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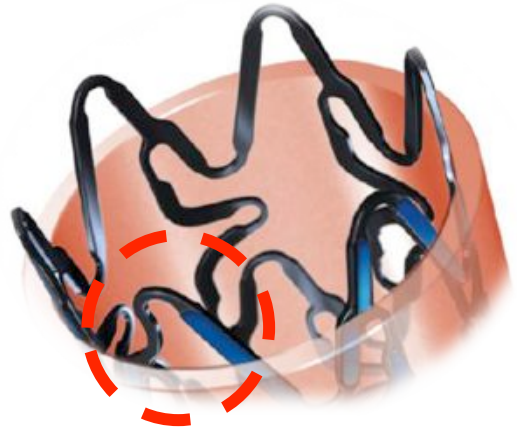
“Cre8 polymer-free DES technology: rationale and pre-clinical data”

Cre8™: polymer-free DES platform

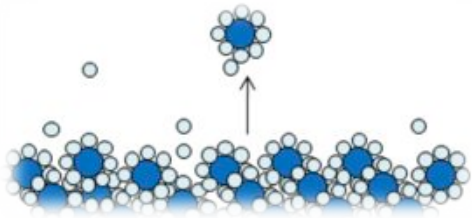
Polymer-free DES eliminates the renowned drawbacks associated to durable polymers or to the breakdown products of absorbable polymers



Cre8™ exclusive features:

Abluminal Reservoir Technology

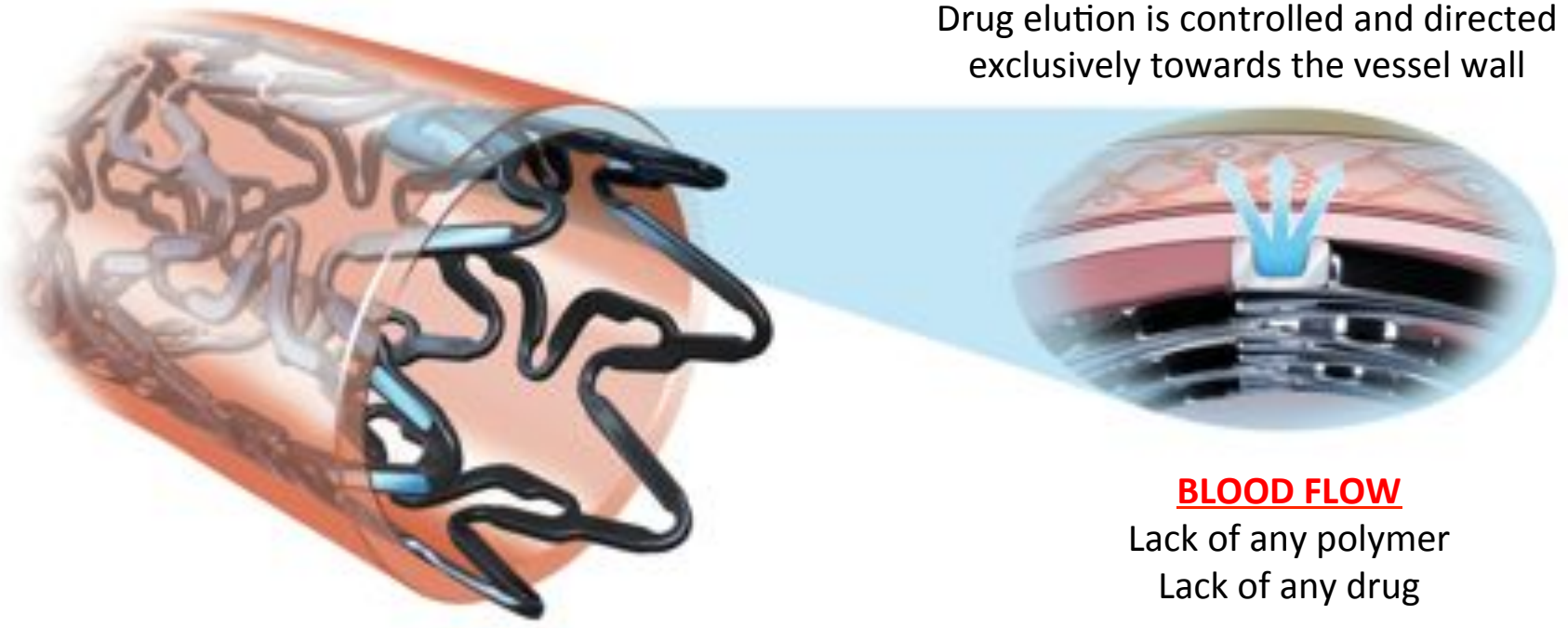
Amphilimus™ Formulation: Sirolimus + organic acid



BIS: Bio Inducer Surface

Abluminal Reservoir Technology

Alvimedica utilizes a proprietary polymer-free drug release system constituted by reservoirs on the stent's outer surface



ARTERIAL WALL

Drug elution is controlled and directed exclusively towards the vessel wall

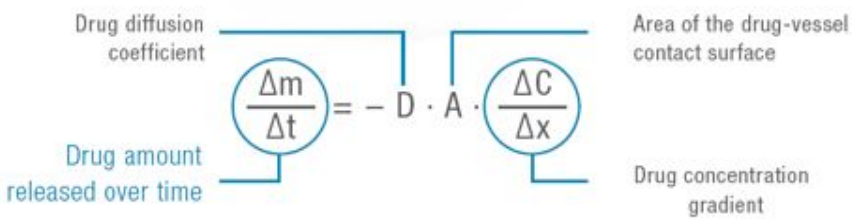
BLOOD FLOW

Lack of any polymer

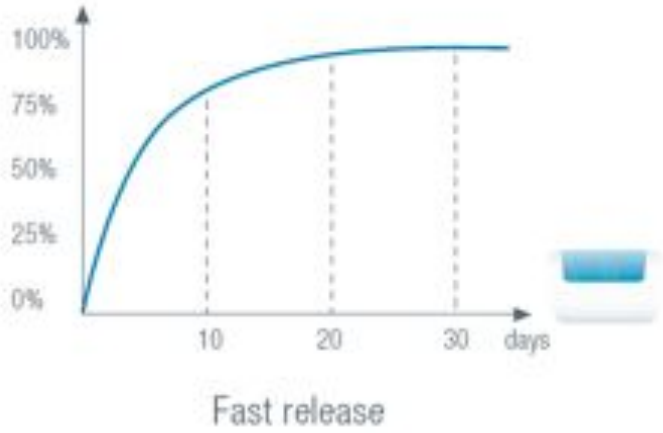
Lack of any drug

Controlled and directed drug elution

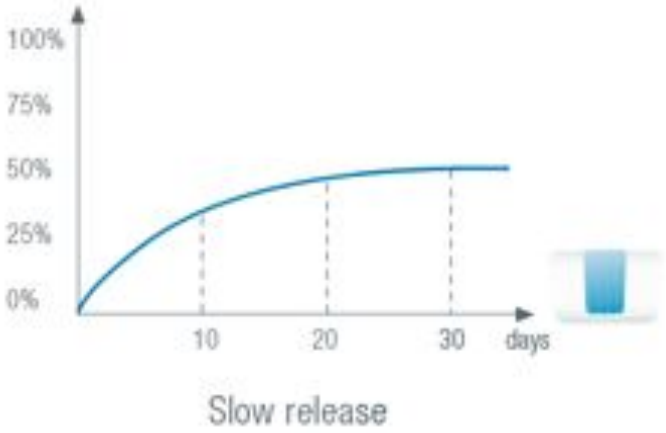
Fick's law



The amount of drug released overtime is proportional to the area of contact and to the drug concentration gradient



