FDA Perspective

Xiaflex
(Collagenase Clostridium Histolyticum)
for Advanced Dupuytren's Disease

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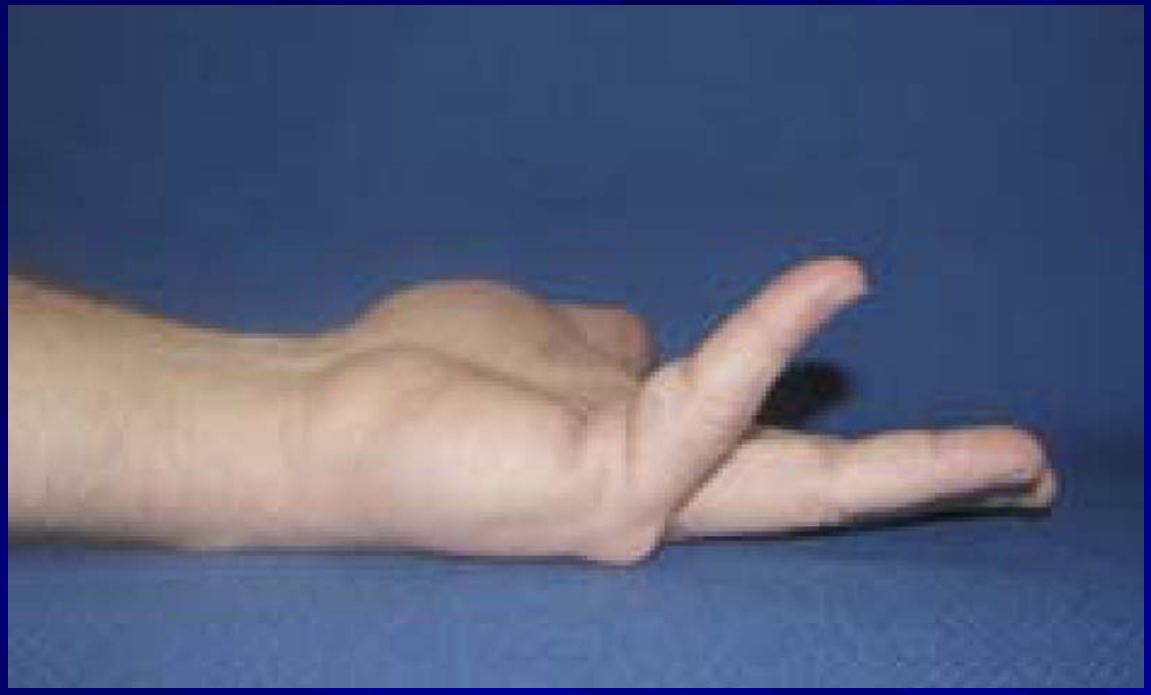
Dupuytren's Contracture (DC)[1]



- Fixed flexion contracture, typically involves the metacarpophalangeal (MP) and/or proximal interphalangeal (PIP) joints
- 5th & 4th fingers are usually involved
- No approved medical therapies; however, surgery (fasciotomy or fasciectomy) can be performed.

1 Picture of hand with Dupuytren's contracture from Dupuytren's Clinic of Nevada.

Xiaflex (Collagenase Clostridium Histolyticum)

Regulatory History	**May 1996 – Orphan Designation for Dupuytren's** **February 2009 – Auxilium submitted Application**
Proposed Indication	**"Advanced Dupuytren's disease"**
Product Background	**Xiaflex consists of two microbial collagenases (AUX-I & AUX-II)** **Isolated & purified from Clostridium histolyticum**
Proposed Mechanism	**Xiaflex injection into a Dupuytren's cord affecting a MP or PIP joint results in collagen lysis resulting in enzymatic disruption of the cord.**
Proposed Dose and Administration	**"By a physician experienced in the diagnosis and management of Dupuytren's."** **Up to 3 injections of 0.58 mg per cord, given at 4-week intervals. If the contracture persists 24 hours after injections, finger extension procedures are recommended.**

Randomized, Double-Blinded, Placebo-Controlled Trials Submitted in the Application (BLA): Patients with Dupuytren's Contracture (DC)[1]

Study #[2] (Full Name)	Treatment Groups	# of intracord injections (Primary Joint)	# of Patients	# of Sites
Trials that provided Primary Support for Efficacy and Safety				
57 (AUX-CC-857)	0.58 mg Xiaflex (n=204) Placebo (n=104)	Up to 3	308	16
59 (AUX-CC-859)	0.58 mg Xiaflex (n=45) Placebo (n=21)	Up to 3	66	5
Supportive Trials				
02 (DUPY-202)	0.58 mg Xiaflex (n=23) 0.29 mg Xiaflex (n=22) 0.145 mg Xiaflex (n=18) Placebo (n=17)	1	80	2
03 (DUPY-303)	0.58 mg Xiaflex (n=23) Placebo (n=12)	Up to 3	35	1
51 (AUX-CC-851)	0.58 mg Xiaflex (n=5) Placebo (n=2)	1	7	3
53 (AUX-CC-853)	0.58 mg Xiaflex (n=17) Placebo (n=6)	Up to 3	23	2

1 Patients had to have a fixed-flexion deformity of at least 1 finger, that was ≥ 20° for a MP or PIP joint associated with a palpable cord.

2 All Studies were in the U.S. except Studies 53 & 59 were in Australia.

Efficacy Results

Trials that served as Primary Support for Efficacy (Studies 57 & 59)

Primary Efficacy Results: % of Patients with Contracture Reduction of Primary Joint to 0-5 degrees[1]

	Study 57 (U.S.)		Study 59 (Australian)	
	Xiaflex 0.58 mg (n=203)	Placebo (n=103)	Xiaflex 0.58 mg (n=45)	Placebo (n=21)
Proportion of patients with clinical success	64%	7%	44%	5%
Difference	57%	—	39%	—
95% CIs for the Difference	(48%, 65%)	—	(18%, 57%)	—

1. 30 days after last injection (**up to 3 injections** on Days 0, 30, & 60)

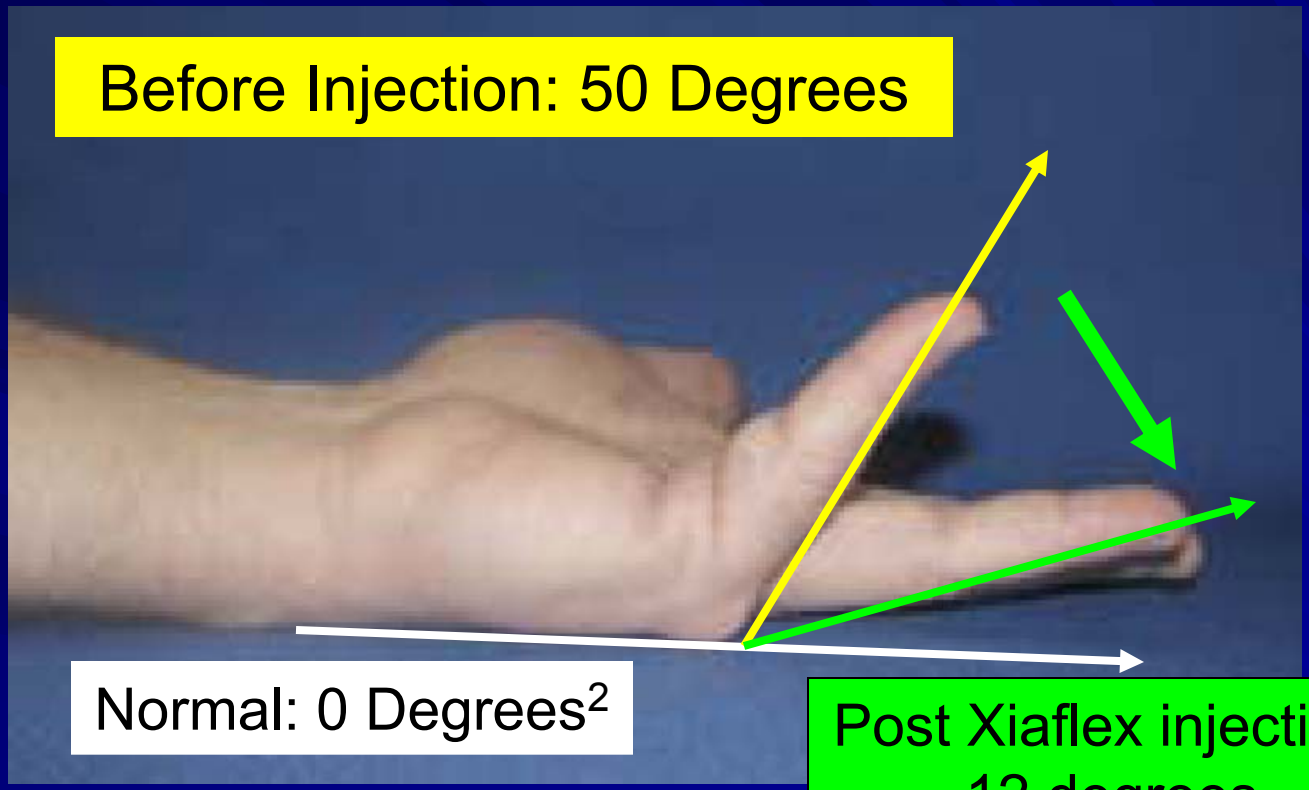
Proportion of Xiaflex-treated patients with contracture reduction to 0° to 5° after 1 injection was 39% & 27% in Studies 57 & 59, respectively

