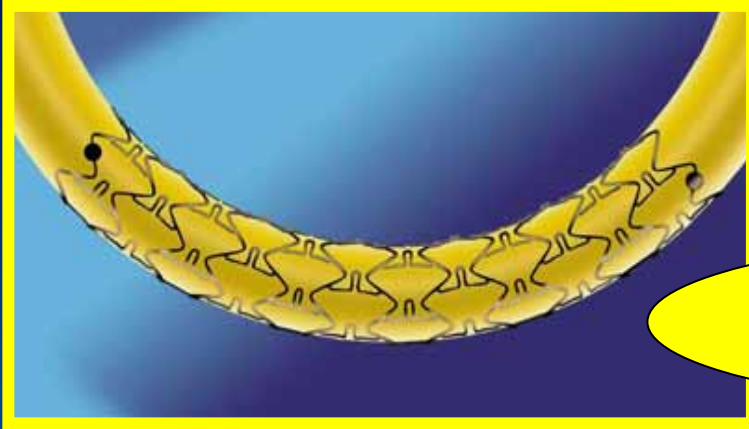


**UPDATE ON JUPITER I AND II CLINICAL TRIALS  
WITH THE SORIN CARBOSTENT TRACROLIMUS  
ELUTING STENT**

*GB Danzi, MD  
Ospedale Maggiore Policlinico  
University of Milan  
Milan - Italy*

# **JANUS CARBOSTENT: THE PLATFORM**



**6 years of clinical use**

## **Distinctive Feature**

**1) CLOSED CELL ARCHITECTURE**



**HOMOGENEOUS EXPANSION**

**2) MIRROR POLISHING**



**THROMBORESISTANCE**

**3) CARBOFILM COATING**

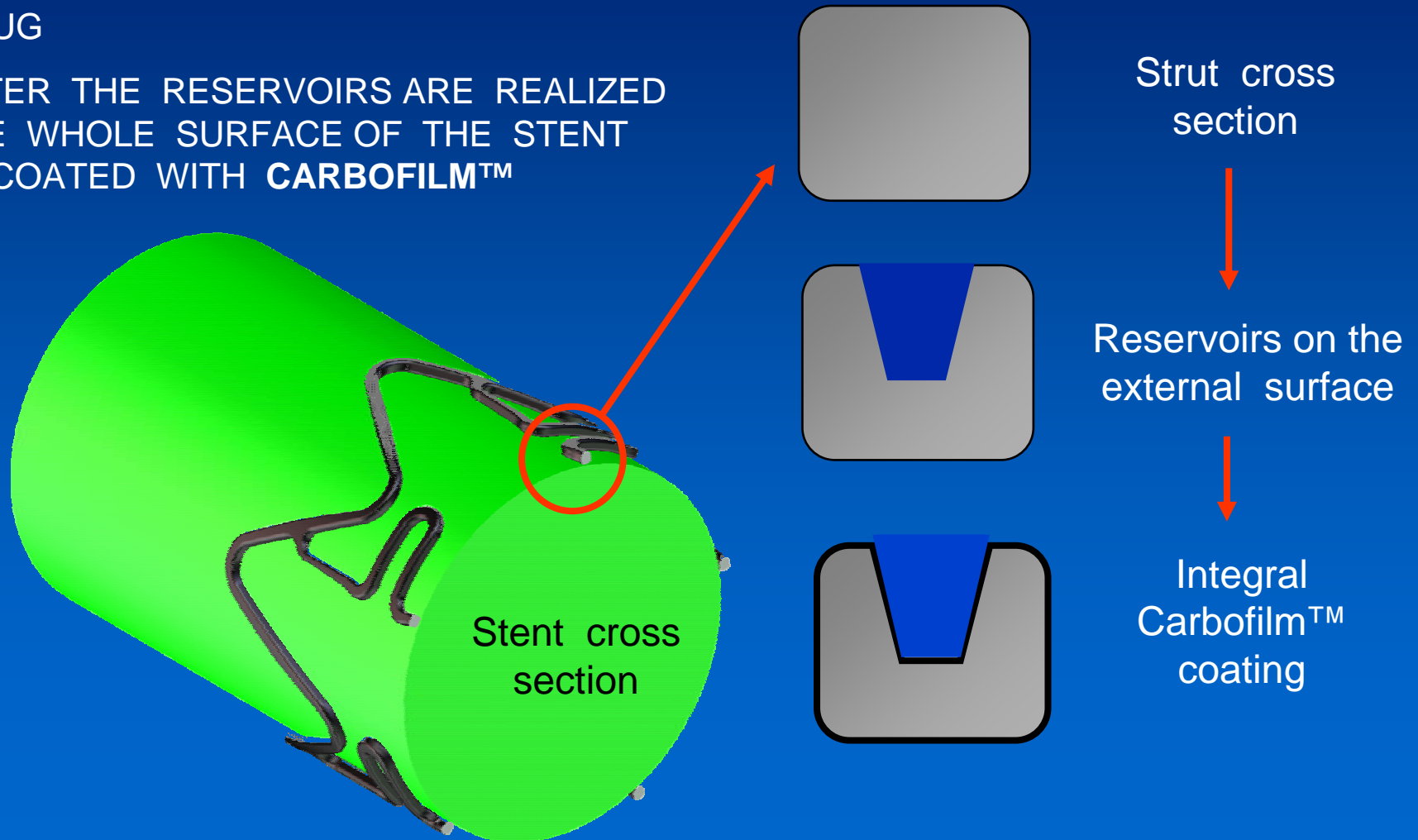


**BIO- & HEMOCOMPATIBILITY**

# RESERVOIRS ON THE SURFACE TO LOAD THE DRUG

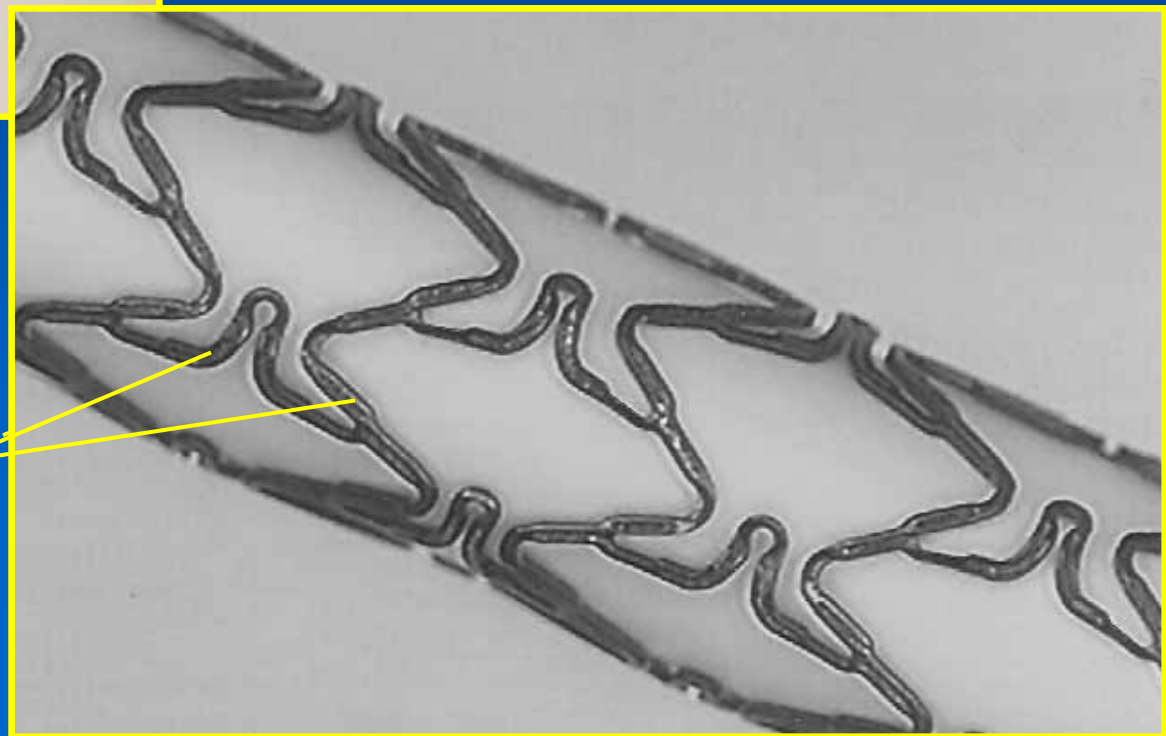
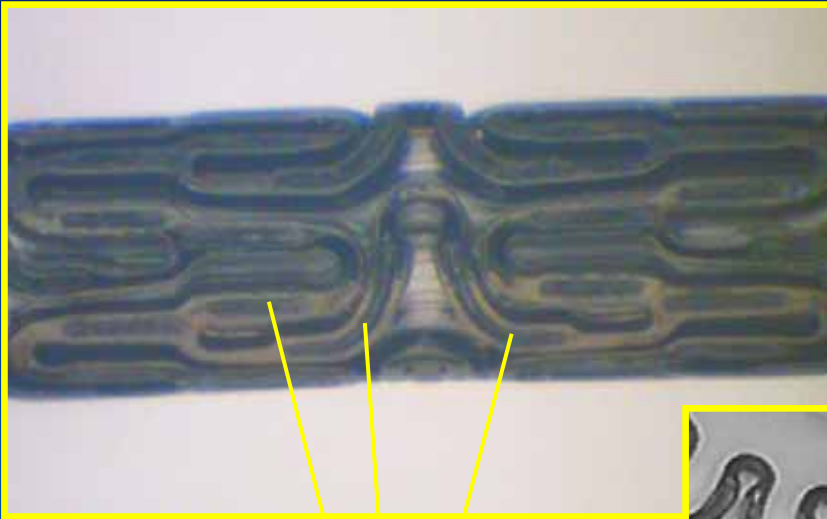
THE EXTERNAL SURFACE OF JANUS CARBOSTENT IS SUITABLY GROOVED TO PROVIDE DEEP RESERVOIRS FOR THE DRUG

AFTER THE RESERVOIRS ARE REALIZED THE WHOLE SURFACE OF THE STENT IS COATED WITH CARBOFILM™



# ***JANUS Carbostent***

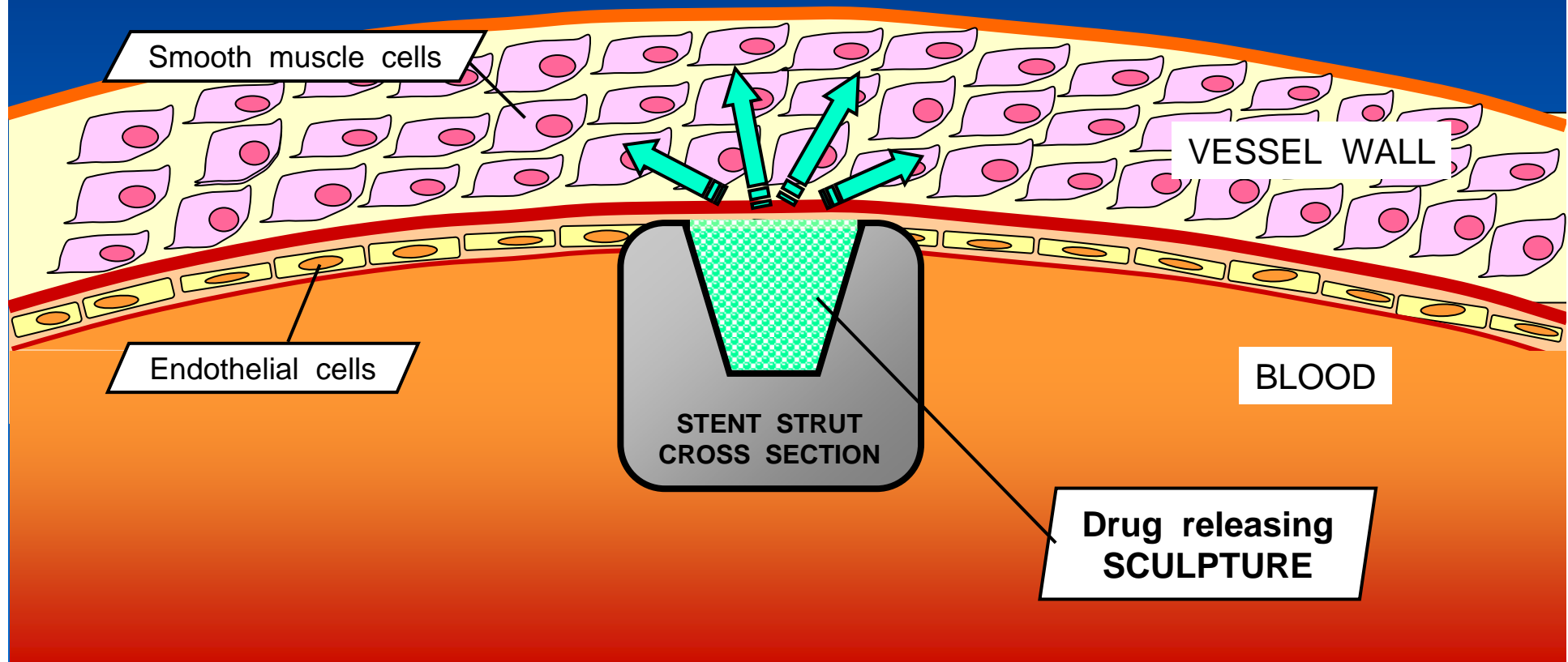
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***Deep drug reservoirs  
on the external surface***

# **JANUS CARBOSTENT RELEASING MECHANISM**

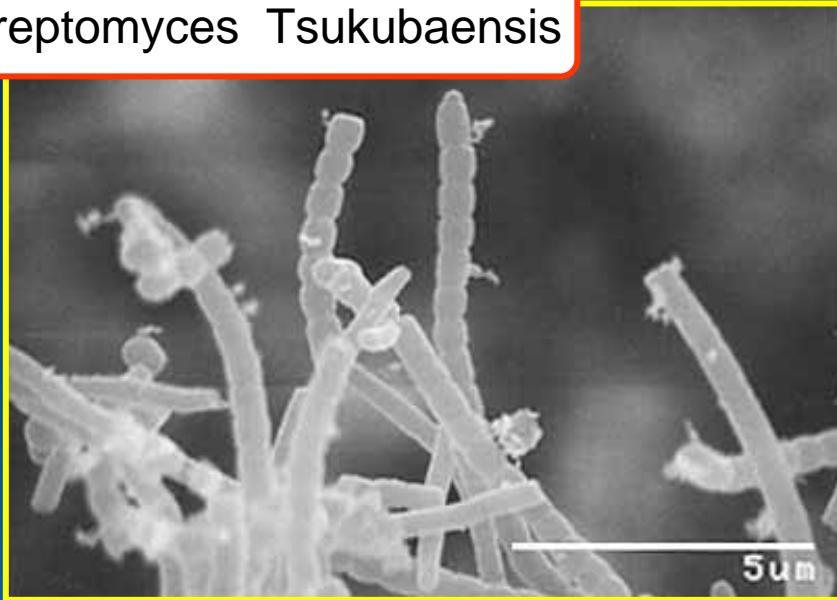
- DEEP SCULPTURES ON THE OUTER STENT SURFACE CONTAIN AND RELEASE THE DRUG ONLY TOWARDS THE VESSEL WALL
- NO DRUG IS LOST INTO THE BLOOD STREAM



# **JANUS CARBOSTENT - The DRUG**

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Streptomyces Tsukubaensis



The first drug which has been selected and tested in combination with Janus Carbostent is ***Tacrolimus (FK 506)***, produced by Fujisawa Pharmaceutical Co. (Japan).

