Apixaban for treatment of embolic stroke of undetermined source (ATTICUS) randomized trial – update of patient characteristics and study timeline after interim analysis

S. Poli[1], C. Meissner[2], H.J. Baezner[3], A. Kraft[4], F. Hillenbrand[5], C. Hobohm[6], J. Liman[7], R. Wachter[8], H. Kimmig[9], R. Huber[10], A. Lindner[11], K. Althaus[12], M. Gawaz[13], U. Ziemann[1], T. Geisler[13]

[1]Eberhard-Karls University of Tubingen, Neurology & Stroke, Tuebingen, Germany; [2]Eberhard-Karls University of Tubingen, Biometry, Tuebingen, Germany; [3]Klinikum Stuttgart, Neurology, Stuttgart, Germany; [4]Hospital Martha-Maria Halle Dölau, Neurology, Halle, Germany; [5]Rems-Murr-Clinic Winnenden, Neurology, Winnenden, Germany; [6]Carl-von-Basedow-Clinic Saalekreis, Neurology, Merseburg, Germany; [7]University Hospital Gottingen, Neurology, Goettingen, Germany; [8]University Hospital Gottingen, Cardiology, Goettingen, Germany; [9]Schwarzwald-Baar Hospital, Neurology, Villingen-Schwenningen, Germany; [10]Medical Campus Lake Constance, Neurology, Friedrichshafen, Germany; [11]Marien Hospital, Neurology, Stuttgart, Germany; [12]University Hospital of Ulm, Neurology, Ulm, Germany; [13]Eberhard-Karls University of Tubingen, Cardiology, Tuebingen, Germany

On behalf of ATTICUS investigators

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Background: Secondary prevention after embolic stroke of undetermined source (ESUS) has not yet been established. ESUS is associated with high risk of recurrent ischemic stroke and clinically silent ischemic lesions. Secondary prevention with aspirin is the current standard therapy in ESUS patients, despite high prevalence of occult atrial fibrillation (AF).

Purpose: To determine whether the direct oral factor Xa inhibitor apixaban, started within 28 days after index stroke, is superior to aspirin in preventing new ischemic lesions in subjects with remote cardiac monitoring. Primary endpoint was detection of new ischemic lesions in flair and diffusion-weighted (DWI) MR imaging at 12 months follow-up.

Methods: The study enrolled ESUS patients with risk profile for cardiac thromboembolism (i.e., left atrium (LA) size $>$45 mm, spontaneous echo contrast in LA appendage, LA appendage flow velocity $\leq$0.2 cm/s, atrial high rate episodes, CHA2DS2-Vasc score $\geq$4, patent foramen ovale). Patients were randomized 1:1 into the aspirin and apixaban arms. Study drug was initiated within 3–28 days after minor/moderate stroke and 14–28 days after major stroke. MRI (Flair/DWI) was conducted within 7 days of AF detection by remote cardiac monitors and at 12 months. ClinicalTrials.gov Identifier: NCT02427126. Funding: The trial is supported by BMS-Pfizer Alliance.

Results: Enrollment was stopped after interims analysis (including 200 patients) due to futility. Overall, 373 patients were screened with 353 being enrolled (178 and 175 in apixaban and ASA arms, respectively). So far, 130 (73.0%) and 120 (68.6%) subjects from apixaban and ASA arms, respectively, completed the study. 2% death, 1.7% withdrawal, and 1.7% were lost to follow-up. 3.9% did not completed the study for other reasons. Mean age of the ATTICUS population was 68.5 years with 51% males. 80% of the subjects suffered from hypertension. Mean systolic blood pressure at enrollment was 132 mmHg, BMI was 27.7, and CHA2DS-VASc-Score was 4.9. So far, adverse events (AE) occurred in 63% of the subjects, 30% was documented as severe. 6.8% cases of recurrent ischemic stroke and no case of hemorrhagic stroke were reported. Only 1 case of severe bleeding was reported in the aspirin arm. Newly detected AF was reported in 80 patients (23%), 42 occurring in the aspirin arm. As required by protocol, latter were immediately switched from aspirin to apixaban. Due to ongoing data clearing, numbers and % will change until presentation.

Conclusions: In contrast to the recently published NAVIGATE and RESPECT ESUS trials, patients enrolled in ATTICUS need to exhibit additional AF predicting factors. Furthermore, mandatory cardiac remote monitoring will help to elucidate the impact of AF and the effects of early oral anticoagulation with apixaban compared to antiplatelet therapy with aspirin on the incidence of new ischemic lesions after ESUS. Preliminary data will be presented and discussed in the context of current literature.