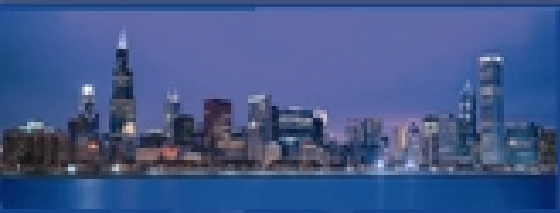


Alfimeprase: Phase 2 Multi-center Trial (NAPA-I)

Safety and Activity of Alfimeprase for Catheter-Directed Thrombolysis in Patients with Lower Extremity Acute Peripheral Arterial Occlusion: Report of a Phase 2, Multi-Center, Multi-National, Open-Label, Dose-Escalation Study (NAPA-1)

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for the Alfimeprase
HA002 Study Investigator**



**Faculty Disclosure
Jacob Cynamon, M.D**

I hereby disclose that I:

- 1. Am a member of the advisory board for Nuvelo.**



Acute PAO: Magnitude and Management of “Leg Attack”

- **Peripheral arterial occlusion (PAO) due to atherosclerosis**
 - Incidence of 5% in men and 2.5% in women
 - Up to 15-20% of chronic PAO patients develop acute PAO
- **Acute PAO management goals**
 - Rapid restoration of arterial patency and blood flow
 - Limb preservation and avoidance of treatment complications
- **Acute PAO management options**
 - Open surgery (e.g., thrombectomy, arterial bypass, endarterectomy)
 - Catheter-directed procedures (e.g., thrombolysis, percutaneous mechanical thrombectomy, angioplasty/stenting)

Acute PAO: Management Causal Chain (Pathway)

Rapid restoration of arterial flow*

Identification of underlying lesions

Facilitation of endovascular treatment

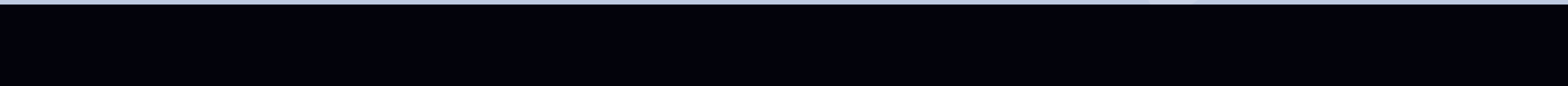
Avoidance of open vascular surgery

Avoidance of perioperative complications

Avoidance of death

Limb salvage

*** = time sensitive
and critical step**



Limitations of Current Thrombolytic Agents (tPA, UK, and rPA)

Limitations:

- Dependency on adequate plasminogen supply
- May not work well on PAI-1 rich, platelet-rich, arterial clots
- Greater than 24 hour mean duration of treatment to achieve flow^{1,2}
- Systemic “lytic state”
- Hypofibrinogenemia
- 5-16% incidence of major hemorrhage
- 1-2% incidence of intracranial hemorrhage (ICH)

