Summary of Clinical Study Report

Apixaban for treatment of embolic stroke of undetermined source (ATTICUS randomized trial)

Multicenter (national, Germany), randomized, blinded (PROBE), parallel group, active controlled, efficacy study (phase III)

[*ATTICUS*]

Name of test drug/investigational product:	Eliquis® (Apixaban)
Indication studied:	Embolic stroke
Development phase of study:	Phase III
EudraCT Number:	2014-005109-19
Protocol identification code:	ATTICUS
Date of the report:	09.12.2022
Version:	1

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- Study initiation date: 17.12.2015
- Date of study completion date (last patient completed): 09.11.2021

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2 Name of Finished Product and Active Substance

Verwendete Prüfpräparate	**Verwendete Wirkstoffe**
ELIQUIS® (Investigational drug)	Apixaban
Aspirin® (Comparator)	Acetylsalicylic acid (ASA)

3 Individual Study Table

N.a.

4 Title of Study

“Apixaban for treatment of embolic stroke of undetermined source (ATTICUS randomized trial)”

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6 Publications

Insights into preliminary Data of the ATTICUS trial Apixaban for treatment of embolic stroke of undetermined source (ATTICUS randomized trial);* T Geisler, T Keller, C Meisner, A Mengel, HJ Bäzner, E Schmid, A Kraft, F Hoffmann, F Hillenbrand, L Niehaus, C Hobohm, J Liman, R Wachter, H Kimmig, W Jung, R Huber, D Lewis, A Lindner, F Schön, M

Schabet, J Brachmann, G Petzold, F Bode, J Meyne, P Hüllemann, M Ebinger, K Althaus, M Görtler, M Gawaz, U Ziemann, S Poli; Presentation at ESC on August 29th, 2021.

Apixaban for TreatmenT of emboliC stroke of Undetermined Source (ATTICUS randomized trial) – first insights; S Poli, T Keller, C Meisner, HJ Bäzner, E Schmid, A Kraft, F Hoffmann, F Hillenbrand, L Niehaus, C Hobohm, J Liman, R Wachter, H Kimmig, W Jung, R Huber, D Lewis, A Lindner, F Schön, M Schabet, J Brachmann, G Petzold, F Bode, J Meyne, P Hüllemann, M Ebinger, K Althaus, M Görtler, M Gawaz, U Ziemann, T Geisler; e-Poster presented online at virtual ESOC in September 2021.

APIXABAN FOR TREATMENT OF EMBOLIC STROKE OF UNDETERMINED SOURCE – ATTICUS RANDOMIZED TRIAL- UPDATE OF PATIENT CHARACTERISTICS AND STUDY TIMELINE AFTER INTERIM ANALYSIS; S. Poli, C. Meisner, A. Mengel, H. Bätzner, M. Wolf, A. Kraft, F. Hoffmann, F. Hillenbrand, L. Niehaus, C. Hobohm, J. Liman, R. Wachter, H. Kimmig, W. Jung, R. Huber, A. Lindner, K. Althaus, J. Meyne, M. Schabet, G. Petzold, J. Brachmann, M. Ebinger, M. Gawaz, U. Ziemann, T. Geisler; Poster presented at WSC in October 2021.

ATTICUS: Apixaban for TreatmenT of embolIC stroke of Undetermined Source; S Poli1*, T Keller2, P Martus3, K Poli1, U Ziemann1, and T Geisler2* (*contributed equally) on behalf of the Steering Committee and ATTICUS investigators; Poster presented at ESOC on May 4th, 2022.

ATTICUS RANDOMIZED CONTROLLED TRIAL - RESULTS OF PRE-SPECIFIED SECONDARY ANALYSES; S. Poli*, T. Keller, P. Martus, K. Poli, U. Ziemann, T. Geisler* (*contributed equally) on behalf of the Steering Committee and the ATTICUS investigators; Poster presented at WSC in October 2022.

