Adventitial Drug Infusion to Prevent Restenosis

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Disclosure

Speaker name: Marianne Brodmann

I have the following potential conflicts of interest to report:

- [x] Consulting
- [ ] Employment in industry
- [ ] Stockholder of a healthcare company
- [ ] Owner of a healthcare company
- [ ] Other(s)

- [x] I do not have any potential conflict of interest
What is Adventitial Drug Delivery (ADD)
The Bullfrog® Micro-Infusion Device

“Painting” the vessel with 0.5 mL per cm of lesion, including 20% contrast to follow the diffusion:
Current Clinical Trials of Adventitial-Perivascular Therapy with Bullfrog Delivery

**Trauma**
- **Vonapanitase**
  - SFA
  - Enrolling

**Recoil**
- **Dexamethasone**
  - DANCE
    - 283 limbs
    - Open-label
    - COMPLETED
  - LIMBO-ATX
    - 120 total subjects
    - 1:1 RCT
    - Enrollment COMPLETE
  - LIMBO-PTA
    - 120 total subjects
    - 1:1 RCT
    - Enrolling

**Signaling**
- **Temsirolimus**
  - TANGO
    - 60 total subjects
    - Dose-escalation RCT
    - Enrolling
The DANCE Trial Tested the Hypothesis that Treating Inflammation Reduces Restenosis

Restenosis results from the inflammatory cascade:

- **Hours**
  - Injury
  - Endovascular Procedure
  - Dexamethasone

- **Days**
  - Transcription
  - Signaling
  - Recruitment

- **Weeks**
  - Migration
  - Proliferation

- **Months**
  - Hyperplasia/Narrowing

Upstream targeting of the early inflammatory process limits or eliminates downstream restenosis, but allows healing and resolution.
The DANCE Trial
Dexamethasone to the Adventitia to eNhance Clinical Efficacy in fem/pop disease

- Multicenter, open-label trial
- SFA and Popliteal
- Primary atherectomy (ATX) or primary angioplasty (PTA) based on investigator decision
- Adventitial drug delivery of dexamethasone (ADD-DEX) in all subjects
- National co-PIs (U.S.):
  - Mahmood Razavi, MD
  - George Adams, MD
- Primary Endpoints:
  - Safety: MALE+POD within 30 days from the procedure
  - Efficacy: Primary patency at 12 months
    - Freedom from angiographic or duplex ultrasound binary restenosis (PSVR ≤ 2.4)
    - Freedom from clinically-driven target lesion revascularization (CD-TLR)
DANCE Statistical Analysis Plan

• The DANCE trial was designed with the intent to compare all treatment results to historical and contemporary control data

• Two performance goals were determined by examination of published DCB pivotal studies (LEVANT 2 and In.PACT SFA)

• **Historical (PTA) Performance Goal**: based on the PTA controls from the DCB pivotal studies

• **Contemporary (DCB) Performance Goal**: based on the combined DCB outcomes from the DCB pivotal studies

• Planned Analyses:
  – Primary: demonstrate superiority to the Historical (PTA) Performance Goal
  – Secondary: demonstrate non-inferiority to the Contemporary (DCB) Performance Goal with a 10% non-inferiority margin
## Determination of Performance Goal

<table>
<thead>
<tr>
<th>12-month primary patency</th>
<th>LEVANT 2&lt;sup&gt;1&lt;/sup&gt;</th>
<th>IN.PACT SFA&lt;sup&gt;2&lt;/sup&gt;</th>
<th>COMBINED</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>PTA</td>
<td>DCB</td>
<td>PTA</td>
</tr>
<tr>
<td>Patent:</td>
<td>71</td>
<td>172</td>
<td>54</td>
</tr>
<tr>
<td>Not Patent:</td>
<td>64</td>
<td>92</td>
<td>49</td>
</tr>
<tr>
<td>Patency rate:</td>
<td>52.6%</td>
<td>65.2%</td>
<td>52.4%</td>
</tr>
</tbody>
</table>

**Historical (PTA) performance goal:** 52.5% 12-month primary patency

**Contemporary (DCB) performance goal:** 72.3% 12-month primary patency

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Comparative Enrollment Characteristics: Criteria with Statistical Differences

Generally, more advanced/complex disease characteristics in the DANCE trial compared to the DCB trials.
Comparison of Patency Rates between DANCE and the Performance Goals

- **Primary analysis:**
  - DANCE-ATX and -PTA 12-month patency rates were each superior to historical performance goal of 52.5% (P<0.001 for both groups)

- **Secondary analysis:**
  - DANCE-ATX and -PTA 12-month patency rates were each non-inferior to the contemporary performance goal of 72.3% (P<0.001 for ATX and P<0.004 for PTA)

- **Sensitivity analysis:**
  - Presence or lack of stent did not statistically affect outcomes

![Graph showing 12-month primary patency rates](chart)

- Combined PTA, 52.5%
- Combined DCB, 72.3%
- DANCE-ATX, 74.8%
- DANCE-PTA, 74.3%
- DANCE-ATX (PP), 78.4%
- DANCE-PTA (PP), 75.5%

(Primary Patency (Error Bars: 95% CI by Normal Approximation))

Brodmann, LINC 2018
DANCE Preliminary 2-Year Primary Patency Kaplan-Meier Estimates (per protocol)

DANCE-ATX Primary Patency (PP)

DANCE-PTA Primary Patency (PP)
DANCE Preliminary 2-Year Freedom from CD-TLR
Kaplan Meier Estimates (per protocol)

DANCE-ATX Freedom from CD-TLR (PP)

DANCE-PTA Freedom from CD-TLR (PP)
Conclusions

- The ADD-DEX procedure in DANCE has produced positive results in both primary atherectomy (in a challenging patient population) and primary angioplasty intervention.
- DANCE patency rates are non-inferior to the performance goal derived from results of paclitaxel-coated DCBs in pivotal trials.
- DANCE patency rates are superior to the performance goal derived from historical PTA treatments (the control arms in the DCB studies).
- Long-term patency rates with DANCE continue to hold up, with 25-month patency rates exceeding 70% on average.