The Concept of DVA for NOP CLTI

Current status

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The Problem in CLTI.

Transmission Failure
ie Big Artery Disease (BAD)

From iliac to the big foot arteries (dorsalis pedis and plantar arteries)

Distribution Failure
ie Small Artery Disease (SAD)

Plantar arch and the small arteries rising from it and from the big foot arteries (tarsal, metatarsal, digital, calcaneal branches)

How common is SAD disease

Angiographic evaluation of 1915 Limbs (90% with CLI)

Any plantar/DP + SAD at high risk for developing CLI

> 50% 2-3 BTA vessel disease

25% arch disease

SAD = Plantar arch and the small arteries rising from it

The No Option Patient (NOP-CLTI)

• Implies No Option for further revascularization
• Options:
  – Palliative amputation
  – Opioids
  – Stem cell therapy
  – Spinal Cord Stimulation
  – Novel methods of Revascularization

Up to 20% of CLTI patients become “no option” ¹

Novel Revasc Options for NOP-CLTI

Venous Arterialization

Surgical Arterialization

Hybrid Foot Vein Arterialization (HFVA)

Endovascular (Percutaneous) Arterialization

Superficial Venous Arterialization

Deep Venous Arterialization

LimFlow: Purpose Built pDVA Therapy
SUPERFICIAL VEIN ARTERIALIZATION (HYBRID)
Superficial venous arterialization (GSV)

Courtesy Schreve
Superficial venous arterialization (GSV)

Courtesy Schreve
1° toe vein

GSV

MMV

Courtesy Ferraresi
DEEP VEIN ARTERIALIZATION
Deep Venous Bypass

Artery

Vein

Surgical VA

Professor Pramook, Vascular Surgeon, Thailand
Failed Intervention
+
No distal target for bypass
Distal anastomosis is difficult as vein is small and prone to twisting.

Valves not easily addressed.
Surgical DVA
PERCUTANEOUS DEEP VEIN ARTERIALIZATION
LimFlow pDVA Procedure Overview

1. Venous Catheter
2. Arterial Catheter
3. Crossing is done.
4. Tapered Covered Crossing Stent
5. Limflow Self-Expanding Covered Extension Stents
6. Valvulotome renders valves incompetent.
7. Forward flow is achieved.
LimFlow System Purpose-Built for pDVA

- **Straight Stent Grafts**
- **Conical Stent Graft**
- **Ultrasound AV Positioning Kit**
- **Push Valvulotome**
## LimFlow Clinical Program

<table>
<thead>
<tr>
<th></th>
<th>Pilot</th>
<th>PROMISE I (US Feasibility)</th>
<th>PROMISE International</th>
<th>PROMISE II (U.S. Pivotal)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong># Patients</strong></td>
<td>7</td>
<td>32</td>
<td>30+</td>
<td>60 – 120</td>
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<tr>
<td><strong># Centers</strong></td>
<td>1</td>
<td>7</td>
<td>12</td>
<td>Up to 20</td>
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<tr>
<td><strong>Protocol</strong></td>
<td>Single-center, prospective, open label</td>
<td>Multi-center, prospective, single-arm</td>
<td>Multi-center, prospective, single-arm</td>
<td>Multi-center, prospective, efficacy and safety study</td>
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<tr>
<td><strong>Countries</strong></td>
<td>Singapore</td>
<td>U.S.</td>
<td>Europe and Singapore</td>
<td>U.S. and Japan</td>
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</tbody>
</table>

PROMISE 1
PROMISE I Study Design

Key Endpoints

Primary safety endpoint
- Amputation Free Survival (AFS) at 30d

Secondary endpoints
- AFS at 6M
- Procedure & Technical Success
- Wound Healing
- Patency

Key Inclusion/Exclusion Criteria

Inclusion:
- Rutherford 5/6
- No-Option CLTI
- Approval by independent review committee

Exclusion:
- Life expectancy <12 months
- Dialysis
- Severe heart failure

Follow-Up Schedule

<table>
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<tr>
<th></th>
<th>BL</th>
<th>1M</th>
<th>3M</th>
<th>6M</th>
<th>9M</th>
<th>1Y</th>
<th>2Y</th>
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<tbody>
<tr>
<td>Wound Assessment</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
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<tr>
<td>TcPO2</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
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<td>Doppler</td>
<td>✓</td>
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<td>✓</td>
<td>✓</td>
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</table>
### Patient and Procedural Characteristics

#### Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
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</thead>
<tbody>
<tr>
<td>Age (Avg, years)</td>
<td>71 (42-94)</td>
</tr>
<tr>
<td>Gender (% Male)</td>
<td>66%</td>
</tr>
</tbody>
</table>