7 Study period (years)

- Date of first enrolment: 05.02.2016
- Date of last enrolment completed (visit of last patient): 09.11.2021

8 Phase of Development

Phase III

9 Objectives

The aim of the study was to show that apixaban has superior efficacy over ASA (standard of care) to reduce the rate of new ischemic lesions detected by cerebral FLAIR/DWI weighted MRI in patients with Embolic Stroke of Unknown Source (ESUS). In terms of saefety,, to show that apixaban is associated with similar risk of major and clinically relevant non-major bleedings defined by ISTH criteria compared to standard of care after ESUS.

The primary endpoint was the occurrence of at least one new ischemic lesion identified by magnetic resonance imaging (axial T2-weighted fluid attenuated inversion recovery MRI (FLAIR) and/or axial diffusion weighted MRI (DWI)) at 12 months when compared to the baseline MRI (FLAIR, DWI) obtained at the time of study drug initiation. MRI at 12 months was directly compared with the baseline MRI to assess for new ischemic lesions.

The secondary endpoints were:

- Combination of recurrent ischemic stroke, hemorrhagic stroke, systemic embolism
- Combination of major adverse cardiovascular events (MACE) including recurrent stroke, myocardial infarction and cardiovascular death.
- Occurrence of new embolic lesions identified by MRI at 12 months (compared with the baseline MRI).
- Combination of major and clinically relevant non-major bleedings defined according to ISTH criteria
- Change of cognitive function (MOCA)
- Quality of Life EQ-5D-5L
-

The exploratory objectives were:

- Incidence of patients with ESUS in whom clinically relevant AF (episodes ≥2minutes) is detected by event recorder during 12 months follow-up.
- Evaluation of the association of different cut-off values for duration of AF and the primary endpoint
- Evaluation of time relation of newly detected AF and new ischemic lesions in FLAIR/DWI MRI
- Comparison of cumulative incidence of new ischemic lesions detected by FLAIR/DWI MRI after event recorder guided conversion from ASA to apixaban during the on-treatment phase aspirin versus apixaban
- Comparison of cumulative incidence of new ischemic lesions in the on-treatment period of apixaban versus aspirin prior to detection of atrial fibrillation
- Association of atrial premature beats in 24h Holter ECG with the occurrence of atrial fibrillation during event recorder monitoring and association with the primary endpoint
- Association of alterations of heart rate variability with the occurrence of AF episodes since presence of impaired heart rate variability is a known strong and significant predictor of new onset AF.
- Analysis for metabonomic, genetic and biomarker markers (ELISA, Multiplex, MALDI-TOF) will be performed to detect novel molecular mechanisms involved in ESUS and AF burden
- Explorative subgroup analyses as described in protocol p. 79

10 Methodology

ATTICUS is a randomized, multicenter, blinded (PROBE), active controlled, parallel-group, open label study (phase III). Patients were randomized 1:1 to Apixaban or usual care (acetylic salicylic acid (ASA, Aspirin®). Usual care was administered as per local practice and/or approved label. Apixaban or usual care was administered from randomization (depending on the severity of stroke and the individual risk for HTI (3-28 days after minor/moderate stroke and 14-28 days after major stroke) until 12 months after study drug initiation. Following randomization, clinical endpoints, information on health status, including blood pressure control was collected at the different visits.

11 Number of Patients

- Planned participants: 600
- Screened participants: approx. 900
- Recruited patients: 371
- Randomized patients: 353
- Drop-outs: 18 + 1 withdrew consent on day of randomization
- Analyzed patients: 352
- Analyzed ITT population: 343
- Analyzed pP patients: 270

12 Diagnosis and Main Criteria for Inclusion and Exclusion

The general criteria for subject selection was adult male and female patients with ESUS. Patients also fulfilling the below outlined inclusion criteria were enrolled in the study. Trial population consisted of both genders. Gender distribution in the trial was supposed to reflect the distribution in the real patient's population (approx. 60% male and 40% female patients), i.e. there was no prior defined quantitative ratio between females and males. Gender differences in outcome are not expected.

