AstraZeneca

Clinical Study Results

Research Sponsor: AstraZeneca UK

Drug Studied: MEDI0382

Study Purpose: This study was done to learn how MEDI0382 works in the liver and about its safety in participants with type 2 diabetes mellitus who were overweight or obese

Protocol Number: D5670C00022

Thank you

Thank you to the participants who took part in the clinical study for the study drug MEDI0382, also called cotadutide.

All of the participants helped researchers learn more about MEDI0382 to help people with non-alcoholic fatty liver disease, non-alcoholic steatohepatitis, or fatty liver. Having type 2 diabetes mellitus, also called T2DM, can cause these conditions.

AstraZeneca UK sponsored this study and believes it is important to share the results of the study with the participants and the public.

An independent non-profit organization called CISCRP helped prepare this summary of the study results. We hope it helps the participants understand and feel proud of their important role in medical research.

If you participated in the study and have questions about the results, please speak with the study doctor or staff at your study site.

Overview of this study

Why was the research needed?

Researchers are looking for a better way to treat non-alcoholic fatty liver disease, non-alcoholic steatohepatitis, or fatty liver. Having T2DM can cause these conditions. Before a drug can be approved for people to receive, researchers do clinical studies to find out how it works and how safe it is.

What treatments did the participants receive?

The participants in this study received MEDI0382 or a placebo. A placebo looks like a drug but does not have any medicine in it.

What were the results of this study?

The main questions the researchers wanted to answer in this study were:

- **Did the participants' glycogen levels in the liver change after receiving MEDI0382?**

  Yes. Overall, the researchers found that the liver glycogen levels, also called sugar stores that are used as energy in the body, changed more in the participants who received MEDI0382, compared with those who received the placebo. Glycogen levels were lower for the participants who received MEDI0382.

- **What medical problems happened during this study?**

  There were 76.2% of participants who had medical problems that the study doctors thought might be related to the study drug during the study. The most common medical problem was nausea.

More details about the results of this study are included later in this summary.

Where can I learn more about this study?

You can find more information about this study on the websites listed on the last page. When a full report of the study results is available, it also can be found on those websites.

Who took part in this study?

The researchers asked for the help of people with T2DM who were also overweight or obese.

In people with T2DM, the body cannot balance and use "glucose" normally. Glucose is a sugar that is used as energy for the body. People with T2DM typically have too much blood glucose and are overweight or obese.

Having T2DM and being overweight or obese can cause a condition called NAFLD/NASH. NAFLD, also called non-alcoholic fatty liver disease, is a condition in which extra fat builds up in the liver. NASH, also called non-alcoholic steatohepatitis, is a form of NAFLD in which there is also inflammation and damage in the liver. These 2 diseases together are called NAFLD/NASH.

The participants in this study were 51 to 77 years old when they joined.

The study included 21 participants in Sweden.

Why was the research needed?

Researchers are looking for a better way to treat people with T2DM who are likely to have NAFLD/NASH. Before a drug can be approved for people to get, researchers do clinical studies to find out how it works and how safe it is.

In people with NAFLD/NASH, there is more fat in the liver than normal. This may cause inflammation and damage in the liver. Inflammation and damage in the liver can lead to liver disease and liver failure. Also, in people with NAFLD/NASH, the body has more energy than normal. The body stores this extra energy as fat in the liver and other parts of the body.

There are currently no treatments for NAFLD/NASH. But, researchers think that treatments that decrease liver fat, inflammation, and liver damage might help prevent liver failure. Researchers also think that treatments that decrease blood glucose levels and body weight will also help people with NAFLD/NASH.

MEDI0382 was designed to act like 2 proteins found in the body that can decrease body weight. These proteins are called "glucagon-like peptide 1", also called GLP-1, and "glucagon".

- **GLP-1** can decrease body weight by decreasing blood glucose levels and hunger.
- **Glucagon** can decrease body weight by decreasing the body's sugar stores, also called glycogen, and hunger. Glucagon causes the breakdown of glycogen to provide the body with energy. Glycogen is a form of glucose that is stored in the liver and can be turned into glucose when blood glucose levels are low. Glucagon also causes the breakdown of fats in the liver, which provides energy when the body is not getting food.

Researchers think that MEDI0382, which acts like both GLP-1 and glucagon, might help people with T2DM who are likely to have NAFLD/NASH. The researchers think that MEDI0382 may help liver health, decrease body weight, and reduce blood sugar levels in patients with T2DM.

But, researchers are not exactly sure how MEDI0382 works in the human body. This is because GLP-1 and glucagon each have opposite effects on glycogen.

