Clinical Study Results

This summary reports the results of only one study. Researchers must look at the results of many types of studies to understand if a study medication works, how it works, and if it is safe to prescribe to patients. The results of this study might be different than the results of other studies that the researchers review.

Sponsor: Pfizer Inc.

Medicine(s) Studied: Danuglipron (PF-06882961)

Protocol Number: C3421008

Dates of Study: 6 January 2021 to 17 November 2021

Title of this Study: A 12-Week Study to Evaluate the Safety, Tolerability and Effects of danuglipron in Adults With Type 2 Diabetes Mellitus Treated With Metformin and Non-Diabetic Adults With Obesity

[A 12-Week, Phase 2A, Randomized, Double-Blind, Sponsor-Open, Placebo-Controlled, Parallel Group Study to Assess the Safety, Tolerability, and Pharmacodynamics of PF-06882961 Titration in Adults With Type 2 Diabetes Mellitus Treated With Metformin and in Non-Diabetic Adults With Obesity]

Date(s) of this Report: 21 June 2022; amended 24 August 2022

– Thank You –

If you participated in this study, Pfizer, the Sponsor, would like to thank you for your participation. This summary will describe the study results. If you have any questions about the study or the results, please contact the doctor or staff at your study site.

Why was this study done?

What are Type 2 Diabetes Mellitus and Obesity?

Type 2 diabetes mellitus (T2DM) is a common form of diabetes where the body does not make enough insulin, or their body cannot use the insulin it makes properly. Over time, T2DM can cause higher than normal levels of sugar in the blood (hyperglycemia) which can harm the health of people with T2DM. People with T2DM are more likely to develop problems with their kidneys, heart, eyes, and nerves. Obesity is a condition in which there is a build-up of body fat to such an extent that it may have a negative effect on health. Obesity can increase the risk of developing T2DM and can cause other types of stress on the body.

What is danuglipron?

Danuglipron (dah-noog-lih-pron, PF-06882961) is an experimental medicine that is taken by mouth and is not yet approved for use by health authorities. Danuglipron stimulates the glucagon-like peptide 1 receptor and may help lower blood sugar levels by increasing insulin secretion. It also increases the feeling of fullness and lowers food intake.

What was the purpose of this study?

The purpose of this study was to learn about the safety and tolerability (impact of danuglipron on the body) of different dosing levels of danuglipron in participants with T2DM treated with metformin and in participants with obesity, without T2DM. Researchers then compared the results of taking danuglipron to the results of taking a placebo to see if there were any differences. The placebo looks like danuglipron but does not contain any active ingredients.

Researchers also wanted to measure the participants' bodies' response to danuglipron by:

- Measuring blood, including glycosylated hemoglobin or HbA1c and blood glucose to see if they change.

- Seeing how well participants tolerated danuglipron as the dose increased gradually over time and whether there were any side effects of taking danuglipron.
- Measuring blood levels of the study drug to see if there were any differences.

Researchers wanted to know:

How many participants in the T2DM group and the obesity (without T2DM) group had medical problems after taking danuglipron when compared to taking placebo and what was the severity of these medical problems?

What happened during the study?

How was the study done?

