Translating Novel Drug Delivery Technologies to Ophthalmic Products – Unique Opportunity for Collaboration Between Academia and Pharmaceutical Industry

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Missouri Life Sciences Summit

March 9, 2010

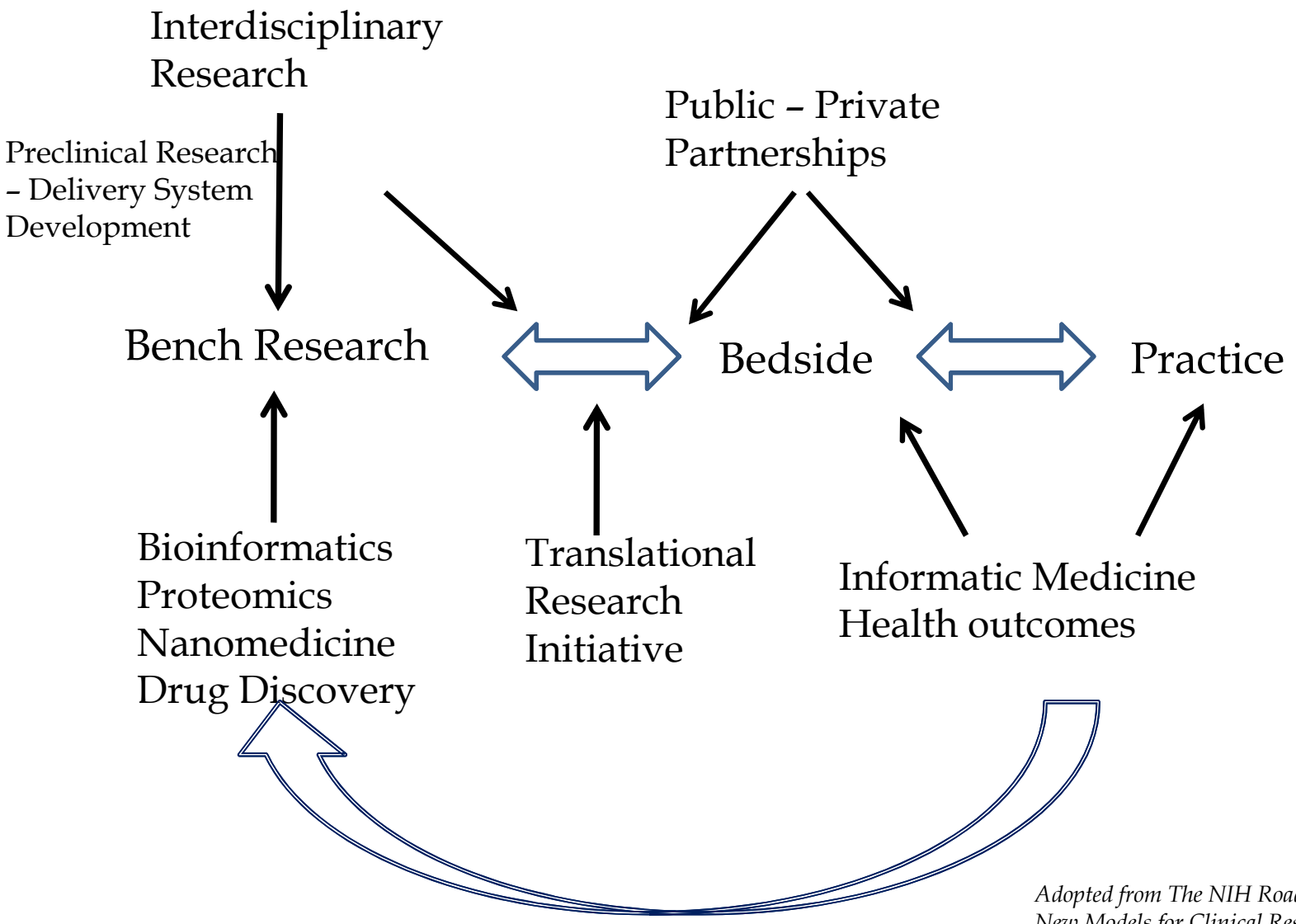
Translational Research

- Current developments in basic discovery sciences have not been mirrored by the same level of progress in understanding the clinical basis of disease and ultimately the development of novel effective therapies. This can be improved by applying translational research throughout the late-stage discovery and exploratory development stages of drug development.

- The American Physiological Society (APS) has defined translational research as 'the transfer of knowledge gained from basic research to new and improved methods of preventing, diagnosing, or treating disease, as well as the transfer of clinical insights into hypotheses that can be tested and validated in the basic research laboratory'.

