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 Studied: PF-07081532 (lotiglipron)

Protocol Number: C3991004

Dates of Study: 27 October 2022 to 22 September 2023

Title of this Study: Trial to Learn About the Study Medicine (PF-07081532) and Rybelsus® in People With Type 2 Diabetes Mellitus and Separately PF-07081532 in People With Obesity

[A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Dose-Ranging, Dose-Finding, Parallel Group Study to Assess Efficacy and Safety of PF-07081532, and Open-Label Oral Semaglutide, in Adults With Type 2 Diabetes Mellitus (T2DM) Inadequately Controlled on Metformin, and Separately PF-07081532 Compared to Matching Placebo in Adults With Obesity but Without T2DM]

Date of this Report: 01 April 2024

– 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. Over time, this can cause higher than normal levels of sugar in the blood. This may harm the health of the person with T2DM.

Insulin is a hormone or chemical messenger that controls the amount of sugar in the blood after eating. A person with T2DM either does not make enough insulin or their body cannot properly use the insulin it makes. Every person needs some sugar in the blood as their body uses this sugar for energy. If a person has T2DM, and there is too much sugar in their blood, this can cause lots of different health problems, including stroke, and may even lead to death.

Some people with T2DM can control the amount of sugar in their blood with diet, but others will need medicine to help them do this.

Obesity is a medical condition. It is seen when a person has excessive or too much body fat that is damaging to their health. Obesity can increase the risk of developing T2DM.

What is lotiglipron?

Lotiglipron is also known as PF-07081532. It is an investigational medicine, which means it is not approved for use outside of research studies. It is taken by mouth.

Lotiglipron is a type of medicine known as a “glucagon-like peptide 1 receptor agonist”. Medicines of this type may help to:

- Keep blood sugar at healthy levels by increasing the amount of insulin released in the blood.
- Slow down the digestion of food and may increase the feeling of fullness after eating. This may lower food intake.

Researchers thought that lotiglipron may help lower blood sugar levels and reduce body weight if taken with proper diet and exercise. However, based on safety concerns and how lotiglipron acted in the body as observed in participants from this study and 2 other studies (C3991040 and C3991047) with lotiglipron, the Sponsor decided to stop this study and the development of lotiglipron.

What was the purpose of this study?

The main purpose of this study was to see if different doses of lotiglipron could:

- **Decrease blood sugar levels** in participants who have T2DM poorly controlled with metformin (Group 1).

  Metformin is a medicine approved to help control sugar levels in the blood.

- **Decrease body weight** in participants who have obesity without T2DM while continuing their diet and exercise (Group 2).

Researchers wanted to know:

- **Did participants with T2DM have lower blood sugar levels after taking lotiglipron for 32 weeks?**
- **Did participants with obesity lose weight after taking lotiglipron for 32 weeks?**
- **What medical problems did participants have during the study?**

What happened during the study?

How was the study done?

Lotiglipron was tested in 2 groups of study participants to find out if it could help participants with T2DM (Group 1) or obesity (Group 2). Semaglutide in tablet form taken by mouth (Rybelsus®) was given to some participants with T2DM for comparison.

> Rybelsus® is a medicine approved to treat T2DM.

Before participants were assigned a study treatment, they all took placebo for 2 weeks during the “run-in” period. During this period, researchers monitored the participants to make sure that participants were taking placebo properly as instructed.

> A **placebo** does not have any medicine in it. Placebo for this study looked like lotiglipron.

Participants in each group were assigned a study treatment, which was taken 1 time daily in the morning.

