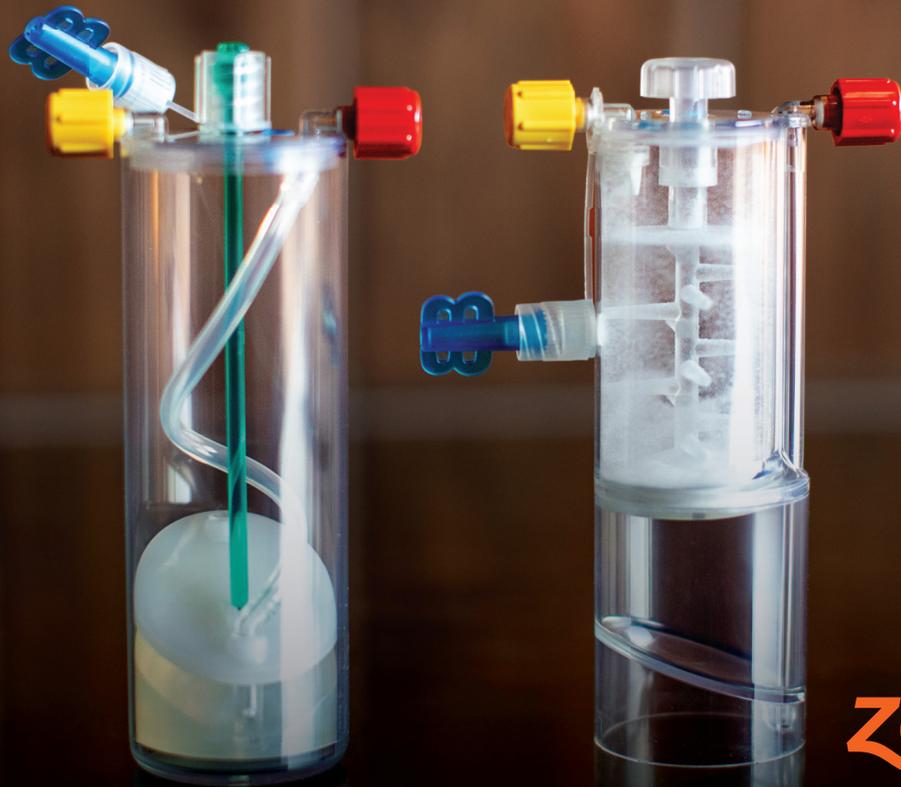


**Pro-Stride**<sup>®</sup>  
APS

**The most trusted choice  
in equine joint care<sup>1</sup>**



**zoetis**

# Veterinarians' go-to regenerative medicine device<sup>1</sup>

There are many options available in the equine regenerative medicine space to manage lameness, making it hard to know what's best. That's why we focus on giving you the facts with clinically relevant equine-specific data and the support you need to effectively manage lameness.

