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Veloxis Hopes Novel Slow-Release Tacrolimus Will Showcase Bioavailability Boost Of "Flat Kinetics"

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Veloxis Pharmaceuticals A/S, aka LifeCycle Pharma, is a step closer in its plan to market a slow-release version of blockbuster immunosuppressant tacrolimus that is not substitutable by the handful of generics that have become available since Astellas Pharma Inc.'s branded Prograf lost U.S. patent protection in 2009.

Veloxis, a Danish company with U.S. offices in Edison, N.J., released top-line results June 21 from a Phase III switch trial in 326 stable kidney transplant patients in which its LCP-Tacro proved non-inferior to Prograf on a composite endpoint of biopsy-proven acute rejection (BPAR), graft loss, death or loss to follow-up at 12 months.

Veloxis had assumed a 6% composite treatment failure rate and set the non-inferiority margin for the trial at 9% to achieve a 95% confidence interval. LCP-Tacro, however, produced a 4.2% rate on the composite endpoint. In the local primary analysis, the treatment failure rate for both therapies was 2.5% (four treatment failures each), while the secondary central analysis showed 2.5% for LCP-Tacro and 4.9% for Prograf.

BPAR results teased out from the central blinded reading of data also showed a trend toward lower rejection rates with LCP-Tacro, with a rejection rate of 0.6% for the tacrolimus produced using Veloxis' MeltDose technology and 3.1% for Prograf.

For the trial, patients who were stable on Prograf either continued with their twice-daily dose or converted to once-daily LCP-Tacro at a lower dose. Veloxis hypothesizes that the smoother PK profile provided by their slow-release drug may lead to better efficacy because it eliminates the peak-to-trough variability associated with twice-daily dosing of Prograf, thus eliminating stress on the body. Patients who took LCP-Tacro also were able to reduce their tacrolimus dose by 20% compared to Prograf, a reflection of the product's improved bioavailability, the company said.

"We had very tight performance around the non-inferiority margin, and we had some directional data that's extremely exciting that we may have actually improved efficacy by modulating pharmacokinetics," William Polvino, president and CEO, said in an interview. "It's very rare when you have a data set that exceeds your own internal expectations."

There were no statistically significant differences between LCP-Tacro and Prograf on adverse events named "of interest": new-onset diabetes, opportunistic infection, malignancy and a set of laboratory measures, although there were numerically more AEs with LCP-Tacro. "On balance, what we're seeing is a very comparable safety and tolerability profile," Polvino maintained.

For Prograf, 81.6% of patients experienced an AE of any kind, while 83.3% experienced one with LCP-Tacro. The difference widened when looking at AEs deemed drug-related, with only 13% of Prograf patients experiencing one compared to 21.6% for LCP-Tacro. That group also experienced more dropouts (21 versus 9), a difference Polvino attributed to an abundance of caution on behalf of investigators in the open-label trial. There was "absolutely no pattern in terms of what time those events occurred or what body systems were affected," he said.

Full data from the trial will be released at coming scientific meetings, Veloxis said.

The second Phase III trial, which tests LCP-Tacro against Prograf in de novo (newly transplanted) kidney transplant patients, is being conducted under a Special Protocol Assessment with FDA. Polvino said the company expects the trial to complete enrollment by the end of this year, and top-line results are anticipated by the end of 2012.

The double-blind, double-dummy, non-inferiority trial is enrolling 540 patients randomized to receive one or the

other of the treatment drugs along with a placebo (dummy) of the other drug. The primary endpoint is proportion of treatment failures based on the same composite endpoint as the first trial after 12 months, with a blinded extension continuing for another year.

The Advantages Of Slow-Release LCP-Tacro

By providing what Polvino calls "flat kinetics," the MeltDose formulation also might be able to cut back on side effects associated with the peaks and troughs experienced by patients dosed twice daily with tacrolimus. In future studies, the company plans to enrich for patients with specific side effects to demonstrate a reduction, he said. For example, he said, physicians say their patients are telling them that they take their Prograf in the morning and by 10 a.m. their hands are shaking so badly they can't write, but by 1 p.m. the tremors stop. "That's a pretty compelling story that says the high peak in the morning is associated with their tremors," Polvino said. "It's quite possible that by eliminating the peak, we can eliminate that side effect."

If it is successful, LCP-Tacro will offer patients the option of taking tacrolimus once a day, as well as the potential for a better safety profile, Sukhumi Bunnapradist, MD, director of kidney transplant research at the Ronald Reagan Medical Center and David Geffen School of Medicine at the University of California, Los Angeles, said in an interview. Typically, a kidney transplant patient initially takes 20-25 pills a day, including an immunosuppression cocktail of two or three drugs for lifetime or for as long as the kidney lasts, he said.

Tacrolimus, either Prograf or one of the approved generics, is taken 12 hours apart, with the evening dose the easiest to miss, so a once-daily dose "could be very beneficial," Bunnapradist said. Also, "what we are hoping to see is whether the new drug would give us more consistency in maintaining the target drug level. What we do know is that they use less drug."

"There also may be a hint" that "maybe with a better absorption profile and more consistent absorption, if you will, you may have better efficacy and a lower rejection rate," but this all needs further study, he said.

