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:	Lotiglipron (PF-07081532)
Protocol Number:	C3991047
Dates of Study:	27 March 2023 to 11 September 2023
Title of this Study:	A Study on How Lotiglipron May Affect the Amounts of Dabigatran and Rosuvastatin in the Blood of People Who Are Overweight or With Obesity [A Phase 1, Open-Label, Fixed-Sequence Study to Estimate the Effect of PF-07081532 Administration on the Single-Dose Pharmacokinetics of Dabigatran and Rosuvastatin in Overweight or Obese Adult Participants]
Date of this Report:	15 September 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 is obesity?

Obesity is a long-term medical condition caused by excessive body fat and can cause serious health problems. People living with obesity have more body fat than those who are overweight.

People who have obesity or are overweight are at a higher risk of Type 2 diabetes, high blood pressure, heart disease, and other health problems.

What is lotiglipron?

Lotiglipron, also known as PF-07081532, is a tablet that is taken by mouth (oral). It is an investigational medicine because it is not approved for use by the health authorities outside of research studies.

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. They may also slow down the digestion of food and may increase the feeling of fullness after eating, which 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 with lotiglipron (C3991004 and C3991040), 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 how lotiglipron may change the amounts of medicines called dabigatran and rosuvastatin in the blood of participants when they are taken together.

Dabigatran and **rosuvastatin** are both approved medicines in the United States (US).

- **Dabigatran** dissolves blood clots and is used to decrease the risk of heart attacks and stroke.
- **Rosuvastatin** is used to reduce levels of bad cholesterol (called “low-density lipoprotein cholesterol” or LDL-C) in the blood.

Researchers chose dabigatran and rosuvastatin for this study as medicines of these types may interact with lotiglipron when they are taken together. This study was not designed to test the effect of lotiglipron on blood sugar levels or body weight.

Researchers wanted to know:

- **How did lotiglipron affect the amounts of dabigatran and rosuvastatin in the participants' blood?**
- **What medical problems did participants have during the study?**

What happened during the study?

How was the study done?

Researchers tested different doses of lotiglipron, along with medicines dabigatran and rosuvastatin, in a group of participants to learn how lotiglipron may change the amounts of dabigatran and rosuvastatin in the participants' blood.

Table 1 shows the study medications (lotiglipron, dabigatran, rosuvastatin) that participants took across the 8 dosing periods, which were planned to last for a total of 54 days. Participants were to stay at the study clinic throughout the 8 dosing periods.

Table 1. What study medications did the participants take in each dosing period?			
Period 1: Dabigatran only (1 dose)	**Period 2:** Rosuvastatin only (1 dose)	**Period 3:** Lotiglipron only (multiple doses)	**Period 4:** Dabigatran (1 dose) **plus** lotiglipron (multiple doses)
Period 5: Rosuvastatin (1 dose) **plus** lotiglipron (multiple doses)	**Period 6:** Lotiglipron only (multiple doses)	**Period 7:** Dabigatran (1 dose) **plus** lotiglipron (multiple doses)	**Period 8:** Rosuvastatin (1 dose) **plus** lotiglipron (multiple doses)

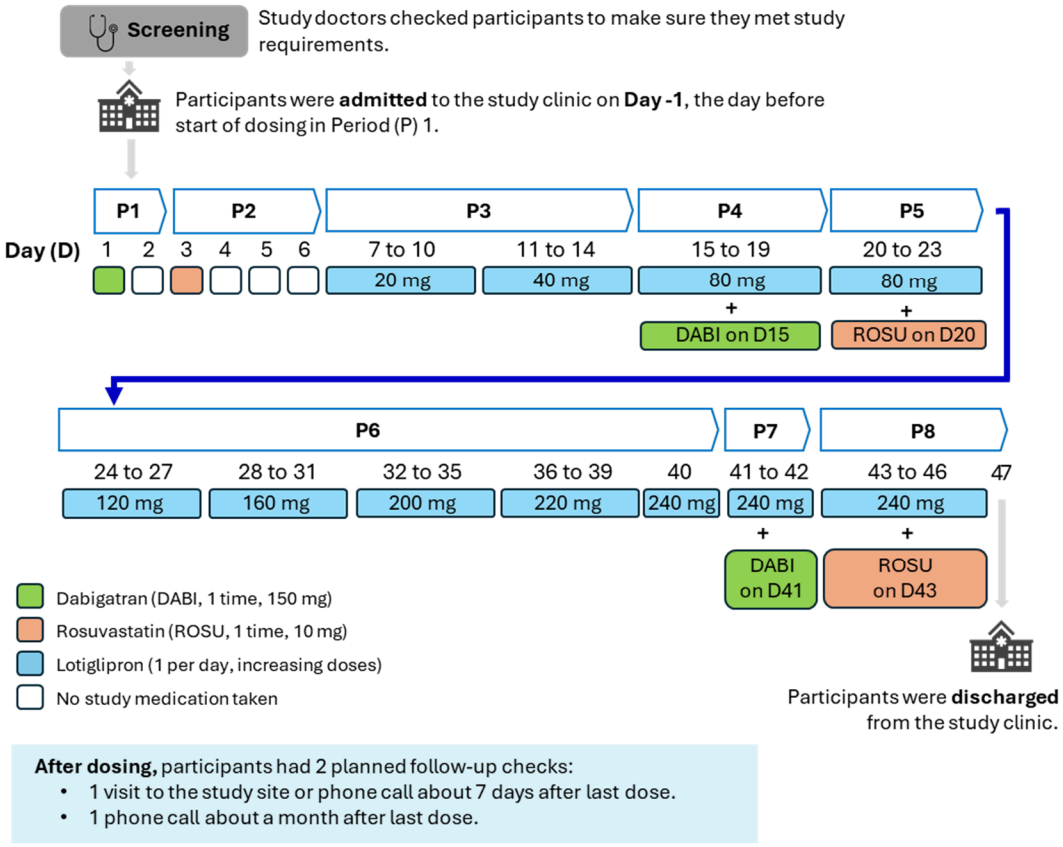
This was an open-label study. This means that researchers and participants knew the medications each participant was taking.

