Lecture overview

- Introduction
- Dosage, administration, presentation
- Indications
- Mechanism of action
- Pharmacology
- Efficacy, safety, contraindications, cautions
- Monitoring
- Selection

Introduction

- The two “new kids on the block” for allergic dermatoses are oclacitinib (Apoquel™) and lokivetmab (Cytopoint®).
- These first-in-class medicines give veterinarians effective and safe additional options to customize atopic dermatitis treatment for canine patients.
- Though these treatments have similar indications, there are some substantial differences in their mechanism of action, administration, contraindications, safety profiles, and other details that require careful consideration when selecting them for different patients.

Dr. Vincent Defalque
Diplomate of the American College of Veterinary Dermatology
North West Veterinary Dermatology Services

New therapies for use in dogs in Canada

apoquel

2016

zoetis

CYTOPOINT

2017

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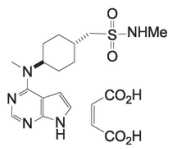
Dosage, Administration, and Presentation

apoquel

- Apoquel™ is an orally-administered film-coated tablet containing oclacitinib maleate.
- It is available in 3 tablet strengths: 3.6 mg, 5.4 mg, and 16 mg.
- Marked with AQ and either S, M, or L on both sides.
- Non-flavoured tablets are scored in half for convenient dosing in dogs:
  - At least 12 months of age
  - Ranging from 3 to 80 kg
- Further division has not been evaluated.
- Packaged in bottles of 100 tablets.
- Administer orally at a dose of 0.4 to 0.6 mg/kg (according to the dosing table) q12h for up to 14 days followed by q24h for maintenance therapy.
- Can be given with or without food.
- Store at controlled room temperature between 20°C to 25°C.



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Dosage, Administration, and Presentation

CYTOPOINT™

- Cytopoint® is a ready-to-use, sterile liquid containing lokivetmab.
- It is available in 1mL vials in four concentrations (10, 20, 30 or 40 mg).
- Packaged in a two-vial carton.
- Must be refrigerated. Store upright at 2°C to 8°C. Prolonged exposure to higher temperatures and/or direct sunlight may adversely affect potency. Do not freeze!
- Administer subcutaneously at a minimum dose of 2 mg/kg.
- For convenience, dosing tables may be used as a guideline.
- Repeat administration every 4-8 weeks as needed in individual patients.
- The product does not contain a preservative.
- Each vial is for single use only, and should be discarded after puncture.

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Dosing tables

apoquel®

Dog body weight (kg)	3.6 mg tablets	5.4 mg tablets	16 mg tablets
3 - 4.4	0.5		
4.5 - 5.9		0.5	
6 - 8.9	1		
9 - 13.4		1	
13.5 - 19.9			0.5
20 - 26.9		2	
27 - 39.9			1
40 - 54.9			1.5
55 - 80			2

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Dosing tables

CYTOPOINT™

Dogs weighing < 2.3 kg

Aseptically withdraw 0.2 mL/kg from a single, 10-mg (Sky) vial and administer subcutaneously.

Dogs weighing 2.3-18.1 kg

Aseptically withdraw the full volume of the appropriate vial according to the dosage table below and administer subcutaneously.

Dog Body Weight (kg)	Presentation			
	10 mg (Sky)	20 mg (Plum)	30 mg (Blush)	40 mg (Navy)
2.3-4.5	1 vial			
4.6-9.1		1 vial		
9.2-13.6			1 vial	
13.7-18.1				1 vial

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Dosing tables

CYTOPOINT™

Dogs weighing > 18.1 kg

A single dose requires a combination of vials, as outlined in the table below. Prior to administration, collect the number of vials indicated under each presentation according to the dog's body weight. Aseptically draw the full volume from each vial into one syringe and administer subcutaneously as a single injection.

Dog Body Weight (kg)	Presentation			
	10 mg (Sky)	20 mg (Plum)	30 mg (Blush)	40 mg (Navy)
18.2-22.7	1 vial +			1 vial
22.8-27.2		1 vial +		1 vial
27.3-31.7			1 vial +	1 vial
31.8-36.3				2 vials
36.4-40.8	1 vial +			2 vials
40.9-45.4		1 vial +		2 vials
45.5-49.9			1 vial +	2 vials
50.0-54.4				3 vials
54.5-59.0	1 vial +			3 vials
59.1-63.5		1 vial +		3 vials
63.6-68.0			1 vial +	3 vials
68.1-72.6				4 vials
72.7-77.1	1 vial +			4 vials
77.2-81.6		1 vial +		4 vials
81.7-86.2			1 vial +	4 vials
86.3-90.7				5 vials

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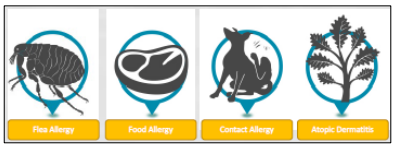
Indications: Broad vs. Narrow

- BROAD: Apoquel™ is labelled for the control of pruritus associated with canine allergic dermatitis (atopic dermatitis, cutaneous adverse food reaction, flea allergy dermatitis, contact allergy). Short or long-term use.



apoquel®

- NARROW: Cytopoint® aids in the reduction of clinical signs of canine atopic dermatitis. Short or long-term use.

CYTOPOINT™

Neuroimmunology

- Pruritus is now understood to result from a complex interaction between the nervous system and the immune system.
- Pruritus results from stimulation of nonmyelinated nerve fibers located in the skin.
- Itch mediators stimulate receptors on itch-specific sensory neurons, which relay signals through the spinal cord to certain brain regions.
- Histamine does not have actually have a big impact!

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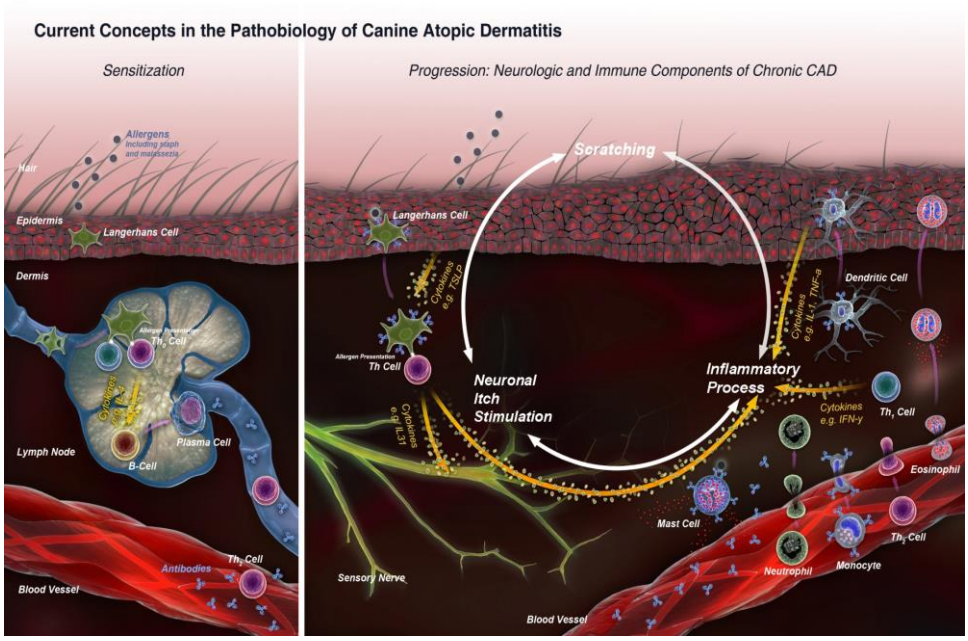
Current Concepts in the Pathobiology of Canine Atopic Dermatitis
Sensitization
Progression: Neurologic and Immune Components of Chronic CAD
Allergens
Including staph and malassezia
Hair
Epidermis
Langerhans Cell
Dermis
Lymph Node
B-Cell
Plasma Cell
Antibodies
Blood Vessel
Scratching
Langerhans Cell
Dendritic Cell
Allergen Presentation
Th Cell
Neuronal Itch Stimulation
Inflammatory Process
Cytokines e.g. IFN-γ
Eosinophil
Mast Cell
Neutrophil
Monocyte
Sensory Nerve
Blood Vessel

