Title Page

ABBREVIATED CLINICAL STUDY REPORT

Study Title:

A randomized, placebo-controlled, double-blind, parallel-group Phase 2a exploratory study with placebo run-in to investigate PK/PD effects, safety, tolerability and pharmacokinetics of REM0046127 oral suspension compared with placebo in subjects with mild to moderate Alzheimer's disease

Brief Title:

A Phase 2a, randomized, placebo-controlled, double-blind study to investigate REM0046127 in mild to moderate Alzheimer's disease

Study Number:

REMAD-02

Study Phase:

Phase 2

Compound:

REM0046127

Indication:

Alzheimer's disease

Study Sponsor:

reMYND NV

Gaston Geenslaan 1
B-3001 Leuven
Belgium

Study Initiation Date:

14 September 2022 (first participant first visit)

Early Study Termination Date:

8 July 2024 (last participant last visit)

The analyses presented in this report are based on a database lock date of 30 August 2024.

Primary Completion Date:

8 July 2024 (last participant last visit)

The analyses presented in this report are based on a database lock date of 30 August 2024.

Regulatory Agency Identifier Number:

Registry	ID
EudraCT	2022-000080-43

Report Date:

Version	Date
Version 1.0	6 December 2024

Compliance Statement:

This study was conducted in compliance with the International Council for Harmonisation (ICH) Good Clinical Practice (GCP), including the archiving of essential documents.

Synopsis

Study Title:

A randomized, placebo-controlled, double-blind, parallel-group Phase 2a exploratory study with placebo run-in to investigate PK/PD effects, safety, tolerability and pharmacokinetics of REM0046127 oral suspension compared with placebo in subjects with mild to moderate Alzheimer's disease

Study Number: REMAD-02

Regulatory Agency Identifier Number(s):

Registry	ID
EudraCT	2022-000080-43

Study Phase: Phase 2

Name of Investigational Intervention: REM0046127

Name of Sponsor/Company: reMYND NV

Number of Study Center(s) and Countries:

This study was conducted at 4 centers in The Netherlands and Spain.

Study Period:

The study was initiated on 14 September 2022 (first participant first visit) and was early terminated on 8 July 2024 (last participant last visit).

Rationale:

Alzheimer's disease (AD) is a ravaging neurodegenerative disease that afflicts 35 million people worldwide – a number projected to triple by 2050 (Scheltens *et al.,* 2021). AD is the leading cause of dementia world-wide. Currently available treatments for AD, cholinesterase inhibitors (donepezil, rivastigmine, and galantamine) and a low-affinity NMDA receptor antagonist (memantine), have only modest effects on the symptoms of the disease and do not prevent disease progression.

Disruption of calcium homeostasis plays an important role in the pathogenesis of Alzheimer's dementia (AD) (LaFerla, 2002). Calcium (Ca^{2+}) is an important second messenger controlling numerous signaling pathways and processes underlying synaptic function and neuronal survival. In AD diseased neurons the levels of cytosolic Ca^{2+} are abnormally elevated which drive the synaptic dysfunction, the development of AD pathology and execution of neuronal cell death. From this perspective therapeutic interventions aimed at lowering these elevated cytosolic levels

are expected to restore normal Ca^{2+} mediated signaling and so preventing the cascade of events leading to neuronal degeneration and consequently the development of AD symptomatology.

REM0046127 is a small molecule that lowers Orai calcium channel activity and thereby lowers elevated cytosolic Ca^{2+} to physiological levels, but not below. Although REM0046127 modulates Orai activity, it does not impact store operated Ca^{2+} entry (SOCE) as primary mechanism which is expected to be of limited tolerability. It was predicted that REM0046127 works both as a symptomatic and as a disease modifying treatment for AD.

REM0046127 was administered for the first time in humans in the Phase 1 study NSC20002. The study participants in this study were young healthy male volunteers who received up to 700mg in the SAD part, and elderly healthy male and female volunteers who received up to 1400mg (700mg bid) in the MAD part, where they were treated for 7 consecutive days with REM0046127. Treatment with REM0046127 was generally well tolerated by all individuals of all cohorts in both SAD and MAD phase. There were no serious adverse events and no adverse events that caused discontinuation of any subject. The results of this study supported further clinical development of REM0046127.

Study REMAD-02 was the first study where REM0046127 will be administered to study participants with Alzheimer's disease.

Objectives, Endpoints, Estimands, and Statistical Methods

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• Assess the tolerability and safety of each dose level	• Incidence of treatment-emergent adverse events
Exploratory	
• Assess the relationships between CSF concentrations of REM0046127 and CSF and blood-based biomarkers and EEG parameters	• EEG power, Synaptic markers, Tau, Aβ, and inflammation and global statistical tests that include EEG parameters and biomarkers
• Compare mean changes from baseline by treatment group for CSF and blood-based biomarkers and EEG	
• Assess plasma and CSF PK parameters of each dose level	• Plasma C_{max}, AUC_{inf}, … • REM0046127 concentrations in CSF

• Compare mean changes from baseline by treatment group on cognitive and functional assessments across the study	• Selected tests from MMSE, ADAS-Cog, Executive function test, computerized test, A-IADL

Methodology:

This was a phase 2, double blind, randomized, placebo-controlled multicenter study with a study duration of up to 3.5 months for each treated study participant. Every study participant had to undergo an up to 28 days screening period, a 14-day placebo run-in period, followed by a 28-day treatment period. Afterwards, (a) follow up visit(s) had to take place.

Number of Participants:

Up to 60 participants were planned, 15 participants were randomized. One participant discontinued the study on day 1, 14 participants were included in the Safety, PK population.

Diagnosis and Main Criteria for Inclusion and Exclusion:

Male and female study participants aged 50 to 85 with mild to moderate Alzheimer's disease according to The National Institute on Aging-Alzheimer's Association (NIA-AA) Research Framework with a clear EEG deficit and with no other clinical, laboratory or neuro-imaging findings that could confound the study results.

Study Interventions, Dose, Mode of Administration, and Batch Number(s):

REM0046127 1400mg (10 mL of 70mg/mL BID, Batch N°202200022), REM0046127 350mg (10 mL of 17.5mg/mL BID, Batch N°202200018), REM0046127 88mg (2.5 mL of 17.5mg/mL BID, Batch N°202200018) or placebo (10 mL or 2.5 mL of placebo BID, Batch N°2022200007, 2022200009 and 2022200011) white to off-white viscous microsuspension for oral administration.

Duration of Study Intervention:

14 days placebo run-in followed by 28-day treatment phase

Summary of Results and Conclusions:

Overt Drug Induced Liver Injury (DILI) in some patients in the 2 highest dose groups, combined with elevated transaminase levels potentially associated with DILI at all dose levels led to early termination of the trial.

Demographic and Other Baseline Characteristics: **(mean +/- SD (min, max)) of Safety, PK population**

	Placebo (n=4)	**88 mg/day (n=5)**	**350 mg/day (n=3)**	**1400 mg/day (n=2)**
Age (years)	69 ± 12 (54, 82)	74 ± 5.3 (66, 80)	76 ± 5.6 (71, 82)	72 ± 19 (58, 85)

Male (%)	2 (50%)	2 (40%)	2 (67%)	0 (0%)
Female (%)	2 (50%)	3 (60%)	1 (33%)	2 (100%)
MMSE at screening	18 ± 1.7 (16, 20)	19 ± 2.3 (15, 21)	19 ± 1.2 (18, 20)	12.5 ± 0.7 (12, 13)
BMI	28 ± 3.0 (24, 31)	23 ± 2.0 (20, 25)	28 ± 6.3 (21, 33)	26 ± 1.0 (25, 26)
ABeta42 (pg/ml)	533 ± 227 (390, 868)	479 ± 113 (278, 550)	689 ± 253 (454, 957)	567 ± 46 (534, 599)
pTau181 (pg/ml)	28 ± 15 (18, 50)	41 ± 21 (26, 78)	30 ± 4.0 (25, 32)	62 ± 36 (36, 87)
pTau181/AB42	0.052 ± 0.011 (0.038, 0.063)	0.089 ± 0.040 (0.050,0.14)	0.046 ± 0.011 (0.033, 0.055)	0.11 ± 0.055 (0.067, 0.15)

Exposure:

All participants started with a placebo run-in phase for 14 days. Participants were exposed to 1400mg/day, 350mg/day, 88mg/day or placebo for 28 days.

Safety Results:

Treatment with REM0046127 was associated with a risk developing Drug Induced Liver Injury (DILI) which resulted in early termination of the trial.

Pharmacokinetic Results:

REM0046127 had a quasi-dose dependent plasma exposure in the 88mg/day to 350mg/day dose range and supra-dose proportional exposure beyond 350 mg/day. Exposure in CSF was sufficient highfor full target engagement in all dose groups tested.

Date and Version of This Report:

Version 1.0, dated 06Dec2024

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List of Abbreviations

AD	Alzheimer's disease
AE	Adverse Events
Aβ	amyloid beta
bid	bis in die - twice a day
Ca2+	Calcium
CSF	cerebrospinal fluid
D	day
DILI	Drug Induced Liver Injury
EEG	electroencephalogram
EOT	end of treatment
h	hour
ICF	informed consent form
IEC	independent ethics committee
IMP	investigational medicinal product
IWRS	Interactive Web Response System
Kd	dissociation constant
NMDA	N-methyl-D-aspartate
PD	pharmacodynamics
PK	pharmacokinetics
SOCE	store operated Ca2+ entry
SUSAR	suspected unexpected serious adverse reaction
t1/2	half-life
TEAE	Treatment Emergent Adverse Event
ULN	upper limit of normal

Ethics

Independent Ethics Committee and/or Institutional Review Board

The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents were submitted to an IEC by the investigator/sponsor and reviewed and approved by the IEC before the study was initiated.

Any amendments to the protocol obtained IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

Appendix 8.2.1: List of IECs includes a list of all IECs.

Competent Authorities

As applicable according to local regulations, the protocol and all protocol amendments were reviewed and approved by each pertinent Competent Authority.

Ethical Conduct of the Study

This study was conducted in accordance with the protocol and consensus ethical principles derived from international guidelines including the Declaration of Helsinki, Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines, applicable ICH GCP Guidelines, and other applicable laws and regulations.

Participant Information and Consent

The investigator or his/her representative explained the nature of the study to the participant and answered all questions regarding the study.

Participants were informed that their participation was voluntary. Participants were required to sign a statement of informed consent that met the requirements of local regulations, ICH guidelines, HIPAA requirements, where applicable, and the IEC and study center.

Investigative sites were instructed to obtain written informed consent before the participant was enrolled in the study and document the date the written consent was obtained. The authorized person obtaining the informed consent was also instructed to sign the ICF. Participants were reconsented to the most current version of the ICF(s) during their participation in the study.

A copy of the ICF(s) was provided to the participant.

1. Introduction

1.1. Background

Dysregulation of calcium signaling plays a central role in the pathogenesis of Alzheimer's disease, and therefore therapeutic intervention to normalize calcium signaling is expected to be therapeutically beneficial (Webber *et al.,* 2023). On the one hand increased intracellular cytosolic calcium and the associated deregulation of Ca^{2+} responsive pathways elicit the characteristic pathophysiology of AD, including accumulation of amyloid-β, hyperphosphorylation of TAU, synaptic dysfunction and neuronal death. On the other hand, neurodegeneration triggered by pathological amyloid-β or TAU requires disturbed calcium signaling. Hence disturbed Ca2+ signaling and AD pathophysiology constitutes a vicious cycle of mutually reinforcing processes which, once set-in motion, lead to neurodegeneration.

1.1.1. REM0046127

REM0046127 is a small molecule intended for the treatment of Alzheimer's dementia (AD). It lowers Orai calcium (Ca^{2+}) channel activity which consequently results in decreased levels of elevated cytosolic Ca^{2+} in AD diseased neurons. Accordingly, REM0046127 restores neuronal synaptic strength, network activity and cognition, reduces exocytosis of protein tau, and reduces brain amyloid beta (Aβ) plaques formation as well as neuronal inflammation, refer to the Investigator's Brochure for more information.

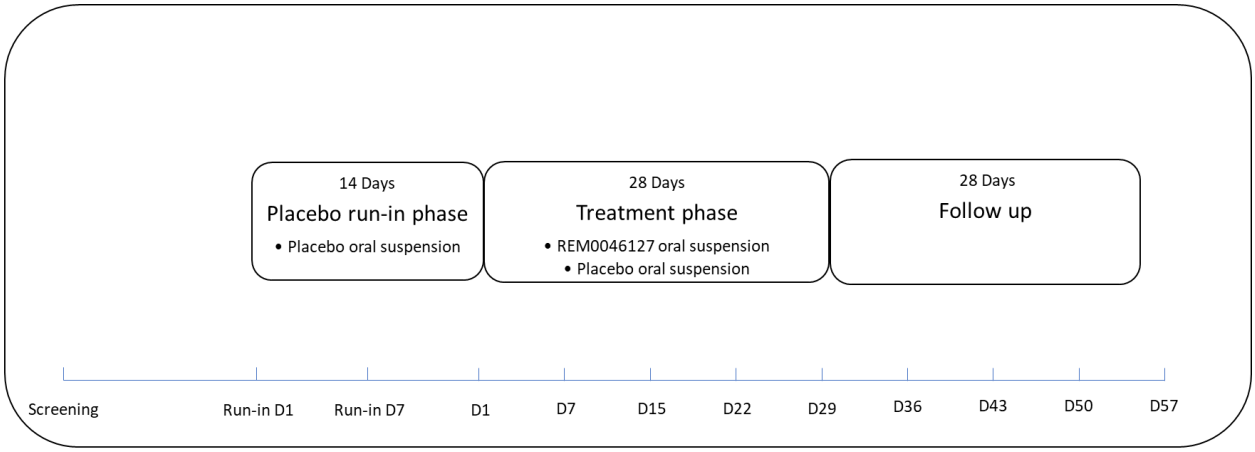
Although REM0046127 modulates Orai activity, it does not impact store-operated Ca^{2+} entry (SOCE) as primary mechanism which would otherwise alter regular receptor mediated signaling which is expected to be of limited tolerability.

Importantly, REM0046127 restrains excessive Ca^{2+} influx only in diseased neurons impacted by the typical changes seen in AD without lowering cytosolic Ca^{2+} below the normal physiological levels even at concentrations >100 times higher than its cellular EC_{50}. No impact on basal Ca^{2+} in healthy neurons is observed. This illustrates that Ca^{2+} homeostasis is normalized but that the physiological functions of cytosolic Ca^{2+} are not impacted. The resulting selective and disease-specific inhibition of calcium influx into Alzheimer-compromised neurons is neuroprotective, and therefore potentially disease-modifying.

Therefore, REM0046127 was a promising drug candidate for the oral treatment of Alzheimer's disease combining potentially cognitive improvement with a slowing of the disease progression in AD patients.

2. Investigational Plan

2.1. Overview of Study Design



D = Day

2.1.1. Discussion of Study Design

The scientific rationale for features of the study design, including chosen control group(s), dose(s), and endpoint(s), as applicable, are discussed in the Scientific Rationale for Study Design section of the protocol Appendix 8.2.3 Study Protocol.

2.1.2. Changes in Study Conduct

All changes in the conduct of the study were implemented by protocol amendment(s), as described in Appendix 8.2.3 Study Protocol.

2.2. Investigators and Study Administrative Structure

Appendix 8.2.2 includes investigator information, study personnel, and the study administrative structure. The study protocol in Appendix 8.2.3 provides additional information on the organization of the study.

2.3. Selection of Study Population

2.3.1. Inclusion/Exclusion Criteria

This study enrolled participants with Alzheimer's Disease. Detailed inclusion and exclusion criteria are provided in Appendix 8.2.3 Study Protocol.

2.3.2. Removal of Participants from Intervention or Study

The specific criteria and procedures for early discontinuation from investigational intervention(s) or withdrawal from the study are described in Appendix 8.2.3 Study Protocol.

2.4. Study Intervention

2.4.1. Study Interventions Administered

The study intervention(s) and arm assignments are outlined in Tables 1 and 2. The justification for the dose(s) selected is described in the justification for dose section of the protocol (Appendix 8.2.3 Study Protocol).

Table 1. Study Intervention(s) Administered

Intervention Label	REM0046127 or Placebo	REM0046127 or Placebo	REM0046127 or Placebo
Intervention Name	REM0046127 70 mg/ml	REM0046127 17.5 mg/ml	Placebo
Intervention Description	White to off-white viscous microsuspension for oral administration	White to off-white viscous microsuspension for oral administration	White to off-white viscous microsuspension for oral administration
Type	Drug	Drug	Drug
Dose Formulation	Other	Other	Other
Unit Dose Strength(s)	70 mg/ml	17.5 mg/ml	0.0 mg/mL
Dosage Level(s)	Cohort 1: 10 ml BID	Cohort 1: 10 ml BID Cohort 2: 2.5 ml BID	Cohort 1: 10 ml BID Cohort 2: 2.5 ml BID
Route of Administration	Oral	Oral	Oral
Use	experimental	experimental	experimental
IMP and NIMP/AxMP.	IMP	IMP	IMP
Sourcing	Provided centrally by the sponsor	Provided centrally by the sponsor	Provided centrally by the sponsor
Packaging and Labeling	IMP was provided in 30 mL amber Kylix bottles. Each bottle and kit were labeled as required per country requirement.	IMP was provided in 30 mL amber Kylix bottles. Each bottle and kit were labeled as required per country requirement.	IMP was provided in 30 mL amber Kylix bottles. Each bottle and kit were labeled as required per country requirement.

Table 2: Study Arm(s)

Arm Title	Placebo run-in	REM0046127	Placebo
Arm Type	placebo	experimental	placebo
Arm Description	Study participants received 10- or 2.5-ml placebo BID from Run-in Day 1 to Run-in Day 14	Study participants received 10 or 2.5 ml REM0046127 17.5 or 70 mg/ml BID from Day 1 to Day 29	Study participants received 10- or 2.5-ml placebo BID from Day 1 to Day 29
Associated Intervention Labels	REM0046127 or Placebo	REM0046127 or Placebo	REM0046127 or Placebo

The manufacturing lot numbers for the study intervention(s) dispensed in this study are in Table 3.

Table 3: Batch numbers for the study intervention

Dose group	IMP administered	Batch N°
REM0046127 1400mg	10 mL of 70mg/mL REM0046127 BID	2022200022
REM0046127 350mg	10 mL of 17.5mg/mL REM0046127 BID	2022200018
REM0046127 88mg	2.5 mL of 17.5mg/mL REM0046127 BID	2022200018
placebo	10 mL or 2.5 mL of placebo BID	2022200007, 2022200009, 2022200011

2.4.2. Measures to Minimize Bias

Method of Assigning Participants to Study Intervention

All participants were centrally randomized to investigational intervention using IWRS. The method used to assign/allocate participants is further described in the Assignment to Study Intervention section of the protocol (Appendix 8.2.3 Study Protocol).

Blinding

This study design included participant, caregiver, investigator and assessor masking.

2.4.3. Study Intervention Compliance

The methods used to assess study intervention compliance are described in the Study Intervention Compliance section of the protocol (Appendix 8.2.3 Study Protocol).

2.5. Study Assessments and Procedures

2.5.1. Planned Measurements and Timing of Assessments

The specific efficacy, PK, PD, and safety assessments, their schedule and measurement/collection methods are provided in the Schedule of Activities and described in the Study Assessments and Procedures sections of the protocol (Appendix 8.2.3 Study Protocol). The collection and assessment of safety information during the study (evaluation, definitions, recording, and reporting of AEs, SAEs and other reportable safety events) is detailed in the Safety Assessments and Adverse Events section of the protocol (Appendix 8.2.3 Study Protocol).

2.6. Data Quality Assurance

2.6.1. Study Monitoring

Study centers were monitored by CRO. Centers were visited at regular intervals and a Visit Log was maintained. Monitors were assigned for reviewing adherence to the protocol; compliance with GCP; and the completeness, accuracy, and consistency of the data. Direct access to

participant medical and laboratory records was permitted to verify entries on the study-specific CRFs.

2.6.2. Laboratory Procedures

Central laboratories were used to analyze the samples (Appendix 8.2.2).

2.6.3. Investigator Responsibilities

The investigators were responsible for all data entered into the CRFs and documented their review and approval of the data, verifying the validity and completeness of the data. The investigator was responsible for appropriate retention of essential study documents.

2.6.4. Clinical Data Management

Case report form data were captured via data entry by study center personnel in a database system owned by a CRO. Data quality checks were applied using manual and electronic verification methods.

2.6.5. Clinical Quality Assurance Audits

Quality audit assessments were not performed for this study.

3. Study Participants

3.1. Disposition of Participants

The disposition of all enrolled study participants is provided in Table 4 and summarized in Figure 1.

Table 4: Participants disposition (n(%))

	REM0046127 1400 mg	REM0046127 350 mg	REM0046127 88 mg	Placebo	Total
Screened					34 (100%)
Did not complete screening					19 (56%)
Randomized	2 (100%)	3 (100%)	6 (100%)	4 (100%)	15 (44%)
Discontinued study treatment early	0 (0%)	1 (33%) [*]	1 (16%) [$]	1 (25%) [*]	3 (20%)
Completed study as per protocol	2 (100%)	2 (66%)	4[**] (66%)	3 (75%)	11 (73%)

[*]Study treatment was discontinued on day 23 upon sponsor request due to the occurrence of potential DILI in other study participants

[$]Study treatment was discontinued on day 1 upon sponsor request due to decision of early termination of the trial – patient did receive only 1 dose of REM0046127 and did not report any adverse events. It was decided not to include this patient in the safety population as it would skew significantly the distribution of reported AEs.

[**]One study participant received unauthorized medication.

n: number of study participants

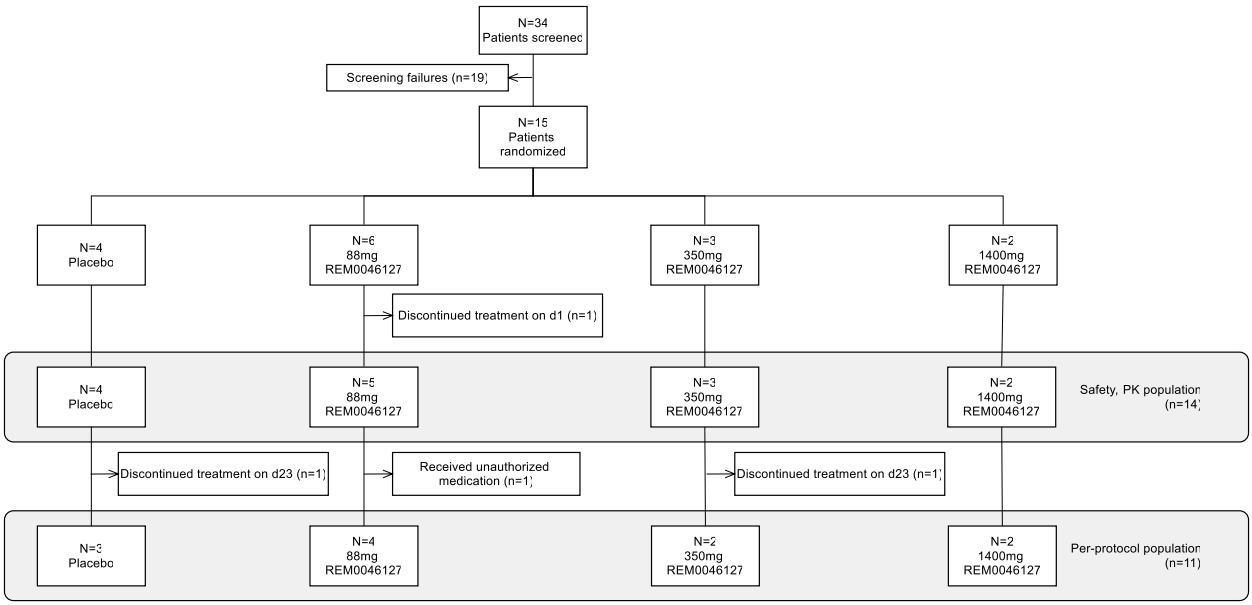


Figure 1: Disposition of participants

3.2. Protocol Deviations

Protocol deviations are presented in Appendix 8.1.1.

A total of 73 protocol deviations were reported, of which none were deemed important.

3.3. Demographic and Other Baseline Characteristics

Table 5: baseline characteristics (mean +/- SD (min, max)) unless otherwise specified) of Safety, PK population

	1400 mg/day (N=2)	**350 mg/day (N=3)**	**88 mg/day (N=5)**	**Placebo (N=4)**
Age (years)	72 ± 19 (58, 85)	76 ± 5.6 (71, 82)	74 ± 5.3 (66, 80)	69 ± 12 (54, 82)
Male (%)	0 (0%)	2 (67%)	2 (40%)	2 (50%)
Female (%)	2 (100%)	1 (33%)	3 (60%)	2 (50%)
MMSE at screening	12.5 ± 0.7 (12, 13)	19 ± 1.2 (18, 20)	19 ± 2.3 (15, 21)	18 ± 1.7 (16, 20)
BMI	26 ± 1.0 (25, 26)	28 ± 6.3 (21, 33)	23 ± 2.0 (20, 25)	28 ± 3.0 (24, 31)
Aβ42 (pg/ml)	567 ± 46 (534, 599)	689 ± 253 (454, 957)	479 ± 113 (278, 550)	533 ± 227 (390, 868)
pTau181 (pg/ml)	62 ± 36 (36, 87)	30 ± 4 (25, 32)	41 ± 21 (26, 78)	28 ± 15 (18, 50)
pTau181/Aβ42	0.11 ± 0.055 (0.067, 0.15)	0.046 ± 0.011 (0.033, 0.055)	0.089 ± 0.040 (0.050,0.14)	0.052 ± 0.011 (0.038, 0.063)

N: total number of study participants in dose group

3.4. Prior and Concomitant Therapy

For the acetylcholinesterase inhibitors donepezil, galantamine, and rivastigmine and the NMDA antagonist memantine, participants were allowed to be stably on such medication for more than 6 months with no expected changes during the study.

Of the 14 participants, 13 received one of these treatments (Table 6). 10 participants received an acetylcholinesterase inhibitor (donepezil, galantamine or rivastigmine) and 3 participants received memantine.

Table 6: concomitant AD treatment (n (%))

	1400 mg/day N=2	**350 mg/day N=3**	**88 mg/day N=5**	**Placebo N=4**
Acetylcholinesterase inhibitor	1 (50%)	1 (33%)	5 (100%)	3 (75%)
Memantine	1 (50%)	1 (33%)	0 (0%)	1 (25%)

n: number of study participants receiving treatment, N: total number of study participants in dose group.

One participant in the 88 mg/day dose group received quetiapine treatment (atypical antipsychotic) from D21-D28. This drug interacts with neuronal pathways triggering cognitive dysfunction; hence this participant was excluded from the efficacy analysis.

3.5. Exposure and Study Intervention Compliance

3.5.1. Exposure

All participants started with a placebo run-in phase for 14 days. Thereafter participants were exposed to 1400mg/day, 350mg/day, 88mg/day or placebo for 28 days.

3.5.2. Dose Modification

Due to adverse events related to drug induced liver injury (DILI) in participants exposed to 1400mg/day and 350mg/day, the study was temporarily put on clinical hold to review safety data. Based on the recommendations of experts in the field of DILI, a protocol amendment was implemented where the dose was reduced to 88mg/day.

3.5.3. Compliance with Intervention

Two study participants, one in the 350mg/day group and one in the placebo group ended their treatment on day 23 at the request of the sponsor, due to suspected DILI observed in other study participants treated.

4. Evaluation of Response to Study Intervention

All data presented includes the Safety/PK population.

4.1. Adverse Events (AEs)

Table 7: Adverse Events Overview

Total number of study participants with at least one:	Placebo (N=4)			88 mg (N=5)			350 mg (N=3)			1400 mg (N=2)			All study participants (N=14)		
	n	%	m	n	%	m	n	%	m	n	%	m	n	%	m
TEAE	3	75	6	5	100	20	3	100	16	2	100	14	13	92.9	56
Serious TEAE	0	0	0	0	0	0	1	33	1	0	0	0	1	7.1	1
Non-Serious TEAE	3	75	6	5	100	20	2	66	15	2	100	14	12	85.7	55
Severe TEAE	0	0	0	0	0	0	1	33	1	0	0	0	1	7.1	1
Fatal TEAE	0	0	0	0	0	0	0	0	0	0	0	0	0	0.0	0
Treatment related TEAE	2	50	2	3	60	4	3	100	7	2	100	9	10	71.4	22
Serious Treatment related TEAE	0	0	0	0	0	0	1	33	1	0	0	0	1	7.1	1
Not-treatment related TEAE	3	75	4	5	100	16	3	100	9	2	100	5	13	92.9	34

n: number of study participants with event, m: number of events, TEAE: treatment emergent adverse events.

The denominator for the percentage calculations is N: total number of subjects in the safety analysis set per treatment.

Treatment related is defined as at least possibly drug related according to the investigator.

Table 8: TEAE by SOC and PT, reported at least 3 times

	Placebo (n=4)			88 mg (n=5)			350 mg (n=3)			1400 mg (n=2)			All study participants (n=14)		
System Organ Class Preferred term	n	%	m	n	%	m	n	%	m	n	%	m	n	%	m
Any TEAE	3	75	6	5	100	20	3	100	16	2	100	14	13	92.9	56
Gastrointestinal disorders	**1**	**25**	**2**	**1**	**20**	**1**	**2**	**67**	**3**	**2**	**100**	**5**	**6**	**42.9**	**11**
Nausea	1	25	1	0	0	0	1	33	1	1	50	1	3	21.4	3
Hepatobiliary disorders*	**0**	**0**	**0**	**1**	**20**	**2**	**3**	**100**	**5**	**2**	**100**	**3**	**6**	**42.9**	**10**
Blood lactate dehydrogenase increased	0	0	0	0	0	0	2	67	2	1	50	1	3	21.4	3

	Placebo (n=4)			88 mg (n=5)			350 mg (n=3)			1400 mg (n=2)			All study participants (n=14)		
System Organ Class Preferred term	n	%	m	n	%	m	n	%	m	n	%	m	n	%	m
Transaminases increased	0	0		1	20	1	1	33	1	1	50	1	3	21.4	3
Injury, poisoning and procedural complications	**1**	**25**	**1**	**3**	**60**	**3**	**1**	**33**	**2**	**2**	**100**	**2**	**7**	**50.0**	**8**
Post lumbar puncture syndrome	1	25	1	2	40	2	1	33	2	1	50	1	5	35.7	6

*Refer to Section 4.1.1 for detailed description of observed AEs related to liver safety

n: number of study participants with event, m: number of events, TEAE: treatment emergent adverse events.

The denominator for the percentage calculations is N: total number of subjects in the safety analysis set per treatment.

4.1.1. Liver Safety Observations

In this study a total of 5 out of 10 patients treated with REM0046127 presented with increased transaminases (≥3 x ULN) at around day 29 of the study – 2/2 (100%) patient in the 1400 mg/day dose group, 2/3 (66%) in the 350 mg/day dose group and 1/5 (20%) in the 88 mg/day dose group. None in the placebo group reported transaminase increases.

A common feature of these transaminase increases is the time of onset, usually noticed either at last day of study drug intake, or at the follow-up visits, peaking days to weeks after study drug discontinuation. The time course to resolution was usually longer than expected (weeks to months after peak transaminase values).

One case fulfilled seriousness criteria and was reported to ethics committees and competent authorities as a suspected unexpected serious adverse reaction (SUSAR).

Narratives for all these cases can be found in Section 7.1 of this CSR.

