mild to moderate depression. Additionally, we aim to assess whether baseline working memory performance or subjective working memory deficits moderate the drug's effect. The secondary objectives are to assess the influence of fampridine on different working memory functions, attention, cognitive flexibility, affective working memory, and mood.

Outcomes	Primary outcome measure: • High-load working-memory performance: d' 3-back as assessed by a letter n-back task (Heck et al., 2022) Secondary outcome measures: • Reaction time (3-back hits) • d' 0-back (Heck et al., 2022) • Adaptive verbal working memory capacity test (SPAN), backward (SCHUHFRIED, 2024). • Verbal episodic memory performance (15 words) measured by immediate and delayed word-list recall task. Adapted from a subtest of the "Verbaler Lern- und Merkfähigkeits-Test" (VLMT; Helmstaedter/Lendt/Lux, 2001). • Accuracy in emotion recognition during the 0-back and 2-back conditions (Affective WM Task). • Depression (MADRS-s (Svanborg/Åsberg, 1994; Svanborg/Åsberg, 2001), self-rating version). • Tower of London (ToL) (Phillips et al., 2001; Shallice, 1982). • Intra-Extra Dimensional Set Shift (IED; Fray, Robbins & Sahakian, 1996). Adapted version for this study from GitHub (Sochat, V., 2016–2017). Lexical ability measured using a phonemic verbal fluency task (S-words). Adapted from a subtest of the Regensburger Wortflüssigkeits-Test (RWT; Aschenbrenner/Tucha/Lange, 2001). Safety outcome measures will be • The most common side effects of fampridine (headache, dizziness and gastrointestinal complaints) are recorded by the participants during the treatment periods at home and at the study centre at the visits using VAS. • AE-recording Assessment of potential confounders • Tiredness and motivation will be rated by the participant using visual analogue scales.
Study Design	Randomized, placebo-controlled, double blind, cross-over
Inclusion- / Exclusion Criteria	Inclusion criteria: • Male or female • Major depressive episode confirmed by the Mini-DIPS. Currently mild to moderate (MADRS: 7-30). • Normotensive. BP: 90/60mmHg - 140/90mmHg. Sufficiently treated hypertensive subjects will be included. • BMI: 19-34.9 kg/m^2 • Age: 18-55 years • Fluent in German • IC as documented by signature Exclusion criteria: • Contraindications to the class of drugs under study, e.g. known hypersensitivity or allergy to 4-aminopyridine • Use of potassium channel blockers within the last 3 months • treatment with OCT 2 inhibitors and -substrates (e.g. cimetidine, propranolol) • Treatment with antidepressants or antipsychotics within the last 3 months and throughout the study period • Current intake of psychoactive drugs (e.g. benzodiazepines, antidepressants, neuroleptics). • Other acute or chronic psychiatric disorder (e.g. psychosis, somatoform disorder, alcohol or drug abuse disorder)

	• Cognitive impairment (MoCA score < 25) • MADRS item 10 > 1 (suicidal tendency) • Risk of lowered seizure threshold (due to e.g. sleep deprivation, withdrawal of alcohol after alcohol abuse, hyponatraemia) • History of seizures • Acute cerebrovascular condition • Acute renal failure or severe renal insufficiency (creatinine clearance < 30 ml/min per 1.73 m^2) • Bradycardia < 50/min during clinical examination. • History of malignant cancers • Walking problems (e.g. due to dizziness) • Other clinically significant concomitant disease states (e.g. hepatic dysfunction, cardiovascular disease, diabetes, asthma) • Clinically significant laboratory or ECG abnormality that could be a safety issue in the study • Severe somatic or neurological comorbidities • Smoking including all nicotine containing smoking systems and devices (>10 cigarettes/units per day), failure to withstand a test day without craving, due to regular consummation pattern • Pregnancy or breast feeding. Intention to become pregnant during the study participation. • Known or suspected non-compliance • Inability to follow the procedures of the study, e.g. due to language or psychological problems of the participant • Participation in another study with an investigational drug within the 30 days preceding and during the present study • Enrolment of the investigator, his/her family members, employees and other dependent persons
Measurements and procedures	Assessment of efficacy: Performance in working memory and other tasks after repeated administration. The assessment will be performed 3 h after the last intake of 10 mg fampridine or placebo at the end of the 7.5-day treatment period (visit 3 and 5). Assessment of safety: • the most common side effects of fampridine via VAS by subjects, • recording Adverse Events.
Study Product / Intervention	Twice daily oral administration of 10 mg fampridine (Fampyra®) for 7.5 days with a wash-out period of at least 6.5 days
Control Intervention	Twice daily oral administration of placebo for 7.5 days
Number of Participants with Rationale	Total of 38 participants. We expect a drop-out rate of approx. 20%. There will be replacement of drop-outs until data for the primary outcome from 38 participants are completed. The estimation of N=38 is based on a power analysis assuming to detect a medium effect size (dz=0.5) of a drug with a power of 85% at two-tailed α=0.05 (see also chapter 3.3.4). Knowing that the sex-distribution of mild to moderate depression is about 2:1 (f:m), we aim for at least 13 male participants.
Study Duration	Study duration is estimated to be 12-15 months
Study Schedule	First-Participant-in (planned): Q2 2025 Last-Participant-Out (planned): Q2 2026

Principal Investigator	Dr. Christiane Gerhards, MD Division of Cognitive Neuroscience University of Basel Birmannsgasse 8, 4055 Basel Phone: +41 61 207 0244 Email: christiane.gerhards@unibas.ch
Study Center	Single-center. University of Basel Division of Cognitive Neuroscience Birmannsgasse 8, 4055 Basel
Statistical Considerations	Linear mixed models will be used to compare the effect of fampridine and placebo on primary and secondary outcome variables. In case of significant deviation from normality for the dependent variable, appropriate non-parametric methods will be used (see also chapter 11.4).
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.

ABBREVIATIONS

AE	Adverse Event
ALT	Alanine Aminotransferase
4-AP	4-aminopyridine
ASR	Annual Safety Repot
AST	Aspartate Aminotransferase
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
CIPS	Collegium Internationale Psychiatriae Scalarum (Internationale Skalen für Psychiatrie)
CTCAE	Common Terminology Criteria for Adverse Events
ClinO	Ordinance on Clinical Trials in Human Research
d' 2-back	d' 2-back as assessed by a letter n-back – a measure of high-load working-memory performance
DIPS	Diagnostisches Interview bei psychischen Störungen
DKF	Departement klinische Forschung
ECG	Electrocardiography
EKNZ	Ethikkommission Nordwest- und Zentralschweiz
eCRF	Electronic Case Report Form
FADP	Federal Act on Data Protection
FOPH	Federal Office of Public Health
FU	Follow-up
GCP	Good Clinical Practice
Gf	Fluid Intelligence
GGT	Gamma-Glutamyltransferase
GMP	Good Manufacturing Practice
GWAS	Genome-wide association studies
HAMD	Hamilton Depression Rating Scale
Ho	Null hypothesis
H1	Alternative hypothesis
HAMD	Hamilton Depression Rating Scale
hCG	Human choriongonadotropin
HR	Heart Rate
HRA	Federal Act on Research involving Human Beings
HumRes	Informationsplattform des BAG zur Humanforschung in der Schweiz, www.humanforschung-schweiz.ch
IC	Informed Consent
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IED	Intra-Extra Dimensional Set Shifting task
IIT	Investigator-initiated trial
IMP	Investigational Medicinal Product

IR	Immediate Release
Kv	Voltage-gated potassium channel
LabKey®	Data management software provided by LabKey, https://www.labkey.com
LDH	Lactatdehydrogenase
LPLV	Last Patient/Participant Last Visit
LTP	Long-Term-Potentiation
MADRS	Montgomery Asberg Depression Rating Scale
MDE	Major Depressive Episode
MRHD	Maximum Recommended Human Dose
MS	Multiple Sclerosis
MTI	Maximum Tolerated Imbalance
MoCA	Montreal Cognitive Assessment
OCT 2	Organic Cation Transporter 2
PANAS	Positive and Negative Affect Schedule
PI	Principal Investigator
PR	Prolonged Release
RWT / S-words	Regensburger Wortflüssigkeits-Test / Lexical ability measured by a phonemic verbal fluency test (S-words)
SADRS	Serious Adverse Drug Reaction
SAE	Serious Adverse Event
SD	Source Data
SDV	Source Data Verification
SOP	Standard Operating Procedure
SPAN	Adaptiver Arbeitsgedächtnistest, SCHUHFRIED
SR	Sustained Release
SUSAR	Suspected Unexpected Serious Adverse Reaction
Studiendatenbank-MCN: Is a local database for study data and is implemented using LabKey®	
TMF	Trial Master File
VAS	Visual Analog Scale
VLMT	Verbaler Lern- und Merkfähigkeits-Test
15 words	Verbal episodic memory performance (15 words) measured by immediate and delayed word-list recall task.
WI	Working Instruction

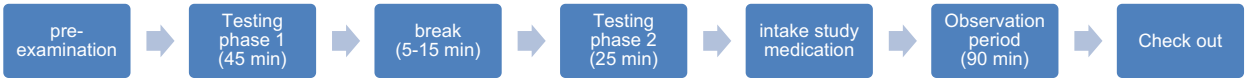
SUMMARY OF THE REVISION HISTORY IN CASE OF AMENDMENTS

Version Nr	Version date	Chapter	Description of changes	Reason for the change
1.0	01/03/2022			Initial version
2.0	13/01/2025	9.3.1 9.3.2	Addition of the responsibilities of the members of the study team. More detailed description of the diagnosis of depression. Clarification of the procedure if a patient is diagnosed with severe depressive symptoms during screening or if a patient develops severe depressive symptoms during participation in the study.	Revision according to the conditions of the EKNZ (1st directive, 17 December 2024):
		11.2, 3.8	Clarification of the description of the determination of the sample size	
2.1	16/01/2025	6.2.1, 6.2.2, 3.2	Clarification of the description of the IMP-kits New authorization holder for Fampyra® in Switzerland: Merz Pharma (Schweiz) AG, Allschwil	corrections
3.0	31/03/2025	9.3.4	Safety FU after regular completion of study participation or after discontinuation of study participation.	FIR Swissmedic, 31.03.2025
		7.1.1, 9.3.1	M.I.N.I. adult replaced by Mini-DIPS for depression diagnosis.	a more suitable tool for our purposes
		5.2, 9.2.2	MADRS self-assessment (instead of the external assessment version) at visits 2-5.	Improvement of comparability between visits, more practical
		9.2.2, 9.3.1 References	Additional references to cognitive tests.	Additional sources to those already mentioned
4.0	24/04/2025	4.2, 5.2, 9.2.2, 12.3.2., 12.3.3, References	Addition of affective working memory task	Assess emotion recognition, which is not yet included in the task battery
5.0	14/07/2025	Synopsis (outcomes), study schedule, 5.2, 9.2.2, 12.3.2, references	Visits 2 and 4: VAS most common side effects, motivation and tiredness new also after completion of psychological testing.	Comparability between the four test days (visits 2–5)
			Digit Span Task replaced with an adaptive verbal working capacity test (SPAN, SCHUHFRIED, 2024)	The adaptive design allows for a more accurate assessment of working memory capacity.
			Precisions concerning descriptions and references of some outcomes.	--
6.0	06/10/2025	Synopsis (in-/exclusion criteria), Study Schedule, 3.8, 7.1.1, 9.3.1	Increase of inclusion age Additional screening for cognitive impairment Correction of the MADRS Score from 0 to 1 as an exclusion criterion	Higher recruitment success Assessment of cognitive function Avoid unnecessary exclusion
7.0	17/11/2025	Synopsis (in-/exclusion criteria), 3.8, 7.1.1, 9.3.1	Change of inclusion criterion MADRS: 7-19 to MADRS: 7-30.	Higher recruitment success

