

VICTORIA CLINICAL STUDY RESULTS

Introduction

Heart Failure affects millions of people. It is life changing and can suddenly have an impact on the patient, their family, the choices they have, the medications and treatment they need, and their future.

This summary describes the initial results from the VICTORIA study. Studies or clinical trials such as this one help to test new medications and treatments to see if they may help patients feel better. In this study the investigational, not yet approved drug vericiguat was used to treat participants (people who agreed to be part of the study) with chronic heart failure. The main question this study wanted to answer was whether vericiguat when given with usual medicine and treatment would help to decrease heart related deaths or stays in the hospital for heart failure.

The VICTORIA study leadership knows how important it is, not only publish the results of the study, but to also share the results, in an understandable format with the participants who volunteered to be in this study as well as others. This summary is intended for participants who may have been involved in this research, as well as their family members, and others who are interested.

Thank-you

The trial leadership wishes to offer our gratitude to all of the participants who volunteered their time to take part in VICTORIA. Without your commitment and willing participation this research would not have been possible.

This summary is for your information only and is meant to help you and others understand the meaning of the results from this clinical study. For medical advice or treatment you should call your doctor. If you were a participant in the study and have questions you should call your study doctor or the staff at the research site.

Study information

Study title:

A Randomized Parallel-Group, Placebo-Controlled, Double-Blind, Event-Driven, Multi-Center Pivotal Phase III Clinical Outcome Trial of Efficacy and Safety of the Oral sGC Stimulator Vericiguat in Subjects With Heart Failure With Reduced Ejection Fraction (HFrEF)

Short study title:

VerIciguaT glObal study in subjects with heart failure with Reduced ejection frAction (VICTORIA)



Why was the research needed?

Heart failure with reduced ejection fraction occurs when the heart muscle is not able to effectively pump enough blood to meet the body's needs. It is a leading cause of heart related deaths around the world. People with chronic (long-term) heart failure who have to stay in the hospital or go back to the hospital tend to be at greater risk compared to those with heart failure who do not need to stay in the hospital. Despite the best current treatments available for those with chronic heart failure the outcomes are often not good.

Vericiguat is a new drug and is known as a soluble guanylate cyclase (sGC) stimulator. Soluble guanylate cyclase (sGC) is an enzyme in the cardiopulmonary system (heart and lungs) that is very important in generating cyclic guanosine monophosphate (cGMP). cGMP is needed for normal function of the heart and blood vessels and is low in heart failure. Vericiguat works to improve cGMP in the body. We believe it may help widen the blood vessels or improve heart function by lowering heart muscle stiffness. It may also help to bring back a more normal size and shape of the heart.

A large number of people with high risk chronic heart failure were studied to show whether or not vericiguat plus best usual care could cut the number of heart related deaths and return stays to the hospital.

Vericiguat is being tested in clinical trials like this one. At this time (May 2020) it has not yet been approved by regulators such as the Food and Drug Administration (FDA) for use outside of a clinical trial. Regulatory agencies will review the information from clinical studies like this one to decide if it should be approved for general use.

What was the main question studied?



In this study the main question was:

- Can the number of cardiovascular (heart related) deaths or heart failure hospitalizations be reduced when the study drug vericiguat is added to best usual care.

Who participated in the study?



The study screened and consented 6857 potential participants from 42 countries (Argentina, Australia, Austria, Belgium, Canada, Chile, China, Colombia, Czech Republic, Denmark, Finland, France, Germany, Greece, Guatemala, Hong Kong, Hungary, Ireland, Israel, Italy, Japan, Malaysia, Mexico, The Netherlands, New Zealand, Norway, Peru, Philippines, Poland, Puerto Rico, Russia, Singapore, South Africa, South Korea, Spain, Sweden, Switzerland, Taiwan, Turkey, United Kingdom, Ukraine, United States). The screening time was 0-30 days allowing time to make sure each participant met the required rules to be in the study. Of the potential participants screened, 5050

were enrolled into the study from September 25, 2016 to December 21, 2018. Participants who were enrolled were followed for a median (midpoint in the range) of 10.8 months.

