

Octopus interim analysis Decision FAQs

These FAQs are provided to update you on the interim results of the Octopus clinical trial. If you have a question that isn't answered in this document, please see below for who to direct your query to.

- If you're an Octopus trial participant, please contact the team at your trial hospital site.
 - If you're on the Registration of Interest waiting list, please contact the UK MS Register contact@ukmsregister.org
 - If you have a general question about Octopus or MS research, please get in touch with the MS Society Help Hub: <https://www.mssociety.org.uk/support-and-community/ms-help-support-services>
- **What are the interim results?**

The interim analysis has found that Alpha Lipoic Acid (also known as ALA) shows early promise as a neuroprotective treatment for progressive MS. Alpha lipoic acid will therefore continue in the Octopus trial.

Unfortunately, metformin didn't show early evidence of promise and will not continue the trial.

- **What do these 'interim analysis' results mean?**

Octopus is the first 'multi-arm multi-stage' trial performed in MS. Multi-arm multi-stage trials are designed to test several drugs at the same time and compare them to a single control group. This type of trial merges what would normally be two consecutive trials into one.

Unlike traditional trials, Octopus uses an 'interim' analysis. This allows researchers to look at early data from the trial, including MRI scans and clinical measures like EDSS. Drugs that show early evidence of promise as potential treatments for people with progressive MS continue in the trial. Those drugs that do not show early promise, leave the trial. This means we get an answer for whether drugs are effective for MS years sooner than would have been using a traditional trial. And it means people spend less time taking ineffective treatments.

The data from the interim analysis shows that Alpha Lipoic Acid (also known as ALA) should continue to the next stage of the trial. But it does not tell us yet whether Alpha Lipoic Acid is effective for progressive MS. People taking Alpha Lipoic Acid or placebo will stay in the Octopus trial. The data showed that metformin should not continue in the trial. People on the metformin arm will leave the trial.

- **When will I find out if I'm staying in the trial?**

Over the coming weeks, all trial participants will be contacted to instruct them on the next steps. All participants should continue taking their trial drugs and attending their visits until they are contacted by their trial hospital site team.

- **When will I find out which trial treatment arm I was on?**

If you are required to stop taking your trial treatment, you will be contacted by your hospital site team. They will let you know which trial treatment you have been taking, and they will inform your GP and local neurologist.

If you are asked to continue taking your trial treatment, then you will have to wait until the final results are released to know which treatment you are taking. We expect this to be early 2029.

- **Will existing participants in Octopus be able to re-enter the trial if their treatment arm isn't continuing?**

If you were still taking part in trial visits and are now contacted to inform you that your participation will end, you can potentially re-enter the trial. If you previously withdrew from the trial and were no longer attending trial visits, then you cannot rejoin the trial.

Eligible participants who indicate they would like to be considered to rejoin the trial will be added back onto the Registration of Interest list by their hospital site. All participants will need to have at least a 6-month break from their last capsule before re-entering the trial, to ensure that previous trial treatments have left your system.

It will take time for hospital sites to contact participants to assess their eligibility to rejoin, as it will depend on their waiting list and the availability in their clinic.

- **If the trial treatment I'm taking isn't continuing to the next stage, do I need to register again to re-enter the trial?**

No, you do not need to register again. If you were recruited to the trial and attending Octopus visits and happy to rejoin the trial, your hospital site will add this to the Registration of Interest portal. This will indicate that you can be contacted to be re-screened.

If/ when there is local capacity, you will be contacted by your hospital site to perform a new eligibility pre-screen. Please note this may not take place immediately as it depends on site capacity and the length of the Registration of Interest list at each site. Hospital sites manage their Registration of Interest list independently.

If you previously withdrew from the trial and were no longer attending the trial visits, then you cannot rejoin the trial.

If you are interested in rejoining Octopus, you will be added back into the list of potential participants managed by your hospital site.

- **If the trial treatment I'm taking isn't continuing to the next stage, will I be prioritised for re-entry to the trial?**

We appreciate you may feel disappointed that your treatment arm isn't continuing and you may be interested in rejoining the trial.