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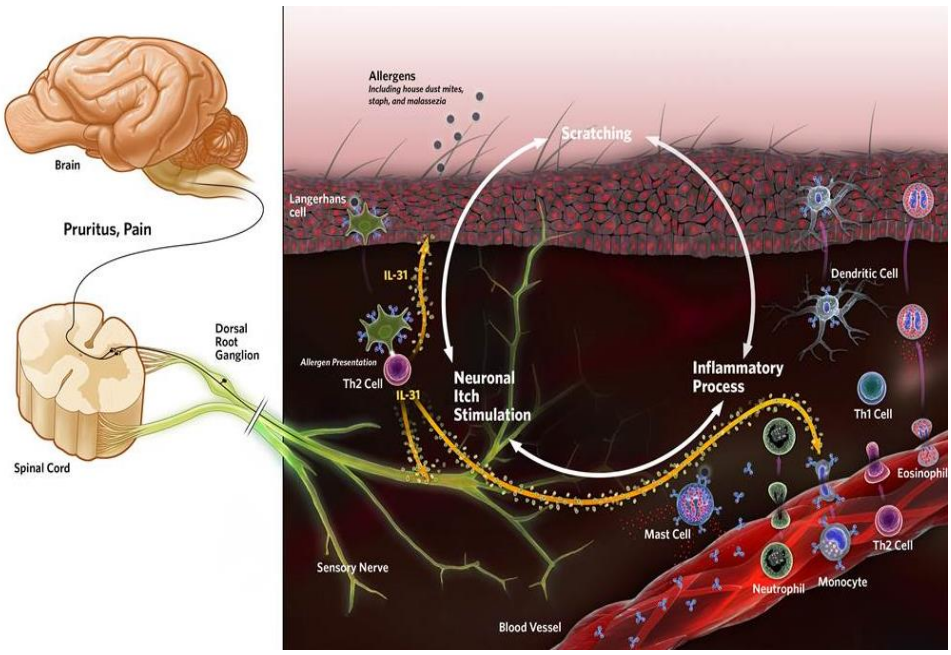
Brain
Pruritus, Pain
Dorsal Root Ganglion
Spinal Cord
Allergens
Including house dust mites, staph, and malassezia
Scratching
Langerhans cell
IL-31
Dendritic Cell
Allergen Presentation
Th2 Cell
Neuronal Itch Stimulation
Inflammatory Process
Th1 Cell
Eosinophil
Mast Cell
Th2 Cell
Sensory Nerve
Neutrophil
Monocyte
Blood Vessel

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What are cytokines ?

- Cytokines are proteins produced by cells such as lymphocytes and keratinocytes.
- They are used for inter-cellular communication.
- Cytokines convey their information by binding to specific receptors on the cell membrane to induce a biologic response.
- After a cytokine binds to its receptor it triggers specific intracellular signaling pathways, one of which is the JAK pathway.
- In the skin, cytokines regulate acute and chronic processes such as neuronal itch simulation and inflammation.

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Cytokines involved in canine allergic skin disease

Veterinary Dermatology

Endorsed by WAVD World Association for Veterinary Dermatology

Vet Dermatol 2015; **26**: 124–e32 DOI: 10.1111/vde.12205

Review: Lymphocytes, cytokines, chemokines and the T-helper 1–T-helper 2 balance in canine atopic dermatitis

Cherie M. Pucheu-Haston*, Petra Bizikova†, Rosanna Marsella‡, Domenico Santoro‡, Tim Nuttall§ and Melissa N. C. Eisenschenk¶

*Department of Veterinary Clinical Sciences, School of Veterinary Medicine, Louisiana State University, 1909 Skip Bertman Drive, Baton Rouge, LA, 70803, USA
†Department of Clinical Sciences, College of Veterinary Medicine, North Carolina State University, 1060 William Moore Drive, Raleigh, NC, 27607, USA
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§Royal (Dick) School of Veterinary Studies, Easter Bush Veterinary Centre, University of Edinburgh, Roslin, EH25 9RG, UK
¶Pet Dermatology Clinic, 9712 63rd Avenue North, Maple Grove, MN, 55369, USA

Correspondence: Cherie M. Pucheu-Haston, Department of Veterinary Clinical Sciences, School of Veterinary Medicine, Louisiana State University, 1909 Skip Bertman Drive, Baton Rouge, LA 70803, USA. E-mail: cpucheu@lsu.edu

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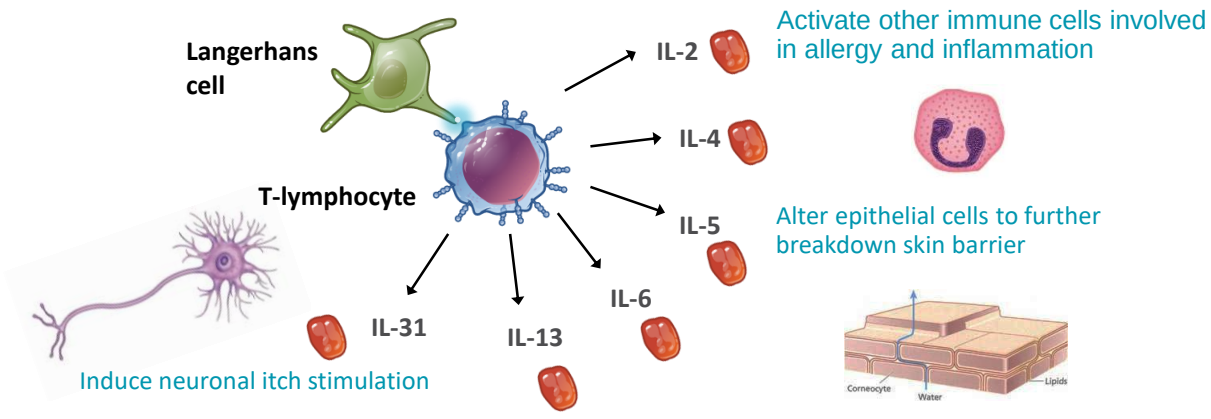
Cytokines involved in canine allergic skin disease



Many cytokines implicated in canine allergic skin disease are secreted from activated T-lymphocytes.
Each of these cytokines plays a specific role in the production of the clinical signs (pruritus and inflammation).

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Interleukin-31 (IL-31)

- IL-31 is a recently identified cytokine implicated in pruritic skin conditions such as canine atopic dermatitis.
- IL-31 binds to a heterodimeric receptor complex. Upon ligand binding, signal transduction cascades such as the Janus kinase-signal transducer and activator of transcription (JAK/STAT) are activated.
- Interleukin-31 could be detected in >50% of serum samples in client-owned dogs with naturally occurring atopic dermatitis, but not in healthy dogs.
- Administration of IL-31 induced pruritus in laboratory beagles.

Veterinary Dermatology

Vet Dermatol 2013; **24**: 48–e12 DOI: 10.1111/j.1365-3164.2012.01098.x

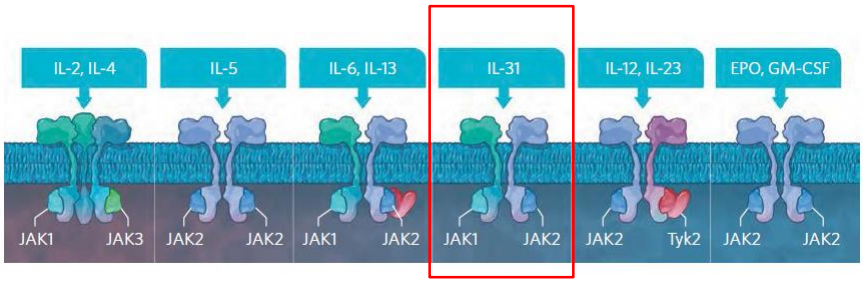
Interleukin-31: its role in canine pruritus and naturally occurring canine atopic dermatitis

Andrea J. Gonzales, William R. Humphrey, James E. Messamore, Timothy J. Fleck, Gregory J. Fici, John A. Shelly, Janet F. Teel, Gary F. Bammert, Steven A. Dunham, Troy E. Fuller and Robert B. McCall

16

Janus kinase (JAK) enzymes

- There are 4 types of JAK enzymes: JAK1, JAK2, JAK3 and TYK2.
- JAK enzymes are attached to the intracellular region of cytokine receptors in varous tissues in the body, including the skin and the nervous system.
- JAK1 is the isoenzyme form most closely associated with pro-allergic, pruritogenic and pro-inflammatory processes mediated by interleukins.
- Cytokine receptors occur in pairs, each corresponding to one of the 4 types of JAK receptors inside the cell.