For the reported SUSAR case the patient affected was a 71-year-old male Caucasian who developed significant transaminase increase first measurable on day 29. In day 36 follow-up visit analysis the values continued to increase, with now additionally LDH approx. 3 times upper limit of normal (ULN) as well as increasing values of total bilirubin (4.94 mg/dl or 4.1 times ULN) with a presence of bilirubinemia and choluria, and also coagulation tests were altered with INR at 1.6 (0.90-1.20 limits according to local laboratory) and decreased prothrombin time at 48.8%. At clinical examination the investigator described a discrete jaundice of the skin and eye corneas. The patient was hospitalized and a transjugular liver biopsy was performed, showing acute hepatitis with a necro-inflammatory pattern with confluent perivenular necrosis and mixed lymphocytic infiltrates. On day 51 transaminases reached a maximum of 37 times the upper limit of normal of AST and 47 times the upper limit of normal for ALT and a total bilirubin of 10.1mg/dL GGT peaked up to 9 times the upper limit of normal at day 76. After treatment

initiation with corticoids 60 mg/day, a notable decrease in transaminases was observed, a slight increase in the prothrombin index (56.4%) and a decrease in total bilirubin (9.1 mg/dl). Given the patient's good clinical condition and the improvement in his blood tests he was discharged and was surveilled by clinical and analytical follow-ups.

Due to this event a clinical hold was put on the study. The study was unblinded to guide further decision making and follow up of the patients.

For the non-SUSAR cases, the maximal elevation of transaminase levels was in the range of 5- to 10-fold the ULN for ALT, with slightly lower (but similar) increases in AST. Other lab parameters remained unaffected, including alkaline phosphatase and total bilirubin. Patients have been followed up until the resolution of the abnormalities.

Apart from the above, transaminase increases < 3 x ULN have been reported for other subjects receiving REM0046127 – all were self-limiting and without associated signs or symptoms:

- Study participant 205 with an AE of elevated transaminase (1.42 x ULN for ALT on Day 51), and
- Study participant 305 did not have a reported AE, but did present with an elevated ALT of 2.26 x ULN on Day 29.

Refer to Figure 2 for a graphical presentation of the ALT elevation over time.

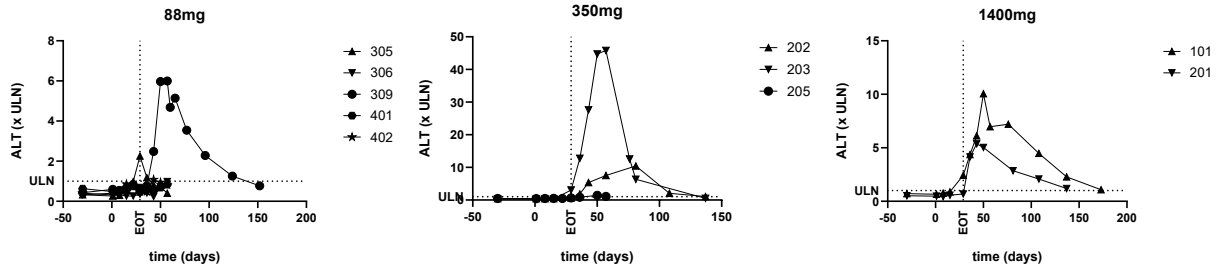


Figure 2: ALT elevation over time, presented as times ULN. (ULN: upper limit of normal; EOT: end of treatment)

4.2. Evaluation of Clinical Laboratory Tests

See Section 7.2 and 7.3.

In total 7 AEs were reported relating to abnormal clinical lab tests:

- 3 cases of increased LDH (study participants 201, 202 and 203; 1 in 1400mg group and 2 in 350 mg group)
- 1 case of decreased PT and decreased aPTT time (study participant 206, 1 in placebo group)
- 1 case of increased blood glucose (study participant 201, 1 in 1400mg group)
- 1 case of increased uric acid (study participant 205, 1 in 350mg group)

All these findings are resolved spontaneously. Some LDH increases reported are probably caused by the reported DILI or transaminase increases.

No other lab abnormalities were reported as AE.

Among treated participants (Safety, PK population), a consequent decrease in total Cholesterol was noted, a finding consistent with observations made in preclinical toxicity studies. The relevance of these findings, their potential relationship with the observed liver function test abnormalities, its relation to study drug intake and its underlying mechanism are still to be elucidated.

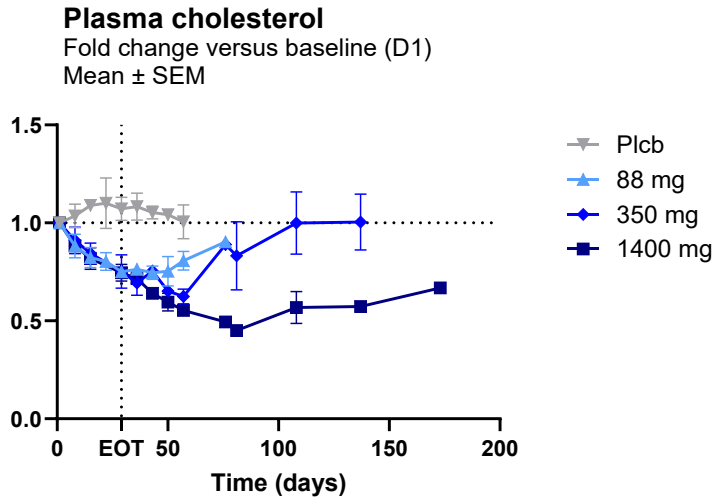


Figure 3: Cholesterol decrease over time, presented as fold change from baseline (D1, day 1; Plcb: placebo; EOT: end of treatment).

4.2.1.1. Vital Signs, Electrocardiograms, Physical Examination Findings

There were no clinically meaningful findings in the vital signs' measurements, physical examination assessments, ECGs, or other observations related to safety in this study. The assessments and observations were comparable across study arms.

4.3. Pharmacokinetics

4.3.1. Dose and Exposure in plasma

REM0046127 reached maximum observed plasma concentration (t_{max}) around 2 hours postdose in all dose groups. The mean terminal elimination half-life ($t_{1/2}$) was 320h, 438h and 396h for the 88, 350 and 1400mg/day groups respectively. Whereas in the Phase 1 SAD/MAD study, the $t_{1/2}$ of the compound after single dose estimated to be 24 hours, it was prolonged in the REMAD-02 study to 6-9 days after 28 days of BID dosing, even up to >13 days when looking at terminal half-life.

C_{max} and AUC_{0-6h} increased with increasing doses and seem to be dose proportional (Table 9 and Table 10). Steady state was not yet reached on day 8, hence for the 88mg/day dose group multiple PK sampling was done on day 22 instead of Day 8.

Although no firm conclusions can be made comparing Day 8 vs Day 22 data (no steady state on Day 8) we can estimate by visual inspection of the concentration-time plots that steady state appears to be reached by day 15 of dosing – and not by Day 8. This is also in line with the estimated half-life of approximately 7-9 days. Terminal half-life of 300+ hours has been deducted from the available data.

Comparing measured concentrations at 3h postdose (i.e. around C_{max}) between Day 22 (88 mg) and Day 29 (350mg and 1400 mg) reveal a quasi-dose-proportional increase in circulating drug levels in the 88 mg/day to 350 mg/day dose range, and supra-dose-proportional beyond 350 mg/day.

All these comparisons have serious limitations because of the limited amount of data that can be compared one-on-one, and the fact that steady state concentrations were not reached before Day 15 of dosing, making the comparison between Day 8 PK and Day 22 PK problematic.

Table 9: 350mg/day and 1400mg/day plasma exposure

	350 mg/day (N=3)	**1400 mg/day (N=2)**
C_{max} D8 (ng/mL) *	2830 (14%)	9890 (48%)
T_{max} D8 (h)*	2	2
AUC $D8_{0-6h}$ (ng.h/mL) *	12066	46716
$t_{1/2}$ (D29-D36) (h)*	215	167
$t_{1/2}$ terminal (h)**	438	396
Css (ng/mL) *	Not Available	Not Available
*Limited N, not all patients have data, dependent on method of calculation		
**Limited N and dependent on method of calculation: range 400-600h Data is shown as Mean (CV%) for Cmax and as Mean for the other parameters. ss: steady state		

Table 10: 88mg/day plasma exposure

	88 mg/day (N=5)
C_{max} D22 (ng/mL)	1199 (18%)
T_{max} D22 (h)	2,4
AUC $D22_{0-6h}$ (ng.h/mL)	5475

$t_{1/2}$ (D29-D36) (h)	141
$t_{1/2}$ terminal (h)	320
Css (ng/mL)	706

Data is shown as Mean (CV%) for Cmax and as Mean for the other parameters.
ss: steady state

4.3.2. Dose and exposure in CSF

REM0046127 exposure was assessed in CSF samples taken at D29 at 3h post last dose. At all dose levels tested, REM0046127 was detected and increased with increasing dose levels. This seems to be dose proportional (Table 11).

Table 11: CSF exposure on day 29 (mean, (min, max))

	1400 mg/day (N=2)	**350 mg/day (N=2)***	**88 mg/day (N=5)**
CSF conc (ng/mL)	84.8 (52.6, 117,0)	28.7 (26,0, 31.5)	5.5 (2.7, 13.3)

*No CSF sample was taken at EOT (end of treatment) for subject 205.

4.3.3. Drug exposure and Safety

In the 1400mg/day dose group, all study participants (2/2) had elevations of transaminases in the range of 5- to 10-fold the upper limit of normal (ULN) for ALT, with slightly lower (but similar) increases in AST. In the 350mg/day group, 1 study participant (1/3) demonstrated a very limited increase in ALT only, up to 1.42x ULN at most, 1 study participant (1/3) had elevations of transaminases in the range of 5- to 10-fold the ULN and 1 study participant (1/3) developed a manifest DILI which required hospitalization. In the 88mg/day dose group, 1 study participant (1/5) had elevations of transaminases in the range of 5- to 10-fold the ULN for ALT, with slightly lower (but similar) increases in AST. All the observed elevations in transaminases started to occur on D29 or later. It seems that the liver toxicity is dose dependent since the observed frequency of liver function test abnormalities was lower in the 88mg/day group. However, the severity of increasing transaminases and DILI did not appear to be dose related. None of the reported/observed transaminase elevations was accompanied by increases in Alkaline Phosphatase, Total Bilirubin, coagulations abnormalities, and/or signs/symptoms – except for the reported SUSAR case.

4.3.4. Drug exposure and Response

The dissociation constant (Kd) of REM0046127 to bind to its target Septin 6 is 0.6 ng/ml (Princen *et al.,* 2024). The concentrations reached in the CSF at all dose groups are above this level with a margin of 7.5, 48 and 131 in the 88, 350 and 1400mg/day dose groups respectively (Figure 4). This means that full target engagement was reached in all dose groups tested.

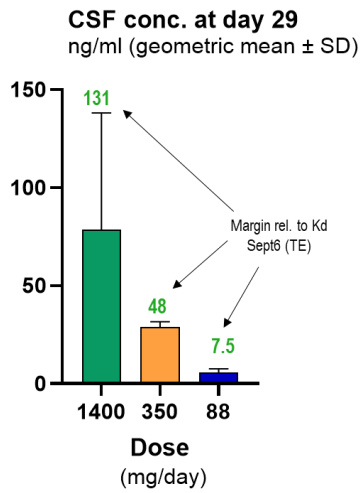


Figure 4: CSF concentrations measured in the different dose groups. In light green, the margin to the Kd of Septin 6 is indicated, which is a measure for the target engagement (TE). See **Table 11** for the number of subjects per group.

5. Conclusions

Overt Drug Induced Liver Injury (DILI) in some patients in the 2 highest dose groups, combined with elevated transaminase levels potentially associated with DILI at all dose levels led to early termination of the trial.

6. References

LaFerla, Nat Rev Neurosci. 2002 (11):862-72. Calcium dyshomeostasis and intracellular signalling in Alzheimer's disease.

Katrien Princen et al. ,Pharmacological modulation of septins restores calcium homeostasis and is neuroprotective in models of Alzheimer’s disease. Science384, eadd6260(2024). DOI:10.1126/science.add6260

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7. Tables, figures and graphs referred to but not included in the text

7.1. Subject narratives

7.1.1. Study participant 101

Death, Date of Death (Study Day): No	**Other Event of Interest:** No
Other SAE: No	**Potential DILI Case:** Yes
AE Leading to Discontinuation: No	

Protocol Number: REMAD-02	**Age (years, at study entry):** 58
Subject Number: 1-101	**Sex:** Female
Height (cm, at study entry or first exam): 170	**Weight (kg, at study entry or first exam):** 75.5
Race/Ethnicity: White/ not Hispanic Or Latino	**Country:** The Netherlands
Assigned Treatment Group: 700 mg BID for 28 days	
Start Date (Study Day) of Study Drug(s) Dosing: 25-Oct-2022	**Stop Date (Study Day) of Study Drug(s) Dosing:** 22-Nov-2022

Event(s) Requiring a Narrative

Preferred Term/ Reported Term	Reason for Narrative	Onset Day/ Onset Date	End Day/ End Date	Investigator Assessment of Severity/ Relationship to Study Drug	Action Taken for Study Drug/Treatment Required	Outcome
HEPATIC ENZYME INCREASED/ ELEVATED LIVER ENZYMES	PDC	29 / 22-Nov-2022	191/ 10-May-2023	Mild/ Related To Study Drug	No action taken / no treatment required	Recovered

Reason for narrative: D: death; SAE: serious adverse event; DC: adverse event leading to discontinuation; EI: event of interest; PDC: potential DILI case.
NR: not reported

Sequence of Events

The patient's medical history includes carpal tunnel syndrome (2010 and 2019), recurrent cystitis (start date 2017), bursitis right shoulder (Nov-2020), post lumbar puncture headache (mild, Feb-2021 and Aug-2021), Covid-19 infection (Jun-2022), Alzheimer's Disease (Nov-2019).

The patient was treated with oral Galantamine @ 16 mg QD since 02-Feb-2021.
On 14-Oct-2022 (day -11), she received a prophylactic influenza vaccine (intramuscular).

At baseline (D1 – randomization), aminotransferase (ALT) was 23 U/L, and within normal limits (10 - 35). On the same day vital signs were as follows: BP 148/92 mmHg, pulse 79 beats per minute (bpm), and temperature 36.9ºC, and BMI was ca 26 kg/m^2.

On 22-Nov-2022 (day 29), Visit 7, the patient developed the nonserious, potential drug induced liver injury (DILI) case of elevation in ALT (85 U/L 2.4x ULN [10-35]) and elevation in aspartate aminotransferase (AST 46 U/L 1.3x ULN [10 - 35]) that were mild in intensity. The patient had no signs or symptoms associated with hepatitis or a drug induced liver injury. Other laboratory test results reported on 22-Nov-2022 (day 29), were lactate dehydrogenase (LDH) 224 U/L (135 - 214), alkaline phosphatase (ALP) 77 U/L (35 - 104), total bilirubin (BILI) 0,27 mg/dL (<1,2), gamma glutamyl transferase (GGT) 35 U/L (0 - 42), and eosinophiles 2,6% (<5,0).
Study drug was stopped on 22-Nov-2022 (day 29) as per protocol.

Transaminase levels were assessed on 29-Nov-2022 (day 36 – EOS visit), 05-Dec-2022 (day 43) and 13-Dec-2022 (day 51), and the results were: ALT 153 4.4 x ULN, 214 7.5 x ULN, and 352 U/L 10.1 x ULN; AST 65 1.8 x ULN, 87 2.5 x ULN, and 132 U/L 3.8 x ULN, respectively. LDH was also elevated at 229 1.1 x ULN, 260 1.2 x ULN and 288 1.3 x ULN respectively. Other liver function tests were within normal limits, with no trends towards increasing.
A slight increase in eosinophiles was noted from 0,6% at baseline to 2,6% at D29 with a maximum of 4% at D43. At D49 the count decreased to 1,2% again.

Other reported Adverse Events for this patient were vomiting (once on 10-Oct-2022, pre-dosing), diarrhea (18-Oct-2022 to 19-Oct-2022), post-lumbar puncture headache (26-Nov-2022 to 28-Nov-2022), and nausea (08-Dec-2022).

During anamnesis the patient and caregiver denied use of illicit drugs, herbal / OTC drugs, except for paracetamol/caffeine 1000/100 mg QD between 26-Nov-2022 and 28-Nov-2022 for an adverse event of postdural puncture headache. No recent history of travels outside Europe, no recent history of exposure to toxins/chemicals, no intake of unusual foods, no intake of dietary supplements was noted upon anamnesis.

A virology panel found a negative serology for recent of active Hepatitis A-B-C, HIV, CMV and EBV – with signs of immunity against EBV, CMV and Hepatitis A.

In a first stage workup, patient was tested for ANA, Anti smooth muscle, AB anti-mitochondrial AB, anti Anti nuclear AB and Anti-liver-kidney microsomal antibod. All titers were reported as being <1:80. Protein electrophoresis revealed no abnormalities.
Ceruloplasmin, Serum ferritin, Serum iron and Transferrin-saturation were all within the reference ranges.

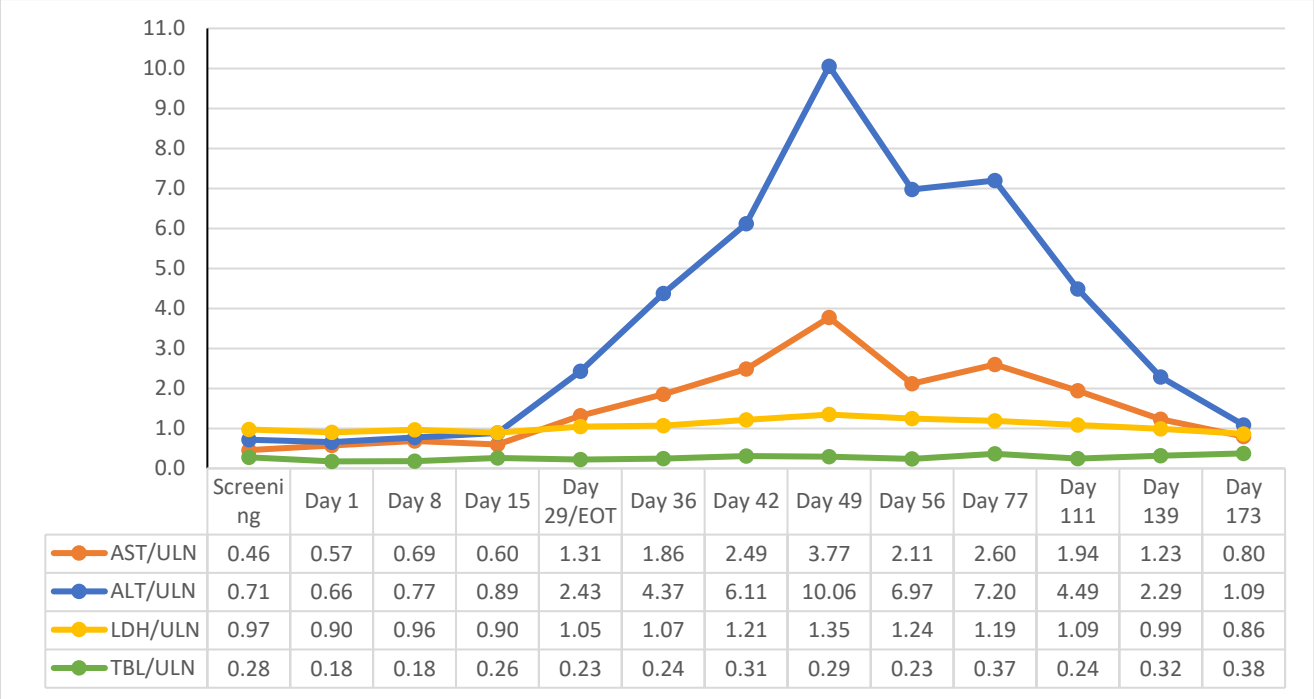
As second stage workup, an ultrasound of the right upper quadrant abdomen was performed on 20-Dec-2022 (D56). The liver ultrasound did not show any underlying pathology.

A clear decrease of ALT and AST values was noted – no changes were seen in total bilirubin. Patient remained asymptomatic.

Patient was followed up via regular consultation with an hepatologist for additional lab testing on days 77, 111 and 139 since first study drug intake, confirming the trend towards normalization of transaminase levels, in the absence of symptoms and/or other functional impact on the liver.

On 13-Mar-2023 (D139), the respective lab values for ALT and AST were at 80 U/l and 43 U/l. No other significant out-of-range values were noted.

Last evaluation was done on Day 173 (17-Apr-2023) after first study drug intake – lab values for AST were within normal limits where ALT was just above. Further follow-up was deemed not necessary per PI's discretion.



	Screening	Day 1	Day 8	Day 15	Day 29/EOT	Day 36	Day 42	Day 49	Day 56	Day 77	Day 111	Day 139	Day 173
AST/ULN	0.46	0.57	0.69	0.60	1.31	1.86	2.49	3.77	2.11	2.60	1.94	1.23	0.80
ALT/ULN	0.71	0.66	0.77	0.89	2.43	4.37	6.11	10.06	6.97	7.20	4.49	2.29	1.09
LDH/ULN	0.97	0.90	0.96	0.90	1.05	1.07	1.21	1.35	1.24	1.19	1.09	0.99	0.86
TBL/ULN	0.28	0.18	0.18	0.26	0.23	0.24	0.31	0.29	0.23	0.37	0.24	0.32	0.38

Figure 5: ALT, AST, LDH, TBL represented as times ULN of participant 101 over time

Evaluation of liver abnormality:

Abnormalities in liver enzymes were restricted to AST and ALT, while GGT, bilirubin, alkaline phosphatase, albumin, and the number and percent of eosinophils remained normal (although eosinophils increased from 0,6% at baseline to 2,6% at the time of the event). LDH increased less than ALT/AST but followed the pattern of transaminases.

No other relevant lab abnormalities have been recorded, except for some urine results compatible with recurrent cystitis.

Ultrasound of the right upper abdomen quadrant was negative for underlying abnormalities.

The case was considered to be probably related to study drug as no underlying hepatic conditions could be identified as possible contributors to a clear differential diagnosis.

This assessment was mainly based on the extent of the observed pattern of increase in ALT, the time course of the decline, the relative eosinophilia at the time of the event and the absence of other known causes of liver dysfunction.

The patient received active medication @ 1400 mg of studydrug QD given as 700 mg BID for 28 days. (Data Safety Monitoring Board, Liver Safety Panel)

Excerpts of Relevant Laboratory Testing:

Table 12: Evolution of ALT of participant 101 over time (absolute values in U/L and as x ULN)

Day	SCR	1	8	15	29	36	42	49	56	77	111	139	173
ALT	25	23	27	31	85	153	214	352	244	252	157	80	38
X ULN	0,71	0,66	0,77	0,89	**2,43**	**4,37**	**6,11**	**10,06**	**6,97**	**7,20**	**4,49**	**2,29**	**1,09**

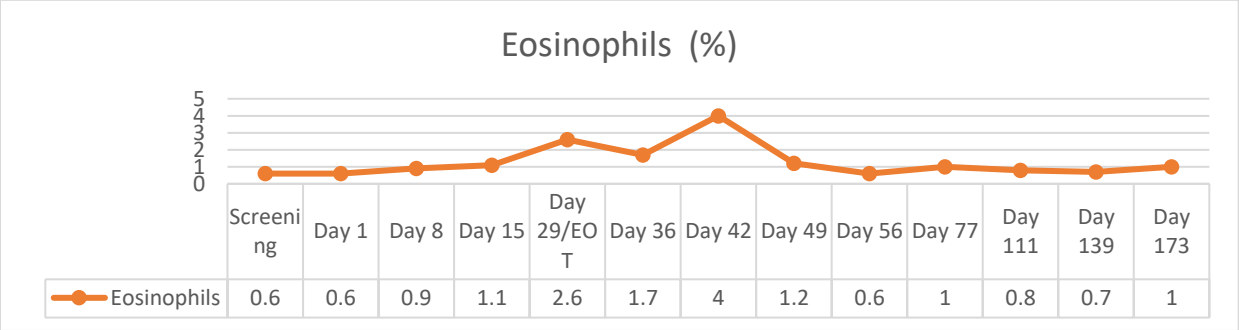


Figure 6: Evolution of % Eosinophils of participant 101 over time

Sponsor's Interpretation and Comment

The Sponsor considered the elevations of ALT and AST to be probably related to the study drug in the absence of other confounding factors

Reported Relevant Adverse Events as per CRF

All Other Adverse Events					
Preferred Term/ Reported Term	**Onset Day/ Onset Date**	**End Day/ End Date**	**Investigator Assessment of Severity/ Relationship to Study Drug**	**Action Taken for Study Drug/Treatment Required**	**Outcome**
VOMITING/ VOMITING (ONCE)	-15/ 10-Oct-2022	-15/ 10-Oct-2022	Moderate / Not Related To Study Drug	None/ NR	Recovered
DIARRHEA / DIARRHEA	-7/ 18-Oct-2022	-6/ 19-Oct-2022	Mild/ Not Related To Study Drug	None/ NR	Recovered
BACK PAIN/ LOCAL BACK PAIN POST LUMBAR PUNCTURE	30/ 23-Nov-2022	53/ 15-Dec-2023	Mild/ Not Related To Study Drug	NAP/ NR	Recovered
POST LUMBAR PUNCTURE SYNDROME / POST-LUMBAR PUNCTURE HEADACHE	33/ 26-Nov-2022	35/ 28-Nov-2022	Mild/ Not Related To Study Drug	Dose Not Changed/ NR	Recovered
NAUSEA / NAUSEA	46/ 08-Dec-2022	46/ 08-Dec-2022	Mild/ Not Related To Study Drug	NAP/ NR	Recovered
WEIGHT DECREASED/ WEIGHT LOSS	77/ 10-Jan-2023	15-12-2023	Mild/ Related To Study Drug	NAP/ NR	Recovered
CYSTITIS/ CYSTITIS	86/ 19-Jan-2023	92/ 25-Jan-2023	Moderate / Not Related To Study Drug	NAP/ NR	Recovered
CONSTIPATION/ CONSTIPATION	86/ 19-Jan-2023	100/ 02-Feb-2023	Moderate / Not Related To Study Drug	NAP/ NR	Recovered

7.1.2. Study participant 201

Death, Date of Death (Study Day): No	**Other Event of Interest:** No
Other SAE: No	**Potential DILI Case:** Yes
AE Leading to Discontinuation: No	

Protocol Number: REMAD-02	**Age (years, at study entry):** 85
Subject Number: 2-201	**Sex:** Female
Height (cm, at study entry or first exam): 144	**Weight (kg, at study entry or first exam):** 52
Race/Ethnicity: White/ not Hispanic Or Latino	**Country:** Spain
Assigned Treatment Group: 700 mg BID for 28 days	
Start Date (Study Day) of Study Drug(s) Dosing: 12-Dec-2022	**Stop Date (Study Day) of Study Drug(s) Dosing:** 02-Jan-2023

Event(s) Requiring a Narrative

Preferred Term/ Reported Term	Reason for Narrative	Onset Day/ Onset Date	End Day/ End Date	Investigator Assessment of Severity/ Relationship to Study Drug	Action Taken for Study Drug/Treatment Required	Outcome
TRANSAMINASES INCREASED/ INCREASED TRANSAMINASES	PDC	36/ 09-Jan-2023	158/ 11-May-2023	Not reported as AE	No action taken / no treatment required	Recovered

Reason for narrative: D: death; SAE: serious adverse event; DC: adverse event leading to discontinuation; EI: event of interest; PDC: potential DILI case.
NR: not reported

Sequence of Events

The patient's medical history includes hypercholesterolemia (2004), stenosis lumbar spinal canal (2005), lower back pain (2011), osteoporosis (2015), Alzheimer's Disease (May-2020), pulmonary thromboembolism (Jul-2022), urinary incontinence (2022), allergic rhinitis (2018) and gait disturbance (2022).

The patient was treated with simvastatine (2018), donepezil (2020), bemiparin (2022) and occasional paracetamol and cetirizine as needed.

At baseline (D1 – randomization), aminotransferase (ALT) was 18 U/L, and within normal limits (10 - 35). On the same day vital signs were as follows: BP 158/70 mmHg, pulse 62 beats per minute (bpm), and temperature 36.1ºC, and BMI was ca 25 kg/m^2.

During study drug treatment (D1 through D29) none of the safety biomarkers indicated any abnormality. No relevant adverse events have been recorded. Patient completed the study as per protocol.

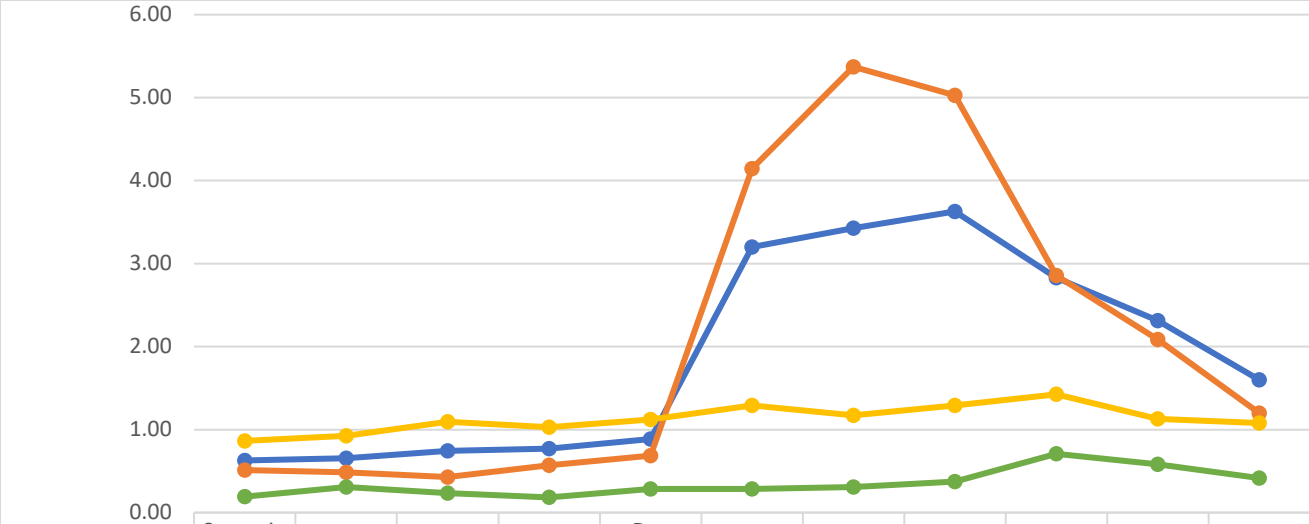
On 09-Jan-2023 (day 36 – EOS visit) the patient developed the nonserious, potential drug induced liver injury (DILI) case of elevation in ALT (145 U/L or 4,1x ULN) and elevation in AST (112 U/L or 3,2x ULN that were mild in intensity. The patient had no signs or symptoms associated with hepatitis or a drug induced liver injury. Other out-of-range laboratory test results were LDH 276 U/L (135 - 214). Some kidney biomarkers (creatinine, eGFR, urea) hovered around the ULN – but normal for age.

Because the elevation of transaminases exceeded 3x ULN, repeat testing was done on 19-Jan-2023 (D45) ALT/AST values increased to 188 U/l and 122 UI/l respectively; or 5,4 x ULN and 3,5 x ULN respectively. LDH increased to 251 U/l (1,2 x ULN). No other clinically relevant lab abnormalities were noted. Patient was asymptomatic.

Follow-up testing was done on 27-Jan-2023 (day 53) – status quo results were observed for ALST/AST (176 U/l and 127 U/l respectively). Patient was asymptomatic.

During follow-up visit on 28-Feb-2023 patient was asymptomatic and doing well. Lab results did show decline in ALT/AST values whilst increasing GGT and LDH. The respective values for ALT and AST were of 100 U/l and 99 U/l respectively; or 2,8 x ULN. LDH was at 305 U/l (1,4 x ULN). Although a doubling of GGT, the values remained within normal ranges (40 U/l with ranges of 6-42 U/l).

Further follow-up on 31-Mar-2023 (day 116) and 03-May-2023 (day 149) showed declining/recovering values for all observed abnormal lab tests – mainly AST and ALT. Despite a still marginal increased ALT and AST - 1.2 and 1.6 x ULN respectively – PI considered the adverse event closed by 11-May-2023 and no further follow-up was warranted.



