Meeting of the Neurological Devices Advisory Panel
NeuroFlo Catheter
December 10, 2012

Jeffrey Toy, Ph.D.
Team Leader
DNPM/ODE/CDRH/FDA
Overview of FDA Presentation

• Regulatory history

• Preclinical

• Clinical Analysis
  » Feasibility
  » “Safety and Efficacy of NeuroFlo Technology in Ischemic Stroke” (SENTIS)

• Statistical Consideration of the SENTIS results
Rationale for Meeting

To solicit Panel’s input on:

Current knowledge of the safety and effectiveness of the NeuroFlo Catheter for use in patients with acute ischemic stroke within 14 hours of symptom onset
Regulatory History

- FloControl catheter 510(k) cleared (2003, 2009)
  - Indication: Selectively stopping or controlling blood flow in the peripheral vasculature, which includes the descending aorta
- NeuroFlo catheter physically identical to FloControl catheter
- NeuroFlo catheter HDE approved (2005)
  - Indication: Treatment of cerebral ischemia resulting from symptomatic vasospasms following aneurismal subarachnoid hemorrhage, secured by either surgical or endovascular intervention for patients who have failed maximal medical management
Regulatory History

• SENTIS trial IDE approved (2005)
  » **Objective**: Demonstrate the safety and efficacy of the NeuroFlo treatment plus medical management relative to medical management alone in improving neurological outcome in ischemic stroke patients
Regulatory History

• NeuroFlo catheter 510(k) submitted (2011)
  » **Indication**: Diversion of cardiac output via partial occlusion of the descending aorta, including in patients with acute ischemic stroke within 14 hours of symptom onset
  » 510(k) found Not Substantially Equivalent (NSE) to predicate FloControl 510(k) – new intended use that alters the intended therapeutic effect of a temporary intravascular occluding catheter
Regulatory History

• NeuroFlo de novo petition (submitted by CoAxia)
  » **Indication**: Selectively stopping or controlling blood flow in the peripheral vasculature, which includes the descending aorta. When used in the descending aorta, balloon inflation results in diversion of cardiac output to the upper torso and core organs, e.g., cardiac, spinal and cerebral vasculature. The NeuroFlo™ Catheter is intended to increase cerebral blood flow in patients with ischemic stroke* and is intended for this use up to 14 hours after symptom onset, in patients who are ineligible for intravenous tPA or thrombectomy.

*In a randomized clinical investigation of stroke patients, use of the NeuroFlo™ Catheter was demonstrated to be safe. The study did not demonstrate a statistically significant improvement in the 90 day ‘return to normal’ Global Outcome Score. Use of the catheter resulted in a reduction of overall mortality and stroke-related mortality.
Regulatory History

• De novo petition under review
• CoAxia requested supervisory review of the 510(k) NSE determination (2012)
• The Center upheld the NSE determination and offered to seek clinical and scientific input from the Neurological Device Advisory Panel (2012)
• Neurological Devices Advisory Panel Meeting
Regulatory History

- Jeffrey Toy, Ph.D. – Team leader
- Natalie Getzoff, M.D. - Neurologist
- Scott Miller, Ph.D. - Biostatistician
- Courtney Millin, Ph.D. – MDR Analyst
- Veronica Sansing, Ph.D. - Epidemiologist
- Carolina Alvarez-Garriga, M.D., DrPH – Epidemiologist
- Hongying Helen Jiang, Ph.D., MS – Epidemiologist
NeuroFlo Catheter
Neurological Devices Advisory Panel

FDA Summary of Preclinical and Clinical Data

Natalie Getzoff, M.D.
DNPMOD/ODE/CDRH/FDA
Outline

- **Preclinical data**
- **Clinical data**
  - Feasibility study
  - SENTIS trial
    - Study overview
    - Safety
    - Effectiveness
Preclinical Data: CBF Swine Study

- Purpose: quantify changes in cerebral blood flow (CBF)
- 6 normal swine
- NeuroFlo device placement similar to SENTIS
- CBF indirectly measured by quantification of microsphere deposition at different time points
Preclinical Data: CBF Swine Study

*Statistically significant difference
Considerations in Analyzing CBF Swine Study Data

• Short term time frame
  » Terminated 90 minutes after balloon deflation
  » No data to demonstrate sustained changes in CBF

• Healthy animal model used
  » Cerebral autoregulation often impaired and arterioles are often maximally dilated in ischemic stroke
  » Unclear if concomitant cardiovascular disease impacts effects of aortic occlusion on CBF
Outline

• Preclinical data
• Clinical data
  » Feasibility study
  » SENTIS trial
    ▪ Study overview
    ▪ Safety
    ▪ Effectiveness
Feasibility Data: Overview