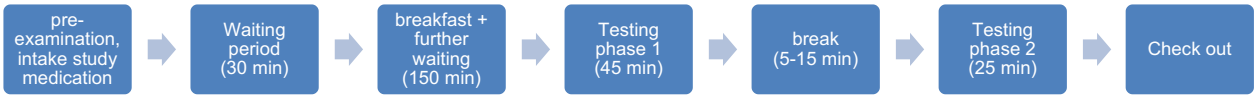
STUDY SCHEDULE

	Duration		**Treatment period 1** (7.5 days)			**Wash-out period** min. visit 3 +7 and max. visit 3 + 28 days	**Treatment period 2** (7.5 days)			**Safety FU**
Visit		**Visit 1**	**Visit 2**		**Visit 3**		**Visit 4**		**Visit 5**	**Visit 6**
Description		Screening	Test day 1	P/V or V/P	Test day 2	Wash-out period	Test day 3	V/P or P/V	Test day 4	FU
Day		within 28 days before Visit 2	1		8		15-36		22-43	24-48
Screening • Written IC, assignment of the subject number • Personal, family and medication history • Psychiatric interview Mini-DIPS • MADRS external assessment, HAMD, PANAS • MoCA • Subjective working memory deficits (VAS), sociodemographics • Physical examination, ECG, laboratory analysis, drug-drug interaction, vital signs	ca. 2 h	x								
Treatment periods • Electronic intake diary • Electronic AE-diary (VAS headache, gastrointestinal discomfort, dizziness)	7.5 days			x				x		
Wash-out period (min. visit 3 +7 and max. visit 3 + 28 days)	1-4 weeks					x				
Test days										
Pre-examination test days • Pregnancy test (Visits 2 and 4) • Sleep duration last 24 hours • AE recording, new medications • VAS headache, gastrointestinal discomfort, dizziness • VAS tiredness, motivation • MADRS-s	15 min		x		x		x		x	
Assignment of the randomization number	5 min		x							
Intake of study medication	5 min		x	x	x		x	x	x	
Waiting time for participants at the study centre: Visits 2 and 4: 90 min observation time after first intake of study medication at the beginning of the treatment periods Visits 3 and 5: 3 hours until final testing. Incl. continental breakfast 30 min after intake of study medication	90 min resp. 3 h		90 min		3 h		90 min		3 h	
Before start of testing • AE recording • VAS headache, gastrointestinal discomfort, dizziness, • VAS tiredness, motivation	5-15 min		(x) (as part of pre-examination)		x		(x) (as part of pre-examination)		x	
Testing Phase – part 1 *(pauses between the tasks: 3-5 min)* • n-back (15 min) • SPAN (10 min) • IED (10 min) • S-words (5 min) • Word-list learning and IR (5 min)	45 min		x		x		x		x	
Break	15 min		x		x		x		x	
Testing Phase – part 2 • Word List SD (5 Min) • Tower of London (ToL) (10 min) • Affective WM Task (15 min)	30 min		x		x		x		x	
After testing phase • AE-recording • VAS headache, gastrointestinal discomfort, dizziness, • VAS tiredness, motivation	5 min		x		(x) (as part of final examination)		x		(x) (as part of final examination)	
Final Examination • AE recording • VAS headache, gastrointestinal discomfort, dizziness • VAS tiredness, motivation	10 min		x		x		x		x	
Follow-up • Completion of AE documentation / occurrence of new AEs since visit 5? • Well-being of the test person • Completion of study participation	5-15 min									x

Visit 2/4 (testing day 1/3)



Visit 3/5 (testing day 2/4)



1 STUDY ADMINISTRATIVE STRUCTURE

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2 ETHICAL AND REGULATORY ASPECTS

The decision of the EKNZ (CEC) and Swissmedic (CA) concerning the conduct of the study will be made in writing to 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

Before recruitment starts, the study will be registered in the WHO-recognized primary registry of the U.S. National Library of Medicine (https://clinicaltrials.gov).

In addition, the study will be registered in the Swiss National Clinical Trials Register (HumRes) in German, also before the start of the study.

2.2 Categorization of study

This clinical trial comes under Category B as fampridine is authorized in Switzerland and it is used in an indication different from that specified in the prescribing information.

2.3 Competent Ethics Committee (CEC)

The principal investigator will obtain approval from the Competent Ethics Committee (EKNZ) before the start of the clinical trial.

No changes are made to the protocol without prior principal investigator and EKNZ 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 for the first visit and for completion, premature termination, interruption and resumption of the clinical trial (ClinO, Art. 38)

The following notifications have to be made by the principal investigator to the EKNZ.

- The first visit of the first participant (FVFP) in the clinical trial within *30 days*.
- The *completion of the study* within *30 days*. Completion of a clinical trial is marked by the last participant's final follow-up visit.
- The *discontinuation, interruption* or resumption of the clinical trial within 15 days. In the notification, the reasons for the discontinuation, interruption or resumption must be stated. An interruption lasting for more than two years is considered to be a premature termination.
- The *summary final report* shall be submitted within one year after completion or premature termination of the clinical trial.

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

The following notifications and reporting have to be made by the principal investigator to the 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.
- Report containing a list of adverse reactions as specified in Articles 40–41 (SAEs, SUSARs) *once a year*. On this basis, the investigator shall submit a report on their severity and causal relationship to the intervention, and on the safety of participants, and shall inform the ethics committee about the general progress of the clinical trial (*DSUR, see chapter 10.4.5*).

2.4 Competent Authority (CA)

The sponsor will obtain approval from Competent Authority (Swissmedic) before the start of the clinical trial.

No changes are made to the protocol without prior sponsor and Swissmedic 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.

2.4.1 Notification and reporting for the first visit and for completion, discontinuation, interruption and resumption of the clinical trial (ClinO, Art. 38)

The following notifications have to be made by the sponsor to Swissmedic:

- The first visit of the first participant (FVFP) in the clinical trial within *30 days*.
- the *completion of the study* within 30 days. Completion of a clinical trial is marked by the last participant's final follow-up visit.
- the *discontinuation, interruption* or resumption of the clinical trial within 15 days. In the notification, the reasons for the discontinuation or interruption must be stated. An interruption lasting for more than two years is considered to be a premature termination.
- the *summary 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 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.
- Report containing a list of adverse reactions as specified in Articles 40–41 (SAEs, SUSARs) *once a year*. On this basis, the investigator shall submit a report on their severity and causal relationship to the intervention, and on the safety of participants, and shall inform the ethics committee about the general progress of the clinical trial (*DSUR, see chapter 10.4.5*).

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 EKNZ and Swissmedic will receive annual safety and interim reports and they will be informed about study stop/end in agreement with local requirements. The EKNZ will also be informed annually about the general progress of the clinical trial.

The safety report can be written and submitted in the format of the Development safety update report (DSUR). See chapter 10.4.5.

2.6 Declaration of interest

The authors certify that they have no intellectual, financial or proprietary conflict and are independent.

2.7 Patient Information and Informed Consent

The investigator explains to each subject 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 subject will be 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 members, friends, their treating physicians or other experts before deciding about their participation in the study. Enough time is given to the subjects.

The subjects are informed that authorized individuals may examine their medical records.

All subjects are given a subject information sheet and a consent form describing the study and providing sufficient information for the subjects to make an informed decision about their participation in the study.

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

The subject should read, understand, and voluntarily agree before signing and dating the informed consent form, and is given a copy of the signed document. The consent form is signed and dated by the

subject and the PI (or her/his designee). The signed consent form it is retained as part of the investigation records.

For details about the recruitment and inclusion procedure see chapter 7.2.

Incidental findings during screening procedure (ECG, laboratory analysis) will be reported to the study participants. We will recommend further support and organize it if needed.

2.8 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.

The investigator has appropriate knowledge and skills in the areas of data security and data protection or is able to ensure compliance by calling in appropriate expertise (Art. 6, ClinO).

Individual subject medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited. Subject confidentiality is ensured by the assignment to each subject a unique subject identification number. For the pseudonymization and coding in this project see chapter 12.3.1.

For data verification purposes, authorized representatives of the sponsor, 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.

2.9 Premature termination of the study

The sponsor 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;
- early evidence of benefit or harm of the experimental intervention.

If the study is terminated earlier than planned, the investigator notifies the EKNZ (CEC) and Swissmedic (CA) according to the provisions of ClinO Article 38 (see chapters 2.3.1 and 2.4.1).

2.10 Protocol amendments

Substantial amendments are only implemented after approval of the EKNZ and Swissmedic 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 EKNZ and Swissmedic. Such deviations shall be documented and reported to the sponsor, the EKNZ and Swissmedic as soon as possible.

All non-substantial amendments are communicated to Swissmedic (CA) as soon as possible and once a year to the EKNZ (CEC) with the safety report / general study progress report of the clinical trial.

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

2.10.1 Reporting to the Competent Ethics Committee (CEC)

Substantial amendments: The following changes are considered to be substantial modifications and have to be reported to the EKNZ by the principal investigator (ClinO, Art. 29):

- modifications affecting the participants' safety and health, or their rights and obligations;
- modifications to the protocol, and in particular modifications based on new scientific findings which concern the trial design, the method of investigation, the endpoints or the form of statistical analysis;
- a change of trial site, or conducting the clinical trial at an additional site;
- a change of sponsor, coordinating investigator or investigator responsible at a trial site;
- the extension of a deadline in accordance with Articles 23, 23*a* and 50; in the application to the ethics committee, the investigator shall indicate whether the application documents are still up-

to-date, particularly with regard to the scientific relevance of the question; if this is not the case, the investigator shall submit updated application documents.

The investigator shall submit to the ethics committee any application documents specified in Annex 3 (ClinO) which are affected by the modification. At the same time, the investigator shall provide information on the reasons for the modification.

In emergency conditions, deviations from the protocol for the protection of the rights, safety and well-being of the trial subjects must be documented and reported to the EKNZ within 7 days; without the prior approval of the sponsor and the EKNZ. In this report, the safety and protective measures taken and the circumstances that made them necessary have to be described. (ClinO, Art. 37)

Other modifications must be notified to the ethics committee in the annual safety report specified in Article 43. (ClinO, Art. 29)

2.10.2 Reporting to the Competent Authority (CA)

Substantial amendments: The following changes are considered to be significant and have to be reported to Swissmedic 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 Swissmedic 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. Swissmedic shall reach a decision within 30 days after receipt of the complete application documents affected by the change.

In emergency conditions, deviations from the protocol for the protection of the rights, safety and well-being of the trial subjects must be documented and reported to Swissmedic within 7 days; without the prior approval of the sponsor and Swissmedic. In this report, the safety and protective measures taken and the circumstances that made them necessary have to be described. (ClinO, Art. 37)

Other modifications which affect the documents submitted to Swissmedic must be notified to Swissmedic as quickly as possible. (ClinO, Art. 34)

3 BACKGROUND AND RATIONALE

3.1 Background and Rationale

In a recent study we investigated the potential cognitive benefits of fampridine for working memory enhancement, leveraging a genome-guided drug repurposing approach (Papassotiropoulos et al., 2024). In this double-blind, randomized, placebo-controlled crossover trial with 43 healthy young adults, fampridine's effect on working memory was assessed after 3.5 days of repeated administration. Independently of baseline cognitive performance, no significant main effect was observed. However, lower baseline performance was associated with higher working memory performance after repeated intake of fampridine compared to placebo (ρ=-0.37, P=0.014, n=43). Analysis with the Jonckheere-Terpstra test confirmed this observation: a significant ordered effect of study medication after repeated administration across participants with low (i.e., low tercile), medium (i.e., middle tercile), and high (i.e., high tercile) baseline working memory performance was detected (z=-2.24, r=-0.34, P=0.025, n=43). Post-hoc tests for each tercile separately revealed a significant main effect of the study medication for the low performance group, with fampridine resulting in better working memory performance compared to placebo (r=0.54, P=0.035, n=15; Figure 3). No significant main effect of study medication was found in the medium (r= 0.17, P=0.59, n=13) or high baseline performance group (r=-0.40, P=0.14, n=15; Figure 3).