- GLP-1 **increases** liver glycogen and **decreases** blood glucose levels.
- Glucagon **decreases** liver glycogen and **increases** blood glucose levels.

So, the researchers want to better understand how MEDI0382 changes glycogen levels in the liver so they can know how exactly MEDI0382 works in the human body.

In this study, the researchers wanted to find out how MEDI0382 works in a small number of participants who were overweight or obese with T2DM. They also wanted to find out if the participants had any medical problems during the study.

What was the purpose of this study?

The main questions the researchers wanted to answer in this study were:

- Did the participants' glycogen levels in the liver change after receiving MEDI0382?
- What medical problems happened during this study?

The answers to these questions are important to know before other studies can be done to find out how MEDI0382 works in the liver in people with T2DM who were likely to have NAFLD/NASH.

What treatments did the participants receive?

The participants received MEDI0382 or a placebo through a needle under the skin, also called an injection. A placebo looks like a drug but does not have any medicine in it. Researchers use a placebo to help make sure any of the effects they see in the participants who received the drug are actually caused by the drug.

The doses of MEDI0382 were measured in micrograms, also known as "µg".

A computer program was used to randomly choose the treatment each participant received. This helps make sure the groups are chosen fairly. Researchers do this so that comparing the results of each treatment is as accurate as possible.

This was a "double-blind" study. This means none of the participants, researchers, study doctors, or other study staff knew what treatment each participant was receiving.

Some studies are done this way because knowing what treatment the participants are receiving can affect the results of the study. When the study ended, the research sponsor found out which treatment the participants got so they could create a report of the study results.

The participants in this study were taking a medication called metformin when they joined the study. Metformin can affect the glycogen levels in the liver, which the researchers were measuring. So, the participants stopped taking metformin for 5 days before starting the study treatment. This is called a "wash-out" period. After this time period, they started taking metformin again. They also stopped taking metformin for the last 5 days of the study treatment.

The chart below shows the treatments the participants received.

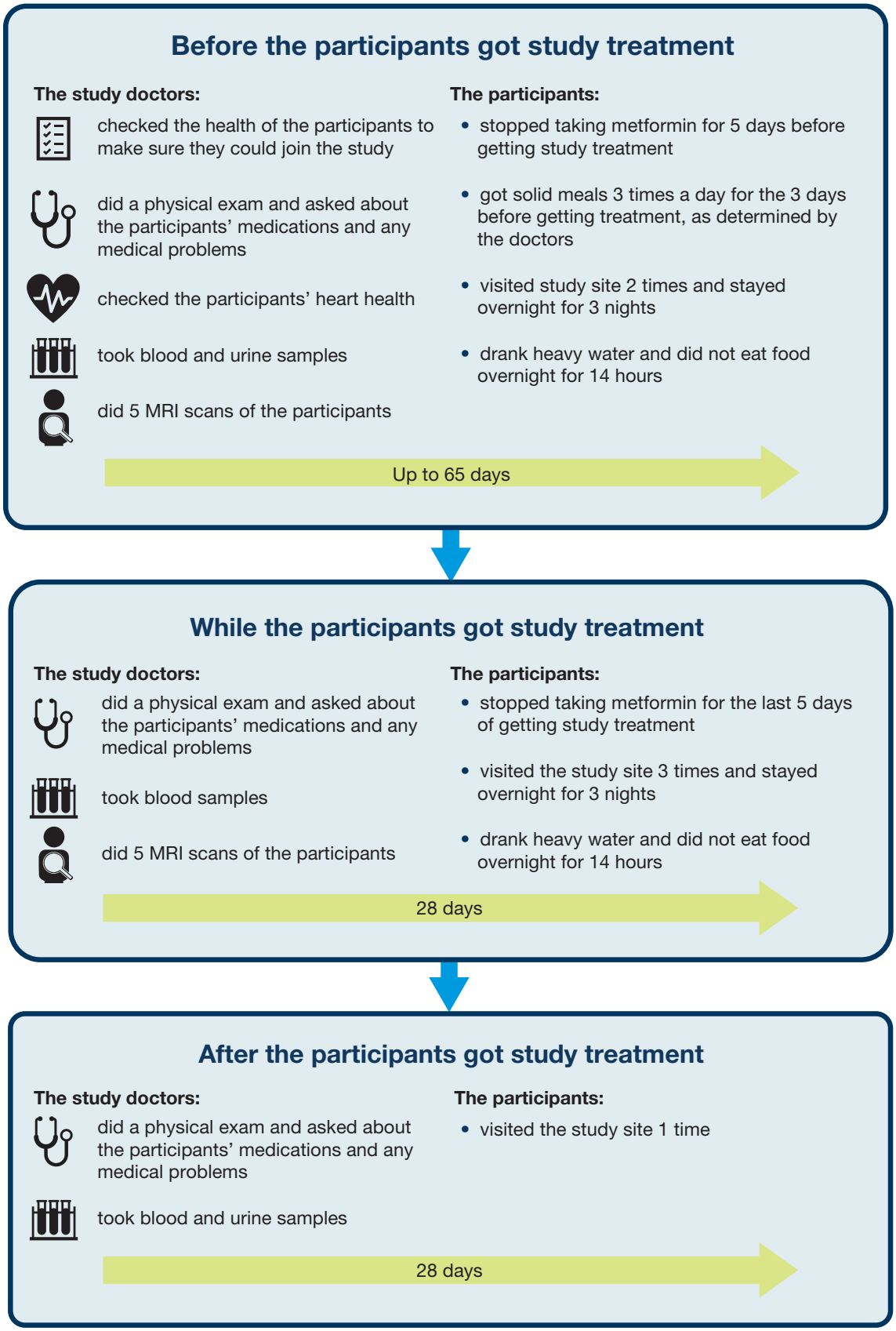
	Group 1	Group 2
	12 participants	9 participants
	MEDI0382, as an injection under the skin • 100 µg for 7 days, then • 200 µg for 7 days, then • 300 µg for 14 days	Placebo, as an injection under the skin
	Once a day for 28 days	

