

MIROCALS Consortium announces top-line results of European trial of low dose Interleukin 2 in Amyotrophic Lateral Sclerosis at 33rd International Symposium on ALS/MND.

About the MIROCALS Trial:

- MIROCALS is a phase 2b randomised placebo-controlled trial investigating the efficacy and safety of low dose interleukin 2 (ld IL2) in people with amyotrophic lateral sclerosis (ALS)
- 220 participants were recruited in 17 ALS Centres in UK and France, randomised to either ld IL2 or placebo for 18 months and followed for up to 21 months.
- Novel features were recruitment of participants early in the disease process, soon after diagnosis, and the systematic collection of blood and cerebrospinal spinal fluid (CSF) to measure cellular and molecular indicators (biomarkers) of disease activity or treatment response.
- The primary outcome measure for efficacy was survival.
- Secondary measures included activities of daily living and motor function, biomarkers for target responses and markers for disease activity.

Primary Results:

- The unadjusted analysis of the primary endpoint of survival showed a modest decrease in risk of death in IL2 treated patients compared with placebo, but this effect did not reach statistical significance
- However, analysis of the primary survival endpoint, adjusted on the primary biomarker of neuronal injury in cerebrospinal fluid, phosphorylated neurofilament heavy chain (CSF pNFH) showed a larger and statistically significant treatment effect on survival.
- This effect was not present in the 21% of participants with high CSF pNFH, which corresponded with aggressive, fast progressing disease.
- These results provide encouraging evidence, from a randomised placebo-controlled drug trial, in support of immune system modification and neuroinflammation as viable targets for altering ALS disease progression.

The MIROCALS (Modifying Immune Response and Outcomes in ALS) Trial Consortium today announces top-line results from the phase 2b trial of low dose Interleukin-2 (ld IL2) in amyotrophic lateral sclerosis (ALS; also known as Motor Neuron Disease, MND). Results were presented to an online audience by Dr Gilbert Bensimon, Centre Hospitalier Universitaire de

Nîmes, on the opening day of the Motor Neurone Disease Association's 33rd International Symposium on ALS/MND.

The MIROCALS trial, conducted in clinics across France and the United Kingdom, in collaboration with eight leading research groups in the UK, France, Italy and Sweden, tested whether low doses of IL2 can alter aspects of the immune system associated with inflammation in the central nervous system, which is believed to play an important role in the speed at which ALS progresses.

Following a 12-week run in period while starting treatment with riluzole (the accepted standard drug treatment), a total of 220 people with ALS attending 17 specialist clinics in the UK and France were randomised in equal proportion to receive subcutaneous injections of low-dose interleukin-2 or placebo for a period of 18 months, with the primary outcome to demonstrate a treatment-related decrease in the rate of death.

The treatment was well tolerated, with adverse events recorded as mostly mild to moderate, occurring across both active treatment and placebo arms. Effective target engagement, measured by elevation in plasma regulatory T cells (Tregs) was also demonstrated, confirming the results of a previous pilot study which showed that IL2 decreases inflammatory markers in the blood.

The primary unadjusted analysis of survival showed a small (19%) but not statistically significant decrease in the risk of death at 21 months.

The primary core biomarker (CSF pNFH) revealed a highly significant association between CSF pNFH levels and survival. Furthermore, pre-planned analysis of efficacy adjusted on the level of CSF pNFH at randomisation showed a significant effect in favour of IL2 on disease progression and survival.

CSF pNFH measurements were critical in the context of developing a 'personalised medicine approach' by defining groups of participants with different responses to IL2. According to CSF pNFH levels, in about 20% of the population no significant treatment effect could be detected in these rapidly progressive patients all with high CSF pNFH levels.

However, 80% of the population had low to moderate CSF pNFH levels, correlating with less aggressive disease progression and for these patients there was a significant decrease in the risk of death of over 40%.

Dr Gilbert Bensimon, lead investigator and project co-ordinator, Centre Hospitalier Universitaire de Nîmes (CHU) comments: *"While the primary unadjusted survival analysis was not significant, the pre-planned adjusted analysis - an approach recommended by the US Food and Drug Administration - shows a positive effect of IL2 on survival. Furthermore, a joint rank analysis of survival and function also showed significant benefit with IL2 compared to placebo. These results indicate that IL2 does have a beneficial effect in ALS, but clearly further studies are needed to see if this effect can be enhanced by different treatment schedules and by exploiting the insights we have gained by integrating CSF pNFH and other biomarkers into the trial design."*

Peripheral changes in immune processes and their knock-on impact on central neuroinflammation have emerged as exciting targets for therapy development. MIROCALS is the first large scale randomised placebo-controlled trial to demonstrate 'proof of principle' in relation to IL2 with the potential to translate into clinical benefit for people living with this devastating condition."

An important feature of the MIROCALS trial is the attention devoted to the rigorous collection and analysis of blood and cerebrospinal fluid samples through the course of the study to

confirm the relevance of emerging disease biomarkers, whilst seeking to identify novel biomarkers and therapeutic targets for future drug development.

