Summary of Changes From I-SPOT Protocol Version 1.2 to Version 2

Throughout document footer changed to November 2015 Version 2

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\*Deceased November, 2015

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The ISPOT study has been expanded to include SHINE subjects treated with IV tPA. Enrollment of this subgroup will address an important area of interplay between blood coagulation mechanisms, hyperglycemia and insulin therapy in the context of AIS. These findings may have an impact on the development of treatment strategies in AIS, including on the role of aggressive measures to lower BG and the potential use of novel antithrombotic agents that may ameliorate some of the hemostatic changes after tPA for stroke.

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Exclusion

1. Current or anticipated use of systemic anticoagulants, intra-arterial fibrinolytics (tPA) or mechanical thrombectomy

After the patient or legally authorized representative agrees to participate and signs informed consent, the patient’s blood will be drawn before study drug is administered. Patients who have received intravenous thrombolytics will have baseline blood samples drawn after tPA infusion has ended and before the start of study drug.

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Subjects who receive thrombolytics will be monitored closely for bleeding and hematoma at the venipuncture site.

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Participants who are enrolled in the I-SPOT study and before the 48 hour blood draw have mechanical thrombectomy performed, intra-arterial thrombolytics or systemic anticoagulants administered will still have blood drawn for the 48 hour I-SPOT laboratory studies.

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A limited number (120) of the I-SPOT subjects will have received intravenous tPA.

Appreciating that biomarker levels may be significantly altered by IV tPA, these data will be analyzed separate from non-tPA treated patients. We will test the primary I-SPOT hypotheses and perform the planned secondary analyses including exploration of the relationship between biomarker levels and actual blood glucose level and with demographic variables such as, race, age, gender, etc. and baseline characteristics such as cardiovascular risk factors, use of VTE prophylaxis, insulin dose, etc. as covariates. Also, appreciating that the rate of change in biomarker levels may be highly variable irrespective of the treatment group, we will explore relationships between biomarker levels and independent factors and covariates at baseline and at 48 hours, with time as a fixed effect.

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Since the start of I-SPOT enrollment, between 19% and 28% of SHINE enrolled patients have been eligible to participate in the I-SPOT study. The most common exclusion to I-SPOT eligibility has been treatment with IV tPA; and the percentage of patients treated acutely with tPA rose from 58% to 68% with the largest increases occurring over the past 6 months. At this rate, we project the sample enrollment size for this cohort to be limited to 195 patients. Enrollment of I-SPOT patients treated with tPA will be limited to 120, with the total ISPOT enrollment remaining at 315 subjects.

The primary analysis of non-tPA-treated ISPOT study subjects will not be compromised. We determined that, given the observed variability in measurements of samples thus far, there is sufficient power to detect even a fairly conservative effect size with a sample of 96 subjects per SHINE group of a total of 192 subjects.

Appreciating that biomarker levels may be significantly altered by IV tPA, data from IV tPA treated I-SPOT subjects (n=120) will be analyzed separate from non-tPA treated subjects. We will test the primary I-SPOT hypotheses and perform the planned secondary analyses as above.