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Safety and efficacy of factor XIa inhibition with milvexian for secondary stroke prevention (AXIOMATIC-SSP): a phase 2, international, randomised, double-blind, placebo-controlled, dose-finding trial

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MS and GJH wrote the first and final drafts of the manuscript and had access to all the data in the study. All co-authors reviewed the draft manuscripts, provided comments, and approved submission. MS, CAM, KT, DB, SEK, HL, GT, GN, AC, AS, PA, ME, BWY, DTa, DTo, LY, PvWM, GSS, AAv, JD, DS, TT, JE, SFA, JRW, ECS, NGP, PML, AAr, DG, HCD, CC, AK, DL, and GJH served on the steering committee. All authors contributed to study design as well as data collection and interpretation. MS and GJH confirm the fidelity of the trial protocol and have verified the accuracy and completeness of the data and reporting of events.
All authors agreed to submit the manuscript for publication.

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See **Online** for appendix

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Summary

Background—People with factor XI deficiency have lower rates of ischaemic stroke than the general population and infrequent spontaneous bleeding, suggesting that factor XI has a more important role in thrombosis than in haemostasis. Milvexian, an oral small-molecule inhibitor of activated factor XI, added to standard antiplatelet therapy, might reduce the risk of non-cardioembolic ischaemic stroke without increasing the risk of bleeding. We aimed to estimate the dose–response of milvexian for recurrent ischaemic cerebral events and major bleeding in patients with recent ischaemic stroke or transient ischaemic attack (TIA).

Methods—AXIOMATIC-SSP was a phase 2, randomised, double-blind, placebo-controlled, dose-finding trial done at 367 hospitals in 27 countries. Eligible participants aged 40 years or older, with acute (<48 h) ischaemic stroke or high-risk TIA, were randomly assigned by a web-based interactive response system in a 1:1:1:1:1:2 ratio to receive one of five doses of milvexian (25 mg once daily, 25 mg twice daily, 50 mg twice daily, 100 mg twice daily, or 200 mg twice daily) or matching placebo twice daily for 90 days. All participants received clopidogrel 75 mg daily for the first 21 days and aspirin 100 mg daily for the first 90 days. Investigators, site staff, and participants were masked to treatment assignment. The primary efficacy endpoint was the

composite of ischaemic stroke or incident covert brain infarct on MRI at 90 days, assessed in all participants allocated to treatment who completed a follow-up MRI brain scan, and the primary analysis assessed the dose–response relationship with Multiple Comparison Procedure–Modelling (MCP-MOD). The main safety outcome was major bleeding at 90 days, assessed in all participants who received at least one dose of the study drug. This trial is registered with ClinicalTrials.gov (NCT03766581) and the EU Clinical Trials Register (2017-005029-19).

Findings—Between Jan 27, 2019, and Dec 24, 2021, 2366 participants were randomly allocated to placebo (n=691); milvexian 25 mg once daily (n=328); or twice-daily doses of milvexian 25 mg (n=318), 50 mg (n=328), 100 mg (n=310), or 200 mg (n=351). The median age of participants was 71 (IQR 62–77) years and 859 (36%) were female. At 90 days, the estimates of the percentage of participants with either symptomatic ischaemic stroke or covert brain infarcts were 16·8 (90·2% CI 14·5–19·1) for placebo, 16·7 (14·8–18·6) for 25 mg milvexian once daily, 16·6 (14·8–18·3) for 25 mg twice daily, 15·6 (13·9–17·5) for 50 mg twice daily, 15·4 (13·4–17·6) for 100 mg twice daily, and 15·3 (12·8–19·7) for 200 mg twice daily. No significant dose–response was observed among the five milvexian doses for the primary composite efficacy outcome. Model-based estimates of the relative risk with milvexian compared with placebo were 0·99 (90·2% CI 0·91–1·05) for 25 mg once daily, 0·99 (0·87–1·11) for 25 mg twice daily, 0·93 (0·78–1·11) for 50 mg twice daily, 0·92 (0·75–1·13) for 100 mg twice daily, and 0·91 (0·72–1·26) for 200 mg twice daily. No apparent dose–response was observed for major bleeding (four [1%] of 682 participants with placebo, two [1%] of 325 with milvexian 25 mg once daily, two [1%] of 313 with 25 mg twice daily, five [2%] of 325 with 50 mg twice daily, five [2%] of 306 with 100 mg twice daily, and five [1%] of 344 with 200 mg twice daily). Five treatment-emergent deaths occurred, four of which were considered unrelated to the study drug by the investigator.

Interpretation—Factor XIa inhibition with milvexian, added to dual antiplatelet therapy, did not substantially reduce the composite outcome of symptomatic ischaemic stroke or covert brain infarction and did not meaningfully increase the risk of major bleeding. Findings from our study have informed the design of a phase 3 trial of milvexian for the prevention of ischaemic stroke in patients with acute ischaemic stroke or TIA.

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Introduction

After a non-cardioembolic mild ischaemic stroke or transient ischaemic attack (TIA), the risk of an early recurrent stroke is high,[1–4] despite guideline recommendations to use dual antiplatelet therapy for 10–90 days followed by antiplatelet monotherapy.[5–8] Individuals with large artery atherosclerosis underlying acute stroke have a higher risk of recurrent stroke than those who have stroke with other causes.[5,9] For these patients, only a few treatment options are available and alternative secondary prevention strategies are needed.

Anticoagulation after acute ischaemic stroke with standard heparins in unselected patients reduces the risk of recurrent ischaemic stroke, deep vein thrombosis, and pulmonary embolism but increases the risk of haemorrhagic stroke and other types of bleeding, which offset the potential benefits.[10] As a result, anticoagulation is not commonly used for secondary prevention in people with non-cardioembolic ischaemic stroke. The combination

of aspirin and anticoagulation with low-dose rivaroxaban, an inhibitor of activated factor X, also reduces the risk of major ischaemic cardiovascular events but increases the risk of major bleeding compared with aspirin alone in patients with stable atherosclerotic vascular disease, including patients who are stable more than 1 month after non-lacunar ischaemic stroke).[11]

As factor XI seems to be important for driving thrombus growth but less important in haemostasis, effective and safer anticoagulation might be achieved by inhibiting activated factor XI.[12] Individuals with congenital factor XI deficiency have a lower risk of ischaemic stroke and venous thromboembolism than those without this deficiency, whereas high plasma concentrations of factor XI are associated with an increased risk of ischaemic stroke.[13] People who are deficient in factor XI rarely have spontaneous bleeding and, if they do, the bleeding is mostly post-traumatic and in tissues with high intrinsic fibrinolytic activity, such as the nasopharynx and genitourinary tract.[13–16]

Phase 2 randomised controlled trials have reported that inhibition or reduction of expression of factor XI by antisense oligonucleotides or inhibition of activated factor XI with monoclonal antibodies or small molecules is associated with lower rates of venous thromboembolism and lower rates of bleeding compared with enoxaparin in patients undergoing knee arthroplasty,[17–20] lower rates of bleeding compared with apixaban in patients with atrial fibrillation,[21] and no significant increase in bleeding compared with placebo in patients with acute non-cardioembolic ischaemic stroke or acute myocardial infarction.[22,23]

Milvexian (BMS-986177/JNJ-70033093) is an orally administered, direct inhibitor of activated factor XI.[24] Phase 1 studies have shown that milvexian is safe and well tolerated at doses up to 200 mg twice daily and 500 mg once daily.[25] A phase 2 randomised controlled trial found that milvexian 200 mg once daily and 50–200 mg twice daily after elective knee arthroplasty significantly reduced the incidence of venous thromboembolism in a dose-dependent manner compared with enoxaparin, with a low risk of bleeding.[20]

The Antithrombotic treatment with FXIa inhibition to Optimize Management of Acute Thromboembolic events for Secondary Stroke Prevention (AXIOMATIC-SSP) study was designed primarily to estimate the dose–response effect of milvexian compared with placebo on the incidence of the composite outcome of symptomatic ischaemic stroke and covert brain infarction at 90 days, and to secondarily assess major bleeding at 90 days, in participants with acute non-cardioembolic ischaemic stroke or high-risk TIA.

Methods

Study design and participants

AXIOMATIC-SSP was a phase 2, international, multicentre, randomised, double-blind, placebo-controlled, dose-finding clinical trial comparing five doses of milvexian with placebo. The trial rationale and design have been published previously.[26] The trial protocol was approved by all relevant regulatory health authorities, appropriate national ethics committees, and local institutional review boards (appendix pp 18–24).[26] The trial was conducted at 367 stroke centres in 27 countries. The steering committee supervised the

conduct of the study. The sponsor selected, contracted, and paid study investigators; provided trial medications; and oversaw site monitoring.

