BMJ Open

Randomised, double-blind, placebo-controlled study investigating Safety and efficAcy of MLC901 in post-traUmatic bRAin Injury: the SAMURAI study protocol

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To cite: Pilipenko P, Ivanova AA, Kotsiubinskaya YV, *et al*. Randomised, double-blind, placebo-controlled study investigating Safety and efficAcy of MLC901 in post-traUmatic bRAin Injury: the SAMURAI study protocol. *BMJ Open* 2022;**12**:e059167. doi:10.1136/bmjopen-2021-059167

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2021-059167).

Received 10 November 2021
Accepted 22 March 2022

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ABSTRACT

Introduction Traumatic brain injury (TBI) is a leading cause of death in young adults globally and 90% of cases are mild TBI. Treatment to facilitate recovery after TBI is needed. Traditional medicine MLC901 (NeuroAiD II) with neuroprotective and neuroproliferative properties in cellular and animal models of brain injury showed TBI-associated cognitive improvement in mild or moderate TBI.

Methods and analysis This is a randomised placebo-controlled trial, with 6-month treatment and 9-month follow-up, to determine the safety and efficacy of MLC901 in improving cognitive function in patients with cognitive impairment following mild TBI. This multicentre trial is conducted at the research centres of six hospitals/institutions in Russia. The primary outcome is to determine the effect of MLC901 on complex attention using the CNS Vital Signs (CNS-VS) online neurological test after 6-month treatment in patients receiving MLC901 compared with placebo. Secondary outcomes include other cognitive domains of CNS-VS and Rivermead Post Concussion Symptoms Questionnaire. The exploratory endpoints include Quality of Life after Brain Injury, Hospital Anxiety and Depression Scale and evaluation of improved neurological parameters 3 months after treatment completion. In addition, treatment compliance, concomitant therapies and adverse events will be collected. Investigators will use a secured online system for data entry.

Ethics and dissemination The study has been approved by the ethic committee of Ministry of Health of the Russian Federation (No: 58074). The results of this study will be published in a peer-review journal and presented at international conferences as poster presentations.

Trial registration number NCT04861688.

Strengths and limitations of this study

- This is a properly powered multicentred phase III randomised placebo-controlled trial that includes a predetermined statistical analysis plan of primary and secondary outcomes.
- It is a multicentre study, thus enhancing generalisability of the findings.
- The most common cognitive deficits with mild traumatic brain injury (TBI) include difficulties with complex attention, executive functioning and memory. CNS-Vital Signs is validated and widely used tool to measure those neurocognitive functioning and those domains of cognitive deficits that will be evaluated as endpoints in this study.
- However, this study will not provide data on moderate to severe TBI and this is a limitation.

INTRODUCTION

Traumatic brain injury (TBI) is a leading cause of disability and death in young adults globally. Causes of TBI are changing worldwide with increases in road traffic injuries, falls and sports-related concussion.[1–3] It was estimated that about half of the population has suffered from a TBI at some moment in their life (around 90% of all TBI cases are mild TBI) and there are about 50 million people experiencing new TBI annually and the burden of TBI is increasing globally.[1 4] Injury to the brain is caused from the mechanical impact of the brain onto the bony surfaces within the skull or from penetration of objects into the skull and diffuse axonal injury as a result of rotational forces as the brain moves within the skull. This injury may also cause brain cells death which can result neurological/cognitive deficits. The most frequent sites of cerebral contusion in closed TBI are the temporal and basal-frontal regions, both of which are associated with cognitive functioning.[5 6] Persistent cognitive deficits can profoundly impact a person's day-to-day functioning, often affecting their ability to return to work and their capacity

to engage in independent living.[6 7] The most common cognitive deficits include difficulties with complex attention, executive functioning, cognitive flexibility and memory. Due to limited understanding of mechanism of injury and deficits, the mutimodel preclinical approach to address the behavioural deficits and evaluation of potential therapeutic agents focusing anxiety and behavioural manifestation is needed.[8–10] Many people recover spontaneously from mild TBI as the brain mobilises surviving elements of the central nervous system in the damaged area to facilitate recovery.[11] However this spontaneous recovery process can be incomplete, and people continue to experience cognitive, emotional and physical impairments.[12–14]

