AstraZeneca

news release

July 14, 2003

EXANTA™ (ximelagatran) SHOWS EFFICACY IN FIRST STUDY FOR TREATMENT OF VENOUS THROMBOEMBOLISM (VTE) – SUPPORTS REGULATORY SUBMISSION

AstraZeneca announced today that data from the *THRIVE Treatment* study show that Exanta™ (ximelagatran), the first in a new class of oral anticoagulants called oral direct thrombin inhibitors (oral DTIs), is as effective as the current standard of care treatment regimen, enoxaparin/warfarin, in the treatment of acute venous thromboembolism (VTE; deep vein thrombosis with or without pulmonary embolism) and secondary prevention of recurrent VTE events. Importantly, the six month long study, presented today at the XIX Congress of the International Society on Thrombosis and Haemostasis (ISTH) in Birmingham, UK, also showed a favourable trend for Exanta in bleeding and mortality rates compared with the standard therapy regimen.

THRIVE Treatment, an international, randomised, multicentre, double-blind study, was designed as a non-inferiority study to compare fixed dose oral Exanta 36mg twice daily with the current standard treatment, enoxaparin (1mg/kg) followed by dose-adjusted warfarin (INR 2.0-3.0). The primary endpoint of the study was achieved, demonstrating the equivalent efficacy of oral Exanta to the standard treatment regimen in the prevention of recurrent VTE over six months. The incidence of recurrent VTE events was 26 Exanta vs 24 enoxaparin/warfarin (estimated cumulative risk 2.1% vs 2.0%), in the ITT (Intention To Treat) analysis.

"The impact of thrombosis is often underestimated, despite the fact that it is the third most common cardiovascular disease worldwide, affecting over five million people each year," said Dr. Hamish Cameron, Vice President, Head of Exanta, AstraZeneca. "The results of *THRIVE Treatment* complement the earlier findings of *THRIVE III*, and further demonstrate the promise of Exanta to be at least as effective as the best type of standard treatment currently available. These studies will form the basis for the regulatory submission for Exanta in the treatment and long-term prevention of VTE, which remains on track for late this year."

Safety and mortality outcomes also showed a favourable trend for Exanta over enoxaparin/warfarin with respect to the risk of major bleeding: 14 Exanta vs 25 standard treatment, (estimated cumulative risk 1.3% vs 2.2%) in the OT (On Treatment) analysis and all-cause mortality: 28 Exanta vs 42 standard treatment, (estimated cumulative risk 2.3% vs 3.4%), ITT analysis.

Laboratory blood tests in the study showed an incidence of liver enzyme elevations in 9.6% of patients receiving Exanta, compared with 2% of patients receiving

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July 14, 2003

enoxaparin/warfarin. These elevations decreased spontaneously whether treatment continued or was stopped. As has been seen in previous studies, these elevations were typically transient and not associated with any specific clinical symptoms. Patients taking Exanta benefit from at least as effective anti-thrombotic protection as those treated with well-controlled warfarin, but without the limitations of warfarin treatment or its requirement for time and cost-intensive coagulation monitoring and dose titration. These promising efficacy results need to be considered alongside the safety profile for Exanta emerging from this study and from other clinical trials, which will define its overall benefit-risk profile.

Exanta has completed phase III studies in a number of indications and is the first oral anticoagulant to reach late stage clinical trials since the development of warfarin more than 50 years ago. To date more than 30,000 patients have been enrolled in the Exanta clinical trial programme. Of the 17,000 patients who have been treated with Exanta, over a third (7,000) have received Exanta treatment for at least six months. The current worldwide market for anti-thrombotics is $9.6 billion.
Exanta is being reviewed in Europe for the prevention of venous thromboembolism (VTE) following elective hip or knee replacement surgery and will be submitted for regulatory approval in the US for the same indication in Q4 2003. In addition to the regulatory submission for the treatment of VTE, scheduled for submission in Europe in the fourth quarter of this year, submissions in the EU and US for the prevention of stroke in atrial fibrillation patients are also planned for the 4Q of 2003.

Exanta is a trademark of the AstraZeneca group of companies.

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Editors' Notes:
The *THRIVE Treatment* study was established from study groups from the *THRIVE II & V* studies.
The **THR**ombin **I**nhibitor in **V**enous thrombo**E**mbolism (*THRIVE*) *Treatment* study involved 2,489 patients with acute deep vein thrombosis (DVT), of whom 37% had confirmed pulmonary embolism. Patients were randomly assigned to, and received, either oral ximelagatran 36mg bid for six months, or subcutaneous enoxaparin 1mg/kg bid for a minimum of five days followed by warfarin (target INR of 2.0-3.0) for six months.
The rationale for 'non-inferiority' studies: As many highly effective treatments are available in various therapeutic areas, placebo-controlled trials are often now considered unethical. Therefore, the concept of non-inferiority testing is increasingly common where the objective of these studies is to demonstrate that a treatment is 'not inferior to' or 'as effective as' a gold standard treatment. This can then enable treatments to be differentiated in terms of their respective additional advantages to the patient and physician, such as convenience or benefit-risk. Exanta met the non-inferiority criterion in the *THRIVE Treatment* study.