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 study participants. The results of this study might be different than the results of other studies that the researchers review.

Sponsor: Pfizer Inc.

Medicine(s) Studied: Palbociclib (PD-0332991)

Protocol Number: A5481027

Dates of Study: 23 March 2015 to 31 August 2020, the study is still ongoing

Title of this Study: A Study Comparing Palbociclib Plus Letrozole Versus Placebo Plus Letrozole for the Treatment of Asian Postmenopausal Women with Advanced Breast Cancer

[A Multicenter, Randomized, Double-Blind Phase 3 Study of Palbociclib (Oral CDK 4/6 Inhibitor) Plus Letrozole Versus Placebo Plus Letrozole for the Treatment of Previously Untreated Asian Postmenopausal Women with ER (+), HER2 (-) Advanced Breast Cancer]

Date(s) of this Report: 15 July 2021

– 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.

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Why was this study done?

What is Advanced Breast Cancer?

Sometimes, breast cancer can spread from the breast to other parts of the body, most often to the bones, lungs, liver, or brain. This is called advanced breast cancer. Advanced breast cancer cannot be treated by surgery or radiation therapy with the intention to cure the cancer, but to slow down the development of the cancer and help the patient live longer. The participants in this study had estrogen receptor-positive [ER (+)] breast cancer, human epidermal growth factor receptor 2 negative [HER2 (-)] advanced breast cancer. The cells of ER (+) breast cancer have receptors that allow them to use the hormone estrogen to grow and HER2 (-) means that the participants have a normal amount of HER2 proteins in the breast cells (too much of this protein means that there is another type of cancer present). This type [ER (+), HER2 (-)] of advanced breast cancer is sensitive to hormonal treatment.

What is Palbociclib?

Palbociclib is a medicine that has been used to treat a specific type of breast cancer known as hormone receptor positive [HR (+)] and HER2 (-). A hormone receptor is a receptor molecule that binds to a specific hormone. A breast cancer is classified as HR (+) if its cells have receptors for the hormones; estrogen and progesterone. Palbociclib targets the functioning of specific proteins or enzymes called cyclin-dependent kinases (CDK4 and CDK6). These enzymes are important for normal cell division and when they are damaged, they may cause cancer cells to grow and spread. Certain cancers, for example, ER (+), are more likely to have disturbances in CDK4 and CDK6. Palbociclib prevents the CDK4 and CDK6 enzymes from functioning which stops the cells from dividing and stops the growth of breast cancer cells.

What was the purpose of this study?

The purpose of this research study was to compare the effect of the study drug, palbociclib, plus letrozole, with placebo plus letrozole to find out which is better for treating advanced breast cancer in Asian women who have not received any previous systemic treatment and have already experienced menopause (stopping of menstrual periods permanently).

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- Palbociclib is an approved medicine.
- Systemic treatment is any medication that travels through your body in the bloodstream to find, damage, or destroy cancer cells. It includes chemotherapy, immunotherapy, hormone therapy, or targeted therapy.
- A placebo looks like the medicine under study but does not contain any medicine. Researchers use a placebo to see if the study medicine works better or is safer than not taking it.
- Letrozole is a hormonal medicine that is approved for the treatment of advanced breast cancer that is sensitive to hormonal treatment. Letrozole is available outside of this research study by a doctor's prescription.

Researchers wanted to know:

Did the participants taking palbociclib plus letrozole have a better progression-free survival (PFS) than participants that were taking placebo plus letrozole?

- Researchers wanted to determine the PFS of participants taking palbociclib plus letrozole and compare it to the PFS of participants taking placebo plus letrozole.
- The PFS is the length of time during and after receiving a treatment for a disease, during which a patient lives with the disease not getting worse.

How participants tolerated palbociclib and whether it caused any medical problems?

- Researchers also wanted to learn more about the safety and tolerability of palbociclib.
- They monitored the participants for any medical problems that happened while they were in the study.

