Informed Consent to Participate in a Clinical Trial

PATIENT INFORMATION AND INFORMED CONSENT

Clinical Trial Title:	**Evaluation of the Safety of Molecular Hydrogen Inhalation in Patients with Mild Cognitive Impairment**
Clinical Trial Protocol Number:	H2-MCI-R1-001-2025
Clinical Trial Sponsor:	H2 Medical Technologies s.r.o.
Name of the Investigator:	Prof. MUDr. David Školoudík, PhD, FESO, FEAN
Study Center Address:	Cerebrovascular Clinic s.r.o. Bieblova 410, 702 00 Moravská Ostrava a Přívoz
Patient identification:	

Dear Sir or Madam,

We would like to invite you to participate in this clinical trial, which aims to evaluate the safety and tolerability of molecular hydrogen inhalation in patients with mild cognitive impairment (MCI). Clinical trials are essential for obtaining scientific evidence regarding the effects of new therapeutic approaches and play a key role in the advancement of modern medicine.

This study is research-based and aims to help physicians better understand the potential benefits of molecular hydrogen in **protecting the brain** and improving cognitive functions—specifically memory, attention, and the ability to concentrate. In scientific terms, this protective effect is called **neuroprotection**.

Neuroprotection refers to a set of strategies that protect brain tissue from damage—for example, during mild, long-term inflammation. The goal is to slow down or halt harmful biochemical processes (processes occurring inside cells that affect their functioning) that can lead to the loss of nerve cells, thereby preserving brain function.

The study is being conducted in the Czech Republic and is intended only for patients who meet predetermined eligibility criteria.

The sponsor of this study is H2 Medical Technologies s.r.o., which is responsible for its organization and funding. The study physician and other healthcare professionals involved in the study will receive financial compensation from the sponsor for their work.

Your participation in this study is entirely voluntary, and it is entirely up to you to decide whether you wish to participate. You will be enrolled in the study only if you provide your written informed consent.

Before making a decision, please carefully review this document, which supplements the information you received during your discussion with the study physician. If any part of the text is unclear, do not hesitate to ask the physician or the study coordinator. You may take this document home with you, review it carefully, and, if necessary, discuss your participation with your family and friends.

If you decide not to participate in the study or withdraw from it at any time, this will not affect your ongoing medical care in any way. If you decide to withdraw from the study, please inform the principal investigator, who will provide you with further instructions on how to safely end your participation.

Thank you for considering participation in this study. Your cooperation is important for the further advancement of medicine and may help improve care for patients with cognitive decline in the future.

1. Why is this study being conducted?

Mild cognitive impairment (MCI) is a condition characterized by a decline in memory, attention, and other mental abilities, but it does not yet affect daily functioning as significantly as dementia. This condition may serve as an early warning sign for the development of Alzheimer's disease or other brain disorders that cause the loss of nerve cells.

One possible cause of MCI is so-called **oxidative stress**—a condition in which the body's balance between harmful substances (known as free radicals) and the defense mechanisms that normally neutralize them is disrupted. These free radicals can damage cells, including brain cells, thereby contributing to the decline in cognitive function. This can be compounded by **chronic inflammation** or **disruptions in cellular metabolism**—that is, the way cells obtain and use energy. All of these factors can lead to a gradual decline in brain function.

Molecular hydrogen (H_2) is a natural gas with antioxidant and anti-inflammatory properties (the ability of substances to neutralize harmful substances, such as free radicals, in the body) that is being studied for its potential to protect brain cells from damage. Research suggests that hydrogen may help neutralize harmful free radicals, reduce inflammatory processes in the brain, and support the proper function of **mitochondria**—that is,
the "powerhouses of the cell," which ensure energy production in every cell, including brain cells. Well-functioning mitochondria are key to brain health because they supply cells with the energy they need and help them cope with stressful conditions. Supporting them may help slow cognitive decline.

The aim of this study is to evaluate the safety and tolerability of molecular hydrogen inhalation in patients with mild cognitive impairment. The study will focus on potential positive effects on cognitive function and will monitor changes in biochemical parameters related to oxidative stress and inflammation.

This study represents an important step toward a better understanding of the effects of molecular hydrogen on brain function, which may contribute in the future to the development of new strategies for the prevention and treatment of cognitive disorders.

2. What is molecular hydrogen inhalation?

Molecular hydrogen (H_2) is a naturally occurring gas that has been extensively studied in recent years for its antioxidant and anti-inflammatory properties. Research suggests that molecular hydrogen

can neutralize free radicals, reduce oxidative stress and inflammatory processes in the body, and thereby support cellular health, including brain function.

