What is ambrisentan and when will it be available in Europe?

Ambrisentan is an investigational selective Endothelin Receptor Antagonist (ERA) being developed as a once daily oral therapy for patients with pulmonary arterial hypertension. Ambrisentan has been granted orphan drug designation for the treatment of PAH in both the United States and European Union.

Endothelin is a small peptide hormone that is believed to play a critical role in the control of blood flow and cell growth. Elevated endothelin blood levels are associated with several cardiovascular disease conditions, including PAH, chronic kidney disease, hypertension, chronic heart failure, stroke and restenosis of arteries after balloon angioplasty or stent implantation. Therefore, many scientists believe that agents that block the detrimental effects of endothelin will provide significant benefits in the treatment of these conditions.

There are two classes of endothelin receptors, endothelin A (ET_A) receptors and endothelin B (ET_B) receptors, which play significantly different roles in regulating blood vessel diameter. The binding of endothelin to ET_A receptors located on smooth muscle cells causes vasoconstriction, or narrowing of the blood vessels. However, the binding of endothelin to ET_B receptors located on the vascular endothelium causes vasodilation through the production of nitric oxide and prostacyclin. The activity of the ET_B receptor is thought to be counter-regulatory, protecting against excessive vasoconstriction.

Myogen Inc. recently announced positive top line results of the ARIES-2 trial, the first pivotal Phase II trial evaluating ambrisentan. The trial met the primary efficacy endpoint of improved exercise capacity, the key secondary endpoint of time to clinical worsening and several other secondary efficacy endpoints. Top line results of the second Phase III trial, ARIES-1 are expected to be announced in Q2 2006.

What Phase 3 studies are currently ongoing with ambrisentan?

In January 2004, Myogen announced the initiation of two pivotal Phase 3 clinical trials, ARIES-1 and ARIES-2, evaluating the safety and efficacy of ambrisentan in patients with PAH. The ARIES trials are randomized, double-blind, placebo-controlled trials of identical design except for the doses of ambrisentan studied and the geographic locations of the investigative sites. Both trials were designed to enrol 186 patients (62 patients per dose group).

ARIES-1 is evaluating once-daily doses of 5 mg and 10 mg of ambrisentan. ARIES-2 evaluated once-daily doses of 2.5 mg and 5 mg of ambrisentan. The primary efficacy endpoint is exercise capacity, measured as the mean change from baseline at 12 weeks in the 6 Minute Walk Distance (6MWD) compared to placebo. Secondary endpoints include time to clinical worsening, World Health Organization (WHO) functional class, SF-36™ Health Survey, and Borg dyspnea index. ARIES-2 enrolled 192 patients primarily from Europe, while ARIES-1 enrolled 202 patients primarily from the United States.

Enrolment in ARIES-1 was completed in November 2005 and top line results are expected in the second quarter of 2006. Enrolment in ARIES-2 was completed in August 2005 and top line results were reported on December 12, 2005.

ARIES-2 Results

The trial met the primary efficacy endpoint of improved exercise capacity, the key secondary endpoint of time to clinical worsening and several other secondary efficacy endpoints.

The primary efficacy endpoint of the ARIES-2 trial was the placebo-corrected mean change in six-minute walk distance (6MWD) at week 12 compared to baseline. Results of the trial demonstrated that with once-daily dosing, 5 mg of ambrisentan improved the placebo-corrected mean 6MWD by 59.4 meters (p=0.0002) and 2.5 mg of ambrisentan improved the placebo-corrected mean 6MWD by 32.3 meters (p=0.0219). For the placebo group, the mean 6MWD at week 12 decreased from baseline by 10.1 meters. Improvements in time to clinical worsening compared to placebo were observed for both the 5 mg dose group (p=0.0076) and the 2.5 mg dose group (p=0.0048).
The trial safety results demonstrated ambrisentan was generally well tolerated. The most frequent adverse event was headache, which occurred in 12.7% of patients in the 5 mg dose group and 7.8% in the 2.5 mg dose group, compared to 6.2% in the placebo group. No patients treated with ambrisentan developed serum aminotransferase concentrations greater than three-times the upper limit of the normal range, compared to one patient in the placebo group. Ambrisentan had no apparent effect on the activity or dosage of warfarin-type anticoagulants commonly prescribed for patients with PAH.

Based on results to date and the properties of ambrisentan, we believe that, if ambrisentan is ultimately approved in Europe, it may offer significant clinical benefit to PAH patients not provided by other PAH therapies.

What clinical benefits might ambrisentan have over other ERA products?

Ambrisentan is an ERA that is selective for the ET_A receptor. The compound demonstrates high potency, high bioavailability and a half-life that we believe is suitable for once daily dosing. In addition, the compound does not induce or inhibit the p450 metabolic pathway.

We believe that a significant opportunity exists for a new class of ERAs that bind selectively to the ET_A receptor in preference to the ET_B receptor. Selective ET_A antagonists are likely to block the negative effects of endothelin by preventing the harmful effects of vasoconstriction and cell proliferation, while preserving the beneficial effects of the ET_B receptor. We believe that the potential clinical benefits of selective ET_A antagonists will position these compounds as the treatment of choice for PAH.

We believe the selectivity and potency of ambrisentan may offer significant advantages over other ERAs, including enhanced and more durable efficacy, safety and ease of use (alone or in combination with other therapies).

What are the possible advantages of ambrisentan having a lower potential for drug-drug interactions than bosentan (Tracleer®)?

Ambrisentan does not interact with either sildenafil (Revatio®) or warfarin.

Bosentan (Tracleer®) has significant interactions with sildenafil (Revatio®) and anticoagulants, two types of drugs that will both be commonly used in PAH patients in future.

Bosentan (Tracleer®) has been found to interact with sildenafil (Revatio®) in a way that raises bosentan (Tracleer®) concentrations in the blood by 50% and lowers sildenafil (Revatio®) levels by 50%.That could, in theory, double the dosage (and cost) of sildenafil (Revatio®) and boost the already high rates of liver-function abnormalities caused by bosentan (Tracleer®).

Bosentan (Tracleer®) also significantly decreases the anticoagulant properties of warfarin leading to potential dosing and INR measurement complications for patients on warfarin therapy.