Ref: *Damian O'Connell and David Roblin; Translational research in the pharmaceutical industry: from bench to bedside;Drug Discovery Today, Volume 11, Issues 17-18,2006, Pages 833-838 .*

Translational Research



Adopted from The NIH Roadmap: envisioning New Models for Clinical Research

Translational Research

- It is a two way process of iterative learning from experimentation. Within the context of the biopharmaceutical drug industry, translational research constitutes the cross-line preclinical and clinical research strategies and experiments that bridge the scientific and operational gaps between *basic* research (bench) and early-stage clinical studies (bedside).

- The integration of this bi-directional thought process can be extremely powerful. An example from bench to bedside includes development of clear aqueous drops of a calcineurin inhibitor for treatment of dry eye syndrome.

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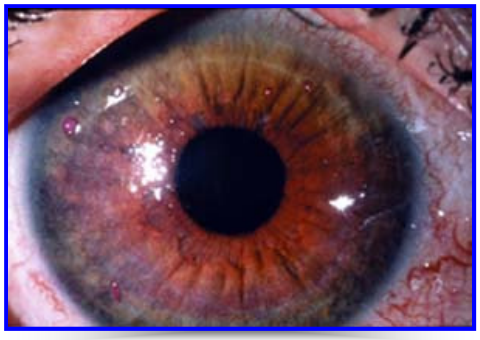
Dry Eye: A Large and Growing Medical Problem



- Chronic Inflammation of the Tear-Producing Lacrimal Gland
- Break-Up of Tear Film: Blurred Vision, Corneal Damage, Pain
- Risk Factors: Lasik, Menopause and Autoimmune Diseases

Significant Medical Need

- **40% of All Ophthalmologist Visits for Dry Eye**
- **10M in U.S./EU Affected**
- **Sjogren's (Dry Eye, Dry Mouth, Inflamed Joints) 1% of Population**
- **Painful, Debilitating Condition**

Current Therapies Fall Short

- **Palliative: OTC Artificial Tears**
- **Restasis® (0.05% CsA emulsion)**
  - Modest Efficacy
  - Irritating/Burning Sensation
  - Poor Compliance

Voclosporin – a Next Generation Calcineurin Inhibitor

Background

- Calcineurin Inhibitors: Down-Regulate Pro-Inflammatory TH-1 Cells
- Oral Formulation
  - Uveitis (Phase III, Lux Biosciences, N= 557)
  - Psoriasis (Phase III Isotechnika; N = ~1,000)
  - Renal Allografts (Phase IIb Isotechnika; n = 334)
- Topical Ophthalmic Formulation
  - Dry Eye, Blepharitis, Conjunctivitis (Lux Biosciences)

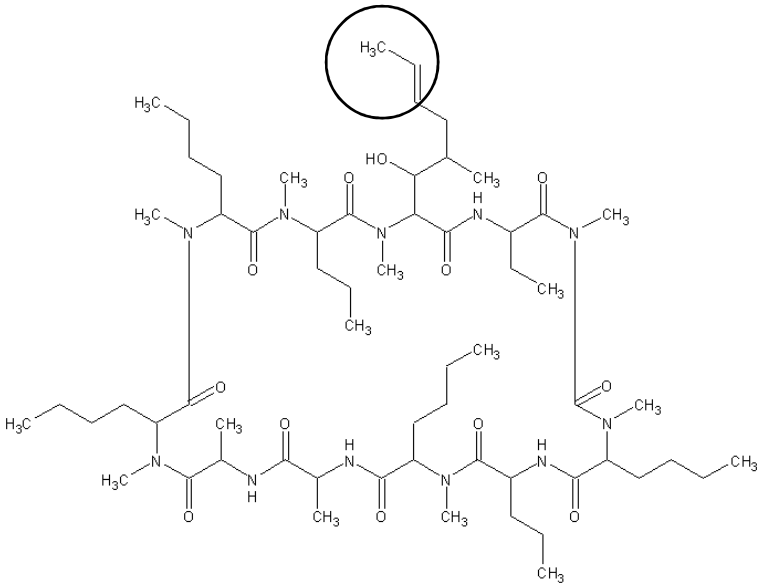
FEATURES

- Rationally Designed Novel Molecule
- 4x Greater Potency vs. Cyclosporine A
- Predictable Dosing
- Extended Therapeutic Window

