Advancing Methods for Equivalence of Ophthalmic Products

A New Vision for the Future

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Director of Operations

PRECLINICAL TESTING FOR DRUGS, BIOLOGICS AND MEDICAL DEVICES

Presentation Summary

- Challenges of Ocular Drug Delivery
- Considerations for Ocular Drug Formulation
- Regulatory View on Bioequivalence
- Non-clinical Models for Totality of Evidence
- Enabling High Quality Cost Effective Generics

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Impact of Ocular Disease

- 285 million people are estimated to be visually impaired worldwide
  - 39 million are blind and 246 have low vision.
- About 90% of the world's visually impaired live in low-income settings.
- The number of people visually impaired from infectious diseases has reduced in the last 20 years

80% of all visual impairment can be prevented or cured.

Source: WHO

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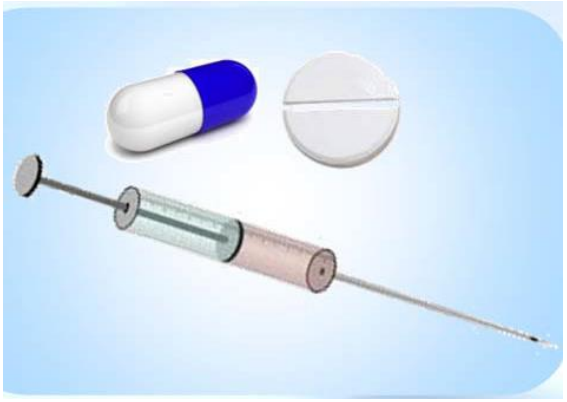
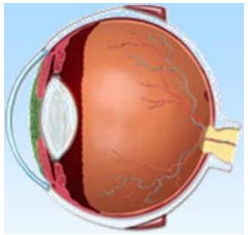
Topical Versus Systemic Delivery

vs



Eye drops allow therapeutic concentrations of drug to be achieved selectively in aqueous humor/ocular tissues



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Getting the Drug In

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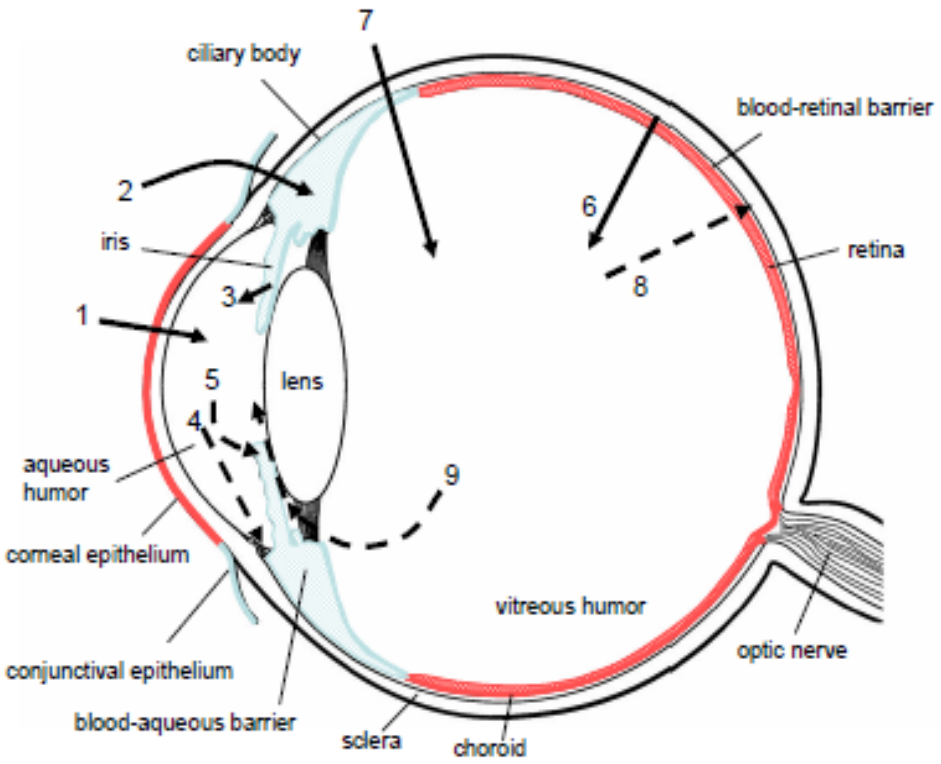
Ocular Barriers

Anterior Segment

Cornea Epithelium
Cornea Stroma
Cornea Endothelium
Conjunctiva
Iris-Ciliary Body (ICB)
Sclera

Posterior Segment

Choroid
Lens
RPE
Retina
Vitreous Humor



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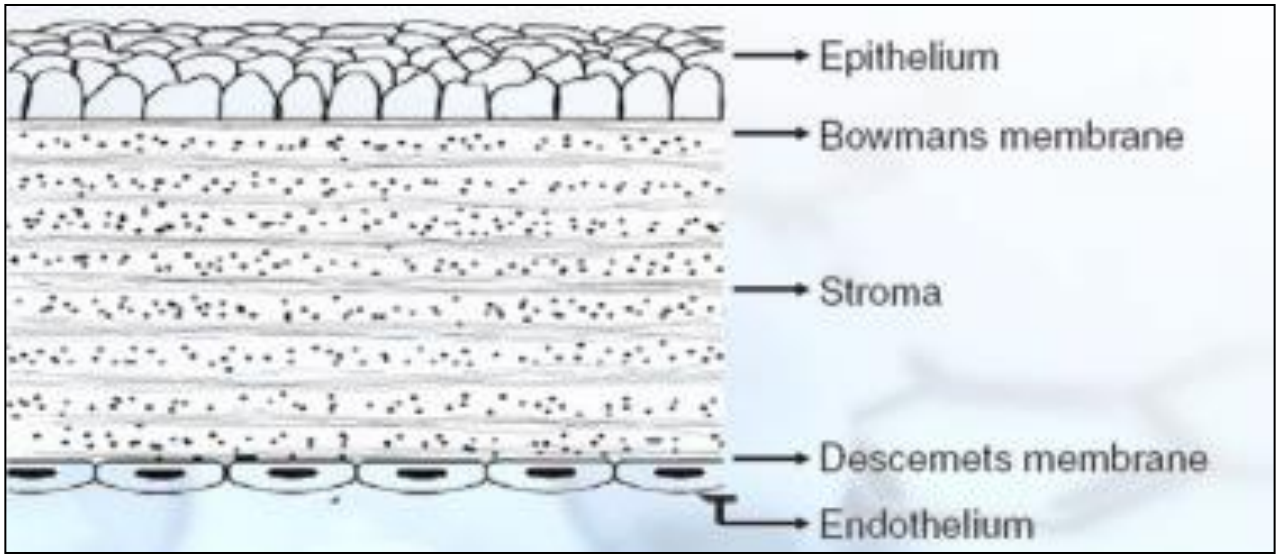
Corneal Barrier

Low Corneal Permeability

Optimizing Log P



Superficial absorption into conjunctiva and sclera and rapid removal by peripheral blood flow

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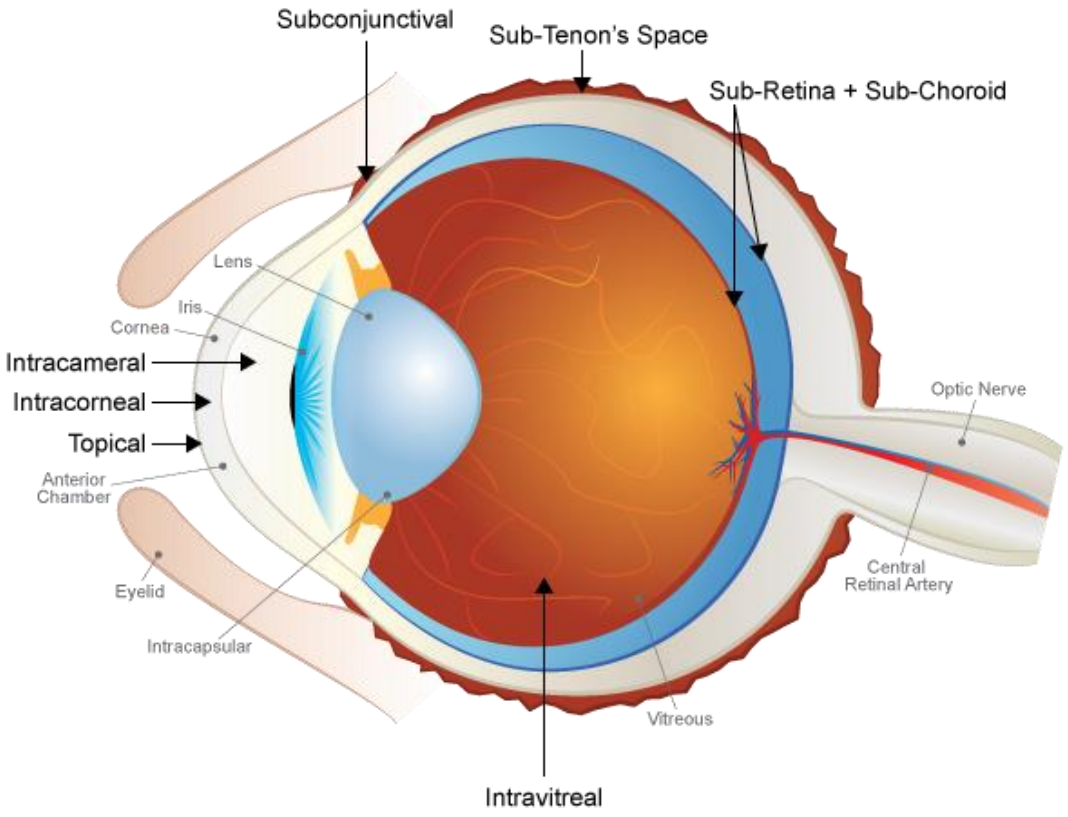
Physiological Factors

- Limited dose volume
- Short residence time
- Dilution and drainage
- Metabolism and transporters
- Multiple barriers
- Local adverse effects



Schoenwald RD. Ocular drug delivery. Pharmacokietic considerations. Clin Pharmacokinet 1990; 18: 255-269

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Ocular bioavailability

- Transport of hydrophilic and macromolecular drugs occurs through scleral route
- Lipophilic small molecule can permeate the cornea, and move into the aqueous humor via *Fickian* diffusion
- Drug needs dual solubility (oil and water soluble) to traverse the corneal epithelium (lipid barrier) then the aqueous humor
- BA assay sensitivity

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Ocular Formulations

Key Components

- Active ingredient(s)
- Vehicle
- Inactive ingredients:
  - Tonicity adjustment
  - Buffer and adjust pH
  - Anti-oxidants
  - Solubilizers
  - Suspending agents and viscosifiers
  - Prevent microbial contamination

Stability of Active Ingredient

- Degradation of active ingredient, due to excessive heat, light exposure, or contamination, can compromise efficacy[1-3]
  - Stable at room temperature (refrigeration not required)
    - For example, bimatoprost is more stable than other PGAs
  - Not sensitive to light or air exposure (storage in colored bottle or lightproof, airtight foil pouch not required)

1. Cantor. *Expert Opin Pharmacother*. 2002;3(12):1753-1762.
2. Paolera et al. *BMC Ophthalmol.* 2008;8:11.
3. Johnson et al. *J Ocul Pharmacol Ther*. 2011;27(1):51-59.

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Tonicity

- Tonicity of an ophthalmic solution needs to be adjusted so that it
  - Exerts an osmotic pressure equal to that of tear fluids (roughly equivalent to 0.9% NaCl ideally)
- Some ophthalmic solutions are necessarily hypotonic to enhance absorption and provide concentration of active ingredient sufficient to achieve efficacy
  - Hypotonic solutions are better tolerated than hypertonic solutions
- Common tonicity-adjusting ingredients include: NaCl, Cl, buffer salts, dextrose, glycerin, propylene glycol, and d-mannitol

Ghate and Edelhauser. *J Glaucoma*. 2008;17(2):147-56.