Working With Tough-To-Formulate Drugs

Tacrolimus is an especially good drug for Veloxis to formulate because it has a narrow therapeutic index, Polvino explained. If the level of drug in the blood gets too low, the organ can be rejected and if it gets too high it can cause toxicity in the transplanted kidney, so flat kinetics is crucial. But tacrolimus isn't the first reformulation Veloxis has tackled.

"We have [already] shown from a manufacturing perspective that we can get approvals using this technology," he said. It's a robust manufacturing process that can be scaled up and transferred to large-scale contract manufacturers without difficulty and without a lot of added cost, he said.

The first drug the firm developed is cholesterol drug Fenoglide, a fenofibrate engineered for increased bioavailability so it can be delivered at low doses. In 2008 Veloxis sold the royalty stream on the product, which was then marketed by Sciele Pharma under a 2007 agreement, to Cowen Healthcare Royalty Partners to help fund its development plans ("Cowen Royalty Buyers In 'Right Place, Right Time," "The Pink Sheet" DAILY, Aug. 21, 2008).

Sciele subsequently was bought out by Shionogi Pharma Inc. in 2009; Shionogi decided in 2010 to terminate its North American licensing agreement for Fenoglide. Veloxis is in the process of helping Cowan Royalty to resume manufacture and sale of the product.

And Veloxis has taken on a new challenge. On June 6, the company announced a grant from the Danish National Advanced Technology Foundation to work with Herlev Hospital in Copenhagen on development of an oral chemotherapeutic agent to potentially replace an unnamed existing IV agent.

In Copenhagen, the company has a team of about 20 formulation scientists "working on our next drug," Polvino said. "We're looking at some very exciting opportunities." Also in the company's pipeline are Atorfen, in Phase II, and LCP-Feno, in Phase I, both for dyslipidemia.

The recent name change goes along with that spirit of creativity and innovation, said Polvino. The old name said "not-so-innovative reformulation."

The LCP-Tacro Commercialization Plan

Veloxis plans to submit U.S. and European marketing applications for LCP-Tacro, which by then should have a brand name that rolls more easily off the tongue, in the first quarter of 2013.

In the U.S. the submission will follow the 505(b)(2) NDA pathway. But the company isn't looking for a quick approval despite being able to rely on the originator's pharmacology, toxicology and carcinogenicity data. Veloxis anticipates the process will take at least a year, including the possibility of an advisory committee outing.

"The clinical program is as robust as any new chemical entity," Polvino said. "We made such a massive change to

the pharmacokinetic profile that we have conducted a very, very large Phase II and Phase III program to define the safety profile and the efficacy."

Veloxis also has a program in liver transplantation and may look to pursue that smaller indication once it has the kidney approval, which represents about 70% of the transplant market, in hand, he said.

Looking ahead, Polvino said he believes that with its emerging profile LCP-Tacro can compete successfully for the unusually large portion of the immunosuppressant market that Prograf has managed to hold onto in the face of generic competition. He estimates that Astellas lost only about half of its $1 billion U.S. market to generics as opposed to the usual 90%, but that it hasn't lost as much in Europe because it was able to introduce its once-daily product Advagraf there. Veloxis estimates the global immunosuppressant market at $5 billion; Astellas garnered $2 billion last year from its tacrolimus franchise.

In the U.S., FDA declared Advagraf "approvable" in 2007, and Astellas has not moved publicly to resolve the agency's concerns ("Astellas' Once-Daily Prograf Receives Mixed Decisions For Three Prophylaxis Claims," "The Pink Sheet" DAILY, Jan. 24, 2007).

"Unlike most markets, there is still a very large proportion of prescriptions being written specifically for the brand [because] doctors treat to a very narrow therapeutic range and want to know that every dose is coming from the same brand, the same manufacturer," Polvino said. "They rely on the consistency of branding to make sure their patients stay in a therapeutic range every day they take the drug."

Nonetheless, Polvino said he thinks Veloxis won't have any trouble getting clinicians to switch to LCP-Tacro. "It's a very small community and very scientifically driven," he said. "With this audience, compliance and convenience have higher consequences than in other settings.... [And] we're going to continue working in the clinical program to show some advantages in terms of some potentially troublesome side effects, like tremors and diabetes."

Also, while the handful of generics now on the market are an AB substitution for Prograf, LCP-Tacro cannot be substituted, he said. Veloxis believes LCP-Tacro's profile allows it to compete directly with both Prograf and Advagraf with sufficient differentiation to command significant pricing. To that end, the company announced in June that it had hired John Weinberg, who formerly headed up Novartis AG's U.S. transplant and infectious disease business, to be senior VP of commercial development and strategic planning.

Veloxis has enticed some partnership interest. Under its old Lifecycle name, the company was showcased as a 2009 top-ten partnering opportunity in inflammation/autoimmune disease at Windhover's Therapeutic Area Partnerships conference ("Partnering Inflammation/Autoimmune Drugs Offers Sizzle And Steak," "The Pink Sheet," Nov. 30, 2009).

While partnering is an option, it is conceivable that Veloxis could hire the sales force required to market LCP-Tacro, Polvino said. It would take only about 20 sales reps to cover the entire U.S. because there are only about 240 transplant centers in the country, of which about half are high-volume transplanters. So, 120 represent the commercial target, he said, adding that about 50 of those are involved in the current Phase III trial.