Mean % Change from Baseline in Contracture Degree[1]

	Study 57 (U.S.)		Study 59 (Australian)	
	Xiaflex 0.58 mg (n=203)	Placebo (n=103)	Xiaflex 0.58 mg (n=45)	Placebo (n=21)
Baseline contracture degree mean (SD)	50 (20)	49 (20)	53 (15)	50 (16)
Contracture degree 30 days after injection, mean (SD)	12 (19)	46 (24)	17 (19)	44 (20)
Mean % decrease from baseline in degree of contracture, 30 days after last injection	79%	9%	71%	14%

1. 30 days after last injection (**up to 3 injections** on Days 0, 30, & 60)

Representation of Mean Change in Fixed Flexion Contracture after Xiaflex Injections[1]



1 Degrees of full extension of primary MP & PIP joints in Study 57.
2 Normal full extension of the MP & PIP joints was considered to be 0 degrees (does not include MP joint hyperextension).

Picture of hand with Dupuytren's contracture from Dupuytren's Clinic of Nevada.

Contracture Recurrence in Xiaflex Studies vs. Recurrence in Surgery Literature

	Recurrence Incidence (# of Patients)	Mean Follow-up (years)	Recurrence Definition
Auxilium-Sponsored Xiaflex Studies			
Xiaflex-treated patients	4% (n=830)	0.6	Contracture increase ≥ 20° with the presence of a palpable cord
Literature Reports: Surgery for Dupuytren's contracture			
Fasciectomy			Severe enough to require another surgery
Foucher 1992	23% (n=107)	5.6	
	6% (n=107)		
Skoff 2004	3% (n=30)	2.7-3.5	
Searle 1992	0% (n=32)	3.2	
Hall 1997	0% (n=67)	4	
Fasciectomy or Fasciotomy			
Dias 2006	15% (n=1037)	2.3	
McFarlane 1990	6%-8% (n=434)	2	
	6%-8% (n=48)	10	
Fasciotomy			
Duthie 1997	66% (n=82)	10	
Van Rijssen 2006	42% (n=55)	2.8	
Foucher 2003	19% (n=100)	3.2	

Subgroup Analysis by Expertise of Investigator Who Performed Injections[1]

	Total # (%) of patients at site	Proportion of Patients with Clinical Success (Primary Efficacy Endpoint)[1]	
		Xiaflex 0.58 mg	Placebo
All Sites in U.S. Study 57	306 (100%)	130/203 (64%)	7/103 (7%)
Hand Surgeons[2]	273 (89%)	114/181 (63%)	7/92 (8%)
Orthopedic Surgeons[3]	33 (11%)	16/22 (73%)	0/11 (0%)
All Sites in Australian Study 59	66 (100%)	20/45 (44%)	1/21 (5%)
Hand Surgeons	27 (41%)	9/19 (47%)	0/8 (0%)
Orthopedic Surgeon	23 (35%)	6/15 (40%)	1/8 (13%)
Rheumatologists	16 (24%)	5/11 (45%)	0/5 (0%)

1. Primary efficacy endpoint: % of patients with contracture reduction to 0° to 5° of the primary joint after up to 3 injections
2. At 1 of these sites either a hand surgeon or a plastic surgery fellow performed injections.
3. At 1 of these sites either a hand surgeon or orthopedic surgeon performed injections.

Safety Results

Exposure to Xiaflex

In the controlled portions of Studies 57 & 59 (through Day 90)

249 Xiaflex-treated patients & 125 placebo-treated patients.

In entire safety database (controlled & uncontrolled studies):

- 1082 Xiaflex-treated patients with 1780 Dupuytren's cords treated with 2630 Xiaflex injections.
- Mean (±SD) duration of safety follow-up for these 1082 patients was 9.5 (±4.6) months.

# of Xiaflex Injections Received	n (%)*
≥ 1	1082 (100%)
1	443 (41%)
2	219 (20%)
3	170 (16%)
4	93 (9%)
5	116 (11%)
6	14 (1%)
7	13 (1%)
8	14 (1%)
* n (%) is the number (%) of patients who received injections	

Major Safety Results (1)

Controlled Portions of Pooled Studies 57 & 59 Through Day 90

	0.58 mg of Xiaflex (n=249)	Placebo (n=125)
Deaths	0 (0%)	0 (0%)
All Serious Adverse Events (SAEs)	7 (3%)	1 (1%)
SAEs involving the injected extremity	5 (2%)	0 (0%)
Adverse Events Leading to Discontinuation (DAEs)	3 (1%)	0 (0%)
Adverse Events	243 (98%)	61 (49%)

Major Safety Results (2)

Controlled and Uncontrolled Portions of 12 Submitted Xiaflex Studies	
	0.58 mg of Xiaflex
Safety results per patient	
# of Xiaflex-treated patients (0.58 mg)	n=1082
Deaths[1]	5/1082 (0.5%)
SAEs involving the treated extremity	11/1082 (1.0%)
Tendon rupture involving the treated extremity	3/1082 (0.3%)
Safety results per Xiaflex injection	
# of Xiaflex injections (0.58 mg)	n=2630
SAEs involving the treated extremity	11/2630 (0.4%)
Tendon ruptures involving the treated extremity	3/2630 (0.1%)

1 Does not include 2 deaths from a pilot academic study of Xiaflex.

SAEs = serious adverse events

Deaths

	Cause of Death	Age in years (Gender)	Past Medical History	# of Xiaflex Injections (0.58 mg)	Time Between Last Xiaflex Injection & Date of Death
Auxilium's Submitted Xiaflex Studies					
1	COPD	68 (male)	COPD	2	208 days
2	Liver cancer	63 (male)	—	3	≥ 76 days
3	MI	77 (male)	CAD	1	157 days
4	MI	79 (male)	DM type II	1	180 days
5	MI	76 (male)	CAD	1	267 days
Pilot Academic Study of Xiaflex					
6	Pulmonary fibrosis	75 (male)	COPD	1	About 365 days
7	Aortic aneurysm rupture	68 (male)	Cardiac disease	1	About 60 days

Serious Adverse Events of Injected Extremity

	Serious Adverse Event (SAE) of the injected extremity	Time Between Last Xiaflex Injection & AE	# of Xiaflex Injections into Cord (0.58 mg)	Treatment/Outcome
Controlled Portions of Studies 57 & 59 Through Day 90				
1	Tendon ruptures	4 days	3	Surgery
2	Tendon ruptures	7 days	1	Surgery
3	Complex regional pain syndrome	13 days	1	Steroids, pregabalin & hand therapy
4	Ligament disorder	20 days	3	Event ongoing
5	Flexor pulley ruptures	43 days	2	Surgery
Open-Label, Uncontrolled Portions of the Xiaflex Studies				
6	Tendon rupture	≤ 7 days	1	Surgery
7	Sensory abnormality of left hand	13 days	2	Resolved
8	Fracture of the tip of right 2nd finger with a ligament tear	14 days	1	Recovered without surgery
9	Tendonitis	14 days	4	Managed conservatively, Outcome unknown
10	Boutonniere deformity	28 days	1	Splint, ongoing
11	Elective amputation right 5th finger	103 days	1	Surgery

11 (1.0%) of 1082 Xiaflex-treated patients had SAEs of injected extremity

3 (0.3%) of 1082 Xiaflex-treated patients had tendon ruptures

Xiaflex-Associated SAEs of Injected Extremity vs. Complications of Surgery for Dupuytren's

Auxilium's Xiaflex Studies: Serious Adverse Events (SAEs) of the Injected Extremity	
SAEs involving the treated extremity	1.0%
Tendon Ruptures	0.3%
Literature Reports: Complications After Fasciectomy or Fasciotomy for Dupuytren's contracture[1]	
Intra-operative complications	**Proportion**
Arterial injury/transection	0-10%
Nerve injuries	0-8%
Post-operative complications	**Proportion**
Complex Regional Pain Syndrome	0-18%
Infection	0-10%
Skin loss	0-5%
Wound healing difficulties	0-4%
Hematoma	0-3%
Amputation	0-0.6%
Gangrene	0-0.1%
Systemic complications (e.g., MI, left ventricular failure, urinary retention)	< 1%

1 Data are from retrospective & prospective observational studies

Common Adverse Events (≥ 5%)[1]

	0.58 mg of Xiaflex (n=249)	Placebo (n=125)
Patients with ≥ 1 Adverse Event (AE)	**243 (98%)**	**61 (49%)**
Edema (mostly hand edema)	73%	5%
Contusion	55%	3%
Injection site hemorrhage	38%	3%
Pain in extremity	35%	5%
Injection site pain	33%	6%
Injection site swelling	24%	6%
Tenderness	24%	0%
Ecchymosis	20%	1%
Lymphadenopathy	12%	0%
Pruritus	11%	1%
Skin laceration	9%	0%
Lymph node pain	8%	0%
Axillary pain	6%	0%
Erythema	6%	0%
Injection site pruritus	5%	0%

1 Controlled Portions of Pooled Studies 57 & 59 Through Day 90. All patients received ≥ 1 dose of study drug

Allergic Reactions

No severe allergic reactions (requiring hospitalization or those associated with respiratory compromise or end-organ dysfunction) were observed.

