FOCUSSCED STUDY RESULTS SUMMARY

Results from a clinical research study of tocilizumab in people with systemic sclerosis

Roche

This results summary has been developed to explain what happened in the focuSSced study (WA29767).

These results are based on information collected up to the end of January 2018.

As you read through this summary, you may wish to refer to the glossary of terms at the end.

What was this study about?

The aim of the focuSSced study was to see how Tocilizumab (TCZ) affected the progression of Systemic Sclerosis (SSc) compared to **placebo**. This study also looked at the safety of TCZ in people with SSc.

Placebo: an inactive drug that looked like TCZ and was given in the same way.

SSc is an autoimmune disease. This means the immune system, which usually fights germs and other illness, attacks healthy parts of the body instead. As a result, with SSc, normal tissue throughout the body, including the skin, lungs and other organs may be replaced by hardened or scar-like tissue, or "sclerosis".

Most people affected by SSc are women between the age of 30 and 50 years. Approximately 1 in 10 people who are affected are male.

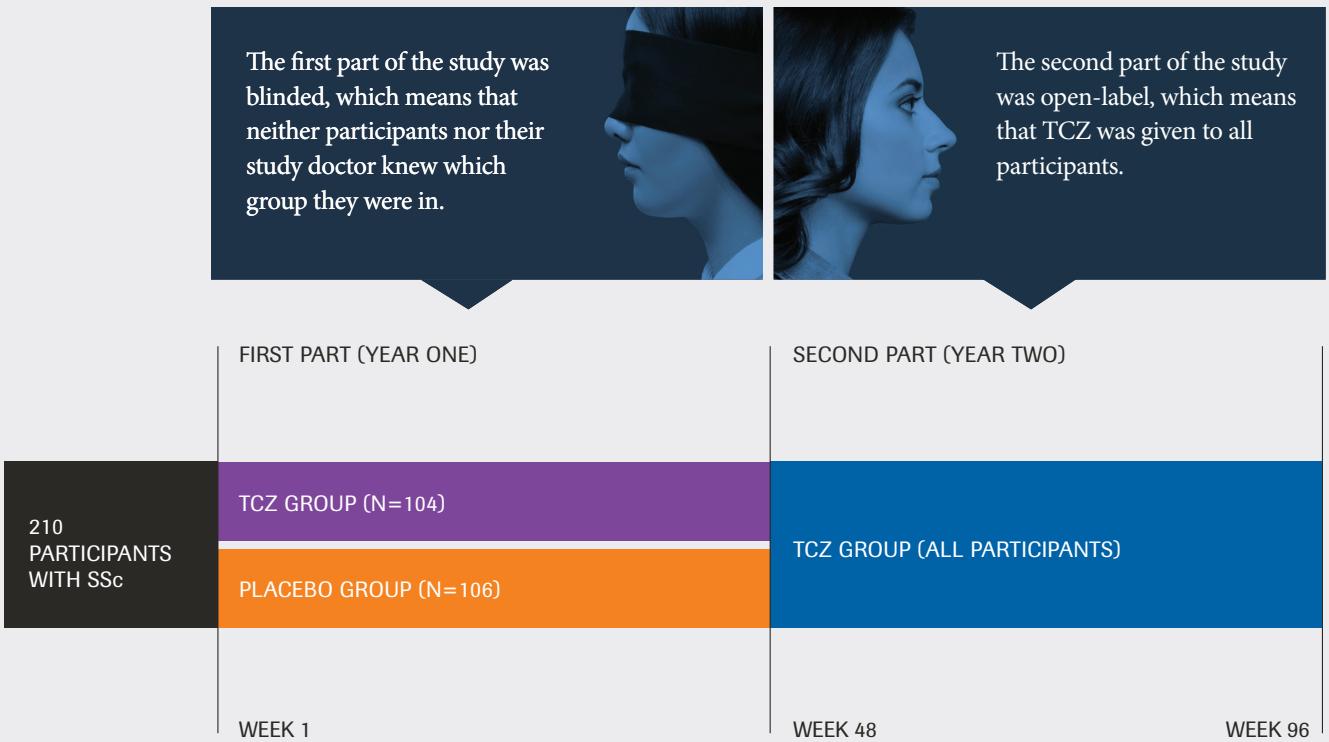
People with SSc may be affected in different ways depending on which tissues are involved. For example, use of fingers and hands and even body movement can be restricted depending on how much skin has thickened or hardened. Shortness of breath and cough may occur if the tissue in the lungs are affected.