¹Ouriel et al., *JVIR* 1994; ²Ouriel et al., *NEJM* 1998

Alfimeprase: Novel Acting Thrombolytic

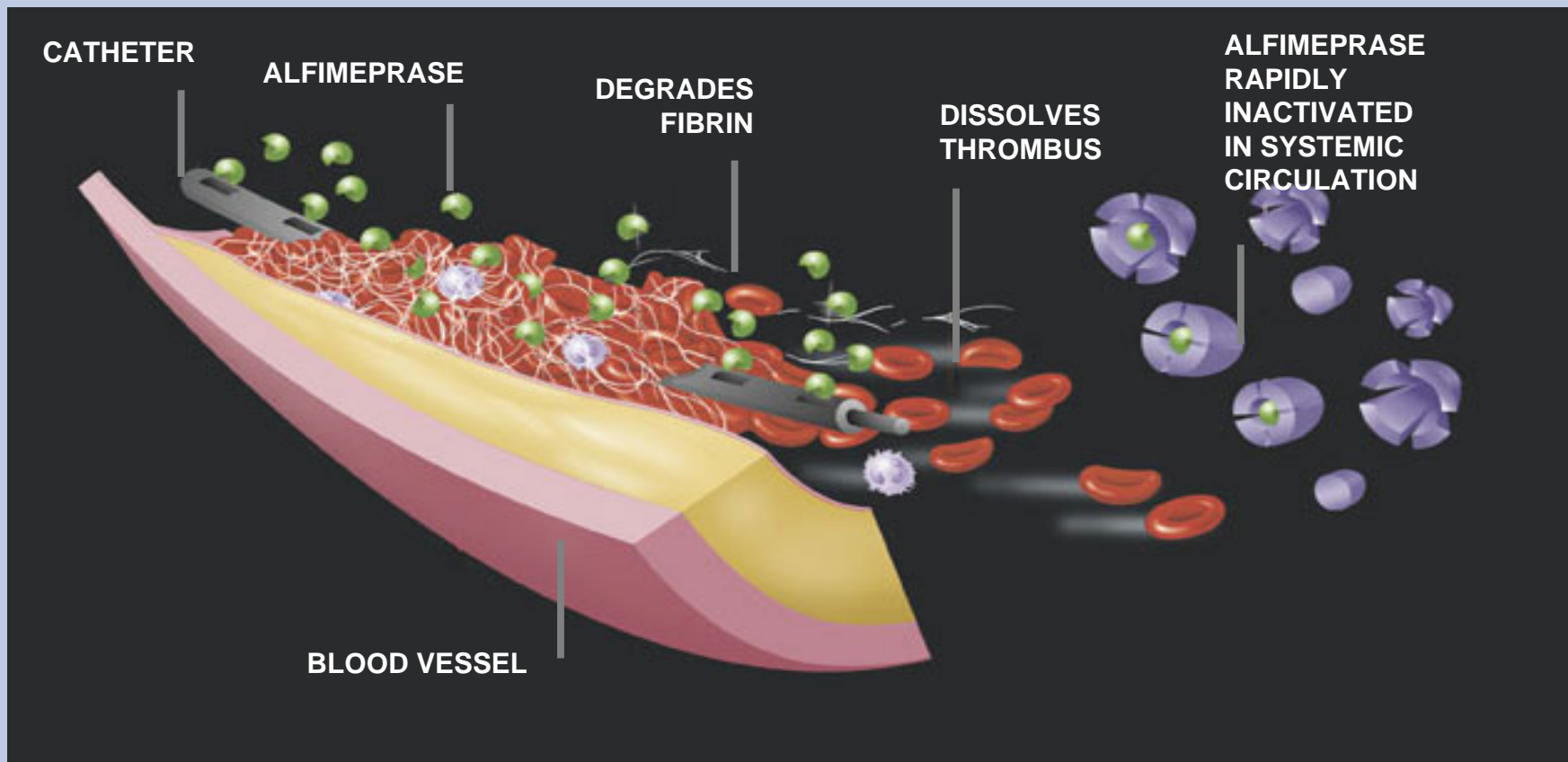
Key characteristics:

- A direct fibrinolytic
- Not plasminogen dependent
- Ability to lyse large clots in 1-4 hours
- Lytic activity confined to the site of drug delivery
- Not inactivated by PAI-1
- No systemic “lytic state” at clinically relevant doses
- Potentially less bleeding including less ICH