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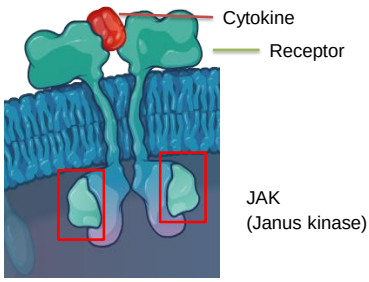
Janus kinase (JAK) enzymes

- The name is taken from the two-faced Roman god of doorways *Janus*.
- JAKs possess two near-identical phosphate-transferring domains.
- One domain exhibits the kinase activity, while the other negatively regulates the kinase activity of the first.



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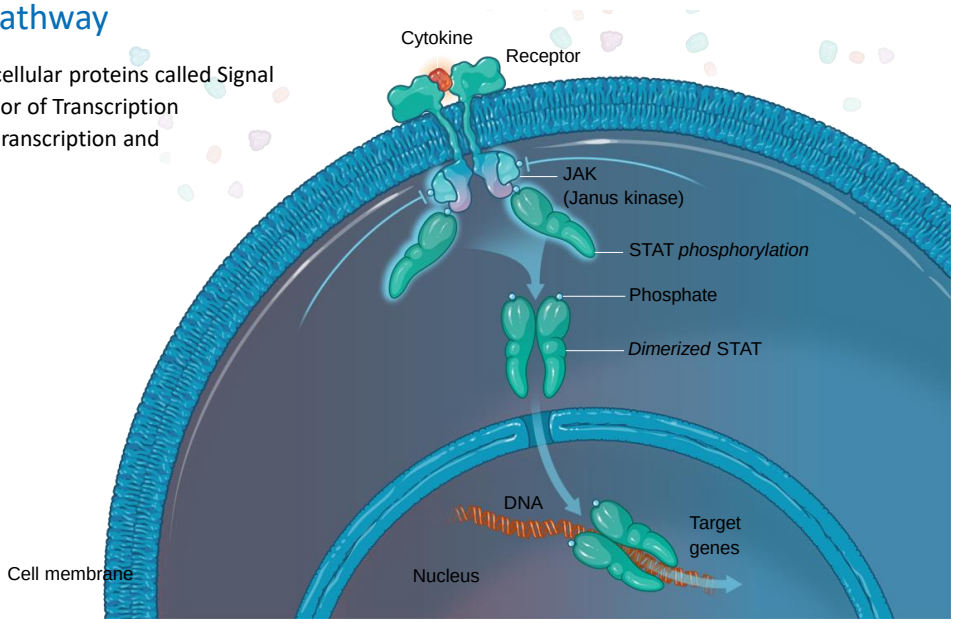
JAK signaling pathway

JAKs activate the intracellular proteins called Signal Transducer and Activator of Transcription (STAT) to induce gene transcription and biological responses.



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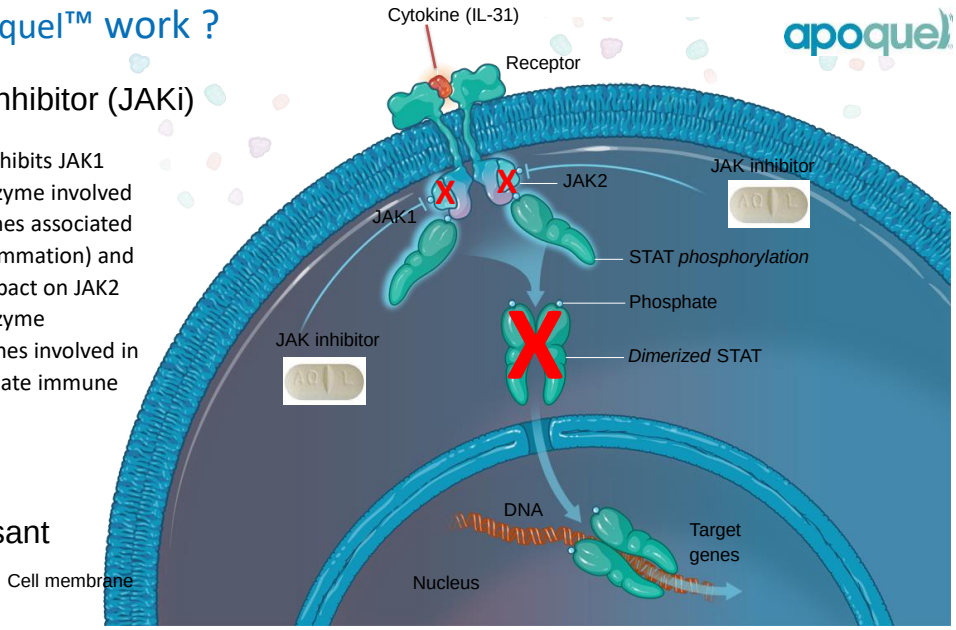
How does Apoquel™ work ?

Selective JAK inhibitor (JAKi)

Oclacitinib primarily inhibits JAK1 (the form of the isoenzyme involved in the action of cytokines associated with pruritus and inflammation) and JAK3, with minimal impact on JAK2 (the form of the isoenzyme associated with cytokines involved in hematopoiesis and innate immune function).

Not a systemic immunosupressant



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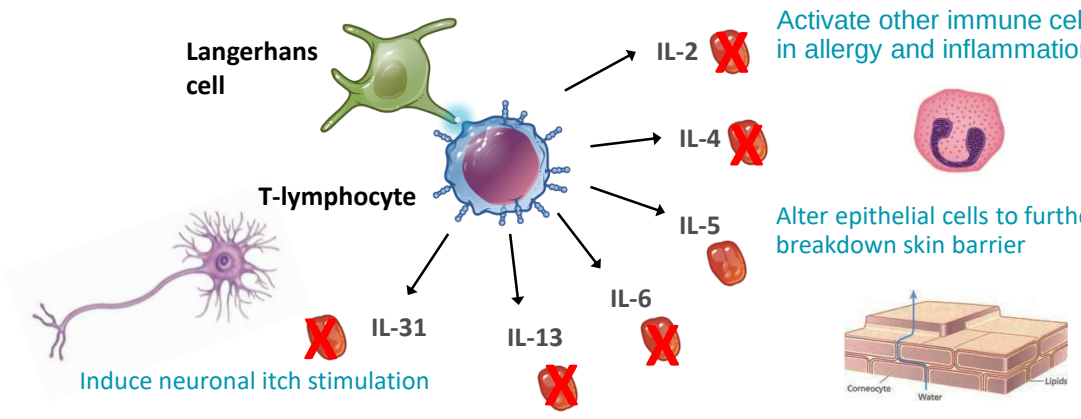
Oclacitinib inhibits the activity of many cytokines (incl. IL-31)



Oclacitinib blocks the activity of pruritogenic and pro-inflammatory cytokines that utilize JAK 1/JAK3. Oclacitinib has both anti-pruritic and anti-inflammatory effects.

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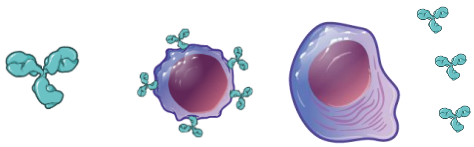
What are antibodies ?



