A study to look at how safe a drug called obinutuzumab was for people with end-stage kidney disease waiting for a kidney transplant – and how this medicine was processed through the body

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) – written for:

- Members of the public
- People who took part in the study

The study started in November 2015 and ended in November 2018. This summary is based on the results known at the time it was written (December 2019). More information may now be known.

One study can't tell us everything about the possible side effects of a medicine and the help that the medicine can give. It takes lots of people in many studies to find out everything we need to know. The results from this study may be different from results from other studies of the same medicine.

- This means that you should not make decisions based on this one summary. Always talk to your doctor or healthcare provider before making any decisions about treatment for your disease.

Contents of the summary

Thank you to the people who took part in this study

The people who took part in this study have helped researchers to answer important health questions about the study drug obinutuzumab and end-stage kidney disease.

We hope this summary helps you to understand the results of this study and how they will be used to improve the care of people with end-stage kidney disease who need a kidney transplant. If you have any questions about these results, please speak with your study doctor.

Key information about this study

- This study was done to find out what effects, good or bad, a medicine called obinutuzumab (the 'study medicine') has on people with chronic kidney disease who need a kidney transplant ('end-stage kidney disease') and whose immune system has been pre-activated, meaning it is likely to fight ('reject') a new kidney from a donor.
- People with an activated immune system have unwanted antibodies (a specific type of protein) in their blood. The number of antibodies can be measured in blood.
- People with end-stage kidney disease whose immune system has been activated to fight a new donor kidney ('transplant rejection') may have a harder time finding a matching donor.
- Obinutuzumab reduces the number of B cells in the body. B cells are part of the immune system that help activate the immune system and make antibodies.
- All the people who took part in this study were given the study medicine.
- This study included 25 people in the United States.
- The main finding was that obinutuzumab could be used safely in people with end-stage kidney disease, but there were some side effects that we talk about later in the summary.
- The study also found that obinutuzumab reduced the number of B cells in people with end-stage kidney disease, but in most people, it reduced the number of unwanted antibodies only a very little and not enough to make it easier to find a matching donor.

1. General information about this study

Why was this study done?

Chronic kidney disease means the kidneys do not work properly and continue to get worse. It can be caused by other medical problems, including diabetes, high blood pressure and cysts in the kidneys.

The kidneys help clean the blood by removing wastes and extra fluid, which are carried from the body in urine. In people with chronic kidney disease, the kidneys do not function as well as in healthy people. When chronic kidney disease gets worse ('end-stage kidney disease'), the best treatment might be for the person to get a new kidney from a healthy person or a person who has died (a 'donor'). This procedure is called a 'kidney transplant.' However, sometimes the body's immune system attacks ('rejects') the new kidney. This is called 'transplant rejection.'

Normally, the body's immune system makes proteins called antibodies that attack outside invaders like bacteria, viruses, and other germs to help prevent or fight infection. In some people with chronic kidney disease, the immune system has been turned on ('pre-activated') to make unwanted antibodies that attack the new kidney as if it were an outside invader. This can happen in people who have been pregnant or have had blood transfusions or another kidney transplant.

Doctors can measure the antibodies in the blood of a person who needs a kidney transplant. A person who has more of these unwanted antibodies is said to be 'sensitized.' A sensitized person has more risk of transplant rejection after getting a kidney transplant than a person who is not sensitized. Approximately 30% of people who are waiting for a kidney transplant are sensitized.

Before a transplant, doctors do tests to see if the donor 'matches' the patient biologically. These tests can tell if a person is sensitized to reject a kidney from a particular donor. Doctors have a harder time finding a matching donor for people who are sensitized. There are currently no medicines that help people with end-stage kidney disease who are sensitized to become 'desensitized' so they can safely get a particular kidney transplant.

Studies have already shown that the study medicine, obinutuzumab, is safe and works well in people with cancers of the blood. However, no proper clinical studies have been done until now to look at how well obinutuzumab works and how safe it is in people with end-stage kidney disease before they get a kidney transplant.

What was the study medicine?

Obinutuzumab (Gazyva®) is a medicine already given to:

- People with a type of blood cancer called chronic lymphocytic leukaemia
- People with a type of blood cancer called follicular lymphoma

Obinutuzumab works by removing a specific type of B cells from the blood. B cells are part of the immune system and help make the antibodies that can attack a new kidney during transplant rejection. By removing this type of B cells, obinutuzumab may help people with end-stage kidney disease who are sensitized to become desensitized. This would help them find a matching donor organ more easily.