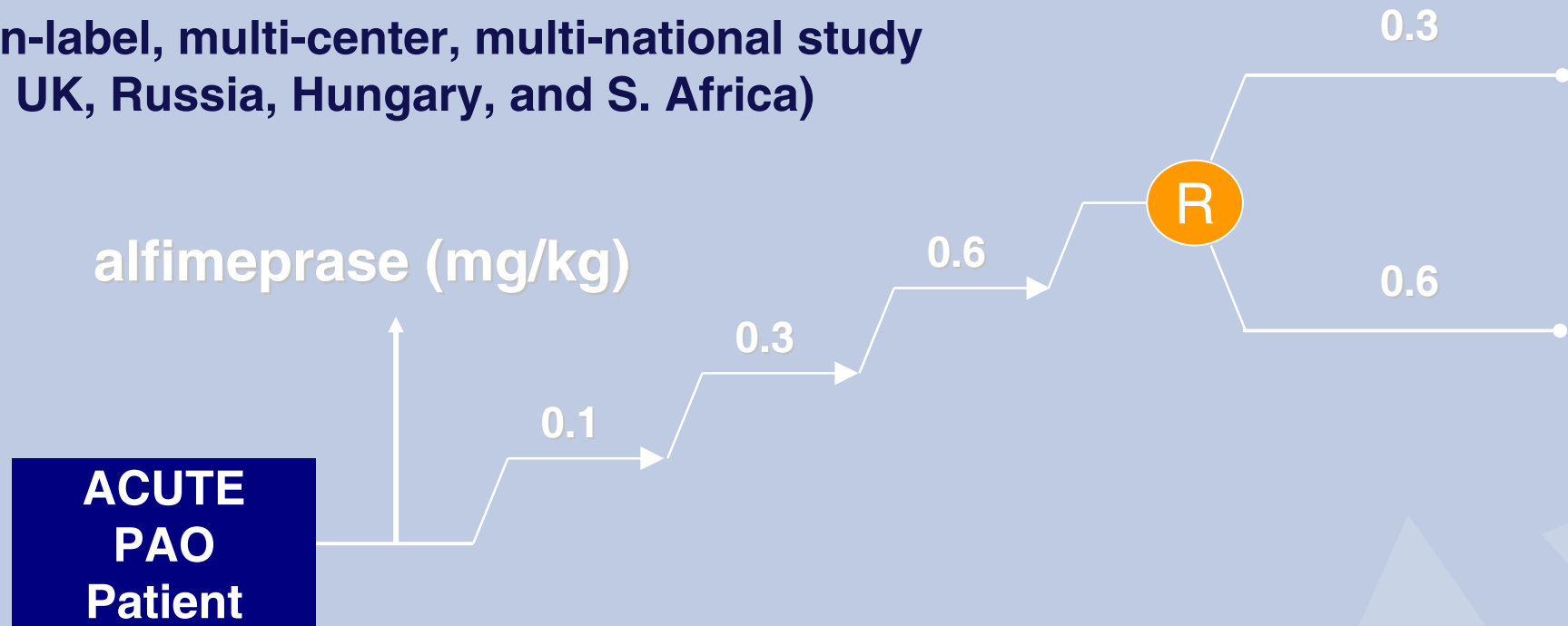
Alfimeprase: Novel Acting Thrombolytic

Systemic Inactivation of Alfimeprase by Alpha-2 Macroglobulin Allows for Potentially Fewer Side Effects



HA002 Alfimeprase PAO Phase 2: Dose Escalation Trial

Open-label, multi-center, multi-national study
(US, UK, Russia, Hungary, and S. Africa)



Primary objectives:

- Adverse event (AE) rate
- Serious adverse event (SAE) rate
- Major bleeding (including ICH) rate

Secondary objectives:

- Determination of alfimeprase activity
- Open-surgery free survival
- Severity of interventions

HA002: Methodology

Subjects

- Adults > 18 years of age with acute PAO of the lower limb
- Onset of symptoms within 14 days of enrollment
- Ischemia severity of SVS/ISCVS class I or IIA

Dosing

- Intrathrombus alteplase 0.1, 0.3, or 0.6 mg/kg via a slit-hole catheter with 1 mL/min manual pulses
- Divided dose with 2/3 and 1/3 of total dose given 2 hours apart

Primary endpoint

- AE, SAE, and major hemorrhage rates up to 30 days after dosing

Secondary endpoints

- Open-surgery free survival at 14 and 30 days
- Patency as defined by restoration of flow
- Increase in ankle-brachial index by ≥ 0.15
- Reduction in severity of planned surgical interventions