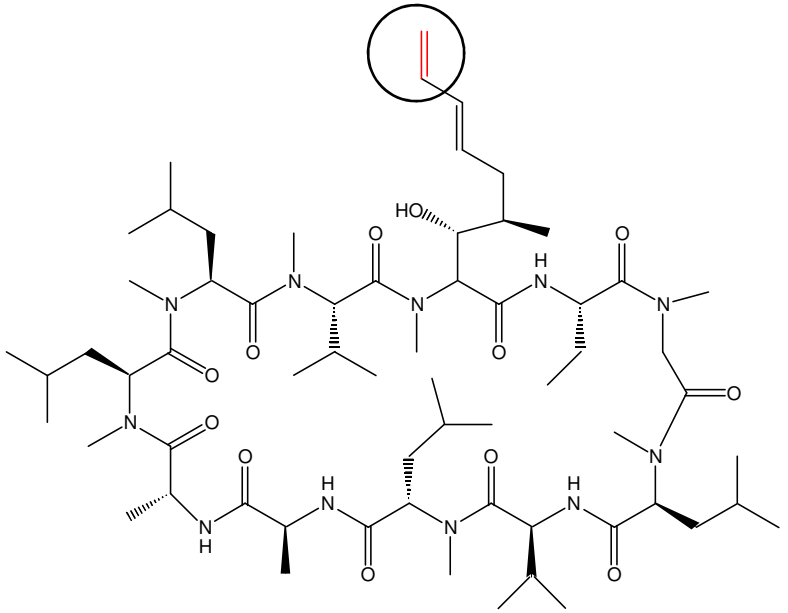
EXPECTED BENEFITS

- High Efficacy and Good Safety: Suitable for Chronic Use (Oral Form)
- High Efficacy and Tolerability, Good Compliance (Topical Form)