To be in the study, participants needed to meet the following criteria:

- Men and women 18 years of age or older
- History of chronic heart failure defined by New York Heart Association (NYHA) Class II – IV (Class II - Mild symptoms to Class IV - severe symptoms)
- Being admitted to the hospital in the last 6 months for heart failure OR treated with intravenous (IV) diuretics for heart failure (diuretics increase the amount of water and salt expelled from your body when you urinate)
- Elevated brain natriuretic peptide (BNP) or NT-proBNP in the 30 days before being enrolled (These are proteins your heart makes. They go up when your heart failure gets worse)
- Left ventricular ejection fraction (LVEF) of less than 45% in the last 12 months before being enrolled in the study. (Ejection fraction is a measurement, by percentage, to show how much blood is pumped out of the left ventricle in your heart with each contraction).

What treatments did the participants take?



After meeting the rules to be enrolled in the study, all participants were assigned at random, to receive either the study drug vericiguat plus best usual care or placebo plus best usual care. Placebo looks the same as the study drug but does not have the medicine in it and offers no treatment effect.

This was a ‘double-blind’ study. This means that neither the study doctor nor the participant knew which treatment the participant was taking.

Participants were started at a dose of 2.5mg once a day then moved up to 5mg once a day and then moved up to 10mg once a day as tolerated. Changes to the dose were based on the review of the participant’s blood pressure and clinical symptoms at each study visit. Visits occurred 2 weeks, 4 weeks and then every 4 months after being enrolled, until the end of the study. All participants followed the same visit schedule and changes to the dose of medication as tolerated.

Vericiguat	Placebo
2526 participants took vericiguat	2524 participants took placebo
Once a day pill	Once a day pill
First dose 2.5mg; Target dose 10mg	First dose 2.5mg; Target dose 10mg
Blood pressure and clinical symptoms were tested after 2 weeks, 4 weeks and every 4 months. The dose was changed based on blood pressure and clinical symptoms.	Blood pressure and clinical symptoms were tested after 2 weeks, 4 weeks and every 4 months. The dose was changed based on blood pressure and clinical symptoms.

What happened during the study?

During the study participants visited their study physician and study team as follows:



- 2 weeks after being enrolled
- 4 weeks after being enrolled
- Every 4 months until the end of the study.
- Follow up phone call 2 weeks after the final visit

Assessments and tests at the visits included:



- Medical history, physical exam, vital signs (blood pressure and heart rate)
- Review of medical events between visits and any side effects
- Routine blood tests
- Quality of life questionnaires
- ECG (tracing of the electrical activity of the heart)

Many participants also gave blood samples for genetic and future biomedical research. Some participants also agreed to be a part of extra imaging (echocardiogram and magnetic resonance imaging [MRI]) studies. These extra tests and studies will help to better understand how the medicine works in chronic heart failure. It may help to develop new tests or treatment options.

What side effects did the participants have?

This section will tell you about adverse reactions also known as side effects which some participants had during the study.

- A side effect is any unfavorable and unintended sign, symptom, or disease that the participant had while in the study even if it is not related to the drug being studied.
- Conditions participants had before the study that got worse were also reported as side effects.
- Side effects that are marked as **serious** can result in death, are life threatening, result in a continuing or significant disability, extend an existing hospital stay, or are an important medical event.
- All side effects in this study were recorded from the time the participant signed the consent form to participate until 14 days after the end of study treatment.
- Potential endpoints (study outcomes) that were recorded and submitted to a clinical events committee for review included; death due to heart problems, being admitted to the hospital for heart problems and urgent heart failure visits. These potential endpoints or outcomes, were expected and not reported as serious side effects.
- This study had an independent data and safety monitoring committee who reviewed the trial data at set time points and closely watched for any safety concerns.

The charts on the next page show the number of **participants that had serious side effects and**

participants who had side effects that were not serious. The side effects were similar but were lower for participants taking vericiguat plus usual care compared to placebo plus usual care.

