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Rationale and design of the AXIOMATIC-SSP phase II trial: Antithrombotic treatment with factor XIa inhibition to Optimize Management of Acute Thromboembolic events for Secondary Stroke Prevention

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Abstract

Background: Individuals with ischemic stroke or transient ischemic attack (TIA) have a high early risk of ischemic stroke despite dual antiplatelet therapy. The risk of ischemic stroke, and associated disability, represents a significant unmet clinical need. Genetic variants resulting in

reduced factor XI levels are associated with reduced risk for ischemic stroke but are not associated with increased intracranial bleeding. Milvexian is an oral small-molecule inhibitor of FXIa that binds activated factor XI with high affinity and selectivity and may reduce the risk of stroke when added to antiplatelet drugs without significant bleeding. We aimed to evaluate the dose-response relationship of milvexian in participants treated with dual antiplate-lets.

Methods: We began a phase II, double-blinded, randomized, placebo-controlled trial at 367 sites in 2019. Participants (N = 2366) with ischemic stroke (National Institutes of Health Stroke Scale score   7) or high-risk TIA (ABCD^2 score   6) were randomized to 1 of 5 doses of milvexian or placebo for 90 days. Participants also received clopidogrel 75 mg daily for the first 21 days and aspirin 100 mg for 90 days. The efficacy endpoint was the composite of ischemic stroke or incident infarct on magnetic resonance imaging. Major bleeding, defined as type 3 or 5 bleeding according to the Bleeding Academic Research Consortium, was the safety endpoint. Participant follow-up will end in 2022.

Conclusion: The AXIOMATIC-SSP trial will evaluate the dose-response of milvexian for ischemic stroke occurrence in participants with ischemic stroke or TIA.

Study rationale

Early stroke occurrence after ischemic stroke or transient ischemic attack (TIA) remains a significant risk despite advances in secondary prevention. Ischemic stroke is largely a thromboembolic disease, and major efforts to reduce the early risk of recurrent stroke in patients with non-cardioembolic stroke have focused on antiplatelet strategies.[1] Improvements in outcome have been associated with novel antiplatelet strategies, but significant residual risk of ischemic stroke and the potential for major bleeding, including intracranial hemorrhage, limit the effectiveness of these options. In a recent trial, patients with minor ischemic stroke and high-risk TIA had a risk of stroke within 90 days of 6.3% when treated with aspirin and 4.6% when treated with the combination of aspirin and clopidogrel with an increase in major bleeding.[1] Clopidogrel is a prodrug that requires activation through the cytochrome P450 2C19 (CYP2C19) system and has reduced efficacy in those with loss of function alleles.[2, 3] Ticagrelor does not require conversion to an active metabolite and is unaffected by the presence of loss of function alleles.[4] In individuals with loss of function alleles, ticagrelor combined with aspirin reduces stroke occurrence better than the combination of clopidogrel combined with aspirin.[3] Cilostazol-based dual antiplatelet therapy seems to be effective in chronic stroke, but the effect against early recurrence has been uncertain.[5, 6] There is an unmet need for an antithrombotic strategy that reduces the risk of ischemic stroke with a low potential to cause serious bleeding.

Emboli that cause stroke may arise from multiple sources in the cardiac and arterial beds.[7] Thrombus formation at the source of embolization may be triggered or amplified by platelet activation and fibrin deposition. These pathways interact, and resulting thrombi are a combination of platelets and fibrin, suggesting that optimization of antithrombotic

strategies can be achieved by targeting both pathways—the dual pathway approach.[8] This hypothesis has been tested in acute and stable arterial disease using a combination of aspirin and the factor Xa (FXa) inhibitor rivaroxaban. In patients with acute coronary syndromes, rivaroxaban added to standard antiplatelet therapy reduced the combined endpoint of stroke, myocardial infarction (MI), and death over standard therapy alone, with an increase in major bleeding and intracranial hemorrhage.[9]

The risk of stroke, MI, and death was reduced by the combination of rivaroxaban and aspirin over aspirin alone in patients with stable coronary or peripheral artery disease.[10] Of note, there was a reduction of 42% in the hazard of stroke (hazard ratio [HR], 0.58; 95% confidence interval [CI], 0.44–0.76), and the absolute benefit was greatest in those with a prior history of stroke.[11] The reduction was consistently noted across different stroke subtypes, suggesting that the dual pathway approach was effective in preventing thromboembolism in multiple stroke subtypes.[12] However, combined therapy with rivaroxaban and aspirin was also associated with an increase in major bleeding compared with aspirin alone (HR, 1.70; 95% CI, 1.40–2.05).[10]