Exploratory Analysis of "Pruritus" AEs[1] by Injection

	Study 57 (U.S.)		Study 59 (Australian)	
	Xiaflex n=203	Placebo n=103	Xiaflex n=45	Placebo n=21
After up to 3 injections	33/203 (16%)	1/103 (1%)	6/45 (13%)	0/21 (0%)
After 1 injection	10/203 (5%)	1/103 (1%)	1/45 (2%)	0/21 (0%)
After 2 injections	15/99 (15%)	0/100 (0%)	4/22 (18%)	0/19 (0%)
After 3 injections	20/45 (44%)	0/91 (0%)	3/8 (38%)	0/18 (0%)

1 Pruritus AEs included Pruritus, Injection Site Pruritus, & Pruritus Generalized

Immunogenicity

- 86% of patients had positive antibodies to AUX-1 and/or AUX-2 after first Xiaflex injection
- 100% of patients had antibodies to AUX-1 & AUX-2 after the fourth Xiaflex injection
- No significant difference in the proportion of Xiaflex-treated patients with positive or negative neutralizing antibody to AUX-I or AUX-2 who achieved the primary endpoint

Special Considerations

Training for Investigators vs. Proposed Training If Approved

		Investigators in Studies 57 & 59	Clinicians in Practice if Approved
Training			
Injection Technique & Finger Extension Procedure	Paper Manual	Yes	Yes
	Video	Yes	Yes
Workshops/Investigator Meetings		Yes	No
"Trained Auxilium personnel"		No	Yes
Simulations		No	No
Other Risk Minimization			
Investigator Brochure		Yes	No
Labeling		N/A	Yes
Attestation of Training[1]		N/A	Yes

1 Physicians must sign a form that states that they understand the injection procedures & Xiaflex risks, & they have viewed a Xiaflex video. If physicians do not sign this form, Xiaflex will not be provided.

Benefit-Risk

Risk-Benefit Overview: Up to 3 Injections[1]

Possible Benefit			
	Xiaflex	Placebo	Number Needed to Treat (NNT)
Patients who had a contracture reduction to 0° to 5°	150/248 (60%)	8/124 (6%)	~ 2
Patients who had a ≥ 50% decrease in contracture from baseline	207/248 (83%)	15/124 (12%)	~ 1

Possible Risk			
	Xiaflex	Placebo	Number Needed to Harm (NNH)
Local AEs (e.g., edema, contusion, pain of extremity)	243/249 (98%)	61/125 (49%)	~ 1*
Tendon Ruptures	2/249 (1%)	0/125 (0%)	~ 125
Other SAEs of injected extremity (not tendon ruptures)	3/249 (1%)	0/125 (0%)	~ 83

1 Based on pooled portions of Studies 57 & 59 through Day 90. Mean (±SD) # of Xiaflex injections given in these trials was 1.7 (±0.8).

* NNH for local reactions was ~ 1 because the incidence of local reactions in patients not given Xiaflex injections would likely be 0%.

Summary

Efficacy: Results from controlled trials demonstrate a statistically significant increase in the proportion of patients achieving almost complete contracture reduction when treated with Xiaflex compared to placebo.

Safety: Xiaflex injection was associated with twice as many AEs compared to placebo, with most being local reactions. SAEs, including tendon ruptures, were uncommon.

Special Considerations: Clinical trial results may represent a "best-case" scenario where the investigators performing injections had extensive professional training and were highly trained in Xiaflex injection & finger extension procedures.

- Return to Main

Risk Management Considerations for Collagenase Clostridium Histolyticum

Arthritis Drugs Advisory Committee

September 16, 2009

Kathryn O'Connell, M.D., Ph.D.
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Division of Risk Management

FDA's Concept of Risk Management

The overall and continuing process of minimizing risks throughout a product's lifecycle to optimize its benefit-risk balance*

*Guidance for Industry
Development and Use of Risk Minimization Action Plans
March, 2005

Risk Management Issue for CCH

- Is required training necessary for CCH?
- An issue because the relationship between tendon rupture and improper administration of the product is unknown
  - Generalizability to clinical practice of trial results obtained by highly trained investigators
  - Unknown relationship between tendon rupture and user factors (i.e., specialty, hand anatomy expertise)
  - Inherent potential damaging effect of collagenase on collagen-containing structures adjacent to cord

Risk Management

Product safety issues are typically managed through:

- Product's package insert
- Sponsor-provided training
- Post-marketing studies
- Post-marketing surveillance

However…

If the seriousness of risks associated with CCH make it necessary to require and enforce training…

- Food and Drug Administration Amendments Act (FDAAA) provides FDA authority to *require* risk evaluation and mitigation strategies (REMS)

- Accordingly, REMS may be required *if, and only if*, the FDA determines that these strategies are necessary to ensure that the benefits of the drug outweigh the risks

REMS

May include one or more of the following:

- **Medication Guide** for patients
- **Communication Plan** for healthcare professionals
- **Elements to Assure Safe Use (ETASU)**
  - Often involve some form of restricted distribution

REMS - Medication Guide

- Provides FDA approved patient-friendly labeling
- Can be required if FDA determines one or more:
  - Patient labeling could help prevent serious adverse events
  - The product has serious risks that could affect patient's decision to use or continue to use
  - Patient adherence to directions is crucial to product effectiveness

REMS - Communication Plan

- FDA approved materials used to aid sponsor's implementation of REMS and/or inform healthcare providers about serious risk(s)
- For example, "Dear Healthcare Professional" letters and other educational materials have been required to alert prescribers to serious risks associated with the use of certain drugs and biologics
- The impact of such letters is not known

REMS - ETASU

- Mandatory prescriber training or certification
- Mandatory certification of dispensers
- Drug administration restricted to certain health care settings
- Mandatory documentation of safe use prior to dispensing
- Mandatory monitoring of patients
- Mandatory enrollment of patients in a registry

REMS -ETASU

- Provide the most strict control over whether the product is used as per FDA approved labeling
- Downside is that ETASU can impose significant burdens on the healthcare system and reduce patient access to treatment
- Thus, ETASU should be used only if the product would otherwise not be approved due to specific serious risk listed in the labeling

FDCA 505-1(f)(3) requires that ETASU…

- Must be commensurate with specific serious risk(s) listed in the labeling
- Can't be unduly burdensome on patient access to the drug
- To minimize the burden on the healthcare delivery system, must, to the extent practicable, conform with elements for other drugs with similar serious risks and be designed for compatibility with established distribution, procurement, and dispensing systems for drugs

Summary

- FDA has the authority to require REMS *if* additional measures (in this case, required training) *are necessary* to ensure the benefits of CCH outweigh the risks

- Risk management for CCH should minimize healthcare system burden and barriers to patient access, to the extent possible within risk mitigation goals

- Return to Main

Q&A Slides Presented to the Arthritis Drugs Advisory Committee

FDA CDER

Arthritis Drugs Advisory Committee

September 16, 2009

BLA: 125338, clostridial collagenase, Auxilium Pharmaceuticals, Inc.

6003-4314 Deep Vein Thrombosis

- 62-year-old ♂ – History of Ledderhose's Disease. Drove a considerable distance to study site
  - Day 0 – AA4500 injection
  - Day 2 – Left knee and calf pain
- Doppler revealed single lower extremity thrombosis – superficial and deep
- Managed with anticoagulants

Pharmacology of AA4500

Cause of the Local Effects?