## See what your peers are saying about Pro-Stride:



**Pro-Stride ranked first amongst equine orthobiologics in:<sup>1</sup>**

✓ **Safety for the horse**

✓ **Consistent and predictable outcomes**

✓ **Most supported by product manufacturer**

✓ **Preferred onset of results**

✓ **Rigorous equine-specific science and research**

✓ **Equine orthobiologic I trust**

**Pro-Stride<sup>®</sup> APS** is the most requested regenerative medicine by horse owners and trainers<sup>1</sup>

## Pro-Stride APS is the most used orthobiologics in cases of:<sup>1</sup>

Mild-moderate OA

Synovitis

Navicular bursa injection

Tendon sheath injection

Medical management of OCD

Post-operative IA injection

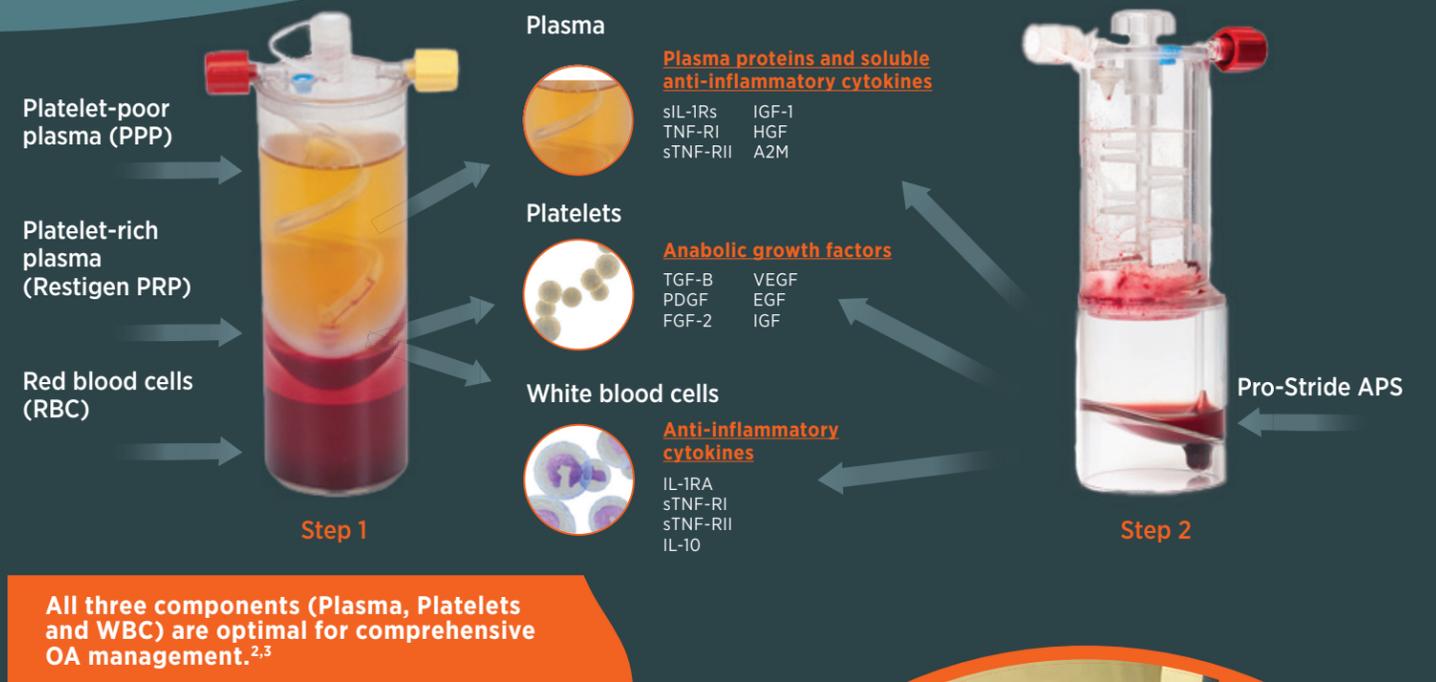
Meniscal injury



Scan to learn more about Pro-Stride.