Molecular hydrogen inhalation is a non-invasive method in which the patient inhales hydrogen mixed with air using a special hydrogen generator. This study will use the H2-Air Blend Inhaler, which produces high-purity, air-diluted hydrogen intended for therapeutic use.

How does inhalation work?

- Inhalation takes place while the patient is seated in a relaxed position, breathing hydrogen gas through a special nasal cannula.
- Each inhalation session lasts 60 minutes and takes place every workday during the intervention phase of the study.
- Inhalation is completely painless and requires no active cooperation from the patient.

What are the potential effects?

- Molecular hydrogen is being studied for its potential to reduce oxidative stress, which plays a role in the development of neurodegenerative diseases.
- Research suggests that it may support healthy brain cell function **and** improve cognitive performance in patients with mild cognitive impairment (MCI).
- In addition to brain function, hydrogen may also have other beneficial effects on inflammatory and metabolic processes in the body.

Contraindications and Limitations

Inhaling molecular hydrogen is considered a safe method; however, there are situations in which it is not appropriate to participate in the study:

- People with an implanted pacemaker—although the direct effect of hydrogen inhalation on pacemaker function is unknown, patients with implanted electronic devices cannot participate in this study. If you have a pacemaker or other electronic implants, please inform the study physician.
- Pregnant women—the safety of molecular hydrogen during pregnancy has not been sufficiently studied. If you are pregnant or planning to become pregnant, you cannot participate in the study. Please inform the study physician.
- Individuals with advanced-stage chronic diseases – if you have a serious medical condition that could significantly affect the course of your participation in the study, participation may not be appropriate. The study physician will determine your eligibility based on an individual assessment.

If you are unsure whether this study is right for you, please contact the study physician, who will discuss all participation criteria with you in detail.

3 What is the course of the study, and what should I be aware of while participating?

If you decide to participate in this study and sign the informed consent form, the doctor will first assess whether you meet all the eligibility criteria. Before the study begins, you will undergo a thorough initial medical examination, which includes a routine physical exam, as well as measurements of your blood pressure, pulse, weight, and height. The doctor will ask you about your medical history, including any medications you are taking, other medical conditions, and your overall health. To monitor the course of the study as accurately as possible, laboratory tests will also be performed during the initial visit, focusing on biochemical markers such as inflammation, metabolic processes, and antioxidant capacity.

The examination will also include neurocognitive tests, such as ALBA and POBAV, which will help doctors assess the status of your cognitive functions at the start of the study. You will also be asked to complete a set of questionnaires focused on quality of life, subjective assessments of memory, and other cognitive abilities, which will provide a comprehensive view of your health status and any changes that may occur during the study.

If the doctor confirms that you meet all the inclusion criteria, you will be enrolled in the intervention phase of the study, which lasts three months. During this time, you will visit the study site every workday, where you will inhale molecular hydrogen for sixty minutes. This inhalation takes place in a relaxed environment and is completely non-invasive. The hydrogen mixture is inhaled through a special nasal cannula, which allows for comfortable breathing throughout the procedure. No active participation is required from the patient during inhalation; you simply need to sit quietly and breathe.

The three-month intervention phase is followed by a monitoring period that lasts another three months. During this phase, you will no longer perform the inhalation, but you will attend regular checkups so that the doctor can assess the long-term effects of molecular hydrogen on your health. The checkups will include the same examinations as at the beginning of the study—laboratory tests, blood pressure and pulse measurements, neurocognitive tests, and completion of questionnaires.

Participation in the study requires adherence to regular visits and cooperation with the study team. It is very important that all scheduled inhalations be performed according to the established schedule, as this is the only way to obtain reliable results regarding the effects of molecular hydrogen. If, for any reason, you are unable to attend a visit or if you experience any side effects, it is essential to inform your doctor or the study coordinator as soon as possible.

Throughout the study, you will be under the supervision of qualified medical staff who will ensure your safety and comfort. If you have any questions or concerns, please do not hesitate to contact the study team. It is also important to know that participation in this study is entirely voluntary, and you may decide to withdraw at any time without it having any impact on your future medical care. The total duration of your participation in the study is six months, during which you will be contributing to research that could lead to better treatment and prevention options for cognitive disorders in the future.