- **AUX I / AUX II efficiently cleave collagen into small fragments**
- **In animal studies, collagen fragments result in:**
  - **Increased capillary permeability**
  - **Hemorrhage**
  - **Rapid localized edema**
  - **Local non-immunological mast cell histamine release**
- **In non-clinical studies response resolves in 2-4 weeks**
- **Inactivated collagenase does not elicit local reactions in animal studies**

AA4500 Injection Site Effects

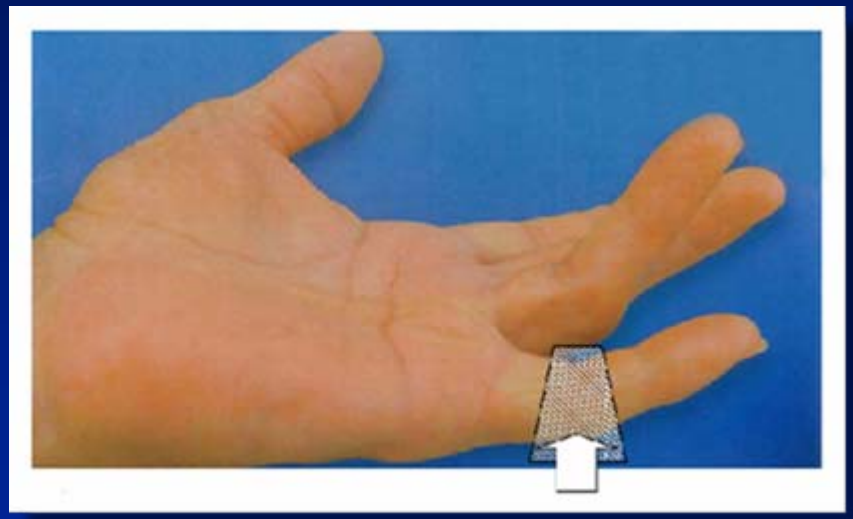
Non-clinical Studies

Study Number(s)	Species & Injection Site	Results
Pharmaco 95-2384	Zucker rats SQ (fat pad)	Fat cell disruption (inflammation)
LAB 1007-1671	Rat IV (extravasation)	No effects on injected vessel Reversible hemorrhage, edema, collagen lysis (interstitial & peritendon) No effects on tendon fibers, nerves, arteries, muscle or bone/cartilage
TRL 507, 510, 520	Dog intrapenile (various locations)	Collagen lysis confined when injection into tunica albuginea Reversible interstitial hemorrhage, edema, inflammation (fibro-vascular proliferation) No effects on arteries, nerves, urethral mucosa (venules disrupted) Reversible arteriolar wall hemorrhage w intact collagen & smooth muscle

AA4500 Clinical Development Experience

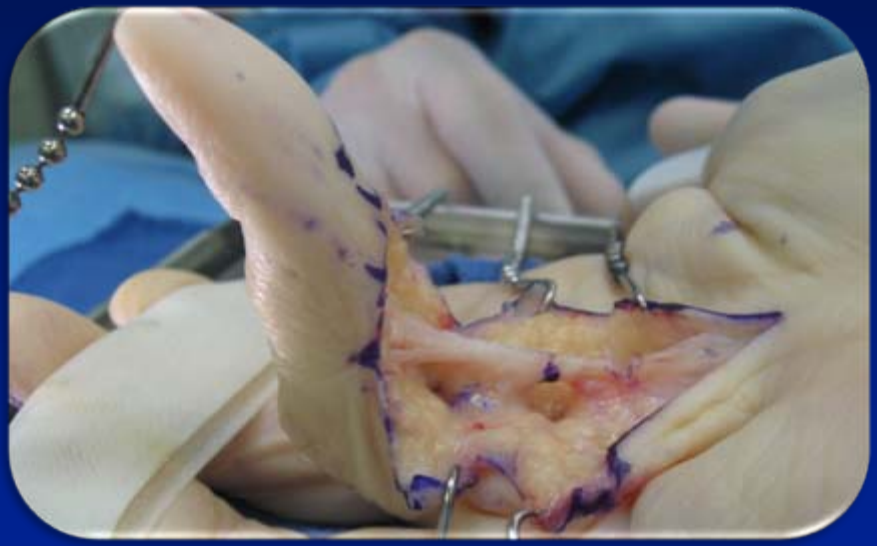
Modifications – Injection Site Recommendations

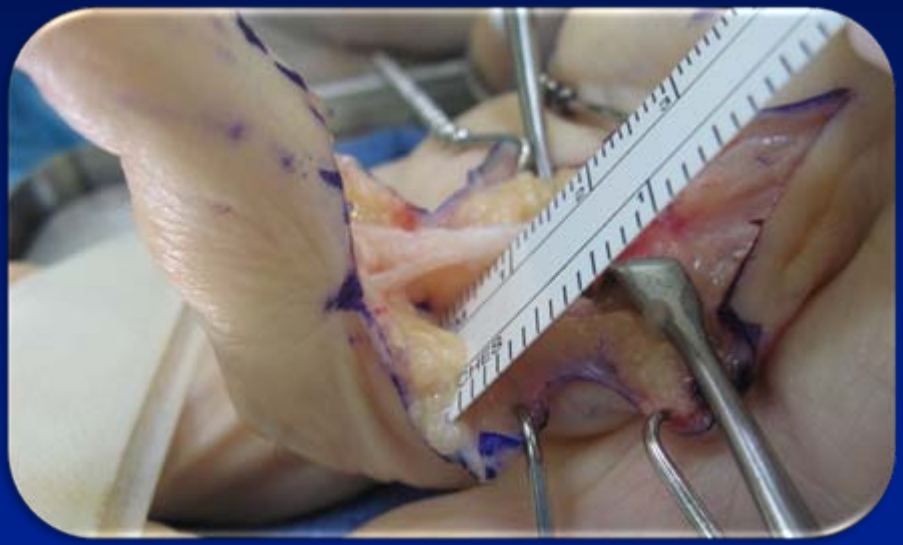
- **Do not inject more than 4 mm distal to the palmar digital crease**



- **Needle insertion into the cord contracting the PIP joint in the fifth finger should never be more then 2 MM to 3 MM in depth**

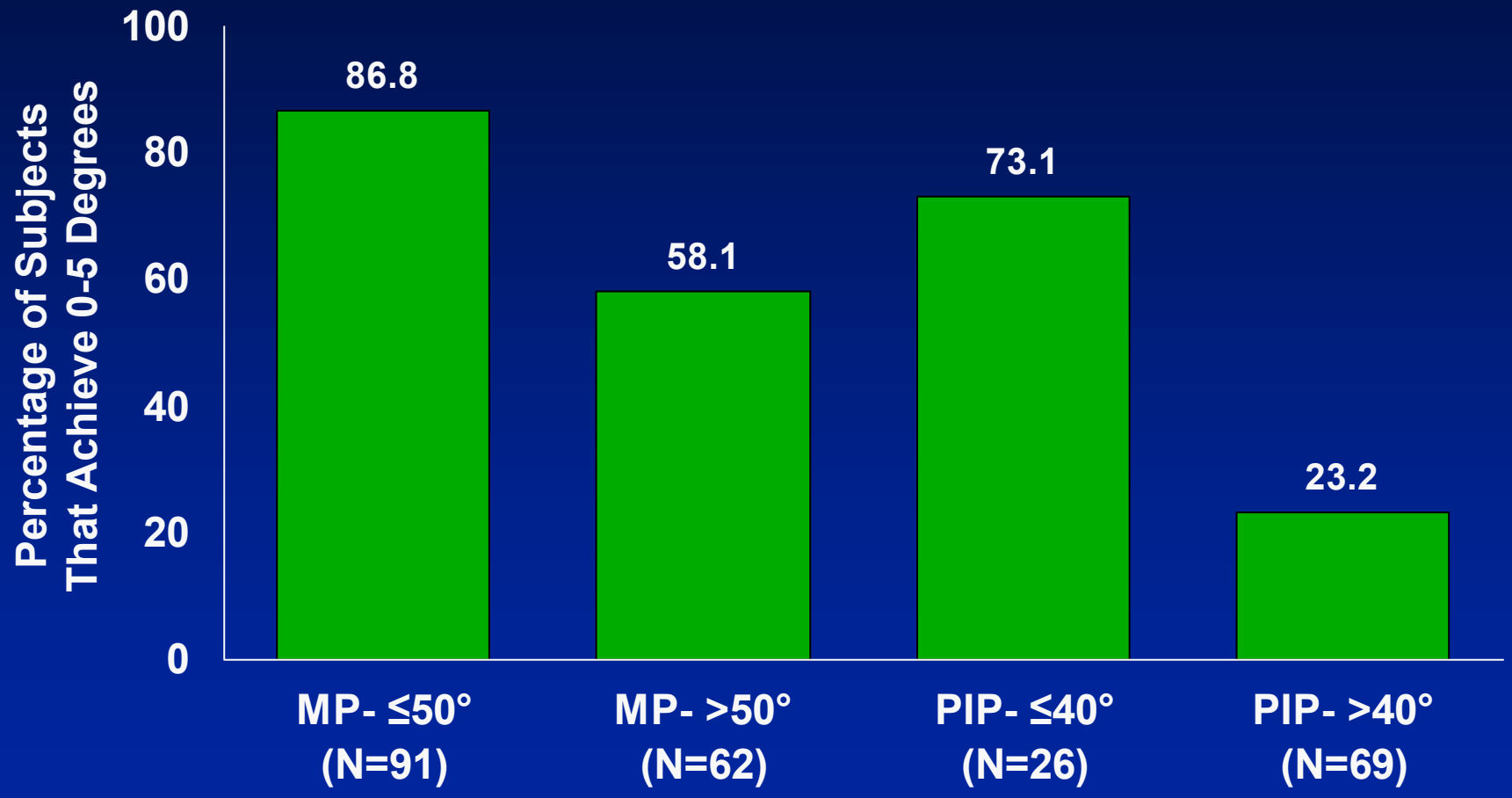
Cord to Flexor Distance





By Baseline Severity and Joint

Studies I-II (AA4500 Only)