Inclusion criteria:

- Must be ≥ 18 years at the time of signing the informed consent.
- ESUS must be defined according to following criteria:
  - ✓ Stroke detected by CT or MRI that is not lacunar
  - ✓ Absence of extracranial or intracranial atherosclerosis causing ≥50% luminal stenosis (according to NASCET) in arteries supplying the area of ischaemia
  - ✓ No major-risk cardioembolic source of embolism [Permanent or paroxysmal atrial fibrillation, sustained atrial flutter, intracardiac thrombus, prosthetic (mechanic) cardiac valve, atrial myxoma or other cardiac

tumors, moderate or severe mitral stenosis, recent (<4weeks) myocardial infarction defined as angiographically confirmed MI, left ventricular ejection fraction less than 30%, valvular vegetations, or infective endocarditis]
    - ✓ No other specific cause of stroke identified (eg, arteritis, dissection, migraine/vasospasm, drug misuse)
- At least one of the following non-major but suggestive risk factors for cardiac embolism:
    - ✓ LA size >45mm (parasternal axis)
    - ✓ Spontaneous echo contrast in LAA
    - ✓ LAA flow velocity <=0.2m/s
    - ✓ Atrial high rate episodes
    - ✓ CHA2DS2-Vasc score >=4
    - ✓ Persistent foramen ovale
- Planned ECG continuous (daily) monitoring (non-invasive or invasive, initiation within 28 days after randomization) or pre-existing event recorder
- Understand and voluntarily sign an informed consent document prior to any study related assessments/procedures
- Able to adhere to the study visit schedule and other protocol requirements.
- Women of childbearing potential (WOCBP) must be using an adequate method of contraception to avoid pregnancy throughout the treatment period of the study or for 2 weeks after the last dose of study medication, whichever is longer, in such a manner that the risk of pregnancy is minimized. The inclusion of WOCBP requires use of a highly effective contraceptive measure according to "Recommendations related to contraception and pregnancy testing in clinical trials" (see http://www.hma.eu/ctfg.html sections 4.1 and 4.3). Contraception should be maintained during treatment and until the end of relevant systemic exposure. WOCBP include any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or is not postmenopausal (defined as amenorrhea ≥ 12 consecutive months; or women on hormone replacement therapy [HRT] with documented serum follicle stimulating hormone [FSH] level > 35 mIU/mL). Even women who are using oral contraceptives, other hormonal contraceptives (vaginal products, skin patches, or implanted or injectable products), or mechanical products such as an intrauterine device or barrier methods (diaphragm, condoms, spermicides) to prevent pregnancy, or are practicing abstinence or where their partner is sterile (eg, vasectomy) should be considered to be of childbearing potential. WOCBP must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 48 hours prior to the start of study medication.
- All subjects must agree to refrain from donating blood while on study drug and for 28 days after discontinuation from this study treatment.
- All subjects must agree not to share medication.
- All WOCBP will be asked to repeat pregnancy tests at each study visit.

<u>Exclusion criteria</u>

- Subjects presenting with any of the following criteria will not be included in the trial:
- History of hypersensitivity to the investigational medicinal product or to any drug with similar chemical structure or to any excipient present in the pharmaceutical form of the investigational medicinal product.
- Participation in other clinical interventional trials or observation period of competing interventional trials.
- Diagnosis of haemorrhage or other pathology, such as vascular malformation, tumor, abscess or other major non-ischaemic brain disease, on baseline head CT or MRI scan
- Clear indication for anticoagulation (atrial fibrillation, mechanical cardiac valves, deep venous thrombosis, pulmonary embolism or known hypercoagulable state)
- Inability to control following risk factors for Hemorrhagic Transformation of fresh cerebral Infarction (HTI) during index hospital stay (i.e. within seven days after index stroke): presence of HTI at the time of anticoagulation, blood pressure >160 mmHg systolic, abnormal blood glucose (fasting glucose level >126 mg/dL or glucose level >200 mg/dL postprandial and low platelet count (less than 100 x10^9/L); multiple measurements allowed.
- Clear indication for dual antiplatelet therapy (e.g. Aspirin® plus Clopidogrel, Aspirin® plus Prasugrel, Aspirin® plus Ticagrelor or Aspirin® plus Dipyridamole)
- Clear stroke-/non-stroke-indication for concomitant long-term therapy with antiplatelets (e.g. acetylsalicylic acid (ASA), Clopidogrel, or Prasugrel) or with non-steroidal anti-inflammatory drugs (NSAID).

