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

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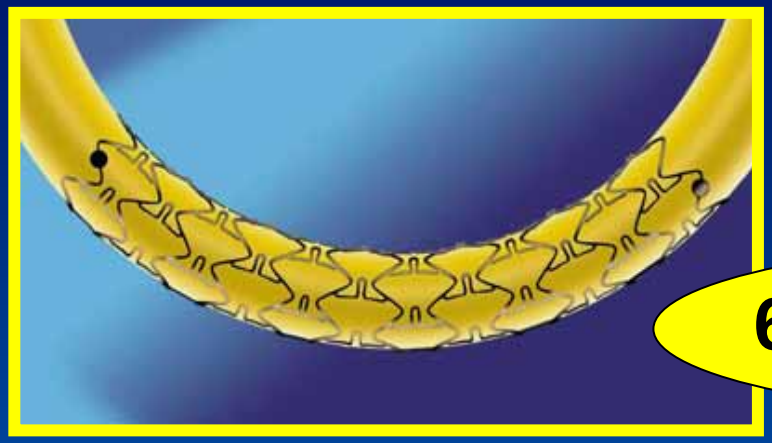
JANUS CARBOSTENT: THE PLATFORM



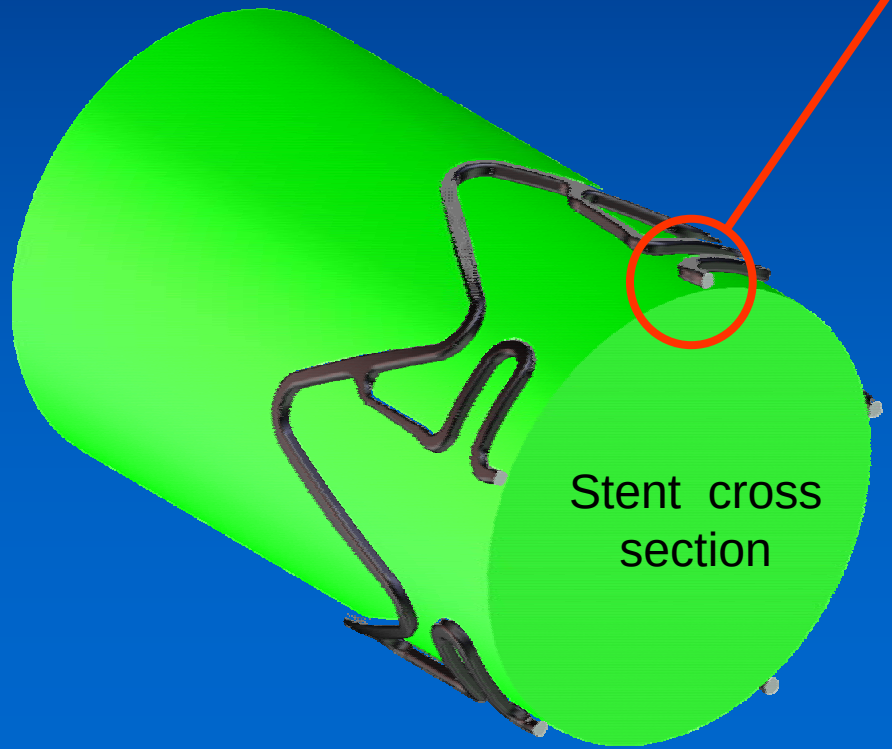
6 years of clinical use

Distinctive Feature	Benefit
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™**