	Screening	Day 1	Day 8	Day 15	Day 29/EOT	Day 36	Day 45	Day 53	Day 85	Day 116	Day 149
AST/ULN	0.63	0.66	0.74	0.77	0.89	3.20	3.43	3.63	2.83	2.31	1.60
ALT/ULN	0.51	0.49	0.43	0.57	0.69	4.14	5.37	5.03	2.86	2.09	1.20
LDH/ULN	0.86	0.93	1.09	1.03	1.12	1.29	1.17	1.29	1.43	1.13	1.08
TBL/ULN	0.19	0.31	0.23	0.18	0.28	0.28	0.31	0.38	0.71	0.58	0.42

Figure 7: ALT, AST, LDH, TBL represented as times ULN of participant 201 over time

Evaluation of liver abnormality:

Abnormalities in liver enzymes were restricted to AST and ALT, while GGT, bilirubin, alkaline phosphatase, albumin, and the number and percent of eosinophils remained normal (although eosinophils increased from 2,5% at baseline to 3,7% at the time of the event). LDH increased less than ALT/AST but followed the pattern of transaminases.

No other relevant lab abnormalities have been recorded, except for some kidney function markers hovering around ULN – but normal for age and stable.

The case was considered to be probably related to study drug as no underlying hepatic conditions could be identified as possible contributors to a clear differential diagnosis.
Patient is on chronic simvastatine treatment – to be noted.

This assessment was mainly based on the extent of the observed pattern of increase in ALT, the time course of the decline, the relative eosinophilia at the time of the event and the absence of other known causes of liver dysfunction.

The patient received active medication @ 1400 mg of study drug QD given as 700 mg BID for 28 days.

Sponsor's Interpretation and Comment

The Sponsor considered the elevations of transaminases to be probably related to the study drug in the absence of other confounding factors – most likely an episode of DILI.

Reported Adverse Events as per CRF

All Other Adverse Events					
Preferred Term/ Reported Term	**Onset Day/ Onset Date**	**End Day/ End Date**	**Investigator Assessment of Severity/ Relationship to Study Drug**	**Action Taken for Study Drug/Treatment Required**	**Outcome**
BLOOD GLUCOSE INCREASED / INCREASED BLOOD GLUCOSE	36/ 09-Jan-2023	70/ 12-Feb-2023	Mild/ Related To Study Drug	None/ NR	Recovered
BLOOD LACTATE DEHYDROGENASE INCREASED / INCREASED LDH	10/ 14-Dec-2022	158/ 11-May-2023	Mild/ Related To Study Drug	None/ NR	Recovered
CONSTIPATION/ CONSTIPATION	80/ 12-Feb-2023		Moderate/ Not Related To Study Drug	None/ NR	resolving
NASAL INJURY/ FRONTAL AND NASAL CONTUSION	94/ 26-Feb-2023	96/ 28-Feb-2023	Mild/ Not Related to Study Drug	None/ NR	Recovered

7.1.3. Study participant 202

Death, Date of Death (Study Day): No	**Other Event of Interest:** No
Other SAE: No	**Potential DILI Case:** Yes
AE Leading to Discontinuation: No	

Protocol Number: REMAD-02	**Age (years, at study entry):** 85
Subject Number: 2-202	**Sex:** Female
Height (cm, at study entry or first exam): 163	**Weight (kg, at study entry or first exam):** 76
Race/Ethnicity: White/ not Hispanic Or Latino	**Country:** Spain
Assigned Treatment Group: 175 mg BID for 28 days	
Start Date (Study Day) of Study Drug(s) Dosing: 05-Dec-2022	**Stop Date (Study Day) of Study Drug(s) Dosing:** 02-Jan-2023

Event(s) Requiring a Narrative

Preferred Term/ Reported Term	Reason for Narrative	Onset Day/ Onset Date	End Day/ End Date	Investigator Assessment of Severity/ Relationship to Study Drug	Action Taken for Study Drug/Treatment Required	Outcome
BLOOD LACTATE DEHYDROGENASE INCREASED/ ABNORMAL VALUES OF LDH AND TRANSAMINASES	PDC	36/ 09-Jan-2023	137/ 21-Apr-2023	Not reported as AE	No action taken / no treatment required	Recovered

Reason for narrative: D: death; SAE: serious adverse event; DC: adverse event leading to discontinuation; EI: event of interest; PDC: potential DILI case.
NR: not reported

Sequence of Events

The patient's medical history includes hypercholesterolemia (2014), hypertension (2014), Alzheimer's Disease (Mar-2020) and several surgeries for inguinal/abdominal hernia repair.

The patient was treated with rivastigmine (Apr-2022) and amlodipine (2014). Flu vaccine and COVID-19 vaccines were given on 30-Nov-2022.

At baseline (D1 – randomization), aminotransferase (ALT) was 15 U/L, and within normal limits (10 - 35). On the same day vital signs were as follows: BP 163/90 mmHg, pulse 73 beats per minute (bpm), and temperature 36.2ºC, and BMI was ca 29 kg/m^2.

During study drug treatment (D1 through D29) none of the safety biomarkers did indicate any clinically significant abnormality. No relevant adverse events have been recorded. Patient completed the study as per protocol. Paracetamol 500mg QD was given between 10-Nov-2022 and 11-Nov-2022 for headache and back pain.

On 09-Jan-2023 (day 36 – EOS visit) the patient developed the nonserious, potential drug induced liver injury (DILI) case of elevation in ALT (65 U/L or 1,8x ULN) and elevation in AST (57 U/L or 1,6x ULN that were mild in intensity. The patient had no signs or symptoms associated with hepatitis or a drug induced liver injury. Other out-of-range laboratory test results were LDH 235 U/L (135 - 214). Ibuprofen 600 mg TID was given between 02-Jan-2023 and 04-Jan-2023 for post-puncture back pain.

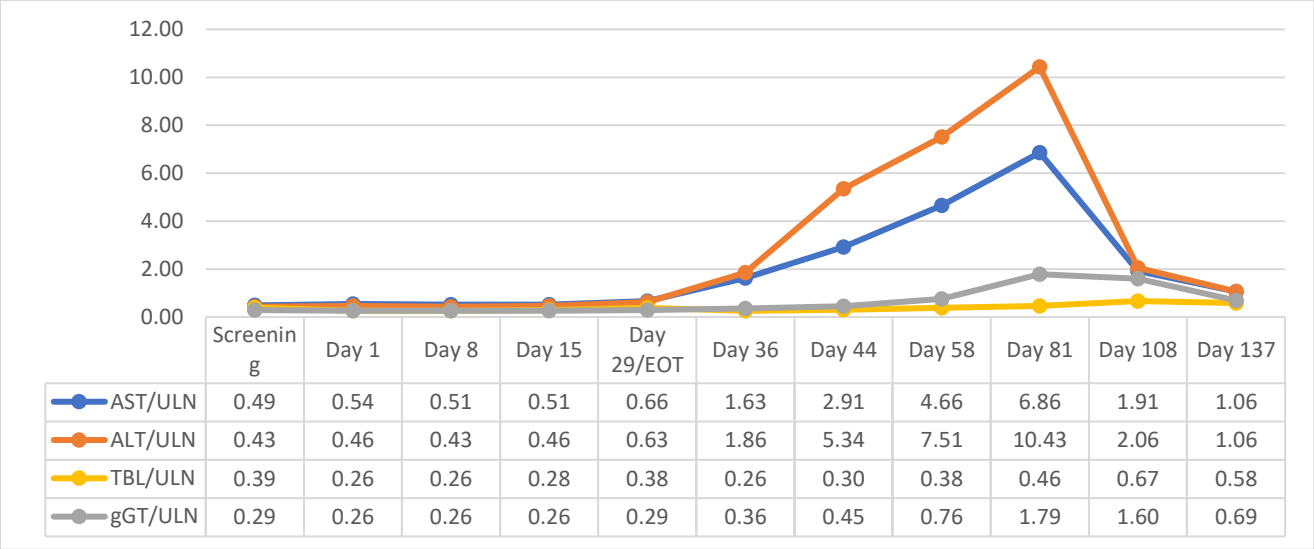
Repeat testing was done on 17-Jan-2023 (D44) ALT/AST values increased to 187 U/l and 102 UI/l respectively; or 5,3 x ULN and 2,9 x ULN respectively. LDH increased to 256 U/l (1,2 x ULN). No other clinically relevant lab abnormalities were noted. Patient was asymptomatic.

Follow-up testing was done on 31-Jan-2023 (D58) – results were observed for ALST/AST of 263 U/l and 163 U/l respectively; or 7,5x ULN and 4,7x ULN respectively. LDH increased up to 281 U/l (1,3x ULN). A slight increase above ULN was noted for ALP (110 U/l with and ULN of 104 U/l).
Patient was asymptomatic. No other relevant abnormalities were noted.

Latest known follow-up visit was done on 23-Feb-2023 (D81). Asymptomatic patient doing well. Lab results do show still increasing values for ALT/AST together with ALP and LDH.
The respective values for ALT and AST are of 365 U/l and 240 U/l respectively; or 10,4 x ULN and 6,9x ULN respectively. LDH is at 292 U/l (1,4 x ULN) and ALP at 142 (1,4x ULN).

Patient remained asymptomatic, but has been referred to hepatology for specialised follow-up.

Further follow-up on days 108 (23-Mar-2023) through 137 (21-Apr-2023) did show gradual decline of transaminase levels back to or around the ULN.



	Screening	Day 1	Day 8	Day 15	Day 29/EOT	Day 36	Day 44	Day 58	Day 81	Day 108	Day 137
AST/ULN	0.49	0.54	0.51	0.51	0.66	1.63	2.91	4.66	6.86	1.91	1.06
ALT/ULN	0.43	0.46	0.43	0.46	0.63	1.86	5.34	7.51	10.43	2.06	1.06
TBL/ULN	0.39	0.26	0.26	0.28	0.38	0.26	0.30	0.38	0.46	0.67	0.58
gGT/ULN	0.29	0.26	0.26	0.26	0.29	0.36	0.45	0.76	1.79	1.60	0.69

Figure 8: ALT, AST, TBL, gGT represented as times ULN of participant 202 over time

Evaluation of liver abnormality:

Abnormalities in liver enzymes were restricted to AST and ALT, while GGT, bilirubin, alkaline phosphatase, albumin, and the number and percent of eosinophils remained normal. LDH increased less than ALT/AST but followed the pattern of transaminases.
ALP increase is noted but is very mild – hardly exceeding ULN.

No other relevant lab abnormalities have been recorded.

The case was considered to be probably related to study drug as no underlying hepatic conditions could be identified as possible contributors to a clear differential diagnosis.

This assessment was mainly based on the extent of the observed pattern of increase in ALT, the time course of the decline, the relative eosinophilia at the time of the event and the absence of other known causes of liver dysfunction.

The patient received active medication @ 350mg of studydrug QD given as 175 mg BID for 28 days.

Sponsor's Interpretation and Comment

The Sponsor considered the elevations of transaminases to be probably related to the study drug in the absence of other confounding factors – most likely an episode of DILI.

Reported Relevant Adverse Events as per CRF

All Other Adverse Events					
Preferred Term/ Reported Term	**Onset Day/ Onset Date**	**End Day/ End Date**	**Investigator Assessment of Severity/ Relationship to Study Drug**	**Action Taken for Study Drug/Treatment Required**	**Outcome**
VOMITING / VOMITING	-24/ 10-Nov-2022	-23/ 11-Nov-2022	Mild/ Not Related To Study Drug	None/ NR	Recovered
HYPOTENSION / HYPOTENSION	-25/ 09-Nov-2022	-25/ 09-Nov-2022	Mild/ Not Related To Study Drug	None/ NR	Recovered
NAUSEA/ NAUSEA	29/ 02-Jan-2023	31/ 04-Jan-2023	Mild/ Not Related To Study Drug	None/ NR	Recovered
POST LUMBAR PUNCTURE SYNDROME/ MILD HOLOCRANIAL HEADACHE	-25/ 09-Nov-2022	-25/ 09-Nov-2022	Mild/ Not Related To Study Drug	None/ NR	Recovered
POST LUMBAR PUNCTURE SYNDROME/ PAIN IN THE LOWER BACK	29/ 02-Jan-2023	31/ 04-Jan-2023	Moderate/ Not Related To Study Drug	None/ NR	Recovered

7.1.4. Study participant 203

Death, Date of Death (Study Day): No	**Other Event of Interest:** No
Other SAE: No	**Potential DILI Case:** Yes
AE Leading to Discontinuation: No	

Protocol Number: REMAD-02	**Age (years, at study entry):** 71
Subject Number: 2-203	**Sex:** Male
Height (cm, at study entry or first exam): 173	**Weight (kg, at study entry or first exam):** 63
Race/Ethnicity: White/ not Hispanic Or Latino	**Country:** Spain
Assigned Treatment Group: 175 mg BID for 28 days	
Start Date (Study Day) of Study Drug(s) Dosing: 07-Dec-2022	**Stop Date (Study Day) of Study Drug(s) Dosing:** 04-Jan-2023

Event(s) Requiring a Narrative

Preferred Term/ Reported Term	Reason for Narrative	Onset Day/ Onset Date	End Day/ End Date	Investigator Assessment of Severity/ Relationship to Study Drug	Action Taken for Study Drug/Treatment Required	Outcome
TRANSAMINASES INCREASED/ ELEVATED LIVER ENZYMES	PDC	29/ 04-Jan-2023	153/ 08-May-2023	Moderate/ Related To Study Drug	No action taken / no treatment required	Recovered
HEPATITIS TOXIC/ TOXIC HEPATITIS	PDC	51/ 26-Jan-2023	374/ NK-Dec-2023	Severe/ Related To Study Drug	No action taken / Treatment required with corticosteroids	Recovered

Reason for narrative: D: death; SAE: serious adverse event; DC: adverse event leading to discontinuation; EI: event of interest; PDC: potential DILI case.
NK: not known

Sequence of Events

The patient's medical history includes hypertension (2008), ventricular dilatation (2018), benign prostate hypertrophy (2021), suspected prostate carcinoma (elevated PSA and CA19.9 – watchful waiting since 2022), Alzheimer's Disease (date to be confirmed).

The patient was treated with oral enalapril/hydrochlorthiazide since 2015 (hypertension), Tiobec (vitamin supplement including niacin) since 04/2022 and Adiro (aspirin) since 11/2022.

At screening patient tested positive for Hepatitis C antibodies. Confirmatory RNA analysis by PCR was negative for HCV and patient was allowed to be enrolled into the trial.

At baseline (D1 – randomization), aminotransferase (ALT) was 16 U/L, and within normal limits (10 - 50). On the same day vital signs were as follows: BP 157/68 mmHg, pulse 54 beats per minute (bpm), and temperature 36.4ºC, and BMI was ca 21 kg/m^2

The patient developed a significant increase of AST and ALT on which was first measurable at end of treatment on day 29 (4th of January 2023) with a value of AST 3,28 fold of ULN and ALT 3,06 fold of ULN and a peak of AST 11,17 fold of ULN and ALT 12,76 fold of ULN at day 36. LDH also increased steadily from day 15 with a peak of 1,48 fold of ULN. No other clinical relevant lab abnormalities were noted.

See also 7.2 Clinical Laboratory Tests – Liver Function Tests.

At control 1 (Day 44), AST and ALT reached values of 21,8-fold of ULN and 27,6-fold of ULN respectively. GGT, total bilirubine and AP values remained within normal limits.
There was no new concomitant medication administered. Daily medication is limited to a vitamin complex (alpha-lipoic acid, B vitamins, vitamin E and vitamin C) and enalapril/hydrochlorothiazide 20/12.5 mg for hypertension since 2015, as well as acetylsalicylic acid since 2022.

During anamnesis the patient and caregiver denied use of illicit drugs, herbal / OTC drugs. No recent history of travel outside Europe, no recent history of exposure to toxins/chemicals, no intake of unusual foods, no intake of dietary supplements was noted upon anamnesis. The patient had no signs or symptoms that could be associated with hepatitis or drug induced liver injury.

A virology panel found a negative serology for recent of active Hepatitis B, HIV, CMV and EBV – with signs of past infection with Hepatitis A. Hepatitis C antibodies were again positive but with negative PCR.

In a first stage workup, patient was tested for ANA, Anti smooth muscle, AB anti-mitochondrial AB, anti Anti nuclear AB and Anti-liver-kidney microsomal antibody. All titers were reported as being <1:80 except for ANA IFT showing a titer of 1:80 with fine speckled and nucleolar fluorescence of nucleus (common finding of limited significance).
Protein electrophoresis revealed no significant abnormalities.
Ceruloplasmin, Serum ferritin, Serum iron and Transferrin-saturation were all within the reference ranges.

As a second stage workup, an ultrasound of the right upper quadrant abdomen was performed on 25-Jan-2023 (D50). The liver ultrasound did not show any significant abnormalities except for the occurrence of simple hepatic cysts and simple cysts on the right kidney – of no clinical importance.

However, the lab results on D50 did demonstrate a further increase of ALT and AST to > 40 x ULN accompanied by an increase of total bilirubin of 1,9 x ULN and rising GGTs. An additional lab on 26-Jan-2023 (D51) confirmed these values as well as total bilirubin exceeding 2 x ULN and impact on coagulation for which patient was referred to hospital emergency department because of an increased INR (1,4) and decreased PT (58,5%). Patient was not admitted to the hospital but put in close follow-up by the hepatologists on ambulatory basis.

An SAE was reported on 31st of January 2023.

On 01-Feb-2023 (D57) patient was re-examined. At clinical examination the investigator described a discrete jaundice of the skin and eye corneas which was observed. However, the patient remained asymptomatic and did not report fatigue, asthenia or signs of any spontaneous bleeding and he reports feeling well. Lab results deteriorated further with ALT/AST values still > 40 x ULN and increasing total bilirubin of > 4 x ULN and decreasing PT (48.8%) and INR of 1,6. ALP remained within normal limits. Based on increasing total bilirubin and after discussion with hepatology, it was decided to hospitalise the patient for close observation on 08-Feb-2023 (D64).

(Translation of report hospitalisation is added at end of document.)

Patient underwent liver biopsy and was put on corticosteroids as empirical therapy. Biopsy results showed acute hepatitis in a necro-inflammatory pattern with confluent necrosis perivenular with mixed infiltrates.

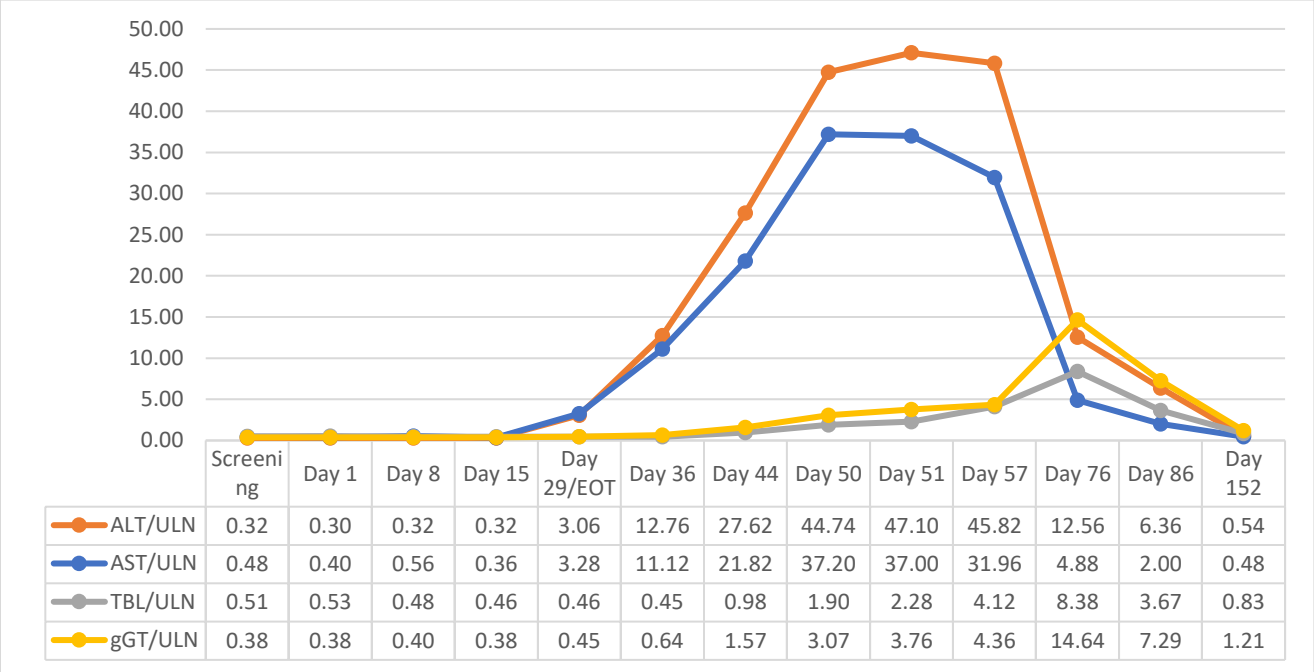
After initiation of corticosteroid therapy, patient improved and was discharged on 20-Feb-2023 (D76).

Still with ALT/AST values of approximately 12x and 5x ULN and total bilirubin at 10,06 mg/dL (or > 8 x ULN) but improving coagulation.

Further follow up did show declining values for ALT, AST and total bilirubine with recovery of hepatic function and normalization of coagulation parameters.

The lab results of 02-Mar-2023 (D86) did show ALT and AST values of 318 U/l and 100 U/l respectively, or 6,3 x ULN and 2 x ULN respectively. Total bilirubin was at 4.4 mg/dL (or 2 x ULN).

Last lab follow-up was done on 08-May-2024 (day 152) with normalised transaminase levels and adequate bilirubine and coagulation parameters.



	Screening	Day 1	Day 8	Day 15	Day 29/EOT	Day 36	Day 44	Day 50	Day 51	Day 57	Day 76	Day 86	Day 152
ALT/ULN	0.32	0.30	0.32	0.32	3.06	12.76	27.62	44.74	47.10	45.82	12.56	6.36	0.54
AST/ULN	0.48	0.40	0.56	0.36	3.28	11.12	21.82	37.20	37.00	31.96	4.88	2.00	0.48
TBL/ULN	0.51	0.53	0.48	0.46	0.46	0.45	0.98	1.90	2.28	4.12	8.38	3.67	0.83
gGT/ULN	0.38	0.38	0.40	0.38	0.45	0.64	1.57	3.07	3.76	4.36	14.64	7.29	1.21

Figure 9: ALT, AST, TBL, gGT represented as times ULN of participant 203 over time

<u>Evaluation of liver abnormality:</u>

Severe case of Drug Induced Liver Injury with ALT/AST elevations exceeding 37 x ULN, accompanied by total bilirubin elevations up to and exceeding 8 x ULN with a clear impact on liver function as demonstrated by the impact on the PT and INR. Eosinophiles (%) reached a peak of 5,7% on Day 36 – i.e. around the start of the liver events.

Ultrasound of the right upper abdomen quadrant was negative for underlying clinical relevant abnormalities.

The case was considered to be definitely related to study drug as no underlying hepatic conditions could be identified as possible contributors to a clear differential diagnosis.

However – patient has been previously exposed to Hepatitis C and Hepatitis A, and – according to the discharge report – the patient was also taking chronically "red rice yeast" as a dietary

supplement to lower cholesterol levels. We were only aware of the vitamin complex (which also contains B vitamins, including niacin) and the enalapril/thiazide combination.
The combination of red yeast rice (which contains monacolin K) and niacin can lead to acute liver necrosis, which can take months to improve.

Given the other occurrences of transaminase increases in other patients, the sponsor is convinced that the study drug plays a significant role in the observed cases. However, it cannot be ruled out that the severe reaction in this patient could be multifactorial/- causal.

The patient received active medication @ 350 mg of studydrug QD given as 175 mg BID for 28 days.

Excerpt of Relevant Laboratory Testing:

Table 13: Evolution of ALT of participant 203 over time (absolute values in U/L and as x ULN)

Day	SCR	1	8	15	29	36	44	50	51	57	76	86	152
ALT	16	15	16	16	153	638	1381	2237	2355	2291	628	318	27
/ULN	0,32	0,30	0,32	0,32	**3,06**	**12,76**	**27,62**	**44,74**	**47,10**	**45,82**	**12,56**	**6,36**	**0,54**

Table 14: Evolution of Total Bilirubin of participant 203 over time (absolute values in mg/dL and as x ULN)

Day	SCR	1	8	15	29	36	44	50	51	57	76	86	152
Tbili	0,61	0,63	0,57	0,55	0,55	0,54	1,17	2,28	2,73	4,94	10,06	4,4	1,00
/ULN	0,51	0,53	0,48	0,46	0,46	0,45	0,98	1,90	2,28	4,12	8,38	3,67	0,83

Table 15: Evolution of PT (%) and INR of participant 203 over time

Day	SCR	1	8	15	29	36	44	50	51	57	76	86	152
PT	90	90,5	90,4	89,5	93,7	86,1	No data	No data	58,5	48,8	61,2	64,9	89
INR	1,10	1,10	1,10	1,10	1,00	1,10	No data	No data	1,40	1,60	1,40	1,30	1,06

Sponsor's Interpretation and Comment

The Sponsor considered the observed changes compatible with a severe case of DILI meeting the Hy's Law criteria – related to study drug

Reported Adverse Events as per CRF

All Other Adverse Events					
Preferred Term/ Reported Term	**Onset Day/ Onset Date**	**End Day/ End Date**	**Investigator Assessment of Severity/ Relationship to Study Drug**	**Action Taken for Study Drug/Treatment Required**	**Outcome**
GASTROINTESTINAL TRACT ADENOMA / TUBULAR ADENOMA	10/ 15-Dec-2022		Mild / Not Related To Study Drug	None/ NR	Ongoing
PSEUDOPOLYP / INFLAMMATORY PSEUDOPOLYP	10/ 15-Dec-2022	10/ 15-Dec-2022	Mild/ Not Related To Study Drug	None/ NR	Recovered
BLOOD LACTATE DEHYDROGENASE INCREASED/ LDH INCREASED	29/ 04-Jan-2023	153/ 08-May-2023	Moderate/ Related To Study Drug	NAP/ NR	Recovering
CHEST PAIN / CHEST PAIN	42/ 15-Feb-2023		Mild/ Related To Study Drug	NAP/ NR	Recovering

Translation Hospitalisation Report – Dr. Fernandez Gomez Javier

Reasons for the consult

Acute hepatitis under study

Antecedents and previous history

71 year old patient, no AMC (drug allergy), no current toxic habits. No DM (Diabetes Mellitus)

AP - AHT on treatment with enalapril - Dyslipidaemia on treatment with "red rice" - Past HCV (RNA neg) detected in 2022. No history of chronic liver disease. - Dilated MCP: dilated LV without hypertrophy - Mild Alzheimer's disease on treatment with rivastigmine patches.

Treatment: aspirin 100 mg/d; enalapril5 mg/d; rivastigmine patches (acetylcholinesterase inhibitor)

Current process

The patient is included in a double-blind phase 2 Clinical Trial with a calcium antagonist (REM0046127), oral suspension 150 mg/12h day for 28 days. At that time he restarted ALZERTA patches. There was an alteration of transaminases at the end-of-drug analysis: 4/1/23 AST/ALT 164/153, visit of 029 (at the end of treatment). Despite discontinuation of the

study drug the liver profile is still altered: 11/1/23: AST. 556/ ALT: 638 19/1/23: 1091/ 1381 BB: 2,1# 25/1/23: 1905/ 2121 bb 2,28
Abdominal echo was performed and was normal.

After outpatient initial clinical control and due to persistent liver damage, he was admitted to complete the study and liver biopsy.

Physical exploration

C and O: cutaneomucous jaundice. Respiratory: m.v.c (vesicular murmur preserved). C: rhythmic, no murmurs. A: hepatomegaly 2 cm discreetly painful, no ascites. EEII (Lower limbs): no alterations. NRL: Glasgow 15p, no hepatic encephalopathy.

Liver profile on admission: AST/ALT: 1211/1854, bilirubin 12.8, quick 45%, INR 1.6, haemogram normal except for platelets 111000. Normal renal function HC (blood culture): negative, UC (urine culture) negative HAV, HCV (RNA), HBV (DNA), HEV (RNA), herpes 1,2,6, herpes zoster, CMV and EBV negative. Parvovirus negative

Liver profile at discharge after starting corticosteroids: AST/ALT 138/603, bilirubin 9.1, AFP 116, platelets 154000, quick 56.4%.
No relevant abnormalities found in the abdominal ultrasound, permeable vessels, no signs of chronic liver disease, no signs of portal hypertension.

Echocardiogram: Left ventricle of normal dimensions and global and segmental motility. EF VE 65% Moderate aortic insufficiency. Valve apparently trivalve, slightly calcified with still preserved opening. Aortic root and ascending aorta poorly visualized. Rest of valves morphologically and functionally normal. Right cavities not dilated and with normal motility of the right ventricle.

TREADMILL EXERCISE ECHOCARDIOGRAM: Exercise increases the motility of all ventricular segments, without the appearance of chest pain or arrhythmias. Adequate HR and BP response reaching a maximal HR of 150 bpm (100% of TMHR) and a maximal BP of 200/95, with 10 METS.

Complementary explorations

Liver haemodynamics with transjugular biopsy. Portal pressure gradient of 10 mmHg Liver biopsy LIVER (TRANSJUGULAR BIOPSY): - ACUTE HEPATITIS WITH NECROINFLAMMATORY PATTERN WITH PERIVENULAR CONFLUENT NECROSIS AND MIXED INFILTRATES.

Evolution

1.Acute severe toxic immune-mediated hepatitis The patient has remained clinically stable throughout his admission An abdominal ultrasound and transjugular liver biopsy were performed, showing clinically significant portal hypertension. Liver biopsy shows perivenular necrosis and lymphocytic infiltrate predominantly in zone 3 (centrolobulillar zone). Staining showing T lymphocytes (CD3+), with a similar proportion of CD4 and CDS.

After starting treatment with corticoids 60 mg/day, a notable decrease in transaminases was observed (at discharge 136/63), a slight increase in the prothrombin index (56.4%) and a decrease in bilirubin (9.1 mg/dl). Given the patient's good clinical condition and the improvement in his blood tests, it was decided to discharge him with recommendation of close clinical and analytical monitoring. Next visit 23/2/23 at 16:00h at Barnaclinic.

2. Chest pain under study. Moderate aortic insufficiency. On day 15 after removing the central line, the patient presented dizziness without dyspnea and oppressive chest pain radiating to the back lasting about 5 minutes. No dyspnea, sat 100% at baseline. EKG with pain showing T neg in V2 and V3, changes that regress in the EKG without pain. After assessment by Cardiology it was decided to carry out an echocardiogram and exercise echocardiogram which showed moderate aortic insufficiency and was negative for ischaemia. Regular check-ups by the cardiologist are recommended.

At discharge treatment with: prednisone 40mg/d, enalapril 5 mg/d, ASA 100mg/d, omeprazole 20 mg/d, septrin forte LMV, acfol 1c/d

Therapeutic plan

Prednisone 50mg/d, enalapril 5 mg/d, ASA 100mg/d, omeprazole 20 mg/d, septrin forte LMV

Other recommendations

Close clinical monitoring Moderate physical exercise

BIOPSY REPORT

MACROSCOPIC DESCRIPTION

823-004532-ABIOPSY

Liver

Three brownish cylinders are received, measuring between 21.7x1 mm and 12.6x1 mm. Blocks: 1/3. IT.

MICROSCOPIC DESCRIPTION

Cylinders of liver parenchyma with preserved architecture, with up to 14 portal spaces. Most of them show a very mild, non-expansive, mixed inflammatory infiltrate (predominantly lymphocytic, with some isolated eosinophils), without erosion of the limiting membrane. No lesions of the biliary epithelium were observed. In the lobule there is a diffuse hepatocytic process with a necroinflammatory pattern with disarray and scattered necroinflammatory foci, although predominantly centrolobular, where there are also foci of perivenular confluent necrosis (with the formation of some central- central necrosis bridges). The lobular inflammatory infiltrate has the same characteristics as the portal infiltrate. No relevant plasma cell component is identified. Absence of fibrosis on trichrome staining.

