

About the ATLAS ACS Clinical Trial Program



Fast facts

- ◆ **The ATLAS ACS clinical trials are global Phase II and Phase III studies evaluating the safety and efficacy of the anticoagulant rivaroxaban combined with standard antiplatelet therapy in patients with recently diagnosed acute coronary syndrome (ACS)**
- ◆ **ATLAS ACS-TIMI 46 is a double-blind, dose-escalation, Phase II study of rivaroxaban in the secondary prevention of ACS in patients who are treated with aspirin alone or aspirin plus a thienopyridine; results were presented at the American Heart Association (AHA) Annual Scientific Sessions in 2008**
- ◆ **ATLAS ACS-TIMI 51 is an ongoing Phase III placebo controlled study, which will enroll up to 16,000 patients, investigating the efficacy and safety of rivaroxaban 2.5 mg twice-daily or 5 mg twice-daily (respectively) combined with standard antiplatelet therapy in the prevention of secondary ACS events**
- ◆ **ATLAS ACS-TIMI 51 is expected to finish in 2011**

Acute Coronary Syndrome (ACS) and unmet medical need

Coronary arteries send oxygen-rich blood to the heart to keep the heart muscle working and healthy. ACS occurs when a coronary artery is blocked by a blood clot, critically reducing blood supply to the heart.

ACS remains a huge public health concern in the US, as about 500,000 people die from ACS every year.¹ In Europe, ACS is the most common cause of death, accounting for more than 741,000 deaths annually.²

The main treatment goal for ACS patients is to prevent death or recurrent ACS by halting the formation of new clots which can cause adverse cardiovascular events.³

Among patients with ACS, antiplatelet therapy with aspirin and, at the physician's discretion, a thienopyridine, such as clopidogrel, reduces both short- and long-term adverse cardiovascular events.^{4,5,6} There remains, however, a high rate (~10%) of MI, stroke, or death among such patients.^{7,8}

A major global initiative in secondary prevention for patients with ACS

The ATLAS ACS (**A**nti-Xa **T**herapy to **L**ower cardiovascular events in addition to aspirin with/without thienopyridine therapy in subjects with **A**cute coronary **S**ndrome) clinical studies are global Phase II and Phase III trials involving up to 19,500 patients, evaluating the safety and efficacy of rivaroxaban in patients with recently diagnosed ACS receiving standard antiplatelet therapy.

The purpose of ATLAS ACS is to determine whether rivaroxaban in addition to standard care reduces the risk of the composite of cardiovascular (CV) death, myocardial infarction (MI), or stroke in subjects with a recent ACS, compared with placebo.

The ATLAS ACS clinical trial program is being conducted in collaboration with the Thrombolysis in Myocardial Infarction (TIMI) Study Group.



ATLAS ACS-TIMI 46 trial⁹

ATLAS ACS-TIMI 46 is a double-blind, dose-escalation, Phase II study of rivaroxaban in the secondary prevention of ACS in patients who are treated with aspirin alone, or aspirin plus a thienopyridine, in addition to standard medical therapy.

The risk of clinically significant bleeding with rivaroxaban versus placebo increased in a dose-dependent manner. Rates of the primary efficacy endpoint were 5.6% (126/2331) for rivaroxaban versus 7.0% (79/1160) for placebo (p=ns). Rivaroxaban reduced the main secondary efficacy endpoint of death, MI, or stroke compared with placebo (87/2331 [3.9%] vs 62/1160 [5.5%]; p=0.0270). Results were presented at the American Heart Association (AHA) annual Scientific Sessions in 2008.

In conjunction with the efficacy seen with lower doses of rivaroxaban and on the basis of the graded increase in bleeding across doses, rivaroxaban 2.5 mg and 5 mg, administered twice-daily, have been selected for further assessment in the large, Phase III clinical trial ATLAS ACS-TIMI 51.

ATLAS ACS-TIMI 51¹⁰

ATLAS ACS-TIMI 51 is an ongoing Phase III placebo controlled study, which will enroll up to 16,000 patients, investigating the efficacy and safety of rivaroxaban 2.5 mg twice-daily or 5 mg twice-daily (respectively) combined with the standard antiplatelet therapy in the prevention of secondary ACS events.

ATLAS ACS-TIMI 51 is expected to finish in 2011.