If you are interested in rejoining Octopus, you will be added back into the list of potential participants managed by your hospital site. Your hospital site team will be in touch based on their capacity and availability. They will need to establish if you are still eligible for the trial. For example, to check if anything in your health has changed which means you are not able to be considered for re-entry. All participants will need to have at least a 6-month break from their last capsule, to ensure study treatments have left your system.

- **Will a new drug arm be added to replace metformin?**

Octopus will continue as a long-term trials platform, and we hope to add further arms to the trial in 2027. The Octopus trial team has been busy in the background researching new drugs which could be introduced to the trial.

Participants who were on the metformin arm of the trial will not be automatically added to the new arm. Participants on the trial will not be able to switch arms.

If you are interested in rejoining Octopus, you will be added back into the list of potential participants managed by your hospital site. Your hospital site team will be in touch based on their capacity and availability. They will need to establish if you are still eligible for the trial. For example, to check if anything in your health has changed that might change your eligibility. All participants will need to have a 6-month break from their last capsule, to ensure study treatments have left your system.

- **If I have been on the waiting list for a long time, will I be prioritised to join the new arms?**

We understand that being on the waiting list can be frustrating. The local trial hospital sites will be working through their lists of potential participants as quickly and fairly as possible. You will be contacted by your hospital site as soon as there is availability for screening.

- **Will I find out if I am on placebo?**

People on ALA and placebo will be told to remain on the study, but for the benefit of the trial, we will not reveal at this stage which of those treatments you are receiving. These participants will find out whether they were receiving ALA or placebo after completion of the next part of the trial.

- **How reliable are these results?**

The data from stage 1 of the trial found:

- Alpha-lipoic acid (ALA) is showing early promise as a **potential** treatment for progressive MS and should continue to the next stage for further testing. Stage 1 of the trial was designed to detect any promise of benefit but does not prove that ALA is effective for progressive MS – the next part of the trial will prove this more definitely.
- There was no evidence of promise for metformin as a potential treatment for progressive MS and it will not continue in the trial.

This data was clear and unambiguous. Further data and a full publication will be shared in the coming months.

- **Can I continue taking metformin if I feel like I'm benefitting from it?**

The Octopus trial can no longer supply the trial treatment to you. The trial was designed to detect even small benefits compared with placebo. And the results found that metformin did not show promise as a neuroprotective treatment for progressive MS. In view of the results, we advise that you do not continue seeking this medication via another source.

Taking drugs that haven't been approved for MS outside of a clinical trial can put you at risk. Participants in clinical trials are screened before they enter the trial, to confirm that it is appropriate for them to take the trial treatment. They then have careful and regular monitoring throughout the trial to ensure that they aren't suffering from any adverse effects. This means that we can make their participation in the trial as safe as possible.

If you're not part of the Octopus trial, and you're considering taking metformin or Alpha Lipoic Acid specifically for your MS, this could put you at risk. Please speak to your doctor or MS nurse if you are considering taking either drug.

- **Were the drugs tested in the trial safe?**

The Trial Management Teams and an independent data monitoring committee regularly reviewed the trial data. Both drugs tested in the trial have side effects. But these were carefully monitored to maintain participant safety.

- **I have already stopped taking part in the trial previously, how can I find out if I was taking metformin?**

If you are no longer taking part in Octopus and not attending visits, you can contact the hospital site where you attended, and they will be able to let you know if you were taking metformin. If you are on Alpha Lipoic Acid or placebo, you will not be able to find which of these you were taking.

- **What does this mean for the future of metformin as a myelin repair drug?**

We didn't find any evidence that metformin is beneficial as a neuroprotective treatment for people with progressive MS.

Other studies have shown that metformin could boost myelin repair in MS. However, these studies have been in smaller groups of people who have lower levels of disability (typically people with relapsing remitting MS). Therefore, it is possible that metformin could be beneficial for people with different types of MS, or those who are less severely affected by it. Some studies are underway to test for any clinical benefit of metformin in people with relapsing-remitting MS.