Fast release

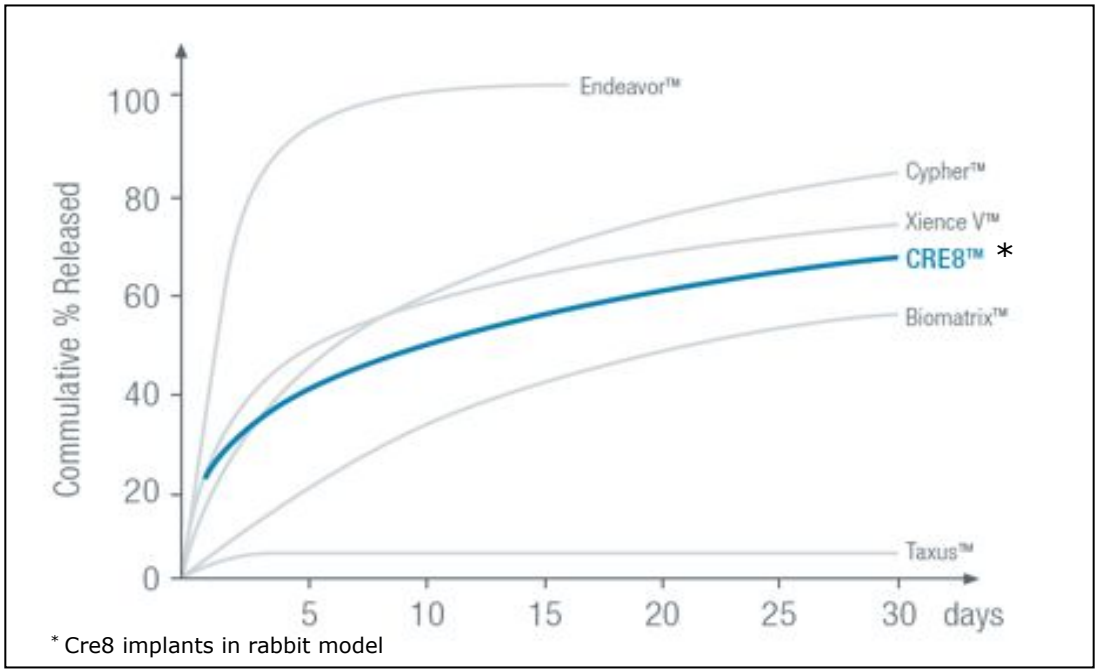


Slow release

The reservoir's design directly impacts on drug amount and release kinetic

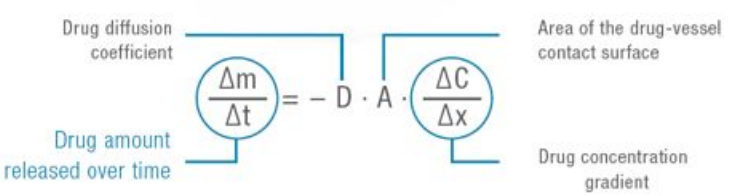
Controlled and directed drug elution

The Cre8™release kinetic has been defined fixing the parameters inside the Fick's law



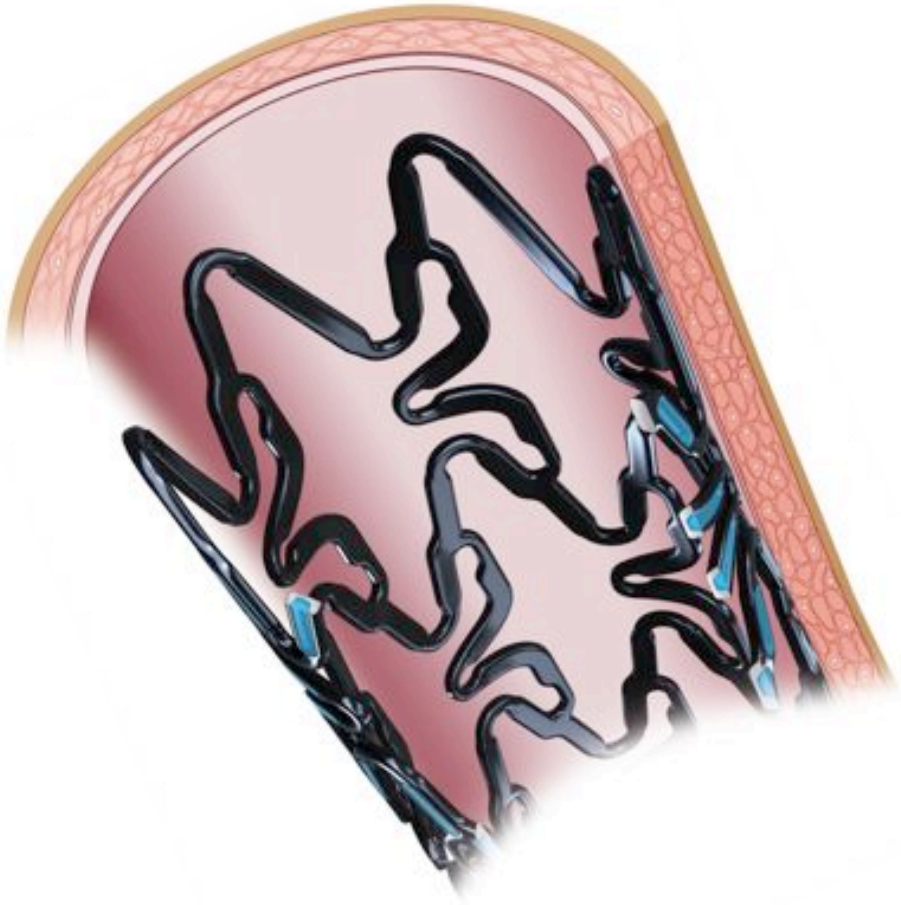
* Cre8 implants in rabbit model

Fick's law



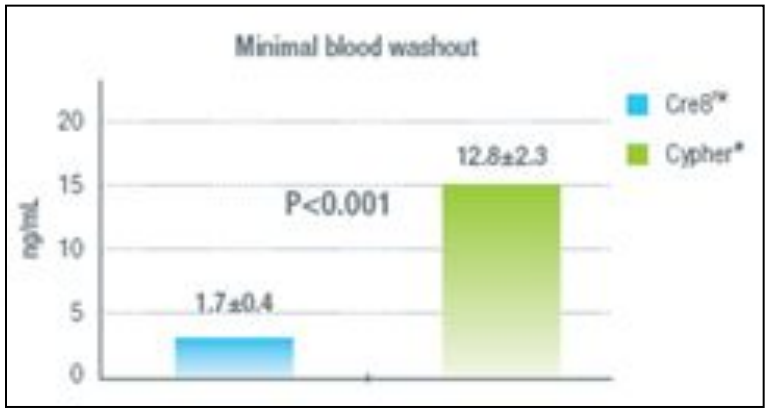
- Peak drug tissue concentration during the first days
- 50% drug elution in approximately 18 days
- 65%-70% drug elution within 30 days
- Complete drug elution within 90 days

Controlled and directed drug elution



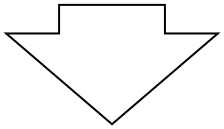
Abluminal release:

- Drug released where needed
- No interaction with endothelization process
- No drug wash-out



