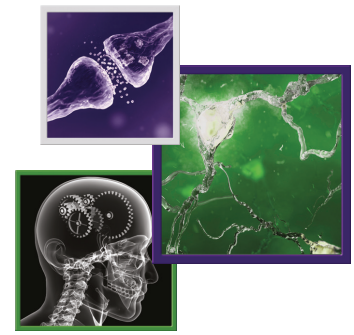
Plain Language Summary of Publication

Neurodegenerative Disease Management



A plain language summary of what clinical studies can tell us about the safety of evobrutinib – a potential treatment for multiple sclerosis

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Summary

What is this summary about?
This summary explains the findings from a recent investigation that combined the results of over 1000 people from three clinical studies to understand the safety of evobrutinib.

Evobrutinib is an oral medication (taken by mouth), being researched as a potential treatment for multiple sclerosis (MS). This medication was also investigated in rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE).

Over 1000 people have taken evobrutinib as part of three separate phase 2 clinical studies. These studies looked at how much of the drug should be taken, how safe the drug is, and how well it might work for treating a certain medical condition.

How to say (double click sound icon to play sound)...

- **Evobrutinib:** ee-voh-BREW-tin-ib
- **Multiple sclerosis:** MUHL-tuh-pl skler-OW-sus
- **Rheumatoid arthritis:** ROO-mah-toyd arth-RIE-tis
- **Systemic lupus erythematosus:** sih-STEM-ik LOO-pus eh-rih-thee-mah-TOE-sis
- **Diarrhoea:** die-ah-REE-ah
- **Tyrosine kinase:** TIE-row-seen KIN-ays

What were the results?
Evobrutinib was well-tolerated by participants in all three studies. The number of side effects reported by participants taking the medication was very similar to those reported by participants taking the placebo (a 'dummy' treatment without a real drug).

The most common side effects in clinical studies were urinary tract infections, headache, swelling of the nose and throat, diarrhoea and blood markers of potential liver damage (these returned to normal once the treatment was stopped).

What do the results mean?
The safety data from all three clinical studies are encouraging and can be used to inform further research into using evobrutinib in MS.

Where can I find the original article on which this summary is based?

You can read the original article published in the *Journal of Neurology, Neurosurgery and Psychiatry* for free at: https://jnnp.bmj.com/content/94/1/1

Future Medicine part of fsg

Who is this article for?

- People with MS (PwMS), their families and carers
- Patient advocates
- Healthcare professionals who treat PwMS, e.g., doctors, nurses, nurse practitioners, physician assistants, etc.

What did this investigation look at?

This report looked at the safety information of evobrutinib from three separate phase 2 clinical studies. Evobrutinib was developed with the goal of treating conditions where the immune system, the body's natural defence system, mistakenly attacks healthy parts of the body (autoimmune conditions).

The beneficial treatment effect that evobrutinib had in people with RA or SLE was not considered good enough to continue investigating this drug for these medical conditions. Early results in MS showed a potential benefit, and further studies are ongoing.

Medical conditions tested with evobrutinib

The three clinical studies combined in this report included people with chronic (long-term) conditions where the immune system – the body's natural defence system – mistakenly attacks healthy parts of the body.

General definitions and symptoms of these autoimmune diseases

Multiple sclerosis

- MS is a disease in which the immune system mistakenly attacks the protective covering of nerve cells, known as the myelin sheath
- The damage can cause a range of symptoms including mobility problems, fatigue, balance issues and problems with thinking and controlling emotions

Rheumatoid arthritis

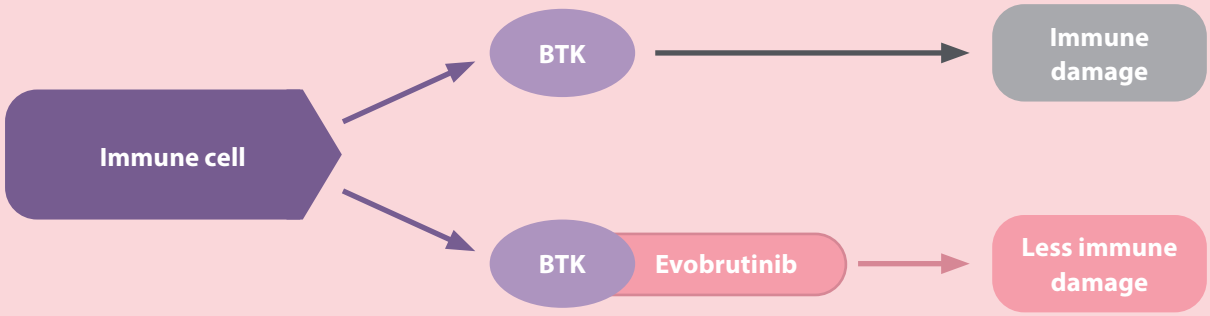
- RA is a disease where the immune system mistakenly attacks healthy cells in the body, causing painful swelling
- This mainly happens in the joints, where it can also damage nearby cartilage and bone, spreading the swelling to nearby tissues