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What happened during the study?

How was the study done?

Researchers tested palbociclib (test medicine) combined with letrozole on a group of study participants with advanced breast cancer to find out if it provided a longer PFS than study participants with advanced breast cancer taking placebo plus letrozole. A description of the how the study was done can be seen in Figure 1 below.

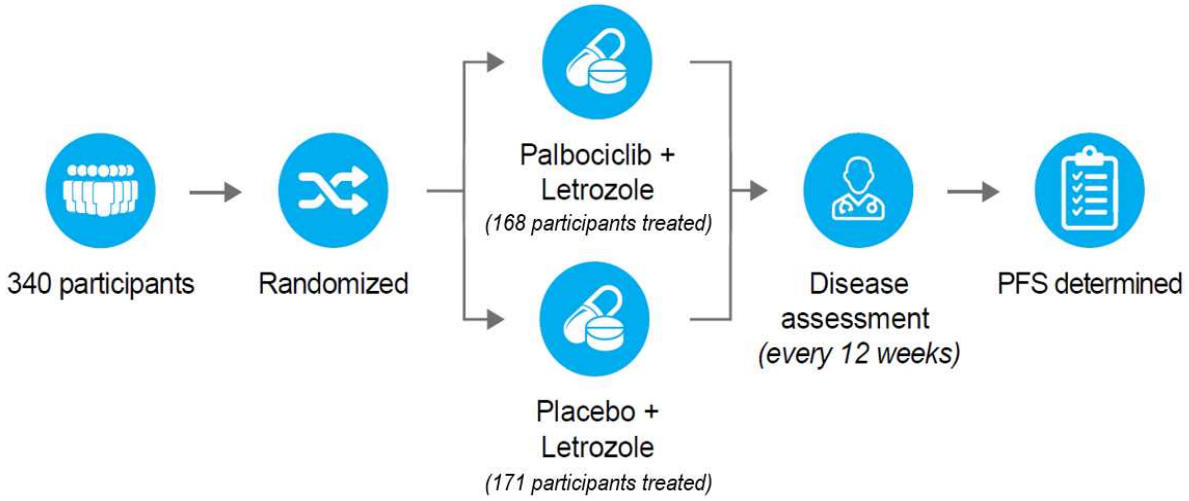

Figure 1. A description of how the study was done.

After the last dose of palbociclib treatment, study participants were contacted by the study team every 6 months to asked about:

- Any changes in the health of the participant
- Any medications the participant was taking

Study participants were assigned to each group by chance alone. Neither the study participants nor the researchers knew who took palbociclib and who took the placebo. This is known as a "blinded" study.

Where did this study take place?

The Sponsor ran this study at 52 locations across Mainland China, Hong Kong, Taiwan, Thailand, and Singapore.

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When did this study take place?

It began 23 March 2015, and the primary completion date was 31 August 2020. Primary completion date corresponds to the date when the last participant was examined or received treatment and that results for the main results were collected. This study is ongoing.

Who participated in this study?

The study included participants with advanced breast cancer, who were between the ages of 18 and 70 years, had already experienced menopause, and had not received any systemic treatment for their advanced disease.

- A total of 340 women participated and 339 women were treated in this study
- All participants were between the ages of 29 and 70 years

Participants were to be treated until disease progression, death or unable to tolerate the treatment, or withdrawal of consent, whichever occurred first. PFS was determined based on the disease progression or death of study participants. Of the 340 participants who started the study, 138 are still participating in the study.

Two hundred and ninety participants discontinued the study treatment because

- The participant died
- The participant was lost to follow-up
- The participant's cancer got worse
- The participant experienced medical problems
- The participants left by their choice or a doctor decided it was best for a participant to stop being in the study

How long did the study last?

The entire study took 5 years to the primary completion date, the study is still ongoing. However, when the primary completion point was reached in August 2020, the Sponsor began reviewing the information collected. The Sponsor then created a report of the results. This is a summary of that report.

