Clinical Study Results

1. Study name

What does this summary cover?

This summary shows the main results from only one clinical study. Researchers look at the results of many studies to decide which investigational medicines work best and are safest for patients.

Title of the study:	A Double-blind, Randomized, Placebo-controlled, Multicenter, Dose Escalation Study to Select and Evaluate an Oral Modified Release Formulation of Omecamtiv Mecarbil in Subjects With Heart Failure and Left Ventricular Systolic Dysfunction
Brief Title:	COSMIC-HF – Chronic Oral Study of Myosin Activation to Increase Contractility in Heart Failure
Protocol Number:	20110151
EU Trial Number	2012-000327-40
US National Clinical Trial Number:	NCT01786512
Date of This Summary	01 May 2017

2. Who sponsored the study?

Who was the sponsor of the study?

Amgen Inc.

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Amgen Inc., the sponsor of this study, along with Cytokinetics, a company collaborating with Amgen, would like to thank everyone who participated in this study and feels it is important to share the results of this study.

3. General information about the clinical trial

Where and when was the study done?

This study took place at 105 centers in 13 countries in Europe, Australia, and North America. The study began in January 2013 and ended in August 2015. The study was completed as planned.

Why was the study done?

This study was done to find out which dose and formulation of a new investigational medicine, called omecamtiv mecarbil, works best in people with heart failure and if omecamtiv mecarbil should undergo further study to determine if it might make people with heart failure live longer and stay out of the hospital. This study had 2 different parts. Participants could only join 1 part of the study (Part 1 or Part 2):

Part 1

- This was the first part of the study.
- Researchers looked at how 2 different doses and 3 different formulations of omecamtiv mecarbil were released into participants' blood and whether they cause any side effects.

Part 2

- This was the second part of the study, which extended findings from Part 1 of the study.
- Researchers chose the best formulation from Part 1 and looked at the following:
    - how it works in the body with longer treatment
    - its effects on the heart and symptoms of heart failure
    - whether it causes any side effects

4. What patients/people were included in this study?

Who took part in the study?

This study included 544 men and women of 32 to 84 years of age with heart failure. People from the following countries took part in the study:

Country	Part 1	Part 2
Belgium	--	14 participants
Bulgaria	15 participants	37 participants
Czech Republic	--	16 participants
Germany	1 participant	29 participants
Hungary	22 participants	26 participants
Italy	--	12 participants
Lithuania	--	21 participants
Netherlands	--	18 participants
Poland	19 participants	73 participants
United Kingdom	--	37 participants
European Union Total	57 participants	283 participants
Australia	--	5 participants
Canada	1 participant	52 participants
United States	38 participants	108 participants

This study was for people from 18 to 85 years of age with chronic heart failure. In Part 1 of the study:

- 76 participants (79%, or about 8 out of 10) were men and 20 (21%, or about 2 out of 10) were women
- Participants ranged in age from 40 to 82 years

- 41 participants (43%, or about 4 out of 10) were under 65 years old

In Part 2 of the study:

- 371 participants (83%, or about 8 out of 10) were men and 77 participants (17%, or about 2 out of 10) were women
- Participants ranged in age from 32 to 84 years
- 239 participants (53%, or about half) were under 65 years old

5. Which medicines were studied?

What investigational medicines were studied?

- Participants received tablets containing the investigational medicine, omecamtiv mecarbil or placebo. A placebo does not contain any medicine and helps researchers compare the effects of a new medicine to taking no medicine. In addition to omecamtiv mecarbil or placebo, participants could also receive other medicines their doctor prescribed to treat their heart failure.
- Neither the participant nor the study doctor could choose whether they received omecamtiv mecarbil or placebo. Participants agreed to be put into a treatment group by chance ("randomized"). This is like flipping a coin or drawing numbers out of a hat.
- Neither the participant nor the study doctor or staff knew which investigational medicine the participant was receiving during the study. This was done to make sure the study results were not influenced in any way.

The figure below shows the investigational medicines the participants took in Part 1 of the study.

Part 1 lasted 7 days

- Participants were enrolled into 1 of 2 dose groups (25 or 50 mg)
- Within each dose group, participants were randomized, to receive 1 of 3 different formulations of omecamtiv mecarbil, which had slightly different ingredients, or the placebo.
- Participants took their assigned study treatment twice a day for 6 days and then once on day 7.
- Participants had a 3 in 4 (75%) chance of receiving omecamtiv mecarbil and a 1 in 4 (25%) chance of receiving the placebo.