All the people taking part in this study were also taking another medicine called intravenous immunoglobulin. This medicine decreases the activity of the whole immune system and may help obinutuzumab remove unwanted antibodies. Additional medicines called mycophenolate mofetil, tacrolimus, and steroids were given to people in the study who received a kidney transplant. These medicines help stop the body from newly making unwanted antibodies at the time of transplant that could damage the new kidney.

What did researchers want to find out?

The main questions that researchers wanted to answer were:

1. How many people in the study had medical problems (that may or may not have been caused by the study medicine) during the study?
2. How many people in the study had medical problems (that may or may not have been caused by the study medicine) after getting a kidney transplant?

Other questions that researchers wanted to answer included:

3. How quickly did the study medicine move through the bodies of people during the study?
4. How much and for how long did the study medicine reduce the number of B cells in the blood of people in the study?
5. How well did the study medicine reduce the number of unwanted antibodies in the blood of people who were sensitized?

What kind of study was this?

This study was a ‘Phase 1b’ study, which means that this was one of the first studies of obinutuzumab in a small number of people with end-stage kidney disease who were sensitized. The researchers did medical tests on the people who took part to find out more about how obinutuzumab works.

This was an ‘open-label’ study, which means that the people in the study and the study doctors knew that obinutuzumab was being given. The study was also uncontrolled, which means that all the people in the study were given obinutuzumab. It was not compared to another drug or to a placebo.

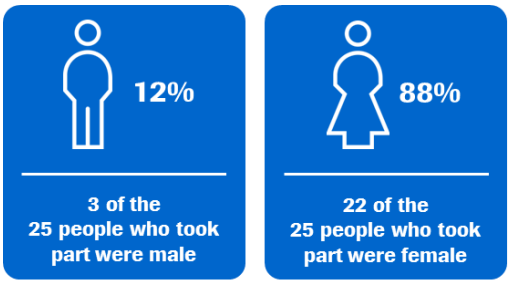
When and where did the study take place?

The study started in November 2015 and ended in November 2018. This summary was written after the study had ended.

The study took place at 7 study centres across the United States.

2. Who took part in this study?

This study included 25 adults with end-stage kidney disease who were waiting for a kidney transplant. Here is more information about the people who took part in the study.



Age range: 29 to 65 years old

People could take part in the study if they:

- Had end-stage kidney disease
- Were recommended by their doctors and needed a kidney transplant, but had not yet had the kidney transplant
- Were sensitized, meaning they had many unwanted antibodies that made it harder to find a matching donor organ and put them at a higher risk of transplant rejection

Note

People who took part in the study had problems with their kidneys for different reasons:

- *9 people had cysts in their kidneys*
- *6 people had diabetes that was affecting their kidneys*
- *4 people had inflammation of their kidneys – called glomerulonephritis*
- *1 person had high blood pressure that was affecting their kidneys*
- *5 people had other medical problems that were affecting their kidneys*

People who took part in the study had been on the waiting list for a kidney transplant for 7 months to 12 years before the study began.

People could not take part in the study if they:

- Had a recent major surgical operation or planned to have major surgery during the study (other than kidney transplant)
- Needed another major organ transplant (such as liver or pancreas) at the same time as a kidney transplant
- Had low levels of white blood cells, platelets, or red blood cells in their body
- Had any other serious health problem, such as cancers, heart problems, liver problems, lung problems, or serious infections

3. What happened during the study?

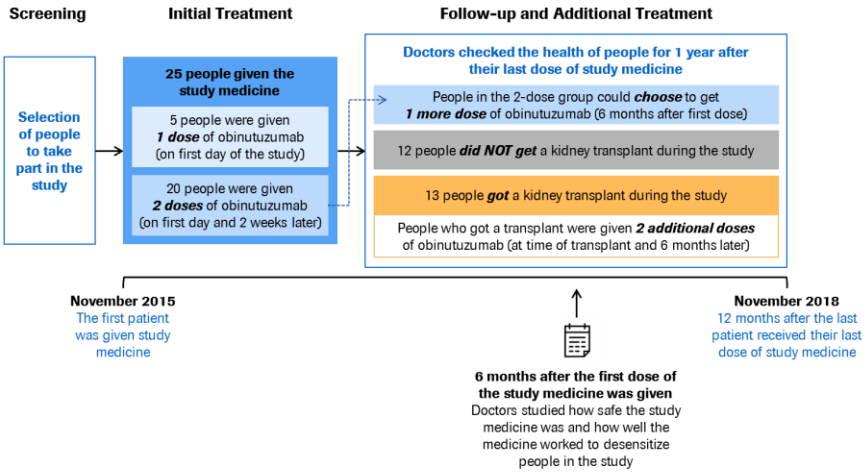
During the study, all 25 people were given:

- **Obinutuzumab** (the study medicine) – given by drip into a vein (infusion) on the first day of the study.
    - 5 people were given the study medicine once – on the first day of the study.
    - 20 people were given the study medicine twice – on the first day of the study and again 2 weeks after their first treatment.
    - People who received a kidney transplant were also given the study medicine at the time of the transplant and then again 6 months after the transplant
- **Intravenous immunoglobulin** – given by drip into a vein (infusion) on the first day of the study and at 3 and 6 weeks after their first treatment. This medicine is given to people who are sensitized to decrease the activity of the immune system and to help remove unwanted antibodies.
- **Mycophenolate mofetil**, **tacrolimus,** and **steroids** – given to people after they received a kidney transplant. These medicines are typically given to people after receiving a kidney transplant to lower the risk of transplant rejection.

The study had 2 main steps:

- **Treatment:** People in the study were given their first dose of obinutuzumab on the first day of the study. Some people were given more doses of obinutuzumab depending on which treatment group they were in and whether they received a kidney transplant (see above). Doctors checked the health of all people in the study for 12 months after their first treatment. Other medicines were also given.
- **Follow-up:** People went back to the study centre for more doctor visits for at least another year after the last dose of obinutuzumab. Study doctors studied the health of people who got a kidney transplant and people who did not.
    - 12 people did not get a kidney transplant during the study.
    - 13 people got a kidney transplant during the study. Doctors continued to check the health of people who got a kidney transplant for at least 1 year after they got their last dose of obinutuzumab.

This picture shows what happened in the study.



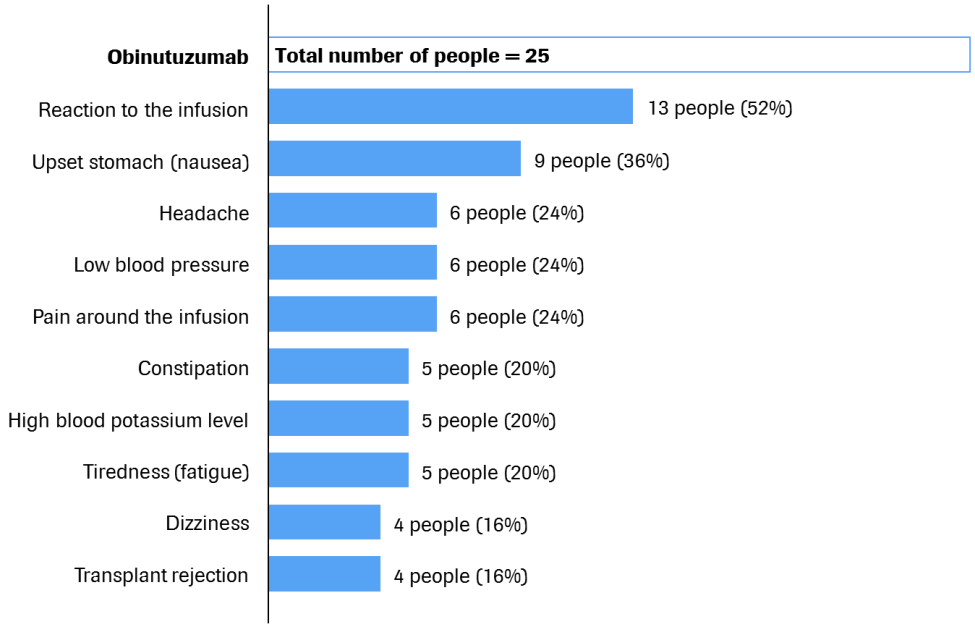
4. What were the results of the study?

Question 1: How many people in the study had medical problems (that may or may not have been caused by their treatment) during the study?

Here, we talk about all medical problems that the people had during the study and whether they were related to the study medicine. Side effects are medical problems believed to be caused by the study medicine. We talk about side effects in Section 5 (What were the side effects of the study medicine?).