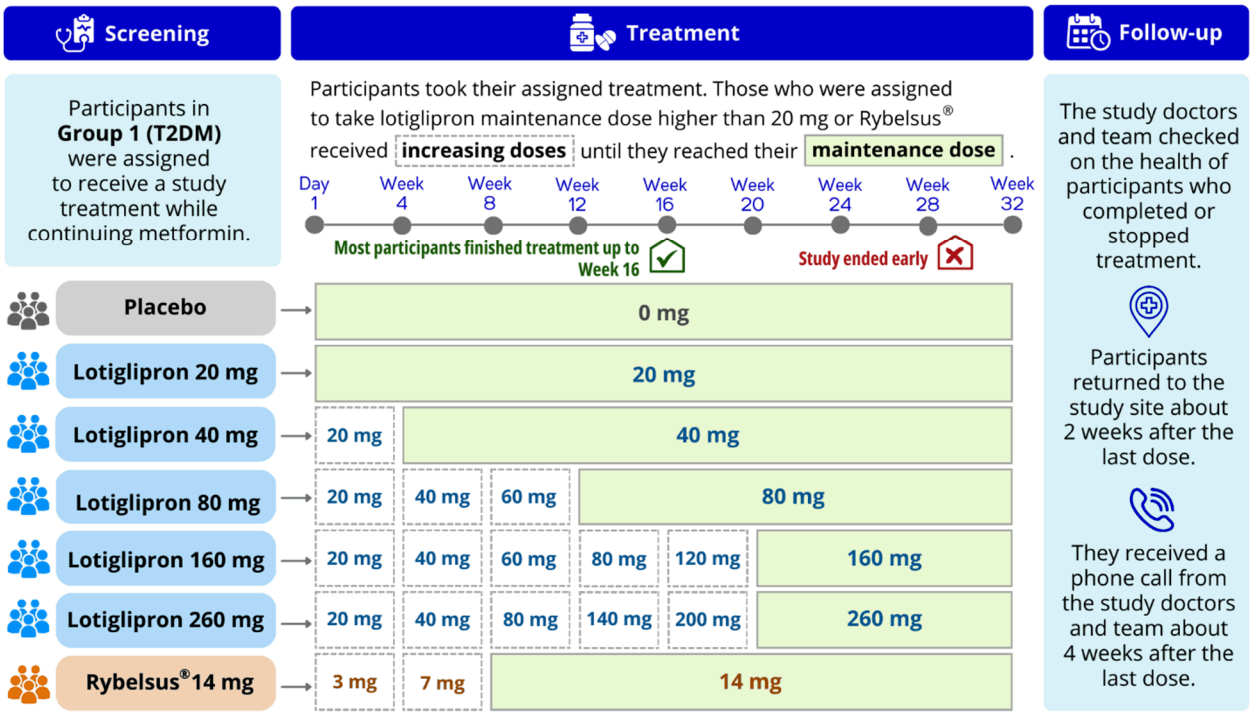
Group 1:	Group 2:
Participants with **T2DM** were assigned by chance to take 1 of 7 study treatments: • **Lotiglipron** in 1 of 5 dose levels with the final dose ("maintenance dose") ranging from 20 to 260 milligrams (mg), • **Placebo**, or • **Rybelsus**® 14 mg	Participants with **obesity** were assigned by chance to take 1 of 6 study treatments: • **Lotiglipron** in 1 of 5 dose levels with the maintenance dose ranging from 80 to 260 mg, or • **Placebo**

Most participants were to take their study treatment for 32 weeks. The first set of participants who signed up were to take their study treatment for about 44 weeks. As shown in Figures 1 and 2 below:

- Participants in Group 1 (Figure 1) who were assigned to take lotiglipron 20 mg as the maintenance dose took this dose throughout the treatment period.
- For those assigned to take a maintenance dose of lotiglipron higher than 20 mg in Groups 1 and 2 (Figures 1 and 2), the starting dose was 20 mg for the first 4 weeks. The dose was increased every 4 weeks until participants reached their assigned maintenance dose, which they took for the remainder of the treatment period.
- For those assigned to take Rybelsus® in Group 1 (Figure 1), the starting dose was 3 mg for the first 4 weeks. The dose was increased to 7 mg for the next 4 weeks. Thereafter, participants took the 14-mg maintenance dose.

Figure 1 below shows what happened to Group 1 participants in this study.

Figure 1. How was the study planned for Group 1?



