Summary of Results for Laypersons

What was the Study Called?

A Phase III, Double-Blind, Randomized Study to Evaluate the Safety and Efficacy of BAL8557 Versus a Caspofungin Followed by Voriconazole Regimen in the Treatment of Candidemia and Other Invasive *Candida* Infections

Why was this Study Needed?

Patients who are immunocompromised (have a weakened immune system) are at risk for fungal infections of the bloodstream and those that spread throughout the body. These types of fungal infections are called invasive fungal infections. When they are caused by an overgrowth of a yeast (a type of fungus) called *Candida*, they are called invasive *Candida* infections. Several types of *Candida* can cause these infections. There are treatments for invasive *Candida* infections. But treatments such as caspofungin and voriconazole may treat only a few types of *Candida*. They may also cause unwanted effects.

There was a need for studying new treatments. Isavuconazole (also known as Cresemba® and BAL8557) is a prescription medicine used to treat invasive fungal infections.

This study was conducted in patients with an invasive *Candida* infection. Most patients also had cancer or another serious health condition that weakened their immune system. The patients received isavuconazole or caspofungin as an intravenous infusion for at least 10 days. For the infusion, a small cannula (needle) was inserted into a vein of their arm.

This study helped answer the question if isavuconazole was the same or better than caspofungin in treating patients with an invasive *Candida* infection. It was also important to find out what unwanted effects the patients had from the study medicines.

This study for isavuconazole took place at 116 clinics worldwide in Argentina, Australia, Belgium, Brazil, Canada, Chile, China, France, Germany, Hungary, India, Israel, Italy, Lebanon, Malaysia, Mexico, New Zealand, the Philippines, Russia, Singapore, South Africa, Spain, Switzerland, Thailand and the US. The study took place from March 2007 to March 2015. When the study ended, the sponsor (Astellas) reviewed all the study information and created a report of the results. This is a summary of that report.

What Kind of Study was This and Who Took Part in it?

This was a "double-blinded" study. This means that the study doctor and the patients did not know which study medicine the patient was taking.

Men and women could take part in the study if:

- They were at least 18 years of age.
- They had an invasive *Candida* infection. This was proven by a test that was done with samples from the patients' blood or other body sites. The samples were taken within 96 hours before treatment assignment.

- They had symptoms of the infection within 96 hours before treatment assignment. These symptoms could include fever, low body temperature or low blood pressure.
- They were able and willing to follow the study instructions.
- Women were not producing milk. They were no longer able to have children. Or they used reliable birth control methods.

Patients could not take part in the study if:

- Women were pregnant or breastfeeding.
- They were allergic to any component of the study medicines.
- They had a medical condition that made it inadvisable for them to take the study medicines.
- They had a high risk for abnormal electrical conduction within the heart.
- Their liver was in poor working condition as shown by the following:
  - The patients had increased blood levels of a liver enzyme (alanine aminotransferase or aspartate aminotransferase) more than 5 times the normal level. Increased blood levels of these liver enzymes indicate that liver cells are damaged.
  - They had increased blood levels of a liver pigment (bilirubin). This is often a sign of liver problems.
  - It was known that they had scar tissue in their liver. Or they had gradual loss of liver function.

Before the start of study treatment, patients were checked to see if they could be in the study. At the study visit on day 1, patients who could be in the study were picked by chance alone for 1 of the treatments:

- Isavuconazole: Patients received 200 mg as a daily intravenous infusion for up to 56 days.
  On study day 11, the study doctor decided if a patient could instead take the dose of study medicine twice a day by mouth (orally). The patient had to have normal levels of a type of white blood cells (neutrophils). The daily oral dose was 200 mg.
- Caspofungin: Patients received 50 or 70 mg of caspofungin as a daily intravenous infusion for up to 56 days.
  On study day 11, the study doctor decided if a patient could instead take an oral dose of voriconazole capsules twice a day (caspofungin does not come in capsules). The patient had to have normal levels of neutrophils. The daily oral dose was 400 mg of voriconazole.

Patients returned to the clinic for regular check-up visits over the study's 10 to 14 weeks. At most visits, the study doctor took samples from the blood and other body sites. The study doctor checked those samples to see if the *Candida* organism was still in the patient's body. At several visits, patients were asked questions about the symptoms of their *Candida* infection.

A total of 450 patients were in the study. A total of 440 patients received at least 1 dose of study medicine.

- 220 patients took isavuconazole.
- 220 patients took caspofungin or caspofungin and voriconazole.

