Clinical Trial Results – Layperson Summary

A study to compare different doses of MSTT1041A with a "placebo" – in patients with severe asthma

See the end of the summary for the full title of the study.

About this summary

This is a summary of the results of a clinical trial called a "study" in this document. This summary is written for:

- members of the public
- **participants** – these are asthma patients who took part in the study

This summary is based on information known at the time of writing.

The study started in September 2016 and finished in July 2019. This summary was written after the study had ended.

No single study can tell us everything about the risks and benefits of a medicine. Many people volunteer in several studies to help us find out everything we need to know. The results from this study may be different from other studies with the same medicine.

- This means that you should not make decisions based on this one summary.
- Always speak to your doctor before making any decisions about your treatment.

Contents of the summary

Thank you to the people who took part in this study

The patients who took part have helped researchers to answer important questions about asthma and different doses of the study medicine.

Key information about this study

- In this study, participants were given different doses of a treatment.
- The treatment was a medicine (MSTT1041A) or no medicine (placebo).
- This study was done to find out if MSTT1041A could be effective for patients with severe asthma.
- Researchers wanted to see what the results would be if treatments were given with MSTT1041A in comparison to treatments with the placebo.
- This study included 502 patients in 15 countries.
- This study found that MSTT1041A was effective in asthma patients at the highest dose tested in this study in comparison to the placebo.
- Side effects were similar in groups that got the study medicine or the placebo.
- This report was written after the study was completed.

1. General information about this study

Why was this study done?

Asthma is a disease of the airways leading to the lungs. Patients with asthma may have coughing, wheezing, and difficulty breathing.

Approximately 300 million people in the world have asthma. Several different types of medicine are used to control asthma.

Patients can have bouts of asthma that are especially serious, and their regular treatment may not seem effective when this occurs. These are called "**asthma exacerbations**", and are experienced by patients who have an advanced form of the disease.

Asthma exacerbations can be triggered by exercise, certain medicines, and breathing in something that irritates the airways. Getting sick from a virus that causes an upper airway infection can also be a trigger.

The triggers for asthma exacerbation cause the body to release a molecule, called "**IL-33**". IL-33 binds to structures on airway cells, called **ST2 receptors**.

When IL-33 molecules are bound to ST2 receptors, it can lead to symptoms seen with asthma exacerbation.

In this study, researchers wanted to test a medicine called **MSTT1041A.** This medicine is also known as "**ST2 mab**".

Researchers wanted to find out if there was a dose of MSTT1041A that was safe and effective for controlling asthma exacerbations in patients.

What was the study medicine?

MSTT1041A, also known as **ST2 mab**, is a medicine that has been given to people in other studies and found to be safe for humans. Here is how the medicine works:

- **IL-33** is a molecule that is released by the body in response to triggers that cause asthma exacerbations.
- IL-33 binds to **ST2 receptors** present on airway cells. This can lead to symptoms seen with asthma exacerbations.
- MSTT1041A is a medicine that also binds to ST2 receptors on airway cells.
- When MSTT1041A is present, it may interfere with the binding of IL-33 to ST2 receptors. This medicine may be able to control asthma exacerbations in patients.

MSTT1041A was compared to a "**placebo**".

- In this study, some patients got MSTT1041A while others got a placebo.
- The placebo looked the same as MSTT1041A but did not contain any real medicine.

What did researchers want to find out?

Researchers did this study to compare the study medicine against the placebo.

The main question that researchers wanted to answer were:

1. What dose of MSTT1041A was effective for reducing the number of asthma exacerbations?

Other questions that researchers wanted to answer were:

2. What dose of MSTT1041A was effective for improving other symptoms for asthma patients?
3. How long does it take for MSTT1041A to be distributed in the body?
4. How safe was MSTT1041A for asthma patients?
5. Did MSTT1041A cause the immune system to make antibodies against this medicine?

What kind of study was this?

There are several ways to describe this study.

- **Phase 2b study**
  Phase 2 studies are carried out to find out if a study medicine is effective for patients. This was a "Phase 2b" study, which means that this study was testing different doses of the study medicine that researchers thought might be useful.
- **Placebo-controlled study**
  Some people got MSTT1041A while others got a placebo. This was done so that all patients got a treatment, and the real effect of the medicine could be compared against the placebo.
- **Randomized study**
  A computer randomly decided which patient joined the medicine groups and which patient joined the placebo group. Researchers and patients had no control over this.
- **Double-blind study**
  The researchers and patients did not know which patient was getting the study medicine and which patient was getting the placebo. That made this a double-blind study.

When and where did the study take place?

