Summary of Results for Laypersons

What was the Study Called?

A Phase IIIb/IV Randomized, Controlled, Open-Label, Parallel Group Study to Compare the Efficacy of Vancomycin Therapy to Extended Duration Fidaxomicin Therapy in the Sustained Clinical Cure of *Clostridium difficile* Infection in an Older Population. This is also known as the EXTEND study.

Why was this Study Needed?

People who have used antibiotics are at risk for *Clostridium difficile (C. difficile)* infection of the colon or large bowel. Antibiotics kill most of the good bacteria in the intestine, which then allows *C. difficile* bacteria to overgrow in the large bowel and cause an infection. They attack the lining of the intestine and cause watery diarrhea. Vancomycin (also known as Vancocin) and fidaxomicin (also known as Dificlir and Dificid) are prescription medicines used to treat *C. difficile* infection. These medicines were compared in 2 studies of more than 1000 patients with *C. difficile* infection. More than half of the patients were 60 years or older. The studies found that the medicines are less effective in treating *C. difficile* infection with increasing age (by decade) in patients age 40 years or older. After patients complete treatment with these medicines, the *C. difficile* infection can come back. This happens more often with increasing age (by decade) in patients 40 years or older. There was a need to study a new treatment option for older patients.

This study was conducted in patients aged 60 years or older with *C. difficile* infection. Half of the patients in this study took standard vancomycin. This meant that they took vancomycin every day for 10 days. The other half took fidaxomicin for an extended length of treatment. This meant that these patients took the same total dose of fidaxomicin over 25 days instead of 10 days; they took fidaxomicin every day from days 1 to 5 and every other day from days 7 to 25. They did not take study medicine on day 6.

This study compared standard vancomycin with fidaxomicin that was taken for an extended length of treatment. It helped answer which of the 2 treatments was better in treating patients aged 60 years or older with *C. difficile* infection. At 30 days after the last dose of study medicine, the study compared the cure of *C. difficile* infection in each treatment group. The infection was considered cured if patients met 2 conditions. First, their infection symptoms had improved 2 days after their last dose of study medicine. And second, their infection had not come back within 30 days after their last dose of study medicine. It was also important to find out what unwanted effects the patients had from the study medicines.

This study for fidaxomicin took place at 86 clinics in Austria, Belgium, Croatia, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Italy, Poland, Portugal, Romania, Russia, Slovenia, Spain, Sweden, Switzerland, Turkey and the UK. The study took place from November 2014 to May 2016. 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 an "open-label" study. This means that all patients knew which of the 2 study medicines they were taking, standard vancomycin or fidaxomicin taken for an extended length of treatment.

Men and women could take part in the study if:

- They were at least 60 years of age.
- They had *C. difficile* infection. They had watery diarrhea 24 hours before treatment assignment. A test showed that they had toxin produced by *C. difficile* bacteria in their stool. The stool samples were taken within 48 hours before treatment assignment.

Patients could not take part in the study if:

- They had taken more than 1 day of treatment for *C. difficile* infection within the past 48 hours.
- They had more than 2 episodes of *C. difficile* infection within the past 3 months.
- They had a life-threatening condition where swelling and inflammation spread into the deeper layers of the large bowel. The large bowel then stops working and widens.
- They were allergic to any component of the study medicines.

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:

- Fidaxomicin taken for an extended length of treatment: Patients took 1 fidaxomicin tablet (200 mg) by mouth twice daily for 5 days. They took no study medicine on day 6. They took 1 fidaxomicin tablet (200 mg) every other day from days 7 to 25.
- Standard vancomycin: Patients took 1 vancomycin capsule (125 mg) by mouth 4 times daily for 10 days.

Patients returned to the clinic for a check-up visit 2 days after the last dose of study medicine. The study doctor checked if their infection symptoms improved. Patients were asked questions about their health in general. Patients also returned to the clinic for a check-up visit 30 days after the last dose of study medicine. The study doctor checked if their *C. difficile* infection had come back. Patients were asked questions about their health in general. Patients returned to the clinic for the last check-up visit 3 months after the start of treatment. The study doctor checked if their *C. difficile* infection had come back. Patients returned to the clinic for an additional check-up visit if their infection did not get cured. Or if their *C. difficile* infection came back within 30 days after the last dose of study medicine.

