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: *Bosulif*®/Bosutinib

Protocol Number: AV001 B1871053

Dates of Study: 15 July 2014 to 17 April 2020

Title of this Study: A Multicenter Phase 3 Randomized, Open-Label Study of Bosutinib Versus Imatinib in Adult Patients With Newly Diagnosed Chronic Phase Chronic Myelogenous Leukemia (Bosutinib trial in First line chrOnic myelogenous leukemia tREatment; BFORE)

[A Multicenter Phase 3 Randomized, Open-Label Study of Bosutinib Versus Imatinib in Adult Patients With Newly Diagnosed Chronic Phase Chronic Myelogenous Leukemia]

Date(s) of this Report: 14 December 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.

Why was this study done?

What is Chronic Myeloid Leukemia?

Chronic myeloid leukemia (CML) is a cancer that begins in cells within the bone marrow. The bone marrow is the spongy inner portion of bones where blood cells are made. Normally, these cells divide into different types of blood cells: white blood cells, red blood cells, and platelets.

Sometimes a mistake happens when the bone marrow cells divide and unhealthy cells are produced. In CML, the unhealthy cells produce a protein called breakpoint cluster region protein/Abelson murine leukemia viral oncogene (BCR-ABL). The protein BCR-ABL causes CML. This protein leads to the production of too many unhealthy cells (leukemic cells) that crowd out healthy cells.

What is Bosutinib?

Tyrosine kinases are proteins in the body that control how cells grow and divide. Bosutinib is a drug that blocks a tyrosine kinase called BCR-ABL, which means that when treated with bosutinib, BCR-ABL is deactivated or is less active. This study compared *Bosulif*®/bosutinib 400 mg and imatinib 400 mg. Both drugs are tablets taken by mouth.

At the time this study began, bosutinib was approved for patients with CML when the initial treatment given is no longer controlling the disease (known as resistance) or has had to be stopped because they could not tolerate it (known as intolerance). Imatinib is a marketed drug approved for the treatment of patients with newly diagnosed CML, and is considered a standard treatment for newly diagnosed/previously untreated CML.

What was the purpose of this study?

The main reason researchers did this study was to provide another choice for the treatment of CML in adult patients who were newly diagnosed. Specifically, researchers wanted to know what percentage (%) of participants receiving bosutinib 400 mg reached a major molecular response (MMR) at 48 weeks after treatment started compared to participants receiving imatinib 400 mg. A major molecular response means that the participant has low levels of BCR-ABL, more specifically, levels of BCR-ABL that are 0.1% or less. In addition, researchers wanted to know about any medical problems participants had during the study.

Researchers wanted to know:

What percentage (%) of participants receiving bosutinib 400 mg reached a MMR at 48 weeks compared to participants receiving imatinib 400 mg? A major molecular response means that BCR-ABL levels were 0.1% or less.

What happened during the study?

How was the study done?

Researchers tested bosutinib on a group of study participants to find out if participants taking bosutinib 400 mg reached MMR at 48 weeks compared to participants taking imatinib 400 mg. Participants were assigned to one of the following treatment groups:

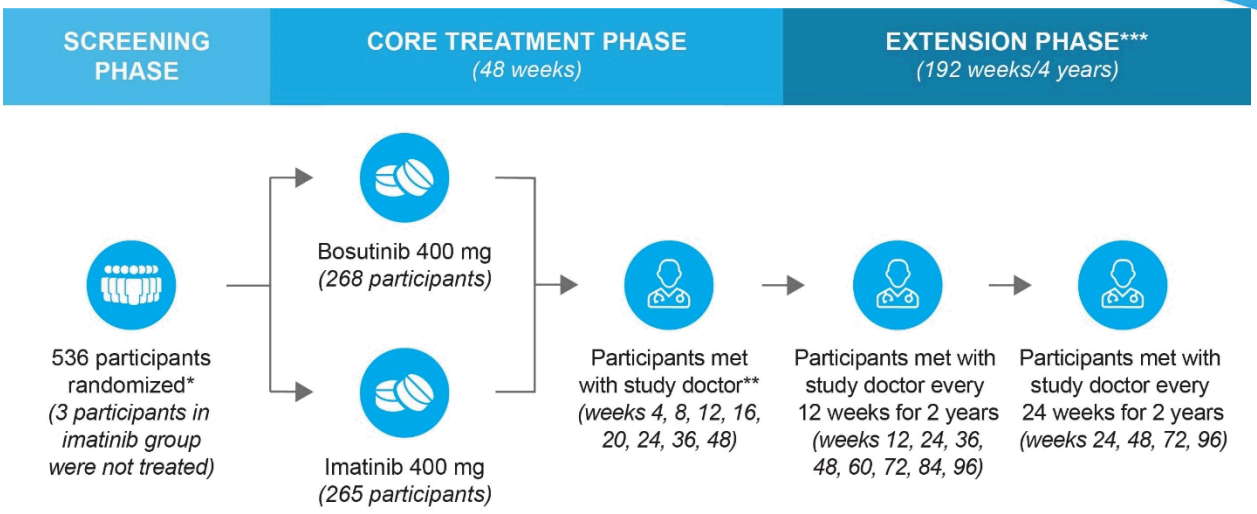
- Bosutinib 400 mg, an investigational drug, which means bosutinib was not approved for use in this country to treat CML as initial therapy when the study started
- Imatinib 400 mg

This was an "open-label" study, which means that doctors and participants knew which treatment participants were receiving. However, the laboratory that evaluated MMR was not aware of which treatment participants received (blinded). Participants were assigned to each treatment group by chance, like a flip of a coin, and had an equal chance of assignment to either treatment group. This is called randomization and is done to make the groups more similar.

Study Plan

During this 48-week treatment period, participants were required to meet with their study doctor every 4 weeks for the first 24 weeks, then at 36 weeks, and at 48 weeks for an exam (Core Treatment Phase).

If participants responded to treatment, they continued to take their assigned treatment for 4 more years (192 weeks) (Extension Phase) after the initial 48 weeks of treatment. Participants met with their study doctor for follow-up visits until they reached 5 years of treatment or until the CML got worse. The participants could continue to receive treatment after the study was completed at the discretion of their treating physician.



* 533 participants were treated

** Evaluation of symptoms and general health.

*** Participants were asked to come in for follow-up visits until they reached the end of the 4 year period or until their condition worsened/disease progressed.

Where did this study take place?

The Sponsor ran this study at 146 locations in 26 countries in 6 regions of the world, including: Australia, Asia, Europe, Middle East, North America, and South Africa.

When did this study take place?

This study began 15 July 2014 and ended 17 April 2020.

Who participated in this study?

Participants in this study had to meet the following inclusion/exclusion criteria: newly diagnosed CML; molecular diagnosis of CML positive for BCR-ABL; no previous treatment except for hydroxyurea or anagrelide; acceptable liver and kidney function; no central nervous system (brain and spinal cord) involvement; and the ability to swallow tablets.

- A total of 311 men participated
- A total of 225 women participated
- All participants were between the ages of 18 years and 84 years

Participants were to be treated until 5 years after starting the study. Of the 536 participants who started the study, 463 participants finished the study.

73 participants (14%; 14 out of 100) did not finish the study because of:

- Participant request: 24 participants (5%; 5 out of 100)
- Participant passed away: 28 participants (5%; 5 out of 100)
- Lost to follow-up: 13 participants (2%; 2 out of 100)
- Missing: 3 participants (1%; 1 out of 100)
- Other reason: 3 participants (1%; 1 out of 100)
- Physician request: (2 participants, or less than 1%, did not finish the study because their doctor decided it was best for a participant to stop being in the study).

Of the 533 participants who received treatment, a total of 314 participants (59%; 59 out of 100) were still receiving the study drug at the end of the 5-year study period in both groups.