Structures: Cyclosporine A & Voclosporin

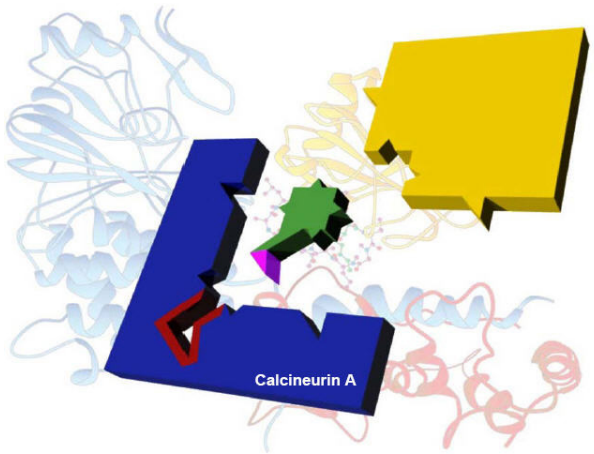


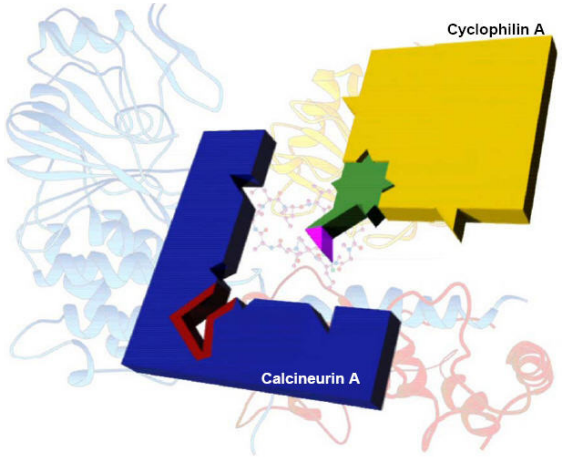
Cyclosporine A

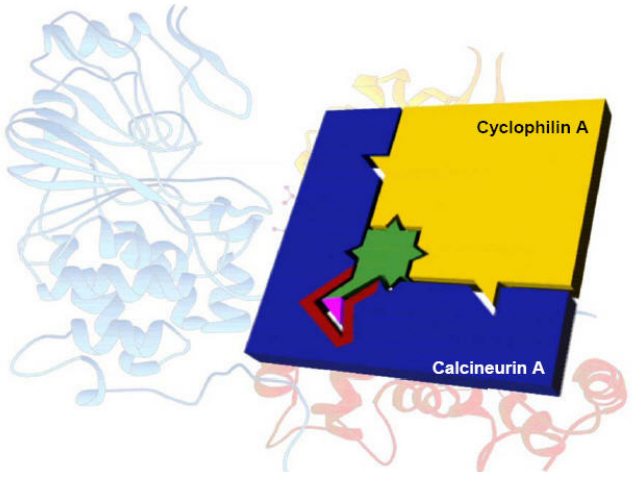


Voclosporin

Voclosporin: ***Higher*** affinity to Calcineurin than CsA







Calcineurin

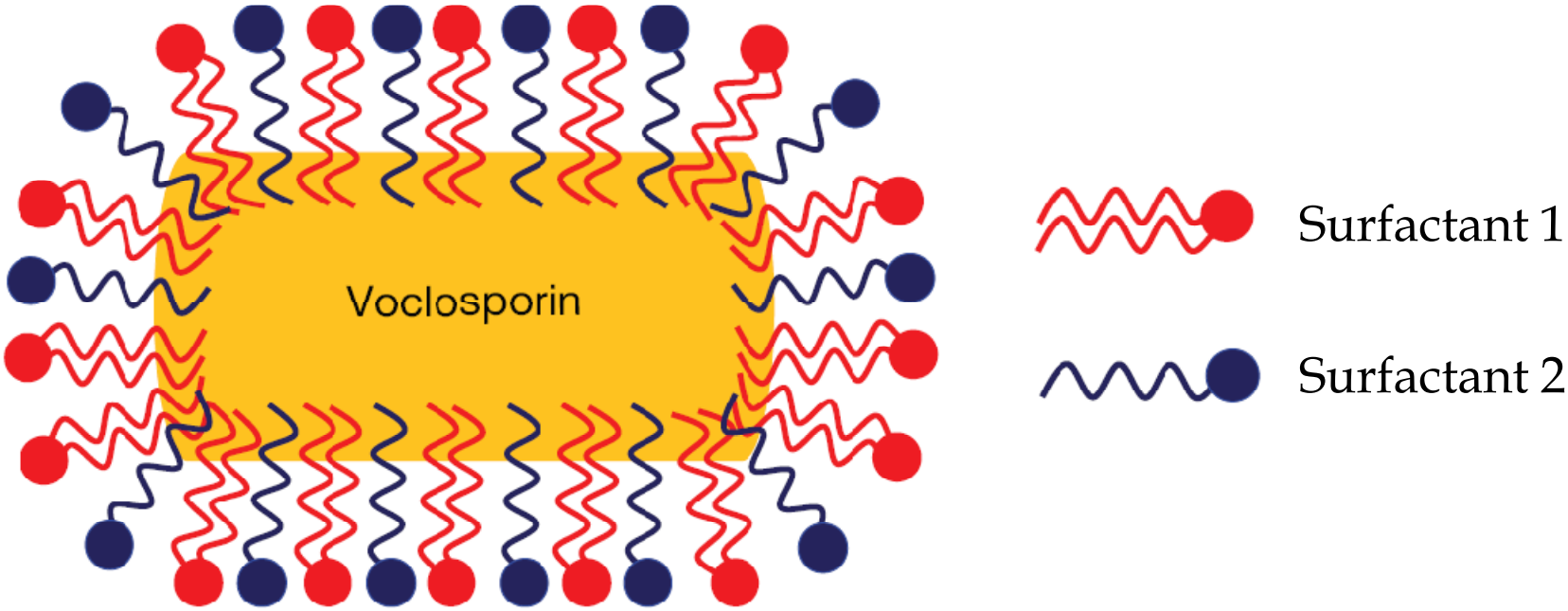
Cyclophilin A

Voclosporin