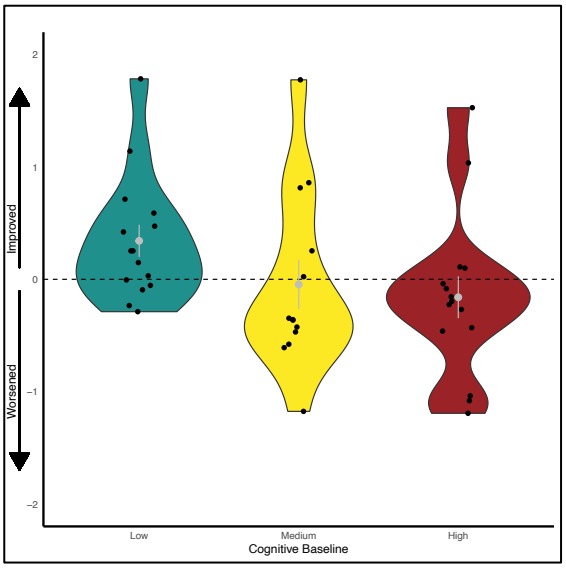

Figure 1. Analysis of the drug effect on the primary outcome per cognitive baseline group, violin plots. Y-axis: individual difference (fampridine – placebo) in d' after repeated administration; values above 0 represent improvement under fampridine, values below 0 represent decrease under fampridine. X-axis: baseline working memory performance (d') stratified in three performance groups (i.e., low, medium, high terciles). Gray dots and vertical lines represent primary outcome measure means and standard errors of the means, respectively.

Additionally, fampridine significantly lowered (P=0.027) the resting motor threshold (rMT), an indicator of cortical excitability, suggesting a neural mechanism linking potassium channel modulation to cognitive function. Importantly, lower rMT was associated with higher baseline working memory performance under placebo conditions (ρ=-0.38, P=0.019).

The findings suggest that fampridine enhances working memory in individuals with lower baseline performance, highlighting its potential therapeutic value in addressing cognitive deficits in psychiatric populations. The study underscores the importance of considering baseline cognitive abilities in pharmacological interventions and sets the stage for future trials in clinical populations with psychiatric disorders, such as depression. Importantly, working memory deficits are often observed in depression (Nikolin et al., 2021)

3.2 Investigational Product (treatment) and Indication

Active study medication consists of a single tablet of fampridine 10mg sustained release (SR) formulated for oral administration (Fampyra®). Authorisation holder in Switzerland:

Merz Pharma (Schweiz) AG
Hegenheimermattweg 57, 4123 Allschwil
Handelsregister: Kanton Basel-Landschaft CHE-101.213.674
Web: https://www.merz.ch/

Fampridine is a potassium channel blocker indicated to improve walking in patients with multiple sclerosis. This was demonstrated by an increase in walking speed (Jeffery and Pharr 2010).

Fampridine, whose active ingredient is prolonged release 4-aminopyridine (4-AP), is a broad-spectrum voltage-dependent potassium channel blocker, which can increase action potential propagation in demyelinated axons (Chwieduk and Keating, 2010). The compound, which is lipid soluble, crosses the axon membrane, blocking the exposed potassium channels; this decreases potassium loss, increases action potentials and conduction, and promotes synaptic and neuromuscular transmission of nerve signals (Chwieduk and Keating, 2010). Prolonged release (De Giglio, De Luca et al., 2019) Fampridine is completely absorbed from the gastrointestinal tract and this more slowly than immediate release (IR) fampridine (Fernandez, Berger et al., 2012). This decreases peak plasma concentration by 50%, which consequently reduces dose-related adverse effects (Fernandez, Berger et al., 2012). SR fampridine should be administered under fasting conditions: administration with food increases peak plasma concentration, leading to increased risk of adverse effects (Weir, Torkin et al., 2013), see also prescribing information of Fampyra®[1].

Apparent first-order terminal elimination half-life $t_{1/2}$ of fampridine is 4.62 h (5.2 to 6.5 h) (Henney, Faust et al., 2011).

3.3 Preclinical Evidence

In rats, fampridine was found to improve short-term memory performance of old, but not young, animals (Barnes, Eppich et al., 1989).

Further it was found to be able to enhance memory as demonstrated in a 72-h retention of passive avoidance task (Haroutunian, Barnes et al., 1985). The effect of fampridine was also investigated in a mouse model of HIV-1 encephalitis. These mice show impaired spatial memory in radial arm water maze tests. Electrophysiology studies revealed a reduction of long-term potentiation (LTP) in the CA1 region of the hippocampus. Systemic administration of fampridine blocked HIV-1-associated reduction of LTP and improved animal performance in the radial arm water maze (Keblesh, Dou et al., 2009).

3.4 Clinical Evidence to Date

Fampridine was investigated in patients with Alzheimer disease. In one study it partially reversed memory deficits (Wesseling, Agoston et al., 1984). In a second study, results indicated no significant difference in total Alzheimer Disease Assessment Scale Scores (Davidson, Zemishlany et al., 1988).

In patients with Multiple Sclerosis, fampridine was investigated in several clinical studies. MS can cause progressive walking impairments, which are improved by Fampridine. Through a blockade of potassium channels, fampridine restores nerve impulse conduction (Tseng, Li et al., 2016), facilitates and enhances synaptic transmission, retards the postsynaptic action potential repolarization (Kasatkina, 2016), and increases the release of acetylcholine (Lugaresi, 2015).

Fampridine also improves cognitive functions in MS. In a clinical trial MS patients receiving a maximum dose of 0.7 mg/kg of body weight per day achieved significantly higher scores in attention span, verbal fluency, planning and graphics and constructive motion (Arreola-Mora, Silva-Pereyra et al., 2019). Another study showed improvement in information processing speed in MS patients receiving 10 mg twice daily for 12 weeks (De Giglio, De Luca et al., 2019).

These findings are consistent with another study, where 40 mg/day led to improvements in attention and concentration in MS patients (Smits et al., 1994). In contrast, no cognitive improvement was reported with a dose of 30–32 mg/day (Rossini et al., 2001; Romani et al., 2004). Considering a long period of administration (9–12 months) at a dose of 20 mg per day, a beneficial effect on both processing speed and working memory has been observed (Pavsic, Pelicon et al., 2015).

3.5 Dose Rationale

The maximum recommended dose of fampridine SR for the treatment of MS is 10 mg twice daily (approximately 12 hours apart) without food (see prescribing information Fampyra®).

[1] https://www.compendium.ch/it/product/1422958-fampyra-ret-tabl-10-mg

In healthy individuals a single dose of fampridine SR 10 mg achieved a mean maximum plasma concentration (C_{max}) of 21.6 ± 3.89 ng/ mL, with a mean time to maximum plasma concentration (T_{max}) of 3.2 ± 1.5 hours (Smith, Swan et al., 2010).

Fampridine is lipid soluble and able to pass the blood–brain barrier (Lemeignan, Millart et al., 1984) and therefore able to reach structures of the prefrontal cortex involved in working memory functions. Cerebrospinal fluid levels of fampridine peak 30–60 min following peak serum concentration (Donovan, Halter ., 2000).

Previous studies examining long-term use of fampridine reported pro-cognitive effects with 10 mg fampridine SR twice daily (see 3.4).

3.6 Explanation for choice of placebo

Placebo is chosen to assess effects of fampridine on memory processes in a cross-over design. Placebo consists of an identically looking tablet (for pharmaceutical ingredients see chapter 8.1.2.) manufactured by

Losan Pharma GmbH
Otto-Hahn-Straße 13
79395 Neuenburg am Rhein
Germany

Placebo is chosen here as main comparator. One reason for this choice is that it is scientific standard and the best method to control for unspecific potentially confounding effects. The inclusion of a placebo in this study design acts as a control measure, aiding in the accurate evaluation of treatment efficacy by creating a comparative baseline against which the effects of the investigational drug can be assessed within the same individuals. This approach is particularly relevant in within-subject designs, as each participant serves as their own control, minimizing variability and enhancing the sensitivity of the study to detect true treatment effects. Moreover, employing a placebo in such studies aligns with ethical considerations by ensuring rigorous evaluation of the investigational drug's effectiveness while minimizing potential bias. The use of a placebo within a within-subject design thus contributes to robust and credible findings by allowing for a more precise understanding of the specific effects of the drug being studied in comparison to baseline responses observed in the absence of active intervention.

3.7 Risks / Benefits

Although 10 mg fampridine twice a day for a short period is generally well tolerated (Smith, Swan et al., 2010) (March and Cardi 2009), and a recent study in healthy participants applying fampridine (10 mg) twice daily over 3.5 days showed no relevant adverse events (Papassotiropoulos et al., 2024), subjects will be informed of the possible risks associated with taking fampridine. Specific risks that participants need to be aware of are listed below:

- The most frequently occurring AEs included dizziness, headache, insomnia and gastrointestinal discomfort. No discontinuations due to AEs were reported in a study with healthy subjects after administration of a single 10 mg dose (Smith, Swan et al., 2010).
- Fampridine is excreted primarily unchanged in the urine (Blight and Henney 2009). Tolerability and incidence of AEs appear to be dose related, occurring more frequently at plasma concentrations > 100 ng/mL (Van Diemen, Polman et al., 1993). We will therefore exclude subjects with renal impairment to avoid higher plasma levels (see chapter 3.5). To assess renal impairment, we will perform creatinine and uric acid levels in plasma.
- Fampridine is excreted primarily through the organic cation transporter 2 (OCT 2). OCT 2 inhibitors or substrates (e.g. Cimetidine, Carvediol, Propanolol and Metformin) may inhibit elimination of fampridine and increase the risk of adverse events. Subjects with concomitant use of OCT 2 – inhibitors are excluded from participation. In subjects with concomitant use of OCT 2-substrates the potential of drug-drug interaction with fampridine will be checked individually. In case of an confirmed increased risk the subject will be excluded from participation.
- Fampridine can cause seizures. We will exclude people with a history of seizures and subjects at risk of lowered seizure threshold due to e.g. sleep deprivation or alcohol withdrawal after alcohol abuse or hyponatraemia (by e.g. drug- induced SIADH).

- Despite the fact that fampridine at therapeutic and supratherapeutic doses is not associated with QT prolongation in healthy subjects (March and Cardi 2009) we will exclude subjects with any clinically significant ECG abnormalities or history of cardiovascular disease.
- Fampridine might cause nausea and dizziness and have an additive effect with alcohol. Participants will be advised to avoid alcohol, illegal substances, and any medication (especially psychoactive) due to possible interactions during the course of the study.
- Subjects will be warned about engaging in activities requiring mental alertness, such as driving a car or operating appliances, machinery, etc. Driving a motor vehicle or operating machinery is not allowed within 24 hours of intake and subjects have to agree to use public transportation or taxi after medication intake for this time period.
- In several in vivo and in vitro studies there was no evidence of drug-related carcinogenicity or mutagenicity (prescribing information Fampyra®).
- For fampridine, no clinical data on exposed pregnancies are available. Administration of fampridine to animals during pregnancy and lactation resulted in decreased offspring viability and growth at doses 6.8 times the maximum recommended human dose (MRHD) of 20 mg/day. In developmental toxicity studies in rats and rabbits, fampridine was administered orally at doses up to 10 and 5 mg/kg/day, respectively, during the period of organogenesis. These doses are approximately 5 times the MRHD. No evidence of developmental toxicity was found in either species at the highest doses tested, which were maternally toxic. For additional safety data, refer to the prescribing information Fampyra®.