DIAGNOSIS

liver (transjugular biopsy):

- acute hepatitis in a necroinflammatory pattern with confluent necrosis

perivenular and mixed infiltrates (see microscopic description and note)

NOTES

The histological pattern observed is compatible with DILI (drug-induced liver injury). There are no changes that may suggest an HAI (autoimmune hepatitis) (signs of chronic disease, plasmatic cells). To be associated with clinical and analytical data and patient evolution

An additional immunohistochemical study is ongoing. An additional report will be issued.

ADDITIONAL REPORT

Immunohistochemical study for subpopulations. The inflammatory component is mainly T (CD3+)

7.1.5. Study participant 205

Death, Date of Death (Study Day): No	**Other Event of Interest:** Yes
Other SAE: No	**Potential DILI Case:** No
AE Leading to Discontinuation: No	

Protocol Number: REMAD-02	**Age (years, at study entry):** 75
Subject Number: 2-205	**Sex:** Male
Height (cm, at study entry or first exam): 173	**Weight (kg, at study entry or first exam):** 100
Race/Ethnicity: White/ not Hispanic Or Latino	**Country:** Spain
Assigned Treatment Group: 175 mg BID for 28 days	
Start Date (Study Day) of Study Drug(s) Dosing: 04-Jan-2023	**Stop Date (Study Day) of Study Drug(s) Dosing:** 27-Jan-2023

Event(s) Requiring a Narrative

Preferred Term/ Reported Term	Reason for Narrative	Onset Day/ Onset Date	End Day/ End Date	Investigator Assessment of Severity/ Relationship to Study Drug	Action Taken for Study Drug/Treatment Required	Outcome
ALANINE AMINOTRANSFERASE INCREASED/ ALT INCREASED	EoI	50/ 22-Feb-2023	113/ 26-Apr-2023	Mild/ Related	No action taken / no treatment required	Recovered

Reason for narrative: D: death; SAE: serious adverse event; DC: adverse event leading to discontinuation; EoI: event of interest; PDC: potential DILI case.

Sequence of Events

The patient's medical history includes benign prostate hypertrophy (2021), hypertension (2012), Alzheimer's Disease (Oct-2020), cholecystectomy (2007) and COVID-19 infection (Sep-2021).

The patient was treated with donepezil (Nov-2020), memantine (Dec-2021), enalapril (2012), tamsulosine (2021) and lorazepam (2021).

At baseline (D1 – randomization), aminotransferase (ALT) was 21 U/L, and within normal limits (10 - 50). On the same day vital signs were as follows: BP 149/87 mmHg, pulse 69 beats per minute (bpm), and temperature 36.2ºC, and BMI was ca 33,5 kg/m^2.

During study drug treatment (D1 through D29) none of the safety biomarkers did indicate any clinically significant abnormality. No relevant adverse events have been recorded, except for a flare of gouty arthritis in Dec-2022 (mild, unrelated).

Patient was terminated early on 27-Jan-2023 (D24) based on recommendations of the DSMB to put a clinical hold on the study due to important transaminase elevations in other patients.

After early termination visit the patient was followed up approximately weekly for safety lab sampling up to 4 weeks after end of study drug intake.

During this FUP there was a slight increase in ALT up to 1.4x ULN on 23-Feb-2023 (D51) with a trend towards normalization on 01-Mar-2023 (D58) where the ALT values were at 1.1x ULN. No other clinically relevant out-of-range values were noted during the entire follow-up period, except for an increased uric acid.

Evaluation of liver abnormality:

Abnormalities in liver enzymes were restricted to ALT – only slightly above ULN.
No other relevant lab abnormalities have been recorded.

The case was considered to be probably related to study drug as no underlying hepatic conditions could be identified as possible contributors to a clear differential diagnosis.

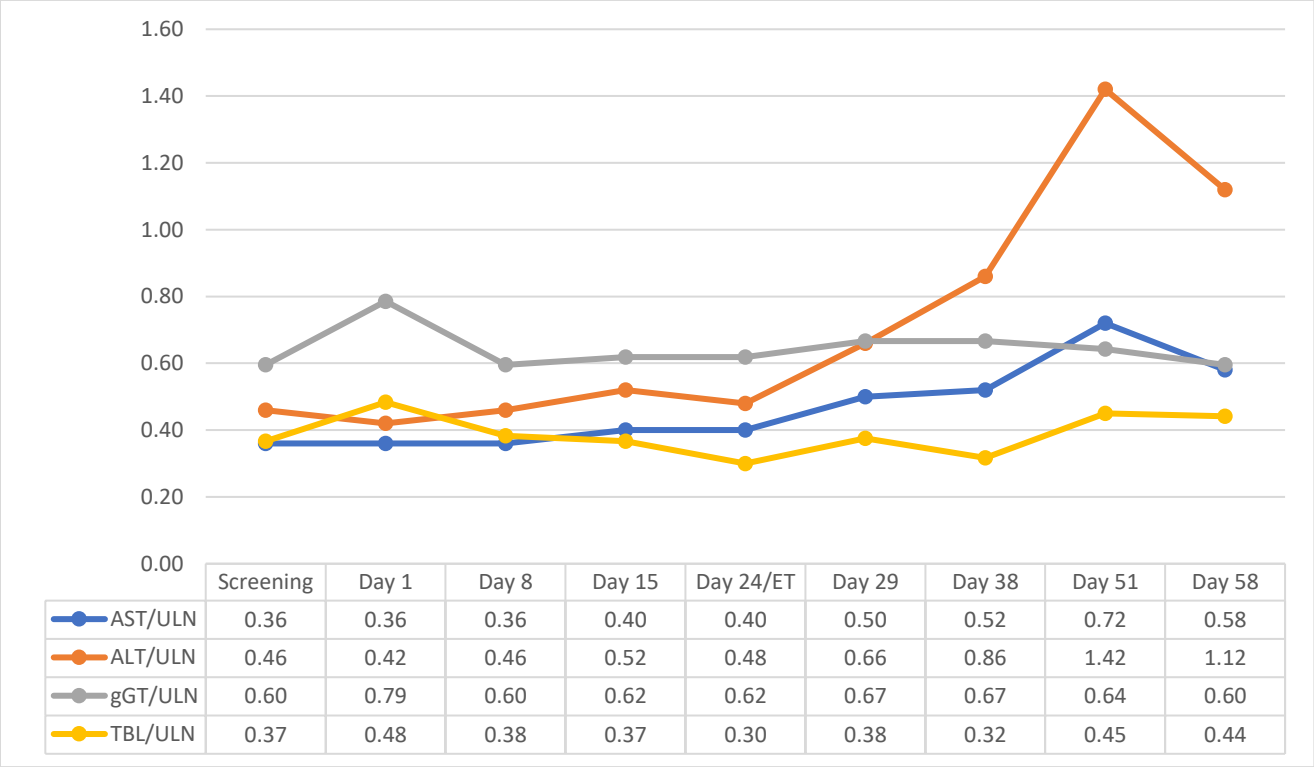
This assessment was mainly based on the extent of the observed pattern of increase in ALT, and the absence of other known causes of liver dysfunction.

The patient received active medication @ 350mg of study drug QD given as 175 mg BID for 28 days.

Excerpt of Relevant Laboratory Testing:

Evolution of ALT over time (absolute values in U/L and as x ULN)

Day	SCR	1	8	15	24	29	38	51	58
ALT	23	21	23	26	24	33	43	71	56
/ULN	0,46	0,42	0,46	0,52	0,48	0,66	0,86	1,42	1,12



	Screening	Day 1	Day 8	Day 15	Day 24/ET	Day 29	Day 38	Day 51	Day 58
AST/ULN	0.36	0.36	0.36	0.40	0.40	0.50	0.52	0.72	0.58
ALT/ULN	0.46	0.42	0.46	0.52	0.48	0.66	0.86	1.42	1.12
gGT/ULN	0.60	0.79	0.60	0.62	0.62	0.67	0.67	0.64	0.60
TBL/ULN	0.37	0.48	0.38	0.37	0.30	0.38	0.32	0.45	0.44

Figure 10: ALT, AST, TBL, gGT represented as times ULN of participant 205 over time

Sponsor's Interpretation and Comment

The Sponsor considered the elevations of transaminases to be probably related to the study drug in the absence of other confounding factors

Reported Adverse Events as per CRF

All Other Adverse Events					
Preferred Term/ Reported Term	**Onset Day/ Onset Date**	**End Day/ End Date**	**Investigator Assessment of Severity/ Relationship to Study Drug**	**Action Taken for Study Drug/Treatment Required**	**Outcome**
GOUTY ARTHRITIS / GOUTY ARTHRITS	-17/ 16-Dec-2022	394/ 01-Feb-2024	Mild/ Not Related To Study Drug	None/ NR	Recovered
DEPRESSION / DEPRESSIVE SYNDROME	1/ 02-Jan-2023		Mild/ Not Related To Study Drug	None/ NR	ongoing
BLOOD URIC ACID INCREASED/ INCREASED URIC ACID	8/ 11-Jan-2023		Mild/ Related To Study Drug	None/ NR	ongoing

7.1.6. Study Participant 305

Death, Date of Death (Study Day): No	**Other Event of Interest:** Yes
Other SAE: No	**Potential DILI Case:** No
AE Leading to Discontinuation: No	

Protocol Number: REMAD-02	**Age (years, at study entry):** 72
Subject Number: 3-305	**Sex:** Male
Height (cm, at study entry or first exam): 167	**Weight (kg, at study entry or first exam):** 70
Race/Ethnicity: White/ not Hispanic Or Latino	**Country:** Spain
Assigned Treatment Group: 44 mg BID for 28 days	
Start Date (Study Day) of Study Drug(s) Dosing: 03-Oct-2023	**Stop Date (Study Day) of Study Drug(s) Dosing:** 02-Nov-2023

Event(s) Requiring a Narrative

Preferred Term/ Reported Term	Reason for Narrative	Onset Day/ Onset Date	End Day/ End Date	Investigator Assessment of Severity/ Relationship to Study Drug	Action Taken for Study Drug/Treatment Required	Outcome
TBD/ INCREASED CK	EI	22/ 24-Oct-2023	29/ 02-Nov-2023	Not reported as AE	No action taken / no treatment required	Recovered
TBD/ INCREASED GGT and ALT	EI	29/ 02-Nov-2023	57/ 27-Nov-2023	Not reported as AE	No action taken / no treatment required	Recovered

Reason for narrative: D: death; SAE: serious adverse event; DC: adverse event leading to discontinuation; EI: event of interest; PDC: potential DILI case.
NR: not reported

Sequence of Events

The patient's medical history includes: hearing loss and tinnitus (2020), arterial hypertension (2008), benign prostate hyperplasia (2014), retinal detachment (21-Feb-2023), Alzheimer's Disease (Mar-2022), depression (Apr-2022) and constipation (2020).

The patient was treated with tamsulosin (2014), dutasteride (2014), donepezil (2022), enalapril (2008) and sertraline (2022).

At baseline (D1 – randomization), all safety parameters were within normal limits (or normal-for-age). On the same day vital signs were as follows: BP 146/86 mmHg, pulse 53 beats per minute (bpm), and temperature 36.2ºC, and BMI was ca 25 kg/m^2.

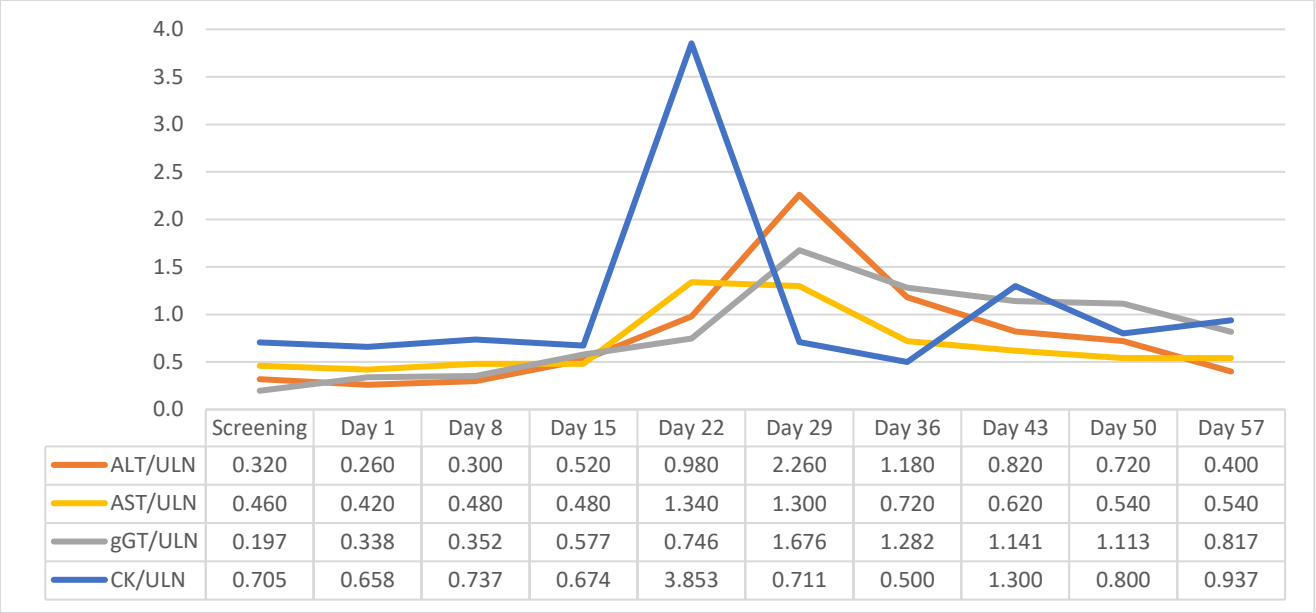
Patient completed the study as per protocol. During study drug treatment (D1 through D29) three mild adverse events have been recorded: cough (starting day -1), aggressiveness towards caregiver/spouse (starting day 8 of treatment) and an episode of drowsiness on day 22.

The AE of "Aggressiveness" was treated with the addition of Quietiapine 25mg starting on 24-Oct-2023 (day 22). Quietiapine treatment was stopped on 31-Oct-2023 (day 29).

On 24-Oct-2023 (day 22) the lab results revealed a mild elevation in CK (732 U/L or 3,8x ULN) accompanied by slight elevations in LDH of 232 U/l (1,03x ULN) and AST (67 U/L or 1,3x ULN).
These abnormalities returned within normal limits on 02-Nov-2023 (day 31) except for a persisting but mild elevated AST (65 U/l or 1,3x ULN). AST returned to normal on 06-Nov-2023 (day 35). Another – isolated – CK abnormality was noted on day 42 (13-Nov-2023) with a CK of 247 U/l (1,3x ULN).

On 31-Oct-2023 (day 29) the lab results showed an increase in gGT and ALT of 119 U/l (1,7x ULN) and 113 U/l (2,26x ULN) respectively. ALT returned to normal levels by day 42 (13-Nov-2023). The elevated gGT levels are gradually declining but still slightly above ULN (79 U/l or 1,1x ULN) by day 49 (20-Nov-2023). gGT levels were back within normal limits on day 57 (27-Nov-2023).

The patient had no signs or symptoms associated with the observed lab abnormalities.



	Screening	Day 1	Day 8	Day 15	Day 22	Day 29	Day 36	Day 43	Day 50	Day 57
ALT/ULN	0.320	0.260	0.300	0.520	0.980	2.260	1.180	0.820	0.720	0.400
AST/ULN	0.460	0.420	0.480	0.480	1.340	1.300	0.720	0.620	0.540	0.540
gGT/ULN	0.197	0.338	0.352	0.577	0.746	1.676	1.282	1.141	1.113	0.817
CK/ULN	0.705	0.658	0.737	0.674	3.853	0.711	0.500	1.300	0.800	0.937

Figure 11: ALT, AST, gGT, CK represented as times ULN of participant 305 over time

Evaluation of the observed abnormalities:

The observed lab abnormalities are thought to be attributable to two different/separate events given their time course and the associated lab abnormalities.

The elevated CK (and associated LDH/AST increase) are typical for an event involving muscle injury – or increased physical activity in an untrained individual. Given the reporting of aggressive behavior towards spouse this might be a possible explanation. Silent stroke could be a potential differential diagnosis, but rather unlikely given the frequent (weekly) visits at the neurologist.

The episode of elevated gGT and ALT was marked by the absence of any other relevant lab abnormality (especially other associated LFTs). Potential explanations for the observed changes in this patient are:

- A temporary rise in gGT/ALT can be explained by the addition of quetiapine for aggressiveness. Quetiapine treatment started on 24-Oct-2023. Changes in gGT/ALT usually occur within the first month of treatment and this is a common reported side effect of Quetiapine use (i.e. in 1-10% of the patients)
- Unreported acute alcohol use (?) or changes in usual lifestyle (due to aggressive behavior towards spouse patient has changed habitat to live with son at first and then with his daughter. This might change usual drinking/living/eating habits)
- Drug-induced episode caused by study drug – but the pattern of LFT changes is not consistent with those seen in Cohort 1 where there was no gGT involvement in the early stages of LFT changes. Also the rate in rise/decline of gGT indicates an acute one-off episode rather than a continuous irritation of the liver or drug accumulation in the liver (circulating half-life of gGT is about 10 days and about 48h for ALT).

No other relevant lab abnormalities have been recorded, or all were normal for age and stable.

Sponsor's Interpretation and Comment

The Sponsor considered the observed lab abnormalities are not related to study drug.

Most Relevant Reported Adverse Events as per CRF

All Other Adverse Events					
Preferred Term/ Reported Term	**Onset Day/ Onset Date**	**End Day/ End Date**	**Investigator Assessment of Severity/ Relationship to Study Drug**	**Action Taken for Study Drug/Treatment Required**	**Outcome**
COUGH / COUGH	-1/ 02-Oct-2023	-1/ 02-Oct-2023	Mild/ Not Related To Study Drug	None/ As needed Algidol	Recovered
AGRESSION / AGGRESSIVENESS	8/ 10-Oct-2023	24/ 26-Oct-2023	Moderate/ Probably Related To Study Drug	None/ Quetiapine 25 mg	Recovered
ANXIETY / ANXIETY ATTACK	47/ 18-Nov-2023	47/ 18-Nov-2023	Mild/ Not Related To Study Drug	None/ None	Recovered
SOMNOLENCE / DROWSINESS	22/ 24-Oct-2023	22/ 24-Oct-2023	Mild/ Not Related To Study Drug	None/ None	Recovered
TRAUMATIC ARTHRITIS/ POST TRAUMATIC ARTHRITIS	31/ 02-Nov-2023	42/ 13-Nov-2023	Mild/ Not Related To Study Drug	None/ None	Recovered
LIMB INJURY/ TRAUMA TO RIGHT HAND	-42/ 22-Aug-2023	-15/ 18-Sep-2023	Mild/ Not Related To Study Drug	None/ None	Recovered

7.1.7. Study Participant 309

Death, Date of Death (Study Day): No	**Other Event of Interest:** No
Other SAE: No	**Potential DILI Case:** Yes
AE Leading to Discontinuation: No	

Protocol Number: REMAD-02	**Age (years, at study entry):** 77
Subject Number: 3-309	**Sex:** Female
Height (cm, at study entry or first exam): 163	**Weight (kg, at study entry or first exam):** 63
Race/Ethnicity: White/ not Hispanic Or Latino	**Country:** Spain
Assigned Treatment Group: 44 mg BID treatment for 28 days	
Start Date (Study Day) of Study Drug(s) Dosing: 07-Feb-2024	**Stop Date (Study Day) of Study Drug(s) Dosing:** 05-Mar-2024

Event(s) Requiring a Narrative

Preferred Term/ Reported Term	Reason for Narrative	Onset Day/ Onset Date	End Day/ End Date	Investigator Assessment of Severity/ Relationship to Study Drug	Action Taken for Study Drug/Treatment Required	Outcome
Drug Induced Liver Injury/ Drug Induced Liver Injury (DILI)	PDC	43/ 19-Mar-2024	152/ 08-Aug-2024	Mild/ Probably	No action taken / no treatment required	Recovered
TRANSAMINASES INCREASED/ WORSENING HYPERTRANSAMINEMIA	PDC	50/ 26-Mar-2024	78/ 24-Apr-2024	Mild/ Probably	No action taken / no treatment required	Recovered

Reason for narrative: D: death; SAE: serious adverse event; DC: adverse event leading to discontinuation; EI: event of interest; PDC: potential DILI case.
NR: not reported

Sequence of Events

The patient's medical history includes mild prodromal Alzheimer's Disease (08-Mar-2023 to 15-Nov-2023), Mild Alzheimer's Disease (15-Nov-2023), arterial hypertension (2013) and gluten intolerance (2013), proneness to vasovagal syncope (2011 to 2020). Two minor surgical procedures upper limb and feet in 2016 and 2021.

The patient was treated with enalapril (2013) and donepezil (Mar-2023).

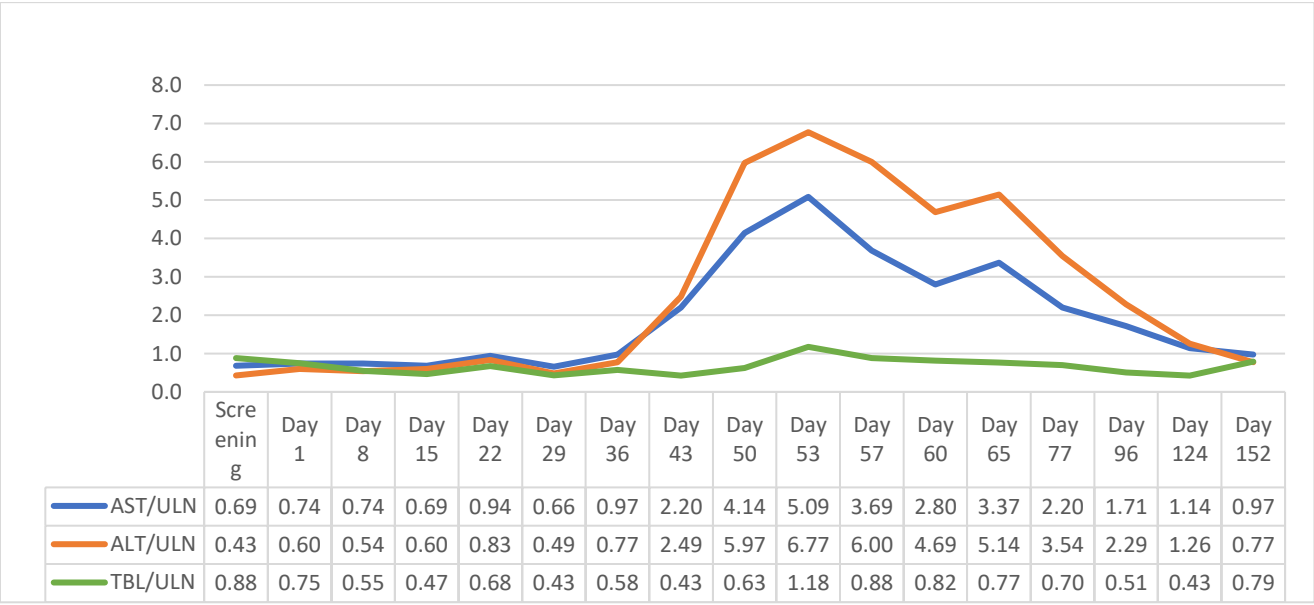
At baseline (D1 – randomization), all safety parameters were within normal limits (or normal-for-age). On the same day vital signs were as follows: BP 123/66 mmHg, pulse 79 beats per minute (bpm), and temperature 35.8°C, and BMI was ca 23.6 kg/m^2.

Patient completed the study as per protocol. During study drug treatment (D1 through D29) one adverse event had been recorded: blepharitis (starting day 2). This AE was treated with the local application of Tobradex eyedrops. The AE was reported to be resolved by day 50.

On Day 29 (end of treatment) all lab results were within normal limits for all tests related to liver safety. Physical examination and all other safety measures were within the expected ranges for age. Even so for Day 36 (Follow-up 1).

However, on Day 43 (Follow-up 2) the lab results revealed a mild elevation in ALT (87 U/L or 2,5x ULN) and AST (77 U/L or 2,2 ULN). No accompanying signs/symptoms were reported, no other clinically relevant abnormalities were noted. These transaminase increases reached a peak around Day 53 with values for ALT and AST of 6,8xULN and 5,1xULN respectively. A marginal rise in total bilirubin of 1,2xULN was seen. No other related lab abnormalities were noted.

These abnormalities gradually declined over the course of the next couple of weeks and returned within normal limits by 08-Jul-2024 (Day 152).



	Screening	Day 1	Day 8	Day 15	Day 22	Day 29	Day 36	Day 43	Day 50	Day 53	Day 57	Day 60	Day 65	Day 77	Day 96	Day 124	Day 152
AST/ULN	0.69	0.74	0.74	0.69	0.94	0.66	0.97	2.20	4.14	5.09	3.69	2.80	3.37	2.20	1.71	1.14	0.97
ALT/ULN	0.43	0.60	0.54	0.60	0.83	0.49	0.77	2.49	5.97	6.77	6.00	4.69	5.14	3.54	2.29	1.26	0.77
TBL/ULN	0.88	0.75	0.55	0.47	0.68	0.43	0.58	0.43	0.63	1.18	0.88	0.82	0.77	0.70	0.51	0.43	0.79

Figure 12: AST, ALT, TBL represented as times ULN of participant 309 over time

A virology panel found a negative serology for recent of active Hepatitis A-B-C, HIV, CMV and EBV – with signs of immunity against EBV, CMV and Hepatitis A.

In a first stage workup, patient was tested for ANA, Anti smooth muscle, AB anti-mitochondrial AB, anti Anti nuclear AB and Anti-liver-kidney microsomal antibod. All titters were reported as being <1:80. Protein electrophoresis revealed no abnormalities.
Ceruloplasmin, Serum ferritin, Serum iron and Transferrin-saturation were all within the reference ranges.

The patient had no signs or symptoms associated with the observed lab abnormalities.

Evaluation of the observed abnormalities:

The observed lab abnormalities are thought to be attributable to an episode of Drug Induced Liver Injury, most likely cause to the intake of study drug.

No other relevant lab abnormalities have been recorded, or all were normal for age and stable.

Sponsor's Interpretation and Comment

The Sponsor considered the observed lab abnormalities are related to study drug – probably an episode of DILI.

Reported Relevant Adverse Events as per CRF

All Other Adverse Events					
Preferred Term/ Reported Term	**Onset Day/ Onset Date**	**End Day/ End Date**	**Investigator Assessment of Severity/ Relationship to Study Drug**	**Action Taken for Study Drug/Treatment Required**	**Outcome**
BLEPHARITIS / BLEPHARITIS	2/ 08-Feb-2024	50/ 26-Mar-2024	Mild/ Not Related To Study Drug	None/ Tobradex topical	Recovered

7.2. Clinical Laboratory Tests – Liver Function tests

7.2.1. Chemistry: Alanine Aminotransferase (ALT)

Table 16: ALT Placebo (U/l)

	N	Geomean	SD	Median	Min	Max	Mean change from baseline
Screening	4	18.52	5.10	18.00	14.00	26.00	
D1	4	19.91	8.04	19.50	13.00	32.00	1.00
D8	4	20.97	7.53	22.00	13.00	31.00	1.05
D15	4	21.77	9.64	22.00	13.00	36.00	1.09
D22	3	18.33	4.16	20.00	14.00	22.00	1.08
D29	4	21.80	9.13	20.50	15.00	36.00	1.09
D36	4	23.84	6.56	24.00	17.00	33.00	1.20
D43	2	23.00	0.00	23.00	23.00	23.00	1.18
D50	2	23.45	2.12	23.50	22.00	25.00	1.21
D57	2	24.37	3.54	24.50	22.00	27.00	1.25

Table 17: ALT 88 mg REM0046127 (U/l)

	N	Geomean	SD	Median	Min	Max	Mean change from baseline
Screening	4	16.4	3.1	16.00	14.00	22.00	
D1	4	15.9	4.3	17.00	11.00	21.00	1.00
D8	4	16.0	2.9	16.00	12.00	19.00	1.00
D15	4	22.1	6.4	25.00	13.00	30.00	1.39
D22	4	26.5	12.9	27.00	13.00	49.00	1.66
D29	4	26.9	42.1	18.00	17.00	113.00	1.69
D36	4	25.8	17.3	21.00	17.00	59.00	1.62
D43	4	31.1	29.5	38.00	12.00	87.00	1.96
D50	4	46.4	79.2	36.00	24.00	209.00	2.91
D57	4	44.4	80.4	29.00	20.00	210.00	2.79

Table 18: ALT 350 mg REM0046127 (U/l)

	N	Geomean	SD	Median	Min	Max	Mean change

							from baseline
Screening	3	17.67	4.36	16.00	15.00	23.00	
D1	3	17.15	3.21	16.00	15.00	21.00	1.00
D8	3	17.67	4.36	16.00	15.00	23.00	1.03
D15	3	18.81	5.77	16.00	16.00	26.00	1.10
D22	1	24.00		24.00	24.00	24.00	1.04
D29	3	48.07	72.67	33.00	22.00	153.00	2.80
D36	3	121.26	337.35	65.00	43.00	638.00	7.07
D43	2	508.18	844.29	784.00	187.00	1381.00	32.80
D50	3	346.97	1198.96	263.00	71.00	2237.00	20.24
D57	3	360.44	1211.07	365.00	56.00	2291.00	21.02

Table 19: ALT 1400 mg REM0046127 (U/l)

	N	Geomean	SD	Median	Min	Max	Mean change from baseline
Screening	2	21.21	4.95	21.50	18.00	25.00	
D1	2	19.77	4.24	20.00	17.00	23.00	1.00
D8	2	20.12	8.49	21.00	15.00	27.00	1.02
D15	2	24.90	7.78	25.50	20.00	31.00	1.26
D22	0						
D29	2	45.17	43.13	54.50	24.00	85.00	2.28
D36	2	148.95	5.66	149.00	145.00	153.00	7.53
D43	2	200.58	18.38	201.00	188.00	214.00	10.14
D50	2	248.90	124.45	264.00	176.00	352.00	12.59
D57	2	156.20	101.82	172.00	100.00	244.00	7.90

7.2.2. Chemistry: Aspartate Transferase (AST)

Table 20: AST Placebo (U/l)

	N	Geomean	SD	Median	Min	Max	Mean change from baseline
Screening	4	21.38	4.92	20.00	18.00	29.00	

D1	4	21.20	4.20	21.00	17.00	27.00	1.00
D8	4	23.24	8.42	22.50	16.00	36.00	1.10
D15	4	20.16	5.56	21.00	14.00	27.00	0.95
D22	3	18.87	2.65	20.00	16.00	21.00	0.96
D29	4	20.89	4.72	20.00	17.00	28.00	0.99
D36	4	25.91	4.99	25.50	21.00	33.00	1.22
D43	2	20.45	2.12	20.50	19.00	22.00	0.97
D50	2	23.49	0.71	23.50	23.00	24.00	1.12
D57	2	22.05	6.36	22.50	18.00	27.00	1.05

Table 21: AST 88 mg REM0046127 (U/l)

	N	**Geomean**	**SD**	**Median**	**Min**	**Max**	**Mean change from baseline**
Screening	4	23.13	1.92	24.0	20.00	25.00	
D1	4	21.39	3.36	21.0	18.00	26.00	1.00
D8	4	22.29	2.51	21.0	20.00	26.00	1.04
D15	4	24.15	4.04	24.0	20.00	31.00	1.13
D22	4	32.11	18.72	33.0	18.00	67.00	1.50
D29	4	29.01	18.49	23.0	23.00	65.00	1.36
D36	4	25.23	8.14	22.0	19.00	36.00	1.18
D43	4	30.27	24.75	31.0	14.00	77.00	1.41
D50	4	38.32	52.59	27.0	23.00	145.00	1.79
D57	4	38.51	44.97	28.0	27.00	129.00	1.80