Additional Studies – AA4500

AUX-860 – Long Term Follow-Up Study

- Two to five year follow-up
- Approximately 350 subjects from studies:
  - AUX-854
  - AUX-856
  - AUX-857/858
  - AUX-859
- Objectives
  - Durability of response
  - Progression of disease
  - Long term safety

Access Management Program (cont.)
Attestation Language

- I have reviewed and understand the procedural steps necessary to properly reconstitute and provide treatment with AA4500 according to location of the Dupuytren's contracture (MP or PIP joint)
- I understand the following risks are associated with AA4500:

  AA4500 should only be injected into the Dupuytren's (collagen) cord. Because AA4500 lyses collagen, care should be taken to avoid injecting into tendons, nerves, blood vessels, or other collagen-containing structures of the hand. Exposure of AA4500 to normal collagen-containing structures may result in damage to those structures and possible permanent injury, such as tendon rupture or ligament damage.
- I will counsel each patient on the risks and benefits of AA4500, and provide each patient with the AA4500 Patient Package Insert

Comparison of Training

Injection Training of Investigators vs. Proposed Physician Training

Areas of Training	Injection Training of Investigators	Proposed Physician Training
Preparation, Injection Technique and Finger Extension	Yes	Improved
Adverse event reporting information	Yes*	Improved
Important safety information section	Yes †	Improved
Adverse events described	Most common†	All ≥ 5%
Injection technique specific to the joint affected	–	Yes
Risk of tendon damage specifically discussed	–	Yes
"Frequently Asked Questions" section based on investigator experience	–	Yes
Self assessment of learning	–	Yes
Sequential completion of training video required before attestation	–	Yes
Training attestation required before use	–	Yes
Consistent training experience	–	Yes

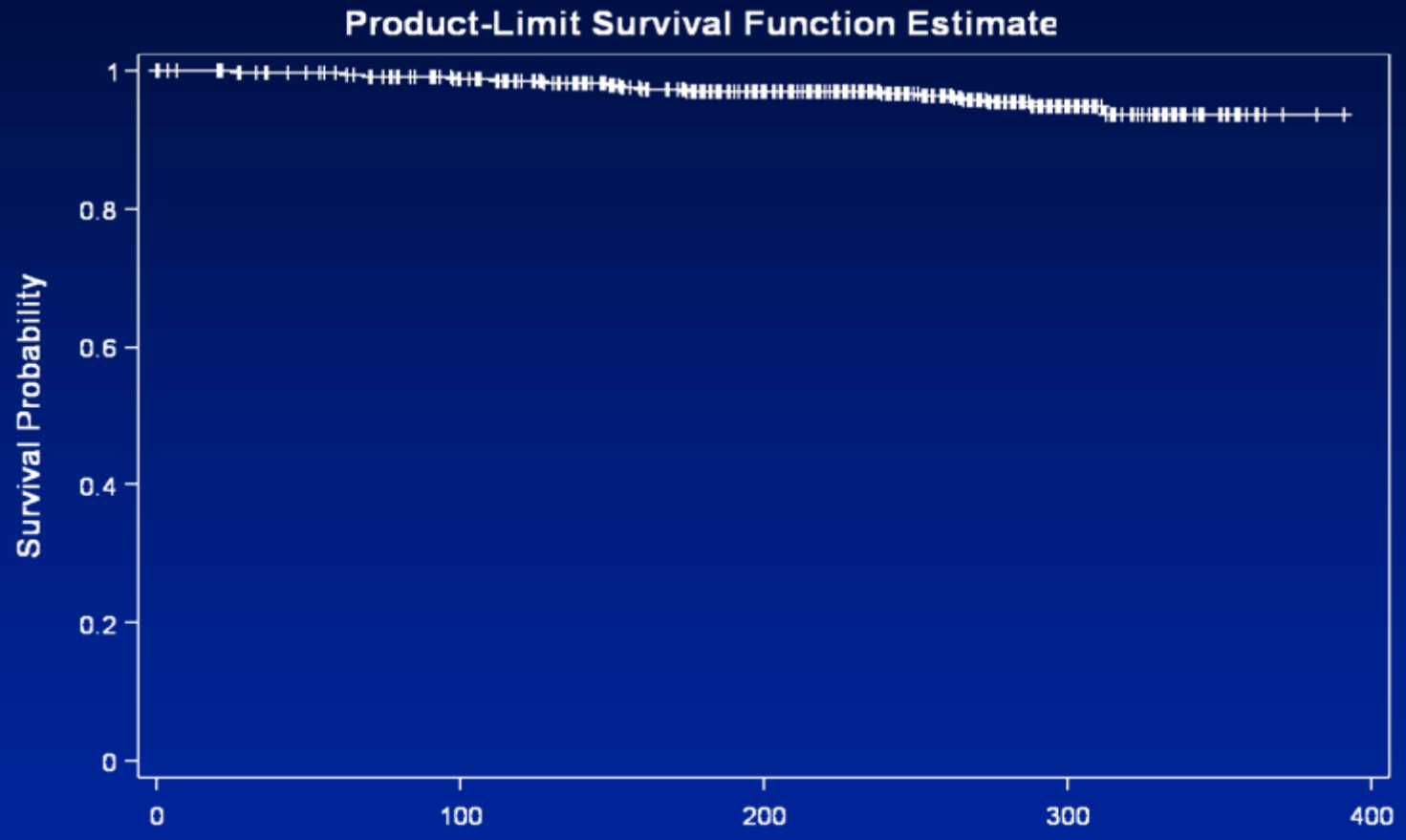
Included in the *Study Protocol / †Investigator's Brochure

Distribution of Primary Joints by Severity and Joint Type

	Study I (N=203)	Study II (N=45)
MP – ≤50°	39.9%	22.2%
PIP –≤40°	10.3%	11.1%
MP – >50°	25.6%	22.2%
PIP – >40°	24.1%	44.4%
	100%	100%

AA4500: Durability of Response

Kaplan-Meier Time to Recurrence



Rate = 3.6% (30/830)

KM @ 360 days = 6.7%±1.7%

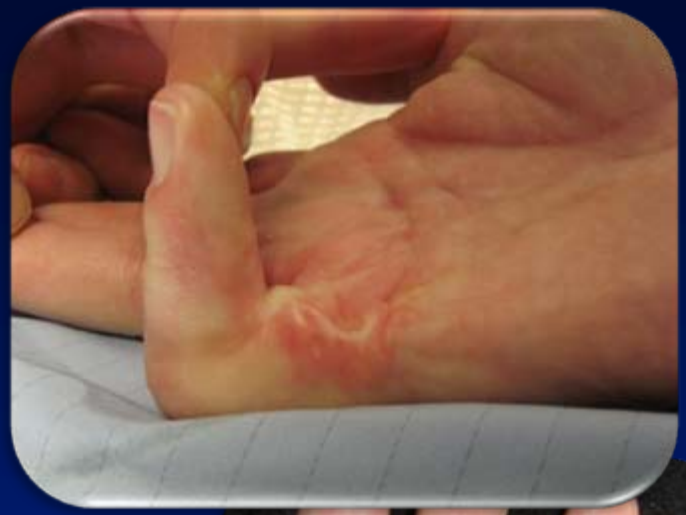
830 successfully treated joints

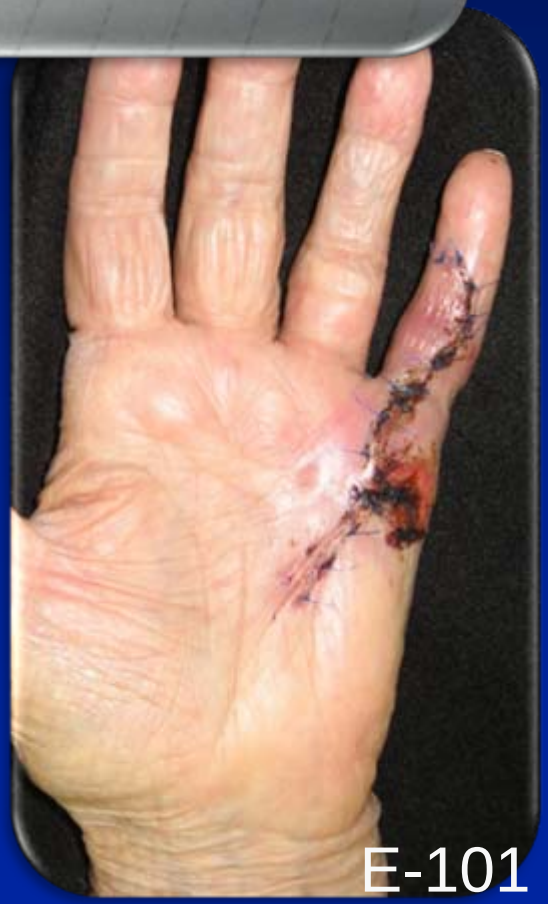
Fasciectomy Results

Results of Surgical Treatment of Dupuytren's Disease in Women: A Review of 109 Consecutive Patients

