# 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:** Lorlatinib (PF-06463922)

**Protocol Number:** B7461001

**Dates of Study:** 08 January 2014 to 24 May 2023

**Title of this Study:** A Study of PF-06463922 in Participants With Advanced Non-Small Cell Lung Cancer

[Phase 1/2 Study of PF-06463922 (an ALK/ROS1 Tyrosine Kinase Inhibitor) in Patients With Advanced Non-Small Cell Lung Cancer Harboring Specific Molecular Alterations]

**Date of this Report:** 23 March 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 advanced non-small cell lung cancer?

Lung cancer is the name for cancer that starts in the lungs. Non-small cell lung cancer (NSCLC) is the most common type of lung cancer. Participants in this study had NSCLC that was “advanced”. When a cancer is spread outside of its location of origin it is called “advanced” or “metastatic” cancer. Some people have NSCLC that is referred to as “anaplastic lymphoma kinase (ALK)-positive” or “c-ros oncogene 1 (ROS1)-positive”. These people have some changes in their genes that can cause cancer cells to grow.

## What is lorlatinib?

Lorlatinib (lor-la-ti-nib) is an investigational cancer medicine that is being tested as a treatment for people with ALK-positive or ROS1-positive lung cancers. There are certain proteins called “kinases” that help cancer cells grow. As they grow, the cancer cells can form into a tumor and spread to other parts of the body, such as the brain. Lorlatinib may be able to block kinases, potentially reducing tumor size and stopping ALK-positive and ROS1-positive lung cancers from being able to grow and spread. Lorlatinib is known as an “ALK-inhibitor” medication.

This was the first study to test lorlatinib in humans. At the time this study began, lorlatinib was not approved for use outside of research studies. Lorlatinib is taken as tablets, by mouth.

## What was the purpose of this study?

The study was conducted in 2 parts: Phase 1 and Phase 2.

The main purpose of this study was to learn about the effects and tolerability of lorlatinib in participants with ALK-positive or ROS1-positive

advanced NSCLC. "Tolerability" refers to how well participants can tolerate taking the study treatment.

Researchers wanted to find out the correct and best (optimal) dose of lorlatinib for treating participants with ALK-positive or ROS1-positive advanced NSCLC. As a part of the safety assessment in Phase 1, researchers checked if participants taking lorlatinib had any dose-limiting toxicities (DLTs). In Phase 2 researchers assessed if participants taking lorlatinib have any positive effects on their cancer.

"DLTs" are certain medical problems caused by taking lorlatinib which require the participant to lower the dose or stop taking the medicine (permanently or temporarily).

### Researchers wanted to know:

- **Phase 1: Did participants taking lorlatinib experience any DLTs?**
- **Phase 2: Did participants taking lorlatinib have a reduction in tumor size?**

## What happened during the study?

### How was the study done?

The study was conducted in 2 parts: Phase 1 and Phase 2.

This was an "open-label" study. This means researchers and participants knew what study medication participants received.

Participants were treated with study medication in "cycles". One cycle is 21 days (3 weeks) in duration. All participants were given lorlatinib

continuously in 21-day cycles until their cancer got worse, they experienced unacceptable medical problems, death or they decided they wanted to stop taking the study medication.

**Phase 1**

For Phase 1, researchers wanted to find the right dose for treating NSCLC. All participants were 'screened' before entering the 'treatment period' to see if they qualified to be in the study. Participants entered the study in small groups of 3 to 17 participants. Each group was given a different dose of lorlatinib, and the participants were watched closely for any medical problems. The doses for each group ranged from 10 mg to 200 mg lorlatinib given either once daily or twice daily. About 28 to 35 days after their last dose, participants had a 'follow-up' visit to check their health. Participants were contacted by telephone every 2 months to assess their overall health, and to collect information on any additional treatment for their cancer. This is called 'survival follow-up'.

Participants were first treated in a group size of 3 participants starting at the dose of 10 mg once daily. Based on the number of DLTs or other medical problems of concern, participants were given increasing dose levels of lorlatinib sequentially. Phase 1 study schema is described in Figure 1.