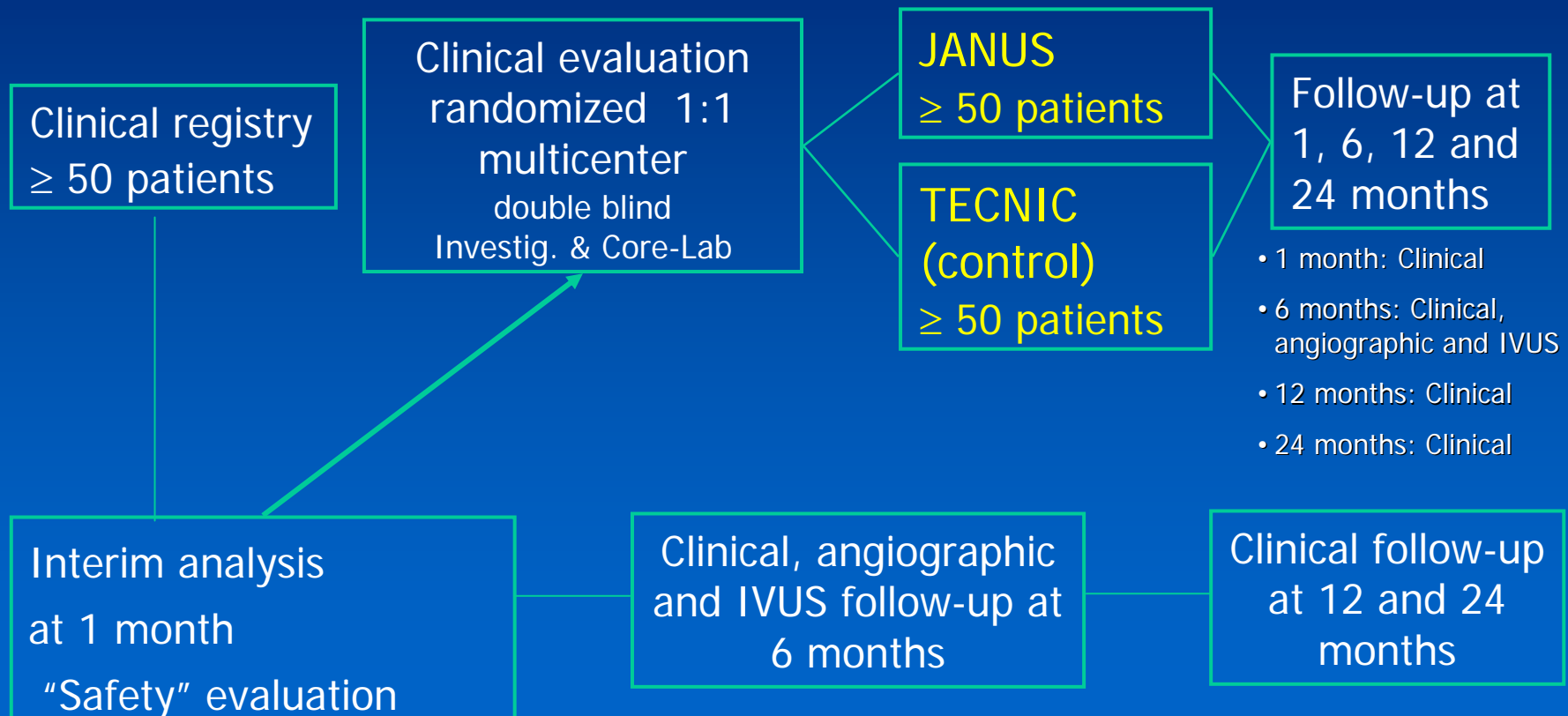
***Tacrolimus*** is the active ingredient of two pharmaceutical products registered in all the main countries of the world: the immunosuppressant Prograf®, used in the treatment of patients after kidney or liver transplantation, and the Protopic®, used in the treatment of atopic dermatitis.

**UPDATE**  
**on**  
**JUPITER I**

# Jupiter I: Study Design

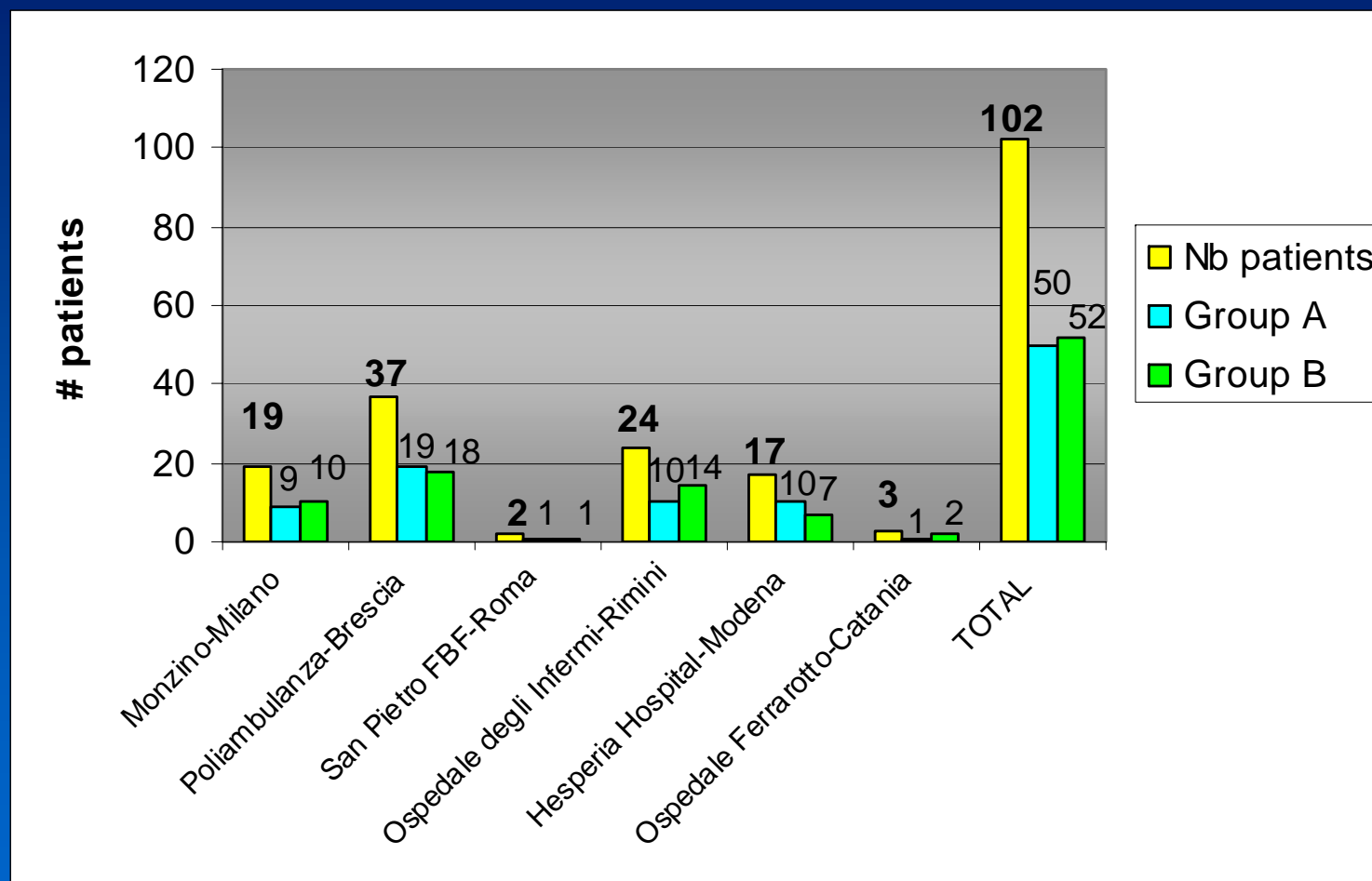
## $\alpha$ phase

## $\beta$ phase





# Jupiter I - $\beta$ : Study Update



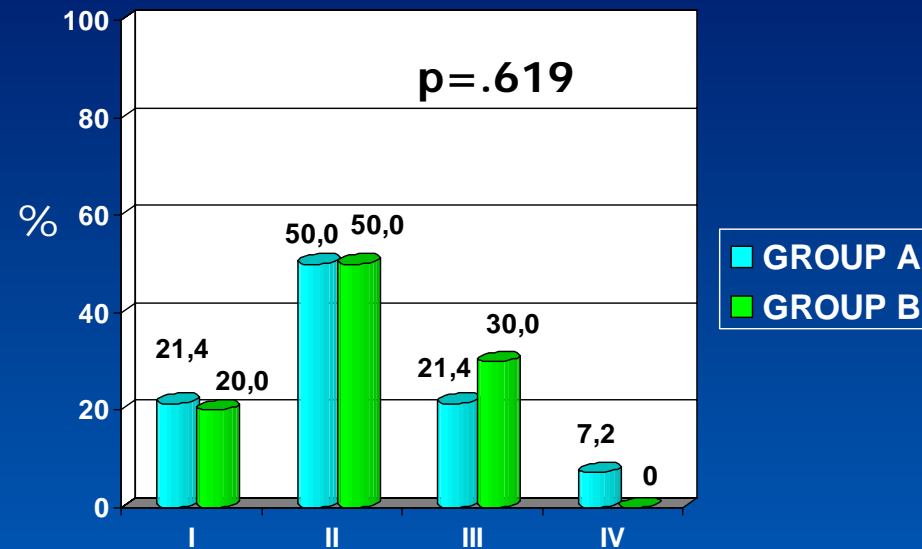
Enrolment completed on December 2004

# Jupiter I - $\beta$ : Base-Line Clinical Characteristics

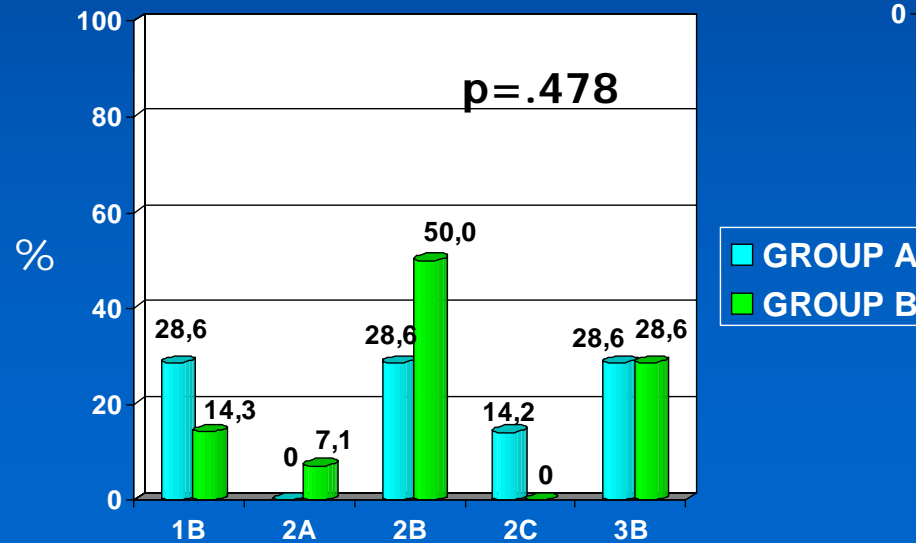
	GROUP A	GROUP B	P value
N° of enrolled pts (102)	50	52	
N° of available pts (92)	46	49	
Male	89.1%	79.6%	.203
Age (yrs)	64.6 $\pm$ 11.6	64.0 $\pm$ 10.4	.788
<u>Clinical Status</u>			.436
Asymptomatic	6.5% (3 pts)	8.2% (4 pts)	
Silent Ischemia	8.7% (4 pts)	8.2% (4 pts)	
Stable Angina	60.9% (28 pts)	42.8% (21 pts)	
Unstable Angina	15.2% (7 pts)	28.6% (14 pts)	
MI	8.7% (4 pts)	12.2% (6 pts)	