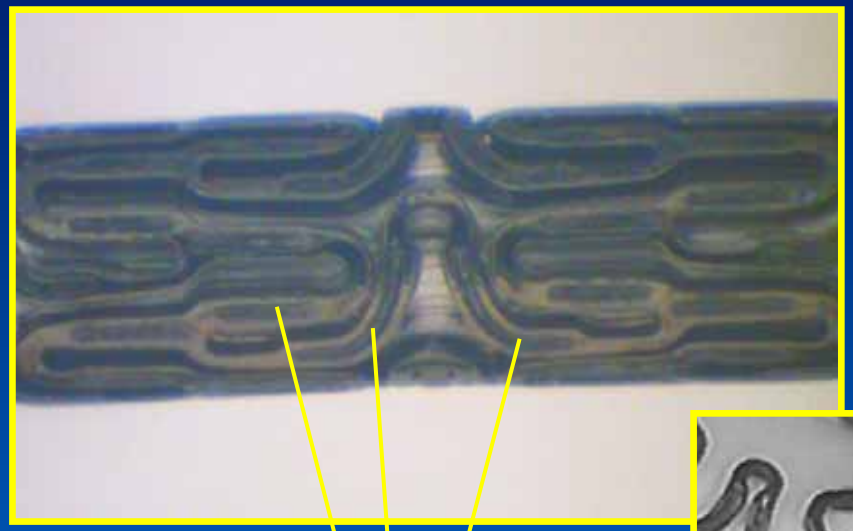


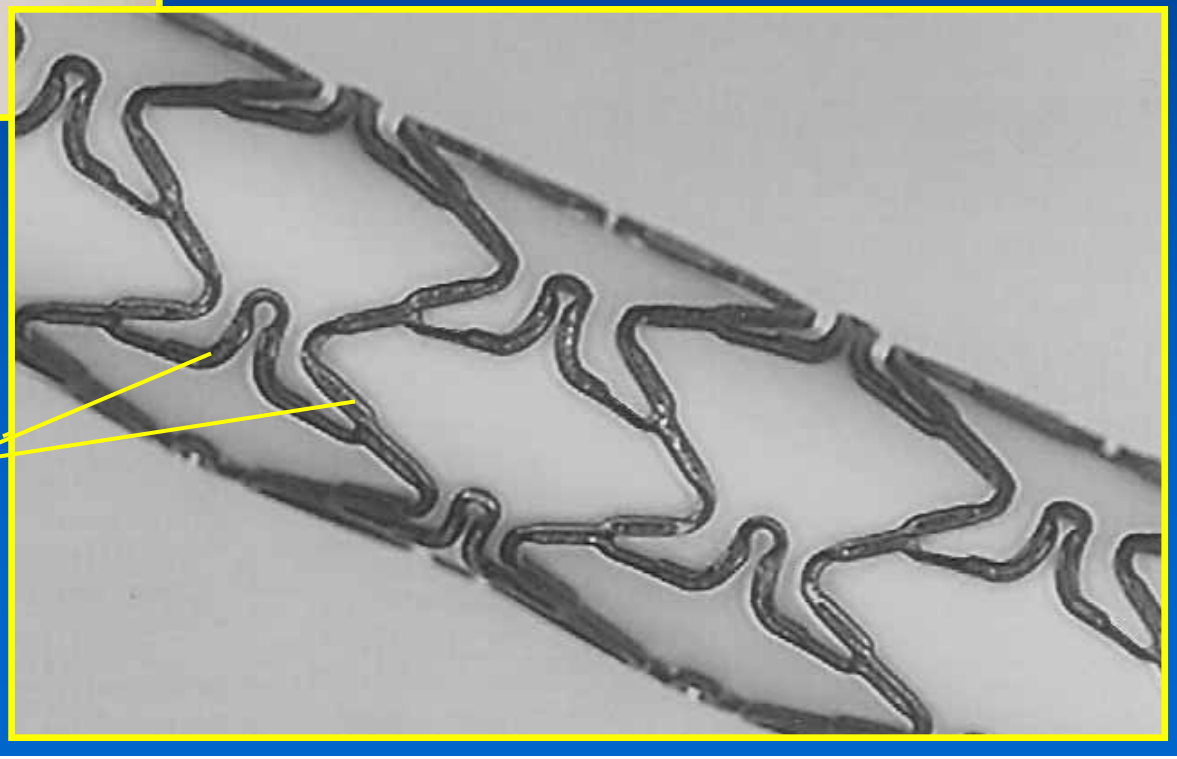
Strut cross section

Reservoirs on the external surface

Integral Carbofilm™ coating

JANUS Carbostent

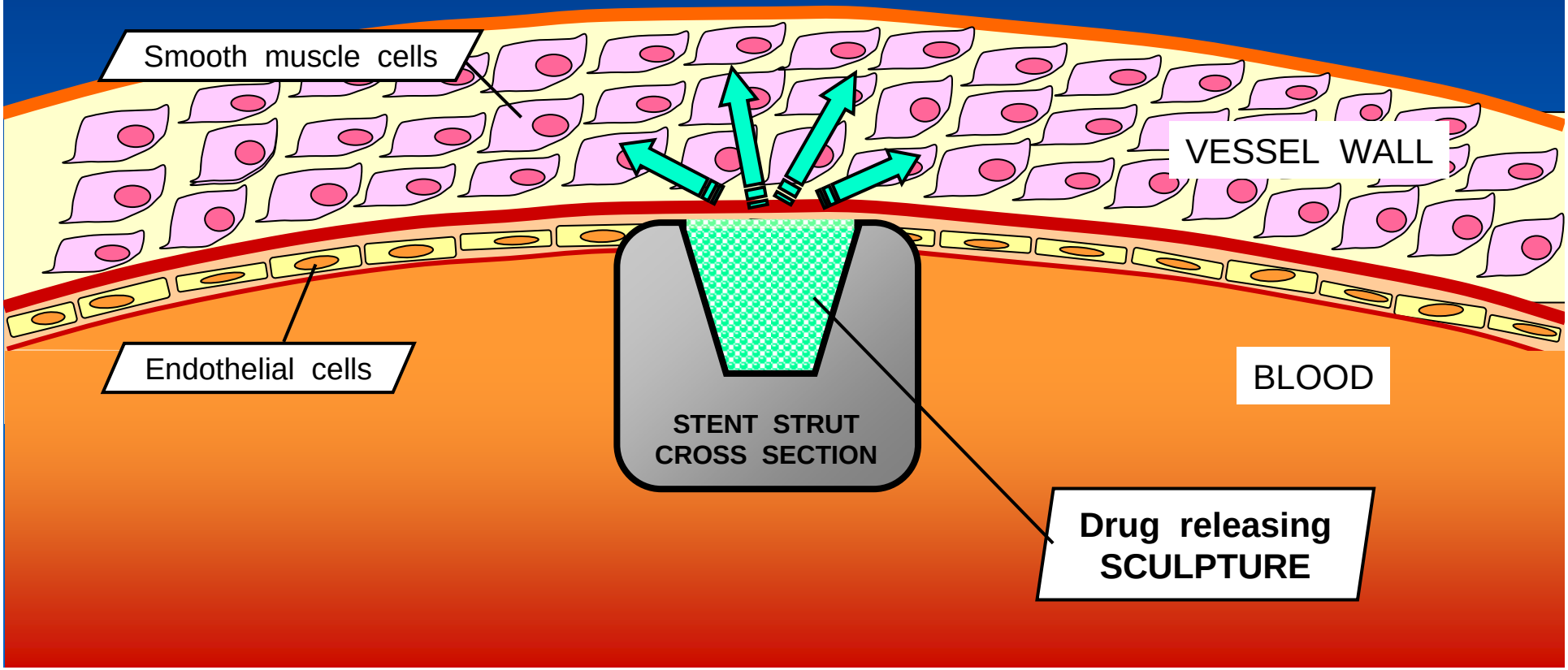




Deep drug reservoirs on the external surface

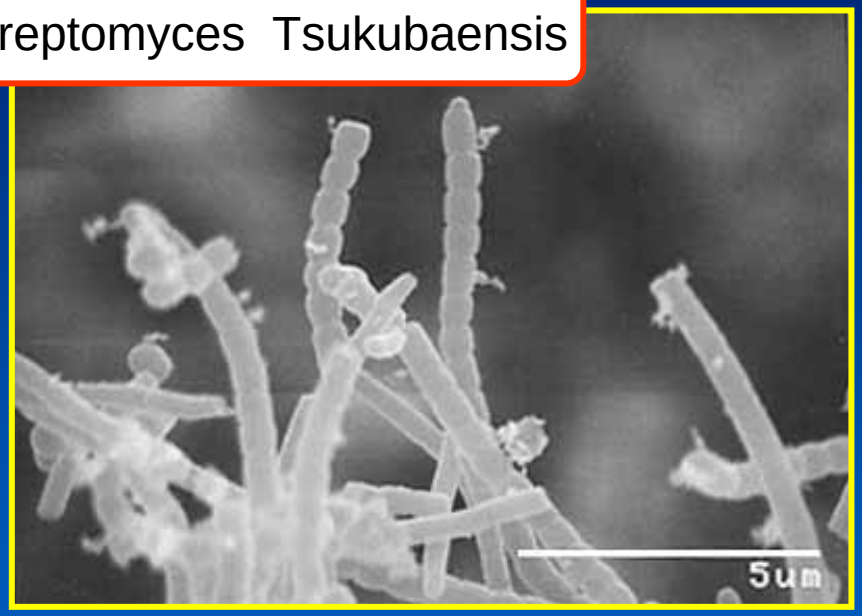
JANUS CARBOSTENT RELEASING MECHANISM

- 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

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

α phase **β phase**

Clinical registry
≥ 50 patients

Clinical evaluation
randomized 1:1
multicenter
double blind
Investig. & Core-Lab

JANUS
≥ 50 patients

TECNIC
(control)
≥ 50 patients

Follow-up at
1, 6, 12 and
24 months

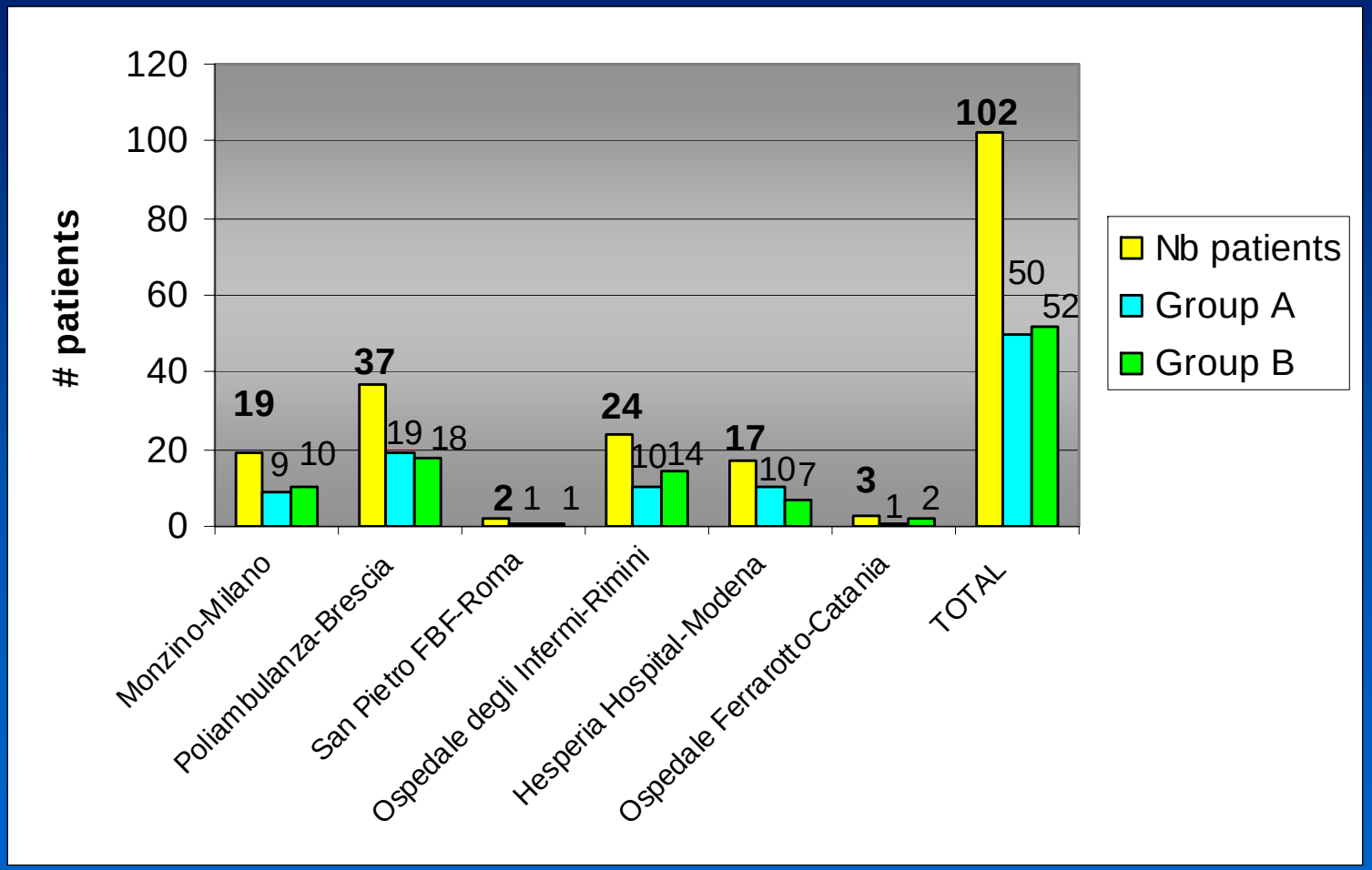
- 1 month: Clinical
- 6 months: Clinical, angiographic and IVUS
- 12 months: Clinical
- 24 months: Clinical

Interim analysis
at 1 month
"Safety" evaluation

Clinical, angiographic
and IVUS follow-up at
6 months

Clinical follow-up
at 12 and 24
months

Jupiter I – β: Study Update



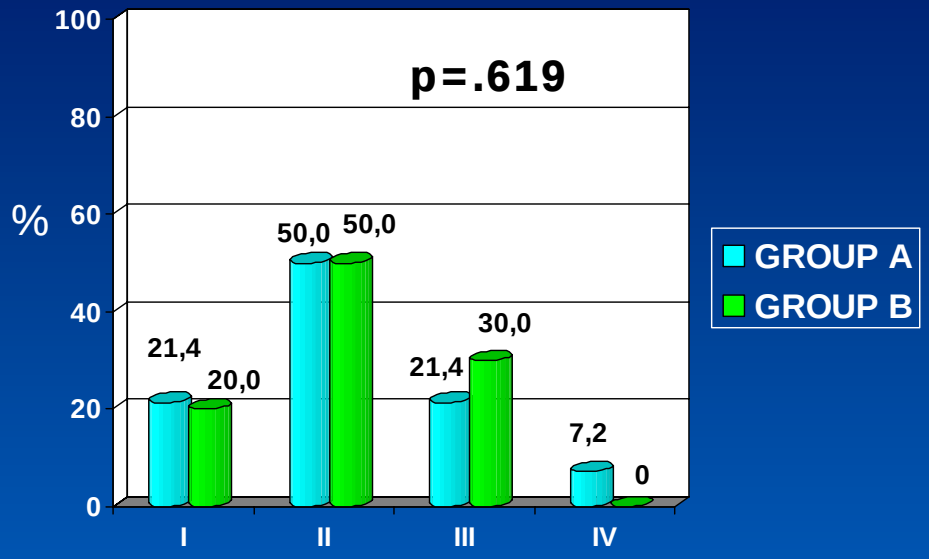
Enrolment completed on December 2004

Jupiter I - β: Base-Line Clinical Characteristics

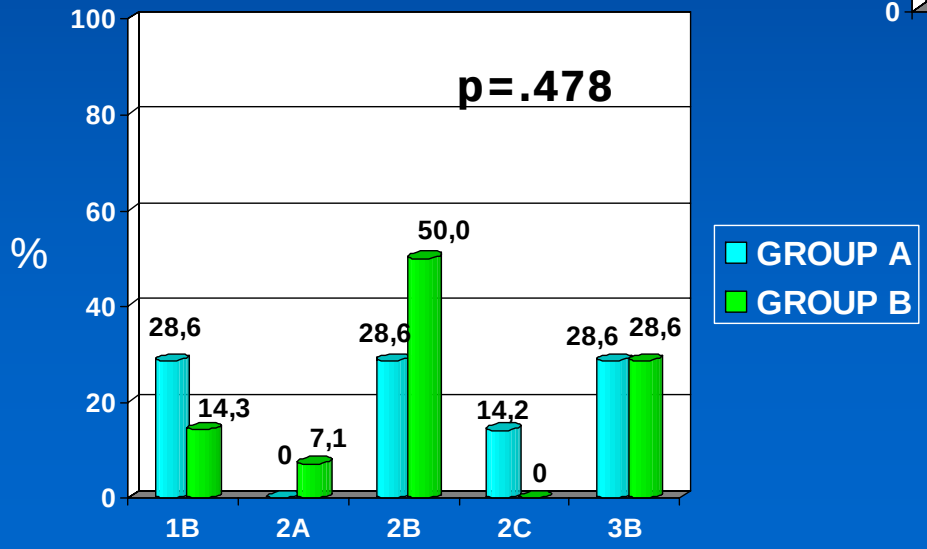
	GROUP A	GROUP B	P value
N° of enrolled pts (102)	50	52	
N° of available pts (92)	46	49	
Male	89.1%	79.6%	.203
Age (yrs)	64.6 ± 11.6	64.0 ± 10.4	.788
Clinical Status			.436
Asymptomatic	6.5% (3 pts)	8.2% (4 pts)	
Silent Ischemia	8.7% (4 pts)	8.2% (4 pts)	
Stable Angina	60.9% (28 pts)	42.8% (21 pts)	
Unstable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

Jupiter I - β: Base-Line Clinical Characteristics

Stable angina



Unstable angina



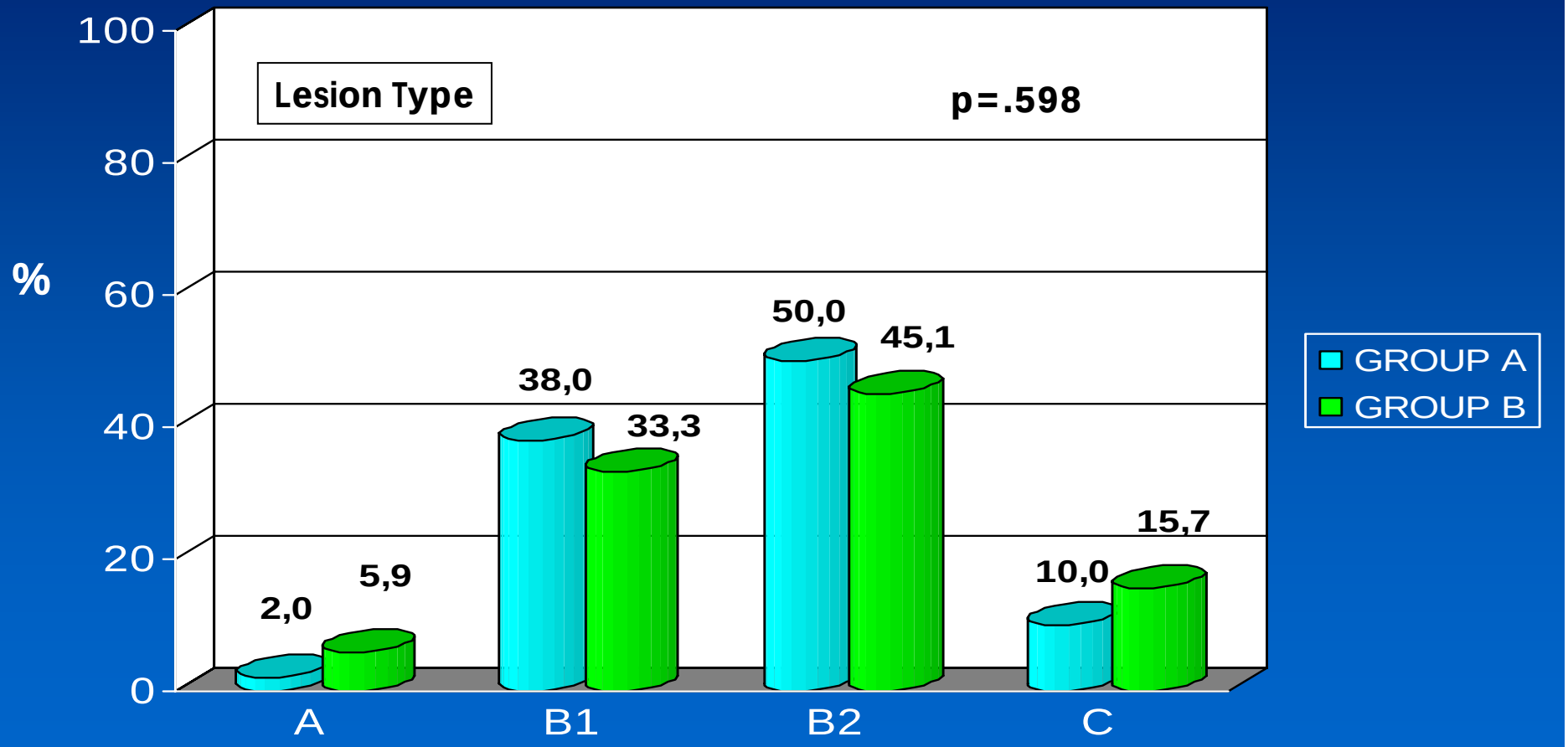
Jupiter I - β: Base-Line Clinical Characteristics