# Pro-Stride<sup>®</sup> APS is a comprehensive orthobiologic device for managing equine osteoarthritis (OA)

## What's in Pro-Stride APS?

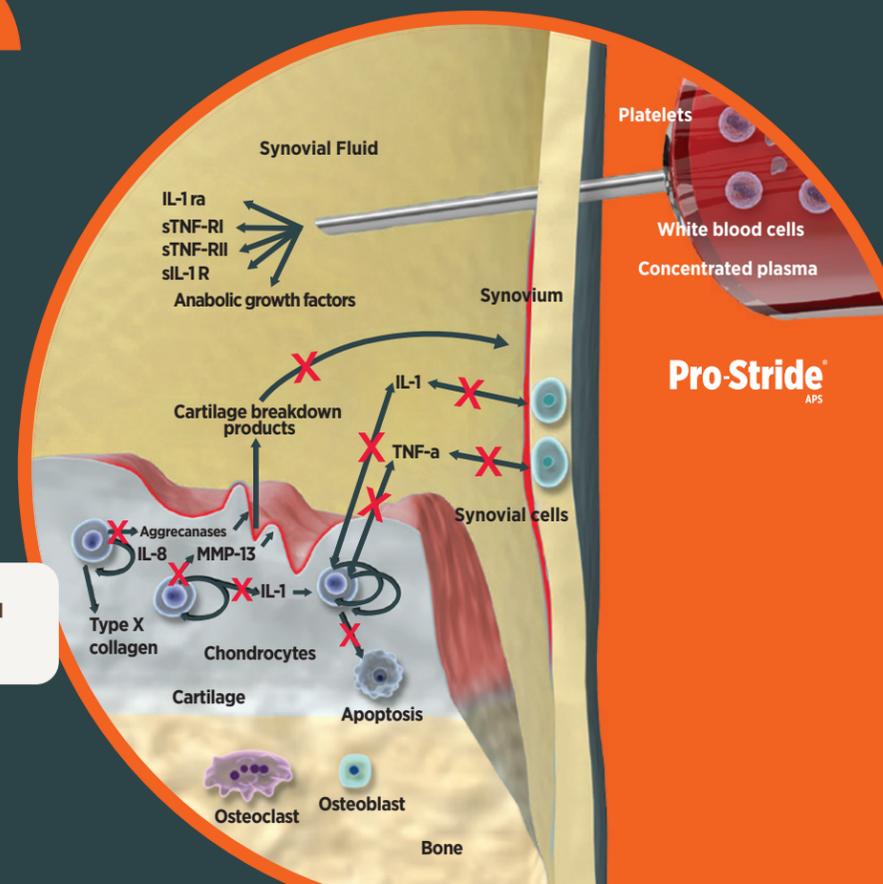


## Comprehensive orthobiologic device for a complex process

OA is a complex process that ultimately breaks down cartilage. Inflammatory proteins like IL-1, TNF-α, MMP-13 and aggrecanase need to be neutralized to prevent joint deterioration.

The Pro-Stride APS device concentrates horses' naturally occurring anti-inflammatory proteins and growth factors to address this complex process.<sup>2</sup>

**X** Pro-Stride inhibits multiple inflammatory pathways and provides growth factors to support healing.



## STUDY 1: COMPARISON OF A2M IN THREE ORTHOBIOLOGIC DEVICES

### Evaluation of plasma protein composition in Restigen® PRP, Pro-Stride APS and PPP compared to Alpha2EQ® devices<sup>4</sup>

#### Study objective

To demonstrate concentrations of Alpha-2-macroglobulin (A2M) and other proteins found following processing with Restigen PRP, Pro-Stride APS and Alpha2EQ devices.

#### Study methods

Thirteen horses in three geographic locations were utilized. Blood samples were obtained and processed by independent veterinarians. Plasma protein analysis was performed by proteomics at Zoetis Veterinary Medical Research and Development in Kalamazoo, MI.



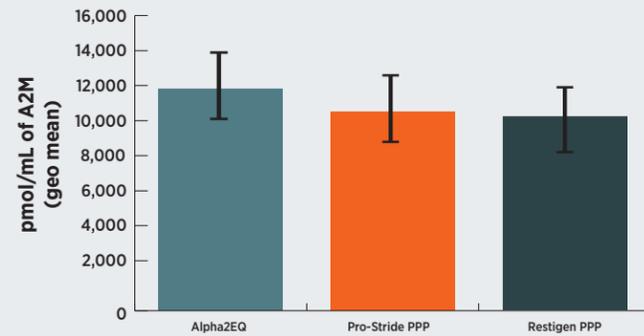
Scan to view the full research study

#### Results

- ✓ A2M concentration of plasma is equivalent between all three devices
- ✓ There are significantly higher concentrations of A2M in the final output of Pro-Stride APS and Restigen PRP versus Alpha2EQ
- ✓ The PPP portion of Pro-Stride APS and Restigen PRP had identical protein profiles as compared to the final output of Alpha2EQ

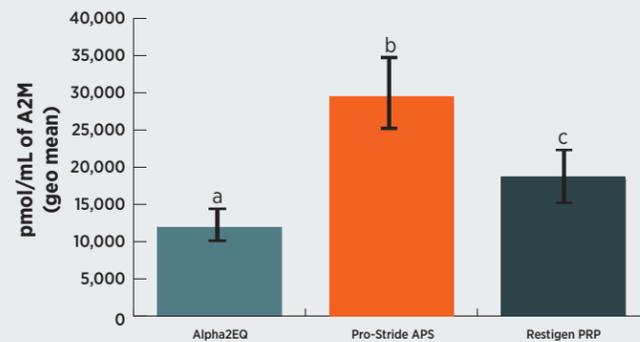
**What does this mean?**  
In the study, the PPP portion of Restigen PRP and Pro-Stride APS is identical to the final output of Alpha2EQ.