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pH

- **Critical for a Topical Ophthalmic**
- **pH adjustment is an important step in formulation:**
  - Influences the comfort and tolerability of the drug product
    - Affects bioavailability Optimizes solubility and permeability
    - Minimizes lacrimation and tear dilution/ drainage of active
  - Provides stability for the active
  - Buffer capacity greatly affects pH tolerability

Surfactants

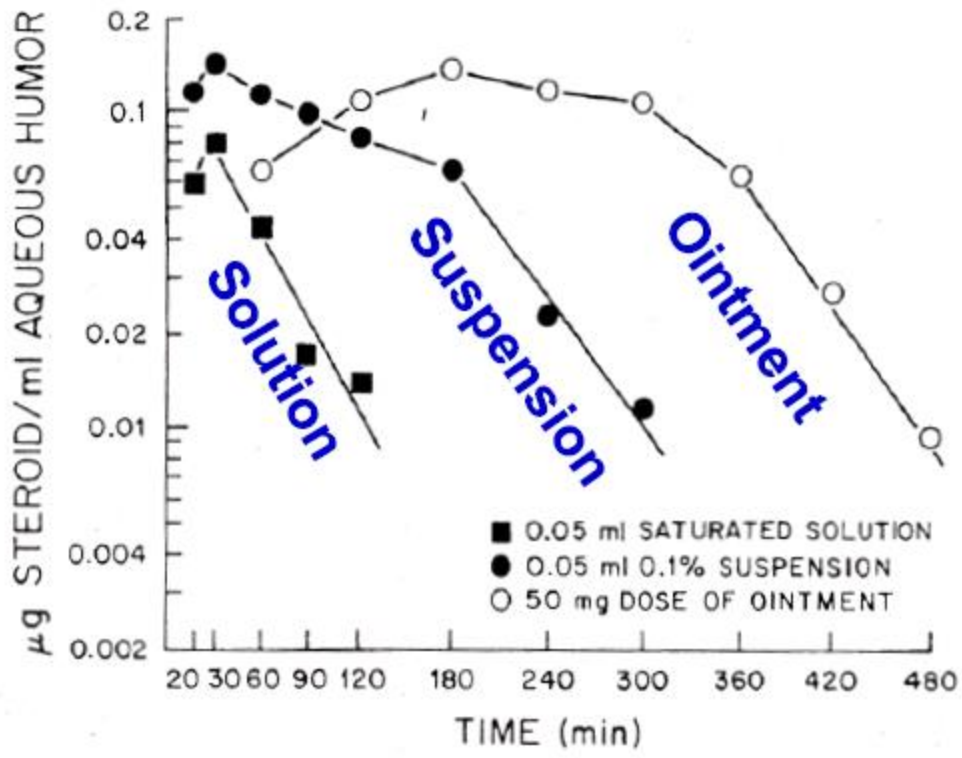
- **Several nonionic surfactants are used in relatively low concentrations to:**
  - Aid in dispersing steroids in suspensions
  - To achieve drug solubility or to improve solution clarity
  - Polysorbate, tyloxapol, polyoxyl 40 stearate
- **The order of surfactant toxicity is:**
  - Anionic > cationic » nonionic
  - Nonionic surfactants preferred for ophthalmic use

Modern Pharmaceutics 4th ed 2006

Viscosifiers

- **Used to increase the viscosity of ophthalmic solutions and suspensions**
  - Improve suspension stability
  - Increase precorneal residence time by decreasing drainage rate and increasing mucoadhesiveness, resulting in potentially increased drug bioavailability
  - Act as a demulcent (protects ocular surface and relieves dryness/irritation)
  - Provide lubrication of the corneal surface
    - Commonly used viscosifiers include: polyvinyl alcohol, sodium carboxymethylcellulose, hydroxypropyl methylcellulose, hydroxyethylcellulose, and carbomers

Impact of Formulation Type



Rabbit study of ^{3}H-fluorometholone

Sieg et al, J Pharm Sci, 1975

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Preservatives

Commonly Used	Historically Used
Benzalkonium chloride (BAK or BAC)	Sorbic acid
PURITE® (stabilized oxychloro complex)	Thiomersal
Polyquad® (polyquaternium-1)	Benzododecinium bromide
Sodium perborate	Chlorobutanol/phenylethanol
sofZia®	Parabens
Polyhexamethylene biguanide (PHMB)	Phenylmercuric acetate or nitrate

Preservatives differ in their mechanism of action, antimicrobial specificities and safety profile

BAK is the most commonly used ophthalmic preservative (72% of ophthalmic solutions)

Abelson and Fink, 1992

OGD View on Complex Drugs

- **Can have Generics (ANDA Approvals)**
  For e.g. – enoxaparin (2011), acyclovir (2013)

- **Can be controversial**
  Citizen petitions/International differences (clinical studies for EMA)/non-biological complex drugs as a new category outside ANDA pathway

- **Are more complex than other ANDA**
  Complex development/Longer reviews

GDUFA Initiatives

GDUFA FY 2014 Regulatory Science Priorities

- Post-market Evaluation of Generic Drugs
- **Equivalence of Complex Products**
- Equivalence of Locally Acting Products
- Therapeutic Equivalence Evaluation and Standards
- Computational and Analytical Tools

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Pathway to FDA Approval

"Currently, generic ophthalmic solutions are expected to have the same active and inactive ingredients in the same concentrations (both active and inactive). If they are not the same, then a study comparing the clinical bioequivalence has to be performed. If the product is anything other than a solution, where manufacturing issues could potentially make a difference, the generic has to have a study demonstrating equivalence, even if the actives and inactives are the same"

Questions from AGS members, answered by Wiley Chambers, MD, FDA Deputy Director for the Division of Transplant and Ophthalmology Products, March 2011

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BE Requirements

- Methods used to define bioequivalence can be found in 21 CFR 320.24, and include:
- FDA may require in vivo or in vitro testing, or both, to measure the bioavailability of a drug product or establish the bioequivalence of specific drug products

  - In Vivo PK – systemic distribution
  - In Vitro – correlated and predicted on human in vivo
  - Mass balance – applicable only when urinary excretion
  - In Vivo PD study – for local acting
  - Clinical trials- BA
  - In vitro dissolution tests
  - Any other deemed suitable by FDA

BE issues for ophthalmic products

Ophthalmic Preparations: AT rating "Probable Bioequivalence to the Branded Product"

Without published head to head clinical studies comparing generic ophthalmic drugs to brand-name agents it is difficult to ascertain whether there is true equivalence

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Ophthalmic Solutions

- Q1& Q2
- +/- 5% inactive ingredients
- Pharmaceutical equivalence results in bioequivalence
- Biowaiver is requested

- Only potential differences may be in Q3 (due to manufacturing processes)
  - Requires evaluation of:
    - Rheology
    - In Vitro release

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Ophthalmic solutions Draft Guidance

- Xalatan draft guidance - 2008

Active ingredient: Latanoprost

Form/Route: Solution/Drops; Ophthalmic

Recommended study: Request for Waiver of *In vivo* Bioequivalence Study Requirements

To qualify for a waiver of the *in vivo* bioequivalence (BE) study requirements under 21 CFR 320.22(b)(1), a generic latanoprost ophthalmic solution product must have the same active and inactive ingredients in the same concentration as the reference listed drug product (RLD).

For an ophthalmic drug product that differs from the RLD in preservative, buffer, substance to adjust tonicity, or thickening agent [(as permitted by the chemistry, manufacturing and controls (CMC) regulations for abbreviated new drug applications (ANDAs), 21 CFR 314.94(a)(9)(iv)], the regulation specifies that the applicant must identify and characterize the differences and provide information demonstrating that the differences do not affect the safety or efficacy of the proposed drug product.

Challenges with suspensions/emulsions

- Pharmaceutical equivalence may not translate to bioequivalence
- Q1 & Q2 formulations may have different physicochemical properties
  - Particle size
  - Size distribution
  - Viscosity
  - Zeta potential
  - pH
- These properties can affect pre-corneal residence time, drug release and rate and extent of drug delivery to the target site

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Issues with bioequivalence

- Differences in extended-release gel vehicles (gellan versus xanthan) can impact corneal residence time.
  - Timoptic-XE (timolol maleate ophthalmic gel-forming solution, Merck) has better surface contact resulting in improved efficacy compared to the generic
- Differences in particle size impacts aggregation resulting altered dosage consistency and concentrations
  - Micro-fine suspension in its Pred Forte (prednisolone acetate) is more uniform, remains longer in the conjunctival sac and minimizes mechanical irritation to the eye compared to generic prednisolone acetate

First ophthalmic emulsion waiver

- Cyclosporine draft guidance – 2013

Active ingredient: Cyclosporine

Form/Route: Emulsion/Ophthalmic

Recommended study: 2 **Options:** ***In Vitro*** **or** ***In Vivo*** **Study**

I. In Vitro option:

To qualify for the in vitro option for this drug product pursuant to 21 CFR 320.24 (b)(6), under which "any other approach deemed adequate by FDA to measure bioavailability or establish bioequivalence" may be acceptable for determining the bioavailability or bioequivalence (BE) of a drug product, all of the following criteria must be met:

i. The test and Reference Listed Drug (RLD) formulations are qualitatively and quantitatively the same (Q1/Q2).

ii. Acceptable comparative physicochemical characterization of the test and RLD formulations. The comparative study should be performed on at least three lots of both test and reference products.

Parameters to measure: Globule size distribution, viscosity, pH, zeta potential, osmolality, surface tension.

Bioequivalence based on (95% CI): Population bioequivalence based on D_{50} and SPAN $(D_{90}-D_{10})/D_{50}$ or polydispersity index for the globule size distribution only (the other parameters do not require population bioequivalence analysis). The population bioequivalence analysis should be performed separately for each peak detected in the globule size distribution of the RLD. The separation of the peaks should be determined by the minimum value located between the peaks of the RLD.

iii. Acceptable comparative in vitro drug release rate tests of cyclosporine from the test and RLD formulations.

Characterization based equivalence

- USP Chapter 1724: Performance tests for semi solid drug products
  - Assess general quality attributes
    - Integrity of the dosage form
  - Assess product performance (e.g. drug release)
    - Relates to in vivo drug performance
- Taken together, quality and performance tests are intended to ensure the identity, strength, quality, purity, comparability and performance of semi-solid drug products
- Provides measurable index to anticipate performance of the dosage form in the clinic

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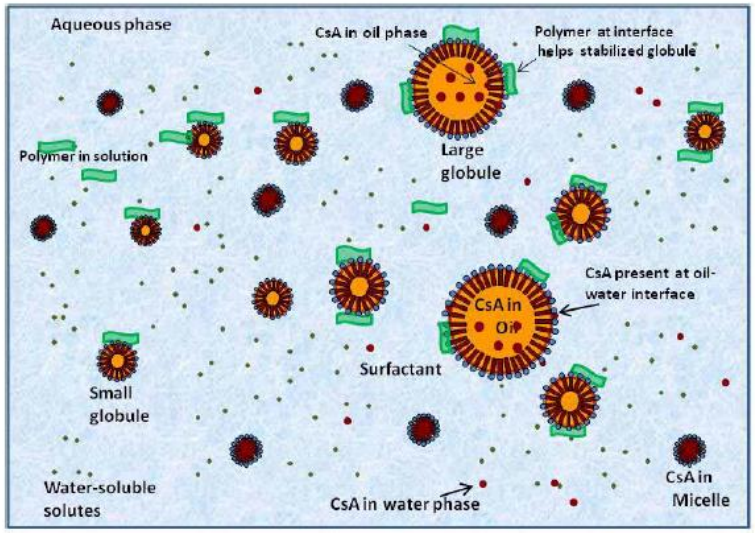
Citizen Petition- Restasis

SCHEMATIC OF EMULSION INFRASTRUCTURE



- Distribution of drug is dependent on Q1Q2, grade of excipients used and manufacture process
- Rate and extent of drug distribution in tissues impacted by amount of drug in the different phases of the emulsion
- Interaction and drug release depends on emulsion and conditions of ocular surface

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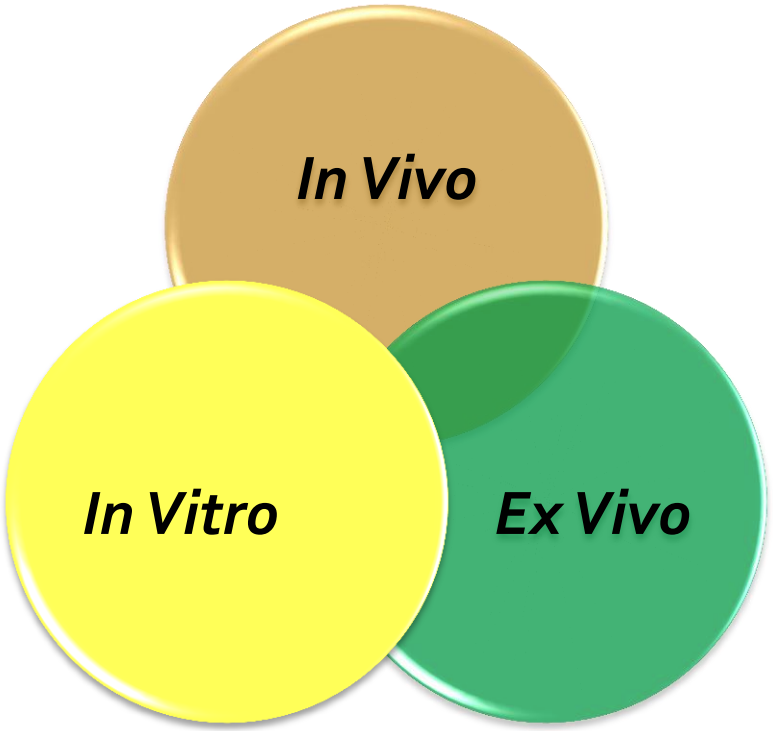
Building Totality of Evidence

- *In Vitro*
  - Rate of release of active ingredient from the vehicle
- *Ex Vivo*
  - Comparative Flux across excised corneal or conjunctival tissue
- *In vivo*
  - Ocular PK and distribution
  - Efficacy (CEP)