  All sexually active female of childbearing potential are requested to use adequate contraception starting 10 days before the first intervention until and including the last visit day, such as oral, injectable, or implantable contraceptives or intrauterine devices. No contraception will be required from women who are sexually inactive or not heterosexually active. To minimize the risk of exposure to IMP we will perform a pregnancy test before administration of study drug on test day 1 and 3 (visits 2 and 4; start of treatment periods).
- All subjects will be informed about possible side effects of medication and advised to inform the investigator about observed side effects due to possible individual differences in metabolism of study medication.

The benefit of the study lies in the clinical implications with regard to treatment of working memory deficits in neuropsychiatric disorders. The benefits are expected to be very relevant for patients with depression and could improve quality of life for these patients.

Therefore, we consider the rather mild and infrequent side effects tolerable in comparison with the potential benefits this study might show.

3.8 Justification of choice of study population

We have recently demonstrated that fampridine can enhance working memory in healthy individuals with lower baseline performance, suggesting it may hold potential for addressing working memory deficits, which are often observed in depression (Nikolin et al., 2021). We will recruit individuals with mild to moderate depression, which does not necessitate antidepressant medication to avoid potential interaction with such medication.

As drug effects may vary between sexes, the study will consider sex as a covariate of potential importance in the statistical analyses. Given the low prevalence of intersex individuals and those with gender identities not congruent with their assigned sex at birth, our study design does not allow consideration of questions related to these conditions.

4 STUDY OBJECTIVES

4.1 Primary Objective

The primary objective of this study is to evaluate if fampridine improves working memory in mild to moderate depression. Additionally, we aim to assess whether baseline working memory performance or subjective working memory deficits moderate the drug's effect.

4.2 Secondary Objectives

The secondary objectives are to assess the influence of fampridine on different working memory functions, attention, cognitive flexibility, affective working memory, and mood.

4.3 Safety Objectives

The study aims to assess tolerability of study medication in terms of incidence of side effects e.g. headache, gastrointestinal discomfort and dizziness and the rate of AEs.

5 STUDY OUTCOMES

5.1 Primary Outcome

High-load working-memory performance: d' 3-back as assessed by a letter n-back task (Heck et al., 2022)

5.2 Secondary Outcomes

- Reaction time (3-back hits)
- d' 0-back (Heck et al., 2022)
- Adaptive verbal working memory capacity test (SPAN) backward (SCHUHFRIED, 2024).
- Verbal episodic memory performance (15 words) measured by immediate and delayed word-list recall task after acute and repeated intake of study medication. Adapted from a subtest of the Verbaler Lern- und Merkfähigkeits-Test (VLMT; Helmstaedter/Lendt/Lux, 2001).
- Accuracy in emotion recognition during the 0-back and 2-back conditions (Affective WM Task)
- Depression (MADRS-s (Svanborg/Åsberg, 1994; Svanborg/Åsberg, 2001), self-rating version).
- Tower of London (ToL; Phillips et al., 2001; Shallice, 1982).
- Intra-Extra Dimensional Set Shift (IED; Fray, Robbins & Sahakian, 1996). Adapted version for this study from GitHub (Sochat, V., 2016–2017).
- Lexical ability measured by a phonemic verbal fluency task (S-words). Adapted from a subtest of the Regensburger Wortflüssigkeits-Test (RWT; Aschenbrenner/Tucha/Lange, 2001).

5.3 Safety Outcomes

- The most common side effects of fampridine (headache, dizziness and gastrointestinal complaints) are recorded by the participants during the treatment phases at home and at the study centre at the visits using VAS. (see chapter 10.1.1)
- AE-recording

5.4 Assessment of potential confounders

- Tiredness and motivation will be rated by the participant using visual analogue scales.

6 STUDY DESIGN

6.1 General study design and justification of design

Pharmacological proof-of-concept study on the effects of 7.5. days of 10 mg fampridine (oral administration) twice daily on cognitive processes, in particular working memory, in 38 patients with mild to moderate depression using the following design:

- randomized
- double-blind (participant, study team)
- placebo-controlled
- cross-over
- counter-balanced

The total duration of the study, from the first participant to the last participant's completion, will be approximately 12-15 months. The duration for each individual participant will range from 4 to 9 weeks, depending on the length of the wash-out phase, the latter being at least 6.5 days (i.e., exceeding 25 half-lives of the active moiety fampridine (t½ = 6 hours)) and up to 27 days. After the screening visit (visit 1), participants will return to the clinic for four test days. Two test days will be conducted during each study period to assess performance in cognitive tasks (see Figure 2).

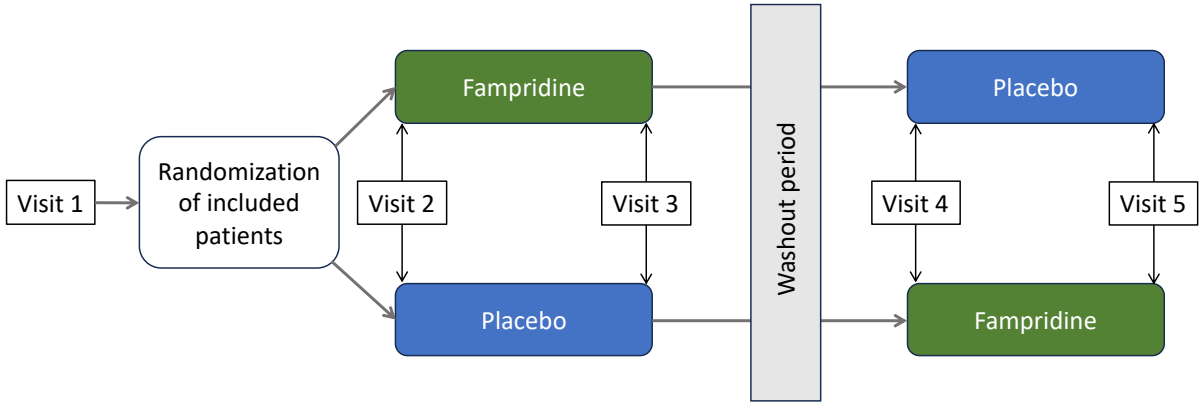

Figure 2. Study design overview. Illustration of the study's double-blind, placebo-controlled, randomized, crossover design. After the 4visit (Visit 1), eligible participants will be randomly assigned to receive either fampridine or placebo as their initial treatment. Following a washout period of at least 6.5 days, participants will switch to the alternate treatment (fampridine or placebo) for the second phase. Baseline assessments of working memory performance will be conducted at visits 2 and 4, before the first dose of either fampridine or placebo. At visits 3 and 5, working memory performance will be reassessed after 7 days of treatment with the respective intervention.

During the screening visit (visit 1), the investigator will explain the study's aims, procedures, the drug being investigated, and potential risks to the participant. Written informed consent will be obtained from all participants, with no time constraints for signing. Participants who are potential candidates for enrolment will be assessed for eligibility based on the inclusion and exclusion criteria during the screening visit. The screening visit will occur within 4 weeks prior to the first test visit (visit 2).

Eligible participants will be randomized on test day 1 (visit 2) to receive either placebo or fampridine first, following a cross-over design. Baseline cognitive testings will be conducted before the first tablet is taken at visits 2 and 4. After completing the test battery, participants will take the first tablet in the study centre and remain under observation for 90 min to monitor for acute side effects. They will then be discharged with 13 tablets to take at home, 2 tablets per day (one in the morning and one in the evening), starting the day of test days 1 and 3 (visits 2 and 4). Participants will have to document every study drug intake via an online tool. Participants will return to the clinic on day 8 for test days 2 and 4 (visits 3 and 5), where they receive the last tablet. At the end of test days 1 and 3 (visits 2 and 4), participants will be interviewed regarding their current well-being. If no complaints or symptoms are reported, they will be allowed to leave. In cases of minor health issues, participants will stay at the clinic under medical supervision until recovery.

Of note, we selected a 7.5-day treatment period based on our previous findings in healthy subjects, where no effect was observed after acute administration, but a significant effect emerged after 3.5 days. Extending the treatment to 7.5 days may further enhance efficacy. A longer treatment period was avoided in this proof-of-concept study to minimize dropout risk and ensure feasibility.

6.2 Methods of minimizing bias

To minimize bias, participants will be randomly allocated to treatment groups (i.e. starting with fampridine or placebo) and study medication will be double-blinded.

6.2.1 Randomization

After pre-examination on visit 2, each eligible participant will be assigned a randomization number. Each eligible participant will be allocated to one of the two randomization groups (Placebo/Verum or Verum/Placebo) according to the maximum tolerated imbalance (MTI) procedures. This allocation will be generated automatically by secuTrial® which contains the randomization list. The randomization list is generated with a clinical trial randomization tool[2] of the National Institute of Health (NIH), USA, by the data manager of the DKF (secuTrial®). This procedure ensures that participants will be randomly allocated to the two groups, while accounting for sex as a covariate of potential importance.

Replacement of dropouts will be carried out after the assignment of the first 38 randomisation numbers. The replacement of all drop-outs will be carried out after assignment of all 38 medication kits is completed. There will be replacement of drop-outs until data for the primary outcome of 38 participants are completed.

Knowing that the sex-distribution of mild to moderate depression is about 2:1 (f:m), we aim for at least 13 male participants.

6.2.2 Blinding procedures

The IMP and the placebo are identically looking tablets to ensure double-blind conditions.

The pharmacy will prepare two kits of study mediation per participant (one per intervention period). Each kit will consist of two intransparent plastic containers, one containing either 14 tablets of blistered fampridine and a drying agent or unblistered placebo and a drying agent (visits 2 and 4 and treatment phase at home) and one containing either one tablet of blistered fampridine and a drying agent or unblistered placebo and a drying agent (visits 3 and 5). It is necessary to keep Fampyra® blistered as long as possible to prevent any contact of fampridine with humidity. After unblistering, Fampridin will stay stable for seven days in a closed container while adding a drying agent (professional / prescribing information Germany Fampyra® SR).

Each kit (and all parts of it) of study medication will be labelled with a randomization number. A staff member not involved in the conduct of the study will open the kit and the plastic container corresponding to the respective intervention period and visit in a separate room (visits 2-5). If Verum is inside she/he will unblister the tablets, if Placebo is inside nothing has to be done. Afterwards he/she hands over the container to the responsible staff member for the participant. On visits 2 and 4 the container will be handed over to the subject for the first intake in the study center and the intake of the study medication at home. During each intervention period a tablet must be taken approximately every 12 hours for 13 times at home. The last (15th) intake of the study medication will be again in the study center (second container for the treatment phase).

The IMP and the placebo are identically looking tablets to ensure double-blind conditions.

6.2.3 Other methods of minimizing bias

The investigators of the test days will be trained and will follow detailed working instructions to ensure that each test day will be conducted in a highly standardized way. All study team members will be blinded to ensure that those assessing the outcomes will be blind to group assignment. Testing will take place at the same location at the premises of the Division of Cognitive Neuroscience, University of Basel for each participant and during the same time window of the day to minimize the influence of diurnal differences in cognitive test performance.

6.3 Unblinding Procedures (code break)

Unblinding will be permitted under these circumstances

- SAE
- AE if knowledge is crucial for further medical approach

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®.