M. U. Anwar, MBBS, S. K. Al Ghazal, MD, R. S. Boome, MBBS

J Hand Surg 2007;32A:





- Complications
  - Recurrence (f/u avg 12 months)
    - 22% women / 19% men
  - Flare reaction – 2%
  - Digital nerve / artery injury – 3%
  - Infection – 2%
  - Loss of flexion / extension

Short Interval Between Injections

Subject Number	Days Between Injections	Joints Treated (Success 0 to 5°)	AEs Reported (Duration Days) Severity Following the Latter Dose
5026-5218	13	L Ring PIP (Yes) R Ring PIP (Yes)	Edema (6) Mild, Pruritus (4) Mild, Contusion (3) Mild, Pain in Ext (1) Mild
5026-5218	10	R Ring PIP (Yes) R Little PIP (Yes)	Edema (6) Mild, Pain in Ext (2) Mild
5026-5211	14	L Middle MP (Yes) L Ring MP (Yes)	Contusion (121) Moderate, Edema (121) Moderate, Skin Laceration (25) Moderate
5026-5204	15	R Index PIP (Yes) L Index PIP (Yes)	Edema (4) Mild, Contusion (8) Mild

ADA Titer: 1st vs. 2nd Treatment Period

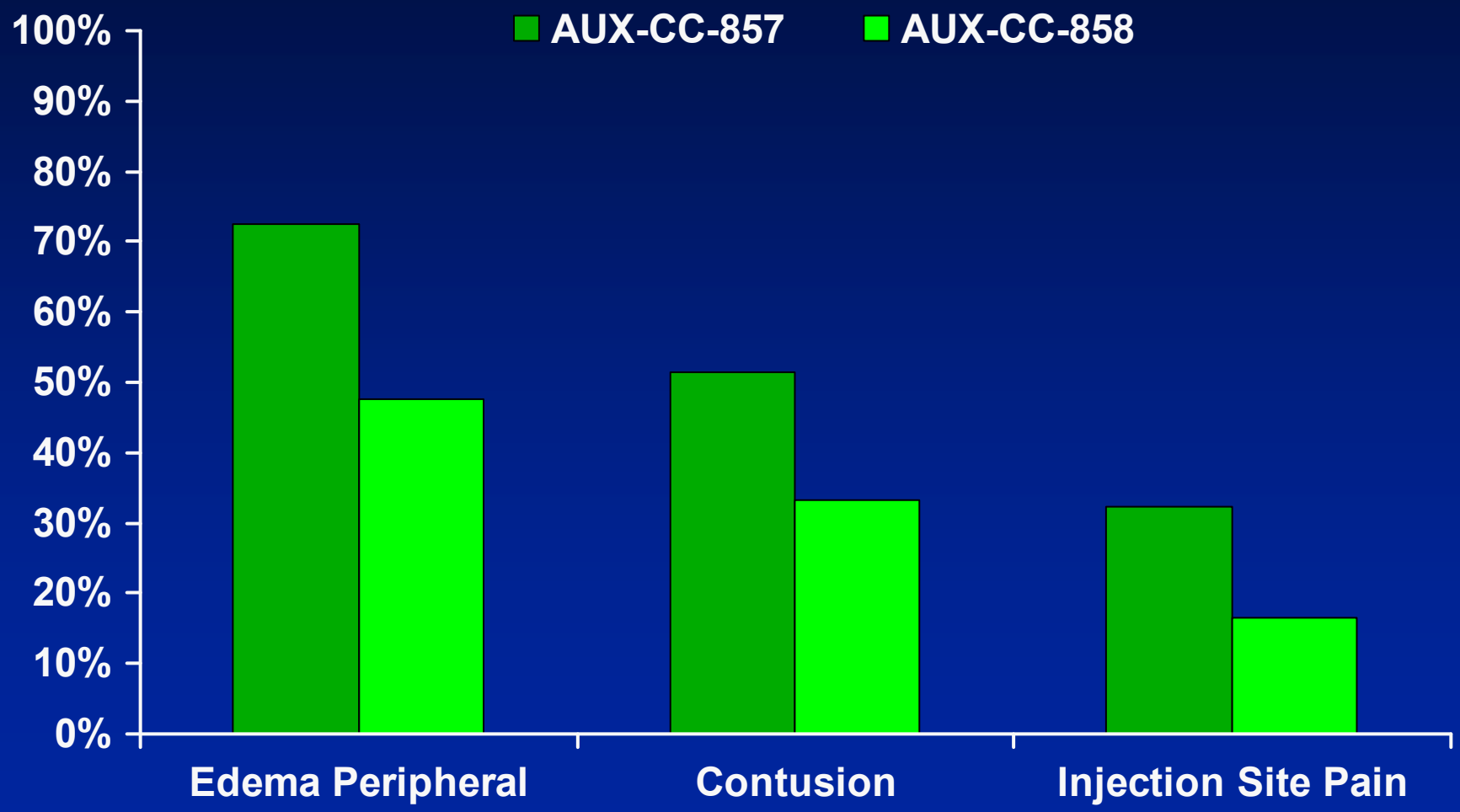
AUX-CC-857	Mean antibody titer 30 days following		
	1st injection	2nd injection	3rd injection
Anti-AUX-I	**167**	**10209**	**53703**
Anti-AUX-II	**99**	**3126**	**16749**

↓ Subjects from Study #857 were recruited into extension Study #858

AUX-CC-858	Mean antibody titer 30 days following				
	1st injection	2nd injection	3rd injection	4th injection	5th injection
Anti-AUX-I	**2512**	**33266**	**100000**	**188799**	**193197**
Anti-AUX-II	**1189**	**9268**	**29444**	**41879**	**39446**