Table 22: AST 350 mg REM0046127

	N	**Geomean**	**SD**	**Median**	**Min**	**Max**	**Mean change from baseline**
Screening	3	19.44	3.79	18.00	17.00	24.00	
D1	3	18.98	1.00	19.00	18.00	20.00	1.00
D8	3	20.86	5.77	18.00	18.00	28.00	1.10
D15	3	18.64	1.15	18.00	18.00	20.00	0.98
D22	1	20.00		20.00	20.00	20.00	1.11
D29	3	45.52	80.84	25.00	23.00	164.00	2.40

D36	3	93.75	297.45	57.00	26.00	556.00	4.94
D43	2	333.59	699.33	596.50	102.00	1091.00	17.11
D50	3	221.82	1018.41	163.00	36.00	1860.00	11.69
D57	3	223.22	851.51	240.00	29.00	1598.00	11.76

Table 23: AST 1400 mg REM0046127 (U/l)

	N	Geomean	SD	Median	Min	Max	Mean change from baseline
Screening	2	18.76	4.24	19.00	16.00	22.00	
D1	2	21.45	2.12	21.50	20.00	23.00	1.00
D8	2	24.98	1.41	25.00	24.00	26.00	1.16
D15	2	23.81	4.24	24.00	21.00	27.00	1.11
D22	0						
D29	2	37.76	10.61	38.50	31.00	46.00	1.76
D36	2	85.32	33.23	88.50	65.00	112.00	3.98
D43	2	102.18	23.33	103.50	87.00	120.00	4.76
D50	2	129.48	3.54	129.50	127.00	132.00	6.04
D57	2	85.59	17.68	86.50	74.00	99.00	3.99

7.2.3. Chemistry: Lactate Dehydrogenase (LDH)

Table 24: LDH Placebo (U/l)

	N	Geomean	SD	Median	Min	Max	Mean change from baseline
Screening	4	179.67	22.46	185.50	153.00	199.00	
D1	4	176.52	33.13	172.50	149.00	221.00	1.00
D8	4	178.01	40.64	184.00	138.00	220.00	1.01
D15	4	165.00	29.68	169.00	137.00	193.00	0.93
D22	3	163.18	43.29	149.00	135.00	216.00	1.00
D29	4	165.66	21.93	167.00	142.00	191.00	0.94
D36	4	182.40	37.38	184.50	151.00	221.00	1.03
D43	2	173.90	46.67	177.00	144.00	210.00	1.01
D50	2	180.10	25.46	181.00	163.00	199.00	1.05
D57	2	169.12	40.31	171.50	143.00	200.00	0.98

Table 25: LDH 88 mg REM0046127 (U/l)

c	N	Geomean	SD	Median	Min	Max	Mean change from baseline
Screening	4	166.23	19.98	173.00	146.00	191.00	
D1	4	168.53	10.52	170.00	154.00	179.00	1.00
D8	4	169.36	24.39	172.00	137.00	198.00	1.00
D15	4	171.34	17.00	167.00	153.00	197.00	1.02
D22	4	187.82	31.14	175.00	159.00	232.00	1.11
D29	4	171.74	16.99	173.00	151.00	197.00	1.02
D36	4	167.44	25.76	160.00	140.00	199.00	0.99
D43	4	160.98	27.73	149.00	137.00	201.00	0.96
D50	4	178.44	34.69	168.00	152.00	241.00	1.06
D57	4	182.45	32.61	183.00	154.00	237.00	1.08

Table 26: LDH 350 mg REM0046127 (U/l)

	N	Geomean	SD	Median	Min	Max	Mean change from baseline
Screening	3	169.56	27.87	158.00	152.00	203.00	
D1	3	164.65	22.94	155.00	150.00	192.00	1.00
D8	3	167.64	30.17	155.00	149.00	204.00	1.02
D15	3	177.06	26.73	166.00	160.00	209.00	1.08
D22	1	169.00		169.00	169.00	169.00	1.09
D29	3	209.14	30.17	225.00	176.00	231.00	1.27
D36	3	236.25	83.51	235.00	168.00	334.00	1.43
D43	2	340.16	138.59	354.00	256.00	452.00	2.00
D50	3	314.19	256.02	281.00	168.00	657.00	1.91
D57	3	291.41	189.58	292.00	159.00	533.00	1.77

Table 27: LDH 1400 mg REM0046127 (U/l)

	N	Geomean	SD	Median	Min	Max	Mean change from baseline

Screening	2	196.16	16.26	196.5	185.00	208.00	
D1	2	195.48	3.54	195.5	193.00	198.00	1.00
D8	2	219.55	19.80	220.0	206.00	234.00	1.12
D15	2	205.52	19.80	206.0	192.00	220.00	1.05
D22	0						
D29	2	231.86	11.31	232.0	224.00	240.00	1.19
D36	2	251.40	33.23	252.5	229.00	276.00	1.29
D43	2	255.46	6.36	255.5	251.00	260.00	1.31
D50	2	281.94	8.49	282.0	276.00	288.00	1.44
D57	2	284.83	27.58	285.5	266.00	305.00	1.46

7.2.4. Chemistry: Total Bilirubin

Table 28: Total Bilirubin Placebo (mg/dl)

	N	**Geomean**	**SD**	**Median**	**Min**	**Max**	**Mean change from baseline**
Screening	4	0.48	0.10	0.47	0.38	0.61	
D1	4	0.37	0.12	0.44	0.22	0.47	1.00
D8	4	0.36	0.11	0.40	0.22	0.47	0.96
D15	4	0.39	0.10	0.40	0.30	0.50	1.04
D22	3	0.34	0.05	0.32	0.30	0.40	0.90
D29	4	0.36	0.19	0.37	0.20	0.66	0.97
D36	4	0.45	0.14	0.42	0.37	0.67	1.22
D43	2	0.44	0.06	0.44	0.40	0.48	1.17
D50	2	0.42	0.06	0.43	0.38	0.47	1.13
D57	2	0.35	0.04	0.35	0.32	0.38	0.93

Table 29: Total Bilirubin 88 mg REM0046127 (mg/dl)

	N	**Geomean**	**SD**	**Median**	**Min**	**Max**	**Mean change from baseline**
Screening	4	0.44	0.32	0.39	0.28	1.06	
D1	4	0.54	0.20	0.51	0.37	0.90	1.00
D8	4	0.42	0.18	0.43	0.24	0.66	0.78
D15	4	0.34	0.13	0.32	0.21	0.56	0.63

D22	4	0.51	0.19	0.48	0.34	0.81	0.95
D29	4	0.34	0.16	0.37	0.17	0.54	0.64
D36	4	0.37	0.25	0.45	0.15	0.69	0.70
D43	4	0.49	0.16	0.51	0.31	0.76	0.91
D50	4	0.45	0.26	0.48	0.15	0.80	0.84
D57	4	0.49	0.32	0.52	0.21	1.06	0.91

Table 30: Total Bilirubin 350 mg REM0046127 (mg/dl)

	N	**Geomean**	**SD**	**Median**	**Min**	**Max**	**Mean change from baseline**
Screening	3	0.50	0.09	0.47	0.44	0.61	
D1	3	0.48	0.17	0.58	0.31	0.63	1.00
D8	3	0.43	0.13	0.46	0.31	0.57	0.90
D15	3	0.43	0.11	0.44	0.34	0.55	0.90
D22	1	0.36		0.36	0.36	0.36	0.62
D29	3	0.48	0.06	0.46	0.45	0.55	1.00
D36	3	0.40	0.12	0.38	0.31	0.54	0.83
D43	2	0.65	0.57	0.77	0.36	1.17	1.47
D50	3	0.83	1.03	0.54	0.46	2.28	1.71
D57	3	1.13	2.54	0.55	0.53	4.94	2.33

Table 31: Total Bilirubin 1400 mg REM0046127 (mg/dl)

	N	**Geomean**	**SD**	**Median**	**Min**	**Max**	**Mean change from baseline**
Screening	2	0.28	0.07	0.28	0.23	0.33	
D1	2	0.28	0.11	0.29	0.21	0.37	1.00
D8	2	0.25	0.04	0.25	0.22	0.28	0.89
D15	2	0.26	0.06	0.27	0.22	0.31	0.94
D22	0						
D29	2	0.30	0.05	0.31	0.27	0.34	1.09
D36	2	0.31	0.04	0.32	0.29	0.34	1.13
D43	2	0.37	0.00	0.37	0.37	0.37	1.33
D50	2	0.40	0.07	0.40	0.35	0.45	1.42

D57	2	0.49	0.40	0.57	0.28	0.85	1.75

7.2.5. Chemistry: Alkalic Phosphatase (ALP)

Table 32: ALP Placebo (U/l)

	N	Geomean	SD	Median	Min	Max	Mean change from baseline
Screening	4	87.88	24.69	91.50	63.00	116.00	
D1	4	85.05	23.87	86.00	62.00	116.00	1.00
D8	4	86.68	19.31	86.00	71.00	110.00	1.02
D15	4	84.86	21.23	82.50	69.00	113.00	1.00
D22	3	91.32	20.95	98.00	70.00	111.00	1.03
D29	4	85.03	20.07	84.00	69.00	110.00	1.00
D36	4	85.91	19.23	86.50	70.00	107.00	1.01
D43	2	80.80	26.87	83.00	64.00	102.00	1.04
D50	2	78.74	26.87	81.00	62.00	100.00	1.02
D57	2	75.93	21.92	77.50	62.00	93.00	0.98

Table 33: ALP 88 mg REM0046127 (U/l)

	N	Geomean	SD	Median	Min	Max	Mean change from baseline
Screening	4	55.01	11.25	56.0	39.00	68.00	
D1	4	56.24	8.53	59.0	43.00	66.00	1.00
D8	4	56.56	12.19	60.0	37.00	69.00	1.01
D15	4	52.96	12.46	57.0	36.00	70.00	0.94
D22	4	53.47	16.52	60.0	33.00	77.00	0.95
D29	4	53.76	18.27	57.0	34.00	81.00	0.96
D36	4	50.33	14.69	54.0	31.00	67.00	0.89
D43	4	51.61	15.83	57.0	30.00	69.00	0.92
D50	4	54.71	14.22	62.0	34.00	71.00	0.97
D57	4	53.75	14.69	60.0	36.00	74.00	0.96

Table 34: ALP 350 mg REM0046127 (U/l)

	N	Geomean	SD	Median	Min	Max	Mean change from baseline
Screening	3	74.11	11.06	76.00	63.00	85.00	
D1	3	74.40	11.27	81.00	62.00	82.00	1.00
D8	3	70.50	17.35	76.00	53.00	87.00	0.95
D15	3	70.18	10.07	72.00	60.00	80.00	0.94
D22	1	57.00		57.00	57.00	57.00	0.92
D29	3	70.32	12.00	71.00	59.00	83.00	0.95
D36	3	69.93	15.39	67.00	58.00	88.00	0.94
D43	2	94.44	4.95	94.50	91.00	98.00	1.16
D50	3	87.57	30.89	109.00	56.00	110.00	1.18
D57	3	97.86	45.24	120.00	55.00	142.00	1.32

Table 35: ALP 1400 mg REM0046127 (U/l)

	N	Geomean	SD	Median	Min	Max	Mean change from baseline
Screening	2	80.99	1.41	81.00	80.00	82.00	
D1	2	91.01	13.44	91.50	82.00	101.00	1.00
D8	2	78.59	11.31	79.00	71.00	87.00	0.86
D15	2	82.96	13.44	83.50	74.00	93.00	0.91
D22	0						
D29	2	86.42	14.14	87.00	77.00	97.00	0.95
D36	2	83.52	12.73	84.00	75.00	93.00	0.92
D43	2	79.36	19.09	80.50	67.00	94.00	0.87
D50	2	77.48	12.73	78.00	69.00	87.00	0.85
D57	2	84.41	14.14	85.00	75.00	95.00	0.93

7.3. Clinical Laboratory Tests - Cholesterol

7.3.1. Chemistry: Total Cholesterol

Table 36: Total Cholesterol Placebo (mg/dl)

	N	Geomean	SD	Median	Min	Max	Mean change

							from baseline
Screening	4	244.62	35.29	244.00	209.00	289.00	
D1	4	220.16	42.52	232.50	164.00	265.00	1.00
D8	4	226.57	36.35	229.00	191.00	266.00	1.03
D15	4	239.33	51.40	243.50	181.00	306.00	1.09
D22	3	224.28	41.43	209.00	197.00	274.00	1.08
D29	4	234.79	46.83	236.00	190.00	291.00	1.07
D36	4	237.25	64.19	230.50	182.00	330.00	1.08
D43	2	205.83	42.43	208.00	178.00	238.00	1.05
D50	2	203.76	47.38	206.50	173.00	240.00	1.04
D57	2	195.72	24.75	196.50	179.00	214.00	1.00

Table 37: Total Cholesterol 88 mg REM0046127 (mg/dl)

	N	Geomean	SD	Median	Min	Max	Mean change from baseline
Screening	4	213.01	34.30	215.0	161.00	249.00	
D1	4	214.04	31.06	215.0	176.00	263.00	1.00
D8	4	187.12	31.22	200.0	154.00	229.00	0.87
D15	4	174.50	36.12	195.0	138.00	210.00	0.82
D22	4	170.91	34.38	181.0	127.00	208.00	0.80
D29	4	160.27	34.36	172.0	120.00	210.00	0.75
D36	4	162.69	31.84	164.0	136.00	215.00	0.76
D43	4	158.93	28.44	172.0	130.00	193.00	0.74
D50	4	157.57	43.32	150.0	106.00	210.00	0.74
D57	4	171.22	34.48	156.0	143.00	224.00	0.80

Table 38: Total Cholesterol 350 mg REM0046127 (mg/dl)

	N	Geomean	SD	Median	Min	Max	Mean change from baseline
Screening	3	206.10	44.52	211.00	164.00	253.00	
D1	3	203.50	23.12	192.00	190.00	231.00	1.00
D8	3	184.38	44.12	174.00	152.00	237.00	0.91
D15	3	171.24	33.13	170.00	142.00	208.00	0.84

D22	1	119.00					0.62
D29	3	150.97	33.62	170.00	115.00	176.00	0.74
D36	3	139.86	34.53	141.00	109.00	178.00	0.69
D43	2	157.98	25.46	159.00	141.00	177.00	0.75
D50	3	135.63	21.13	126.00	123.00	161.00	0.67
D57	3	124.30	23.25	117.00	108.00	152.00	0.61

Table 39: Total Cholesterol 1400 mg REM0046127 (mg/dl)

	N	**Geomean**	**SD**	**Median**	**Min**	**Max**	**Mean change from baseline**
Screening	2	217.37	10.61	217.50	210.00	225.00	
D1	2	241.75	15.56	242.00	231.00	253.00	1.00
D8	2	213.49	3.54	213.50	211.00	216.00	0.88
D15	2	197.45	6.36	197.50	193.00	202.00	0.82
D22	0						0.00
D29	2	179.99	2.83	180.00	178.00	182.00	0.74
D36	2	172.97	4.24	173.00	170.00	176.00	0.72
D43	2	154.84	9.90	155.00	148.00	162.00	0.64
D50	2	143.43	6.36	143.50	139.00	148.00	0.59
D57	2	120.66	25.46	122.00	104.00	140.00	0.50

7.3.2. Chemistry: HDL Cholesterol

Table 40: HDL Cholesterol Placebo (mg/dl)

	N	**Geomean**	**SD**	**Median**	**Min**	**Max**	**Mean change from baseline**
Screening	4	55.35	9.45	59.00	43.00	63.00	
D1	4	52.50	5.85	53.00	46.00	59.00	1.00
D8	4	53.45	8.83	54.00	45.00	63.00	1.02
D15	4	57.61	4.65	57.00	53.00	64.00	1.10
D22	3	58.40	6.66	62.00	51.00	63.00	1.06
D29	4	52.56	9.43	56.50	40.00	60.00	1.00
D36	4	54.80	8.02	56.50	45.00	63.00	1.04
D43	2	58.45	3.54	58.50	56.00	61.00	1.02

D50	2	56.48	2.12	56.50	55.00	58.00	0.98
D57	2	60.45	3.54	60.50	58.00	63.00	1.05

Table 41: HDL Cholesterol 88 mg REM0046127 (mg/dl)

	N	Geomean	SD	Median	Min	Max	Mean change from baseline
Screening	4	68.36	12.60	63.0	59.00	90.00	
D1	4	68.22	18.32	64.0	53.00	98.00	1.00
D8	4	62.94	8.71	64.0	54.00	77.00	0.92
D15	4	58.85	9.29	59.0	50.00	74.00	0.86
D22	4	58.52	10.11	55.0	49.00	71.00	0.86
D29	4	53.16	11.27	50.0	45.00	73.00	0.78
D36	4	54.47	8.72	53.0	45.00	69.00	0.80
D43	4	56.48	6.69	55.0	48.00	64.00	0.83
D50	4	52.60	14.93	55.0	33.00	73.00	0.77
D57	4	58.93	11.86	59.0	50.00	79.00	0.86

Table 42: HDL Cholesterol 350 mg REM0046127 (mg/dl)

	N	Geomean	SD	Median	Min	Max	Mean change from baseline
Screening	3	60.69	21.08	69.0	40	81	
D1	3	58.38	20.42	68.0	38	77	1.00
D8	3	52.57	19.86	62.0	33	71	0.90
D15	3	52.36	18.01	63.0	34	67	0.90
D22	1	34.00					0.89
D29	3	50.65	19.43	58.0	32	70	0.87
D36	3	43.84	13.32	52.0	30	54	0.75
D43	2	47.48	2.12	47.5	46	49	0.66
D50	3	37.74	8.50	35.0	32	48	0.65
D57	3	35.09	8.14	32.0	30	45	0.60

Table 43: HDL Cholesterol 1400 mg REM0046127 (mg/dl)

	N	Geomean	SD	Median	Min	Max	Mean change

							from baseline
Screening	2	74.30	22.63	76.00	60.00	92.00	
D1	2	83.84	19.80	85.00	71.00	99.00	1.00
D8	2	71.58	16.26	72.50	61.00	84.00	0.85
D15	2	66.33	26.87	69.00	50.00	88.00	0.79
D22	0						
D29	2	62.74	24.04	65.00	48.00	82.00	0.75
D36	2	57.30	12.73	58.00	49.00	67.00	0.68
D43	2	52.87	15.56	54.00	43.00	65.00	0.63
D50	2	51.12	19.80	53.00	39.00	67.00	0.61
D57	2	29.34	14.14	31.00	21.00	41.00	0.35

7.3.3. Chemistry: LDL Cholesterol

Table 44: LDL Cholesterol Placebo (mg/dl)

	N	Geomean	SD	Median	Min	Max	Mean change from baseline
Screening	4	158.30	39.87	160.00	120.00	208.00	
D1	4	139.55	40.28	149.00	91.00	188.00	1.00
D8	4	145.77	39.99	154.50	103.00	188.00	1.04
D15	4	153.26	52.22	163.00	95.00	220.00	1.10
D22	3	146.14	37.24	128.00	127.00	192.00	1.16
D29	4	153.11	43.06	160.50	107.00	203.00	1.10
D36	4	154.53	59.16	155.50	99.00	240.00	1.11
D43	2	128.31	49.50	133.00	98.00	168.00	1.08
D50	2	122.64	56.57	129.00	89.00	169.00	1.03
D57	2	116.29	38.89	119.50	92.00	147.00	0.98

Table 45: LDL Cholesterol 88 mg REM0046127 (mg/dl)

	N	Geomean	SD	Median	Min	Max	Mean change from baseline
Screening	4	130.78	29.07	142.00	89.00	167.00	
D1	4	128.94	24.92	142.00	94.00	158.00	1.00

D8	4	109.23	30.90	119.0	76.00	147.00	0.85
D15	4	105.31	32.65	131.0	71.00	137.00	0.82
D22	4	102.41	31.33	128.0	64.00	130.00	0.79
D29	4	99.71	27.55	104.0	68.00	136.00	0.77
D36	4	102.26	26.19	103.0	80.00	142.00	0.79
D43	4	95.72	25.99	104.0	69.00	123.00	0.74
D50	4	92.78	36.38	88.0	54.00	142.00	0.72
D57	4	104.09	27.42	92.0	81.00	138.00	0.81

Table 46: LDL Cholesterol 350 mg REM0046127 (mg/dl)

	N	**Geomean**	**SD**	**Median**	**Min**	**Max**	**Mean change from baseline**
Screening	3	128.60	33.71	121.0	104.00	169.00	
D1	3	119.70	21.52	122.0	99.00	142.00	1.00
D8	3	108.02	30.86	97.0	89.00	146.00	0.90
D15	3	98.78	22.37	90.0	85.00	126.00	0.83
D22	1	77.00					0.63
D29	3	90.38	13.11	89.0	79.00	105.00	0.76
D36	3	83.88	17.44	77.0	73.00	105.00	0.70
D43	2	93.53	19.09	94.5	81.00	108.00	0.82
D50	3	89.53	14.98	86.0	78.00	107.00	0.75
D57	3	76.42	14.50	77.0	63.00	92.00	0.64

Table 47: LDL Cholesterol 1400 mg REM0046127 (mg/dl)

	N	**Geomean**	**SD**	**Median**	**Min**	**Max**	**Mean change from baseline**
Screening	2	116.28	18.38	117.0	104	130	
D1	2	127.16	34.65	129.5	105	154	1.00
D8	2	118.74	28.99	120.5	100	141	0.93
D15	2	110.12	24.75	111.5	94	129	0.87
D22	0						
D29	2	102.43	25.46	104.0	86	122	0.81
D36	2	100.31	21.92	101.5	86	117	0.79

D43	2	83.41	19.09	84.5	71	98	0.66
D50	2	81.24	9.19	81.5	75	88	0.64
D57	2	54.99	33.94	60.0	36	84	0.43

7.4. Treatment-emergent adverse events by Meddra system organ class (SOC) and preferred term (PT)

Table 48: TEAE by SOC and PT

	Placebo (n=4)			**88 mg (n=5)**			**350 mg (n=3)**			**1400 mg (n=2)**			**All study participants (n=14)**		
System Organ Class Preferred term	n	%	m	n	%	m	n	%	m	n	%	m	n	%	m
Any TEAE	3	75	6	5	100	20	3	100	16	2	100	14	13	92.9	56
Blood and lymphatic system disorders	**1**	**0**	**1**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**1**	7.1	**1**
Thrombocytopenia	1	25	1	0	0	0	0	0	0	0	0	0	1	7.1	1
Cardiac disorders	**0**	**0**	**0**	**0**	**0**	**0**	**1**	**33**	**1**	**0**	**0**	**0**	**1**	7.1	**1**
Chest pain	0	0	0	0	0	0	1	33	1	0	0	0	1	7.1	1
Eye disorders	**0**	**0**	**0**	**1**	**20**	**1**	**0**	**0**	**0**	**0**	**0**	**0**	**1**	7.1	**1**
Blepharitis	0	0	0	1	20	1	0	0	0	0	0	0	1	7.1	1
Gastrointestinal disorders	**1**	**25**	**2**	**1**	**20**	**1**	**2**	**67**	**3**	**2**	**100**	**5**	**6**	42.9	**11**
Constipation	0	0	0	0	0	0	0	0	0	2	100	2	2	14.3	2
Diarrhea	0	0	0	0	0	0	0	0	0	1	50	1	1	7.1	1
Dyspepsia	0	0	0	1	20	1	0	0	0	0	0	0	1	7.1	1
Flatulence	1	25	1	0	0	0	0	0	0	0	0	0	1	7.1	1
Nausea	1	25	1	0	0	0	1	33	1	1	50	1	3	21.4	3
Pseudopolyp	0	0	0	0	0	0	1	33	1	0	0	0	1	7.1	1
Vomiting	0	0	0	0	0	0	1	33	1	1	50	1	2	14.3	2
General disorders and administration site conditions	**0**	**0**	**0**	**1**	**20**	**1**	**0**	**0**	**0**	**0**	**0**	**0**	**1**	7.1	**1**
Pyrexia	0	0	0	1	20	1	0	0	0	0	0	0	1	7.1	1
Hepatobiliary disorders	**0**	**0**	**0**	**1**	**20**	**2**	**3**	**100**	**5**	**2**	**100**	**3**	**6**	42.9	**10**
Alanine aminotransferase increased	0	0	0	0	0	0	1	33	1	0	0	0	1	7.1	1

Blood lactate dehydrogenase increased	0	0	0	0	0	0	2	67	2	1	50	1	3	21.4	3
Drug-induced liver injury	0	0	0	1	20	1	0	0	0	0	0	0	1	7.1	1
Hepatic enzyme increased	0	0	0	0	0	0	0	0	0	1	50	1	1	7.1	1
Hepatitis toxic	0	0	0	0	0	0	1	33	1	0	0		1	7.1	1
Transaminases increased	0	0		1	20	1	1	33	1	1	50	1	3	21.4	3
Infections and infestations	**0**	**0**	**0**	**2**	**40**	**2**	**0**	**0**	**0**	**1**	**50**	**1**	**3**	21.4	**3**
Bronchitis	0	0	0	1	20	1	0	0	0	0	0	0	1	7.1	1
Cystitis	0	0	0	0	0	0	0	0	0	1	50	1	1	7.1	1
Pneumonia	0	0	0	1	20	1	0	0	0	0	0	0	1	7.1	1
Injury, poisoning and procedural complications	**1**	**25**	**1**	**3**	**60**	**3**	**1**	**33**	**2**	**2**	**100**	**2**	**7**	50.0	**8**
Limb injury	0	0	0	1	20	1	0	0	0	0	0	0	1	7.1	1
Nasal injury	0	0	0	0	0	0	0	0	0	1	50	1	1	7.1	1
Post lumbar puncture syndrome	1	25	1	2	40	2	1	33	2	1	50	1	5	35.7	6
Investigations	**1**	**25**	**2**	**0**	**0**	**0**	**1**	**33**	**1**	**2**	**100**	**2**	**4**	28.6	**5**
Activated partial thromboplastin time shortened	1	25	1	0	0	0	0	0	0	0	0	0	1	7.1	1
Blood glucose increased	0	0	0	0	0	0	0	0	0	1	50	1	1	7.1	1
Blood uric acid increased	0	0	0	0	0	0	1	33	1	0	0	0	1	7.1	1
Prothrombin time shortened	1	25	1	0	0	0	0	0	0	0	0	0	1	7.1	1
Weight decreased	0	0	0	0	0	0	0	0	0	1	50	1	1	7.1	1
Musculoskeletal and connective tissue disorders	**0**	**0**	**0**	**2**	**40**	**3**	**1**	**33**	**1**	**1**	**50**	**1**	**4**	28.6	**5**
Back pain	0	0	0	0	0	0	0	0	0	1	50	1	1	7.1	1
Gouty arthritis	0	0	0	0	0	0	1	33	1	0	0	0	1	7.1	1
Neck pain	0	0	0	1	20	2	0	0	0	0	0	0	1	7.1	2
Traumatic arthritis	0	0	0	1	20	1	0	0	0	0	0	0	1	7.1	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**0**	**0**	**0**	**0**	**0**	**0**	**1**	**33**	**1**	**0**	**0**	**0**	**1**	7.1	1
Gastrointestinal tract adenoma	0	0	0	0	0	0	1	33	1	0	0	0	1	7.1	1
Nervous system disorders	**0**	**0**	**0**	**1**	**20**	**1**	**0**	**0**	**0**	**0**	**0**	**0**	**1**	7.1	**1**
Somnolence	0	0	0	1	20	1	0	0	0	0	0	0	1	7.1	1
Psychiatric disorders	**0**	**0**	**0**	**1**	**20**	**3**	**1**	**33**	**1**	**0**	**0**	**0**	**2**	14.3	**4**
Aggression	0	0	0	1	20	1	0	0	0	0	0	0	1	7.1	1

Anxiety	0	0	0	1	20	2	0	0	0	0	0	0	1	7.1	2
Depression	0	0	0	0	0	0	1	33	1	0	0	0	1	7.1	1
Respiratory, thoracic and mediastinal disorders	**0**	**0**	**0**	**2**	**40**	**3**	**0**	**0**	**0**	**0**	**0**	**0**	**2**	14.3	**3**
Cough	0	0	0	1	20	2	0	0	0	0	0	0	1	7.1	2
Sputum increased	0	0	0	1	20	1	0	0	0	0	0	0	1	7.1	1
Vascular disorders	**0**	**0**	**0**	**0**	**0**	**0**	**1**	**33**	**1**	**0**	**0**	**0**	**1**	7.1	**1**
Hypotension	0	0	0	0	0	0	1	33	1	0	0	0	1	7.1	1

n= NUMBER OF STUDY PARTICIPANTS WITH EVENT, m = NUMBER OF EVENTS, AE = ADVERSE EVENT, TEAE = TREATMENT EMERGENT AE.
THE DENOMINATOR FOR THE PERCENTAGE CALCULATIONS IS N: THE TOTAL NUMBER OF STUDY PARTICIPANTS IN THE SAFETY ANALYSIS.

8. Appendices

8.1. Patient Data Listings

8.1.1. Protocol Deviations

Institute	Deviation Nr.	Grade	Type	Patient	Root cause and Corrective / Preventive Action
Brain Research Center Amsterdam	1	Minor	Study Procedures	101	No dipstick was done on urine, but urine was sent to Spranger and analyzed. Corrective action: site retrained and worksheet for CRC is adapted to document dipstick analysis.
Brain Research Center Amsterdam	2	Minor	Study Procedures	101	Test for coding was done for 120 seconds instead of 90 seconds (as per training slides). This was noted by accident as monitor asked another question about the test. As action, one-pager instruction sheet was created and shared with the site.
Brain Research Center Amsterdam	3	Minor	Study Procedures	101	EEG only performed in afternoon due to technical issues in the morning. Siesta was reached and EEG was taken successfully in the afternoon with some delay. As action, direct number of person at Siesta was provided to site for quicker assistance.
Brain Research Center Amsterdam	4	Minor	Study Procedures	101	Weight was not taken by mistake. As per note in source documents, site is aware.
Brain Research Center Amsterdam	5	Minor	Study Procedures	101	PK sampling done 210 minutes after IMP administration (time window till 195 minutes). Reason indicated by site is run out of cognitive tests: Schedule of assessment is hard to folloy-up. Site is aware of time window.
Brain Research Center Amsterdam	6	Minor	Study Procedures	103	For computerized test, different timepoints are indicated (3 tests, 0 tests, 3 tests). Note by site in eCRF: failure due to test not functioning well on computer. System crashed halfway. As action, instruction in manual are refreshed e.g. use of chrome, removal of cache. Second test will be deleted. .
Brain Research Center Amsterdam	7	Minor	Other	103	Missing IMP was noted by patient in diary. As action, info is entered by CRC in eCRF on IMP form (when form became available in system).
Brain Research Center Amsterdam	8	Minor	Other	103	Missing IMP was noted by patient in diary. As action, info is entered by CRC in eCRF on IMP form (when form became available in system).
Fundacio ACE Barcelona	1	Minor	Study Procedures	201	Non-compliance with the 12-hour interval between one medication and another from Ruin-in D1 to Run-in D14/The patient was retrained by the research team.