	GROUP A	GROUP B	P value
Risk factors	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

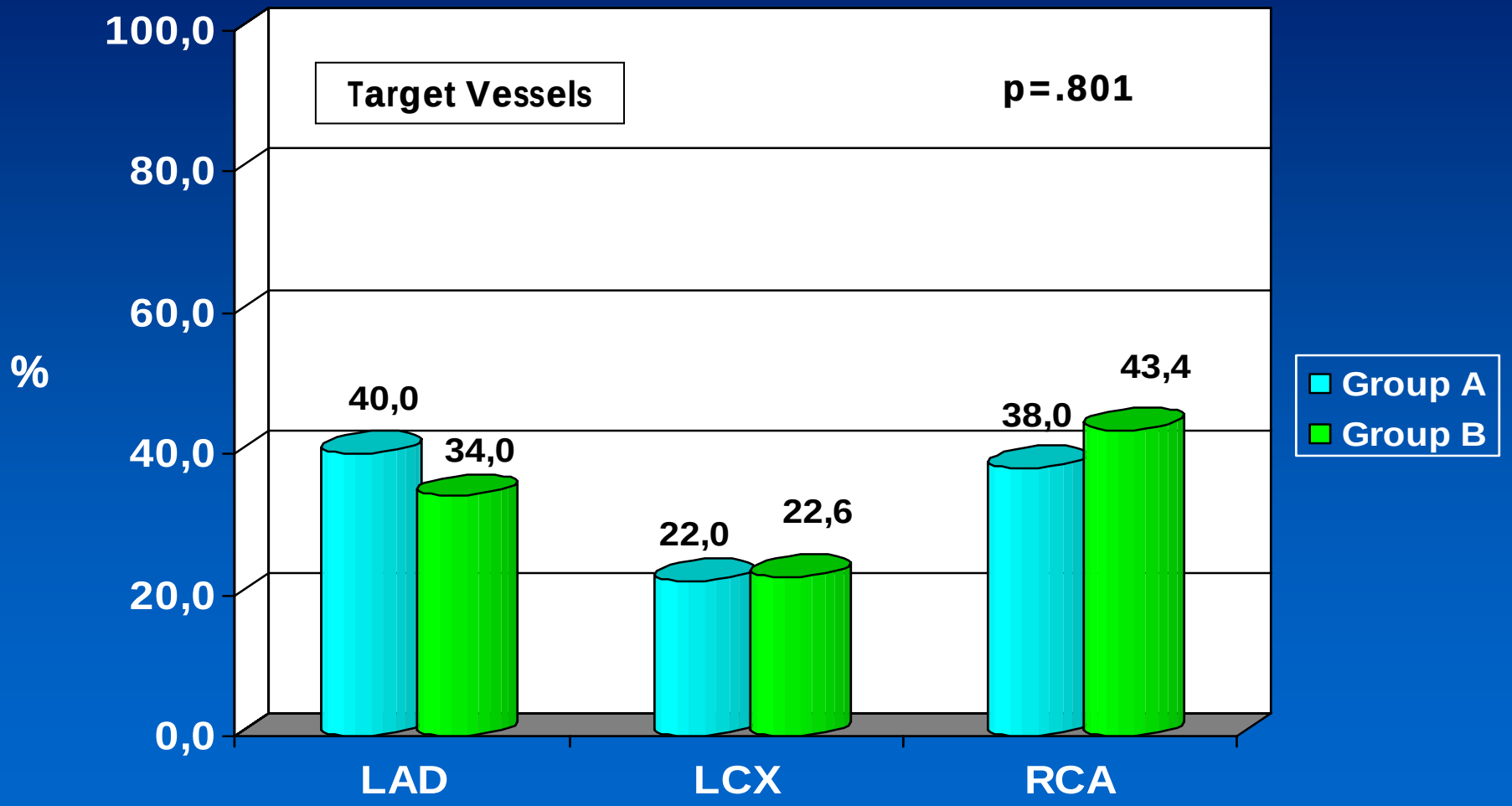
Jupiter I - β: Target lesion characteristics

	GROUP A	GROUP B	P value
N° of available lesions (103)	50	53	
De Novo	100%	100%	
Lesion morphology			.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

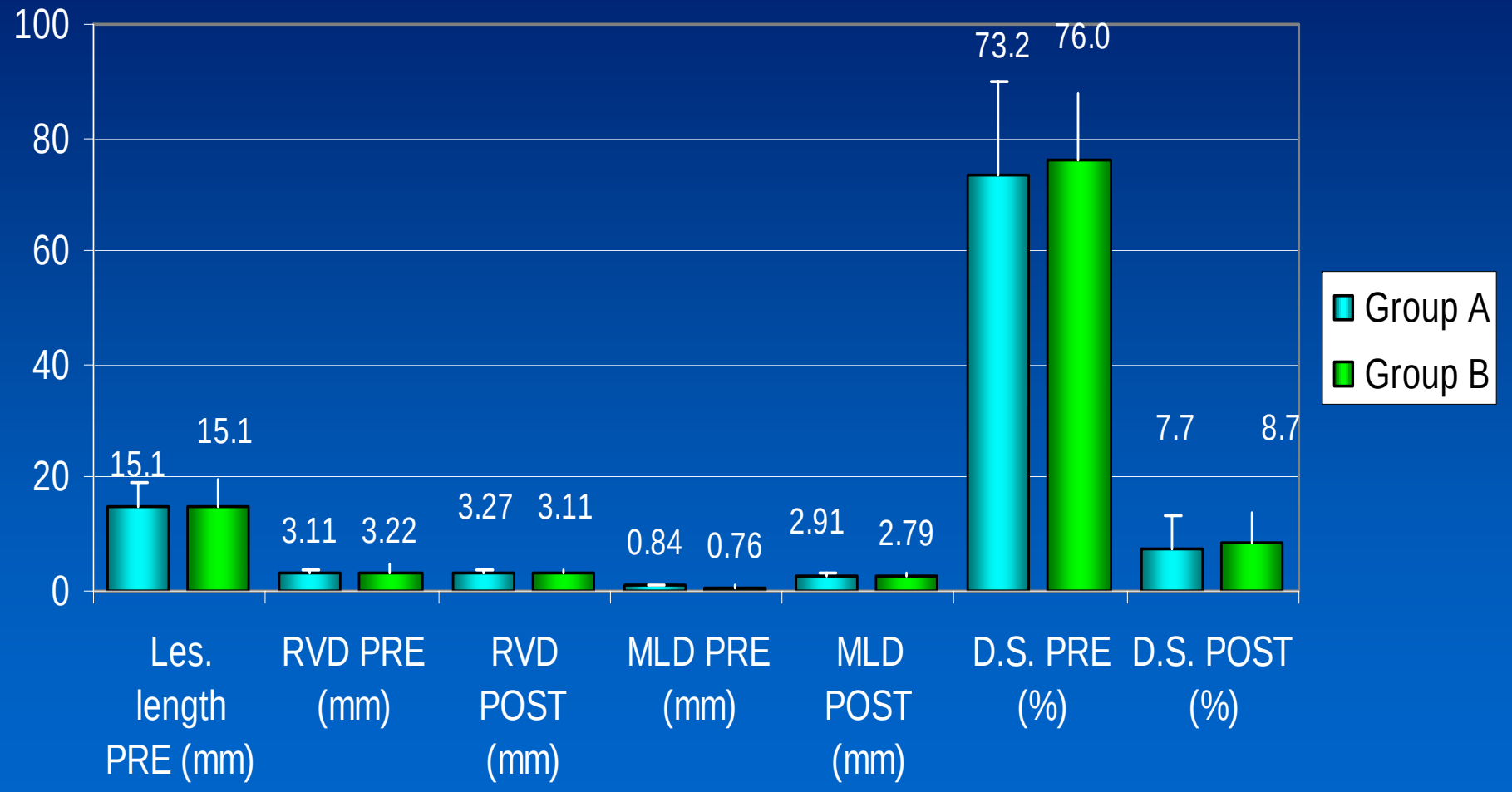
Jupiter I - β: Target lesion characteristics



Jupiter I - β: Target lesion characteristics



Jupiter I - β : Procedural angiographic data



Jupiter I - β : Procedural data

	GROUP A	GROUP B	P value
Stenting procedure	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 ± 2.86	15.36 ± 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 - β : Preliminary in-hospital MACE

	GROUP A 50	GROUP B 52
MACE		
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 - β : Preliminary 30-day follow-up

	GROUP A	GROUP B
	50	52
MACE		
Death	0%	0%
MI	0%	3.8% (2)
TLR	0%	0%
CABG	–	–
Re-PTCA	–	–
Re-PTCA + Stent	–	–
Total events	0%	3.8% (2)
Sub-acute Thrombosis	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: 2.3µg/mm2

Clinical evaluation randomized
1:1
16 centers in Europe
double blind
(Investigator & Core-Lab)