4. What are the benefits of participating in the study?

Participation in this study may not provide you with any direct health benefits, as the primary goal is to gain scientific insights into the safety and potential effects of molecular hydrogen on cognitive function. Nevertheless, your participation may be beneficial both to you and to future patients who could benefit from this method in the future.

Thanks to regular medical checkups, you will be under the careful supervision of a team of healthcare professionals who will monitor your overall health, cognitive function, and biochemical parameters. This means that during the study, you can gain valuable information about your health that would not otherwise be part of routine medical care. If any health issues are identified during the examinations, you will be informed of them, and your doctor may recommend appropriate follow-up tests or measures.

Your participation in this study is also important from the perspective of medical research. The results of this study may contribute to a better understanding of the effects of molecular hydrogen on brain function in the future and potentially lead to the development of new approaches to the prevention and treatment of cognitive disorders. Thanks to you and other participants, it will be possible to collect important data that can help doctors better understand this new therapeutic approach and assess its benefits and safety.

Although we cannot guarantee that inhaling molecular hydrogen will provide you with immediate benefits, your participation has broader significance and may help not only you but also other patients in the future.

5. What are the risks associated with participating in the study?

Based on available scientific evidence and previous studies, inhaling molecular hydrogen is considered a safe method with a minimal risk of side effects. Research to date shows that molecular hydrogen is well tolerated and has no toxic properties. Nevertheless, it is important to note that, as with any other experimental treatment, there is a possibility of adverse reactions, although they are rare and usually mild.

Possible side effects that have been reported in connection with the inhalation of molecular hydrogen include:

- mild irritation of the respiratory tract, particularly in individuals with chronic respiratory conditions such as asthma or chronic obstructive pulmonary disease
- a sensation of dizziness or mild nausea, usually of short duration, which may be related to individual sensitivity to hydrogen inhalation
- mild dryness in the mouth or throat, which may be caused by prolonged inhalation without adequate hydration
- transient headache, which has been reported in some cases but has not yet been definitively linked to hydrogen inhalation

If you experience any unusual medical condition or symptoms during the study, it is important to inform the study physician or another member of the study staff. In the event of any more serious symptoms, please contact a doctor as soon as possible so that the situation can be assessed in a timely manner and necessary measures can be taken if needed.

The tests you will undergo during the study are non-invasive and do not pose any significant health risks. Blood draws will be performed using standard methods and should not cause any long-term complications.

During the study, it is important that you avoid taking any new medications without first consulting the study physician. This also applies to over-the-counter medications and dietary supplements that could affect the study results. If you need to undergo any other treatment during the study or find yourself in a situation requiring emergency medical care, inform your treating physician of your participation in the study and then contact the study team.

We recommend that you carry your clinical trial participant card with you for the duration of the study; it contains basic information about the study and the study team's contact information. This will ensure that, in the event of any health problem, appropriate medical care can be provided quickly and effectively.

6. What other treatment options are available outside of the study?

Currently, there is no specific treatment that can completely halt or reverse mild cognitive impairment (MCI). The standard approach for patients with this condition typically involves a combination of pharmacological and non-pharmacological measures that may help slow the progression of cognitive decline and improve quality of life.

During the study, you will continue your usual treatment and take all prescribed medications at the same doses as before entering the study. It is important that your treatment remains stable, as any changes could affect the assessment of the effects of molecular hydrogen inhalation. If it becomes necessary to adjust the dosage of any of your medications during the study, you will be informed, and any changes will be discussed with the study physician.

Common approaches outside of this study primarily include cognitive training, which involves various mental activities and exercises aimed at improving memory, attention, and other cognitive functions. Some patients may also benefit from lifestyle modifications, such as regular physical activity,

a healthy diet rich in antioxidants and omega-3 fatty acids, and stress reduction through relaxation techniques.

Pharmacological treatment in some cases involves the administration of medications intended for the treatment of Alzheimer's disease, such as cholinesterase inhibitors (e.g., donepezil, rivastigmine) or NMDA receptor antagonists (memantine). However, these medications are not routinely prescribed for patients with MCI, and their use depends on the physician's individual assessment.

In this study, molecular hydrogen inhalation will be used as a complementary method to current standard of care. Its effects on cognitive function will be monitored to determine its potential benefits for patients with MCI. If you decide not to participate in the study, you may continue to use commonly available treatment options under the guidance of your treating physician.

7. Who is not eligible to participate in this study?

Not everyone is eligible to participate in this study. Certain groups of patients are excluded from participation for safety reasons or because their participation could potentially influence the study results.