A total of 364 patients were in the study. A total of 362 patients received at least 1 dose of study medicine.

- 181 patients took fidaxomicin for an extended length of treatment.
- 181 patients took standard vancomycin.

	Number of Patients
Age Group	
Aged 60 to 74 years	165
Aged 75 years and older	197
Sex	
Men	151
Women	211
Clinic Location	
European Union Countries	336
Austria	4
Belgium	1
Croatia	9
Czech Republic	27
Denmark	2
Finland	4
France	27
Germany	17
Greece	44
Hungary	28
Italy	35
Poland	37
Portugal	3
Romania	44
Slovenia	10
Spain	14
Sweden	11
The UK	19
Outside of European Union	26
Russia	14
Switzerland	5
Turkey	7

What Were the Study Results?

This study was conducted in patients aged 60 years or older with *C. difficile* infection. Half of the patients took standard vancomycin; they took vancomycin daily for 10 days. The other half took fidaxomicin for an extended length of treatment; they took the same total dose of fidaxomicin over 25 days instead of the usual 10 days. This study tested which of the 2 treatments was better in treating patients aged 60 years or older with *C. difficile* infection.

At 30 days after the last dose of study medicine, the study compared the cure of *C. difficile* infection in each treatment group. This meant that patients' infection symptoms had improved 2 days after their last dose of study medicine. And their infection had not come back within 30 days after their last dose of study medicine.

At 30 days after the last dose of study medicine, the *C. difficile* infection was cured in 70.1% of patients who took fidaxomicin for an extended length of treatment. The *C. difficile* infection was cured in 59.2% of patients who took standard vancomycin. The study showed

that fidaxomicin taken for an extended length of treatment was better than standard vancomycin in treating patients aged 60 years or older with *C. difficile* 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 adverse reactions experienced by more than 1 patient who received at least 1 dose of study medicine while taking part in this study.

The adverse reactions experienced by more than 1 patient were constipation and itching. Only the patients who took fidaxomicin for an extended length of treatment had these adverse reactions.

Adverse Reaction	Fidaxomicin Taken for Extended Length of Treatment (out of 181 patients)	Standard Vancomycin (out of 181 patients)
Constipation	4 (2.2%)	0
Itching	3 (1.7%)	0

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

Three patients who took fidaxomicin for an extended length of treatment experienced serious adverse reactions. Six patients who took standard vancomycin experienced serious adverse reactions. Four of the 6 patients experienced 1 serious adverse reaction each. The other 2 patients experienced 2 serious adverse reactions each.

The table below shows the serious adverse reactions.

Serious Adverse Reaction	Fidaxomicin Taken for Extended Length of Treatment (out of 181 patients)	Standard Vancomycin (out of 181 patients)
Inability of the heart to adequately pump blood to supply oxygen to the body	0	1 (0.6%)
Partial or complete functional blockage of the small and/or large bowel	0	1 (0.6%)
Study medicine did not work	0	1 (0.6%)
Bile duct stone	1 (0.6%)	0
Allergic reaction to medicine	1 (0.6%)	0
Infection with *Clostridium*	0	1 (0.6%)
Infection with *Klebsiella*	0	1 (0.6%)
Severe illness in which the bloodstream is overwhelmed by bacteria	0	1 (0.6%)
Sleepiness, the state of feeling drowsy, ready to fall asleep	0	1 (0.6%)
Dry, red, itchy rash	0	1 (0.6%)
Itching	1 (0.6%)	0

More than half of the patients in this study were 75 years or older. Patients of that age usually have other health conditions and an increased risk of dying.

A total of 69 patients died during the study due to a variety of reasons: 33 who took fidaxomicin for an extended length of treatment and 36 who took standard vancomycin. Most of the patients who died were at least 75 years old. Of the 69 patients who died, the death of 1 patient could have been related to this patient's study medicine (standard vancomycin). This patient experienced serious adverse reactions of severe illness in which the bloodstream is overwhelmed by bacteria and inability of the heart to adequately pump blood to supply oxygen to the body.

Where Can I Learn More About This Study?

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

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 fidaxomicin, please discuss these with your doctor.

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