## Figure 1: Study Schema for Phase 1


### Phase 2

Phase 2 of the study was started after researchers decided on the correct dose of lorlatinib (100 mg once daily) in Phase 1. Participants were placed in different groups based on the type of NSCLC they had and the type of treatments they had already tried. Some of the participants in this study

had already taken chemotherapy, an ALK-inhibitor medication called crizotinib (in the form of capsules), or other ALK-inhibitor medications. A total of 275 participants were assigned to the following treatment groups:

- Group 1: Participants with advanced ALK-positive NSCLC who had not received previous treatments (30 participants).
- Group 2: Participants with advanced ALK-positive NSCLC whose cancer got worse despite previously taking crizotinib (27 participants).
- Group 3: Participants with advanced ALK-positive NSCLC whose cancer got worse despite previously taking either crizotinib and 1 or 2 regimens of chemotherapy or another ALK-inhibitor medication (60 participants).
- Group 4: Participants with advanced ALK-positive NSCLC whose cancer got worse despite taking 2 prior ALK-inhibitor medications. These participants may also have had chemotherapies (65 participants).
- Group 5: Participants with advanced ALK-positive NSCLC whose cancer got worse despite taking 3 prior ALK-inhibitor medications. These participants may also have had chemotherapies (46 participants).
- Group 6: Participants with advanced ROS1-positive NSCLC. These participants may or may not have had pervious treatments (47 participants).

All participants assigned in Groups 1-6 took 100 mg lorlatinib once daily.

For Phase 1, researchers assessed the safety and tolerability of lorlatinib by looking at the DLTs and medical problems participants had during the study. For Phase 2, researchers measured the effect of lorlatinib on participants' cancer by looking at scans and images of their tumors to evaluate their growth before, during and after treatment. Researchers also

measured the effect of lorlatinib in participants whose NSCLC had spread to the brain.

## Where did this study take place?

The Sponsor ran this study at 47 locations in 14 countries in Asia, Australia, Europe, and North America.

## When did this study take place?

It began on 08 January 2014 and ended on 24 May 2023.

## Who participated in this study?

The study included participants who had ALK-positive or ROS1-positive advanced NSCLC.

### Phase 1

A total of 54 participants were included and treated in Phase 1 of the study.

- A total of 22 men participated
- A total of 32 women participated
- All participants were between the ages of 27 and 82 years

Of the 54 participants who received at least 1 dose of lorlatinib, 46 participants (85.2%) permanently discontinued from the study because of the following reasons:

- Death (35 participants)
- Lost to follow-up (2 participants)
- Refused further follow-up (5 participants)
- Other reasons (4 participants)

All 54 participants permanently stopped the study treatment because of death (3 participants [5.6%]), medical problems related to lorlatinib (2 participants [3.7%]), medical problems not related to lorlatinib (4 participants [7.4%]), and due to other reasons (45 participants [83.3%]).

**Phase 2**

A total 276 participants were enrolled and assigned study treatment in Phase 2. Out of the 276 participants assigned, 275 participants received lorlatinib treatment. One participant did not receive study treatment and discontinued from the study (the participant died before receiving study treatment).

- A total of 118 men participated
- A total of 157 women participated
- All participants were between the ages of 19 and 85 years

Of the 275 participants who received at least 1 dose of lorlatinib, 214 participants (77.8%) permanently discontinued from the study because of the following reasons:

- Death (151 participants)
- Lost to follow-up (8 participants)
- Refused further follow-up (34 participants)
- Other reasons (20 participants)
- Lost to follow-up due to other reasons (1 participant)

All 275 participants permanently stopped the study treatment because of death (9 participants [3.3%]), medical problems related to lorlatinib (13 participants [4.7%]), medical problems not related to lorlatinib

(23 participants [8.4%]), and due to other reasons (231 participants [84.0%]).

### How long did the study last?

The amount of time each participant was involved in the study varied. The entire study took approximately 9 years and 5 months to complete.

When the study ended in May 2023, 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?

### For Phase 1, did participants taking lorlatinib experience any DLTs?

During Phase 1, researchers assessed how many participants in each group had DLTs during their first 21-day treatment cycle, and what the DLTs were.