Factor XI (FXI) is the precursor of the coagulation protease factor XIa (FXIa). While FXIa makes relatively modest contributions to hemostasis, it is involved in thrombus growth and stabilization[13] (Fig. 1). Epidemiologic and Bayesian randomization studies in individuals born with FXI deficiency suggest that FXI(a) inhibition is a promising strategy for secondary stroke prevention.[14, 15] Patients with FXI deficiency have a significantly lower risk for stroke than matched controls with normal FXI levels, whereas patients with high FXI levels have an increased risk for recurrent stroke.[16] Spontaneous hemorrhage in FXI-deficient patients is rare. Bleeding most commonly occurs with trauma to tissues with high intrinsic fibrinolytic activity, such as the nose and genitourinary tract.[17] Studies of deep venous thrombosis prophylaxis have demonstrated a reduction in venography-defined thrombosis and favorable bleeding profiles with reduction in FXI levels or inhibition of FXIa.[18–20] The potential for a therapeutic effect with low risk of bleeding makes FXI and FXIa promising targets for secondary stroke prevention.

Milvexian (BMS-986177/JNJ-70033093) is a direct-acting, high-affinity inhibitor of human coagulation FXIa.[21] Milvexian binds rapidly and reversibly to FXIa and exhibits high selectivity and specificity for FXIa over other proteases of the blood coagulation cascade and anticoagulant systems. Fig. 2 shows the x-ray crystal structure of milvexian bound to the FXIa protease domain.[21] As opposed to thrombin and FXa inhibitors which act on the common coagulation pathway required for hemostasis, milvexian acts on FXIa, reducing the contribution of this feedback loop to thrombin generation without affecting thrombin activation of FV and FVIII. Activation of FV and FVIII also amplify the generation of thrombin (Fig. 1). Milvexian is predicted to have limited effects on hemostasis and could provide the first opportunity to determine whether clinically effective antithrombic activity can occur without significant increases in bleeding risk. Pre-clinical studies and human trials have assessed its safety, pharmacokinetic (PK) and pharmacodynamic (PD) effects. At doses that preserved hemostasis, milvexian exhibited robust antithrombotic efficacy in the prevention and treatment of arterial thrombosis in a rabbit electrically induced carotid artery

thrombosis (ECAT) model.[22] Administration of milvexian also resulted in dose-dependent inhibition of thrombosis in a rabbit arterio-venous shunt model.[23]

Phase I studies of milvexian demonstrated that it was safe and well tolerated at doses up to 200 mg twice daily (BID) and 500 mg once daily (QD).[24] The drug is rapidly absorbed after oral administration, with a time to peak of 2 to 4 hours. The primary elimination routes are through cytochrome P450 enzyme (CYP) metabolism, specifically CYP3A, with relatively low renal excretion (<20%) and the dose range of 20 – 200 mg is generally dose proportional.[25–27] The drug has a terminal elimination half-life of 11 to 18 hours, supporting either BID or QD dosing.[24] Milvexian increases the activated partial thromboplastin time (aPTT) in a concentration-dependent manner.[24] Milvexian is well tolerated in participants with mild or moderate hepatic impairment and demonstrated a similar PK profile as in healthy subjects.[28] After accounting for protein-binding, the exposure-response relationship with the aPTT overlapped with that observed in healthy study participants, indicating that the biologic effect of milvexian was unchanged in hepatic impairment.[28] In participants with severe renal impairment, milvexian had a modest increase in drug exposure compared to those with normal renal function.[27] Based on preclinical data, milvexian has a low potential for interactions as a perpetrator (i.e., a drug that causes an effect on the substrate drug) or substrate. Studies with moderate and strong CYP3A4 inhibitors indicated relatively small and modest milvexian plasma exposure increases, respectively, due to changes in the half-life as expected based on the metabolic profile of milvexian.[26] Strong CYP3A4 induction with rifampin resulted in modest decreases in milvexian concentration.[25] The dose range of 25 mg QD to 200 mg BID was selected based on pre-clinical blood concentration targets from the rabbit ECAT model and the phase I human study.[22, 24] The goal of the dose range selected was to enable an assessment of the exposure-response in stroke prevention and enable an evaluation of the FXIa mechanism of action.

Post-operative FXIa inhibition with milvexian in participants undergoing total knee arthroplasty was effective for preventing venous thromboembolism and was associated with a low risk of clinically relevant bleeding compared with enoxaparin in a phase II trial.[20] Following administration of milvexian at daily doses from 25 to 400 mg, a significant dose-response was noted for the incidence of venous thromboembolism after elective knee arthroplasty with BID and QD regimens. The incidence of venous thromboembolism was significantly lower with daily milvexian doses of 100 mg or more compared to enoxaparin 40 mg QD. Bleeding of any severity occurred in 4% of milvexian-treated patients and 4% of enoxaparin-treated patients. Major or clinically relevant non-major bleeding occurred in fewer milvexian patients than those treated with enoxaparin (1% vs 2%). No major bleeding was observed with the use of milvexian.