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In Vitro Release Testing

- The underlying principal is to determine the diffusion of the active ingredient
  - From the semi-solid matrix
  - Across a membrane
  - Into an appropriate medium
  - Representing the clinical use of the semi solid dosage form as close as possible

SUPAC Guidance used as the basis of study design parameters and criteria

In Vitro Release Testing

- Diffusion cell system
- Synthetic membrane

  Appropriate inert synthetic membranes such as polysulfone, cellulose acetate/nitrate mixed ester, polytetrafluoroethylene 70 μM
- Receptor medium

  Appropriate receptor medium such as aqueous buffer for water soluble drugs or a hydro-alcoholic medium for sparingly soluble drugs or another medium with proper justification
- Number of samples: 6 recommended
- Sample applications: Infinite dose condition
- Sampling time

  Multiple sampling times over an appropriate time period to generate an adequate release profile and to determine the drug release rate (a 6-hour study period with not less than five samples)

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In Vitro Release Testing

- Apparatus
- Selection of Membrane
- Solubility of API in receptor medium
- Method Validation

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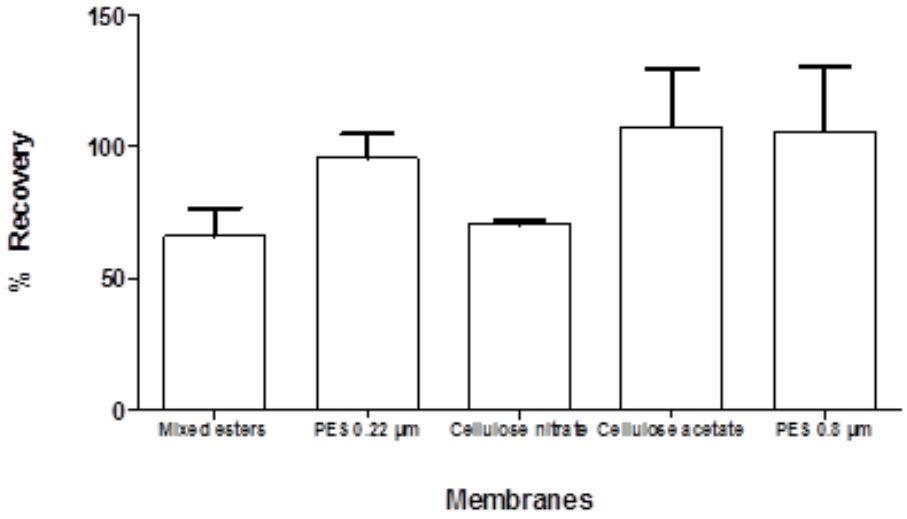
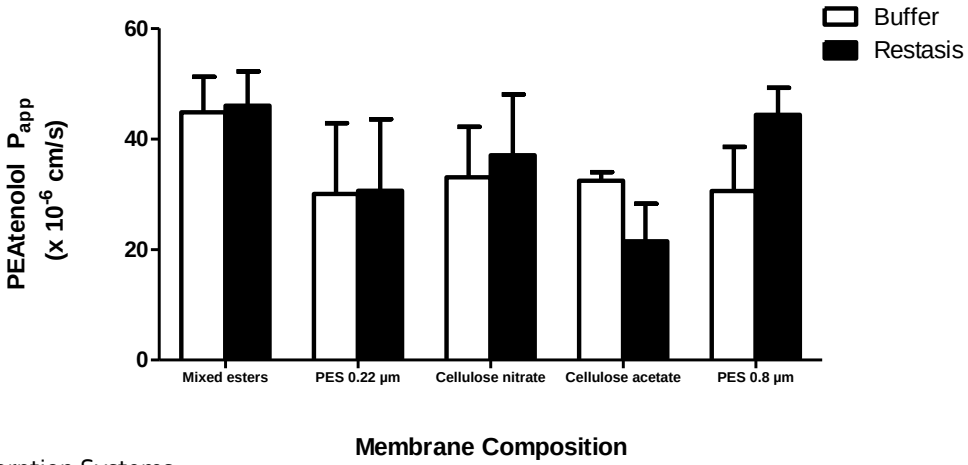
Suitability Assessments



- Recovery Assessment
  - Membrane binding
  - Extraction procedures



- Compatibility
  - Tolerability
  - PE atenolol

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Ex Vivo Corneal and Conjunctival Permeability/Flux

- Freshly excised corneal and conjunctival tissue from Dutch-belted rabbit eyes
- Low-volume Vertical Diffusion Ussing Chamber
- Buffer/Analytical Matrix: Glutathione-Bicarbonate Ringer (GBR) - pH 7.4
- Unidirectional Flux Assessment across excised corneal or conjunctival tissue
- N=6 replicates per treatment group
- Suitable high and low permeability reference standards
- Flux and Percent Recovery
- Post-experiment tissue integrity results (atenolol P_{app})

Rabbit Cornea Permeability: System Validation

	Cornea P_{app} (x 10^{-6} cm/s)	SD	Conjunctiva P_{app} (x 10^{-6} cm/s)	SD
Acebutalol	4.68	0.39	3.24	0.94
Acetazolamide	1.28	0.26	3.39	1.23
Apraclonidine	3.11	1.78	12.6	4.74
Atenolol	1.84	0.46	4.95	1.19
Betaxolol	32.0	4.42	5.24	1.94
Brimonidine	28.8	1.22	6.73	2.03
Brinzolamide	0.91	0.93	5.15	1.28
Bufarolol	19.0	4.56	3.58	0.58
Ciprofloxacin	0.42	0.35	4.48	3.31
Clonidine	46.7	8.73	12.6	4.52
Dexamethasone	5.08	0.71	4.38	0.22
Dexamethasone Acetate	BLQ	N/A	BLQ	N/A

Rabbit Cornea Permeability: System Validation

	Cornea P_{app} (x 10^{-6} cm/s)	SD	Conjunctiva P_{app} (x 10^{-6} cm/s)	SD
Dorzolamide	0.99	0.35	4.17	1.51
Ethoxzolamide	21.1	2.81	1.90	0.80
Fluorescein	1.07	0.42	3.84	1.04
Latanoprost	0.07	0.14	BLQ	N/A
Latanoprost acid	96.8	83.0	2.59	2.22
Levolbunolol	19.5	1.70	5.51	3.70
Moxifloxacin	8.91	0.94	5.98	3.49
Propranolol	23.9	8.37	2.48	1.65
Testosterone	27.6	5.37	2.20	2.47
Timolol	37.0	6.41	5.15	2.62

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Variability: Intra and Inter-Assay

	Atenolol		Antipyrine	
	DB Cornea CV	DB Conjunctiva CV	DB Cornea CV	DB Conjunctiva CV
Week 1	28%	25%	16%	40%
Week 2	25%	19%	6%	18%
Week 3	32%	22%	8%	48%
Week 4	40%	45%	12%	53%
Week 5	38%	33%	9%	27%
Week 6	27%	47%	6%	24%
Week 7	19%	27%	9%	10%
Week 8	26%	26%	7%	9%
Week 9	59%	32%	47%	39%
Week 10	24%	38%	6%	20%
Average	**32%**	**31%**	**13%**	**29%**
Range	**19-59%**	**19-47%**	**6-47%**	**9-53%**
Median	**28%**	**30%**	**8%**	**26%**

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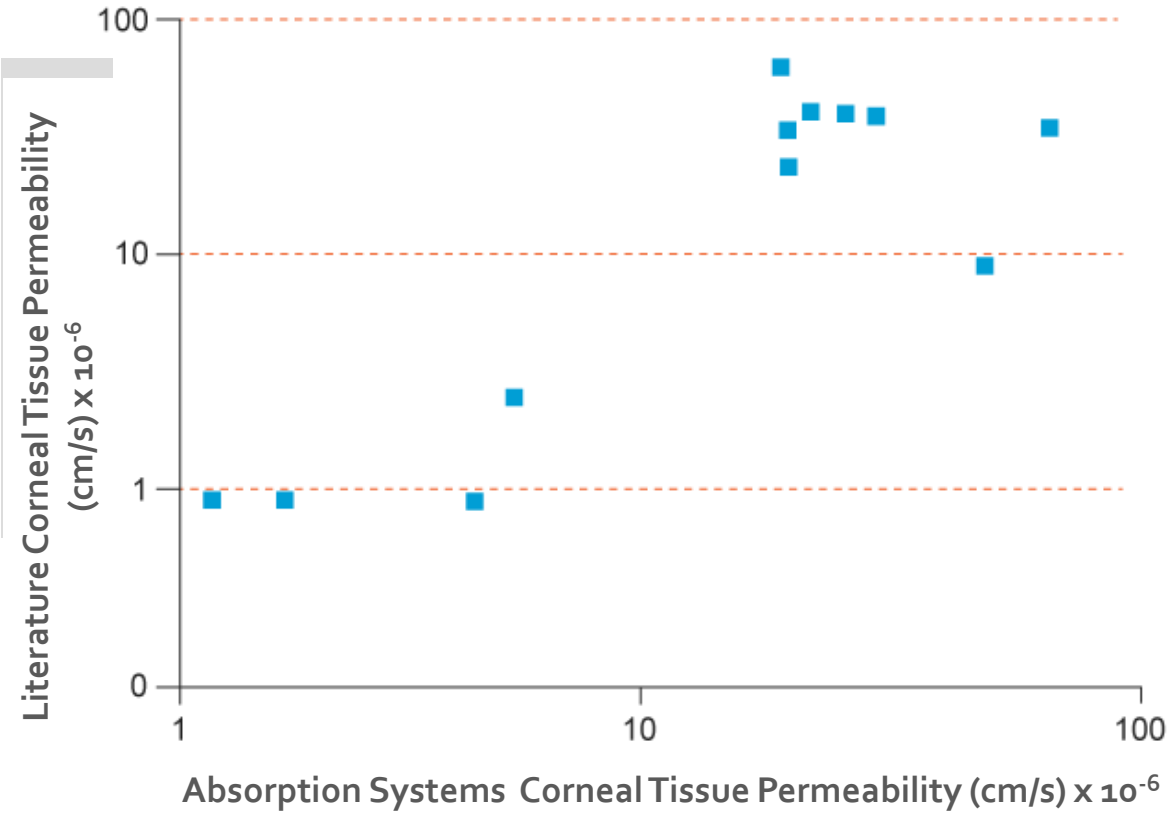
Model Discrimination

Corneal Permeability vs. Literature Values



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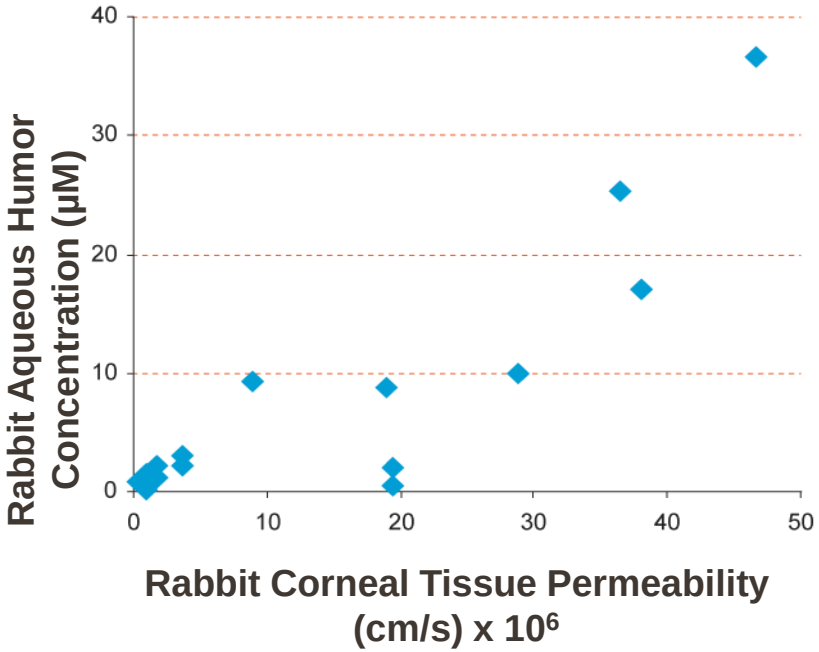
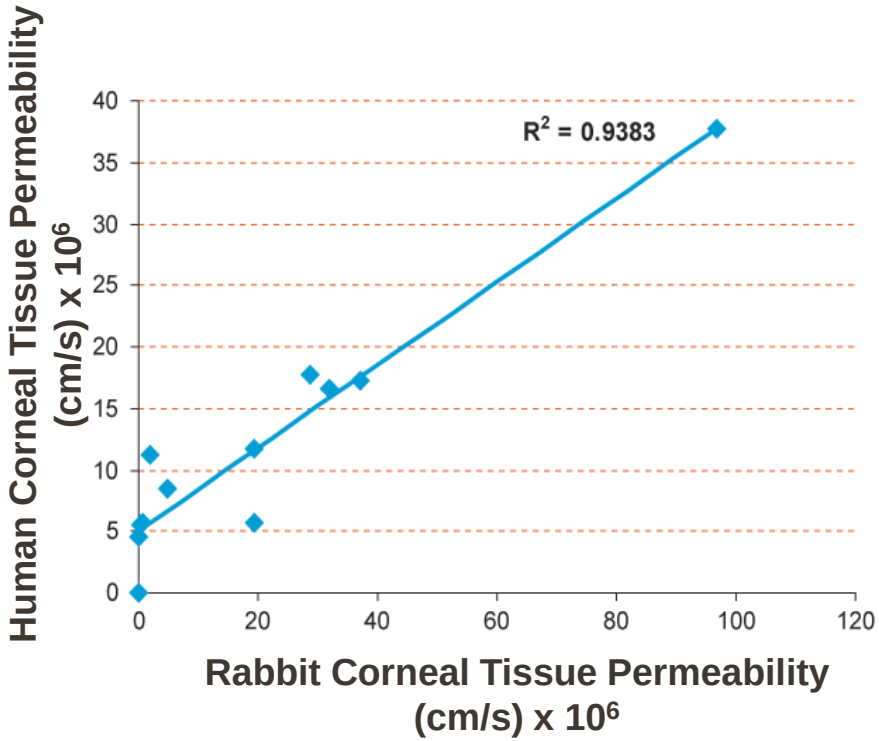
Rabbit vs Human