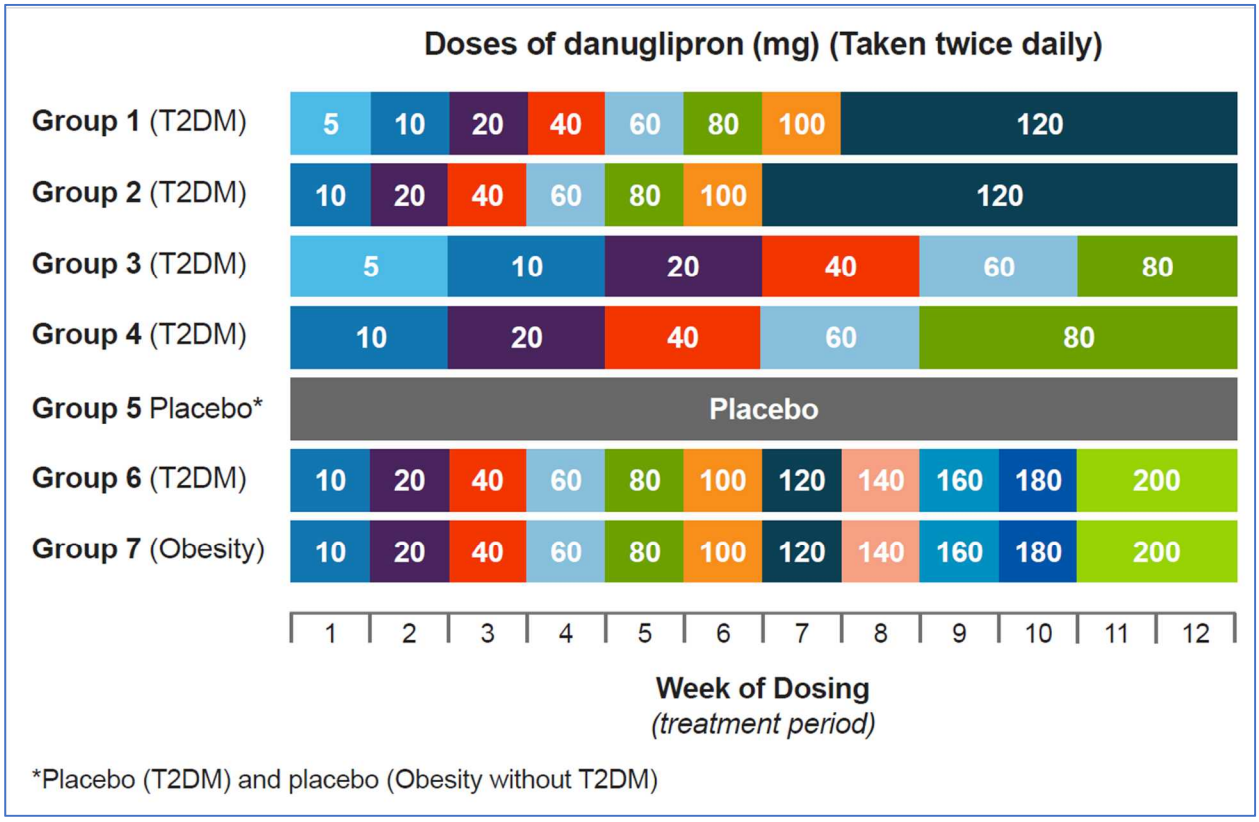
Researchers tested different doses of danuglipron on a group of adult participants with T2DM being treated with metformin and a group of adult participants with obesity but without T2DM to compare the number of participants in both groups who had medical problems and the severity of these medical problems.

Participants with T2DM were put into 1 of 6 treatment groups by chance alone, like the flip of a coin. This is known as a "randomized" study. Randomization is done to make the groups more similar for characteristics like age and sex. In 5 groups the T2DM participants received danuglipron and in 1 group participants received the placebo. Participants with obesity (without T2DM) were put into 1 of 2 treatment groups also by chance. In 1 group the obesity participants received danuglipron and in the other group participants received the placebo.

Participants in all 6 groups that received danuglipron were given the study medicine at a low starting dose (5 mg of danuglipron) or high starting dose (10 mg of danuglipron) and the dose was increased every 1 or 2 weeks to reach different target doses (80 mg, 120 mg, or 200 mg of danuglipron), depending on which group they were put into.

