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Actelion antibiotic cadazolid to meet Phase III endpoints but hesitation persists on efficacy range – experts

High drug levels tamp down antibiotic resistance concerns

Specific *C. difficile* ribotypes should be focus for current trials

One-month follow-up may be inadequate to prove recurrence efficacy

Actelion's [VTX:ATLN] Phase III trials for *Clostridium difficile* (*C. difficile*) drug cadazolid are likely to succeed based on the antibiotic's mechanism of action (MOA) and previous data, experts agreed. However, earlier trial populations could prove difficult to draw extrapolations to how many *C. difficile* forms the drug will be effective against in the pivotal studies, some said.

The safety profile did not raise alarms, but experts debated on whether a one-month or three-month follow-up would be enough to prove cadazolid can prevent infection recurrence.

The two identical Phase III trials compare cadazolid against vancomycin and each have 640 patients (NCT01983683 and NCT01987895), ClinicalTrials.gov states. The trials' primary completion date is in June 2016.

Actelion declined to comment.

Cadazolid works by inhibiting *C. difficile* protein synthesis, leading to suppression of spore and toxin formation, the company website states.

MOA/earlier data bolster Phase III prospects with caveats

As cadazolid stays in the gut and is not absorbed, drug concentration remains at very high levels in the lumen, over and above the minimum inhibitory concentration required to combat the bacteria, Dr Dimitri Drekonja, assistant professor of medicine, University of Minnesota, Minneapolis, said. As such, the Phase III trials should reach their endpoint, clinical cure at the end of 10-day treatment, Drekonja said.

Because *C. difficile* is exposed to high drug levels at the very start of treatment, antibiotic resistance is less likely to occur versus bacteria exposed to just enough drug to kill it, said Dr Oliver Cornely, professor, Clinical Trials Unit Infectious Diseases, University Hospital of Cologne, Germany.

Cadazolid's MOA draws confidence in Phase III trials because the antibiotic prevents toxin formation, so it speeds up a patient's recovery from diarrhea, Dr Farrin Manian, infectious disease physician, Massachusetts General Hospital, Boston said. One secondary endpoint includes time to resolution of diarrhoea.

Cadazolid is likely to be effective against different types of *C. difficile* in Phase III based on a Phase II clinical trial and preclinical data, said Mamun Rashid, a preclinical investigator and associate, Clinical Microbiology Division, Karolinska Institutet, Stockholm, Sweden. The widespread efficacy range is due to the drug's function in protein synthesis, Rashid added.

During Phase II trials, clinical cure was achieved in 76.5% patients who received 250mg, 80% in 500mg and 68.4% in 1,000mg of cadazolid twice-daily (Gerding et al. J Antimicrob Chemother 2015 Oct 3. pii: dkv300).

The Phase II trial covered 14 different types of *C. difficile*. During in vitro trials, cadazolid showed bactericidal effect against *C. difficile* isolates with more than 99.9% killed in 24 hours and was more bactericidal than vancomycin (Locher et al. Antimicrob Agents Chemother. 2014 Feb; 58(2): 892- 900). Toxigenic strain ATCC9689 and hypervirulent ribotype 027 strain 13366 were included in the experiments, the study states.

While the Phase II data demonstrates efficacy against different *C. difficile* types, its 84-patient sample size might be too small to draw conclusions for the Phase III studies, Manian said. Only 12 out of 84 Phase II subjects had 027 ribotype, he added, this type should be the focus of trials as it is the most prevalent. The Phase III programme does not screen for specific ribotypes.

In the larger Phase III trials, there will be a wider representation of different stages of *C. difficile* infection, which could affect how quickly subjects respond to cadazolid, said Tim Long, assistant professor, pharmaceutical science, Marshall University, Huntington, West Virginia. Also, the Phase III trials' larger sample size would likely have subjects 60 years and older or subjects with compromised immune systems who could take longer to recover or become easily reinfected, he added.

Side-effect profile benign

If there were any side effects, they would be gastrointestinal (GI) because of the drug's endurance in the lumen, Long said. Because patients are already experiencing GI discomfort, patients wouldn't mind if they experience some mild additional GI-related side effects because the cadazolid treatment period is only 10 days, he said.

During the Phase I trial, the most frequent adverse event reported was headache but it is unclear if this is a systemic issue because the drug is not absorbed, as demonstrated by high levels of the drug detected in subject faecal samples, Manian said.

Cadazolid's potential allergy and drug interactions are unclear, Drekonja said. Pfizer's [NYSE:PFE] Zyvox (linezolid), an antibiotic against Gram-positive bacteria with a comparable structure to cadazolid, can cause various side effects depending on its own drug-drug interactions, he said. However, linezolid is absorbed in the body, he said.

Experts debate recurrence secondary endpoint

Key Opinion Leaders

Brandon Bookstaver
Dimitri Drekonja
Farrin Manian
Mamun Rashid
Oliver Cornely
Tim Long

Company

*Actelion Pharmaceuticals Ltd [View Contacts](#)
Pfizer, Inc. [View Contacts](#)

Drug(s)

*Cadazolid
[Zyvox](#)

Topic

Product Development

Event Calendar

[Phase III Trial End](#)
[Phase III Trial End](#)

Indications

[Clostridium Difficile Infection \(C. Difficile \)](#)

Country

Switzerland

Clinical Trials

[NCT01983683](#)
[NCT01987895](#)

Mechanism(s)

[Bacterial Protein Synthesis Inhibitor](#)
[Protein Synthesis Inhibitor](#)

Intelligence Grade

Strong evidence

[Email Analyst](#)

While the Phase III trials have a secondary endpoint of sustained cure after a month, a three-month timeline would have been better, Long said. That period would be long enough to allow subjects' gut microflora to normalise, meaning patients would be less susceptible to secondary infections. The extended duration could add more clout to the company' secondary infection prevention claims, Brandon Bookstaver, associate professor, pharmacy, South Carolina College of Pharmacy, Columbia, said .

However, three months might be too long for a follow-up as that timeframe allows for a higher chance of reinfection besides the primary infection, Drekonja and Manian said. Three to four weeks is the time frame where most patients get reinfected anyway, Bookstaver added.

Twenty to 30% of patients are re-infected with *C. difficile* due to resilient spores, Drekonja and Manian said. For these patients, the dormant spores have been in the lumen from the primary infection and resurface after treatment, Drekonja said. Environmental spores can also start another infection, he said.

The drug's ability of spore prevention ensures the likelihood of reinfection is reduced even after cadazolid treatment has stopped, Manian added.

Spores acquired in the environment are particularly critical because *C. difficile* patients are hospital-bound, thus increasing infection opportunities, Drekonja added.

Actelion has a market cap of CHF 15.4bn (USD 15.5bn).

by Reynald Castaneda in London

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