New Limus Delivering Devices for Above and Below Knee Occlusive Disease

When to Expect Results?

Professor Andrew Holden

LINC 2021 1.27.21
Disclosure

Professor Andrew Holden

I have the following potential conflicts of interest to report:

- [x] Consulting – Advisory Board Member for Medtronic, Gore, Boston Scientific, Philips
- [ ] Employment in industry
- [ ] Stockholder of a healthcare company
- [ ] Owner of a healthcare company
- [x] Other(s) – Clinical Investigator for Abbott, e-Femoral, Biotronik, Surmodics

- [ ] I do not have any potential conflict of interest
Background

• Paclitaxel-eluting devices have shown a sustained patency benefit and reduced re-intervention rates when compared to standard of care angioplasty/bare-metal stents in femoro-popliteal disease

• A meta-analysis in 2018 raised safety concerns regarding Paclitaxel-eluting devices and stimulated interest in alternative anti-restenotic strategies

• While recent and accumulating evidence suggests the original safety concerns were the result of factors such as trial design, inadequate patient numbers, incomplete follow-up and forms of unintended trial bias, it is still important to evaluate alternative anti-restenotic strategies
Background – Mechanisms of Action

Paclitaxel (Cytotoxic) 
Interferes with cell division

Cytotoxic drugs halt cell division, inducing apoptosis

Rapid transfer (via excipient) allows acute delivery, especially beneficial if no artificial reservoir is present

Limus (Cytostatic) 
Interferes with cell growth

Cytostatic drugs hold a cell in G₀ phase, arresting growth

Prolonged elution (via polymeric ‘reservoir’) allows sustained delivery, especially beneficial when stent is present

Challenge for Limus – delivering devices in lower limb arterial disease is to achieve adequate tissue concentrations over a sustained period without a permanent scaffold.
BTK Use of Coronary Limus Eluting Stents

• Clear patency advantage over angioplasty and bare metal stents
• Clinical advantages including reduced reintervention and amputation
• Largely limited to short proximal tibial lesions
New Limus Technologies for Above Knee Disease

- MedAlliance Selution DCB
- Concept Medical Magic Touch DCB
- Biotronik BRight DCB
- Illumina NiTiDES SES
- Efemoral Vascular Scaffold System
Sirolimus-Eluting Balloon with Sustained Release

Proprietary MicroReservoir Technology
- Creation of MicroReservoirs combining sirolimus & biodegradable polymer
- Sirolimus - a proven safe & effective cytostatic drug
- Offering a wider therapeutic range

MicroReservoirs: Miniature Drug-Delivery Systems
- Optimal size MicroReservoirs to achieve pharmaco-kinetic release profile comparable to best in class DES
- Consistent and predictable drug release
- Sustained therapeutic effect for up to 90 days.

Cell Adherent Technology (CAT™)
Proprietary amphipathic lipid technology which binds MicroReservoirs to the balloon surface
- Contains and protects micro-reservoirs during insertion and inflation
- Enhances drug retention and bioavailability, allowing for a lower drug dose concentration on the balloon surface (1 μg/mm²).
- Optimizes transfer of MicroReservoirs to the tissue and maximizes the cellular uptake of sirolimus.