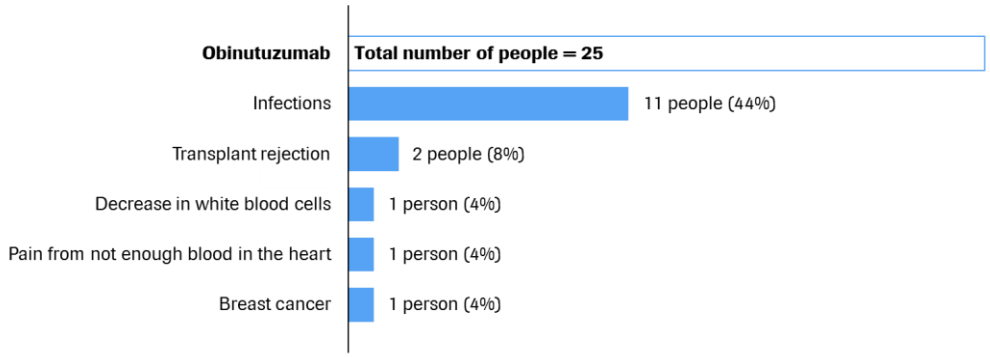
In this study, 23 out of the 25 people who were given obinutuzumab (92%) had at least one medical problem during the study. This picture shows the most common medical problems that happened during the first 6 months of the study.

What were the most common medical problems during the study?



"Serious medical problems" were medical problems that required the patient to go to hospital to be treated. These problems may or may not have been related to the study medicine. Serious medical problems happened in 13 out of the 25 people (52%) during the first 6 months of the study. No people died in this study. This picture shows the serious medical problems that happened during the study (some people had more than one serious medical problem).

How many people had each of these serious medical problems during the study?



The most common types of serious infections that happened during the study were:

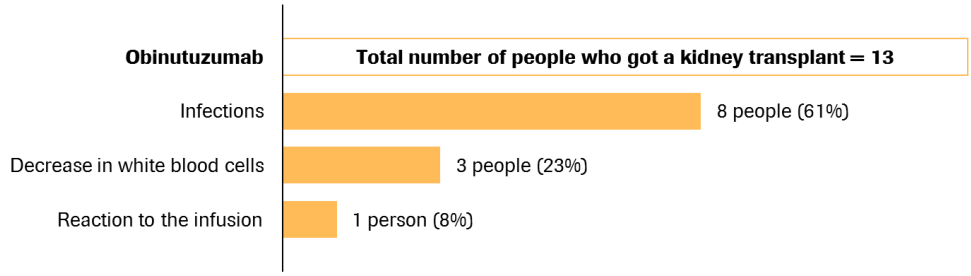
- Lung infection (pneumonia). This happened in 3 people.
- Infection of the wound from kidney transplant surgery. This happened in 2 people.

Question 2: How many people in the study had medical problems (that may or may not have been caused by the study medicine) after receiving a kidney transplant?

The researchers also looked at medical problems in people who got a kidney transplant and whether the medical problems were related to the study medicine. The researchers wanted to know if there were medical problems that happened in people who were given obinutuzumab and who got a kidney transplant.

- 12 out of the 13 people (92%) who got a kidney transplant during the study had medical problems.
- 6 people (46%) who got a kidney transplant had serious medical problems.
- The study doctors looked carefully at medical problems that may be related to obinutuzumab, shown in the picture below.

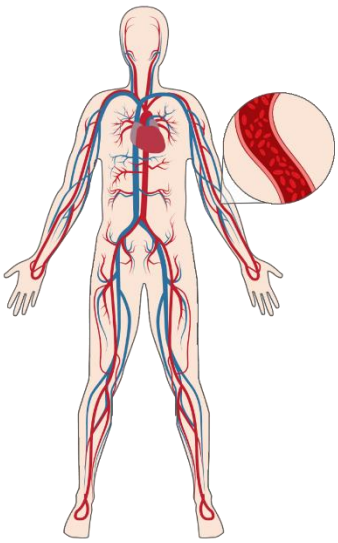
How many people who received a kidney transplant had each of these medical problems during the the study?



Question 3: How quickly did the study medicine move through the bodies of people during the study?

Researchers wanted to know how quickly the study medicine moved through the bodies of people in the study. Researchers tested this by measuring how much obinutuzumab was in the participants' blood at different times during the study.