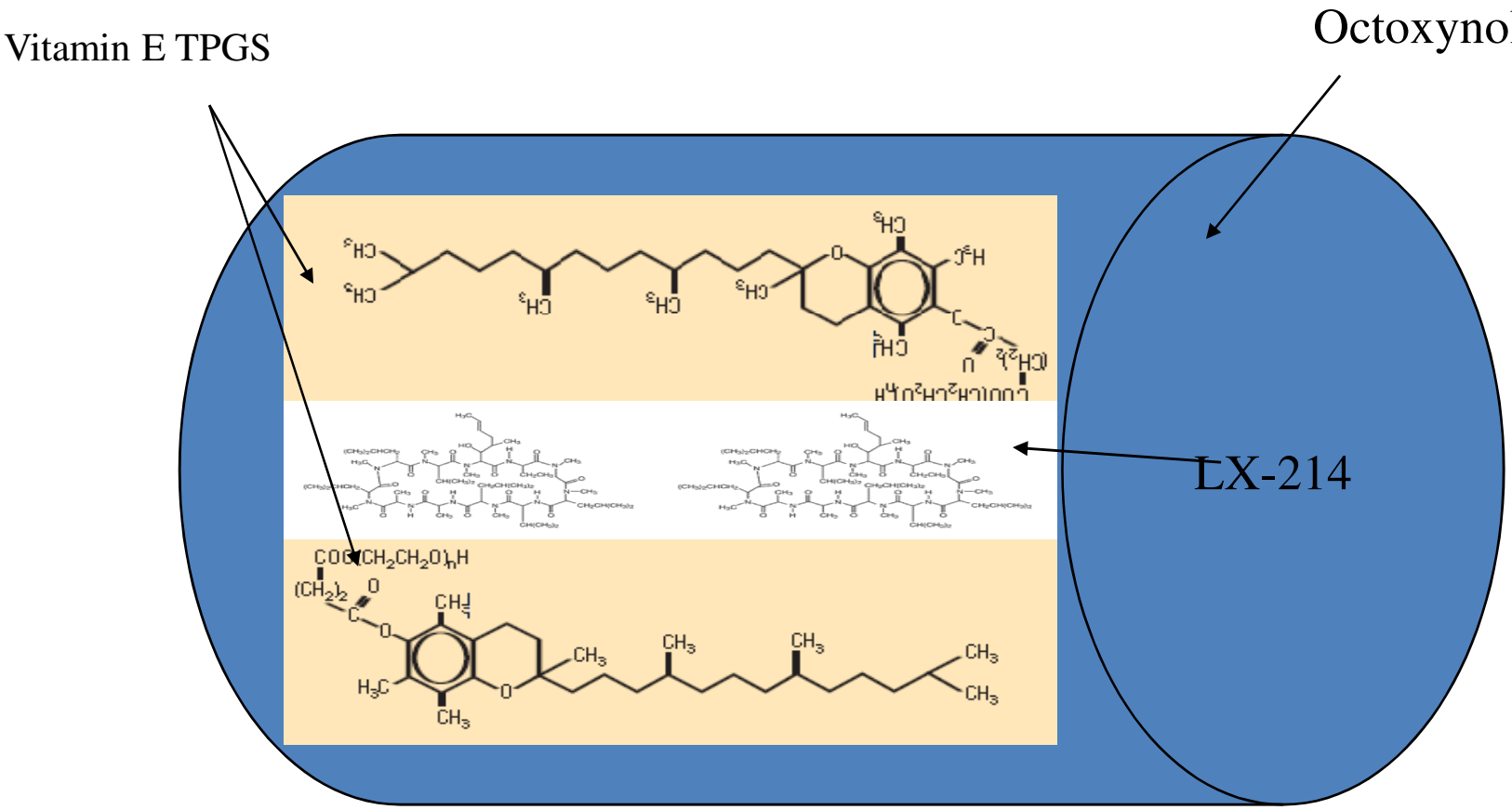
Cyclosporine A

Latch Region

Mixed NanoMicellar Formulation: Voclosporin



Nanomicellar structure of formulation Voclosporin



Voclosporin: Proprietary Topical Product with Best-in-Class Potential

- **Proprietary Topical Formulation: Clear Solution**
- **Easy to Use: Eye Drop, Single Use Vial, Patient Administered**