1. Drug concentration evident in MicroReservoirs and tissue - Data on file at M.A. Med Alliance SA
<table>
<thead>
<tr>
<th>Trial Code</th>
<th>No.</th>
<th>Type</th>
<th>Endpoint</th>
<th>Region</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SUCCESS PTA</strong></td>
<td>722</td>
<td>Post Market Trial</td>
<td>CD TLR @ 12 M</td>
<td>Europe/Asia/LAM</td>
<td>Enrollment about to start</td>
</tr>
<tr>
<td><strong>SELUTION FIM</strong></td>
<td>50</td>
<td>Single Arm</td>
<td>LLL @ 6M</td>
<td>Germany</td>
<td>2 Y Final Data Available</td>
</tr>
<tr>
<td><strong>SELUTION SFA IDE</strong></td>
<td>286</td>
<td>Review with FDA</td>
<td></td>
<td>US &amp; Europe</td>
<td>Enrollment to start in 2021</td>
</tr>
<tr>
<td><strong>PRESTIGE</strong></td>
<td>25</td>
<td>Single Arm</td>
<td>Freedom from TLR @ 6M</td>
<td>Asia</td>
<td>12 M FU – LBT @ LINC 2021</td>
</tr>
<tr>
<td><strong>PRESTINE</strong></td>
<td>75</td>
<td>Single Arm</td>
<td>Freedom from TLR @ 6M</td>
<td>Asia</td>
<td>Enrollment Completed</td>
</tr>
<tr>
<td><strong>SELUTION BTK IDE</strong></td>
<td>330</td>
<td>Review with FDA</td>
<td></td>
<td>US &amp; Europe</td>
<td>Enrollment to start in 2021</td>
</tr>
<tr>
<td><strong>STEP (Foot Trial)</strong></td>
<td>20</td>
<td>Single Arm</td>
<td>Freedom from Occlusion @ 30 D</td>
<td>Austria</td>
<td>Enrollment about to start</td>
</tr>
<tr>
<td><strong>SAVE</strong></td>
<td>84</td>
<td>RCT vs POBA</td>
<td>Primary Patency @ 6 M</td>
<td>Europe</td>
<td>Recruiting</td>
</tr>
<tr>
<td><strong>ISABELLA</strong></td>
<td>40</td>
<td>Single Arm</td>
<td>Primary Patency @ 6 M</td>
<td>Asia</td>
<td>Enrollment Completed</td>
</tr>
<tr>
<td><strong>SELUTION AVF IDE</strong></td>
<td>268</td>
<td>Review with FDA</td>
<td></td>
<td>US &amp; Europe</td>
<td>Enrollment to start in 2021</td>
</tr>
<tr>
<td><strong>SELUTION ED</strong></td>
<td>66</td>
<td>RCT vs Sham</td>
<td>IIEF-6 score @ 6w</td>
<td>Europe</td>
<td>Enrollment to start in 2021</td>
</tr>
</tbody>
</table>
## Clinical Trial Programme: ~2000 Patients

<table>
<thead>
<tr>
<th>Trial Name</th>
<th>No.</th>
<th>Design</th>
<th>End Points</th>
<th>Location</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SELUTION FIM</strong></td>
<td>50</td>
<td>Single Arm</td>
<td>LLL @ 6M</td>
<td>Germany</td>
<td>2 Y Final Data Available</td>
</tr>
<tr>
<td><strong>SUCCESS PTA (SFA &amp; CLI)</strong></td>
<td>722</td>
<td>Post Market Trial</td>
<td>CD TLR @ 12 M</td>
<td>Europe/Asia/LAM</td>
<td>Enrollment about to start</td>
</tr>
<tr>
<td><strong>SELUTION SFA IDE</strong></td>
<td>286</td>
<td>Review with FDA</td>
<td></td>
<td>US &amp; Europe</td>
<td>Enrollment to start in 2021</td>
</tr>
<tr>
<td><strong>SAVE</strong></td>
<td>84</td>
<td>RCT</td>
<td>Recruiting</td>
<td>Europe</td>
<td>Recruiting</td>
</tr>
<tr>
<td><strong>ISABELLA</strong></td>
<td>40</td>
<td>Single Arm</td>
<td>Primary Patency @ 6 M</td>
<td>Asia</td>
<td>Enrollment Completed</td>
</tr>
<tr>
<td><strong>SELUTION AVF IDE</strong></td>
<td>268</td>
<td>Review with FDA</td>
<td></td>
<td>US &amp; Europe</td>
<td>Enrollment to start in 2021</td>
</tr>
<tr>
<td><strong>ED</strong></td>
<td>66</td>
<td>RCT vs Sham</td>
<td>IIEF-6 score @ 6w</td>
<td>Europe</td>
<td>Enrollment to start in 2021</td>
</tr>
</tbody>
</table>

**SELUTION FIM** – PI T Zeller  
**SUCCESS PTA** – PI M Lichtenberg
BRight Novel Sirolimus Derivative Drug Coated Balloon

Description of Design Components

- **Drug**: Novel Sirolimus derivative 2 μg/mm²
- **Base layer**: Human Natural Product
- **Catheter Platform**: Passeo-35

