The choice of a unique formulation, coupled with a prolonged polymer-free elution, maximizes DES efficacy

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Disclosures

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• Research grants to institution:
  Boston Scientific, Heartflow
Why -limus drugs are less effective in diabetics

FACT #1:
Direct Resistance of diabetic cells to –limus drugs
Direct resistance of VSMCs to \(-\)limus drugs

Dysregulation of the Mammalian Target of Rapamycin and \(p27^{Kip1}\) Promotes Intimal Hyperplasia in Diabetes Mellitus

**Normal patient**
- Quiescent status: ERK NON ACTIVE, mTOR NON ACTIVE, P27 HIGH CONCENTRATION
- Proliferative status: ERK ACTIVE, mTOR ACTIVE, P27 LOW CONCENTRATION

**Diabetic patient**
- Proliferative status: ERK HYPER ACTIVE, mTOR ACTIVE, P27 VERY LOW CONCENTRATION

10 times higher \("-\)limus\) concentration is needed in the diabetic cell to achieve similar inhibition seen in non-diabetic cell!
Why -limus drugs are less effective in diabetics

FACT #2: Effect of other hormones
Overweight is a risk factor for diabetes and for CVD.

90% of diabetic patients (Type 2) are overweight or obese
(Obesity Society Feb. 2015)
**Leptin: Effects at vascular level**

Leptin is a hormone secreted by adipocytes (cells distributed ubiquitously throughout the body, also perivascularly, particularly in overweight patients) with specific vascular effects.

**Pathological status** (Hyperleptinaemia)

- **RESTENOSIS**
- **PERMANENT INFLAMMATORY STATUS**
- **PLAQUE PROGRESSION**
- **PRO-THROMBOTIC STATUS**

**Angiogenesis**
- endothelial cell proliferation ↑
- VSMC proliferation ↑
- GM-CSF/G-CSF ↑
- proliferation hematopoietic progenitors

**Immune system**
- Activation of monocytes
- T-cell activation

**Atherogenesis**
- Platelet aggregation ↑
- VSMC proliferation ↑
- ROS production ↑
- MCP-1 upregulation
- IL-6, TNF-α ↑

- 9 times higher “olimus” concentration is needed to block leptin-induced hyperplasia.
Why -limus drugs are less effective in diabetics

Reasons for “-limus” drugs lower efficacy in diabetics:

1. Direct Resistance of diabetic cells to –limus drugs

   ➔ 10 times higher “-limus” drug concentration is needed to achieve similar inhibition of non DM cells

2. Contribution of other hormones in limiting “-limus” action on cell proliferation

   ➔ 9 times higher “-limus” drug concentration is needed to stop Leptin-induced hyperplasia

To improve PCI efficacy in diabetic patients we need to increase the «-limus» drug concentration inside the diabetic cells!
Unique technology for very high efficacy in diabetics:

Amphilimus™ formulation
Sirolimus and Fatty Acid are eluted together

Combined effect

Sirolimus

- Immunosuppressant
- Anti-proliferative action
- Anti-microbial
- Inhibitor of inflammatory cell activities
- High potency

Fatty Acid

- Sustained drug elution timing
- Modulated drug bioavailability
- Raised homogeneous drug distribution
- Enhanced drug stability

Proprietary technology

Amphilimus™ Formulation
**The key role of Fatty Acids in diabetes for ATP generation**

**Two pathways for ATP generation:**
1. Glucose pathway (30%)
2. Fatty acid pathway (70%)

- Membrane protein overexpression leads to higher fatty acids bindings/translocation.

Membrane Fatty Acid Transporters as Regulators of Lipid Metabolism: Implications for Metabolic Disease - Glatz J; 2010 Physiol Rev 90: 367–417
Unique technology for very high efficacy in diabetics:

Abluminal Reservoir Technology
Alvimedica utilizes a proprietary polymer-free drug release system constituted by reservoirs on the stent's abluminal surface.

