

PLANNED COMBINED SAFETY  
ANALYSIS FOR STENTS  
UTILIZING BIOLIMUS A9<sup>®</sup>  
AND BIODEGRADABLE  
POLYMER

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# Stent Thrombosis: the question

- Events are rare
- Predictors are poorly defined
- Results cannot be generalized from one drug-polymer combination to another

# Stent Thrombosis: the question

- Current regulatory evaluation of new molecular entities requires 2000 patient exposure based on the following assumptions
  - Expected ST rate ~1% for bare metal stents
  - Power to detect doubling in rate of ST for a new stent
- There may be an interest in increasing the power to detect adverse events that occur infrequently and late through studies with
  - Larger total exposure (patient-years)

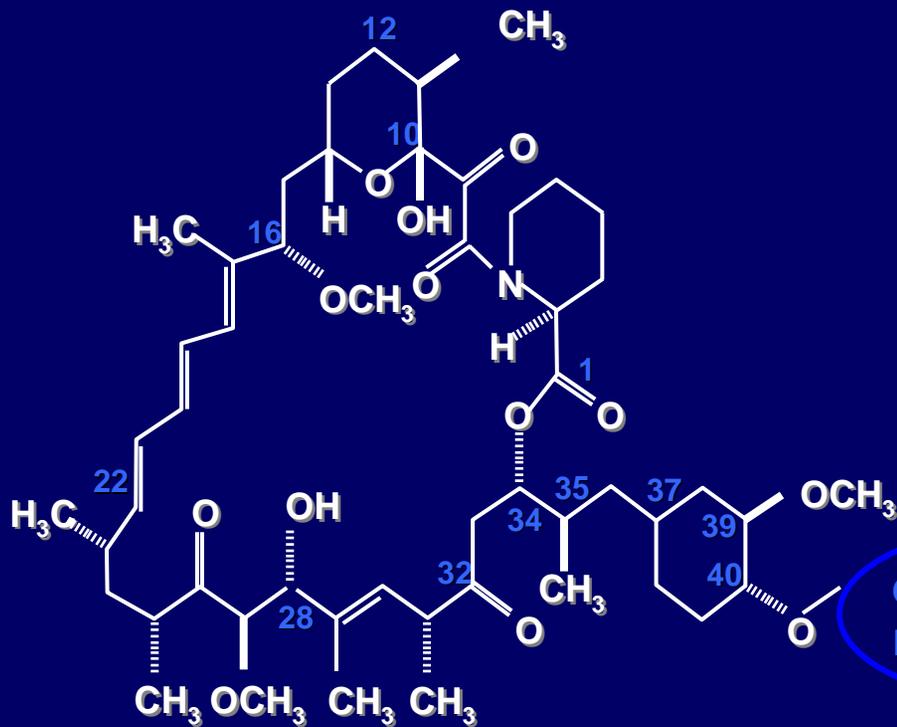
# Stent Thrombosis: The question

- Where different stent platforms use the same drug-polymer combination, combining data may improve the power to detect rare adverse events
  - anticipated and unanticipated

# Biolimus A9 Stent Programs

- Biolimus A9 and the biodegradable polymer is under investigation in several stent platforms:
  - Biosensors, Devax, Terumo, and Xtent
- Each stent platform has a series of trials designed to demonstrate safety and effectiveness to support approvals
- The trials vary according to stent type and target patient population

# *Bioluminus A9 and Biodegradable Polymer*



Sirolimus  
Everolimus  
Zotarolimus  
**Bioluminus A9**

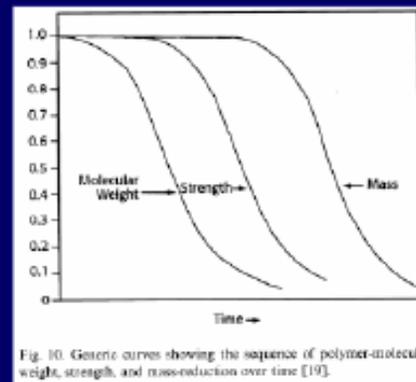
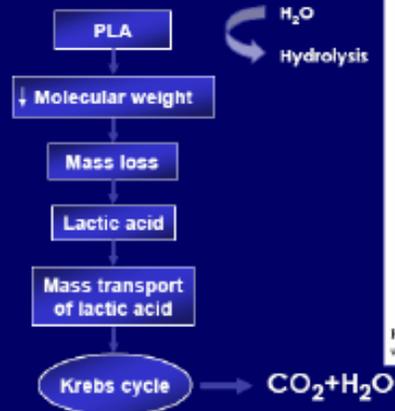
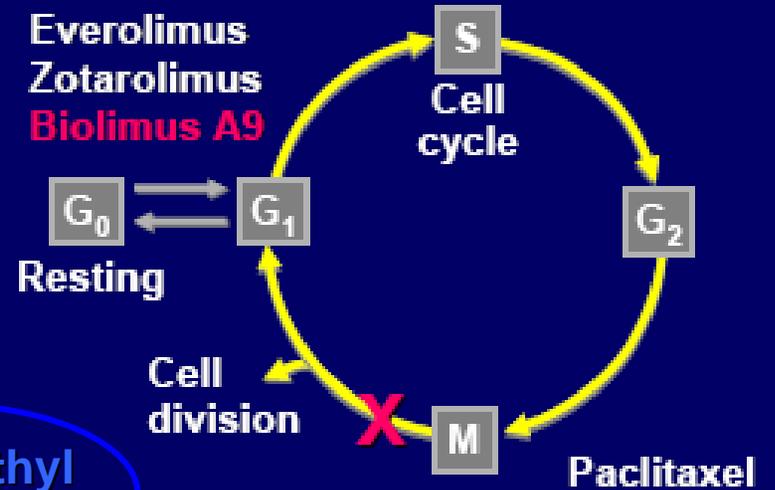