TCZ is a medicine that blocks the activity of Interleukin-6 (IL 6). IL-6 is a protein that is involved with the immune system and is known to have a key role in inflammation. Increased levels of IL-6 are seen in people with SSc.

Inflammation: occurs when a tissue is damaged or injured in some way. Tissue may become reddened, warm, swollen or painful. If this happens the tissue is said to be inflamed.

What happened during the study?

The focuSSced study was about 2 years long and was divided into two parts. Each part was 48 weeks long.

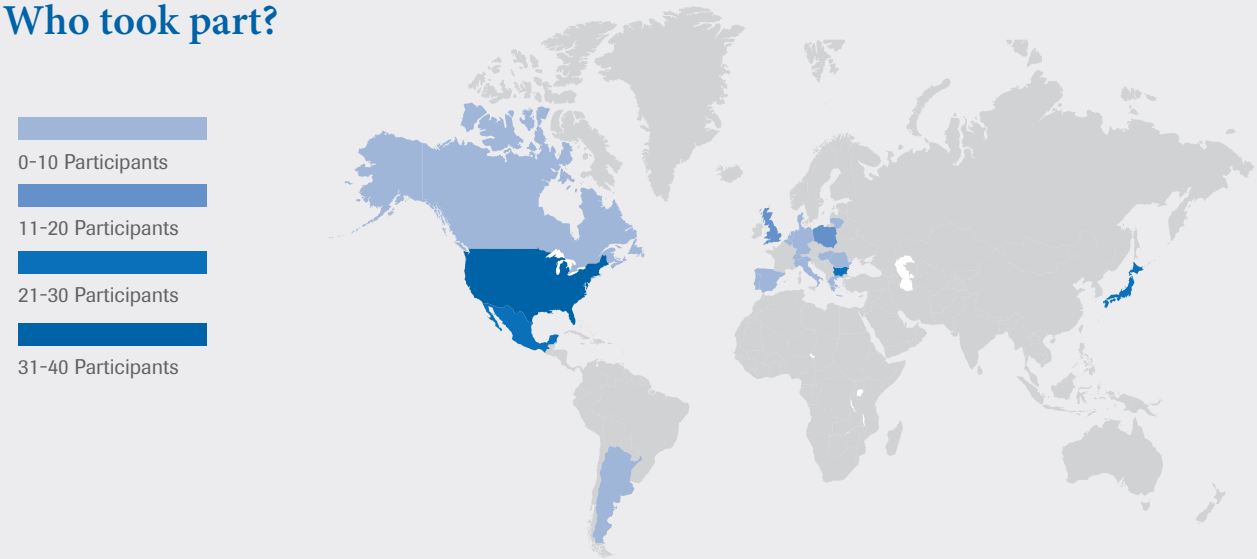


In the first part, participants were randomly assigned (like flipping a coin) to be given TCZ or placebo. There was an equal chance of being given TCZ or placebo. In this study 104 participants received TCZ and 106 participants received placebo.

In the second part, all participants received TCZ for 48 weeks. Every participant, whether they received TCZ or placebo in the first part, received TCZ in the second part.

During clinic visits, participants were checked to assess their SSc as well as any other medical issues. This included checking the skin, breathing, and safety as well as completion of questionnaires to see how participants were feeling.

Who took part?



210 participants

in 20 countries

from 75 clinics

48 years
The average age of participants in this study

81%
The percentage of women in the study

17 months
The average time since diagnosis of SSc, which means that about half the participants had been diagnosed in the 17 months before they started the study

Average: a number that represents the middle or most common value in a group of data.