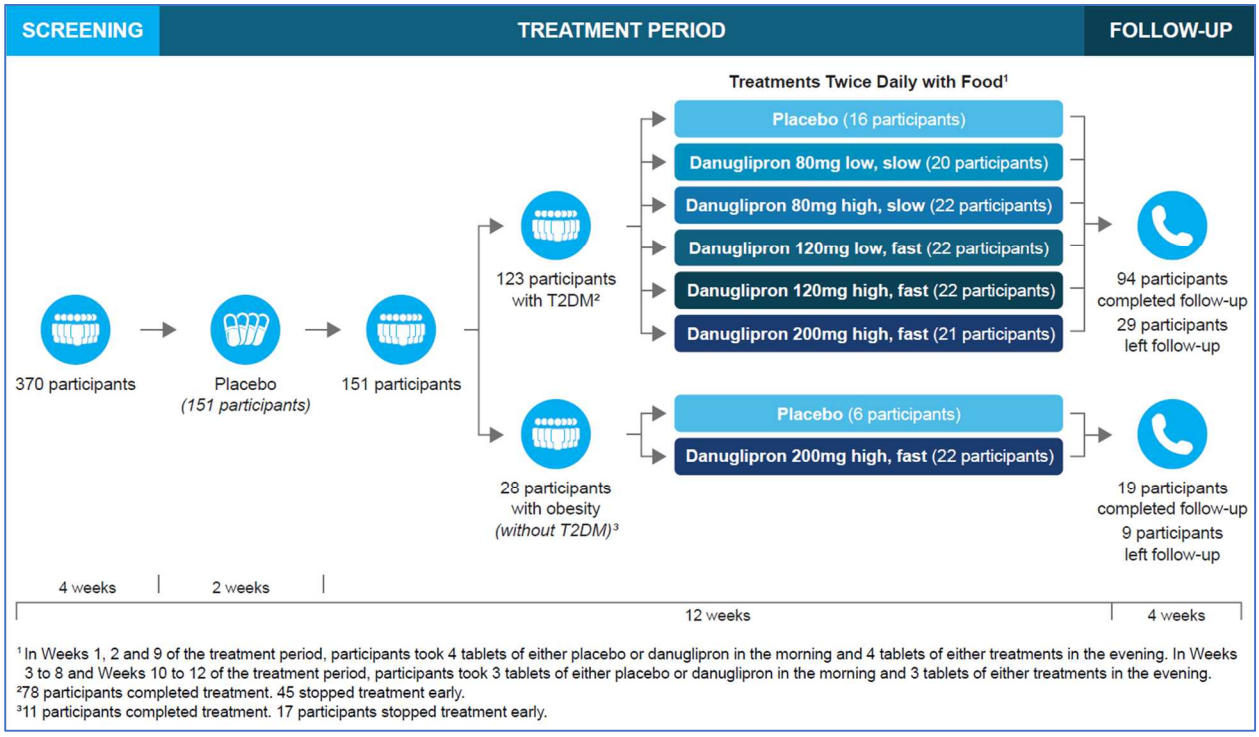
For example, participants in Group 1 were given a low starting dose of danuglipron (5 mg), which doubled every week to reach the target dose of 120 mg; these are fast titration steps. A shortened format for this is "danuglipron X mg Y, Z" where X is the target dose, Y is the low or high starting dose, and Z is the fast or slow titration steps.

The steps involving dose increases with the corresponding groups are shown in more detail in the image below.



After the screening period, all participants took placebo for around 2 weeks. Participants then began taking danuglipron or placebo twice daily for 12 weeks based on which treatment group they were randomized into. This part of the study was "double-blinded". This means the participants and study doctors did not know who was given which treatment during this part of the study. Researchers use "double-blinded" studies to make sure that the results of the study were not influenced in any way. Finally, participants completed a follow-up visit which lasted 4 weeks after taking their last dose of danuglipron or placebo.

The study design is shown in the image below.



[1] In Weeks 1, 2 and 9 of the treatment period, participants took 4 tablets of either placebo or danuglipron in the morning and 4 tablets of either treatments in the evening. In Weeks 3 to 8 and Weeks 10 to 12 of the treatment period, participants took 3 tablets of either placebo or danuglipron in the morning and 3 tablets of either treatments in the evening.
[2] 78 participants completed treatment. 45 stopped treatment early.
[3] 11 participants completed treatment. 17 participants stopped treatment early.

The 6 danuglipron dose groups and placebo group are detailed below; all doses were administered twice daily over 12 weeks:

- Group 1 (T2DM): starting dose of 5 mg of danuglipron with dose increased weekly to 120 mg of danuglipron (120 mg low, fast).
- Group 2 (T2DM): starting dose of 10 mg of danuglipron with dose increased weekly to 120 mg of danuglipron (120 mg high, fast).
- Group 3 (T2DM): starting dose of 5 mg of danuglipron with dose increased every 2 weeks to 80 mg of danuglipron (80 mg low, slow).
- Group 4 (T2DM): starting dose of 10 mg of danuglipron with dose increased every 2 weeks to 80 mg of danuglipron (80 mg high, slow).
- Group 5: placebo (T2DM) and placebo (obesity without T2DM)
- Group 6 (T2DM): starting dose of 10 mg with dose increased weekly to 200 mg of danuglipron (200 mg high, fast).
- Group 7 (obesity without T2DM): starting dose of 10 mg with dose increased weekly to 200 mg of danuglipron (200 mg high, fast).

Where did this study take place?

The Sponsor ran this study at 38 locations in the United States.

When did this study take place?

It began 6 January 2021 and ended 17 November 2021.

Who participated in this study?

The study included participants who had T2DM who were being treated with metformin and participants with obesity but without T2DM.