[2] https://ctrandomization.cancer.gov/

The principal investigator or a representative will report to the sponsor within 24 hours and document the unblinding. Not involved study team members will not be informed about the result.

7 STUDY POPULATION

7.1 Eligibility criteria

7.1.1 Inclusion criteria

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

- Male or female
- Major depressive episode confirmed by the Mini-DIPS Open Access Interview (Margraf et al., 2017)
- Currently mild to modrate (MADRS external assessment: 7-30). See section 9.3.1 for details
- Normotensive (BP: 90/60mmHg - 140/90mmHg). Sufficiently treated hypertensive subjects will be included.
- BMI: 19 - 34,9 kg/m^2
- Age: 18 - 55 years
- Fluent in German
- IC as documented by signature

7.1.2 Exclusion criteria

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

- Contraindications to the class of drugs under study, e.g. known hypersensitivity or allergy to 4-aminopyridine
- Use of potassium channel blockers within the last 3 months
- Treatment with OCT 2 inhibitors and -substrates (e.g. cimetidine, propranolol)
- Treatment with antidepressants or antipsychotics within the last 3 months and throughout the study period
- Current intake of psychoactive drugs (e.g. benzodiazepines, antidepressants, neuroleptics).
- Other acute or chronic psychiatric disorder (e.g. psychosis, somatoform disorder, alcohol or drug abuse disorder)
- Cognitive impairment (MoCA< 25)
- MADRS item 10 > 1 (suicidal tendency)
- Risk of lowered seizure threshold (due to e.g. sleep deprivation, withdrawal of alcohol after alcohol abuse, hyponatraemia)
- History of seizures
- Acute cerebrovascular condition
- Acute renal failure or severe renal insufficiency (creatinine clearance < 30 ml/min per 1.73 m^2)
- Bradycardia < 50/min during clinical examination.
- History of malignant cancers
- Walking problems (e.g. due to dizziness)
- Other clinically significant concomitant disease states (e.g. hepatic dysfunction, cardiovascular disease, diabetes, asthma)
- Clinically significant laboratory or ECG abnormality that could be a safety issue in the study
- Severe somatic or neurological comorbidities
- Smoking including all nicotine containing smoking systems and devices (>10 cigarettes/units per day), failure to withstand a test day without craving, due to regular consummation pattern
- Pregnancy or breast feeding. Intention to become pregnant during the study participation.
- Known or suspected non-compliance
- Inability to follow the procedures of the study, e.g. due to language or psychological problems of the participant
- Participation in another study with an investigational drug within the 30 days preceding and during the present study
- Enrolment of the investigator, his/her family members, employees and other dependent persons

7.2 Recruitment and pre-screening

Study participants will be searched in the German speaking part of Switzerland using the following websites mcn.unibas.ch and markt.unibas.ch. We will also advertise the study in print and online media (including social media) and in public transportation and via flyers.

After contacting us, the interested person will be sent the "Subject information sheet and informed consent form" together with some administrative information. If the subject is still interested in participating, a study team member will call the subject to inform him/her about the study and answer his/her questions. Afterwards, a pre-screening (phone call) with a check of the main in- and exclusion criteria will be performed. If the subject meets all inclusion criteria and none of the exclusion criteria and is interested in participating the screening visit will be fixed.

The pre-screening documents of subjects eligible for a study participation will be filed as part of the Source Data (SD) in the participant's dossier.

The pre-screening documents of subjects NOT eligible for a study participation will be kept in an pseudonymous form until LPLV. Then they will be shredded.

For screening procedures see chapter 9.3.1.

A study compensation of CHF 450 including travel expenses will be paid at the end of the second test visit. Screening Failures and Drop-Outs receive a pro rata temporis compensation.

After obtaining informed consent, each participant will be assigned a participant number. At visit 2, eligible participants are randomly assigned to treatment group (i.e. either fampridine or placebo first) following the order of the randomization list imported into secuTrial®. For detailed procedure see chapter 6.2.1 (randomization) and 12.2 (coding).

7.3 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. There will be a final examination after withdrawal for whatever reason. The investigator also has the right to withdraw participants from the study if it is in the best interest of the participant.

The following reasons result in withdrawal:

- Adverse events challenging the health of the participant if continuing the study
- Adverse events prohibiting cognitive testing
- Intake of psychoactive substances within 3 days before test days (e.g. benzodiazepines, neuroleptics, cannabis)
- Start of a treatment with antidepressants during the study
- Sleep deprivation (24 hours without sleep)
- Positive pregnancy test (test day 1 or test day 3)
- More than 2 tablets were not taken in one of the two treatment periods (according to the online diary and/or the number of tablets returned) at visit 3/5.
- Non-Compliance
- Administrative troubles
- Severe protocol violations

Withdrawal date and reason will be listed in the participant enrolment log. Safety data will be analyzed for all participants, who received at least one dose of study medication.

7.4 Contraception and pregnancy

All female participants of childbearing potential are requested to use adequate contraception starting 10 days before the first intervention period until the final visit, such as oral, injectable, or implantable contraceptives or intrauterine devices. Women who declare that they remain sexually inactive 10 days before the first intervention period until the last visit and confirm this by signing a declaration are exempt from the requirement to use contraception.

To minimize the risk of exposure to IMP we will perform a pregnancy test before administration of the study drug on test day 1 and 3.

If despite all contraceptive measures a pregnancy occurs the pregnant participant must be withdrawn immediately from the clinical study. Any pregnancy during the treatment phase of the study and within 30 days after discontinuation of study medication will be reported to the sponsor within 24 hours.

For documentation and reporting and handling of pregnancies see chapters 10.3 and 10.4.4.

8 STUDY INTERVENTION

8.1 Identity of Investigational Products

8.1.1 Experimental Intervention

Active study medication consists of 15 tablets (7.5 days) of fampridine 10 mg formulated for oral administration taken in the morning and evening approximately 12 h apart without food. Tablets must be administered as a whole: do not divide, crush, chew, or dissolve Fampyra® tablets.

There will be a washout period of at least 6.5 days equalling over 40 half-lives of the active substance fampridine ($t_{½}$ = 4.62 h) between experimental and control intervention.

The permitted time window for the start of the second treatment phase is as follows:

- Visit 3 plus at least 7 days AND
- Visit 3 plus max. 28 days

8.1.2 Control Intervention

One identically looking placebo tablet formulated for oral administration consisting of

Placebo Tabletten zu Fampyra® 10 mg

Beschreibung:			
Spezifikation:	**Bezeichnung Inhaltsstoff:**		**Menge/Einheit:**
Tablettenkern:			
Ph. Eur.	Cellulose mikrokristallin 200		289 mg
Ph. Eur.	Cellulose mikrokristallin 101		122 mg
Ph. Eur.	Hypromellose 6		47 mg
Ph. Eur.	Magnesiumstearat pflanzlich		9,4 mg
Ph. Eur.	Siliciumdioxid hochdispers		2,4 mg
		Summe:	470 mg
Tablettenfilm:			
Ph. Eur.	Hypromellose 6		5,90 mg
Ph. Eur.	Polyethylenglycol		0,90 mg
Ph. Eur.	Titandioxid		1,20 mg
		Summe:	8 mg
		Gesamtsumme:	478 mg

8.1.3 Packaging, Labelling and Supply (re-supply)

Packaging, labelling and supply will be provided by the Pharmacy of the University Hospital Basel (see chapter 6.2.2).

8.1.4 Storage Conditions

The IMP will be stored at a maximum of 25° C and protected from light and humidity until initiation at the pharmacy. Thereafter the IMP will be stored for the entire study until last participant out at the same conditions 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

See chapter 8.1.1

8.2.2 Control Intervention

See chapter 8.1.2.

8.3 Dose

No modifications needed.

8.4 Compliance with study intervention

Each subject will be provided with a personal login to secuTrial® to be able to document the intake of the investigational product directly after intake. A study team member will send a note if entry is missing to remind the subject of intake of the investigational product.

All subjects have to return the container on the following test days in order to control the container for not used tablets and for correct disposal of remaining tablets after study end.

Blinding is warranted (see chapters 6.2.1 and 6.2.2., Randomization and Blinding).

8.5 Data Collection and Follow-up for withdrawn participants

Not needed. Subject withdrawn because of (S)AE will be followed up until resolution or stabilization.

8.6 Trial specific preventive measures

In case of headache, pain or fever, paracetamol is allowed and has to be recorded as concomitant medication. Nonsteroidal and anti-inflammatory medication is allowed and has to be recorded as concomitant medication.

8.7 Concomitant Interventions (treatments)

Treatments with OCT 2 inhibitors (e.g. cimetidine, trimethoprim, propranolol, carvedilol, metformin) are prohibited during the course of the study as they may inhibit elimination of fampridine and increase the risk of adverse events.

All concomitant treatment will be recorded in the eCRF.

8.8 Study Drug Accountability

The supplies from and the returns to the pharmacy of the USB for destruction will be documented at the pharmacy and also by the study coordinator on the site in the IMP accountability log. This log documents the IMPs received from the pharmacy, the kits used by each participant, and the return to the pharmacy of used and unused kits. This documentation includes the following information: delivery date, delivered kits, batch number, expiry date. The administration of the IMP to the participants is recorded in the participant dossier.

8.9 Return or Destruction of Study Drug

Used and unused kits will be returned to the pharmacy of the University Hospital Basel (USB) for destruction. The pharmacy will destroy and dispose them duly in accordance to hospital policy and the local directives.

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 13)

9.2 Assessments of outcomes

9.2.1 Assessment of primary outcome

- High-load working memory performance after repeated (i.e., 7.5 days) intake of study medications (visit 3 and 5)
  We will use the letter n-back task (Heck, Fastenrath et al., 2014)) which includes a 3-back task assessing working memory. The 3-back task requires participants to respond to a letter repeat with two intervening letters (for example, **S**−m−b−**s**−g-…). Performance will be quantified with the d' measure controlling for false positives. We will use parallel versions (different sequences) for the four test days. Primary outcome will be performance after repeated intake of study medication.

9.2.2 Assessment of secondary outcomes

Performance in other working memory-related tasks and other n-back outcomes will be measured as follows:

- Reaction time (for correct 3-back responses).
  Performance in a 0-back task (d') as a measure of attention. We will use parallel versions (different sequences) for the test days.
- Verbal working memory capacity will be assessed with an adaptive working memory test (SPAN) (SCHUHFRIED, 2024). The SPAN is a computer-based, adaptively administered test based on item response theory (Rasch model; Rasch, 1980). In the study, test form S2 (backward digit span) is used, which captures both storage capacity and executive functions (Baddeley, 2010). Adaptive administration allows for precise, efficient, and individually tailored assessment while minimizing floor and ceiling effects.
  Test scoring is based on the estimation of a continuous person parameter (θ) using weighted maximum likelihood (Warm, 1989). This parameter reflects the individual's latent working memory ability and is additionally converted into a digit span score with decimal precision, allowing for nuanced interpretation (Gignac & Weiss, 2015).
- Verbal episodic memory performance measured by immediate and delayed word-list recall task after acute and repeated intake of study medication. In this test a list of 15 selected words will be presented to the participants with a rate of one word per two seconds and the participant should recall the words immediately in writing (immediate recall). Around 15 minutes later the participants are asked to recall the words again (short delay). Number of correct words recalled in each stage is considered as the participant's immediate and delayed recall score respectively. We use the four 15-words wordlists A-D out of the following Test: Verbaler Lern-und Merkfähigkeitstest, VLMT (Helmstaedter/Lendt/Lux, 2001).
- Lexical ability measured by phonemic verbal fluency test (S-words) after acute and repeated intake of study medication; adapted from a subtest of the Regensburger Wortflüssigkeits-Test (RWT; Aschenbrenner/Tucha/Lange, 2001). In this task participants should name orally as many words as possible initiating with a special letter in one minute (e.g. Mary, Milk, Mouse, etc. for the letter M). The number of unique meaningful words will be considered as the participant's score. For each test day we will use a different letter (B, K, P, M).
- Planning and Problem solving, key aspects of executive functioning, will be measured with the "Tower of London" (ToL) test (Freiburger Version, Kaller, C.P. et al., Schuhfried GmbH). In this test, participants will be tasked to rearrange colour balls to match a target arrangement in as few moves as possible (ToL; Shallice, 1982). The raw score for planning ability (number of correctly solved trials with the minimum number of ball placements) is considered as the participants score. Parallel versions will be used for the four test days.
- Cognitive Flexibility will be assessed through the "Intra-Extra Dimensional Set Shifting (IED)" task. Participants are asked to use the given feedback to work out a rule that determines which stimulus (shapes and lines in different combinations) is correct. After six correct responses, the stimuli and/or rule changes. The shifts in rule are initially intra-dimensional and then later

extra-dimensional. (IED; Fray, Robbins, & Sahakian, 1996). The highest reached level is considered as the participant's score. Parallel version will be used for the four test days.