MCL901 (NeuroAiD II), containing extracts of nine herbal components, is a simplified formulation of MLC601 (NeuroAiD), a traditional medicine that was registered with the Sino-Food and Drug Administration (Sino-FDA) in August 2001 for the treatment of stroke.[15] MLC901 has similar safety and efficacy profiles as its precursor MLC601,[16] but has several advantages that can improve patient compliance.

Non-clinical studies

MLC901 and MLC601 have been shown to demonstrate neuroprotective, anti-inflammatory and neurorestorative properties in animal and cellular models of cerebral ischaemia and other brain injuries.[16 17] Along with enhanced neuronal survival and recovery, cognitive and neurological improvements occurred with MLC901 and MLC601 following TBI.[18 19] In an animal model wherein TBI was induced by lateral fluid percussion, MLC901 was shown to decrease brain lesions induced by TBI. It also prevented the increase of serum S-100 beta and neuron-specific enolase, which are markers to predict the neurologic outcome in human patients with TBI. These effects were associated with an upregulation of vascular endothelial growth factor as well as an increase of endogenous hippocampal neurogenesis and gliogenesis around the lesion. The suppression of temporal order memory in the 'what-where-when' task in rats after TBI was restored by MLC901.[18] Furthermore, MLC601 treatment after TBI in rats significantly improved neurological and motor outcomes which were correlated with attenuation in contusion volume, fewer apoptotic neurons and less microgliosis.[19]

Clinical studies

There are extensive clinical efficacy, safety and feasibility studies and experience of MLC901 and MLC601 in stroke.[15 20–25] A pilot randomised controlled trial of MLC901 (BRAin Injury and Neuroaid Supplementation (BRAINS)) in adults with impaired Cognitive Failures Questionnaire (CFQ) at baseline revealed excellent safety profile of MLC901 and significant improvements in complex attentions and executive functioning in mild to moderate TBI, following 6 months of treatment compared with placebo.[26] Additionally, there was a small improvement in the cognitive domain of quality of life. It was concluded that a full-scale multicentre clinical trial is needed to determine clinical efficacy of MLC901 in adults following TBI on cognitive functioning, symptoms and quality of life. A randomised, double-blind, placebo-controlled study in moderate to severe TBI showed significant improvement of Modified Rankin Scale (mRS) and Glasgow outcome scale (GOS) in MLC901 group compared with placebo following 6-month treatment.[27]

Another study called NEurological Prognosis after Brain Trauma and Use of NEuroaid (NEPTUNE) in 32 adult patients, aimed to assess the effects of MLC601 on the functional and neurological outcome of patients with non-surgical moderate TBI when given within 2 days of injury.[28] All patients were followed for 6 months. On Barthel Index (BI), the MLC601 group had higher median values compared to the control group at all timepoints, reaching significance at month 3 and 6. Trajectories of BI over time showed significant improvement of BI in MLC601 group from time of discharge to month 3–6.

Since 2001 when it was first marketed in China and subsequently in other countries, there have been minimal serious side effects reported to date with the use of MLC901. Clinical safety has been demonstrated in published clinical trials which reported the more common adverse events (AEs) being gastrointestinal (nausea, vomiting, discomfort, diarrhoea, dry mouth) and headache which were mostly mild and transient.[15 22 23 29–39] Furthermore, there were no overall increase in serious AEs related to underlying diseases, and no effect on haematological, haemostatic and biochemical parameters or ECG in normal and patients who had stroke, even when started 48 hours of stroke onset.[20 21 40] The therapeutic dose of MLC901 is two capsules three times a day. With only herbal ingredients, MLC901 is expected to have a comparable or even better safety profile than its precursor. In the proposed study, MLC901 is given in patients with mild TBI.