Dose 1: 25 mg (omecamtiv mecarbil or placebo)			
11 participants took placebo	10 participants took Formulation 1	14 participants took Formulation 2	13 participants took Formulation 3

Dose 2: 50 mg (omecamtiv mecarbil or placebo)			
10 participants took placebo	11 participants took Formulation 1	11 participants took Formulation 2	14 participants took Formulation 3

The figure below shows the investigational medicines participants took in Part 2 of the study:

Part 2 lasted almost 6 months

- Based on the results of Part 1, researchers chose 1 formulation to test in Part 2.
- Participants were randomized to 1 of 2 doses of omecamtiv mecarbil or the placebo.
- Participants took their assigned treatment twice a day for 20 weeks and once on the last day of the study.
- Participants had a 2 in 3 chance (66%) of receiving omecamtiv mecarbil and a 1 in 3 chance (33%) of receiving the placebo.
    - 150 participants took 25 mg omecamtiv mecarbil
    - 146 participants started taking 25 mg omecamtiv mecarbil and could increase their dose to 50 mg after 8 weeks
    - 149 participants took the placebo

6. What were the side effects?

What are side effects (sometimes called adverse reactions)?

All medicines can cause side effects, or unwanted medical problems that may happen when you take a medicine. In a clinical study, the study doctors record side effects that they think may be caused by the investigational medicine each patient is receiving. These are also called "adverse reactions." Only side effects that the study doctor thought may be related to the study treatment a participant was receiving are reported in this summary.

What side effects related to the treatment (also called "adverse reactions") were seen?

When reporting side effects in this study, the study doctor did not know if the participant was receiving omecamtiv mecarbil or the placebo. A side effect was recorded as "serious" if it caused death, was life threatening, required the participant to stay in a hospital, or caused a birth defect. No participant died due to a side effect in either Part 1 or 2 of this study.

The table below shows how many participants had side effects that were considered related to treatment in Part 1 of the study:

Side Effects During Part 1 of the Study		
	omecamtiv mecarbil (73 participants)	**placebo (21 participants)**
How many participants had non-serious side effects?	11 participants (15%)	2 participants (10%)
How many participants had serious side effects?	2 participants (3%)	0 participants (0%)
How many participants died from side effects?	0 participants (0%)	0 participants (0%)
How many participants stopped taking the study medicine because of side effects?	2 participants (3%)	0 participants (0%)

During Part 1, the following serious side effects occurred in the omecamtiv mecarbil group and no participants in the placebo group:

- unstable angina (reduced blood flow to the heart resulting in chest pain) – 1 participant
- myocardial ischemia (reduced blood flow to the heart) – 1 participant

The table below shows non-serious side effects that happened to at least 2% (or about 2 out of 100) of participants during Part 1 of this study.

Non-Serious Side Effects During Part 1 of the Study		
Non-serious side effect	**omecamtiv mecarbil (73 participants)**	**placebo (21 participants)**
Constipation	0 participants (0%)	1 participant (5%)
High blood pressure	0 participants (0%)	1 participant (5%)
Headache	2 participants (3%)	0 participants (0%)

The table below shows how many participants had side effects in Part 2 of the study.

Side Effects During Part 2 of the Study		
	omecamtiv mecarbil (296 participants)	**placebo (149 participants)**
How many participants had non-serious side effects?	31 participants (11%)	22 participants (15%)
How many participants had serious side effects?	12 participants (4%)	2 participants (1%)
How many participants died from side effects?	0 participants (0%)	0 participants (0%)
How many participants stopped taking the study medicine because of side effects?	13 participants (4%)	7 participants (5%)

The table below shows the serious side effects in Part 2 that occurred in at least 0.4% (or about 4 out of 1,000) of participants.

Serious Side Effects During Part 2 of the Study		
Serious side effect	**omecamtiv mecarbil (296 participants)**	**placebo (149 participants)**
Unstable angina (chest pain that happens suddenly and becomes worse over time)	2 participants (1%)	0 participants (0%)
Angina pectoris (chest pain caused by reduced blood flow to the heart)	2 participants (1%)	0 participants (0%)
Increased levels of the heart protein Troponin I	2 participants (1%)	0 participants (0%)
Heart attack	0 participants (0%)	2 participants (1%)
Congestive cardiac failure (heart failure)	0 participants (0%)	1 participant (1%)

The table below shows the non-serious side effects that occurred in at least 0.5% (or about 5 out of 1,000) of participants in Part 2 of this study.

Non-serious Side Effects During Part 2 of the Study		
Non-serious side effect	**omecamtiv mecarbil (296 participants)**	**placebo (149 participants)**
Headache	2 participants (1%)	3 participants (2%)
Dizziness	4 participants (1%)	1 participant (1%)
Tiredness	3 participants (1%)	1 participant (1%)
Angina pectoris (chest pain caused by reduced blood flow to the heart)	2 participants (1%)	0 participants (0%)
Increased levels of alkaline phosphatase in the blood	2 participants (1%)	0 participants (0%)
Postural dizziness (dizziness when standing up)	2 participants (1%)	0 participants (0%)
Difficulty breathing	2 participants (1%)	0 participants (0%)
Sweating too much	2 participants (1%)	0 participants (0%)
Low blood pressure	2 participants (1%)	2 participants (1%)
Nausea	2 participants (1%)	0 participants (0%)
Orthostatic hypotension (sudden drop in blood pressure when standing up)	2 participants (1%)	0 participants (0%)
Increased levels of the heart protein Troponin I	2 participants (1%)	1 participants (1%)

This section only shows the most frequently reported side effects. Information about other side effects may be available at the websites listed at the end of this summary.

