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.
Medicines Studied:	Ervogastat (DGAT2i), Clesacostat (ACCi)
Protocol Number:	C2541013
Dates of Study:	15 June 2020 to 21 February 2024
Title of this Study:	A Study to Learn the Effects of Ervogastat (DGAT2i) Given Alone or Together with Clesacostat (ACCi), Compared to Placebo, in People With Non-alcoholic Steatohepatitis and Stage 2 or 3 Fibrosis [A Phase 2, Randomized, Double-Blind, Double-Dummy, Placebo-Controlled, Dose-Ranging, Dose-Finding, Parallel Group Study to Assess Efficacy and Safety of PF-06865571 (DGAT2i) Alone and When Co-administered With PF-05221304 (ACCi) in Adult Participants With Biopsy-Confirmed Non-alcoholic Steatohepatitis and Fibrosis Stage 2 or 3]
Date of this Report:	19 December 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 Non-alcoholic Steatohepatitis (NASH)?

Non-alcoholic steatohepatitis, or NASH, is a serious condition where the liver has a high level of fat and is swollen (or inflamed). This can lead to stiffness or scarring (fibrosis) of the liver. Liver fibrosis is divided into 4 different stages. The stages of liver fibrosis are, minimal scarring (Stage 1), mild scarring (Stage 2), moderate scarring (Stage 3), and severe scarring (Stage 4). People with NASH can develop fibrosis, liver damage, and in some, it can lead to death.

What are ervogastat and clesacostat?

Ervogastat (errr-vo-gaa-stat) and clesacostat (kle-saa-co-stat) are two medicines being studied for the treatment of NASH with liver fibrosis. In this study, ervogastat is being tested alone and together with clesacostat. Both ervogastat and clesacostat are referred to as study medications.

Ervogastat blocks a specific protein and reduces the levels of a type of fat called triglycerides which are made by the liver. Clesacostat blocks another protein and reduces production of new fat by the liver. Researchers think that reducing the amount of these fats in the liver may help to control or slow down liver damage in people with NASH and liver fibrosis.

What was the purpose of this study?

The purpose of this study was to learn if the study medications (ervogastat alone or given together with clesacostat) improve NASH with liver fibrosis, compared to placebo. A placebo does not have any medicine in it, but it looks just like the study medication.

Researchers wanted to know:

- **How many participants had resolution of NASH without worsening of fibrosis, or fibrosis that reduced by 1 stage or more without worsening of NASH, or both, assessed by a liver biopsy, after 48 weeks of treatment?**

What happened during the study?

How was the study done?

This study was done in 3 phases.

Screening phase (10-16 weeks before study start): In this phase, researchers identified the participants who could take part in the study, based on liver scans (which imaged the liver using ultrasound to check the amount of fat and stiffness of liver), blood tests, and liver biopsy. Liver biopsy involved removal of a tiny piece of the liver so that it could be examined under a microscope to evaluate the amount of steatosis (fat), inflammation, and fibrosis in the liver. Once found eligible, participants took placebo for 2 weeks, to get familiarized with the dosing instructions for the study, before they started the study medication.

Treatment phase (up to 48 weeks): In this phase, researchers learnt about the effects of ervogastat alone, and when given together with clesacostat, compared with placebo. Participants took the study medication together as 3 tablets, by mouth, twice daily (either ervogastat alone, ervogastat with clesacostat, or placebo) (Figure 1). Participants were assigned to 1 of 7 treatment groups in a random way using a computer program. This process is called “randomization”. This means that each person had an equal chance of being assigned to 1 of the 7 groups. The 7 groups were:

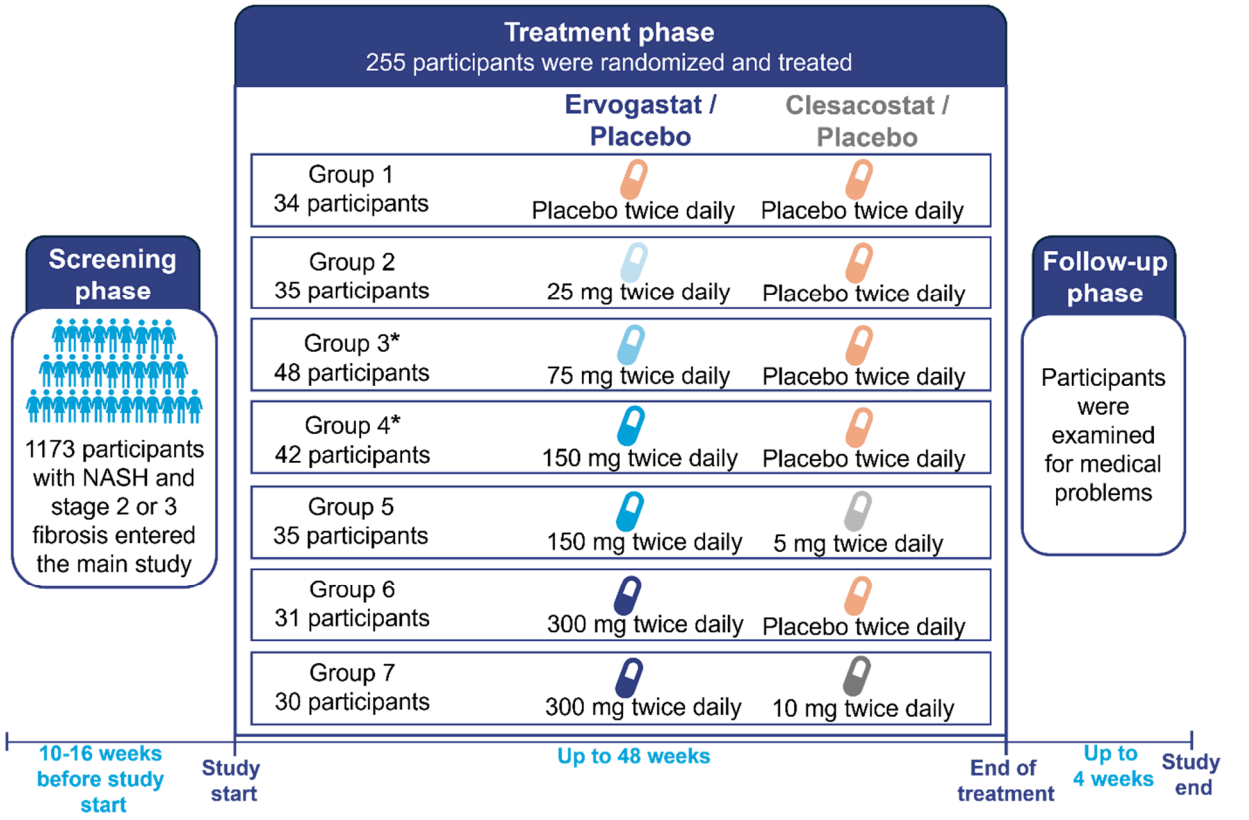
- **Group 1-** Placebo, twice daily
- **Group 2-** Ervogastat 25 mg, twice daily
- **Group 3-** Ervogastat 75 mg, twice daily and 150 mg once daily- combined and reported together under 75 mg twice daily
- **Group 4-** Ervogastat 150 mg, twice daily and 300 mg, once daily- combined and reported together under 150 mg twice daily
- **Group 5-** Ervogastat 150 mg with clesacostat 5 mg, twice daily
- **Group 6-** Ervogastat 300 mg, twice daily
- **Group 7-** Ervogastat 300 mg with clesacostat 10 mg, twice daily

Participants and researchers did not know who took placebo, ervogastat, or ervogastat + clesacostat. This is known as “double-blind”.

Researchers performed a liver biopsy, during the Screening phase and at the end of treatment (Week 48). In addition to liver biopsies, researchers also collected blood and urine samples from the participants at multiple visits to assess safety and response to the study medications. Researchers also assessed liver fat or steatosis using a highly sensitive magnetic resonance imaging tool in participants at selected study sites in Canada, Puerto Rico, and the United States of America.

Follow-up phase (up to 4 weeks): After completion of the treatment phase, researchers monitored the participants’ health and checked for any medical problems. The Figure 1 below shows the study design in detail.

Figure 1: Study design



*Group 3 and *Group 4= Includes participants randomized to once-daily dose at the same total daily dose

Where did this study take place?

The Sponsor ran this study at 107 locations in 11 countries in North America, Asia, and Europe.

When did this study take place?

It began on 15 June 2020 and ended on 21 February 2024.

Who participated in this study?

The study included participants who were 18 years or older and had NASH confirmed by liver biopsy, with stage 2 or 3 fibrosis.

- A total of 101 men participated
- A total of 154 women participated
- All study participants were between the ages of 23 and 76 years.