---

**Overview of the delivery system**

<table>
<thead>
<tr>
<th>Specification</th>
<th>Specification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Usable length</td>
<td>130 cm</td>
</tr>
<tr>
<td>Introducer sheath compatibility</td>
<td>6F minimum</td>
</tr>
<tr>
<td>Guide wire compatibility</td>
<td>0.035 inch, over-the-wire design</td>
</tr>
<tr>
<td>Nominal pressure (NP)</td>
<td>7 atm (all sizes)</td>
</tr>
<tr>
<td>Rated burst pressure (RBP)</td>
<td>14 atm (all sizes)</td>
</tr>
</tbody>
</table>

---

**Study Device Matrix**

<table>
<thead>
<tr>
<th>Balloon diam</th>
<th>Balloon Length</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>80 mm</td>
</tr>
<tr>
<td>5 mm</td>
<td>X</td>
</tr>
<tr>
<td>6 mm</td>
<td>X</td>
</tr>
</tbody>
</table>

---

Human Natural Product

Drug-layer

BIOTRONIK Novel Sirolimus derivative

Base-layer

Human Natural Product + Sirolimus Derivative Coated Balloon
## Bright First-In-Human Study

| **Objective** | To assess the safety and clinical performance of the BRight DCB in the treatment of symptomatic PAD due to de novo stenosis of the superficial femoral and proximal popliteal artery |
| **Design** | - Prospective, multi-center, first-in-human single arm study  
  - N= 50 patients |
| **Primary Endpoint** | 6 month Late Lumen Loss (LLL) of the target lesion by QVA (corelab reviewed) |
| **Key Secondary Endpoints** | At 1, 6 and 12 months:  
  - MAE (device or procedure related death within 30 days post index procedure, major index limb amputation, cd TLR)  
  - cd TLR, cd TVR  
  - Primary Patency (DUS PSVR ≤ 2.5 and the absence of cd TLR)  
  - Target limb amputation (minor, major)  
  - All-cause of death |
| **Participating sites** | - Patrice Mwipatayi (CCI), Royal Pert Hospital (Perth, AUS)  
  - Andrew Holden, Auckland Regional Public Health (Auckland, NZ)  
  - Carsten Ritter, Fiona Stanley Hospital (Perth, AUS)  
  - Vikram Puttaswamy, Royal North Shore Hospital (Sydney, AUS) |
| **Study Status** | FPI anticipated in January 2021 |
Efemoral™ Vascular Scaffold System
Bioresorbable Sirolimus-Eluting Scaffolds

- Efemoral bioresorbable scaffolds with FlexStep™ technology optimized for high radial strength and flexibility to accommodate skeletal motion through inter-scaffold spaces
- Proprietary sirolimus coating to prevent restenosis and maintain patency
- Scaffold strut thickness similar to peripheral metal stents
- Standard balloon-expandable delivery system
One hundred (n=100) patients with symptomatic peripheral arterial disease (Rutherford-Becker Category 2-4) due to a single de novo stenotic or occlusive atherosclerotic lesion in the femoropopliteal artery

• Prospective, single arm, multi-center trial
• Reference Vessel Diameter (RVD) ≥ 5.5 and ≤ 6.5 mm; lesion length ≤90 mm
• Single target lesion treated with a single Efemoral EVSS
• Clinical endpoints include RB category and clinically-driven target lesion revascularization
• Quantitative imaging endpoints include duplex-derived peak-systolic velocity ratio and angiographically-derived in-scaffold/in-segment late lumen loss and % diameter stenosis
EFEMORAL I Clinical Study

Residual stenosis and dissection following balloon inflation

Widely patent after EVSS deployment

Pre-procedure  Post-balloon angioplasty  Post-EVSS deployment
New Limus Technologies for Below Knee Disease

- MedAlliance Selution DCB
- Concept Medical Magic Touch DCB
- Surmodics Sundance DCB
- Abbott Esprit BTK Everolimus Eluting Resorbable Scaffold
Surmodics SUNDANCE DCB

**DEVICE SPECIFICATIONS**

- Length: 150 cm OTW
- Balloon Diameter: 2.0 – 4.0 mm
- Balloon Length: 20 – 220 mm
- Rated Burst Pressure: 16 ATM
- Minimum Introducer: 5 Fr
- Sirolimus Drug Coating
Surmodics SWING First-in-Human Trial