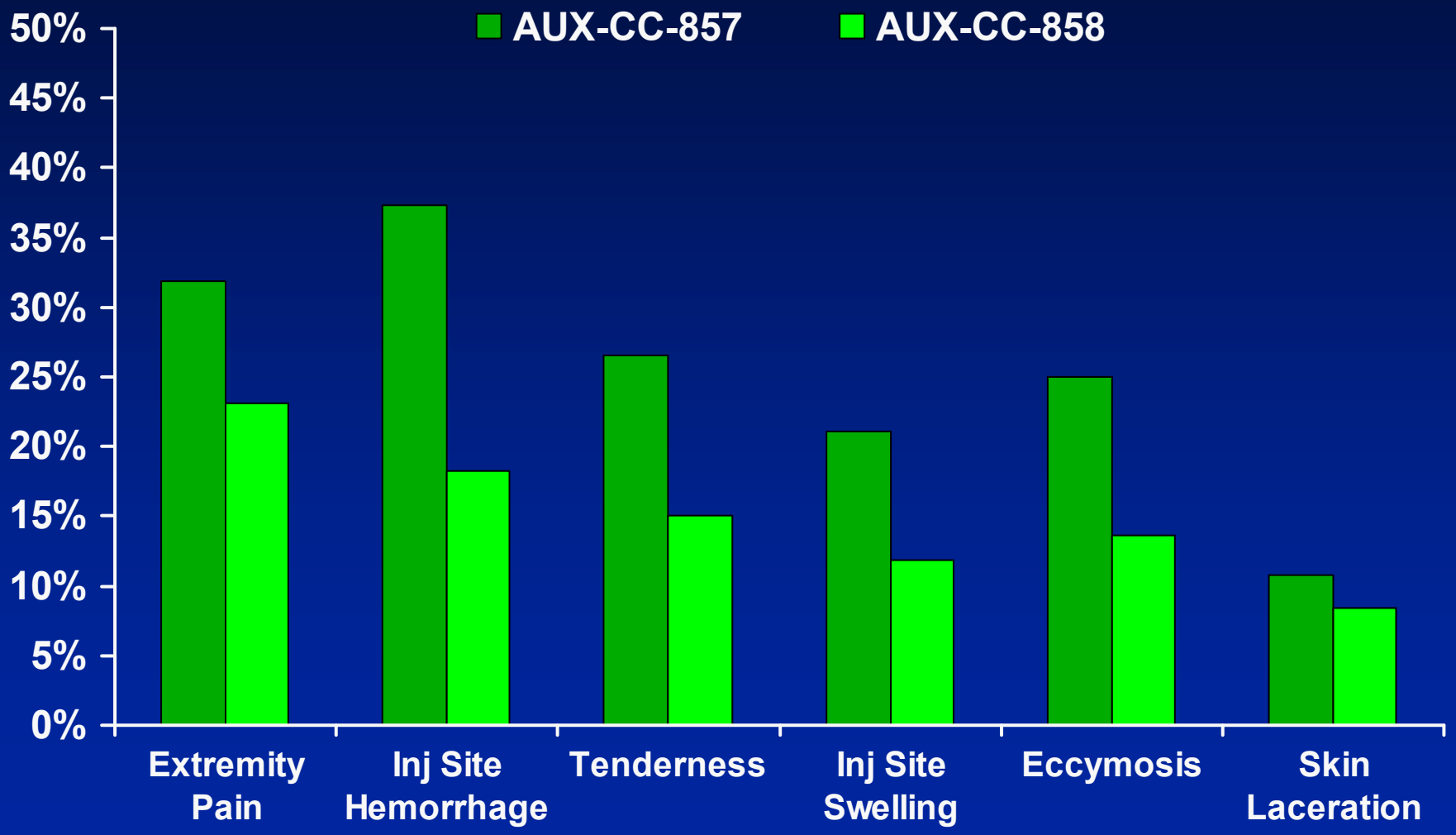
AUX-CC-857 vs. AUX-CC-858

Most Common Local Symptoms ≥5%



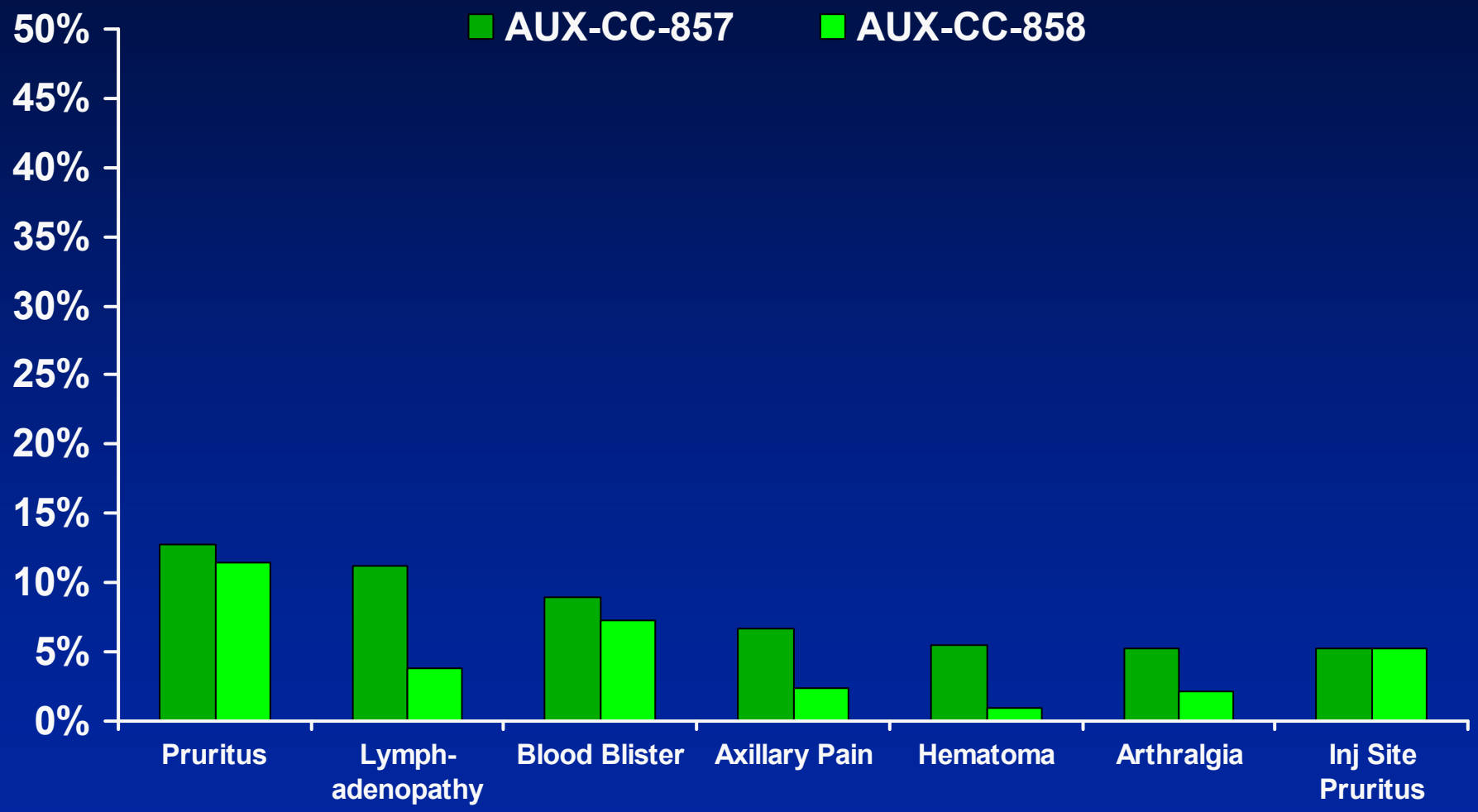
AUX-CC-857 vs. AUX-CC-858

Most Common Local Symptoms ≥5%



AUX-CC-857 vs. AUX-CC-858

Most Common Local Symptoms ≥5%



AA4500 Clinical Development Experience

Training Reinforcement Timeline

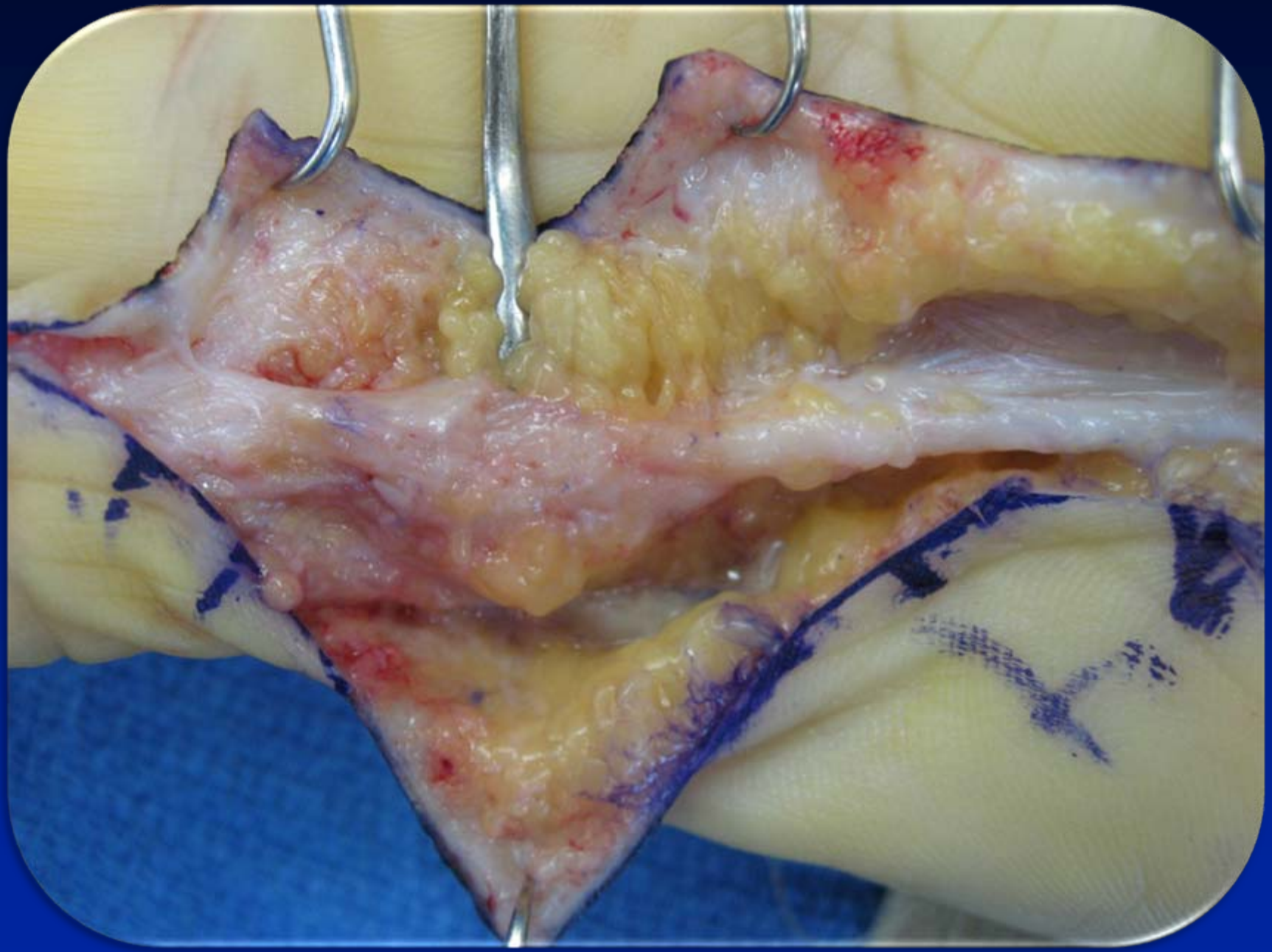
- **Prior to the training reinforcement**
  - 734 AA4500 injections
    - 446 MP cords
    - 288 PIP cords