- Antibodies are Y-shaped proteins produced by mature B-cells (plasma cells).
- They are used by the immune system to identify and neutralize foreign substances.
- Five isotypes (classes) of immunoglobulins are recognized in mammals on the basis of their molecular weight and antigen binding capacity: IgA, IgD, IgE, IgG and IgM.
- Approximately 80% of all antibodies in humans and companion animals are of the IgG class.

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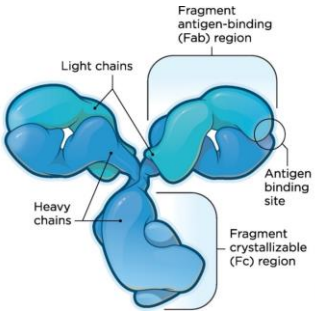
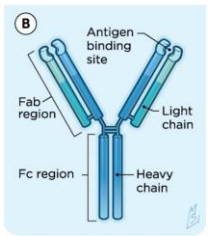
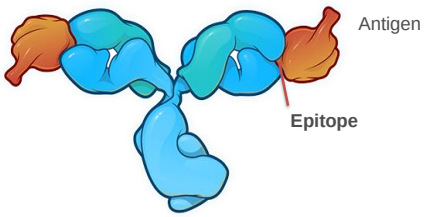
Antibody structure and epitope

- All antibodies contain 2 heavy and 2 light chains.
- Each light chain contains 1 variable region and 1 constant region.
- Each heavy chain contains 1 variable region and 3 constant regions.
- An epitope is the region of an antigen that is recognized by the antibody.







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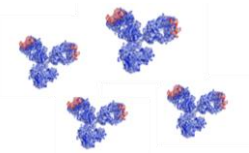
What are monoclonal / therapeutic antibodies ?



- Monoclonal antibodies (mAbs) are a single pure homogeneous antibody preparation produced by a single lineage of B-cells.
- They all have the same sequence and recognize a single epitope.
- They can be designed to selectively bind different molecules to identify, neutralize or block their intended target.
- Biological therapy: therapeutic mAbs are used medically to block a patient's soluble protein (e.g. a cytokine), a receptor on a cell, or infectious agents such as viruses or bacteria.

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mAb nomenclature

Prefix	Target/Disease Infix	Source Infix	Suffix
	-k(i)- interleukin	-o- mouse	
	-l(i)- immune system	-xi- chimeric	
	-le(s)- inflammatory lesions	-zu- humanized	
variable	-t(u)- tumor	-u- human	-mab
	-b(a)- bacterium	-vet- veterinary	
	-f(u)- fungus		
	-v(i)- virus		

Lo-ki-vet-mab

WHO International Nonproprietary Names (INN)
United States Adopted Names (USAN)

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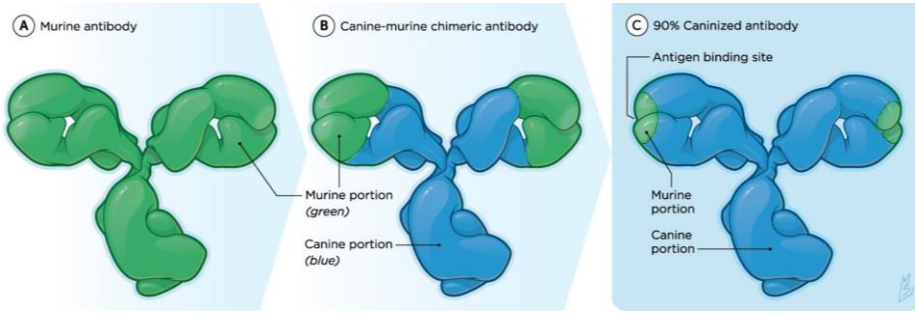
What is lokivetmab ?

- Lokivetmab is a “caninized” chimeric antibody.
- Only the antigen binding site is murine. The rest is canine.
- DO NOT USE IN CATS!



Less Immunogenic

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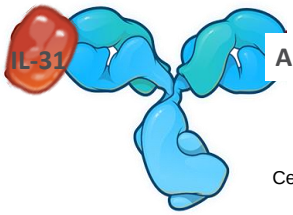
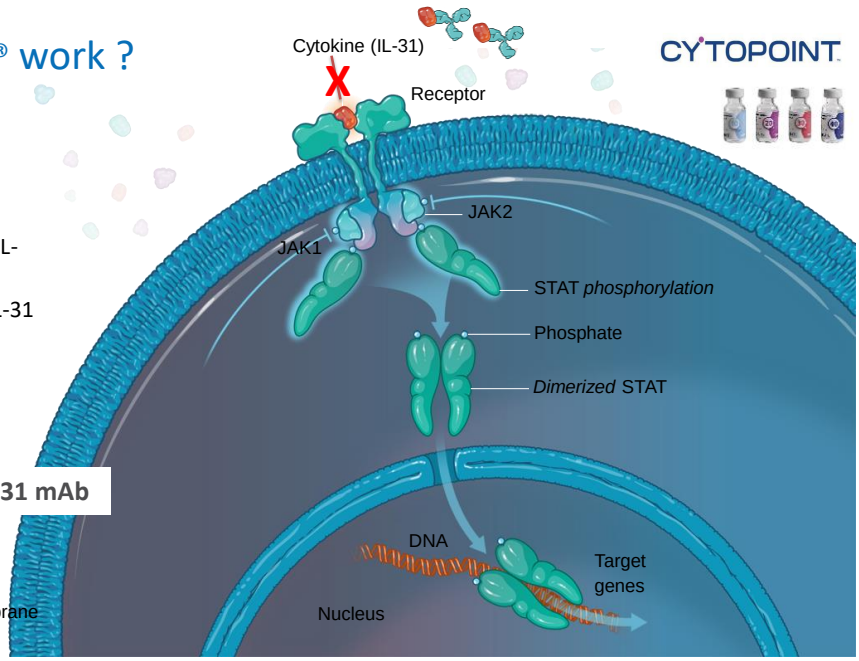
How does Cytopoint® work ?

Anti-IL-31 mAb

Lokivetmab is a caninized monoclonal antibody, targeted specifically to a single cytokine: IL-31. It works by "soaking up" or neutralizing soluble circulating IL-31 produced by lymphocytes, preventing it from activating cell receptors and inducing pruritus.





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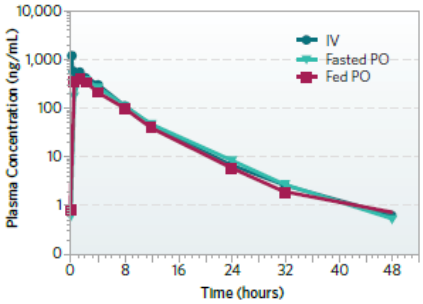
Absorption

apoquel®

- Apoquel™ has an ideal pharmacokinetic profile.
- Rapidly and well absorbed following oral administration in dogs.
- Average time to maximum plasma concentration (T_{max}) is < 1 hour.
- Terminal half-life ($t_{1/2}$) = 4.1 hours.
- High oral bioavailability (89%).
- Low protein binding (66.3%-69.7%).
- No significant impact of prandial state (can be given with or without food).



Mean oclacitinib plasma concentration - time profiles after IV and oral administration in dogs under fed and fasted conditions.

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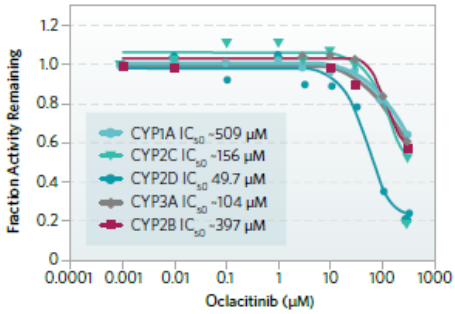
Metabolism

- Apoquel™ minimally inhibits cytochrome P450 isoenzymes therefore minimizing the potential for any clinically-relevant drug-drug interaction.
- Inhibitory concentrations (IC50s) are 50-fold greater than the observed maximum plasma concentration (Cmax) values at the labelled dose.