• “Phase I” (n=17) and “Phase II” (n=6)
• Purpose: To assess the safety and effectiveness of the NeuroFlo catheter for augmented perfusion of the brain following acute ischemic stroke
• Assessment measures:
  » SAEs to 30 days
  » NIHSS scores at 24 hours post-procedure, 5-7 and 30 days post-procedure
    ▪ Success = ≥ 3 point decrease in NIHSS score at 24 hours post-procedure
Feasibility Study: Results

• Safety:
  » SAEs in full feasibility dataset (n=26)
    ▪ 5 SAEs in 27% (7/26) subjects
    ▪ 2 device- or procedure-related SAEs in 2/26 subjects (7.7%)
  » 3 deaths (15%), none device- or procedure-related
  » Total AEs: 23 events in 26 subjects

• Effectiveness:
  » Phase I: 7/17 (41.1%) subjects with ≥ 3 point decrease in NIHSS score at 24 hours post-procedure
  » Phase II: 5/6 (83.3%) subjects with ≥ 3 point decrease in NIHSS score at 24 hours post-procedure
Feasibility Study: CBF Data

• Single-arm study of 17 subjects

• Variables assessed
  » CBF assessed with transcranial doppler in 16/17 subjects
  » Cerebral perfusion assessed in 10/17 subjects by
    ▪ Angiography (n=7)
    ▪ SPECT scan (n=2)
    ▪ PET scan (n=1)
Feasibility Study: CBF Data

• Reported results:
  » CBF increased > 15% in 12 of 16 subjects (mean 25%, 0-89%)
  » “Angiograms improved in 3 of 6 (50%) patients. Perfusion also improved by PET and SPECT scan.”
  » 2 subjects died of “stroke progression”

• Several limitations:
  » Small sample size
  » Uncontrolled
  » Correlation to clinical benefit not available, because 90 day clinical outcomes not assessed
  » Unclear impact from different assessment methods
Panel Question

CoAxia proposes the following indications for use for the NeuroFlo Catheter:

“The CoAxia NeuroFlo™ Catheter is intended for use in selectively stopping or controlling blood flow in the peripheral vasculature, which includes the descending aorta. When used in the descending aorta, balloon inflation results in diversion of cardiac output to the upper torso and core organs, e.g., cardiac, spinal and cerebral vasculature. The NeuroFlo™ Catheter is intended to increase cerebral blood flow in patients with ischemic stroke* and is intended for this use up to 14 hours after symptom onset, in patients who are ineligible for intravenous tPA or thrombectomy.

“*In a randomized clinical investigation of stroke patients, use of the NeuroFlo™ Catheter was demonstrated to be safe. The study did not demonstrate a statistically significant improvement in the 90 day ‘return to normal’ Global Outcome Score. Use of the catheter resulted in a reduction of overall mortality and stroke-related mortality.”
Panel Question

Please discuss if the available data (including the SENTIS trial results and other NeuroFlo pre-clinical and clinical data) demonstrate effectiveness in increasing cerebral blood flow in patients with acute ischemic stroke within 14 hours of symptom onset.
Panel Question

• Please discuss the role of increased cerebral blood flow as a complement to or surrogate for the primary effectiveness endpoint to assess effectiveness of device treatment for acute ischemic stroke.

• If increased cerebral blood flow is used as an endpoint in an acute ischemic stroke trial, please discuss the advantages and disadvantages of the following assessment measures:
  » Increase in overall cerebral blood flow;
  » Increase in regional or local cerebral blood flow; or
  » Increase in collateral blood flow.
Panel Question

- If cerebral blood flow changes are used as an endpoint in an acute ischemic stroke trial, please discuss the following:
  - Appropriate measurement technique(s) to assess cerebral blood flow or collateral flow;
  - The amount of blood flow change that is clinically relevant; and
  - The duration of blood flow change necessary to be considered clinically relevant.
Outline

- Preclinical data
- Clinical Data
  » Feasibility Study
  » SENTIS trial
    ▪ Study overview
    ▪ Safety
    ▪ Effectiveness
SENTIS Study Overview

Objective: “to demonstrate the safety and efficacy of the NeuroFlo treatment plus medical management relative to medical management alone in improving neurological outcome in ischemic stroke patients.”
SENTIS Study Overview

- Multi-center, randomized, controlled, prospective, assessor-blinded trial
- 1:1 randomization
  - NeuroFlo: device treatment plus medical management
  - Control: medical management alone
- Primary analysis population: mITT
- Other cohorts:
  - ITT
  - mAT
Key Inclusion Criteria

- New hemispheric cortical dysfunction due to acute cerebral ischemia
- Baseline NIHSS 5-18
- NeuroFlo procedure will start within 14 hours of symptom onset
Key Exclusion Criteria

- Pre-existing mRS ≥ 2
- > ⅓ middle cerebral artery territory
- New intracranial bleed
- Use of thrombolytic drug or clot retriever during current stroke episode
- Rapidly improving neurologic status
- NeuroFlo group specific exclusion criteria:
  » Aortic diameters outside the device-defined limits
  » Evidence of aortic aneurysm
  » High grade iliac stenosis or tortuosity
Prespecified Safety Endpoints

• Primary:
  » Comparison in incidence of SAEs
  » From time of enrollment through 90 days of follow-up.