- A total of 73 men participated

- A total of 78 women participated
- All participants were between the ages of 21 to 75

Participants were to be treated until the end of the 12-week treatment period. There were a total 151 participants who were treated with danuglipron or placebo, of which 123 participants had T2DM and 28 participants had obesity (without T2DM).

In the T2DM group:

A total of 45 participants (37%) did not finish the double-blind treatment period. The most common reason for not finishing the treatment period was because of medical problems (32 participants [26%]). Of the 29 participants (24%) who did not finish the follow-up period, the most common reason was because of medical problems (14 participants [11%]).

In the Obesity (without T2DM) group:

A total of 17 participants (61%) did not finish the double-blind treatment period. The most common reason for not finishing the treatment period was because of medical problems (12 participants [43%]). Of the 9 participants (32%) who did not finish the follow-up period, the most common reasons were because of medical problems, the participants left by choice and the participants were lost to follow-up (3 participants each [11%]).

How long did the study last?

Study participants were in the study for 22 weeks. The entire study took just over 10 months to complete.

When the study ended in November 2021, the Sponsor began reviewing the information collected. The Sponsor then created a report of the results. This is a summary of that report.

What were the results of the study?

How many participants in the T2DM group and the obesity (without T2DM) group had medical problems after taking danuglipron when compared to taking placebo and what was the severity of these medical problems?

In the T2DM Group

Of the 123 participants with T2DM, the 3 most common medical problems reported by participants were nausea (35 out of 123 [28%] participants), vomiting (32 out of 123 [26%] participants) and diarrhoea (16 out of 123 [13%] participants). In participants who took danuglipron, the range of nausea varied from 20% to 48% across the different groups (Groups 1 to 4 and Group 6), compared to 13% with participants who took the placebo (Group 5). The range of vomiting varied from 18% to 41% across the different groups (Groups 1 to 4 and Group 6), compared to 13% with participants who took the placebo (Group 5). The range of diarrhoea varied from 5% to 23% across the different groups (Groups 1 to 4 and Group 6), compared to 13% with participants who took the placebo (Group 5).

There was a total of 247 medical problems reported by participants with T2DM. Of the 247 medical problems, 172 (70%) were of mild intensity. There were 68 out of 247 (28%) medical problems that were of moderate intensity. There were 7 out of 247 (3%) severe medical problems.

In the Obesity (without T2DM) group

Of the 28 participants with obesity (without T2DM), the 3 most common medical problems reported by participants were nausea (13 out of 28 [46%] participants), vomiting (10 out of 28 [36%] participants) and dizziness (4 out of 28 [14%] participants). In participants who took danuglipron (Group 7), 59% of participants reported nausea, 45% of participants reported vomiting and 18% of

participants reported dizziness. No participants reported nausea, vomiting and dizziness in the placebo group (Group 5).

There was a total of 57 medical problems reported by participants with obesity (without T2DM). Of the 57 medical problems, 33 (58%) were of mild intensity. There were 23 out of 57 (40%) medical problems that were of moderate intensity. There was 1 out of 57 (2%) severe medical problem.

Danuglipron may be considered generally safe and tolerable for participants with T2DM and participants with obesity (without T2DM).

This does not mean that everyone in this study had these results. This is a summary of just some of the main results of this study. Other studies may have different results.

What medical problems did participants have during the study?

The researchers recorded any medical problems the participants had during the study. Participants could have had medical problems for reasons not related to the study (for example, caused by an underlying disease or by chance). Or, medical problems could also have been caused by a study treatment or by another medicine the participant was taking. Sometimes the cause of a medical problem is unknown. By comparing medical problems across many treatment groups in many studies, doctors try to understand what effects a study medication might have on a participant.

The 3 most common medical problems reported by participants with T2DM were nausea, vomiting and diarrhoea. The 3 most common medical problems reported by participants with obesity (without T2DM) were nausea, vomiting and dizziness.

A total of 79 out of 123 participants (64%) in the T2DM group had at least 1 medical problem. A total of 18 T2DM participants (15%) stopped study treatment but

continued in the study, and 14 T2DM participants (11%) left the study because of medical problems.

A total of 22 out of 28 participants (79%) in the obesity (without T2DM) group had at least 1 medical problem. A total of 9 participants (32%) stopped study treatment but continued in the study, and 3 participants (11%) left the study because of medical problems.

The most common medical problems –reported by more than 10% of participants with T2DM are shown in Table 1 in page 11 and more than 10% of participants with obesity (without T2DM) in Table 2 in page 12.