Design of Studies

ATLAS ACS-TIMI 46 Trial

A double-blind, dose-escalation, Phase II study of rivaroxaban in the secondary prevention of ACS in patients who are treated with aspirin alone or aspirin plus a thienopyridine

Study design	<ul style="list-style-type: none"> ◆ Multi-center, randomized, double-blind, parallel-group, Phase II dosing and safety study ◆ Pre-defined study period of 6 months
Interventions	<p>Stratum 1: Low-dose aspirin and either:</p> <ul style="list-style-type: none"> ◆ One of three doses of rivaroxaban (5 mg, 10 mg, or 20 mg) taken once-daily ◆ Twice-daily rivaroxaban with total daily amount equaling (5 mg, 10 mg, or 20 mg) ◆ Placebo <p>Stratum 2: Low-dose aspirin and a thienopyridine, such as clopidogrel and either:</p> <ul style="list-style-type: none"> ◆ One of four doses of rivaroxaban (5 mg, 10 mg, 15 or 20 mg) taken once-daily ◆ Twice-daily rivaroxaban with total daily amount equaling (5 mg, 10 mg, 15 or 20 mg) ◆ Placebo
Number of patients	<ul style="list-style-type: none"> ◆ Almost 3,500 patients from 297 sites in 27 countries
Primary efficacy endpoint	<ul style="list-style-type: none"> ◆ Composite of death, MI, stroke or severe recurrent ischemia requiring revascularization up to 6 months post enrolment
Secondary efficacy endpoint	<ul style="list-style-type: none"> ◆ Composite of death, MI or stroke up to 6 months post enrolment
Primary safety endpoint	<ul style="list-style-type: none"> ◆ Clinically significant bleeding (TIMI major, TIMI minor, or bleeding requiring medical attention)*
RESULTS	
Primary efficacy endpoint	<ul style="list-style-type: none"> ◆ Compared with placebo, rivaroxaban tended to reduce the primary efficacy endpoint of death, myocardial infarction, stroke, or severe recurrent ischaemia requiring revascularisation across the entire population from 7.0% to 5.6% (HR 0.79, 95% CI 0.60-1.05, P=0.10), however, no statistically significant difference was shown
Secondary efficacy endpoint	<ul style="list-style-type: none"> ◆ Rivaroxaban compared with placebo was associated with a significant reduction in the secondary endpoint, the composite of death, MI, or stroke by 31% (from 5.5% to 3.9%, HR 0.69, 95% CI 0.50-0.96, P=0.03)
Primary safety endpoint	<ul style="list-style-type: none"> ◆ Rivaroxaban was associated with clinically significant major bleeding, which increased in a dose dependant fashion ◆ TIMI major bleeding increased vs. placebo in: <ul style="list-style-type: none"> • 'Aspirin' only stratum: 0.0% to 1.2% (p=0.17) • 'Aspirin' + clopidogrel stratum: 0.2% to 1.2% (p=0.03)



ATLAS ACS-TIMI 51 Trial

A Phase III safety and efficacy study of rivaroxaban in the secondary prevention of ACS in patients who are treated with aspirin alone or aspirin plus a thienopyridine

Study design	<ul style="list-style-type: none"> ◆ Multi-center, randomized, event-driven, double-blind, parallel-group, placebo controlled study ◆ Pre-defined study period of 6 months
Interventions	<p>Stratum 1: Standard antiplatelet therapy of low-dose aspirin and either:</p> <ul style="list-style-type: none"> ◆ One of two doses of oral rivaroxaban (2.5 mg and 5 mg) taken twice daily ◆ Placebo <p>Stratum 2: Low-dose aspirin and a thienopyridine, such as clopidogrel and either:</p> <ul style="list-style-type: none"> ◆ One of two doses of oral rivaroxaban (2.5 mg and 5 mg) taken twice daily ◆ Placebo
Number of patients	◆ Up to 16,000 patients worldwide
Primary efficacy endpoint	◆ Reduction in the risk of the composite of CV death, MI, or stroke
Primary safety endpoint	◆ Major bleeding events not associated with coronary artery bypass graft (CABG) surgery

*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.

References

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About Rivaroxaban

Rivaroxaban is a novel oral anticoagulant that was invented in Bayer Schering Pharma's Wuppertal laboratories in Germany, and is being jointly developed by Bayer HealthCare and Johnson & Johnson Pharmaceutical Research & Development, L.L.C. In clinical studies, rivaroxaban has been shown to be effective in preventing VTE in adult patients following elective hip or knee replacement surgery. It has a rapid onset of action with a predictable dose response and high bioavailability, no requirement for coagulation monitoring, as well as a limited potential for food and drug interactions. Rivaroxaban is marketed under the brand name Xarelto® for VTE prevention in adult patients following elective hip or knee replacement surgery, and it is the only new oral anticoagulant that has consistently demonstrated superior efficacy over enoxaparin for this indication. Xarelto® is approved in more than 100 countries worldwide and has been successfully launched in more than 75 countries by Bayer Schering Pharma achieving the market leader position among the new oral anticoagulants.

The extensive clinical trial program supporting rivaroxaban makes it the most studied oral, direct Factor Xa inhibitor in the world today. More than 65,000 patients are expected to be enrolled into the rivaroxaban clinical development program, which will evaluate the product in the prevention and treatment of a broad range of acute and chronic blood-clotting disorders, including stroke prevention in patients with atrial fibrillation, secondary prevention of acute coronary syndrome, and VTE prevention in hospitalized, medically ill patients.

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



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