A2M concentration of plasma by device



No statistical difference

A2M concentration in final outputs



a,b,c: Significant difference (p<0.05)

	A2M	Plasma proteins and soluble anti-inflammatory cytokines (TNF-RI, IGF-1)	Platelet-derived growth factors (PDGR, VEGF and others)	WBC-derived anti-inflammatory cytokines (IL1-ra, IL-10 and others)
Pro-Stride APS (3mL)	2.7X concentrated over plasma	✓	✓	✓
Restigen PRP (6mL)	1.8X concentrated over plasma	✓	✓	✓
Pro-Stride or Restigen PPP portion from device 1 (30 mL)	Plasma A2M and other protein composition equivalent between devices	✓		
Alpha2EQ (30 mL)	Plasma A2M and other protein composition equivalent between devices	No published data		

## STUDY 2: COMPARATIVE ANALYSIS OF MEDIATORS IN FOUR DEVICES

### Pro-Stride APS and Restigen PRP concentrate desirable anti-inflammatory mediators for an improved comprehensive solution for osteoarthritis management<sup>5</sup>

#### Study objective

To quantify the concentration of A2M, immunomodulatory cytokines and TGF-β1 in Alpha2EQ, Pro-Stride APS, Restigen PRP and Arthrex ACP.

#### Study methods

Blood samples from six horses were processed to make each device. The concentrations of IL-1β, IL-4, IL-6, IL-10, IL-17a, TNF-α, TGF-β1, IL-1Ra and A2M were measured and compared.



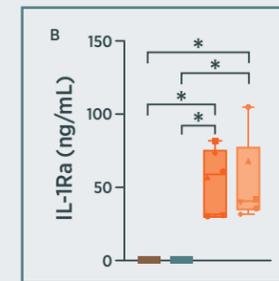
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Previous work has shown that Alpha2EQ is equivalent to Platelet Poor Plasma (PPP). Review study 1 for more information.



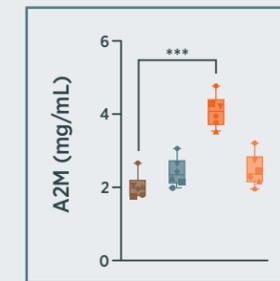
#### Results

**KEY**  
Alpha2EQ (blue)  
Arthrex ACP (grey)  
Pro-Stride APS (orange)  
Restigen PRP (dark blue)



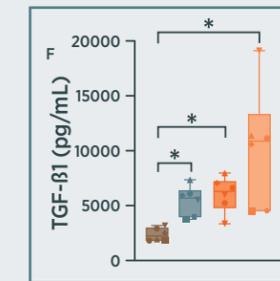
Pro-Stride APS and Restigen PRP had significantly higher IL-1Ra concentrations compared to Alpha2EQ and Arthrex ACP.

- ✓ IL-1Ra was below the level of detection in Arthrex ACP and Alpha 2EQ



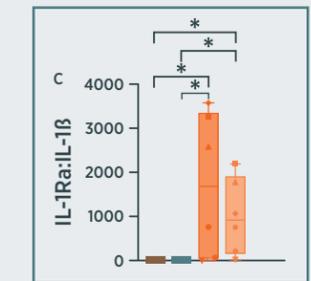
Pro-Stride APS had the highest concentration of A2M, significantly greater than Alpha2EQ.

- ✓ No significant differences were found in the concentrations of IL-1β, IL-4, IL-6, IL-10, and IL-17a between devices



TGF-β1 levels were significantly higher in Pro-Stride APS, Restigen PRP, and Arthrex ACP compared to Alpha2EQ.

- ✓ This protein is important in cartilage maintenance and repair



Both Pro-Stride APS and Restigen PRP exceeded the ratio of >100:1 of IL-1Ra:IL-1β, which is needed to promote joint health, while Alpha2EQ and Arthrex ACP did not.

Pro-Stride and Restigen are leukocyte rich (contain WBCs) while Alpha2EQ and Arthrex ACP contain no or low WBCs (leukocyte poor). Leukocyte-rich preparations provide higher concentrations of IL-1Ra, which is important for healing.

#### What does this mean?

Pro-Stride APS and Restigen PRP, which have higher concentrations of IL-1Ra, A2M and TGF-β1 than Alpha2EQ and Arthrex ACP, may be more effective in modulating inflammation and promoting healing.

### STUDY 3: SHORT-TERM NSAID ADMINISTRATION

#### Effect of a Single Dose Administration of NSAIDs on Pro-Stride APS and Restigen PRP<sup>6</sup>



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#### Results

A single dose of ketoprofen, flunixin meglumine, phenylbutazone or firocoxib did not significantly alter the cytokine or growth factor profile of Pro-Stride APS or Restigen PRP when blood was obtained 6 hours post-administration.