Group 1 (T2DM) – When the study ended:

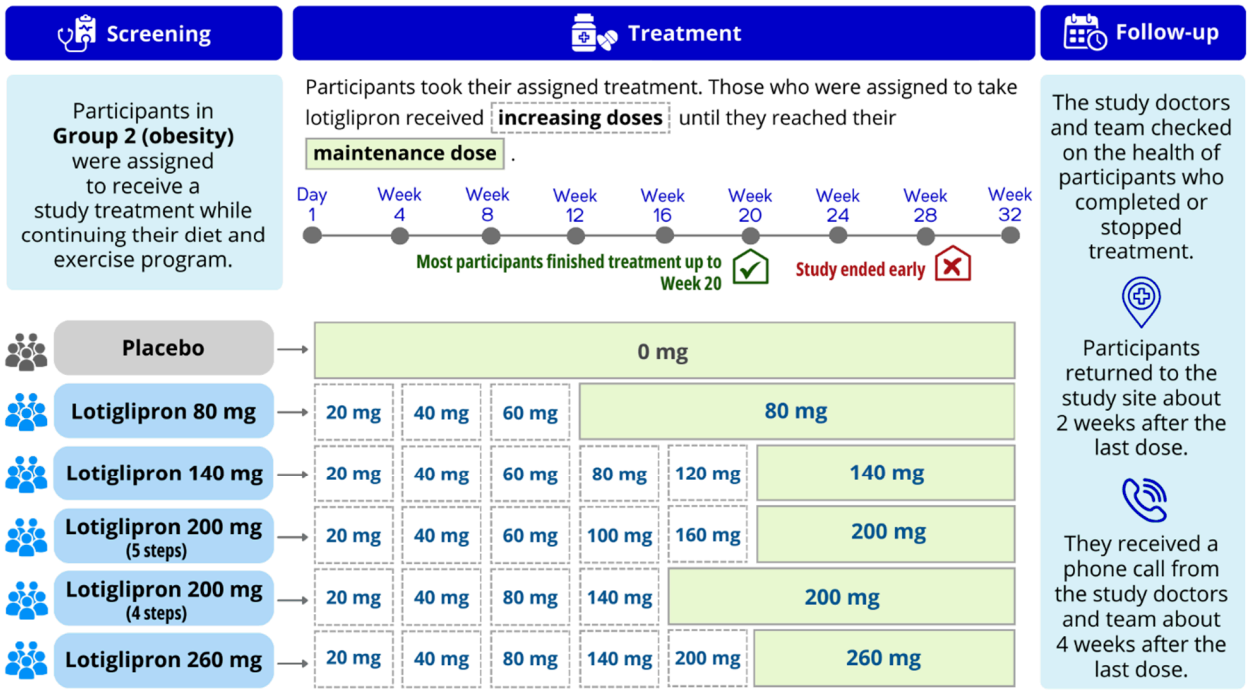
- At least 85% of participants in the 20 mg, 40 mg, and 80 mg lotiglipron groups and 14 mg Rybelsus® group reached their assigned maintenance dose.
- At least 8% of participants in the 160 mg and 260 mg lotiglipron groups reached their assigned maintenance dose.

The table below shows how many participants in Group 1 reached their maintenance dose when the study ended:

Placebo	Lotiglipron 20 mg	Lotiglipron 40 mg	Lotiglipron 80 mg	Lotiglipron 160 mg	Lotiglipron 260 mg	Rybelsus® 14 mg
75 out of 75 participants (100%)	73 out of 73 participants (100%)	71 out of 72 participants (99%)	62 out of 73 participants (85%)	7 out of 72 participants (10%)	6 out of 74 participants (8%)	70 out of 73 participants (96%)

Figure 2 below shows what happened to Group 2 participants in this study.

Figure 2. How was the study planned for Group 2?



Group 2 (Obesity) – When the study ended:

- At least 80% of participants in the 80 mg lotiglipron group reached their assigned maintenance dose.
- At least 44% of participants in the 140 mg, 200 mg (5 steps and 4 steps), and 260 mg lotiglipron groups reached their assigned maintenance dose.