- *In Vivo* Rabbit and Human Corneal Permeability





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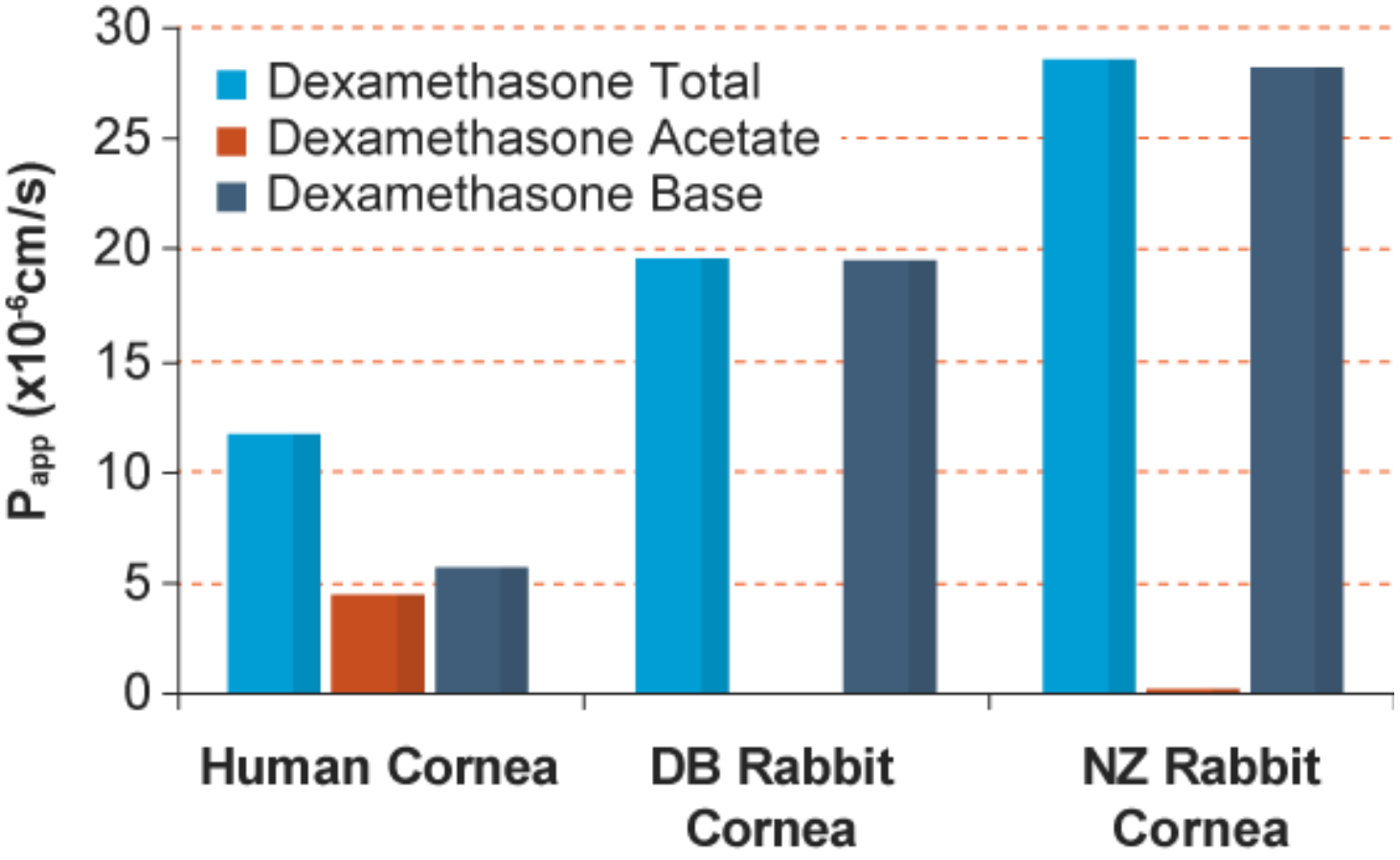
Esterase Activity Across Tissues



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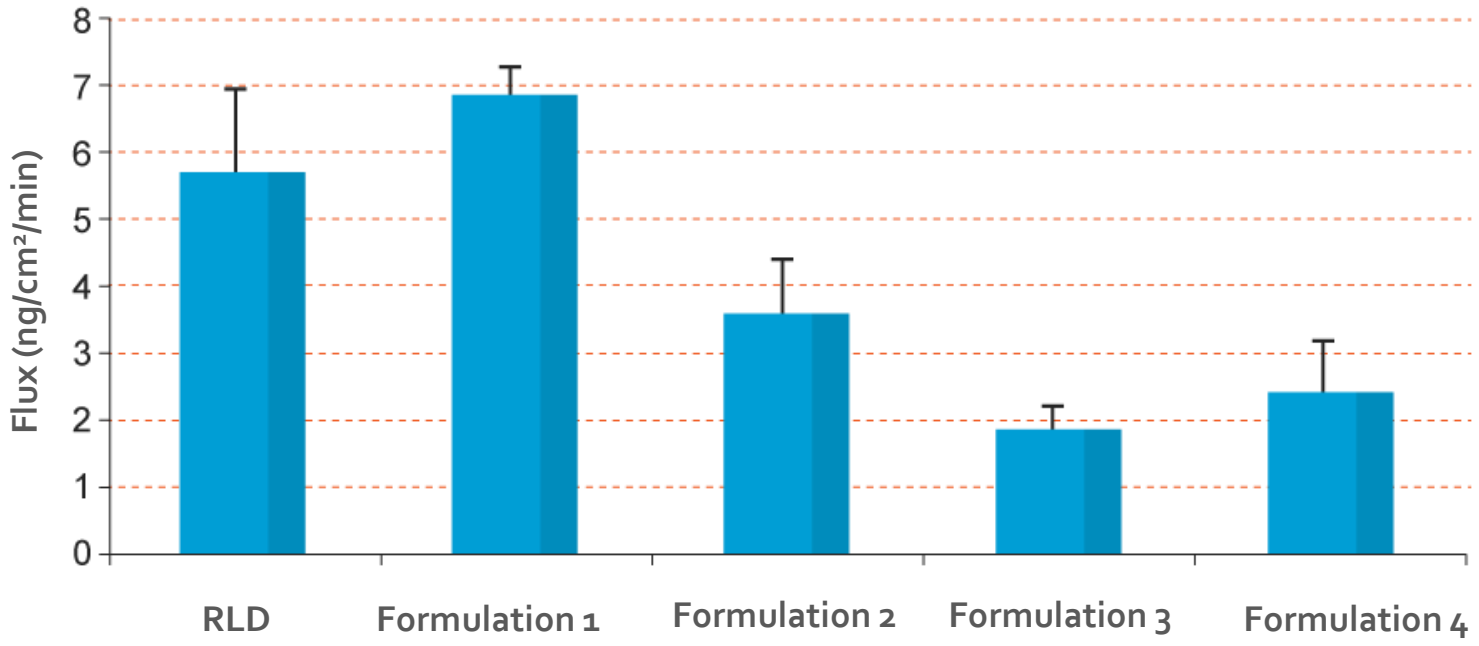
Formulation Comparison

Flux across excised rabbit corneal tissue



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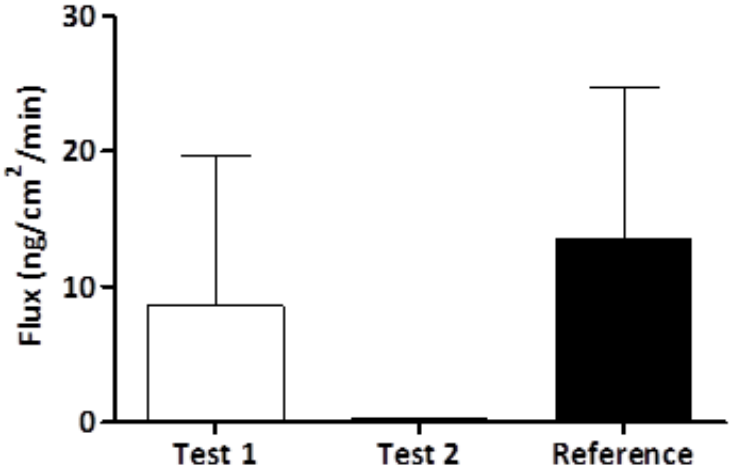
Bimatoprost comparative study



Group	N	Donor	Receiver and Time Points
Test 1	4/group	1.5 mL of each formulation	Plain GBR buffer, sample at T=30, 60, 90, 120, 150 and 180 min
Test 2			
Reference			

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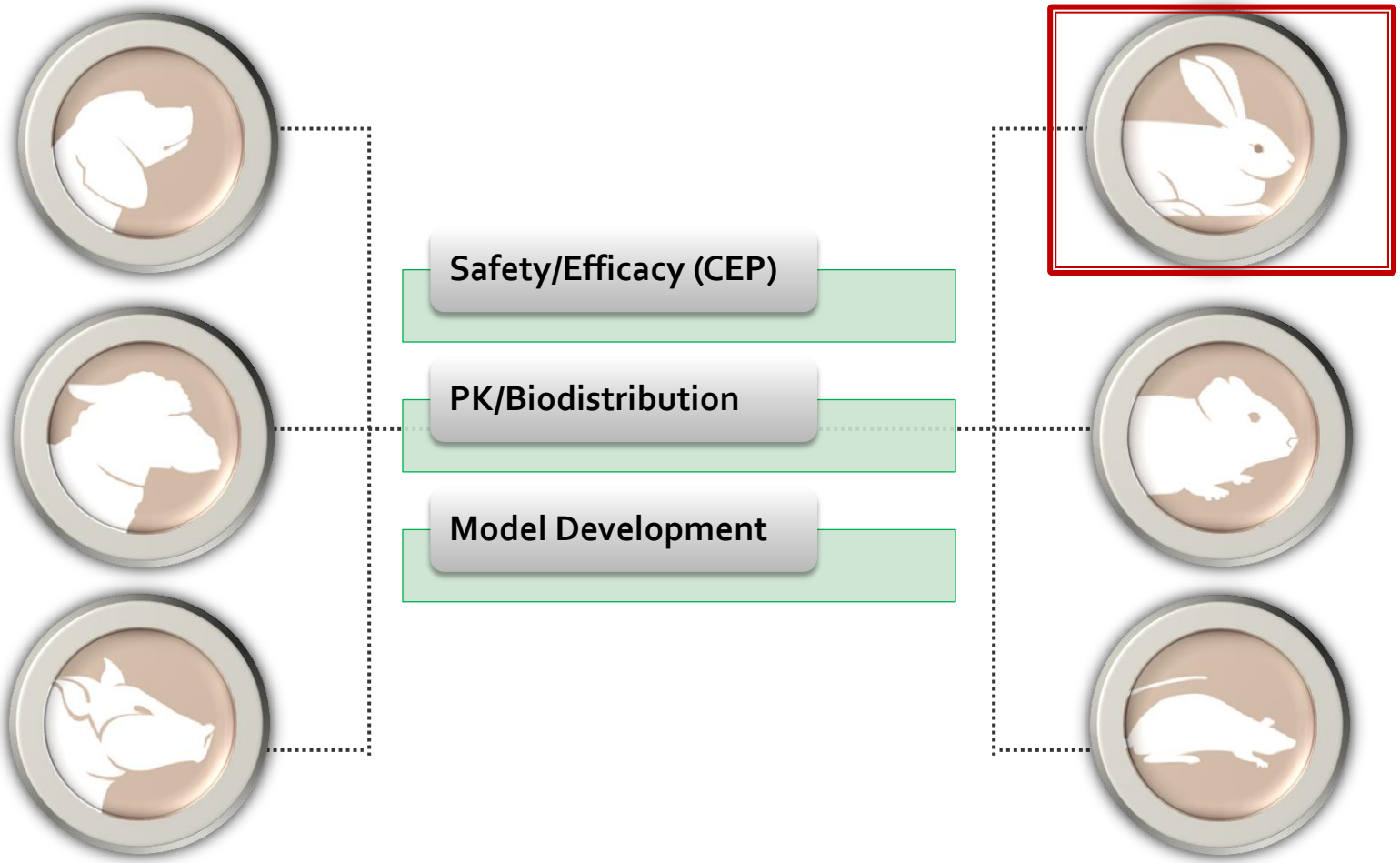
In Vivo Models