### STUDY 4: LONG-TERM NSAID ADMINISTRATION

#### The Effect of Prolonged Administration of NSAIDs on Concentrations of Cytokines and Growth Factors in Pro-Stride APS and Restigen PRP<sup>7</sup>



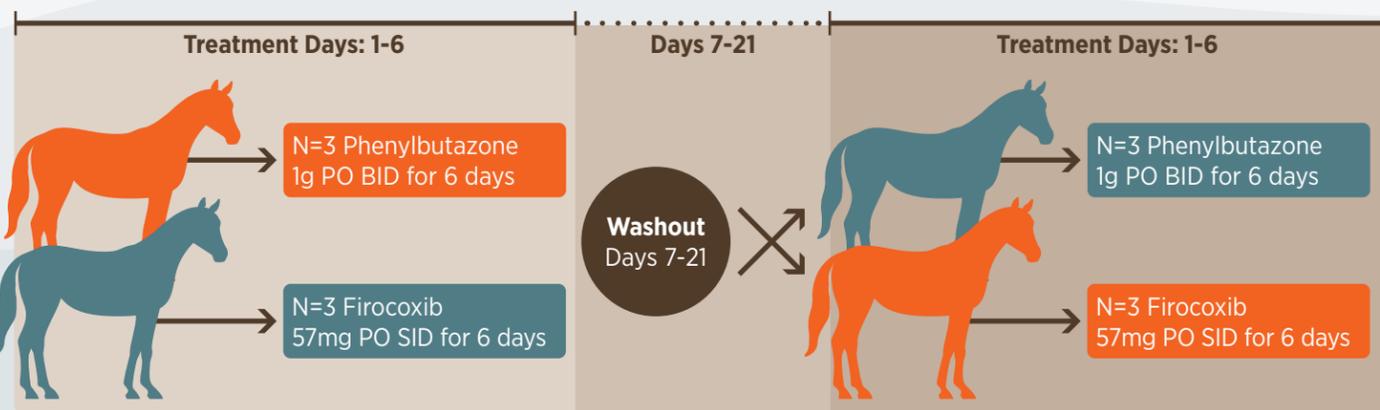
Scan to view the full research study

#### Study objective

To determine the effects of firocoxib and phenylbutazone on concentrations of growth factors and cytokines in Pro-Stride APS and Restigen PRP devices when given for six consecutive days.

#### Study methods

Prospective cross-over study using six research horses at the University of Pennsylvania.



Blood collection and evaluation of end solution from Restigen PRP and Pro-Stride APS devices were conducted at days 0 (pre-treatment), 7, 14 & 21 for each group

**Looking at:**  
**Platelet & leukocyte concentrations**  
**Cytokines:** IL-1 $\beta$ , IL-10, IL-6, IL-8, TNF $\alpha$   
**Growth factors:** FGF-2, TGF- $\beta$ , PDGF

#### Results

There were no statistically significant differences in concentrations of cytokines or growth factors in either Pro-Stride APS or Restigen PRP before or after 6 days of administration of firocoxib or phenylbutazone.

#### What does this mean?

There was no impact on the final output of Restigen or Pro-Stride in horses receiving long-term NSAID administration, so there's no need to stop administration prior to blood collection.