The table below shows how many participants in Group 2 reached their maintenance dose when the study ended:

Placebo	Lotiglipron 80 mg	Lotiglipron 140 mg	Lotiglipron 200 mg (5 steps)	Lotiglipron 200 mg (4 steps)	Lotiglipron 260 mg
64 out of 64 participants (100%)	53 out of 66 participants (80%)	37 out of 64 participants (58%)	38 out of 65 participants (59%)	43 out of 66 participants (65%)	28 out of 64 participants (44%)

Throughout the study for Groups 1 and 2, the researchers monitored each participant's health. Participants had blood tests and other health checks done.

For Groups 1 and 2, the results in participants taking lotiglipron were compared to the results in participants taking placebo. For Group 1, the results in participants taking Rybelsus® were also compared to the results in participants taking placebo.

- Participants and researchers did not know who took lotiglipron and who took placebo. This is known as a "blinded" study.
- Participants and researchers knew if participants were taking Rybelsus®.

Where did this study take place?

The Sponsor ran this study at 78 locations in 7 countries.

- Bulgaria
- Canada
- Czech Republic
- Hungary
- Japan
- Poland
- United States, including Puerto Rico

When did this study take place?

It began on 27 October 2022 and ended on 22 September 2023.

Who participated in this study?

The study included 2 groups of adult participants who met different requirements:

- **Group 1:** Participants who have T2DM poorly controlled with metformin.
- **Group 2:** Participants who have obesity based on their body mass index who did not have T2DM.

In total, 902 participants joined this study and 901 took study treatment.

Group 1:

512 participants with **T2DM** took study treatment:

- 280 (55%) men and 232 (45%) women participated.
- Participants were 28 to 76 years old.

Group 2:

389 participants with **obesity** took study treatment:

- 152 (39%) men and 237 (61%) women participated.
- Participants were 18 to 76 years old.

None of the participants finished the treatment period. The most common reason for this was because the Sponsor ended the study early due to safety concerns that are explained on the next page.

A total of 42 participants did not finish the follow-up period.

- 21 participants could not be reached when contacted for follow-up.
- 20 participants left by their choice before the study was ended early.
- 1 participant, who took placebo in Group 1, died from cardiac arrest, which is when the heart suddenly stops beating.

How long did the study last?

It was planned for participants to be in the study for about 36 to 48 weeks. The entire study ran for about 47 weeks before it was ended early.

When the study ended in September 2023, the Sponsor began reviewing the information collected. The Sponsor then created a report of the results. This is a summary of that report.

The Sponsor decided to stop this study and the development of lotiglipron. This was because of safety concerns and how lotiglipron acted in the body as observed in participants from this study and 2 other studies (C3991040 and C3991047) with lotiglipron.

Across these 3 studies:

- Some participants were observed to have high levels of liver enzymes in their blood, such as alanine aminotransferase (ALT) and aspartate aminotransferase (AST). High levels of these liver enzymes may be a sign of a medical condition like liver disease or liver injury.
- Some participants had unexpectedly high amounts of lotiglipron in their blood. This may have been caused by lotiglipron reducing the ability of the liver to break down medicines, including lotiglipron, in the body.
- No participant had liver failure, and no participant with high levels of liver enzymes needed medications.

After the Sponsor's decision to stop this study and the development of lotiglipron, all participants were instructed to stop taking the study treatment and to finish their follow-up visits. Participants with high levels of liver enzymes had follow-up checkups until their liver enzymes decreased and became similar to levels before their first dose of study treatment.

What were the results of the study?

Did participants with T2DM have lower blood sugar levels after taking lotiglipron for 32 weeks?

Did participants with obesity lose weight after taking lotiglipron for 32 weeks?

It was not possible to answer these 2 questions because the study ended before participants could complete 32 weeks of treatment.