To take part in the study, participants needed to have active SSc. This meant that their SSc symptoms had been getting worse in the 6 months before their first study visit, or that they had been diagnosed with SSc in the 1.5 years before their first study visit.

How to read these results

In this section of the report, we have summarized the results* up to the end of the first part of this study (week 48). Each result will show the average change in SSc experienced by participants from the time they started the study until the end of the first part of the study (week 48).

For each result, we will show the change for both the TCZ group and the placebo group. This will allow you to see the difference between these two groups.

Statistically significant means the difference seen between two groups is unlikely to be due to chance

Any individual change is thought to be clinically meaningful if it is a change that a patient or their doctor would consider important.

* The results presented in this report may not reflect your individual experience with this study because they are collected from the overall group of participants.

What did the study show?

Here, we report the key results for 210 participants, of whom 104 received TCZ and 106 received placebo.

104
TCZ

106
Placebo

Understanding skin change measurement

Measuring skin thickness over time can tell us if SSc in the skin is getting better or worse. The modified Rodnan Skin Score (mRSS) test measures skin thickness. This test is completed by a healthcare professional who feels the skin across 17 different parts of the body and gives each area a score between 0 (for no thickening) and 3 (for severe thickening). The scores are added together to give a total score between 0 and 51. If the mRSS gets smaller over time, then skin is getting thinner and SSc may be improving.

How did participants' skin change during this study?

The average skin thickness at the start of the study, as measured by the mRSS, was 20. This represents moderate skin thickening.

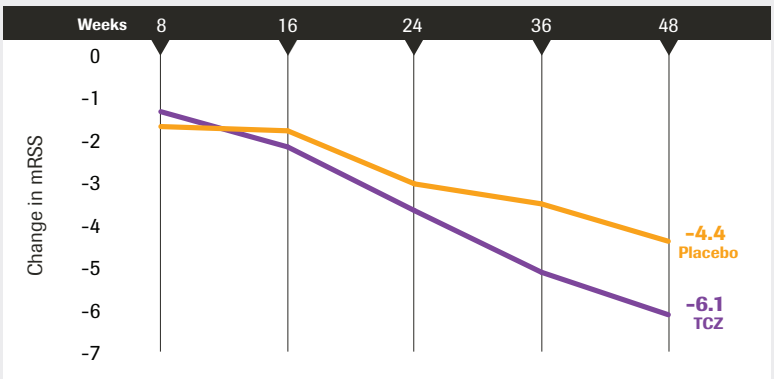
The line graph shows how the mRSS changed during the first part of the study. A decrease in mRSS means it's improving. In this study the mRSS decreased over time in both the TCZ group and the placebo group.

In the **TCZ group** the mRSS decreased by an average of **6.1 points**.
In the **placebo group** the mRSS decreased by **4.4 points**.

Although the change appears to be greater for the TCZ group, the amount of change is similar between the two groups and is not considered statistically significant. This means that on average the improvement in the placebo group is not considered to be different from the improvement seen in the TCZ group.

As statistical significance was not shown for the mRSS, none of the other clinical measurements in the study can be considered statistically significant.

Modified Rodnan Skin Score (mRSS)

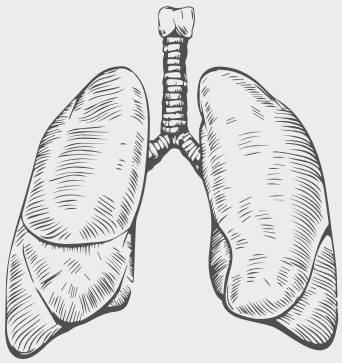


Average (95% Confidence interval [95% CI]) at week 48 for the TCZ group is -6.1 (-7.7 to -4.6) and for the placebo group is -4.4 (-6.0 to -2.9)

Understanding lung function measurement

Scarring of the lungs is a frequent complication for patients with SSc. Scar tissue that has replaced normal lung tissue cannot take oxygen into the body, which can lead to trouble breathing. For some patients, the scarring in their lungs is life limiting.