Evidence to date suggests that inhibition of FXIa is a promising target for antithrombotic therapy for ischemic stroke, and has the potential to reduce thrombin generation enough to prevent thrombotic vascular occlusion or embolization without impairing hemostasis.

Design

Overview

Antithrombotic treatment with factor XIa inhibition to Optimize Management of
Acute Thromboembolic events for Secondary Stroke Prevention (AXIOMATIC-SSP
[ClinicalTrials.gov Identifier: NCT03766581]) is an international, phase II, randomized,
double-blind, placebo-controlled, dose-ranging clinical trial examining the safety and
efficacy of milvexian in patients with acute ischemic stroke or high-risk TIA. The main
objective is to determine the dose-response relationship of milvexian in participants with
acute ischemic stroke or TIA who are treated with aspirin and clopidogrel. The main
secondary objective is to assess the rate of major bleeding in this population compared with
placebo. Between January 2019 and December 2021, we randomized 2,366 participants at
367 sites in 27 countries. The main results will be available in 2022.

Study population

Key inclusion criteria are listed in Table 1. Individuals   40 years of age who have had
an ischemic stroke or high-risk TIA were recruited and randomized within 48 hours of
the onset of symptoms. Qualifying strokes were defined as symptomatic non-lacunar acute
brain infarcts visible on neuroimaging (computed tomography [CT] or magnetic resonance
imaging [MRI]) and relevant to the clinical symptoms. Participants were required to have a
National Institutes of Health Stroke Scale (NIHSS) score of   7 at the time of randomization
(scores range from 0–42, with higher scores indicating greater stroke severity). Petechial
hemorrhagic transformation of the index infarct and cerebral microbleeds were permitted.
Qualifying TIA was defined as acute onset of neurologic deficits attributable to brain
ischemia with complete resolution of deficit and no brain infarction on neuroimaging
and with an ABCD^2 score   6 (scores range from 0–7, with higher scores indicating
a greater risk of stroke) or motor symptoms.[29] All participants were required to have
visible intracranial or extracranial atherosclerotic plaque of any degree, but not complete
occlusion on an imaging study, and a premorbid modified Rankin score (mRS) of   3. After
approximately 450 patients had been randomized and the data monitoring committee (DMC)
had reviewed the safety and efficacy data, enrollment of participants who had received
thrombolytic therapy and/or mechanical thrombectomy for the treatment of the index stroke
was permitted. Additional requirements were that 24 hours had passed between the acute
recanalization therapy and the first dose of study medication, provided that neuroimaging
excluded hemorrhagic transformation of the acute infarct and all other study criteria were
met.

Key exclusion criteria are summarized in Table 2. Potential participants were excluded if
there was evidence of large vessel dissection, intracranial tumor (other than meningioma), or
arteriovenous malformation that could explain the symptoms. Also excluded were those with
a history of hemorrhage in the brain or spinal cord, and those with conditions that, in the
opinion of the investigator, would contradict anticoagulant therapy. A requirement for dual
antiplatelet therapy beyond 21 days or planned use of anticoagulants, with the exception of
heparin or low molecular weight heparin for maintaining the patency of indwelling catheters,

were exclusions. Known SARS-CoV-2 infection within 4 weeks prior to screening was also an exclusion.

Study treatment and visits

Following informed consent, participants were randomized to milvexian or matching placebo plus open-label uncoated aspirin 100 mg and clopidogrel (loading dose of 300–600 mg, followed by 75 mg/day). Clopidogrel was administered for 21 days, while aspirin and milvexian or matching placebo were continued until Day 90 (Fig. 3). Randomization was initially to milvexian in QD doses of 25 mg and BID doses of 25 mg, 50 mg, 100 mg, and, after review of safety and efficacy data by the independent DMC, to 200 mg BID also. Despite the delayed start of randomization to the 200-mg BID dose, the study targeted at 2:1 randomization between placebo and each milvexian dose to occur by the end of enrollment. No dose adjustments were made to milvexian, aspirin, or clopidogrel after randomization. A baseline MRI brain scan was performed according to a standardized study-specific protocol (Supplementary Table 1) and was recommended prior to randomization. Milvexian dosing was started within 6 hours of the baseline scan. In instances where the baseline MRI could not be performed within 48 hours of symptom onset, it could be acquired post-randomization, but no later than 72 hours from symptom onset. Study visits occurred at 21 and 90 days, with a telephone contact at 60 days. In approximately 450 patients, central laboratory tests were also obtained at 60 days. An end-of-study MRI brain scan was obtained at 90 days, with a telephone contact at 97 days. The NIHSS, the Montreal Cognitive Assessment (MoCA), and the Digit Symbol Substitution Test (DSST) were collected at the Day 1, Day 21, and Day 90 visits and following any new clinical stroke. Blood samples for safety markers were collected at Day 1 (baseline), Day 21, Day 60, and Day 90 visits while PK, PD, and biomarker samples were collected between Day 1 to Day 4, Day 21, and Day 90 visits (Appendix 1).