In vitro inhibition of canine liver cytochrome P450 isoenzymes by oclacitinib.

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Clearance

- Major clearance route is metabolism with minor contributions from renal and biliary elimination.
- The main route of excretion is via the urine (51%), with a significant amount also excreted in the feces (38%).
- Transformed into one major metabolite, and several smaller metabolites.
- No accumulation.

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Absorption and distribution

CYTOPOINT

- Monoclonal antibodies have unique pharmacologic features.
- A subcutaneous injection deposits the mAb into the interstitial space.
- There is 50-100% bioavailability when the antibody is injected.
- The mAb is then transported out of the interstitial space into the bloodstream in one of several ways:
  - Via lymphatic circulation
  - Direct absorption into capillaries
  - By receptor-mediated cell uptake (endocytosis) and transfer to the bloodstream.
- mAbs are held in the bloodstream (low tissue distribution) by barriers to capillary diffusion and lymphatic transport back to the blood.
- In general, mAb targets are circulating in blood or on cell surfaces, not inside cells.

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Catabolism and clearance

CYTOPOINT

- mAbs are cleared from the body in several ways:
  - Through binding to their target
  - Via anti-mAb antibodies in circulation
  - By flow out of capillaries into the interstitial space, where they are taken up by cells.
- mAbs are catabolized (not metabolized) to peptides and amino acids within cells.
- mAbs that attach to the FcRn (Fc neonatal receptor) within the endosome are protected from catabolization and are recycled back into the blood or lymph which extends the half-life of the antibody.
- Hepatic and renal elimination is minimal. In a radiolabeled mAb study in mice, only 3.6% of the mAb was found in the liver, and 2-3% in the kidney.
- The kidneys can only filter molecules with a molecular weight cutoff of approximately 30-50 kDa, and mAbs, being large macromolecules, are not filtered.

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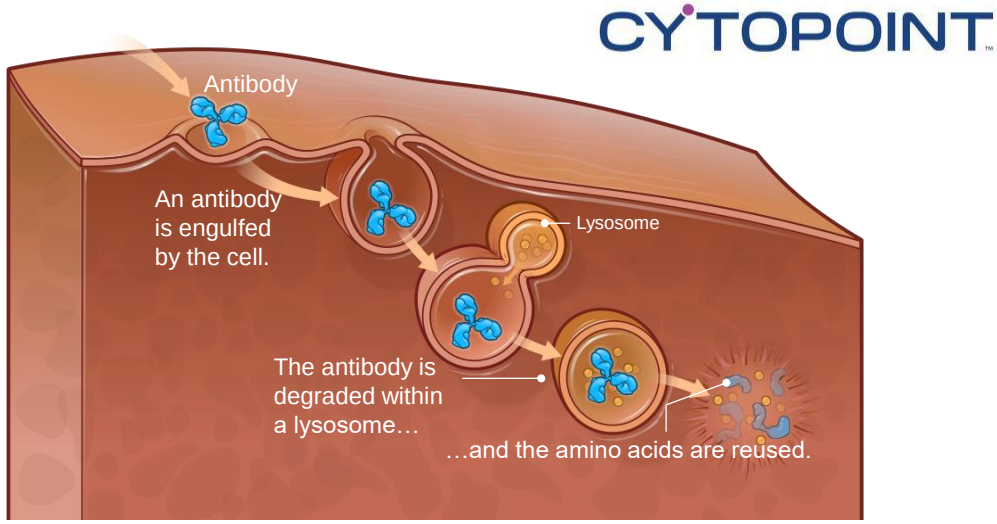
mAbs are processed by the body through degradation



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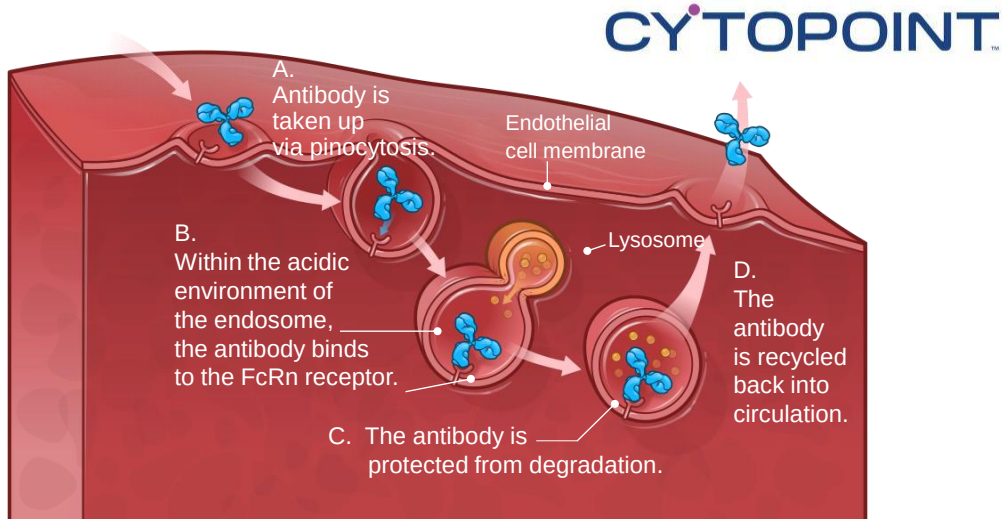
mAbs are recycled and reused by the body



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Apoquel™ vs. Cytopoint®

	apoquel	CYTOPOINT
Treatment type	Traditional pharmaceutical (drug)	Biopharmaceutical (biological)
Regulated by	Health Canada	Canadian Food Inspection Agency (CFIA)
Size	Small molecules	Large MW protein (macromolecule)
Route/ Frequency	Oral Daily (short duration)	Injectable (SQ) Monthly or less often (long period of time)
Specificity	Less targeted Blocks the activity of several cytokines	Single target Extreme specificity (IL-31 only)
Target	Intracellular (JAK enzymes)	Extracellular (circulating cytokine)
Metabolism, clearance	Hepatic, renal metabolism and elimination	Protein catabolism Minimal hepatic and renal elimination

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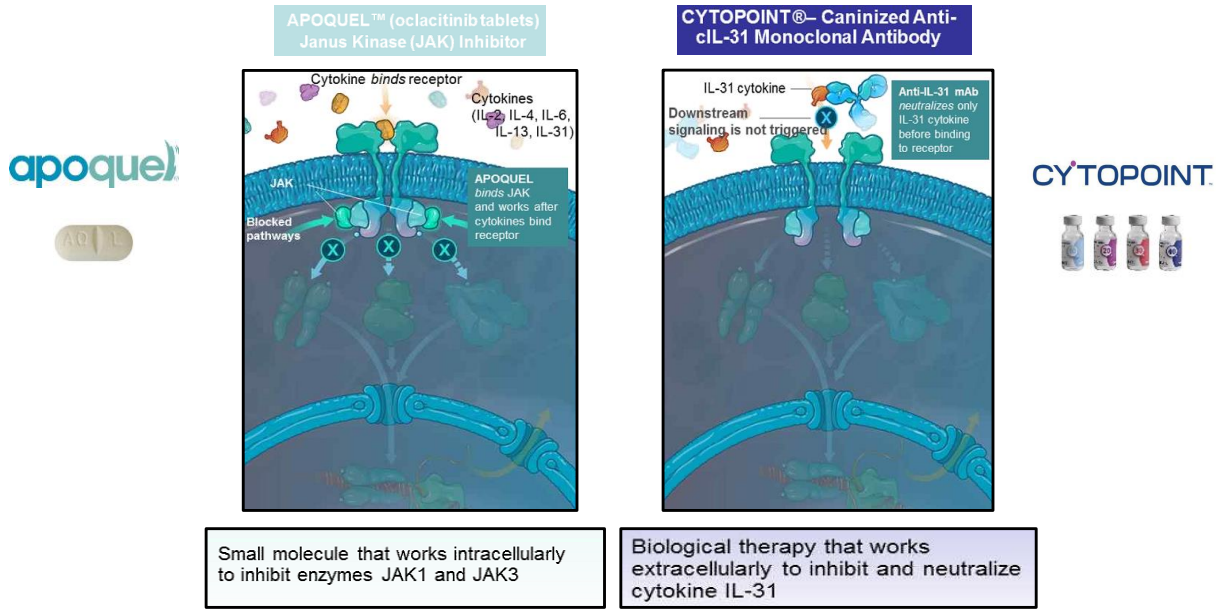
Apoquel™ vs. Cytopoint®