# Jupiter I - $\beta$ : Base-Line Clinical Characteristics

Stable angina



Unstable angina



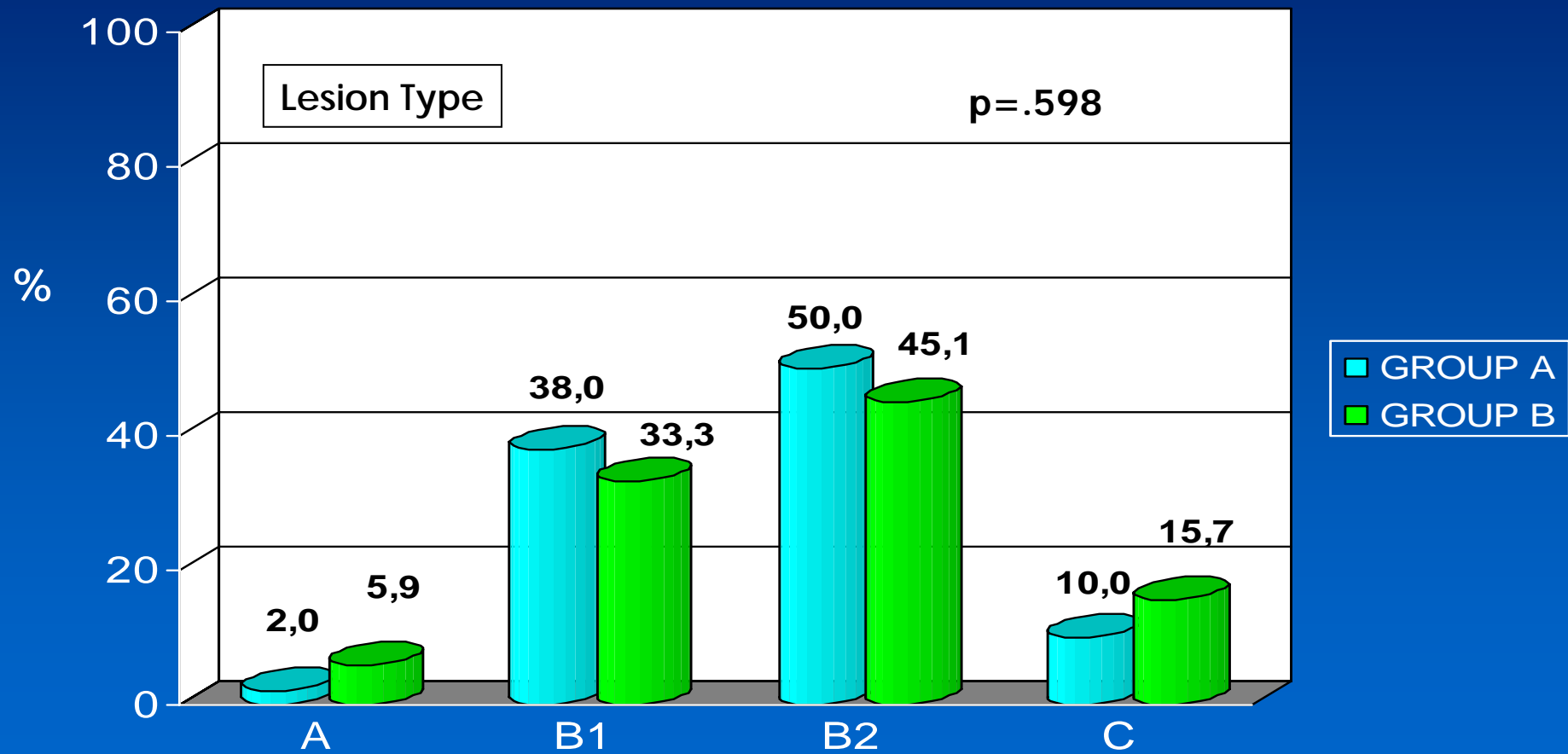
# Jupiter I - $\beta$ : Base-Line Clinical Characteristics

	GROUP A	GROUP B	P value
<u>Risk factors</u>	46	49	
Smokers	37.0% (17 pts)	42.9% (21 pts)	.557
Diabetes	17.4% (8 pts)	28.6% (14 pts)	.197
ID Diabetes	4.3% (2 pts)	2.0% (1 pts)	.520
NID Diabetes	13.0% (6 pts)	26.5% (13 pts)	.101
Hypertension	69.6% (32 pts)	59.2% (29 pts)	.291
Hypercholesterolemia	63.0% (29 pts)	79.6% (39 pts)	.074
Family history of CAD	21.7% (10 pts)	22.4% (11 pts)	.934

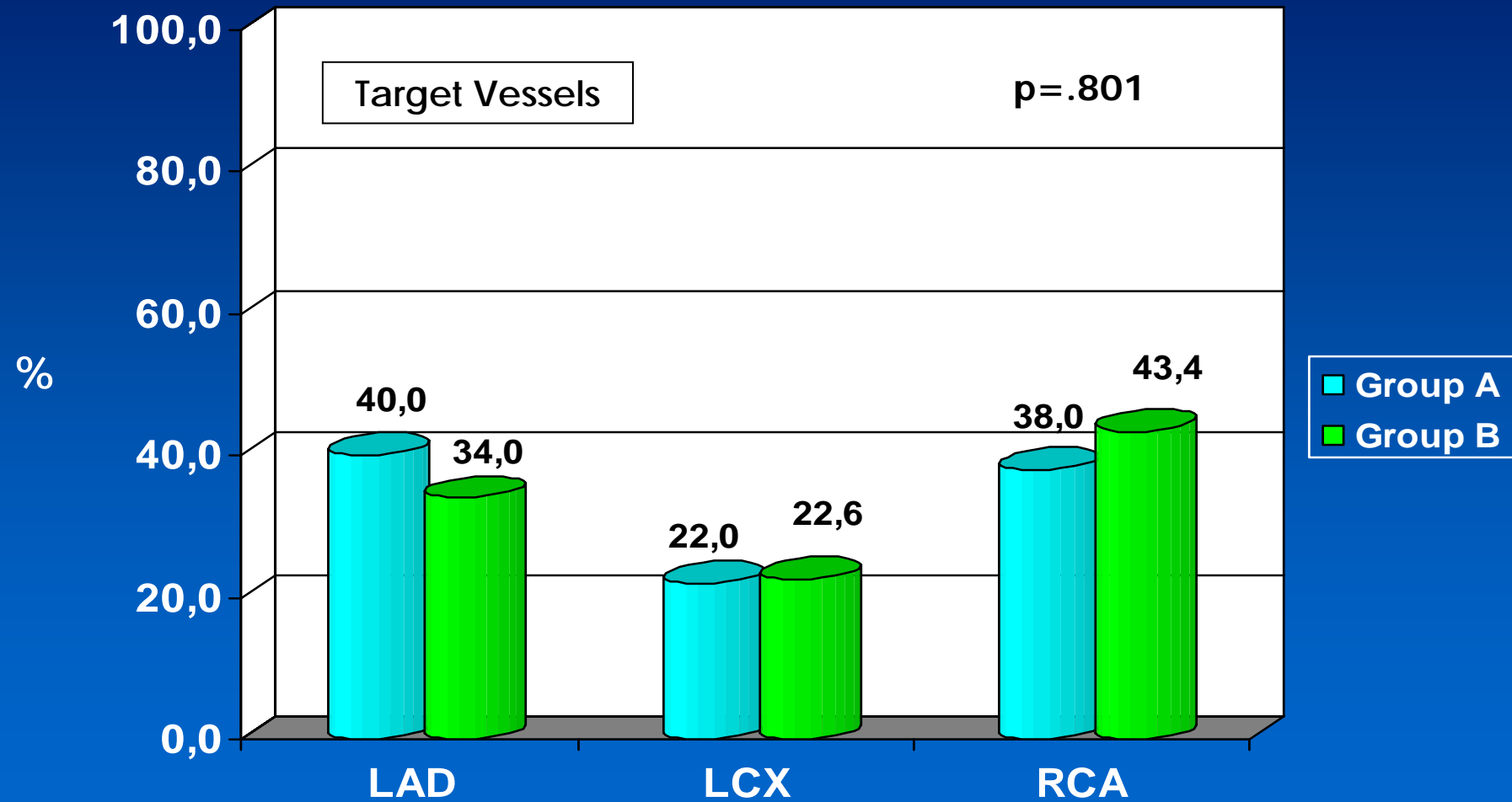
# Jupiter I - $\beta$ : Target lesion characteristics

	GROUP A	GROUP B	P value
N° of available lesions (103)	50	53	
De Novo	100%	100%	
<b>Lesion morphology</b>			.942
Concentric	46.0% (23/50 les)	45.3% (24/53 les)	
Eccentric	54.0% (27/50 les)	54.7% (29/53 les)	
Calcification	10.0% (5/50 les)	9.4% (5/53 les)	.923
Tortuosity	12.0% (6/50 les)	3.8% (2/53 les)	.119
Bifurcation	0%	0%	
Ostial Lesion	0%	0%	
Total Chronic Occlusion	2.0% (1/50 les)	0%	.301

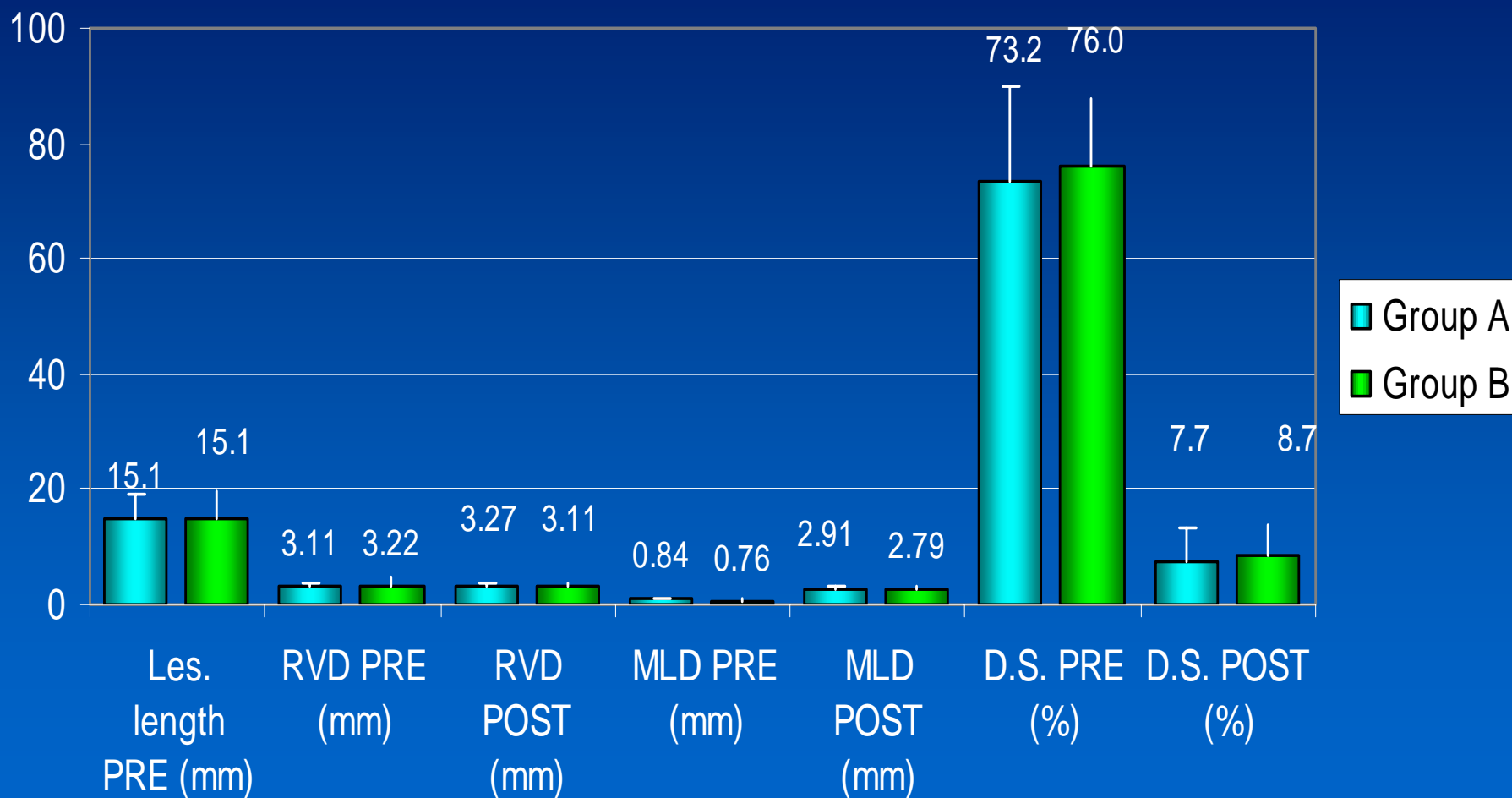
# Jupiter I - $\beta$ : Target lesion characteristics



# Jupiter I - $\beta$ : Target lesion characteristics



# Jupiter I - $\beta$ : Procedural angiographic data





# Jupiter I - $\beta$ : Procedural data

	GROUP A	GROUP B	P value
<u>Stenting procedure</u>	50	53	.923
Direct stenting	10.0% (5/50 les)	9.4% (5/53 les)	
Predilation	90.0% (45/50 les)	90.6% (48/53 les)	
N° stent / lesion	1.08	1.00	
Max. stent depl. pressure (atm)	15.29 $\pm$ 2.86	15.36 $\pm$ 2.59	.893
Postdilation	52.0% (26/50 les)	50.9% (27/53 les)	.915
Dissection	0%	0%	
Procedural success	100%	100%	
TIMI flow 3	100%	100%	
Residual stenosis <20%	100%	100%	

# Jupiter I - $\beta$ : Preliminary in-hospital MACE

	GROUP A	GROUP B
	50	52
<u>MACE</u>		
Death	0%	0%
MI	0%	3.8% (2)
TLR	0%	0%
CABG	—	—
Re-PTCA	—	—
Re-PTCA + Stent	—	—

Total events

0%

3.8% (2)

Acute Thrombosis

0%

0%

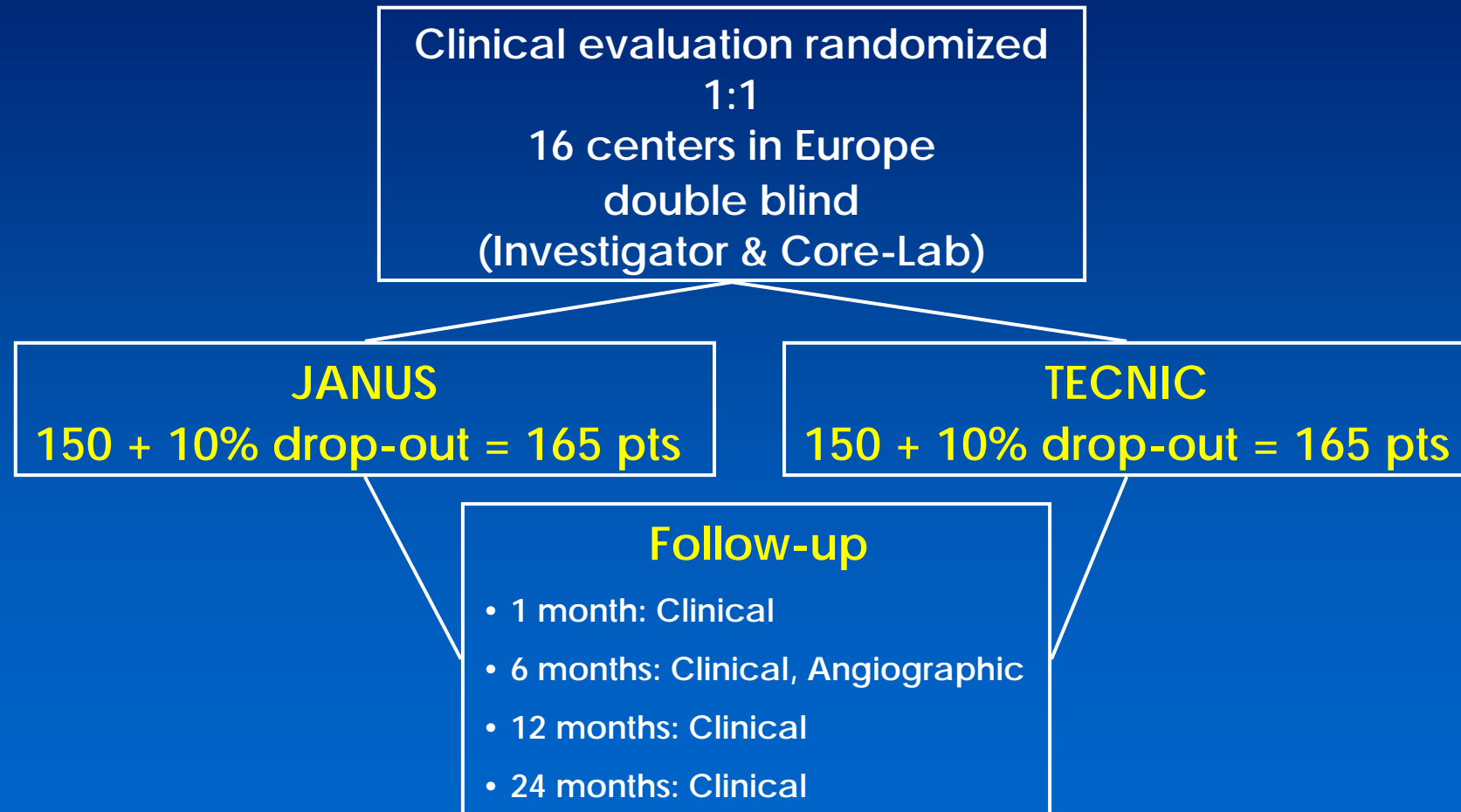
# Jupiter I - $\beta$ : Preliminary 30-day follow-up

	GROUP A	GROUP B
	50	52
<u>MACE</u>		
Death	0%	0%
MI	0%	3.8% (2)
TLR	0%	0%
CABG	—	—
Re-PTCA	—	—
Re-PTCA + Stent	—	—
Total events	0%	3.8% (2)
<u>Sub-acute Thrombosis</u>	0%	0%

The 6-month follow-up results will be available on October 2005

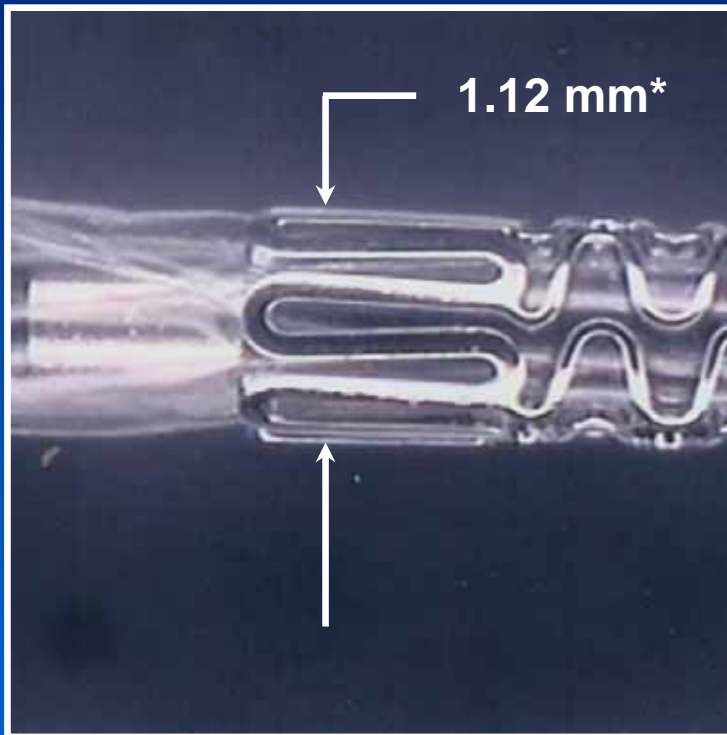
**JUPITER II**  
**preliminary**  
**clinical data**

# Jupiter II: Study Design with high dose: 2.3 $\mu$ g/mm<sup>2</sup>

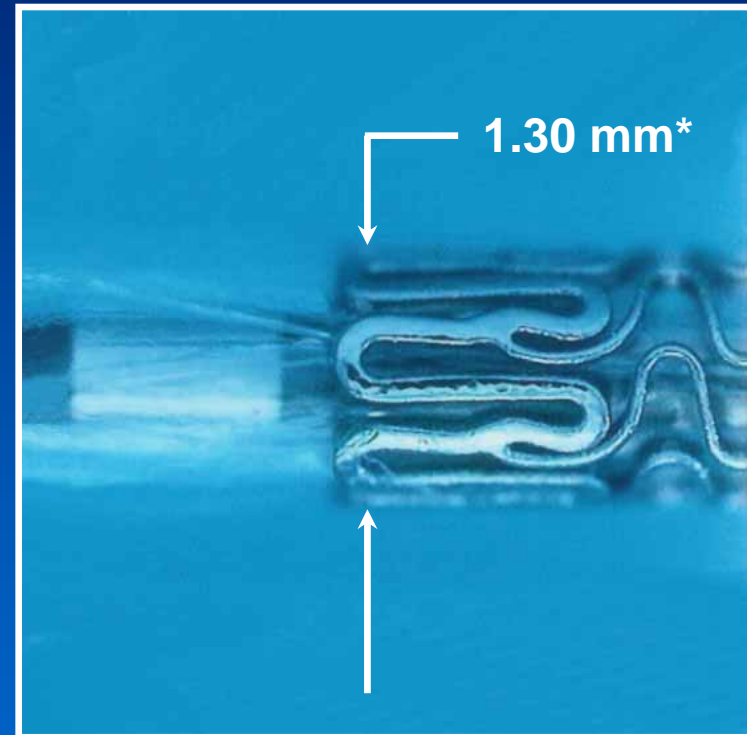


## ***Profile Increased by Polymer Coating***

Polymer coatings used as drug carriers for DES contribute to ***increase the device profile*** in comparison to the platform stents



**Bx Sonic™**  
(3.0 x 18 mm)

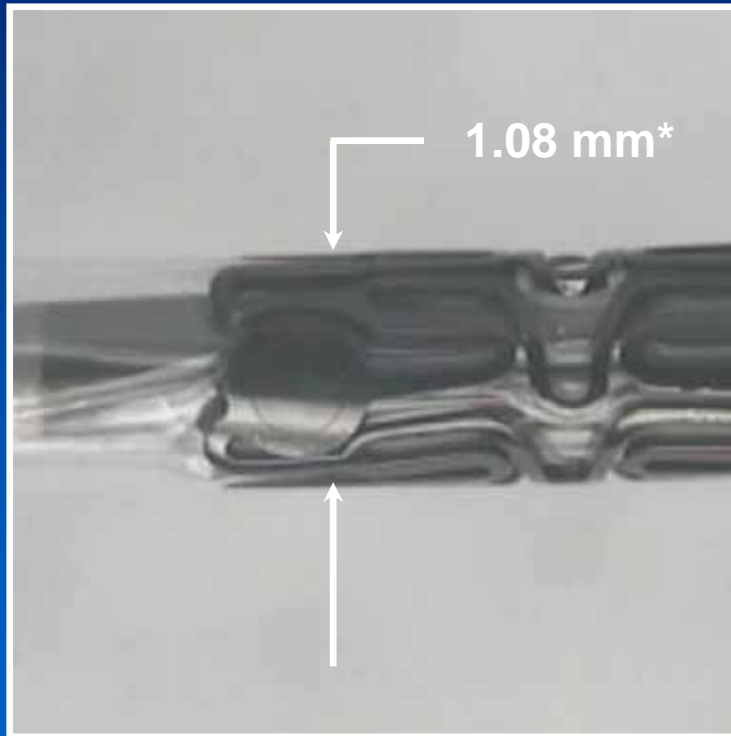


**Cypher Select™**  
(3.0 x 18 mm)

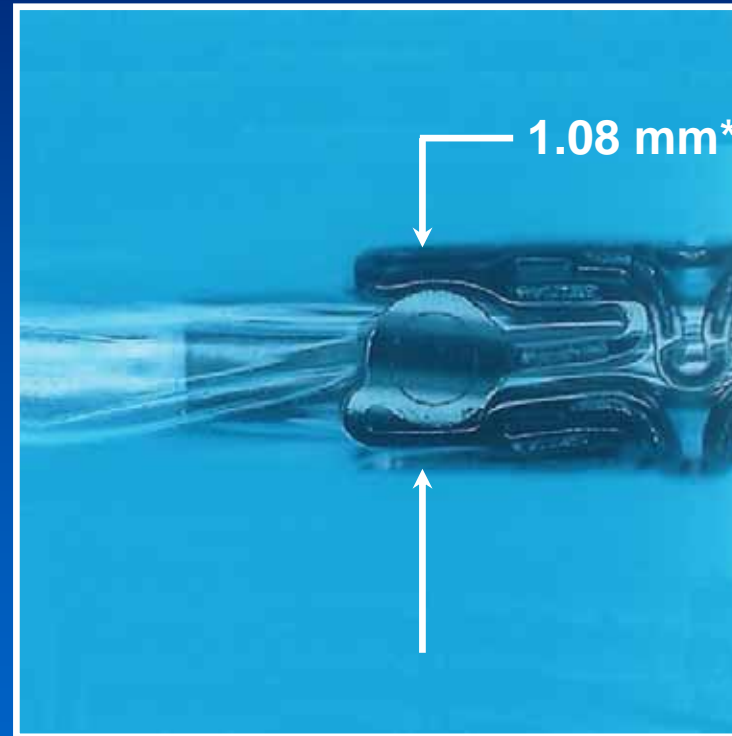
\* Crossing profiles measured according to ASTM F2081-01

# No Profile Increase Avoiding A Polymer Coating

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**Tecnic Carbostent™**  
(3.0 x 15 mm)



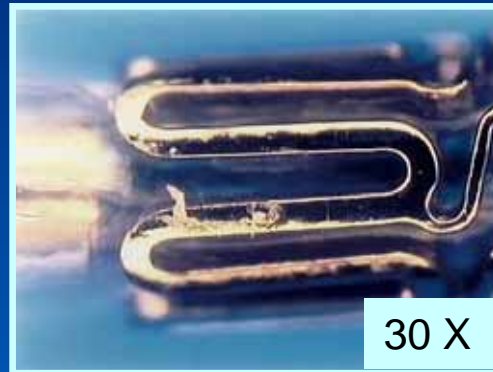
**Janus Carbostent™**  
(3.0 x 15 mm)

\* Crossing profiles measured according to ASTM F2081-01

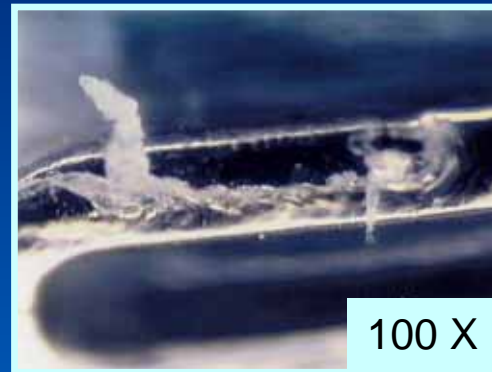
# Polymer Coating Fragility

The polymer coatings and matrices used as drug carriers for DES are relatively soft and fragile. During stent delivery and implant they are exposed to the risk of scratches and peeling, especially when the **Direct Stenting technique** is used.

Cypher

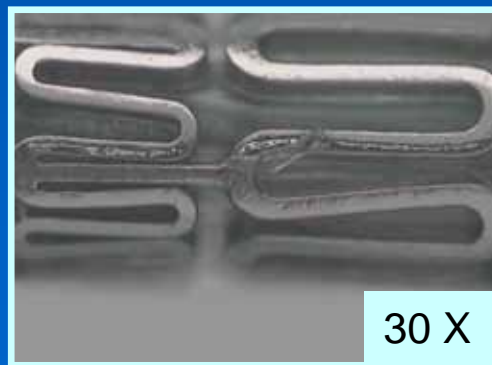


30 X

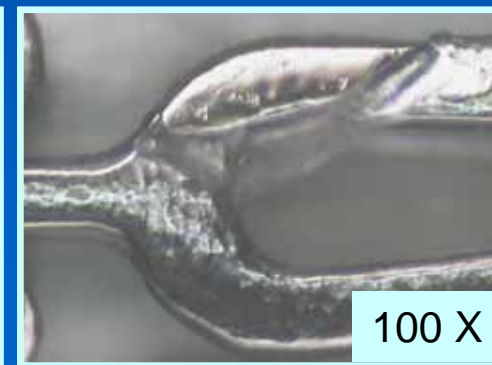


100 X

Taxus



30 X



100 X

After 1 "round trip" through the guiding catheter and into a diseased coronary artery



# Integrity of Incorporated Drug

**JANUS Carbostent** has no polymeric coating on its surface.

The drug is deposited directly into the reservoirs created on the abluminal stent surface and is protected during delivery, even when the ***Direct Stenting technique*** is used.