HA002: Alfimeprase in Acute PAO

Final Safety Results

Safety Measure	Alfimeprase 0.1 mg/kg N=16	Alfimeprase 0.3 mg/kg N=49	Alfimeprase 0.6 mg/kg N=48	Alfimeprase total N=113
Any SAE ^{1,2}	25 %	29 %	48 %	36.3 %
Major hemorrhages ³	0 %	4 % ⁴	10 %	6.2 %
Hypotension	6 %	2 % ⁴	19 %	9.7 %
Peripheral embolism	0 %	2 %	4 %	2.7 %
ICH or Death	0 %	0 %	0 %	0 %

¹ 65.9% of reported SAEs were deemed not related or unlikely to be related to study drug

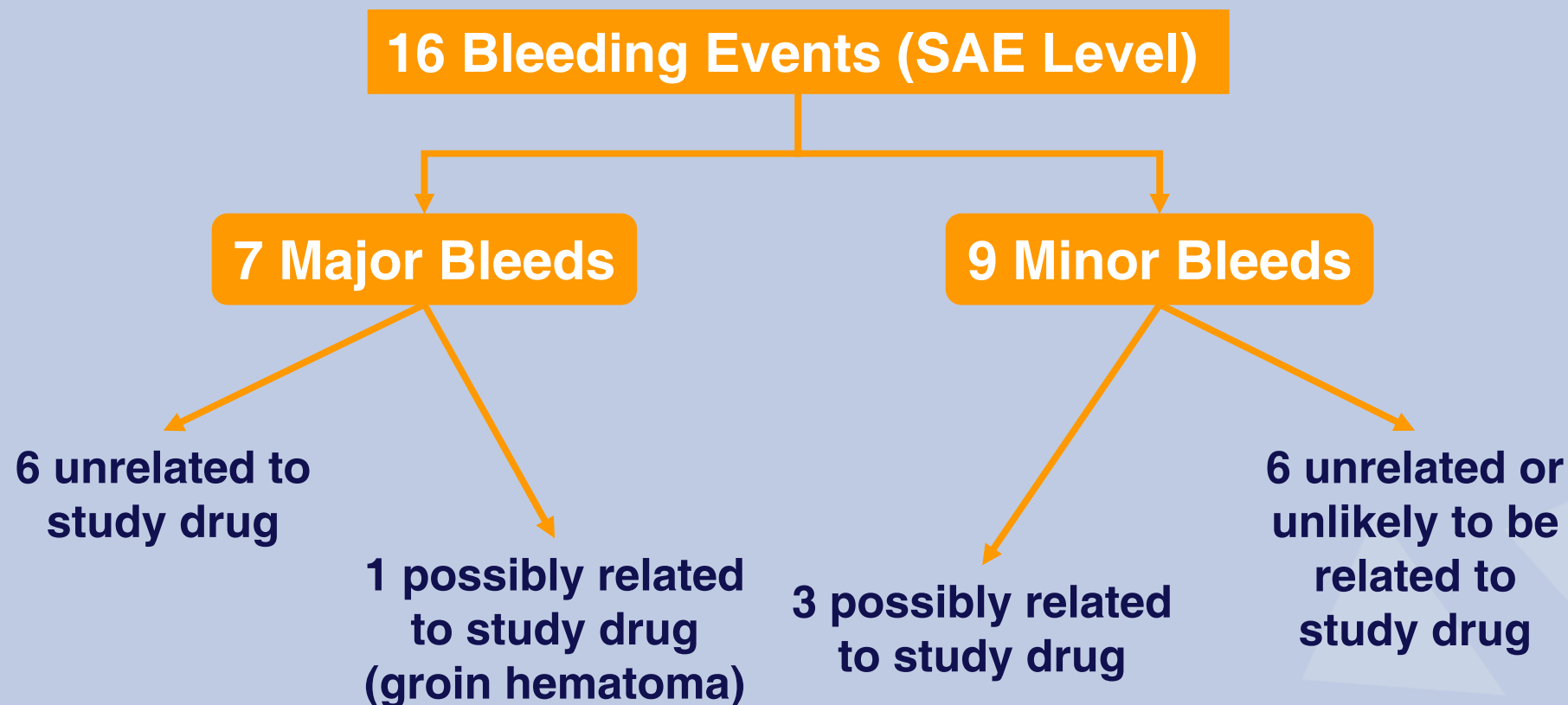
² Only 2.3% of SAEs were deemed to have a definite relationship to study drug