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Examples in human medicine

Product	XELJANZ® (tofacitinib citrate)	Xolair® Omalizumab FOR SUBCUTANEOUS USE
Company	Pfizer	NOVARTIS
Target	JAK enzymes	Immunoglobulin E
Indication	Rheumatoid arthritis	Allergic asthma Chronic idiopathic urticaria

Apoquel™ compared to placebo

apoquel

Veterinary Dermatology

Vet Dermatol 2013; **24**: 587–e142 DOI: 10.1111/vde.12088

A blinded, randomized, placebo-controlled trial of the efficacy and safety of the Janus kinase inhibitor oclacitinib (Apoquel®) in client-owned dogs with atopic dermatitis

Sallie B. Cosgrove*, Jody A. Wren*, Dawn M. Cleaver*, Kelly F. Walsh*, Stacey I. Follis*, Vickie I. King*, Jezaniah-Kira S. Tena* and Michael R. Stegemann†

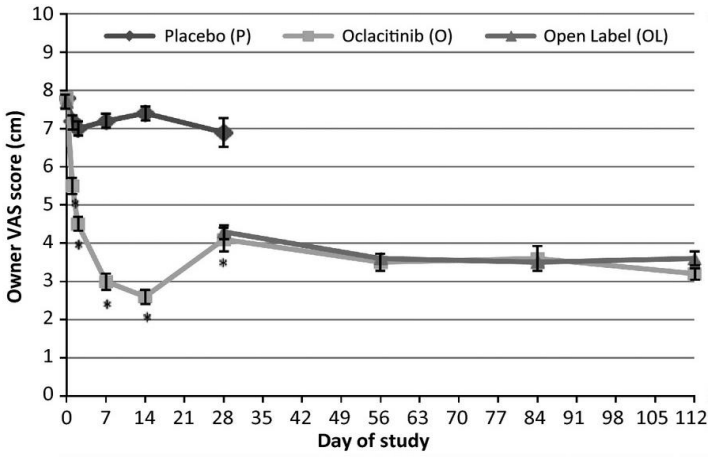
Source of funding:

zoetis

299 client-owned atopic dogs, 18 practices
Apoquel™ compared to placebo for 4 weeks
Adverse effects reported
Study provides evidence of the effectiveness of oclacitinib compared to placebo

Dr. Vincent Defalque
Diplomate of the American College of Veterinary Dermatology
North West Veterinary Dermatology Services

Apoquel™ compared to placebo



Visual analog scale (VAS) for placebo and oclactinib.
*Significant treatment difference at $P < 0.05$.

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Apoquel™ compared to placebo

Adverse reactions observed during days 0–16 [a]	Oclacitinib (n = 152) [n (%)]	Placebo (n = 147) [n (%)]
Diarrhoea	7 (4.6)	5 (3.4)
Vomiting	6 (3.9)	6 (4.1)
Anorexia	4 (2.6)	0
New dermal, epidermal or subcutaneous mass [b]	4 (2.6)	4 (2.7)
Lethargy	3 (2.0)	2 (1.4)

Adverse health events occurring in dogs in the placebo and oclacitinib-treated groups.

40

Apoquel™ compared to prednisolone

Veterinary Dermatology

Vet Dermatol 2014; **25**: 512–e86 DOI: 10.1111/vde.12166

Efficacy of oclacitinib (Apoquel®) compared with prednisolone for the control of pruritus and clinical signs associated with allergic dermatitis in client-owned dogs in Australia

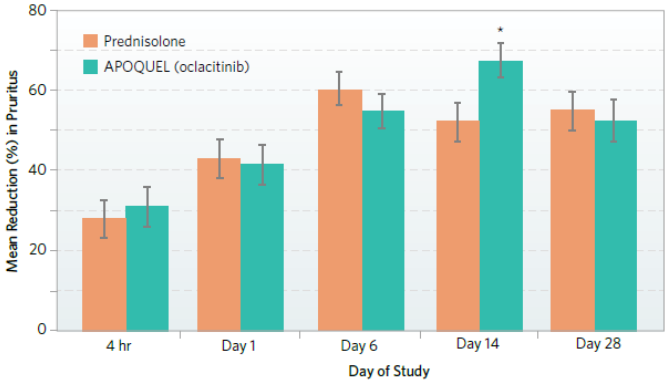
Caroline Gadeyne*, Peter Little†, Vickie L. King‡, Nigel Edwards†, Kylie Davis† and Michael R. Stegemann*

Source of funding:

zoetis

123 client-owned allergic dogs, 12 practices
Apoquel™ compared to prednisolone 5 mg tablets (Delta-Cortef®, Zoetis) for 4 weeks
Adverse effects reported
Response in both treatment groups was rapid (4 hours)

Apoquel™ compared to prednisolone



PRESUMPTIVE DIAGNOSIS BY VETERINARY INVESTIGATOR	PERCENT (%) OF APOQUEL DOGS WITH DIAGNOSIS	PERCENT (%) OF PREDNISOLONE DOGS WITH DIAGNOSIS
Atopic dermatitis	96.7%	98.4%
Flea allergy dermatitis	32.8%	40.3%
Contact dermatitis	47.5%	41.9%
Food hypersensitivity	23.0%	19.4%

Day of Study	4 hr	1	6	14	28
Prednisolone	28	43	60	52	55
APOQUEL	31	41	55	67	52
p value	0.655	0.797	0.351	0.019	0.721

Visual analog scale (VAS) for prednisolone and oclactinib.
*Significant treatment difference at $P < 0.05$.

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North West Veterinary Dermatology Services

Apoquel™ compared to prednisolone

Abnormal clinical sign	Prednisolone-treated dogs [*n* = 62; *n* (%)] [b, c]	Oclacitinib-treated dogs [*n* = 61; *n* (%)] [b c]
Pyoderma, including folliculitis	6 (9.7)	6 (9.8)
Dermatitis	3 (4.8)	2 (3.3)
Dermatomycosis	0 (0.0)	2 (3.3)
Otitis externa	1 (1.6)	2 (3.3)
Haematuria	0 (0.0)	2 (3.3)
Emesis	2 (3.2)	2 (3.3)
Lameness	0 (0.0)	2 (3.3)
Diarrhoea	2 (3.2)	1 (1.6)
Lethargy	3 (4.8)	1 (1.6)
Pinnal irritation	2 (3.2)	0 (0.0)

Adverse health events occurring in 2 or more dogs in the prednisolone and oclacitinib-treated groups.

43

Apoquel™ compared to Atopica®

Veterinary Dermatology

Vet Dermatol 2015; **26**: 23–e8 DOI: 10.1111/vde.12186

A blinded, randomized clinical trial comparing the efficacy and safety of oclacitinib and ciclosporin for the control of atopic dermatitis in client-owned dogs

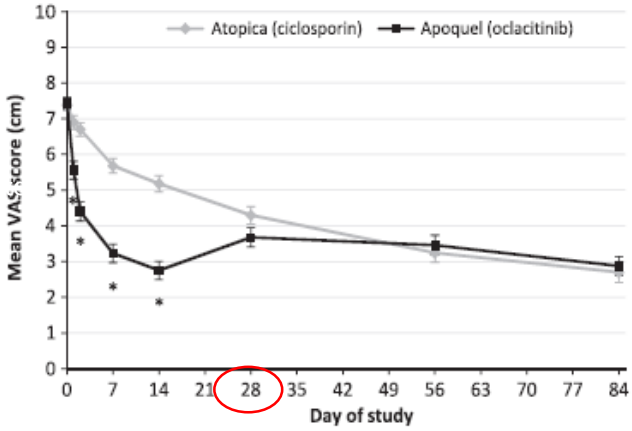
Peter R. Little*, Vickie L. King†, Kylie R. Davis*, Sallie B. Cosgrove† and Michael R. Stegemann‡

Source of funding:

226 client-owned atopic dogs
Apoquel™ compared to Atopica® for 12 weeks
Adverse effects reported
Apoquel™ had a faster onset of action and less gastrointestinal side effects than Atopica®

Dr. Vincent Defalque
Diplomate of the American College of Veterinary Dermatology
North West Veterinary Dermatology Services

Apoquel™ compared to Atopica®



Visual analog scale (VAS) for ciclosporin and oclactinib.
*Significant treatment difference at $P < 0.05$.