In March 2017, when the primary objective of the study was met, one participant treated at 200 mg of lorlatinib once daily reported a DLT. The participant reported mild to moderate central nervous system problems which included aphasia (problem with understanding, talking, writing, or reading due to brain damage), cognitive disorder (mental illness affecting thoughts and learning), damage to vision, and abnormal dreams.

However, most of the participants who took either 150 mg or 200 mg of lorlatinib once daily had other medical problems that caused them to temporarily stop or lower their dose of lorlatinib. Using this information,

the researchers decided that 100 mg once daily was the well-tolerated and optimal dose of lorlatinib for treating participants with NSCLC.

When the study ended in May 2023, one participant treated at 100 mg of lorlatinib twice daily reported to have a DLT known as tinnitus (ringing in the ear).

## For Phase 2, did participants taking lorlatinib have a reduction in tumor size?

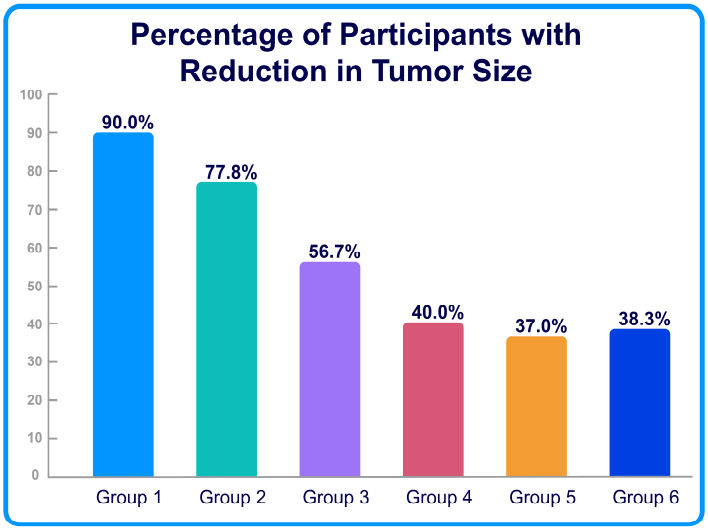
To answer this question, the researchers measured the "objective response rate" (ORR), which is the percentage of participants whose cancer got better (their tumor shrank or disappeared on images). Researchers measured the percentage of participants whose tumor decreased/shrank under therapy (called 'partial response' [PR]) and/or disappeared (called 'complete response' [CR]) after treatment.

There were participants in each group who showed a reduction in tumor size after taking lorlatinib. The ORR for each group is shown in Figure 2 on the next page.

One out of 30 (3.3%) participants in Group 1, 2 out of 60 (3.3%) participants in Group 3, 2 out of 65 (3.1%) participants in Group 4, 3 out of 47 (6.4%) participants in Group 6 had the best response recorded with no signs of cancer and whose tumor completely disappeared (CR).

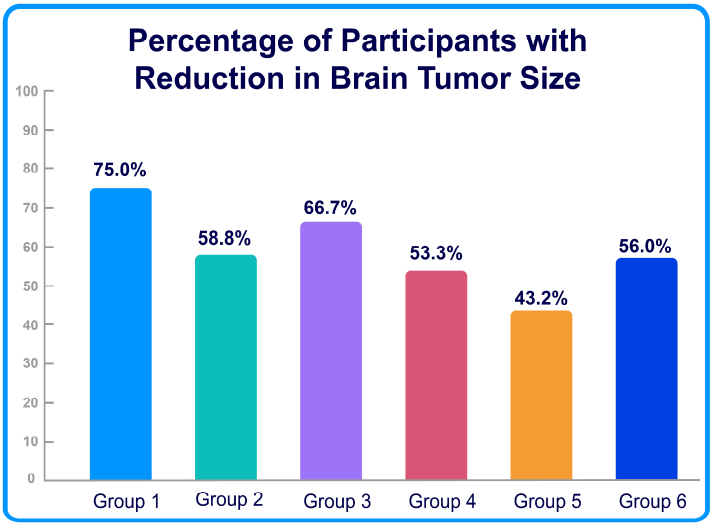
A total of 26 participants (86.7%) in Group 1, 21 participants (77.8%) in Group 2, 32 participants (53.3%) in Group 3, 24 participants (36.9%) in Group 4, 17 participants (37.0%) in Group 5, and 15 participants (31.9%) in Group 6 had their tumor shrink by 30% or more under therapy that qualified for PR.