³ No major hemorrhages were deemed probably or definitely related to study drug

⁴ Not related to study drug

HA002: Alfimeprase in Acute PAO

Bleeding Events



- SAE bleed defined as bleeding that is fatal, life-threatening, requires hospitalization, results in significant disability, or that poses significant medical hazard
- Major bleed defined as bleeding that requires an operation or transfusion, results in death, or any ICH

HA002: Alfimeprase in Acute PAO

Final Activity Results (Intention to Treat) ¹

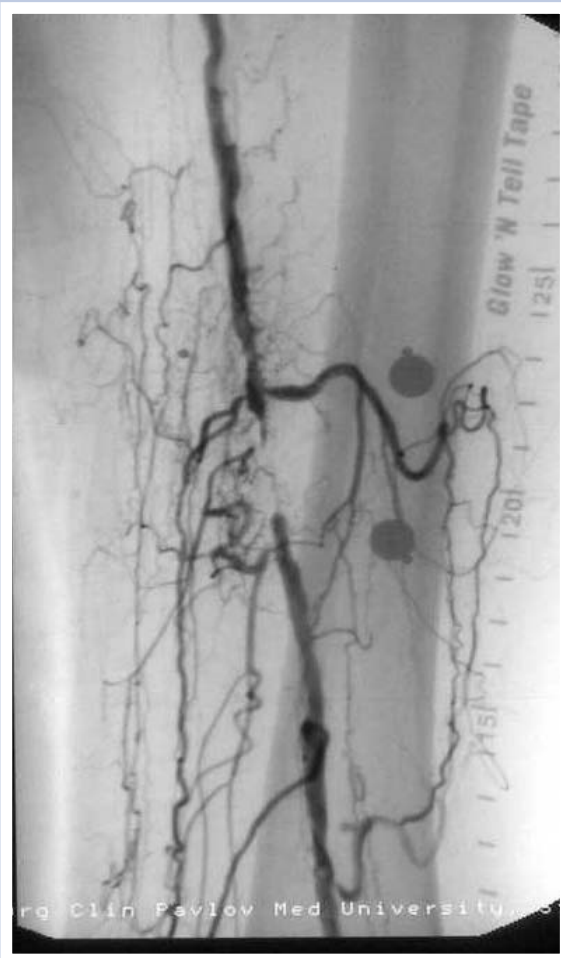
Activity Measure	Alfimeprase 0.1 mg/kg N=16	Alfimeprase 0.3 mg/kg N=49	Alfimeprase 0.6 mg/kg N=48	Alfimeprase total N=113
30-Day Open-Vascular Surgery-Free Survival	69 %	61 %	52 %	58 %
Partial to complete clot lysis (grade 1, 2 or 3 patency) ²	50 %	76 %	73 %	73 %
Restoration of Arterial Flow (grade 2 or 3 patency) ²	31 %	55 %	60 %	54 %
Increase in ABI by ≥ 0.15	50 %	74 %	85 %	78 %

¹ An interim analysis presented at Vascular 2004 included activity results for “evaluable subjects.” The current presentation is based on intention to treat (ITT) analysis. In ITT, previously unevaluable angiograms are now considered as grade 0.