Below are instructions on how to read Table 1 and Table 2

Instructions for Understanding Table 1 and Table 2.

- The **1st** column of Tables 1 and 2 lists medical problems that were commonly reported during the study in either the T2DM group or obesity (without T2DM) group. All medical problems reported by more than 10% of participants are listed in both tables.
- The **2nd -7th** columns in Table 1 and the **2nd-3rd** columns in Table 2 tell how many of the participants in each treatment group (treated with danuglipron or placebo) reported each medical problem. Next to this number is the percentage of the participants taking danuglipron or placebo who reported the medical problem.
- Using these instructions, you can see that in the T2DM group, 4 out of the 20 participants (20%) who took danuglipron 80 mg (low, slow) reported nausea. A total of 2 out of the 16 (13%) participants taking a placebo reported nausea.

Table 1. Commonly reported medical problems by study participants in the T2DM group

	Danuglipron					Placebo
Medical Problem	**Group 3** **80 mg low, slow** **20 Participants**	**Group 4** **80 mg high, slow** **22 Participants**	**Group 1** **120 mg low, fast** **22 Participants**	**Group 2** **120 mg high, fast** **22 Participants**	**Group 6** **200 mg high, fast** **21 Participants**	**Group 5** **Placebo** **16 Participants**
Nausea	4 out of 20 participants (20%)	5 out of 22 participants (23%)	6 out of 22 participants (27%)	8 out of 22 participants (36%)	10 out of 21 participants (48%)	2 out of 16 participants (13%)
Diarrhoea	2 out of 20 participants (10%)	1 out of 22 participants (5%)	5 out of 22 participants (23%)	5 out of 22 participants (23%)	1 out of 21 participants (5%)	2 out of 16 participants (13%)
Vomiting	5 out of 20 participants (25%)	4 out of 22 participants (18%)	6 out of 22 participants (27%)	9 out of 22 participants (41%)	6 out of 21 participants (29%)	2 out of 16 participants (13%)
Belly pain above the belly button	1 out of 20 participants (5%)	3 out of 22 participants (14%)	2 out of 22 participants (9%)	1 out of 22 participants (5%)	0 out of 21 participants (0%)	1 out of 16 participants (6%)
Indigestion	1 out of 20 participants (5%)	1 out of 22 participants (5%)	2 out of 22 participants (9%)	5 out of 22 participants (23%)	1 out of 21 participants (5%)	0 out of 16 participants (0%)
Decreased appetite	1 out of 20 participants (5%)	2 out of 22 participants (9%)	4 out of 22 participants (18%)	1 out of 22 participants (5%)	4 out of 21 participants (19%)	1 out of 16 participants (6%)
Low blood sugar levels	1 out of 20 participants (5%)	3 out of 22 participants (14%)	0 out of 22 participants (0%)	3 out of 22 participants (14%)	1 out of 21 participants (5%)	1 out of 16 participants (6%)

Headache	1 out of 20 participants (5%)	3 out of 22 participants (14%)	1 out of 22 participants (5%)	1 out of 22 participants (5%)	0 out of 21 participants (0%)	1 out of 16 participants (6%)

Did study participants have any serious medical problems?

A medical problem is considered "serious" when it is life-threatening, needs hospital care, or causes lasting problems.

No participants in either the T2DM or the obesity (without T2DM) groups had serious medical problems.

No participants died during the study.

Table 2. Commonly reported medical problems by study participants in the Obesity (without T2DM) group

Medical Problem	Group 7 Danuglipron 200 mg high, fast 22 participants	Group 5 Placebo 6 participants
Nausea	13 out of 22 participants (59%)	0 out of 6 participants (0%)
Vomiting	10 out of 22 participants (45%)	0 out of 6 participants (0%)
Belly pain above the belly button	3 out of 22 participants (14%)	0 out of 6 participants (0%)
Dizziness	4 out of 22 participants (18%)	0 out of 6 participants (0%)

Where can I learn more about this study?

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

The full scientific report of this study is available online at:

www.clinicaltrials.gov
www.pfizer.com/research/research_clinical_trials/trial_results

Use the study identifier **NCT04617275**
Use the protocol number **C3421008**

Please remember that researchers look at the results of many studies to find out which medicines can work and are safe for study patients.

Again, if you participated in this study,
thank you for volunteering.
We do research to try to find the best ways to help patients, and you helped us to do that!