- Processing of emotional information (0-back) and its alteration through reduced affective working memory capacity (2-back) will be assessed using a newly developed affective working memory task. The task follows a classic N-back paradigm with two conditions: 0-back and 2-back. Emotional faces (happy, sad, neutral; male/female) from the Karolinska Directed Emotional Faces set (Lundqvist et al., 1998) are presented for 1500 ms with a 1350 ms inter-stimulus interval. Participants indicate whether each stimulus is a "hit" or "non-hit," based on the current stimulus (0-back) or compared to the stimulus two trials prior (2-back). The severity of depressive symptoms will be assessed using MADRS-s (Svanborg/Åsberg, 1994; Svanborg/Åsberg, 2001), self-rating version. For visits 2-5, this refers to the previous week. The MADRS-s consists of 9 items assessing subjects' mood, inner tension, sleep, appetite, ability to concentrate, initiative, emotional involvement, pessimism and zest for life. Each item is scored between 0 and 6. The total score is calculated by summing the answers of the ten items, ranging between 0 and 54 (higher scores indicate increased severity).

9.2.3 Assessment of potential confounders

- Tiredness and motivation will be rated by the participant using visual analogue scales.

9.2.4 Assessment of safety outcomes

Adverse events: All clinically relevant (S)AEs occurring after the participant has signed the informed consent until follow up visit will be fully recorded in the participants eCRF. Description of (S)AE, time of onset, duration and resolution. Assessment of intensity, relationship to study drug and measures taken.

The following very common AEs, which are already described in the prescribing information for Fampyra® (version January 2022), are excluded from recording, but will be measured as a possible confounding factor using VAS during the treatment periods (morning/evening) and also at all four visits in the study centre:

- headache,
- gastrointestinal complaints such as dyspepsia, abdominal pain, constipation and nausea,
- dizziness.

All other clinically relevant AEs will be fully recorded. See chapter 10.3 for documentation of Adverse Events.

SAEs will 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.

Laboratory parameters: No laboratory parameters will be assessed after completed screening.

Vital signs (BP, HR) will be taken as described in screening procedures.

9.3 Procedures at each visit

9.3.1 Screening visit (visit 1)

During the screening visit the investigator explains to the subject 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 without limiting time for signature. Subjects who are candidates for enrolment into the study will be evaluated for eligibility during the screening visit by an investigator (inclusion, exclusion criteria). Screening visit will take place within 2 weeks before first test visit and consists of

- Assessment of personal and family history
- Assessment of medication history
- Physical examination (including body weight and height)
- VAS subjective working memory problems (ranging from not impaired to heavily impaired)
- Sociodemographic self-assessment questionnaire

The following questionnaires will be used to assess psychiatric disorders:

- Mini-DIPS Open Access (Margraf et al., 2017). We will use a shortened version to avoid redundancy and focus on relevant inclusion and exclusion criteria.
- Clinician rating of depression severity: MADRS external assessment (Schmidtke et al.,1988 (German version), HAMD (Hamilton 1960, German version CIPS 1977)
- Affect will be measured using the PANAS (Breyer et al., 2016)
- Montreal cognitive assessment test (MoCA) for detection of cognitive impairment (Nasreddine et al., 2005). We will use a shortened version scoring between 0 and 29. A score of 25 or over is considered to be normal.
- Assessment of clinical properties for characterizing patient's disorder: duration of illness, duration of current episode, characteristics of current episode (melancholic vs. nonmelancholic)

HAMD and PANAS are not used to diagnose depression in this study; instead, they are employed to further characterize the patient population. Affect will be measured using the PANAS (Positive and Negative Affect Schedule) questionnaire. It is self-report questionnaire that measures the intensity of positive and negative emotional states over a specific period. (Krone et al., 1996). To evaluate the intensity of depression the HAMD (Hamilton Depression Rating Scale) will be used. It includes a series of questions related to mood, behaviour, and physical symptoms that will be asked by an clinical trained personnel. (Schmitt et al., 2012).

Diagnosis of major depression: Mental disorders will be assessed using the Mini-DIPS (Margraf et al., 2017). The Mini-DIPS is a brief diagnostic interview for mental disorders. It offers a quick yet reliable diagnostic assessment of mental disorders according to DSM-5 and ICD-10. The Mini-DIPS provides an overview of the general burden of the persons examined and enables the documentation of important anamnestic information for practice and research. In addition to the interview guide, the short interview provides supplementary information and diagnostic checklists based on the DSM-5 criteria for all listed mental disorders. It will be used **to confirm the clinical diagnosis** of a major depressive episode and assess the severity of suicidality, and to exclude other relevant mental disorders such as bipolar disorder, schizophrenia, drug and alcohol dependency and others. The duration is about 20 minutes in a shortened version. To diagnose a current Major Depressive Episode (MDE) using Mini-DIPS, the individual must have experienced a consistently depressed mood or a marked loss of interest or pleasure in most activities for at least two weeks. Additionally, at least five symptoms must be present during this period, including significant changes in appetite or weight, sleep disturbances (insomnia or hypersomnia), psychomotor agitation or retardation observable by others, fatigue or loss of energy, feelings of worthlessness or excessive guilt, diminished ability to concentrate or make decisions, or recurrent thoughts of death, suicidal ideation, or a suicide plan. These symptoms must cause clinically significant distress or impairment in social, occupational, or other important areas of functioning, and cannot be attributed to the physiological effects of a substance or another medical condition. The Mini-DIPS uses structured questions to systematically assess these criteria and ensure a reliable diagnosis.

The severity of the depressive symptoms will be assessed by the diagnostic interview MADRS (Schmidtke et al.,1988 (German version)). The MADRS consists of 10 items assessing subjects' apparent and reported sadness, inner tension, sleep, appetite, ability to concentrate, initiative, emotional involvement, pessimism and zest for life. Each item is scored between 0 and 6. The total score is calculated by summing the answers of the ten items, ranging between 0 and 60 (higher scores indicate increased severity). A score of 7 or higher indicates a mild depressive episode (score 7-19). A score of 20 or higher indicated moderate depression and a score of 34 or higher severe depression. Only subjects with a clinically confirmed depression and a mild or lower moderate severity will be included. In case of suicidal thoughts (MADRS Item 10 > 1) or a MADRS score > 30, the subject is excluded and advised to consult a psychologist/psychiatrist.

In cases of severe depressive symptoms, with or without suicidality, a timely clinical appointment will be arranged at the Acute Outpatient Clinic or the Central Admissions of the Psychiatric University Hospital Basel. If patients feel unable to cope with their situation until their scheduled appointment at the hospital, they are encouraged to contact us directly or to seek an earlier consultation at the UPK.

For patients with mild to moderate, but clinically relevant, depressive symptoms, those who are not currently undergoing psychological treatment will be advised to consult a psychologist or psychiatrist. Patients with moderate symptoms will be advised to do so as soon as possible, while patients with mild symptoms will be advised to seek consultation if their symptoms do not improve within the next few weeks.

Addresses of recommended professionals will be provided. Furthermore, it will be documented if participants begin psychological treatment during their study participation.

A trained psychologist experienced in diagnosing psychiatric conditions carries out the diagnostic interview. The final decision on inclusion/exclusion is the responsibility of the investigator.

Screening for cognitive impairment: To ensure internal validity when assessing working memory in individuals with mild to moderate depressive disorder, global cognitive screening with the Montreal Cognitive Assessment (MoCA) will be performed, in order to detect subtle cognitive impairments (such as mild cognitive impairments other etiologies or dementia syndromes), that might confound the measurements. The MoCA was chosen because it is a brief, well-validated screening instrument with superior sensitivity for detecting mild and subtle cognitive deficits relative to other brief screens. (Tsoi et al., 2015). Screening with the MoCA at enrolment will allow prespecified exclusion or stratification of participants whose global cognitive deficits could confound interpretation of working-memory outcomes related to depression, and permit adjustment for baseline global cognition in statistical models to reduce residual confounding. Participants with MoCA results below 25 points, suggesting possible mild neurocognitive disorder, will be excluded and be recommended to get a comprehensive neuropsychological evaluation.

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”.
- Twelve lead ECG with formal readings (Wilson, Einthoven, Goldberger), device: Schiller AT10, will be taken and rated by a specialist familiar with the study medication at the “Ambulantes Studienzentrum” (ASZ), University Hospital Basel (USB)
- Venous blood samples (2.7 ml and 4.7 ml) will be taken at “Ambulantes Studienzentrum” (ASZ), University Hospital Basel (USB), to measure:
    - Blood count (incl. platelets) / hemoglobine / hematocrit
    - Blood chemistry including: sodium, potassium, chloride, calcium, phosphate, creatinine, uric acid, bilirubin, alkaline phosphatase, LDH, AST, ALT, GGT, pancreatic amylase, albumin, total protein (+Alb./Glob.), C-reak. Protein, creatine kinase.
    - To further investigate abnormal laboratory findings during the screening, the investigator has the possibility to measure other blood values in order to clarify certain findings relevant for in- or exclusion.

Laboratory values outside the reference range of the laboratory and considered clinically relevant will lead to exclusion of the subject from study participation.

Blood samples will be analyzed by the laboratory of University Hospital Basel. Blood samples will be discarded directly after analysis.

Clinically significant abnormal ECG readings will result in exclusion of the subject.

If a test or exam result suggest that further medical evaluation or treatment may be necessary, the participant will be notified and advised to see their care provider for further evaluation or treatment.

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

Screening failures equal to participants not meeting all inclusion criteria or meeting one or more of the exclusion criteria. Excluded participants will be listed on a screening failure log.

The investigator or the sponsor notifies the EKNZ and the Swissmedic of the first study participant, in accordance to Art 23a ClinO. If the first participating person is not included in the trial within two years following the issuance of the last authorization, the trial is considered interrupted. The clinical trial may not be commenced until an application for an extension of the time limit has been approved. The application for the extension is submitted to the EKNZ, and to Swissmedic. (see also chapter 2.3.1 and 2.4.1).

9.3.2 Test days (visits 2 - 5)

At the beginning of the visits 2 and 4, all female participants will perform a pregnancy test. Pregnancy test will be performed in a urine sample. A one-step hCG (monoclonale anti-hCG antibodies) urine pregnancy

test will be used for qualitative (visual) determination of hCG in urine specimen for early detection of pregnancy.

Women who declare that they remain sexually inactive 10 days before the first intervention period until the last visit and confirm this by signing a declaration are exempt from the requirement to use contraception.