• Secondary:
  » 90 day Mortality/Survival
  » New Intracranial Hemorrhage
  » Symptomatic Intracerebral Hemorrhage
  » Index Stroke Related SAE
Primary Effectiveness Endpoint

- Estimate the effect of NeuroFlo treatment as compared to control using the global test outcome at 90 days.

- Components for the global test measurement were NIHSS, mRS, BI, and GOS.
  - NIHSS = 0 or 1, mRS = 0 or 1, BI = 95 - 100, GOS = 5

- Result of the global test is an overall odds ratio:
  - Assesses the association between treatment and a favorable outcome at 90 days
  - OR > 1 favors treatment
  - OR < 1 favors control
Prespecified Secondary Effectiveness Endpoints

- Primary Efficacy Endpoint Component Analysis
- Acute improvement in NIHSS (change in NIHSS ≥ 3 points or NIHSS ≤ 2) 24 hours post-procedure
- Stroke Impact Scale (SIS) as collected at 30 and 90 days
- Hospital length of stay
- mRS Shift Analysis
- Dichotomized mRS (0-2 versus 3-6)
- Entry Severity Responder Analysis
- Subject Disposition Upon Discharge

- No effectiveness endpoint assessed cerebral blood flow
Subject Accountability

• **Enrolled: 515 subjects at 72 sites**
  » Control: 257 subjects randomized
  » NeuroFlo: 258 subjects randomized
  ▪ 28 Exclusions:
    – 25 due to anatomical ineligibility via angiography
    – 3 due to rapid neurological improvement
    – No significant difference between NeuroFlo, control, and NeuroFlo Exclusions groups in
      » Demographics
      » Mortality
      » Endpoints
  ▪ Final NeuroFlo N=230
Outline

• Preclinical data
• Feasibility data
• SENTIS trial
  » Study overview
  » Safety
  » Effectiveness
Primary Safety Endpoint Analysis

- **NeuroFlo (N=230)**
  - 174 SAEs in 43.9% (101/230) subjects
- **Control (N=257)**
  - 177 SAEs in 42.8% (110/257) subjects
- \( p = 0.923 \)
Primary Safety Endpoint Considerations

• **Overall SAE rate:**
  » Does not differentiate between events associated or unassociated with the device or procedure
  » Weights all SAEs equally, but some SAEs may have more clinical concerns than others
## SAEs by Treatment Group and Organ System

<table>
<thead>
<tr>
<th>SAE Type</th>
<th>NeuroFlo (N=230)</th>
<th>Control (N=257)</th>
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<tr>
<td></td>
<td># Events</td>
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<tr>
<td>Other</td>
<td>21</td>
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</tr>
</tbody>
</table>
NeuroFlo Related* SAEs

- SAEs 8/230 (3.4%)
  - Neurological deterioration with new stroke and hemorrhage – fatal SAE (1)
  - Femoral artery occlusion/thrombosis with limb ischemia – limb amputation (1)
  - Femoral artery occlusion/thrombosis (2)
  - Pseudoaneurysm (2)
  - Pulmonary Edema (1)
  - Right groin abscess (1)

*Adjudicated by DSMB as device- and/or procedure-related
## All AEs by Treatment Group and Organ System

<table>
<thead>
<tr>
<th>Adverse Event Type</th>
<th>NeuroFlo (N=230)</th>
<th>Control (N=257)</th>
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</thead>
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<td># Subj</td>
</tr>
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<td>221</td>
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<tr>
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<td>111</td>
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<tr>
<td>Pulmonary</td>
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<td>65</td>
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<td>Renal</td>
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<td>70</td>
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<tr>
<td>Neurological – Bleeding</td>
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<td>41</td>
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<tr>
<td>Neurological – Other</td>
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<td>116</td>
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<tr>
<td>Gastrointestinal</td>
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<td>70</td>
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<tr>
<td>Laboratory</td>
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<td>121</td>
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<td>Vascular</td>
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<td>50</td>
</tr>
<tr>
<td>Other</td>
<td>301</td>
<td>150</td>
</tr>
</tbody>
</table>
NeuroFlo Related* Non-Serious AEs

- Non-serious AEs: 36 events in 35/230 subjects (15.2%)
  - Hematoma (18)
  - Hypertension (3)
  - Pain (3)
  - Ecchymosis (2)
  - Hypotension (2)
  - Aortic injury (1)
  - Arrhythmia (1)
  - Bleeding, access site (1)
  - Decreased R femoral pulse (1)
  - Diminished pulse (1)
  - Pseudoaneurysm (1)
  - Renal dysfunction (1)
  - Popliteal trifurcation thrombosis (1)

*Adjudicated by DSMB as device- and/or procedure-related
Panel Question

The SENTIS trial met its primary safety endpoint of no statistically significant elevation in the rate of serious adverse events (SAEs) in the NeuroFlo-treated group relative to the Control group. Specifically, there were 174 SAEs in 101/230 (43.9%) NeuroFlo subjects and 177 SAEs in 110/257 (42.8%) control subjects. However, there were SAEs not seen in the control group that were adjudicated as related to the NeuroFlo treatment. In light of all of the available safety data:
Panel Questions

• Please discuss the safety of the NeuroFlo device in the SENTIS population (patients with acute ischemic stroke treatable within 14 hours from symptom onset, with baseline NIHSS score of 5-18, and without evidence of massive infarct or hemorrhage).