- 160 (60%; 60 out of 100) participants in the bosutinib group were still receiving bosutinib at the end of the study period. 154 (58%; 58 out of 100) participants in the imatinib group were still receiving imatinib at the end of the study period.
- 219 (41%; 41 out of 100) participants discontinued treatment. The most common reasons for discontinuing treatment (occurring in ≥5% of participants) were:
    - 100 participants (19%; 19 out of 100) stopped treatment due to a medical problem. 67 participants (25%; 25 out of 100) in the bosutinib group stopped treatment because of a medical problem and 33 participants (13%; 13 out of 100) in the imatinib group stopped treatment because of a medical problem.
    - 56 participants (11%; 11 out of 100) stopped treatment because they did not respond to treatment as expected (treatment failure). 13 participants (5%; 5 out of 100) in the bosutinib group and 43 participants (16%;

16 out of 100) in the imatinib group stopped treatment because of treatment failure.

How long did the study last?

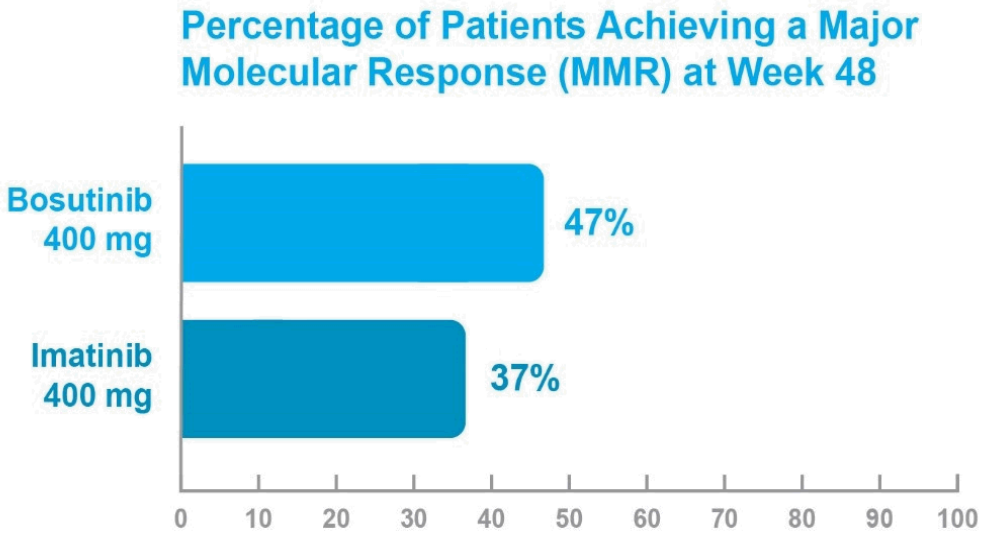
Study participants were in the study for 5 years. The entire study took almost 6 years to complete.

The Sponsor began reviewing the information collected in 2016 and the created a report of the results. The study ended in April 2020 and another report was created that included longer-term information. This is a summary of the 2020 report.

What were the results of the study?

What percentage (%) of participants receiving bosutinib 400 mg reached a MMR at 48 weeks compared to participants receiving imatinib 400 mg?

47% (47 out of 100) of participants receiving bosutinib 400 mg achieved MMR at Week 48, while 37% (37 out of 100) of participants receiving imatinib 400 mg achieved MMR at Week 48.



Based on these results, researchers decided that the results are likely the result of the medication and not due to chance. Bosutinib may be an option for treating patients with newly diagnosed CML.

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 treatment 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.

527 participants out of 533 (99%; 99 out of 100) participants in this study had at least 1 medical problem. 496 participants out of 533 (93%; 93 out of 100) participants had medical problems that the researchers thought were caused by one of the study drugs.

Of the 268 participants treated with bosutinib, 265 participants (99%; 99 out of 100) had medical problems. Of the 265 participants treated with imatinib, 262 of the 265 (99%; 99 out of 100) participants had medical problems.