There will be a short examination consisting of assessment of concomitant medication and intake / consumption of psychoactive substances, sleep duration last 24 hours, and adverse events.

On test days 1 and 3 (visits 2 and 4), subjects should take breakfast at home no later than 2 hours before the planned intake of the first tablet at our study center. After a brief examination, baseline cognitive performance is measured before taking the study medication. After taking the first tablet at the start of both study phases, the subjects remain at the study centre for observation for at least 90 minutes to monitor possible acute side effects. Intake of study medication will take place at approx. the same time point for each subject at test day 2 and 4 (visits 3 and 5). We will provide a continental breakfast to be eaten 30 min after intake of study medication. Testing will take place at approx. the same time for each subject to minimize the influence of diurnal differences in cognitive test performance. After intake of study medication on test days 2 and 4 (visits 3 and 5), there will be a 3-h waiting period before the cognitive test battery will be administered. A parallel version of the test battery will be administered on each test day. For the duration of the different study parts see table 1 (Duration of Study parts, page 14).

At the end of each test day, participants will be asked about their current wellbeing. If there are no complaints / symptoms they will be dismissed. In case of minor health problems the participant will have to stay in the study center until recovery under medical control. In case of more severe incidents staff will act according to chapter 10.

Assessments in participants who prematurely stop the study: There will be a final examination after withdrawal during test days for whatever reason. The examination consists of recording adverse events and assessing vital signs.

At the last visit (visit 5 - last regular visit / 6 -safety follow-up), or at the time point of dropping out of the study: For patients who developed severe depressive symptoms, with or without suicidality, a timely clinical appointment will be arranged at the Acute Outpatient Clinic or the Central Admissions of the Psychiatric University Hospital Basel. If patients feel unable to cope with their situation until their scheduled appointment at the hospital, they are encouraged to contact us directly or to seek an earlier consultation at the UPK.

For patients with mild to moderate, but clinically relevant, depressive symptoms, patients will be advised to consult a psychologist or psychiatrist if their symptoms do not improve within the next few weeks. Addresses of recommended professionals will be provided.

All visits of the study are conducted in the Division of Cognitive Neuroscience of the University of Basel.

Study staff involved: The cognitive tests on the test days (visits 2-5) will be conducted by a psychologist or trained study staff. The preparation of the study medication (deblistering) at the beginning of the treatment phases is carried out by a member of the study team who is not further involved in the conduct of the study. The tablets are dispensed by the psychologists, the investigator or trained study staff (see also chapter 6.2.2, randomization and blinding). The study coordinator is responsible for maintaining the study's drug accountability log.

9.3.3 Treatment periods

During the visits 2 and 4 (test days 1 and 3) every subject will be supplied with a plastic container containing 14 tablets of IP to be taken twice per day during the following 7 days, the first tablet on site after baseline cognitive performance testing and the second in the evenings of visits 2 and 4 (test days 1 and 3) and the last tablet in the evenings before visits 3 and 5 (test days 2 and 4). Each subject receives a total of 15 verum tablets and 15 placebo tablets. The last tablets on visits 3 and 5 will be given to the participants by a staff member in the study center.

During the treatment days, the participants document the intake of the tablets twice a day (morning/evening) and the most common side effects via visual analog scales via a separate personal

login directly in secuTrial® (s. chapter 8.4 - Compliance with study intervention, and chapter 9.2.4 – assessment of safety outcomes).

9.3.4 Safety follow-up

After the washout period for fampridine of at least 5 half-lives (approximately 30 hours) after Visit 5, we will perform a safety check. Within 2 to 7 days after completion of the second treatment phase (Visit 5), an investigator will contact each subject by telephone to inquire about adverse events that have occurred since visit 5 and/or about the outcome of open adverse events and to ensure that subjects are doing well.

A safety follow-up will also take place after an early study termination if the first treatment phase has already started (from Visit 2).

10 SAFETY

The Sponsor's SOPs provide more detail on safety reporting.

During the entire duration of the study, all adverse events (AE) and all serious adverse events (SAEs) are collected, fully investigated and documented in source documents and case report forms (CRF). Study duration encompassed the time from when the participant signs the informed consent until the last protocol-specific procedure has been completed.

For the assessment and documentation of (serious) adverse events see the chapters 10.2 and 10.3.

For the reporting of (serious) adverse events see chapter 10.4.

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.

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 jeopardise 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 sponsor evaluates the SAE that has been reported regarding seriousness, causality and expectedness. If the event is related to the investigational product and is both serious and unexpected, it is classified as a SUSAR.

In case of double-blinded studies, unblinding may be needed to determine a SUSAR. The sponsor should not disclose the treatment allocation to the investigator, nor to the study staff, in order not to make the subject ineligible.

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

10.2.1 Assessment of causality

Both Investigator and Sponsor make a causality assessment of the event to the study investigational medicine product, 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

Adverse events will be categorized as 1=mild, 2=moderate, 3=severe, 4=life-threatening, 5=death (according to CTCAE, NIH 2021).

10.3 Documentation

10.3.1 Serious Adverse Events (SAE)

The sponsor's SOPs provide more detail on safety reporting.

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 final examination.

10.3.2 Adverse Events (AE)

The following information needs to be collected for adverse events:

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

In addition, we document the study phase in which an AE occurred and the visit.

For assessment of safety outcomes see chapters 9.2.3.

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 principal investigator of the study. The principal investigator will re-evaluate the SAE and return the form to the site.

SAEs 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 EKNZ via BASEC by the principal investigator and to Swissmedic via sponsor *within 7 days*, if the event is life-threatening or fatal, *or within 15 days* (all other events).

IMPORTANT: The reporting obligations of SUSAR also apply if the principal investigator or the sponsor becomes aware of a suspected case that has arisen in Switzerland after termination of the clinical trial, or if the investigator or the sponsor only becomes aware of such a suspected case after termination of the clinical trial.

10.4.3 Reporting of immediate safety and protective measures

All suspected new risks and relevant new aspects of known adverse reactions that require immediate safety-related measures, must be reported to the sponsor-investigator within 24 hours. The sponsor-investigator must report these measures within 7 days to the EKNZ via BASEC and to Swissmedic.

10.4.4 Reporting and handling of pregnancies

Pregnant participants must be withdrawn immediately from the clinical study. Any pregnancy during the treatment phase of the study and within 30 days after discontinuation of study medication will be documented and reported to the sponsor within 24 hours.

The course and outcome of the pregnancy should be followed up carefully, and any abnormal outcome regarding the mother or the child should be documented and reported.

10.4.5 Periodic reporting of safety and general progress of the clinical trial

Once a year, the principal-investigator submits to the EKNZ a list of the safety events including the severity of the events, their causality to the intervention and the safety of the study participants. The start date for the safety report is the sponsor's first authorisation to conduct a clinical trial in any country worldwide.

The principal-investigator also informs the EKNZ about the general progress of the clinical trial.

The safety report / general study progress report is submitted *once a year* to the EKNZ via principal-investigator and to Swissmedic via sponsor-investigator.

The safety report / general study progress report is submitted throughout the duration of the clinical trial, and the last submission of the safety report will cover the Last Patient Last Visit (LPLV).

The safety report can be written and submitted in the format of the Development safety update report (DSUR) in compliance to ICH Harmonised Guideline E2F for commercial and non-commercial sponsor.

The safety report and the general study progress report can be merged in one single report. If a pregnancy occurs during the course of the study, we will submit the study information and informed consent form for pregnant participants (based on the Swissethics template) to the EKNZ for evaluation."

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

Occurrence during a visit to the study centre

In case of minor health problems the participant will have to stay under medical control in our department.

In case of major health problems the participant will be transferred to the emergency department in the University Hospital of Basel (USB). The responsible investigator will inform the health care provider about the participation in the study. For unblinding see 6.3.

The investigator is responsible for assessing the severity of the health problems.

Information about the outcome in all above-mentioned cases will be collected until full recovery and stored in the participants dossier and in the eCRF.

Occurrence during treatment periods

Will be assessed using daily online ratings by participants. The Investigator will contact patients if extends and frequency exceeds a SOP defined level.

11 STATISTICAL METHODS

11.1 Hypothesis

a) Fampridine improves working memory functions in patients with mild to moderate depression.
b) Patients' baseline working memory performance or subjective working memory problems moderate the effect of fampridine on working memory functions. Specifically, we expect that patients with lower baseline working memory performance or more profound subjective working memory problems will exhibit a greater improvement in working memory functions when treated with fampridine.

11.2 Determination of Sample Size

In our recent cross-over study (Papassotiropoulos, Freytag et al., 2024) investigating the effect of fampridine on working memory performance in healthy subjects, we observed a large effect size (dz = 0.82) for drug-related improvements in individuals with low baseline working memory performance (i.e., lowest tercile). This effect size (dz = 0.82) accounts for within-person correlation and standard deviations observed in the published study. However, for the proposed study in a clinical population, we do not expect to replicate such a large effect size due to the increased variability and noise typically present in clinical samples. Consequently, we have adopted a more conservative approach, estimating a moderate effect size of dz = 0.5 (assuming similar within-person correlation and standard deviations as in the published paper). Based on this effect size and assuming a power of 85% at two-tailed α=0.05, the estimated sample size is N=38 (software: G-power 3.1). Considering an expected drop-out rate of 10–20%, we plan to recruit a sample of 45–50 participants. There will be replacement of drop-outs until data for the primary outcome from 38 participants are completed.

While the estimated sample size of 38 participants is justified as detailed above, unknown factors might influence the expected effect size. Although an interim analysis could provide a better estimate of the effect size, it carries the risk of introducing unintentional downstream biases due to unblinding, which may affect the integrity of the study moving forward. For this reason, we would prefer to refrain from conducting an interim analysis in this case.

11.3 Statistical criteria of termination of trial

Statistical criteria of termination of trial: As soon as at least 38 participants will have complete data for the primary outcome. For subjects still enrolled at that time point see 11.4.1.

11.4 Planned Analyses

All analyses will be performed with the software R. The differences between the experimental conditions (placebo, verum) will be analyzed using linear mixed models in combination with analysis of variance (SS II), with treatment, period, and sequence as fixed effects and subject IDs as the random effect of the mixed model. Sex, age and baseline cognition will be inserted as covariates.

In case of significant interactions between covariates and experimental condition, post-hoc tests will be applied to describe the interaction.

To control for possible confounders, we will also consider, tiredness, motivation, headache, gastrointestinal discomfort, dizziness, mood as assessed by MADRS-s (self-rating version), potassium blood concentration at screening, body weight and duration of washout period as covariates (each covariate entering the statistical analysis separately). In case of a significant interaction between independent variables of interest and covariates, *post-hoc* analysis will be applied to describe the interaction effect.

In case of significant deviation from normality for the dependent variable, appropriate non-parametric methods will be used.

11.4.1 Datasets to be analyzed, analysis populations

We will apply a Per-Protocol-Analysis, i.e. the analysis of the primary and secondary outcome measures will be only performed with those participants, who have complete data for primary outcome. Before unblinding, the logfiles of the n-back task will be reviewed for completeness and compliance. There will be replacement of Drop-Outs until primary outcome data of 38 participants are completed. Drop-Outs will be thoroughly described to assess the reason(s) for dropping out.

We will recruit up to 4 subjects more towards the end of the trial to prevent under-recruitment due to Drop-Outs. If more than 38 subjects will complete all tests and investigations their data will also be analyzed.

11.4.2 Analysis for the primary outcome

A significance level of $p < 0.05$ will be considered as significant.