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What were the results of the study?

Did the participants taking palbociclib plus letrozole have a longer PFS than participants that were taking placebo plus letrozole?

Researchers determined the median PFS (in months) for participants with advanced breast cancer taking palbociclib plus letrozole and for participants taking placebo plus letrozole (Figure 2). The median is the middle number in a set of values when these values are arranged from smallest to largest.

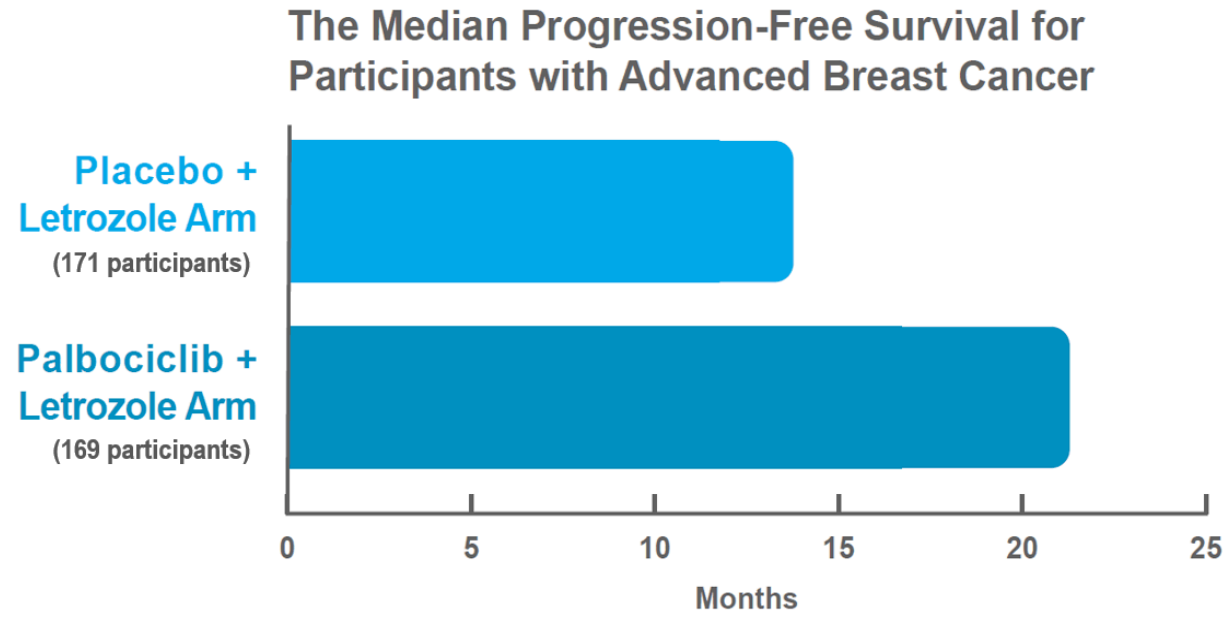

Figure 2. The median PFS of participants with advanced breast cancer.

Researchers found that participants who took palbociclib plus letrozole had a longer median PFS (22 months) in comparison to the participants taking placebo plus letrozole (median PFS of 14 months).

The hazard ratio (HR) was 0.677 (95% confidence interval [CI]: 0.529, 0.867) which favored the palbociclib plus letrozole group. The HR is a comparison between the probability of events in a treatment group (palbociclib plus letrozole), compared to the probability of events in a control group (placebo plus letrozole).

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- An HR of 1 means that both groups (treatment and control) are experiencing an equal number of events at any point in time.
- The 95% CI is a range with an upper and lower number calculated from a sample. Because the true population HR is unknown, this range describes possible values that the HR could be.