- Ocular PK and Biodistribution
  - Male or female NZW (prequalified)
  - N=3 or 5 per group
  - Topical dosing –QD both eyes
  - Sampling schedule: 12- 18 time points
  - Matrices: Plasma, Aqueous humor, Cornea, Conjunctiva, Iris/ciliary body, Retina/choroid and Sclera
- Efficacy/Clinical End Point
  - Glaucoma (IOP measurements)
  - Dry Eye (TBUT, Schirmer)
  - Wet AMD (laser)

Preclinical Models



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Interspecies Comparison

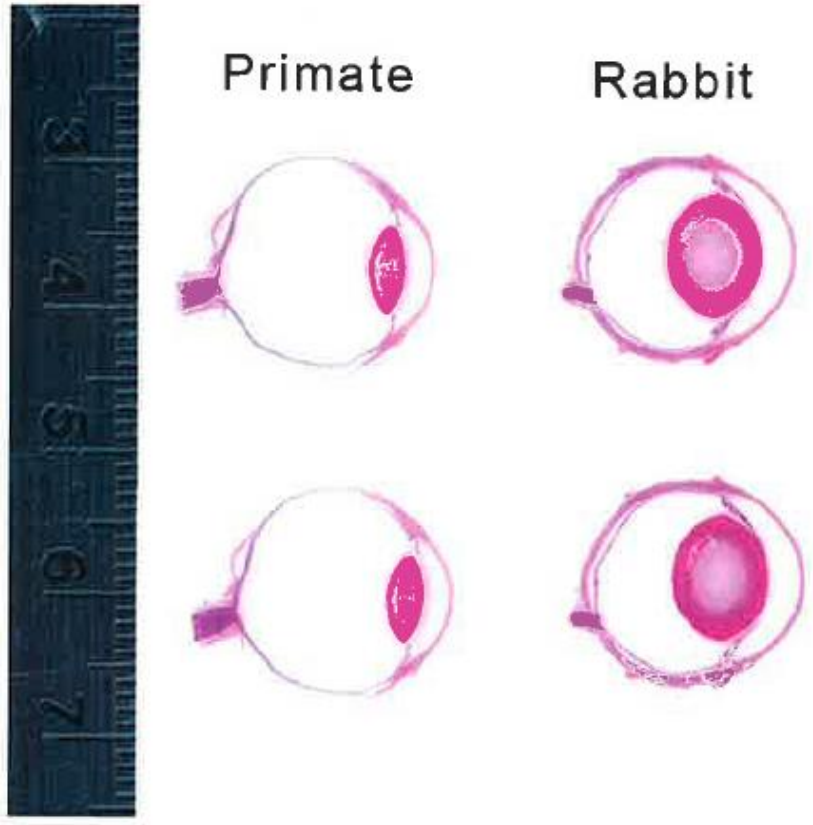
Eye	Radius (mm)	Area (sq mm)
Rabbit[b]	9	1018
Monkey	9.5	1134
Human[a]	12	1810

[a] Tripathi RC, et al., In The Eye, ed. Hugh Davson, 3rd Ed., Academic Press, NY. 1984, Pg 5

[b] Prince JH, et al., Anatomy and Histology of the Eye and Orbit of Domestic Animals. Charles Thomas, Springfield, IL. 1960, pg. 268.

Eye	Vitreous Humor Volume (mL)	Ratio
Rat	0.02	200
NZW Rabbit	1.5	2.7
Cyno Monkey	1.5	2.7
Human	4.0	1.0

Short B (2008). *Tox Path., 36*: 49.



Short B (2008). *Tox Path., 36*: 49.

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Species Differences

Factor	Rabbit	Human
Tear volume (mL)	5-10	7-30
Tear turnover rate (mL/min)	0.6-0.8	0.5-2.2
Spontaneous blinking rate	4-5 times/hour	6-15 times/min
Nictitating membrane	Present	Absent
Lacrimal punctum/puncta	1	2
pH of lacrimal fluids	7.3-7.7	7.3-7.7
Milliosmolarity of tears	305	305
Corneal thickness (mm)	0.4	0.52
Corneal diameter (mm)	15	12
Corneal surface area (cm2)	1.5-2.0	1.04
Ratio of conjunctiva:cornea surface	9	17
Aqueous humor volume (mL)	0.25-0.3	0.1-0.25
Aqueous humor turnover (mL/min)	3-4.7	2-3

Species Selection

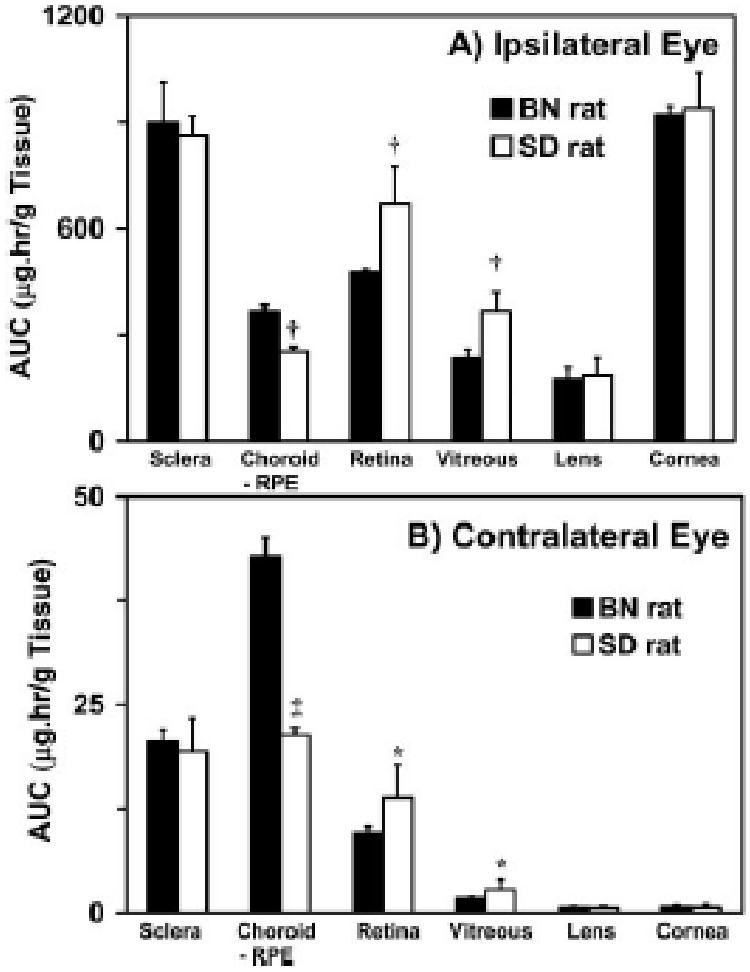
	Human (mL)	Dog (mL)	Rabbit (mL)	Pig (mL)
Anterior chamber	0.3	0.4	0.3	0.3
Posterior chamber	0.06	0.2	0.06	--
Lens volume	0.2	0.5	0.2	0.5
Vitreous volume	3.9	3.2	1.5	3.0

- Typical dose: ~50 uL in the rabbit
- Rabbit – ocular tissue separate
- Rat – pool tissues from both eyes

Effect of Melanin Binding On Ocular Tissue Exposure

- Study conducted in Sprague Dawley albino and Brown Norway pigmented rats
- Celecoxib was dosed in ipsilateral eye only, but tissues were collected in both dosed and undosed eyes

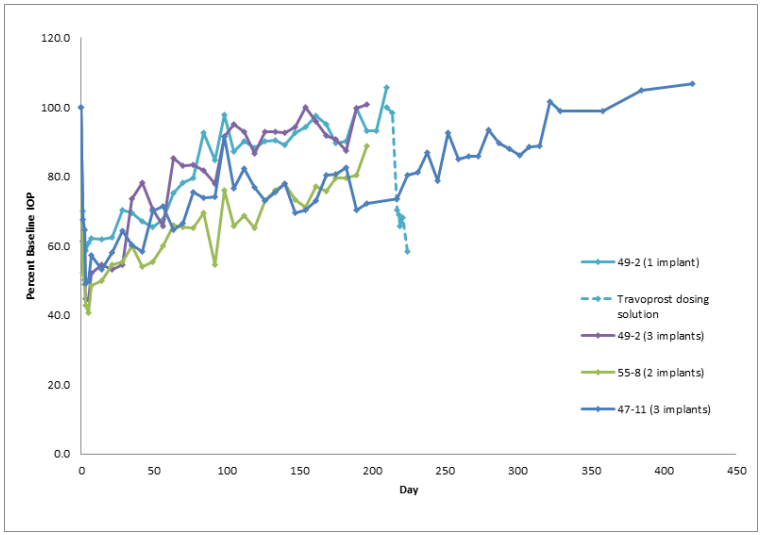
Cheruvu et al., IOVS 2008: 49(1), 333-341

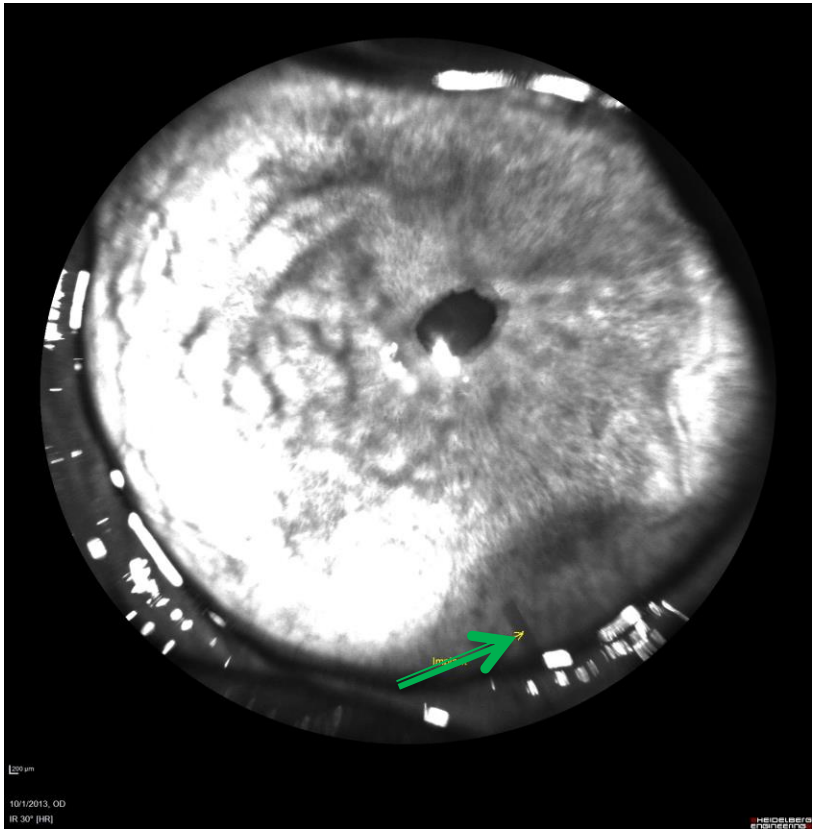


ABSORPTION SYSTEMS®

Clinical End Point -Glaucoma

- Drug eluting device
- Implanted in anterior chamber of Beagle dog
- IOP measurements
- Study Duration: Over 1 year





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Correlation with human data

Reference Compound	Mechanism of Action	Human			Rabbit		
		Used Clinically	Concentration	Response	Used Experimentally	Concentration	Response
β-Blockers: Betaxolol	β-selective adrenergic blocking agent, ↓ aqueous formation	Yes	0.25%, 0.5%, 1%	>-3 mmHg	Yes	0.01%	-3 mmHg
Levobunolol	Non-selective adrenergic blocking agent, ↓ aqueous formation	Yes	0.25%, 0.5%, 1%	-8 mmHg (2 hrs)	Yes	0.5% - 2%	-4 mmHg
						0.25%, 0.5%, 1%-4%, 6%, 8%	-4mmHg (1 hr)
L-Timolol	"	Yes	0.25%, 0.5%	> -5 mmHg	Yes	0.5%, 1%, 2%	
D-Timolol	"	No	0.1%, 0.5%, 1%, 2%	> -5 mmHg (2 hrs)	Yes		-5 mmHg (2 hrs)