- Concomitant systemic therapy with strong inhibitors of cytochrome P450 3A4 (CYP3A4) and P-glycoprotein (P-gp), i.e. azole-antimycotics (e.g. ketoconazole, itrakonazole, voriconazole and posaconazole) and human immunodeficiency virus (HIV)-protease inhibitors.
- Contraindication to investigational medications
- Planned or likely therapy with fibrinolytic agents within 48 hours of first study medication
- History of intracranial, intraocular, spinal, retroperitoneal or atraumatic intra-articular bleeding
- Gastrointestinal bleed or major surgery within 3 months
- Planned or likely revascularization (any angioplasty or vascular surgery) within the next 3 months
- TIA or minor stroke induced by angiography or surgery
- Severe non-cardiovascular comorbidity with life expectancy <3 months
- Women of childbearing age not practicing reliable contraception who do not have documented negative pregnancy test result
- Severe renal failure, defined as Creatinine Clearance (CreaCl, Cockroft-Gault) <15 ml/min
- Severe hepatic insufficiency (Child-Pugh score B to C),
- Active liver disease, including but not limited to
    a) Persistent ALT, AST, AP greater than twice the upper limit of the normal range
    b) Active hepatitis A
    c) Active hepatitis C (positive HCV RNA)
    d) Active hepatitis B (HBs antigen +, anti HBc IgM +)
    e) Hep B/C serology testing only upon suspicion of active disease
- Contraindications against performance of MRI (pacemaker/ICD), previous implantation non-MRI capable prostheses
- Anemia (hemoglobin level less than 100 g/L)
- Patients considered unreliable by the investigator, or having a life expectancy less than the expected duration of the trial because of concomitant disease, or having any condition which, in the opinion of the investigator, would not allow safe participation in the study (e.g., drug addiction, alcohol abuse)
- Pregnancy, breast feeding or ineffective contraception is present.

13 Test investigational medicinal product

Test investigational medicinal product: ELIQUIS® /Apixaban (provided by the manufacturer BMS/Pfizer)
ELIQUIS® /Apixaban is approved for prevention of ischemic stroke and systemic embolisms with non-valvular atrial fibrillation in adults since December 20th, 2012 in EU.

Dose: 5 mg or reduced dose of
2.5 mg in patients who meet two of the following three criteria:
1. age ≥ 80 years, 2. body weight < 60 kg and 3. serum creatinin ≥ 1,5 mg/dl (133 Micromol/l

Mode of administration: oral

Product information (Batch listing):

Drug Product or Commercial Batch No.	Alternate Drug Product or Commercial Batch No.	IRO Number	Label Batch	Material No.	Drug Description	Strength	Container Range Beginning No.	Container Range End No.	Comments
3J76929	3G73711	01CV185417	AAB2726	1363539	Apixaban Tablet	5 mg	258305	258454	
3G74763	N/A	02CV185417	AAB2730	1363538	Apixaban Tablet	2.5 mg	261805	261854	
AAC0884	5A88010	03CV185417	AAJ7112	1363539	Apixaban Tablet	5 mg	263535	263684	
AAC9014	N/A	04CV185417	AAJ7113	1363538	Apixaban Tablet	2.5 mg	264205	264254	
AAC0884	5A88010	05CV185417	AAM0345	1363539	Apixaban Tablet	5 mg	265670	265744	
AAC0884	5A88010	06CV185417	AAU3213	1363539	Apixaban Tablet	5 mg	274457	274606	
AAC9014	N/A	07CV185417	AAJ7113	1363538	Apixaban Tablet	2.5 mg	263875	263924	SAP Batch AAJ7113.6A
AAC0884	5A88010	08CV185417	AAU3213	1363539	Apixaban Tablet	5 mg	273607	273831	SAP Batch AAU3213.6A
AAC9014	N/A	09CV185417	AAM0348	1363538	Apixaban Tablet	2.5 mg	266055	266106	
AAC0884	5A88010	10CV185417	AAU3213	1363539	Apixaban Tablet	5 mg	273832	273903	SAP Batch AAU3213.7A
AAK2833	N/A	11CV185417	AAT9368	1363538	Apixaban Tablet	2.5 mg	272832	272856	
AAT0503	AAT4023	12CV185417	ABG1121	1363539	Apixaban Tablet	5 mg	335351	335450	
AAT0503	AAT4023	13CV185417	ABG1121	1363539	Apixaban Tablet	5 mg	335201	335350	SAP Batch ABG1121.1A
AAK2833	N/A	14CV185417	AAT9368	1363538	Apixaban Tablet	2.5 mg	272732	272781	SAP Batch AAT9368.1A
ABC5248	N/A	15CV185417	ABS6987	1363538	Apixaban Tablet	2.5 mg	343381	343390	