Systemic lupus erythematosus

- SLE is a disease in which the immune system mistakenly attacks body tissues, causing extensive swelling and damage to affected organs
- Areas affected include joints, skin, brain, kidneys, and blood vessels
- The disease has flares (periods of symptoms) with different symptoms depending on what damage is being caused

Evobrutinib

- In the three studies, evobrutinib tablets were taken orally once or twice a day
- Evobrutinib works by attaching tightly to a protein called Bruton's tyrosine kinase (BTK), which is made by immune cells and may play a role in autoimmune diseases
- Evobrutinib stops BTK from working, which may reduce the immune system attacks on healthy parts of the body seen in MS, RA and SLE
- This may reduce damage to surrounding tissues and slow down the disease



What do we know so far about evobrutinib?

In all three studies, the medication was proven to be well-tolerated. They compared the number of side effects in people taking the medication and those taking the placebo. Since the numbers of side effects were very similar between the two groups, the medication was found to be as safe as the placebo.

Although the beneficial treatment effect that evobrutinib had in people with RA or SLE was not considered good enough to continue investigating, the results from all three clinical studies are encouraging and can be used to inform further research into using evobrutinib in MS.

So far, the efficacy results from the phase 2 clinical study on MS have successfully shown that it can reduce brain lesions (areas of damaged brain tissue). However, larger phase 3 studies are required to confirm how well evobrutinib works before it can be approved for use.

Phase 3 study :
A study that compares how safe and effective a new treatment is against the best currently available treatment (the standard treatment) or placebo ('sugar pill').

Who took part in this investigation?

Within each clinical study, people taking evobrutinib or placebo were similar in age, weight, sex, and length of time since diagnosis. This evens out any difference that may not be due to the effects of the medication. This is also the reason why data collected from larger populations are more reliable. When there are more people involved, the effect of individual differences on the results is reduced.

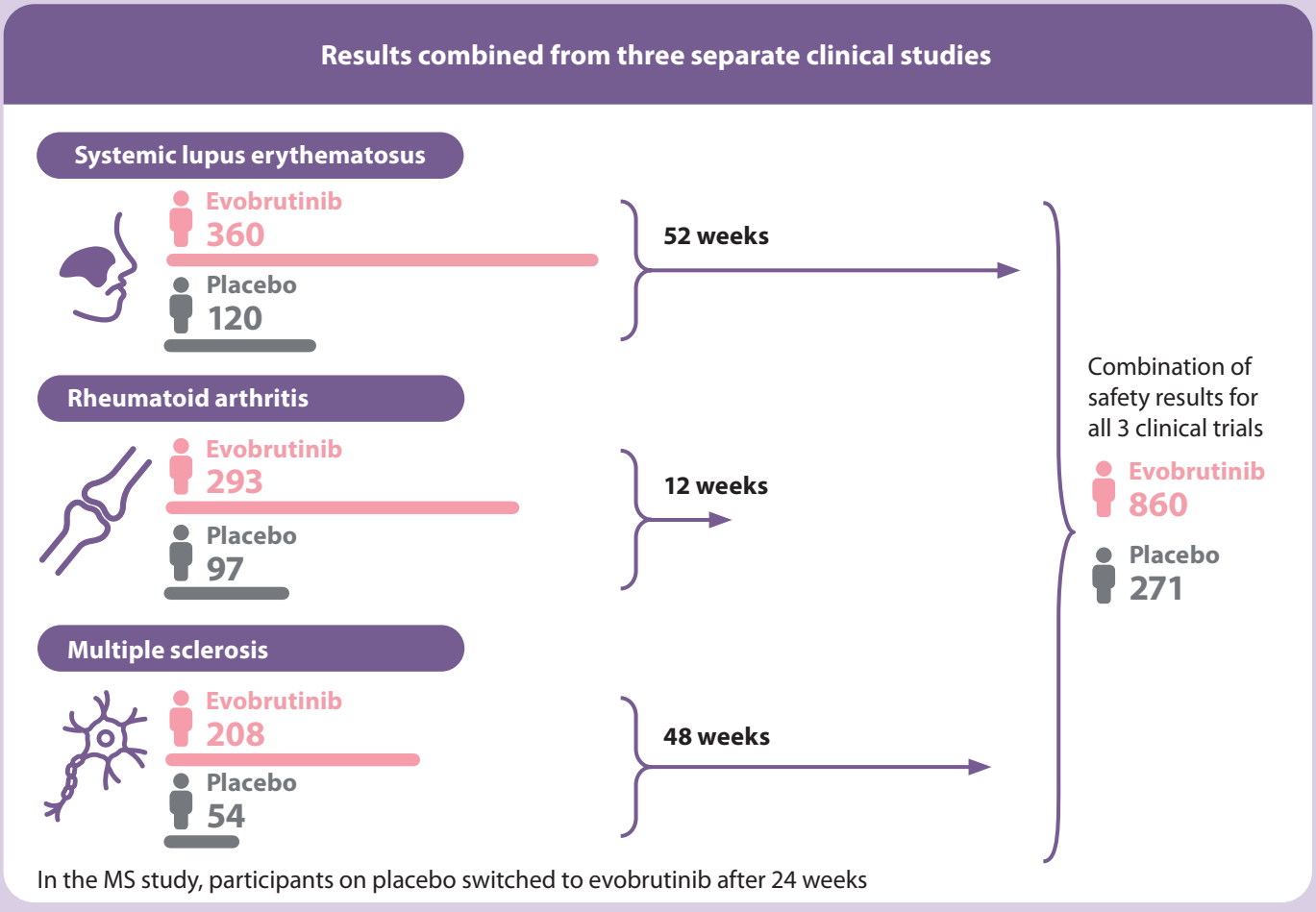
Phase 2 clinical studies typically involve a few hundred patients, monitored over the course of several months or years. However, the number of participants during phase 2 studies is not large enough to show whether the medication will work well for most patients. These phase 2 studies help investigators prepare the methods that will be scaled up for phase 3 clinical studies, which will look at how well evobrutinib treatment works on a bigger MS population and how safe it is.