### STUDY 5: TREATING SYNOVITIS

#### Effects of Pro-Stride APS in horses with acute synovitis<sup>8</sup>



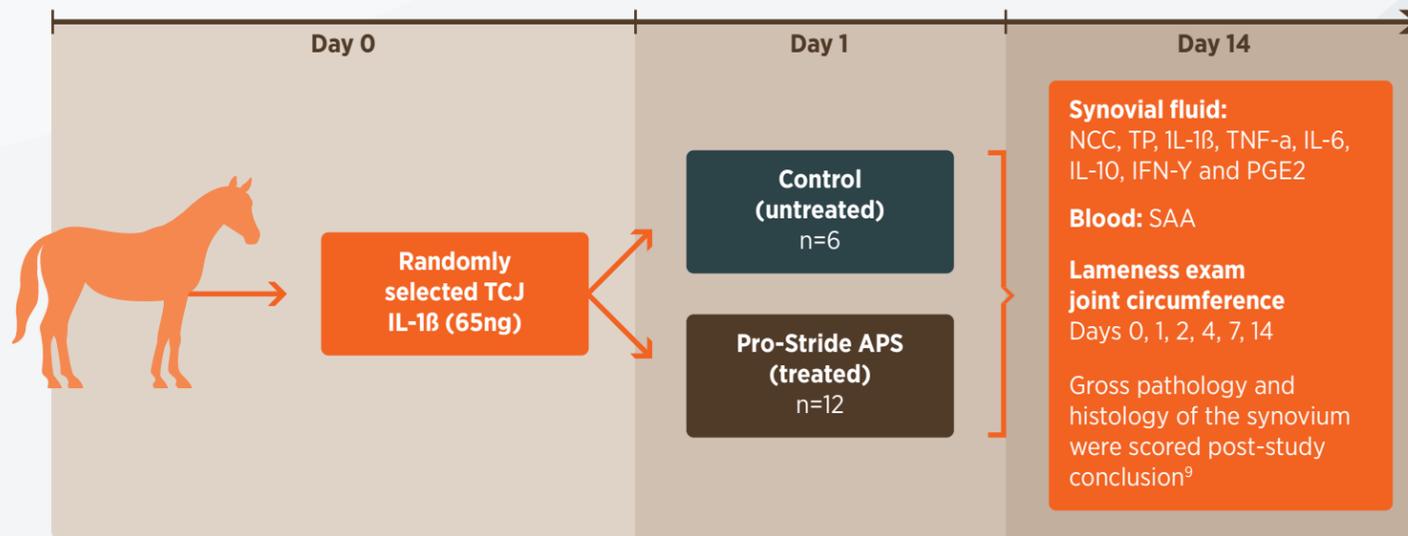
Scan to view the full research study

#### Study objective

To investigate the effects of a single intra-articular Pro-Stride injection on horses with acute IL-1 $\beta$ -induced synovitis.

#### Study methods

Randomized control study using 18 research horses at the University of Pennsylvania New Bolton Center.



#### Results

- ✓ IL-1 $\beta$  effectively induced synovitis
- ✓ No significant differences in synovial fluid, cytokine or SAA concentrations between groups
- ✓ No significant differences in lameness parameters between groups
- ✓ Gross and histopathology scores of Pro-Stride APS-treated joints were similar to normal joints
- ✓ Untreated control joints showed more damage (synovial hyperemia, edema, discoloration and hemisiderosis)



#### What does this mean?

In the study, Pro-Stride APS appeared to have a disease-modifying effect in this synovitis model, protecting the joint from acute inflammation.

## STUDY 6: METABOLIC IMPACT OF IA TRIAMCINOLONE & PRO-STRIDE APS

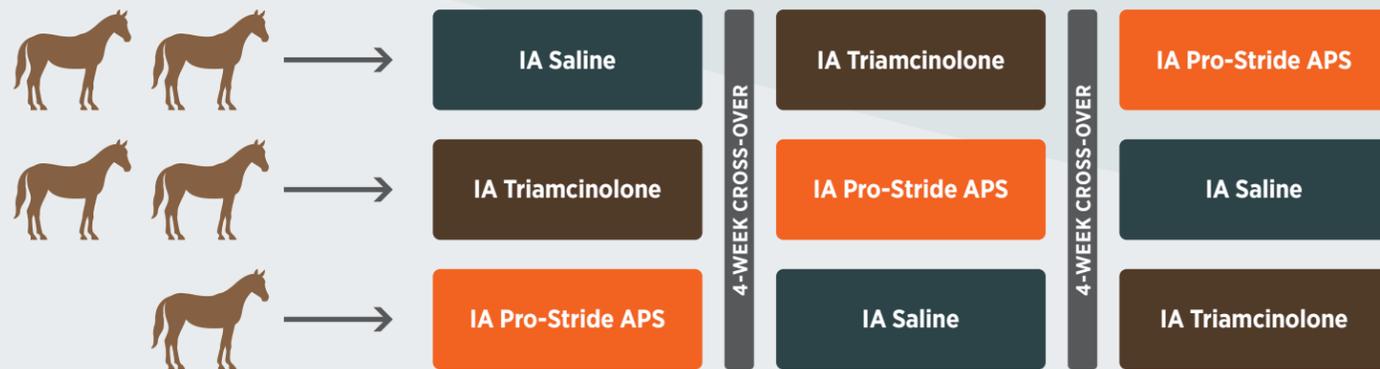
### Intra-articular (IA) triamcinolone acetonide (TA) induced significant and prolonged metabolic disturbances, while Pro-Stride APS and saline did not<sup>10</sup>

#### Study objective

To compare the metabolic effect between IA administration of TA, Pro-Stride APS and saline.