Study objectives and endpoints

The primary efficacy endpoint was the composite of incident ischemic stroke during the treatment period or new covert brain infarction detected by the comparison of 90-day and baseline MRIs. All images were read independently by 2 blinded neuroradiologists, and disagreements were resolved by consensus. A new infarct was determined if the 90-day MRI demonstrated a new lesion on the diffusion weighted sequences or the fluid attenuated inversion recovery sequence consistent with an ischemic infarct. Clinically overt strokes were determined by site investigators following standardized definitions. Briefly, to qualify as an outcome event, a clinical diagnosis of stroke required a sustained increase in the NIHSS score of 3 points that was not explained by other factors, such as infection, or was confirmed by imaging as a new infarct.

The secondary endpoint of major bleeding was determined by the occurrence of types 3 and 5 bleeding, according to the Bleeding Academic Research Consortium (BARC) classification system (Appendix 2).[30] Secondary endpoints also included the volume and number of new infarcts detected by MRI imaging and the rate of clinical bleeding of any type with milvexian compared to placebo. Bleeding was additionally evaluated utilizing International Society on Thrombosis and Haemostasis (ISTH) and PLATelet inhibition and

patient Outcomes (PLATO) criteria. Central laboratory samples were used to determine the dose-response relationship to PD markers as well as the PK of milvexian.

Study organization

AXIOMATIC-SSP was sponsored by Bristol Myers Squibb, in collaboration with Janssen Pharmaceuticals, Inc. A steering committee, chaired by the principal investigator and composed of national leaders, experts in stroke and thrombosis, and sponsor representatives, supervised the conduct of the study to ensure standards of high quality were met and was responsible for the scientific aspects of the trial. An independent DMC, whose membership includes experts in stroke, clinical trials, thrombosis, and statistics, had access to unblinded data and was responsible for the safety of participants in the trial. No formal interim analyses were performed. An administrative interim analysis was performed by the sponsor using personnel who had no other connection to the study when approximately 1600 participants had been randomized to facilitate subsequent program development. The principal investigator, steering committee, and all study personnel involved with the study conduct, sites, and vendors were blinded to the results of this analysis.

Statistical considerations

Sample size calculations for the primary endpoint were performed for detecting a dose-response effect, with generalized Multiple Comparisons and Modeling (gMCP-Mod) using simulations with the Dose-Finding package in R statistical analysis software.[31, 32] Simulations of 2500 clinical trials were performed, assuming a true incidence for placebo of 15%, a plateau-shaped dose-response relationship with maximum relative risk reduction of 32% for milvexian 100 or 200 mg BID relative to placebo, and 25 mg QD as the lowest dose added to the ordered BID dose regimens.[33, 34] Candidate models included an E_{max} model, a logistic model, and an exponential model.

Using these assumptions, a total of 2100 participants allocated in a 2:1:1:1:1:1 ratio to the placebo and milvexian 25 mg QD, 25 mg BID, 50 mg BID, 100 mg BID, and 200 mg BID groups would provide approximately 80% power to demonstrate a dose-response relationship, with a 1-sided type I error of 0.049. Accounting for up to 10% of participants with missing images at day 90, a sample size of approximately 2350 patients was targeted.

All randomized participants will be included in the analysis of the primary endpoint if they have either a symptomatic ischemic stroke event by day 90 or an evaluable MRI at the day 90 visit. Because of the COVID-19 pandemic, all day 90 visit MRIs will be included in the primary analysis, regardless of timing. All other efficacy analyses will be performed on a randomized (intent-to-treat [ITT]) population up to day 90.

If a dose-response relationship exists, then fitted estimates for the incidence of the primary endpoint will be calculated in each of the treatment groups using the weighted average of fitted models, with weights determined from the Akaike information criteria (AIC) for each model. The observed incidence of the primary endpoint will be summarized by treatment group using the fitted model from the gMCP-Mod procedure. The gMCP-Mod will incorporate the event proportion at each dose level, and then the logit scale will be used during the rest of the gMCP-Mod procedure.

To assess the robustness of the primary efficacy analysis, additional sensitivity analyses will be carried out using the following approaches:

- A sensitivity analysis will repeat the primary analysis, but include MRIs obtained up to Day 106.

- The primary analysis will be repeated using all participants randomized, counting any event-free participants without a Day 90 MRI as having no event (analysis #1) or as having an event (analysis #2).

- The primary analysis will be repeated excluding participants with a protocol deviation meeting predefined criteria having the potential to affect interpretation of major safety or efficacy endpoint analyses, if 5% of participants have such a deviation.