Target Profile vs. Restasis

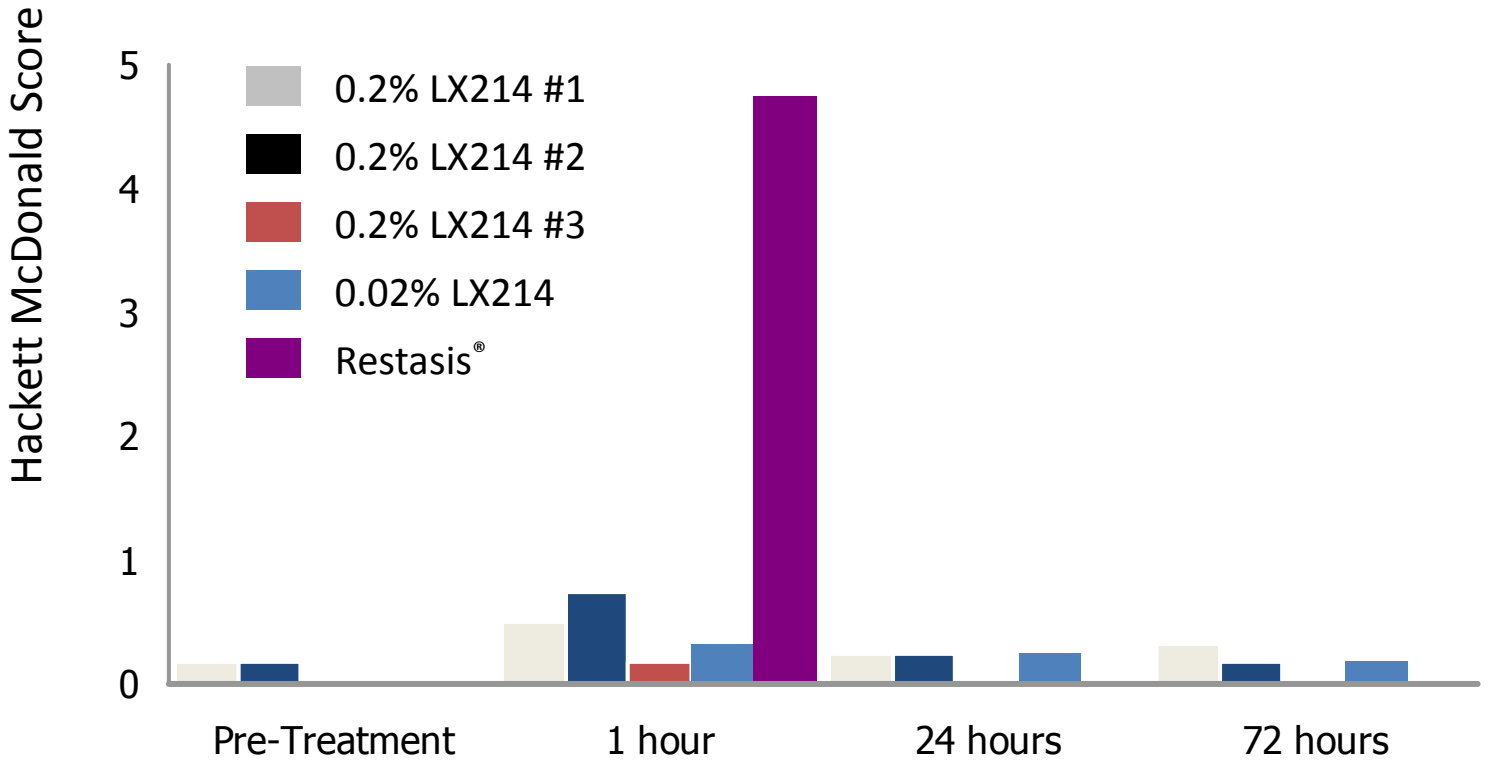
- **High Tissue Concentration of Next Generation Calcineurin Inhibitor: Expect Better Efficacy**
- **Less Irritating than Restasis® in Animal Eyes: Expect Better Tolerability**
- **Potential for QD Dosing Based on pK Data: Expect Better Compliance**

Voclosporin Pilot Tolerability Study Design

- Repeat Dose Tolerability Study
  - New Zealand white Rabbits (3-4 KG)
  - One drop (50 ul) of a LX214 formulation or Restasis® per eye
  - LX214 formulations tested:
    - 0.2% LX214 with varying amounts of excipients (total of 12 formulations tested: 3 Groups of 4 formulations each)
    - 0.02% LX214 with varying amounts of excipients (total of 4 formulations tested)
    - n=3 eyes tested per formulation (Total n=12 eyes/group x 4 groups = 48 eyes)
    - N=4 eyes tested for Restasis®
  - Treated every 30 minutes for 4 treatments
  - Hackett-MacDonald microscopic ocular examination and scoring done at 1, 24, & 72 hours after treatment

Voclosporin: Not Irritating to the Eye

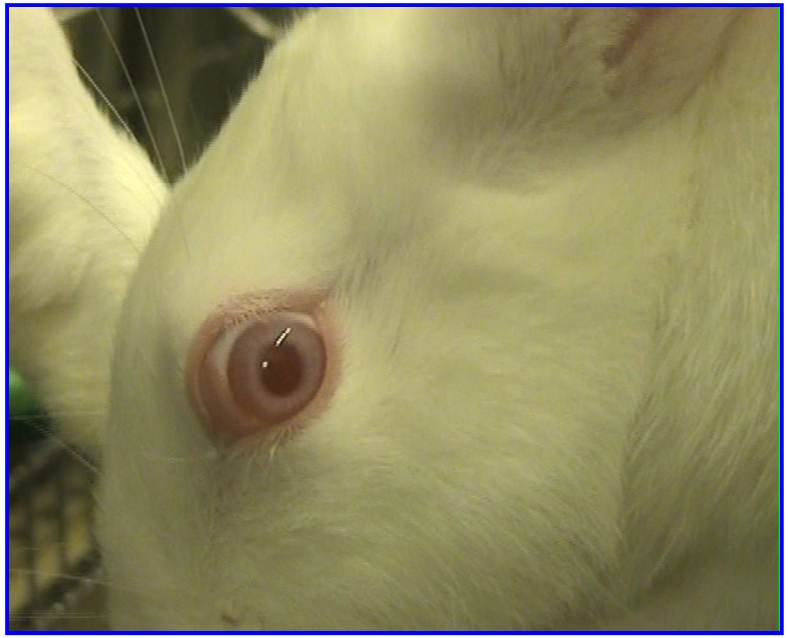
Mean Microscopic Ocular Exam Scores (NZW Rabbits, N=48 Eyes)