45

Apoquel™ compared to Atopica®

Abnormal health event	Ciclosporin (N=112) [n (%)]	Oclacitinib (N=114) [n (%)]
Vomiting	49 (43.8)	16 (14.0)
Pyoderma	13 (11.6)	13 (11.4)
Otitis externa	16 (14.3)	12 (10.5)
Unspecified skin lump	6 (5.4)	8 (7.0)
Lethargy	6 (5.4)	7 (6.1)
Abnormal test result	3 (2.7)	5 (4.4)
Diarrhoea	17 (15.2)	4 (3.5)
Fungal skin infection	5 (4.5)	4 (3.5)
Skin lesion NOS	5 (4.5)	4 (3.5)
Elevated liver enzymes	9 (8.0)	3 (2.6)
Leucopenia	3 (2.7)	3 (2.6)
Erythema	5 (4.5)	2 (1.8)
Haematuria	3 (2.7)	2 (1.8)
External parasite	2 (1.8)	2 (1.8)
Urinary tract disorder NOS	2 (1.8)	2 (1.8)
Lymphopenia	1 (0.9)	2 (1.8)
Pruritus	1 (0.9)	2 (1.8)
Dermatitis	6 (5.4)	1 (0.9)
Anorexia	3 (2.7)	1 (0.9)
Neutropenia	3 (2.7)	1 (0.9)
Pinnal irritation	3 (2.7)	1 (0.9)
Urinary bladder disorder NOS	3 (2.7)	0 (0.0)

Adverse health events occurring in 2 or more dogs in the ciclosporin and oclacitinib-treated groups.

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Apoquel™ compared to Atopica®

A retrospective study comparing the incidence of cutaneous histiocytoma development in atopic dogs treated with oclacitinib and ciclosporin

E.J. HIGH*, A.T.H. LAM*, L. FERRER*

533 client-owned atopic dogs treated with Apoquel™
654 client-owned atopic dogs treated with Atopica®
Cutaneous histiocytoma development may be higher (2.6% versus 0.6%) in dogs treated with Apoquel™ compared to those treated with Atopica®
Additional research is needed to determine a causal relationship and pathomechanisms between oclacitinib and cutaneous histiocytomas

Source of funding:

Self-funded

North American Veterinary Dermatology Forum

2017

Apoquel™ administration for > 6 months does not significantly increase incidence of malignancies

THURSDAY, APRIL 11, 2019

RESIDENT ABSTRACTS

Comparison of malignancies and nonmalignant skin masses in 339 allergic dogs receiving long-term (> 6 months) oclacitinib with age and breed matched control population

B. LANCELLOTTI*, J. ANGUS*, H. EDGINTON*, W. ROSENKRANTZ†

339 client-owned atopic dogs treated with Apoquel™ for > 180 days
321 client-owned allergic dogs NOT treated with Apoquel™
Minimum of 2 years of follow up or death/euthanasia within 2 years
Incidence of malignancies and skin masses in the oclacitinib group (16.2%, 57.2%, respectively) vs. controls (12.5%, 60.1%, respectively) not statistically different
Age of death in the oclacitinib group vs. controls not statistically different

Source of funding:

Self-funded

North American Veterinary Dermatology Forum

2019

Apoquel™ administration is not associated with increased risk of UTI or subclinical bacteriuria

Source of funding:

Veterinary Dermatology

Vet Dermatol 2017; **28**: 485–e113 DOI: 10.1111/vde.12450

The frequency of urinary tract infection and subclinical bacteriuria in dogs with allergic dermatitis treated with oclacitinib: a prospective study

Andrew C. Simpson*, Jennifer R. Schissler*, Rod A.W. Rosychuk* and A Russell Moore†

47 client-owned atopic dogs
Received Apoquel™ for > 180 days
No lower urinary tract signs
Negative urine bacterial cultures
Gastrointestinal side effects noted in 7.3% of patients

Cytopoint® compared to placebo

Source of funding:

Veterinary Dermatology

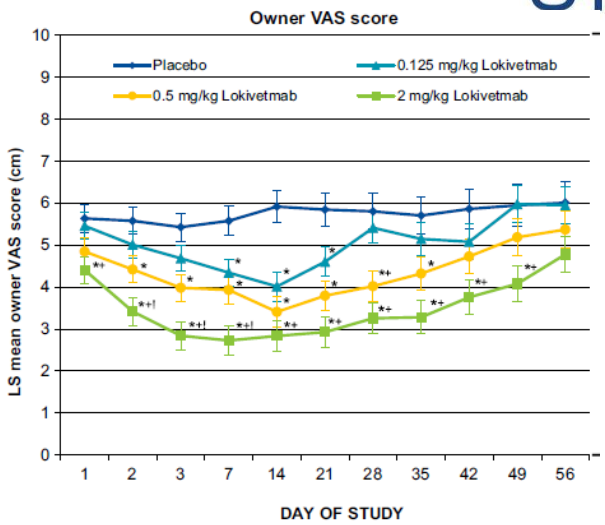
Vet Dermatol 2016; **27**: 478–e129 DOI: 10.1111/vde.12376

A blinded, randomized, placebo-controlled, dose determination trial of lokivetmab (ZTS-00103289), a caninized, anti-canine IL-31 monoclonal antibody in client owned dogs with atopic dermatitis

Gina M. Michels*, Deborah S. Ramsey*, Kelly F. Walsh*, Olivier M. Martinon†, Sean P. Mahabir*, Jacquelien D. Hoevers*, Rodney R. Walters† and Steven A. Dunham†

211 client-owned atopic dogs, 15 practices
A single Cytopoint® injection at 3 different dosages compared to placebo for 8 weeks
Adverse effects reported
Cytopoint® at minimum dose of 0.5 mg/kg reduced pruritus compared to placebo for at least 1 month
Level and duration of response increased with increasing dose

Cytopoint® compared to placebo



Visual analog scale (VAS) for placebo and lokivetmab.
*Significant treatment difference at $P < 0.05$.

Cytopoint® compared to placebo

Adverse events observed during days 0–56 [a]	Placebo (*n* = 52) [*n* (%)]	Lokivetmab (mg/kg) 0.125 (*n* = 55) [*n* (%)]	0.5 (*n* = 54) [*n* (%)]	2.0 (*n* = 50) [*n* (%)]
Vomiting	1 (1.9)	3 (5.5)	2 (3.7)	4 (8.0)
Diarrhoea	0 (0.0)	1 (1.8)	2 (3.7)	3 (6.0)
Pyoderma	2 (3.8)	4 (7.3)	3 (5.6)	2 (4.0)
Lethargy	0 (0.0)	1 (1.8)	0 (0.0)	2 (4.0)
Anorexia	0 (0.0)	0 (0.0)	0 (0.0)	2 (4.0)
Dermatitis	2 (3.8)	0 (0.0)	4 (7.4)	1 (2.0)
Otitis externa	2 (3.8)	1 (1.8)	3 (5.6)	1 (2.0)
Anxiety	0 (0.0)	0 (0.0)	2 (3.7)	0 (0.0)
Aural haematoma	2 (3.8)	0 (0.0)	0 (0.0)	0 (0.0)

Adverse health events occurring at least once in >2% of the placebo and lokivetmab-treated groups.