Number of participants with serious side effects during the study

	Vericiguat	Placebo
How many participants had serious side effects	826 out of 2519 (32.8%)	876 out of 2515 (34.8%)

Number of participants with side effects that were not serious during the study

	Vericiguat	Placebo
How many participants had side effects	2027 out of 2519 (80.5%)	2036 out of 2515 (81%)

Based on results from earlier studies with vericiguat, this study closely watched participants for **symptomatic hypotension (abnormally low blood pressure with symptoms)** and **syncope (temporary loss of consciousness)**. The chart below shows the number of participants who had symptomatic hypotension and syncope. **The results were similar between the two groups, but participants taking vericiguat plus usual care did have more symptomatic hypotension and syncope compared to participants taking placebo plus usual care.**

Number of participants with symptomatic hypotension and syncope during the study

	Vericiguat	Placebo
Symptomatic hypotension	229 out of 2519 (9.1%)	198 out of 2515 (7.9%)
Syncope	101 out of 2519 (4.0%)	87 out of 2515 (3.5%)

Anemia or a lowering of blood hemoglobin was a side effect that occurred more in participants taking vericiguat. The chart below shows the number of participants in each group who had anemia during the study.

Number of participants with anemia during the study

	Vericiguat	Placebo
Anemia	192 out of 2519 (7.6%)	143 out of 2515 (5.7%)

Description of the participants enrolled in the study

Participants included in the study

Average age	67 years old
Men	3842 out of 5050 (76%)
Women	1208 out of 5050 (24%)
Enrolled within 3 months of their heart failure hospitalization	3378 out of 5050 (66.9%)
Enrolled between 3 and 6 months from their heart failure hospitalization	871 out of 5050 (17.2%)
Not hospitalized but had IV diuretics within 3 months of being enrolled into the study	801 out of 5050 (15.9%)
Average ejection fraction	29%
Median (midpoint in the range) NT-proBNP	2816 pg/mL

- Participants were well treated, with usual guideline-based care medicine and heart failure treatments. Guideline-based means medicine or treatment that is prescribed based on what is the best care and treatment for the disease.
- Despite use of the usual guideline-based care medicines and heart failure treatments already being taken, their worsening heart failure qualified them for this study.
- Use of usual guideline-based care medicine and heart failure treatments was similar between the vericiguat and placebo participants.
- More than 80% of participants taking vericiguat and placebo followed the study treatments.
- After about 12 months in the study 89.2% of vericiguat participants and 91.4% of placebo participants reached the target vericiguat dose of 10mg.

What were the main results of the study?

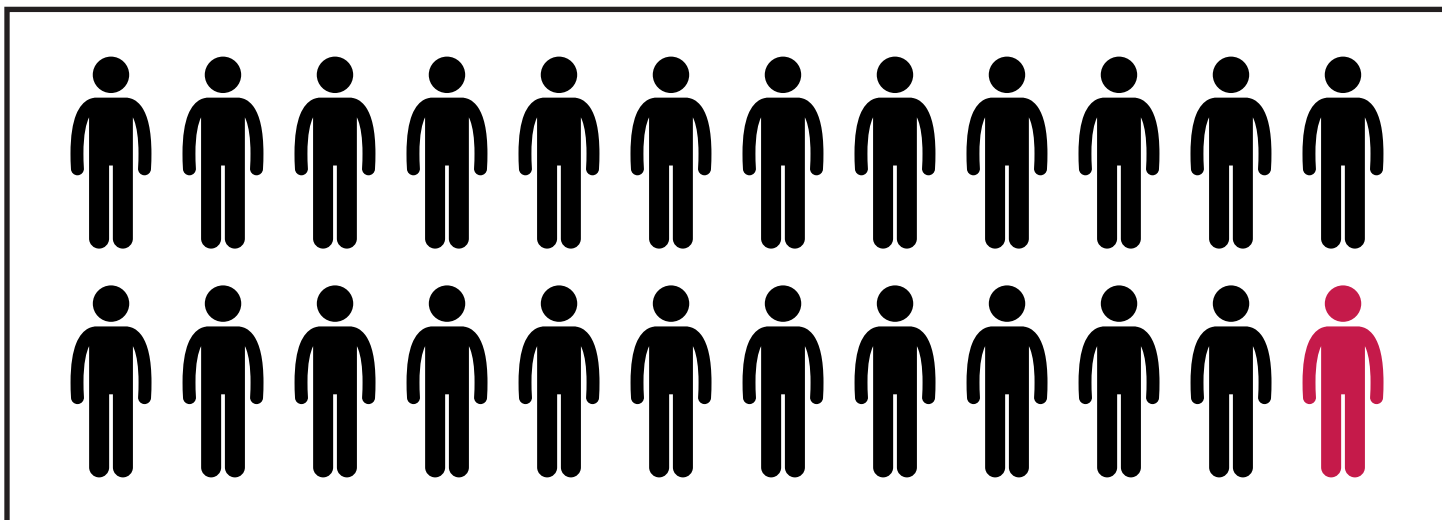
- This section includes the results for all participants in the study.
- **The study results below only answer the main question the study was asking, 'Can the number of heart related deaths or heart failure hospital stays be reduced when the study drug vericiguat is added to best usual care?'**
- More results, looking at other outcomes and features in the study will continue to be shared in the future.
- Statistical plans for reviewing the data were put in place before the study started and approved by international regulatory agencies. These plans included estimates of how many participants needed to be included in the study and how many heart failure events would occur. These statistical plans were needed in order to review the data and know whether the study drug, vericiguat was working.