• A Prospective, Multi-Center, Single-Arm, Feasibility Study to Access the Safety and Performance with the SUNDANCE™ Drug Coated Balloon for the Treatment of De Novo or Restenotic Lesions in Infra-Popliteal Arteries - SWING Study

• 35 Subjects

• 36-Month Follow-up

• 8 Centers in Australia, Austria, Germany, Latvia, New Zealand

• Expected enrollment completion – Quarter 2 / CY21
Abbott ESPRIT™ Drug-Eluting Resorbable Scaffold

**EVEROLIMUS**
- 100 µg/cm² dose density
- Elution rate matched to restenosis cascade
- Cytostatic; broad therapeutic range

**PDLLA RESORBABLE COATING**
- Uniform drug delivery
- Provides sustained drug elution to maximize long term patency without downstream particulates

**PLLA Resorbable Scaffold**
- 99 µm strut thickness†
- Balloon expandable
- Resists recoil; provides a platform for sustained drug delivery
- Resorbs in a benign, controlled manner (~36 months)

**PORCINE MODEL**
Baseline
1 Month

©2020 Abbott. All rights reserved. LIFE BTK 2020.9.23.ver1.0
EspritÔ BTK Everolimus Eluting Resorbable Scaffold
LIFE-BTK Randomized Multicenter Clinical Trial

PIVOTAL INVESTIGATION OF SAFETY AND EFFICACY FOR BTK TREATMENT

Prospective, randomized multicenter, US and OUS single-blind, trial
225 patients randomized
2:1 Esprit™ BTK vs. PTA

6-MONTH PRIMARY ENDPOINTS

SAFETY ENDPOINT:
MALE+POD

EFFICACY ENDPOINT:
Primary Patency + Limb Salvage

5-YEAR FOLLOW-UP

TRIAL LEADERSHIP
Ramon Varcoe MBBS, MS, FRACS, PhD; Sahil Parikh MD, FACC, FSCAI; Brian DeRubertis MD, FACS

10 patients enrolled to date
Vessel Preparation Devices

• Improve the results of angioplasty with reduced residual stenosis and dissection
• May also improve drug delivery and retention in the vessel wall
• Devices agnostic to specific drugs

Cagent Serranator – PRELUDE BTK

Reflow Medical Spur Stent – DEEPER LIMUS Trial
The Temporary Spur Stent System* (Reflow Medical)

- Following Spur treatment, treat area with commercially available Limus-based coated balloon
- Circumferential tines enable controlled penetration of vessel plaque, calcium, artery wall
  - Enhance drug uptake
  - Minimize recoil
  - Reduce dissections

* For clinical investigational use only
# DEEPER LIMUS Trial

**DEEPER LIMUS**

<table>
<thead>
<tr>
<th>DEEPER LIMUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Goal N= 30; actively enrolling)</td>
</tr>
</tbody>
</table>

| Prospectively, single-center Spur* + LIMUS-coated DCB |
| PI: Prof. M. Brodmann Univ. Graz, Austria |

### Primary Safety Endpoint:
6-month composite of All-Cause Mortality, Major Amputation and Clinically Driven Target Lesion Revascularization (CD-TLR)

### Secondary Endpoints:
1. LLL at 6 months by QVA
2. Primary patency at 6 months by QVA
3. Freedom from MALE and POD at 30 days
4. Freedom from MALE at 6 and 12 months
5. Improvement in Rutherford at 3, 6, 12 months
6. Wound healing/WiFl at 6 and 12 months

- Study start-up: April, 2020
- Single arm: Spur* + commercially available, limus based coated balloon
- Primary endpoint results anticipated: Q1 2022
- Angiographic and ultrasound core lab adjudication
- Independent safety oversight
- Total follow up period out to one year
- 100% device and procedure success to this point

Number of patients treated as of 1.13.21 – 12 patients

* For clinical investigational use only
New Limus Delivering Devices for Above and Below Knee Occlusive Disease

When to Expect Results?

Professor Andrew Holden

LINC 2021 1.27.21