Sirolimus DCB for Infrapopliteal Interventions: Selution SLR Clinical Evidence Base and Selution 4BTK Trial Update

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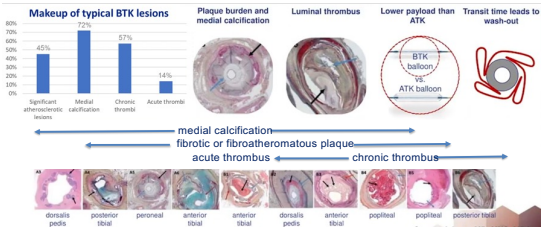
Conflicts

• InspireMD	*Research Funding (Co-PI)*
• MedAlliance/Cordis	*Advisory Board, Equity*
• Aveera	*Advisory Board, Equity*
• Protexa	*Advisory Board, Equity*
• Pulse Therapeutics	*Advisory Board, Equity*

The Challenge of BTK Intimal Drug Delivery



Nanula, et al. JACC 2018;72:2152-63

Series of Negative DCB BTK Studies

	Study	Endpoint Measure	DCB Group	PTA Group	Difference	Outcome
DCB	In.PACT DEEP (JACC 2014;64_1568-76)	12-month Freedom from Restenosis	59.0%	64.5%	-5.5%	Further studies discontinued due to safety concerns
		12-month Freedom from CD-TLR	88.1%	86.5%	1.6%	
		12-month Freedom from Major Amp	91.2%	96.4%	-5.2%	
	BioLUX P-II (JACC Intv 2015;8:1614-22)	6-month Freedom from Restenosis	46.9%	58.6%	-11.7%	Negative efficacy result
	SINGA-PACLI (Radiology 2021;300(3):715-724)	6-month superior Primary Patency	43%	38%	5%	Did not meet primary endpoints
		12-month Freedom from Major Amp	59%	78%	-19%	
	Lutonix BTK (J Inv Cardl 2019;31(5):205-11)	6-month Primary Efficacy Endpoint *	74.5%	63.5%	11.0%	Did not meet primary endpoint, signal dropout at 12 months
		12-month Primary Efficacy Endpoint	60.4%	60.9%	-0.5%	
DES	SAVAL (Vasc Med. 2023 Dec;28(6):571-580)	12-month Primary Patency	68.0%	76.0%	-8.0%	Did not meet primary effectiveness and safety endpoints
		12-month Freedom from Major Adverse Event	91.6%	95.3%	-3.7%	

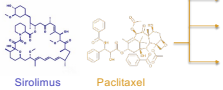
* Composite of freedom from major amputation, target lesion occlusion, or CD-TLR

Adapted from G. Adams, VIVA 2020

Sirolimus vs Paclitaxel

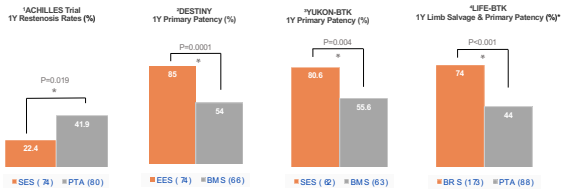
Similar but different

Sirolimus	Paclitaxel
ANTI-RESTENOTIC	ANTI-RESTENOTIC
CYTOSTATIC	CYTOTOXIC
10'000 FOLD SAFETY MARGIN	100 FOLD SAFETY MARGIN
WIDE THERAPEUTIC RANGE	NARROW THERAPEUTIC RANGE
ANTI-INFLAMMATORY	X
LOW TISSUE ABSORPTION	FAST TISSUE ABSORPTION
SHORT TISSUE RETENTION	LONG TISSUE RETENTION



Wessely, Rainer et al. JACC, vol 47, no. 4, 2006, pp. 708-714.

Limus Drugs Perform Well on Short Stents/Scaffolds in BTK



1. J Am Coll Cardiol. 2012 Dec 4;60(22):2290-5. 2. J Vasc Surg. 2012 Feb;55(2):390-8. 3. Eur Heart J. 2011 Sep;32(18):2274-81. 4. Varcoe, Ramon L., et al. *NEJM* (2023). doi: 10.1056/NEJMoa2305637.
* Primary efficacy endpoint defined as freedom from Amputation above the ankle of the target limb; Occlusion of the target vessel, CD-TLR, Binary restenosis of the target lesion

Sirolimus Eluting Balloon Design Goals

- **INCREASE DRUG UPTAKE**
  - Difficult to get Sirolimus to enter the arterial tissue within 30 to 180 seconds of balloon dilatation; hence some kind of "instant glue" required to transfer the drug from the balloon to the tissue efficiently
- **EXTEND DRUG RETENTION**
  - Sirolimus must be continuously delivered over time, so some form of "time release mechanism" must be employed to maintain therapeutic levels
- **LIMIT DRUG EMBOLIZATION**
  - Protect from WASH-OFF during balloon delivery and to protect from EMBOLIZATION during balloon deployment