Forced Vital Capacity (FVC), is the amount of air a person can force out of their lungs after taking a very deep breath in. FVC is a measurement of lung function. Percent predicted Forced Vital Capacity (ppFVC) is a measure of how an individual's FVC compared with what is expected for that individual. In this study, measurements were taken to understand if lung function was changing. An increased score meant lung function improved.

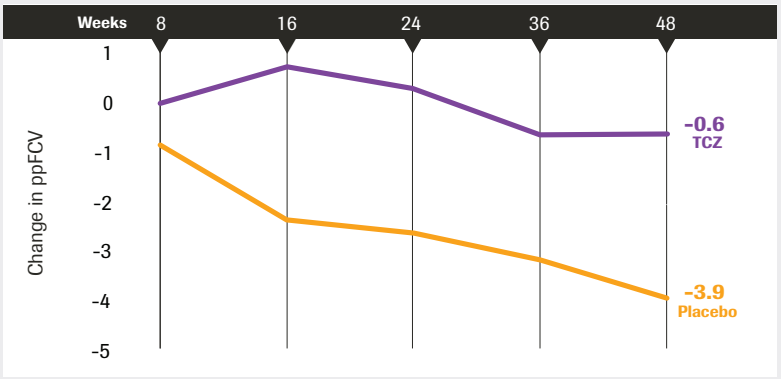


How did participants' lung function change?

The line graph shows how the FVC as a measure of participants' lung function changed during the first part of the study. A decrease in score would mean that the lungs are doing worse. In this study, on average, there was almost no change **(0.6 points)** in lung function in the **TCZ group**; however, the lung function decreased (worsened by **3.9 points**) for participants in the **placebo group**.

This was considered a clinically meaningful effect on lung function for participants in the TCZ group.

Percent Predicted Forced Vital Capacity (ppFVC)



Average (95% CI) at week 48 for TCZ group is -0.6 (-2.4 to 0.9) and for the placebo group is -3.9 (-4.8 to -1.6)

Understanding treatment failure

We collect certain kinds of information to help us understand if a drug is working. If any of the following happened to a participant during the study, the treatment was considered not to have worked for that participant:

- Death
- Worsening of lung function (by measuring FVC)
- Increase in skin thickness (by measuring mRSS score)
- A side effect considered to be related to SSc

Collecting information on how many participants experience 'treatment failure' is important because it can give us information on whether a drug is working or not.

How many participants experienced treatment failure?

Less participants in the **TCZ group (23 participants, 22%)** had treatment failure compared to the **placebo group (37 participants, 35%)**.

Percent of participants experiencing treatment failure

Understanding participant and doctor reported outcomes

In clinical studies, we often use questionnaires to ask participants how they feel they are managing with their disease, both in terms of their symptoms and their ability to carry out day-to-day tasks. In this study, questionnaires helped us understand how SSc was affecting the daily life of participants and if they noticed any change to their SSc during the study.

The Health Assessment Questionnaire Disability Index (HAQ-DI)

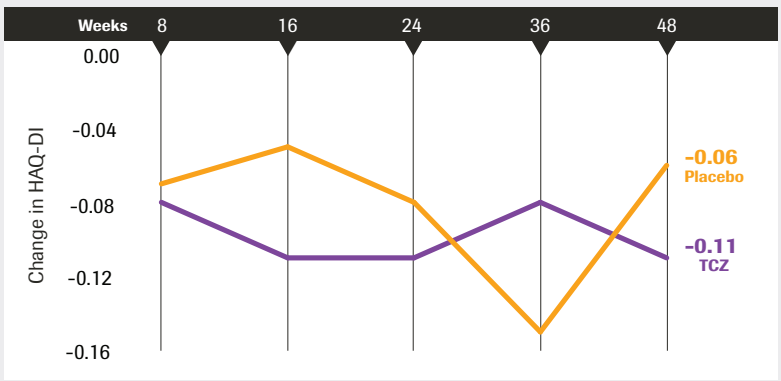
In the Health Assessment Questionnaire Disability Index (HAQ-DI), participants were asked to rate how much difficulty they had when completing daily activities. Examples of daily activities include getting dressed, standing up, eating and walking.