JANUS
150 + 10% drop-out = 165 pts

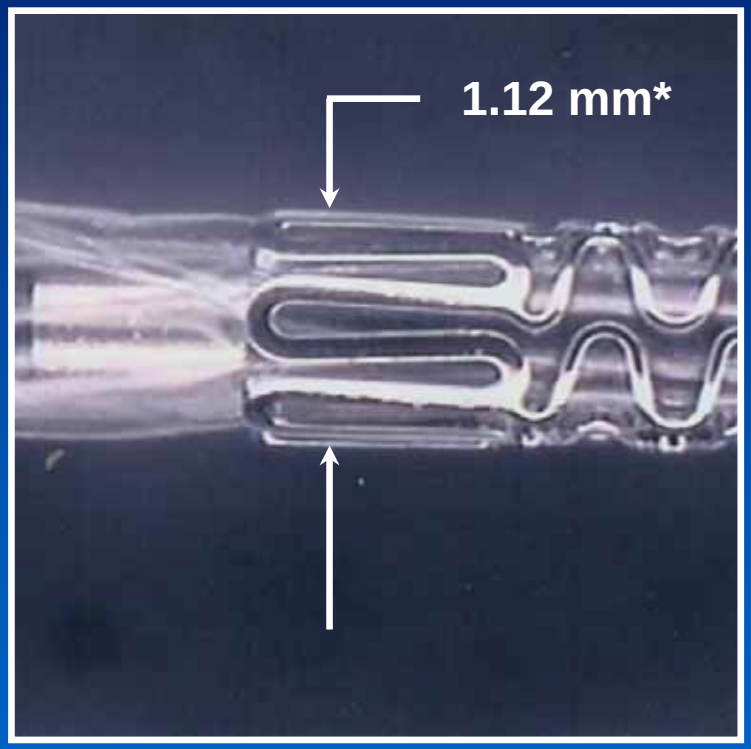
TECNIC
150 + 10% drop-out = 165 pts

Follow-up

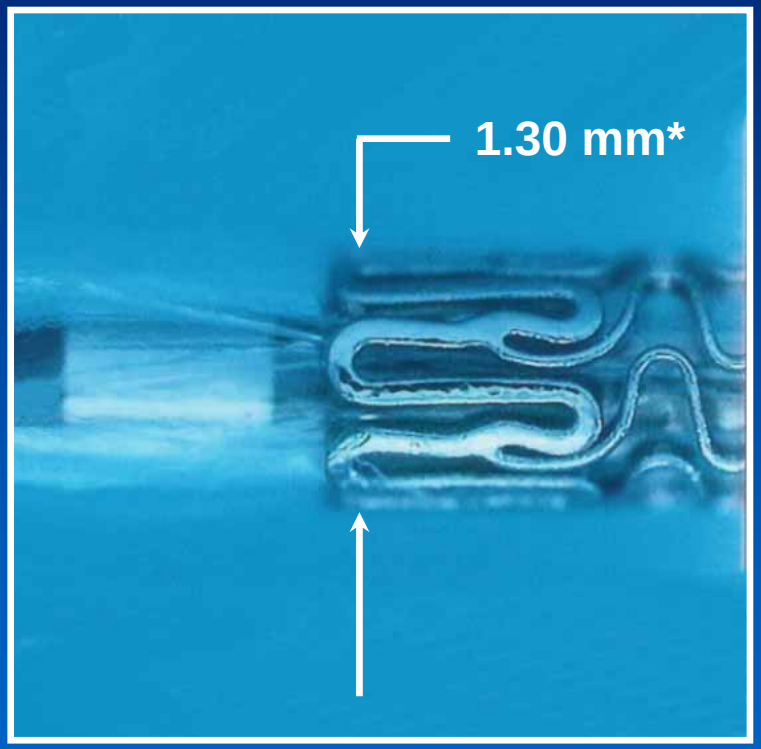
- **1 month: Clinical**
- **6 months: Clinical, Angiographic**
- **12 months: Clinical**
- **24 months: Clinical**

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



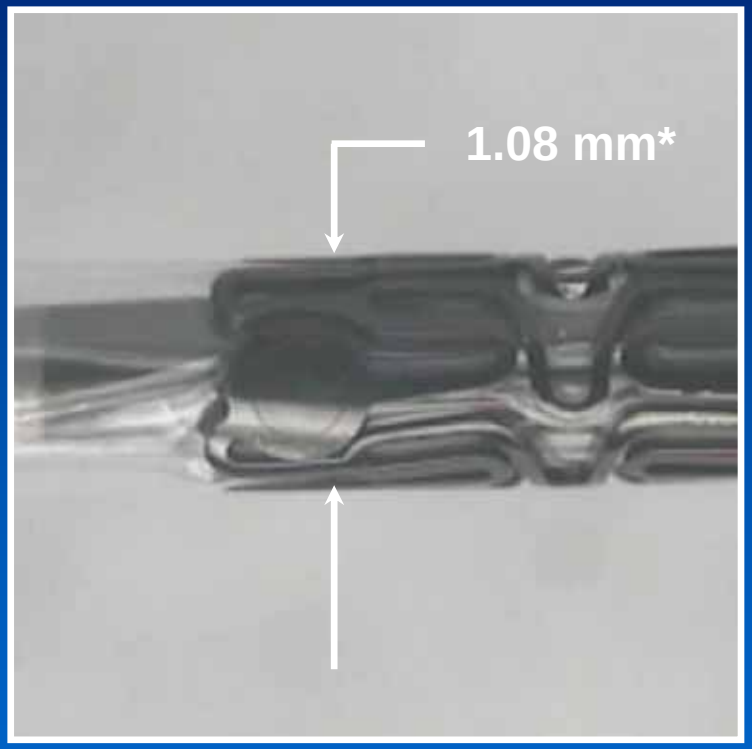
Bx Sonic™
(3.0 x 18 mm)



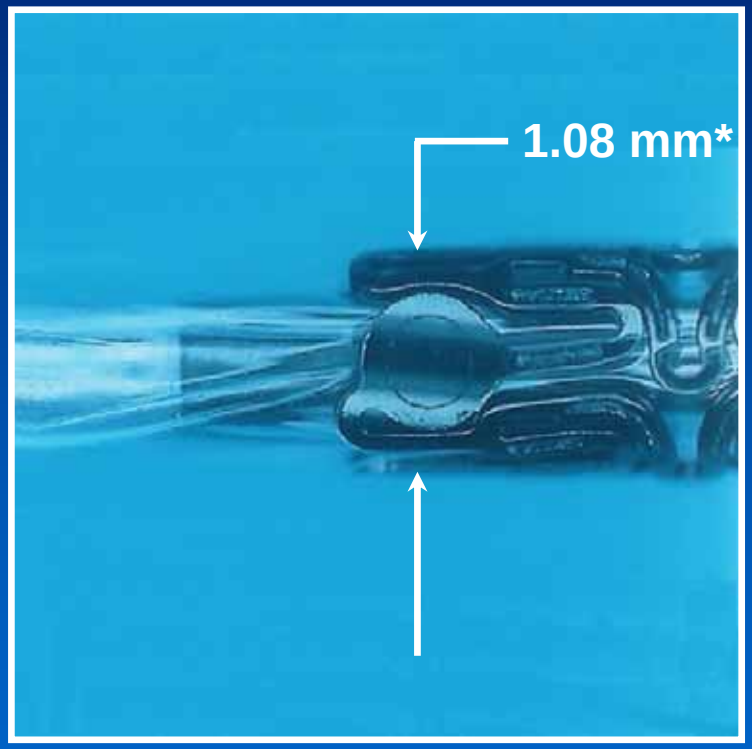
Cypher Select™
(3.0 x 18 mm)

* Crossing profiles measured according to ASTM F2081-01

No Profile Increase Avoiding A Polymer Coating



Tecnic Carbostent™
(3.0 x 15 mm)



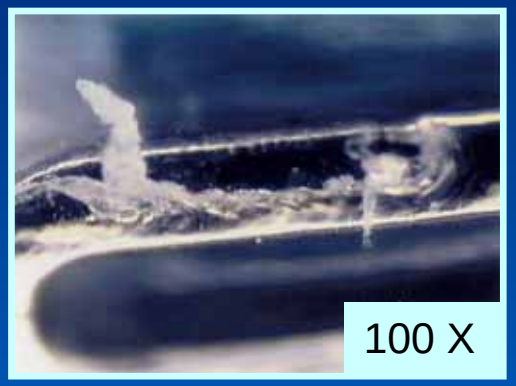
Janus Carbostent™
(3.0 x 15 mm)

* Crossing profiles measured according to ASTM F2081-01

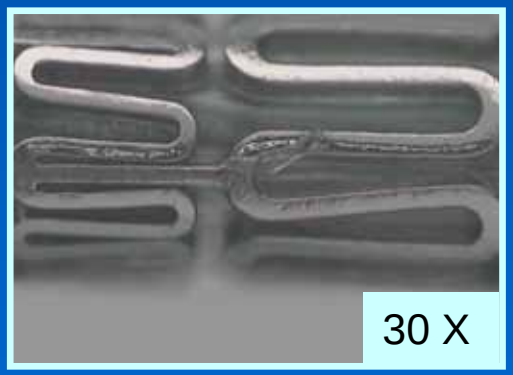
Polymer Coating Fragility

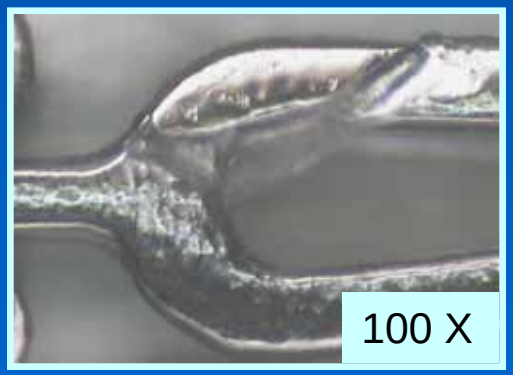
The polymer coatings and matrices used as drug carriers for DES are relatively soft and fragile. During stent delivery and implant they are exposed to the risk of scratches and peeling, especially when the ***Direct Stenting technique*** is used.

