

# Workshop 3 – Discussion Guide

Recommendations for:

## Regulatory Issues for Approving Therapeutic Interventions for Acute Stroke Treatment

Chairpersons:

*Jim Grotta, Kevin McKenna and Ralph Sacco*

### Goal

To understand the FDA regulations and expectations towards gaining approval for potentially effective drug(s) or device therapies for stroke, and to develop recommendations for a clinical trial program strategy by academic and industry investigators.

### Objectives

- I. To understand the current FDA regulatory guidelines/milestones to gain ultimate approval for:
  - a. Potential solitary neuroprotective drug
  - b. Combinations of neuroprotectives or combination of neuroprotective + lytic
  - c. Potential device + drug
  
- II. Determine which guidelines:
  - Are either:
    - a. “Real”, i.e., established and fixed, or
    - b. “Perceived” and variable therefore open to negotiation?
  - And either:
    - c. Make sense, or
    - d. Should be challenged?

**✓ Fixed or ✓ Variable & ✓ Logical or ✓ Needs to be Challenged**

- III. Develop recommendations for a clinical trial strategy that will include the following broad topics:
  - Pre-phase three data
  - Clinical trial outcomes

- Phase three study design
- Multiple therapy trials

## **Consensus Discussion**

Listed below are these topics with a menu of pertinent questions and concerns that might be addressed in developing such a strategy.

### **1. Pre-Phase 3 Data:**

- a. How much and what pilot data needed? Is it necessary to escalate to maximal tolerated dose in pilot studies? How much reliance on preclinical data for dosing and safety? When is enough data enough?
- b. What is FDA attitude toward Bayesian approach to dose finding/safety pilot studies?
- c. In the investigation of an agent to treat ischemic stroke, how much safety data from hemorrhagic stroke patients is needed to obviate the need for pretreatment imaging.

### **2. Clinical Trial Outcomes:**

- a. Are there standard outcomes that the FDA would like to see in all trials? What is the view on global outcome statistics?
- b. Can surrogate endpoints such as MRI, clot lysis by TCD or other vascular imaging, biomarkers of tissue damage etc. be used in phase 2 trials? In phase 3? What validation is needed?
- c. What endpoint domains commonly employed in stroke trials would warrant specific mention in product labels e.g., physical disability, communicative disability, and impairments/neurological recovery.

### **3. Phase 3 Studies:**

- a. Need for two positive phase 3 trials? One phase 2 and one phase 3? Two trials in the US? One in the US and one “elsewhere”? One positive trial approved under subpart H of the regulations similar to that used in the approval of oncology drugs?
- b. What is the role of futility analysis?
- c. What are the views on stopping rules for early termination of trials?
- d. What steps can be taken to facilitate communication between Independent Data Monitoring Boards and the FDA with respect to the results of interim analysis? “Seamless” transit from phase 2 to phase 3 as in NINDS tPA trial?

### **4. Multiple Therapies:**

- a. Need for separate arms for individual components of a combination? When is Combination vs. “Best Standard” OK? Factorial design? Bayesian approach to efficacy studies?
- b. How to “add on” to existing therapy such as TPA? For patients who qualify for IV TPA within 3 hours, do all trials have to be TPA plus drug X vs. TPA? What data are needed about a new drug to justify a non-TPA arm in patients

who otherwise qualify for TPA, i.e. drug X vs TPA? What about alternative TPA doses or routes? How to develop a 6 hour trial allowing TPA—2 arms? = drug X vs. standard therapy (TPA in those who qualify and not in others) vs. 4 arms = drug X with or without TPA in those who qualify for TPA, and drug X vs. placebo in those who don't?

- c. How to translate experience from other disciplines that have seen success with small incremental steps of combinations such as neurooncology, cardiology etc to FDA attitude towards stroke therapy? Orphan drug status?

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### **Group 3 Consensus Recommendations:**