Janus

After 1 “round trip” through the guiding catheter and into a diseased coronary artery

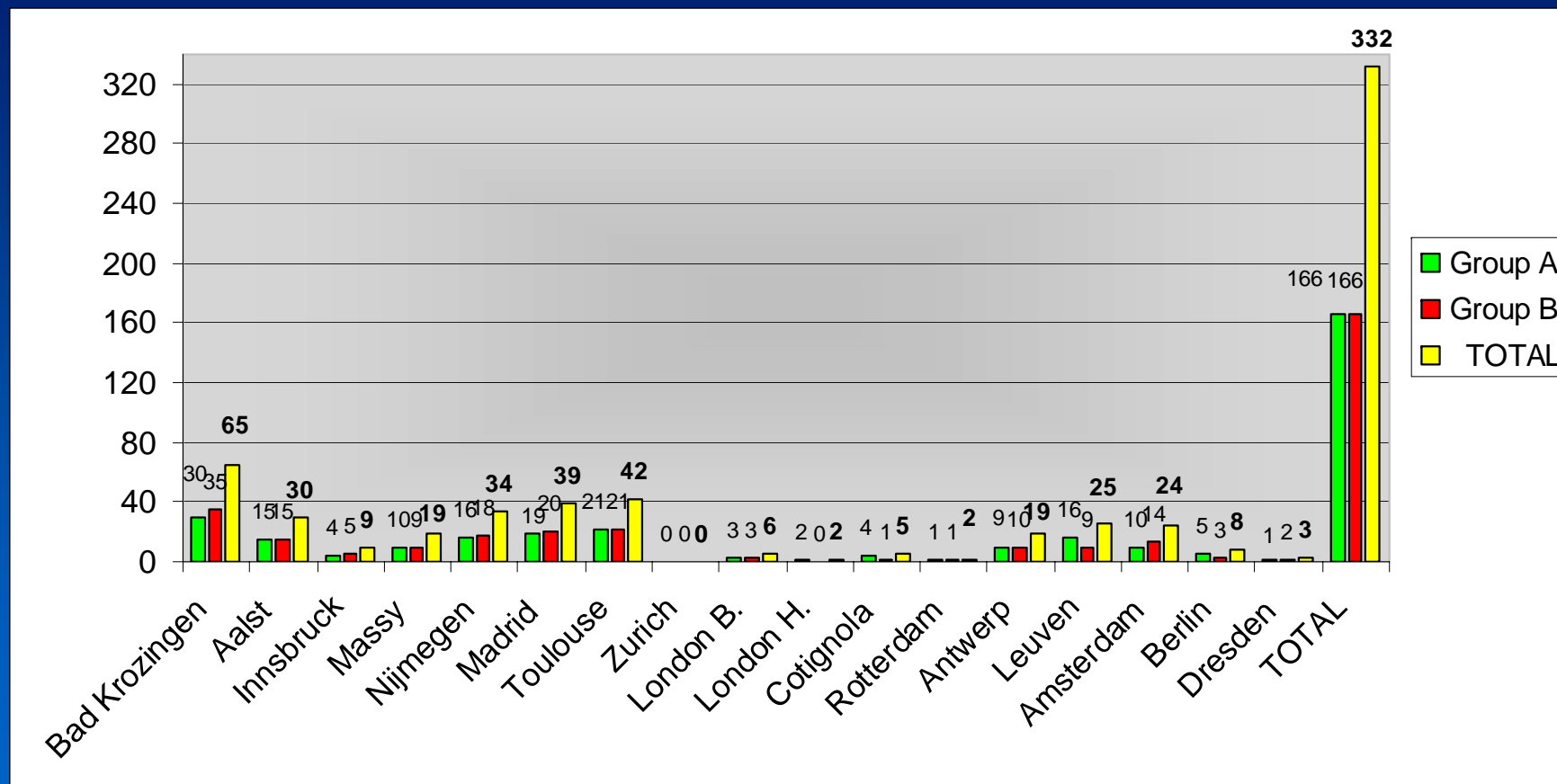


30 X

# Jupiter II: Participating centers

COUNTRY	INVESTIGATOR
FRANCE (2)	Dr. Morice (PI) – Massy Prof. Carrié - Toulouse
THE NETHERLANDS (3)	Dr. Aengevaeren-Nijmegen Prof. Serruys - Rotterdam Dr. De Winter - Amsterdam
BELGIUM (3)	Dr. De Bruyne, Dr. Wijns - Aalst Dr. Verheye – Antwerp Dr. Dubois - Leuven
GERMANY (3)	Prof. Neumann, Prof. Bestehorn – Bad Krozingen Dr. Hoffmann - Berlin Dr. Hempel - Dresden
SPAIN (1)	Prof. Macaya - Madrid
U.K. (2)	Prof. Di Mario, Prof. Ilsey - London
ITALY (1)	Dr. Cremonesi – Cotignola
AUSTRIA (1)	Prof. Pachinger - Innsbruck
SWITZERLAND (1)	Prof. Amann - Zurich

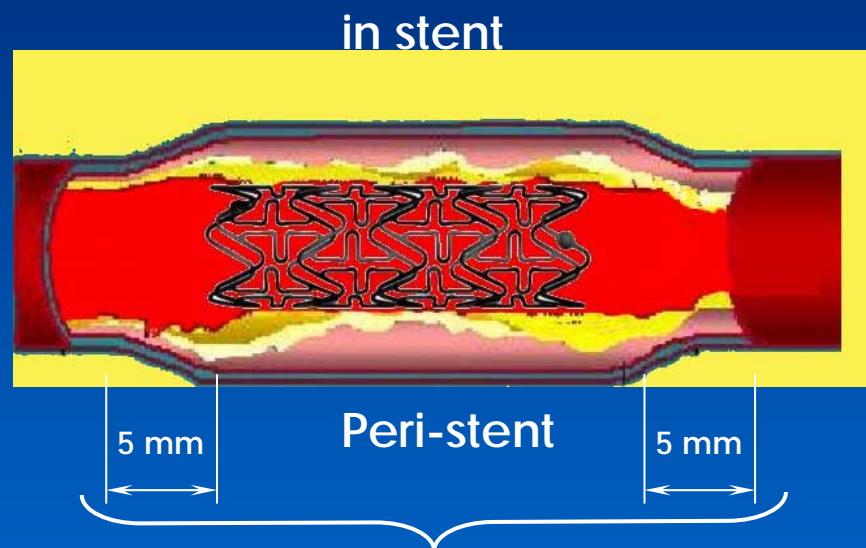
# Jupiter II: Enrolment



Enrolment Completed as for Dec. 2004

# Jupiter II: Primary Endpoint

Assessment of in-stent and peri-stent "Late Lumen Loss (LLL)" at 6 month follow-up by Quantitative Coronary Angiography (QCA)



In-stent: measurement within the stented area

Peri-stent: measurement within the stented segment and within 5 mm proximal and distal to the stent edges

# Jupiter II: Base-Line Clinical Characteristics

	GROUP A	GROUP B	p value
N° of enrolled pts (332)	166	166	
N° of available pts (272)	159	159	
Male	75.5%	74.8%	.8967
Age (yrs)	63.7 ± 10.0	63.7 ± 9.7	.9773
<b><u>Clinical Status</u></b>			
Asymptomatic	5.7% (9 pts)	4.4% (7 pts)	.6079
Silent Ischemia	8.2% (13 pts)	6.9% (11 pts)	.6711
Stable Angina	66.0% (103 pts)	62.9% (100 pts)	.5580
Unstable Angina	15.1% (24 pts)	17.6% (28 pts)	.5442
MI	5.0% (8 pts)	8.2% (13 pts)	.2589
<b><u>CAD</u></b>			
Single vessel disease	61.6% (98 pts)	59.8% (95 pts)	.7305
Multivessel disease	38.4% (61 pts)	40.2% (64 pts)	.7305

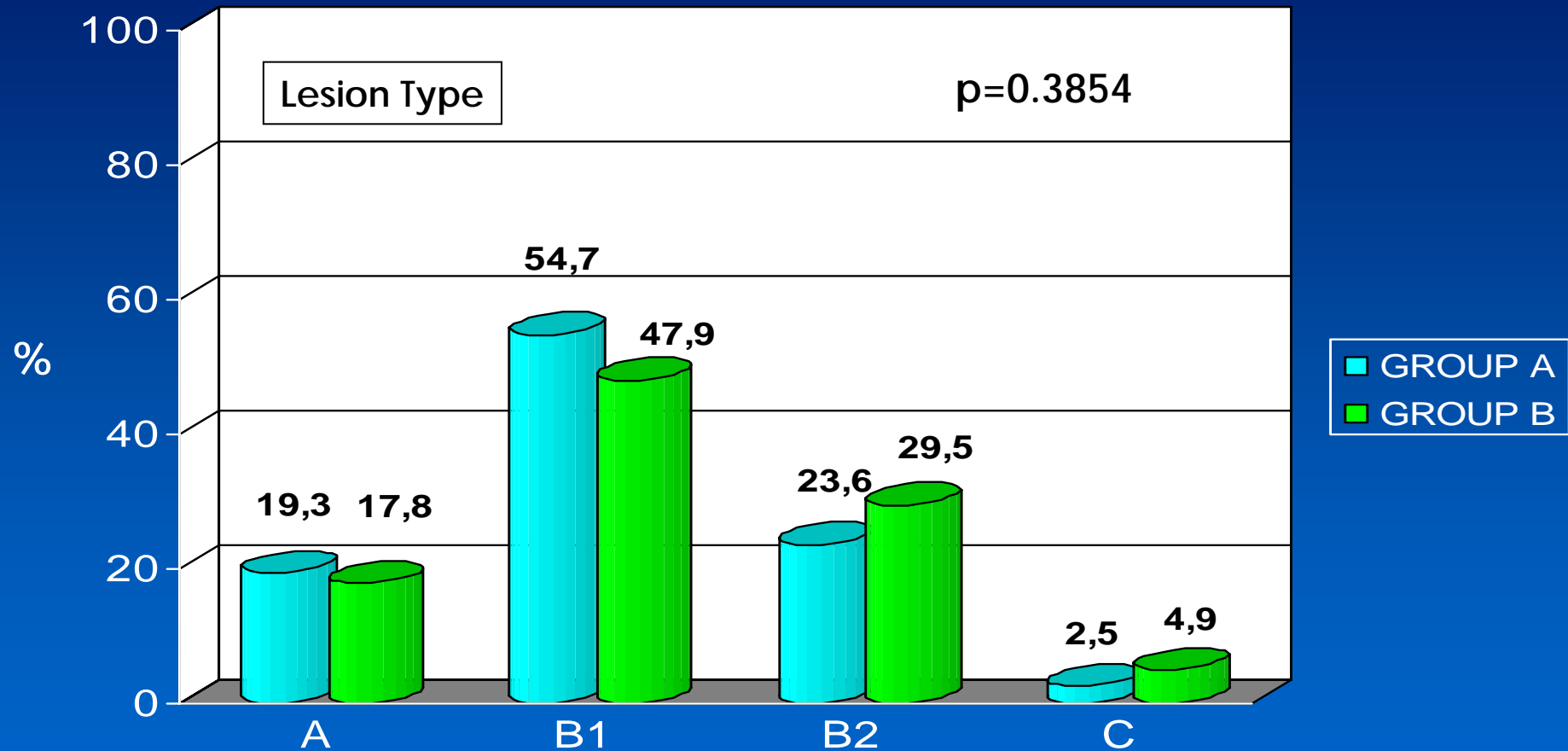
# Jupiter II: Base-Line Clinical Characteristics

	GROUP A	GROUP B	p value
<u>Risk factors</u>	159	159	
Smokers	38.4% (61 pts)	44.0% (70 pts)	.3052
Diabetes	19.5% (31 pts)	17.6% (28 pts)	.6652
ID Diabetes	6.3% (10 pts)	2.5% (4 pts)	.1698
NID Diabetes	13.2% (21 pts)	15.1% (24 pts)	.6293
Hypertension	62.9% (100 pts)	57.2% (91 pts)	.3028
Hypercholesterolemia	69.2% (110 pts)	67.3% (107 pts)	.7178
Family history of CAD	7.7% (44 pts)	28.9% (46 pts)	.8034
Other Pathology	6.9% (11 pts)	9.4% (15 pts)	.4130

