ABOUT THE ATLAS ACS TIMI TRIAL PROGRAM

FAST FACTS

- ATLAS ACS* TIMI is a global program of clinical trials that may involve up to 19,500 patients, evaluating the safety and efficacy of rivaroxaban in patients with recently diagnosed acute coronary syndrome (ACS) who are receiving standard antiplatelet therapy
- The ATLAS ACS TIMI clinical trials are being conducted in collaboration with the Thrombolysis in Myocardial Infarction (TIMI) Study Group, which is affiliated with Harvard Medical School
- Results from the Phase II ATLAS ACS TIMI 46 trial were presented during the late-breaking clinical trial session at the American Heart Association (AHA) annual Scientific Sessions in November 2008
- The ATLAS ACS TIMI 51 Phase III trial is expected to start in December 2008

*Anti-Xa Therapy to Lower cardiovascular events in addition to Aspirin with/without thienopyridine therapy in Subjects with Acute Coronary Syndrome

What is ACS?

- Acute coronary syndrome (ACS) is a very common and life-threatening result of coronary heart disease (CHD). It occurs when a coronary artery is blocked by a blood clot, critically reducing blood supply to the heart.[1]
- ACS heart conditions include:
  - Myocardial infarction (MI, or heart attack)
  - Unstable angina (a very serious condition that indicates a heart attack could soon occur)
- Risk factors for ACS include family history, high cholesterol, high blood pressure, diabetes and tobacco use.[2,3]
- Despite available therapies, the risk of illness or death for patients diagnosed with ACS remains high:
  - Almost 30% of patients who leave the hospital after an ACS event are re-admitted within the first six months.[4]
- The main treatment goal for ACS patients is to prevent death or recurrent ACS by stopping the growth of existing clots and halting the formation of new clots.

ATLAS ACS TIMI 46: A Phase II dose-finding study

As a Phase II dose-finding study, ATLAS ACS TIMI 46 trial was designed to explore the safety and efficacy of rivaroxaban at escalating total daily doses, ranging from 5 mg up to 20 mg. Rivaroxaban was administered at once-daily and twice-daily intervals, assessing eight different dosing regimens in total. Results of this trial are important to help identify which doses of rivaroxaban will be used in the large scale Phase III clinical trial, which is expected to begin in December 2008.

The ATLAS ACS TIMI 46 program included 297 sites in 27 countries, and enrolled nearly 3,500 patients.

The treatment groups

The ATLAS ACS TIMI 46 study was randomized, placebo-controlled, and double-blinded, meaning neither the study doctors nor the patients knew which drugs the patients received (rivaroxaban or placebo).

All patients received standard antiplatelet therapy of low-dose aspirin and, at the physician's discretion, a thienopyridine, such as clopidogrel. Patients were then randomized to additionally receive either rivaroxaban or a placebo for six months.

ATLAS ACS TIMI 46: Secondary Prevention in Acute Coronary Syndrome

Phase II dose-finding study of rivaroxaban in the secondary prevention of acute coronary syndrome in patients who are treated with aspirin alone or aspirin alone or aspirin plus a thienopyridine (compounds such as clopidogrel, which prevent platelet aggregation).

Study design	Randomized, double-blinded, parallel-group, multicenter
Patient numbers	Nearly 3,500 patients
Interventions	➢ Rivaroxaban total daily doses of 5 mg, 10 mg, 15 mg and 20 mg either as once-daily or twice-daily regimen ➢ Placebo ➢ Treatments given for 6 months
Endpoints	Safety: Assessed using the endpoint of clinically significant bleeding, using the TIMI scale* Primary Efficacy: Composite of death, MI, stroke or severe recurrent ischemia requiring revascularization Secondary Efficacy: Composite of death, MI or stroke

*The TIMI scale is one of the most well-known risk scoring methods for a patient hospitalized with a heart attack. Using a patient's current vital health information as a guide, the TIMI scale provides a numeric value for the patient's potential prognosis, including short-term risk of death.

ATLAS ACS TIMI 51: A pivotal Phase III study

The ATLAS ACS TIMI 51 trial is a global, Phase III clinical study designed to evaluate the safety and efficacy of rivaroxaban in addition to standard care in reducing the risk of the composite of cardiovascular (CV) death, MI, or stroke in patients with recent ACS compared with placebo.

The treatment groups

The ATLAS ACS TIMI 51 study is randomized, event-driven, placebo-controlled and double-blinded, meaning neither the study doctors nor the patients will know which drugs the patients will receive (rivaroxaban or placebo).

The ATLAS ACS TIMI 51 trial is expected to begin in December 2008 with a potential to enrollment of up to 16,000 ACS patients. All patients will receive standard antiplatelet therapy of low-dose aspirin and, at the physician's discretion, a thienopyridine, such as clopidogrel. Patients will then be randomized to additionally receive either rivaroxaban at doses of 2.5 mg or 5 mg, or placebo, twice-daily for at least six months.

ATLAS ACS TIMI 51 Trial: Secondary Prevention in Acute Coronary Syndrome

Phase III study of rivaroxaban in the secondary prevention of acute coronary syndrome in patients who are treated with aspirin and thienopyridine therapy (compounds such as clopidogrel, which prevent platelet aggregation), given at their physician's discretion.

Study design	Randomized, double-blinded, parallel-group, event-driven, multicenter
Patient numbers	Up to 16,000 patients
Interventions	➢ Rivaroxaban total daily doses of 5 mg, 10 mg, as twice-daily regimen ➢ Placebo ➢ Treatments given for at least 6 months
Primary endpoint	Efficacy: Assessed using the composite of CV death, MI, or stroke Safety: Assessed using TIMI major bleeding events not associated with coronary artery bypass graft (CABG) surgery

To learn more about thrombosis please visit www.thrombosisadviser.com

To learn more about 'Xarelto' please visit www.xarelto.com

References

1. American Heart Association. Heart Disease and Stroke Statistics : 2008 Update At-a-Glance. 2008: 14.
2. Smith SC Jr et al. J Am Coll Cardiol 2006; 47: 2130-9.
3. NCEP Expert Panel. Circulation 2002; 106: 3143-421.
4. Turpie AGG. Am J Manag Care 2006; 12: S430-4.