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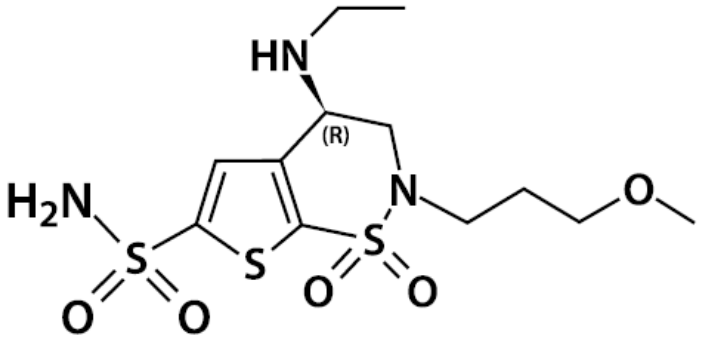
Case Study 1 – Brinzolamide ophthalmic suspension (Azopt®)



- 1% ophthalmic suspension
- Specific, non-competitive, reversible inhibitor of carbonic anhydrase II (CA II)
- Suppresses formation of AH and thereby reduces IOP
- RLD: Azopt® (Alcon), FDA approved in 1998
- No approved generic in the US

ABSORPTION SYSTEMS®

In Vivo PK and Ocular biodistribution

- Comparative ocular distribution study of test formulation versus the reference of brinzolamide
- Dosed in the eyes of male New Zealand White Rabbits for 1, 3, 5, 7, and 14 days
- Ocular compartments analyzed:
  - Cornea and conjunctiva have the most direct contact with the drug suspension after topical administration.
  - Aqueous humor shows the levels of the test article that passed into the anterior chamber.
  - Iris/ciliary body to see how much test article reached the tissue that is the site of its pharmacodynamic action

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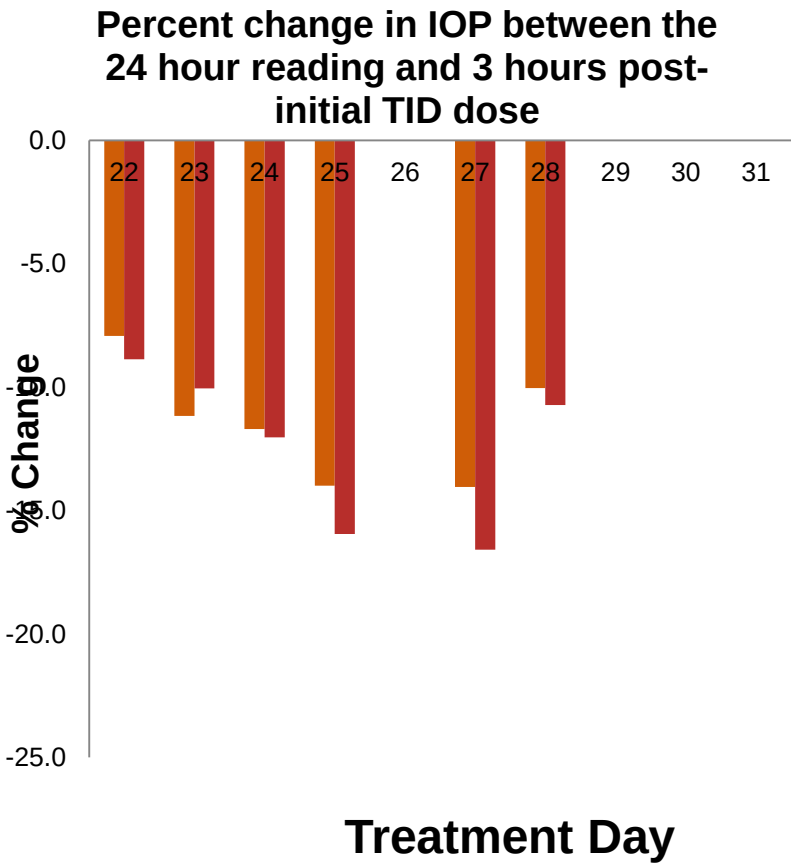
Clinical End Point

- Steroid Induced Hypertensive Model
- Model Induction: 2-3 weeks
- Daily IOP measurements



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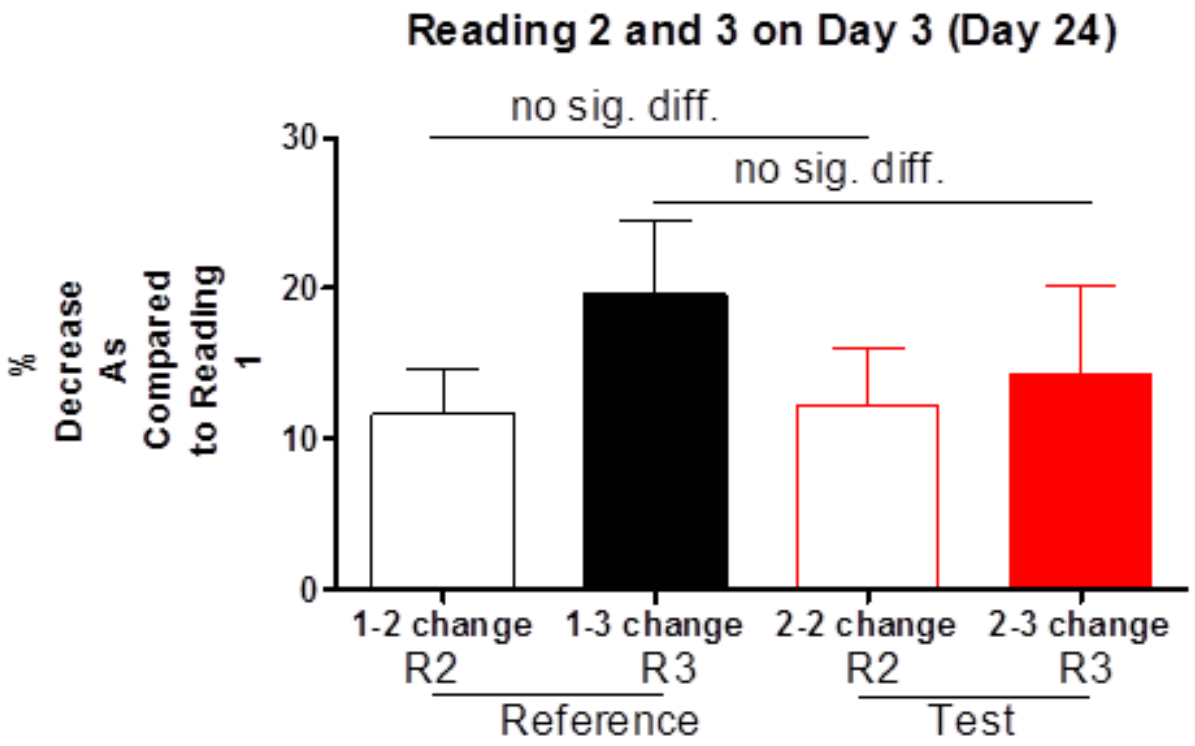
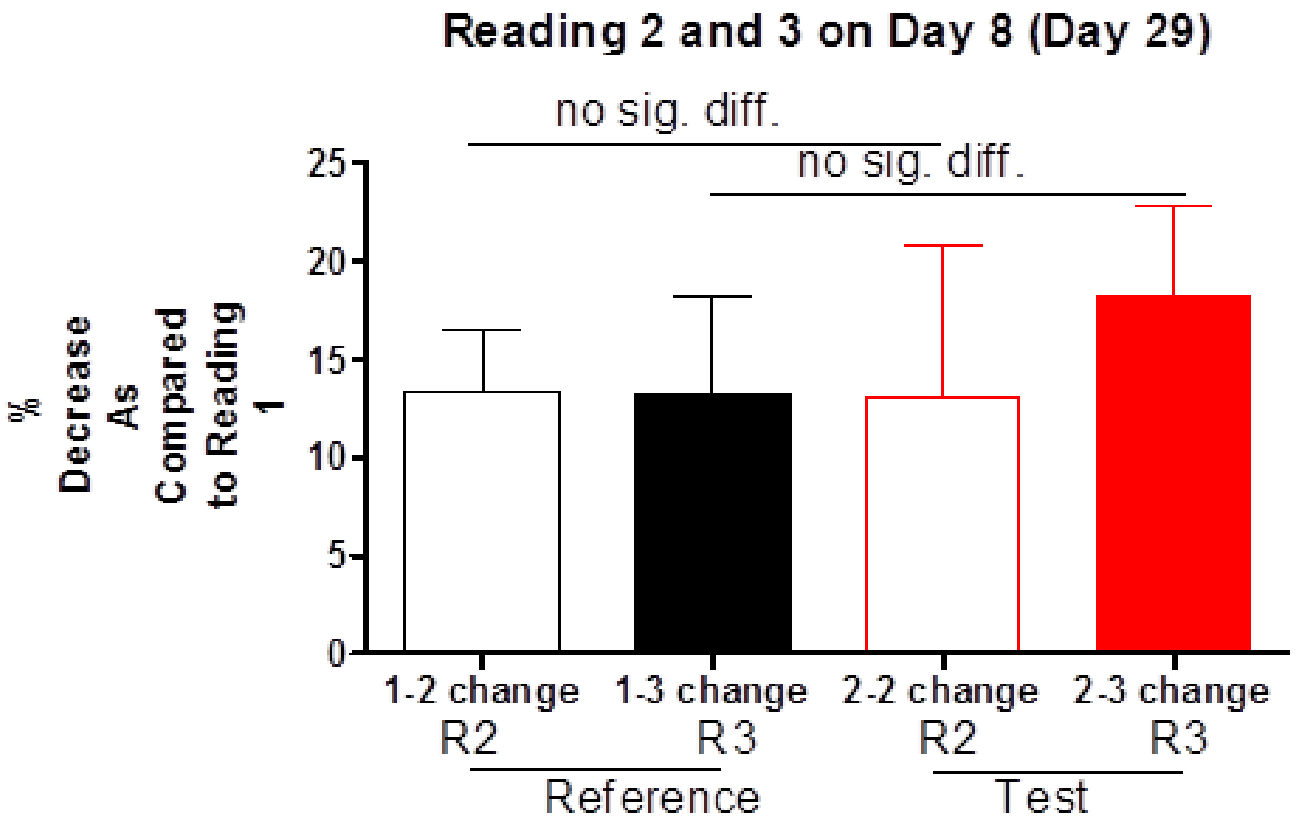
Glaucoma - Reference versus test

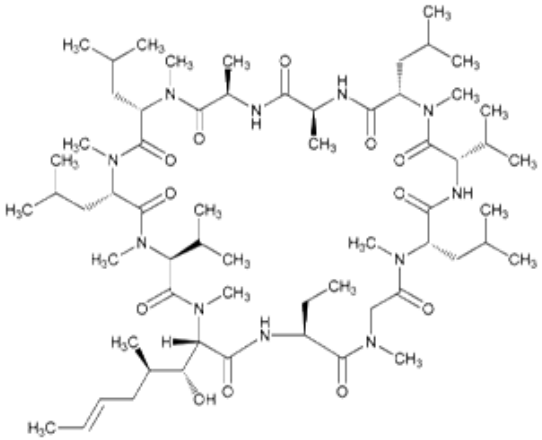


ABSORPTION SYSTEMS®

Reference versus test

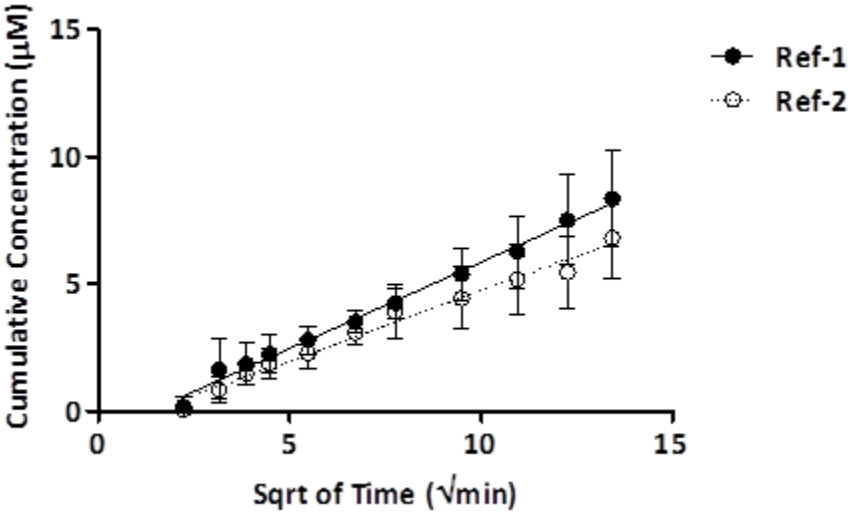


Case Study 2 – Cyclosproine ophthalmic emulsion (Restasis®)



