

MIROCALS clinical trial

Information Sheet DA

MIROCALS (Modifying Immune Response and Outcomes in Amyotrophic Lateral Sclerosis) is a clinical trial taking place in the UK and France. It will test a new potential therapy for ALS, the most common form of MND. The drug to be tested is called Interleukin-2.


This information sheet explains how Interleukin-2 works and how it may be used to treat MND, the criteria that need to be met for a person to take part and what taking part in the trial will involve. A full, much more detailed explanation of the study will be provided by a trial doctor to everyone who takes part. This information sheet contains an outline of the study only.

Not everyone can participate in a trial. There are several rules, or criteria, that people with MND must meet to participate in this trial and some criteria that will exclude people from participating. The most important criterion is that **to be eligible to take part you cannot have ever received riluzole (or not for more than 3 weeks)**. A summary of the inclusion criteria is listed on pages 3-4.

To visit the MIROCALS website, go to www.mirocals.eu. The content is split into the following sections:

1. **Background and aims of the trial**
2. **Taking part in the trial: who, where, when, how**
3. **IL-2 for people unable to take part in the trial**
4. **I think I am eligible to take part, who do I contact?**

Disclaimer: *Please note that information provided in this information sheet is based on a review of the currently available literature. This information sheet was written by the MND Association staff who are not clinicians and so any information provided in this sheet should not be considered a clinical advice. You should always discuss potential treatments with your clinician.*

 This symbol is used to highlight **our other publications**. To find out how to access these, see *Further information* at the end of this sheet.

What do the words and abbreviations mean?

Biomarker:	Unique biological signature of a specific disease, or group of diseases.
Cerebrospinal fluid (CSF):	Cushioning fluid encasing the brain and spinal cord.
Interleukin-2 (IL-2):	Substance found in the immune system that regulates activity of white blood cells.
Lumbar puncture:	Medical procedure in which a thin needle is introduced into the spine to collect cerebrospinal fluid.
Magnetic Resonance Imaging (MRI):	A type of scan that can visualise certain areas of the body (most often the brain).
Placebo:	An inactive compound ('dummy drug') given to half of participants in most clinical trials.
Regulatory T Cell (Treg):	Immune cell helping to protect nerve cells against damage.

1: Background

Amyotrophic Lateral Sclerosis (ALS) is the most common form of motor neurone disease (MND). Although ALS is not a disease of the immune system, there is evidence from studies of patients that the levels of some types of immune cells in the blood can play a role in the speed at which the disease progresses.

One particular immune cell, called a Regulatory T Cell (or 'Treg') is thought to play a part in helping to protect nerve cells against damage. The drug Interleukin-2 can increase the levels of Tregs in the blood and so might be able to protect motor neurones in ALS.

The purpose of this study is to test the safety and effectiveness of low doses of Interleukin-2 in people with ALS and, in particular, to find out if it may slow down the advance of the disease.

What is Interleukin-2 and how does it work?

Interleukin-2 (IL-2) is a substance naturally produced by the body. Its main role is to promote the production of Tregs. Increasing IL-2 levels in people with ALS can reduce the inflammation that occurs around motor neurones and may therefore slow down the progression of the disease.

Has it been tested before?

High dose IL-2 is already used to treat certain forms of cancer. Due to some of its adverse effects on the immune system, smaller doses of this drug are recommended to use for non-cancerous diseases.

Studies have previously been conducted with people with various autoimmune diseases (e.g., type-1 diabetes) and ALS (IMODALS study) to identify the lowest effective IL-2 dose that would still trigger increase in Tregs. Results of these studies showed that low doses of IL-2 are sufficient to activate expansion of Tregs without any serious side effects.

Purpose of the trial

From June 2017, a Phase II clinical trial will be recruiting 216 people recently diagnosed with ALS across 16 centres in the UK and France over a period of 18 months. The trial will assess the efficacy (effectiveness) and safety of low doses of IL-2 when administered over the course of 18 months.



For further information about how clinical trials are conducted, see: Information sheet D – *Clinical trials*.

Aims of the trial

MIROCALS aims to determine the effects IL-2 has on people with ALS and, in particular, if it has the potential to slow down the progression of the disease. To test this, the team will measure the effect of IL-2 on survival, changes in day-to-day activities and quality of life. In addition, they will be carefully monitoring any side effects that people may experience when taking this drug.

As this is a placebo-controlled trial, it is important for people taking part to understand that only one half of the participants will be given IL-2, whereas the other half will receive an inactive agent (placebo). All participants will be randomly allocated to one of these groups.

As a secondary goal, the researchers will search for biomarkers, unique biological signatures, in the blood and cerebrospinal fluid (CSF). Finding biomarkers for ALS would allow us to show whether a drug is working, monitor the progression of the disease, and speed up diagnosis.



For further information about biomarkers, see: Information Sheet G: *Biomarkers*.