Key subgroup analyses will be performed for demographic variables, index event type (ischemic stroke or TIA), time from onset to first dose, location of atherosclerosis, baseline NIHSS score, prior ischemic stroke or TIA, hypertension, thrombolysis/thrombectomy, prior antiplatelet therapy, and prior statin therapy.

For other events, incidence within each treatment group and the associated relative risk reduction between each milvexian arm and placebo will be presented. NIHSS, mRS, MoCA, and DSST (subtest of WAIS-IV) will be summarized at baseline, on Days 21 and 90, and at the time of a new stroke event.

Analysis of all safety data will be performed on participants treated with 1 dose of double-blind drug. The proportion of participants with major bleeding events (BARC types 3 and 5), as well as BARC-, ISTH-, and PLATO-defined criteria, will be summarized by treatment group. Additional summaries will include characteristics of cerebral microbleeds, hemorrhagic transformation of ischemic stroke, and asymptomatic intracranial bleeding. Adverse event and laboratory data, as well as PK and PD data, will be summarized.

Study conduct during the COVID-19 pandemic

Our trial was conducted during the COVID-19 pandemic resulting in a number of operational and logistical challenges. Innovative changes were instituted to overcome challenges imposed by the pandemic. Remote site initiation visits and remote source data verification were permitted for experienced sites, provided on-site monitoring would occur as soon as travel restrictions were removed. For patients who were unable to attend follow-up study visits in-person, qualified health care professionals visited them at home for safety and endpoint assessments. Direct shipment of investigational products from study centers to participants, via courier with proper temperature control, was arranged. AXIOMATIC-SSP study-specific guidance along with the sponsor's general guidance for the conduct of clinical research during the pandemic were provided to study centers to ensure the safety and welfare of patients, sites, and study members while assuring study compliance.

Discussion

The dual pathway approach, combining an anticoagulant with antiplatelet therapy for stroke prevention, holds promise but requires careful dose-finding to ensure adequate inhibition of thrombosis without increasing the risk for major bleeding. FXIa inhibition with milvexian offers the potential to reduce thrombosis without impeding hemostasis, a significant advantage over previous generations of anticoagulants. AXIOMATIC-SSP is, to our knowledge, the largest dose-finding trial for secondary stroke prevention with the dual pathway approach conducted to date. We combined imaging evidence of new infarctions with clinical stroke events to achieve a placebo event rate sufficient to allow completion of the trial within a reasonable time-frame. This model of arterial thromboembolism has significant advantages in assessing efficacy and safety over previous approaches that developed antithrombotic doses for stroke prevention in a population subject to venous thromboembolism. The results will provide dosing data for a larger phase III trial.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgment:

Glossary

CT	computed tomography
MRI	magnetic resonance imaging
NIHSS	National Institutes of Health Stroke Scale
CTA	computed tomography angiography
MRA	magnetic resonance angiography
mRS	modified Rankin score
TIA	transient ischemic attack
IV	intravenous
INR	international normalized ratio
aPTT	activated partial thromboplastin time

| **ULN** | upper limit of normal |

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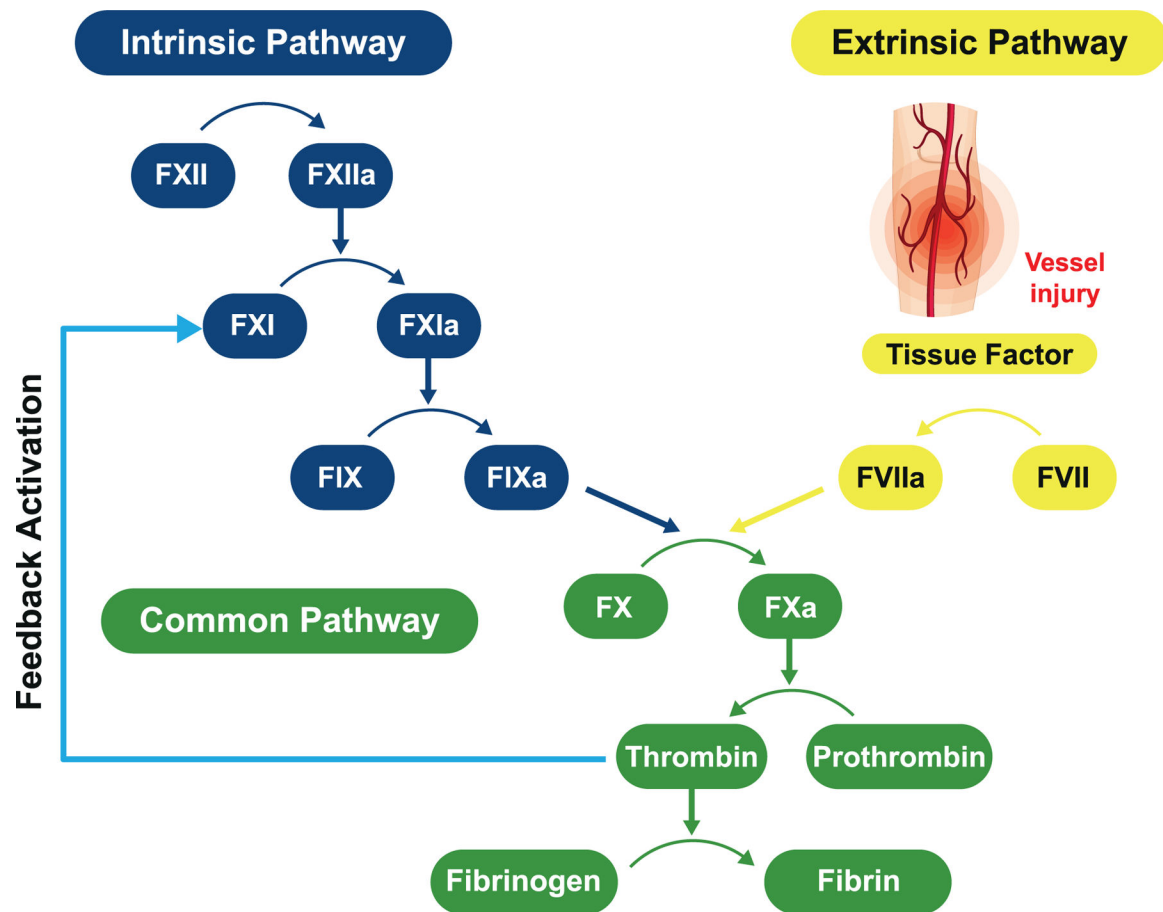
Fig. 1. Coagulation pathway.