Aims

The study aims to determine the efficacy of MLC901 in improvement of cognitive functioning of adult patients with long-term (1–12 months) cognitive impairment following mild TBI and to assess the safety of MLC901 in these patients.

Objectives

The objectives of the study are to determine the effect of MLC901 in cognitive functioning of patients with mild TBI after 6 months of MLC901 administration. The primary objective of the study is to determine the effect on changes in complex attention, the secondary, on changes in executive functioning, processing speed, memory (visual and verbal), reaction time and postconcussion symptoms, and the exploratory on changes in quality of life, level of anxiety and depression. Another exploratory objective is to assess changes of improved neurological parameters after 9 months.

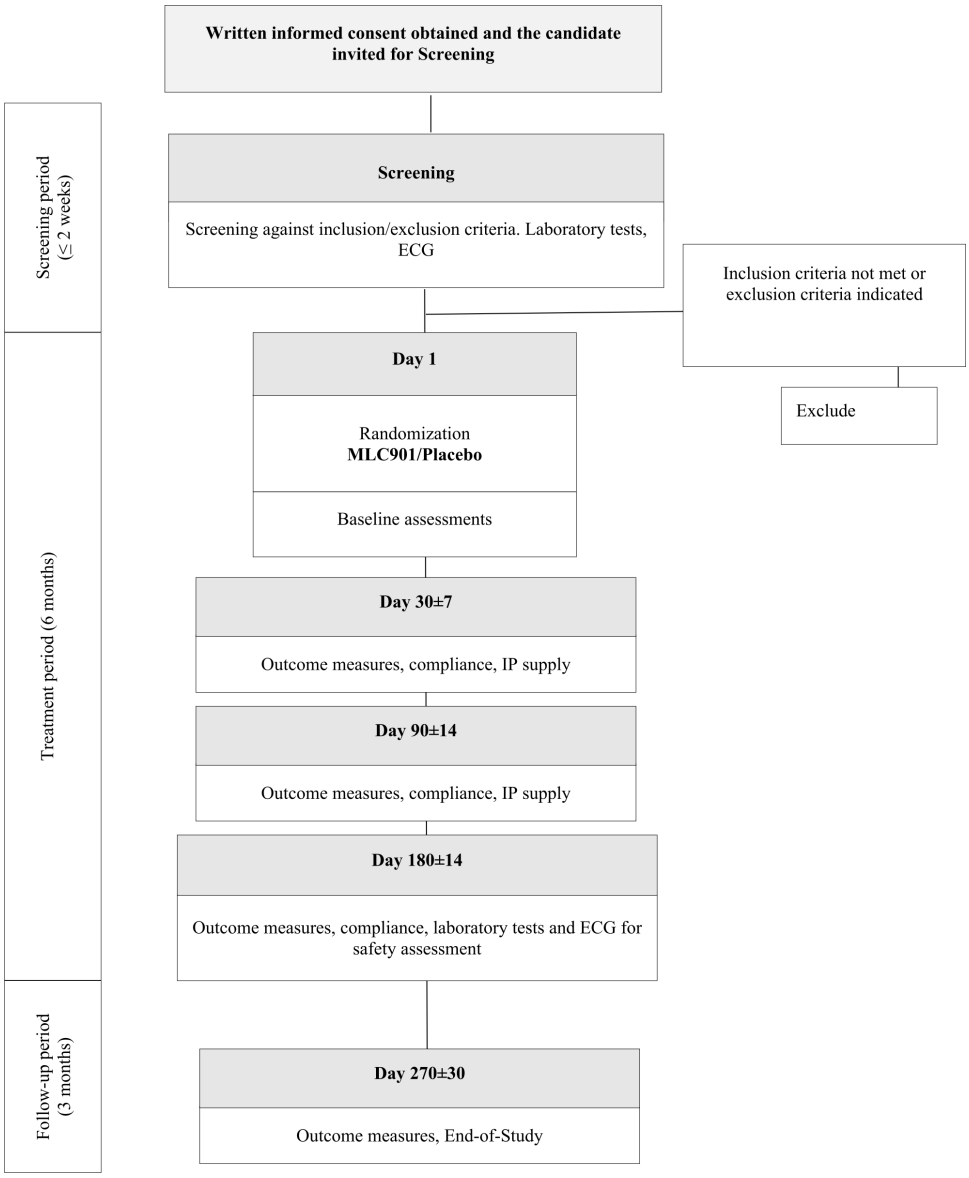

Figure 1 Summary of study design.

METHODS AND ANALYSIS

Study design

This is a 9-month randomised, double-blind, placebo-controlled, multicentre trial known as Safety and efficAcy of MLC901 in cognitive recovery post-traUmatic bRAin Injury (SAMURAI) performed in Russia. The study consists of three periods: screening period, 6-month treatment period and 3-month follow-up period. The summary of study design is given in figure 1.

Enrolment

The study will be conducted in Russia according to International Conference on Harmonisation-Good Clinical Practice (ICH/GCP) guidelines. Central and local ethics committee approval has been obtained before commencing the trial at clinical sites. The key inclusion criteria are male or female, aged 18–65 years, diagnosed with mild TBI, which occurred 1–12 months prior to enrolment to the study. Mild TBI is defined as an external force from an incident causing injury to the brain and resulting in an altered level of consciousness, evidenced by any of the following: Glasgow Coma Scale (GCS) 13–15, loss of consciousness for up to 30 min, dazed and confused at the time of injury or post-TBI amnesia of <24 hours duration, CFQ score >30. The key exclusion criteria are moderate or severe TBI (GCS<13), coexisting severe morbidity or psychiatric condition which in the investigator's judgement may jeopardise the patient by his/her participation in the study or may hamper his/her ability to perform and complete the procedures required in the study, and use of hormonal contraceptives.

Randomisation

After consenting to participate in the study and completing the baseline assessment, eligible participants will be randomised to receive either MLC901 or placebo using 1:1 stratified permuted block randomisation. This approach will help to stratify by study centre,

time since injury (1–3 months/4–12 months) and gender. Centralised stratified permuted block randomisation will be done using Interactive Web Response System. The randomisation number will be generated by the system automatically after the investigator enters the patient data into the system. The study team, including the biostatistician, will be unblinded only after database has been locked. After the patient signs the Informed consent form (ICF) at the screening visit (online supplemental 1), he/she will be assigned the screening number that is assigned in the order of enrolment. The randomisation code will be assigned to each patient that passed the screening and was found eligible. The randomisation code of each patient will be recorded in the source records and the patient's Case Report Form (CRF).

Study treatments

MLC901 is provided in capsule form containing 400 mg of dry extracts from nine herbs (*Radix Astragali*, *Radix Salviae miltiorrhizae*, *Radix Paeoniae rubra*, *Rhizoma chuanxiong*, *Radix Angelicae sinensis*, *Carthamus tinctorius*, *Prunus persica*, *Radix polygalae* and *Rhizoma Acori tatarinowii*). The dose will be two capsules taken orally three times per day for 6 months. Matching placebo capsules contains dextrin and magnesium stearate and they are visually indistinguishable from the active pills. Both MLC901 and placebo are provided by Moleac Pte Ltd.