Kaplan-Meier plots (graphs) are used to show what the probability of PFS is at a certain time point. It usually compares two treatment groups in a study and was used to compare the palbociclib plus letrozole group and the placebo plus letrozole group in this study. The Kaplan-Meier Plot of PFS is shown below in Figure 3. This figure shows that participants in the palbociclib plus letrozole group had a higher probability of PFS than participants in the placebo plus letrozole group for most of the follow-up time.

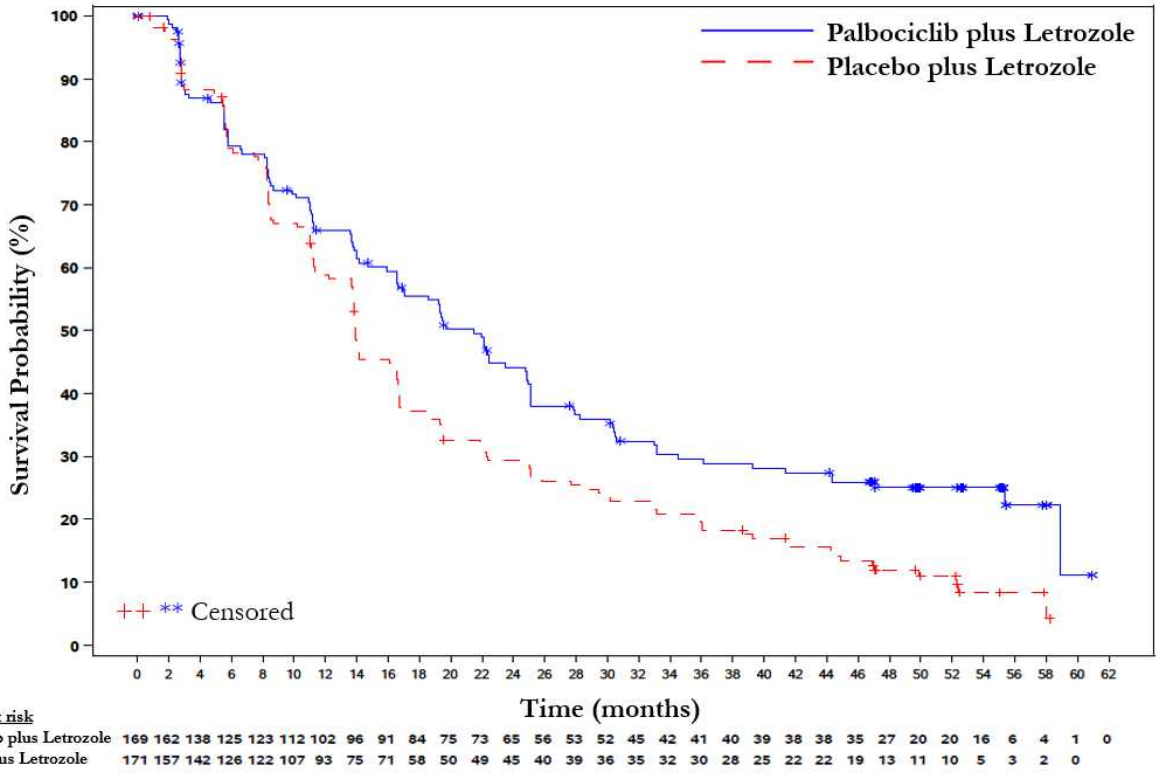

Figure 2. Kaplan-Meier Plot of PFS.

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Researchers have decided that the results are not likely the result of chance. The addition of palbociclib to letrozole may help prolong the PFS of participants with advanced breast cancer and could be used as a treatment for advanced breast cancer.

This does not mean that everyone in this study had these results. These are just some of the main findings 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.

Three hundred and twenty three out of 339 (95%) participants who received treatment in this study had at least 1 medical problem. A total of 18 participants discontinued the study because of medical problems. The most common medical problems, those reported by more than 20% of participants taking palbociclib plus letrozole, are described below.