• Please discuss any additional measures that may reduce the risk of these SAEs associated with use of the NeuroFlo device in the SENTIS population.
Prespecified Secondary Safety Endpoint

90 Day All-cause Mortality

» NeuroFlo: 11.3% (26/230)
» Control: 16.3% (42/257)
» Nominal p = 0.087 (by Cochran-Mantel-Haenszel test)

90 Day Survival

» NeuroFlo: 88.5% (214/230)
» Control: 84.2% (217/257)
» Nominal p = 0.099 (by log rank test)
Prespecified Secondary Safety Endpoint

90 Day Survival

Estimated probability of survival

Time (days)

Log-rank p=0.099

NeuroFlo
Control
Panel Question

The SENTIS trial resulted in a 90-day all-cause mortality rate of 11.3% in the NeuroFlo group vs. 16.3% in the control group (p = 0.087 using Cochran-Mantel-Haenszel test). Survival at 90 days by Kaplan-Meier was 88.5% (83.6%, 92.0%) and 84.2% (79.1%, 88.1%) in the NeuroFlo and Control groups, respectively (p = 0.099 by log-rank test). Please discuss the clinical significance of these findings.
Prespecified Secondary Safety Endpoints

**New Intracranial Hemorrhage**

- NeuroFlo: 26.1% (60/230), 60 events
- Control: 27.6% (71/257), 74 events
- \( p=0.702 \) (nominal)
Prespecified Secondary Safety Endpoints

Symptomatic Intracranial Hemorrhage

- Measured at 24 hours post-procedure
- NeuroFlo: 1.3% (3/230), 3 events
- Control: 0.8% (2/257), 2 events
- Nominal p=0.565
Prespecified Secondary Safety Endpoints

Index Stroke-Related SAEs at 90 days

- NeuroFlo: 20.9% (48/230), 55 events
- Control: 23.7% (61/257), 70 events
- Adjusted Odds Ratio (OR) = 1.20
- Nominal p = 0.449 (nominal)
- No statistically significant difference between groups
Post Hoc Secondary Safety Endpoint

Stroke-related deaths defined by CoAxia as:
- Deaths due to stroke
- Systemic complications associated with stroke
- New stroke

<table>
<thead>
<tr>
<th></th>
<th>NeuroFlo</th>
<th>Control</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>90 Day Stroke-related mortality</td>
<td>7.4% (17/230)</td>
<td>14.4% (37/257)</td>
<td>0.0111*</td>
</tr>
<tr>
<td>90 Day Survival</td>
<td>92.4% (88.1-95.2)</td>
<td>85.3% (80.3-89.2)</td>
<td>0.0146^</td>
</tr>
</tbody>
</table>

*by Cochran-Mantel-Haenszel test; ^by log rank test
Post Hoc Secondary Safety Endpoint

90 Day Stroke-Related Survival

![Graph showing the estimated probability of survival over time for different groups. The y-axis represents the estimated probability of survival, ranging from 0.6 to 1.0. The x-axis represents time in days, ranging from 0 to 90. The graph indicates a comparison between NeuroFlo and Control groups, with a Log-rank p-value of 0.015.]
Stroke Related Mortality Analysis: Interpretation Challenges

- Performed in the absence of a statistically significant primary effectiveness analysis
- Post hoc defined endpoint and analysis
- No corresponding $p < 0.05$ in all-cause mortality (NeuroFlo 11.3%, control 16.3%, $p=0.099$)
Panel Question

CoAxia conducted a post hoc analysis of multiple effectiveness and safety endpoints using SENTIS results, and found stroke-related mortality to be decreased for NeuroFlo-treated subjects (90-day stroke-related mortality: NeuroFlo 7.4%, Control 14.4%, nominal p=0.011). Survivorship at 90 days by Kaplan-Meier was 92.4% (88.1%, 95.2%) in the NeuroFlo group and 85.3% (80.3%, 89.2%) in the Control group, p = 0.0146 using log-rank test. For the purpose of this analysis, stroke-related mortality is defined as deaths that were adjudicated to have been due to stroke, systemic complications associated with stroke, or new stroke. Post hoc analyses are challenging to interpret, especially if conducted in the setting of a non-significant primary endpoint. Please discuss the clinical significance of this post hoc analysis finding.
Outline