Pregnant and breastfeeding women cannot participate in this study because the safety of inhaling molecular hydrogen in pregnant women has not yet been sufficiently studied, and it is unknown whether it could affect fetal development. Therefore, all women of childbearing age who have the potential to become pregnant must undergo a pregnancy test at the beginning of the study. This requirement does not apply to postmenopausal women or women who have undergone surgical sterilization, such as tubal ligation or hysterectomy. If you are a woman of childbearing age and decide to participate in the study, you will be asked to use effective contraception for the duration of the study and for at least one day after your last inhalation. Reliable contraception is considered to be a combination of hormonal contraception (oral contraceptive pills, hormonal implants, intrauterine device, long-acting injections) and barrier methods (condom, diaphragm, spermicidal membrane, or cervical cap). Using only one barrier method is not sufficient. If you become pregnant or suspect you are pregnant during the study, inform the study physician immediately.

Another group of patients who cannot participate in the study are those with an implanted pacemaker or other active electronic implant. Although inhaling molecular hydrogen does not pose a direct risk to pacemaker users, there are not yet sufficient studies to confirm its absolute safety in this specific group of patients. For safety reasons, therefore, these patients are not permitted to participate.

Patients with severe chronic diseases in an advanced stage, whose life expectancy is less than five years, are also excluded from the study. The study focuses on long-term monitoring of cognitive functions; therefore, it is important that participants be in a relatively stable state of health to allow for an objective evaluation of the effects of inhaling molecular hydrogen.

Another exclusion criterion is the use of dietary supplements or medications that could influence the study results. If you regularly take other products that affect cognitive function, metabolism, or oxidative stress (such as antioxidants, anti-inflammatory supplements, or neuroprotective agents), you must consult with the study physician regarding your eligibility to participate.

Individuals with other neurological or psychiatric conditions besides dementia are not eligible to participate in the study. If you suffer from, for example, epilepsy, schizophrenia, bipolar disorder, or another serious neurological or psychiatric condition, this study is not suitable for you.

If you are unsure whether you meet the eligibility criteria for the study, we recommend consulting with the study physician, who will provide you with detailed information and help assess your eligibility for enrollment in the study.

8. Will I be informed of new findings during the study?

Throughout the study, you will be regularly informed of any new developments that could affect your safety, the course of the study, or your decision to continue participating. If new findings regarding the inhalation of molecular hydrogen emerge during the research—whether from this study or other scientific sources—the study team will provide you with this information.

If new findings suggest any changes in the assessment of benefits and risks or could influence your decision to continue in the study, you will have the opportunity to reconsider your decision. If necessary, you will be offered the opportunity to sign an amendment to the informed consent form that reflects these new facts. This amendment will contain all relevant information so that you have sufficient grounds to make an informed decision about your continued participation.

Your safety and your ability to make free and informed decisions are the study team's top priority. If you have any questions or would like more information about the current status of the study, please do not hesitate to contact the study physician or study coordinator at any time.

9. What will happen to my personal data?

All personal data and health information collected as part of this study will be protected and processed in accordance with the applicable laws of the Czech Republic, including the General Data Protection Regulation (GDPR) and other relevant legal regulations.

All data recorded during the study will be sent to the sponsor only in encrypted form, which means that your name and other personally identifiable information will not be included in the transmitted data. Data that could be used to identify you will not leave the investigating physician's office and will remain secure within the healthcare facility where the study is being conducted.

Access to your personal data will be limited solely to those responsible for conducting the study. This includes the principal investigator and his or her team, authorized representatives of the study sponsor, such as monitors and auditors, individuals authorized by national regulatory authorities (e.g., the State Institute for Drug Control—SÚKL), and members of the ethics committee who oversee the conduct of the study. All of these individuals are bound by a duty of confidentiality and may not share the provided data with third parties outside the scope of this study.

You have the right to access your data held in your medical records and study documentation. If you feel that certain information is inaccurate or that its processing does not comply with legal regulations, you have the right to request that the data controller correct or delete it.

If you have any questions regarding the processing of your personal data as part of the study, you may contact the study physician or the authorized representative of the study sponsor at any time. The protection of your personal data is one of the study's top priorities, and all measures are in place to ensure its maximum security.

10. Are there any financial costs associated with my participation in the study? Am I entitled to reimbursement of expenses?