Cypher



Taxus





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.*

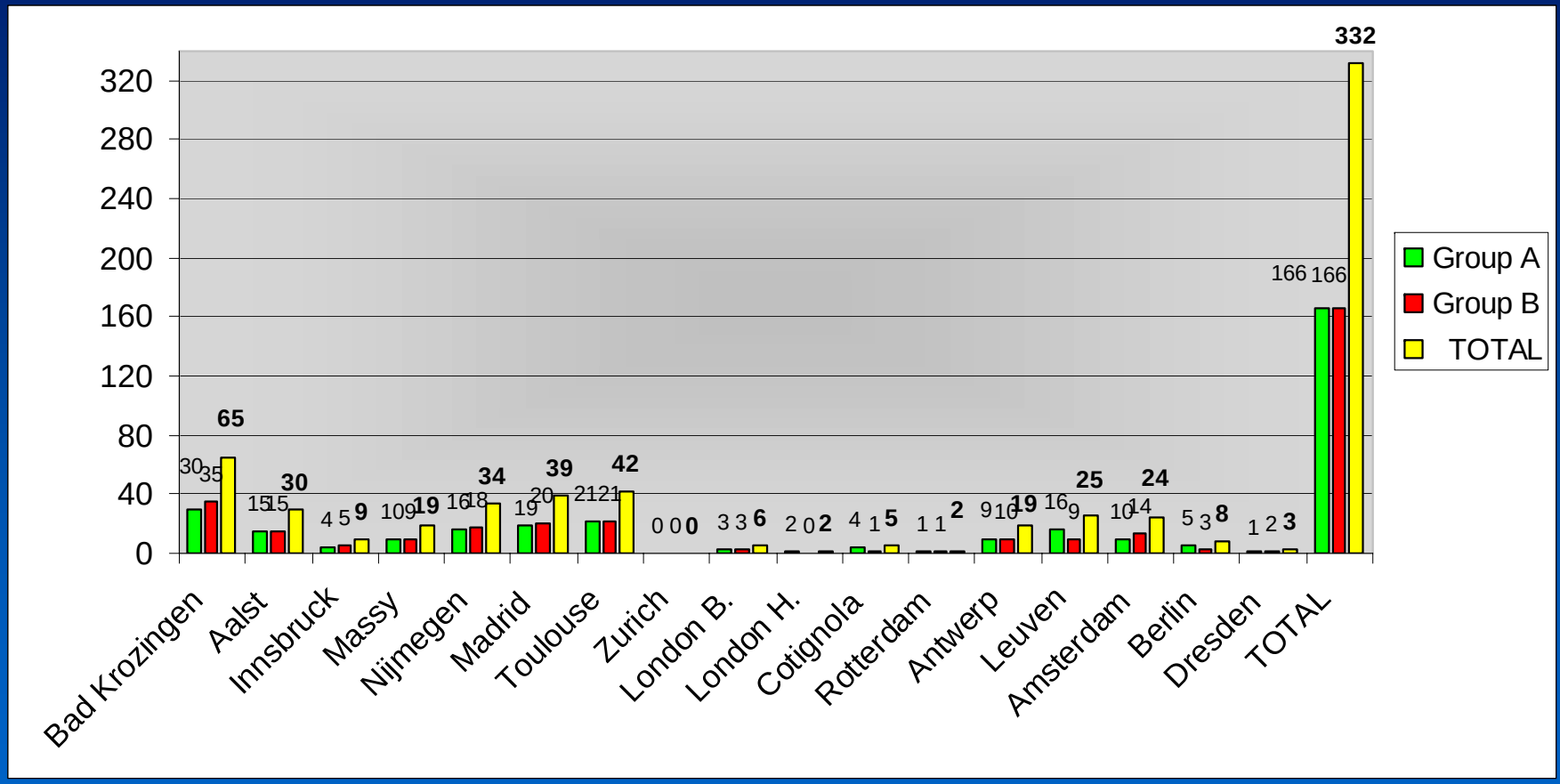
Janus

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

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

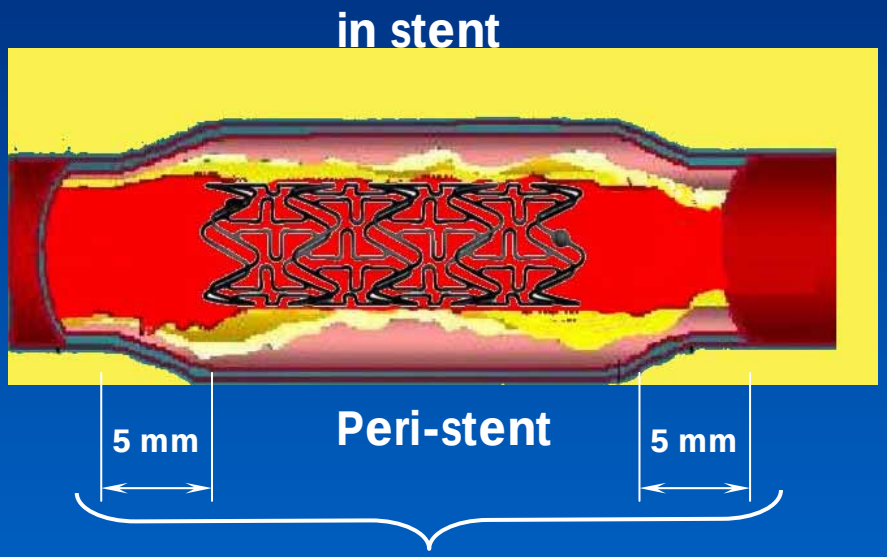
Jupiter II: Enrolment



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
Clinical Status			
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
CAD			
Single vessel disease	61.6% (98 pts)	59.8% (95 pts)	.7305
Multivessel disease	38.4% (61 pts)	40.2% (64 pts)	.7305

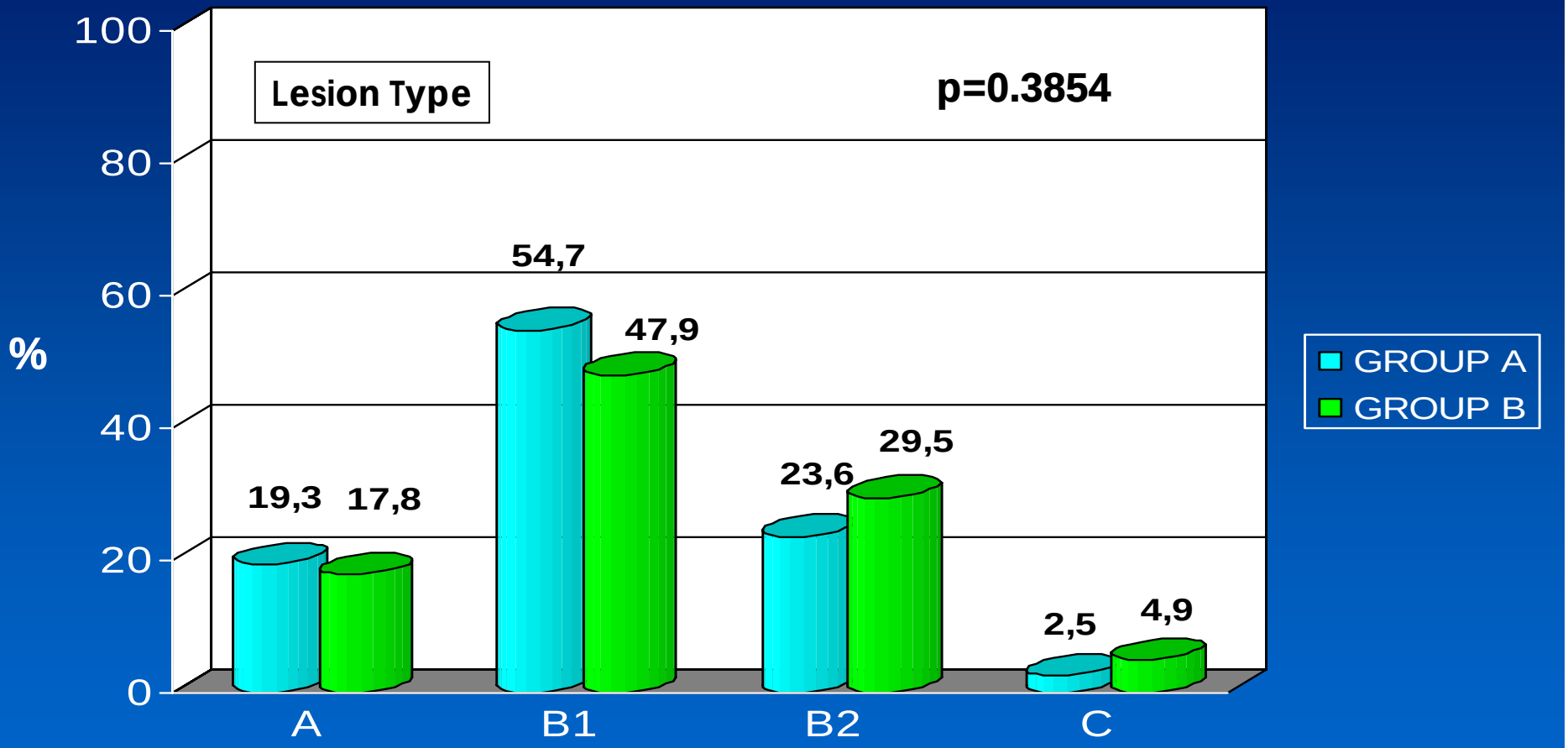
Jupiter II: Base-Line Clinical Characteristics

	GROUP A	GROUP B	p value
Risk factors	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

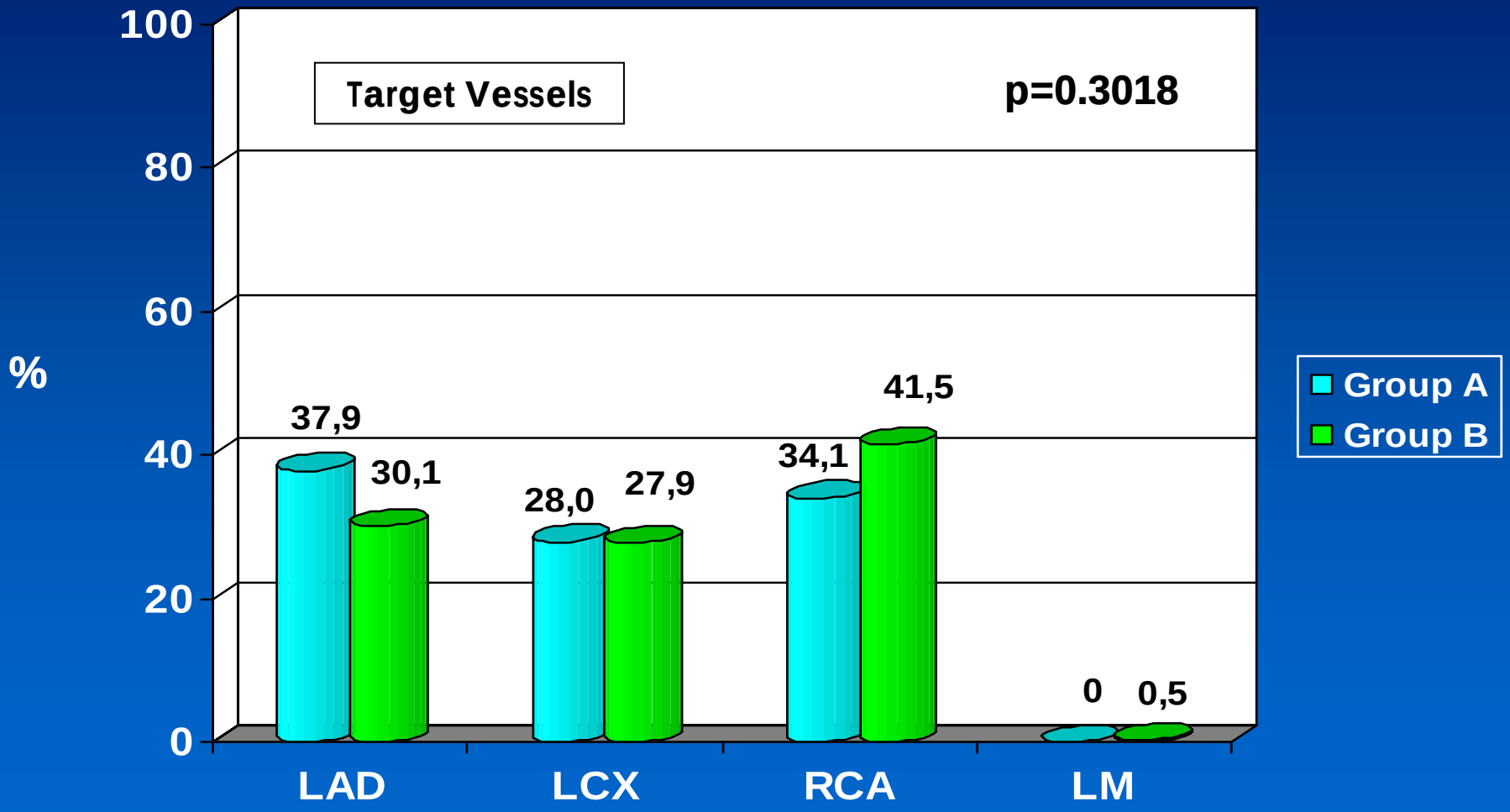
Jupiter II: Target lesions Characteristics

	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)	.0399
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