At baseline, 1 and 3 months, participants will be given their supply of capsules in blister cards by the researcher. All participants will continue to receive standard medical care, with any changes in medical treatment being recorded. If a participant misses one dose, he/she will be advised to take the dose as soon as he/she remembers or with the next dose. If more than one dose is missed (eg, missed a whole day), the participant will be advised to take one dose as soon as they remember and then to continue treatment as usual. No more than eight capsules should be taken in one 24-hour period. Participants will be asked not to discard any capsules that they have not taken. Subjects will bring the dispensed study medication (including sachets and blisters) to each visit. Any leftover capsules (eg, capsules that participants had forgotten to take) will be collected by the investigator at the end of each time period (at 1, 3 and 6 months). The investigator will check subject compliance by counting the number of returned capsules at specified time points and record the number of missed capsules. All cases of lost or damaged capsules should be documented. Treatment compliance will be calculated by the investigator. Any detected overdose should be reported on CRF. In case of a compliance deviation, all subjects should be reinstructed about the dosing requirements during study contacts.

Primary outcomes

Changes in complex attention score will be assessed by CNS Vital Signs (CNS-VS), an online neuropsychological test battery developed as a routine clinical screening instrument.[41]

Secondary outcomes

Changes in cognitive functioning scores will be assessed by other cognitive domains of CNS-VS such as executive functioning, processing speed, verbal and visual memory and reaction time. During CNS-VS testing (primary and secondary outcomes), after the patient undergoing seven cognitive tests, the system automatically calculates scores for domains. Psychometric properties of CNS-VS have been extensively studies, including test–retest reliability, sensitivity, concurrent validity with other psychometric tests and discriminant validity in different clinical settings (various level of TBI severity, mild cognitive impairment, depression, etc)[41–43] The tests in CNS-VS are also sensitive to malingerers and patients with conversion disorders. The psychometric characteristics of the tests in the CNS-VS battery are very similar to the characteristics of the conventional neuropsychological tests on which they are based.[41 44] CNS-VS is free from practice effect and therefore is suitable for use as a serial assessment measure. In a study of Gualtieri,[41–43] CNS-VS complex attention score was compared between patients with postconcussion syndrome and mild brain injury (with loss of consciousness less than 20 min and/or transient posttraumatic amnesia not more than 24 hours) and normal patients. CNS-VS complex attention score was assessed at 100.41 in the subgroup on normal patients, as compared with an average of 92.8 in the mild brain injury or patients with postconcussion syndrome subgroups. These results suggest that a difference in complex attention score in the range of 8–10 is clinically important and distinguish normal subjects from subjects with some level of post brain injury impairment.

The Rivermead Post-Concussion Symptoms Questionnaire (RPQ) assesses neurobehavioural sequelae and consists of two subscales including the RPQ3, which includes symptoms of headaches, dizziness and nausea, and the RPQ13 comprising 13 other common symptoms such as restlessness, noise and light sensitivity, sleep disturbance, blurred vision and balance difficulties. Participants are to state the extent of each symptom they experience in comparison to the time before accident, on 5-point scale ranging from 0 (not experienced) to 4 (severe problem). The two subscales have revealed good test–retest reliability and adequate external construct validity.[45 46]

Exploratory outcomes

The Quality of Life after Brain Injury instrument (QOLIBRI)[47] contains two parts. The first part assesses satisfaction with health-related quality of life and is composed of 6 overall items and 29 items allocated to four subscales: thinking, feelings, autonomy and social aspects. The second part, devoted to 'bothered' questions, is composed of 12 items in two subscales: negative feelings and restrictions. The six subscales meet standard psychometric criteria. In addition, two items evaluate medical-oriented aspects. The QOLIBRI showed good construct validity in the TBI group.[47]

Mood will be assessed by the Hospital Anxiety and Depression Scale (HADS).[48] The scale has been widely used for assessing levels of anxiety and depression in patients with medical problems including TBI. The scale consists of 14 questions that ask participants to rate the extent to which they have been feeling in the past week, yielding separate subscale scores for anxiety and depression. The subscale scores range from 0 to 21 (0–7 normal, 8–10 mild, 11–14 moderate and 15–21 severe). The measure has demonstrated good test–retest reliability[49] and good sensitivity and specificity.[50]

In case of any improvement in any of the above parameters after 6 months of MLC901 treatment, changes in improved parameters in the same adult patients after 9 months of treatment initiation (ie, 3 months after treatment completion) will be assessed.