- After treatment on the first day of the study, the total amount of obinutuzumab was similar in the 5 people who were given 1 dose (on average, 345 µg per mL of blood) and in the 20 people who were given 2 doses before they received the second dose (on average, 378 µg per mL of blood).
- The total amount of obinutuzumab in the 20 people who were given 2 doses was higher after they got the second dose 2 weeks after the first dose (on average, 541 µg per mL of blood).
- Over time, the total amount of obinutuzumab in the people in the study decreased. Obinutuzumab moved through the bodies of people in the study at a speed that was similar to what has been measured in people with cancer who were treated with obinutuzumab.

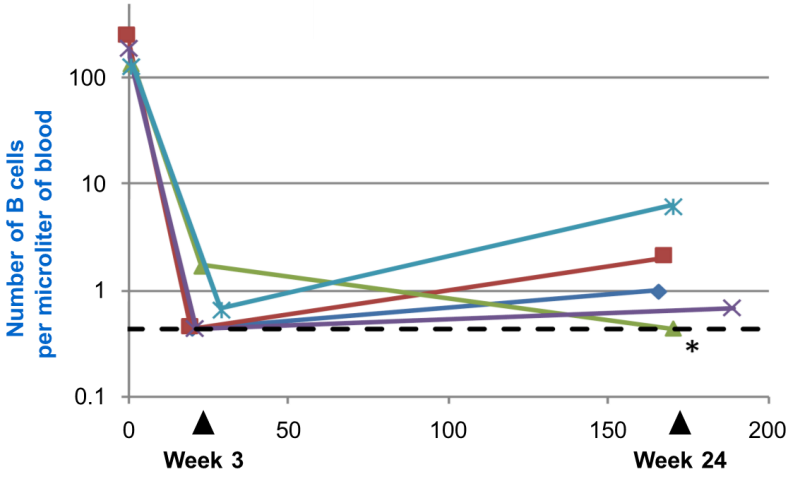


Question 4: How much and for how long did the study medicine reduce the number of B cells in people?

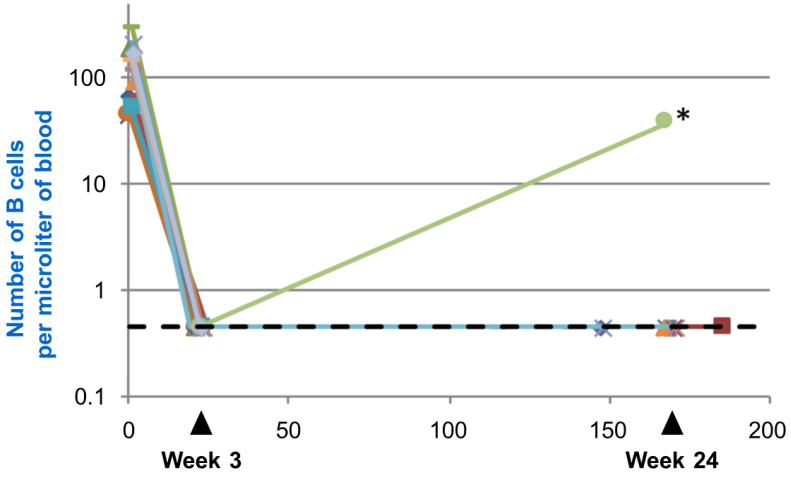
Obinutuzumab works by removing a specific type of B cells from the blood. Researchers measured how many of these B cells people had at different times during the study. They wanted to see if the study medicine was doing what it is supposed to do – remove specific types of B cell in the body.

- In people who were given 1 dose of obinutuzumab, the number of the specific type of B cells that obinutuzumab removes was much lower 3 weeks after the start of the study and was still low 24 weeks after the start of the study.
- In people who were given 2 doses of obinutuzumab, the specific type of B cells that obinutuzumab removes were almost completely gone 3 weeks after the start of the study and were still almost completely gone in most people 24 weeks after the start of the study.

How did the number of B cells in the bodies of people who were given 1 dose of obinutuzumab change over time?



How did the number of B cells in the bodies of people who were given 2 doses of obinutuzumab change over time?



Each colored line on the graphs shows the B cell measurements from 1 person who was given obinutuzumab.
* The green line (marked with '*') represents a person whose body made antibodies against obinutuzumab, so obinutuzumab may have not worked as well to reduced the number of B cells in the blood.

Question 5: How well did the study medicine reduce the number of unwanted antibodies in the blood that caused people to be sensitized?