Of the 533 participants, 106 participants (20%; 20 out of 100) stopped taking study treatment because of medical problems. Of the participants treated with bosutinib, 68 of the 268 participants (25%; 25 out of 100) stopped taking bosutinib because of medical problems. Of the participants treated with imatinib, 38 of the 265 participants (14%; 14 out of 100) stopped taking study treatment because of medical problems. The most common medical problems – those reported by at least 10% of participants – are described below.

Below are instructions on how to read Table 1 Most Common Medical Problems.

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 ≥10% of participants are listed.
- The **2nd** column tells how many of the 268 participants taking bosutinib reported each medical problem. Next to this number is the percentage of the 268 participants taking bosutinib who reported the medical problem.
- The **3rd** column tells how many of the 265 participants taking imatinib reported each medical problem. Next to this number is the percentage of the 265 participants taking imatinib who reported the medical problem.
- Using these instructions, you can see that 10 participants out of the 268 (4%) participants taking bosutinib reported muscle cramps. A total of 81 participants out of the 265 (31%) participants taking imatinib reported muscle cramps.

Table 1: Commonly reported medical problems by study participants

Medical Problem	Bosutinib 400 mg (268 Participants)	Imatinib 400 mg (265 Participants)
Loose stools	201 out of 268 participants (75%)	107 out of 265 participants (40%)
Feel like throwing up	100 out of 268 participants (37%)	112 out of 265 participants (42%)
Low platelets	96 out of 268 participants (36%)	53 out of 265 participants (20%)
Increase in liver enzyme-alanine aminotransferase (ALT)	90 out of 268 participants (34%)	16 out of 265 participants (6%)
Increase in liver enzyme-aspartate aminotransferase (AST)	69 out of 268 participants (26%)	18 out of 265 participants (7%)
Rash	62 out of 268 participants (23%)	39 out of 265 participants (15%)
Stomach pain	61 out of 268 participants (23%)	25 out of 265 participants (9%)
Low red blood cells	59 out of 268 participants (22%)	60 out of 265 participants (23%)
Headache	59 out of 268 participants (22%)	41 out of 265 participants (16%)

Medical Problem	Bosutinib 400 mg (268 Participants)	Imatinib 400 mg (265 Participants)
Feeling tired	57 out of 268 participants (21%)	54 out of 265 participants (20%)
Increase in pancreas enzyme-lipase	56 out of 268 participants (21%)	30 out of 265 participants (11%)
Throwing up	55 out of 268 participants (21%)	54 out of 265 participants (20%)
Joint pain	48 out of 268 participants (18%)	49 out of 265 participants (19%)
Fever	46 out of 268 participants (17%)	30 out of 265 participants (11%)
Nose/throat infection	37 out of 268 participants (14%)	33 out of 265 participants (13%)
Common cold	36 out of 268 participants (13%)	30 out of 265 participants (11%)
Difficulty passing stools	36 out of 268 participants (13%)	17 out of 265 participants (6%)
Feeling weak	34 out of 268 participants (13%)	24 out of 265 participants (9%)
Low white blood cell type that fights infection	33 out of 268 participants (12%)	61 out of 265 participants (23%)
Back pain	32 out of 268 participants (12%)	25 out of 265 participants (9%)

Medical Problem	Bosutinib 400 mg (268 Participants)	Imatinib 400 mg (265 Participants)
Not feeling hungry	30 out of 268 participants (11%)	17 out of 265 participants (6%)
Cough	30 out of 268 participants (11%)	26 out of 265 participants (10%)
Itching	30 out of 268 participants (11%)	10 out of 265 participants (4%)
Difficulty breathing	29 out of 268 participants (11%)	15 out of 265 participants (6%)
Pain in upper stomach	28 out of 268 participants (10%)	27 out of 265 participants (10%)
Urinary tract infection	27 out of 268 participants (10%)	20 out of 265 participants (8%)
Leg/arm pain	26 out of 268 participants (10%)	39 out of 265 participants (15%)
Increased blood pressure	26 out of 268 participants (10%)	29 out of 265 participants (11%)
Swelling in hands/feet	20 out of 268 participants (8%)	43 out of 265 participants (16%)
Low total white blood cells	18 out of 268 participants (7%)	34 out of 265 participants (13%)
Increase in enzyme-creatine phosphokinase	14 out of 268 participants (5%)	33 out of 265 participants (13%)