**ARTERIAL WALL**
*Drug elution is controlled and directed exclusively towards the vessel wall*

**BLOOD FLOW**
*No polymer*  
*No drug*
Abluminal Reservoir is the ONLY polymer-free technology able to provide the same elution kinetic obtained by the most effective polymeric DES.

- Peak drug tissue concentration during the first days
- 50% drug elution in approximately 18 days
- 65%-70% drug elution within 30 days
- Complete drug elution within 90 days

The Reservoir shape defines drug release kinetic (Fick law)
Abluminal Reservoirs, contrary to polymers, allow a mix of substances to be simultaneously eluted for a maximized synergetic effect.

**Polymers**

Polymers act as a “filter” (porosity) determining which molecules are very fast released (small ones) and those slowly released (big ones).

**Abluminal Reservoir**

Abluminal Reservoir allows different substances to be simultaneously eluted - the kinetic release is fixed by the reservoir shape.
Can drug distribution be further optimized to maximize DES efficacy?

Cre8 EVO: New Stent Architecture (EvenArt)
New Stent Architecture for maximized efficacy (EvenArt)

An innovative stent architecture has been developed to improve even more the homogeneous drug distribution within the vessel wall, in particular in case of complex coronary anatomies and pathologies like those of diabetic patients.
Shortened pitch with reduced crown width and different link number/ pattern enhance Elution Profile in challenging anatomies/ conditions.
DRUG/EFFICACY matrix

Pharmaceutical Solution

Cre8™

Geometrical Solution

Cre8™ EVO - EvenArt

Reservoirs closer to each others

Amphilimus™ formulation
#2: Cre8™ EVO - New Stent Architecture (EvenArt) and delivery system for better Deliverability/ Conformability

Vessel features in diabetic patients

<table>
<thead>
<tr>
<th>Feature</th>
<th>Description</th>
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<tr>
<td>VESSEL CALIBRE</td>
<td>smaller sized vessels</td>
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<td>VESSEL INVOLVEMENT</td>
<td>higher incidence of multivessel disease</td>
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<tr>
<td>LOCATION OF LESIONS</td>
<td>proximal segments, LM</td>
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<tr>
<td>TYPE OF LESIONS</td>
<td>CTO and bifurcation lesions</td>
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<tr>
<td>COLLATERAL CIRCULATION</td>
<td>impaired circulation</td>
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<tr>
<td>CORONARY ARTERY CALCIFICATION</td>
<td>increased coronary artery calcifications</td>
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Cre8™ EVO new stent architecture, coupled with enhanced delivery system, allows for excellent device **Deliverability** and **Conformability** in any anatomy; even in the most challenging patients/ settings (diabetics)
Cre8™ EVO - Features summary

**DES features**

- Polymer-free DES
- Reservoir Technology
- Amphipilimus Formulation (Sirolimus 0.9 $\mu$g/mm$^2$ + FA)
- EvenArt stent architecture
- Bio Inducer Surface (pure Carbon surface)
- Zero stent shortening upon expansion
- 2 Platinum markers @ stent ends
- Co-Cr thin stent strut: 70/80 µm

**Delivery System features**

- Balanced and hydrophilic coated shaft
- Short balloon tapers
- RBP = 18atm for the entire product catalogue (from 2.25 to 4.5mm)

### NOMINAL LENGTHS [mm]

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Conclusions

• Reasons for lower DES efficacy in diabetics:
   VSMCs of diabetic patients are less responsive to –limus drugs.
   High blood levels of the hormone leptin, which stimulates VSMCs proliferation, are often present in diabetic and overweight patients.

• A prolonged elution of the Amphlimus™ formulation from Abluminal Reservoirs, allows for higher –limus drug concentration to re-establish VSMCs inhibition and prevent in-stent restenosis.

• Cre8™ EVO, with its new stent architecture and delivery system, can:
   Further advance DES efficacy specifically in complex anatomies/patients (diabetics).
   Provide excellent device Deliverability and Conformability
Thank you for your attention!

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