## Figure 2: Percentage of Participants With Reduction in Tumor Size




The researchers also assessed if lorlatinib would help participants with NSCLC that had spread to the brain. As shown in Figure 3 below, there were participants in each group who showed a reduction in brain tumor size after taking lorlatinib.

## Figure 3: Percentage of Participants With Reduction in Brain Tumor Size



Four out of 8 (50.0%) participants in Group 1, 6 out 17 (35.3%) participants in Group 2, 8 out of 33 (24.2%) participants in Group 3, 15 out of 45 (33.3%) participants in Group 4, 9 out of 37 (24.3%) participants in Group 5, and 10 out of 25 (40.0%) in Group 6 had the best response recorded with no signs of cancer and whose brain tumor completely disappeared (CR).

A total of 2 participants (25.0%) in Group 1, 4 participants (23.5%) in Group 2, 14 participants (42.4%) in Group 3, 9 participants (20.0%) in Group 4, 7 participants (18.9%) in Group 5, and 4 participants (16.0%) in Group 6 had their brain tumor shrink by 30% or more under therapy that qualified for PR.

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.

All 54 (100%) participants in Phase 1 and 274 out of 275 (99.6%) participants in Phase 2 of this study had at least 1 medical problem. A total of 6 (11.1%) participants in Phase 1 and 35 (12.7%) participants in Phase 2 permanently discontinued the study treatment because of medical problems. The most common medical problems – those reported by more than 10% of participants in Phase 1 and Phase 2 – are described below.

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

### Instructions for Understanding Table 1.

- The **1st** column of Table 1 lists medical problems that were commonly reported during Phase 1 of the study. All medical problems reported by more than 10% of participants in Phase 1 are listed.
- The **2nd** column tells how many of the 54 participants taking lorlatinib reported each medical problem. Next to this number is the percentage of the 54 participants taking lorlatinib who reported the medical problem.
- Using these instructions, you can see that 41 out of the 54 (75.9%) participants taking lorlatinib reported high level of cholesterol in the blood.

### Instructions for Understanding Table 2.

- The **1st** column of Table 2 lists medical problems that were commonly reported during Phase 2 of the study. All medical problems reported by more than 10% of participants in Phase 2 are listed.
- The **2nd** column tells how many of the 275 participants taking lorlatinib reported each medical problem. Next to this number

is the percentage of the 275 participants taking lorlatinib who reported the medical problem.

- Using these instructions, you can see that 232 out of the 275 (84.4%) participants taking lorlatinib reported high level of cholesterol in the blood.

**Table 1. Commonly reported medical problems reported by more than 10% of study participants in Phase 1**

| Medical Problem | Lorlatinib (54 participants) |
|---|---|
| **High level of cholesterol in the blood** | 41 out of 54 participants (75.9%) |
| **Swelling (or fluid retention)** | 35 out of 54 participants (64.8%) |
| **Nerve damage to the extremities such as hands, feet, or arms** | 33 out of 54 participants (61.1%) |
| **Fatigue** | 30 out of 54 participants (55.6%) |
| **High level of triglycerides (a type of fat) in the blood** | 25 out of 54 participants (46.3%) |
| **Inability to think, learn, and remember** | 22 out of 54 participants (40.7%) |
| **Low red blood cell count** | 19 out of 54 participants (35.2%) |

| Table 1. Commonly reported medical problems reported by more than 10% of study participants in Phase 1 | |
|---|---|
| **Medical Problem** | **Lorlatinib (54 participants)** |
| **Shortness of breath** | 17 out of 54 participants (31.5%) |
| **Speech and language abnormalities** | 16 out of 54 participants (29.6%) |
| **Mood effects which include depression (extreme sadness) and mania (extremely high mood)** | 15 out of 54 participants (27.8%) |
| **Weight increased** | 15 out of 54 participants (27.8%) |
| **Vision disorder** | 14 out of 54 participants (25.9%) |
| **Pain in a joint** | 14 out of 54 participants (25.9%) |
| **Backpain** | 14 out of 54 participants (25.9%) |
| **Diarrhea** | 14 out of 54 participants (25.9%) |
| **Nausea** | 14 out of 54 participants (25.9%) |
| **Liver test enzyme (aspartate aminotransferase) increased** | 13 out of 54 participants (24.1%) |
| **Headache** | 13 out of 54 participants (24.1%) |

| Table 1. Commonly reported medical problems reported by more than 10% of study participants in Phase 1 | |
|---|---|
| **Medical Problem** | **Lorlatinib (54 participants)** |
| **Constipation** | 12 out of 54 participants (22.2%) |
| **Cough** | 12 out of 54 participants (22.2%) |
| **Increased amount of protein (lipase) that help break down fat** | 12 out of 54 participants (22.2%) |
| **Nose and throat infection** | 12 out of 54 participants (22.2%) |
| **Increased amount of an enzyme (amylase) that changes starches and complex sugars into simple sugars** | 10 out of 54 participants (18.5%) |
| **Cancer got worse** | 10 out of 54 participants (18.5%) |
| **Abdominal pain** | 9 out of 54 participants (16.7%) |
| **Infection affecting the larger airways of the lungs** | 9 out of 54 participants (16.7%) |
| **Ringing in ear** | 9 out of 54 participants (16.7%) |
| **Vomiting** | 9 out of 54 participants (16.7%) |

| Table 1. Commonly reported medical problems reported by more than 10% of study participants in Phase 1 | |
|---|---|
| **Medical Problem** | **Lorlatinib (54 participants)** |
| **Liver test enzyme (alanine aminotransferase) increased** | 8 out of 54 participants (14.8%) |
| **Dizziness** | 8 out of 54 participants (14.8%) |
| **Fever** | 8 out of 54 participants (14.8%) |
| **Urinary tract infection** | 8 out of 54 participants (14.8%) |
| **Arm or leg pain** | 7 out of 54 participants (13.0%) |
| **Lung infection (pneumonia)** | 7 out of 54 participants (13.0%) |
| **Upper abdominal pain** | 6 out of 54 participants (11.1%) |
| **High blood pressure** | 6 out of 54 participants (11.1%) |
| **Low potassium levels in the blood** | 6 out of 54 participants (11.1%) |
| **Low magnesium levels in the blood** | 6 out of 54 participants (11.1%) |
| **Muscle pain** | 6 out of 54 participants (11.1%) |
| **Rash** | 6 out of 54 participants (11.1%) |

| Table 2. Commonly reported medical problems reported by more than 10% of study participants in Phase 2 | |
|---|---|
| **Medical Problem** | **Lorlatinib (275 participants)** |
| **High level of cholesterol in the blood** | 232 out of 275 participants (84.4%) |
| **High level of triglycerides (a type of fat) in the blood** | 189 out of 275 participants (68.7%) |
| **Swelling (or fluid retention)** | 155 out of 275 participants (56.4%) |
| **Nerve damage to the extremities such as hands, feet, or arms** | 136 out of 275 participants (49.5%) |
| **Inability to think, learn, and remember** | 86 out of 275 participants (31.3%) |
| **Shortness of breath** | 86 out of 275 participants (31.3%) |
| **Fatigue** | 84 out of 275 participants (30.5%) |
| **Pain in a joint** | 84 out of 275 participants (30.5%) |
| **Weight increased** | 77 out of 275 participants (28.0%) |
| **Diarrhea** | 69 out of 275 participants (25.1%) |