# Jupiter II: Target Lesions Characteristics

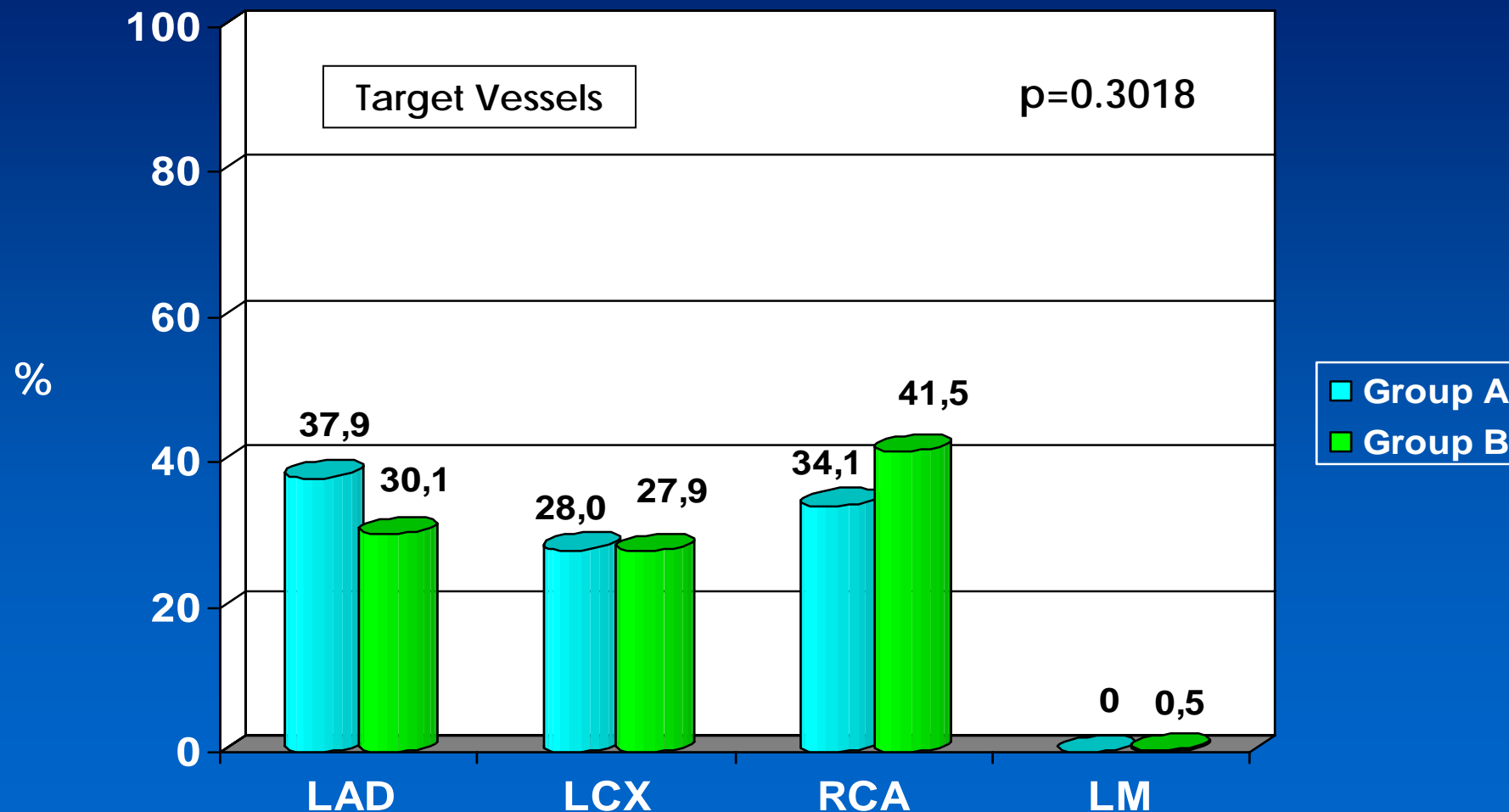
	GROUP A	GROUP B	p value
N° of lesions (365)	182	183	
De Novo	98.9% (178/180 les)	99.5% (181/182 les)	.6219
Concentric	53.4% (87/163 les)	47.7% (83/174 les)	.2979
Eccentric	46.6% (76/163 les)	52.3% (91/174 les)	.2979
Calcification	17.2% (31/180 les)	21.4% (39/182 les)	.3110
Tortuosity	6.7% (12/180 les)	13.1% (24/183 les)	<b>.0399</b>
Bifurcation	0%	2.7% (5/183 les)	.0608
Ostial Lesion	0.6% (1/180 les)	1.1% (2/183 les)	1.000
Total Chronic Occlusion	0%	1.1% (2/183 les)	.4987

# Jupiter II: Target Lesions Characteristics

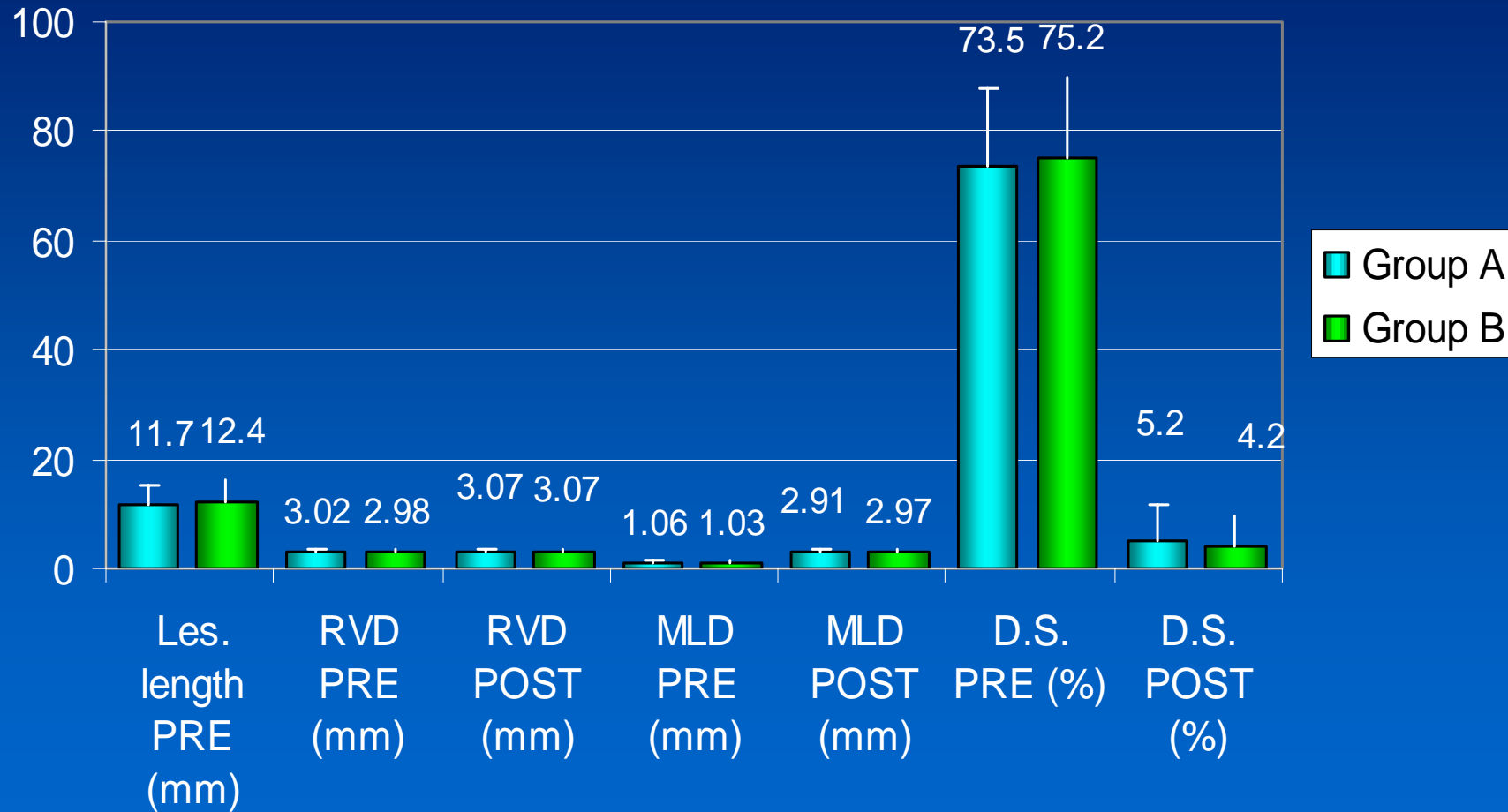




# Jupiter II: Target Lesions Characteristics



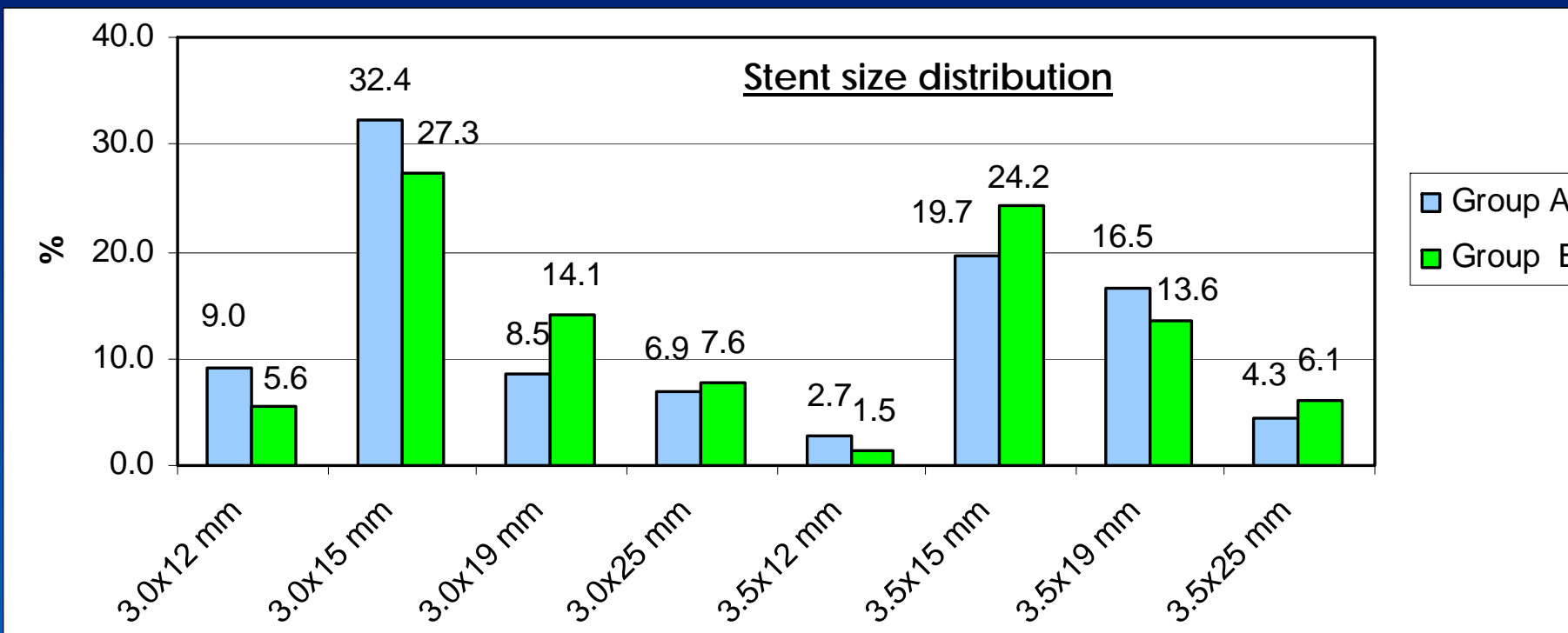
# Jupiter II: Procedural angiographic data



# Jupiter II: Procedural data

	GROUP A	GROUP B	p value
<u>Stenting procedure</u>	182	183	
Direct stenting	82.4% (150 les)	72.7% (133 les)	.0258
Postdilation after direct stenting	15.3% (23/150 les)	14.3% (19/133 les)	
N° stent / lesion	1.03	1.08	
MIP (atm)	13.74 ± 2.93	13.62 ± 3.00	.6942
Postdilation	16.9% (29/172 les)	18.4% (33/179 les)	.6989
Dissection	1.1% (2/182 les)	3.8% (7/183 les)	.1743
Procedural success	99.4% (170/171 les)	99.4% (172/173 les)	1.000
TIMI flow 3	100%	100%	
Residual stenosis >20%	0.6% (1/1)	0.6% (1/183)	1.000

# Jupiter II: Procedural data



# Jupiter II: Preliminary in-hospital MACE

	GROUP A 159	GROUP B* 159	p value
<u>MACE</u>			
Death	0%	0%	
MI	0.63% (1)	0.63% (1)	1.0000
TLR	1.26% (2)	0%	.3260
CABG	0%	0%	
Re-PTCA	0.63% (1)	0%	
Re-PTCA + Stent	0.63% (1)	0%	
<b>Total events</b>	<b>1.89% (3)</b>	<b>0.63% (1)</b>	<b>.3812</b>
<u>Acute Thrombosis</u>	0%	0%	

\* 1 protocol deviation censored

# Jupiter II: Preliminary 30-day follow-up\*

	GROUP A	GROUP B	p value
<u>Clinical status</u>	159	159	
<u>MACE</u>			
Death	0%	0%	
MI	0.8%	0%	.3772
TLR	0%	0%	
CABG	0%	0%	
Re-PTCA	0%	0%	
Re-PTCA + Stent	0%	0%	
Total events	0.8% (1)	0%	.3772
<u>Sub-acute Thrombosis</u>	1.6% (2)	0%	.3246

The 6-month follow-up results will be available on October 2005

\* Clinical events not yet adjudicated by Critical Event Committee

# Conclusion: Clinical Studies

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- Initial clinical outcomes are showing a positive performance in term of MACE, incidence of acute and subacute thrombosis in both groups;
- The preliminary Jupiter II 30-day results demonstrate low rate of clinical events in both groups confirming at short term that the two stents in evaluation have a comparable clinical safety (MACE and Thrombosis);
- Janus is the latest innovative DES platform, designed for resolving major limitations of current DES with polymer coatings.