Of the 256 participants who started the study, 255 were treated and 229 finished the treatment phase. Twenty-six (26) participants did not finish the treatment phase because, either:

- They decided to leave the study,
- They developed/experienced medical conditions preventing continued participation in the study,
- They did not return to the study sites for continued follow-up, and
- They had other non-safety related reasons to discontinue from the treatment phase of the study.

How long did the study last?

Study participants were in the study for up to 1.5 years. The entire study took about 4 years to complete and dosed less than the planned number of participants due to difficulty with recruitment during the COVID-19 pandemic.

When the study ended in February 2024, the Sponsor began reviewing the information collected. The Sponsor then created a report of the results. This is a summary of that report.

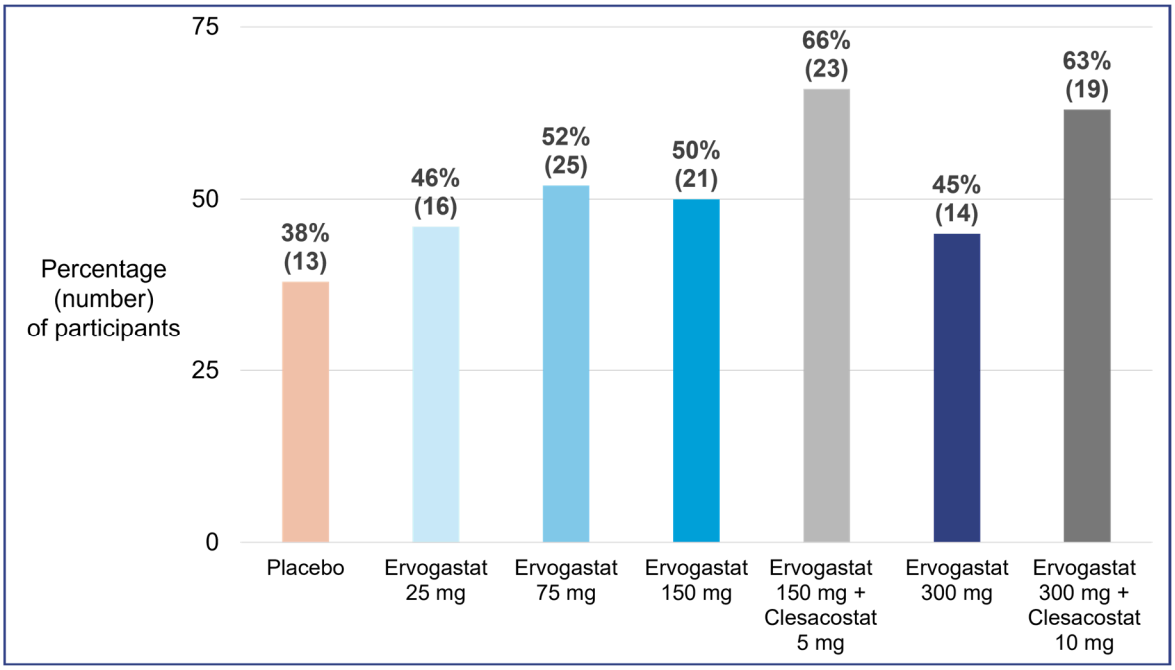
What were the results of the study?

How many participants had resolution of NASH without worsening of fibrosis, or fibrosis that reduced by 1 stage or more without worsening of NASH, or both, assessed by a liver biopsy, after 48 weeks of treatment?

- The results from 255 participants who received treatment were assessed. Of these, 212 had evaluable liver biopsies from Screening and Week 48. For the remaining 43 participants, liver biopsies were either:
  - not performed at Week 48 (36 participants), or
  - the liver sample was non-evaluable (7 participants).
- With respect to the study results, these 43 participants were considered to have not responded to their assigned study medication.
- In the ervogastat + clesacostat treated groups, a higher percentage of participants had resolution of NASH symptoms without worsening of fibrosis or had improvement in fibrosis by 1 or more stage without worsening of NASH, or both, compared to those who took placebo.
- Both combinations of ervogastat with clesacostat were more effective than placebo.
- Ervogastat alone, at the doses tested, was no more effective than placebo. This was likely due to the relatively small number of participants in the treatment groups, and a large response to placebo for the improvement in fibrosis by 1 stage or more.

- Figure 2 below shows the results in detail.