Amphilimus™ Formulation

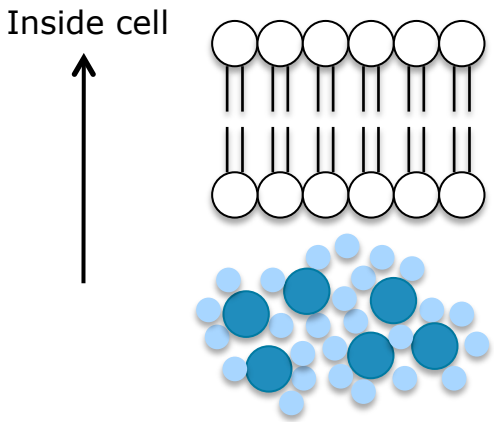
Sirolimus + organic acid



Specific properties/contributions	
Sirolimus (m-Tor inhibitor drug)	Organic acid (Amphiphilic carrier)
• Immunosuppressant • Anti-proliferative action • Anti-microbial • Inhibitor of inflammatory cell activities • High potency	• Sustained drug elution timing • Modulated drug bioavailability • Raised homogeneous drug distribution • Enhanced drug stability

Homogeneous drug distribution

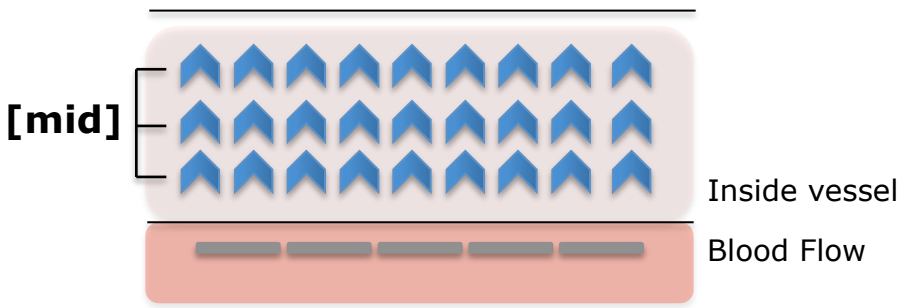
Cell Membrane



Formulated Drug

Sirolimus molecule is 4 times bigger than the organic acid molecule

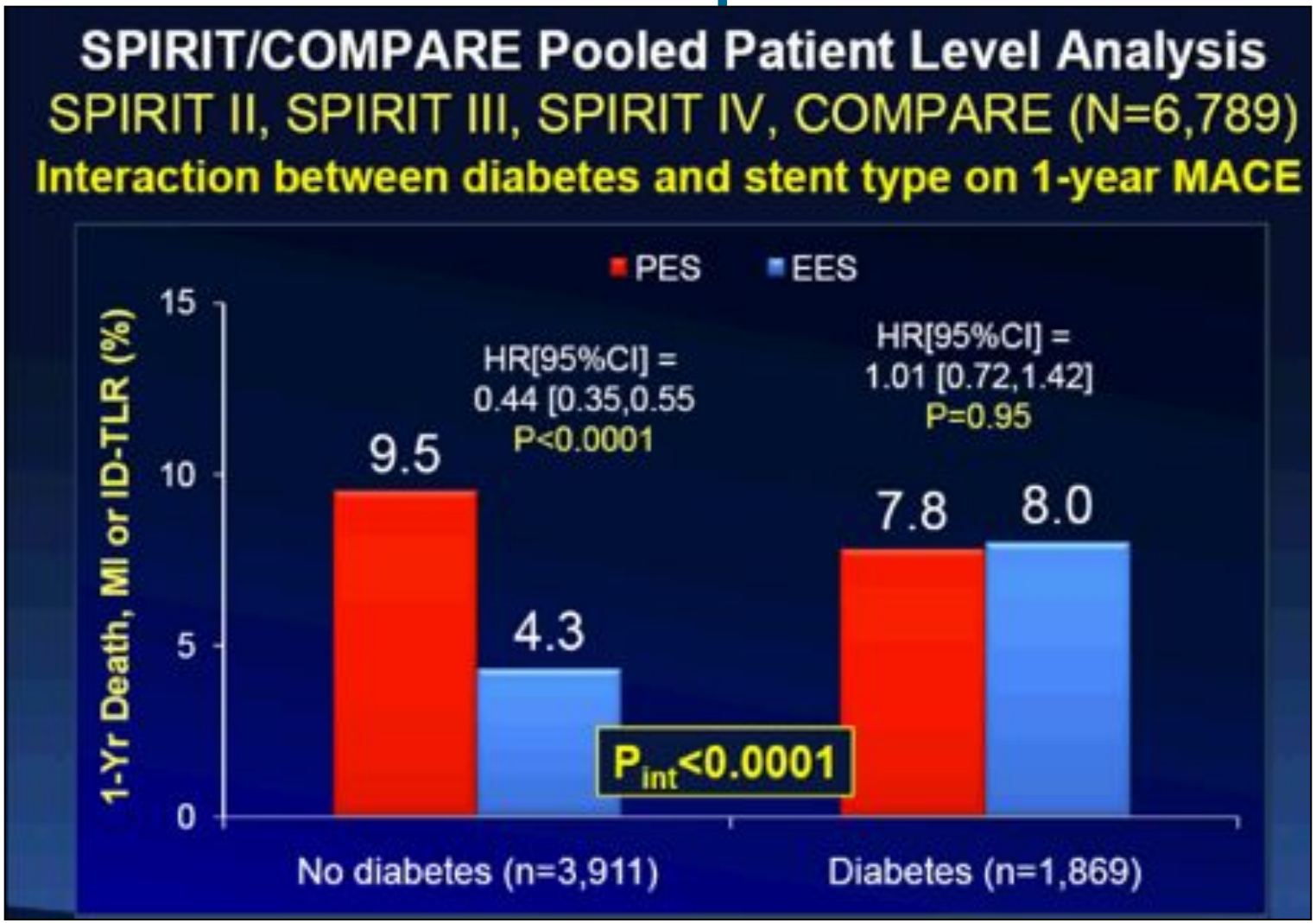
Distribution inside the vessel wall



Formulated drug

Amphiphilic small molecules are characterized by an excellent permeability through cell membrane that allows an homogeneous distribution and a uniform action on the whole tissue.

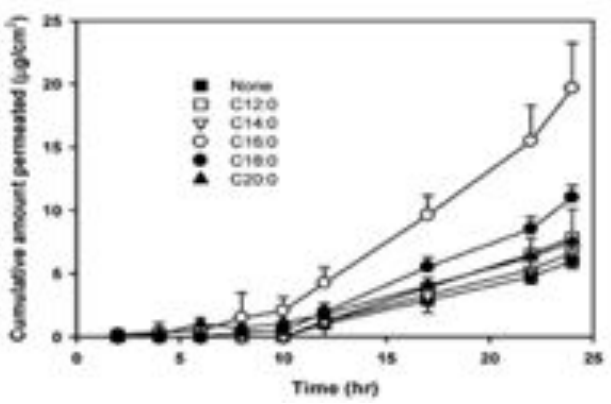
Xience (2nd gen DES) efficacy equals Taxus in diabetic patients



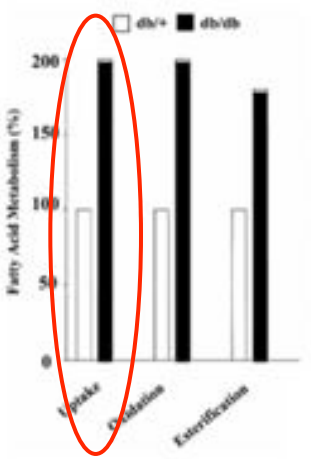
Amphilimus Formulation = Sirolimus + Organic Acid (fatty acid)

Cre8^{TM} employs a permeation enhancer (fatty acid) in its formulation.