Study flow

The study will consist of three periods: screening, treatment period for 6 months and follow-up period after 3 months of treatment completion. At screening and baseline visit, a score of >30 of CFQ will be used to determine if the patient is experiencing cognitive impairment. Demographic data, medical history, concomitant medication, physical examination and vital signs will be collected. Baseline cognitive assessments and safety evaluation will be done as day 1 (visit 2). Further safety and efficacy assessments will be conducted at months 1, 3 and 6 (visits 3, 4 and 5). End of study assessment (visit 6) will be at the follow-up visit, 3 months after treatment completion, that is, 9 months from the start of treatment. The details of study visits and assessments are in table 1.

Safety will be assessed by physical examination, AEs/serious adverse events (SAEs) reporting, ECG and laboratory investigations (complete blood count, serum total protein, serum aspartate transaminase, serum alanine transaminase, serum glucose, serum creatinine, serum total bilirubin, serum alkaline phosphatase) and urinalysis.

Efficacy of MLC901 will be evaluated by improvement in cognitive functioning of patients with long-term cognitive impairment following mild TBI, in terms of changes from the baseline. The following tests will be done: cognitive functioning (complex attention, executive functioning, processing speed, visual and verbal memory, reaction time) assessed by CNS-VS, RPQ, QOLIBRI, HADS at months 1, 3, 6 and 9.

Sample size consideration

An estimate of 20 for SD of change in complex attention from baseline to 6 months was obtained from the BRAINS pilot study of MLC901 in 78 patients with mild or moderate TBI.[26] A minimally clinically meaningful difference of −10 in the mean change in complex attention, using CNS-VS, per group was determined. Target power: 80%. Two-sided significance level: 5%. The proportion of subjects in groups 1:1. Hypotheses: H_0: $M_T \geq M_R$, H1: $M_T < M_R$, where M_T is an arithmetical mean of change of complex attention score after 6 months of treatment, compared with baseline, in the MLC901 group, and M_R is an arithmetical mean of change from baseline of complex attention score after 6 months of treatment in the placebo group (lower score of complex attention is better). One hundred and twenty eight subjects are required to detect a clinically meaningful difference of −10 in the mean changes in complex attention between MLC901 and placebo arms with 80% power at a two-sided 5% significance level. The sample size is increased to 182 subjects (91 per arm) to allow for 30% dropouts.

Statistical analysis

Data on demographics, laboratory results, vital signs, physical examination will be presented using the following descriptive statistics: number of observations, percentages, mean, SD, median, quartiles, minimum and maximum values. These baseline differences and differences in outcomes at 1, 3, 6 and 9-month follow-up will be summarised using means, SD, medians, quartiles, minimums and maximums. Baseline value for all parameters is defined as the most recent estimate before first drug intake.

Efficacy analysis

Primary analysis will employ the intention-to-treat (ITT) population, sensitivity analyses will be performed using ITT population with last observation carried forward imputations and per protocol population.

Primary efficacy endpoints

Change in complex attention score, determined using CNS-VS computer cognitive testing system, after 6 months of treatment compared with baseline in the group of patients receiving MLC901, compared with the placebo group. For primary endpoint analysis for each patient, the difference in complex attention scores, determined using CNS-VS computer testing, after 6 months of therapy compared with baseline, will be calculated. Mixed effects model (PROC MIXED) will be used with adjustments for baseline and potential covariates. All timepoints will be used for the model. The participant and site will be used as the random effects. Model selection will be undertaken with each outcome using standard selection heuristics. Covariates will be selected based on improving the overall efficiency of the model. Baseline and age, gender, time since injury (1–3 months/4–12 months) and study centre will be included as covariates in the mixed-effects model. Descriptive statistics will be calculated to change in complex attention in each group, as well as mean values obtained by the method of least squares from the mixed effects model. Superiority of MLC901 over placebo will be claimed if H0: $LSM_T \geq LSM_R$ is rejected and thereafter H1: $LSM_T < LSM_R$ is accepted at significance level of 5%, where LSM_T is a least square mean of change from baseline of complex attention score after 6 months of treatment assessed by the mixed model repeated measures analysis in the MLC901 group and LSM_R is a least square mean of change from baseline of complex attention