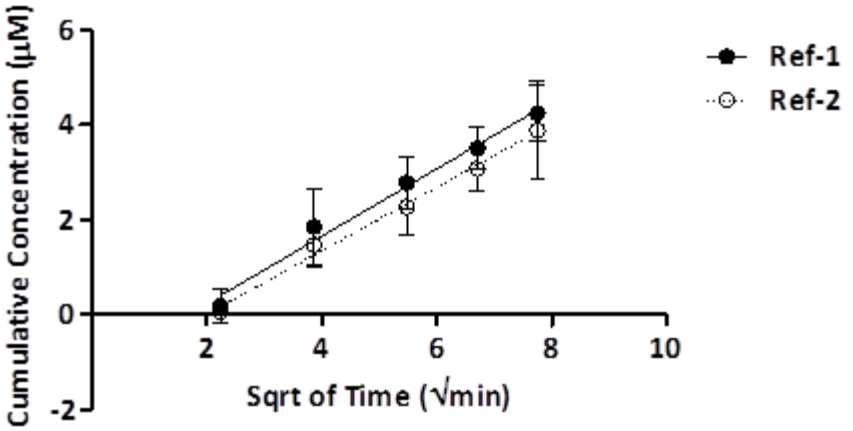
- 0.05% emulsion
- Launched by Allergan in 2003
- First, and still the only FDA approved prescription drug for chronic dry eye disease
- Just 2 drops a day allows to "attack" the underlying inflammatory characteristic of the disease and allow patients to produce natural tears

IVRT Profiles – Reference versus Reference



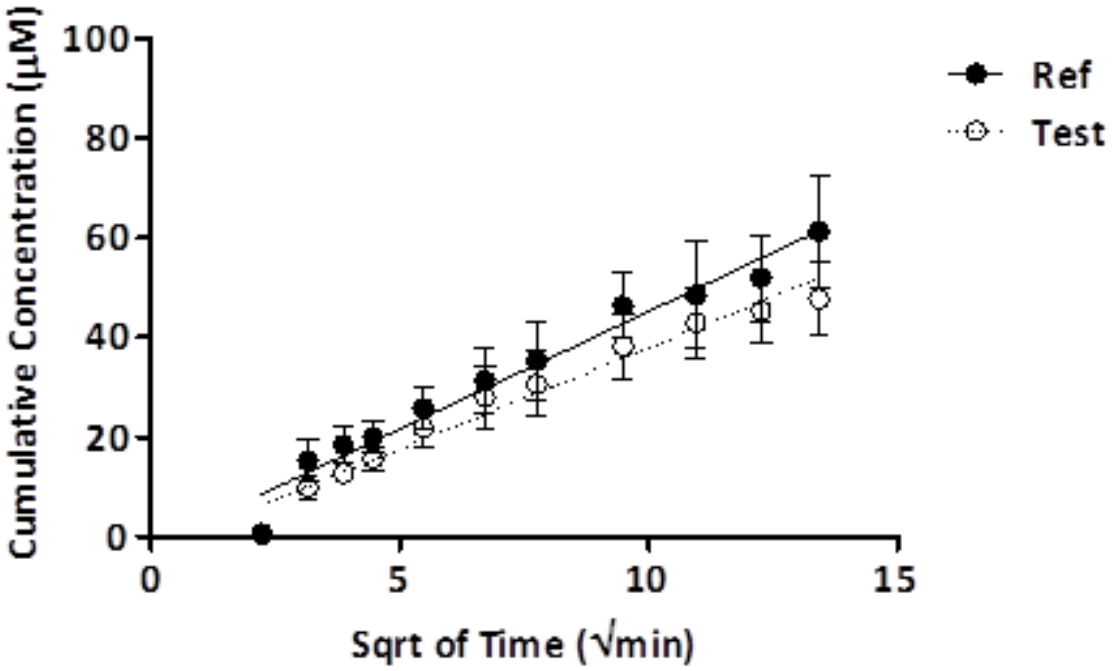
IVRT Profiles from Ref-1 and Ref-2 (Up to 180 min) (Mean ± SD)

IVRT Profiles from Ref-1 and Ref-2 (Up to 60 min) (Mean ± SD)



ABSORPTION SYSTEMS®

IVRT Profiles – Test versus Reference



IVRT Profiles from Test and Reference(Up to 60 min) (Mean ± SD)

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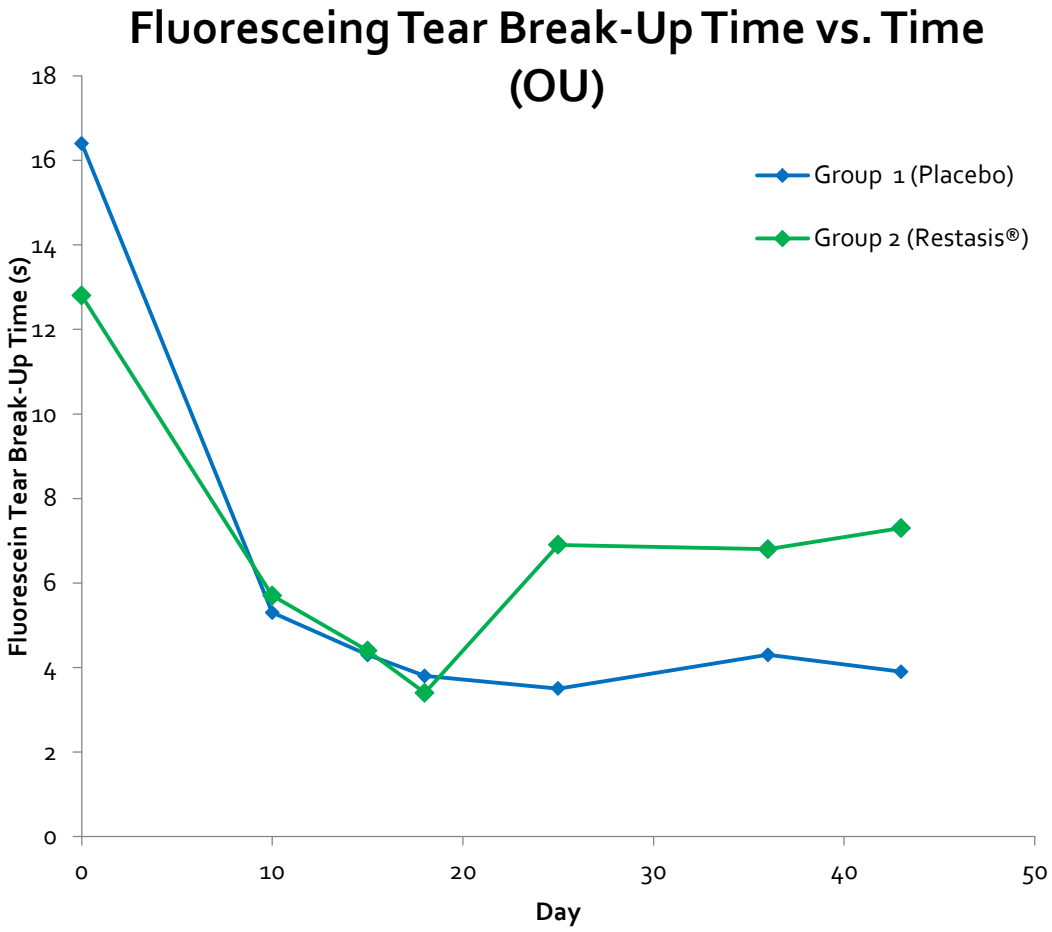
Clinical End Point -Dry Eye / KCS

- Topical administration of Atropine
- Increased airflow & low humidity (<20%)
- Fluorescein Tear Breakup Test
- Schirmer Tear Test



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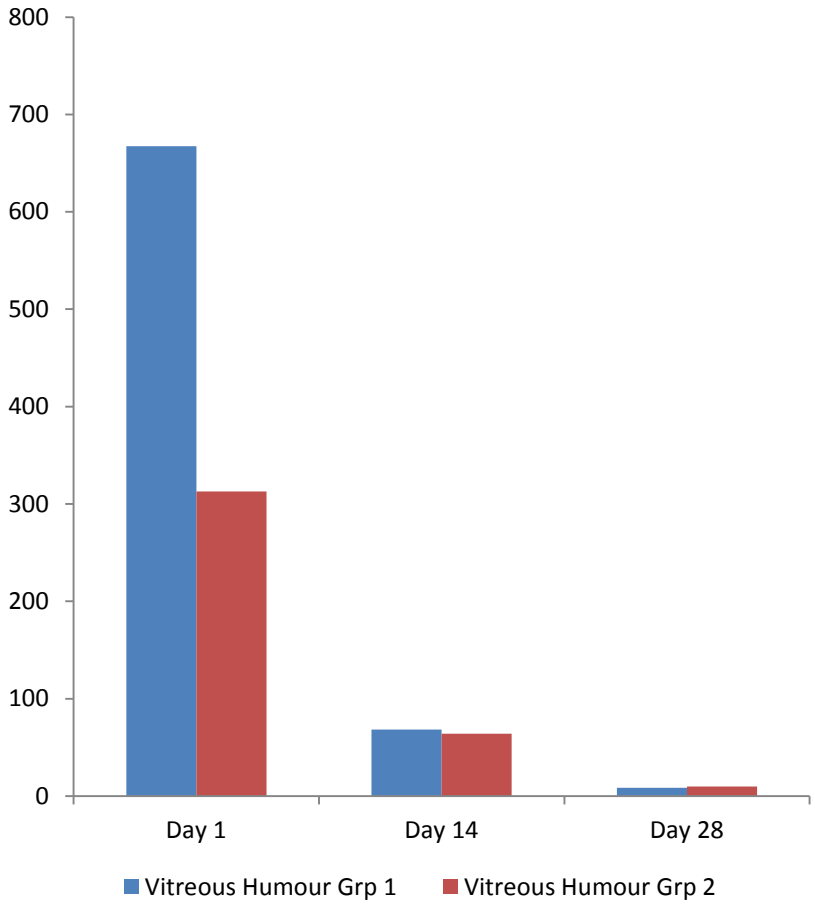
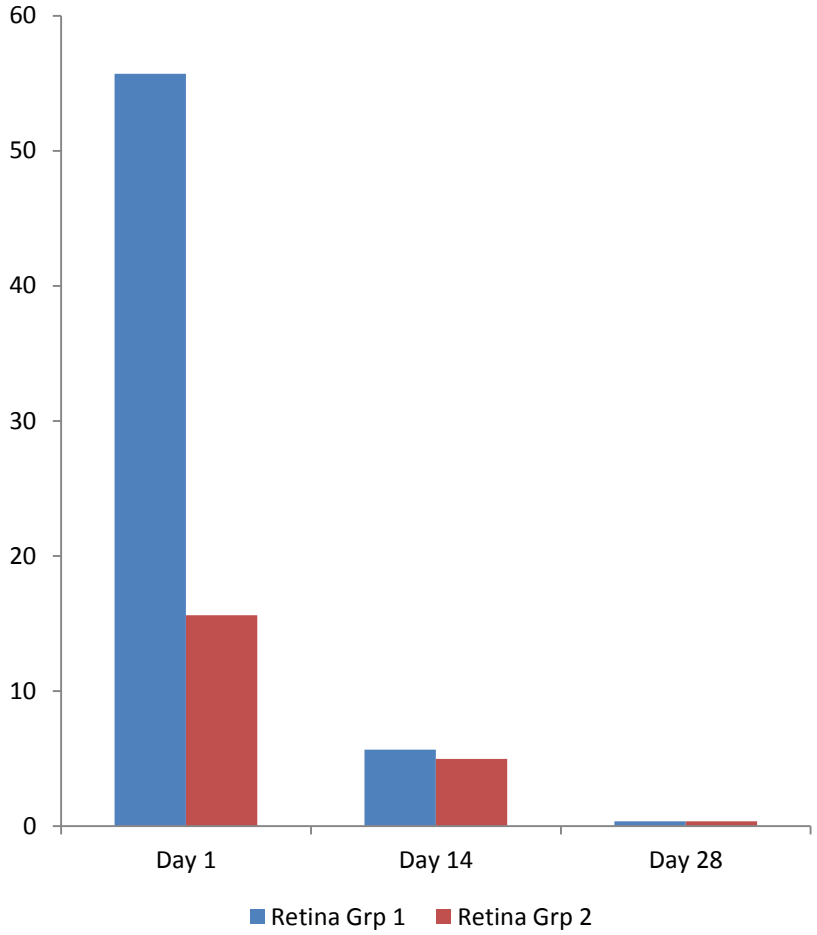
Avastin/Lucentis

- Treatment for age related macular degeneration (wet/neovascular form of AMD)
- Anti-VEGF therapies
- Intra-vitreal injection

