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ALS Pursues First-of-its-Kind Antiobiotic Superiority Trial

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After years of what has appeared to be a never-ending debate over the acceptable margins and endpoints for noninferiority trials of antibiotics, Advanced Life Sciences Holdings Inc. has decided it is time to move on by conducting a first-of-its-kind superiority study comparing its experimental drug Restanza (cethromycin) against azithromycin in treating community-acquired bacterial pneumonia (CABP).

The biotech, which received a complete response letter after a negative advisory panel vote last year, is conducting the 800-patient Phase III efficacy trial of Restanza 300 mg under a special protocol assessment agreement with the FDA. (See *BioWorld Today*, June 3, 2009, and Aug. 3, 2009.)

ALS President and Chief Financial Officer John Flavin noted that the FDA over the past few years has held numerous workshops and advisory committee meetings to aid the agency in determining regulatory requirements for antibiotic studies.

The agency in March 2009 issued new draft guidance documents for noninferiority trials in CABP - the first new guidelines issued in more than a decade - which left many companies unsure of their path forward for development of their products.

The FDA this past December again convened a meeting of its Anti-Infective Drugs Advisory Committee to discuss its guidance document and to help regulators determine endpoints and other clinical trial design issues pertaining to development of antibacterial products specifically for CABP.

The committee voted 14 to 2 that historical data supported the use of all-cause mortality as a primary endpoint in a CABP noninferiority study - a conclusion that the same committee came to at an April 2008 meeting. (See *BioWorld Today*, April 3, 2008.)

Most panelists agreed that all-cause mortality would be a "hard" endpoint with less chance of bias.

Panelists also said that a noninferiority margin of 10 percent was acceptable.

The committee also voted 12 to 4 that historical data supported the use of clinical response as a primary endpoint in a CABP noninferiority trial.

But while many firms believed that the outcome of last December's advisory committee meeting and the FDA's draft guidance, once finalized, would finally put to bed the issue of margins and endpoints for noninferiority trials, it did not, Flavin lamented.

"It is clear that the FDA is still determining what the appropriate parameters are for a noninferiority trial design for pneumonia," he told *BioWorld Today*.

Flavin noted that the FDA last week held another workshop on the topic, "wherein these same issues continue to be debated."

The crux of the problem with testing antibiotics, he explained, is the lack of any placebo-controlled trials to define the treatment effect of an agent.

But given the life-threatening nature of pneumonia, most agree that it would be unethical to conduct a placebo-controlled trial in that population, Flavin pointed out.

Fate was unkind to ALS last year when the FDA's advisory panel that examined Restanza convened shortly after the agency issued its new draft guidelines for noninferiority studies in CABP, with panelists voting 11 to 3, with one abstention, that the drug's data failed to demonstrate efficacy under the new requirements.

"Our results were held to that new standard, despite the fact that our trials were set up and initiated in 2005 under prior guidance from the FDA," Flavin said.

That same panel, however, reversed itself when it came to Restanza's safety, voting 11 to 3, with one abstention, that the firm's Phase III results demonstrated clearly that the drug was safe in treating CABP.

The FDA in late July 2009 issued a complete response letter on Restanza's application indicating that regulators could not approve it in its current form and that additional clinical data would be needed to demonstrate efficacy.

"This has occurred with many companies with the guidance changes, and you need to go back and do more work, which we understood and undertook that mission coming out of our complete response letter," Flavin said.

Focusing on a superiority study design for its new trial

is "not only good science," but Flavin said it also would be "good business as well if we are successful in achieving the superiority outcome that we expect to achieve, given the data we have around Restanza's activity against macrolide-resistant *Streptococcus pneumoniae*, both in vitro and in clinical data."

Flavin noted that ALS' trial is the "first" prospectively designed superiority study to be conducted in CABP.

In the double-blind pivotal superiority study, ALS plans to compare the efficacy and safety of once-daily Restanza 300 mg over seven days against azithromycin, with a primary efficacy endpoint of clinical cure rate in a macrolide-resistant *S. pneumoniae* population.

With the U.S. resistance rates as high as 40 percent to standard-of-care macrolide antibiotics, such as azithromycin, Restanza, which belongs to a new class of drugs known as ketolides, would provide prescribers and patients a much needed option in treating CABP, Flavin insisted.

He noted that ALS' Phase III study's protocol includes several "unique" features, such as the inclusion of patient-reported outcome measures, which he said have the potential to generate a more robust demonstration of effectiveness and establish Restanza as a new standard of care in treating pneumonia.

While noninferiority trials are designed to determine that a drug is not meaningfully less efficacious than the comparator drug, a superiority study would give prescribers and patients the ability to see a clear differential advantage of a certain medication, Flavin explained.

And from a patient's and physician's point of view, "you want to be able to show clear differential advantages, which this study can do," he added.

With no clear resolution about the future of noninferiority trials in CABP, superiority trials pose fewer challenges, Flavin argued.

ALS' trial, he contended, will "open up a new door to advance the science," which Flavin said was a better option than the FDA holding more meetings and hearings with "the same outcome every time," and continuing to "frustrate" drugmakers throughout that process.

"Let's move something forward," he said.