However, the difference in ischemic stroke was significant, with the per-year death rate in the warfarin group (n=23) of 0.72% compared with 1.36% in the aspirin group (n=55; p=0.005).

The main secondary outcome occurred at a rate of 12.7% per year in warfarin-treated patients versus 12.15% per year in the aspirin-treated group (p=0.33). Major hemorrhage per year, however, occurred in 1.78% of patients in the warfarin group versus 0.87% in patients who were taking aspirin (p<0.001). Significant differences were observed in gastrointestinal hemorrhage (p=0.01) and "all other bleeds" (p=0.01). Importantly, no difference in intracerebral or intracranial bleeding was found; combined, the annual rates were 0.27% in the warfarin group compared with 0.22% in the aspirin group (p=0.82).

The authors concluded that there was no overall difference for the primary outcome, although there was a suggestive benefit with warfarin at 4 years and beyond. Warfarin reduced ischemic stroke risk throughout follow-up, but patients who were on the drug had more major hemorrhages than those in the aspirin group (1.78% vs 0.87%). Intracerebral and intracranial outcomes were similar. No significant difference was observed for the main secondary outcome.

Given no overall benefit of warfarin and increased risk of bleeding, the study found no compelling evidence to use warfarin for all patients. Based on effectiveness in preventing stroke and the possible benefit of warfarin after 4 years, analyses are underway to better identify patients that will benefit from warfarin or aspirin.

AXIS 2 Clinical Outcomes No Different Than Placebo

Written by Rita Buckley

AX200 was a novel and promising drug candidate with a comprehensive preclinical and clinical package that fulfilled Stroke Therapy Academic Industry Roundtable (STAIR) and European Stroke Organization recommendations; yet, no difference was observed in clinical outcome or imaging compared with placebo in acute ischemic stroke patients, according to results from the AX200 for the Treatment of Ischemic Stroke Phase 3 trial [AXIS-2; NCT00927836]. E. Bernd Ringelstein, MD, Westfälische Wilhelms Universität Münster, Münster, Germany, reported outcomes from the study.

AXIS 2 was a randomized, double-blind, placebo-controlled, two-arm, multinational, multicenter trial that included 328 patients with acute ischemic stroke in the middle cerebral artery territory. The objective was to demonstrate the efficacy of AX200 (rhG-CSF; filgrastim) versus placebo. The most relevant inclusion criteria were that patients had to be <9 hours from symptom onset, have a National Institute of Health Stroke Scale (NIHSS) of 6 to 22, have a diffusion-weighted imaging lesion >15 cm^3, and be aged ≤85 years. Recombinant tissue plasminogen activator (rtPA) was allowed if patients were still eligible after lysis (ie, had an NIHSS of at least 6).

Patients were randomized to receive 135 µg/kg of AX200 over 72 hours intravenously or placebo, with one-third given over 30 minutes as a priming dose. The primary endpoint was modified Rankin scale (mRS) score at Day 90. The secondary endpoint was NIHSS at Day 90. Additional analyses were performed on infarct growth, adverse events, mortality, cytokines, and hematology.

The study was conducted at 51 sites in 7 countries. Intention-to-treat (ITT; n=323) and per-protocol analyses (n=272) were performed. Patients had a mean age of 63±10 years, and there were no significant differences in demographics. Hematology tests showed an expected increase in white blood cells and monocytes and a small decrease in platelets. No significant differences were observed in serious adverse events.

There were no significant differences between AX200 and placebo patients in the primary efficacy endpoint (mRS at Day 90) in either the ITT or per-protocol groups, and there was broad overlap in confidence intervals (Figure 1). The same outcome was seen in the secondary endpoint (NIHSS at Day 90; Figure 2). No significant differences between the AX200 and control groups were observed in the subgroup analysis for rtPA pretreatment, either.

Figure 1. mRS Day 90 AXIS200 Efficacy Endpoint.