7. What were the overall results of the study?

How did omecamtiv mecarbil act in the body?

During Part 1 of the study:

- Researchers looked at how 2 different doses and 3 different formulations of omecamtiv mecarbil were released into participants' blood. They did this by studying blood samples collected from the participants.
- All 3 formulations released similar amounts of omecamtiv mecarbil in the blood.

- The highest and average amount of omecamtiv mecarbil released into the blood was similar for all 3 formulations.
- Researchers found that the differences from participant to participant in the amount of omecamtiv mecarbil released into the blood was best controlled by Formulation 1 and chose this formulation to test in Part 2.

During Part 2 of the study:

- Researchers tested Formulation 1 and measured the average amount of omecamtiv mecarbil and the highest amount of omecamtiv mecarbil in the blood after both 2 weeks and 12 weeks of treatment.
- They found that levels of omecamtiv mecarbil in participants' blood reached the amount researchers expected.

How did omecamtiv mecarbil affect participants' heart function compared with the placebo?

During Part 2 of the study, researchers looked at how taking omecamtiv mecarbil or placebo affected participants' heart function using the following measurements:

Systolic ejection time, or SET

The SET is the amount of time the heart spends contracting during 1 heartbeat. After 20 weeks of treatment, researchers found that:

- SET stayed the same for participants taking the placebo, and increased for participants taking omecamtiv mecarbil.

Stroke volume

The stroke volume is the amount of blood pumped by the heart with each heartbeat. After 20 weeks of treatment, researchers found that:

- Stroke volume decreased for participants taking the placebo and increased for participants taking omecamtiv mecarbil.

Left ventricular end systolic diameter, or LVESD

The LVESD is the diameter of the left side of the heart at the end of the heart's contraction. An increase in LVESD is one sign that heart function has become worse. After 20 weeks of treatment, researchers found that:

- LVESD decreased for participants taking omecamtiv mecarbil and those taking the placebo, with a greater decrease in participants taking omecamtiv mecarbil.

Left ventricular end diastolic diameter, or LVEDD

The LVEDD is the diameter of the left side of the heart just before it begins to contract. An increase in LVEDD is one sign that heart function has become worse. After 20 weeks of treatment, researchers found that:

- LVEDD increased in participants taking the placebo and decreased in participants taking omecamtiv mecarbil.

Heart rate

The heart rate is the number of times the heart beats each minute. An increase in heart rate is one sign that heart function has become worse. After 20 weeks of treatment, researchers found that:

- Heart rate slightly increased in participants taking the placebo and decreased in participants taking omecamtiv mecarbil.

These are just some of the main results of the study. More results may be available at the websites listed at the end of this summary.

8. How has this study helped patients and researchers?

What is important to know about these results?

- Part 1 of this study was designed to find out which of the 3 formulations of omecamtiv mecarbil should be tested in Part 2. Researchers found the amount of omecamtiv mecarbil released into the blood over 12 hours was best controlled by Formulation 1 and chose this formulation to test in Part 2.
- During Part 2, researchers found the expected levels of omecamtiv mecarbil in participants' blood after 12 weeks of treatment with Formulation 1.

Some participants in this study had side effects that the study doctor thought could be associated with study treatments. In Part 1, no serious side effects occurred in more than 1 participant in the omecamtiv mecarbil group. Calculated as a percentage, 1 participant is the same as 1.4%, or about 14 out of 1,000 people. In Part 2, some serious side effects occurred in 2 participants in both the omecamtiv mecarbil and placebo groups. Calculated as a percentage, this is the same as 1%, or 1 out of 100 people.

These results are only for this clinical study, which looked at 544 people with heart failure. The results for any individual could have been better or worse than the results for their group. Also, no single clinical study can give a complete picture of the benefits and risks of an investigational medicine. Other studies may find different results. It takes many studies to know whether a medicine might one day be a treatment option for certain patients.

9. Are there plans for further studies?

Will there be more studies with omecamtiv mecarbil?

If more clinical studies are done with omecamtiv mecarbil, they may be listed on public websites, such as those below. Search for study medicine name "omecamtiv mecarbil" on these or other websites:

- www.clinicaltrials.gov
- www.clinicaltrialsregister.eu
- amgentrials.com

10. Where can I find more information about this study?

Where can I learn more?

To find out more about this study, check these websites:

- www.clinicaltrials.gov use the study identifier "NCT01786512"
- www.clinicaltrialsregister.eu use the study identifier "2012-000327-40"

The study sponsor has committed to making research results available to the public. This summary is provided as part of that commitment and should not be used for any other purpose. It should not be considered to make a claim for any product or to guide treatment decisions.

If you participated in the study and have questions about the study results, the doctor or staff at your study site may be able to answer them.