14 Duration of treatment

Apixaban or usual care (acetylsalicylic acid) were administered from study drug initiation (3-28 days after minor/moderate stroke and 14-28 days after major stroke) until **12 months** after study drug initiation.

15 Reference therapy

Reference therapy: acetylsalicylic acid

Dose: 100 mg

Mode of administration: oral

Product information (Batch listing):
Not available – ASA was given as standard of care therapy (open label)

16 Criteria for evaluation

16.1 Efficacy

The primary endpoint was “new ischemic lesion identified by MRI” (for a detailed definition c.f. section 9)

16.2 Safety

Adverse/severe adverse events (see Appendix)

17 Statistical methods

Primary aim of the study was to show superiority of Apixaban vs. ASA regarding the primary endpoint „new ischemic lesion identified by MRI” (yes/no). The primary analysis was a Mantel Hanszel Chi-Square-Test stratified for study

center with a one-sided level of significance of 0.025 in an adaptive design according to Bauer and Köhne. The interim analysis (stage 1) was planned to be done after 200 patients who reached t=12 months of treatment, a maximum of 400 patients should be recruited in stage 2 of the study (total number n=600), the exact number depending on the observed results in stage 1. Further details of this design can be found in the study protocol pp 65/66, and p 67. All other analyses were not intended confirmatorily. Secondary outcomes as listed in section 9 were analyzed using methods for time to event data (Kaplan Meier estimates, Log Rank test). Safety analysis was planned to be done descriptively.
After the futile interim analysis, which required 12 months follow up for all patients, it was decided to finish the planned therapy for all patients already randomized and to use all patients in the final analysis (n=352 ITT).

18 Summary/Conclusions

18.1 Efficacy Results

In the **interim analysis (stage 1)**, 165 patients (87 Apixaban, 78 ASA) could be evaluated, in 35 patients the primary endpoint was not available. A recurrent stroke was observed in 10 of 87 patients treated with Apixaban (11.5%) and in 6 of 78 patients (7.7%) treated with ASA. The odds ratio ASA vs. apixaban was 0.63 in favour of ASA (two-sided 95% CI 0.22-1.78, p = 0.74 (one-sided for superiority of Apixaban, p = 0.53, two-sided).

For **stage 2**, a one-sided p-value of 0.00514 would have been necessary to reach a successful overall result. With the maximum of 400 patients and an overall rate of 9.7% recurrent strokes, an odds ratio of 2.83 in favour of Apixaban would have been required. Based on this results, the following decisions were taken: Stopping for futility but continuation of study treatment and follow up for each recruited patient for 12 months according to protocol

In the **pooled analysis (stage 1 + 2)** for 325 of 352 patients in the ITT population, in 23 of 169 patients in the Apixaban group (13.6%), and in 25 of 156 patients in the ASA group (16.0%) a recurrent stroke was observed (odds ratio 1.27 in favour of Apixaban, two-sided 95% CI 0.68-2.37, p = 0.29 one- sided for superiority of Apixaban, p = 0.57, two-sided). Thus, in the final ITT analysis, the study result was negative but with a very small effect in favour of Apixaban.

