**Title: AXIOMATIC-SSP: Milvexian in Additon to Aspirin and Clopidogrel for Secondary Stroke Prevention**

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**What is the rationale behind using Milvexian in addition to DOACs in patients with ischemic stroke?**

So, patients who've had a recent ischemic stroke or high risk TIA have an absolute risk of a stroke within the first 90 days between six and 10%. So, really quite high. We've made some advances with antiplatelet agents, using aspirin in combination with clopidogrel. And most lately, aspirin with ticagrelor, these things, however, have come at a cost of increased bleeding. So, the standard of care at the moment for minor ischemic stroke, high risk TIA, is dual antiplatelet therapy. The reason we chose to add this factor XIa inhibitor on top of dual antiplatelet therapy is that we wanted the comparator to be the best standard of care available to us. It also gave us the opportunity to test the safety of this agent in combination with antiplatelet agents. And certainly at phase two, when we don't have evidence of efficacy, we did not want to lead patients in the trial without the standard of care. So as a result, patients in AXIOMATIC-SSP received one of five doses of milvexian on top of aspirin and clopidogrel for the first 21 days. And then the aspirin from day 22 to day 90.

**What was the study design?**

So, we looked at patients who had high risk TIA defined as having an ABCD 2 Score of six or seven or motor symptoms, or mild to moderate stroke, NIH Stroke Scale of seven or less, and we randomised them within 48 hours of symptom onset. So very rapidly, after the occurrence of the index event. The strokes were non-lacunar and noncardioembolic, so we avoided patients who had an indication for anticoagulation and also small vessel disease which appears from previous studies to respond less well to antithrombotic therapy. All patients, whether they came in with TIA or stroke had to have visible atherosclerosis in a feeding vessel. So it could be in the aortic arch, in the carotids in the vertebral arteries, depending on the area of the brain that was affected. They were randomised to one of five doses of milvexian or matching placebo, and the doses had a 16-fold range from 25 milligrammes once a day to 200 milligrammes twice a day. Everyone was on dual antiplatelet therapy, aspirin and clopidogrel for the first 21 days. And then on aspirin, 100 milligrammes a day by itself from day 22 to day 90. Our composite efficacy endpoint was a combination of symptomatic ischemic stroke and covert infarcts. So these are infarcts we detect on MRI, looking at the 90-day MRI compared to a baseline MRI, so we know they've occurred during the period of this study.

**What are the Key Outcomes?**

In the primary outcome, which combined covert infarcts with symptomatic ischemic stroke, we saw numeric reductions in this outcome for the 50 mg twice a day and 100 mg twice a day doses. But overall, we did not see a dose response curve. However, when we look at each component separately, what you note is that the covert infarcts don't respond at all. However, symptomatic ischemic stroke did respond. Every dose of milvexian, apart from the highest dose, had a lower rate of stroke than placebo. And there was a 30% reduction compared to placebo for doses between 25 mg twice a day and 100 mg twice a day. This all occurred with really outstanding safety. There were no fatal bleeds. There was no increase in intracranial haemorrhage or hemorrhagic transformation of the ischemic stroke. Most of the bleeds that we saw were GI bleeds. And the rate in our trial ranged from 0.6% to 1.5%. Again, there wasn't a dose response for bleeding. However, numerically increased in the 50 mg of BID dose and higher doses.

**What are the next steps for Phase III Trials for the use of milvexian?**

So, you know, the real prime function of a dose-finding trial, such as AXIOMATIC-SSP, is to find a dose that we can take forward. Here, we have three doses with efficacy that was actually higher than we predicted at the outset and an outstanding safety when combined with antiplatelet trials. So, the next step is an adequately powered phase three trial, and I think, likely, to study a similar population to the one we studied in phase two. So, that should start as quickly as possible.

**If this use of milvexian is implemented in clinical practice, what could be the impact on both clinicians and patients?**

So, you know, I think that if we get to the stage where things work as we expect, there'll be a huge impact on patients. Stroke is a devastating condition and we have about 12.2 million strokes each year in the world, and it results in significant disability. So, looking at these patients who are at highest risk of death or disability due to stroke, and reducing the chance of that occurring, I think is of great benefit. What's limited us in the past is the bleeding hazard. And what we see early on is benefit without a significant increase in bleeding. And I do want to say that I... That we have to be careful in our claims. It's not the case that we expect no bleeding. We will see some bleeding with all antithrombotics but we hope that the trade-off is as we predict, and the serious bleeding just doesn't occur. So, this has a potential to really revolutionise stroke prevention. For clinicians, I think that having a very effective tool in the toolbox is important. If things work as they did at phase two, I think we're going to have to be more conscious as clinicians of the underlying stroke subtype, and particularly look early for atherosclerosis underlying the stroke.”