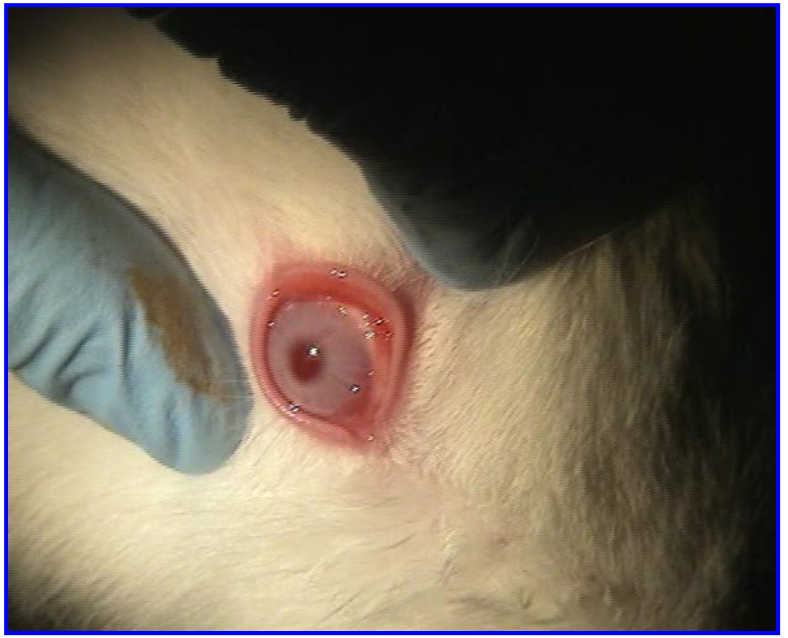
1-Day Repeat Dose Ocular Tolerability Test: Voclosporin vs. Restasis®

Four Applications (50 µL Application per Eye), Applied 30 Min Apart

LX-214

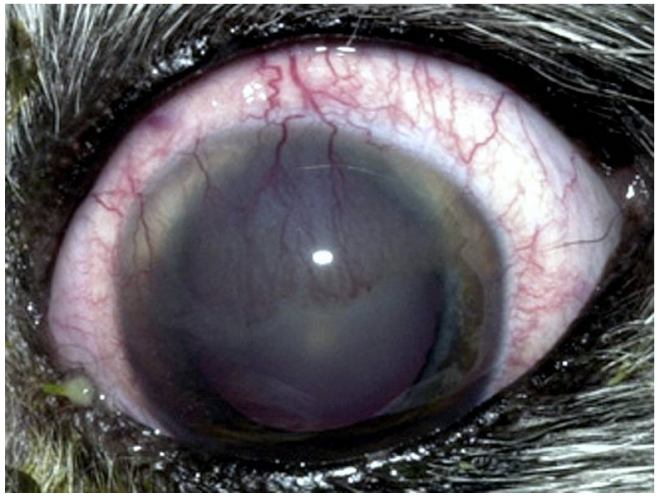


Restasis®

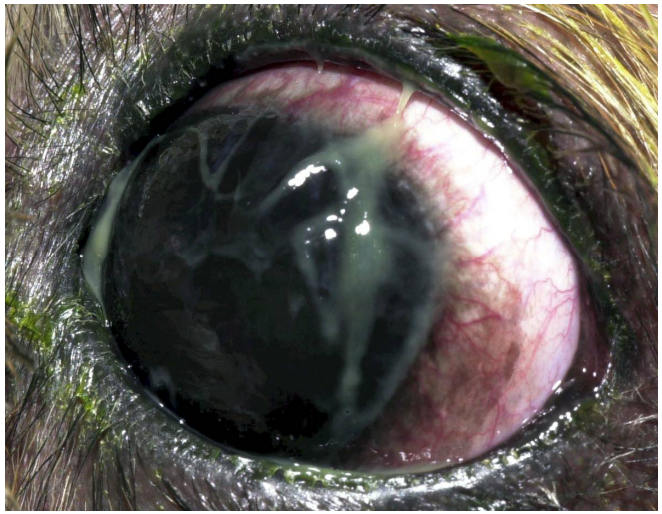


Voclosporin Pilot Efficacy Study
Canine Keratoconjunctivitis Sicca

- Severe dry eye - similar to human dry eye
- Immune-mediated lacrimal gland destruction
- Clinical parameters include corneal vascularization, pigmentation, mucus discharge
- Schirmer tear test (STT) <10 mm/min (normal 15-21 mm/min)
- >85% well-controlled using topical CsA