In the per protocol population, 261 patients were included (142 Apixaban, 119 ASA) results were comparable. (18/142 = 12.7% new ischemic leasions (Apixaban) vs. 22/119, 18.5% (ASA), p=0.29 two-sided, p=0.097 one-sided in favour of Apixaban).

For secondary outcomes (Combination of recurrent ischemic stroke, hemorrhagic stroke, systemic embolism (14 events Apixaban, 13 events ASA) Combination of major adverse cardiovascular events (MACE) including recurrent stroke, myocardial infarction and cardiovascular death. (18 vs. 19 (mit deaths) 15 vs 15 (ohne deaths), Combination of major and clinically relevant non-major bleedings defined according to ISTH criteria (5 vs. 9), Change of cognitive function (MOCA, p= 0.64), Quality of Life (EQ-5D, p=0.66, VAS p=0.079) no differences between study arms were observed.

18.2 Safety Results

Detailed results of the AEs and SAEs can be found in Appendix 1, pp 169-261. AEs and SAEs were not different between both study groups: AEs (page 169) were observed in 131 patients in the Apixaban group (73.6%)-and in 123 patients in the ASA group (70.7%). SAEs (page 241) were observed in 52 (29.2%) of patients in the Apixaban group and in 55 (31.6%) of patients in the ASA group. In a more detailed analysis taking into account the medication prior to the respective event, 1.56 AEs per patient year were observed in the Apixaban group and 1.64 AEs in the ASA group. Restricting the analysis to events with at least possible relationship to the study drug, we found 0.35 (Apixaban) vs. 0.29 per patient year.

18.3Conclusion

The major findings of ATTICUS are: 1) early anticoagulation either unguided or delayed by CEM after ESUS and additional risk factors was associated with equal risk for NIL and equally low risk for major and CRNM bleedings 2) Preselection criteria with high likelihood for atriopathy and stroke recurrence and paroxysmal AF were associated with a high rate (>25% of patients) of detected AF episodes ≥ 2minutes in CEM requiring anticoagulation therapy 3) there were signals of a benefit of early (unguided) anticoagulation in elderly patients (≥75 years) without increased bleeding risk.

The ATTICUS trial showed that pre-selection of ESUS patients offers a high chance to predict early AF in patients with ESUS requiring anticoagulation. Further evidence is needed whether patients with additional signs of atrial cardiomyopathy benefit from early anticoagulation. We observed signals of a benefit of early anticoagulation in elderly patients, a finding that deserves further exploration. Both, early anticoagulation with apixaban at full dose or anticoagulation guided by ICM (i.e., switch from ASA to apixaban upon AF detection) appeared to be safe without occurrence of any intracardial haemorrhage favouring the concept of early anticoagulation in high-risk patients until AF has been excluded.

This study was futile with respect to the primary and also with respect to secondary endpoints.

Three further statistical considerations might be important:
Comparison of sample size estimation and observed effect: In the study protocol (page 67), no assumed effect size is documented. A two-stage adaptive design was chosen instead. Thus, it is not possible to compare results from the planning phase to the observed results.
Comparison of stage 1 and stage 2: It should be noted that results in the (planned) first stage of the study (n=165) with 11.5% new leasions in Apixaban and 7.7% in ASA were different to the (unplanned) second stage (n=160) with 24.4% in the ASA vs. 15.9% in the Apixaban group (p-value stage 0.012, interaction stage arm 0.146, logistic regression analysis).
Consequences for further studies: However, using the result of the 325 patients of both study phases, 13.6% new lesions in Apixaban vs. 16% in ASA, leads to a total of about 7.900 patients necessary for a study to show superiority of Apixaban vs. ASA.

19 Appendices

Appendix 1: Descriptive Statistics (ATT_Anhang1_Deskription_final_20JAN23.pdf)