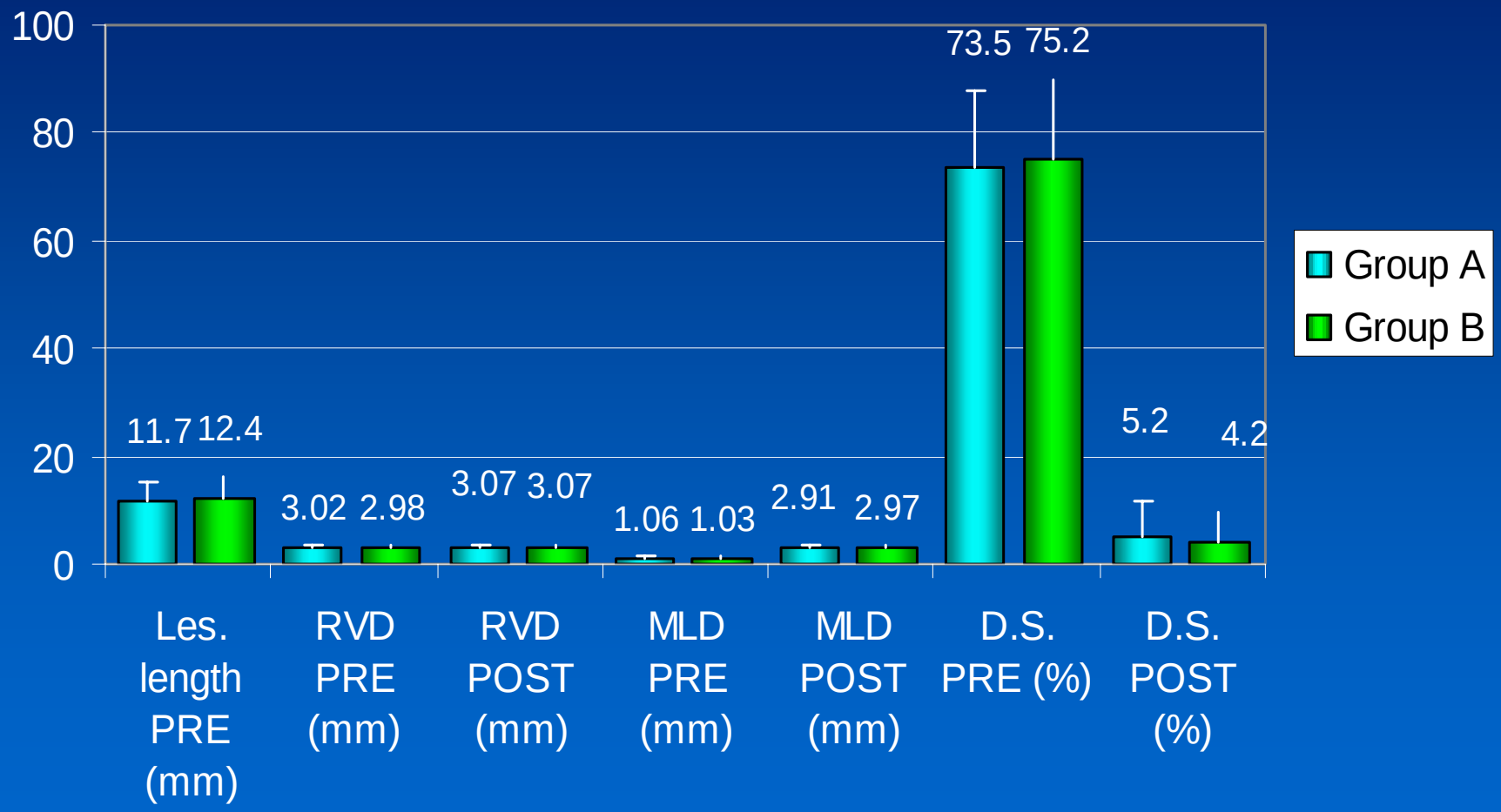
Jupiter II: Target lesions Characteristics



Jupiter II: Target lesions Characteristics



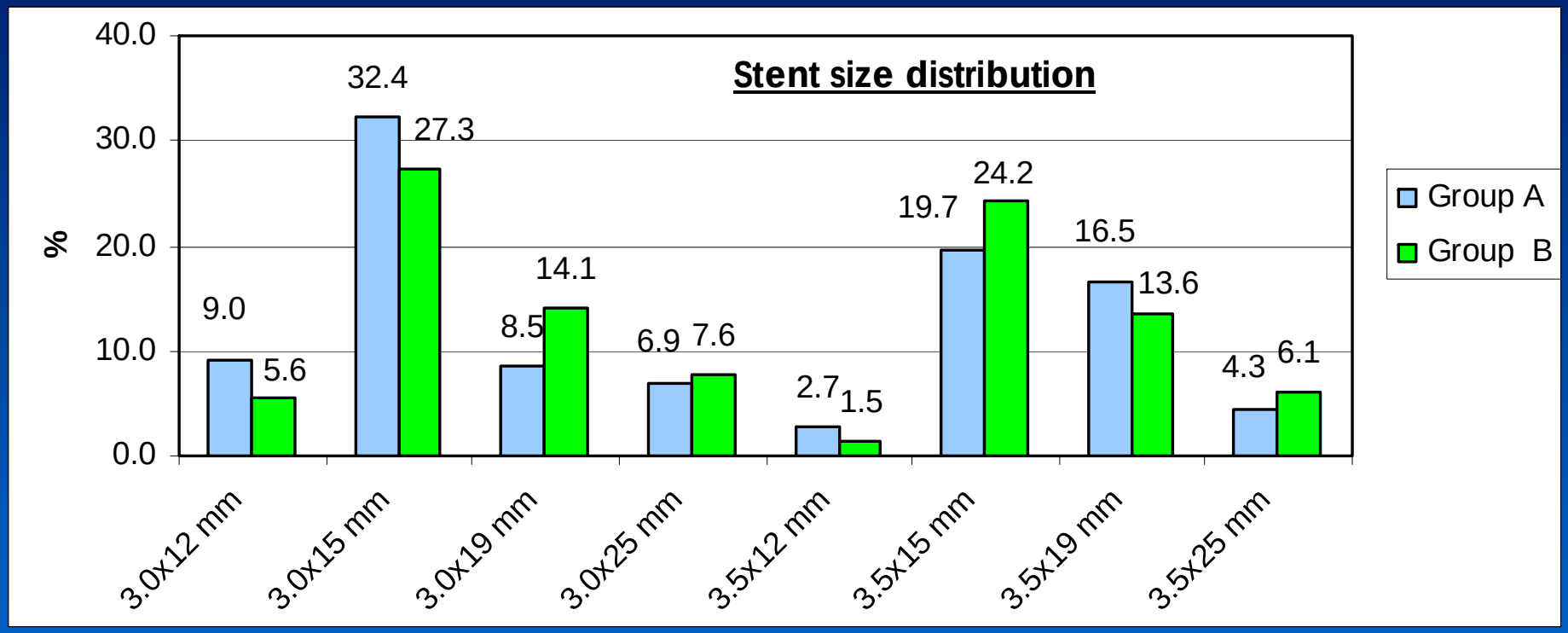
Jupiter II: Procedural angiographic data



Jupiter II: Procedural data

	GROUP A	GROUP B	p value
Stenting procedure	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
MACE			
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%	
Total events	1.89% (3)	0.63% (1)	.3812
Acute Thrombosis	0%	0%	

* 1 protocol deviation censored

Jupiter II: Preliminary 30-day follow-up*

	GROUP A	GROUP B	p value
Clinical status	159	159	
MACE			
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
Sub-acute Thrombosis	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

- **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:

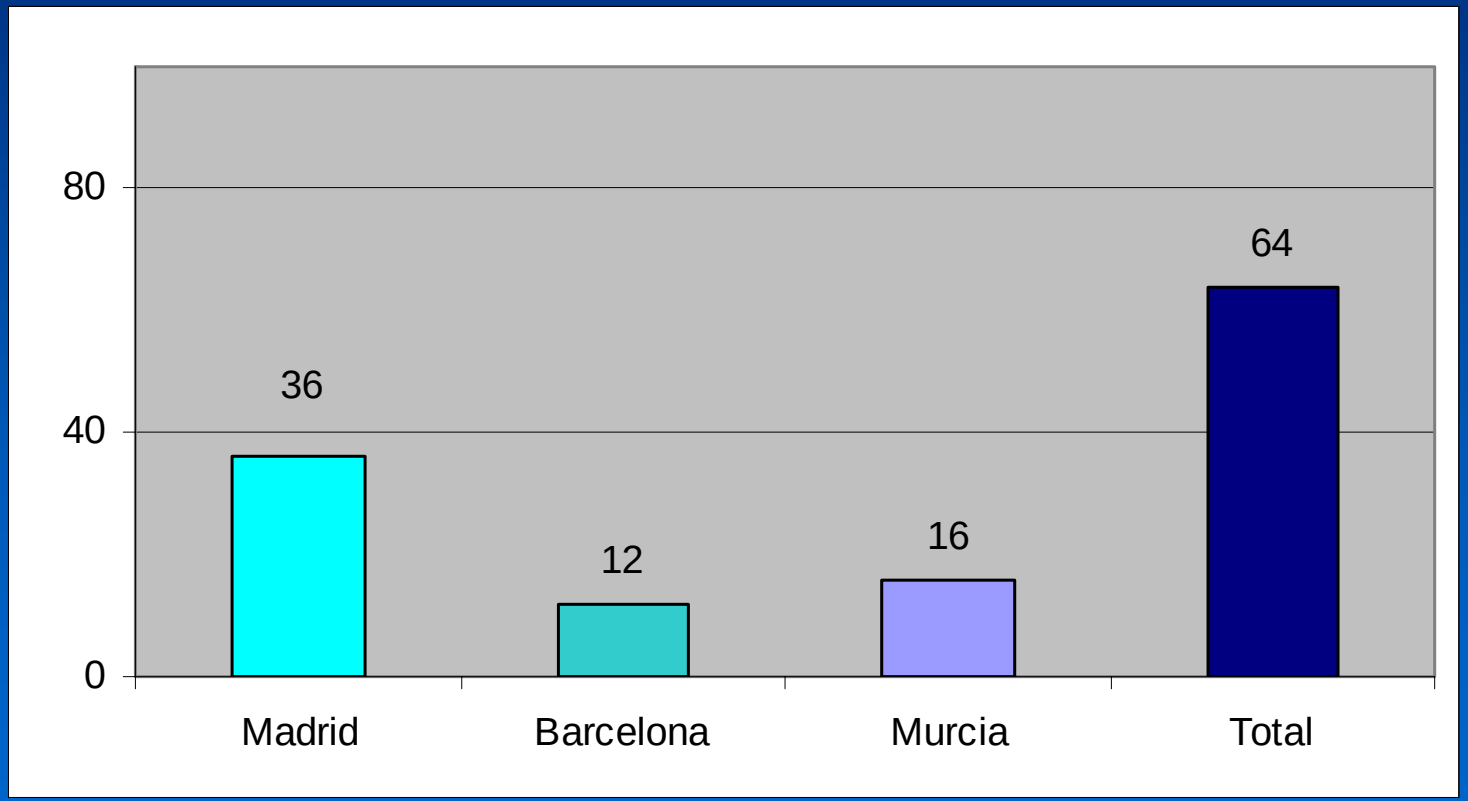
- Late Lumen Loss (in-stent + edges) by QCA at 9 month f-up

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:

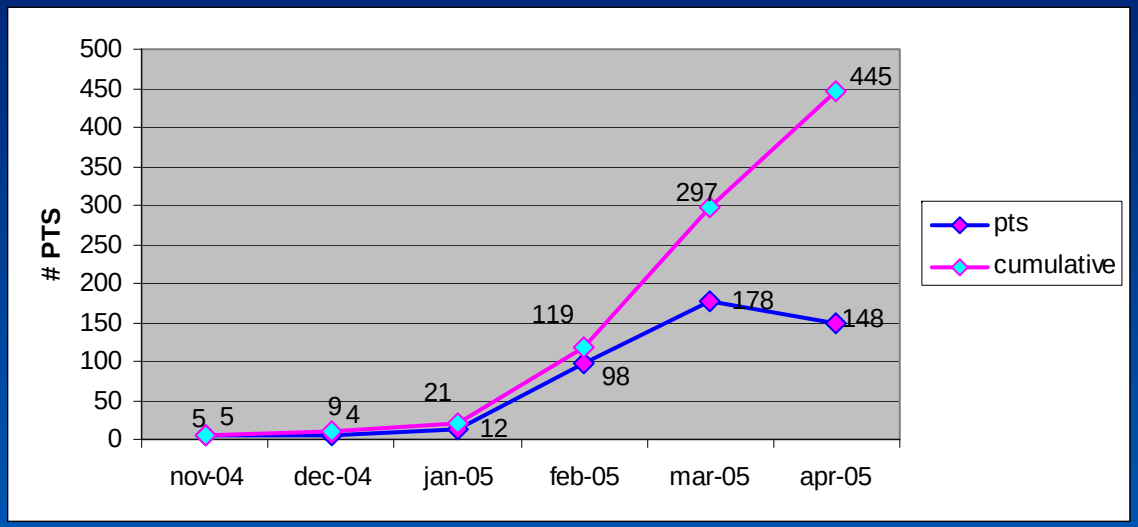
- Incidence of MACE within discharge, 30 days, 6, 12 & 24 months
- Thrombosis rate within discharge, 30 days, 6, 12 & 24 months (acute, sub-acute & late thrombosis)
- Clinical performances of Janus Carbostent, during implant procedure