• Preclinical data
• Feasibility data
• SENTIS trial
  » Study overview
  » Safety
    ▪ Endpoints
    ▪ Adverse Events (AEs)
  » Effectiveness
Primary Effectiveness Endpoint

• Estimate the effect of NeuroFlo treatment as compared to control using the global test outcome at 90 days

• Odds ratio (OR) for improved outcome = 1.17 (95% CI [0.81,1.67]), p=0.407

• Results were similar for mAT and ITT cohorts

• Supported by lack of difference between the NeuroFlo and control groups when the four components of the global endpoint were analyzed separately
Panel Question

The SENTIS trial used a global test-type endpoint with multiple components to assess effectiveness. Please discuss your interpretation of this global endpoint in evaluating clinical outcomes in subjects enrolled in SENTIS.
### Prespecified Secondary Effectiveness Endpoints

#### Primary Efficacy Endpoint Component Analysis
(covariate adjusted, excluding NeuroFlo Exclusions)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Proportion of subjects with favorable response</th>
<th>Odds Ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Treatment (N=230)</td>
<td>Control (N=257)</td>
<td></td>
</tr>
<tr>
<td>NIHSS (0 or 1)</td>
<td>28.5%</td>
<td>30.6%</td>
<td>0.98 (0.63, 1.54)</td>
</tr>
<tr>
<td>mRS (0 or 1)</td>
<td>31.2%</td>
<td>31.5%</td>
<td>1.11 (0.71, 1.74)</td>
</tr>
<tr>
<td>BI (95-100)</td>
<td>50.2%</td>
<td>45.6%</td>
<td>1.38 (0.89, 2.13)</td>
</tr>
<tr>
<td>GOS (5)</td>
<td>33.0%</td>
<td>33.9%</td>
<td>1.06 (0.68, 1.65)</td>
</tr>
</tbody>
</table>
Prespecified Secondary Effectiveness Endpoints

Acute Improvement in NIHSS

• Assessed 24 hours post-procedure
• NeuroFlo: 41.9%
• Control: 37.0%
• Adjusted OR = 1.24 (95% CI [0.85-1.82])
• $p = 0.260$ (nominal)
Prespecified Secondary Effectiveness Endpoints

mRS Shift Analysis

- No statistically significant shift in the distribution of the full range of mRS scores
Prespecified Secondary Effectiveness Endpoints

Dichotomized mRS Score (0-2 vs. 3-6) at 90 days

- NeuroFlo: 48.2%
- Control: 44.2%
- OR = 1.34 [0.86-2.10]
- \( p = 0.314 \) (nominal)
Prespecified Secondary Effectiveness Endpoints

“Entry Severity Responder Analysis”

- Sliding dichotomy mRS
  - Baseline NIHSS of ≤ 7 needs a mRS of 0 at 90 days
  - Baseline NIHSS of 8 to 14 needs a mRS of 0 to 1 at 90 days
  - Baseline NIHSS of ≥ 15 needs a mRS of 0 to 2 at 90 days

- OR = 1.03 (95% CI [0.66-1.62])
- p = 0.809 (nominal)
Prespecified Secondary Effectiveness Endpoints

Stroke Impact Scale (SIS) at 30 and 90 Days

<table>
<thead>
<tr>
<th></th>
<th>NeuroFlo (N=174)</th>
<th>Control (N=197)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n/N</td>
<td>135/159</td>
<td>145/167</td>
</tr>
<tr>
<td>30 days (mean ± SD)</td>
<td>60.9 ± 26.1</td>
<td>60.5 ± 28.8</td>
</tr>
<tr>
<td>90 days (mean ± SD)</td>
<td>68.4 ± 25.3</td>
<td>67.7 ± 24.5</td>
</tr>
</tbody>
</table>

• $p = 0.402$ (nominal)
Prespecified Secondary Effectiveness Endpoints

Hospital Length of Stay

- NeuroFlo: 10.5 days ± 11.8 days
- Control: 8.8 days ± 9.2 days
- $p = 0.151$ (nominal)
- No statistically significant difference between the groups, overall or by region
### Prespecified Secondary Effectiveness Endpoints

#### Subject Disposition Upon Discharge

<table>
<thead>
<tr>
<th></th>
<th>NeuroFlo (N=147)</th>
<th>Control (N=167)</th>
</tr>
</thead>
<tbody>
<tr>
<td>At Home</td>
<td>32.7%</td>
<td>38.9%</td>
</tr>
<tr>
<td>In Facility</td>
<td>63.3%</td>
<td>54.5%</td>
</tr>
<tr>
<td>Died before discharge</td>
<td>4.1%</td>
<td>6.6%</td>
</tr>
</tbody>
</table>

- Assessed only on US subjects
- Overall p = 0.549
- No statistically significant difference between NeuroFlo and control groups for any disposition status
Panel Question