Fundacio ACE Barcelona	2	Minor	Study Procedures	201	Do not record abnormalities fron urine dipstick. The nurse team not collect the information/ The research team is reminded that all the procedures detailed in the protocol must be carried out.
Fundacio ACE Barcelona	3	Minor	Study Procedures	201	Do not record abnormalities from urine dipstick. The nurse team not collect the information/ The research team is reminded that all the procedures detailed in the protocol must be carried out.
Fundacio ACE Barcelona	4	Minor	Study Procedures	202	Non-compliance with the 12-hour interval between one medication and another. The patient exceeded the time +/-1h window permitted from Run-in D1/The patient was retrained by the research team.
Fundacio ACE Barcelona	5	Minor	Study Procedures	203	Do not record abnormalities from urine dipstick. The nurse team not collect the information/ The research team is reminded that all the procedures detailed in the protocol must be carried out.
Fundacio ACE Barcelona	6	Minor	Study Procedures	203	Non-compliance with the 12-hour interval between one medication and another. The patient exceeded the time +/-1h window permitted on D25/ The patient was retrained by the research team.
Fundacio ACE Barcelona	7	Minor	Study Procedures	203	For mistake the study team did the CT instead the MRI in the screening/ The study team is reminded that all the procedures detailed in the protocol must be carried out.
Fundacio ACE Barcelona	8	Minor	Study Procedures	206	For mistake the study team did the CT instead the MRI in the screening/ The study team is reminded that all the procedures detailed in the protocol must be carried out.
Fundacio ACE Barcelona	9	Minor	Study Procedures	205	The patient took an extra placebo dose. The patient mistakenly took the placebo dose (run-in) in the morning on the day of visit 4 (D1 treatment phase) and then at 14h the study medication was taken/The patient was retrained by the research team.
Fundacio ACE Barcelona	10	Minor	Study Procedures	202	The picture recognition task was not done in the PCTS test. The rater was reminded that in case of any problem they can contact to REMAD@exeter.ac.uk or or tried to ask the monitor for help to solve it at the moment.
Fundacio ACE Barcelona	11	Minor	Study Procedures	205	The PCTS test was not done in the ED visit. The rater have technical issues. According to the Rater Marta Ibarrola, she tried to enter the test with her password and an incorrect password message appeared and there was no button to reset it. She tried it many times but she couldn't access the test. She also did not send an email to REMAD@exeter.ac.uk or tried to ask the monitor for help to solve it at the moment.
Fundacio ACE Barcelona	12	Minor	Study Procedures	206	The PCTS test was not done in the ED visit. The rater have technical issues. According to the Rater Marta Ibarrola, she tried to enter the test with her password and an incorrect password message appeared and there

					was no button to reset it. She tried it many times but she couldn't access the test. She also did not send an email to REMAD@exeter.ac.uk or tried to ask the monitor for help to solve it at the moment.
Fundacio ACE Barcelona	13	Minor	Study Procedures	201	Did not record abnormalities from urine dipstick. The nurse team did not collect the information
Fundacio ACE Barcelona	14	Minor	Study Procedures	201	MMSE Screening_ D. recall section. There is data available. There is an open query (#15) where Charo Cuevas answers that there is no data but the CRA assures that this data is available.
Fundacio ACE Barcelona	15	Minor	Study Procedures	201	Visit 2 (Run-in D1): Did not meet the 12h interval between morning and evening doses. The patient exceeded the time +/-1h window permitted from Run-in D1 to Run-in D7.
Fundacio ACE Barcelona	16	Minor	Study Procedures	201	Visit 3 (Run-in phase D2): The patient exceeded the time +/-1h window permitted from Run-in D1 to Run-in D7. The patient exceeded the time +/-1h window permitted from Run-in D8 to Run-in D14. The patient was retrained by the research team.
Fundacio ACE Barcelona	17	Minor	Study Procedures	201	Visit 4 (Day 1). Quantitative EEG Event Log Day 1. ERP. Number counted is missing. There is a comment in the field : started then forgot to count
Fundacio ACE Barcelona	18	Minor	Study Procedures	201	Visit 5 (Day 8). Do not record abnormalities from urine dipstick. The nurse team did not collect the information.
Fundacio ACE Barcelona	19	Minor	Study Procedures	201	Visit 7 (Day 29) according to Protocol V3.0 (19-Jul-2022). Quantitative EEG Event Log Day 1. ERP. 'Start counting with'; field is missing. There is a comment in the field :missing;
Fundacio ACE Barcelona	20	Minor	Study Procedures	201	Visit 7 (Day 29) according to Protocol V3.0 (19-Jul-2022). Quantitative EEG Event Log Day 1. ERP. Number counted; field is missing. There is a comment in the field : ;missing;
Fundacio ACE Barcelona	21	Minor	Study Procedures	201	Visit 8 (Day 36) according to Protocol V3.0 (19-Jul-2022). Do not record abnormalities from urine dipstick. The nurse team did not collect the information
Fundacio ACE Barcelona	22	Minor	Study Procedures	202	Visit 2 (Run-in D1): Did not meet the 12h interval between morning and evening doses. The patient exceeded the time +/-1h window permitted from Run-in D1.
Fundacio ACE Barcelona	23	Minor	Study Procedures	202	Visit 4 (Day 1). The picture recognition task was not done in the PCTS test. The rater had technical issues. (In the eCRF it is said that Computerized test is done;)
Fundacio ACE Barcelona	24	Minor	Study Procedures	202	Visit 4 (Day 1). Do not record abnormalities from urine dipstick. The nurse team did not collect the

					information. There is a comment in the field : missing data;.
Fundacio ACE Barcelona	25	Minor	Study Procedures	203	Visit 4 (Day 1). Do not record abnormalities from urine dipstick. The nurse team not collect the information
Fundacio ACE Barcelona	26	Minor	Study Procedures	203	Visit 6 (Day 15). Did not meet the 12h interval between morning and evening doses. The patient exceeded the time +/-1h window permitted on D25
Fundacio ACE Barcelona	27	Minor	Safety	203	Visit After Visit 8 (Follow-up) according to V3,0 (19-Jul-2022) On Thursday January 26, The patient was diagnosed with a toxic hepatitis. The AE was recorded as a severe adverse event in the eCRF on the same day, but was not submitted as a SAE because the SAE fields of the eCRF were blocked and they could not enter the required information. The problem was resolved on Monday 30, by Andreas Redl from Datamedrix. According to the explanations given, to be able to enter the data, a special right was defined in the eCRF that had to be removed so that the coordinator could register the information in the defined fields. The SAE was submitted on Tuesday, January 31.
Fundacio ACE Barcelona	28	Minor	Safety	203	Visit After Visit 8 (Follow-up) according to V3,0 (19-Jul-2022): The uploaded follow up SAE reports from patient 203, were incorrectly named as initial report. Therefore, in the eCRF system 6 “initial” SAE reports referring to patient 203 are entered, but all 6 reports are related to the same SAE. It was escalated to NSC and Sponsor.
Fundacio ACE Barcelona	29	Minor	Informed Consent	204	Visit 1 (Screening). The ICF of Patient 204 is not complete. He did not write his name next to the signature. It also missing the completion the section on whether the patient establishes restrictions regarding the future use of the samples. This patient was screening failure
Fundacio ACE Barcelona	30	Minor	Study Procedures	205	Visit 1 (Screening) EEG event Log. Some questions where not made to the patient and the information is missing. The questions not performed were the following: - when did you go to bed last time? -When did you fall asleep? - When did you get up today morning? - How much did you sleep? - How many times did you wake up during the night?
Fundacio ACE Barcelona	31	Minor	Study Procedures	205	Visit 1 (screening) Biocalibration. It was not recorded. There is a comment in the eCRF: i forgot to record the biocalibration so it goes biocolstart and after i went on with the EEG estrins grade and ERP. I did another calibration all the end after the oddball;
Fundacio ACE Barcelona	32	Minor	Study Procedures	205	Visit 4 (Day 1). The patient took an extra placebo dose. The patient mistakenly took the placebo dose (run-in) in the morning on the day of visit 4 (D1

					treatment phase) and then at 14h the study medication was taken.
Fundacio ACE Barcelona	33	Minor	Study Procedures	205	Visit 5 (Day 8). Did not meet the 12h interval between morning and evening doses. The patient exceeded the time +/-1h window permitted on D14
Fundacio ACE Barcelona	34	Minor	Study Procedures	205	Early Discontinuation. The PCTS test was not done. The rater had technical issues. According to the Rater Marta Ibarrola, she tried to enter the test with her password and an incorrect password message appeared and there was no button to reset it. She tried it many times but she couldn't access the test.
Fundacio ACE Barcelona	35	Minor	Study Procedures	205	Early discontinuation. EEG event Log. Some questions where not made to the patient and the information is missing. The questions not performed were the following: 2 -When did you fall asleep? 5 - How many times did you wake up during the night?
Fundacio ACE Barcelona	36	Minor	Study Procedures	206	Visit 6 (Day 15). EEG event Log. Some questions where not made to the patient and the information is missing. The questions not performed were the following: 1 - when did you go to bed last time? 2 - When did you fall asleep? 4 - How much did you sleep? 5 - How many times did you wakee up during the night?
Fundacio ACE Barcelona	37	Minor	Study Procedures	206	Visit 6 (Day 15). ERP: Lost counting. There is a comment in the field : missing;
Fundacio ACE Barcelona	38	Minor	Study Procedures	206	Early discontinuation. The PCTS test was not done. The rater had technical issues. According to the Rater Marta Ibarrola, she tried to enter the test with her password and an incorrect password message appeared and there was no button to reset it. She tried it many times but she couldn't access the test.
Fundacio ACE Barcelona	39	Minor	Other	n/a	The date reported is the one from the Screening of the first patient recruited at this site. Original CVs of Karan Chugani, Claire Braboszcz and Ángel Blanco are missing in the ISF. Signed copies were sent by email. They belong to an external team to the ACE center.
Madrid	1	Minor	Study Procedures	401	V2 (Run-in phase 1). Computerized Cognitive test: program crashed in step 4. In the system appeared as completed
Madrid	2	Minor	Study Procedures	401	V4 (Day 1). Computerized Cognitive test: program crashed in step 5 In the system appeared as completed and closed automatically.
Madrid	3	Minor	Safety	401	Visit Follow-up (Day 50) Subject 401, bilateral pneumonia with asthmatic exacerbation, hypoxemic respiratory failure and mild hyponatremia, bilateral pleural effusion on radiographs. The site had issues with entering the SAE in the eCRF. The CRA helped the site during his monitoring Visit on the 11-Apr-

					2024. The event started on the 06-Apr-2024 and ended on the 09-Apr-2024. The event was rated as not related to the study drug.
Madrid	4	Minor	Study Procedures	402	Visit Day 29. Computerized Cognitive test: program crashed and subtest 4 and 5 could not be finalized.
Sevilla	1	Minor	Study Procedures	305	Extension of the screening period. A File Note explaining the case has been filed in the ISF
Sevilla	2	Minor	Study Procedures	306	Extension of the screening period. A File Note explaining the case has been filed in the ISF
Sevilla	3	Minor	Study Procedures	307	Extension of the screening period. A File Note explaining the case has been filed in the ISF
Sevilla	4	Minor	Study Procedures	308	Extension of the screening period. A File Note explaining the case has been filed in the ISF
Sevilla	5	Minor	Study Procedures	309	Extension of the screening period. A File Note explaining the case has been filed in the ISF
Sevilla	6	Minor	Study Procedures	305	Day 43 (Visit 10). Urine dipstick not done
Sevilla	7	Minor	Study Procedures	305	Day 50 (Visit 11). Urine dipstick not done
Sevilla	8	Minor	Study Procedures	305	Day 57. (Visit 12) Urine dipstick not done
Sevilla	9	Minor	Study Procedures	306	Day 1 (V04). The PCTS test was not completed for a technical problem. In the eCRF it is stated that the test was done without any comment
Sevilla	10	Minor	Other	309	Run-in phase Day 8 (V03). The subject doesn't take one administration. The son referred that the subject had anxiety.
Sevilla	11	Minor	Other	309	Day 8 (V05). The subject doesn't take the medication from 09-Feb-24 to 11-Feb-2024 (3 days). the subject took up mediation again on 12-Feb-2024. Besides, there may have been an error in administration by the caregiver who has used 4 intakes of 2.5 mL from each bottle instead of 3 intakes.
Sevilla	12	Minor	Study Procedures	310	Run-in phase Day 1 (V02). Coding is not performed due to visuoperceptive impairment.
Sevilla	13	Minor	Study Procedures	310	Run-in phase Day 1 (V02). PCTS test was not completed. It was completed up to test 3. There were problems with test 4, as it did not finish. The page was refreshed, and the problem persisted. After consulting with the back-up monitor, the exercise was completed, without being able to perform test 2.
Sevilla	14	Minor	Study Procedures	311	Run-in phase Day 1 (V02). Letter fluency test could not be performed since the patient did not understand the instructions.
Sevilla	15	Minor	Study Procedures	311	Run-in phase Day 1 (V02). PCTS test was not completed. There were 3 tries.

Sevilla	16	Minor	Study Procedures	311	Day 1 (V04). Visit 04 was not totally completed due to decision of the Sponsor of terminating the study
Sevilla	17	Minor	Informed Consent	316	Screening visit. HIP/CI V3,0 (12/02/2024) the patient wrote 12/00/24 by mistake. The name of the investigator. The patient wrote Dr. Fansso instead of Dr. Franco.
Sevilla	18	Minor	Study Procedures	308	Patient 308 (Start of Screening: 18OCT2024; Run in phase start om 27NOV2024) exceeded the screening period of 28 days due to scheduling issues for the CSF sampling assessments.
Sevilla	19	Minor	Study Procedures	311	Patient 311 (Start of Screening: 10Jan2024; Randomized: 18Mar2024) exceeded the screening period of 28 days due to scheduling issues for the CSF sampling assessments.
Sevilla	20	Minor	Study Procedures	315	Patient 315 (Start of Screening: 07Feb2024; Randomized: 01Apr2024) exceeded the screening period of 28 days due to scheduling issues for the CSF sampling assessments.
Sevilla	21	Minor	Study Procedures	309	No vital signs were measured at this visit for this patient.
Sevilla	22	Minor	Study Procedures	306	Day 22: Pk samples times not taken according to protocol by mistake of the study team

8.2. Study Information

8.2.1. List of IECs

Name	Address	e-mail	Phone
Stichting Beoordeling Ethiek Biomedisch Onderzoek	Dr. Nassaulaan 10, 9401 HK Essen The Netherlands	info@stebo.nl	+31 592 405 871
Comité de ética de la investigación con medicamentos de la fundación de gestió sanitaria del hospital de la santa Creu i Sant Pau	Sant Antoni Ma Claret, 167 08025 Barcelona Spain	santpau@santpau.cat	+34 93 291 90 00

8.2.2. List and description of investigators and other important participants in the study

8.2.2.1. Site List

	Site	Adress	PI	Study Coordinator/Study Nurse
1	Brain Research Center Amsterdam	Cronenburg 2, 1081 GN Amsterdam, The Netherlands	Jort Vijverberg e.vijverberg@amsterdamumc.nl	Merel van der Maas M.vanderMaas@brainresearchcenter.nl
2	Fundación ACE	Calle Marqués de Sentmenat 57, Barcelona 08029, Spain	Dr. Mercé Boada Rovira mboada@fundacioace.com	Mar Buendía mbuendia@fundacioace.com
3	FISEVI Hospital Universitario Virgen del Rocío	Hospital Universitario Virgen del Rocío Avd. Manuel Siurot, s/n Sevilla 41013 Spain	Dr. Emilio Franco Macías efranco17@fgmail.com	Andrea Luque Tirado mandrea.nps@gmail.com
4	Hospital Clínico San Carlos	Hospital Clínico San Carlos, Servicio de Neurología, Baja Sur, Consulta 58.	Dr. Jordi Matias-Guiu	Marta Palacios Sarmiento marta13_12@hotmail.com

8.2.2.2. CRO, Sponsor and Third Party Team List

Surname	First name	Function	e-mail
Safety reporting and DSMB			
Funk	Daniel	PV	dfunk@neuroscios.com
Frölich	Lutz	DSMB	lutz.froelich@zi-mannheim.de
Beubler	Eckhard	DSMB	eckhard.beubler@medunigraz.at
Schmidt	Reinhold	DSMB	reinhold.schmidt@medunigraz.at
Sponsor: reMYND NV			
De Witte	Koen	CEO	koen.de.witte@remynd.com
Griffioen	Gerard	CSO	gerard.griffioen@remynd.com
Nuytten	Mieke	PM	mieke.nuytten@remynd.com
Steven	Ramael	MM	steven.ramael@ext.remynd.com
CRO: NeuroScios GmbH, Willersdorferstrasse 7, 8061 St. Radegund/Graz, Austria			
Temel	Philipp	PM	ptemel@neuroscios.com

Schöffmann	Ina	PM	ischoeffmann@neuroscios.com
Helmberg	Nikola	CEO	nhelmberg@neuroscios.com
Redl	Andreas	eCRF/ Data Management	a.redl@datamedrix.com
Central Laboratory- Safety: Labor Dr. Spranger, Lindberghstr. 9-13, 85051 Ingolstadt, Germany			
Bauer	Norbert	Spranger/Lab	norbert.bauer@ingolab.de
Bartram	Thies	Spranger/Lab	thies.bartram@ingolab.de
Central Laboratory – PK: Charles River Laboratories, Den Bosch, The Netherlands			
Korsten	John	Study Director	john.korsten@crl.com

8.2.3. Protocol and protocol amendments

8.2.3.1. Amendments to Study Protocol (Summaries of Changes)

DOCUMENT HISTORY	
Document	**Date**
Version 4.1	5-Jul-2023
Version 4.0	16-Mar-2023
Version 3.0	19-Jul-2022
Version 2.0	28-Apr-2022
Version 1.0	28-Mar-2022

Version 4.1 (05-Jul-2023)

Overall Rationale for the Change:

Remove the ERP measurement from the EEG assessment.

Section # and Name	Description of Change	Brief Rationale
3 Objectives and Endpoints	Remove ERP from exploratory analysis	Procedure too complicated for the patient population
8.1.2 EEG	ERP removed	Procedure too complicated for the patient population

Version 4.0 (16-Mar-2023)

Overall Rationale for the Change:

To adapt the study design and reduce the dosage of IMP in order to manage liver risk after observed transient increases in transaminases.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis	Cohort 2 and 3 added with lower doses	Limit compound accumulation to prevent liver risk
1.3 SoA	Add a visit at D22 and at D43, D50 and D57 Change PK sample collection	An additional safety lab to detect liver parameters early on and to follow up safety parameters until 28 days after EOT
3 Objectives and Endpoints	Clarify the description and add global statistical test	To align with SAP
9 Statistical Considerations	Updated description on efficacy analyses and interim analysis	To align with SAP
5.2 Exclusion criteria	Add criteria on liver risk	Exclude patients with increased liver sensitivity

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis	Cohort 2 and 3 added with lower doses	Limit compound accumulation to prevent liver risk
6.1 IMP Administered	Highest dose removed	Limit compound accumulation to prevent liver risk
7.1.1 Stopping criteria	Liver chemistry stopping criteria added	Patient safety
Throughout	Minor editorial and document formatting revisions	Minor, therefore have not been summarized

Version 3.0 (19-July-2022)

Overall Rationale for the Change:

The overall rationale for the amendment is to implement the comments received from the Competent Authority of Spain and to simplify the concomitant medication section (6.9).

Section # and Name	Description of Change	Brief Rationale
5.2 Exclusion criteria	Added that subjects with known sensitivity to IMP should be excluded	Added upon request of Spanish CA
6.9 Prior and Concomitant medications	Simplified the description of allowed and forbidden medication	Updated for clarity
Throughout	Minor editorial and document formatting revisions	Minor, therefore have not been summarized

Version 2.0 (28-April-2022)

Overall Rationale for the Change:

The overall rationale for the amendment is to implement the comments received from the Ethics Committee in The Netherlands and to consider treatment guidelines for AD patients in Spain.

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities	Made the cognitive tests on Day 15 optional	To reduce the burden to the patients
5.1 Inclusion criteria	Chronic medication to be taken at least 3 months prior to screening	To eliminate AEs caused by starting new medication
	Allow patients to be treated with an NMDA antagonist	To better reflect treatment practice in Spain
9.2 Statistical analysis	CSF biomarkers change from baseline will be analyzed via an ANCOVA model	Correction

Section # and Name	Description of Change	Brief Rationale
Throughout	Minor editorial and document formatting revisions	Minor, therefore have not been summarized

All protocol versions can be provided upon request.

8.2.3.2. Final Protocol Version 4.1 – 5 July 2023

Title Page

Protocol Title:

A randomized, placebo-controlled, double-blind, parallel-group Phase 2a exploratory study with placebo run-in to investigate PK/PD effects, safety, tolerability and pharmacokinetics of REM0046127 oral suspension compared with placebo in subjects with mild to moderate Alzheimer's disease

Protocol Number:

REMAD-02

Compound:

REM0046127

Brief Title:

A Phase 2a, randomized, placebo-controlled, double-blind study to investigate REM0046127 in mild to moderate Alzheimer's disease

Study Phase:

Phase 2a

Sponsor Name:

reMYND NV

Legal Registered Address:

Gaston Geenslaan 1

B-3001 Leuven

Belgium

Regulatory Agency Identifier Number(s):

EudraCT	2022-000080-43

Sponsor Signature Page

Final protocol date: Version 4.1: 05 July 2023

A randomized, placebo-controlled, double-blind, parallel-group Phase 2a exploratory study with placebo run-in to investigate PK/PD effects, safety, tolerability and pharmacokinetics of REM0046127 oral suspension compared with placebo in subjects with mild to moderate Alzheimer's disease

Sponsor Signatory:

Koen De Witte
Managing Director
reMYND
Gaston Geenslaan 1,
B-3001 Leuven-Heverlee, Belgium

July 5, 2023 | Date

Signature

Medical Monitor Name and Contact Information can be found in the study-specific manual

Protocol Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Version 4.1	5-Jul-2023
Version 4.0	16-Mar-2023
Version 3.0	19-Jul-2022
Version 2.0	28-Apr-2022
Version 1.0	28-Mar-2022

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8.1.2 EEG	ERP removed	Procedure too complicated for the patient population

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5.2 Exclusion criteria	Add criteria on liver risk	Exclude patients with increased liver sensitivity
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Section # and Name	Description of Change	Brief Rationale
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5.1 Inclusion criteria	Chronic medication to be taken at least 3 months prior to screening	To eliminate AEs caused by starting new medication

Section # and Name	Description of Change	Brief Rationale
	Allow patients to be treated with an NMDA antagonist	To better reflect treatment practice in Spain
9.2 Statistical analysis	CSF biomarkers change from baseline will be analyzed via an ANCOVA model	Correction
Throughout	Minor editorial and document formatting revisions	Minor, therefore have not been summarized

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List of Abbreviations

Abbreviation	Definition
Aβ	Amyloid beta
θ power	Theta power
ACTH	Adrenocorticotropin Hormone
AD	Alzheimer disease/Alzheimer dementia
AE	Adverse Event
A-IADL	Amsterdam Instrumental Activities of Daily Living
ALT	Alanine Aminotransferase
AP	Alkaline phosphatase
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
AUC0-∞	Area under the plasma concentration vs. time curve, between 0 and infinity
AUC0-t	Area under the plasma concentration vs. time curve, between 0 and the last detectable concentration
BID	Bis in die (twice a day)
BMI	Body Mass Index
BP	Blood Pressure
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CK	Creatine-kinase
CL	Clearance
Cmax	Maximum Concentration
CONSORT	Consolidated Standards of Reporting Trials
(e)CRF	(electronic) Case report form

CRO	Clinical Research Organization
CSF	Cerebrospinal fluid
C-SSRS	Columbia Suicide Severity Rating Scale
CT	Computer Tomography
CV	Coefficient of Variation
D	Day
DSMB	Drug Safety Monitoring Board
EC50	half maximal effective concentration
ECG	Electrocardiogram
ED80	Effective dose to achieve desired effect in 80 %
EEG	Electroencephalography
ERP	Event-Related Potential
FAS	Full analysis set
FIH	First in Human
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practices
GFAP	Glial fibrillary acidic protein
GFR	Glomerular Filtration Rate
gamma-GT	Gamma Glutamyl Transpeptidase (UI/L)
GMP	Good Manufacturing Practice
GOT	Glutamic Oxaloacetic Transaminase (UI/L)
GPT	Glutamic Pyruvic Transaminase (UI/L)
h	Hour(s)
HAM-D	Hamilton Rating Scale for Depression

HBV	Hepatitis B Virus
HBsAg	Hepatitis B Virus surface antigen
HCV	Hepatitis C Virus
HDL	High Density Lipoprotein
HIV	Human Immunodeficiency Virus
HR	Heart Rate (beats/min)
HRT	Hormonal Replacement Therapy
IB	Investigators Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
INR	International Normalized Ratio
IRB	Institutional Review Board
i.v.	intravenous
IWRS	Interactive Web Response System
kg	Kilogram
LDH	Lactate Dehydrogenase
LDL	Low Density Lipoprotein
m2	Squared meters
MAD	Multiple Ascending Dose
MANOVA	Multivariate Analysis Of Variance
MANCOVA	Multivariate Covariance Analysis
MCH	Mean Corpuscular Hemoglobin

MCV	Mean Corpuscular Volume (fL)
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligrams
mL	Milliliter
MMRM	Mixed Model with Repeated Measures
MMSE	Mini Mental State Examination
MRI	Magnetic Resonance Imaging
MRT	Mean Residence Time
N	Number
Nf-L	Neurofilament Light
NIA-AA	National Institute on Aging—Alzheimer's Association
NMDA	N-methyl-D-aspartate
PD	Pharmacodynamics
PK	Pharmacokinetics
PT	Prothrombin Time
pTau	Phospho Tau
RBC	Red Blood Cells
ROC	Receiver Operator Characteristic
SAS	Safety analysis set
SAD	Single Ascending Dose
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SoA	Schedule of Activities

SOCE	Store-operated Ca2+ entry
SRC	Safety Review Committee
SUSAR	Suspected unexpected serious adverse reaction
t1/2	Biological half-life (h)
Tau	Tau protein
TEAEs	Treatment related Adverse Events
Tmax	Time for reaching maximum concentration
UN	Unstructured covariance structure
Vd	Distribution Volume
WBC	White Blood Cells
WONCBP:	Woman of Nonchildbearing Potential

1. Protocol Summary

1.1. Synopsis

Protocol Title:

A randomized, placebo-controlled, double-blind, parallel-group Phase 2a exploratory study with placebo run-in to investigate PK/PD effects, safety, tolerability and pharmacokinetics of REM0046127 oral suspension compared with placebo in male and female subjects with mild to moderate Alzheimer's disease

Brief Title:

A Phase 2a, randomized, placebo-controlled, double-blind study to investigate REM0046127 in mild to moderate Alzheimer's disease

Agency Identifier Number(s):

EudraCT 2022-000080-43

Rationale:

REM0046127 is a small molecule intended for the oral treatment of subjects suffering from Alzheimer's disease (AD). The pharmacological mechanism of REM0046127 is based on modulating Orai calcium (Ca^{2+}) channel activity to normalize neuronal Ca^{2+} homeostasis in AD-diseased neurons. This mechanism is central in the AD-disease cascade and is therefore expected to modulate fast-acting mechanisms like restoration of impaired synaptic function, neuronal network activity (EEG), secretion of tau into CSF and synaptic CSF biomarkers to improve cognition (symptomatic). It is also expected to influence processes with slower kinetics like brain amyloid plaques formation and neuronal cell death to slow or even stop disease progression over time (neuroprotection).

Objectives, Endpoints

Objectives	**Endpoints** *All readouts are defined as mean change from baseline at day 29 for active compared to placebo, unless otherwise specified*
Primary	
• Assess the tolerability and safety of each dose level	• Incidence of treatment-emergent adverse events
Exploratory	
• Assess the relationships between CSF concentrations of REM0046127 and	• EEG power, Synaptic markers, Tau, Aβ, and inflammation (see Table 1:

CSF and blood-based biomarkers and EEG parameters	CSF Biomarkers) and global statistical tests that include EEG parameters and biomarkers
• Compare mean changes from baseline by treatment group for CSF and blood-based biomarkers and EEG	
• Assess plasma and CSF PK parameters of each dose level	• Plasma Cmax, AUCinf, … • REM0046127 concentrations in CSF
• Compare mean changes from baseline by treatment group on cognitive and functional assessments across the study	• Selected tests from MMSE, ADAS-Cog, Executive function test, computerized test, A-IADL

Overall Design:

This is a randomized, double-blind, placebo-controlled, parallel arm study with 28-day treatment duration with a 14-day placebo run-in in subjects with mild to moderate Alzheimer disease.

Brief Summary:

The purpose of this study is to measure effects on CSF biomarkers, EEG and safety with REM0046127 oral suspension compared with placebo in subjects with mild to moderate Alzheimer disease.

- The study duration will be up to 3.5 months for each treated subject
- Each subject will start with a 14-day placebo run-in period, followed by a 28-day treatment period and 28-day follow-up period
- Visit frequency: every week
- Number of Subjects: at least 30 subjects with an upper limit of 60 subjects.
- Study Design:
    - Cohort 1:
        - 7 patients
        - randomized 1:1:1
        - placebo: 350mg REM0046127 (175mg BID):1400 mg REM0046127 (700mg BID)
    - Cohort 2a:
        - Up to 12 patients
        - randomized 1:2
        - placebo: 87.5mg REM0046127 (43.75mg BID)
        - a Drug Safety Monitoring Board (DSMB) meeting will be performed after 6 patients completed Visit 10 (D43).
    - Cohort 2b: (optional - only in case a higher dose is tested)
        - Up to 12 patients

- randomized 1:2
- placebo: up to 175 mg REM0046127 (87.5mg BID)
- a DSMB meeting will be performed after 6 patients completed Visit 10 (D43).

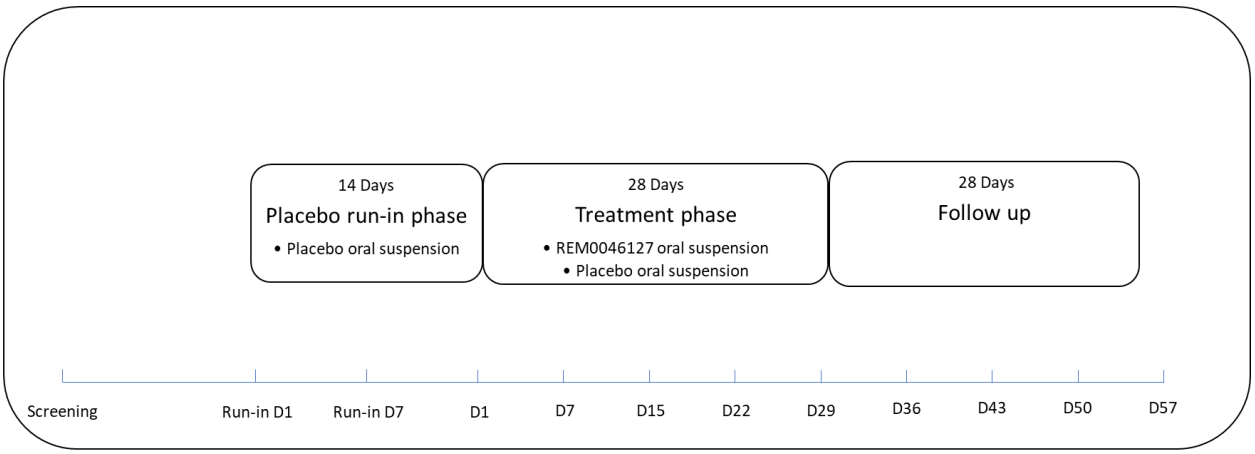
- Cohort 3:
  - Up to 45 patients
  - Dosages to be selected with the DSMB and PIs after safety evaluation of the different adaptions for Cohort 2. Therapeutic dosage expected to be in the range of 20-90 mg BID. Depending on the safety assessment, PK data and biomarker effects, the dosage could be lowered or increased, but will not exceed the highest dose tested in cohort 2 – proven safe and well-tolerated according to DSMB.
  - Adaptive randomisation after statistical interim analysis

Data Monitoring/Other Committee:

A Drug Safety Monitoring Board (DSMB) will be established to monitor the safety and scientific integrity of the trial, and to make recommendations to the sponsor. Refer to Section 10.1.6.1 for more information on the DSMB.