By combining the safety data from three phase 2 studies, this report looked at a larger number of participants tested with evobrutinib to gain a better understanding of the medication's overall level of safety.

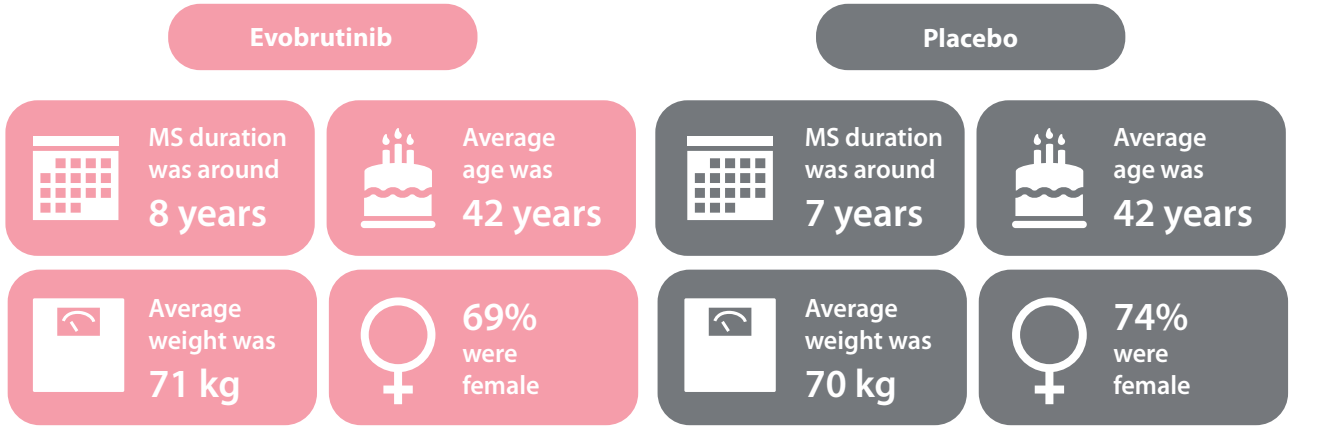
A total of 1132 people who had MS (480 people), RA (390 people) or SLE (480 people) took part in the three clinical studies:

- 861 participants were treated with evobrutinib
- 271 participants were treated with a placebo (for some or all of the time they were in the study)

As these are separate clinical studies, each one ran for a different length of time (including the length of time people received a placebo).