The study started in September 2016 and finished in July 2019. The study took place in:

- Argentina
- Belgium
- Bulgaria
- Canada
- Czech Republic
- Germany
- New Zealand
- Peru
- Poland
- Romania
- Russia
- South Africa
- South Korea
- Ukraine
- United States

This summary was written after the study had ended.

2. Who took part in this study?

There were 502 asthma patients who received treatment. Patients came from Central and Eastern Europe (56%), Latin America (12%), North America (24%), and from Western Europe and rest of the world (8%).

The majority of the patients were female (66%). Most of the patients were white (84%). The most common (median) age of patients was 53 years. The youngest patient was 18 years old. The oldest patient was 75 years old.

There were 4 treatment groups:

Placebo Total = 127 patients 84% white 65% women and 35% men Average age = 51 years	**MSTT1041A – 70 mg** Total = 127 patients 83% white 64% women and 36% men Average age = 52 years
MSTT1041A – 210 mg Total = 127 patients 86% white 71% women and 29% men Average age = 53 years	**MSTT1041A – 490 mg** Total = 127 patients 84% white 65% women and 35% men Average age = 51 years

What was required in order for patients to participate in this study

1. Provide written consents to volunteer in this study.
2. Be between 18 and 75 years old.
3. Have a body mass index of 18 to 38 kg/m^2 and weigh at least 40 kg.
4. Agree to use family planning methods to prevent pregnancies while participating in this study.
5. Have asthma that is documented by a doctor.
6. Have evidence of uncontrolled asthma.
7. Use asthma medicine (high dose inhaled corticosteroid therapy and one other medicine).
8. Take a breathing test that measures the force of a patient's breath and meet the requirements to participate in the study.

What conditions disqualified patients from participating in this study

1. Mothers who were breast-feeding or intending to get pregnant.
2. Having symptoms that were like asthma, but that were not due to the traditional form of the disease.
3. Recent history of smoking.
4. History or evidence of substance abuse that would interfere with the study.
5. Asthma exacerbation within 4 weeks prior to screening
6. Hospital procedure due to asthma with 12 months prior to screening (intubation for respiratory failure).
7. Presence of other long-term disease that could interfere with the study.
8. Known allergies to products used in the study.

3. What happened during the study?

The "**treatment**" was either the study medicine or the placebo. Patients did not know what they were getting.

- At the start of the study (Week 0), everyone got a treatment that was a placebo.
- At Week 2, patients had to meet further requirements in order to continue in the study.
- At Week 2, each patient (who met the requirements allowing the patient to continue in study) was assigned to a treatment group (medicine or placebo) at random by a computer.

The treatment groups were:

1. Placebo – no medicine
2. MSTT1041A – 70 mg
3. MSTT1041A – 210 mg
4. MSTT1041A – 490 mg

How and when were treatments administered?
Each treatment included 4 injections to the stomach area (subcutaneous abdominal injections). Treatments were given once every 4 weeks, from Week 2 to Week 50.

What happened after treatment started?
The study lasted from Week 0 to Week 54. Patients came in to the clinic to get their treatment. During the visit, patients gave blood samples and underwent other tests for the study. Patients answered questions so researchers could learn about other effects of the treatments. Patients visited the clinic until Week 70 for follow-ups.

4. What were the results of the study?

Five hundred and two asthma patients got at least one treatment; 468 patients completed the 54-week study.

Question 1: 1. What dose of MSTT1041A was effective for reducing the number of asthma exacerbations?

Researchers compared results for the MSTT1041A groups against the placebo group. Patients in the highest MSTT1041A dose group (490 mg) saw a 43% reduction in the number of asthma exacerbations compared to placebo.

While the other MSTT1041A dose groups also saw reductions (22% and 37%), these were not as significant.

Question 2: What dose of MSTT1041A was effective for improving other symptoms for asthma patients?

Patients answered several questions about their asthma symptoms and how the disease was affecting their lives. They reported a somewhat better outcome in the highest dose group (490 mg), compared to the placebo group.

The highest dose group also saw a slightly longer time before the first asthma exacerbation episode (time before onset), compared to the placebo group.

Question 3: How long does it take for MSTT1041A to be distributed in the body?

It took 7 days after MSTT1041A injections for the level in blood to reach its highest concentration. It took 12 weeks of treatment (once every 4 weeks) before medicine levels found in blood reached a concentration that did not change much (steady state).

Question 4: How safe was MSTT1041A for asthma patients?

Researchers compared side effects of patients who got the study medicine with those who got the placebo.

The number of side effects and how severe they were – were generally the same for patients who got MSTT1041A and those who got the placebo. Therefore, MSTT1041A was considered safe at all the doses tested in this study.