Thrombin also activates FV and FVIII which amplify the generation of thrombin and are unaffected by inhibition of FXIa.

FXII, factor XII; FXIIa, activated factor XII; FXI, factor XI; FXIa, activated factor XI; FIX, factor IX; FIXa, activated factor IX; FVIIa, activated factor VII; FVII, factor VII; FX, factor X; FXa, activated factor X.

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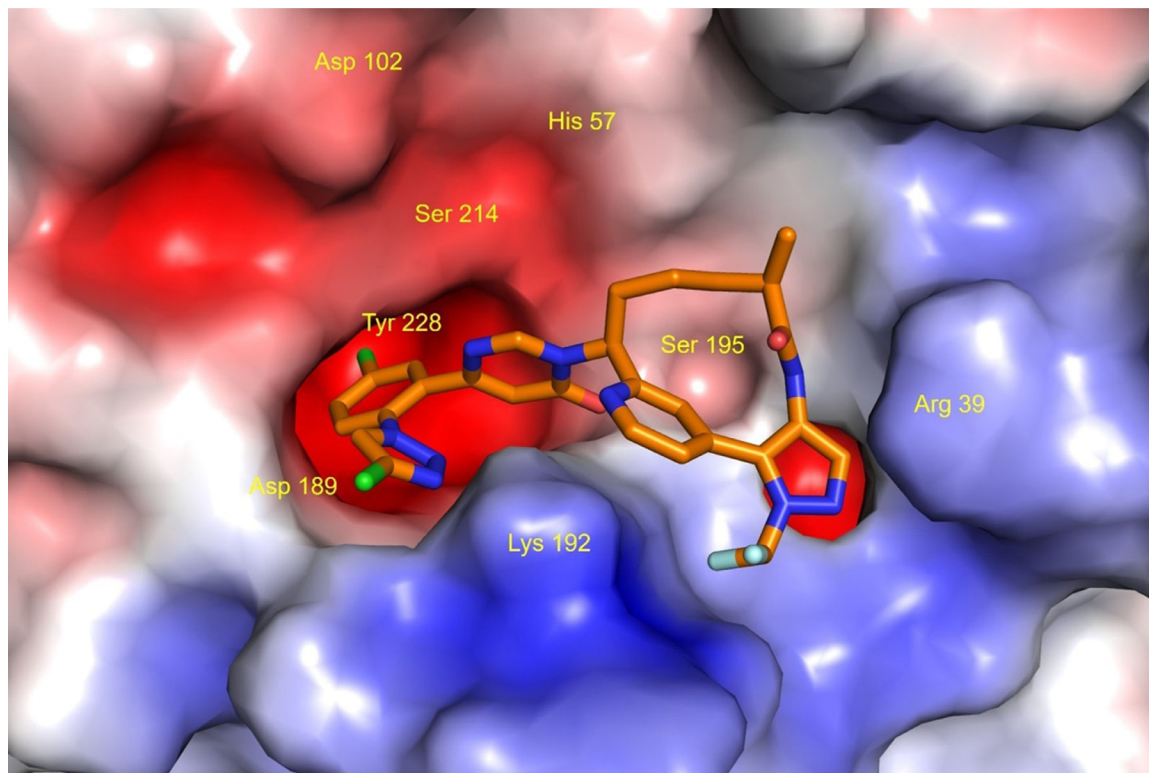
Fig. 2. X-ray crystal structure of milvexian bound to factor XIa (Protein Data Bank ID: 7MBO). Milvexian is represented as a stick model (atom colors: C, orange; O, red; N, blue; Cl, green; F, light blue; H, not shown). The molecular surface of Factor XIa is displayed colored by electrostatic potential (blue: positive; red: negative; white: neutral). Amino acid labels are displayed for the catalytic triad residues (His57, Asp102, Ser195) and selected residues (Arg39, Asp189, Lys192, Tyr228) that are within a distance of 3.5 angstroms from milvexian. This illustration was created using the PyMOL Molecular Graphics System, version 1.7.6.0, Schrödinger, LLC, New York.
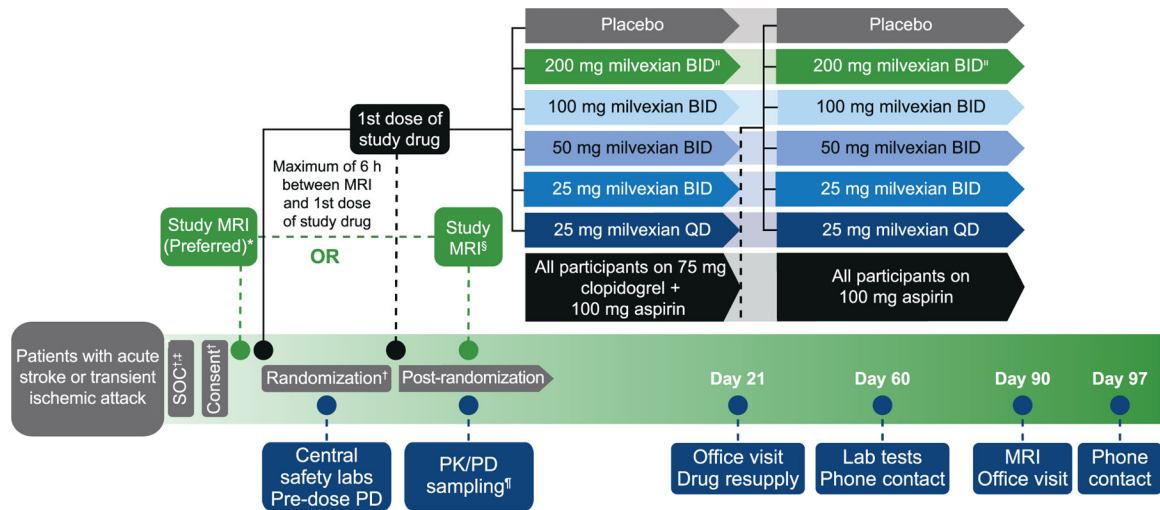
Fig. 3. AXIOMATIC-SSP study design

BID, twice daily; MRI, magnetic resonance imaging; QD, once daily; SOC, standard of care; PD, pharmacodynamic; PK, pharmacokinetic; LD, loading dose.

*Within 48 hours of index event and prior to randomization.

†300 mg clopidogrel LD + 100 mg aspirin.

‡600 mg clopidogrel LD permitted.