Information about the participants with multiple sclerosis



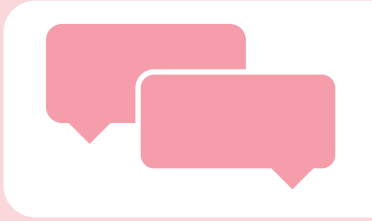
What were the safety results across the three clinical studies?

Summary of the safety results across the three phase 2 trials of evobrutinib:

- The percentage of participants taking evobrutinib who experienced side effects (66%) was similar to that of participants taking placebo (62%).
- Of these side effects, the most common were urinary tract infections, headache, swelling of the nose and throat, diarrhoea and blood markers of potential liver damage.
- Similar percentages of serious side effects were seen in participants taking evobrutinib (6%) and those taking placebo (5%).
- The percentage of participants who stopped taking evobrutinib due to treatment-related side effects (9%) was similar to those who stopped taking placebo due to side effects (10%).
- 2–3% of participants treated with evobrutinib and 0–2% of participants treated with placebo showed signs of liver injury.
- Blood tests looked at the levels of two proteins produced by the liver, where higher levels of these can suggest liver damage. Participants on evobrutinib in all three studies had levels slightly higher than those on the placebo but did not report any symptoms, and their results returned to normal once the treatment was stopped.

What were the main conclusions?

Safety information from over 1000 participants in evobrutinib clinical trials found that the number of side effects reported by those taking the medication was very similar to the effects reported by those taking the placebo. Therefore, the medication can be considered well-tolerated, which is particularly important when considering that MS, RA and SLE are chronic diseases and long-term medication is needed. This combined analysis of safety data is useful for follow-up studies of evobrutinib in MS and helps encourage patients in further studies that this drug is a good candidate for treatment.



Questions from this research that can be used to talk to your doctor or nurse about your MS care

- What does this information mean for me?
- How can we use this information to make decisions about my MS care?

Are there any plans for further studies?

Currently, a long-term follow-up study of the phase 2 study is evaluating the long-term safety of evobrutinib in people with MS – and how the disease activity progresses over time in those taking it. The phase 3 MS study will test how well the medication works to control symptoms in a larger population and how safe it is compared to a standard MS treatment.

Who sponsored this report?

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Are there any plans for further studies?

More information on the three phase 2 clinical studies can be found on the website: https://clinicaltrials.gov/ by searching for the following trial numbers (ClinicalTrials.gov Identifier): NCT02975349 for multiple sclerosis, NCT03233230 for rheumatoid arthritis, and NCT02975336 for systemic lupus erythematosus.

Further information on evobrutinib can be found on the MS Trust website: https://mstrust.org.uk/a-z/evobrutinib

The full title of the primary article discussed here is:
Characterisation of the safety profile of evobrutinib in over 1000 patients from phase II clinical trials in multiple sclerosis, rheumatoid arthritis and systemic lupus erythematosus: an integrated safety analysis.

You can find the full primary article and access it free of charge here: https://doi.org/10.1136/jnnp-2022-328799

The full title of the article presenting results of the phase 2 MS trial is:
Placebo-Controlled Trial of an Oral BTK Inhibitor in Multiple Sclerosis

You can find the phase 2 MS trial article and access it free of charge here:
https://www.nejm.org/doi/full/10.1056/nejmoa1901981

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Financial & competing interests disclosure

X Montalban has received speaking honoraria and travel expenses for participation in scientific meetings, has been a steering committee member of clinical trials or participated in advisory boards of clinical trials in the past years with Abbvie, Actelion, Alexion, Biogen, Bristol-Myers Squibb/Celgene, EMD Serono, Genzyme, Hoffmann-La Roche, Immunic, Janssen Pharmaceuticals, Medday, Merck, Mylan, Nervgen, Novartis, Sandoz, Sanofi-Genzyme, Teva Pharmaceutical, TG Therapeutics, Excemed, MSIF and NMSS.

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MC Genovese is an employee of and has financial interests in Gilead.

D Tomic is an employee of Ares Trading SA, Eysins, Switzerland, an affiliate of Merck KGaA, and received stock or an ownership interest from Novartis.

D Parsons-Rich was an employee of EMD Serono Research & Development Institute, Inc., Billerica, MA, USA, an affiliate of Merck KGaA, at the time of the study, and is currently an employee of and has received stock from Pfizer.

C Le Bolay and H Guehring are employees of Merck Healthcare KGaA, Darmstadt, Germany.

A Kao is an employee of and received stock or an ownership interest from EMD Serono Inc., Billerica, MA, USA, a healthcare business of Merck KGaA.

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