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Manuscript Number: STROKE/2023/043198R3

Title: Effect of the Factor XIa Inhibitor Asundexian According to Baseline Infarct Pattern and on MRI Covert Infarct Outcomes

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Effect of the Factor XIa Inhibitor Asundexian According to Baseline Infarct Pattern and on MRI Covert Infarct Outcomes

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Short title (50 characters, maximum): Asundexian and covert infarcts

Abstract word count: 247

Total word count: 6,524

Tables: 3

Table 1. Participant Characteristics According to Baseline Acute Infarct Pattern: Single Small Subcortical Infarct vs. Multiple, Large, or Cortical Infarcts

Table 2. Effect of Asundexian on Covert Brain Infarcts
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Figure 1. Participant flow diagram
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ABSTRACT

Background: Exploratory analysis of the phase 2 PACIFIC-Stroke randomized trial suggested that asundexian, an oral factor XIa inhibitor, prevents recurrent stroke and TIAs in patients with atherosclerotic stroke. In this post-hoc exploratory analysis, we hypothesized that asundexian would be more effective in patients enrolled with large, multiple or cortical acute infarcts on MRI than in patients enrolled with a single small subcortical acute infarct, and that asundexian would prevent incident cortical covert infarcts.

Methods: In this placebo-controlled double-blinded randomized controlled trial, patients with mild-to-moderate non-cardioembolic ischemic stroke were assigned to asundexian (10 mg, 20 mg, or 50 mg once daily) or placebo, in addition to antiplatelet therapy. Brain MRIs were required within 72 hours of randomization and repeated at 26 weeks or at discontinuation of study drug.

Results: Of 1,808 randomized patients, 1780 (98.5%) had interpretable baseline MRIs of which 1628 (91.5%) had one or more DWI positive acute infarcts. MRI follow-up was obtained in 1,439 patients, of whom 1,358 had no symptomatic stroke during the trial period. Compared with placebo, asundexian 50 mg daily conferred a trend toward reduced risk of recurrent ischemic stroke or incident covert infarcts (hazard ratio [HR] 0.71, 95% CI 0.45-1.11) and recurrent ischemic stroke or TIA (secondary outcome; HR 0.59, 95% CI 0.33-1.06) that was not evident in patients with single small subcortical infarcts (HRs 1.14, 95% CI 0.62-2.10 and 0.93, 95% CI 0.28-3.06). Incident cortical covert infarcts were reduced in patients taking asundexian 50 mg, but the difference was not statistically significant (crude incidence ratio 0.56, 95% CI 0.28-1.12).

Conclusions: These exploratory, unconfirmed results suggest that asundexian may prevent new embolic infarcts but is not small artery occlusion. The hypothesis that subtypes of covert brain infarcts respond differently to anticoagulant prophylaxis should be tested in future trials.

Registration: NCT04304508; https://clinicaltrials.gov/study/NCT04304508.

NON-STANDARD ABBREVIATIONS AND ACRONYMS

CAD: coronary artery disease

DWI: diffusion weighted imaging

MRI: magnetic resonance imaging

NIHSS: National Institutes of Health Stroke Scale

OCEANIC: Oral faCtor Eleven A iNhibitor asundexIan as novel anti-thrombotiC

PACIFIC: Program of AntiCoagulation via Inhibition of FXIa by the oral Compound BAY 2433334 non-cardioembolic Stroke

TIA: transient ischemic attack

INTRODUCTION

Asundexian is a one of a new generation of oral direct inhibitors of activated coagulation factor XI (FXIa) that may prevent thrombosis with less associated bleeding than currently available anticoagulants[1]. In the phase 2 Program of AntiCoagulation via Inhibition of FXIa by the oral Compound BAY 2433334 non-cardioembolic Stroke (PACIFIC-Stroke) randomized controlled trial, treatment with asundexian in doses of 10 mg, 20 mg, or 50 mg daily was not associated with a reduction in the combined primary endpoint of recurrent symptomatic stroke or covert brain infarction on MRI at or before 6 months[2]. However, in the subgroup of patients with

imaging evidence of extra- or intra-cranial atherosclerosis or those in whom the qualifying stroke mechanism was large artery atherosclerosis, there was a significant reduction in symptomatic recurrent ischemic stroke or incident transient ischemic attack[2].

In PACIFIC-Stroke, study participants were mandated to have brain MRI at entry and at 26 weeks or at the time of discontinuation of study drug. The objectives of this post-hoc and exploratory analysis were to: a) determine the effect of asundexian according to patterns of infarction defined on baseline MRI, including those enrolled with single small subcortical infarction compared with other patterns, and b) determine the effect of asundexian on MRI-defined covert brain outcomes including small subcortical infarction. We hypothesized that asundexian would: a) be more effective in patients enrolled with multiple or cortical acute infarcts rather than a single small subcortical infarct at trial entry, and b) be more effective at preventing new cortical infarcts than small subcortical infarcts.

METHODS

This study followed Consolidated Standards of Reporting Trials guidelines[3] for clinical trials. Study data cannot be shared. The study was approved by institutional review boards at each site and was done with written informed consent of the participants.

PACIFIC-Stroke was an international, randomized, placebo-controlled, double-blind, parallel group, dose-finding Phase II trial. Patients were randomly assigned in a 1:1:1:1 ratio to receive one of three asundexian dosages (BAY 2433334; 10 mg, 20 mg, and 50 mg once daily) or placebo, in addition to required background antiplatelet therapy chosen by the local investigator. Randomized was done online by computer, stratified by whether participants were anticipated to receive single or dual antiplatelet therapy as standard of care. Patients 45 years of

age or older with non-cardioembolic ischemic stroke were eligible for participation within 48 hours of symptom onset (or last known to be without symptoms) if intended to be treated with antiplatelet therapy during study, if able to undergo a baseline MRI (either prior to or within 72 hours after randomization), and if willing to adhere to study procedures. The main exclusion criteria were prior ischemic stroke within 30 days of index event, history of atrial fibrillation or suspicion of cardioembolic stroke, active bleeding or history of major bleeding, uncontrolled hypertension, estimated glomerular filtration rate of <30 mL/min/1·73 m^2, significant liver disease, or contraindication to MRI. The trial is registered at clinicaltrials.gov (NCT NCT04304508). The full trial protocol has been published[2].

Recruitment was conducted in two parts. Part A was confined to patients with minor ischemic strokes (National Institutes of Health Stroke Scale [NIHSS] score ≤7 at randomization), whereas Part B broadened eligibility to additionally include moderate ischemic strokes (NIHSS score of 8 to 15) and extended participation to patients who had undergone intravenous thrombolysis and/or endovascular therapy. Transition from Part A to Part B eligibility criteria occurred after recruitment of the initial 829 participants following the recommendation of an independent data monitoring committee after a pre-planned review of safety data. Etiologic subtype of the qualifying ischemic stroke was classified by the site investigators using the TOAST criteria[4].

Participants were followed for a minimum of six months, up to a maximum of 12 months. All participants were required to undergo at least two MRIs that met study requirements. In addition to the baseline MRI (obtained following the index stroke either prior to randomization or within 72 hours after randomization), participants underwent a final study MRI at 26 weeks or as soon as possible after early termination of assigned study treatment. Part A participants

147 additionally underwent a study MRI at 13 weeks used for safety assessment for the transition to
148 Part B but not for identification of the primary outcome unless no later study MRI was available.
149 The MRI sequence protocol was intended to reflect routine clinical practice for acute stroke
150 imaging, based on standards from the American College of Radiology (ACR)[5]. Required
151 sequences were diffusion-weighted imaging (DWI), apparent diffusion coefficient (ADC), fluid-
152 attenuated inversion recovery (FLAIR), and a hemorrhage-sensitive sequence which could be
153 either T2*weighted gradient-recalled echo (T2* GRE) or susceptibility-weighted imaging (SWI)
154 according to existing site protocols. Slice orientation was oblique axial. Requirements included
155 slice thickness ≤5 mm, pixel sizes no larger than 0.9375 mm by 0.9375, and slice gap ≤2 mm.
156 Within these tolerances, sites were allowed to use their local acute stroke protocol. Adherence to
157 sequence parameters was verified by having each site scan a phantom (ACR phantom or a water
158 bottle) prior to enrolling participants, and by central visual review of each MRI.
159 MRI data were transmitted to the central MRI Core Laboratory at the University of
160 Calgary for independent interpretation by two radiologists--one primary reader who reviewed all
161 scans from all patients and one of three secondary readers--blinded to participant data and
162 treatment assignment. Differences were resolved by consensus. Incident brain infarcts were
163 identified by direct comparison of the baseline MRI with the follow-up study MRI. Radiologist
164 readers were required to demonstrate good agreement for brain infarcts (kappa value ≥0.60) on
165 an independent test set. Kappa values for the identification of new infarcts for each pair of
166 readers, based on a set of 50 PACIFIC-Stoke cases, were 0.74, 0.77, and 0.90, indicating good to
167 excellent agreement. Infarcts were defined according to Standards for Reporting Vascular
168 Changes on Neuroimaging (STRIVE)[6] and were classified according to small or large size (small
169 being defined as <15 mm axial diameter in the chronic phase, or up to 20 mm in axial diameter

in the acute phase to take swelling into account[6]), by location (involving the cortex or purely subcortical), and whether they were positive on diffusion weighted imaging (DWI). To be considered positive on DWI, infarcts had to either show restricted diffusion on the apparent diffusion coefficient (ADC) map or be small enough (5 mm axial diameter or less) that the restricted diffusion would not be expected to be visible on ADC. Infarction that was contiguous with the acute baseline infarction and in the same vascular territory was defined as *extension* of previous infarction, while infarcts that occurred remote to the region of previous infarction were termed *new infarcts*.

Statistical analysis

Incident covert infarcts were defined as those that were seen on either the 13-week or 26-week study-mandated MRI in participants without a history of symptomatic recurrent ischemic stroke after the baseline MRI. Pre-specified patient categories of incident covert infarcts were defined as patients with new infarction including either new infarcts or extension of baseline infarction; extension of baseline infarction only; single new small subcortical infarct only; multiple, large, or cortical new infarcts; and one or more cortical new infarcts. Baseline infarct patterns were grouped according to pre-specified categories of any DWI positive lesion; a single small subcortical DWI lesion; multiple DWI positive lesions of any size or location; multiple, large, or cortical DWI positive lesions; and one or more cortical DWI lesions.

Characteristics of patients with different infarct patterns were compared using the chi-square test or Fisher's exact test for categorical variables or two-sample t-test for continuous variables.

The primary outcome for the first objective (effect of asundexian according to baseline infarct pattern) was recurrent symptomatic stroke or incident covert brain infarction, matching

193 the primary outcome of the PACIFIC trial; the two secondary outcomes were recurrent
194 symptomatic stroke or TIA, and incident covert infarction. The primary outcome for the second
195 objective (effect of asundexian on different types of new corvert infarcts) was incident cortical
196 covert brain infarcts; secondary outcomes were any new infarct or extension of prior infarcts,
197 any new infarct, extension of prior infarct only, new single small subcortical infarct, and new
198 multiple or large size or cortical infarcts.

199 Crude incidence ratios (CIRs) were used to determine the effect of asundexian on one or
200 more incident covert infarcts seen on either the 13-week or 26-week MRI in different patient
201 groups compared with placebo. The crude incidence ratio is the ratio of the proportion with new
202 covert infarcts in the asundexian treatment group to the proportion with new covert infarcts in
203 the placebo group. Cox regression with hazard ratios were used to determine the association of
204 asundexian treatment with the incidence of new symptomatic stroke, or the combination of new
205 symptomatic stroke or TIA. Patients randomized to each group were analyzed in that group.
206 Participants missing MRI data were excluded. Because the analyses in MRI subgroups were
207 exploratory, no corrections for multiple comparisons were made. Analyses were performed using
208 SAS v9.4 (Cary, NC).

209

210 **RESULTS**

211 A total of 1,808 participants underwent randomization at 196 sites in 23 countries between June
212 15, 2020, and July 22, 2021. Self-reported race was 83% white (1505 participants), 1% Black
213 (18), 15% Asian (268), and <1% other (3). Participants came from Western Europe and Australia
214 (1007; 56%), Eastern Europe (524; 29%), Asia (254; 14%), and North America (23; 1%). The
215 flow of enrollment is shown in Figure 1. Overall, 1,780/1,808 (98%) participants had analyzable

baseline MRI (Figure 1) and 1,439 (79.5%) had follow-up MRI. Characteristics of participants with and without baseline and follow-up MRI are shown in Supplemental Table S1; the participants without MRIs were older and less likely to be diagnosed with small vessel or cardioembolic stroke types. Participants were followed for a median of 10.6 months (interquartile range [IQR] 8.1 to 12.4). After excluding participants with new symptomatic stroke and those who were missing follow-up MRI, there were 1,385 participants without symptomatic stroke for analysis of incident covert infarcts (Figure 1).

Participant Characteristics According to Baseline Pattern of Infarction

At baseline, a DWI positive lesion, from which baseline infarct pattern could be determined, was seen in 1,628/1,780 (91.5%). The participants with clinically diagnosed stroke without DWI positive lesions had lower NIHSS, more frequent history of prior ischemic stroke, and were less likely to be female (Supplemental Table S2).

Among the 1,628 with DWI positive lesions, there were 474 (29%) with a single small subcortical infarct, 737 (45%) with multiple DWI lesions, 180 (11%) with bilateral DWI lesions, and 696 (43%) with one or more cortical DWI positive lesions. Examples of infarct patterns are shown in Figure 2. A comparison of participants with single small subcortical infarcts to participants with other DWI patterns (multiple, large, or cortical DWI positive lesions), overall and stratified by asundexian dose, is shown in Table 1. The participants without single small subcortical infarcts had higher NIHSS and were more likely to have a history of coronary heart disease or peripheral arterial disease.

Asundexian Effect According to Baseline Pattern of Infarction

The effects of asundexian on the pre-specified main trial outcome (recurrent symptomatic ischemic stroke or incident covert brain infarcts), exploratory trial outcome (recurrent

symptomatic stroke or TIA), and on incident covert brain infarction according to baseline infarct patterns are shown in Table 2. For analyses of incident covert brain infarction, 102/1,780 participants with symptomatic stroke during follow-up and 341/1,780 participants (19.2%) without an MRI follow up were excluded.

For all study outcomes, there was little evidence for an effect of asundexian in patients randomized with a single small subcortical infarct, with HRs and CIRs close to one. In contrast, for patients enrolled with multiple, large, or cortical DWI positive infarcts the HR for symptomatic stroke or TIA was less than one, although not statistically significant. The lowest HRs were seen for patients with cortical DWI positive infarcts at baseline. For example, in patients with one or more cortical infarcts the HR for recurrent symptomatic stroke or TIA in asundexian 50 mg compared with placebo was 0.59 (95% CI 0.33 to 1.06). For the outcome of incident covert brain infarction, the CIR was reduced only in the patients enrolled with cortical DWI positive infarcts treated with asundexian 50 mg compared with placebo (CIR 0.79, 95% CI 0.44 to 1.40) although the confidence limits were wide and the result was not statistically significant.

Effect of Asundexian on Subtypes of Incident Covert Brain Infarcts

Among the participants without symptomatic stroke and who had a follow-up MRI, there were 252/1,358 (18.6%) who had an incident covert brain infarction, either new infarcts or extension of a baseline infarct, detected on either the 13-week or 26-week study MRI or MRI repeated at the time of study drug discontinuation. Among the 252 participants with incident covert brain infarction, 220/252 (87.3%) had new infarcts, defined as one or more infarcts remote from the index areas of infarction, while 32/252 (12.7%) had only extension of baseline areas of infarction.

Among the 220 participants with new brain infarcts, 104 (47.3%) had an incident single small subcortical infarct only, while 116 (52.7%) had multiple, large, or cortical new infarcts. Any incident cortical infarcts were seen in 58/220 (26.4%).

The effects of asundexian on different types of covert brain infarct outcomes are shown in Table 3 and graphically displayed in Figure 3. There was little evidence of an effect of asundexian on new infarcts or the combination of new infarcts or extension of existing infarcts, with CIRs close to one. The CIR for extension of baseline infarction was reduced with asundexian 50 mg (0.49) but the confidence limits were wide (95% CI 0.15 to 1.62). There was a trend for reduced risk of new cortical infarcts with asundexian 50 mg (CIR 0.56) but the confidence limits crossed one (95% CI 0.28 to 1.12) and the interaction p value was not significant (p_{int} 0.17).

DISCUSSION

In this large phase 2 study of patients with mostly mild ischemic stroke, MRI-defined brain infarction was incorporated as part of a composite endpoint to increase the number of ischemic events for analysis as well as to assess the effect of asundexian on this important outcome. Given the phase 2 design, the trial was not powered to show significant differences in the CIR of new covert brain infarcts in asundexian treatment arms compared with placebo. Most patients (91.5%) presented with a DWI positive lesion at baseline, which was similar to the pooled sensitivity of DWI for acute ischemic stroke from a systematic review and meta-analysis[7]. In exploratory analyses, we failed to find statistically significant effects of asundexian according to the baseline pattern of infarction; however, the HR was substantially less than one for recurrent ischemic stroke and TIA in patients enrolled with multiple, large, or cortical infarcts. In

additional exploratory analyses we found a trend for lower risk of new covert cortical infarcts in patients randomized to asundexian 50 mg daily; however, the confidence limits were wide such that the effects were not statistically significant. Taken together, the evidence from these exploratory analyses, while not statistically significant, raise the possibility that asundexian prevents embolic infarction in patients whose qualifying event was not a single small subcortical infarct but may not prevent small vessel occlusion. A larger, phase 3 trial is needed to confirm these results, as well as the impact of asundexian on bleeding.

One of the reasons for including MRI endpoints in this phase 2, dose-finding study, was to increase the number of ischemic events for analysis. For that purpose, the use of MRI was successful. MRI of adequate quality were obtained in 98% of the participants at baseline and in 80.8% of the participants without recurrent symptomatic stroke in follow-up. The number of patients with MRI-defined incident covert brain infarction at 26 weeks (252) exceeded the number with recurrent symptomatic stroke within 26 weeks (89) by almost three-fold. These findings show that patients with acute symptomatic stroke are at high risk in the short term for new covert brain infarcts, as well as for symptomatic recurrence. Overall, 14.8% of the participants had a new MRI-defined infarct within the next 26 weeks. With more than 1,400 patients with follow-up brain MRIs, this is one of the largest studies to date on the incidence of new covert infarction in the months following symptomatic stroke. Previously, several smaller (50 to 340 patients) cohort studies in which routine MRI was performed 7 to 90 days after acute ischemic stroke reported that 10% to 47% had new infarcts seen on MRI[8-16], usually without new symptoms. Patients with new covert infarcts had a higher risk for future symptomatic stroke[9]. More research will be needed to better define the relationship between incident covert brain infarcts and stroke outcomes including risk for recurrence.

Acquiring and systematically analyzing brain MRI also helped define a patient subgroup with an ischemic stroke mechanism that may be more responsive to factor XIa inhibition. The reduced risk of symptomatic recurrence in patients with large, cortical, or multiple acute infarcts and the fewer incident covert infarcts seen in cortical regions suggests the possibility that factor XI inhibition with asundexian may prevent embolism. In contrast, there was little evidence that the addition of asundexian to routine antithrombotic management prevented recurrent symptomatic stroke in patients enrolled with a single small subcortical infarct, and it was not effective in preventing new small subcortical infarcts.

While the associations observed in this study were not statistically significant, owing to in part to the phase 2 study design, confidence in these exploratory findings is increased by concordance with the results of genetic studies and other exploratory analyses of the PACIFIC-Stroke trial. Genetic polymorphisms that reduce factor XI levels decrease the risk of ischemic stroke overall, without reducing the risk of lacunar stroke[17]. Additionally, in exploratory analyses of PACIFIC-Stroke the effect of asundexian was greater in patients with evidence of large artery atherosclerosis or history of atherosclerotic cardiovascular disease[2], which is consistent with an asundexian effect on preventing atheroembolism but not small artery occlusion. The reasons for this differential effect on atheroembolism and small artery occlusion are not clear. More research, including using animal and tissue models, is needed to better understand the relationships between vessel diameter, endothelial dysfunction, factor XI activity, pathological thrombus formation, and vessel occlusion.

The experience in PACIFIC-Stroke lends support to the use of imaging-defined covert brain infarction as a surrogate endpoint for phase 2 trials of stroke prevention. Post-hoc exploratory analyses of the MRI data provided support for a potential asundexian effect in an

important subgroup. However, interpretation of the MRI endpoint may need to account for the different mechanisms of infarction. As with symptomatic ischemic stroke, covert infarction can be caused by diverse mechanisms including cardioembolism, large artery atherosclerosis, and small vessel occlusion. When the treatment has differential effects according to stroke mechanism, then the overall burden of new covert infarcts will not be the best surrogate. Furthermore, because they are asymptomatic or clinically unrecognized covert infarcts are unlikely to be large or involve eloquent areas of cortex, and thus more likely to be small and subcortical. Therefore, the total burden of covert infarcts tends to be strongly influenced by progression of cerebral small vessel disease. For drugs that target embolism from cardiac or atherosclerotic sources, an MRI surrogate of cortical covert infarcts, rather than total covert infarcts, should be preferred.

There are some limitations to this study. The main limitation is the sample size, with small numbers of participants in each infarct pattern group. PACIFIC-Stroke was a phase 2 study designed to provide information to select the optimal dose of asundexian, based on safety and preliminary evidence of efficacy, for a future phase 3 trial. Consequently, the exploratory effect estimates presented in this study have wide confidence limits and are not statistically significant. However, the finding that asundexian may be more effective in preventing atheroembolic stroke than small artery occlusion is consistent with other exploratory analyses of the trial data and with human evidence from Mendelian randomization, raising confidence in the results. Multiple post-hoc comparisons were made without adjustment; therefore, the nominal p values should not be taken at face value and the findings need to be confirmed in future research. MRI follow-up was absent in 20.5% due, at least partly, to the difficulties in obtaining routine follow-up during the global Covid-19 pandemic. However, participants with and without MRI were similar except that

those without MRI were older. A lower prevalence of small vessel and cardioembolic stroke types among those without MRI may reflect a lack of diagnostic MRI information, or alternatively the infarct patterns could have been truly different. Bias due to missing follow-up cannot be excluded, and the analyses presented here cannot be considered fully intent-to-treat. A more intensive, higher-resolution MRI research protocol might have detected even more covert infarcts; however, we chose to use a more pragmatic, standardized MRI protocol, with central review, based on clinical imaging standards. Using a clinically applicable protocol makes our findings more relevant to routine clinical care. Study Steering Committee participation was based on national leadership in relevant stroke organizations and trials, without specifically considering sex and racial diversity. Study participants were predominantly European or Asian; therefore, future studies will be needed to confirm the applicability to other race and ethnic groups.

In summary, in this analysis of PACIFIC-Stroke we found that patients with acute non-cardioembolic ischemic stroke are at high risk of subsequent symptomatic and covert brain infarction, and that inhibition of factor XIa activity with asundexian may have some effect in preventing recurrent symptomatic stroke and cortical infarction in patients with embolic infarcts. In contrast, we did not find evidence to support an effect of asundexian in patients with single small subcortical infarcts. These findings should be regarded with caution, given the low confidence related to the small sample size of this phase 2 study. Nonetheless, the availability of study-specified baseline and follow-up MRIs facilitated new hypotheses about the pathophysiology of recurrent stroke and incident covert brain infarct and response to asundexian that could be tested in new trials. Based in part on the results of these analyses, the ongoing phase 3 Oral faCtor Eleven A iNhibitor asundexIan as novel anti-thrombotiC –STROKE

(OCEANIC-STROKE) randomized controlled trial has been designed to test whether oral factor XI inhibition reduces the risk of symptomatic recurrence in patients with acute non-cardioembolic ischemic stroke and evidence of cerebrovascular or systemic atherosclerosis.

FUNDING SOURCES

The study was sponsored by Bayer AG.

DISCLOSURES

All coauthors, except C-HC who reports no disclosures, or their institutions received financial support from Bayer for participation in the PACIFIC-Stroke trial. HM and PC are employees of Bayer. VC additionally reports honoraria and travel support from Boehringer Ingelheim and Ever Pharma, and participated in a Data Safety board, Steering Committee of Pacific AF and Stroke, paid to Ars Umbria. SC additionally reports research grants and consulting fees from Boehringer Ingelheim, Bristol Myers Squibb, Sanofi Aventis, and Boston Scientific; consulting fees from Portola; and honoraria from Boehringer Ingelheim and Bristol Myers Squibb.

SUPPLEMENTAL MATERIAL

Supplemental Tables S1-S2

APPENDIX

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Table 1. Participant Characteristics According to Baseline Acute Infarct Pattern on MRI and Asundexian Dose: Single Small Subcortical Infarct vs. Multiple, Large, or Cortical Infarcts

	Multiple, large, or cortical DWI+ (N=1154)	Single small subcortical DWI+ (N=474)	P-value*
Overall			
Number of patients	1154	474	
Age	66.98 (9.92)	66.95 (9.89)	0.95
Female	388 (33.6%)	152 (32.1%)	0.55
NIHSS	2.95 (2.39)	2.62 (1.91)	0.003
History of Prior stroke	160 (13.9%)	80 (16.9%)	0.12
History of CAD or peripheral arterial disease	137 (11.9%)	40 (8.4%)	0.04
Placebo Arm			
Number of patients	289	122	
Age	66.38 (10.05)	67.24 (10.29)	0.44
Female	94 (32.5%)	37 (30.3%)	0.66
NIHSS	3.03 (2.32)	2.61 (1.97)	0.07
History of Prior stroke	38 (13.1%)	26 (21.3%)	0.04
History of CAD or peripheral arterial disease	33 (11.4%)	10 (8.2%)	0.33
Asundexian 10 Arm			
Number of patients	272	131	
Age	66.94 (10.33)	66.37 (9.86)	0.60
Female	93 (34.2%)	45 (34.4%)	0.98
NIHSS	2.97 (2.53)	2.67 (1.92)	0.19
History of Prior stroke	43 (15.8%)	20 (15.3%)	0.89
History of CAD or peripheral arterial disease	31 (11.4%)	14 (10.7%)	0.83
Asundexian 20 mg			
Number of patients	289	112	
Age	67.46 (9.11)	67.27 (9.99)	0.86
Female	100 (34.6%)	29 (25.9%)	0.09
NIHSS	2.66 (2.24)	2.65 (1.90)	0.94
History of Prior stroke	40 (13.8%)	17 (15.2%)	0.73

History of CAD or peripheral arterial disease	32 (11.1%)	5 (4.5%)	0.04
Asundexian 50 mg			
Number of patients	304	109	
Age	67.14 (10.17)	67.00 (9.47)	0.90
Female	101 (33.2%)	41 (37.6%)	0.41
NIHSS	3.15 (2.46)	2.53 (1.86)	0.008
History of Prior stroke	39 (12.8%)	17 (15.6%)	0.47
History of CAD or peripheral arterial disease	41 (13.5%)	11 (10.1%)	0.36

Table 1 Legend: Values are mean (standard deviation) or number (percentage). DWI+, DWI positive; NIHSS, National Institute of Health Stroke Scale; CAD, coronary artery disease. *P value is for the comparison of all participants with single small subcortical ischemic stroke (N=474) to multiple, large, or cortical DWI positive (n=1154).

Table 2. Effect of Asundexian According to Baseline Pattern of Acute Infarction on DWI

Recurrent symptomatic stroke or incident covert infarction (primary trial outcome)

	Placebo	10 mg	20 mg	50 mg	10 mg vs. Placebo	20 mg vs. Placebo	50 mg vs. Placebo	P_{int}
All patients	82/456 (18.0%)	88/455 (19.3%)	93/450 (20.7%)	78/447 (17.4%)	1.00 (0.77-1.30)	1.08 (0.84-1.40)	0.96 (0.73-1.26)	-
DWI+ lesion	76/411 (18.5%)	84/403 (20.8%)	91/401 (22.7%)	75/413 (18.2%)	1.05 (0.80-1.38)	1.13 (0.87-1.47)	0.97 (0.73-1.28)	0.42
No DWI lesion	6/ 39 (15.4%)	4/ 43 (9.3%)	2/ 39 (5.1%)	2/ 29 (6.9%)	0.50 (0.16 - 1.60)	0.38 (0.08 - 1.69)	0.50 (0.11 - 2.21)	
Single small subcortical DWI+	16/122 (13.1%)	24/131 (18.3%)	20/112 (17.9%)	18/109 (16.5%)	1.28 (0.72-2.27)	1.23 (0.68-2.22)	1.14 (0.62-2.10)	0.81
No single small subcortical DWI+	66/ 328 (20.1%)	64/ 315 (20.3%)	73/ 328 (22.3%)	59/ 333 (17.7%)	0.94 (0.70 - 1.26)	1.05 (0.79 - 1.40)	0.90 (0.66 - 1.22)	
Multiple, large, or cortical DWI+	60/289 (20.8%)	60/272 (22.1%)	71/289 (24.6%)	57/304 (18.8%)	1.00 (0.74-1.36)	1.10 (0.82-1.48)	0.92 (0.67-1.26)	0.95
No multiple, large, or cortical DWI+	22/ 161 (13.7%)	28/ 174 (16.1%)	22/ 151 (14.6%)	20/ 138 (14.5%)	1.05 (0.64 - 1.75)	1.01 (0.59 - 1.72)	0.99 (0.57 - 1.71)	
One or more cortical DWI+	37/175 (21.1%)	34/172 (19.8%)	38/182 (20.9%)	24/167 (14.4%)	0.89 (0.59-1.32)	0.92 (0.62-1.36)	0.71 (0.45-1.11)	0.42
No cortical DWI+	45/ 275 (16.4%)	54/ 274 (19.7%)	55/ 258 (21.3%)	53/ 275 (19.3%)	1.09 (0.77 - 1.55)	1.22 (0.86 - 1.73)	1.14 (0.80 - 1.61)	

Recurrent symptomatic stroke or TIA (exploratory trial outcome)

	Placebo	10 mg	20 mg	50 mg	10 mg vs. Placebo	20 mg vs. Placebo	50 mg vs. Placebo	
All patients	38/456 (8.3%)	35/455 (7.7%)	28/450 (6.2%)	24/447 (5.4%)	0.92 (0.58-1.46)	0.74 (0.45-1.21)	0.64 (0.38-1.06)	-
DWI+ lesion	35/411 (8.5%)	35/403 (8.7%)	26/401 (6.5%)	23/413 (5.6%)	1.02 (0.64-1.64)	0.76 (0.46-1.26)	0.65 (0.39-1.11)	0.99
No DWI lesion	3/ 39 (7.7%)	0/ 43 (0.0%)	2/ 39 (5.1%)	1/ 29 (3.4%)	-	0.66 (0.11, 3.95)	0.42 (0.04, 4.05)	
Single small subcortical DWI+	6/122 (4.9%)	5/131 (3.8%)	5/112 (4.5%)	5/109 (4.6%)	0.76 (0.23-2.50)	0.93 (0.28-3.05)	0.93 (0.28-3.06)	0.74
No single small subcortical DWI+	32/ 328 (9.8%)	30/ 315 (9.5%)	23/ 328 (7.0%)	19/ 333 (5.7%)	0.98 (0.60, 1.62)	0.70 (0.41, 1.20)	0.58 (0.33, 1.02)	
Multiple, large, or cortical DWI+	29/289 (10.0%)	30/272 (11.0%)	21/289 (7.3%)	18/304 (5.9%)	1.12 (0.67-1.86)	0.71 (0.40-1.24)	0.59 (0.33-1.06)	0.37
No multiple, large, or cortical DWI+	9/ 161 (5.6%)	5/ 174 (2.9%)	7/ 151 (4.6%)	6/ 138 (4.3%)	0.50 (0.17, 1.49)	0.84 (0.31, 2.26)	0.76 (0.27, 2.14)	
One or more cortical DWI+	21/175 (12.0%)	21/172 (12.2%)	11/182 (6.0%)	10/167 (6.0%)	1.05 (0.57-1.92)	0.48 (0.23-1.00)	0.49 (0.23-1.05)	0.17

No cortical DWI+	17/ 275 (6.2%)	14/ 274 (5.1%)	17/ 258 (6.6%)	14/ 275 (5.1%)	0.81 (0.40, 1.65)	1.08 (0.55, 2.13)	0.82 (0.40, 1.66)	

Incident covert infarction among patients who did not have a symptomatic stroke

	Placebo	**10 mg**	**20 mg**	**50 mg**	**10 mg vs. Placebo**	**20 mg vs. Placebo**	**50 mg vs. Placebo**	
All patients	59/ 327 (18.0%)	64/355 (18.0%)	68/345 (19.7%)	61/331 (18.4%)	1.00 (0.73-1.38)	1.09 (0.80-1.50)	1.02 (0.74-1.41)	-
DWI+ lesion	54/301 (17.9%)	60/319 (18.8%)	68/ 323 (21.1%)	58/ 312 (18.6%)	1.05 (0.75-1.46)	1.17 (0.85-1.62)	1.04 (0.74-1.45)	0.79
No DWI lesion	5/ 26 (19.2%)	4/ 36 (11.1%)	0/ 22 (0.0%)	2/ 18 (11.1%)	-	-	0.58 (0.13 - 2.66)	
Single small subcortical DWI+	13/94 (13.8%)	20/ 111 (18.0%)	16/ 96 (16.7%)	14/93 (15.1%)	1.30 (0.69-2.48)	1.21 (0.61-2.37)	1.09 (0.54-2.19)	0.80
No single small subcortical DWI+	46/ 233 (19.7%)	44/ 244 (18.0%)	52/ 249 (20.9%)	46/ 237 (19.4%)	0.91 (0.63 - 1.33)	1.06 (0.74 - 1.51)	0.98 (0.68 - 1.42)	
Multiple, large, or cortical DWI+	41/207 (19.8%)	40/208 (19.2%)	52/227 (22.9%)	44/219 (20.1%)	0.97 (0.66-1.44)	1.16 (0.80-1.66)	1.01 (0.69-1.48)	0.77
No multiple, large, or cortical DWI+	18/ 120 (15.0%)	24/ 147 (16.3%)	16/ 118 (13.6%)	16/ 111 (14.4%)	1.09 (0.62 - 1.91)	0.90 (0.48 - 1.69)	0.96 (0.52 - 1.79)	
One or more cortical DWI+	22/ 117 (18.8%)	19/ 125 (15.2%)	28/142 (19.7%)	17/115 (14.8%)	0.81 (0.46-1.41)	1.05 (0.63-1.73)	0.79 (0.44-1.40)	0.65
No cortical DWI+	37/ 210 (17.6%)	45/ 230 (19.6%)	40/ 203 (19.7%)	43/ 215 (20.0%)	1.11 (0.75 - 1.64)	1.12 (0.75 - 1.67)	1.14 (0.76 - 1.69)	

Table 2 Legend: Values are proportion (n/N) with percentage or effect estimate (95% confidence interval). For the outcome of "Recurrent symptomatic stroke or incident covert infarction" and "Incident covert infarction", crude incidence ratios and their 95% confidence intervals are shown. For the outcome of "Recurrent symptomatic stroke or TIA ", hazard ratios (HRs) and their 95% confidence intervals are shown. DWI+, DWI positive lesion. P_{int}, p value for interaction for those with versus without that baseline DWI pattern.

Table 3. Effect of Asundexian on Types of New Covert Brain Infarcts

	Placebo (N=327)	10 mg (N=355)	20 mg (N=345)	50 mg (N=331)	10 mg vs. Placebo	20 mg vs. Placebo	50 mg vs. Placebo
New infarcts or extension of prior infarcts	59 (18.0%)	64 (18.0%)	68 (19.7%)	61 (18.4%)	1.00 (0.73-1.38)	1.09 (0.80-1.50)	1.02 (0.74-1.41)
One or more new infarcts	51 (15.6%)	51 (14.4%)	61 (17.7%)	57 (17.2%)	0.92 (0.64 -1.32)	1.13 (0.80-1.59)	1.10 (0.78-1.56)
Extension of prior infarcts only	8 (2.4%)	13 (3.7%)	7 (2.0%)	4 (1.2%)	1.50 (0.63-3.57)	0.83 (0.30-2.25)	0.49 (0.15-1.62)
New single small subcortical infarct	27 (8.3%)	20 (5.6%)	23 (6.7%)	34 (10.3%)	0.68 (0.39-1.19)	0.81 (0.47-1.37)	1.24 (0.77-2.01)
New multiple or large size or cortical new infarcts	24 (7.3%)	31 (8.7%)	38 11.0%)	23 (6.9%)	1.19 (0.71-1.98)	1.50 (0.92-2.44)	0.95 (0.55-1.64)
New cortical infarcts	16 (4.9%)	15 (4.2%)	17 (4.9%)	10 (3.0%)	0.94 (0.52-1.69)	0.89 (0.50-1.57)	0.56 (0.28-1.12)

Table 3 Legend: Values are proportion (n/N) with percentage or crude incidence ratio (95% confidence interval) for MRI-defined incident covert infarction. DWI+, DWI positive lesion.

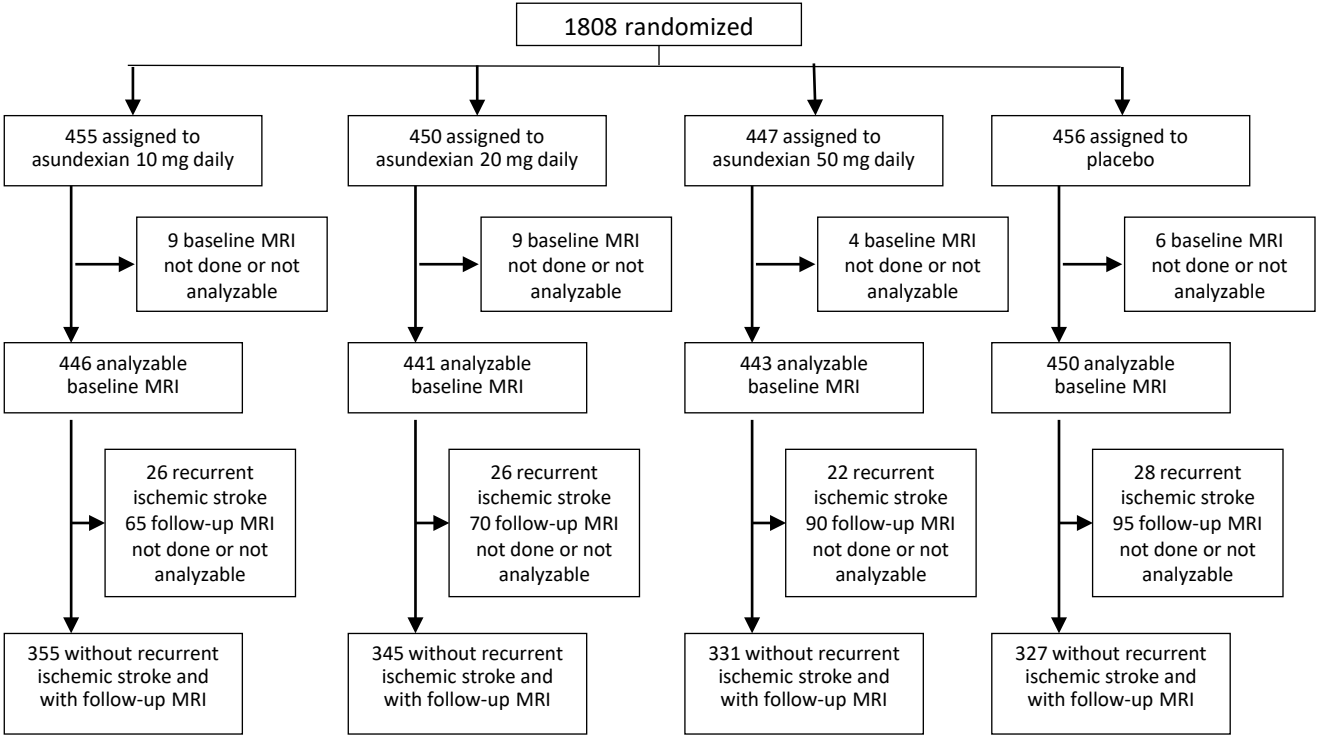
Figure 1. Study flow diagram

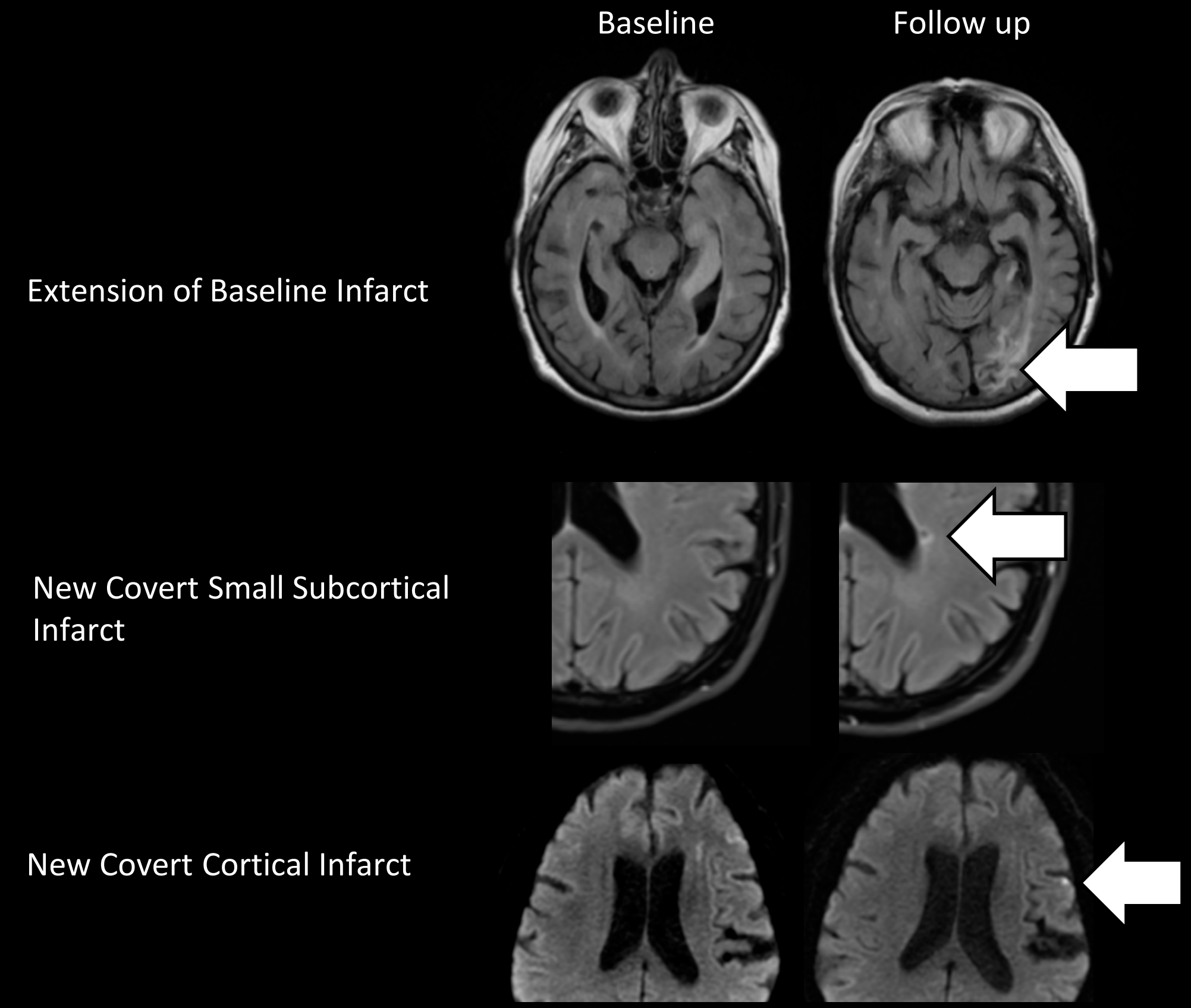
Figure 2. Examples of Infarct Patterns

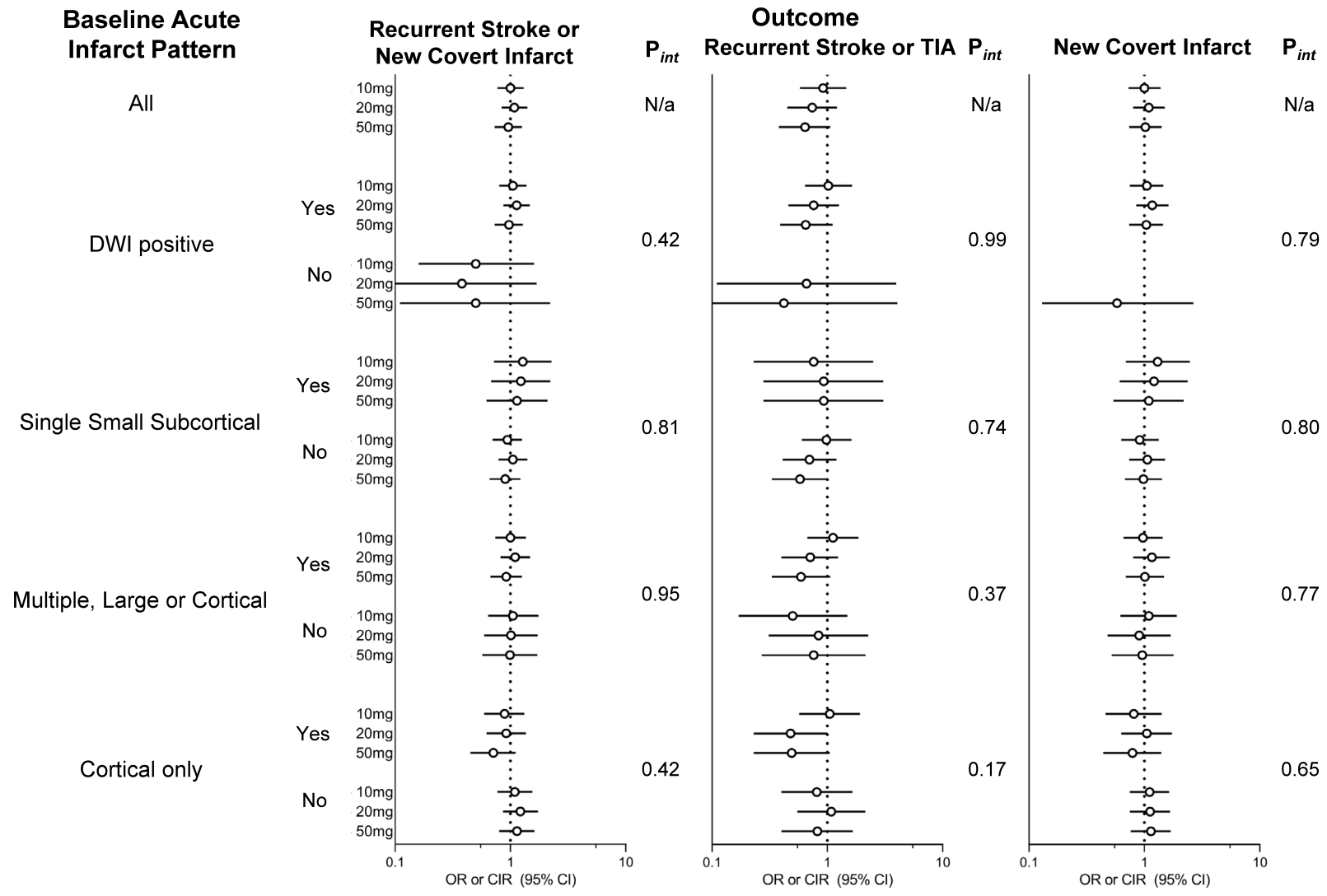
Figure 2 Legend: Top row: At baseline (left) there is an acute infarct in the anterior medial temporal lobe visible on the FLAIR sequence. At follow up (right) there is evidence of new infarction in the posterior temporal and occipital lobe (arrow) that is also in the territory of the posterior cerebral artery, adjacent to the previous area of infarction. Middle row: Adjacent to the left lateral ventricle, a single, small (3 mm diameter) subcortical infarct (arrow) is visible on the FLAIR sequence at follow-up (right) that was not present at baseline (left). Bottom row: There is a new small cortical infarct visible in the left frontal cortex on the DWI sequence (arrow) at follow-up (right) that was not visible on the baseline image (left).

Figure 3. Forest plot: Effect of Asundexian According to Baseline Acute Infarct Patterns

Figure 3 Legend: For the outcome of "Recurrent symptomatic stroke or incident covert infarction" and "Incident covert infarction", crude incidence ratios and their 95% confidence intervals are graphed. For the outcome of "Recurrent symptomatic stroke or TIA ", hazard ratios (HRs) and their 95% confidence intervals are graphed. Point estimates to the left of 1 indicate that asundexian was better than placebo. Numbers for CIRs, HRs, and CIs are given in table 3. DWI, diffusion weighted imaging, P_{int}, interaction p value.


1808 randomized
455 assigned to asundexian 10 mg daily
450 assigned to asundexian 20 mg daily
447 assigned to asundexian 50 mg daily
456 assigned to placebo
9 baseline MRI not done or not analyzable
9 baseline MRI not done or not analyzable
4 baseline MRI not done or not analyzable
6 baseline MRI not done or not analyzable
446 analyzable baseline MRI
441 analyzable baseline MRI
443 analyzable baseline MRI
450 analyzable baseline MRI
26 recurrent ischemic stroke 65 follow-up MRI not done or not analyzable
26 recurrent ischemic stroke 70 follow-up MRI not done or not analyzable
22 recurrent ischemic stroke 90 follow-up MRI not done or not analyzable
28 recurrent ischemic stroke 95 follow-up MRI not done or not analyzable
355 without recurrent ischemic stroke and with follow-up MRI
345 without recurrent ischemic stroke and with follow-up MRI
331 without recurrent ischemic stroke and with follow-up MRI
327 without recurrent ischemic stroke and with follow-up MRI


Baseline
Follow up
Extension of Baseline Infarct
New Covert Small Subcortical Infarct
New Covert Cortical Infarct


Baseline Acute Infarct Pattern
Outcome
Recurrent Stroke or New Covert Infarct
P int
Recurrent Stroke or TIA
P int
New Covert Infarct
P int
All
DWI positive
Yes
No
Single Small Subcortical
Yes
No
Multiple, Large or Cortical
Yes
No
Cortical only
Yes
No
10mg
20mg
50mg
N/a
0.42
0.81
0.95
0.42
0.99
0.74
0.37
0.17
0.79
0.80
0.77
0.65
0.1
1
10
OR or CIR (95% CI)