1) Fatty acids are used to improve trans-dermal and skin delivery of many different drugs.*



2) Cardiac fatty acid uptake is double in diabetic mice model.**



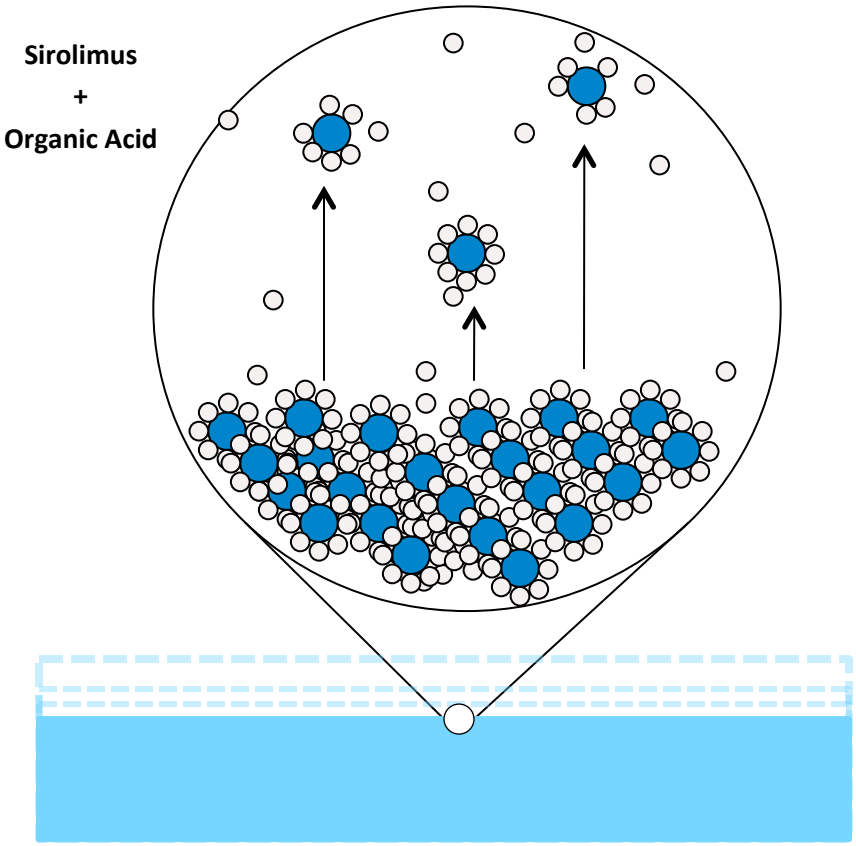
Drug + Permeation enhancer = **Increased drug concentration (diabetes)**