Finally, it is important for the researchers to work out whether participants in the trial react to the same treatment in exactly the same way, or in very different ways. Any differences may be partly due to each person's unique genetic make-up, so researchers will analyse participants' DNA. This will allow them to determine how a person's genetic profile may affect their responsiveness to IL-2 (or riluzole) treatment, leading to more personalised treatments and more efficient drug trials in the future.

MIROCALS brain imaging study (ANNALS-QuICT)

People who are eligible for the MIROCALS trial will also have the opportunity to take part in an optional brain imaging study run by researchers at the Brighton and Sussex Medical School. This would involve having an MRI brain scan twice during the study: once during the first three months when participants are taking only riluzole and again 4-6 months after starting the study treatment. It is hoped that these detailed scans will enhance understanding of how and why brain cells become damaged in ALS. Any UK-based participant of MIROCALS will be eligible to travel to Brighton for the MRI scans for which travel costs can be reimbursed.

2: Taking part in the trial

Where will the trial take place?

The following five centres are currently recruiting participants in the UK:

Brighton: Royal Sussex County Hospital

London: King's College Hospital

Royal London

Hospital

National Hospital for Neurology and Neurosurgery

Sheffield: Royal Hallamshire Hospital

Glasgow: Queen Elizabeth University Hospital

How are people selected for the trial?

Not everyone can participate in a trial. There are several criteria that people with ALS must meet to participate in this trial (inclusion criteria) and some criteria that may exclude people from participating (exclusion criteria). Some important inclusion criteria are listed below (this isn't the full list).

In addition to these criteria, once the researchers have reached their target number of participants, they will not be able to include any more.

Inclusion criteria (who can take part?)

To be eligible to take part in the initial stage of the clinical trial, participants need to meet the following criteria:

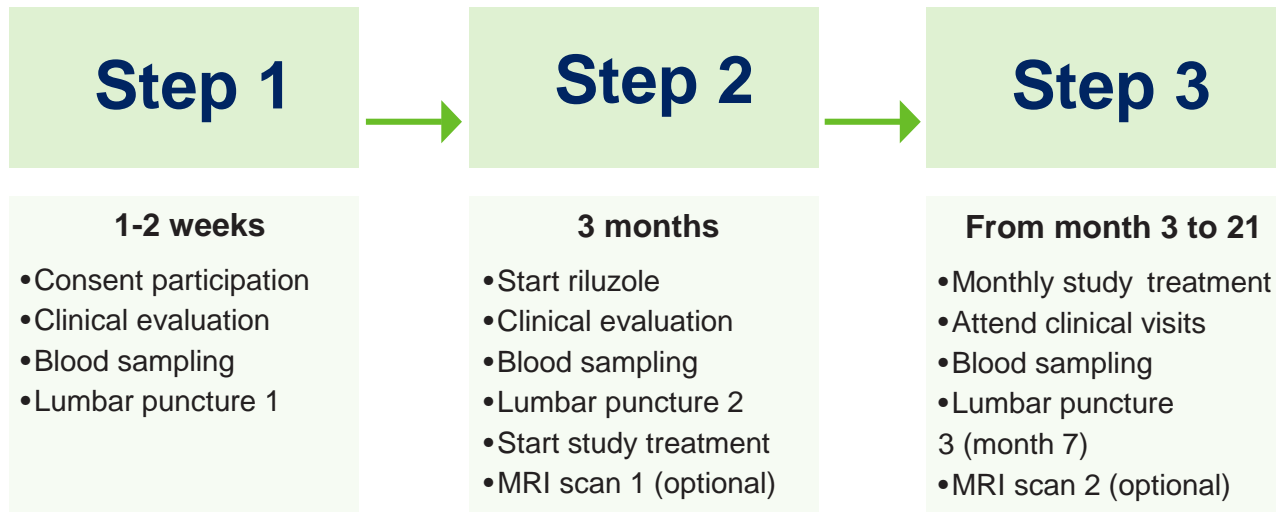
- Age between 18 and 76
- Recently diagnosed with ALS (with a disease duration of 24 months or less, starting from the time of first symptoms)
- No prior or present riluzole treatment (or within less than 3 weeks of exposure)
- Willingness to undergo lumbar punctures (this entails a thin needle being introduced gently into the spine under local anaesthesia)

Exclusion criteria (who cannot take part?)

- People without sufficient capacity to give informed consent
- People using assisted ventilation (e.g., NIV or tracheostomy)
- People fed through gastrostomy or nasogastric tube
- Pregnant women
- People with severe cardiac and pulmonary disease, past or present autoimmune disorders, treated asthma, chronic steroid treatment, specific viral infection, diagnosis of cancer within 5 years prior inclusion
- People who have ever taken riluzole for more than 3 weeks

What would I have to do if I took part?

The study is divided into three stages: step 1 is an initial screening phase; during the three-month step 2 participants will be taking riluzole only. In the final stage, step 3, participants will continue on riluzole and also be having treatment injections.