Please discuss any relevant treatment effect identified in the data from the SENTIS trial and if any identified effects are clinically meaningful.
Post Hoc Subgroup Analyses

- Several subpopulations with potential clinical benefit identified
  - Numerous exploratory analyses
  - None prespecified
Results of Some Post Hoc Subgroup Analyses

<table>
<thead>
<tr>
<th>SENTIS Cohort*</th>
<th>Evaluable Subjects</th>
<th>NeuroFio (n=226)</th>
<th>Control (n=261)</th>
<th>mRS 0-2 Outcome</th>
<th>Stroke-Related Mortality</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Odds Ratio^</td>
<td>Nominal p-value+</td>
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<tr>
<td>TFSO ≤ 5 hrs</td>
<td>76</td>
<td>60.60% (20/33)</td>
<td>37.20% (16/43)</td>
<td>4.69</td>
<td>0.011</td>
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<tr>
<td>TFSO ≤ 6 hrs</td>
<td>128</td>
<td>56.30% (36/64)</td>
<td>40.60% (26/64)</td>
<td>3.11</td>
<td>0.011</td>
</tr>
<tr>
<td>Baseline NIHSS 8-14</td>
<td>214</td>
<td>50.00% (54/108)</td>
<td>37.70% (40/106)</td>
<td>1.84</td>
<td>0.043</td>
</tr>
<tr>
<td>Age &gt;70 yrs</td>
<td>246</td>
<td>42.60% (46/108)</td>
<td>34.80% (48/138)</td>
<td>1.98</td>
<td>0.044</td>
</tr>
<tr>
<td>Age &gt;80 yrs</td>
<td>102</td>
<td>40.80% (20/49)</td>
<td>22.60% (12/53)</td>
<td>4.03</td>
<td>0.013</td>
</tr>
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</table>

* Based on the predefined 'modified as-treated' population. ^ Odds ratios are adjusted by age and baseline NIHSS scores; + p values not calculated with Alpha spend applied;
**Results of Some Post Hoc Subgroup Analyses**

<table>
<thead>
<tr>
<th>Analysis</th>
<th>NeuroFlo (n=247)</th>
<th>Control (n=242)</th>
<th>Odds Ratio</th>
<th>Nominal p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shift analysis “less final global disability”</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>0.092</td>
</tr>
<tr>
<td>mRS 0-2 vs 3-6</td>
<td>49.4% (122 / 247)</td>
<td>43.4% (105 / 242)</td>
<td>1.54 (0.99-2.40)</td>
<td>0.053</td>
</tr>
<tr>
<td>mRS 0-4 vs 5-6</td>
<td>84.6% (209 / 247)</td>
<td>76.4% (185 / 242)</td>
<td>1.90 (1.10-3.29)</td>
<td>0.021</td>
</tr>
<tr>
<td>Sliding dichotomoy</td>
<td>50.2% (124 / 247)</td>
<td>43.0% (104 / 242)</td>
<td>1.43 (0.98-2.08)</td>
<td>0.067</td>
</tr>
</tbody>
</table>

**Unique study cohort**
- **Subjects excluded:**
  - “Stroke mimics”
  - Those with missing data
- **NeuroFlo Exclusion subjects included in the NeuroFlo group, though no NeuroFlo treatment received**
Panel Question

Please discuss whether the benefits from use of the NeuroFlo device outweigh the risks of its use in the patient population enrolled in the SENTIS trial. Please discuss these benefits and risks in the context of alternative treatments (including non-device therapies) approved or cleared for the intended condition and patient population, as this is a component of FDA’s final regulatory decision with respect to benefit-risk determination.
Panel Question

After failing to meet any pre-specified primary and secondary effectiveness endpoints, CoAxia conducted multiple post hoc analyses and identified several subgroups in whom they state that the NeuroFlo device shows larger treatment effect (e.g., subjects >70 years or subjects with baseline NIHSS score between 8 and 14). FDA has concerns that, due to the post hoc nature of these subgroup analyses, the results may represent false positive findings. Taking these concerns into consideration, please discuss the benefits and risks in the identified subgroups.
CoAxia NeuroFlo catheter
FDA presentation
Statistical component

Scott W. Miller, Ph.D.
DBS/OSB/CDRH/FDA
Overview

• Pre-specified primary analysis
  » Global test

• Type I error inflation
  » Secondary analyses
  » Post hoc analyses
Overview

- Pre-specified primary analysis
  » Global test
- Type I error inflation
  » Secondary analyses
  » Post hoc analyses
Pre-specified primary effectiveness analysis: global test

• Global test
  » 4 components: NIHSS, mRS, BI, GOS
• Each component classified as favorable or unfavorable
• Global test assumes the odds ratio for treatment is about the same for each component
• NOT a simple combination of the 4 (composite outcome)
## Global test vs. Composite