# DIABETEs and drug Eluting Stent

## The DIABETES III Trial



# Diabetes III

## STUDY DESIGN:

### Multicenter:

- Madrid: Hospital Clinico San Carlos, Prof. Macaya, Dr. Sabaté (PIs)
- Barcelona: Hospital de Bellvitge, Dr. Cequier
- Murcia: Hospital Virgen de Arrixaca, Dr. Valdes

Spanish Prospective Trial (80 pts will be enrolled)

START OF THE STUDY: December 2004

AIM OF THE STUDY: To evaluate the efficacy of Janus Carbostent on the inhibition of neointimal proliferation, assessed by QCA at 9 month follow-up, in diabetic patients. The obtained results will be compared to an historical cohort treated with bare metal stent (DIABETES I trial)

# Diabetes III

## PRIMARY ENDPOINT:

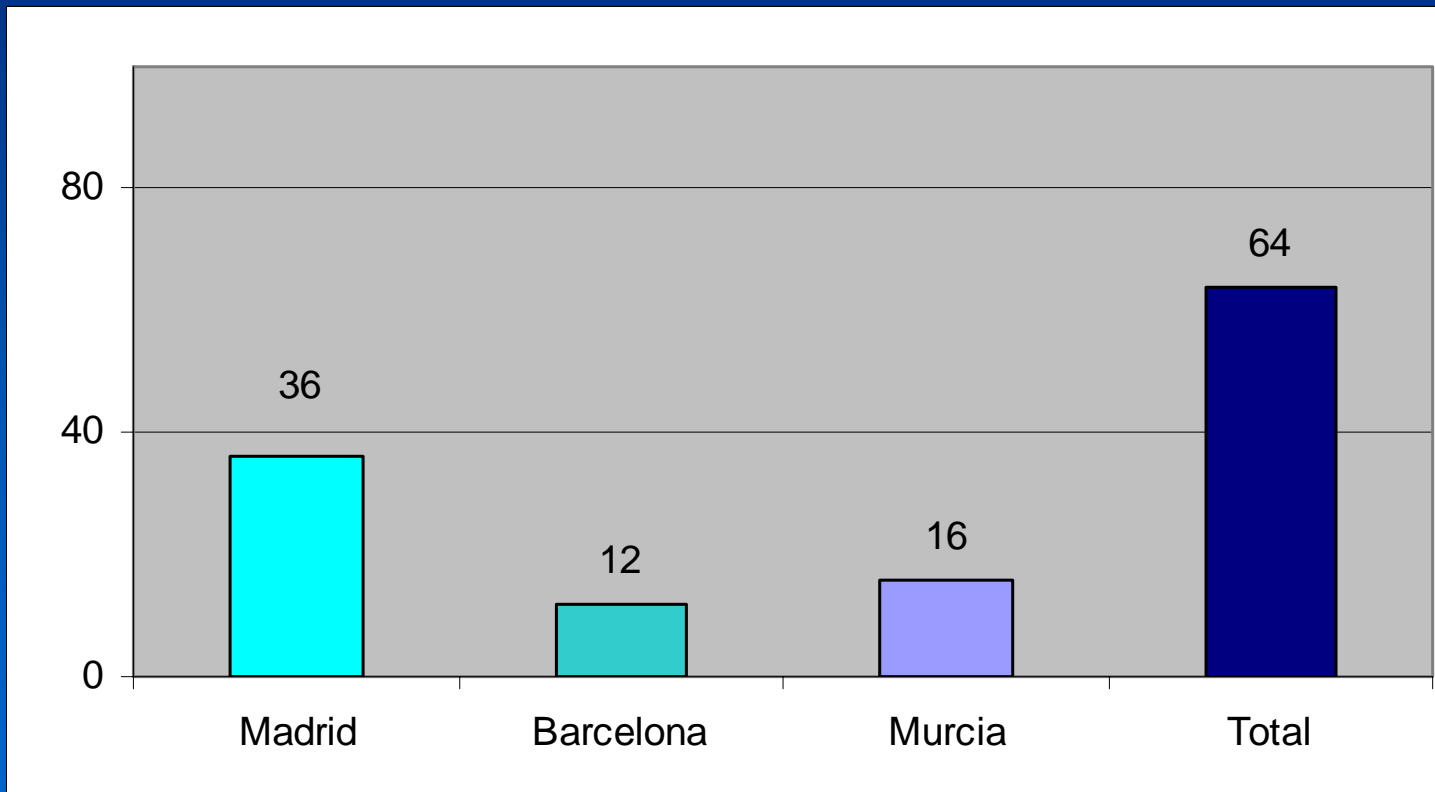
- Late Lumen Loss (in-stent + edges) by QCA at 9 month f-up

## SECONDARY ENDPOINTS:

- In-stent + edges neointimal hyperplasia area by IVUS at 9 month f-up
- Binary restenosis rate, MLD and mean luminal diameter at 9-month f-up
- MACE at 1, 9, 12 and 24 month f-up
- Occurrence of complications attributable to DES: late stent thrombosis, edge effect, late stent malapposition, coronary aneurysm

# Diabetes III

Enrolment started in December 2004



# eJANUS

# eJanus

## STUDY DESIGN:

European, Multicenter (100-200), Prospective Registry  
Based on electronic CRFs

START OF THE STUDY:      November 2004

## AIM OF THE STUDY:

Assessment of clinical performances of Janus Carbostent in the treatment of de novo or restenotic lesions in “real world” population

## STUDY POPULATION:

All “real world” patients (2500 pts) with stable/unstable angina, documented ischemia or AMI who are scheduled to undergo coronary angioplasty of de novo or restenotic lesion(s) in native coronary arteries

# eJanus

## PRIMARY ENDPOINTS:

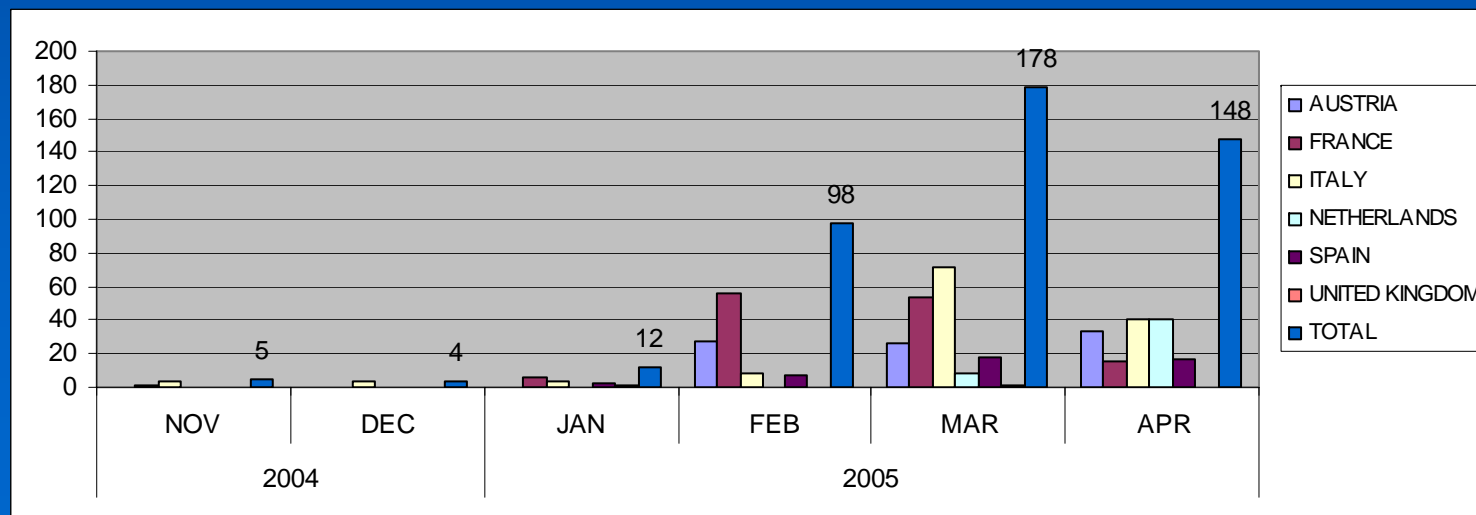
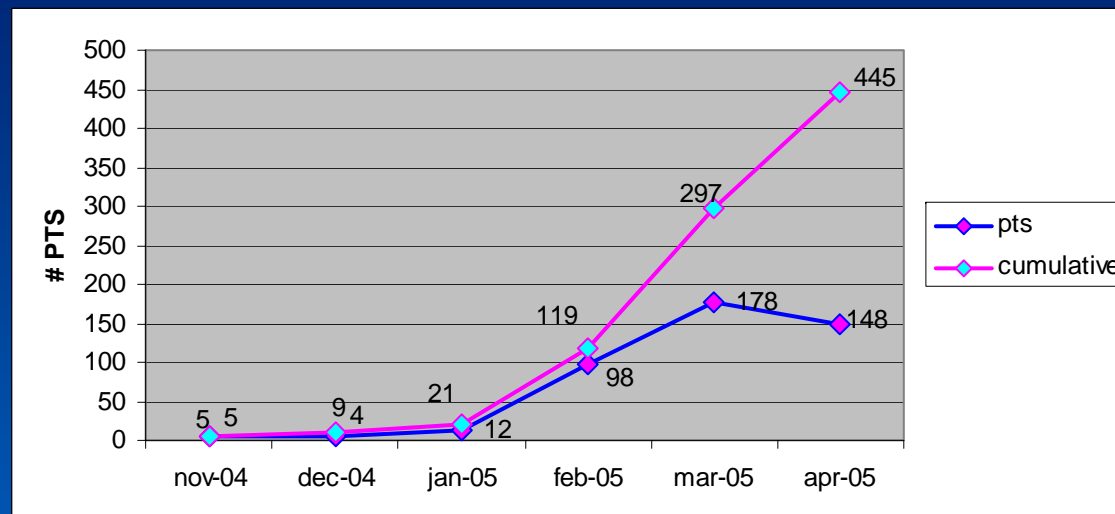
- Incidence of MACE within discharge, 30 days, 6, 12 & 24 months
- Thrombosis rate within discharge, 30 days, 6, 12 & 24 months (acute, sub-acute & late thrombosis)
- Clinical performances of Janus Carbostent, during implant procedure

## SECONDARY ENDPOINT:

- Clinically driven TLR at 6 months

# eJanus Enrolment Update

## Enrolment started in November 2004



***SORIN JANUS CARBOSTENT***

***FUTURE DEVELOPMENTS***



## ***POSSIBILITY TO REALIZE DIFFERENT RESERVOIRS***

The shape and size of the reservoirs can be selected in order to:

**1) CONTAIN DIFFERENT AMOUNT OF DRUG**

**2) ADJUST THE RELEASE KINETIC**

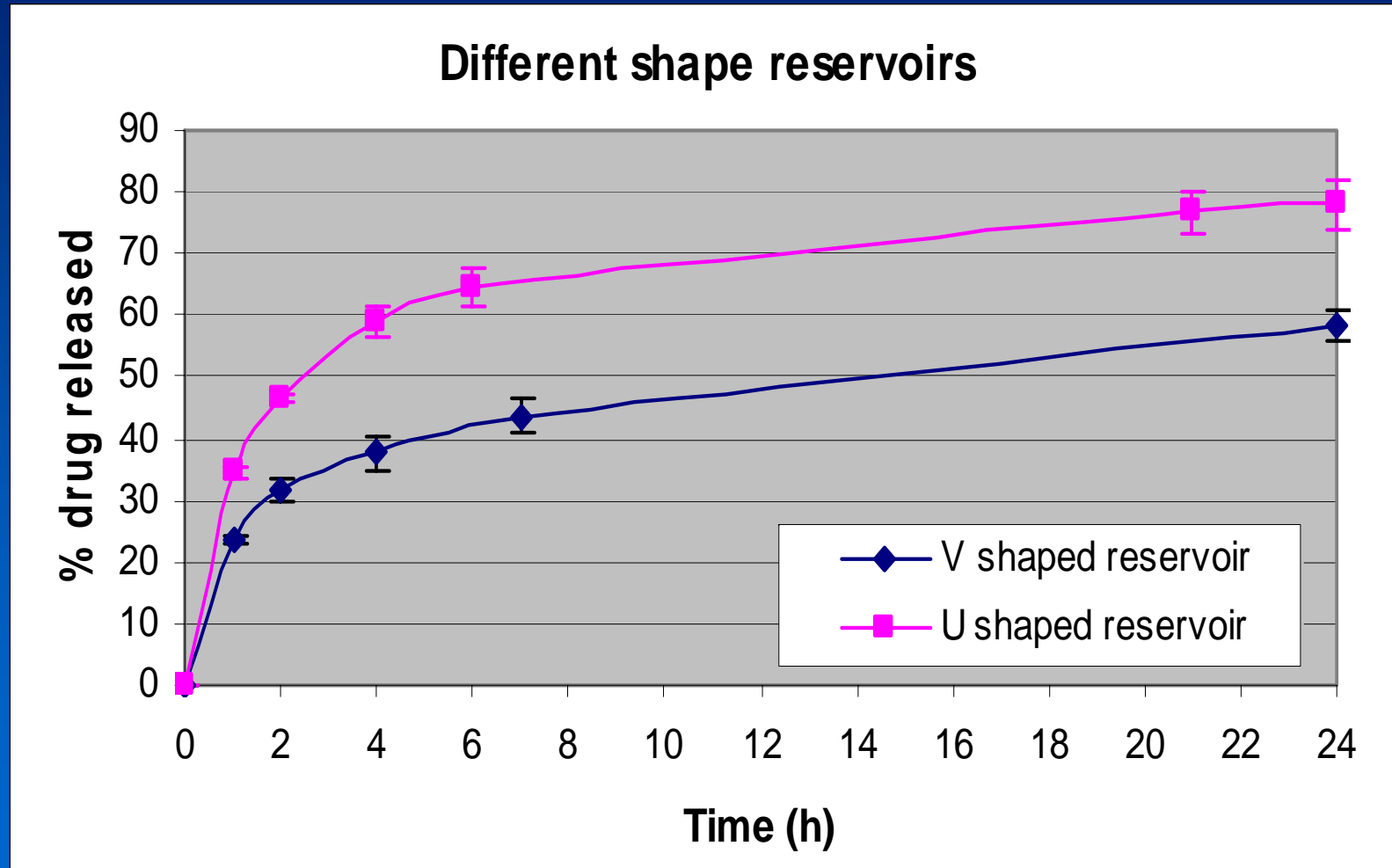
***“U” shaped reservoirs***



***“V” shaped reservoirs***

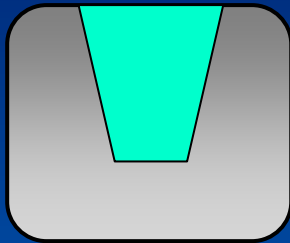


# EFFECT OF THE RESERVOIR SHAPE ON RELEASE KINETIC

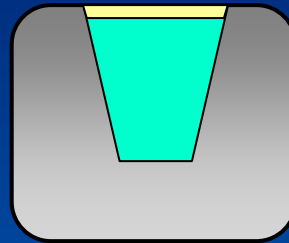


## Carriers: a choice not an obligation.

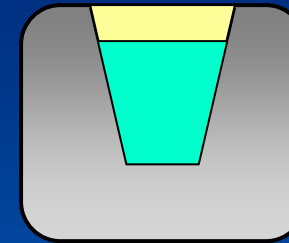
With Janus platform no additional carrier is strictly required, but the widest choice of drug formulations and excipients can be used to realize more sophisticated release profiles.