“A key strength of MIROCALS has been the collaboration of leading European research groups in immunology, biomarker development and genomics” says Professor Nigel Leigh, co-lead and chief trial investigator, of Brighton and Sussex Medical School. *“There remain many questions to address, but the wealth of data and samples accumulated are supporting ongoing research to better understand the factors that drive ALS disease progression. These will hopefully open the door to new therapeutic avenues and more personalised approaches to treatment, to deliver even more positive outcomes in future trials.*

Additional analysis of samples and data, maintained in a central biobanking facility in France, are being performed across various MIROCALS consortium laboratories in the UK, Italy, and Sweden, with further findings to be announced in the coming months.

“ALS is a relentlessly progressive and devastating disease that robs people of their independence and ultimately their lives” says Dr Brian Dickie, Director of Research for the UK-based Motor Neurone Disease Association. *“Taking part in clinical trials requires a significant commitment from people with ALS and we are so grateful of everyone who volunteered for this important and ground-breaking study.”*

Dr Bensimon adds, *“There is still work to be done with sample analysis to understand the beneficial biological effects that we believe are occurring, as well as addressing issues around drug formulation and administration. But the priority will be the discussion with drug regulatory agencies on the next steps to hopefully add this promising treatment to the ‘tool kit’ of therapeutic options available to the medical and patient community.”*

For more information, please visit: <https://www.mndassociation.org/research/clinical-trials/mirocals/>

For information or to request interviews with Dr Gilbert Bensimon, lead investigator and project co-ordinator, Centre Hospitalier Universitaire de Nîmes (CHU) or Professor Nigel Leigh, co-lead and chief trial investigator, of Brighton and Sussex Medical School please email communications@mndassociation.org

About amyotrophic lateral sclerosis (ALS) / motor neuron disease (MND)

- It attacks the nerves that control movement so muscles no longer work. ALS does not usually affect the senses (sight, sound and feeling)
- It can leave people locked in a failing body, unable to move, talk and eventually breathe.
- Some people may experience changes in thinking and behaviour, with a proportion experiencing a rare form of dementia.
- It affects around 45,000 people in Europe.
- It kills a third of people within a year and more than half within two years of diagnosis.
- There is no cure.

About the MIROCALS trial

- The cause of ALS is not fully understood. Although ALS is not considered to be primarily an immunological disease, it is clear that immunological and inflammatory mechanisms contribute significantly to motor nerve cell damage.
- Low dose IL-2 increases the number of certain immune cells, known as Regulatory T-cells ('Tregs') in the blood, which contribute to the control of this inflammatory response.
- Previous research has shown that there is a strong relationship between the numbers of Tregs in the blood and the speed of progression of ALS. A pilot study (IMODALS): Immune Modulation in ALS) demonstrated that low dose IL-2 increased the number of Tregs and improved their ability to influence other immune cell responses that contribute to nerve cell damage.
- The MIROCALS trial investigated the use of low dose IL-2 over a more prolonged (18 month) treatment period, in the hope of slowing disease progression by redressing the balance between mechanisms that drive the disease process and those that enhance protection and even repair.
- People with ALS were recruited to the trial shortly after diagnosis, in order to test the treatment at a relatively early stage in the disease process.

About The MIROCALS Consortium

- The MIROCALS Consortium is coordinated by [The Centre Hospitalier Universitaire de Nîmes](#), sponsor of the study. It is scientifically led by Dr Gilbert Bensimon (Project Coordinator) of [The Centre Hospitalier Universitaire de Nîmes](#), France and Professor Nigel Leigh (Chief Trial Investigator) of [Brighton and Sussex Medical School](#), Brighton, UK.
- The strong partnership combined the experienced clinical trial regulatory and monitoring expertise of Irish-based [ICON plc](#), with treatment management logistics led by the UK-based company [WGK Clinical Services](#) and biobanking expertise provided by the French not-for-profit organization [Généthon](#).
- The scientific contributors include leading investigators from several cutting-edge European laboratories: [Humanitas Research Hospital](#), Italy; and [King's College London](#), UK have led investigations into immunological aspects of the project, while work on brain biomarkers for monitoring disease progression is headed by [Goeteborgs Universitet](#), Sweden and [Queen Mary University of London](#). The investigation of gene expression is coordinated by the [University of Sheffield](#), UK and gene sequencing studies by [King's College London](#), UK. [Généthon](#), Paris is responsible for the MIROCALS biobank, with the [MND Association](#) providing guidance on ethical aspects and the dissemination of information.
- The MIROCALS study receives funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No. 633413, with additional grants from the Motor Neurone Disease Association supported by the J P Moulton Charitable Foundation and the Garfield Weston Foundation, the French Health Ministry from Programme Hospitalier de Recherche Clinique, My Name's5 Doddie Foundation, Association Francaise contre les Myopathies, MND Scotland and Association pour la Recherche sur la SLA.