	Number of Patients
Age Group	
Aged 18 to 45 years	104
Aged older than 45 years and up to 65 years	173
Aged older than 65 years and up to 75 years	89
Aged older than 75 years	74
Sex	
Men	269
Women	171
Clinic Location	
European Union Countries	101
Belgium	39
France	13
Germany	35
Hungary	2
Italy	9
Spain	3
Outside of European Union	339
Argentina	15
Australia	6
Brazil	25
Canada	18
Chile	4
China	2
India	26
Israel	71
Lebanon	3
Malaysia	5
Mexico	10
New Zealand	2
The Philippines	3
Russia	4
Singapore	8
South Africa	2
Switzerland	3
Thailand	79
The US	53

What Were the Study Results?

This study was conducted in patients with an invasive *Candida* infection. This study tested if isavuconazole was the same or better than caspofungin in treating their infection. The study compared the patients after they had received the study medicine as an intravenous infusion for 10 days.

The study showed that the invasive *Candida* infection was cured in 60.3% of patients in the isavuconazole group and 71.1% of patients in the caspofungin group. The study did not show that isavuconazole was the same or better than caspofungin in treating the infection.

What Adverse Reactions did Patients Have?

A lot of research is needed to know whether a medicine causes a medical problem. So when new medicines are being studied researchers keep track of all medical problems that patients have while they are in the study. These medical problems are called "adverse events" and are recorded whether or not they might be caused by the treatment taken. An "adverse reaction" is any medical problem or "adverse event" that is judged by the study doctor to be possibly caused by a medicine or treatment used in the study.

The table below shows the most common adverse reactions experienced by patients who received at least 1 dose of study medicine while taking part in this study.

More patients in the isavuconazole group than in the caspofungin group had fever. More patients in the caspofungin group than in the isavuconazole group had increased blood level of a liver or bone enzyme (alkaline phosphatase). None of the patients in the caspofungin group had pain surrounding the injection site.

Adverse Reaction	Isavuconazole (out of 220 patients)	Caspofungin (out of 220 patients)
Vomiting	8 (3.6%)	7 (3.2%)
Nausea or the urge to vomit	7 (3.2%)	5 (2.3%)
Fever	5 (2.3%)	1 (0.5%)
Pain surrounding the injection site	5 (2.3%)	0
Diarrhea	4 (1.8%)	7 (3.2%)
Decreased blood level of potassium	4 (1.8%)	7 (3.2%)
Increased blood level of a liver enzyme (GGT)	3 (1.4%)	6 (2.7%)
Increased blood level of a liver or bone enzyme (alkaline phosphatase)	2 (0.9%)	6 (2.7%)

An adverse reaction is considered "serious" when it is life-threatening, causes lasting problems or needs hospital care.

A total of 19 patients in the isavuconazole group and 12 patients in the caspofungin group experienced serious adverse reactions.

The table below shows the most common serious adverse reactions.

Serious Adverse Reaction	Isavuconazole (out of 220 patients)	Caspofungin (out of 220 patients)
Lack of enough red blood cells (anemia)	1 (0.5%)	2 (0.9%)
Increased blood level of liver enzyme	2 (0.9%)	2 (0.9%)
Below-normal blood level of oxygen	2 (0.9%)	0
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Serious Adverse Reaction	Isavuconazole	Caspofungin
Sudden inability of kidneys to filter waste products from the blood	2 (0.9%)	0
Sudden abnormal buildup of fluid in the lungs	2 (0.9%)	0
Shortness of breath	2 (0.9%)	0
Low blood pressure	2 (0.9%)	0

A total of 107 patients died during the study: 55 in the isavuconazole group and 52 in the voriconazole group. Most of the deaths were related to the serious health conditions the patients had when they entered the study. Of the 107 patients who died, the deaths of 4 patients (3 in the isavuconazole group and 1 in the caspofungin group) could have been related to the study medicines they took. These patients experienced serious adverse reactions of progressive failure of the lungs, liver, kidney, and clotting mechanisms; severe illness in which the bloodstream is overwhelmed by a type of bacteria (*Klebsiella*); sudden inability of kidneys to filter waste products from the blood; and infection caused by use of a catheter.

Where Can I Learn More About This Study?

After evaluating the results of this clinical study Astellas may perform additional studies to better understand isavuconazole.

This summary of the clinical study results is available online at http://www.astellasclinicalstudyresults.com.

Please remember that researchers look at the results of many studies to find out how well medicines work and which adverse reactions they might cause. If you have questions about isavuconazole, please discuss these with your doctor.

Sponsors contact details:

Astellas Pharma Global Development
1 Astellas Way
Northbrook, IL 60062
USA