Participants had 2 planned follow-up checks within 1 month after their last dose of the study medications.

Researchers took blood and urine samples from participants throughout the study. Researchers also checked the participants' health and asked them how they were feeling.

Figure 1 shows what happened in the study.

Figure 1. How was this study done?



Because of safety concerns and how lotiglipron acted in the body of participants in this study and 2 other lotiglipron studies, some changes in this study's plan were made:

- Only 16 participants (out of the planned 24 participants) were dosed in the study. Eight (8) participants were not dosed as the study was terminated early.
- The highest dose (260 mg) planned to be given in this study was lowered to 240 mg; therefore, dosing in Periods 6 and 7 was shortened. These changes were allowed in the study plan to ensure the safety of participants.

Where did this study take place?

The Sponsor ran this study at 1 location in the US.

When did this study take place?

It began on 27 March 2023 and ended on 11 September 2023.

Who participated in this study?

This study included healthy people who met the following study requirements:

- 18 years of age of older
- a body mass index (BMI) of 25 or greater

BMI Categories:

- Below 18.5 = underweight
- 18.5 to 24.9 = normal weight
- 25 to 29.9 = overweight
- 30 or greater = obesity

Sixteen (16) participants joined the study. A total of 5 men and 11 women, between the age of 21 and 60 years, participated.

Out of 16 participants, 14 (87.5%) finished all dosing periods. There were 2 participants who did not finish dosing:

- One (1) participant stopped dosing in Period 8 (rosuvastatin plus lotiglipron) because of a medical problem they had in the study.
- Another participant stopped dosing in Period 4 (dabigatran plus lotiglipron) because of their own decision (not related to safety).

How long did the study last?

Each participant was in the study for about 4 months. The study ran for about 6 months 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 with lotiglipron (C3991004 and C3991040). 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 medication 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 medication.

What were the results of the study?

How did lotiglipron affect the amounts of dabigatran and rosuvastatin in the participants' blood?

To answer this question, study doctors took blood samples from participants throughout the study. They measured the **total amounts of dabigatran and rosuvastatin in the blood over time** throughout the dosing periods.

Researchers compared the results during these periods:

Periods 1 and 2		**Periods 4, 5, 7, and 8**
Days when participants took dabigatran and rosuvastatin **without lotiglipron.**	→ **to** ←	Days when participants took dabigatran and rosuvastatin **with lotiglipron.**

Study results showed that, compared to when dabigatran and rosuvastatin were taken without lotiglipron:

- The total amount of dabigatran in the participants' blood was **lower by about 20%** when it was **taken with lotiglipron**.
- The total amount of rosuvastatin in the participants' blood was **higher by about 2 times** when it was **taken with lotiglipron**.

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 unknown 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.

All 16 participants had at least 1 medical problem during the study.

The most common medical problems – those reported by 40% or more participants – are described in Table 2 below. Most of these medical problems are related to the digestive system.

Below are instructions on how to read Table 2.

Instructions for Understanding Table 2.

- The **1st** column of Table 2 lists medical problems that were commonly reported during the study. All medical problems reported by 40% of participants or more are listed.
- The **2nd** column tells how many of the 16 participants in the study reported each medical problem. Next to this number is

the percentage of participants in the study who reported the medical problem.

- For example, using these instructions, you can see that 12 out of 16 participants (75%) in the study reported indigestion.

Table 2. Commonly reported medical problems by study participants

Medical Problem	Overall (16 Participants)
Indigestion	12 out of 16 participants (75%)
Diarrhea	11 out of 16 participants (69%)
Constipation	10 out of 16 participants (63%)
Nausea	10 out of 16 participants (63%)
Vomiting	10 out of 16 participants (63%)
Flatulence (gas)	7 out of 16 participants (44%)
Headache	7 out of 16 participants (44%)

There was 1 participant who stopped dosing in the study because of a medical problem they had. This participant, along with 2 other participants, had high levels of liver enzymes called AST and ALT during Period 8, when they were dosed with rosuvastatin and lotiglipron. The AST and ALT levels of these participants were more than 3 times the normal highest level.

> The level of liver enzymes helps tell how well the liver is working. **High levels of liver enzymes** in the blood may be a sign of a medical condition like liver disease or liver injury.

Researchers believe that the high liver enzyme levels in these 3 participants may be related to lotiglipron.

With these results, researchers wanted to see whether lotiglipron, dabigatran, and rosuvastatin acted differently in the body of participants with high liver enzyme levels compared to those with normal liver enzyme levels.

Researchers found that the amounts of rosuvastatin and lotiglipron in the blood were higher in the 3 participants with high liver enzyme levels than in the remaining 13 participants with normal liver enzyme levels. The amount of dabigatran in the participants' blood was the same regardless of the participants' liver enzyme levels.

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.

One (1) out of 16 participants (6.3%) had a serious medical problem. This was the same participant who stopped dosing because of the medical problem of high liver enzyme levels. The researchers considered this medical problem as medically important because of large increases in the participant’s liver enzyme levels.

Researchers believe that this serious medical problem might be related to lotiglipron.

No participant died during the study.

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 **C3991047**

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

www.clinicaltrials.gov	Use the study identifier **NCT05788328**

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!