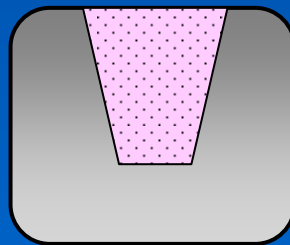
**RESERVOIR FILLED  
WITH ONE DRUG**



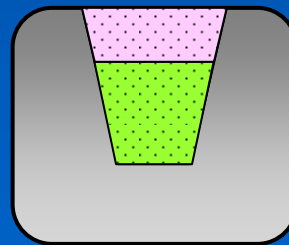
**ONE DRUG  
+  
POLYMER COVER  
FOR SLOWER RELEASE**



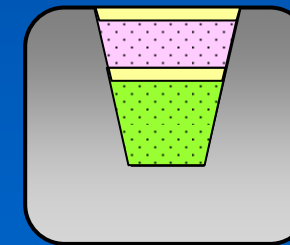
**THICKER POLYMER  
COVER FOR EVEN  
SLOWER RELEASE**



**RESERVOIR FILLED WITH  
A POLYMER MATRIX  
CONTAINING THE DRUG**



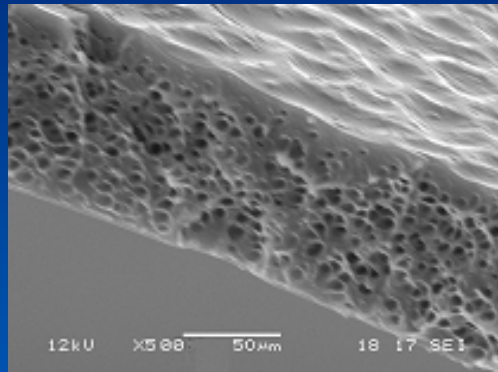
**TWO POLYMER  
MATRICES CONTAINING  
TWO DIFFERENT DRUGS**



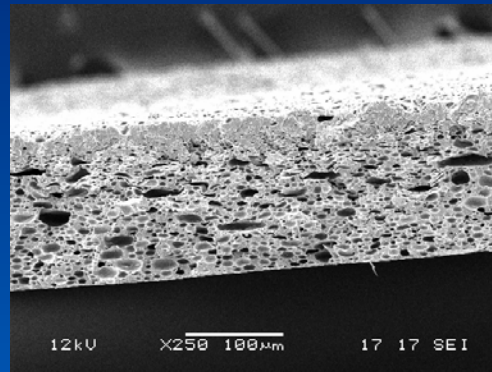
**TWO POLYMER  
MATRICES CONTAINING  
TWO DIFFERENT DRUGS  
+  
TWO POLYMER COVERS**

# ***SEM images of Sorin proprietary carriers under evaluation***

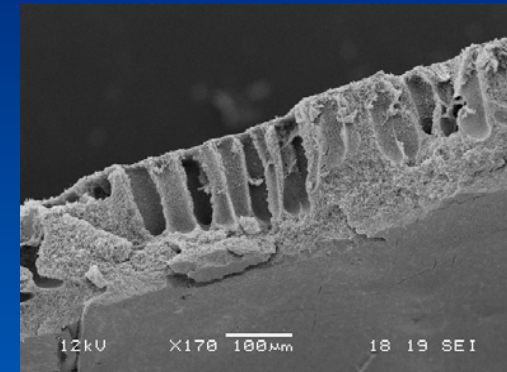
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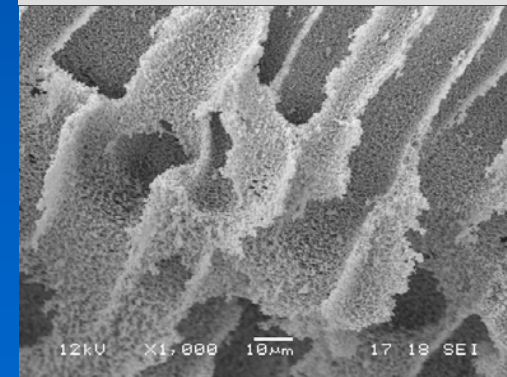
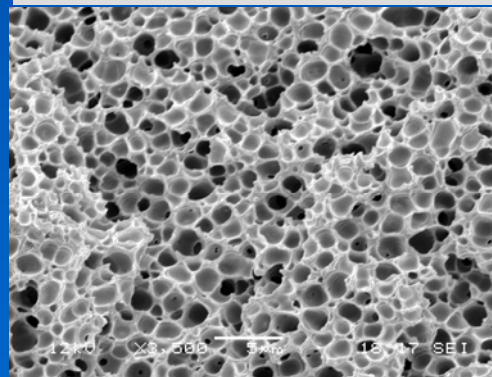
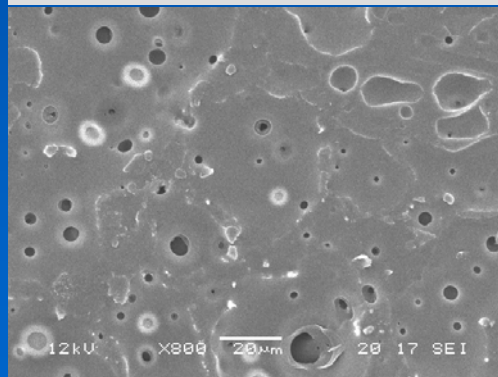
**Porous matrix with top coat**



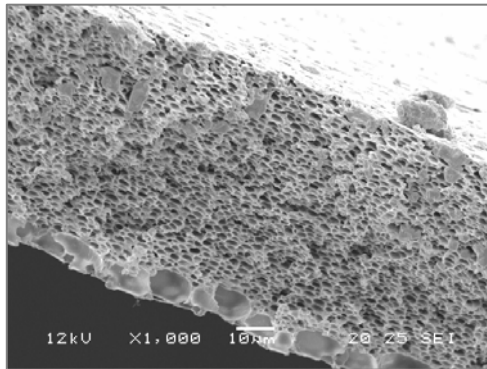
**Porous matrix**



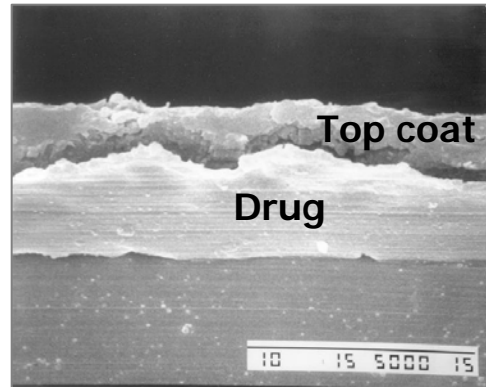
**Tubular matrix**



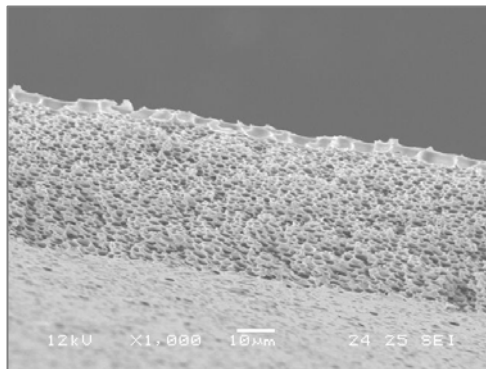
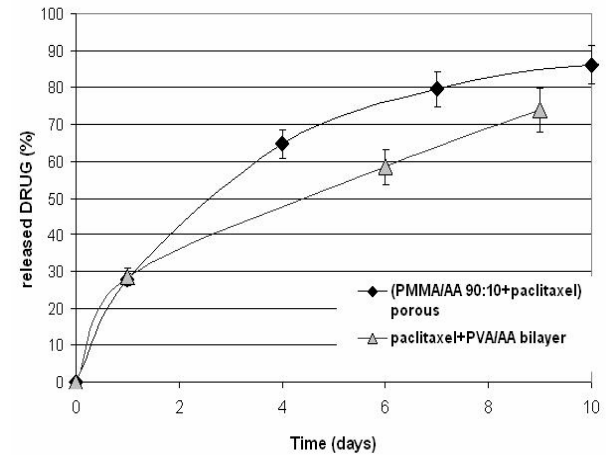
# INFLUENCE OF POLYMER MATRICES ON THE RELEASE KINETIC



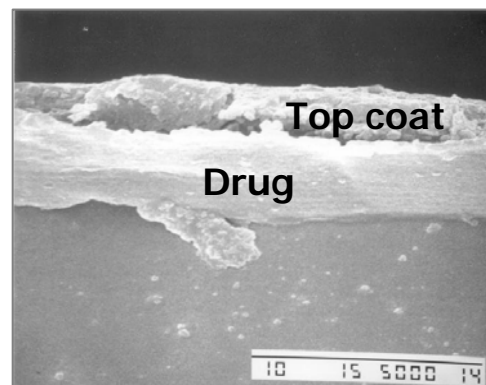
**Porous matrix**  
Drug: tacrolimus  
Porous film: PMMA/AA 90:10



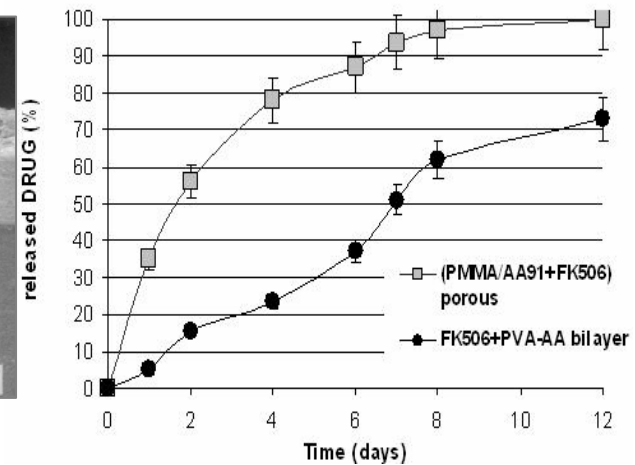
**Thin polymeric bilayer**  
metallographic section  
Drug: tacrolimus  
Top coating: PVA/AA



**Porous matrix**  
Drug: paclitaxel  
Porous film: PMMA/AA 90:10

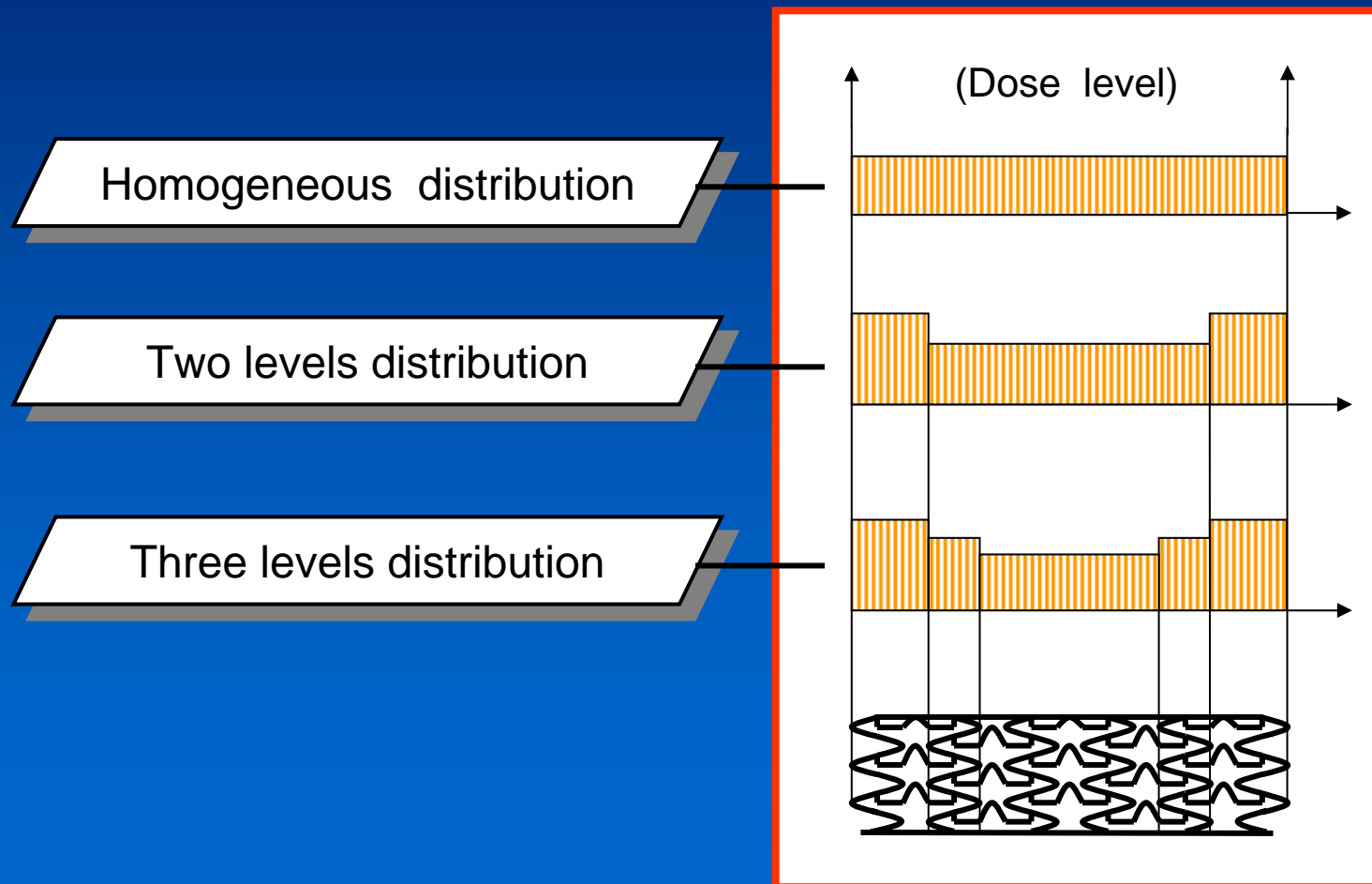


**Thin polymeric bilayer**  
metallographic section  
Drug: paclitaxel  
Top coating: PVA/AA



# ***LONGITUDINAL DOSE DISTRIBUTION***

**Variable dose distribution along the longitudinal axis of the stent can be achieved filling the reservoirs with different amount of drug**



# LONGITUDINAL DRUG / DOSE DISTRIBUTION

Suitable amount of different drugs can be loaded selectively along the longitudinal axis of the stent to provide synergic therapeutic effects