What happened during this study?

This study was done in 2 parts, called Part A and Part B. This summary is for Part A. The participants in Part A were not in Part B.

The participants were in Part A for about 4 months. But, the entire study for both parts took about 3 years to finish. The study started in May 2018 and ended in April 2021.

The chart below shows what happened during the study.



What were the results of this study?

This is a summary of the main results from Part A of this study overall. The results each participant had might be different and are not in this summary. A full list of the questions that researchers wanted to answer can be found on the websites listed at the end of this summary. When a full report of the study results is available, it can also be found on these websites.

Researchers look at the results of many studies to decide which treatments work best and are safest. Other studies may provide new information or different results. Always talk to a doctor before making any treatment changes.

Did the participants' glycogen levels in the liver change after receiving MEDI0382?

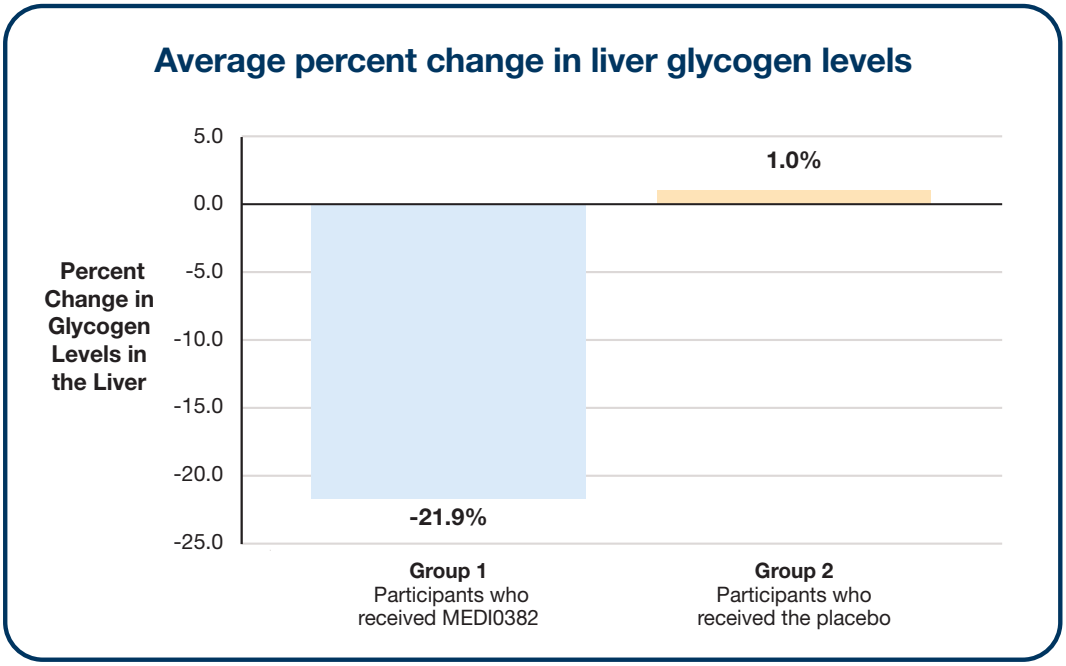
Yes. Overall, the researchers found that the glycogen levels changed more in the participants who received MEDI0382 compared with the participants who received the placebo. The participants who received MEDI0382 had a **decrease** in glycogen in the liver, compared with the participants who got the placebo. This means that MEDI0382 works in a similar way to **glucagon** in the liver.