Table 1 Schedules of study procedures

Procedure	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6
Time window, days	Day −14 to −1	Day 1	Day 30±7	Day 90±14	Day 180±14	Day 270±30
Informed consent form	X*					
Inclusion/exclusion criteria assessment	X					
Medical history	X	X†				
Prior/concomitant medication review	X	X†	X	X	X	X
Pregnancy test	X				X	
Demographic data (age, race)	X					
Height, weight, BMI calculation‡	X					
Collection of baseline characteristics (including social information)		X				
Date/time of TBI and injury characteristics including worst recorded GCS score	X					
Cognitive Failures Questionnaire (CFQ)	X					
Randomisation		X§				
CNS-Vital Signs (cognitive assessment)		X	X	X	X	X
Quality of life assessment (QOLIBRI)		X	X	X	X	X
Mood assessment (HADS)		X	X	X	X	X
Postconcussion symptoms (RPQ)		X	X	X	X	X
Physical examination	X	X	X	X	X	X
12-Lead ECG	X				X	
Vital signs	X	X	X	X	X	X
Clinical laboratory tests (Haematology, blood chemistry, urine)	X				X	
Compliance assessment			X	X	X	X
Adverse event monitoring		X	X	X	X	X
Investigational product supply		X	X	X		
Study drug administration		Day 1–Day 180±14 days				

*Informed consent form must be obtained prior to performing any study-related procedures.
†Not necessary if complete information was obtained on screening.
‡Body weight and height will be obtained without outerwear and shoes; BMI=weight (kg)/height (m^2).
§Subjects will be randomised just prior to dosing. Further drug intake will be done according to the randomisation scheme.
BMI, body mass index; GCS, Glasgow Coma Score; HADS, Hospital Anxiety and Depression Scale; RPQ, Rivermead Post Concussion Symptoms Questionnaire; TBI, traumatic brain injury.

score after 6 months of treatment assessed by the mixed model repeated measures analysis in the placebo group (lower score of complex attention is better).

Secondary efficacy endpoints and exploratory efficacy endpoints

The same approach as for primary endpoint will be used for analysis of secondary efficacy endpoints and exploratory endpoints, and completely similar hypotheses are be formulated as for the analysis of the primary endpoint. Mixed-effects models will be used to analyse the change in values from baseline, adjusted for covariates and baseline estimates. No sensitivity analysis will be performed for secondary endpoints. No adjustments

will be made for multiple comparisons, hypotheses will be tested hierarchically, hypothesis testing by secondary endpoints will be taken into account if statistically significant differences between groups for the primary endpoint are confirmed. For all comparisons, a critical significance level of 0.05 was chosen.

Safety analysis

Safety analysis will be performed in the safety population. Regardless of the reason for the completion of the study, the data of all patients who received at least one dose of investigational product according to the assignments will be included in the safety analysis. AEs will be coded using MedDRA dictionary. Incidences of treatment emergent AEs/SAEs will be calculated for assessment of AEs. Incidences of AEs reported during the study will be presented as number of patients with AE in total and in each treatment group. Number of AEs per each severity category and per causal relationship with the study drug will be presented. Incidences of AEs will be compared between the MLC901 and the placebo group. The proportion of patients with at least one AE will be compared in the MLC901 group and in the placebo group.

Study administration and oversight

This study will be carried out at six clinical sites at various healthcare institutions of the regional hospital or private research centres in Russia, led by the principal investigator (PP) and other site investigators (AAI, YVK, VNG). Steering committee chaired by the principal investigator will provide oversight of the conduct of the trial and ensures the study runs in a manner that is safe for study participants and also provides appropriate safety and efficacy data to the sponsor. An independent data safety and monitoring board is established to safeguard the interests of the study participants and to monitor the blinded safety data to make recommendation whether study should be continued, be modified, be analysed as an interim, or be terminated. An independent Scientific Advisory Board (SAB) is established to provide strategic scientific advice and recommendations for study.