An internal Safety Review Committee (SRC) will be established to decide on dose modifications when safety concerns in a subject are observed. Refer to Section 10.1.6.2 for more information on the SRC.

1.2. Schema



D = Day

Schedule of Activities (SoA)

	Screening [1]	Placebo Run-in Phase 14 days		Treatment Phase 28 days					Early Discontinuation	Follow-up 28 days			
Visit #	1	2	3	4	5	6	7	8	E/D	9	10	11	12
Study Day Study Visit Window		Run-in D1 (Day -14)	Run-in D8 (Day -7) Phone call ± 2	Day 1 treatment phase ± 1	Day 8 ± 1	Day 15 ± 1	Day 22 ± 1	Day 29[2] ± 1		Day 36 ± 3	Day 43 ± 3	Day 50 ± 3	Day 57 ± 3
Procedure													
Informed consent	X												
Inclusion and exclusion criteria	X			X									
Demography	X												
Physical examination	X	X		X	X	X	X	X	X	X	X[3]	X[3]	X[3]
Vital signs	X	X		X	X	X	X	X	X	X	X[3]	X[3]	X[3]
Medical history	X												
Current medical conditions	X												
MRI[4]	X												
MMSE	X			X				X	X				
ADAS-COG and executive function test[5]		X		X		(X)[6]		X	X				
Computerized cognitive test		X		X		(X)[7]		X	X				

[1]Screening should be performed within 28 days prior to Run-in D1. It's mandatory to start with the non-invasive screening assessments before performing any of the invasive screening assessments. If a subject fails one of the in-/exclusion criteria, the subject will be a screen failure and no further assessments will be done.

[2] MMSE, ADAS-COG and executive function test, computerized cognitive test, Amsterdam IADL Questionnaire, C-SSRS can also be done on Day 28

[3] Only in case of complaints or AEs

[4] Can be deleted in case an MRI or CT from the last 6 months is already available.

[5] Comprehension, Orientation, Word recall, Delayed Word recall, Spoken language ability and Word finding difficulty will be assessed from ADAS-COG. Letter Fluency Test and Coding Test will be assessed for executive function. Refer to section 8.2.1.2. and 8.2.1.3.

[6] optional

[7] optional

	Screening [1]	Placebo Run-in Phase 14 days		Treatment Phase 28 days					Early Discontinuation	Follow-up 28 days			
Visit #	1	2	3	4	5	6	7	8	E/D	9	10	11	12
Study Day Study Visit Window		Run-in D1 (Day -14)	Run-in D8 (Day -7) Phone call ± 2	Day 1 treatment phase ± 1	Day 8 ± 1	Day 15 ± 1	Day 22 ± 1	Day 29[2] ± 1		Day 36 ± 3	Day 43 ± 3	Day 50 ± 3	Day 57 ± 3
Amsterdam IADL Questionnaire[8]				X				X	X				
C-SSRS	X			X				X	X				
12-lead ECG	X			X			X	X	X	X			
EEG[9]	X			X		X		X	X				
Biological samples[10]													
Laboratory safety tests	X			X	X	X	X	X	X	X	X	X	X
Blood sampling for PK analysis, 1, 2 or 6 samples[11]					X 1 sample	X 1 sample	X 6 samples	X 2 samples		X 1 sample	X 1 sample	X 1 sample	X 1 sample
Blood sampling for Blood-based and Plasma Biomarkers	X			X	X	X	X	X	X	X	X	X	X
CSF sampling	X[12]							X[13]					
Randomization				X									
Dispensing of IMP kits		X		X	X	X							
Training/ check on study medication		X		X	X	X	X	X					

[8] To be completed by the caregiver
[9] Quantitative EEG (qEEG). Refer to section 8.1.2.
[10] Refer to the laboratory manual for instructions on the collection, storage and shipping of these samples.
[11] Visit 5, Visit 6: 1 PK sample to be taken pre-dose. Visit 7: 6 PK samples to be taken pre-dose, 0.5-1-2-3-6hr after morning dose. Visit 8: 2 PK samples to be taken pre-dose and 3hrs after morning dose; on Visit 9, 10, 11 and 12: 1 PK sample to be taken.
[12] If a recent CSF sample is available, to be evaluated with the sponsor if this can be used.
[13] CSF sample to be taken 3hrs (+/- 15 mins) after morning dose

	Screening [1]	Placebo Run-in Phase 14 days		Treatment Phase 28 days					Early Discontinuation	Follow-up 28 days			
Visit #	1	2	3	4	5	6	7	8	E/D	9	10	11	12
Study Day Study Visit Window		Run-in D1 (Day -14)	Run-in D8 (Day -7) Phone call ± 2	Day 1 treatment phase ± 1	Day 8 ± 1	Day 15 ± 1	Day 22 ± 1	Day 29[2] ± 1		Day 36 ± 3	Day 43 ± 3	Day 50 ± 3	Day 57 ± 3
intake and patient diary[14]													
Return of IMP for drug accountability				X	X	X	X	X	X				
IMP administration[15]		X	X	X	X	X	X	X					
AE review		←=========→		←=========→					X	X	X	X	X
SAE review		←=========→		←=========→					X	X	X	X	X
Concomitant medication review		←=========→		←=========→					X	X	X	X	X

[14] Subjects need to complete a diary card to record daily dosing times, AEs and ConMeds
[15] At Visit 4, no morning dose should be administered. The IMP administration will start with the evening dose. At Visit 5, 6, 7 and 8 the morning dose of IMP is administered on site, under the supervision of the study staff.

2. Introduction

2.1. Study Rationale

Alzheimer's disease (AD) is a ravaging neurodegenerative disease that afflicts 35 million people worldwide – a number projected to triple by 2050 (Scheltens *et al.,* 2021). AD is the leading cause of dementia world-wide. Currently available treatments for AD, cholinesterase inhibitors (donepezil, rivastigmine, and galantamine) and a low-affinity NMDA receptor antagonist (memantine), have only modest effects on the symptoms of the disease and do not prevent disease progression.

Disruption of calcium homeostasis plays an important role in the pathogenesis of Alzheimer's dementia (AD) (LaFerla, 2002). Calcium (Ca^{2+}) is an important second messenger controlling numerous signaling pathways and processes underlying synaptic function and neuronal survival. In AD diseased neurons the levels of cytosolic Ca^{2+} are abnormally elevated which drive the synaptic dysfunction, the development of AD pathology and execution of neuronal cell death. From this perspective therapeutic interventions aimed at lowering these elevated cytosolic levels are expected to restore normal Ca^{2+} mediated signaling and so preventing the cascade of events leading to neuronal degeneration and consequently the development of AD symptomatology.

REM0046127 is a small molecule that lowers Orai calcium channel activity and thereby lowers elevated cytosolic Ca^{2+} to physiological levels, but not below. Although REM0046127 modulates Orai activity, it does not impact store operated Ca^{2+} entry (SOCE) as primary mechanism which is expected to be of limited tolerability. It is predicted that REM0046127 works both as a symptomatic and as a disease modifying treatment for AD.

REM0046127 was administered for the first time in humans in the Phase 1 study NSC20002. The subjects in this study were young healthy male volunteers who received up to 700mg in the SAD part, and elderly healthy male and female volunteers who received up to 1400mg (700mg bid) in the MAD part, where they were treated for 7 consecutive days with REM0046127. REM0046127 was safe and well tolerated in all dose levels tested. The results of this study support further clinical development of REM0046127.

Study REMAD-02 is the first study where REM0046127 will be administered to subjects with Alzheimer's disease.

2.2. Background

Dysregulation of calcium signaling plays a central role in the pathogenesis of Alzheimer's disease, and therefore therapeutic intervention to normalize calcium signaling is expected to be therapeutically beneficial (LaFerla, 2002). On the one hand increased intracellular cytosolic calcium and the associated deregulation of Ca^{2+} responsive pathways elicit the characteristic pathophysiology of AD, including accumulation of amyloid-β, hyperphosphorylation of TAU, synaptic dysfunction and neuronal death. On the other hand, neurodegeneration triggered by pathological amyloid-β or TAU requires disturbed calcium signaling. Hence disturbed Ca2+ signaling and AD pathophysiology constitutes a vicious cycle of mutually reinforcing processes which, once set-in motion, lead to neurodegeneration.

2.2.1. REM0046127

REM0046127 is a small molecule intended for the treatment of Alzheimer's dementia (AD). It lowers Orai calcium (Ca^{2+}) channel activity which consequently results in decreased levels of elevated cytosolic Ca^{2+} in AD diseased neurons. Accordingly, REM0046127 restores neuronal synaptic strength, network activity and cognition, reduces exocytosis of protein tau, and reduces brain amyloid beta (Aβ) plaques formation as well as neuronal inflammation, refer to the Investigator's Brochure for more information.

Although REM0046127 modulates Orai activity, it does not impact store-operated Ca^{2+} entry (SOCE) as primary mechanism which would otherwise alter regular receptor mediated signaling which is expected to be of limited tolerability.

Importantly, REM0046127 restrains excessive Ca^{2+} influx only in diseased neurons impacted by the typical changes seen in AD without lowering cytosolic Ca^{2+} below the normal physiological levels even at concentrations >100 times higher than its cellular EC_{50}. No impact on basal Ca^{2+} in healthy neurons is observed. This illustrates Ca^{2+} homeostasis is normalized but that the physiological functions of cytosolic Ca^{2+} are not impacted. The resulting selective and disease-specific inhibition of calcium influx into Alzheimer-compromised neurons is neuroprotective, and therefore potentially disease-modifying.

Therefore, REM0046127 is a promising drug candidate for the oral treatment of Alzheimer's disease combining potentially cognitive improvement with a slowing of the disease progression in subjects.

2.2.1.1. Non-Clinical Data

The available non-clinical data supports the potential of REM0046127 as a safe treatment option for AD. Refer to the Investigator's Brochure (IB) for a description of the available non-clinical data.

2.2.1.2. Clinical data

The safety of a single oral administration of 6 different dose levels up to 700 mg (SAD) and multiple oral administration during 7 days of 2 different dose levels up to 1400 mg (MAD) of REM0046127 was assessed in a phase 1 study in healthy volunteers (study NSC20002, ClinicalTrials.gov identifier NCT04672135). Forty-three healthy young male subjects were treated with REM0046127 in the SAD part: 6 with 4 mg, 7 with 35 mg, 6 with 70 mg, 6 with 200 mg and 12 with 700 mg (of which 6 in fasted condition and 6 in fed condition). 13 subjects were treated with REM0046127 in the MAD part: 8 healthy young subjects with 700 mg, and 4 elderly male and 1 elderly female subject with 1400 mg.

Based on the results of the Phase 1 study, single and multiple administrations up to 7 days of REM0046127 were considered generally safe and well-tolerated at all dose levels tested. No SAEs were reported. Refer to the Investigator's Brochure section 4.1 and 4.2 for a more detailed description of the available clinical data.

2.3. Benefit/Risk Assessment:

2.3.1. Risk Assessment

2.3.1.1. Potential Risks related to REM0046127

This is the second study in which REM0046127 is administered in humans. Based on recently observed AEs in Cohort 1 of this study, there is a **potential** risk of Drug Induced Liver Injury (DILI).

In the ongoing phase 2a study there were a total of 5 patients which presented with increased transaminases starting at around 4-5 weeks after initiating study drug treatment. One patient was hospitalized (SUSAR #1) due to important transaminase increases and functional liver impairment (increased total bilirubin, decreased coagulation). Refer to the Investigator's Brochure for a more detailed description of the available clinical data.

Overall, the significant increase in ALT observed in these 5 patients of the phase 2a study suggests an intrinsic hepatotoxicity mechanism. As a consequence, the dose regimen of REM0046127 was adapted and all patients with abnormal liver parameters will be closely monitored and are subject to follow-ups until values return to normal ranges.

In Section 10.5 of this protocol further guidance is given on the necessary follow-up in case of suspected DILI cases.

2.3.1.2. Potential Risks related to Study Procedures

MRI

According to current knowledge, MRI procedures pose no risk to human health. MRI use is generally biologically safe, has no radiation exposure and is painless. Due to the tight tube, claustrophobic subjects may experience anxiety. Known hazards only arise from metal parts or electronic implants in the body. Rapid movements in the magnetic field should be avoided as they may cause temporary dizziness or a metallic taste in the mouth.

EEG

A routine EEG is associated with minimal risk and is completely painless. However, irregularities can occur if the electrodes detach from the scalp due to heavy sweating, for example, which would distort the evaluation. Muscle twitches of the eyes can also falsify the EEG. For this reason, patients should follow the instructions of the doctor or healthcare professional exactly during the examination.

Blood Draw

Blood draw carries a small risk of pain, excessive bleeding, fainting or light-headedness, haematoma under the skin at the site of the needle insertion and a minor risk of infection.

Lumbar puncture for CSF collection

Lumbar puncture carries the risk of post-dural-puncture headache (common) and local bleeding and/or infections (rare).

2.3.1.3. Measures to Minimise the Risk for the Subjects in the Study

To minimize the risks for the subjects in the study, the following measures will be taken:

- Specific Stopping rules are implemented in the protocol (see section 7.1.1)
- For each subject, each AE will be recorded from the time of providing consent until the end of his/her participation in the study. At each study visit, the study personnel will inquire about medical complaints, laboratory safety tests and a full physical examination will be performed.
- As this is the first study assessing treatment with REM0046127 in subjects with AD who will be treated for 28 days, a drug safety monitoring board (DSMB) will be established. The DSMB will be empowered to make recommendations on further study conduct. The DSMB will convene as specified in Section 10.1.6.1.
- When safety concerns in a subject are observed, the dose of such patient will be reduced after evaluation by the SRC as described in Section 10.1.6.2

2.3.2. Benefit Assessment

REM0046127 may improve cognitive decline which may improve daily living for patients with mild to moderate AD. The results of the study might help people with a similar condition in the future.

This is the first clinical trial investigating the concept of regulating calcium homeostasis via the Orai pathway. This study will increase the knowledge and give guidance on future development using this pathway.

2.3.3. Overall Benefit Risk Conclusion

Considering the measures taken to minimize the risk for the subjects in the study, the Sponsor believes that the potential risks associated with study participation are justified by the anticipated benefits that may be afforded to the subjects in the study, and to subjects with AD in general.

3. Objectives and Endpoints

Objectives	Endpoints *All readouts are defined as mean change from baseline at day 29 for active compared to placebo, unless otherwise specified*
Primary	
• Assess the tolerability and safety of each dose level	• Incidence of treatment-emergent adverse events
Exploratory	
• Assess the relationships between CSF concentrations of REM0046127 and CSF and blood-based biomarkers and EEG parameters	• EEG power, Synaptic markers, Tau, Aβ, and inflammation (see Table 1: CSF Biomarkers) and global statistical tests that include EEG parameters and biomarkers
• Compare mean changes from baseline by treatment group for CSF and blood-based biomarkers and EEG	
• Assess plasma and CSF PK parameters of each dose level	• Plasma Cmax, AUCinf, … • REM0046127 concentrations in CSF
• Compare mean changes from baseline by treatment group on cognitive and functional assessments across the study	• Selected tests from MMSE, ADAS-Cog, Executive function test, computerized test, A-IADL

Table 1: CSF Biomarkers

Related to …	Biomarker
Synaptic plasticity	Panel of 17 synaptic markers as described by Nilsson et al., 2021, including total Neurogranin and Neuronal Pentraxin 2
	GAP43
Tau	total-Tau

Related to …	Biomarker
	pTau181
aBeta	aβ40 & Aβ42
Inflammation	GFAP
	YKL-40
	sTREM2
Neuronal cell-loss	Neurofilament Light (Nf-L)

Additional CSF and/or blood-based biomarkers may be measured which relate to (i) synaptic function, (ii) blood-brain-barrier integrity, (iii) brain lipid metabolism, (iv) APP processing, (v) inflammation, (vi) microglia activity, (vii) the autophagy lysosomal system, (viii) the ubiquitin proteasome system, (ix) gene regulation, or other future research.

4. Study Design

4.1. Overall Design

- **Overall Design**: This is a phase 2, randomized, placebo-controlled, multicenter study
- **Study Population**: Subjects with mild to moderate AD
- **Blinding**: Double-blind
- **Assignment of IMP**: If the screening has been successfully passed, the subject will be randomized after the placebo run-in phase on Day 1 to one of the treatment arms.
- **Study duration**: Up to 3.5 months for each treated subject. Every subject must undergo a 14-day placebo run-in period, followed by a 28-day treatment period. On days 36 (±3), day 43 (±3), 50 (±3) and 57 (±3) a follow up visit will take place.
- **Data monitoring committee**:

  A Drug Safety Monitoring Board (DSMB) will be established to monitor the safety and scientific integrity of the trial, and to make recommendations to the sponsor. Refer to Section 10.1.6.1 for more information on the DSMB.

  An internal Safety Review Committee (SRC) will be established to decide on dose reductions when safety concerns in a subject are observed. Refer to Section 10.1.6.2 for more information on the SRC.

4.2. Scientific Rationale for Study Design

This is the first study in subjects with AD. The purpose of this study is to explore if there is a clinically meaningful PK/PD effect for REM0046127 in patients with mild to moderate AD. The proposed sample size of 30 subjects is based on (i) power calculations to allow demonstration of an improvement with treatment relative to placebo in CSF Tau and EEG with $p \leq 0.05$ and power of at least 80% and (ii) the implied study duration.

4.3. Justification for Dose

For Cohort 1 the REM0046127 dose levels were selected based on the results from the PK and safety data of the Phase 1 trial and the PK/PD results in animal models. The high dose corresponds to the highest dose tested in phase 1 MAD study and was selected to exclude under-dosing. The low dose corresponds to the anticipated ED80, based on CSF exposures in Phase I. CSF concentration needed for an 80% effect (EC80) is 7.3 ng/ml based on target engagement in AD pre-clinical models. In human subjects (n=7) at 700 mg/day the lowest observed REM0046127 concentration in all subjects during the dosing period was **19.1 ng/ml**. This results in a dose of 269 mg/day, rounded to **350 mg/day** to be 4 times less than the high dose.

From Cohort 2 onwards, the REM0046127 dose levels were selected based on the results from the PK and safety data of Cohort 1 in this trial. The dose of Cohort 2a falls below the "rule of 2" concept of 100 mg (Chen *et al.,* 2013) and corresponds to $1/4^{th}$ of the lowest dose tested in Cohort 1.

CSF concentration needed for an 80% effect (EC80) is 7.3 ng/ml based on target engagement in AD pre-clinical models. In human subjects, after 29 days of dosing (Cohort 1 data) the REM0046127 CSF concentration was on average 28.8 ng/mL at the lowest dose. Assuming linear decline of CSF concentration when lowering the dose, the anticipated CSF concentrations for the dose of Cohort 2 would be 7.2 ng/mL.

4.4. End-of-Study Definition

The end of the study is defined as the date of the last visit of the last subject in the study or last scheduled procedure shown in the schedule of activities for the last subject in the study globally.

A subject is considered to have completed the study if the subject has completed all periods of the study including the last visit or the last scheduled procedure shown in the SoA.

5. Study Population

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Subjects are eligible to be included in the study only if all the following criteria apply:

1. Mild to moderate AD as characterized by the following clinical, cognitive, and functional criteria.
    a. Biomarker profile reflecting AD, according to The National Institute on Aging—Alzheimer's Association (NIA-AA) Research Framework based on Screening CSF Aβ1-42 and p-tau concentrations
    b. Clear EEG deficit as assessed by the EEG reader
    c. MMSE score above 12 (preferably above 16) and a maximum of 24
2. A brain imaging study, such as magnetic resonance imaging (MRI) and/or computed tomography (CT) scan having been performed within last 6 months from day of the Screening visit or during the Screening phase of this study consistent with the clinical diagnosis of AD and excluding other potential causes of dementia. If there has been a significant change in clinical status suggestive of stroke or other possible central neurological disease with onset between the time of the last MRI or CT and the Screening evaluation, an MRI scan should be repeated during Screening procedures if considered appropriate by the Investigator
3. Age 50 to 85
4. BMI above 18 and below 30 kg/m2
5. If taking concomitant medications, treated with stable doses of drugs essentially required for chronic medical conditions which do not lead to exclusion, during a period of at least 3 months prior to screening, and dose regimen is expected to remain stable during the conduct of the study
6. If taking an approved cholinesterase inhibitor or NMDA antagonist for treatment of Alzheimer’s disease, treated with a stable dose for at least 6 months prior to the screening visit and the dose is not expected to change during the study as per investigators judgement, or must be off such Alzheimer medication for a period of 8 weeks prior to screening
7. Willing and able to give informed consent.
8. Have a caregiver who assists the participant every day and has intimate knowledge of the participant’s cognitive, functional, and emotional states and of the participant’s personal care. The caregiver must be willing to accompany the participant to all study visits and to supervise IMP administration as well as report adverse events. The caregiver must be willing and able to give informed consent for their own participation and be able to read and write

9. Be able to read, write, speak clearly for the cognitive tests, with eyesight and hearing sufficient to enable completion of the cognitive tests

5.2. Exclusion Criteria

Subjects are excluded from the study if any of the following criteria apply:

1. COVID-19 positive test at the screening visit
2. Clinical, laboratory or neuro-imaging findings consistent with:
    i. Other primary degenerative dementia, (dementia with Lewy bodies, fronto-temporal dementia, Huntington's disease, Creutzfeldt-Jakob Disease, Down's syndrome, etc.)
    ii. Other neurodegenerative condition (Parkinson's disease, amyotrophic lateral sclerosis, etc.)
    iii. Cerebrovascular disease (major infarct, one strategic or multiple lacunar infarcts, extensive white matter lesions > one quarter of the total white matter)
    iv. Other significant central nervous system diseases (e.g. severe head trauma, tumors, subdural hematoma or other space occupying processes, etc.)
    v. Seizure disorder
    vi. Other infectious, metabolic or systemic diseases affecting central nervous system (syphilis, present hypothyroidism, present vitamin B12 or folate deficiency, serum electrolytes out of normal range, juvenile onset diabetes mellitus, etc.)
3. Current presence of a clinically significant major psychiatric disorder according to the criteria of the DSM-IV, or symptom that could affect the subject's ability to complete the study
4. Current clinically significant systemic illness, e.g., neoplasia, that is likely to result in deterioration of the subject's condition or affect the subject's safety during the study
5. History of liver disease, including Gilbert's disease or alcohol abuse
6. Active liver disease or jaundice, or out-of-range values of alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, gamma-glutamyl transferase (GGT), Alkaline Phosphatase (ALP) and/or lactate dehydrogenase (LDH)
7. History of severe post-lumbar puncture syndrome
8. Abnormalities in the blood clotting system or abnormal coagulation status
9. Women of childbearing potential.

    Refer to Appendix X for the definitions of woman of nonchildbearing potential.
10. Male subjects with female partners of child-bearing potential who are unwilling or unable to adhere to contraception requirements

11. Participation in another clinical study during the last 3 months
12. Wheelchair-bound or bed-ridden
13. Hypersensitivity to the IMP, or components thereof, or significant drug or other allergies that, in the opinion of the investigator, contraindicates participation in the study
14. Any other criteria which in the opinion of the Investigator causes the subject not to qualify for the study

5.3. Lifestyle Considerations

5.3.1. Meals and Dietary Restrictions

- The study medication should be administered together with food.
- The subjects should abstain from caffeine and nicotine 90 minutes prior to starting their cognitive testing session.

5.4. Screen Failures

A screen failure occurs when a subject who has consented to participate in the clinical study is not subsequently assigned to IMP/entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) for reasons expected to be temporary (e.g. a laboratory value), may be invited for a new assessment within the screening window. Rescreened subjects that are rescreened outside the screening window need to have all screening procedures repeated and should be assigned a new subject number for every screening/rescreening event.

6. Investigational Medicinal Product (IMP) and Concomitant Therapy

6.1. IMP Administered

Table 2: IMP Administered

IMP Label	REM0046127 or Placebo	REM0046127 or Placebo	REM0046127 or Placebo
IMP Name	REM0046127 35 mg/ml[1]	REM0046127 17.5 mg/ml	Placebo
IMP Description	White to off-white viscous microsuspension for oral administration	White to off-white viscous microsuspension for oral administration	White to off-white viscous microsuspension for oral administration
Type	drug	drug	drug
Dose Formulation	microsuspension	microsuspension	microsuspension
Unit Dose Strength(s)	35.0 mg/ml	17.5 mg/ml	0.0 mg/mL
Dosage Level(s)	2.5 ml BID[1]	2.5 ml BID[1]	2.5 ml BID[1]
Route of Administration	oral	oral	oral
Use	experimental	experimental	placebo
IMP	IMP	IMP	IMP
Sourcing	Provided centrally by the sponsor	Provided centrally by the sponsor	Provided centrally by the sponsor
Packaging and Labeling	IMP will be provided in 30 mL amber Kylix bottles. IMP kits will contain 1 bottle of IMP. Each bottle and kit will be labeled as required per country requirement.	IMP will be provided in 30 mL amber Kylix bottles. IMP kits will contain 1 bottle of IMP. Each bottle and kit will be labeled as required per country requirement.	IMP will be provided in 30 mL amber Kylix bottles. IMP kits will contain 1 bottle of IMP. Each bottle and kit will be labeled as required per country requirement.

[1]Dosage levels can be adjusted, see section 6.6

There will be 2 types of kits:

- **REM0046127 IMP**, containing 1 amber Kylix bottle with IMP.
- **Dosing kits,** containing oral dosing syringes for dosing of the IMP

Table 3: Study Arm(s)

Arm Title	Placebo run-in	REM0046127	Placebo
Arm Type	placebo	experimental	placebo
Arm Description	Subjects will receive 2.5 ml placebo BID from Run-in Day 1 to Run-in Day 14[1]	Subjects will receive 2.5 ml REM0046127 17.5 or 35 mg/ml BID from Day 1 to Day 29[1]	Subjects will receive 2.5 ml placebo once a day from Day 1 to Day 29[1]
Associated Intervention Labels	REM0046127 or Placebo	REM0046127 or Placebo	REM0046127 or Placebo

[1]Dosage levels can be adjusted, see section 6.6

6.2. Preparation, Handling, Storage, and Accountability

6.2.1. Handling of IMP

1. REM0046127 IMP kits should be stored at 2°C to 8°C. Dosing kits should be stored at ambient temperature.

1. The investigator or designee must confirm appropriate conditions (eg, temperature) have been maintained during transit for all IMP received, and any discrepancies are reported and resolved before use of the IMP.
2. Only subjects enrolled in the study may receive IMP, and only authorized site staff may supply IMP.
3. All IMP must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
4. The investigator, or designee is responsible for IMP accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
5. Further guidance and information for the final disposition of unused IMPs are provided in the study manual.

6.2.2. IMP administration

The subject should take the IMP twice a day (in the morning and evening) with assistance from the caregiver, and IMP administration time and date should be documented in the patient's diary. IMP should be administered together with food. During Visit 5, 6, 7 and 8, the morning dose of IMP should be administered on site under supervision of the site staff. Refer to the IMP administration instructions for further guidance.

6.3. Assignment to IMP

6.3.1. Placebo Run-in Phase

IMP kit number allocation will be performed by the IWRS system. During the Placebo Run-in Phase, all subjects will be allocated to Placebo.

6.3.2. Treatment Phase

IMP kit number allocation will be performed by the IWRS system.

IMP administration will start on the evening of Visit 4.

6.4. Blinding

This is a double-blind study in which subjects/care providers/investigators/outcomes assessors, etc. are blinded to IMP. The IWRS will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a subject's intervention assignment is warranted. Subject safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator may, at the investigator's discretion, contact the sponsor to discuss the situation prior to unblinding a subject's intervention assignment unless this could delay emergency treatment for the subject. If a subject's intervention assignment is unblinded, the sponsor must be notified within 24 hours of this occurrence.

Sponsor safety staff may unblind the IMP assignment for any subject with an SAE. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the subject's intervention assignment, may be sent to investigators in accordance with local regulations and/or sponsor policy.

Cohort 1 is unblinded to the sponsor after all subjects completed Visit 8.

6.5. IMP Compliance

As IMP will be administered to the subject at home by the caregiver, compliance with IMP will be assessed at each visit. Compliance will be assessed by counting the vials and checking the remaining amount in the vials during the site visits and documented in the source documents and relevant form. Deviation(s) from the prescribed dosage regimen should be recorded.

A record of the quantity of IMP dispensed to and administered by each subject must be maintained and reconciled with IMP and compliance records. Treatment start and stop dates, including dates for treatment delays and/or dose reductions will also be recorded.

6.6. Dose Modification

6.6.1. Dose modification for an individual subject after treatment initiation

Lab values and AEs will be monitored during each visit after D1. If clinically significant values do not return to normal/baseline within a period judged reasonable by the investigator, this will need to be submitted within 24h to the SRC. The SRC will evaluate the desirability of a dose reduction for the subject by adjusting the dosing volume, without unblinding the initial dose received by such subject. Refer to the study manual for further guidance.

6.6.2. Dose modification at treatment initiation for a treatment arm

In case of repeated observations across subjects, the DSMB can decide to adjust the dose level at treatment initiation as per DSMB charter.

6.7. Continued Access to IMP after the End of the Study

No IMP will be provided after the end of the study. After completion of the study, regular medical care will be provided to the study participants by their treating physician.

6.8. Treatment of Overdose

There is no specific antidote available in case of overdosing REM0046127.

In the event of an overdose, the investigator/treating physician should:

- Closely monitor the subject for any AE/SAE and laboratory abnormalities
- Document the quantity of the excess dose as well as the duration of the overdose.

6.9. Prior and Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, recreational drugs, vitamins, and/or herbal supplements) or other specific categories of interest that the subject is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

The concomitant medication should have no impact on the efficacy read-outs, i.e., CSF biomarkers and EEG. Medications that may interfere with these outcomes if initiated or discontinued include the acetylcholinesterase inhibitors donepezil, galantamine and rivastigmine and the NMDA antagonist memantine or fixed-combination treatments containing the above-mentioned agents.

Hence, subjects should be treatment-naïve, or off such Alzheimer medication for a period of 8 weeks prior to the screening visit. For the acetylcholinesterase inhibitors donepezil, galantamine, and rivastigmine and the NMDA antagonist memantine, it is allowed to be stably on such medication for more than 6 months with no expected changes during the study.

For benzodiazepines (including zolpidem/zopiclone) it is allowed to be stably on such medication for more than 6 months with no expected changes during the study.

Subjects that are treated with psychostimulants, antipsychotics or that are chronically taking opioids or other centrally acting analgesics do not qualify for enrolment.

For all other medication treating chronic conditions: during the conduct of the study including a period of 3 months prior to the Screening visit subjects should be treated only with stable doses of these drugs essentially required for their chronic medical conditions (which do not lead to exclusion). Changes of the drug regimen should be limited to unforeseeable conditions that require acute medical intervention.

7. Discontinuation of IMP and Subject Discontinuation/Withdrawal

Discontinuation of specific sites or of the study as a whole are detailed in Appendix 1.

7.1. Discontinuation of IMP

In rare instances, it may be necessary for a subject to permanently discontinue IMP. If IMP is permanently discontinued, the subject should, if possible, conduct an early discontinuation visit. See the SoA for data to be collected at the time of discontinuation of IMP and follow-up and for any further evaluations that need to be completed.

7.1.1. Liver Chemistry Stopping Criteria

7.1.1.1. Individual Stopping Rules pertaining to elevated transaminases or other liver health markers:

Subjects must be withdrawn from treatment if:

- ALT or AST >5 x ULN; or
- ALT or AST >3 x ULN AND total bilirubin >2 x ULN; or
- ALT or AST ≥ 3 x ULN **and** international normalized ratio (INR) > 1.5; or
- ALT or AST >3 x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).

Subjects will be monitored for drug-induced liver injury (DILI) from randomization to approximately 30 days following the last administration of study drug (refer to Protocol Appendix 10.5 for detailed procedures).