Figure 2: Percentage (number) of participants with resolution of NASH symptoms without worsening of fibrosis, or improvement of fibrosis by 1 or more stage without worsening of NASH, or both, at Week 48



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.

Overall, 193 out of 255 [76%] participants in this study experienced at least 1 medical problem. A total of 6 participants left the study, and 4 other participants stopped the study medication, because of medical problems. The most common medical problems – those reported by 5% or more of the participants in any group – are described below.

Below are instructions on how to read Table 1.

Instructions for Understanding Table 1.

- The **1st** column of Table 1 lists medical problems that were commonly reported during the study. All medical problems reported by 5% or more of the study participants are listed.
- The **2nd** column tells how many of the 34 participants taking placebo reported each medical problem. Next to this number is the percentage of the 34 participants taking placebo who reported the medical problem.

- The **3rd** column tells how many of the 156 participants taking ervogastat alone reported each medical problem. Next to this number is the percentage of the 156 participants taking ervogastat alone who reported the medical problem.
- The **4th** column tells how many of the 65 participants taking ervogastat + clesacostat reported each medical problem. Next to this number is the percentage of the 65 participants taking ervogastat + clesacostat who reported the medical problem.
- Using these instructions, you can see that 0 out of the 34 participants taking placebo, 8 out of the 156 [5%] participants taking ervogastat alone, and 2 out of the 65 [3%] participants taking ervogastat + clesacostat reported back pain.

Table 1. Commonly reported medical problems reported in 5% or more study participants in any group

Medical Problem	Placebo (34 Participants)	All doses of Ervogastat alone (156 Participants)	All doses of Ervogastat + Clesacostat (65 Participants)
Back pain	0 participants	8 out of 156 participants (5%)	2 out of 65 participants (3%)
Common cold	1 out of 34 participants (3%)	3 out of 156 participants (2%)	6 out of 65 participants (9%)

Table 1. Commonly reported medical problems reported in 5% or more study participants in any group

Medical Problem	Placebo (34 Participants)	All doses of Ervogastat alone (156 Participants)	All doses of Ervogastat + Clesacostat (65 Participants)
Constipation	0 participants	5 out of 156 participants (3%)	4 out of 65 participants (6%)
Cough	2 out of 34 participants (6%)	6 out of 156 participants (4%)	1 out of 65 participants (2%)
COVID-19	2 out of 34 participants (6%)	13 out of 156 participants (8%)	3 out of 65 participants (5%)
Diarrhoea	1 out of 34 participants (3%)	14 out of 156 participants (9%)	5 out of 65 participants (8%)
Feeling sick	2 out of 34 participants (6%)	7 out of 156 participants (5%)	4 out of 65 participants (6%)
Fever	2 out of 34 participants (6%)	7 out of 156 participants (5%)	2 out of 65 participants (3%)
Headache	4 out of 34 participants (12%)	8 out of 156 participants (5%)	5 out of 65 participants (8%)
Infection in any part of the urinary tract	1 out of 34 participants (3%)	5 out of 156 participants (3%)	4 out of 65 participants (6%)

Table 1. Commonly reported medical problems reported in 5% or more study participants in any group

Medical Problem	Placebo (34 Participants)	All doses of Ervogastat alone (156 Participants)	All doses of Ervogastat + Clesacostat (65 Participants)
Inflammation of the nose and throat	4 out of 34 participants (12%)	10 out of 156 participants (6%)	2 out of 65 participants (3%)
Inflammation of the sinuses	0 participants	8 out of 156 participants (5%)	3 out of 65 participants (5%)
Joint pain	2 out of 34 participants (6%)	7 out of 156 participants (5%)	5 out of 65 participants (8%)
Pain in upper part of the stomach	3 out of 34 participants (9%)	4 out of 156 participants (3%)	2 out of 65 participants (3%)
Pain while performing study procedures	0 participants	1 out of 156 participants (less than 1%)	4 out of 65 participants (6%)
Poorly controlled diabetes	4 out of 34 participants (12%)	16 out of 156 participants (10%)	4 out of 65 participants (6%)

Table 1. Commonly reported medical problems reported in 5% or more study participants in any group			
Medical Problem	Placebo (34 Participants)	All doses of Ervogastat alone (156 Participants)	All doses of Ervogastat + Clesacostat (65 Participants)
Stomach pain	1 out of 34 participants (3%)	11 out of 156 participants (7%)	1 out of 65 participants (2%)
Tiredness	0 participants	8 out of 156 participants (5%)	1 out of 65 participants (2%)

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.