<table>
<thead>
<tr>
<th>Subject</th>
<th>Scale</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NIHSS</td>
<td>Favorable</td>
</tr>
<tr>
<td></td>
<td>mRS</td>
<td>Unfavorable</td>
</tr>
<tr>
<td></td>
<td>BI</td>
<td>Unfavorable</td>
</tr>
<tr>
<td></td>
<td>GOS</td>
<td>Favorable</td>
</tr>
</tbody>
</table>
### Global test vs. Composite (continued)

<table>
<thead>
<tr>
<th>Number of favorable components</th>
<th>Composite</th>
<th>Global</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Unfavorable</td>
<td>Strong pull to OR&lt;1</td>
</tr>
<tr>
<td>1</td>
<td>Unfavorable</td>
<td>Minor pull to OR&lt;1</td>
</tr>
<tr>
<td>2</td>
<td>Unfavorable</td>
<td>Pulls OR = 1</td>
</tr>
<tr>
<td>3</td>
<td>Unfavorable</td>
<td>Minor pull to OR&gt;1</td>
</tr>
<tr>
<td>4</td>
<td>Favorable</td>
<td>Strong pull to OR&gt;1</td>
</tr>
</tbody>
</table>

*Assume a control subject with similar covariates has 2 favorable components*
Primary effectiveness outcome

<table>
<thead>
<tr>
<th>Primary Effectiveness Outcome (Global test)</th>
<th>Odds Ratio* (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.17 (0.81, 1.67)</td>
<td>0.407</td>
</tr>
</tbody>
</table>

SENTIS trial anticipated an odds ratio of 1.7

Adjusted for: age, gender, baseline NIHSS, time from symptom onset, and baseline glucose level.

*Covariate-adjusted using mITT population
## Assessing global test assumption

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Proportion of subjects with favorable response</th>
<th>Odds Ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIHSS (0 or 1)</td>
<td>Treatment (N=230)* 28.5%</td>
<td>Control (N=257) 30.6%</td>
<td>0.98 (0.63, 1.54)</td>
</tr>
<tr>
<td>mRS (0 or 1)</td>
<td>31.2%</td>
<td>31.5%</td>
<td>1.11 (0.71, 1.74)</td>
</tr>
<tr>
<td>BI (95-100)</td>
<td>50.2%</td>
<td>45.6%</td>
<td>1.38 (0.89, 2.13)</td>
</tr>
<tr>
<td>GOS (5)</td>
<td>33.0%</td>
<td>33.9%</td>
<td>1.06 (0.68, 1.65)</td>
</tr>
</tbody>
</table>

Covariate-adjusted
*Excludes NeuroFlo exclusion subjects*
Assessing global test assumption

<table>
<thead>
<tr>
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<td></td>
</tr>
<tr>
<td>mRS (0 or 1)</td>
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<td>1.11 (0.71, 1.74)</td>
<td>0.648</td>
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<tr>
<td></td>
<td>Control (N=257) 31.5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BI (95-100)</td>
<td>Treatment (N=230)* 50.2%</td>
<td>1.38 (0.89, 2.13)</td>
<td>0.150</td>
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<tr>
<td></td>
<td>Control (N=257) 45.6%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GOS (5)</td>
<td>Treatment (N=230)* 33.0%</td>
<td>1.06 (0.68, 1.65)</td>
<td>0.806</td>
</tr>
<tr>
<td></td>
<td>Control (N=257) 33.9%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Covariate-adjusted
*Excludes NeuroFlo exclusion subjects
### Assessing global test assumption

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Covariate-adjusted

*Excludes NeuroFlo exclusion subjects*
Assessing global test assumption

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<tbody>
<tr>
<td>NIHSS (0 or 1)</td>
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<td>1.06 (0.68, 1.65)</td>
</tr>
</tbody>
</table>

Covariate-adjusted
*Excludes NeuroFlo exclusion subjects
Number of favorable components by treatment group

<table>
<thead>
<tr>
<th>Number of favorable components</th>
<th>NeuroFlo (N=230)</th>
<th>Control (N=257)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 of 4</td>
<td>46.0%</td>
<td>51.0%</td>
</tr>
<tr>
<td>1 of 4</td>
<td>15.9%</td>
<td>8.8%</td>
</tr>
<tr>
<td>2 of 4</td>
<td>5.8%</td>
<td>8.4%</td>
</tr>
<tr>
<td>3 of 4</td>
<td>10.6%</td>
<td>10.0%</td>
</tr>
<tr>
<td>4 of 4</td>
<td>21.7%</td>
<td>21.7%</td>
</tr>
</tbody>
</table>
Panel Question

The SENTIS trial used a global test-type endpoint with multiple components to assess effectiveness. Please discuss your interpretation of this global endpoint in evaluating clinical outcomes in subjects enrolled in SENTIS.
Overview

• Pre-specified primary analysis
  » Global test
• Type I error inflation
  » Secondary analyses
  » Post hoc analyses
Issues with the secondary analyses