However, researchers noted the following results before Week 32:

- **Group 1 (T2DM):**
  After 16 weeks of treatment, a larger decrease in blood sugar levels was seen in participants on lotiglipron and those on Rybelsus® compared to those on placebo.
- **Group 2 (Obesity):**
  After 20 weeks of treatment, a larger decrease in body weight was seen in participants on lotiglipron compared to those on placebo.

Because this study ended earlier than planned, the results described above do not tell us if lotiglipron could help participants with T2DM or participants with obesity.

No future studies are planned with lotiglipron because of safety concerns and how lotiglipron acted in the body as observed in participants from this study and 2 other studies with lotiglipron.

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.

Overall, researchers found that:

- Lotiglipron was better tolerated by participants with T2DM (Group 1) than by participants with obesity (Group 2).
- In 5% of participants in this study, high levels of liver enzymes in the blood were observed when lotiglipron was taken at repeated doses of 40 mg or higher.

Because of safety concerns and how lotiglipron acted in the body as observed in participants from this study and 2 other studies with lotiglipron, the Sponsor decided to stop this study and the development of lotiglipron.

Group 1 (T2DM):

During the study, 303 out of 512 participants (59.2%) in Group 1 had at least 1 medical problem.

A total of 51 participants (10.0%) stopped taking the study treatment because of medical problems. One (1) participant (0.2%) left the study because of medical problems.

Group 2 (Obesity):

During the study, 317 out of 389 participants (81.5%) in Group 2 had at least 1 medical problem.

A total of 97 participants (24.9%) stopped taking the study treatment because of medical problems. Two (2) participants (0.5%) left the study because of medical problems.

The most common medical problems – those reported by more than 5% of participants in the total group – are listed in the tables below.

- Table 1 for Group 1 (participants with T2DM)
- Table 2 for Group 2 (participants with obesity)

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

Instructions for Understanding Table 1 and Table 2.

- The **1st** column of each table lists medical problems that were commonly reported in Group 1 (**Table 1**) and Group 2 (**Table 2)** during the study. All medical problems reported by more than 5% of participants in the total group are listed.

- The **next** columns up to the **2nd** to the last column tell how many of the participants taking placebo, different doses of lotiglipron, or Rybelsus® (only Group 1, Table 1) reported each medical problem. Next to these numbers are the percentages of these participants who reported the medical problem.
- The **last** column tells how many of the participants overall, across the different treatment groups shown in the previous columns, reported each medical problem. Next to this number is the percentage of these participants who reported the medical problem.
- For example, in Table 1 (for Group 1), you can see that 3 out of 75 participants (4.0%) in the placebo group reported nausea. A total of 11 out of 73 participants (15.1%) in the 20 mg lotiglipron group reported nausea.

Table 1. Commonly reported medical problems by study participants in Group 1 (T2DM)

Medical Problem	Placebo 75 Participants	Lotiglipron 20 mg 73 Participants	Lotiglipron 40 mg 72 Participants	Lotiglipron 80 mg 73 Participants	Lotiglipron 160 mg 72 Participants	Lotiglipron 260 mg 74 Participants	Rybelsus® 14 mg 73 Participants	Total 512 Participants
Nausea	3 participants (4.0%)	11 participants (15.1%)	17 participants (23.6%)	21 participants (28.8%)	14 participants (19.4%)	19 participants (25.7%)	10 participants (13.7%)	95 participants (18.6%)
Diarrhea	1 participant (1.3%)	8 participants (11.0%)	9 participants (12.5%)	8 participants (11.0%)	4 participants (5.6%)	8 participants (10.8%)	6 participants (8.2%)	44 participants (8.6%)
Vomiting	1 participant (1.3%)	1 participant (1.4%)	6 participants (8.3%)	11 participants (15.1%)	6 participants (8.3%)	11 participants (14.9%)	6 participants (8.2%)	42 participants (8.2%)
Constipation	1 participant (1.3%)	2 participants (2.7%)	7 participants (9.7%)	3 participants (4.1%)	4 participants (5.6%)	6 participants (8.1%)	4 participants (5.5%)	27 participants (5.3%)