* Drug Delivery, 15:373-379, 2008

** Cardiac fatty acid uptake and metabolism in db/+ and db/db mice. Curr Cardiol Rev. 2008 February; 4(1): 12-21

BIS: Bio Inducer Surface

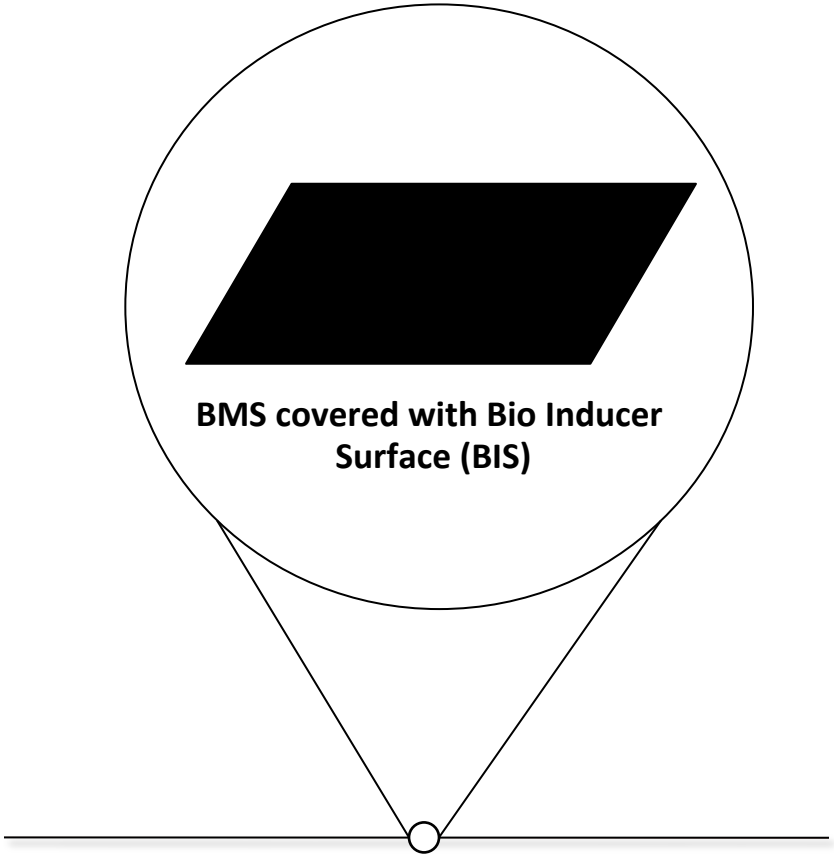
Cre8™ during drug release



CID Amphilimus™ Formulation

- *Sustained drug elution*
- *Modulated drug bioavailability*

Cre8™ after drug release

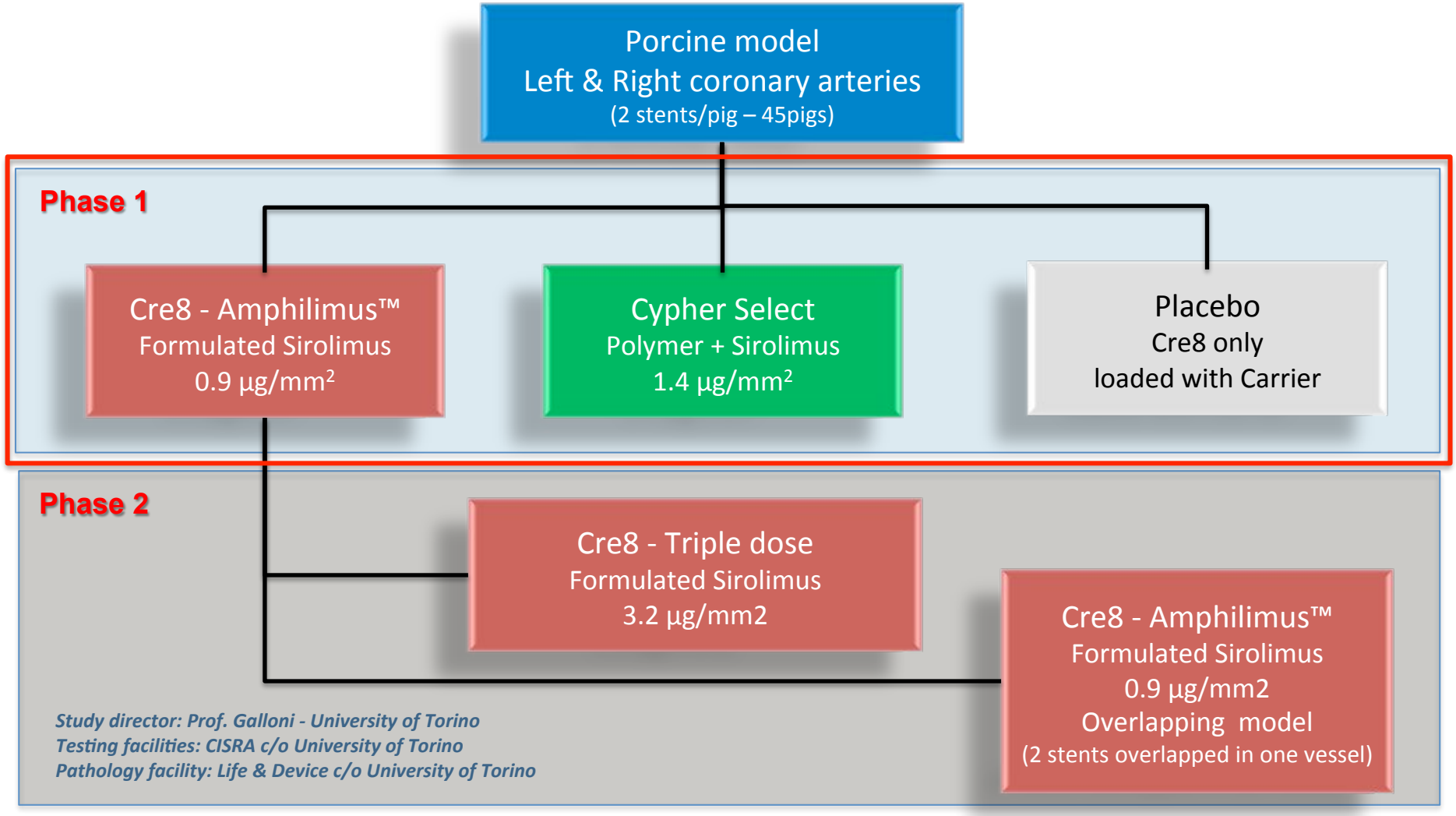


Pure carbon coating

- *Excellent haemo/bio compatible features*
- *No late inflammatory stimuli*

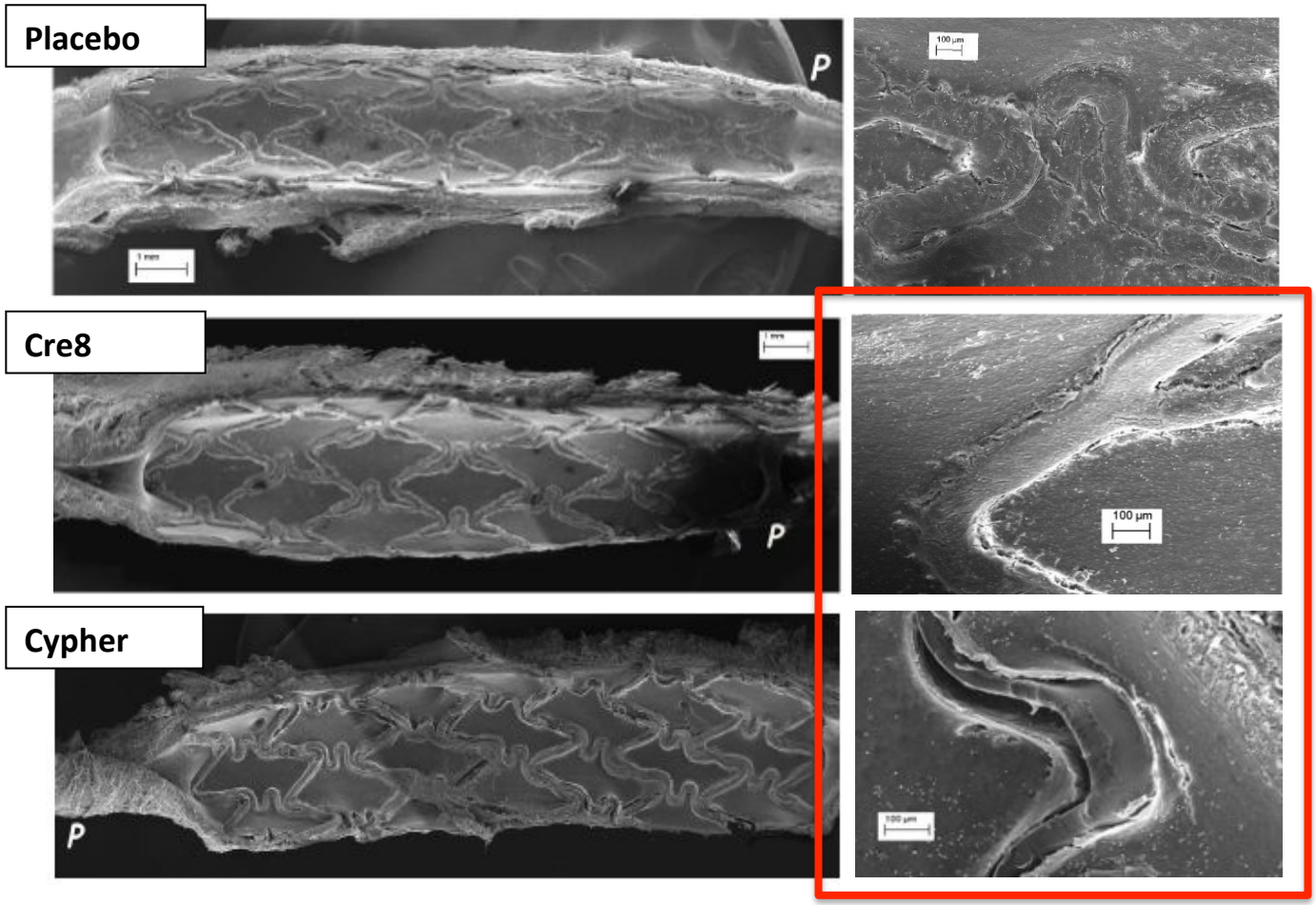
Cre8™ Pre-Clinical studies

Cre8™: Preclinical study in pig model*