7.1.1.2. Study Stopping Rules

From Cohort 2 onwards, these are the study stopping rules pertaining to elevated transaminases and other liver health markers. The study must be stopped for any of the following reasons:

If ≥ 3 subjects are withdrawn from treatment/ the study due to a confirmed study-related increase in:

- ALT or AST >8 x ULN; or
- ALT or AST >5 x ULN for more than 2 weeks; or
- ALT or AST >3 x ULN AND total bilirubin >2 x ULN or INR >1.5 x ULN; or
- ALT or AST ≥ 3 x ULN **and** international normalized ratio (INR) > 1.5; or
- ALT or AST >3 x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever rash, and/or eosinophilia (>5%);

Subject Discontinuation/Withdrawal from the Study

- A subject may withdraw from the study at any time at the subject's own request for any reason (or without providing any reason).

- A subject may be withdrawn at any time at the discretion of the investigator for safety, behavioral, or compliance reasons.
- At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA. See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- The subject will be permanently discontinued from the IMP and the study at that time.
- If the subject withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a subject withdraws from the study, the subject may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

7.2. Lost to Follow up

A subject will be considered lost to follow-up if the subject repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible, counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether the subject wishes to and/or should continue in the study.
- Before a subject is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls, and if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.
- Should the subject continue to be unreachable, the subject will be considered to have withdrawn from the study.

8. Study Assessments and Procedures

- Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the subject's routine clinical and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the timeframe defined in the SoA.
- In the event of a significant study-continuity issue (eg, caused by a pandemic), alternate strategies for subject visits, assessments, medication distribution and monitoring may be implemented by the sponsor or the investigator, as per local health authority/ethics requirements.
- Safety or laboratory results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

8.1. Efficacy Assessments

Planned timepoints for all efficacy assessments are provided in the SoA.

8.1.1. Biomarkers

CSF and blood-based samples will be collected to assess the pharmacodynamic effect of REM0046127 on CSF and blood-based biomarkers related to Synaptic plasticity, Tau, aBeta, Inflammation, Neuronal cell-loss and other processes related to AD. Biomarkers for endpoints are listed in

Table 1: CSF Biomarkers. Samples will be collected according to the schedule described in the SoA and as detailed in laboratory manual provided separately to sites.

For CSF and blood-based biomarker samples, approximately 20 mL of CSF and approximately 60 mL of blood will be collected for biomarker measurements.

With subjects' consent, samples may be used for further research by Sponsor to the understanding of dementia diseases, the development of related or new treatments, or research methods.

8.1.2. Electroencephalogram (EEG)

EEG will be obtained to assess the pharmacodynamic effect of REM0046127 on quantitative EEG (qEEG). EEG recordings will be performed by a trained member of the investigational team according to the schedule described in the SoA and as described in the EEG manual. EEG recordings will be submitted to and graded by a central EEG reader.

8.2. Safety Assessments

Planned timepoints for all safety assessments are provided in the SoA.

8.2.1. Cognitive Scales and Functional Assessments

8.2.1.1. Mini-Mental State Examination (MMSE)

The MMSE is a brief 30-point questionnaire used to assess cognitive impairment with lower scores indicating greater impairment. The MMSE assesses 11 categories of cognition including orientation to time, memory, attention, concentration, naming, repetition, comprehension, and the ability to create a sentence and to copy two intersecting polygons. MMSE scores outside of the target severity of disease and score range, inclusive, will be excluded from participation in this study. The MMSE will be administered by a trained member of the investigational team. At each site, the same individual, whenever possible, will perform the MMSE evaluation on a specific subject throughout the study.

8.2.1.2. ADAS-Cog 6

The ADAS-cog is a structured scale that evaluates memory, orientation, attention, reasoning, language, and constructional praxis. Higher scores indicate greater impairment. A selection of 6 assessments as indicated below will be used as a cognitive measure of clinical effect. These specific ADAS-cog items will be administered by a trained member of the investigational team. At each site, the same individual, whenever possible, will perform the ADAS-cog evaluation on a specific subject throughout the study.

Comprehension	The ability to understand the meaning of words and language over the course of the test is assessed by the test administrator
Orientation	The subject will be asked its first and last name, the day of the week, date, month, year, season, time of day, and location.
Spoken language ability	The ability to use language is evaluated throughout the duration of the test.
Word Finding Difficulty	The word-finding ability is assessed throughout spontaneous conversation with the test administrator.
Word Recall	The subject will be given three chances to recall as many words as possible from a list of 10 words that were shown
Delayed Word Recall	At the end of the test, the subject will be requested again to recall as many words as possible from a list of 10 words that were shown

8.2.1.3. Executive function tests

Letter Fluency	The subject will be given a letter of the alphabet. They will need to tell as many words as they can that begin with that letter in 60 seconds. They cannot use names of people, places or numbers. This will be done 3 times with 3 different letters.
Coding	The subject will receive a paper with boxes with numbers from 1-9 in the top part and a special mark in the bottom part that is specific for that number. They will receive rows with random numbers in the top part which they will need to complete with the corresponding mark in the bottom part.

8.2.1.4. Computerized cognitive test battery

A set of 4 cognitive tests selected from the FLAME battery (Brooker et al., 2020) will be used, delivered entirely online. The subject will need to perform the following tasks:

Digit Vigilance	A target digit from 1 to 9 is randomly selected and constantly displayed to the right-hand side of the screen. Digits are then presented one at a time in the centre of the screen. The subject is required to respond as quickly as possible every time a digit matches the target digit. Correct detections, the speed of the detections and responses made in error (false alarms) are recorded.
Choice Reaction Time	The two possible stimuli in this task that can appear on screen. Equal amounts of each stimuli type will be displayed. The volunteer is required to respond with the correct response key as quickly as possible every time the stimuli appear on screen. The accuracy and speed of each is response is recorded.
Delayed Visual Recognition (Picture Recognition)	At the start of the battery pictures are presented for an equal time on screen. At the end of the battery the original pictures plus very similar distractor pictures are presented one at a time in a counterbalanced order. For each picture the subject has to indicate whether or not it was the precise picture shown earlier, as quickly and accurately as possible. Each picture remains on the screen until a response is made. The accuracy and speed of each response is recorded.
Simple Reaction Time	The subject is required to respond as quickly as possible when a stimulus is presented in the centre of the screen. The subject is informed that the stimuli will be presented one at a time and that they will remain there until a response is made. The speed of each response is recorded.

8.2.1.5. Amsterdam Instrumental Activities of Daily Living (A-IADL) questionnaire

The questionnaire consists of 75 items, measuring impairments in instrumental activities of daily living (IADL). The A-IADL questionnaire will be completed by the caregiver and will be administered according to the timepoints indicated in the SoA.

8.2.2. Medical History

- Medical and surgical history, prior and concurrent medications including cholinesterase inhibitor and memantine use, and current medical conditions will be recorded at the Screening Visit.
- Medical history will include history of cognitive impairment and psychiatric history.

8.2.3. Physical Examinations

- Full physical examination including general appearance, head and neck, eyes, respiratory, heart, abdomen, joints, peripheral circulation, skin, neurological, height (only at the screening visit) and weight. For height and weight measurements, the participant is allowed to wear indoor, daytime clothing with no shoes.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.4. Vital Signs

- Body temperature, blood pressure (BP) and heart rate will be measured. The BP measurements will be taken in the opposite arm as the blood draws, and after a 5-minute rest in the supine position.
- Blood pressure and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Planned timepoints for all assessments are provided in the SoA.

8.2.5. Electrocardiograms

- For routine safety monitoring of patients, 12-lead ECG(s) will be obtained as outlined in the SoA (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals (Fridericia's formula).
- In the case of clinically significant ECG assessments, an AE form must be completed.

8.2.6. Brain MRI

- A brain MRI will be obtained as per the sites standard practice if no MRI or CT was performed within 6 months prior to screening.

8.2.7. Clinical Safety Laboratory Tests

- See Appendix 2 for the list of clinical laboratory tests to be performed and the SoA (Section 1.3) for the timing and frequency.
- The investigator must review the laboratory results, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory results must be retained with source documents.

- All laboratory tests with values considered clinically significantly abnormal during participation in the study or after the last dose of IMP should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.
    - If clinically significant values do not return to normal/baseline within a period judged reasonable by the investigator, the etiology should be identified, and the sponsor notified by submitting it within 24h to the SRC.
    - All protocol-required laboratory tests, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA (Section 1.3).
    - If laboratory values from non-protocol-specified laboratory tests performed at the institution's local laboratory require a change in subject management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded.
- Abnormal laboratory values that are deemed by the Investigator to be 'not clinically significant' (without clinical symptoms or not requiring any intervention either treatment or extra assessments) shall not be recorded as an adverse event on the CRFs.
- Blood will be collected according to standard operating procedures of the hospital.

8.2.8. Suicidal Ideation and Behavior Risk Monitoring

Subjects being treated with IMP that could influence brain activity should be monitored appropriately and observed closely for suicidal ideation and behavior (SIB) or any other unusual changes in behavior, especially at the beginning and end of the course of intervention, or at the time of dose changes, either increases or decreases. Subjects who experience signs of SIB should undergo a risk assessment. All factors contributing to SIB should be evaluated and consideration should be given to discontinuation of the IMP.

When informed consent or assent has been given, families and caregivers of subjects should be alerted about the need to monitor subjects for the emergence of unusual changes in behavior, as well as the emergence of suicidal ideation and behavior and to report such symptoms immediately to the study investigator.

8.2.8.1. C-SSRS

Baseline assessment of suicidal ideation and behavior/intervention-emergent suicidal ideation and behavior will be monitored during the trial using Columbia-Suicide Severity Rating Scale (C-SSRS). Planned timepoints for all assessments are provided in the SoA.

8.3. Adverse Events (AEs) Serious Adverse Events (SAEs), and Other Safety Reporting

The definitions of adverse events (AEs) and serious adverse events (SAEs) can be found in Appendix 3.

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following

up (see Section 7). This includes events reported by the subject (or, when appropriate, by a caregiver, or the subject's legally authorized representative).

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

All AEs and all SAEs will be collected from the signing of the informed consent form (ICF) until the follow-up visit at the timepoints specified in the SoA (Section 1.3).

All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators need to seek information on AEs or SAEs until 30 days after end of treatment. After this period, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and the investigator considers the event to be reasonably related to the IMP or study participation, the investigator must promptly notify the sponsor.

8.3.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the subject is the preferred method to inquire about AE occurrences.

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the subject is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Appendix 3.

8.3.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of an IMP under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of an IMP under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, institutional review boards (IRBs)/independent ethics committees (IECs), and investigators.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

8.4. Pharmacokinetics

- Blood samples of approximately 5 mL per timepoint and CSF samples of approximately 10 mL will be collected for measurement of plasma/CSF concentrations of REM0046127 as specified in the SoA (Section 1.3).
- Instructions for the collection and handling of biological samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.
- Plasma samples will be used to evaluate the PK of REM0046127. Area under the curve [AUC], maximum observed concentration [C_{max}], time to C_{max} [T_{max}], half-life [$T_{½}$], volume of distribution [V_d], clearance [CL] will be calculated using the trapezoidal method.
- Genetic analyses will not be performed on these plasma/CSF samples.
- IMP concentration information that would unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

8.5. Genetics

Genetics will not be evaluated in this study.

8.6. Medical Resource Utilization and Health Economics

Medical resource utilization and health economics parameters are not evaluated in this study.

9. Statistical Considerations

9.1. Analysis Sets

For the purposes of analysis, the following analysis sets are defined:

Subject Analysis Set	Description
Full analysis set (FAS)	All randomized subjects.
Core analysis set (CAS)	All randomized subjects with baseline MMSE of 14-20
Safety analysis set (SAS)	All subjects who are exposed to investigational intervention.

The core analysis set and the full analysis set will be used to analyze endpoints related to the efficacy and biomarker objectives and the safety analysis set will be used to analyze the endpoints and assessments related to safety.

For the efficacy analyses by treatment group subjects will be included in the analyses according to the planned investigational intervention; whereas for safety analyses, subjects will be included in the analyses according to the investigational intervention they actually received.

9.2. Statistical Analyses

9.2.1. General Considerations

The SAP will be finalized prior to database lock and will include more detailed descriptions of the statistical analyses described in this section.

Unless specifically noted otherwise in the SAP, continuous variables will be summarized using the following descriptive statistics: n (non-missing sample size), mean, standard deviation, median, maximum and minimum. The frequency and percentages (based on the non-missing sample size) of observed levels will be reported.

No adjustments for multiple comparisons are planned.

Efficacy and biomarker outcomes will be analyzed using two complementary approaches. In the main approach, CSF concentrations of REM0046127 will be the primary “intervention” variable and in the second approach randomized treatment group will be the intervention variable.

Mean changes from baseline in efficacy and biomarker outcomes measured once post-baseline (day 29) will be analyzed via analysis of covariance and outcome measures with > 1 post-baseline assessment will be analyzed via a mixed-effects model for repeated measures (MMRM).

9.2.2. Safety Analyses

Pre-treatment adverse events (AEs) are defined as those which develop or worsen or become serious during the pre-treatment period.

Treatment-emergent adverse events (TEAEs) are defined as AEs that develop or worsen or become serious during the post-treatment period.

All AEs are to be coded using the current version of MedDRA. Summaries of all TEAEs in each treatment group will include:

- The overview of AEs, summarizing number (%) of participants with any TEAE/serious TEAE.
- The number and percentage of participants with at least one TEAE by System-Organ Class and Preferred Term.
- Summary of TEAEs by intensity (Grades 1 to 5), presented by System-Organ Class and Preferred Term.
- Summary of TEAEs by causal relationship to the trial IP, by System-Organ Class and Preferred Term.

Serious TEAEs will be summarized and presented as number and percent of participants in each treatment group.

TEAEs leading to treatment discontinuation will be summarized and presented as number and percentage of participants in each treatment group and overall.

9.2.3. Efficacy Analyses

The relationship between CSF concentrations of REM0046127 and efficacy and biomarker outcomes will be assessed using correlations and by ANCOVA in which CSF concentrations of REM0046127 will be the intervention variable of interest. The ANCOVA models will include linear, quadratic and cubic terms for CSF concentration with final models including the higher order terms only if they are statistically significant. The ANCOVA models will also include age, baseline MMSE score, and baseline score of the dependent variable as continuous covariates. These analyses will be conducted on the CAS and FAS, with results from the CAS being the primary evaluation.

MMRM models will include age, baseline MMSE score, and baseline score of the dependent variable as continuous covariates, the two-way interactions of these variables with Visit, along with the intervention variable (either CSF concentration of REM0046127 as a continuous variable or randomized treatment group as a categorical covariate) and the interaction of the intervention variable with Visit.

Spearman's correlations between CSF levels of REM0046127 and absolute values and changes from baseline to last observation in all efficacy and biomarker endpoints will be assessed.

9.2.4. Pharmacokinetic analysis

Plasma PK parameters will be calculated using non-compartmental methods. The peak drug concentration (Cmax), the time to peak drug concentration (Tmax), Tlast and Clast, the time to and concentration of the last quantifiable drug concentration, and the area under the curve from dosing to 6hr post dose (AUC_{0-6}).

CSF concentrations will be measured using a qualified assay. A CSF to plasma ratio will be determined if possible, using the nearest plasma timepoint.

9.3. Interim Analysis

An interim analysis will be performed after cohort 2 to define the dose levels of cohort 3. Sample size adjustments might be assessed in this interim analysis. While a planned sample of 18 subjects is based on an effect found in CSF total tau, preclinical results indicate that the EEG biomarker theta power and CSF p-Tau may be more sensitive and show an even larger effect (see section 9.4). An analysis of initial subjects' data will determine if sample size should be adjusted.

9.4. Sample Size Determination

Sample size estimates are determined based on power of detecting differences in (i) mechanism-based biomarkers and (ii) functional EEG by using respectively the available data on (i) total Tau in CSF and (ii) EEG theta power.

9.4.1. Total Tau in CSF

While meta-analytic effect sizes for differences between AD and MCI as well as AD and healthy controls are available (see ALZBIOMARKER Version 3 on Alzforum.org), the present trial is concerned with treatment effects in AD. Using the full difference between AD and healthy controls would be an optimistic treatment effect. Instead of relying on these dramatic differences between a disease state and a healthy state, a more realistic approach that uses a fraction of these effects will be used. Total tau will be used as the example.

A treatment ratio AD: treated of 2.37 is observed in hTau mice. The effect size of differences between AD and healthy controls for total tau is Cohen's d equal to 2.477, matching closely to the pre-clinical treatment ratio observed. Half of this effect (d = 1.2385) is a more realistic effect size to expect from this trial and is used for determining sample size. With 80% power and an alpha level of .05, a total sample of 18 would be sufficient to detect an effect size of d equal to 1.2385. For equal groups, the 18 subjects would be split into groups of 6 subjects per arm. This sample of 18 subjects would have 80% power to detect a d effect size difference equal to1.2385 at an alpha level of .05. In reality, for a constant sample size, the power will be higher as the inter-subject variability will be managed by using the change from baseline, which has not been possible in the studies in mice as only the CSF could be taken at sacrifice in those pre-clinical studies. Also the PK/PD analysis across all subjects provides for a higher power under constant total sample size versus a simple comparison between 2 arms.

Other tau markers such as phospho-tau 231 and phospho-tau 217, more closely linked to pathology, have even larger effect sizes for differences, being two to four times larger, respectively, requiring either an even smaller sample size at constant power or providing a higher power at constant total sample size.

9.4.2. EEG theta power

Preclinical data for theta power indicate that a large effect size might be present for detecting group differences. With a group mean difference of 0.081736 and a pooled standard deviation of 0.05261665, the Cohen's d is equal to 1.5534. With 80% power and an alpha level of .05, 15 subjects would be necessary to detect an effect size of 1.5534.

Theta power may be more sensitive than CSF measures, but it is currently unknown how large of a treatment effect will be present in CSF, so a larger sample size of 30 subjects will be attempted. It is also possible that the preclinical data could offer misleading effect sizes, so they will be used as a general guide on how small the study could become, with an interim analysis planned to determine if less subjects will be sufficient (see section 9.3).

10. Supporting Documentation and Operational Considerations

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
    - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) international ethical guidelines.
    - Applicable ICH Good Clinical Practice (GCP) guidelines
    - Applicable laws and regulations
- The protocol, protocol amendments, ICF, investigator's brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the sponsor or CRO and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study subjects.
- The Sponsor or CRO will be responsible for the following, as applicable:
    - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
    - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
    - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies, European Medical Device Regulation 2017/745 for clinical device research, and all other applicable local regulations

10.1.2. Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

- The investigator or the investigator's representative will explain the nature of the study, including the risks and benefits, to the potential subject and their caregiver and answer all questions regarding the study.
- Potential subjects must be informed that their participation is voluntary. They will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/IEC or study center. The caregiver will be required to sign the caregiver ICF.
- The medical record must include a statement that written informed consent was obtained before the subject was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICFs.
- Subjects must be reconsented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the subject and their caregiver.
- A subject who is rescreened is not required to sign another ICF if the rescreening occurs within 30 days from the previous ICF signature date.

10.1.4. Recruitment strategy

Subjects will be recruited from the internal databases of subjects previously evaluated at the clinical sites who have indicated that they are willing to be contacted about future studies, or via referrals within the sites network. Subjects can also be screened via online tools e.g. social media and local study advertisements at the investigative site.

10.1.5. Data Protection

- Subjects will be assigned a unique identifier by the sponsor. Any subject records or datasets that are transferred to the sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.
- The subject must be informed that their personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject who will be required to give consent for their data to be used as described in the informed consent.
- The subject must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The contract between sponsor and study sites specifies responsibilities of the parties related data protection, including handling of data security breaches and respective communication and cooperation of the parties.
- Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.

10.1.6. Committees Structure

10.1.6.1. Drug Safety Monitoring Board (DSMB)

An independent DSMB (Drug safety and monitoring board) will be established and will meet periodically to review patient safety. Prospectively defined sets of criteria, as outlined in the DSMB charter, will be developed to guide the committee on anticipated risk decisions.

10.1.6.2. Safety Review Committee (SRC)

An internal Safety Review Committee (SRC) will be established to decide on dose adjustments when safety concerns in a subject are observed. If clinically significant abnormal laboratory values or moderate or severe AEs do not return to normal/baseline within a period judged reasonable by the investigator and assessed by the investigator as possibly related to the IMP, the SRC needs to be informed within 24h to decide on the dose reduction. The SRC will evaluate the desirability of a dose reduction for the subject without unblinding the initial dose received by such subject.

10.1.6.3. Early Safety Data Review

- Subject safety will be continuously monitored by the medical monitor, which includes safety signal detection at any time during the study.
- An initial safety review for this study is planned for the first 6 subjects who are dosed and have provided safety data for at least 14 days or until V6 after administration of study treatment in the treatment phase.
- All safety data collected will be summarized and reviewed by the DSMB for agreement of next steps.
- In particular, data will be reviewed by the sponsor for identification of events that would potentially contribute to a requirement to adjust the study. Interim meetings will be held immediately by the DSMB in following cases:
    - Two occurrences of the same or similar serious adverse event (SAE) assessed as probably or possibly related to dosing with the IMP.
    - Two or more different subjects with the same or similar severe AE assessed as probably or possibly related to dosing with the investigational product.
    - Four or more subjects with the same or similar moderate AE which is possibly or probably related to dosing with investigational product.

10.1.7. Dissemination of Clinical Study Data

Study information from this protocol will be posted as required on publicly available clinical trial registries before enrolment of study subjects begins.

At the conclusion of the study, after the data are analyzed, a clinical study report will be prepared.

Summaries of the results of the study will be posted on publicly available clinical trial registries as required.

10.1.8. Data Quality Assurance

- All subject data relating to the study will be recorded on electronic CRFs unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.
- Guidance on completion of CRFs will be provided in the eCRF completion guidelines.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source documents.
- Monitoring details describing strategy, including definition of study critical data items and processes (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan.
- The sponsor or designee is responsible for the data management of this study, including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (eg, contract research organizations).
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 25 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.9. Source Documents

- Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data, and its origin can be found in the source data location list.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The sponsor or designee will perform monitoring to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.10. Study and Site Start and Closure

First Act of Recruitment

The study start date is the date on which the clinical study will be open for recruitment of subjects.

The first act of recruitment is the date first subject signs the ICF and will be the study start date.

Study/Site Termination

The sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

For study termination:

- Discontinuation of further IMP development

For site termination:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines.
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of subjects by the investigator.
- Total number of subjects included earlier than expected.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the subject and should assure appropriate subject therapy and/or follow-up.

10.1.11. Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2. Appendix 2: Clinical Safety Laboratory Tests

- The tests detailed in Table 4: Protocol required Safety Laboratory Tests will be performed by a central laboratory, except for the Routine urine analysis, this will be performed at the clinical trial units.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
- Investigators must document their review of each laboratory safety report.

Table 4: Protocol required Safety Laboratory Tests

Laboratory Tests[16]	**Parameter**	
Hematology	Platelet count	
	Red blood cell (RBC) count	
	RBC indices	Mean corpuscular volume (MCV) Mean corpuscular hemoglobin (MCH) %Reticulocytes
	White blood cell (WBC) count with differential:	Neutrophils Lymphocytes Monocytes Eosinophils Basophils
	Hemoglobin	
	Hematocrit	
Coagulation	PT APTT INR	

[16] Hematology, coagulation, biochemistry, routine urine analysis and hormone biomarkers to be performed each time as per the SoA.

Biochemistry	Magnesium Sodium Potassium Chloride Calcium Creatinine Urea GFR uric acid total bilirubin total protein albumin AP AST	ALT gamma-GT LDH CK Glucose Cholesterol HDL LDL Lipase
Routine urine analysis	pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick Microscopic examination (only if blood or protein is abnormal)	
Hormone Biomarkers	Cortisone, Testosterone (males), Oestradiol (females), Adrenocorticotropin Hormone (ACTH)	
Other screening tests[17]		
Serology	HIV, HCV (antibody), HBV (HBsAg)	

[17] To be performed only at screening

10.3. Appendix 3: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition

- An AE is any untoward medical occurrence in a clinical study subject, temporally associated with the use of IMP, whether or not considered related to the IMP.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of IMP.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease, or more severe than expected for the subject's condition)
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition
- New condition detected or diagnosed after IMP administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either IMP or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
- Lack of efficacy or failure of expected pharmacological action per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events <u>not</u> Meeting the AE Definition

- Any abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.
- Medical or surgical procedure (lumbar puncture): the condition that leads to the procedure is the AE.

- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:

a. Results in death

b. Is life threatening

The term *life threatening* in the definition of *serious* refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires insubject hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the subject has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outsubject setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent or significant disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as important medical events that that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
    - Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood

dyscrasias, convulsions not resulting in hospitalization, or development of intervention dependency or intervention abuse.

10.3.3. Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information.
- It is **not** acceptable for the investigator to send photocopies of the subject's medical records to the Sponsor in lieu of completion of the required form.
- There may be instances when copies of medical records for certain cases are requested by Sponsor or delegated Pharmacovigilance Service Provider. In this case, all subject identifiers, with the exception of the subject number, will be redacted on the copies of the medical records before submission.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to one of the following categories:

- Mild:
  A type of adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- Moderate:
  A type of adverse event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research subject.
- Severe:
  A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

Assessment of Causality

- The investigator is obligated to assess the relationship between IMP and each occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship.
- A *reasonable possibility* of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to IMP administration, will be considered and investigated.
- For causality assessment, the investigator will also consult the IB and/or product information, for marketed products.
- The investigator must review and provide an assessment of causality for each AE/SAE and document this in the medical notes There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.
- The investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a subject dies during participation in the study or during a recognized follow-up period, the investigator will provide the CRO and the sponsor with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally submitted documents.
- The investigator will submit any updated SAE data to the CRO and the sponsor within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting to the Sponsor or CRO via an Electronic Data Collection Tool or provided SAE Reporting Form

- The primary mechanism for reporting an SAE to the Sponsor or CRO will be the e eCRF.
- If the electronic system is unavailable, then the site will use the paper SAE reporting form to report the event within 24 hours.
- The site will enter the SAE data into the eCRF database as soon as it becomes available.
- After the study is completed at a given site, the eCRF database will be taken offline to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study subject or receives updated data on a previously reported SAE after the electronic data collection tool has been taken offline,

then the site can report this follow- up information on a paper SAE form or to the to the Sponsor or CRO by telephone.

SAE Reporting to Sponsor or CRO via SAE Report Form

- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE Reporting Form within the designated reporting timeframes.

10.4 Appendix 4: Contraceptive and Barrier Guidance

Woman of Nonchildbearing Potential (WONCBP)

Women in the following categories are considered WONCBP:

1. Premenopausal female with permanent infertility due to one of the following:
    a. Documented hysterectomy
    b. Documented bilateral salpingectomy
    c. Documented bilateral oophorectomy
    d. For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), investigator discretion should be applied to determining study entry.

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

- Postmenopausal female
    a. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
        i. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
        ii. Females on HRT must discontinue HRT to allow confirmation of postmenopausal status and to be eligible for study enrollment.

10.5. Appendix 5: Liver Safety: Suggested Actions and Follow-up Assessments

Phase 2 liver chemistry stopping criteria are designed to assure participant safety and to evaluate liver event etiology.

Phase 2 Liver Chemistry Stopping Criteria and Follow-Up Assessments

<table>
<tr><th colspan="2">Liver Chemistry Stopping Criteria</th></tr>
<tr><td>ALT or AST-absolute</td><td>ALT or AST ≥ 5 x ULN</td></tr>
<tr><td>Bilirubin[1,2]</td><td>ALT or AST ≥ 3 x ULN and total bilirubin ≥ 2 x ULN</td></tr>
<tr><td>INR[2]</td><td>ALT or AST ≥ 3 x ULN and international normalized ratio (INR) > 1.5</td></tr>
<tr><td>Symptomatic[3]</td><td>ALT or AST ≥ 3 x ULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity</td></tr>
<tr><th colspan="2">Suggested Actions, Monitoring, and Follow-up Assessments</th></tr>
<tr><th>Actions</th><th>Follow-Up Assessments</th></tr>
<tr><td>• Immediately discontinue study intervention.
• Report the event to the sponsor and CRO within 24 hours.
• Enter the event in the eCRF as an adverse event (AE) and complete a serious adverse event (SAE) CRF if the event also met the criteria for an SAE.[2]
• Perform follow-up assessments as described in the Follow Up Assessment column.
• Monitor the participant until liver chemistry test abnormalities resolve, stabilize, or return to baseline.
MONITORING:
<u>If ALT or AST ≥ 3 x ULN AND total bilirubin ≥ 2 x ULN or INR > 1.5:</u>
• Repeat liver chemistry tests (include ALT, aspartate transaminase [AST], alkaline phosphatase, total bilirubin, and INR) and</td><td>• Viral hepatitis serology[4]
• Obtain blood sample for pharmacokinetic (PK) analysis within 24h after the most recent dose5.
• Obtain, glutamate dehydrogenase (GLDH)
• Fractionate bilirubin, if total bilirubin ≥ 2 x ULN.
• Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE form.
• Record use of concomitant medications (including acetaminophen, herbal remedies, and other over-the-counter medications) on the concomitant medications CRF.
• Record alcohol use
If ALT or AST ≥ 3 x ULN AND total bilirubin ≥ 2 x ULN or INR > 1.5 or in case of ALT or AST > 5 x ULN: obtain the following in addition to the assessments listed above:</td></tr>
</table>

perform liver event follow up assessments within **24 hours.** • Monitor participant twice weekly until liver chemistry test abnormalities resolve, stabilize, or return to baseline. • A hepatology consultation is recommended. **<u>If ALT or AST ≥ 3 x ULN AND total bilirubin < 2 x ULN and INR ≤ 1.5:</u>** • Repeat liver chemistry tests (include ALT, AST, alkaline phosphatase, total bilirubin, and INR) and perform liver chemistry follow-up assessments within **24 to 72 hours.** • Monitor participants weekly until liver chemistry abnormalities resolve, stabilize, or return to baseline. • Permanently discontinue study intervention and continue participant in the study for any protocol specified follow up assessments.	• Antinuclear antibody (ANA), anti-smoothmuscle antibody (SMA), anti-mitochondrial antibody,anti-liver-kidney microsomal antibodies, anti-soluble liver antigen • Quantitative total immunoglobulin G, M, E or A1, A2, beta and gamma globulins • Serology for CMV IgG and IgM, HepA-B-C IgG and IgM, EBV IgG-IgM, HIV • Ceruloplasmin, serum ferritin, serum iron and binding capacity. • Liver imaging (ultrasound, magnetic resonance, or computed tomography) to evaluate liver disease; share anonymized report with sponsor • Liver biopsy may be considered and discussed with local specialist if available, for instance: o In participants when serology raises the possibility of autoimmune hepatitis (AIH) o In participants when suspected DILI progresses or fails to resolve on withdrawal of study intervention o In participants with acute or chronic atypical presentation • If liver biopsy conducted share anonymized report with sponsor

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation testing is unavailable, **record the absence/presence of detectable urinary bilirubin on dipstick** which is indicative of direct bilirubin elevations suggesting liver injury.
2. All events of ALT or AST ≥ 3 x ULN **and** total bilirubin ≥ 2 x ULN (for participants with known Gilbert's syndrome these criteria only apply if total bilirubin ≥2xULN, and direct bilirubin >2xULN and at least doubled from baseline value) or ALT or AST ≥ 3 x ULN **and** INR > 1.5 may indicate severe liver injury **(possible 'Hy's Law') and must be reported to sponsor in an expedited manner and as an SAE if SAE criteria met (excluding studies of hepatic impairment or cirrhosis)**. The INR stated threshold value will not apply to participants receiving anticoagulants.
3. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or hypersensitivity (such as fever, rash, or eosinophilia).

4. PK sample may not be required for participants known to be receiving placebo or noncomparator interventions. Record the date/time of the PK blood sample draw and the date/time of the last dose of study intervention prior to the blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the participant's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the laboratory manual.

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