A decrease in score means that participants thought they had less difficulty completing daily activities at week 48 compared to the start of the study.

What were the HAQ-DI results for this study?

In the **TCZ group** the HAQ-DI scores improved by an average of **0.11 points** and in the **placebo group** the HAQ-DI scores improved by an average of **0.06 points**. Although the change appears to be greater for the TCZ group, these changes in HAQ-DI scores are similar. This means that on average the improvement in the placebo group is not considered to be different from the improvement seen in the TCZ group.

Health Assessment Questionnaire Disability Index (HAQ-DI)



Average (95% CI) at week 48 for the TCZ group is -0.11 (-0.22 to -0.01) and for the placebo group is -0.06 (-0.16 to 0.05)

Visual Analog Scale for Global Assessment

Participants and doctors (also known as clinicians) rated the participants' SSc status on a visual scale, called a Visual Analog Scale for Global Assessment. They each put a mark on a 100-mm flat line to rate overall effects of SSc. These responses told us how participants and their doctors felt the overall effects of SSc changed during the first part of the study.

A decrease in score means that participants and doctors thought that the participants' SSc status got better.

On a scale of 0–100 where would you rate the overall effect your systemic sclerosis has on you at this time?

Place a vertical mark on the line to indicate your answer

0 **100**

Has no effect at all **Worst possible effect**

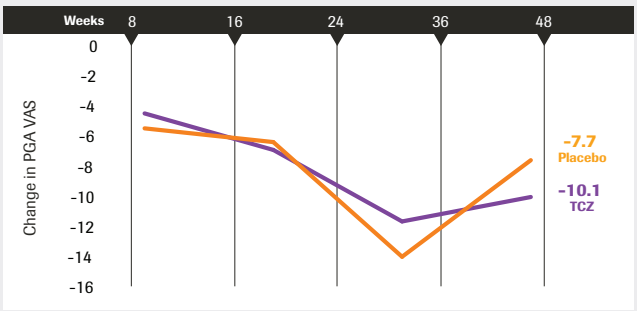
What were the Global Assessment results for this study?

Scores in the **TCZ group** improved on average by **10.1 points**, according to participants.
Scores in the **placebo group** improved on average by **7.7 points** according to participants.

Scores in the **TCZ group** improved on average by **22.5 points**, according to doctors.
Scores in the **placebo group** improved on average by **20.0 points** according to doctors.

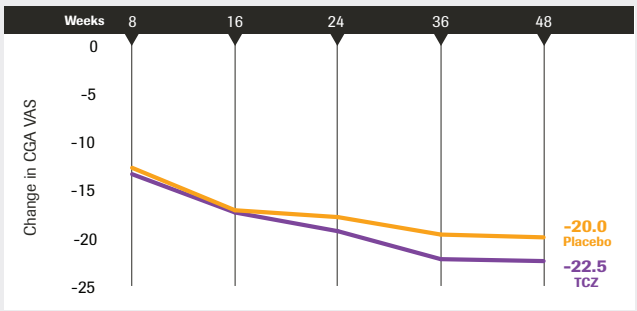
Although the change appears to be greater for the TCZ group, on average, the improvement in the placebo group is not considered to be different from the improvement seen in the TCZ group.

Patient's Global Assessment (PGA)



Average (95% CI) at week 48 for the TCZ group is -10.1 (-14.8 to -5.4) and for the placebo group is -7.7 (-12.3 to -3.0)

Clinician's Global Assessment (CGA)



Average (95% CI) at week 48 for the TCZ group is -22.5 (-27.3 to -17.6) and for the placebo group is -20.0 (-24.8 to -15.2)

Understanding safety and adverse events (side effects)

An adverse event (AE) is any unfavorable medical event that happens after taking medicine. Adverse events may or may not be caused by the medicine. Serious adverse events (SAEs) are those that can require hospital care, cause lasting problems or are life threatening/cause death.