Table 2. Commonly reported medical problems by study participants in Group 2 (obesity)

Medical Problem	Placebo 64 Participants	Lotiglipron 80 mg 66 Participants	Lotiglipron 140 mg 64 Participants	Lotiglipron 200 mg (5 steps) 65 Participants	Lotiglipron 200 mg (4 steps) 66 Participants	Lotiglipron 260 mg 64 Participants	Total 389 Participants
Nausea	8 participants (12.5%)	34 participants (51.5%)	30 participants (46.9%)	38 participants (58.5%)	40 participants (60.6%)	32 participants (50.0%)	182 participants (46.8%)
Constipation	5 participants (7.8%)	14 participants (21.2%)	15 participants (23.4%)	15 participants (23.1%)	23 participants (34.8%)	17 participants (26.6%)	89 participants (22.9%)
Diarrhea	12 participants (18.8%)	10 participants (15.2%)	10 participants (15.6%)	16 participants (24.6%)	17 participants (25.8%)	17 participants (26.6%)	82 participants (21.1%)
Vomiting	1 participants (1.6%)	7 participants (10.6%)	10 participants (15.6%)	21 participants (32.3%)	19 participants (28.8%)	22 participants (34.4%)	80 participants (20.6%)
Stomach acid reflux or heartburn	1 participants (1.6%)	10 participants (15.2%)	6 participants (9.4%)	5 participants (7.7%)	13 participants (19.7%)	6 participants (9.4%)	41 participants (10.5%)
Headache	5 participants (7.8%)	7 participants (10.6%)	4 participants (6.3%)	7 participants (10.8%)	9 participants (13.6%)	5 participants (7.8%)	37 participants (9.5%)
Poor appetite	5 participants (7.8%)	5 participants (7.6%)	7 participants (10.9%)	3 participants (4.6%)	8 participants (12.1%)	8 participants (12.5%)	36 participants (9.3%)
Tiredness	5 participants (7.8%)	7 participants (10.6%)	5 participants (7.8%)	6 participants (9.2%)	5 participants (7.6%)	5 participants (7.8%)	33 participants (8.5%)
Indigestion	2 participants (3.1%)	6 participants (9.1%)	4 participants (6.3%)	6 participants (9.2%)	9 participants (13.6%)	4 participants (6.3%)	31 participants (8.0%)
Pain in the stomach area	4 participants (6.3%)	3 participants (4.5%)	6 participants (9.4%)	2 participants (3.1%)	10 participants (15.2%)	4 participants (6.3%)	29 participants (7.5%)
Urinary tract infection (UTI)	2 participants (3.1%)	2 participants (3.0%)	2 participants (3.1%)	6 participants (9.2%)	5 participants (7.6%)	3 participants (4.7%)	20 participants (5.1%)

During the study, 44 out of 901 participants (5%) across Groups 1 and 2 had high levels of 1 or both of the following liver enzymes in the blood:

- Alanine aminotransferase (ALT)
- Aspartate aminotransferase (AST)

For these participants, the ALT and AST levels were more than 3 times the upper limit of normal (ULN). This means that the results were 3 times greater than the normal highest level.

The tables below show how many participants in each group had high levels of ALT and AST in the blood during the study.

- Table 3 for Group 1 (participants with T2DM)
- Table 4 for Group 2 (participants with obesity)

Table 3. Participants in Group 1 (T2DM) with high ALT and AST levels

Liver Enzyme	Placebo 75 Participants	Lotiglipron 20 mg 73 Participants	Lotiglipron 40 mg 72 Participants	Lotiglipron 80 mg 73 Participants	Lotiglipron 160 mg 72 Participants	Lotiglipron 260 mg 74 Participants	Rybelsus® 14 mg 73 Participants	Total 512 Participants
ALT more than 3 times the ULN	0 participants (0%)	0 participants (0%)	5 participants (6.9%)	6 participants (8.3%)	4 participants (5.6%)	8 participants (11.0%)	0 participants (0%)	23 participants (4.5%)
AST more than 3 times the ULN	0 participants (0%)	0 participants (0%)	3 participants (4.2%)	3 participants (4.2%)	3 participants (4.2%)	3 participants (4.1%)	0 participants (0%)	12 participants (2.4%)