Ocular Bio-distribution

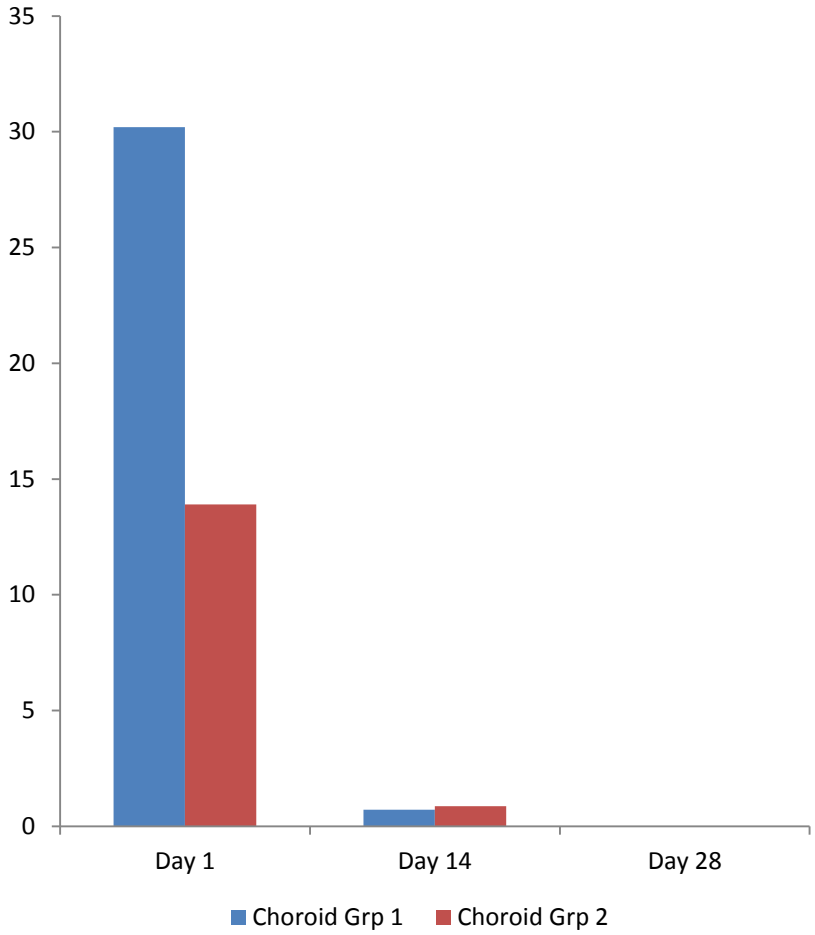


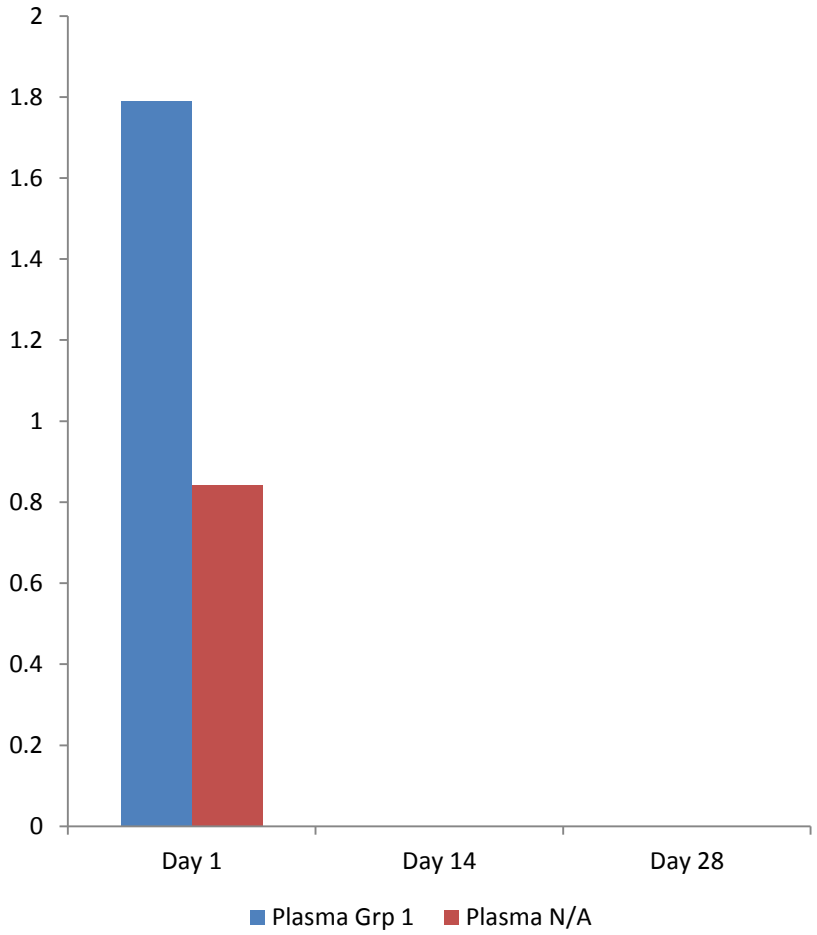


Y axis -Concentrations: µg/mL

ABSORPTION SYSTEMS®

Ocular Bio-distribution



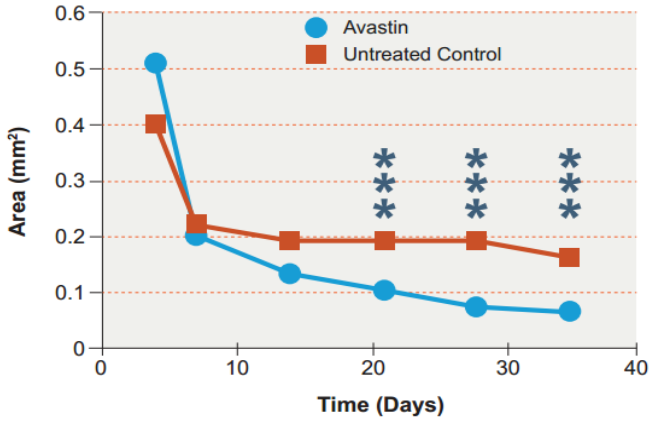


Y axis - Concentrations: µg/mL

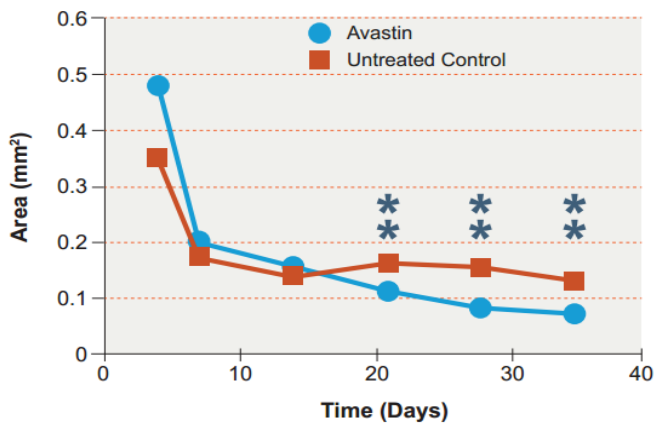
ABSORPTION SYSTEMS®

Clinical End Point -Wet AMD

- Laser Induced Choroidal Neovascularization (CNV)
- Analysis of vascular leakage via Fluorescein Angiography



OD: right eye
Overall combined mean for each group per day.
*p<0.05 **p<0.01 ***p<0.001

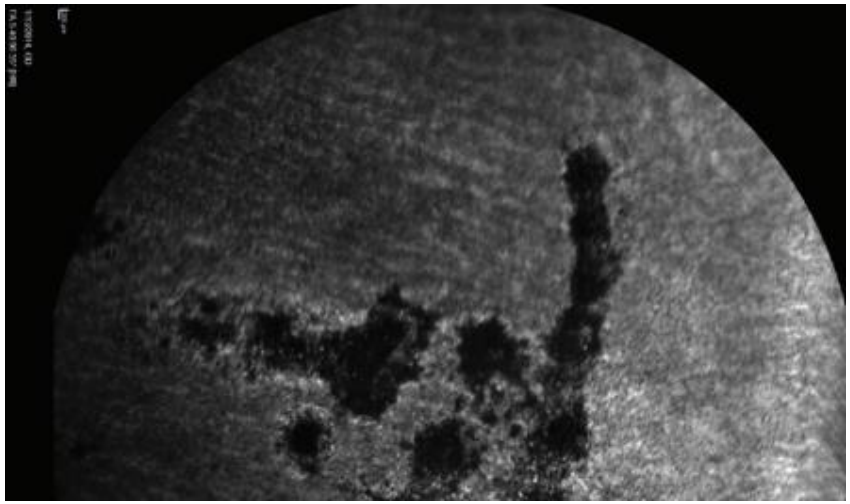


OS: left eye
Overall combined mean for each group per day.
*p<0.05 **p<0.01 ***p<0.001

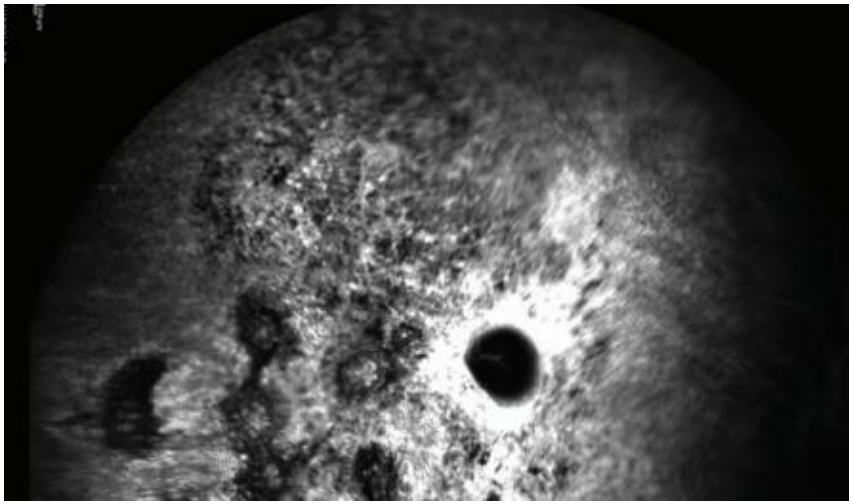
ABSORPTION SYSTEMS®

Wet AMD

- Fluorescein angiography



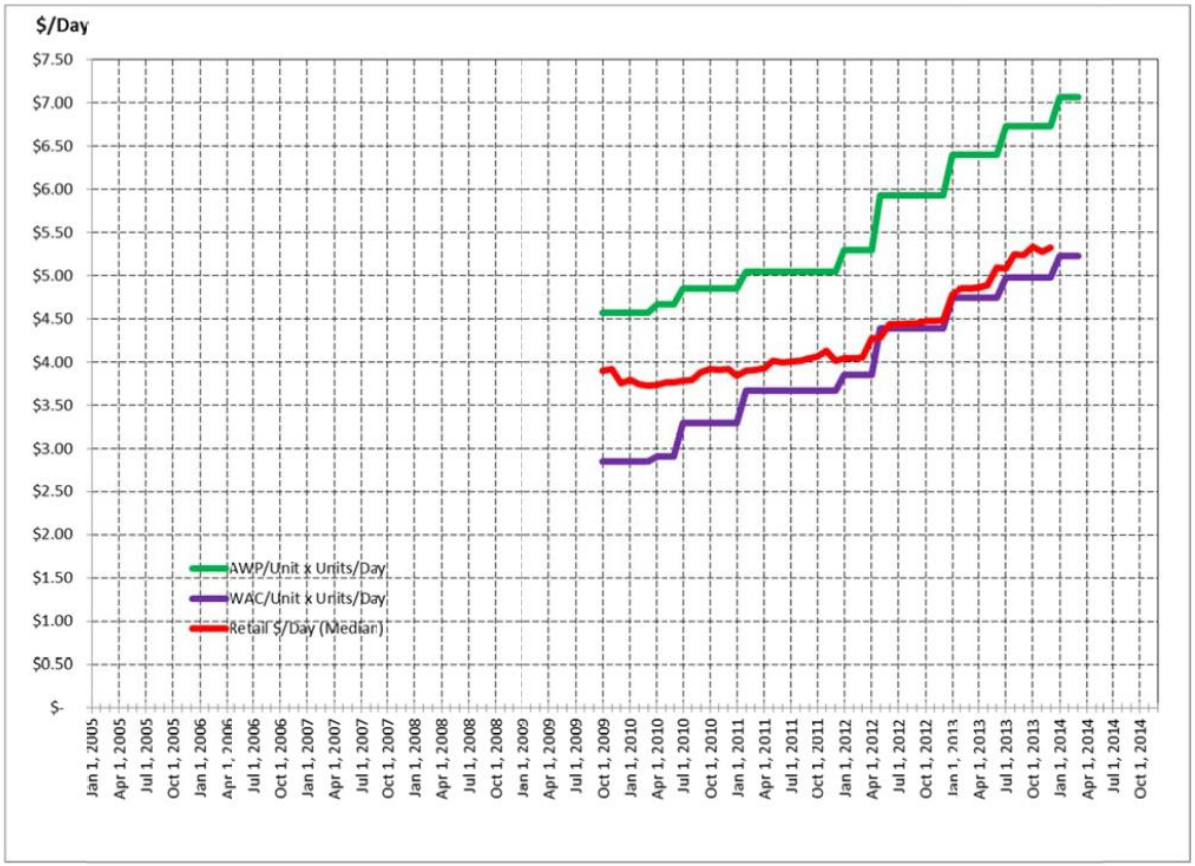
Positive Control Avastin



Control Treatment

Patient Perspective: Price per day of therapy

Brimonidine tartrate 0.15% ophthalmic solution (Sandoz): 2005 - 2013



Schondelmeyer S, 2014

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Patient Perspective