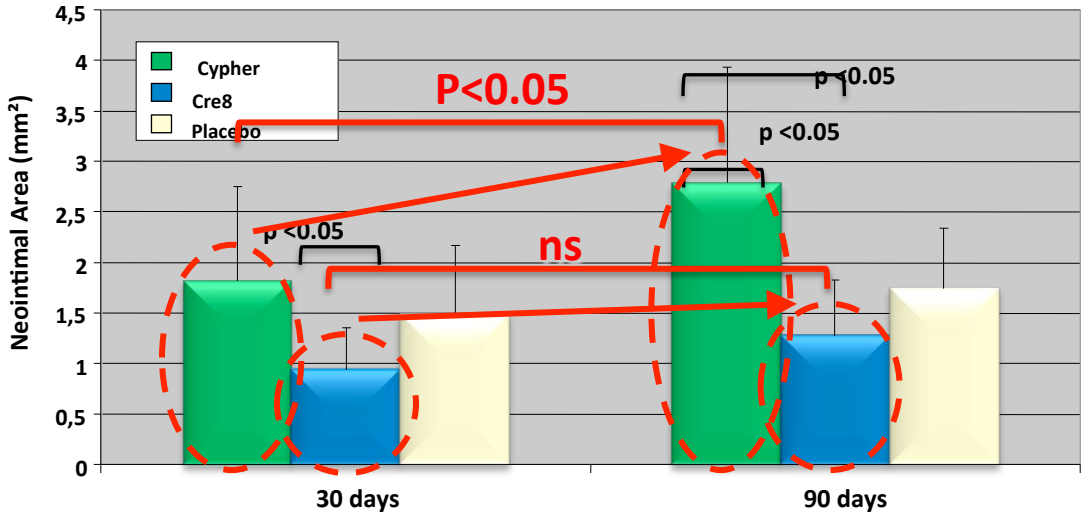
* EuroIntervention, 2012

Endothelization @ 7days*

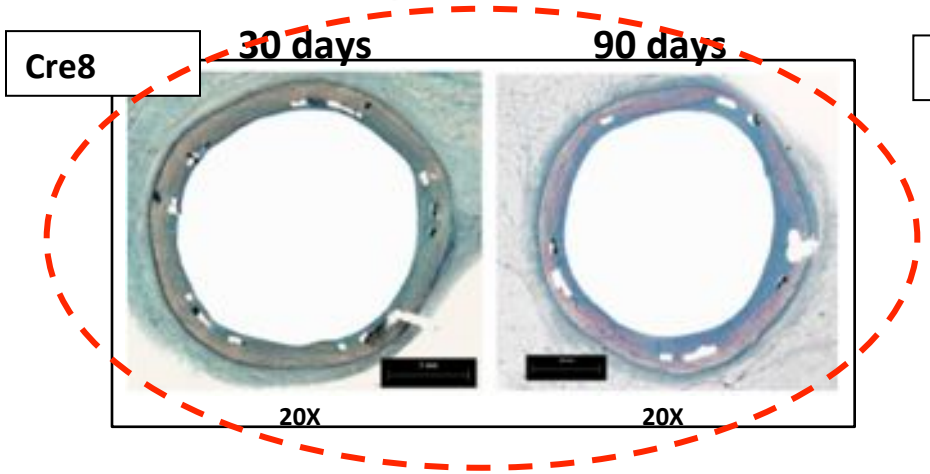


* Published on Eurointervention, November 2011

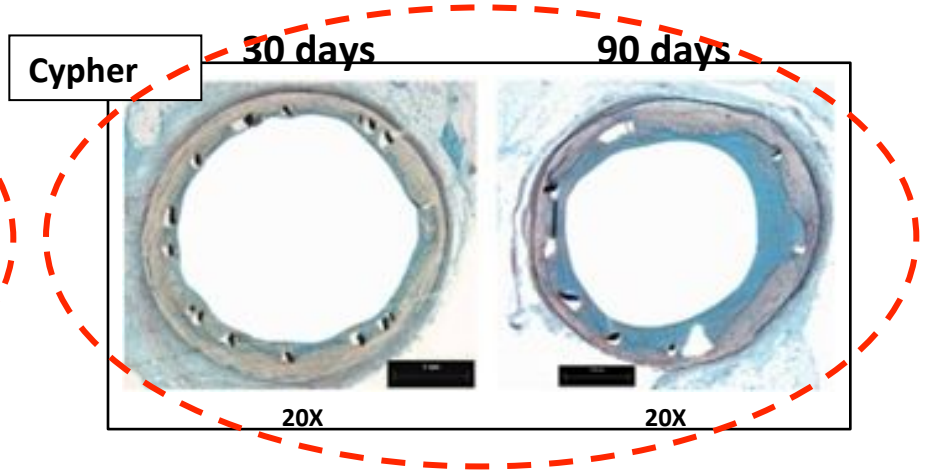
Histomorphometric results*



Stability between 30d & 90d



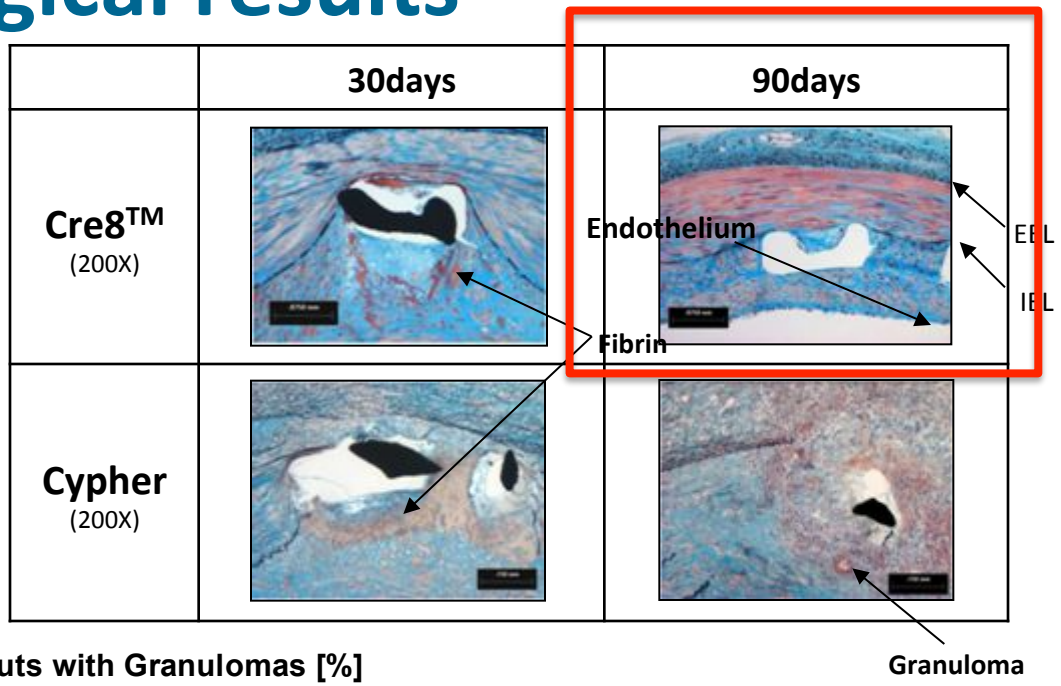
Worsening between 30d & 90d

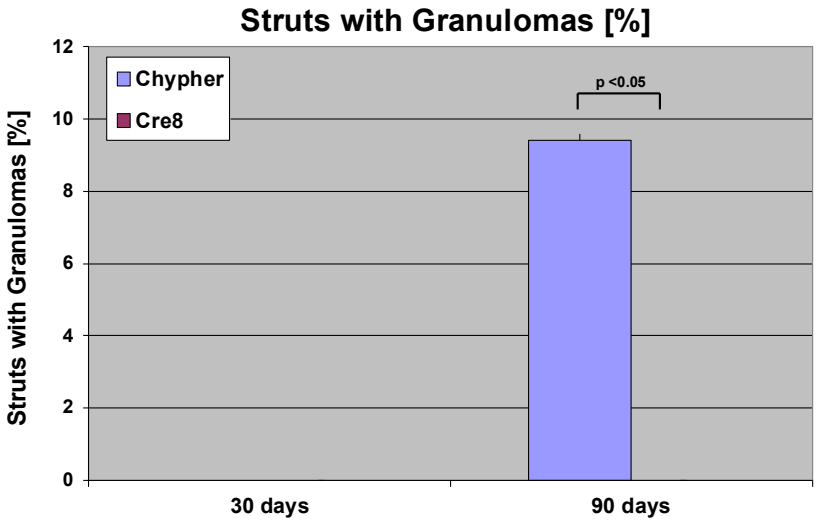


* Published on Eurointervention, November 2011

Histological results*

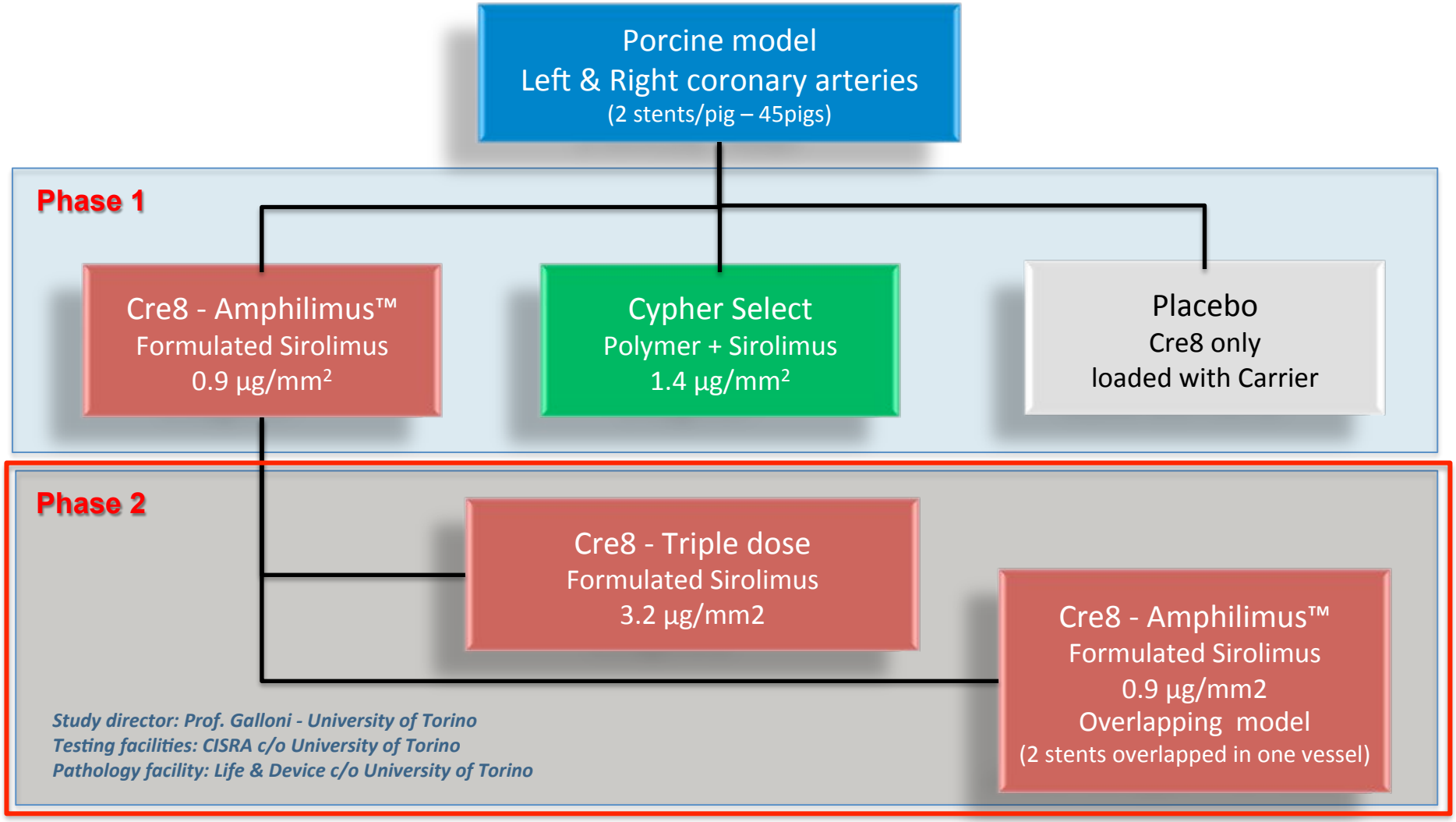
- **Cre8™** ***= Negligible inflammatory response at both follow-up times***