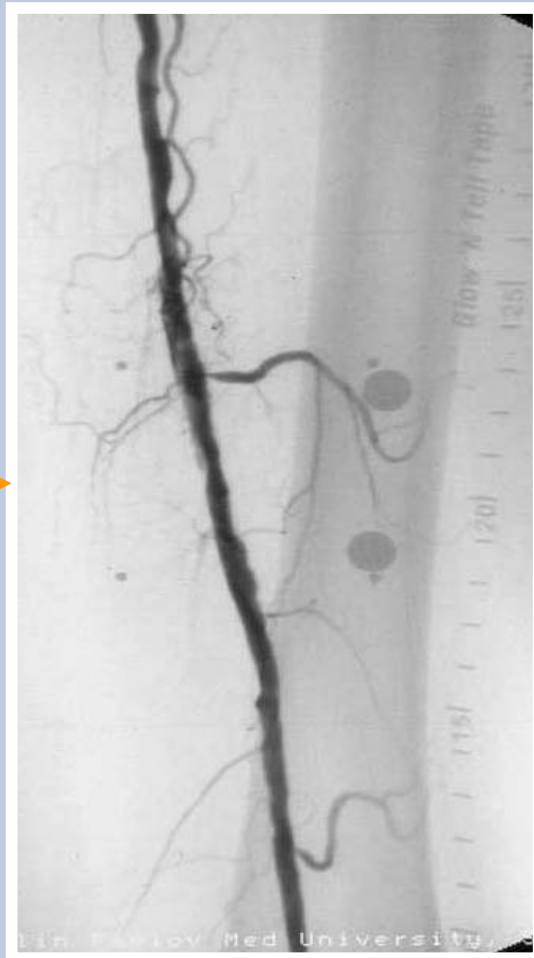
² Patency classifications:

- 0=no thrombolysis, defined as no change in the occlusion from baseline
- 1=incomplete (partial) thrombolysis without flow
- 2=incomplete (partial) thrombolysis with flow
- 3=near-complete or complete thrombolysis with flow

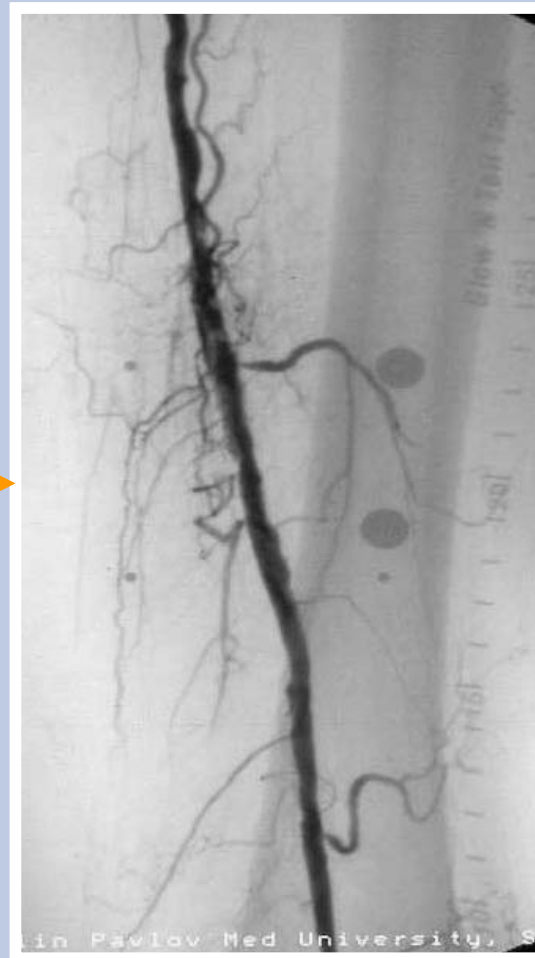
Resolution of “Leg Attack” (Left SFA Acute PAO)



Diagnostic (baseline) angiogram



2 hours after 1st dose



2 hours after 2nd dose

HA002: Discussion

This final analysis of 113 subjects reveals that:

- Alfimeprase was generally safe and well-tolerated in acute PAO
- SAE, major hemorrhage, and hypotension rates were dose-related
- ICH and death rates were zero in this phase 2 study in acute PAO
- Hypotensive episodes were easily managed by standard therapy
- 52% to 69% of subjects were able to avoid surgical intervention
- Investigators reported thrombolysis rates up to 76% and restoration of arterial flow rates up to 60%, **4 HOURS** after initiation of therapy
- Based on an anatomic endpoint (restoration of flow) and a physiologic endpoint (increase in ABI), there was dose-related activity
- Alfimeprase warrants further study in subjects with “Leg Attack”