The researchers wanted to know if obinutuzumab helped to lower the number of unwanted antibodies in the blood that cause people to be sensitized and gives them a higher risk of transplant rejection. They counted the number of antibodies in blood samples from people in the study by using a special test that measures a type of light waves called fluorescence. When the fluorescence in blood samples from sensitized person is reduced by 50% or more, doctors consider that person to be desensitized.

- Only 2 out of 25 people (8%) in the study had fluorescence reduced by 50% or more and were considered desensitized
- 23 out of 25 people (92%) were still sensitized even after obinutuzumab treatment

5. What were the side effects?

In Section 4, we talked about all medical problems that happened during the study that may or may not have been caused by obinutuzumab. In this section, we talk about side effects (also known as 'adverse reactions'). Side effects are medical problems that the study doctor believed were related to obinutuzumab.

Common and serious side effects are listed in the following sections.

Most common side effects

During the study, 16 out of the 25 people (64%) had a side effect believed to be related to obinutuzumab treatment. The most common side effect was a reaction to the infusion, which happened in 13 people (52%).

The typical symptoms of reaction to the infusion were:

- Chills
- Nausea
- Low blood pressure

Serious side effects

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

During the study, 2 out of the 25 people (8%) had a serious side effect believed to be related to obinutuzumab treatment:

- One person who was given 1 dose of obinutuzumab had a serious lung infection (pneumonia).
- One person who was given 2 doses of obinutuzumab had a serious lung infection (pneumonia) and a serious bacterial infection called nocardiosis. This person left the study because of these side effects.
- No people died during the study.

6. How has this study helped research?

The information presented here is from a single study of 25 people with end-stage kidney disease who were waiting to have a kidney transplant. The people in the study were sensitized. This means that they had more unwanted antibodies in their blood. People with unwanted antibodies have a harder time finding a matching kidney and have a higher risk of transplant rejection after getting a kidney transplant than people who are not sensitized. These results helped researchers learn more about how obinutuzumab works in people with chronic kidney disease who are sensitized.

There were only 25 people in this study, so it's hard to know whether other people with end-stage kidney disease would have the same results. Also, all of the people in the study were given obinutuzumab, so there was no way to compare the results to people who were not given obinutuzumab.

Overall, this study showed that obinutuzumab was safe to use in people with end-stage kidney disease. The side effects were similar to side effects seen in previous studies of obinutuzumab in people with other diseases. Obinutuzumab did not help all of the people in the study who needed a kidney transplant and who were sensitized because the medicine did not reduce the number of unwanted antibodies in many of the people.

7. Are there plans for other studies?

At the time of writing this summary, no more studies were planned to look at obinutuzumab in people with end-stage kidney disease who are waiting for a kidney transplant.

Other studies are being done to look at how safe obinutuzumab is and how well it works in people with kidney problems caused by a disease of the immune system called lupus.

8. Where can I find more information?

You can find more information about this study on these websites:

- https://clinicaltrials.gov/ct2/show/NCT02586051
- https://forpatients.roche.com/

If you want to find out more about the results of this study, the full title of the relevant scientific paper is: "Safety, pharmacokinetics, and pharmacodynamic activity of obinutuzumab, a type 2 anti-CD20 monoclonal antibody for the desensitization of candidates for renal transplant." The authors of the scientific paper are: Robert R. Redfield, Stanley C. Jordan, Stephan Busque, Flavio Vincenti, E. Steve Woodle, and others. The paper is published online in the journal *American Journal of Transplantation* (https://onlinelibrary.wiley.com/doi/full/10.1111/ajt.15514).

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

If you have any more questions:

- Visit the ForPatients website and fill out the contact form – https://forpatients.roche.com/
- Contact a representative at your local Roche office.

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

- Talk to the study doctor or staff at the study hospital or clinic.

If you have questions about your own treatment:

- Talk to the doctor in charge of your treatment.

Who organised and paid for this study?

This study was organised and paid for by F. Hoffmann-La Roche Ltd whose main office is in Basel, Switzerland.

Full title of the study and other identifying information

The full title of this study is: “A Study of Obinutuzumab to Evaluate Safety and Tolerability in Hypersensitized Adult Participants With End Stage Renal Disease Awaiting Transplantation.”

The study is known as ‘THEORY’ or Study WT29749.

- The protocol number for this study is: WT29749.
- The ClinicalTrials.gov identifier for this study is: NCT02586051.