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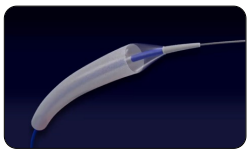
SELUTION SLR™ Drug-Eluting Balloon Technology

2 key features define the unique performance of SELUTION SLR™ DEB



CELL ADHERENT TECHNOLOGY (CAT)™
- Phospholipid blend containing and protecting MicroReservoirs at 1 µg/mm² Sirolimus dose[1]
- **Enhanced Drug Transfer Efficiency**

MicroReservoirs
- ~4 µm spheres of Sirolimus mixed with biodegradable polymer[1]
- **Sustained Drug Release**

1. Cordis 2024 Data on file.

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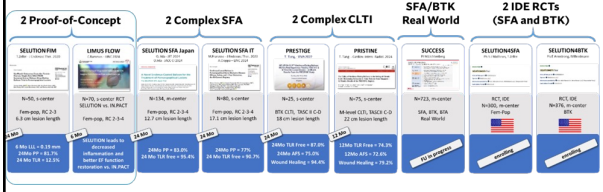
SELUTION SLR™ Drug-Eluting Balloon (DEB) in PAD – Clinical Program Overview

Clinical evidence from 9 Studies and more than 1,800 patients



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Early experience with SELUTION SLR in BTK

PRESTIGE (N=25) – 24 mo follow up available

ClinicalTrials.gov ID: NCT04071782

- **OBJECTIVES**
  - To evaluate the 6 months safety and performance outcome of the SELUTION SLR™ DEB on the treatment of **long tibial occlusive lesions (TASC C and D)** in patients with CLTI
- **DESIGN**
  - Prospective, non randomized single-center trial, single arm
  - Treatment of 25 patients from Asia
- **PRIMARY ENDPOINTS**
  - Freedom from device or procedure related mortality through 30 days
  - Freedom from target lesion revascularization (TLR)at 6 months and 12 months
- **SECONDARY ENDPOINTS**
  - Freedom from major target limb amputation
  - Primary patency rate at 6 and 12M
  - Technical success (ie, able to cross and dilate lesion to achieve <30% residual stenosis)
  - Clinical success (ie, improvement of Rutherford classification at follow up)
  - Wound healing(ie, complete closure of wound / >70% healed)

PRISTINE (N=75) – 12 mo follow up available

ClinicalTrials.gov ID: NCT04534257

- **OBJECTIVES**
  - To evaluate the safety and performance outcome of the SELUTION SLR™ DEB for the treatment of infra inguinal occlusive lesions (TASC C and D) in CLTI
- **DESIGN**
  - Prospective, non randomized single center trial, single arm
  - Treatment of 75 patients from Asia
- **PRIMARY ENDPOINTS**
  - Freedom from device and procedure related mortality through 30 days.
  - Freedom from clinically driven target lesion revascularization (TLR) within 6 months post index procedure.
- **SECONDARY ENDPOINTS**
  - Freedom from clinically driven TLR at 6 and 12 month follow up
  - Freedom from major target limb amputation within 6 and 12 months post index procedure
  - Primary patency at 6 and 12 month follow-up
  - Clinical success at follow-up

Tjun Yip Tang and Tze Tec Chong, Singapore General Hospital

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SELUTION SLR™ DEB in BTK Evidence (PRESTIGE & PRISTINE)

PRESTIGE[1] **n=25, single operator**

Baseline
- Long segment infrapopliteal disease
- **44% ESRD**
- 100% Rutherford 5 (tissue loss)
- **64%** moderate/severe calcification

Sustained Outcomes out to 24 months
- Freedom TLR: **87.0% (20/23)**
- Amputation-free survival (AFS): **75% (18/24)**
- Wound healing: **94.4% (17/18)**

PRISTINE[2] **n=75, multi operator**

Baseline
- TASC C&D
- More advanced wounds. **23% R6** , 68% R5, 9% R4
- Higher calcification (**88% mod/sever calcification**)
- Higher risk of amputation (**67% mod/high risk**)

Outcomes out to 12 months
- Freedom from TLR: **74%**
- Amputation free survival: **72.6%**
- Wound healing rate: **79.2%**

1. PRESTIGE Single Arm Study - Tang TY – VIVA 2022 oral presentation (Clinicaltrial.gov NCT04071782)
2. PRISTINE Registry – T.Chong – CIRSE 2023 oral presentation (Clinicaltrial.gov NCT04534257)