Step 1

Once you have given your consent to take part in the study, you will be asked to undertake a detailed 'screening' evaluation to confirm that you meet all of the eligibility criteria for the trial.

Step 2

If it is confirmed that you are eligible for the study, you will start taking riluzole, the only current treatment that slows down progression of ALS. After three months you will be re-screened for eligibility to continue in the study based on your tolerance of riluzole (anyone with ALS who starts taking riluzole is assessed after three months).

Step 3

If it is confirmed that riluzole doesn't cause you side effects, a computer system will randomly allocate you to one of the two trial groups; either the group that will receive a 'placebo', or the group that will receive IL-2. Neither you nor your study doctor will know which group you've been allocated to.

You will then begin to receive treatment injections (either IL-2 or placebo) that you will give yourself once a day for five days every 4 weeks (total of 19 5-day cycles). During the first visit at the clinic, you or your carer will be shown how to administer the injection (in some cases, visiting nurse can administer the injections).

Throughout the 18-month period you will be asked to visit the clinic every 2-3 months for routine checks of your symptoms. At some of these visits you will also be asked to complete assessments similar to those you underwent at your inclusion visit.

After the study is finished, you can continue taking riluzole which will be prescribed to you by your GP or neurologist. However, you will not be provided with the IL-2

treatment as the data of its safety and any beneficial effects will still be unknown until the data has been analysed.

Why will a placebo be used?

It is important to note that half of the participants in the trial will not receive the IL-2 treatment. This 'control' group is essential if the trial is to demonstrate convincingly whether IL-2 provides benefits over the 'placebo' drug. Placebo is a 'dummy drug' that has no beneficial (or adverse) effects.

Neither the participant nor their doctor will know whether they are receiving IL-2 or the placebo. This is called a double-blind study.



For further information about how clinical trials are conducted, see: Information sheet D – *Clinical trials*.

3: IL-2 treatment for people unable to take part in the trial

We are aware that the majority of people living with ALS will not be eligible to take part due to their current treatment with riluzole or that they've had ALS symptoms for longer than 24 months.

The reason for the 24 months cut-off is to increase the chances of a positive effect by involving people at a relatively early stage of their disease.

The reason for recruiting people who are not yet taking riluzole is because the researchers want to try to gain a better understanding of how riluzole is working in the body and whether some people respond better to the drug than others. This information might be helpful in designing more effective 'riluzole-like' drugs in the future.

As low dose IL-2 is still an experimental treatment, it is not currently available as an NHS treatment for ALS. However, if the trial does indicate that IL-2 provides benefits for people living with ALS then a much larger Phase III trial may still need to be conducted, to provide sufficient evidence to satisfy the drug licensing authorities.

The MND Association and MND Scotland understand that people with ALS need to hold the hope that research will find an answer to the disease. Please be aware that clinical trials are not treatments, but medical experiments that may or may not be successful.

The results of the trial are due in **autumn 2021**.

What should I consider before taking part?

Location of the centres and travel should be taken into consideration by people who wish to participate. The trial in Scotland is taking place in Glasgow, so if accepted onto the trial, patients will need to travel to Glasgow. Support by a carer might be especially necessary due to the length of the study and the likely progression of the disease symptoms. Please make sure to carefully discuss your participation in the study with your carer before agreeing to take part.

I think I am eligible to take part, what next?

Please remember that if someone has ever taken riluzole they are not eligible to take part.

If you think that you are eligible to take part, please contact Katherine McGuigan, Senior Research Nurse (details below), or another member of the research team, who will provide you with next steps.

4: How do I find out more?

Further information

MND Scotland

For more information on MIROCALS, or to register your interest in the trial, please speak to Steven Henderson on:

T: 0141 232 7600

E: Steven.Henderson1@nhs.net

Sackler Clinical Research Facility,
5th Floor Neurosciences Building
Zone 3,
Queen Elizabeth University Hospital,
1345 Govan Road,
Glasgow
G51 4TF

You can also speak to another member of the research team on 0141 232 7600.

For general information on MND and MND Scotland please visit www.mndscotland.org.uk, call 0141 332 3903 or email info@mndscotland.org.uk.

MND Association

You may find these information sheets from the MND Association

helpful: D – *Clinical trials*

G – *Biomarkers*

We also provide the following guides:

Living with motor neurone disease – our main guide to help you manage the impact of the disease

Caring and MND: support for you – comprehensive information for unpaid or family carers, who support someone living with MND

Caring and MND: quick guide – the summary version of our information for carers

You can download most of MND Associations publications at www.mndassociation.org/publications.

We welcome your views

Your feedback is really important to us, as it helps improve our information for the benefit of people living with MND and those who care for them. If you would like to provide feedback on any of our information sheets, you can access an online form at: **www.surveymonkey.co.uk/r/infosheets_research**

You can request a paper version of the form or provide direct feedback by email: research@mndassociation.org.

Thanks to the MND Association of England, Wales and Northern Ireland for creating this Information Guide on MIROCALS.