- **Cypher** ***= Presence of granulomas @90days significantly higher than Cre8™ (p<0.05)***





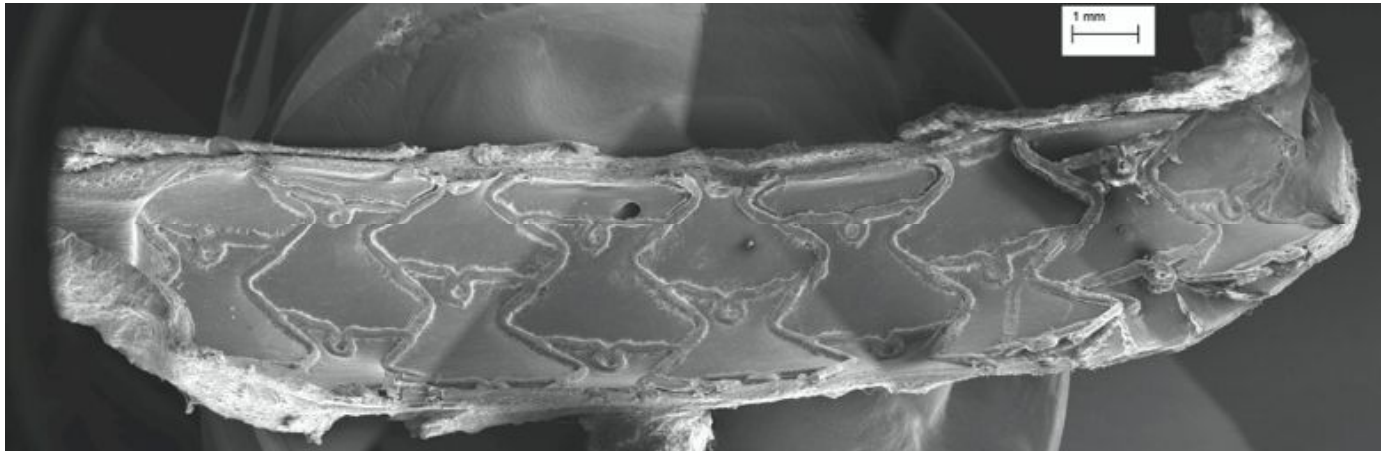
* Published on Eurointervention, November 2011

Cre8™: Preclinical study in pig model*

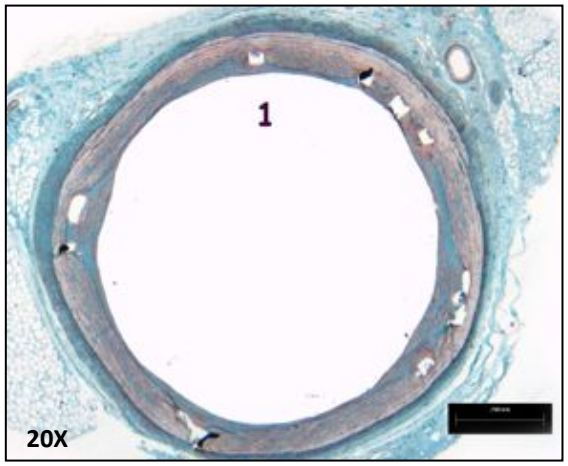


* EuroIntervention, 2012

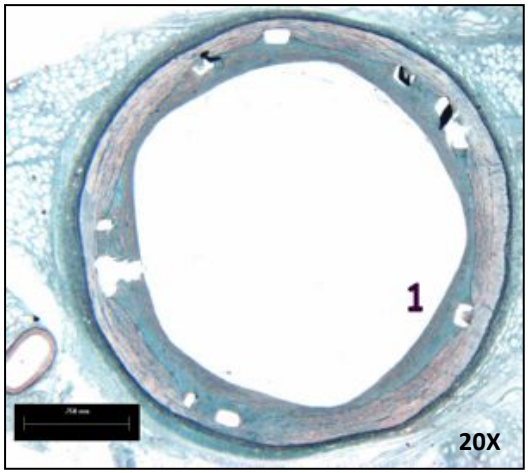
Cre8 – triple Sirolimus dose @ 7, 30 & 90 days



*SEM picture: **7 days**. Whole stent endothelized.*

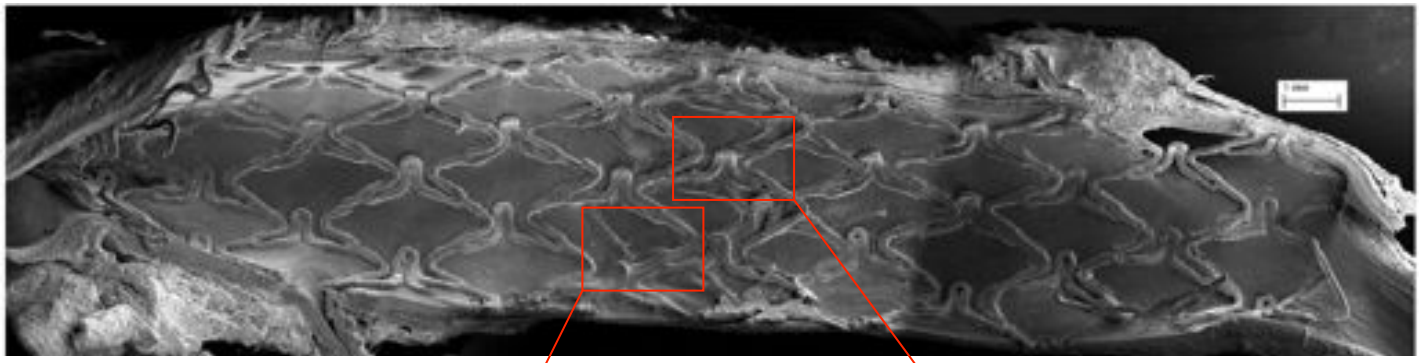


*Histological section at **30 days**.*
Traces of blood clots and fibrin near stent struts.
Thin neointima.