Fig. 10. Generic curves showing the sequence of polymer-molecular weight, strength, and mass-reduction over time [19].

# ***Biolimus A9 and Biodegradable Polymer Four DES Platforms***

<b>Company</b>	<b>Stent Platform (s) Primer Coating</b>	<b>Drug / Polymer</b>	<b>Delivery System</b>
<b>BIOSENSORS</b>	BioMatrix® DES 316L Stainless Steel Parylene C	<b>Biolimus A9: PLA 1:1</b> <b>15.6 µg / mm</b> <b>Abluminal</b>	<b>TIGER Delivery System</b> <b>Rapid Exchange</b>
<b>DEVAX</b>	Axxess™ Plus Nitinol (SE) Parylene N/C	<b>Biolimus A9: PLA 1:1</b> <b>22 µg / mm</b> <b>Abluminal</b>	<b>Covered Sheath</b> <b>Rapid Exchange</b>
<b>TERUMO</b>	Nobori Stent 316L Stainless Steel Parylene C	<b>Biolimus A9: PLA 1:1</b> <b>15.6 µg / mm</b> <b>Abluminal</b>	<b>Nobori Delivery System</b> <b>Rapid Exchange</b>
<b>XTENT</b>	Custom NX™ DES Cobalt Chrome Parylene C	<b>Biolimus A9: PLA 1:1</b> <b>16.7 µg / mm</b> <b>Abluminal</b>	<b>Sheath Protected</b> <b>Adjustable Balloon</b> <b>Lengths</b>

# ***Biolimus A9 Clinical Evaluations***

<b>Phase I Drug Safety Studies</b>				
<b>Clinical Trial</b>	<b>Study Design</b>	<b>N</b>	<b>Follow-Up</b>	<b>Platform</b>
Phase 1 Single Ascending Dose	Randomized, double blind, placebo control	28	30 days	Biolimus A9 <sup>®</sup>
Phase 1 Multiple Ascending Dose	Randomized, double blind, placebo control	19	30 days	Biolimus A9 <sup>®</sup>
<b>DES Platform PK Studies</b>				
<b>Biosensors STEALTH PK</b>	Single Arm Registry	27	12 mos	BioMatrix <sup>®</sup>
<b>Terumo NOBORI PK</b>	Single Arm Registry	20	12mos	Nobori <sup>™</sup>

Specific pre-clinical evaluations &  
Independent PK studies for each platform  
(n=94 pts)

## *DES Platform Clinical Evaluations*

<b>DES Platform FIM and Feasibility Studies</b>				
<b>Clinical Trial</b>	<b>Study Design</b>	<b>N</b>	<b>Follow-Up</b>	<b>Platform</b>
<b>Biosensors</b> STEALTH FIM	RCT vs. Bare Metal S-Stent	120	1 -5 years	BioMatrix®
<b>Devax</b> AXXESS PLUS	Prospective Registry	139	1 year	AXXESS
<b>Devax</b> AXXENT	Prospective Registry	33	1-5 years	AXXENT
<b>Xtent</b> CUSTOM I	Prospective registry	30	1-5 years	Custom NX
<b>Xtent</b> CUSTOM II	Prospective registry	100	1-5 years	Custom NX
<b>Xtent</b> CUSTOM III	Prospective Registry	90	1-5 years	Custom NX