§Within 72 hours of index event and up to 24 hours after randomization; clinical neuroimaging is recommended for eligibility assessment if MRI is done post-randomization (to minimize protocol deviation in case of negative imaging findings).

¶Relative to the 1st or 2nd dose of study drug.

ǁThe 200-mg BID cohort was added after 450 participants from the lower doses completed the day 21 visit.

Table 1.

Key inclusion criteria.

Participant and target disease characteristics

Ischemic stroke: a neurological deficit attributable to a non-lacunar acute brain infarction detected by neuroimaging (CT or MRI) and relevant to the clinical symptoms

AND

NIHSS score 7 at time of randomization

AND

Evidence of relevant intracranial or cervical arterial atherosclerotic plaque, ulceration, or thrombus in a feeding artery documented by imaging (either Doppler ultrasound or CTA or MRA or catheter angiography)

AND

mRS 3 before the index event (pre-morbid)

TIA: acute onset neurological deficit attributable to focal ischemia of the brain by history or examination, with complete resolution of the deficit and no brain infarction on neuroimaging (CT or MRI)

AND

ABCD² score 6 or motor symptoms

AND

Evidence of relevant intracranial or cervical arterial atherosclerotic plaque, ulceration, or thrombus in a feeding artery documented by imaging (either Doppler ultrasound or CTA or MRA or catheter angiography)

AND

mRS 3 before the index event (pre-morbid)