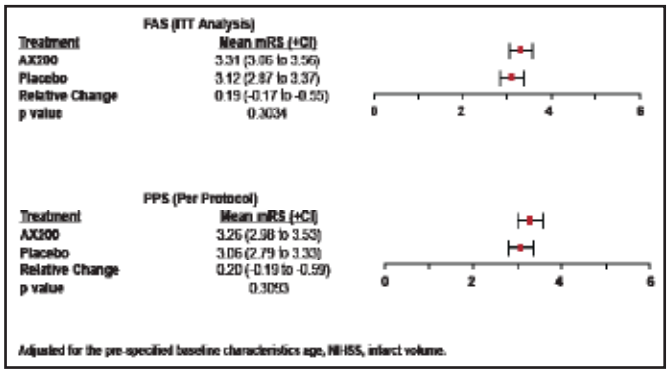

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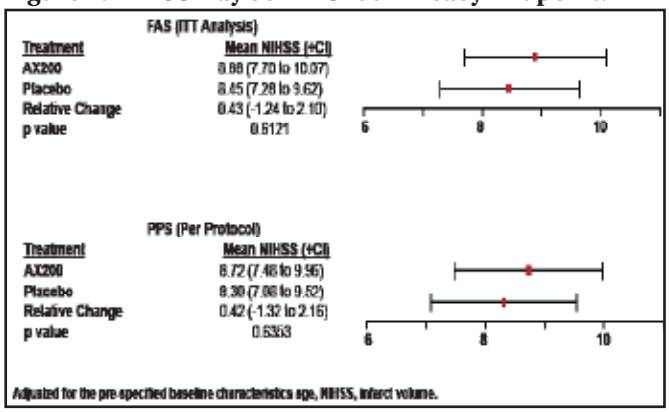
Figure 2. NIHSS Day 90 AXIS200 Efficacy Endpoint.



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The p value for mortality at 90 days was 0.4042 (Fisher's exact test); for the mRS Day 90 shift analysis, it was 0.2938, adjusted for the prespecified baseline characteristics, age, NIHSS, and infarct volume. There were no significant differences between the treatment and control groups in infarct volume.

As a stroke drug candidate, AX200 had a high validation level in animal studies (>30 publications in various stroke models), fulfilling STAIR criteria. AXIS Phase 2a data indicated that recombinant granulocyte colony-stimulating factor is well tolerated and safe in acute stroke.

Safety and tolerability were confirmed in AXIS 2, and showed the predicted pharmacokinetic and pharmacodynamic profile of AX200 in the blood. However, there were no differences between AX200 and placebo treatment in clinical outcome or imaging. No reasons for the failure are evident at present, but data analyses are ongoing.

SAMMPRIS: 30-Day Outcomes After Angioplasty and Stenting

Written by Rita Buckley

Symptomatic intracranial stenoses are an important cause of stroke, which has a high risk of recurrence with medical therapy [Chimowitz MI et al. *N Engl J Med* 2005]. Yet, the Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Arterial Stenosis trial [SAMMPRIS; NCT00576693] found that treatment with aggressive medical management (AMM) was superior to AMM plus percutaneous transluminal angioplasty and stenting (PTAS) [Chimowitz MI et al. *N Engl J Med* 2011]. Colin Derdeyn, MD, FAHA, Washington University School of Medicine, St. Louis, Missouri, USA, presented a detailed analysis of 30-day outcomes from the stenting arm of the SAMMPRIS trial.

The number of patients who underwent angioplasty/stenting was 213. Post hoc analyses were all bivariate, without Bonferroni correction for multiple comparisons, and event rates were small. A total of 60 variables were used in the analysis.

At 30 days, there were 7 parenchymal brain hemorrhages, one of which was asymptomatic, and 6 subarachnoid hemorrhages (SAH), one of which was asymptomatic; the others were caused by wire perforation or vessel rupture.

Postprocedure timing of intraparenchymal hemorrhage (IPH; n=7) ranged from immediate to 3 days. One case was symptomatic immediately postprocedure; 4 occurred within 4 to 24 hours; one occurred 2 days after the procedure; and another occurred at 3 days. All were distributed within the vascular territory of the targeted artery and were most likely secondary to reperfusion.

The interval between the qualifying event and PTAS ranged from 3 to 32 days. Outcomes were typically severe; 4 were fatal; one had an mRS score of 5 and another had 2; and one was asymptomatic. Significant and select factors for IPH included baseline percent of stenosis (central; p=0.011); preangiography diameter stenosis (DS; mm; p=0.01); JPEG review (p=0.042); and preangiography DS (mm; p=0.058). This suggests a common theme of small vessel diameter as a risk factor for IPH after stenting.

Six patients had periprocedural subarachnoid hemorrhages. All were recognized during or immediately after the procedure. Three were most likely guidewire perforations or vessel rupture. Obvious perforation was controlled with coil or glue occlusion of the vessel (n=2).

Two suspected cases of occult perforation were confirmed with CT imaging during or immediately after the procedure; one was asymptomatic, and the other was related to wire perforation.

Significant factors for wire perforation included stent diameter (p=0.051), preangiography percent stenosis (local; p=0.012), and max balloon inflation time (sec; p=0.005). These factors suggest that small vessel diameter predisposes one to SAH after stenting.

Ischemic complications in treated lesions included 12 local perforator distributions, 5 embolic strokes, and 2 delayed stent occlusions that occurred at 4 and 6 days. Both complications resulted in large ipsilateral strokes.