

## Transcript - SPAN2 Podcast

Welcome to our overview on the Stroke Preclinical Assessment Network, or SPAN2, based on the final results presented by Dr. Patrick Lyden. The discussion today draws directly from the primary document and supporting presentation, encompassing the major innovations and findings from this pivotal trial.

Absolutely. The goal behind SPAN2 was ambitious – to address the long-standing gap between promising animal stroke therapies and clinical translation. By executing studies across six major research labs and using diverse animal models, the network aimed to push toward more rigorous and relevant preclinical findings.

To set the stage, SPAN2 was created in response to persistent failures in translating animal model successes to real clinical therapies. One major insight from Dr. Lyden's primary document is that increased methodological rigor often reveals much less treatment effect than initially suggested – and with full rigor, those effects sometimes disappear entirely.

That's a crucial point. The SPAN2 network tested five distinct compounds—each with its own proposed mechanism. This included BPN7332, a LOX inhibitor; tatCN19o, a CaMKII inhibitor; NVX508 for oxygen delivery; GSK2256294A as an epoxide hydrolase inhibitor; and uric acid, which had mixed results in SPAN1. They applied these to four animal models representing real-world patient diversity.

Right, and with that diversity came complexity. The team enforced strict masking with a triple-dummy design, ensuring unbiased results even with the challenge of administering multiple drugs and placebos. Ultimately, after multiple interim analyses and high standards for statistical significance, none of the agents crossed the defined efficacy boundary. Even the most promising candidate showed only a marginal effect.

In summary, while no effective neuroprotective drug emerged, SPAN2 proved that large, multicenter, rigor-driven preclinical trials in stroke research are not only possible but necessary. This framework lays crucial groundwork for future discovery efforts in the field.

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