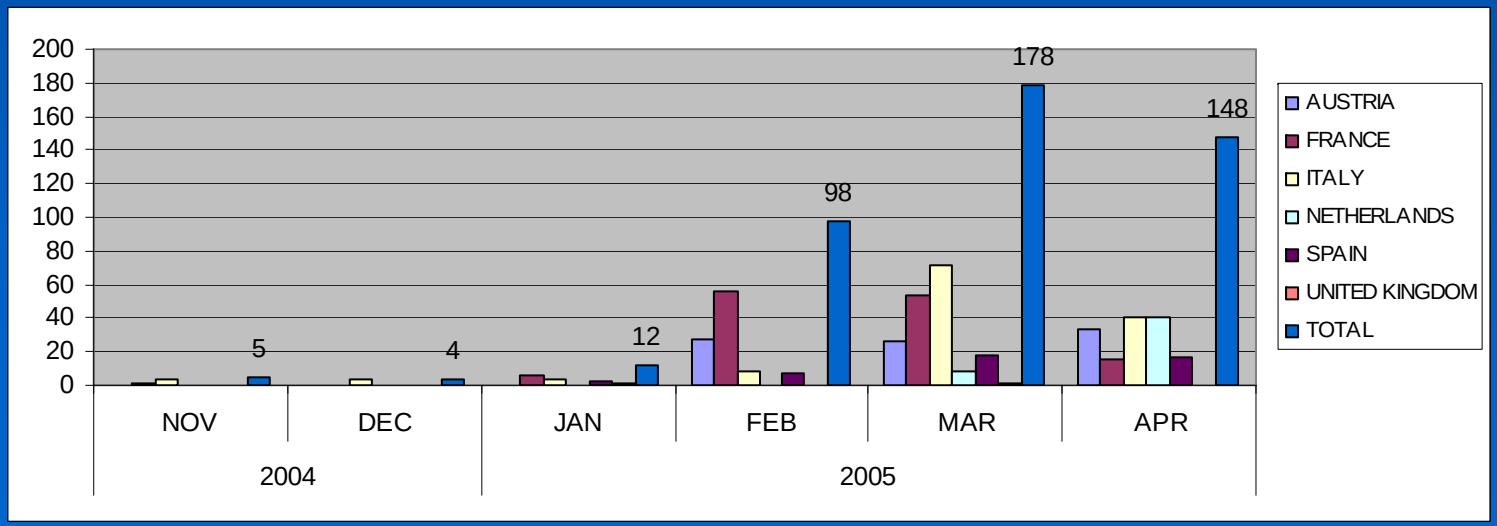
SECONDARY ENDPOINT:

- 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

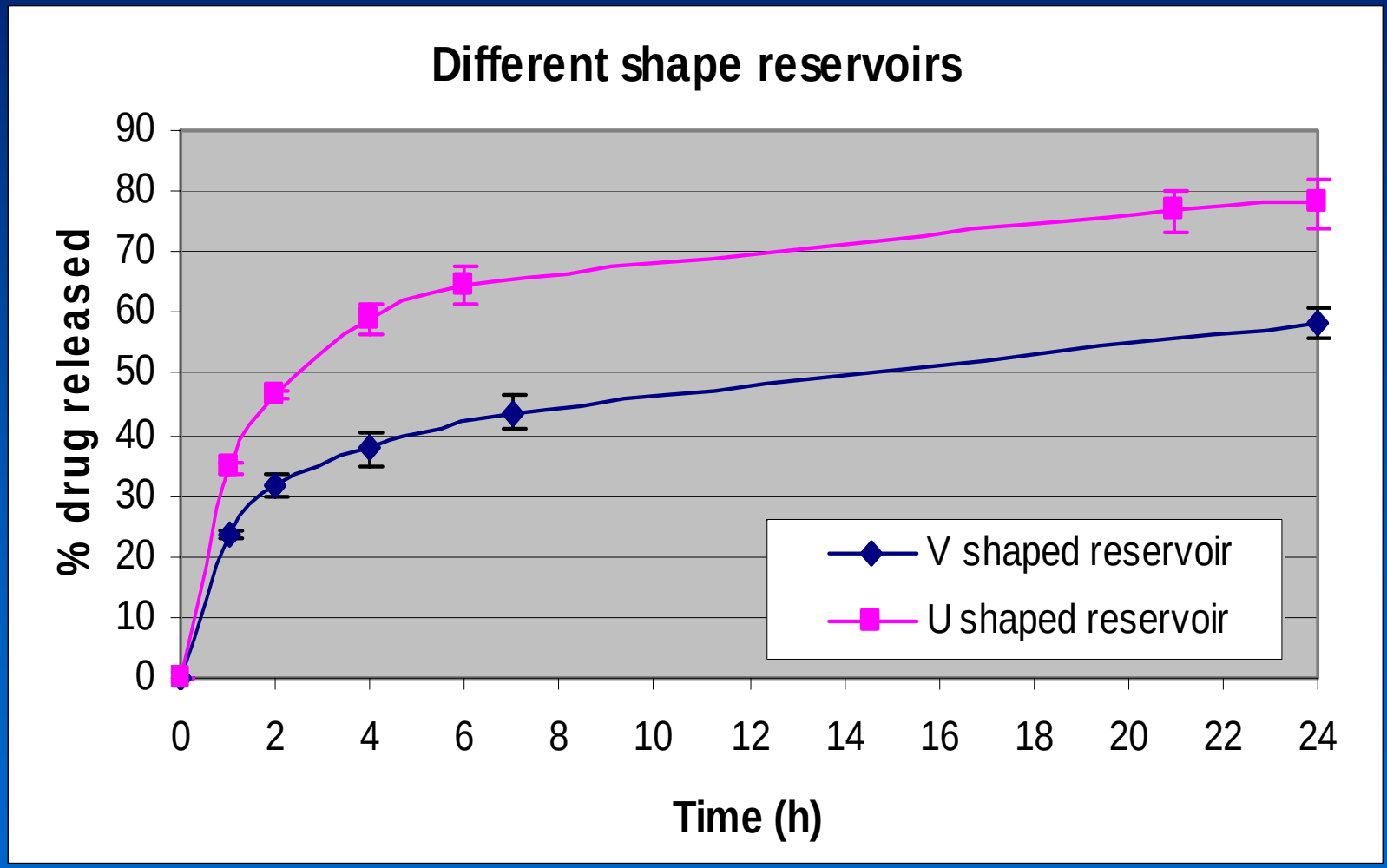
"U" shaped reservoirs



"V" shaped reservoirs

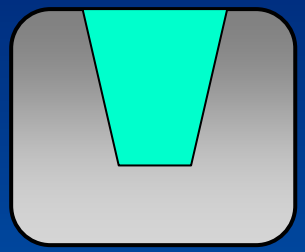


EFFECT OF THE RESERVOIR SHAPE ON RELEASE KINETIC

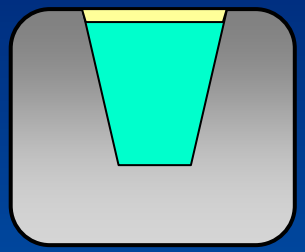


Carriers: a choice not an obligation.

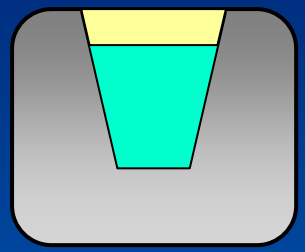
With Janus platform no additional carrier is strictly required, but the widest choice of drug formulations and excipients can be used to realize more sophisticated release profiles.



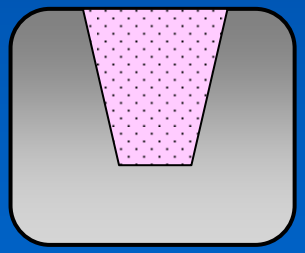
RESERVOIR FILLED WITH ONE DRUG



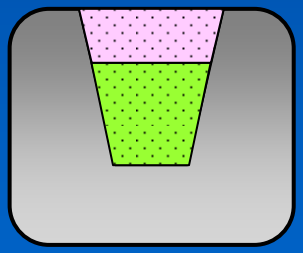
ONE DRUG + POLYMER COVER FOR SLOWER RELEASE



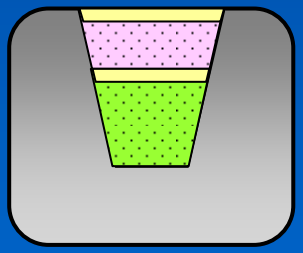
THICKER POLYMER COVER FOR EVEN SLOWER RELEASE