The main results of the study showed that participants who took vericiguat plus best usual care had *significantly less* heart related deaths or heart failure that required them to return



and stay in the hospital compared to participants who took placebo plus best usual care.

Based on this study the results showed that 4.2 out of 100 participants treated with the study drug vericiguat had less readmissions to the hospital for heart failure or less heart related death than those who did not take it. This means that **24 participants would need to be treated with vericiguat for 1 participant to benefit or have less readmission to the hospital for heart failure or die from a heart related death.** See diagram below.



This study also looked at the occurrence of heart related death and heart failure requiring a stay in the hospital as separate events.

Heart related death alone

Based on this study the results showed that 1 out of 100 participants treated with the study drug vericiguat would not have a heart related death. This means that 99 participants would need to be treated with the study drug vericiguat for 1 participant to not have a heart related death. **There was a small decrease in heart related death for those participants who took the study drug vericiguat.**

Hospital stays for heart failure alone

Based on this study the results showed that 3.2 out of 100 participants treated with the study drug vericiguat did not have to return and stay in the hospital for heart failure during the study. This means that 31 participants would need to be treated with the study drug vericiguat for 1 participant to not have to stay in the hospital for heart failure. **In this study, taking the study drug vericiguat had a significant benefit in reducing the number of participants having to go back and stay in the hospital for heart failure.**

How has the study helped patients and researchers?

There are millions of people around the world who have heart failure. Those living with chronic heart failure have an increased risk of death and having to stay in the hospital. This study included a high-risk group of participants with chronic heart failure. Besides treatment with vericiguat or placebo, all participants in this study were treated with the best usual care, medicine and treatment for their heart failure.

- Vericiguat is a once a day medication.
- It is easy to adjust.
- It was well tolerated (few side effects) and generally safe.
- It does not need any testing of kidney function or electrolytes (essential minerals found in your blood, sweat or urine).
- In this study participants who took vericiguat plus best usual care had less stays in the hospital for heart failure and less heart related deaths compared to participants on placebo plus usual care.
- This study has helped to better understand how vericiguat plus best usual care may help people who have worsening heart failure.

At this time vericiguat is not approved by regulators for use outside of a clinical trial. The regulators will review the information and results from this study and others that have been done with vericiguat to decide if it can be approved or if other studies may be needed.

This summary is for your information only and is meant to help you and others understand the results from this clinical study. For medical advice or treatment you should call your doctor. If you were a participant in the study and have questions you should call your study doctor or the staff at the research site.

Where can I learn more about the study?

More information on this study can be found on the websites listed below:



- <https://clinicaltrials.gov/ct2/show/NCT02861534>
- <https://www.clinicaltrialsregister.eu/ctr-search/search?query=VICTORIA%2C+vericiguat>
- <https://thecvc.ca/victoria/>
- <https://www.nejm.org/doi/full/10.1056/NEJMoa1915928>
- <https://thecvc.ca/wp-content/uploads/2017/01/VICTORIA-ACC-LBCT-Slides-Website.pdf>

Additional study information

Protocol number: MK-1242-001-04

EU Trial number: 2016-000671-25

US clinical trials.gov number: [NCT02861534](https://clinicaltrials.gov/ct2/show/NCT02861534)

Study sponsor: Merck and Bayer co-sponsored this study

Academic collaboration: Canadian VIGOUR Centre (CVC) and Duke Clinical Research Institute (DCRI)

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For more information about this study you can contact thecvc@ualberta.ca