Data management

The investigators are responsible for the accuracy and timely entry of the data into the electronic case report form (eCRF). The study monitor will review the eCRFs and other study documents and verify the primary data to confirm that ICH GCP study is conducted in accordance with the regulatory requirements and the study protocol. The investigators must retain copies of key documents for a period specified by the ICH GCP and regulatory requirements.

Trial status

SAMURAI is an ongoing study. Patient enrolment began on 23 August 2021 and is anticipated to complete on 30 November 2022.

Patient and public involvement

Patients with TBI were involved in the study design at the pilot stage of the trial, but neither patients nor other public representatives will be involved in the conduct, reporting or dissemination of the research findings. All study participants will be informed about the main study results and will have an opportunity to receive the main study journal publication on request.

ETHICAL AND DISSEMINATION

Approval from the ethic committee of Ministry of Health of Russian Federation as well as respective local ethic committee have been obtained for this study. ICF as approved by the ethics committee will be used to explain to the patient the nature, purpose and potential risks of their participation prior to performing any study-related procedures.

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Acknowledgements The authors thank Dr Robert Gan and Dr Htar Htar Nwe from Moleac Pte Ltd in coordinating the formatting and review of the manuscript among authors, study team from Atlant Clinical Ltd for Clinical Research Organization (CRO) services in clinical trial management, site management and study conduct.

Contributors The SAMURAI study is an industry-sponsored study and the protocol was written by the study team of Moleac Pte Ltd. All authors have contributed equally in the conceptualisation, design and approval of the protocol and this manuscript. PP is the chair of steering committee as well as the principal investigator and AAI, YVK and VNG are site investigators as well as the members of the steering committee. AYK is a subinvestigator. MM is the chair of DSMB. VF is the chair of SAB.

Funding The SAMURAI study is an industry-sponsored study funded by the Moleac Pte Ltd, Singapore.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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INFORMED CONSENT FORM

Protocol Title: A randomized double-blind, placebo-controlled, multi-center trial to investigate the efficacy and safety of NeuroAiD II™ (MLC901) to improve cognitive functioning in non-surgical mild traumatic brain injury patients

Protocol number: #EFSA2020_03

I confirm that:

1. I have read and understood all of this "Patient information sheet and Informed consent form" provided information concerning participation in this clinical trial, I have been given all necessary explanations and clarifications concerning conduction of the clinical trial
2. I have had an opportunity to ask questions concerning this clinical trial and I have got the comprehensive answers to all my questions
3. I have had enough time to make a decision on my participation in this clinical trial, and I have not been forced in my decision
4. By signing this document, I provide my voluntary consent to participation in this clinical trial and I do agree to follow all study procedures and to comply with all patient's responsibilities
5. I understand that I can voluntarily stop my participation in the clinical trial at any moment without any negative consequences and without any explanations
6. I understand that in case of study results publication my personal data will not be disclosed
7. I was provided with a properly signed and dated copy of "Patient information sheet and Informed consent form" on 14 pages

I agree:

1. To participate in this clinical study
2. That all my medical data will be collected, analyzed, and transferred to the Sponsor as described in this document
3. That Sponsor, Representatives of Sponsor and other authority representatives will have direct access to my medical data, as described in this document

Patient family name, name and second name (patient should write them down personally in block-letters)

……..

Patient signature ……..Date (DD-MM-YYYY) …….

Family name, name and second name of Investigator (should be written in block-letters)

……..……..

Signature of Investigator……...…… Date (DD-MM-YYYY) ..…….…….

This document was dated and signed in 2 hard copies: 1 copy is kept by Investigator, 1 copy is kept by patient