#### Study methods

Five metabolically normal horses, front metacarpophalangeal joint randomly assigned to one of three treatment groups.



#### TRH, OST & bloodwork schedule



KEY	
	TRH (first) + OST (second)
	Resting ACTH, Cortisol, Insulin, Glucose, T3, T4 & FT4d

IR horses are predisposed to hyperinsulinemia-associated laminitis; the use of Pro-Stride APS may be a safer alternative than triamcinolone.



#### Results

- ✓ A single 9mg dose of IA triamcinolone induced significant and prolonged metabolic changes, including:

##### Steroid-induced adrenal insufficiency

- Abnormal thyrotropin-releasing hormone (TRH) test results
- Abnormal resting hypocortisolemia

##### Steroid-induced insulin resistance

- Abnormal oral sugar test results
- Abnormal resting hyperinsulinemia



#### What does this mean?

✓ Use IA triamcinolone with caution in IR horses due to induced hyperinsulinemia.

✓ A single dose of TA can cause a significant and prolonged suppression of cortisol, and ACTH as well as significant increases in insulin and glucose.

✓ Run TRH and/or OST tests before IA triamcinolone or wait at least 7 days post-injection to perform these tests.



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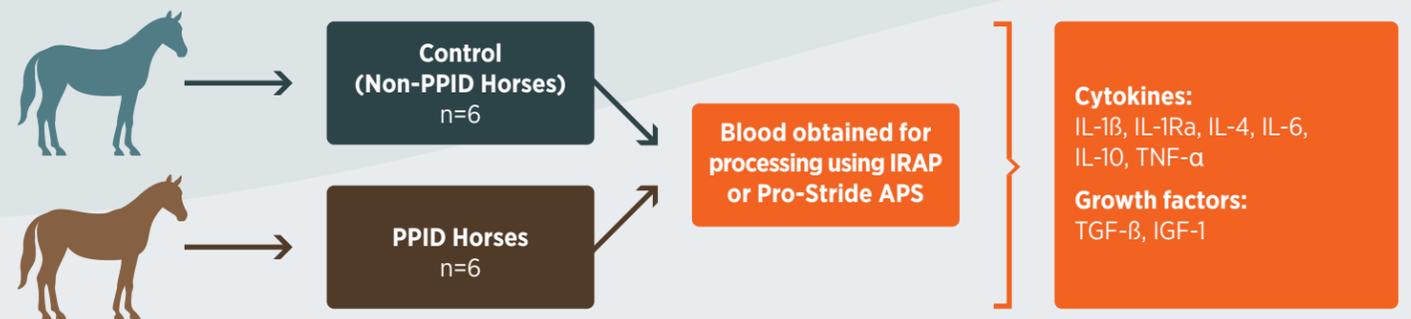
## STUDY 7: ORTHOBIOLOGICS IN PPID HORSES

### No changes in end output from Pro-Stride APS or IRAP in horses with PPID<sup>11</sup>

#### Study objective

To determine if the cytokine profiles of IRAP (autologous conditioned serum, ACS) and Pro-Stride APS are affected in horses with PPID.

#### Study methods



TGF- $\beta$  is crucial for cartilage maintenance, enhancement of cartilage repair and protection of cartilage against IL-1.



#### Results

##### CYTOKINE PROFILES

- ✓ No difference in PPID vs. non-PPID horses
- ✓ No difference in Pro-Stride APS vs. IRAP

##### GROWTH FACTOR PROFILES

- ✓ No difference in PPID vs. non-PPID horses
- ✓ Significantly more TGF- $\beta$  in Pro-Stride APS vs. IRAP in both groups



#### What does this mean?

✓ PPID status has no impact on the output of cytokines and growth factors in Pro-Stride APS and can be considered a first-line therapy in these populations.

✓ Pro-Stride APS contains more TGF- $\beta$  than IRAP, a protein important for cartilage maintenance and repair.



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## STUDY 8: METABOLIC IMPACT OF IA BETAMETHASONE

### Metabolic disturbances were observed after IA injection of betamethasone<sup>12</sup>

#### Study objective

To monitor the effects of IA betamethasone in both insulin dysregulated (ID) and non-ID (metabolically normal) horses.