Eligible participants were aged 40 years or older with non-cardioembolic ischaemic stroke or high-risk TIA seen within 48 h of symptom onset. Qualifying strokes were symptomatic non-lacunar acute brain infarcts visible on neuroimaging (CT or MRI) with a US National Institutes of Health Stroke Scale (NIHSS) score of 5 or lower. After safety review, the NIHSS score inclusion criterion was extended to 7 or lower (see later in this section for changes to eligibility). Qualifying TIAs were acute-onset neurological symptoms attributable to focal brain ischaemia that cause motor deficits or an ABCD2 (age, blood pressure, clinical features, duration of TIA, and presence of diabetes) score of 6 or higher with complete resolution of the deficit and no brain infarction on neuroimaging.[27] All participants had imaging evidence of visible intracranial or extracranial atherosclerotic plaque, ulceration, or thrombus of any degree (but not complete occlusion) in a feeding artery and a premorbid modified Rankin scale (mRS) score of 3 or lower.[26]

We excluded individuals with any of the following: a history of haemorrhage in the brain or spinal cord or a condition that would exclude anticoagulant therapy; SARS-CoV-2 infection within 4 weeks before screening; imaging evidence of large vessel dissection; an intracranial tumour (other than meningioma) or arteriovenous malformation that could explain the qualifying symptoms; an estimated glomerular filtration rate of <15 mL/min per 1·73 m^2; clinically meaningful liver disease (aspartate aminotransferase or alanine aminotransferase >3×upper limit of normal); treatment with strong inducers or inhibitors of both P-glycoprotein and cytochrome P450 isoenzyme 3A4 in the 7 days before randomisation or planned ongoing treatment during the study; planned use of anticoagulants (except for heparins for maintaining the patency of indwelling catheters); or a requirement for dual antiplatelet therapy beyond 21 days.

After approximately 450 participants had been randomly assigned and the independent data monitoring committee had reviewed the safety and efficacy data, the protocol was changed on Oct 9, 2020, to allow enrolment of participants who had received thrombolytic therapy or mechanical thrombectomy, or both, for the treatment of the index stroke, as well as those with an NIHSS score of 6 or 7. Enrolment after acute standard-of-care treatment was permitted if at least 24 h had passed between the acute recanalisation therapy and the first dose of study medication, neuroimaging had excluded haemorrhagic transformation of the acute brain infarct, and all other study criteria were met.[26]

Written informed consent was obtained from each participant or their legally authorised representative before any study-driven procedures were done. The study was conducted in accordance with the Declaration of Helsinki.

Randomisation and masking

Participants were randomly assigned by use of an interactive web-based response system (appendix pp 32–35). The system was programmed before the study started and the service was provided by an interactive response technology vendor. This vendor had no other role besides providing the randomisation service in the study. Eligible participants were

randomly allocated (in a 1:1:1:1:1:2 ratio) to receive one of five oral doses of milvexian (25 mg once daily, 25 mg twice daily, 50 mg twice daily, 100 mg twice daily, or 200 mg twice daily) or matching placebo, in addition to open-label uncoated aspirin (100 mg per day) and clopidogrel (loading dose of 300–600 mg, followed by 75 mg per day; dose selection is described in the appendix pp 39–40). The randomisation scheme originally included 50 mg once-daily and 100 mg once-daily groups, but randomisation to these groups was terminated to reduce the required sample size but maintain focus on twice-daily dosing (keeping 25 mg once daily as the lowest dose). All capsules of milvexian and placebo were identical in appearance, and all participants received a study medication (milvexian or placebo) twice a day to prevent unblinding of the once daily group. Randomisation to the highest dose group of 200 mg twice daily was not permitted until the data monitoring committee had reviewed the safety and efficacy data in at least the first 800 participants and concurred that it was safe to randomly assign participants to this dose. Randomisation to the 200 mg twice-daily group began after 1387 participants had been randomly assigned to other doses or matching placebo. Investigators, site staff, and participants were masked to treatment assignment during the trial until the last participant either completed 90 days of follow-up or withdrew early, and the database was locked.

Procedures

Participants were randomly assigned within 48 h of symptom onset. A baseline MRI brain scan was done according to a study-specific protocol[26] and was recommended before randomisation. If the baseline MRI could not be done before randomisation, it could be acquired up to 24 h after randomisation but no later than 72 h from symptom onset.

The study drug (milvexian or placebo) was started immediately after randomisation (within 48 h of symptom onset in all participants) and no later than 6 h after the baseline MRI brain scan in those with a baseline MRI scan before randomisation. Clopidogrel was administered for 21 days following randomisation, while aspirin and either milvexian or a matching placebo were continued until day 90. Participants who were not taking clopidogrel before the index event or who had not already received a loading dose of clopidogrel as standard of care were loaded with 300–600 mg of clopidogrel. Treatment with aspirin before enrolment that was different than 100 mg daily (eg, a loading dose of 300 mg) was allowed. No dose adjustments were made to milvexian, aspirin, or clopidogrel after randomisation.

Study visits were scheduled for day 21 (±7 days) and day 90 (±7 days), with a telephone contact to assess safety at 60 and 97 days after randomisation The requirement for visits to be within specific time windows was relaxed to accept visits without restriction due to the unpredictability of measures instituted to combat the COVID-19 pandemic. Adherence to the allocated study drug was assessed by interview and pill count at each visit. If the study drug was discontinued permanently, participants were followed up as per protocol and included in the intention-to-treat analysis.

An end-of-study MRI brain scan was obtained at the day 90 visit (±7 days). During the COVID-19 pandemic, we accepted brain scans obtained outside this window. Two neuroradiologists masked to treatment allocation read all images independently, and disagreements were resolved by consensus between the readers.

Outcomes

The primary efficacy endpoint was the composite of symptomatic ischaemic stroke during the 90 days after randomisation or new covert brain infarction, detected by comparing MRI brain scans at baseline and day 90. Site investigators determined symptomatic ischaemic strokes according to standardised study definitions (appendix pp 25–26). A diagnosis of symptomatic ischaemic stroke required a sustained (>24 h) increase in the NIHSS score of 3 or more points that was not explained by other factors or was confirmed by imaging as a new brain infarct. A new covert brain infarct was determined if the day 90 MRI showed a new lesion on the diffusion-weighted imaging (DWI) or fluid-attenuated inversion recovery (FLAIR) sequences that was consistent with an ischaemic brain infarct and if the participant had not had a new symptomatic ischaemic stroke after randomisation.

The safety endpoint of major bleeding, a secondary endpoint, was ascertained by the occurrence of type 3 and type 5 bleeding, according to the Bleeding Academic Research Consortium (BARC) classification system, with a slight modification.[28,29] The modification was that we included symptomatic haemorrhagic transformation of brain infarction in the BARC type 3c classification, in addition to intracranial haemorrhage, if new focal neurological symptoms caused a deterioration in the NIHSS score of 4 or more points or death, and there was symptomatically relevant haemorrhage into at least 30% of the infarct volume, corresponding to the Heidelberg criteria classification of parenchymal haematoma type 2.[29] Bleeding was also assessed with the International Society on Thrombosis and Haemostasis (ISTH) and PLATelet inhibition and patient Outcomes (PLATO) criteria.[26] Additionally, occurrence of clinical bleeding of any type with milvexian was compared with placebo.

Key secondary efficacy analyses were a descriptive analysis of the primary endpoint, individual components of the primary composite efficacy endpoint, and the composite of symptomatic ischaemic stroke, myocardial infarction, and all-cause mortality. Other secondary endpoints were the volume and number of new brain infarcts detected by MRI; measures of stroke severity, neurological function, and cognitive function (NIHSS, mRS score, Montreal Cognitive Assessment [MOCA], and Digit Symbol Substitution Test of the Wechsler Adult Intelligence Scale, Fourth Edition [WAIS-R]); and pharmacokinetic and pharmacodynamic measures. Analyses for these other secondary endpoints are ongoing and these endpoints will be reported separately.

Statistical analysis

We aimed to have at least 80% power, with a one-sided type I error of α=0·049, to detect a dose–response effect of milvexian on the primary efficacy outcome at 90 days (appendix p 29).[26,30–32]

The primary efficacy endpoint analysis population comprised all randomised participants who had a symptomatic ischaemic stroke up to day 90 or an evaluable MRI scan from the day 90 visit. All other efficacy outcomes were analysed in the intention-to-treat population, which comprised all randomized participants, irrespective of treatment initiation or discontinuation up to day 90. Because symptomatic ischaemic stroke was both a

component of the composite primary endpoint and a secondary outcome in its own right, prespecified analyses for symptomatic ischaemic stroke were done in both the primary endpoint analysis population and the intention-to-treat population. The safety analysis population comprised all participants who received at least one dose of study medication, and safety was analysed according to the treatment assigned at randomisation.

We calculated proportions of participants with events by day 90, and relative risks and corresponding two-sided 90·2% CIs for the primary endpoint (model-based dose–response using a bootstrap procedure), and 95% CIs otherwise, to compare the milvexian groups with placebo. The Kaplan-Meier technique was used to estimate and plot the cumulative incidence of clinically symptomatic ischaemic strokes and major bleeding over time.

The Multiple Comparison Procedure–Modelling (MCP-MOD) examined whether a dose–response relationship existed and estimated a fitted incidence for the primary efficacy variable based on three candidate models (E_{max}, logistic, and exponential). The existence of a dose–response trend was shown by the significance of at least one of the three candidate models at the 0·049 level of significance; model-based estimates for the incidence of the primary efficacy endpoint were calculated in each of the treatment groups with the weighted average of the three fitted models by use of Akaike's Information Criterion to determine weights, regardless of the significance of the model (appendix pp 29–32).[26,33] Sensitivity analyses comprised inclusion of MRI scans obtained up to day 106 in the primary efficacy analysis, including all randomised participants (counting any event-free participants without a day 90 MRI scan as having no event or as having an event) and excluding participants with a protocol deviation if at least 5% of participants had such a deviation.

When approximately 1600 participants had been randomly assigned, the sponsor carried out an administrative interim analysis with personnel who were not involved in the study. As specified in the protocol, no decision regarding study conduct was made as a result of this analysis. The aim was to facilitate subsequent planning and development of the milvexian secondary stroke prevention programme. The steering committee and all personnel involved in the study were masked to the results of this administrative interim analysis. An independent data monitoring committee had access to unblinded data and was responsible for the safety of participants in the trial and the integrity of the study. Major protocol amendments are listed in the appendix (pp 27–28).

This trial is registered with ClinicalTrials.gov (NCT03766581), and the EU Clinical Trials Register (2017-005029-19), and is now completed.

Role of the funding source

AXIOMATIC-SSP was sponsored by Bristol Myers Squibb and Janssen Pharmaceuticals, which designed the trial in collaboration with the principal investigator and steering committee. The sponsor collected data, did the statistical analysis, and contributed to interpretation of the data, and funded editorial support. The sponsor reviewed and provided comments on the manuscript, but sponsor approval was not required for submission of the manuscript for publication.

Results

Between Jan 27, 2019, and Dec 24, 2021, 2799 individuals were screened, and 2366 (85%) were randomly allocated to either placebo (n=691) or one of five doses of milvexian (n=1635; figure 1; table 1). 22 participants were randomly allocated to 50 mg once daily milvexian and 18 to 100 mg once daily milvexian, before randomisation to these groups was terminated; data from these two dose groups are included in baseline characteristics (combined milvexian group in table 1 and by dose in the appendix pp 2–3), patient disposition (figure 1), and safety, but not in the efficacy tables.

Baseline demographic and clinical characteristics were balanced between treatment groups (table 1, appendix pp 2–3, 7). The median age of participants was 71 years (IQR 62–77), 834 (35%) of 2366 participants were aged 75 years or older, 859 (36%) were female, 1884 (80%) were White, 408 (17%) were Asian, and 48 (2%) were Black. Ischaemic stroke was the index event for the majority of participants. For those with stroke (n=1790), the median NIHSS score at randomisation was 2 (IQR 1–3) and 1722 (96%) of participants had a NIHSS score of 0–5.

Before randomisation, 271 (11%) of 2366 participants received acute treatment for ischaemic stroke (intravenous administration of tissue plasminogen activator, endovascular treatment, or both); 656 (28%) participants were taking aspirin and 274 (12%) were taking clopidogrel.

The median time from the index event to the first dose of study drug was 35·2 h (IQR 27·3–44·0), and 393 (17%) of 2366 participants were treated with the study drug within 24 h of symptom onset. We completed a baseline MRI brain scan in 1940 (82%) participants within 48 h of symptom onset.

32 randomised participants (nine in the placebo group and 23 in the milvexian groups) did not receive any study drug (figure 1). Vital status was known at the end of the trial for 2295 (97%) of 2366 randomised participants, including those who completed the study and those who died. 23 (1%) of 2366 participants died before the end of the study, four (<1%) were lost to follow-up, 66 (3%) withdrew consent, and one participant withdrew for another reason.

Exposure to the study drug was similar between the placebo and milvexian groups; 502 (74%) of 682 participants assigned placebo and 1187 (72%) of 1652 assigned milvexian received the study drug for at least 84 days (ie, within the window for the 90-day follow-up visit), and the mean duration of study drug exposure was 76·3 (SD 29·0) days in the placebo group, and 74·9 (30·4) days in the combined milvexian group.

Overall, 585 (25%) of 2366 randomised participants did not complete the 90-day treatment phase (162 [23%] of 691 in the placebo group and 423 [25%] of 1675 in the milvexian group), mainly due to adverse events (82 [12%] of 691 in the placebo group and 271 [16%] of 1675 in the milvexian group). Among treated participants, a new diagnosis of atrial fibrillation was the most common reason for discontinuation of treatment (25 [4%] of 682 participants in the placebo group and 52 [3%] of 1652 in the milvexian group). COVID-19-

related discontinuations, including intercurrent COVID-19 (three [<1%] of 691 participants in the placebo group and nine [1%] of 1675 in the milvexian group), site closures, or inability to collect key safety information, or a combination of the above, accounted for treatment discontinuations in 16 (2%) of 691 participants in the placebo group and 32 (2%) of 1675 participants in the milvexian group. Occurrence of symptomatic ischaemic stroke constituted an adverse event and a primary outcome event, and 37 (nine [1%] of 682 in the placebo group and 28 [2%] of 1652 in the milvexian group) ischaemic stroke events led to treatment discontinuation. Across milvexian doses, discontinuation due to adverse events ranged from 44 (14%) of 325 in the 25 mg once-daily group to 79 (23%) of 344 in the 200 mg twice-daily groups. The day 90 MRI scan was completed in 2139 (90%) of 2366 participants.

At 90 days after randomisation, the primary efficacy outcome of the composite of symptomatic ischaemic stroke or covert brain infarcts occurred in 104 (17%) of 625 participants in the placebo group, 50 (16%) of 308 participants in the milvexian 25 mg once-daily group, 53 (18%) of 287 participants in the 25 mg twice-daily group, 43 (14%) of 306 participants in the 50 mg twice-daily group, 41 (15%) of 277 participants in the 100 mg twice-daily group, and 52 (16%) of 317 participants in the 200 mg twice-daily group who had an evaluable MRI image from the day 90 visit (table 2; appendix p 12). No significant dose–response was detected for the primary efficacy outcome because each of the p values corresponding to the three candidate models did not reach significance at the 0·049 level. Model-based estimates of relative risk compared with placebo were 0·99 (90·2% CI 0·91–1·05) with 25 mg milvexian once daily, 0·99 (0·87–1·11) with 25 mg twice daily, 0·93 (0·78–1·11) with 50 mg twice daily, 0·92 (0·75–1·13) with 100 mg twice daily, and 0·91 (0·72–1·26) with 200 mg twice daily.

Sensitivity analyses for the primary endpoint comprised all randomised participants (counting any event-free participants without a day 90 MRI scan as having no event or as having an event) and MRI scans obtained only up to day 106 in the primary efficacy analysis, and excluded participants with a protocol deviation potentially affecting interpretation of key endpoints. Results in sensitivity analyses were consistent with the main analysis (appendix pp 36–38).

The occurrence of covert brain infarcts could be ascertained only in the primary analysis population defined as having paired baseline and day 90 MRI scans (table 2), whereas symptomatic ischaemic stroke could be identified in the entire intention-to-treat population (appendix p 13). The incidence of incident covert brain infarcts was similar across treatment groups, with no apparent treatment effect (primary analysis population; table 2). In the intention-to-treat population, symptomatic ischaemic stroke was reported in 38 (5%) of 691 participants in the placebo group, 15 (5%) of 328 participants in the 25 mg milvexian once-daily group, 12 (4%) of 318 participants in the 25 mg twice-daily group, 13 (4%) of 328 participants in the 50 mg twice-daily group, 11 (4%) of 310 participants in the 100 mg twice-daily group, and 27 (8%) of 351 participants in the 200 mg twice-daily group (appendix p 13). Compared with placebo, there were fewer ischaemic strokes in all milvexian dose groups except for the 200 mg milvexian twice-daily group. These findings were consistent across predefined subgroups of index event type, age, and sex (appendix

p 14). Most symptomatic ischaemic strokes occurred within 30 days of randomisation (appendix p 15).

Myocardial infarction and all-cause death were rare (table 3; appendix pp 4–5). The secondary composite endpoint of ischaemic stroke, myocardial infarction, or all-cause death occurred in 42 (6%) of 691 placebo-assigned participants and 17 (5%) of 328 participants in the 25 mg milvexian once-daily group, 15 (5%) of 318 participants in the 25 mg twice-daily group, 16 (5%) of 328 participants in the 50 mg twice-daily group, 16 (5%) of 310 participants in the 100 mg twice-daily group, and 33 (9%) of 351 participants in the 200 mg twice-daily group (table 3). Treatment-emergent deaths (ie, those that occurred on or after the date of the first dose of study drug and within 7 days of the last dose) occurred in five participants and were considered not related to the study drug in four instances by the investigator (table 4). One participant randomly assigned to 100 mg milvexian had an unwitnessed treatment-emergent death due to an unknown cause, which was considered to be related to the study drug by the site investigator.

The safety outcome of the composite of modified BARC type 3 and type 5 bleeding occurred in four (1%) of 682 participants treated with at least one dose of placebo, two (1%) of 325 participants assigned to 25 mg milvexian once daily, two (1%) of 313 participants assigned to 25 mg twice daily, five (2%) of 325 participants assigned to 50 mg twice daily, five (2%) of 306 participants assigned to 100 mg twice daily, and five (1%) of 344 participants assigned to 200 mg twice daily (table 4). There was no meaningful dose–response with respect to bleeding, acknowledging the small number of events (figure 2; table 4). Intracranial haemorrhage (including symptomatic haemorrhagic transformation of ischaemic stroke) occurred in two (<1%) participants who received placebo, three (1%) participants who received 50 mg milvexian twice daily, and one participant who received 200 mg milvexian twice daily. There were no fatal bleeding events.

Any BARC type bleeding was observed in 54 (8%) of 682 participants treated with placebo, 35 (11%) of 325 participants treated with 25 mg milvexian once daily, 27 (9%) of 313 participants treated with 25 mg twice daily, 40 (12%) of 325 treated with 50 mg twice daily, 40 (13%) of 306 treated with 100 mg twice daily, and 35 (10%) of 344 treated with 200 mg twice daily. Most participants who had a bleeding event did so by day 21 (appendix p 16). The results of the secondary composite safety outcome of major bleeding and clinically relevant nonmajor bleeding by ISTH criteria are shown in the appendix (p 6).

Although the adverse events associated with milvexian were similar to those seen with placebo (table 4), more adverse events were reported in the renal and urinary disorder system organ class in the 200 mg milvexian twice-daily group (47 [14%] of 344) compared with the placebo (25 [4%] of 682), 25 mg once daily (nine [3%] of 325), 25 mg twice daily (eight [3%] of 313), 50 mg twice daily (ten [3%] of 325), and 100 mg twice daily (nine [3%] of 306) groups.

Discussion

This phase 2, randomised, dose-finding trial of milvexian versus placebo, in addition to standard dual antiplatelet therapy, for participants with acute non-lacunar ischaemic stroke or high-risk TIA, had six main findings. First, there was no significant dose–response across milvexian doses (ranging from 25 mg once daily to 200 mg twice daily) for the primary composite efficacy endpoint of symptomatic ischaemic stroke and incident covert brain infarction. Second, there was no significant dose–response for the main composite safety endpoint of major bleeding, which was infrequent (1–2%) in the trial population. Third, in a prespecified secondary analysis, milvexian was associated with fewer symptomatic ischaemic strokes than placebo at all doses except for 200 mg twice daily. Fourth, milvexian had no effect on covert infarcts; across all participants, this type of event contributed 66% (227 of 343) of primary outcome events. Fifth, there were some increases in major bleeding (BARC type 3), of mostly gastrointestinal origin, at milvexian doses of 50 mg twice daily and higher. Sixth, there was no meaningful increase in intracranial haemorrhage or symptomatic haemorrhagic transformation of brain infarction (modified BARC type 3c) with milvexian versus placebo, and there was no fatal bleeding (BARC type 5) in the study. These findings suggest a range of milvexian doses (between 25 mg twice daily and 100 mg twice daily) that could be appropriate for further investigation in a properly powered phase 3 trial.

AXIOMATIC-SSP is the largest clinical trial of activated factor XI inhibition added to standard antiplatelet therapy for secondary stroke prevention. Systematic bias was minimised by the randomised, double-blind, placebo-controlled design. Vital status follow-up was complete in 97% of participants, with attrition balanced between groups. The primary composite endpoint comprised a spectrum of infarct severity combining covert and symptomatic infarcts. The primary composite outcome event rate of 17% in the placebo group was consistent with the pre-study estimated rate of 15% in the placebo group that underpinned the sample size calculations, and the reduction in the relative risk of symptomatic ischaemic stroke with 100 mg milvexian twice daily (0·65; 95% CI 0·33 to 1·25) was consistent with the pre-study estimated 32% reduction in the relative risk of the composite primary efficacy endpoint with 100 mg milvexian twice daily. This effect size would be clinically important if replicated in an appropriately powered phase 3 study.

A recently completed dose-finding trial of another inhibitor of activated factor XI for secondary stroke prevention showed similar results for the composite endpoint of symptomatic ischaemic stroke and covert brain infarcts.[22] No treatment effect on covert stroke was apparent in either trial.[22] The discordance in the presence of a reduction in symptomatic ischaemic stroke and the absence of an effect on MRI evidence of covert brain infarction in both trials suggests that MRI evidence of covert brain infarction might not be a valid marker of symptomatic ischaemic stroke or response to anticoagulation.[33–35] Covert infarcts might be caused by haemodynamic or inflammatory mechanisms that do not respond to anticoagulants. It is also possible that inhibition of activated factor XI reduces the size of pathological thrombi but might not suppress small thrombi underlying covert infarcts. The potential modification of the effect of treatment by infarct topography requires further research in adequately powered datasets.

Although the number of bleeding events was low, we found no consistent dose–response in major bleeding and no meaningful increase in intracerebral haemorrhage with milvexian added to dual antiplatelet therapy for secondary stroke prevention. Similar findings were noted in a recent trial of another activated factor XI inhibitor in participants with acute myocardial infarction.[23] These results are in contrast to the dose-dependent increase in bleeding, shown with the addition of activated factor X inhibitors to dual antiplatelet therapies in individuals with acute coronary syndromes[36,37] and is consistent with the hypothesis that activated factor XI does not play a major role in haemostasis.

The increase in ischaemic stroke events in the 200 mg milvexian twice daily group compared with placebo is unexplained. It contrasts with the efficacy of 200 mg milvexian twice daily in the AXIOMATIC-TKR study of patients undergoing knee replacement surgery, which showed a significant reduction in venous thromboembolism with this dose compared with enoxaparin.[20] Discontinuation due to adverse events was twice as high in the 200 mg milvexian twice-daily group as in the placebo group because ischaemic stroke was defined as both an adverse event and an outcome event in our trial. We found a higher incidence of renal adverse events in the 200 mg twice-daily dose group than in the placebo or other dose groups. This finding was not seen in animal studies,[25] in which exposure was higher than in our study, nor in the phase 2 knee replacement study.[20] We were not able to identify any potential mechanisms that could link milvexian with renal dysfunction related to therapeutic effects or off-target effects. Randomisation to the 200 mg milvexian twice-daily group did not begin until 1387 participants had been randomly assigned, so we cannot exclude a potential influence of unmeasured confounders in this dose group and, given the small number of events in this group, we also cannot exclude a random chance finding.

Limitations of the study included a study treatment completion rate of 75%, mainly due to adverse events and operational difficulties during the COVID-19 pandemic. The study treatment completion rate was similar between treatment groups but might have reduced our power to detect a dose–response. Women were a minority of the trial population, similar to other stroke trials.[38] We included covert brain infarcts as a surrogate for clinical ischaemic stroke in the composite primary outcome to enable sufficient statistical power to detect a dose–response in this phase 2, dose-finding trial. As anticipated, incident covert brain infarcts contributed most of the primary outcome events, but the validity of MRI evidence of covert brain infarction as a surrogate marker of symptomatic stroke in studies of antithrombotic therapy is uncertain.[34,35]

The results of this phase 2 study showed that the combination of anticoagulation with milvexian and standard antiplatelet treatment in patients with acute ischaemic stroke or TIA and visible arterial atherosclerosis did not result in a consistent dose–response for the composite primary endpoint of ischaemic stroke and covert infarct. Similarly, no meaningful dose–response was observed for the safety endpoints of BARC modified type 3 and type 5 bleeding. A phase 3 trial (NCT05702034) is ongoing to assess whether the reduction in symptomatic ischaemic stroke with the 25 mg milvexian twice-daily dose versus placebo, with an acceptable bleeding profile, can be confirmed in a larger and broader population of patients with acute TIA or ischaemic stroke.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Declaration of interests

MS has received consulting fees from Janssen, HLS Therapeutics, and Bayer; and has served in a leadership or fiduciary role for the Canadian Stroke Consortium. CAM has received honoraria from Bristol Myers Squibb and Boehringer Ingelheim. KT has received honoraria from Bayer, Daiichi Sankyo, Bristol Myers Squibb, Otsuka, Novartis, and Abbott Medical. DB has received consulting fees from Bristol Myers Squibb, Bayer, Ipsen, and Boehringer Ingelheim; and has received honoraria from Novo Nordisk, HUMAN BioPlazma, and Parexel. SEK has received grants or contracts from Bristol Myers Squibb; and has received consulting fees from Bristol Myers Squibb. HL has received consulting fees from Bristol Myers Squibb; has participated on steering committees or advisory boards for Bristol Myers Squibb, the US National Institute of Neurological Disorders and Stroke, and Coherex Medical; and is on the Editorial Board for *Medscape Neurology*. GT has received consulting fees from Bristol Myers Squibb. GN has received financial support from Bristol Myers Squibb. AC has participated on a steering committee for Bristol Myers Squibb; has received grants or contracts from Bristol Myers Squibb; and has previously served as the President of the Cerebrovascular Section of Polish Neurological Society, honorary president of the Polish Neurological Society, and in a leadership role for the Angels Initiative— Poland. PA has participated on a steering committee for Bristol Myers Squibb and Janssen; has received grants or contracts from Sanofi, Bristol Myers Squibb, AstraZeneca, Pfizer, Merck, AltheraPharm, and the French Government; has received consulting fees from Bayer, Novartis, and Novo Nordisk; has received honoraria from Viatris and Sanofi; and has participated in an advisory board for Novartis. ME has received grants or contracts from Bayer; has received consulting fees from Bayer; has received honoraria from Abbott, Boehringer Ingelheim, Pfizer, Amgen, GSK, Sanofi, and Novartis; has participated on data safety monitoring boards or advisory boards for Bristol Myers Squibb, Bayer, AstraZeneca, Boehringer Ingelheim, Daiichi Sankyo, Amgen, and Covidien; has served in a leadership or fiduciary role for the European Academy of Neurology, German Neurological Society (DGN), International Society for Cerebral Blood Flow and Metabolism, American Heart Association/American Stroke Association, European Stroke Organisation, World Stroke Organization, German Center for Cardiovascular Research (DZHK), and German Center for Neurodegenerative Diseases (DZNE); and has been a recipient of materials from Amgen. DTa has received consulting fees from QuantaIX Neuroscience, Babylink, and Pi-cardia, and for being a national leader in a randomised controlled trial. DTo has received honoraria from Abbott, Alexion, AstraZeneca, Bayer, Boehringer Ingelheim, Medtronic, and Pfizer. LY has participated in steering committees for Bristol Myers Squibb and Janssen Research & Development; has received honoraria from Bayer, Bristol Myers Squibb, Pfizer, Boehringer Ingelheim, and Daiichi Sankyo; and has received support for attendance at the World Stroke Congress from the World Stroke Organization Future Stroke Leaders Program. PvWM has received contracts and support for attending an investigator meeting from Bristol Myers Squibb; and has served as a national leader and member of a steering committee for Bristol Myers Squibb. GSS has received support from and participated on a steering committee for Bristol Myers Squibb; has received grants or contracts from Boehringer Ingelheim; has received consulting fees from Bristol Myers Squibb and Boehringer Ingelheim; and has participated in an advisory board for Bristol Myers Squibb. AAv has received grants and honoraria from Bayer. JD has received support from Bristol Myers Squibb; has received grants from Pfizer; and has received honoraria from Pfizer, Daiichi Sankyo, and AstraZeneca. DS has received contracts, support for attending a steering committee meeting, and materials and drugs for performing the trial from Bristol Myers Squibb. TT has received grants from the University of Gothenburg, Sahlgrenska University Hospital, and Wennerstrom's Foundation; and has received consulting fees from Bayer, Inventiva Pharma, Bristol Myers Squibb, and Portola Pharmaceuticals. JE has received travel support from Bristol Myers Squibb for attending steering committee meetings. SFA has received grants from Bayer and Boehringer Ingelheim; and has received honoraria from Novo Nordisk and Abbott. JRW has served as President Elect of the Austrian Society of Neurology. ECS has received honoraria from Bristol Myers Squibb, Daiichi Sankyo, and Boston Scientific. NGP has served as the President of the Russian National Society of Preventive Cardiology. PML has received grants from Bristol Myers Squibb and Janssen; has received honoraria from Boehringer Ingelheim and Pfizer; has received support for attending the Global Stroke Alliance; has participated on a data safety monitoring board or advisory board for RapidAI; and has served as the President of the Chilean Stroke Association. DG has received grants or contracts, or both, from the US National Heart, Lung and Blood Institute and the US National Institutes of Health; has received consulting fees from Bristol Myers Squibb, Ionis, Janssen, and Anthos Therapeutics; and has participated on a steering committee for Bristol Myers

Squibb. HCD has received support from Bristol Myers Squibb; has received grants from Boehringer Ingelheim and AstraZeneca; has received honoraria from Boehringer Ingelheim, Pfizer, Sanofi, and Bristol Myers Squibb; has received support for attending meetings or travel, or both, from Boehringer Ingelheim; and has participated on data safety monitoring boards or advisory boards for Actelion, the German Research Council, and the ELAN Study. RAB has received consulting fees from and has participated on a steering committee for Bristol Myers Squibb. CC has received honoraria from Bristol Myers Squibb and Amgen; and has participated on data safety monitoring boards or advisory boards for AstraZeneca and Biogen. GA, MD, and CP are employees and shareholders of Bristol Myers Squibb. AK and DL are employees and shareholders of Bristol Myers Squibb; and have a pending patent application related to this study. GJH has received consulting fees from Bristol Myers Squibb, Janssen Research & Development, and Bayer; has received honoraria from Janssen Medical Affairs; has received honoraria for participating on a data safety monitoring board for AC Immune; and has received honoraria from the American Heart Association for serving as an Associate Editor for *Circulation*. SIB, AS, BWY, and AAr declare no competing interests.

Data sharing

The Bristol Myers Squibb data-sharing policy is available online. Requests for data sharing will be reviewed by an independent data review committee for scientific rationale, analysis plan, and requestor experience and qualifications. The protocol can be accessed in the appendix (pp 41–203) and additional information is available under the EU Clinical Trials Register and on ClinicalTrials.gov.

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Research in context

Evidence before this study

Observational data from individuals with inherited factor XI deficiency have led us to hypothesise that adding a novel inhibitor of activated factor XI, milvexian, to standard antiplatelet therapy after ischaemic stroke or transient ischaemic attack (TIA) might reduce the risk of brain infarction without meaningfully increasing the risk of bleeding complications. We searched PubMed for randomised clinical trials without any language restrictions, published from database inception to May 14, 2023, using the search terms “ischaemic stroke” OR “transient ischaemic attack” AND “factor XI inhibitor” OR “milvexian” AND “clinical trial” OR “randomised trial”. Before initiation of our study, no studies examining factor XI inhibitors for secondary stroke prevention had been conducted. A phase 2b dose-finding trial assessing another factor XI inhibitor (asundexian) for stroke prevention was conducted concurrently with our study; the results of this trial were not available before our study was completed. This trial did not demonstrate a significant dose–response for the composite endpoint of symptomatic stroke or covert brain infarction.

Added value of this study

AXIOMATIC-SSP is, to the best of our knowledge, the largest phase 2 dose-finding trial of an inhibitor of activated factor XI for secondary stroke prevention and the only such trial of milvexian. Milvexian, at doses ranging from 25 mg once daily to 200 mg twice daily, did not produce a dose–response for the primary composite endpoint of symptomatic ischaemic stroke and incident covert brain infarction. However, milvexian was associated with numerically fewer symptomatic ischaemic strokes than placebo at all doses except for 200 mg twice daily. Milvexian was also associated with an increase in major bleeding events (Bleeding Academic Research Consortium [BARC] type 3), mostly gastrointestinal, at doses of 50 mg twice daily and higher. Milvexian did not increase the incidence of symptomatic intracerebral haemorrhage (BARC type 3c) compared with placebo, and there were no fatal bleeding events (BARC type 5).

Implications of all the available evidence

Although we found no significant dose–response relationship for the composite efficacy endpoint of symptomatic ischaemic stroke or covert brain infarction, the reduction in occurrence of symptomatic ischaemic stroke with a range of doses of milvexian is consistent with the findings of the phase 2 trial of milvexian for venous thromboembolism prophylaxis after knee arthroplasty. Our data have informed the dose selection for a phase 3 randomised, placebo-controlled trial (NCT05702034) that has been initiated to assess the safety and efficacy of milvexian for the prevention of ischaemic stroke in patients with acute TIA or ischaemic stroke.

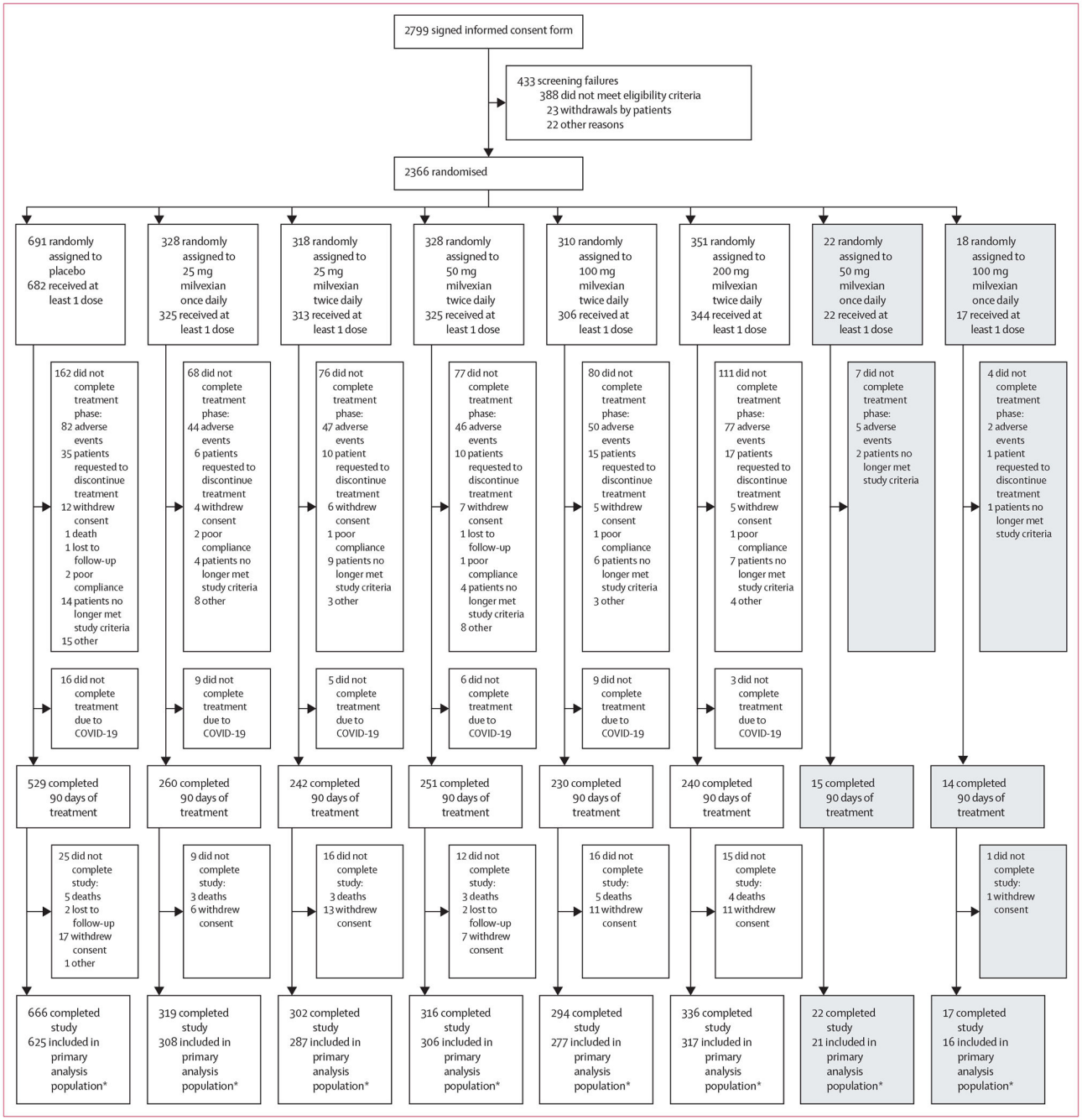

Figure 1: Trial profile

The shaded boxes show dose groups that were terminated early. The outcome event of stroke was also counted as an adverse event. *The primary analysis population comprised all patients with a primary endpoint event up to day 90 or an evaluable MRI from the day 90 visit.

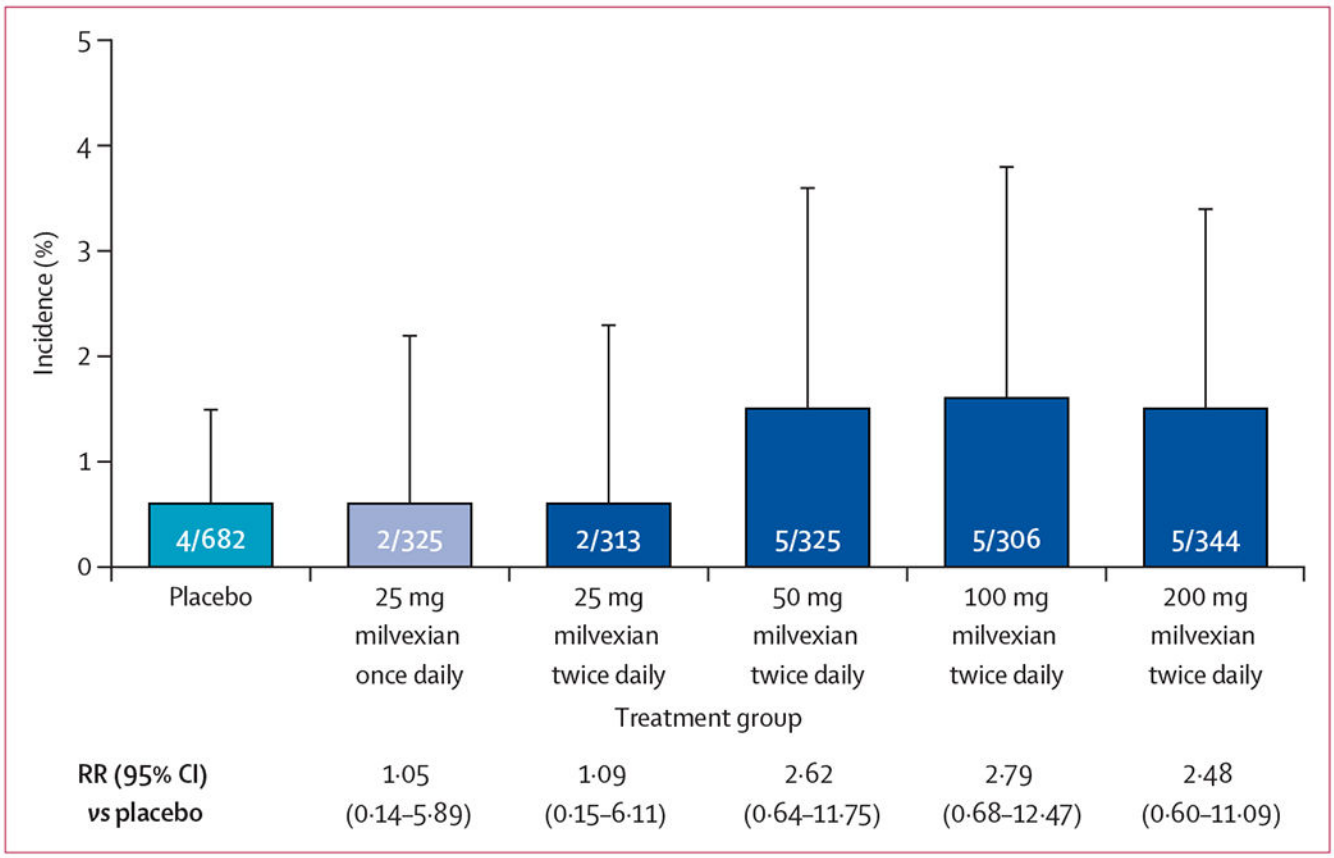

Figure 2: BARC type 3 and type 5 bleeding events

BARC type 3 bleeding events: haemoglobin drop 3 g/dL, requiring transfusion or surgery, or intracerebral haemorrhage. No type 5 (ie, fatal) bleeding events were observed. The figure includes all patients who received at least one dose of study drug, except for those in the dose groups that were terminated early. BARC=Bleeding Academic Research Consortium. RR=relative risk.

Table 1:

Baseline characteristics in the intention-to-treat analysis set

	Total (n=2366)	Placebo (n=691)	Combined milvexian* (n=1675)	25 mg milvexian once daily (n=328)	25 mg milvexian twice daily (n=318)	50 mg milvexian twice daily (n=328)	100 mg milvexian twice daily (n=310)	200 mg milvexian twice daily (n=351)
Median age (years)	71 (62–77)	70 (62–77)	71 (62–78)	72 (64–79)	72 (62–79)	70 (62–77)	71 (63–77)	71 (62–78)
Age category (years)								
<65	720 (30%)	208 (30%)	512 (31%)	90 (27%)	97 (31%)	108 (33%)	92 (30%)	106 (30%)
≥65 to <75	812 (34%)	255 (37%)	557 (33%)	110 (34%)	97 (31%)	109 (33%)	107 (35%)	121 (34%)
≥75	834 (35%)	228 (33%)	606 (36%)	128 (39%)	124 (39%)	111 (34%)	111 (36%)	124 (35%)
Sex								
Female	859 (36%)	254 (37%)	605 (36%)	109 (33%)	118 (37%)	121 (37%)	112 (36%)	128 (36%)
Male	1507 (64%)	437 (63%)	1070 (64%)	219 (67%)	200 (63%)	207 (63%)	198 (64%)	223 (64%)
Race								
White	1884 (80%)	549 (79%)	1335 (80%)	257 (78%)	246 (77%)	260 (79%)	251 (81%)	288 (82%)
Asian	408 (17%)	122 (18%)	286 (17%)	59 (18%)	63 (20%)	56 (17%)	51 (16%)	57 (16%)
Black	48 (2%)	15 (2%)	33 (2%)	5 (2%)	6 (2%)	8 (2%)	3 (1%)	5 (1%)
Other†	26 (1%)	5 (1%)	21 (1%)	7 (2%)	3 (1%)	4 (1%)	5 (2%)	1 (<1%)
Conditions								
Hypertension	1835 (78%)	549 (79%)	1286 (77%)	255 (78%)	240 (75%)	251 (77%)	242 (78%)	266 (76%)
Diabetes mellitus	732 (31%)	222 (32%)	510 (30%)	103 (31%)	102 (32%)	87 (27%)	95 (31%)	106 (30%)
Hypercholesterolaemia	1407 (59%)	398 (58%)	1009 (60%)	192 (59%)	176 (55%)	195 (59%)	193 (62%)	226 (64%)
Median eGFR (mL/min per 1·73 m^2)‡	82 (68–98)	83 (69–99)	82 (67–96)	80 (66–96)	84 (68–98)	82 (67–96)	80 (67–94)	84 (68–98)
Smoking	1236 (52%)	374 (54%)	862 (51%)	174 (53%)	149 (47%)	164 (50%)	166 (54%)	188 (54%)
Median blood pressure (mmHg)								
Systolic	145 (132–159)	145 (132–160)	144 (131–159)	143 (130–159)	146 (131–160)	144 (131–158)	145 (130–160)	142 (132–156)
Diastolic	80 (72–89)	80 (72–89)	80 (72–89)	80 (72–89)	80 (73–90)	80 (74–90)	80 (70–89)	80 (72–87)

	Total (n=2366)	Placebo (n=691)	Combined milvexian* (n=1675)	25 mg milvexian once daily (n=328)	25 mg milvexian twice daily (n=318)	50 mg milvexian twice daily (n=328)	100 mg milvexian twice daily (n=310)	200 mg milvexian twice daily (n=351)
Previous event								
Stroke	331 (14%)	91 (13%)	240 (14%)	44 (13%)	52 (16%)	38 (12%)	51 (16%)	48 (14%)
TIA	205 (9%)	60 (9%)	145 (9%)	32 (10%)	31 (10%)	20 (6%)	30 (10%)	29 (8%)
No event	1871 (79%)	551 (80%)	1320 (79%)	259 (79%)	240 (75%)	273 (83%)	236 (76%)	281 (80%)
Previous vascular disease								
Coronary artery disease	268 (11%)	84 (12%)	184 (11%)	33 (10%)	34 (11%)	36 (11%)	38 (12%)	40 (11%)
Pulmonary artery disease	108 (5%)	42 (6%)	66 (4%)	14 (4%)	17 (5%)	10 (3%)	19 (6%)	6 (2%)
Qualifying event								
Ischaemic stroke	1790 (76%)	526 (76%)	1264 (75%)	238 (73%)	240 (75%)	251 (77%)	229 (74%)	278 (79%)
TIA	571 (24%)	163 (24%)	408 (24%)	89 (27%)	77 (24%)	77 (23%)	81 (26%)	73 (21%)
Median NIHSS score for stroke qualifying event	2 (1–3)	2 (1–3)	2 (1–3)	2 (1–3)	2 (0–3)	2 (1–3)	2 (1–4)	2 (0–3)
Median time from symptom onset to first dose (h)	35·2 (27·3–44·0)	35·3 (27·3–43·7)	35·1 (27·2–44·2)	36·0 (26·5–44·5)	37·3 (28·4–45·3)	33·4 (26·8–43·8)	34·2 (28·0–43·3)	35·5 (27·5–44·7)
<12 h	80 (3%)	21 (3%)	59 (4%)	15 (5%)	15 (5%)	10 (3%)	8 (3%)	9 (3%)
12–24h	313 (13%)	99 (14%)	214 (13%)	47 (14%)	38 (12%)	43 (13%)	37 (12%)	44 (13%)
>24–48 h	1859 (79%)	539 (78%)	1320 (79%)	253 (77%)	244 (77%)	262 (80%)	248 (80%)	282 (80%)
>48 h	75 (3%)	21 (3%)	54 (3%)	9 (3%)	14 (4%)	8 (2%)	13 (4%)	9 (3%)
Not reported§	39 (2%)	11 (2%)	28 (2%)	4 (1%)	7 (2%)	5 (2%)	4 (1%)	7 (2%)
tPA, EVT, or both¶	271 (11%)	81 (12%)	190 (11%)	33 (10%)	20 (6%)	29 (9%)	31 (10%)	77 (22%)

Data are n (%) or median (IQR). Sex was defined as biological sex assigned at birth and race was self-identified by participants. The intention-to-treat analysis set includes all participants who were randomly assigned to a treatment, regardless of whether they received study drug or not. Percentages might not total 100% due to rounding.

eGFR=estimated glomerular filtration rate. EVT=endovascular therapy. NIHSS=US National Institutes of Health Stroke Scale. TIA=transient ischaemic attack. TPA=tissue plasminogen activator.

*Includes participants in the discontinued milvexian 50 mg once-daily and 100 mg once-daily groups.

†Includes Native Hawaiian and other Pacific Islander.

‡Denominators are 2321 for total, 678 for placebo, 1643 for milvexian combined, 323 for 25 mg once daily, 313 for 25 mg twice daily, 324 for 50 mg twice daily, 303 for 100 mg twice daily, and 341 for 200 mg twice daily.

[§] While the specific time was not reported, the site indicated that the participant met inclusion criteria.

[¶] 258 participants (81 placebo and 190 combined milvexian) received thrombolytic therapy (252 alteplase, one reteplase, and five tenecteplase); among the 258 participants who received thrombolytic therapy, ten (four placebo and six combined milvexian) also received EVT. 13 participants (3 placebo and 10 combined milvexian) received EVT alone.

Table 2:

Proportional and model-based assessment in the primary efficacy endpoint analysis population

	Placebo (n=625)	25 mg milvexian once daily (n=308)	25 mg milvexian twice daily (n=287)	50 mg milvexian twice daily (n=306)	100 mg milvexian twice daily (n=277)	200 mg milvexian twice daily (n=317)
Participants with composite event*	104 (17%)	50 (16%)	53 (18%)	43 (14%)	41 (15%)	52 (16%)
Symptomatic ischaemic stroke	38 (6%)	15 (5%)	12 (4%)	13 (4%)	11 (4%)	27 (9%)
Covert infarcts	66 (11%)	35 (11%)	41 (14%)	30 (10%)	30 (11%)	25 (8%)
Model-based estimate for composite event (90·2% CI)†	16·8% (14·5 to 19·1)	16·7% (14·8 to 18·6)	16·6% (14·8 to 18·3)	15·6% (13·9 to 17·5)	15·4% (13·4 to 17·6)	15·3% (12·8 to 19·7)
RR (90·2% CI), model-based analysis†	..	0·99 (0·91 to 1·05)	0·99 (0·87 to 1·11)	0·93 (0·78 to 1·11)	0·92 (0·75 to 1·13)	0·91 (0·72 to 1·26)
Risk difference (90·2% CI) versus placebo, model-based analysis‡	..	−0·1 (−1·7 to 0·8)	−0·2 (−2·4 to 1·6)	−1·2 (−4·0 to 1·7)	−1·4 (−4·6 to 2·0)	−1·5 (−5·1 to 3·9)

Data are n (%) unless otherwise indicated. The primary efficacy endpoint analysis population includes all randomised participants with a day 90 MRI scan. The MCP-MOD analysis assessed three models. The p values for each of the trends, assessed across all doses, were as follows: logistic model, p=0·37; Sigmoidal E_{max} model, p=0·48; exponential model, p=0·58. Significance values controlled for the use of multiple models. Model-based estimates used results-weighted averaging, with weights consistent with relative probability (regardless of significance) of each model.

MCP-MOD=Multiple Comparison Procedure–Modelling. RR=relative risk.

*Percentages might not equal symptomatic ischaemic stroke plus covert infarcts percentages due to rounding.

†Primary analysis of the primary endpoint using MCP-MOD.

‡MCP-MOD dose–response relationship of milvexian (model-averaged).

Table 3:

Secondary efficacy analyses (descriptive analysis)

	Placebo	25 mg milvexian once daily	25 mg milvexian twice daily	50 mg milvexian twice daily	100 mg milvexian twice daily	200 mg milvexian twice daily
Participants with symptomatic ischaemic stroke or covert infarcts *	104/625 (17%)	50/308 (16%)	53/287 (18%)	43/306 (14%)	41/277 (15%)	52/317 (16%)
Risk difference (95% CI) versus placebo, descriptive analysis	..	−0·4 (−5·5 to 4·6)	1·8 (−3·5 to 7·2)	−2·6 (−7·5 to 2·3)	−1·8 (−6·9 to 3·3)	−0·2 (−5·3 to 4·8)
RR (95% CI), based on descriptive analysis	..	0·98 (0·72 to 1·33)	1·11 (0·82 to 1·50)	0·84 (0·61 to 1·17)	0·89 (0·64 to 1·24)	0·99 (0·73 to 1·34)
Participants with new covert brain infarction detected by MRI at day 90 *	66/625 (11%)	35/308 (11%)	41/287 (14%)	30/306 (10%)	30/277 (11%)	25/317 (8%)
Risk difference (95% CI) versus placebo	..	0·8 (−3·5 to 5·1)	3·7 (−1·0 to 8·4)	−0·8 (−4·9 to 3·4)	0·3 (−4·1 to 4·7)	−2·7 (−6·5 to 1·1)
RR (95% CI)	..	1·08 (0·73 to 1·58)	1·35 (0·94 to 1·95)	0·93 (0·62 to 1·40)	1·03 (0·68 to 1·54)	0·75 (0·48 to 1·16)
Composite of non-fatal new ischaemic stroke, non-fatal myocardial infarction, and all-cause death during the treatment period †	42/691 (6%)	17/328 (5%)	15/318 (5%)	16/328 (5%)	16/310 (5%)	33/351 (9%)
Risk difference (95% CI) versus placebo	..	−0·9 (−3·9 to 2·1)	−1·4 (−4·3 to 1·6)	−1·2 (−4·1 to 1·7)	−0·9 (−4·0 to 2·1)	3·3 (−0·2 to 6·9)
RR (95% CI)	..	0·85 (0·49 to 1·47)	0·78 (0·44 to 1·38)	0·80 (0·46 to 1·41)	0·85 (0·49 to 1·49)	1·55 (1·00 to 2·40)
All and non-fatal new ischaemic stroke during the treatment period †	38/691 (5%)	15/328 (5%)	12/318 (4%)	13/328 (4%)	11/310 (4%)	27/351 (8%)
Risk difference (95% CI) versus placebo	..	−0·9 (−3·8 to 1·9)	O Γ> ‘st V Ÿ	−1·5 (−4·3 to 1·2)	−2·0 (−4·6 to 0·7)	2·2 (−1·1 to 5·5)
RR (95% CI)	..	0·83 (0·46 to 1·49)	0·69 (0·36 to 1·30)	0·72 (0·39 to 1·33)	0·65 (0·33 to 1·25)	1·40 (0·87 to 2·25)
Participants with myocardial infarction †	2/691 (<1%)	1/328 (<1%)	2/318 (1%)	1/328 (<1%)	2/310 (1%)	3/351 (1%)
Risk difference (95% CI) versus placebo	..	0·0 (−0·8 to 1·5)	0·3 (−0·6 to 2·0)	0·0 (−0·8 to 1·5)	0·4 (−0·6 to 2·1)	0·6 (−0·4 to 2·3)
RR (95% CI)	..	1·05 (0·07 to 11·75)	2·17 (0·21 to 32·28)	1·05 (0·07 to 11·75)	2·23 (0·21 to 33·17)	2·95 (0·47 to 29·64)
All-cause death †	5/691 (1%)	3/328 (1%)	3/318 (1%)	2/328 (1%)	5/310 (2%)	4/351 (1%)
Risk difference (95% CI) versus placebo	..	0·2 (−1·0 to 2·0)	0·2 (−1·0 to 2·1)	−0·1 (−1·2 to 1·6)	0·9 (−0·5 to 3·1)	0·4 (−0·8 to 2·3)

	Placebo	25 mg milvexian once daily	25 mg milvexian twice daily	50 mg milvexian twice daily	100 mg milvexian twice daily	200 mg milvexian twice daily
RR (95% CI)	..	1·26 (0·20 to 5·73)	1·30 (0·21 to 5·92)	0·84 (0·11 to 4·26)	2·23 (0·61 to 8·12)	1·57 (0·36 to 6·51)

Data are n/N (%), unless otherwise indicated. Symptomatic ischaemic stroke is the same as new ischaemic stroke.

RR=relative risk.

*Based on primary efficacy endpoint analysis population, including all randomised participants with a day 90 MRI scan.

†Based on intention-to-treat analysis set, which comprised all participants who were randomly assigned to a treatment, regardless of whether they received the study drug.

Table 4:

Adverse events and bleeding by BARC type in the safety analysis set

	Placebo (n=682)	25 mg milvexian once daily (n=325)	25 mg milvexian twice daily (n=313)	50 mg milvexian twice daily (n=325)	100 mg milvexian twice daily (n=306)	200 mg milvexian twice daily (n=344)	All milvexian* (n=1652)
Adverse events	399 (59%)	190 (58%)	186 (59%)	192 (59%)	193 (63%)	211 (61%)	996 (60%)
Risk difference, % (95% CI)	..	−0·0% (−6·7 to 6·5)	0·9% (−5·8 to 7·6)	0·6% (−6·0 to 7·1)	4·6% (−2·2 to 11·1)	2·8% (−3·7 to 9·1)	1·8% (−2·6 to 6·2)
Serious adverse events	94 (14%)	37 (11%)	39 (12%)	41 (13%)	42 (14%)	54 (16%)	221 (13%)
Risk difference, % (95% CI)	..	−2·4% (−6·6 to 2·3)	−1·3% (−5·7 to 3·5)	−1·2% (−5·5 to 3·6)	−0·1% (−4·6 to 5·0)	1·9% (−2·6 to 6·8)	−0·4% (−3·7 to 2·6)
Most common adverse events (>5%)†							
Hypertension	56 (8%)	21 (6%)	24 (8%)	24 (7%)	20 (7%)	20 (6%)	111 (7%)
Constipation	44 (6%)	22 (7%)	17 (5%)	20 (6%)	20 (7%)	24 (7%)	106 (6%)
Most common serious adverse events (>1%)†							
Ischaemic stroke	21 (3%)	9 (3%)	6 (2%)	10 (3%)	7 (2%)	11 (3%)	47 (3%)
Stroke in evolution	5 (1%)	2 (1%)	4 (1%)	1 (<1%)	1 (<1%)	8 (2%)	17 (1%)
Transient ischaemic attack	8 (1%)	1 (<1%)	4 (1%)	1 (<1%)	4 (1%)	4 (1%)	14 (1%)
Ischaemic cerebral infarction	3 (<1%)	1 (<1%)	3 (1%)	2 (1%)	1 (<1%)	3 (1%)	10 (1%)
Acute kidney injury	3 (<1%)	0	0	1 (<1%)	0	4 (1%)	5 (<1%)
Discontinuation due to adverse events	83 (12%)	44 (14%)	47 (15%)	46 (14%)	51 (17%)	79 (23%)	274 (17%)
Ischaemic stroke	9 (1%)	6 (2%)	4 (1%)	3 (1%)	3 (1%)	8 (2%)	28 (2%)
Atrial fibrillation	25 (4%)	16 (5%)	9 (3%)	5 (2%)	13 (4%)	9 (3%)	52 (3%)
Renal impairment	0	0	0	0	0	5 (1%)	5 (<1%)
Treatment-emergent death‡	0	1 (<1%)	1 (<1%)	1 (<1%)	2 (1%)	0	5 (<1%)
Ischaemic stroke	0	0	0	0	0	0	0
Cardiovascular related	0	0	1 (<1%)§	0	1 (<1%)¶	0	4 (<1%)
Non-cardiovascular related	0	1 (<1%)‖	0	1 (<1%)**	1 (<1%)**	0	1 (<1%)
All BARC types	54 (8%)	35 (11%)	27 (9%)	40 (12%)	40 (13%)	35 (10%)	186 (11%)
Type 1: not actionable	41 (6%)	26 (8%)	16 (5%)	28 (9%)	25 (8%)	22 (6%)	124 (8%)

	Placebo (n=682)	25 mg milvexian once daily (n=325)	25 mg milvexian twice daily (n=313)	50 mg milvexian twice daily (n=325)	100 mg milvexian twice daily (n=306)	200 mg milvexian twice daily (n=344)	All milvexian* (n=1652)
Type 2: requiring assessment or treatment	9 (1%)	7 (2%)	9 (3%)	7 (2%)	10 (3%)	8 (2%)	43 (3%)
Type 3a: haemoglobin drop 3–5 g/dL or transfusion	2 (<1%)	1 (<1%)	1 (<1%)	1 (<1%)	2 (1%)	3 (1%)	8 (<1%)
Type 3b: haemoglobin drop ≥5 g/dL or requiring surgical intervention	0	1 (<1%)	1 (<1%)	1 (<1%)	3 (1%)	1 (<1%)	7 (<1%)
Modified type 3c: intracranial haemorrhage, including symptomatic haemorrhagic transformation	2 (<1%)	0	0	3 (1%)	0	1 (<1%)	4 (<1%)
Type 4: CABG-related	0	0	0	0	0	0	0
Type 5: fatal	0	0	0	0	0	0	0
Adverse events of special interest							
Drug-induced liver injury	0	0	0	0	0	0	0
Accidental overdose	2 (<1%)	0	1 (<1%)	1 (<1%)	0	0	4 (<1%)
Overdose	0	1 (<1%)	0	0	0	0	1 (<1%)

Data are n (%), unless otherwise indicated. Includes all participants who received at least one dose of study drug. Individual terms reflect MedDRA preferred terms.

BARC=Bleeding Academic Research Consortium. CABG=coronary artery bypass graft. MedDRA=Medical Dictionary for Regulatory Activities.

*Includes participants randomly assigned to milvexian 50 mg and 100 mg once daily.

†Includes adverse events in more than 5% of participants and serious adverse events in more than 1% of participants randomly assigned to the groups shown in the table.

‡Includes all deaths with the date of death occurring on or after the date of the first dose and within 7 days after the last dose of blinded study drug.

§Cause of death was heart failure.

¶Cause of death was sudden cardiac arrest.

//Cause of death was infectious colitis.

**Cause of death was pneumonia.