To answer this question, the researchers measured the level of glycogen in the participants' livers before they received any study treatment and again after they received study treatment for 28 days. The researchers took several measurements of glycogen across a 24-hour time period after the participants had their morning meal. For the results below, the researchers used the glycogen measurement taken 4 hours after the morning meal, before and after receiving treatment. The researchers compared the levels to see how much the participants' glycogen levels changed after getting study treatment. The researchers did this by calculating the average percentage of change in glycogen levels.

The average percentage that the participants' glycogen levels changed was:

- **–21.9%** for the participants who received **MEDI0382**. This means that, overall, the participants who received MEDI0382 had their liver glycogen levels **decrease** by 21.9%.
- **1.0%** for the participants who received the **placebo**. This means that, overall, the participants who received the placebo had their liver glycogen levels **increase** by 1.0%.

The graph below shows these results.



What medical problems happened during this study?

This section is a summary of the medical problems the participants had during the study that the study doctors thought might be related to the study drug. These medical problems are called "adverse reactions". An adverse reaction is considered "serious" when it is life-threatening, causes lasting problems, or requires hospital care.

These adverse reactions may or may not be caused by the study drug. A lot of research is needed to know whether a drug causes an adverse reaction. These adverse reactions have been, and will continue to be, reviewed together with all of the available data for MEDI0382.

The websites listed at the end of this summary may have other information about adverse reactions or other medical problems that happened during this study.

Did any adverse reactions happen during this study?

	All participants (out of 21 participants)
How many participants had adverse reactions?	76.2% (16)
How many participants had serious adverse reactions?	0.0% (0)
How many participants stopped getting study treatment due to adverse reactions?	9.5% (2)

What serious adverse reactions happened during this study?

No serious adverse reactions happened during this study.

What adverse reactions happened during this study?

The table below shows the most common adverse reactions. These adverse reactions happened in 2 or more participants. There were other adverse reactions, but these happened in fewer participants.

Most Common Adverse Reactions

Adverse reaction	All participants (out of 21 participants)
Nausea	47.6% (10)
Indigestion	38.1% (8)
Feeling tired	33.3% (7)
Vomiting	28.6% (6)
Decreased appetite	19.0% (4)
Headache	19.0% (4)
Constipation	14.3% (3)
Dizziness	14.3% (3)
Diarrhea	9.5% (2)
Excessive sweating	9.5% (2)
Pain in the belly	9.5% (2)

How has this study helped patients and researchers?

This study helped researchers learn more about how MEDI0382 works in the liver in people with T2DM who were also overweight and were likely to have NAFLD/NASH.

Researchers look at the results of many studies to decide which treatments work best and are safest. This summary shows only the main results from this one study. Other studies may provide new information or different results.

Further clinical studies with MEDI0382 are planned.

Where can I learn more about this study?

You can find more information about this study on the websites listed below. If more information about the study results is available, it can also be found here.

- www.clinicaltrials.gov Once you are on the website, type **"NCT03555994"** into the search box and click **"Search"**.
- www.clinicaltrialsregister.eu Once you are on the website, click **"Home and Search"**, then type **"2017-005081-22"** in the search box and click **"Search"**.
- www.AstraZenecaClinicalTrials.com Once you are on the website, type **"D5670C00022"** into the search box and click **"Find a Study"**.

Full Study Title: An Exploratory Phase 2, Randomised, Double-blind, Placebo-controlled, and Open-label Active Comparator Study to Evaluate the Effect of MEDI0382 on Hepatic Glycogen Metabolism in Overweight and Obese Subjects with Type 2 Diabetes Mellitus

AstraZeneca Protocol Number: D5670C00022

National Clinical Trials Number: NCT03555994

EudraCT Number: 2017-005081-22

AstraZeneca UK sponsored this study and has its headquarters in Cambridge, UK.

The phone number for the AstraZeneca Information Center is +1-877-240-9479.

Thank you

Clinical study participants belong to a large community of people who take part in clinical research around the world. They help researchers answer important health questions and find medical treatments for patients.

CISCRP

The Center for Information & Study on Clinical Research Participation (CISCRP) is a non-profit organization focused on educating and informing the public about clinical research participation. CISCRP is not involved in recruiting participants for clinical studies, nor is it involved in conducting clinical studies.

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