RESERVOIR FILLED WITH A POLYMER MATRIX CONTAINING THE DRUG

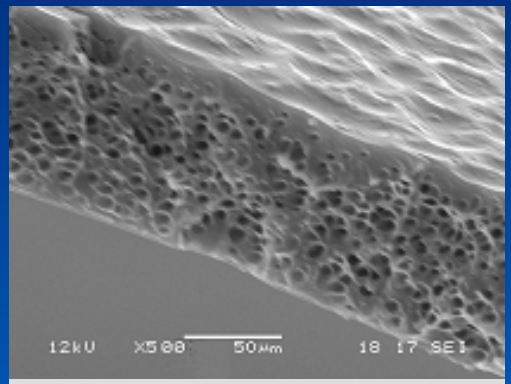


TWO POLYMER MATRICES CONTAINING TWO DIFFERENT DRUGS

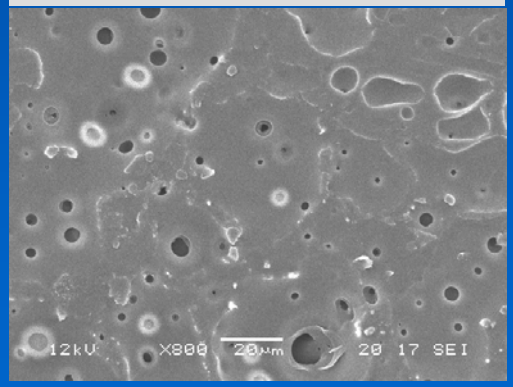


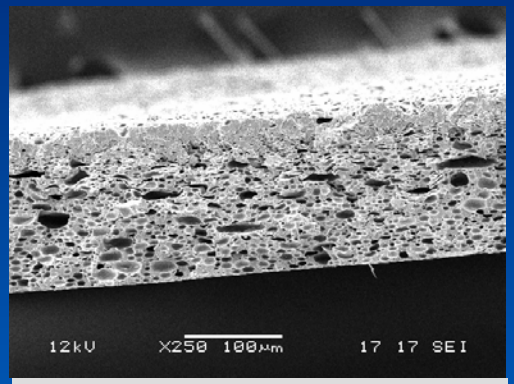
TWO POLYMER MATRICES CONTAINING TWO DIFFERENT DRUGS + TWO POLYMER COVERS

SEM images of Sorin proprietary carriers under evaluation

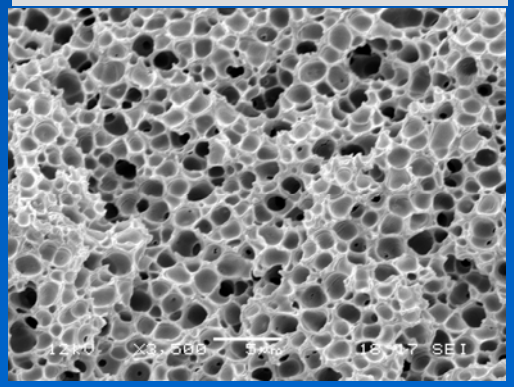


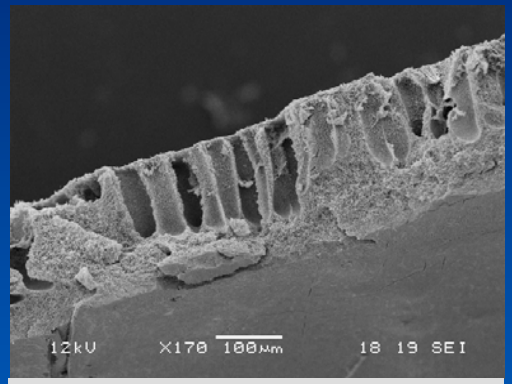
Porous matrix with top coat



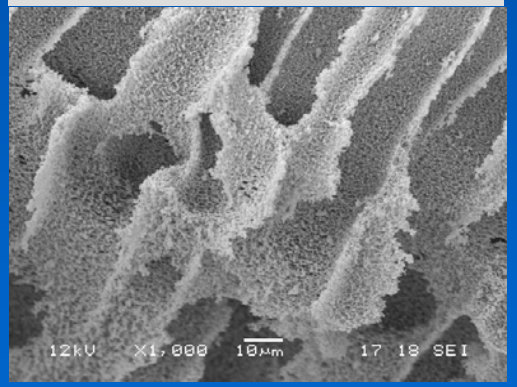


Porous matrix

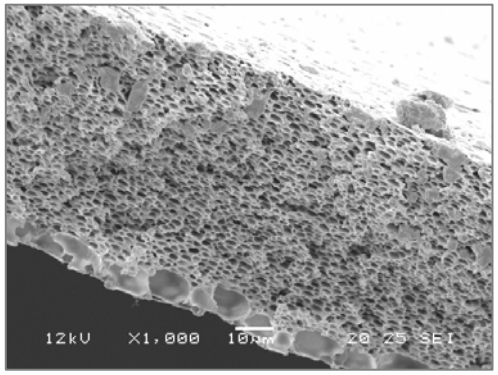




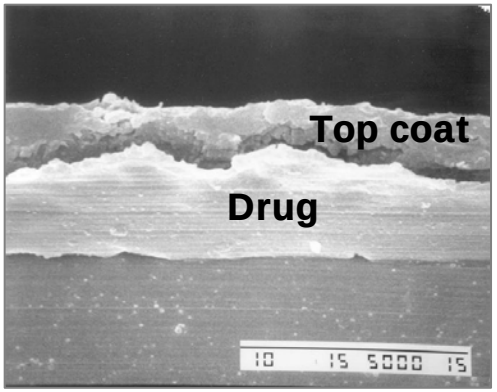
Tubular matrix



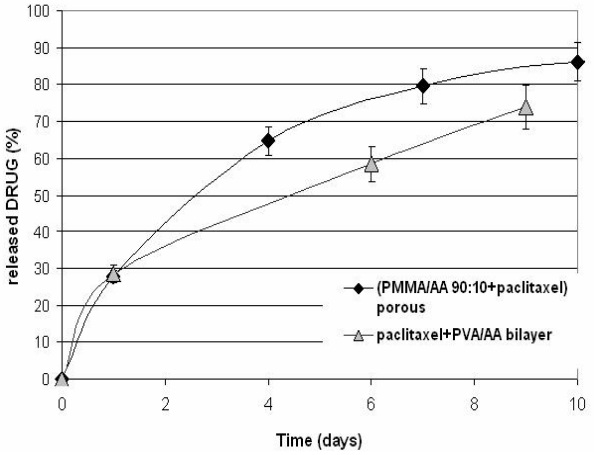
INFLUENCE OF POLYMER MATRICES ON THE RELEASE KINETIC

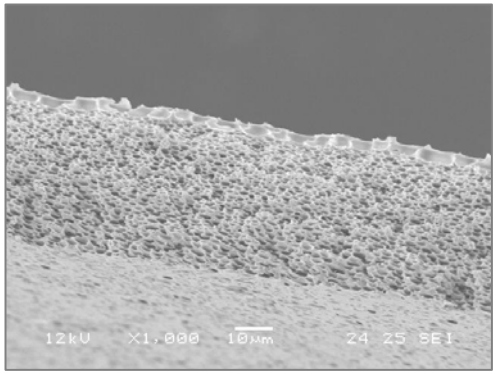


Porous matrix
Drug: tacrolimus
Porous film: PMMA/AA 90:10

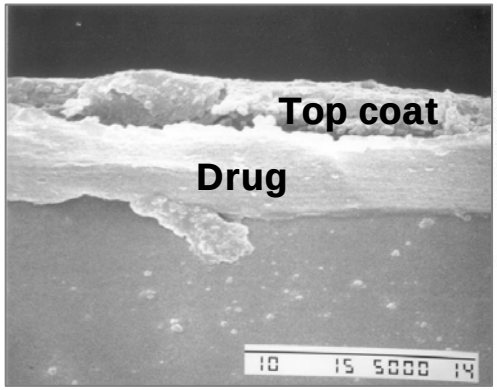


Thin polymeric bilayer
metallografic section
Drug: tacrolimus
Top coating: PVA/AA

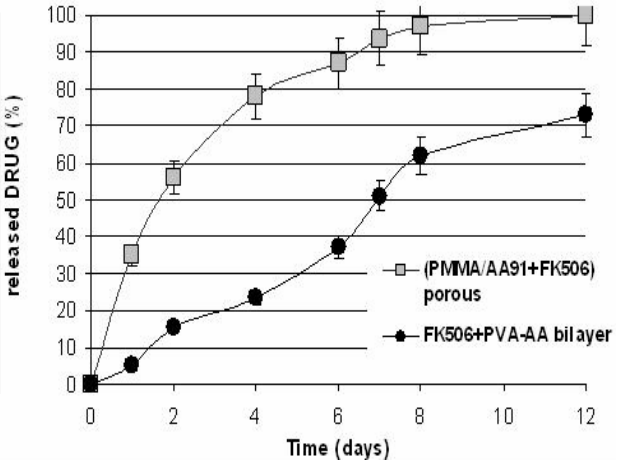




Porous matrix
Drug: paclitaxel
Porous film: PMMA/AA 90:10

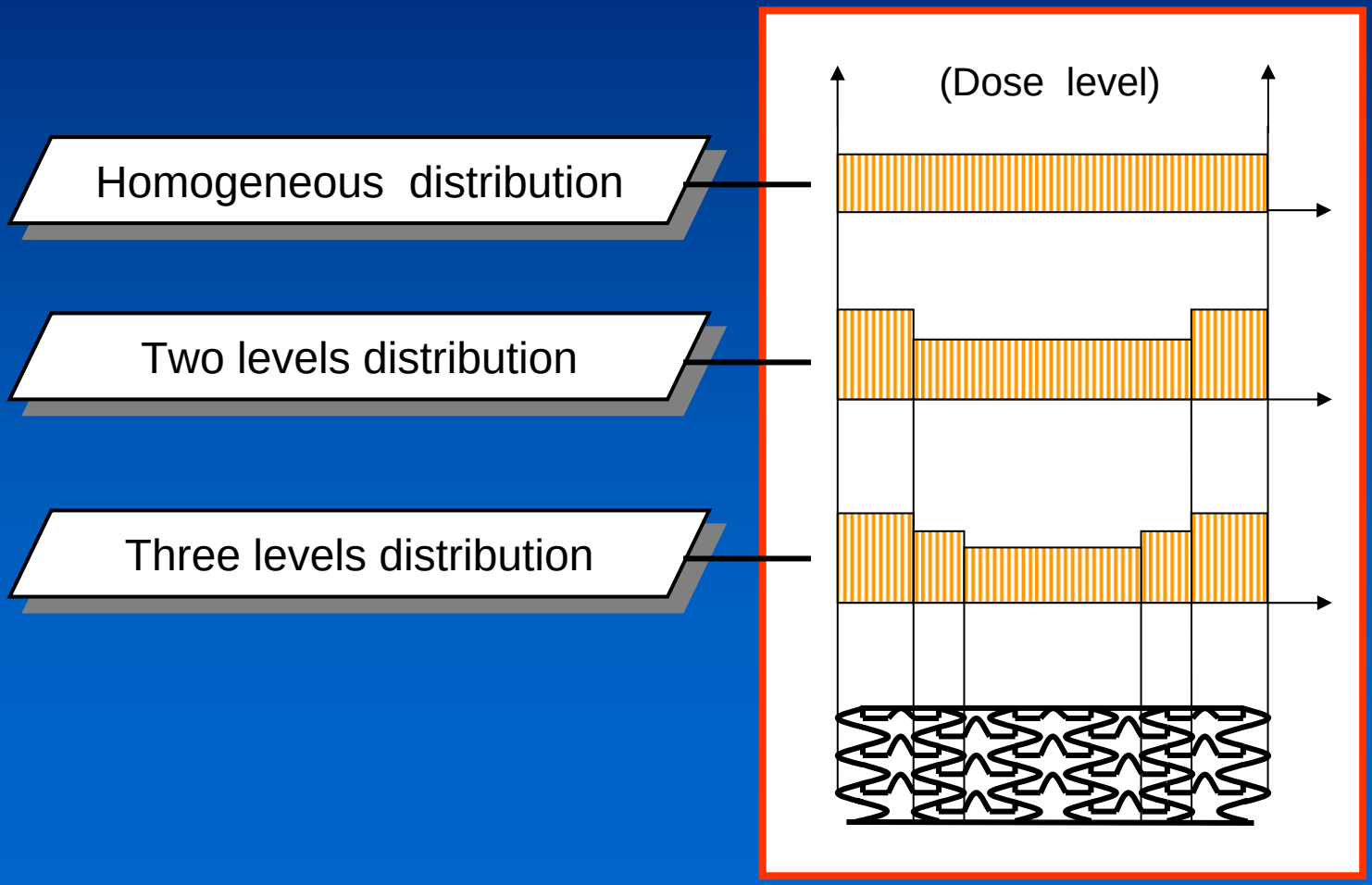


Thin polymeric bilayer
metallografic section
Drug: paclitaxel
Top coating: PVA/AA



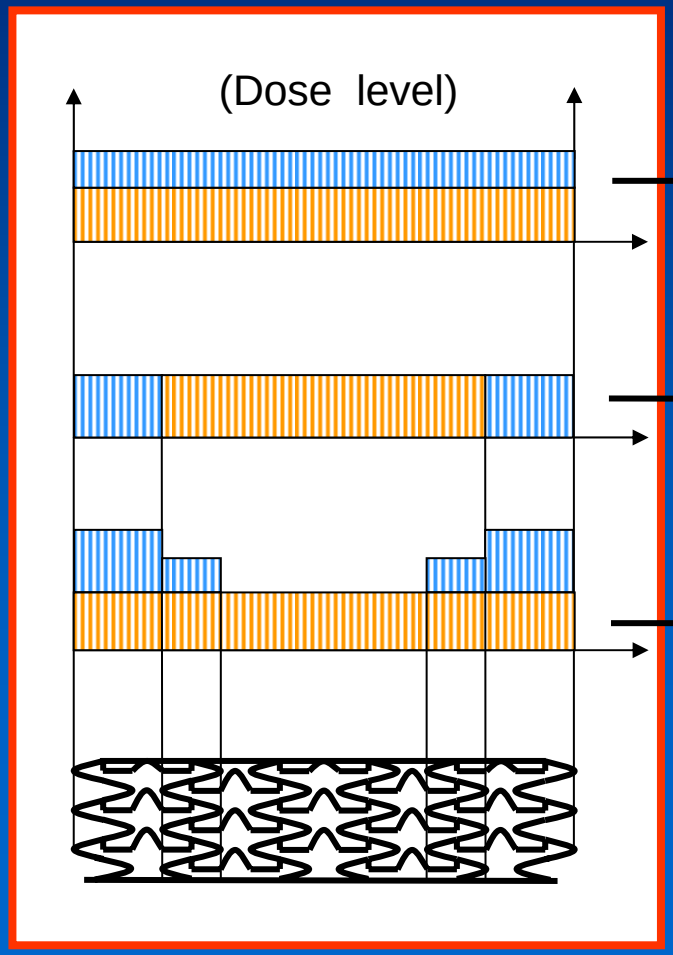
LONGITUDINAL DOSE DISTRIBUTION

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



Homogeneous distribution of two different drugs

Two different drugs in two different areas

Three levels distribution