Question 5: Did MSTT1041A cause the immune system to make antibodies against the medicine?

Antibodies are molecules made by the body in response to something foreign. Antibodies can sometimes be made against certain types of medicine. These antibodies are known as “anti-drug antibody” or “ADA”.

In the entire study, 2% of patients were found to have ADA specific to MSTT1041A, before starting the treatment.

After treatment, 7% of patients tested positive for ADA specific to MSTT1041A.

Having ADA against a certain medicine can lead to less medicine in your body because ADA can remove the medicine. In this study, researchers did not study the effect of ADA on the study medicine.

5. What were the side effects?

Side effects are unwanted medical problems (such as a headache) that happen during the study and are related to the treatment given during the study.

- Not every patient in a study has all or any of the side effects seen in the study.
- Common side effects and serious side effects are listed in the following sections.

Most common side effects

During the treatment period, there was no trend seen in the dose of the study medicine and the number of side effects.

The percentage of patients in each group who reported a side effect were:

- 3% (4 out of 127 patients) for the placebo group
- 12% (15 out of 127 patients) for the MSTT1041A – 70 mg group
- 6% (7 out of 126 patients) for the MSTT1041A – 210 mg group
- 8% (10 out of 122 patients) for the MSTT1041A – 490 mg group

The most common side effect was reported to be at the injection site, where patients said there was pain, redness, or something similar. Injection site reactions were reported more frequently by patients who got the study medicine than by those who got placebo.

Among 127 patients who got the placebo, 4 patients reported a total of 9 side effects. There were 6 different side effects, and 3 of the same side effect – as one patient (1%) reported the same side effect (injection site reaction) on 3 different days.

Among 375 patients who got the medicine, 32 patients (6%) reported a total of 178 side effects. There were 18 side effects that were all different. There were 160 side effects there were all the same - injection site reactions reported by 23 patients (5%).

Serious side effects

A side effect is considered “serious” if it is life threatening, needs hospital care, or causes lasting problems.

There was one serious side effect reported for a patient in the 70 mg group. The patient developed purplish-colored, lace-like blood veins in the skin. The condition, called “livedo reticularis”, could be due to issues with blood vessels or abnormal blood circulation near the skin surface. This incident was thought to be related to the study medicine.

Asthma was commonly reported in this study by patients who experienced serious and severe forms of the disease. However, asthma was not a side effect caused by any dose of the study medicine.

There were two deaths in this study. One patient in the 210 mg group died following a bout of asthma exacerbation. The other patient in the 490 mg group had an unexplained death. The two deaths in this study were not thought to be caused by the study medicine.

6. How has this study helped research?

This study investigated 3 different doses of the study medicine in asthma patients.

Researchers found out that only the highest dose of the medicine had a significant effect on reducing the number of asthma exacerbations in patients who experience severe asthma.

This study helped researchers learn that the study medicine was almost as safe as the placebo, at the doses tested.

Researchers also learned what concentration of medicine was in the body after taking a certain dose.

In addition, they learned that the immune system of some patients made ADA against this medicine.

7. Are there plans for other studies?

Other studies are not planned at this time for this medicine in asthma patients. However, there are other studies testing this medicine in other diseases.

8. Where can I find more information?

You can find more information about this study on the websites listed below:

- World Health Organization clinical trials registry:
  http://apps.who.int/trialsearch/Trial2.aspx?TrialID=NCT02918019

- USA clinical trials registry:
  https://clinicaltrials.gov/ct2/show/NCT02918019

- EU clinical trials registry:
  https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2016-001549-13

Who can I contact if I have questions about this study?

If you have any further questions after reading this summary:

- Visit the ForPatients platform and fill out the contact form
  https://forpatients.roche.com/en/About.html
  or contact a representative at your local Roche office.

If you took part in this study and have any questions about the results:

- Speak with the study doctor or staff at the study hospital or clinic.

Who organized and paid for this study?

This study was organized and paid for by Genentech, Inc., South San Francisco, CA, USA. Genentech is part of F. Hoffmann-La Roche Ltd., with headquarters in Basel, Switzerland.

Full title of the study and other identifying information

The full title of this study is: “A Phase 2b, Randomized, Double-blind, Placebo-controlled, Multicenter, Dose-ranging Study to Assess the Efficacy and Safety of MSTT1041A in Patients with Uncontrolled Severe Asthma”.

- The protocol number for this study is GB39242.
- This study is known by a short name, which is “ZENYATTA”.
- The ClinicalTrials.gov identifier for this study is NCT02918019.
- The EudraCT number for this study is 2016-001549-13.