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SUCCESS PTA STUDY 6-MONTH FU

74% claudication, 26% CLTI

Objectives
- Collect real world safety, efficacy, health economics and Patient Reported Outcome Measure (PROM) data on the use of the SELUTION SLR™ DEB

Design
- Global post-market surveillance study of the SELUTION SLR™ DEB (SFA, BTK, Foot)
- 723 patients in 27 sites around Europe, Asia and South America

Primary Endpoint
- Clinically Driven Target Lesion Revascularization (CD-TLR) at 12M

Secondary Endpoints
- Device success & Procedure success
- Major Adverse Limb Events (MALE) composite endpoint
- Death
- TLR & TVR - including time to first CD-TLR
- Target limb revascularization, thrombosis at the target site and amputation
- Change in Rutherford score, ABI from baseline and EQ5D
- Wound status

Follow-up
- Clinical Follow-up: 6 months, 1 year
- Telephone Follow-up: 2, 3, 4, 5 years

PI
- Michael Lichtenberg, Arnsberg, Germany

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SUCCESS PTA STUDY 6-MONTH FU

Patient and lesion characteristics

Patient Characteristics	Full Cohort (N = 720)	Claudicants (N = 534)	CLTI (N = 186)
Age (years)	70.7 ± 9.9	70.0 ± 9.6	72.8 ± 10.3
Male	65.0% (468/720)	63.9% (341/534)	68.3% (127/186)
Diabetes Mellitus	37.9% (273/720)	33.0% (176/534)	52.2% (97/186)
Lesion Characteristics	**Full Cohort (N = 821*)**	**Claudicants (N = 604*)**	**CLTI (N = 217*)**
Lesion Segments Location			
SFA	64.1% (932/1453~)	68.4% (721/1054**)	52.9% (211/399**)
POP (POP1,POP2)	23.9% (347/1453~)	22.6% (238/1054**)	27.3% (109/399**)
BTK	9.8% (143/1453**)	6.8% (72/1054**)	17.8% (71/399**)
Other *	2.1% (31/1453~)	2.2% (23/1054**)	2.0% (8/399**)
RVD - Target Lesion (mm)	5.2 ± 1.5	5.3 ± 0.9	4.8 ± 2.5
ATK	5.3 ± 0.9	5.4 ± 0.8	5.1 ± 1.0
BTK	3.4 ± 1.1	3.7 ± 0.9	3.2 ± 1.1
Multi-vessel	4.9 ± 1.3	5.1 ± 1.2	4.5 ± 1.3
Lesion Length - Target Lesion (mm)	128.4 ± 101.8	128.4 ± 102.6	128.2 ± 99.6
ATK	132.0 ± 105.0	132.4 ± 105.2	130.5 ± 105.0
BTK	104.0 ± 80.0	85.0 ± 64.1	116.6 ± 87.4
Multi-vessel	119.5 ± 85.3	110.2 ± 84.0	138.4 ± 86.7
Diameter Stenosis Target Lesion (%)	91.6 ± 11.2	91.3 ± 11.6	92.5 ± 10.3
Total occlusion at baseline (100% DS)	42.1% (346/821)	41.7% (252/604)	43.3% (94/217)
MLD – Target lesion (mm)	1.0 ± 2.1	0.9 ± 1.5	1.1 ± 3.3
Calcification Grade 3	20.0% (164/820)	19.9% (120/603)	20.3% (44/217)
Calcification Grade 4	16.3% (134/820)	15.6% (94/603)	16.4% (60/217)

* Number of individual lesions (each lesion may cover multiple vessel districts)
** Number of lesion segments (each segment covering one vessel district)
~ Other: bypass, iliac, profunda, common femoral artery

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SUCCESS PTA STUDY 6-MONTH FU

Clinical outcomes up to 180 days

	Full Cohort		Claudicants		CLTI	
	30 days	180 days	30 days	180 days	30 days	180 days
Death	0.7% (5/710)	1.8% (12/657)	0% (0/525)	0.2% (1/501)	2.7% (5/185)	7.1% (11/156)
Major Cardiac Event (MI, stroke, cardiovascular death)	0.4% (3/707)	1.1% (7/649)	0.2% (1/525)	0.8% (4/501)	1.1% (2/182)	2.0% (3/148)
CD-TLR	0.4% (3/705)	2.5% (16/647)	0.4% (2/525)	2.2% (11/501)	0.6% (1/180)	3.4% (5/146)
Thrombosis	0% (0/705)	0% (0/645)	0% (0/525)	0% (0/500)	0% (0/180)	0% (0/145)
Target limb amputation						
Major target limb amputation	0.7% (5/705)	1.1% (7/646)	0% (0/525)	0% (0/500)	2.8% (5/180)	4.8% (7/146)
Minor target limb amputation	0.7% (5/705)	0.8% (5/646)	0% (0/525)	0% (0/500)	2.8% (5/180)	3.4% (5/146)
MALE Composite Endpoint (Severe limb ischemia leading to an intervention to target limb or major vascular amputation)	1.8% (13/705)	5.9% (38/649)	0.8% (4/525)	4.0% (20/501)	5.0% (9/180)	12.2% (18/148)

