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## Product Discovery & Development

# Life beyond Orenicia

By Michael Flanagan  
Senior Writer

Hoping both to complement Orenicia abatacept and extend the life of its rheumatoid arthritis franchise, **Bristol-Myers Squibb Co.** agreed last week to pay \$85 million up front plus almost \$1 billion in possible milestones for ALD518, a mAb against interleukin-6 in Phase IIa testing. **Alder Biopharmaceuticals Inc.** believes its ALD518 has biological advantages that will make it better than **Roche's** Actemra tocilizumab, a mAb against IL-6 receptor, and thinks it could even compete with TNF inhibitors in the front-line RA setting.

Jeremy Levin, SVP of strategic transactions at BMS, told BioCentury that the pharma has had its eye on ALD518. "In our view, IL-6 plays a key role in the inflammation cascade and was a target that we wanted to have an opportunity to access," he said, particularly now that the pathway's therapeutic pathway has been validated by Actemra.

"Actemra proved that IL-6 is an effective access point for treating rheumatoid arthritis," said Alder President and CEO Randall Schatzman. "We just think that there is a better way to target the biology" that will result in better safety and efficacy.

Whereas Actemra targets the IL-6 receptor (CD126), ALD518 is directed against the IL-6 ligand.

"Comparing the two as targets, the antigen load of the receptor in the body is about 1,000-fold higher than the IL-6 cytokine itself, so at the end of the day we should be able to treat the disease with far less drug on board because there are less molecules to neutralize," said Schatzman.

Actemra's label also warns of a 6.9% rate of infusion reactions, which the biotech's CSO John Latham attributed to the antibody's glycosylation, which causes some amount of antibody-dependent cellular cytotoxicity (ADCC) wherever the antibody binds.

"ALD518 is aglycosylated so there is no ADCC, which should result in a cleaner safety profile," he said. "We haven't seen a single infusion reaction in the 300-plus people who have received ALD518."

Schatzman noted Actemra has a half-life of six days, so it must be dosed monthly, while ALD518's half-life is 30 days and could

allow for dosing as infrequently as every three months.

Actemra is only available for IV administration, and while an IV formulation of ALD518 is being tested in the Phase IIa trial, the biotech also is conducting a Phase I trial of a subcutaneous version in healthy volunteers. The subcutaneous ALD518 will begin a dose-ranging Phase II program next year.

A number of other IL-6 programs are in or near the clinic. The most advanced appears to be CNTO 136, an antibody against IL-6 from **Johnson & Johnson's** Centocor Ortho Biotech Inc. unit that is in Phase II testing for RA.

BMS identified ALD518 as the program it wanted based on its product profile as well as its stage of development. "What we are trying to construct is a robust Phase III portfolio by 2011," Levin said.

Levin believes ALD518 will complement Orenicia. The CTLA-4-Ig fusion protein is approved to treat juvenile idiopathic arthritis as well as moderately to severely active RA in adults, where it is indicated for use as monotherapy or concomitantly with disease-modifying anti-rheumatic drugs (DMARDs) other than TNF inhibitors.

"Orenicia works at the T cell level, so it inhibits the costimulation of T cells and prevents stimulation of the inflammation cascade. This is in contradistinction with how ALD518 works, which is by interdicting a specific pro-inflammatory cytokine," he said. "From a medical and scientific perspective, this means that by having Orenicia and ALD518, you have two completely different approaches and, potentially, different weapons for physicians to add to their toolbox."

Levin also noted Orenicia has been marketed since 2005. "If ALD518 proves successful, then it will come to market for RA in several years time," he said. "So you've got the ability with this program and its associated patent life to extend our RA franchise significantly."

BMS plans to begin Phase III testing of ALD518 in 2011. In addition to RA, Levin believes the program has potential in other autoimmune disorders, including Crohn's disease and lupus.

Schatzman noted that a subset of patients, "somewhere between 20-40%, who are under-responders to TNF inhibitors," would be obvious candidates for ALD518. Moreover, he said,

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**Randall Schatzman,  
Alder Biopharmaceuticals**

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the mAb's safety and efficacy could allow it to compete in the front-line market with the TNF inhibitors.

Schatzman pointed to two pieces of evidence to suggest ALD518 might prove superior to the TNF inhibitors.

First, he said the Phase I studies have demonstrated ALD518 brings about a prolonged and complete suppression of C-reactive protein, a surrogate marker for IL-6 activity, beyond what other agents are able to achieve.

Second is that data for ALD518 in RA patients in the Phase IIa trial. Although the results have not been publicly disclosed, "obviously our partner has reviewed it and was favorably impressed," Schatzman said.

Alder intends to publish the data in a peer-reviewed journal and present them at upcoming rheumatology meetings.

According to Levin, BMS also was impressed by the speed at which Alder was able to take ALD518 forward using its yeast-based antibody expression system, as well as features of the antibody such as its aglycosylation.

Schatzman noted that Alder's yeast-based system "would give us some pricing flexibility since it costs about 1/10th or even 1/20th as much to produce antibodies as compared to in mammalian cells."

BMS licensed exclusive rights to ALD518 for all indications, except cancer, for \$85 million up front, up to \$764 million in development and regulatory milestones and more than \$200 million in potential sales milestones, plus royalties.

The biotech has an option to receive an equity investment of up to \$20 million from the pharma in the event of an IPO. BMS has an option to co-develop and commercialize the product in cancer outside the U.S.

ALD518 is in Phase II testing for fatigue and cachexia related to non-small cell lung cancer (NSCLC).

Roche markets Actemra (RoActemra - EU) for RA in the EU and in Australia, Brazil, India, Japan and Switzerland. A complete response for the agent is under review by FDA.

**Chugai Pharmaceutical Co. Ltd.**, which is majority owned by Roche, co-developed Actemra and markets it in Japan.

#### COMPANIES AND INSTITUTIONS MENTIONED

**Alder Biopharmaceuticals Inc.**, Bothell, Wash.

**Bristol-Myers Squibb Co.** (NYSE:BMJ), Princeton, N.J.

**Chugai Pharmaceutical Co. Ltd.** (Tokyo:4519), Tokyo, Japan

**Johnson & Johnson** (NYSE:JNJ), New Brunswick, N.J.

**Roche** (SIX:ROG), Basel, Switzerland

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