**FIM and Feasibility Safety Studies**  
(n=472 pts)

Not available for sale in the United States

# *DES Platform Clinical Evaluations*

<b>Pivotal Studies</b>				
<b>Company /Clinical Trial</b>	<b>Study Design / Sample Size</b>	<b>N</b>	<b>Follow-Up</b>	<b>Platform</b>
<b>Biosensors</b> STEALTH II	Randomized, Single Blind, DES Control (Taxus)	1,600	1-5 years	BioMatrix®
<b>Biosensors</b> LEADERS	Randomized, Single Blind, DES Control (Cypher Select)	1,700	1-5 years	BioMatrix®
<b>Devax</b> DIVERGE	Prospective Registry	700	1-5 years	Axxess
<b>Terumo</b> NOBORI 1 1st Ph	Randomized, Single Blind DES Control (Taxus Express)	120	1-5 years	Nobori™
<b>Terumo</b> NOBORI 1 2nd Ph	Randomized, Single Blind DES Control (Taxus Liberte)	240	1-5 years	Nobori™
<b>Terumo</b> NOBORI CORE	Prospective Registry (Cypher historical control)	100	1-2 years	Nobori™
<b>Xtent</b> CUSTOM IV & V	Pivotal RCTs	3000	1-5 years	Custom NX

Pivotal studies supporting approval for intended use  
(n ≈ 5,500pts)

Each trial program intended to stand alone.

# *DES Platform Clinical Evaluations*

## Registries and Post Market Studies

<b>Biosensors</b> BEACON	Single Arm Registry	292	1-5 years	BioMatrix®
<b>Biosensors</b> Continuous ACCESS	Single Arm Registry	>1000	1-5 years	BioMatrix®
<b>Devax</b> Continuous AXXESS	Single Arm Registry	1000	1-5 years	AXXESS
<b>Terumo</b> NOBORI 2	Single Arm Registry	1600	1-5 years	Nobori™
<b>Xtent</b> CUSTOM Registry	Single Arm Registry	> 4000	1-5 years	Custom NX

Additional Registries and Post Market Studies  
(n≈7,500 pts)

# Combined Safety Analysis for Biolimus A9 Stents

- Biolimus A9 and the biodegradable polymer are the common thread for all these studies
- Combining data across these trials might increase power to detect rare adverse events

# Combined Safety Analysis for Biolimus A9 Stents

## Objectives

Secondary safety analysis to combine data from individual studies to yield a more precise estimate of safety of the use of Biolimus A9 and the biodegradable polymer

- Exploratory analysis of safety not intended to replace requirements for each individual stent platform
- Comparison of independent effects due to drug-polymer combination vs. patient and trial level covariates

# Combined Safety Analysis for Biolimus A9 Stents

## Methods

- Pooling or exchangeability not possible because of differences in platforms and patients
- Minimum requirements to combine data:
  - Common definitions
  - Common methods of data acquisition and adjudication
  - Presence of common controls (bare metal, DES)
  - Adjustment for confounders at patient and trial level

# Combined Safety Analysis for Biolimus A9 Stents

## Methods

- Mega-analysis of data from the randomized trials and registries of stenting of *de novo* coronary artery stenoses to estimate the safety of each device and compare the Biolimus stents to the control stents
  - Hierarchical regression model (using survival methods to account for varying follow-up duration)
  - Adjustment for confounders on a patient and trial level

# Combined Safety Analysis for Biolimus A9 Stents

## Methods

- A hierarchical survival analysis will be used to link the predictor variables to the expected value of the (binary-valued) safety outcomes for each patient in each trial.
- Either frequentist or Bayesian methods could be applied.

# Combined Safety Analysis for Biolimus A9 Stents

## Adjustment for Confounders Patient level

- Total stent length
- Reference vessel diameter (RVD)
- Multivessel treatment
- Diabetes
- Ejection Fraction
- Number of diseased vessels
- Acute coronary syndrome presentation

# Combined Safety Analysis for Biolimus A9 Stents

## Adjustment for Confounders

### Trial Level

- U.S. versus outside U.S. trials
- Presence of blinding of patients and evaluators to treatment assignment
- Stent platform
- Bifurcation lesion treatment
- Left main coronary artery treatment
- Interactions between platform and the drug-polymer combination would be considered.

# Combined Safety Analysis for Biolimus A9 Stents

## Registry versus RCT

- Propensity score methods to match registry patients to the randomized patients
- Registry group patients for whom there are no randomized patients with similar characteristics would be excluded to increase robustness to model misspecification
- Sensitivity analysis to exclude all registry patients

# Combined Safety Analysis for Biolimus A9 Stents: Anticipated Results

Anticipated results include estimates and confidence intervals for event rates (stent thrombosis) for

- Biolimus stents
- Biolimus platforms
- Patient subsets
- And in comparison to bare metal and drug-eluting controls

# Combined Safety Analysis for Biolimus A9 Stents: Conclusions

- A pre-specified combined safety analysis could be performed at varying time points with varying durations of follow-up and yield greater precision regarding safety
- This analysis could also identify predictors of stent thrombosis with greater certainty
- If a consistent effect is attributable to this drug-polymer combination across platforms, a combined mega-analysis would increase the power to detect this effect