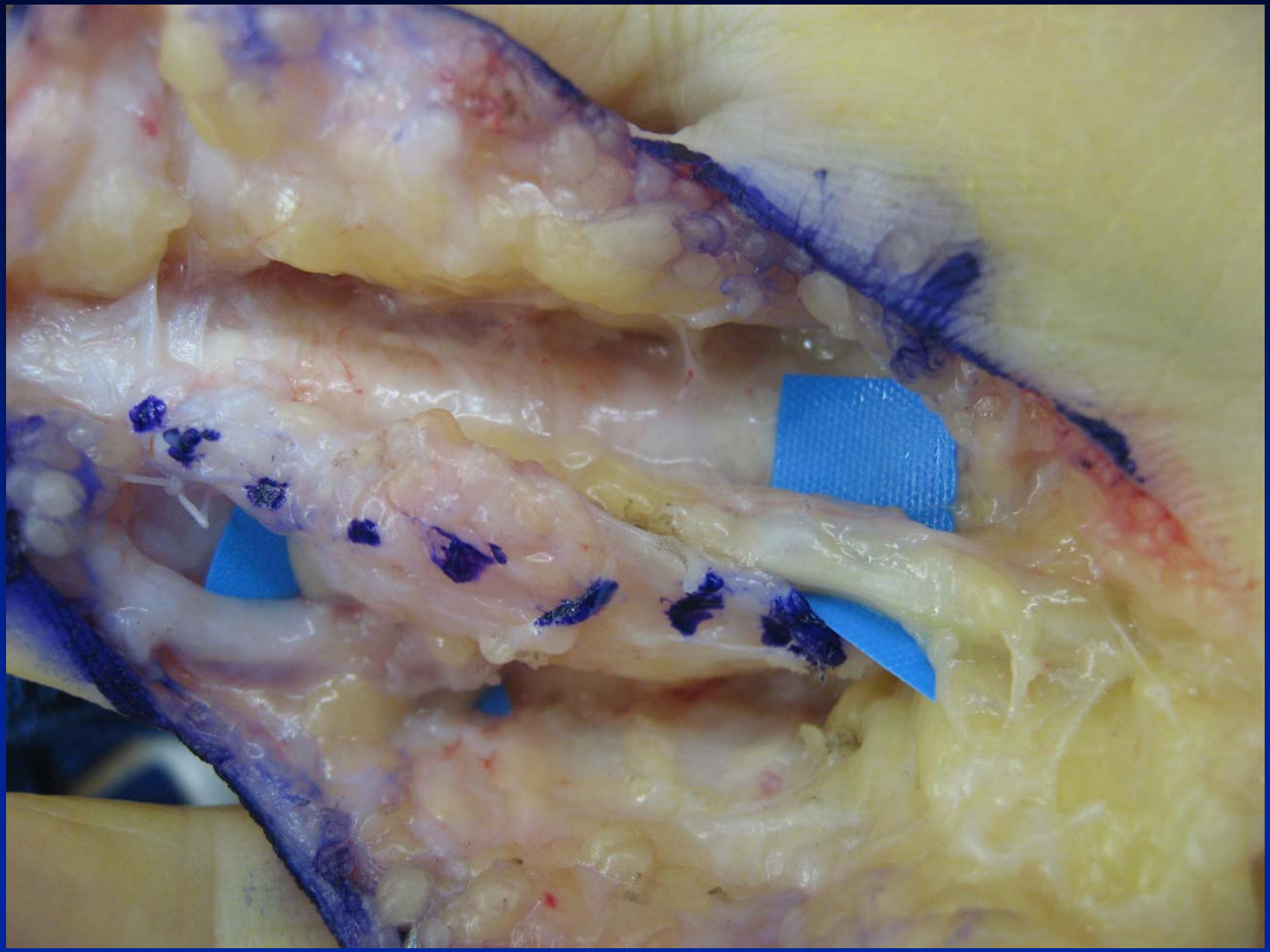
2 Tendon ruptures

- **Following the training reinforcement**
  - 1896 AA4500 injections
    - 1027 MP cords
    - 869 PIP cords

Single tendon rupture

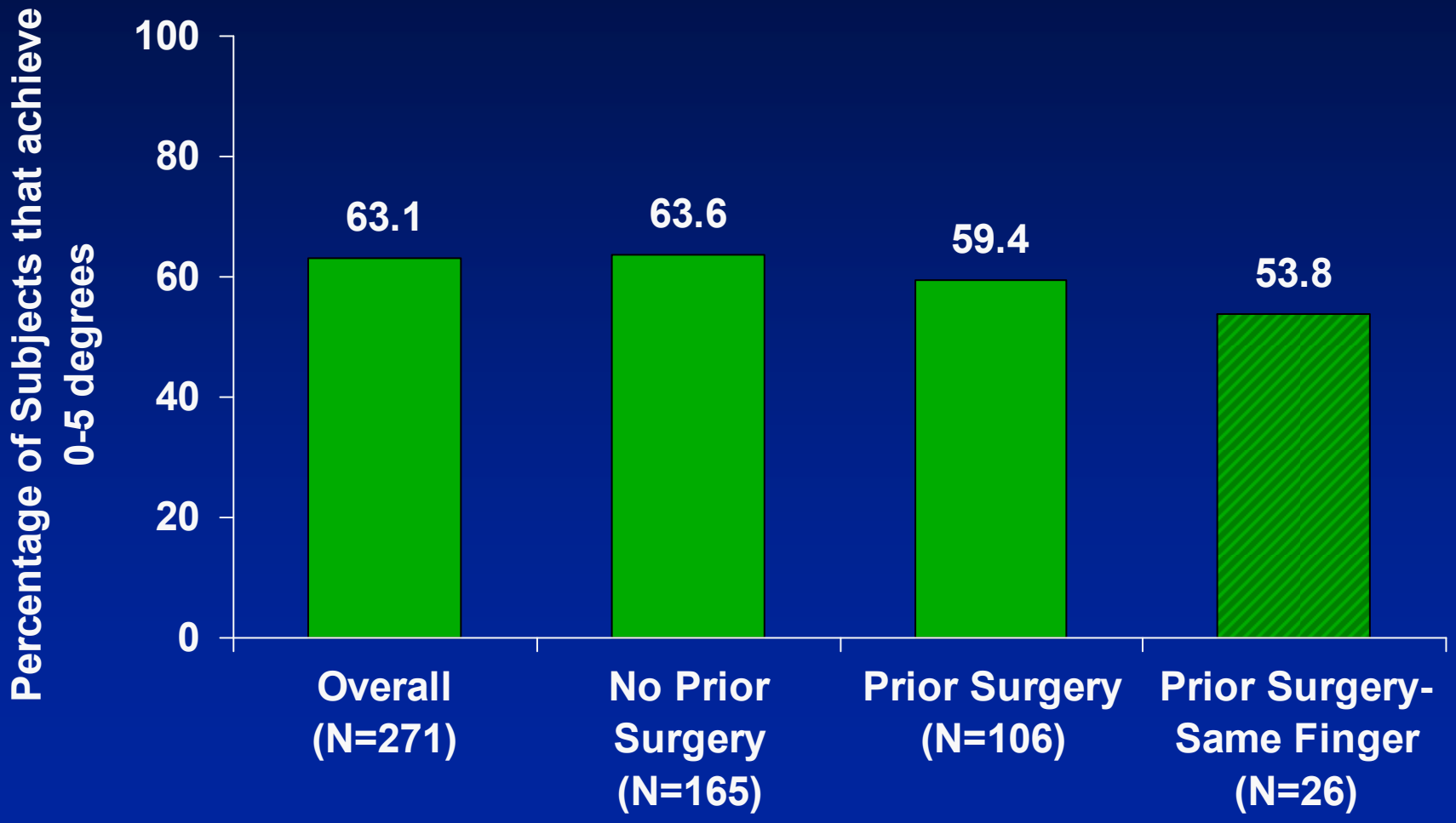
- **Injection training program designed with this experience**





Clinical Success – Prior Surgery

Study I, II, III – AA4500 Only



Published Data

Hamilton RG et al, Journal of Urology, 1986, 135, 641 – 647:

- Of the 44 Peyronie's subjects tested, only 1 gave a binding response
  - <1% binding relative to immobilized control IgE
  - Uncertain specificity/relationship to treatment
- No clinical manifestations