Additional criteria

- Body habitus suitable for MRI and no contraindications to the performance of an MRI
- No contraindications to clopidogrel or aspirin and suitable for treatment with aspirin 100 mg per day for 90 days
- Participants who received thrombolytic therapy or mechanical thrombectomy (without stenting) for the treatment of the index event could be enrolled if all conditions were met:
    - 24 hours elapsed between end of IV thrombolytic use/thrombectomy and first dose of study medication
    - Neuroimaging (either clinical imaging or study MRI) after IV thrombolytic therapy/post-thrombectomy excluded any hemorrhagic transformation
    - NIHSS 7 at time of randomization
    - Post-thrombolytic therapy/post-thrombectomy INR 1.5 and aPTT 1.4× ULN prior to study treatment administration
    - No contraindications were identified that, in the opinion of the investigator, would preclude the start of study medication (eg. large infarct volume, procedure-related bleeding)
    - All other study criteria were met

CT, computed tomography; MRI, magnetic resonance imaging; NIHSS, National Institutes of Health Stroke Scale; CTA, computed tomography angiography; MRA, magnetic resonance angiography; mRS, modified Rankin score; TIA, transient ischemic attack; IV, intravenous; INR, international normalized ratio; aPTT, activated partial thromboplastin time; ULN, upper limit of normal.

Table 2.

Key exclusion criteria.

- Predicted inability to swallow study medication

- Women who are pregnant or breastfeeding

- Any condition that, in the opinion of the investigator, contraindicates anticoagulant therapy or would have an unacceptable risk of bleeding such as a large infarct volume (per investigator discretion) or uncontrolled hypertension

- Hemorrhage, intracranial tumor, arteritis, large vessel dissection, AVM, or other pathology that could account for index symptoms must be excluded by CT or MRI interpreted locally

- Symptomatic carotid stenosis or intracranial artery stenosis for which endarterectomy or angioplasty is planned within 90 days

- Any condition for which chronic anticoagulation is indicated and expected to be initiated (eg, NVAF, DVT, PE)

- Requirement for continued use of DAPT for >21 days or non-aspirin antiplatelet therapy or anticoagulant for another medical condition (eg, prophylaxis for venous thromboembolism)

- History of hemorrhage into the brain, subarachnoid hemorrhage, subdural hematoma, or spinal cord hemorrhage except CMB and minor hemorrhagic transformation of prior infarct manifesting as scattered petechiae (HI1 according to Heidelberg classification)[35]

- History of clinically meaningful hepatic disease and/or clinically significant abnormal liver function

- Any of the following laboratory results outside of the ranges specified below prior to study treatment administration, confirmed by repeat:

  – Hemoglobin <9 g/dL

  – Platelet count <100,000 mm^3

  – aPTT >1.4× ULN

  – INR >1.5

  – AST or ALT >3× ULN

- Intracranial tumor (except meningioma, which is permitted) or aneurysm > 5 mm or AVM (except treated aneurysm without history of intracranial bleed, which is permitted)

- History of ESRD with eGFR <15 mL/min/1.73 m^2 or requiring dialysis

- Planned use of anticoagulants, including warfarin or other vitamin K antagonists, oral thrombin and factor Xa inhibitors, bivalirudin, hirudin, argatroban, unfractionated heparin, and LMWH, with the exception of heparin or LMWH used to maintain patency of indwelling catheters

- Anticipated concomitant chronic (>14 days) use of systemic NSAIDs; NSAID use (including COX-2 inhibitors) prior to randomization is allowed

- Use of combined P-gp and strong CYP3A4 inhibitors or combined P-gp and strong CYP3A4 inducers in the 7 days prior to randomization, or the need for ongoing treatment with concomitant oral or intravenous therapy with combined P-gp and strong CYP3A4 inhibitors or combined P-gp and strong CYP3A4 inducers during the study

- Planned concomitant use of omeprazole or esomeprazole after randomization for the duration of clopidogrel treatment (eg, H2 blockers [except cimetidine] and other PPIs are allowed)

- History of or any of the following findings on 12-lead ECG prior to study drug administration: atrial fibrillation, atrial flutter, complete heart block, or Mobitz II second-degree heart block

- Known SARS-CoV-2 infection within 4 weeks prior to screening

AVM, arteriovenous malformation; CT, computed tomography; MRI, magnetic resonance imaging; NVAF, non-valvular atrial fibrillation; DVT, deep vein thrombosis; PE, pulmonary embolism; DAPT, dual antiplatelet therapy; CMB, cerebral microbleed; HI1, hemorrhagic infarction type 1; aPTT, activated partial thromboplastin time; ULN, upper limit of normal; INR, international normalized ratio; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ESRD, end-stage renal disease; eGFR, estimated glomerular filtration rate; LMWH, low molecular weight heparin; NSAID, non-steroidal anti-inflammatory drug; COX-2, cyclo-oxygenase 2; P-gp, P-glycoprotein; CYP3A4, cytochrome P450 3A4; PPI, proton pump inhibitor; ECG, electrocardiogram; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.