#### Comorbidities

<table>
<thead>
<tr>
<th>Condition</th>
<th>Percentage</th>
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</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>69%</td>
</tr>
<tr>
<td>Type I</td>
<td>13%</td>
</tr>
<tr>
<td>Type II</td>
<td>56%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>88%</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>34%</td>
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</tbody>
</table>

#### Target Vessels

- Anterior Tibial: 3%
- Posterior Tibial: 84%
- Peroneal: 13%

#### Procedural Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
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</thead>
<tbody>
<tr>
<td>Success Rate</td>
<td>97%</td>
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</tbody>
</table>
Primary Endpoint: Amputation Free Survival

6M AFS = 74%

Days Post LimFlow Index Procedure

| # at risk | 32 | 28 | 22 | 22 | 18 | 17 | 13 | 10 | 9 | 8 |

Prob. of AFS
Primary Endpoint: Amputation Free Survival

Amputation Free Survival

6M AFS = 74%

Data on File, LimFlow
At 6 months, an additional 38% of patients were adjudicated as healing, though not 100% healed. Note: All enrolled patients presented with nonhealing ulcers on the target foot.
ALPS MULTICENTER REGISTRY
The retrospective analysis was conducted to:
- Evaluate results of no-option CLI patients treated with LimFlow

Method
- Sites in Alkmaar, Leipzig, Paris and Singapore
- Analysis of consecutive patients treated with LimFlow
- From 11 July 2014 to 11 June 2018
# The ALPS Multi Centre Study Design

## Key Endpoints

**Primary Endpoint**
- Amputation Free Survival (AFS) at 6 Months

**Secondary Endpoints**
- Wound Healing
- Limb Salvage
- Survival
- At 6, 12, 24 Months

## Key Inclusion/Exclusion Criteria

**Inclusion:**
- Rutherford 5/6
- No-Option CLTI

**Exclusion:**
- Acute limb ischemia
- Extensive tissue loss or infection which precluded limb salvage
- Known deep vein thrombosis
ALPS Patient Characteristics (n=32)

Baseline Characteristics (n = 32)
- Median Age (years): 67 ± 14
- Gender (Men): 63%
- SVS WIfI (High Risk): 78%

Comorbidities
- Diabetes (Type II): 66%
- Renal Insufficiency: 53%
- Dialysis Dependent: 16%
- Immunosuppression: 25%

Rutherford Classification
- Class 5: 69%
- Class 6: 31%

SVS WIfI Classification
- Wound: 100%
- Ischemia: 38%
- Infection: 38%
- Severity: 25%
ALPS Procedural Characteristics

**Target Vessels**

- Anterior Tibial: 4%
- Posterior Tibial: 10%
- Popliteal: 86%

**Procedural Characteristics**

| Success Rate | 97% |
ALPS Amputation Free Survival (n=31)

AFS, Survival, Freedom From Amputation

- 6 Months: AFS = 84%
- 12 Months: AFS = 71%
- 24 Months: AFS = 67%
ALPS AFS, Survival, Freedom From Amputation (n=31)

AFS, Survival, Freedom From Amputation

Months Post LimFlow Procedure

- **6 Months**
  - AFS = 84%
  - Survival = 94%
  - FFA = 87%

- **12 Months**
  - AFS = 71%
  - Survival = 84%
  - FFA = 80%

- **24 Months**
  - AFS = 67%
  - Survival = 80%
  - FFA = 80%
ALPS Complete Wound Healing

Complete Wound Healing

- **6 Month Complete Wound Healing = 37%**
- **12 Month Complete Wound Healing = 69%**
- **24 Month Complete Wound Healing = 73%**

Days Post LimFlow Index Procedure

- **Survival**
- **Freedom From Amputation**
- **Complete Wound Healing**
ALPS Average TcPO$_2$ Results

Statistically Significant Rise after 45 Days
ALPS CASE EG
82 Female
Severe Rest Pain & non healing wound x 6 months
Diabetic Hypertensive

Distal Foot Angioplasty Failed
Severe Calcium

Arterial Flow to Venous Arch achieved

LimFlow Case 15
Non healing for 6 months

LimFlow Case 15

Fully Healed 3 months
Conclusions

• This is the largest study of No-Option CLTI patients treated with LimFlow showing mid and long-term results.
• In this complex group of patients, LimFlow has high technical success and Amputation Free Survival rates up to 24 months.
• Long-term findings from this study are very promising.
• In selected patients with No-Option CLTI, pDVA could be a recommended treatment to prevent amputation and heal wounds.
The Concept of DVA for NOP CLTI

Current status

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