| Table 2. Commonly reported medical problems reported by more than 10% of study participants in Phase 2 | |
|---|---|
| **Medical Problem** | **Lorlatinib (275 participants)** |
| **Mood effects which include depression (extreme sadness) and mania (extremely high mood)** | 68 out of 275 participants (24.7%) |
| **Cough** | 68 out of 275 participants (24.7%) |
| **Nausea** | 60 out of 275 participants (21.8%) |
| **Headache** | 57 out of 275 participants (20.7%) |
| **Fever** | 53 out of 275 participants (19.3%) |
| **Dizziness** | 51 out of 275 participants (18.5%) |
| **Constipation** | 50 out of 275 participants (18.2%) |
| **Arm or leg pain** | 50 out of 275 participants (18.2%) |
| **Vision disorder** | 47 out of 275 participants (17.1%) |
| **Low red blood cell count** | 46 out of 275 participants (16.7%) |
| **Back pain** | 46 out of 275 participants (16.7%) |

| Table 2. Commonly reported medical problems reported by more than 10% of study participants in Phase 2 | |
|---|---|
| **Medical Problem** | **Lorlatinib (275 participants)** |
| **Vomiting** | 46 out of 275 participants (16.7%) |
| **Liver test enzyme (aspartate aminotransferase) increased** | 44 out of 275 participants (16.0%) |
| **Liver test enzyme (alanine aminotransferase) increased** | 42 out of 275 participants (15.3%) |
| **Increased amount of protein (lipase) that help break down fat** | 39 out of 275 participants (14.2%) |
| **Nose and throat infection** | 39 out of 275 participants (14.2%) |
| **Muscle pain** | 38 out of 275 participants (13.8%) |
| **Lung infection (pneumonia)** | 38 out of 275 participants (13.8%) |
| **Increased amount of an enzyme (amylase) that changes starches and complex sugars into simple sugars** | 35 out of 275 participants (12.7%) |
| **High blood pressure** | 35 out of 275 participants (12.7%) |
| **Rash** | 33 out of 275 participants (12.0%) |

| Table 2. Commonly reported medical problems reported by more than 10% of study participants in Phase 2 | |
|---|---|
| **Medical Problem** | **Lorlatinib (275 participants)** |
| **Chest pain** | 32 out of 275 participants (11.6%) |
| **Inability to sleep** | 30 out of 275 participants (10.9%) |
| **Cancer got worse** | 29 out of 275 participants (10.5%) |

# 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.

**Phase 1**

Thirty-three (33) out of 54 (61.1%) participants had serious medical problems. The most common serious medical problem was participants’ cancer getting worse (9 participants [16.7%]). Common serious medical problems reported by more than 5% of participants were: shortness of breath and lung infection (in 4 participants [7.4%] each), coughing up blood, mental status changes, and seizure (in 3 participants [5.6%] each).

Researchers thought that 8 out of 54 (14.8%) participants had serious medical problems that were related to taking lorlatinib. These serious medical problems were:

- Seizure (2 participants [3.7%])
- Mental status change, cognitive effects (a person’s inability to think, learn, and remember) cataract (clouding of the eye lens), muscle weakness and skin rash, hallucination, headache, increased amount of lipase, and nervous system symptoms (all in 1 participant [1.9%] each)

A total of 35 participants died in Phase 1 of the study. Thirty-three participants died due to disease under study and 2 participants died due to an unknown cause. None of these deaths were related to the study treatment.

## Phase 2

A total of 135 out of 275 (49.1%) participants had serious medical problems. The most common serious medical problems were participants' cancer getting worse (29 participants [10.5%]) and lung infection (19 participants [6.9%]).

Researchers assessed that 27 out of 275 (9.8%) participants had serious medical problems that were related to taking lorlatinib. Serious medical problems reported in more than 1 participant included cognitive effects (3 participants [1.1%]) and lung failure (2 participants [0.7%]).

A total of 151 participants died during Phase 2 of the study. Out of 151 participants, 129 participants died due to disease under study, 13 participants due to an unknown cause, and 9 participants died due to other reasons. None of these deaths were 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 B7461001 |

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

| | |
|---|---|
| www.clinicaltrials.gov | Use the study identifier **NCT01970865** |
| www.clinicaltrialsregister.eu | Use the study identifier 2013-002620-17 |

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!