Participation in the study is entirely voluntary, and there is no financial compensation for participants. All costs for medical examinations, laboratory tests, and study procedures are fully covered by the study sponsor, so participants incur no expenses related to treatment or examinations conducted as part of the study.

To compensate for any inconvenience associated with traveling to the study site and the time spent during visits, the study sponsor will provide reimbursement in the form of financial compensation.

Detailed information about how expenses will be reimbursed, including the rules and conditions for reimbursement, will be provided by the study staff during your initial visit. If you have any questions regarding the costs associated with study visits or the reimbursement process, please do not hesitate to contact the study team.

11. Am I insured during the study?

All participants in this study are insured in accordance with the applicable legislation of the Czech Republic governing clinical trials of medical devices. The insurance covers any potential health complications or harm that may arise as a result of participation in the study or the use of the investigational medical device.

The insurance was arranged with HDI Versicherung AG, and details regarding the scope of coverage are specified in the insurance policy (2103787). If you would like to review the insurance documentation or obtain more detailed information about the scope of coverage, you may request it from your study physician.

In the event that any health complications arise during the study that could be related to your participation, it is important to inform your study physician immediately. In such a case, you will be provided with appropriate medical care, and if a connection to your participation in the study is established, you are entitled to compensation in accordance with applicable laws.

If you have any questions regarding insurance or would like to learn more about compensation options in the event of harm to your health, please do not hesitate to contact the study team.

12. Compensation for Study Participants

All study participants will receive compensation in the following order according to the visit schedule, taking into account the duration, frequency, and protocol of this clinical study.

- After every 5 inhalation visits (once a week, for a total of 12 weeks), each patient will receive one gift card to a retail store worth 500 CZK
- After each follow-up visit (once a month, 7 follow-up visits), a gift card to a retail store worth 1,000 Kč

13. Contacts

You always have the option to schedule additional consultations with the principal investigator listed on page 1 or with another principal investigator.

- **Principal Investigator**: Prof. MUDr. David Školoudík, PhD, FESO, FEAN Tel: +420 739 782 970
  Email: skoloudik@email.cz
- **Study Coordinator**: PharmDr. Milan Krajíček
  Tel: +420 777 719 781
  Email: milan.krajicek@h2global.group

If you have any questions regarding your rights in the study, you may contact the relevant ethics committee that reviewed and approved the study:

Ethics Committee of Ostrava

University Hospital Tel.: 597

372 542

Email: eticka.komise@fno.cz

PATIENT INFORMED CONSENT

Clinical Trial Name:		
Clinical Trial Protocol Number:		
Patient Identification:		**Social Security Number:**

Please read this form carefully. If you have any questions or would like more information, please ask your study doctor.

I, ..., hereby confirm that the purpose of this clinical trial, its course, the procedures that must be followed, and the potential risks and benefits have been explained to me in detail. I have had the opportunity to review the Patient Information sheet, which I have read carefully, and I fully understand all the information provided to me.

I agree to participate in this clinical trial and confirm that I am aware of my right to withdraw from the trial at any time, without having to provide a reason and without any impact on my future health care. I had the opportunity to ask the study physician any questions regarding the study, and all my questions were answered in a clear and satisfactory manner.

I agree to follow the study physician's instructions and to cooperate with the study as agreed.

I have been informed about the protection of my personal data within the scope of this study. I understand that all data regarding my health status obtained during the study will be processed and stored in accordance with applicable laws, including the General Data Protection Regulation (GDPR—Regulation (EU) 2016/679 of the European Parliament and of the Council). Personal data that allows for my direct identification will not be disclosed to third parties without my consent and will be processed solely for the purposes of this study. Data provided to the study sponsor will be anonymized so that I cannot be directly identified.

I have been informed of my rights regarding the processing of personal data, including the right to access the data, to have it corrected, to restrict its processing, to have it erased, and to file a complaint with the relevant supervisory authority. If I have any questions or concerns regarding the processing of my data, I may contact the study team.

By signing this document, I am not waiving any of my legal rights, and I confirm that I have had sufficient time to consider my participation in the study.

I voluntarily choose to participate in this study under the conditions set forth above.

I have received one copy of the Patient Information and the Informed Consent Form, while the other copy remains on file at the study center.

Patient

Patient's Name:	Handwritten Signature:	Date:

Principal Investigator (to be completed in person by the principal investigator who informed the patient about the study)

Investigator's Name:	Handwritten signature:	Date:

Witness (if the patient is unable to sign personally)

Patient's name:	Handwritten signature:	Date: