Neuroprotective efficacy observed during short survival periods may not necessarily apply to more extended survival periods, and some stroke-impaired behaviors recover naturally in rodent models 1-2 weeks after stroke. The objective of the present study was driven by the hypothesis that acute LAU-0901 plus NPD1-induced neuroprotection endures in animals allowed to survive for several weeks after focal ischemic insult. Two small bioactive molecules were investigated: LAU-0901 (LAU), a PAF-R antagonist that blocks pro-inflammatory signaling, and neuroprotection D1 (NPD1), which activates cell-survival pathways, and their combination exerts potent anti-inflammatory activity in the brain. Male Sprague-Dawley rats were subjected to 2h of middle cerebral artery occlusion (MCAo) by an intraluminal filament and treated with vehicle, LAU (IP), NPD1 (IV) or LAU+NPD1 at three hours after onset of MCAo. Rats received neurobehavioral examinations during MCAo (60 min) and then on days 1, 2, 3, and 7, as well as weekly during an eight-week survival period. This is followed by ex vivo MRI using 11.7 T on weeks 4 and 8. Physiological variables showed no significant differences among groups. No adverse behavioral side effects were observed after the administration of LAU, NPD1, or LAU+NPD1. LAU and NPD1 treatments alone significantly improved the behavior compared to the vehicle on day 1 (33 and 31%), day 7 (38 and 32%), and week 4 (39% and 36%). Combinatory treatment with LAU+NPD1 dramatically improved total neurological score on days 1 (by 36%), 2 (38%), 3 (36%), 7 (42%), and on weeks 4 (44%), 5 (by 43%), 6 (45%), 7 (44%), and 8 (47%) when compared to the vehicle group. MRI analysis is ongoing. In conclusion, these data suggest that LAU and NPD1 alone provide high-grade neuroprotection in the MCAo model. The combinatory treatment also offers dramatic neuroprotection in the MCAo model; however, improvement does not significantly differ from LAU-0901 and NPD1 alone at this stage in the research.