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North West Veterinary Dermatology Services

Cytopoint® compared to Atopica®


CYTOPOINT

Veterinary Dermatology

Vet Dermatol 2017; **28**: 593–e145 DOI: 10.1111/vde.12478

A blinded, randomized clinical trial evaluating the efficacy and safety of lokivetmab compared to ciclosporin in client-owned dogs with atopic dermatitis

Hilde Moyaert*, Leen Van Brussel*, Stasia Borowski*, Monica Escalada*, Sean P. Mahabir†, Rodney R. Walters† and Michael R. Stegemann*

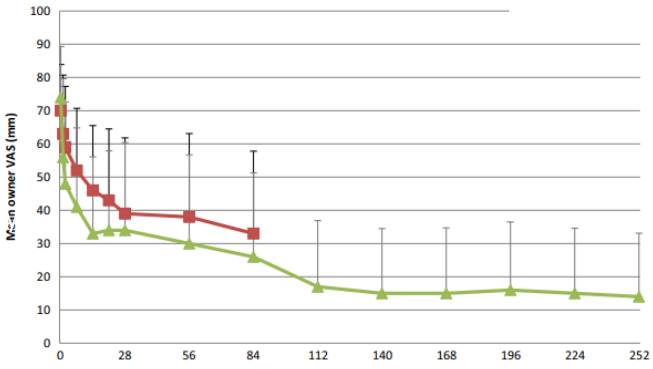
Source of funding:

zoetis

274 client-owned atopic dogs, 40 practices, 4 countries
Monthly Cytopoint® injections compared to Atopica® for 12 weeks
Adverse effects reported
Cytopoint® is noninferior to Atopica® for pruritus reduction

Cytopoint® compared to Atopica®

CYTOPOINT™



	0	1	2	7	14	21	28	56	84	112	140	168	196	224	252
Ciclosporin	70	63	59	52	46	43	39	38	33						
Lokivetmab	74	56*	48*	41*	33*	34*	34*	30*	26*	17	15	15	16	15	14

Visual analog scale (VAS) for ciclosporin and lokivetmab.
*Significant treatment difference at $P < 0.05$.

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Cytopoint® compared to Atopica®

Study period	Ciclosporin (*n* = 132) [*n* (%)] D0–D84	Lokivetmab (*n* = 142) [*n* (%)] D0–D84
Digestive tract disorders (55.3% versus 26.1% versus 19.8%)*		
Vomiting	49 (37.1)	22 (15.5)
Diarrhoea	47 (35.6)	19 (13.4)
Systemic disorders (12.9% versus 19.0% versus 8.6%)*		
Lethargy	11 (8.3)	14 (9.9)
Anorexia	5 (3.8)	7 (4.9)
Hyperthermia	0 (0.0)	3 (2.1)
Skin and appendage disorders (15.2% versus 18.3% versus 22.2%)*		
Bacterial skin infection	1 (0.8)	10 (7.0)
Dermatitis and eczema	6 (4.5)	8 (5.6)
Pruritus	9 (6.8)	6 (4.2)
Erythema	1 (0.8)	4 (2.8)
Alopecia	0 (0.0)	3 (2.1)
Ear and labyrinth disorders (8.3% versus 12.7% versus 12.4%)*		
Otitis externa	4 (3.0)	8 (5.6)
External ear disorder NOS	1 (0.8)	4 (2.8)
Otitis NOS	5 (3.8)	4 (2.8)
Musculoskeletal disorders (0.8% versus 2.8% versus 3.7%)*		
Lameness	1 (0.8)	3 (2.1)

Adverse health events occurring at least once in >2% of the ciclosporin and lokivetmab-treated groups.

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Contraindications

- Apoquel™

Should not be given to dogs with known or suspected allergy or intolerance to oclacitinib maleate or any other components of this product.
Not for use in dogs less than 12 months of age.
Not for use in dogs with serious infections, evidence of immune suppression or evidence of malignant neoplasia.
Not for use in breeding dogs, pregnant or lactating bitches.

- Cytopoint®

DO NOT USE IN CATS

Dr. Vincent Defalque
Diplomate of the American College of Veterinary Dermatology
North West Veterinary Dermatology Services

Cautions

- Apoquel™

Has not been evaluated :
- In dogs less than 3 kg.
- In combination with glucocorticoids, cyclosporine, or other immunosuppressive agents.

- Cytopoint®

Has not been tested in breeding dogs, pregnant or lactating bitches.

Monitoring

- Apoquel™

Rare development of leukopenia (neutropenia).
Complete blood count (for example at 2-3 months, at 6 months, then annually) .
Occasional development of demodicosis and cutaneous histiocytoma.

- Cytopoint®

No monitoring necessary or recommended.

General considerations

- Apoquel™ and Cytopoint® work in ~70% of dogs.
- Lack of response to Apoquel™ does not mean Cytopoint® will not be effective, and vice-versa. It is a matter of *trial and error*.
- Work on allergic pruritus. Pruritus caused by other conditions such as infection may not respond.
- Anecdotally, may be less effective against the otitis component of allergy in some dogs.
- Not all-in-one miracle treatments. Must be used along with other elements of multimodal therapy such as infection and parasite control.

Apoquel™ vs. Cytopoint®

	apoquel	CYTOPOINT
Indication	Control of pruritus associated with allergic dermatitis in dogs Control of atopic dermatitis in dogs	Aids in the reduction of clinical signs associated with atopic dermatitis in dogs
Owner compliance	Oral, once daily for maintenance	SQ injection, once every 4-8 weeks
Owner preference	Drug	Biological
Age	Dogs >1 year of age	Can be given to dogs of any age
Contraindications	Severe infections, neoplasia Immunocompromised patient	Can be given with any concurrent condition
Caution	Not studied with other immunomodulatory drugs	Can be given with any medication

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General considerations

- Apoquel™ and Cytopoint® work in ~70% of dogs.
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- Anecdotally, may be less effective against the otitis component of allergy in some dogs.
- Not all-in-one miracle treatments. Must be used along with other elements of multimodal therapy such as infection and parasite control.

FRIDAY, APRIL 12, 2019

ORIGINAL ABSTRACTS

Identification and characterization of monoclonal antibodies targeting feline IL-31

T.J. FLECK*, G. BAMMERT*, *, S. MAHABIR*, C. JAVENS, B. GALVAN, S. STEINIGER, A. GONZALES*, S. DUNHAM*

**Veterinary Medicine Research and Development, Zoetis Inc., Kalamazoo, MI USA*

Abstract: The use of lokivetmab (Cytopoint®), a monoclonal antibody (mAb) targeting canine interleukin-31 (IL-31), for the treatment of canine allergic and atopic dermatitis has proven the therapeutic benefit of targeting IL-31 in canine disease. To evaluate the role of IL-31 in feline allergic and atopic dermatitis we have generated monoclonal antibodies (mAbs) and speciated derivatives targeting feline IL-31. Each mAb was evaluated for its ability to bind feline IL-31 and inhibit IL-31 mediated signaling in a feline cell line. Several mAbs were found to bind and neutralize the function of feline IL-31. Here we present the affinity (sub nanomolar to low picomolar) and *in vitro* potency (IC_{50} = 3.7 – 15 □g/mL) of three progenitor antibodies and several speciated derivatives. We also explored the *in vivo* efficacy of one antibody in a feline model of IL-31-induced pruritus. In this model eight cats per group were treated with either placebo or mAb (2 mg/kg, subcutaneously). Feline IL-31 was intravenously administered (1 □g/kg) prior to mAb administration and 7 days post mAb administration. Pruritic behavior was evaluated using a categorical scoring system in 1 min intervals over the course of 1 h after IL-31 injection. The results of this study demonstrated that a single 2 mg/kg subcutaneous dose resulted in statistically significant reduction of pruritus ($P < 0.0001$) for at least 1 week when compared to a placebo group administered mAb buffer. These data demonstrate the ability of anti-IL-31 antibodies to effectively inhibit IL-31-induced pruritus in a model of feline disease.

Sources of funding: Zoetis, Inc. funded this study.

Conflict of Interest: The authors are employed by Zoetis, Inc.

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North West Veterinary Dermatology Services