In clinical studies, adverse event information is collected to make sure safety is carefully monitored and any unfavorable medical events are recorded.

This study looked at whether TCZ is safe for patients with SSc compared to placebo, by recording the number and type of adverse events in all participants.

How many participants experienced a serious adverse event?

Less participants in the **TCZ group** had serious adverse events compared to the **placebo group**. Overall, **13 participants (12%)** treated with **TCZ** and **18 participants (17%)** treated with **placebo** had a serious adverse event.

Less participants in the **TCZ group (6 participants, 6%)** stopped treatment because of an adverse event compared to the **placebo group (11 participants, 10%)**.

At least one Serious Adverse Event

Stopped treatment due to Adverse Event

The three most common Serious Adverse Events in both the TCZ and placebo groups were:

	Infections and infestations diseases that are caused by other organisms living in or on your body that are not usually there	Cardiac disorders problems with your heart or blood vessels	Skin and subcutaneous tissue disorders problems that affect the skin and the tissues underneath the skin
TCZ			
Placebo			

Safety in the focuSSced study was similar to that seen in other studies of TCZ.

What was the overall outcome of the study?

Skin thickness (measured using mRSS) was the main factor used to look at the effect of TCZ on SSc. Those who received TCZ had similar changes in skin thickness compared to those who received placebo, after 48 weeks. This means that TCZ had the same effect as placebo on skin thickness in SSc.

Worsening lung function was seen less among participants in the TCZ group compared to those in the placebo group.

Fewer participants in the TCZ group had 'treatment failure' compared to the placebo group.

Those who received TCZ had similar changes in how SSc affected their daily lives compared to those who received placebo.

Finally, fewer participants in the TCZ group had serious adverse events compared to the placebo group.

The results of this study suggest that TCZ and placebo had similar effects on SSc. No new safety issues were identified with TCZ use in participants in the focuSSced study.

Thank you

As a clinical study participant, you belong to a large community of people around the world who advance the field of medicine. Your huge contribution and dedication have helped researchers answer important health questions.

We would like to thank you for participating. We are so grateful for your commitment and contribution to SSc research. We acknowledge and thank you for the time and effort it took to attend the scheduled visits and complete the many assessments.

Glossary

Adverse event (AE): Any unfavorable medical event that happens after taking medicine. Adverse events may or may not be caused by the medicine.

Average: A number that represents the middle or most common value in a group of data.

Blinded: When a clinical study is blinded, it means that neither participants nor their study doctor knows which group they are in and therefore do not know which treatment is being received.

Clinically meaningful: Any individual change is thought to be clinically meaningful if it is a change that a patient or their doctor would consider important.

Inflammation: Occurs when a tissue is damaged or injured in some way. Tissue may become reddened, warm, swollen or painful. If this happens the tissue is said to be inflamed.

Placebo: An inactive drug that looked like TCZ and was given in the same way.

Serious adverse event (SAE): One that can require hospital care, cause lasting problems or is life threatening/causes death.

Statistically significant: The difference seen between two groups is unlikely to be due to chance.

95% Confidence interval (95% CI): 95% of the time the true value of a measure should fall within this range. Confidence interval indicates a range of values that is likely to include the true value. In general, higher confidence levels relate to wider confidence intervals, and lower confidence level relate to narrower intervals.

Where can I find more information?

You can find more information about this study by visiting **clinicaltrials.gov** and searching for the focuSSced study using the study number: NCT02453256 or by going on **clinicaltrialsregister.eu**.

If you have any further questions, please talk to your study doctor or you may reach out to a representative at your local Roche office.

Visit **forpatients.roche.com** for more information/contact details.

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Grazie Mulțumesc

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Tak skal du have

dir Thank You

Dziękuję Ci Dank je

ありがとうございました Merci

Tak skal du have Obrigado