Medical Problem	Bosutinib 400 mg (268 Participants)	Imatinib 400 mg (265 Participants)
Muscle pain	13 out of 268 participants (5%)	48 out of 265 participants (18%)
Muscle cramps	10 out of 268 participants (4%)	81 out of 265 participants (31%)
Swelling around the eye	4 out of 268 participants (2%)	44 out of 265 participants (17%)

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. The serious medical problems reported by at least 1% of participants are listed in Table 2 below.

166 participants (31%, or 31 out of 100 participants) out of 533 participants in the study had serious medical problems.

- 98 participants (37%; 37 out of 100) out of 268 in the bosutinib group had a serious medical problem.
- 68 participants (26%; 26 out of 100) out of 265 in the imatinib group had a serious medical problem.

28 participants (5%; 5 out of 100) passed away during the study. 14 deaths were in the bosutinib group and 14 deaths were in the imatinib group. Of those participants given bosutinib, researchers believe that no deaths were related to bosutinib. Of those participants given imatinib, researchers believe that 1 death was related to imatinib.

Below are instructions on how to read Table 2 Most Common Serious Medical Problems.

Instructions for Understanding Table 2.

- The **1st** column of Table 2 lists serious medical problems that were reported during the study. All medical problems reported by ≥1% of participants are listed.
- The **2nd** column tells how many of the 268 participants taking bosutinib reported each serious medical problem. Next to this number is the percentage of the 268 participants taking bosutinib who reported the serious medical problem.
- The **3rd** column tells how many of the 265 participants taking imatinib reported each serious medical problem. Next to this number is the percentage of the 265 participants taking imatinib who reported the medical problem.
- Using these instructions, you can see that 5 out of the 268 (2%) participants taking bosutinib reported a fever. One participant out of the 265 (less than 1%) participants taking imatinib reported a fever.

Table 2: Commonly reported serious medical problems by study participants

Serious Medical Problem	Bosutinib 400 mg (268 Participants)	Imatinib 400 mg (265 Participants)
Lung infection	8 out of 268 participants (3%)	5 out of 265 participants (2%)
Stomach flu	6 out of 268 participants (2%)	1 out of 265 participants (less than 1%)
Increase in liver enzyme-alanine aminotransferase (ALT)	6 out of 268 participants (2%)	0 out of 265 participants (0%)
Fever	5 out of 268 participants (2%)	1 out of 265 participants (less than 1%)
Loose stools	5 out of 268 participants (2%)	1 out of 265 participants (less than 1%)
Reduced blood flow to heart	4 out of 268 participants (2%)	0 out of 265 participants (0%)
Sudden kidney failure	4 out of 268 participants (2%)	0 out of 265 participants (0%)
Fluid around the lung	4 out of 268 participants (2%)	1 out of 265 participants (less than 1%)
Skin infection	3 out of 268 participants (1%)	2 out of 265 participants (1%)

Table 2: Commonly reported serious medical problems by study participants		
Serious Medical Problem	**Bosutinib 400 mg (268 Participants)**	**Imatinib 400 mg (265 Participants)**
Low red blood cells	1 out of 268 participants (less than 1%)	3 out of 265 participants (1%)
Blood infection	0 out of 268 participants (0%)	3 out of 265 participants (1%)

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.clinicaltrials.gov	Use the study identifier **NCT02130557**
www.clinicaltrialsregister.eu	Use the study identifier **2013-005101-31**

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!