The dependent variable is the primary outcome (i.e. d' 3-back after repeated (i.e., 7 days) administration of study medication). The independent variable of interest is the experimental condition (placebo or verum). We will also conduct correlation analyses between the delta (i.e. verum primary outcome – placebo primary outcome) and a) baseline working memory performance, defined as the mean d' score from the 3-back task assessed during visits 2 and 4 prior to drug administration, and b) subjective working memory problems as defined by the respective visual analog scale during the screening visit. If a significant correlation is observed, we will perform post-hoc analyses to evaluate the effect of the study medication following repeated administration, stratifying participants into respective sub groups.

11.4.3 Analyses for secondary outcomes

Secondary outcome measures will be treated statistically the same way as the primary outcome measure. These analyses will be considered exploratory, i.e. no Bonferroni correction for multiple comparisons will be applied.

11.4.4 Interim analyses

No interim analyses are planned.

11.4.5 Safety analysis

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

11.4.6 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.

Deviation from the original statistical plan will be performed, if reviewers demand specific analyses. In addition, should in the meantime other studies report 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 beside our planned analyses.

11.4.7 Handling of missing data and drop-outs

Missing data will be recorded as NA.

Drop-Outs see chapter 11.4.1.

12 QUALITY ASSURANCE AND CONTROL

12.1 Responsibilities

The sponsor is responsible for implementing and maintaining quality assurance and quality control systems with written SOPs and Working Instructions. The PI is responsible for training of all involved study personnel.

12.2 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. Additionally, the year of birth is used for the laboratory and ECG in the context of the screening.

The telephone screening will be performed before assignment of the subject code as described above. This document will be coded with a separate numeric code and the age of the interested person. The telephone screening form does not contain any other identifying information. For subjects signing the informed consent, the telephone screening form becomes part of the participant dossier. For individuals who do not sign the consent form, the telephone screening form is sorted in coded form and shredded after LPLV.

The participant number of subjects who have signed the informed consent are listed in the electronic combined Screening, Enrolment and Identification Log (Subject Master List, SML). Subjects not having signed the informed consent, will not be entered in the SML. The SML will be kept under lock and key. Access to the participant identification list will have only authorized study team members.

Data will not be anonymised after statistical analysis. They will be stored coded. After the study has been completed, only the people authorised by the sponsor for the archiving in the Divisions of Molecular and Cognitive Neuroscience, University of Basel, will have access to the key list.

12.3 Data handling and record keeping / archiving

12.3.1 Case Report Forms (CRF)

Study data is recorded with electronic Case Report Forms (eCRF). secuTrial® will be used for the eCRF. For each enrolled study participant an 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. We will use a coded identification consisting of a participant number (see chapter 12.2.2).

Authorized for eCRF entries is mainly the investigator, the psychologist, the study coordinator, and other staff members involved in the conduct of the study. Some questionnaires can be completed by study participants themselves. There are separate logins for the participants. The DMP for secuTrial® contains a detailed authorisation matrix. secuTrial® has a detailed audit trail so that every relevant change is traceable and assignable to the person who made it.

(see contract with “Departement Klinische Forschung” (DKF), University Hospital Basel)

12.3.2 Logfiles psychological testing

The following tasks are not entered into the eCRF (secuTrial®) but are collected directly using (web-based) software. The psychological tests will take place at the study centre. The following overview shows the affected tests, the software used, type of collected data, server location and if a study-specific contract, (which also regulates data protection in detail and ensures equivalence to Swiss data protection law) has to be concluded.

Test	Software	Categories of data *	Server location	study-specific contract needed for Software
3-Back Affective WM-Task	Presentation® Neurobehavioral Systems (NBS)[3], Inc., USA	coded	University of Basel (local execution of the software, local storage of log files, no data transfer)	No (licence per device on which the software is running)
Adaptive working memory capacity test (SPAN)	WTS market place, SCHUHFRIED GmbH[4], Österreich	coded	SCHUHFRIED GmbH, Österreich	Yes
15 Words	SoSci-Survey[5]	coded	sciCORE[6], Unibas, CH	No
Tower of London (ToL)	WTS market place, SCHUHFRIED GmbH[7], Österreich	coded	SCHUHFRIED GmbH, Österreich	Yes
Intra-Extradimensional-Dimension (IED)	In-house development by a research group at the UPK Basel with JavaScript-Framework „jspsych“.	coded	University of Basel, CH	Yes, the MIT license (GitHub)[8]

* All of the tools listed generate log files that do NOT contain any information that identifies the subjects. The following information required to assign the log files to the individual test subjects is entered for all tools: code, visit, version of the test for parallel versions, in some cases a study identifier. In addition, the log files are provided with a date and time stamp.

The logfiles will be transferred to a secure electronical archive (Studiendatenbank-MCN) regularly to guarantee originality and to prepare the data for data analysis.

During the data collection phase, data collected with soSci-Survey (sciSCORE), Presentation and WTS the data are backed-up and cannot be changed by the study team. The originality is thus ensured.

We transfer the data continuously to the secure electronical archive (Studiendatenbank-MCN). The data on the servers will be deleted after LPLV at the latest.

12.3.3 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. labor analysis, ECG and pre-screening documentation)
- AE-documentation, concomitant medication
- Mini-DIPS interview documentation
- MADRS and HAMD during screening (both external rating)
- MoCA
- S-Words task
- Administrative documents: visit checklists, individual visit overview, etc.

Direct data entry with secuTrial® by staff members

[3] https://www.neurobs.com/index_html
[4] https://marketplace.schuhfried.com/de/TOL__//__https://marketplace.schuhfried.com/de
[5] www.soscisurvey.de
[6] Center for Scientific Computing at the University of Basel (sciCORE)
[7] https://marketplace.schuhfried.com/de/TOL__//__https://marketplace.schuhfried.com/de
[8] The utilized IED Test is a modified version of a publicly available test dataset obtained from GitHub repository. The repository is licensed under the MIT license, which permits its use in this context.

- Checklist in-/exclusion criteria (investigator)
- Pre-examination visits 2-5 (pregnancy test on visits 2 and 4, etc,)
- Study completion form

Direct data entry with secuTrial® by participants:

- Questionnaires: VAS subjective working memory deficits, sociodemographic data, MADRS-s (self-rating version) (visits 2-5)
- IMP-intake and VAS during treatment periods
- PANAS

Direct data entry with Presentation® by participants:

- n-back
- Affective WM-Task

Direct data entry with SoSci-Survey by participants

- 15 Words

Direct data entry by participants (SCHUFRIED GmbH, Mödling, Österreich)

- Tower of London (ToL)
- Adaptive verbal working memory capacity test (SPAN) backward

Direct data entry by participants (University of Basel)

- Intra-Extra Dimensional Set Shift (IED)

12.3.4 Record keeping / Archiving

The sponsor retains all data relating to the clinical trial until the expiry date of the last delivered batch of the medicinal product under investigation, but for at least twenty years after completion or premature termination of the clinical trial. The principal investigator retains all documents necessary for the identification and follow-up of the trial participants and all other original data for at least twenty years after completion or discontinuation of the clinical trial.

All study related data will be archived in the archives of the Division of Cognitive and Molecular Neuroscience, University of Basel, and in case of the eCRF additionally in the electronic archive-system of the University Hospital Basel.

All electronically captured psychological test data (see 12.3.2) will be archived in a read only status in Studiendatenbank-MCN for at least twenty years (for further information on Studiendatenbank-MCN/LabKey® see chapter 12.3.4).

12.4 Data management

12.4.1 Data management systems

SecuTrial® (eCRF) runs on a server maintained by the IT-department of the University Hospital Basel. The data management group at the Department of Clinical Research (DKF) of the University Hospital Basel implements the eCRF. The user administration and user training is performed by a data manager of the DKF 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

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 a secure data repository and access via a web browser. 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.

Studiendatenbank MCN and SoSci-Survey run on a server maintained by the IT-department of the University of Basel. The data manager of the Division of Cognitive Neuroscience is responsible for the implementation of the tasks, for the user administration and for the user training. Back-up is performed according to processes of the IT-department of the University of Basel. LabKey® has a detailed audit trail so that every relevant change is traceable and assignable to the person who made it. Back-up of the LabKey® database is done by sciCORE, University of Basel, on daily basis. An additional text-file-based

database dump is stored within the Linux or Macintosh file-system deployed by the Psychology IT-Department. This is done occasionally, e.g. when the data collection is finished.

The *source data (including all electronically captured psychological test logfiles, see 12.3.2*) will be stored on a Linux or Macintosh file-system with restricted user access (main file-system). The meta-information of the source data (SHA-1 hashes as 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 LabKey® in a study specific folder (main study folder). The relevant content of the source data that is necessary for creating an analytical database is additionally uploaded to LabKey® (main study folder). The analytical database is created as text-files with time-stamps based on the uploaded or manually entered raw data. These text-files are stored and accessible within the LabKey® file-system.

For source data, we do not expect that any changes will be done. Therefore, we store the meta-information of the source data to be able to verify that the files are in the original state. All other information is documented and stored within LabKey®.

12.4.2 Data security, access and back-up

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 all other used electronic systems, participants are only identified by a unique participant number and the age in years.

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.

12.4.3 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 principal investigator by the data manager of the DKF according to internally defined processes. The exported data will be archived by the data manager MCN in the Studiendatenbank-MCN and printed version from the CRFs by the study coordinator (see 12.3.4).

The electronic data collected by direct data by the participants during the psychological assessments 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.

12.4.4 Electronic and central data validation

secuTrial®: Data entered into the eCRF can be validated for completeness and discrepancies automatically as defined during setup of the data base. 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).

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.

An independent monitor from the DKF Basel will review the data entered into the eCRF. The monitor will raise queries using the query management system implemented. Designated investigators and the study coordinator have to respond to the query and confirm or correct the corresponding data. Thereafter the monitor can close the query.

For source data (including all electronically captured psychological test logfiles) we use different levels of *validation*: As a first step, we evaluate for each subject, visit and computer if all expected files or entries are available and stored in the correct sequence (via the time-stamp). If this basis checks fail, we manually curate the source data, if possible; manual data curation is documented in text-files stored together with the source data or in LabKey®. After performing these basic checks, the data is copied and stored in the final storage space of a study in the main file-system. At the same time-point the meta-information of each file is stored in LabKey®. When uploading the relevant content of the raw data, we further validate if the file-content corresponds to the expected design of a task or survey, if possible (this is data-dependent). Furthermore, within LabKey® we track for each subject, visit and task if there are exclusion reasons (filter-

variables). While creating the final analytical database we apply these filter-variables to the data. An audit trail system maintains a record of initial entries and changes (time and date of changes, user identification of entry and changes). Reasons for changes can be added by a commentary. The data entered or uploaded in the LabKey® study folder will be reviewed by the investigator.

12.5 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.

Monitoring will be provided by the DKF Basel (see contract). Monitoring will be performed according to the separate monitoring plan.

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

12.6 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.

12.7 Confidentiality and Data Protection

Participant's confidentiality will be maintained at all times. Personnel from the sponsor, the principal investigator, DKF Basel, 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

The main publication will be created by Ms. Magdalena Ridder, Prof. Dominique de Quervain, Prof. Andreas Papassotiropoulos, Prof. Annette Brühl, Dr. Nathalie Schicktanz and Dr. Christiane Gerhards.

No publication or communication involving the results of the study is authorized without prior written consent from the Prof. de Quervain, Prof. Andreas Papassotiropoulos and Prof. Annette Brühl.

14 FUNDING AND SUPPORT

Funding of the trial: Getrud Thalman Fond and intramural funds of the Research Cluster Molecular and Cognitive Neurosciences, University of Basel.

15 INSURANCE

The sponsor declares that he has taken out an insurance policy for the total study length, covering the participants in respect of the risks involved in this study. A copy of the certificate is filed in the investigator site file and in the trial master file. 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.

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