A Novel Oral Anticoagulant is Planned to be Developed for Patients with Prosthetic Heart Valves or Chronic Renal Dysfunction

SUNNYVALE, CA - MARCH 8, 2013. Armetheon, Inc., a clinical stage biopharmaceutical company, announced today that it plans to develop its novel oral anti-coagulant (OAC), tecarfarin (ATI-5923), for a patient population which includes those who have prosthetic heart valves or chronic renal dysfunction. In these patients, currently available OACs are contra-indicated or inadequate. Tecarfarin, a potentially best-in-class OAC, was designed to avoid cytochrome P450 (CYP) related metabolism that is a major cause of safety and efficacy problems related to the use of warfarin (Coumadin®), the current standard of care. In a recently completed phase 3 pivotal clinical trial (EMBRACE-AC), tecarfarin was shown to be safe and effective as an OAC in patients with prosthetic heart valves in addition to those with other conditions such as atrial fibrillation or venous thromboembolism, independent of their CYP status.

"Anti-coagulation is challenging in patients with prosthetic heart valves, where non-monitored oral anti-coagulation therapies are not indicated, and where a safe and effective alternative to warfarin would address an important clinical burden," commented Lord Ajay Kakkar, Professor of Surgery, University College London, England.

In December 2012, following a number of fatalities, the FDA informed health care professionals and the public that the novel non-monitored OAC which directly inhibits thrombin should not be used in patients with mechanical heart valves. Experts now recommend that none of the novel non-monitored OACs be used in patients with any type of prosthetic valves.

One of the major causes of unpredictable variability in warfarin anticoagulation response leading to bleeding complications or stroke is its metabolism by the enzyme, CYP2C9. This variability is further exacerbated if patients have a genetic variant of this enzyme.

"Tecarfarin was specifically designed not to be metabolized by any CYP enzymes, which means it may require less monitoring than warfarin. Some monitoring, according to experts, may still be needed to ensure patient compliance. Data from EMBRACE-AC trial showed that tecarfarin is a more effective OAC than warfarin in patients with a CYP2C9 genetic variant taking at least one CYP2C9 inhibitor despite close monitoring, " said Dr Peter Milner, Executive Chairman of Armetheon and partner at AshHill Pharmaceutical Investments. He added, "for approval of tecarfarin, we anticipate only one more pivotal clinical trial will be required which could be a 'real world,' open label study involving about 2500 pre-defined patients".

Recent research indicates that patients with chronic renal dysfunction or failure have reduced or variable activity of CYP enzymes such as CYP2C9 and CYP3A4 as well as the transporter permeability glycoprotein (P-gp). This may explain warfarin's suboptimal performance in this patient population. Currently marketed novel non-monitored OACs (in particular, Factor Xa inhibitors) are eliminated via the kidney and most of them are metabolized via CYP3A4 enzymes in addition to interacting with the P-gp. This may explain the significant variability in anticoagulation response to the novel non-monitored OACs in patients with chronic renal dysfunction or failure.

"Genetic and other sources of variability in the drug metabolizing enzymes CYP3A4 and CYP2C9 or transport related proteins such a P-gp could lead to unpredictable variability in plasma levels of drugs that are metabolized/eliminated through these pathways, particularly if they are used with concomitant medications that may be inhibitors of these metabolic/elimination pathways," said Professor Leslie Z. Benet, former Chairman and Professor of Biopharmaceutical Sciences at University of California San Francisco (UCSF), a world-renowned expert in pharmacokinetics, CYP-dependent drug metabolism and P-gp dependent drug transport.

Unlike many of the novel non-monitored OACs and warfarin, tecarfarin is not metabolized by CYP enzymes or transported by P-gp in addition to not being excreted via the kidney.

"For oral anticoagulation, we believe tecarfarin if approved will be an important clinical tool in addition to warfarin and the novel non-monitored OACs. We are preparing to meet with the FDA and the EMA to propose a clinical trial design and final registration package for tecarfarin in these two regions," said Dr M. (Ken) Kengatharan, President & COO of Armetheon and a General Partner at Atheneos Capital. He added, "we expect to submit for marketing authorization in the US and the EU in less than 4 years. With an increasing use of CYP variant genetic testing and the recent uptick in patient self-monitoring perhaps due to reimbursement by healthcare providers, we strongly believe the time to develop and commercialize tecarfarin is now".

About anti-coagulation therapy in special populations

Oral anticoagulants, are used to slow down or stop the formation of blood clots in the out-patient environment. Currently available anticoagulants include warfarin (Coumadin®) that inhibits vitamin K epoxide (VKOR) and the novel non-monitored OACs that directly either inhibit thrombin or Factor Xa. In patients with prosthetic heart valves, OACs are given to prevent clot formation within these valves. Patients with mechanical heart valves generally remain on warfarin sometimes in combination with aspirin while most patients with bioprosthetic valves are eventually switched to aspirin. However, experts now recommend that the novel non-monitored OACs should not to be used in these patients.

In patients, who have a genetic variant of metabolizing enzymes such as CYP2C9, anticoagulation therapy is difficult to manage well, even if closely monitored, particularly if they take medicines or foods that affect these enzymes. Recent data shows that these drug metabolizing enzymes are down regulated in patients with chronic renal dysfunction or failure which may explain the sub-optimal anti-coagulation control with warfarin or with the novel non-monitored OACs in these patients.

Monitoring the effectiveness of warfarin in many cases requires patients to travel frequently to a local clinic to have their anticoagulation status checked and, if needed, doses adjusted. Recently, perhaps due to reimbursement by healthcare providers, there has been an increase in patient self-monitoring and management of anticoagulation therapy that is currently only applicable to VKOR inhibitors such as tecarfarin. Ultimately, this system could provide many patients with a cost-effective management of anticoagulation therapy with a better patient compliance than with new oral non-monitored OACs.

About Tecarfarin

Tecarfarin (ATI-5923) is potentially a best-in-class orally active vitamin K epoxide (VKOR) inhibitor that was specifically designed to avoid CYP2C9 dependent metabolism and to avoid transport by P-gp. This may mean tecarfarin will need less monitoring than warfarin, potentially resulting in better patient compliance if used together with widely available self-monitoring systems. Unlike the novel non-monitored OACs, tecarfarin has an antidote, vitamin K that is readily available and can be used to rapidly reverse the anticoagulation effect of tecarfarin in an emergency. If approved, tecarfarin could become a superior anticoagulation management solution to warfarin.

About Armetheon

Armetheon, Inc. is a privately held San Francisco Bay area based clinical stage biopharmaceutical company focused on the development of novel drugs for highly unmet need. The company has 3 programs in mid - to late - clinical stage development. Armetheon's current investors include AshHill Pharmaceutical Investments and Atheneos Capital. For more information: www.armetheon.com

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