Table 4. Participants in Group 2 (obesity) with high ALT and AST levels

Liver Enzyme	Placebo 64 Participants	Lotiglipron 80 mg 66 Participants	Lotiglipron 140 mg 64 Participants	Lotiglipron 200 mg (5 steps) 65 Participants	Lotiglipron 200 mg (4 steps) 66 Participants	Lotiglipron 260 mg 64 Participants	Total 389 Participants
ALT more than 3 times the ULN	1 participant (1.6%)	2 participants (3.2%)	6 participants (9.5%)	2 participants (3.2%)	8 participants (12.1%)	1 participant (1.6%)	20 participants (5.2%)
AST more than 3 times the ULN	0 participants (0%)	1 participant (1.6%)	2 participants (3.2%)	1 participants (1.6%)	2 participants (3.0%)	0 participants (0%)	6 participants (1.6%)

Researchers wanted to see whether lotiglipron was handled by the body differently in participants with high ALT and AST levels compared to those without high ALT and AST levels. Researchers measured the following:

- Amount of lotiglipron in the blood before the morning dose was taken. This is also called the "**trough concentration (C-trough)**". Researchers adjusted the computed results according to the dose that each participant took. This makes the comparison fair even if participants took different doses.
- Amount of lotiglipron found in the blood after the morning dose of lotiglipron. This is also called the "**post-dose amount**".

Researchers found that, on average, C-trough and post-dose amounts of lotiglipron were greater among participants with high ALT and AST levels compared to participants without high ALT and AST levels.

These greater C-trough and post-dose amounts of lotiglipron in the blood among participants with high ALT and AST levels were seen as early as Week 4 of treatment and peaked (maximum increases of lotiglipron) at Week 8 of treatment.

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.

Group 1 (T2DM):

During the study, 11 out of 512 participants (2.1%) in Group 1 had at least 1 serious medical problem. No specific serious medical problem was reported by more than 1 participant in any group.

A total of 3 participants reported the following serious medical problems involving high levels of liver enzymes in the blood.

- High liver enzymes in the blood – 1 participant in the 160 mg lotiglipron group.
- Abnormal liver function test results – 1 participant in the 80 mg lotiglipron group.
- Elevated liver function test results – 1 participant in the 260 mg lotiglipron group.

Researchers believe that 2 of the serious medical problems listed above – abnormal liver function test results and elevated liver function test results – may be related to lotiglipron.

Researchers also believe that the following serious medical problem reported by a participant may be related to Rybelsus®:

- Fainting – 1 participant in the Rybelsus® 14 mg group.

Group 2 (Obesity):

During the study, 10 out of 389 participants (2.6%) in Group 2 had at least 1 serious medical problem. No specific serious medical problem was reported by more than 1 participant in any group.

A total of 3 participants reported the following serious medical problems involving high levels of liver enzymes in the blood. Researchers believe that these serious medical problems may be related to lotiglipron:

- High levels of liver enzymes in the blood – 1 participant in the 80 mg lotiglipron group and 1 participant in the 200 mg (4 steps) lotiglipron group.
- High levels of ALT and alkaline phosphatase (an enzyme found in the liver and other body organs) in the blood – 1 participant in the 200 mg (4 steps) lotiglipron group.

In this study, 1 participant died. This participant, who took placebo in Group 1 (T2DM), died from cardiac arrest. Researchers do not believe that this serious medical problem was related to the study treatment.

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.

For more details on your study protocol, please visit:

www.pfizer.com/research/research_clinical_trials/trial_results	Use the protocol number **C3991004**

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

www.clinicaltrials.gov	Use the study identifier **NCT05579977**
www.clinicaltrialsregister.eu	Use the study identifier **2022-002834-15**

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