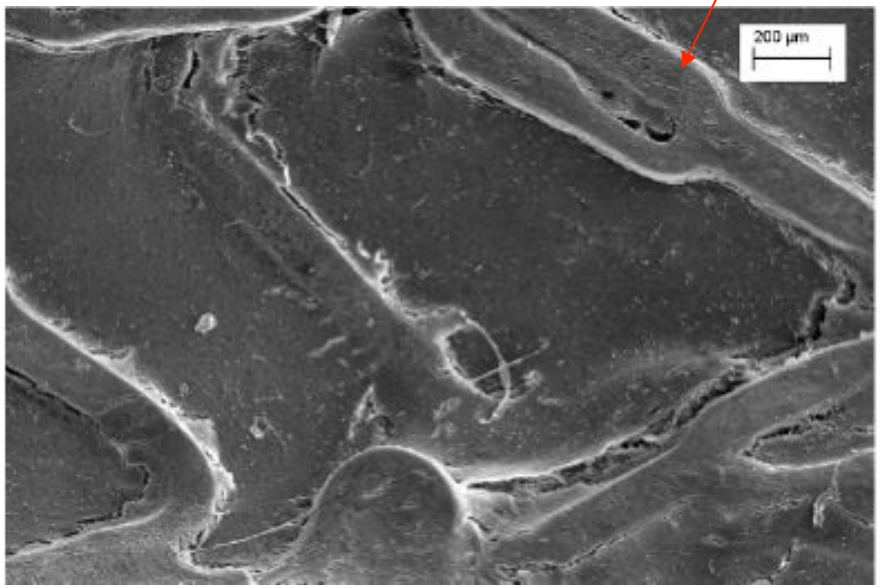


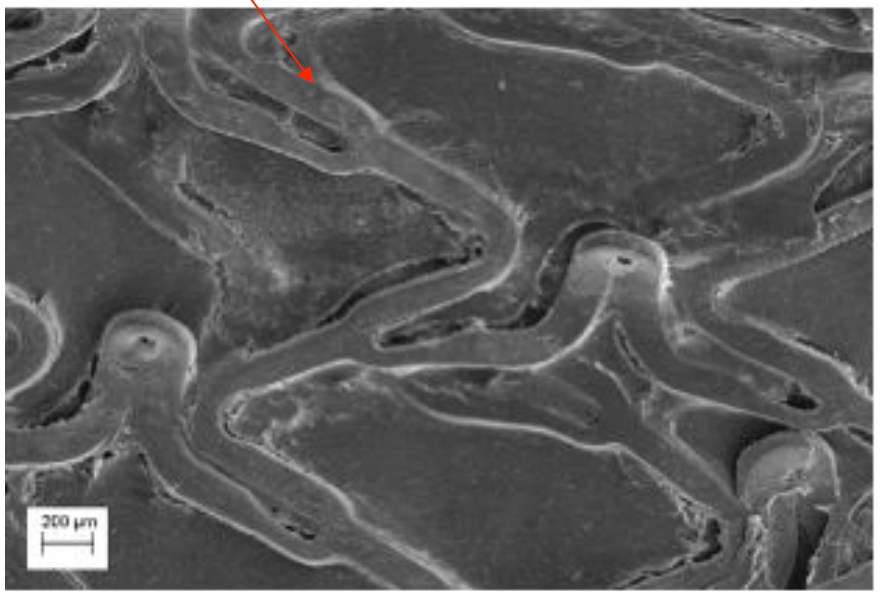
*Histological section at **90 days** .*
Regular and very thin Neointima , no inflammation or blood clots.

Overlapping stent model @ 7 days



SEM: Whole stent appears endothelialized.



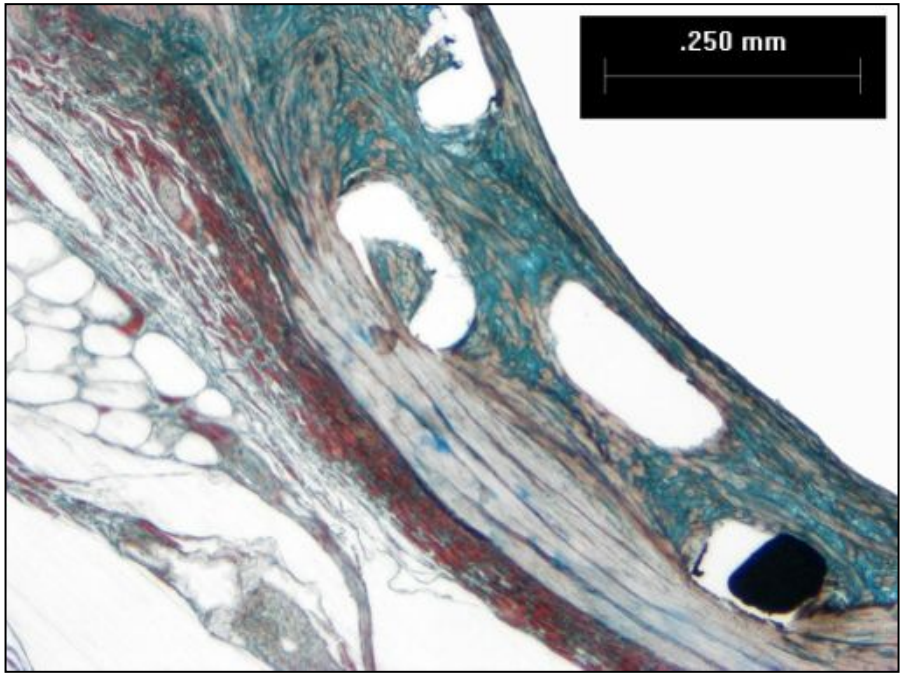


SEM: Magnification of overlapped areas.

Overlapping stent model @ 90 days

*Histological sections at **90 days**.*
Regular and thin neointima , continuous endothelium.
No inflammatory cells or blood clots.

*Histological section at **90 days**.*
Overlapped area magnification.



Conclusions

The new polymer-free **CID DES technology proposes a pioneering solution** – **Cre8™** - which maximizes efficacy and safety from both platform and pharmaceutical perspectives:

- **BIS Polymer-free platform**:
  - Deep abluminal reservoirs for targeted and prolonged drug elution
  - Bio-inducer surface (BIS) coating for excellent blood compatibility and fast device endothelization
- **Innovative Amphilimus™ Formulation**:
  - First time ever use of an organic acid (amphiphilic carrier) to enhance drug bioavailability, permeability and sustain drug elution over time
  - The combination of Sirolimus with an organic acid should contribute to maximize overall safety and efficacy (i.e. diabetics)