Nineteen (19) participants out of 255 [7%] had serious medical problems.

- Eleven (11) out of 156 [7%] participants who received ervogastat alone had at least 1 serious medical problem.
- Seven (7) out of 65 [11%] participants who received ervogastat + clesacostat had at least 1 serious medical problem.
- One (1) out of 34 [3%] participants in the placebo group had at least 1 serious medical problem.
- No participant died during the study.

- The most common serious medical problems reported by the study participants – are described below.

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 the participants are listed.
- The **2nd** column tells how many of the 34 participants taking placebo reported each medical problem. Next to this number is the percentage of the 34 participants taking the study medication who reported the medical problem.
- The **3rd** column tells how many of the 156 participants taking ervogastat alone reported each medical problem. Next to this number is the percentage of the 156 participants taking ervogastat alone who reported the medical problem.
- The **4th** column tells how many of the 65 participants taking ervogastat + clesacostat reported each medical problem. Next to this number is the percentage of the 65 participants taking ervogastat + clesacostat who reported the medical problem.
- Using these instructions, you can see that 0 out of the 34 participants taking placebo, 1 out of the 156 [less than 1%] participants taking ervogastat alone, and 0 out of the 65 participants taking ervogastat + clesacostat reported abnormal blood pooling in the liver.

Table 2. Commonly reported serious medical problems by study participants

Medical Problem	Placebo (34 Participants)	All doses of Ervogastat alone (156 Participants)	All doses of Ervogastat + Clesacostat (65 Participants)
Abnormal blood pooling in the liver	0 participants	1 out of 156 participants (less than 1%)	0 participants
Back pain	0 participants	0 participants	1 out of 65 participants (2%)
Breast cancer	0 participants	1 out of 156 participants (less than 1%)	0 participants
Cancer of the glands that produce saliva	0 participants	1 out of 156 participants (less than 1%)	0 participants
Constipation	0 participants	1 out of 156 participants (less than 1%)	0 participants
COVID-19	0 participants	1 out of 156 participants (less than 1%)	0 participants

Table 2. Commonly reported serious medical problems by study participants

Medical Problem	Placebo (34 Participants)	All doses of Ervogastat alone (156 Participants)	All doses of Ervogastat + Clesacostat (65 Participants)
Enlarged prostate gland that is not cancerous	0 participants	0 participants	1 out of 65 participants (2%)
Fever	0 participants	1 out of 156 participants (less than 1%)	0 participants
Formation of a blood clot in a vein	0 participants	1 out of 156 participants (less than 1%)	0 participants
Hardening of the arteries that supply blood to the heart	0 participants	0 participants	1 out of 65 participants (2%)
Heart attack	0 participants	0 participants	1 out of 65 participants (2%)
Inflamed and narrowed airways in the lungs	0 participants	1 out of 156 participants (less than 1%)	0 participants

Table 2. Commonly reported serious medical problems by study participants

Medical Problem	Placebo (34 Participants)	All doses of Ervogastat alone (156 Participants)	All doses of Ervogastat + Clesacostat (65 Participants)
Inflammation of the appendix	1 out of 34 participants (3%)	0 participants	0 participants
Kidney damage	0 participants	1 out of 156 participants (less than 1%)	0 participants
Liver injury caused by other medication	0 participants	1 out of 156 participants (less than 1%)	0 participants
Long-standing inflammation of the pancreas	0 participants	0 participants	1 out of 65 participants (2%)
Long-standing lung disease that makes it difficult to breathe	0 participants	1 out of 156 participants (less than 1%)	0 participants

Table 2. Commonly reported serious medical problems by study participants			
Medical Problem	**Placebo (34 Participants)**	**All doses of Ervogastat alone (156 Participants)**	**All doses of Ervogastat + Clesacostat (65 Participants)**
Recent swelling in the gall bladder	0 participants	1 out of 156 participants (less than 1%)	0 participants
Sudden bleeding in the liver	0 participants	1 out of 156 participants (less than 1%)	1 out of 65 participants (2%)
Swelling and pain in the joints	0 participants	0 participants	1 out of 65 participants (2%)

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 **C2541013**

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

www.clinicaltrials.gov	Use the study identifier **NCT04321031**
www.clinicaltrialsregister.eu	Use the study identifier **2019-004775-39**

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!