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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 occurring in more than 20% of participants taking palbociclib are listed. The severity of the medical problems shown in Table 1 ranged from mild, moderate, severe/medically significant, life-threatening, or resulted in death. However, none of the medical problems shown in Table 1 was associated with death.
- Some medical problems were grouped together because they were the same problem but reported differently. For example, "White blood cell decreased," and "leukopenia" or "Neutrophil count decreased" and "Neutropenia". These are known as clustered medical problems. For example, 144 of 168 (86%) participants taking palbociclib experienced a low white blood cell count, including the white blood cells known as leukocytes (leukopenia). These medical problems were grouped under the leukopenia cluster. Clustered medical problems are marked with a star (*) and written in capital letters in column **1** of Table 1.
- The **2nd** column tells how many of the 168 participants taking palbociclib reported each medical problem. Next to this number is the percentage of the 168 participants taking the study medication who reported the medical problem.
- The **3rd** column tells how many of the 171 participants taking a placebo reported each medical problem. Next to this number is the percentage of the 171 participants taking the placebo who reported the medical problem.
- Using these instructions, you can see that 165 out of the 168 (98%) participants taking palbociclib reported a low white blood cell count (for the white blood cells known as neutrophils [neutropenia]). A total of 56 out of the 171 (33%) participants taking a placebo reported an increase in liver enzymes (alanine aminotransferase). An increase in liver enzymes may indicate liver damage.

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Table 1. Commonly reported medical problems by study participants (Medical problems reported in at least 20% of study participants taking palbociclib)

Medical Problem	Palbociclib (168 Participants)	Placebo (171 Participants)
LOW WHITE BLOOD CELL (NEUTROPHILS) COUNT (NEUTROPENIA)*	165 out of 168 participants (98%)	29 out of 171 participants (17%)
LOW WHITE BLOOD CELL (LEUKOCYTES) COUNT (LEUKOPENIA)*	144 out of 168 participants (86%)	22 out of 171 participants (13%)
LOW BLOOD PLATELETS (THROMBOCYTOPENIA)*	82 out of 168 participants (49%)	0 out of 171 participants (0%)
LOW RED BLOOD CELL COUNT*	77 out of 168 participants (46%)	3 out of 171 participants (2%)
Increase in liver enzymes (alanine aminotransferase)	56 out of 168 participants (33%)	56 out of 171 participants (33%)
Increase in liver enzymes (aspartate aminotransferase)	58 out of 168 participants (35%)	48 out of 171 participants (28%)
INFECTIONS*	52 out of 168 participants (31%)	53 out of 171 participants (31%)

Did study participants have any serious medical problems?

A medical problem is considered "serious" when it is life-threatening, needs hospital care, results in death, or causes lasting problems. Forty-two out of 339 participants (12%) had serious medical problems. A larger percentage of participants in the palbociclib plus letrozole group than in the placebo plus letrozole group had at least 1 serious medical problem during the study.

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Below are instructions on how to read Table 2.

Instructions for Understanding Table 2.

- The **1st** column of Table 2 lists serious medical problems that were reported during the study. The severity of the medical problems shown in Table 2 ranged from mild, moderate, severe/medically significant, life-threatening, or resulted in death. One medical problem shown in Table 2 resulted in death
- Clustered medical problems are marked with a star (*) and written in capital letters in column **1** of Table 2.
- The **2nd** column tells how many of the 168 participants taking palbociclib reported each serious medical problem. Next to this number is the percentage of the 168 participants taking the study medication who reported the serious medical problem.
- The **3rd** column tells how many of the 171 participants taking a placebo reported each serious medical problem. Next to this number is the percentage of the 171 participants taking a placebo who reported the serious medical problem.
- Using these instructions, you can see that 4 out of the 168 (2%) participants taking palbociclib reported an infection. A total of 5 out of the 171 (%) participants taking a placebo reported an infection.