• Sponsor has highlighted some comparisons with nominal p<0.05
  » A subset of the analyses

• Concerns with interpretation
  » Interpreting secondary analyses challenging in the absence of significant primary analysis and no multiplicity adjustment
Issues with the post hoc analyses

• Sponsor has highlighted some comparisons with nominal p<0.05
  » A subset of the post hoc analyses
• Concerns with interpretation
  » Post hoc analyses are generally not recommended, typically considered hypothesis-generating
Impact of multiple analyses on type I error rate inflation

- Performing multiple unadjusted analyses increases the type I error
- Several methods to control type I error can be pre-specified
- SENTIS trial did not plan to use any of these methods
  » Protocol: “No hypothesis tests will be performed for the secondary outcomes because there are no plans to make labeling claims for these”
Type I error rate inflation

<table>
<thead>
<tr>
<th>Number of independent hypothesis tests</th>
<th>Probability of at least 1 comparison with $p&lt;0.05$</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>40%</td>
</tr>
<tr>
<td>20</td>
<td>64%</td>
</tr>
<tr>
<td>30</td>
<td>79%</td>
</tr>
<tr>
<td>40</td>
<td>87%</td>
</tr>
</tbody>
</table>
Pre-specified safety outcomes assessed

Pre-specified primary safety outcome
» Overall SAE rate

Pre-specified secondary safety outcomes
• Mortality/survival
  – Rate at 90 days
  – Overall survival through 90 days
• New ICH rate through 90 days
• sICH rate
• Index stroke-related SAE rate
Pre-specified primary effectiveness outcome (global test)

- Adjusted for covariates
- Unadjusted

- Not statistically significant
Pre-specified secondary effectiveness outcomes

- NIHSS (adjusted and unadjusted)
- mRS (adjusted and unadjusted)
- BI (adjusted and unadjusted)
- GOS (adjusted and unadjusted)
- Acute improvement in neurologic function at 24 hours
- Stroke Impact Scale at 30 and 90 days
- Hospital length of stay for index stroke
- Distribution of mRS scores at 90 days
- Patient disposition upon hospital discharge [US subjects only]
- mRS dichotomized (0-2 vs. 3-6) at 90 days
- Entry severity responder analysis

- No difference between treatment groups
Non-prespecified (post hoc) outcomes assessed

- Stroke-related mortality
- Baseline NIHSS score between 8-14
- Age
  - >70 years
  - >80 years
- Time from symptom onset (TFSO)
  - ≤ 5 hours
  - ≤ 6 hours
- Additional mRS categorizations using different cutpoints
CoAxia conducted a post hoc analysis of multiple effectiveness and safety endpoints using SENTIS results, and found stroke-related mortality to be decreased for NeuroFlo-treated subjects (90-day stroke-related mortality: NeuroFlo 7.4%, Control 14.4%, nominal p=0.011). Survivorship at 90 days by Kaplan-Meier was 92.4% (88.1%, 95.2%) in the NeuroFlo group and 85.3% (80.3%, 89.2%) in the Control group, p = 0.0146 using log-rank test. For the purpose of this analysis, stroke-related mortality is defined as deaths that were adjudicated to have been due to stroke, systemic complications associated with stroke, or new stroke. Post hoc analyses are challenging to interpret, especially if conducted in the setting of a non-significant primary endpoint. Please discuss the clinical significance of this post hoc analysis finding.
Statistical Conclusion

• SENTIS trial failed to demonstrate statistical significance on:
  » Pre-specified primary effectiveness outcome
  » All pre-specified secondary outcomes

• Primary effectiveness outcome (global test) trend largely driven by BI component

• SENTIS analyzed numerous post hoc outcomes
  » Some have nominal p<0.05 (e.g. stroke-related mortality)

• Post hoc analyses lead to an elevated risk of false positive findings

• Type I error rate uncontrolled and unknown
Meeting of the Neurological Devices Advisory Panel
NeuroFlo Catheter
December 10, 2012

Quynh Hoang
Neurodiagnostic and Neurosurgical Devices Branch Chief
DNPM/ODE/CDRH/FDA
Key Points about SENTIS

- **Objective**: demonstrate the safety and efficacy of the NeuroFlo treatment plus medical management relative to medical management alone in improving neurological outcome in ischemic stroke patients.
- **Study did not assess cerebral blood flow**
- **Outcomes**:
  - Achieved primary safety endpoint (no significant difference in SAE rate between groups)
  - Failed to achieve statistical significance on primary effectiveness endpoint
  - Failed to achieve statistical significance on all secondary effectiveness endpoints
  - Post hoc analyses identified several subgroups with nominal p value < 0.05
- **Limitations**:
  - Interpreting secondary analyses challenging in the absence of significant primary analysis and no multiplicity adjustment
  - Post hoc analyses are typically viewed as hypothesis generating