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#### Results

- ✓ IA betamethasone caused:
  - Rapid and significant suppression of ACTH and cortisol in all study horses for 24-48 hours
  - A significant increase in glucose in metabolically normal horses between 8-48 hours post-administration
- ✓ There were no metabolically normal horses that exceeded the current OST cutoff for ID diagnosis following IA betamethasone
- ✓ All ID horses maintained a reliable ID response to the OST throughout the study

**What does this mean?**  
Betamethasone exhibits similar, albeit shorter, negative metabolic effects vs. TA. As IR horses are predisposed to hyperinsulinemia-associated laminitis, use of orthobiologics may be a safer alternative.

## STUDY 9: HISTOLOGICAL & CYTOLOGICAL CHANGES SEEN POST-IA ARTHRAMID® VET INJECTION

### Arthramid Vet induced a foreign body response when used IA in horses<sup>13</sup>

#### Study objective

To characterize the synovial integration process of a 2.5% synthetic cross-linked injectable polyacrylamide hydrogel (2.5 iPAAG).



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#### Results

- ✓ Injection resulted in a foreign body synovitis at 14 and 42d post-injection, consisting of cellular infiltration, hyperplasia, hypertrophy and hypervascularity of the synovium
- ✓ Significantly higher synovial fluid TNCC at 14, 42 and 90d post-injection

**What does this mean?**  
These findings may be inconsistent with what is normally considered desirable for joint health.

## A comparison of lameness management solutions

**Pro-Stride has the most concentrated and comprehensive mix of healing and anti-inflammatory properties of the commercially available orthobiologics<sup>4, 5</sup>**

Category of lameness treatment	Brand name	Processing time	Concern for repeat injections (Immune response)	Foreign body response	Ability to also utilize PPP	Induces shift from M1 to M2 macrophages	Negative impact on metabolic system	Anti-inflammatory proteins	White blood cells	Platelets	Growth factors
APS: Autologous protein solution	Pro-Stride APS	<20 minutes	No	No	✓	✓ <sup>14</sup>	No <sup>10,11</sup>	✓	✓	✓	✓
PRP: Platelet-rich plasma	Restigen® PRP	15 minutes	No	No	✓	✗	No <sup>10,11</sup>	✓	✓	✓	✓
	ProVet® APC	3 minutes	No	No	✗	✗	Unknown	✓	✓	✓	✓
	Precise- PRP™	None	Possible due to universal donor pool	Unknown	✗	✗	Unknown	✓	✗	✓	✓
PPP: Platelet-poor plasma	Alpha2EQ® A2M	20 minutes	No	No	✗	✗	Unknown	✓	✗	✗	Limited, not platelet derived
ACS: Autologous conditioned serum	IRAP*	24 hours	No	No	✗	✗	Unknown	✓	✗	✗	✓
Synthetic polyacrylamide gels	Arthramid Vet	None	Yes <sup>13**</sup>	Yes <sup>13</sup>	N/A	✗	Unknown	✗	✗	✗	✗
	Noltrex®	None	Yes**	Unknown	N/A	✗	Unknown	✗	✗	✗	✗
Bovine derived elastin & collagen	Spryng®	None	Yes	Unknown	N/A	✗	Unknown	✗	✗	✗	✗
Amnion based (Do not contain stem cells)	AniCell®	None	Yes <sup>15***</sup>	Unknown	N/A	✗	Unknown	✓	✗	✗	✓
	RenoVo®	None	Yes <sup>15***</sup>	Unknown	N/A	✗	Unknown	✓	✗	✗	✓
	Hilltop Bio Strydaflex®, Regenflex RT®	None	Yes <sup>15***</sup>	Unknown	N/A	✗	Unknown	✓	✗	✗	✓
Corticosteroids	Triamcinolone®	None	Yes	No	N/A	✗	Yes <sup>10</sup>	✗	✗	✗	✗

\*IRAP recommends a three-dose series of injections

\*\*No long-term data available with repeat injections

\*\*\*These are allogenic derived products

# HEALING WITH HORSE POWER

 REGENERATIVE MEDICINE DEVICES



**Restigen**<sup>®</sup>  
PRP

Minimize variability with  
a proven therapy for soft  
tissue injury.



**CenTrate**<sup>®</sup>  
BMA

Unlock advanced stall-  
side healing with the  
power of stem cells.



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