Table 2. Serious medical problems reported by study participants who received a treatment

Serious Medical Problem	Palbociclib (168 Participants)	Placebo (171 Participants)
INFECTIONS*	4 out of 168 participants (2%)	5 out of 171 participants (3%)
Increased fluid around lungs	3 out of 168 participants (2%)	0 out of 171 participants (0%)
Broken ankle	2 out of 168 participants (1%)	0 out of 171 participants (0%)

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Table 2. Serious medical problems reported by study participants who received a treatment

Serious Medical Problem	Palbociclib (168 Participants)	Placebo (171 Participants)
Uncontrolled spread and growth of cancer cells	2 out of 168 participants (1%)	0 out of 171 participants (0%)
Fever	2 out of 168 participants (1%)	0 out of 171 participants (0%)
Blood cancer of the bone marrow	1 out of 168 participants (1%)	0 out of 171 participants (0%)
Uncontrolled bleeding in the brain	1 out of 168 participants (1%)	0 out of 171 participants (0%)
Clinical death	1 out of 168 participants (1%)	0 out of 171 participants (0%)
Cancer continued to grow or spread	1 out of 168 participants (1%)	1 out of 171 participants (1%)
Shortness of breath	1 out of 168 participants (1%)	1 out of 171 participants (1%)
Fall	1 out of 168 participants (1%)	0 out of 171 participants (0%)
Low white blood cell count with fever	1 out of 168 participants (1%)	0 out of 171 participants (0%)
Broken bone	1 out of 168 participants (1%)	0 out of 171 participants (0%)
Abnormal liver function	1 out of 168 participants (1%)	1 out of 171 participants (1%)
Fluid leaking in space around the lung	1 out of 168 participants (1%)	0 out of 171 participants (0%)
High blood pressure	1 out of 168 participants (1%)	0 out of 171 participants (0%)
Low blood sodium	1 out of 168 participants (1%)	0 out of 171 participants (0%)
Liver injury	1 out of 168 participants (1%)	0 out of 171 participants (0%)
Stage II cancer of the ovaries	1 out of 168 participants (1%)	0 out of 171 participants (0%)
BLOOD CLOT IN LUNG ARTERY*	1 out of 168 participants (1%)	0 out of 171 participants (0%)
Thyroid cancer	1 out of 168 participants (1%)	0 out of 171 participants (0%)
LOW BLOOD PLATELETS*	1 out of 168 participants (1%)	1 out of 171 participants (1%)
Partial or complete tear of a tendon	1 out of 168 participants (1%)	0 out of 171 participants (0%)
High blood calcium	0 out of 168 participants (0%)	2 out of 171 participants (1%)
Coronary artery (blood vessel) disease	0 out of 168 participants (0%)	1 out of 171 participants (1%)
Dizziness	0 out of 168 participants (0%)	1 out of 171 participants (1%)
Ear disorder	0 out of 168 participants (0%)	1 out of 171 participants (1%)
Liver damage caused by medication	0 out of 168 participants (0%)	1 out of 171 participants (1%)
Broken bone of lower limb	0 out of 168 participants (0%)	1 out of 171 participants (1%)

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Table 2. Serious medical problems reported by study participants who received a treatment

Serious Medical Problem	Palbociclib (168 Participants)	Placebo (171 Participants)
Broken wrist	0 out of 168 participants (0%)	1 out of 171 participants (1%)
Thyroid mass	0 out of 168 participants (0%)	1 out of 171 participants (1%)

Seventy-nine participants died (all causes) in the palbociclib plus letrozole group during the study. Death of one participant (1%) was reported as palbociclib plus letrozole treatment related. However, the study treatment causality could not be fully excluded by the treating doctor. The conclusive death reason was unknown. Eighty-six participants died (all causes) in the placebo plus letrozole group during the study. Most of the deaths happened more than 30 days after the participants received the last dose of treatment and were caused by advanced breast cancer.

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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	Use the study identifier **NCT02297438**
www.pfizer.com/research/research_clinical_trials/trial_results	Use the protocol number **A5481027**

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

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

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