Proportions are defined by the number of eligible patients who completed follow up OR experienced the

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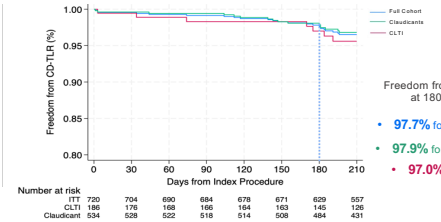
SUCCESS PTA STUDY 6-MONTH FU

Freedom from CD-TLR - KM curve



Number at risk

ITT	720	704	690	684	678	671	629	557
CLTI	186	176	168	166	164	163	145	126
Claudicant	534	528	522	518	514	508	484	431

Freedom from CD-TLR at 180 days:

- **97.7%** for Full Cohort
- **97.9%** for Claudicants
- **97.0%** for CLTI

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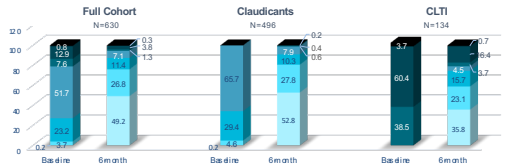
SUCCESS PTA STUDY 6-MONTH FU

Rutherford classification at 6-month FU (paired anaylsis)



85.4% improved at least of 1 category

86.9% improved at least of 1 category

79.9% improved at least of 1 category

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SELUTION4BTK Trial

Objectives
- To demonstrate the superior efficacy and equivalent safety of the SELUTION SLR™ 014 DEB compared to plain (uncoated) balloon angioplasty in the treatment of peripheral arterial disease (PAD) in the BTK arteries in CLTI patients

Design
- Prospective, multi-center, single blinded, RCT (1:1)
- 376 patients (min 50% in USA)
- 60 sites in USA, Europe, Asia & New Zealand

Primary Endpoints
- Efficacy: Hierarchical composite efficacy endpoint determined by Win Ratio method 6 months post-procedure according to the following hierarchy of outcomes: Major (Above-ankle) amputation, CD-TLR , Target lesion occlusion, Transverse View Area Loss (TVAL%) by angiography.
- Safety: Freedom from the composite of Major Adverse Limb events (MALE) & and all-cause perio-operative death (POD) at 30 days

Follow-up
- 1, 6 months
- 1, 2, 3, 4, 5 years

PIs
- US: Ehrin Armstrong
- EU: Marianne Brodmann

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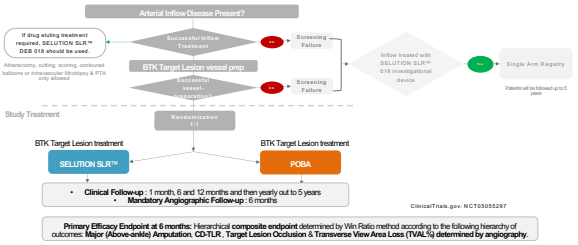
SELUTION SLR™ DEB BTK-IDE study



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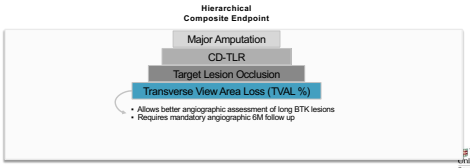
SELUTION4BTK Trial- Unique Study Design Features

- ✓ Inclusion of both **angiographic** and clinical endpoints in the primary endpoint to overcome limitations of duplex ultrasound assessment of BTK lesions
- ✓ Use of novel Win Ratio for the primary endpoint at 6 Months
  - Prioritizes outcome measures by clinical relevance



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Conclusions

- SELUTION SLR™ DEB is a new generation drug eluting technology with:
  - Increased Drug uptake allowing for lower drug dose of 1µg/mm²
  - Extended Drug Retention with sustained sirolimus release
- Single- armed studies have shown early promising results with SELUTION SLR™ DEB in treatment of patients with CLI and below-the-knee lesions in complex real-world population
- **SELUTION4BTK RCT is currently enrolling** (Drs. Brodmann and Armstrong)
- This global IDE trial will evaluate the safety and efficacy of the SELUTION SLR™ DEB versus POBA in treatment of patients with BTK disease

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