- **When will I find out whether the Octopus trial treatments are working?**

The interim analysis found that Alpha Lipoic Acid shows early promise as a treatment for people with progressive MS. Metformin did not show any promise as a treatment for people with progressive MS and so it is not continuing in the trial.

However, we will only know for certain whether Alpha Lipoic Acid is safe and effective for people with progressive MS when we see the final results of the second part of the Octopus trial. To find the full answer, the trial needs to continue to recruit participants to determine if the trial treatment works in slowing disability progression, and whether it is safe enough for clinical use. We anticipate that the final results will be available in early 2029.

- **Can I now receive Alpha Lipoic Acid on the NHS?**

No. The results of the interim analysis of stage 1 data tell us that Alpha Lipoic Acid shows **early promise** as a treatment for progressive MS. We do not know yet if Alpha Lipoic Acid works.

We will only know for certain whether they are safe and effective for people with progressive MS when we see the final results. To find the full answer, the trial needs to continue to recruit participants to determine if the trial treatment works in slowing disability progression, and also to test whether it is safe enough for clinical use. Testing the treatment in a bigger group gives the trial more "power". This gives us a higher chance of showing if the treatment is beneficial and safe for people with progressive MS.

We anticipate that the final results will be available in 2029. This will tell us whether it is effective at slowing progression in MS. If the results are positive, we will work on making the treatment available on the NHS.

- **As Alpha Lipoic Acid shows promise, should I now take it to help my MS?**

No. The results of the interim analysis of stage 1 data tell us that Alpha Lipoic Acid shows **early promise** as a treatment for progressive MS. We do not know yet if Alpha Lipoic Acid is safe and effective as a treatment for progressive MS.

We will only know for certain whether Alpha Lipoic Acid is safe and effective for people with progressive MS when we see the final results of the second stage of Octopus. To find the full answer, the trial needs to continue to recruit participants to determine if the trial treatment works in slowing disability progression. Testing the treatment in a bigger group gives the trial more “power”. This gives us a higher chance of showing if the treatment is beneficial and safe for people with progressive MS.

Taking drugs that haven’t been approved for MS outside of a clinical trial can put you at risk. The Alpha Lipoic Acid used in the trial is of high quality and manufactured to required standards. It is not the same as what people could get in a health food shop or online.

Participants in clinical trials are screened before they enter the trial, to confirm that it is appropriate for them to take the trial treatment. They then have careful and regular monitoring throughout the trial to ensure that they aren’t suffering from any adverse effects. Alpha Lipoic Acid and metformin both have potential for side-effects that can only be managed if you are being carefully monitored. This means that we can ensure people remain safe while they are taking one of these treatments in the trial but taking either of these treatments without careful monitoring could put you at significant risk. Taking one of these medications is also likely to mean that you would be ineligible to re-join the trial in the future.

- **What are the differences between Stage 1 and Stage 2 of Octopus?**

The first 375 participants who joined the study were part of Stage 1. They had MRI scans during the first 2 years of follow-up. People recruited after this joined Stage 2 and did not have MRI scans.

All the participants in Stage 1 and Stage 2 are testing the same trial treatments. Apart from MRI, all participants have the same visit schedule and the same assessments, like the 9-Hole Peg Test and Timed 25-Foot Walk. Once all the participants with MRI scans had completed at least 18 months of follow-up, we analysed the data for all the Octopus participants recruited so far. This included all of the data collected from Stage 1 participants. And some of the clinical data from Stage 2 participants.

Recruitment for Stage 2 began before we had the results for Stage 1, meaning that we could seamlessly transition from one stage of the trial to the next if any of the trial treatments showed early promise. This is part of the innovative ‘multi-arm multi-stage’ design of Octopus, which means the team do not have to stop and set up a new trial.

The data from the interim analysis found that alpha lipoic acid shows early promise as a treatment for progressive MS and will continue to Stage 2 of the trial. Metformin didn’t and therefore will not continue the trial. Participants taking alpha lipoic acid and the placebo will continue in the trial. Further participants are needed to join to ensure the trial has enough information to tell us if these treatments work.