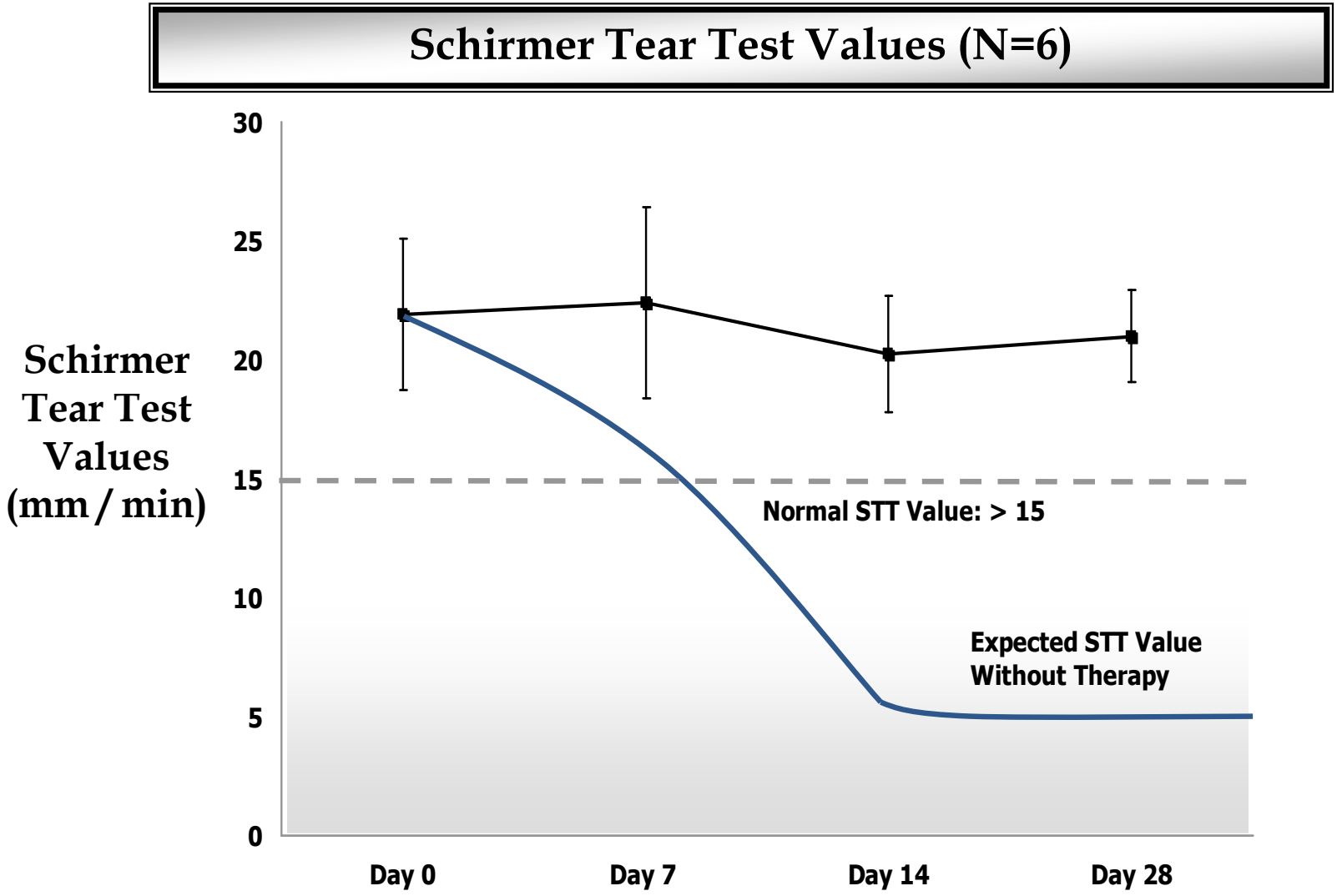


Early canine KCS



Chronic canine KCS

Voclosporin Pilot Efficacy Study – Canine KCS

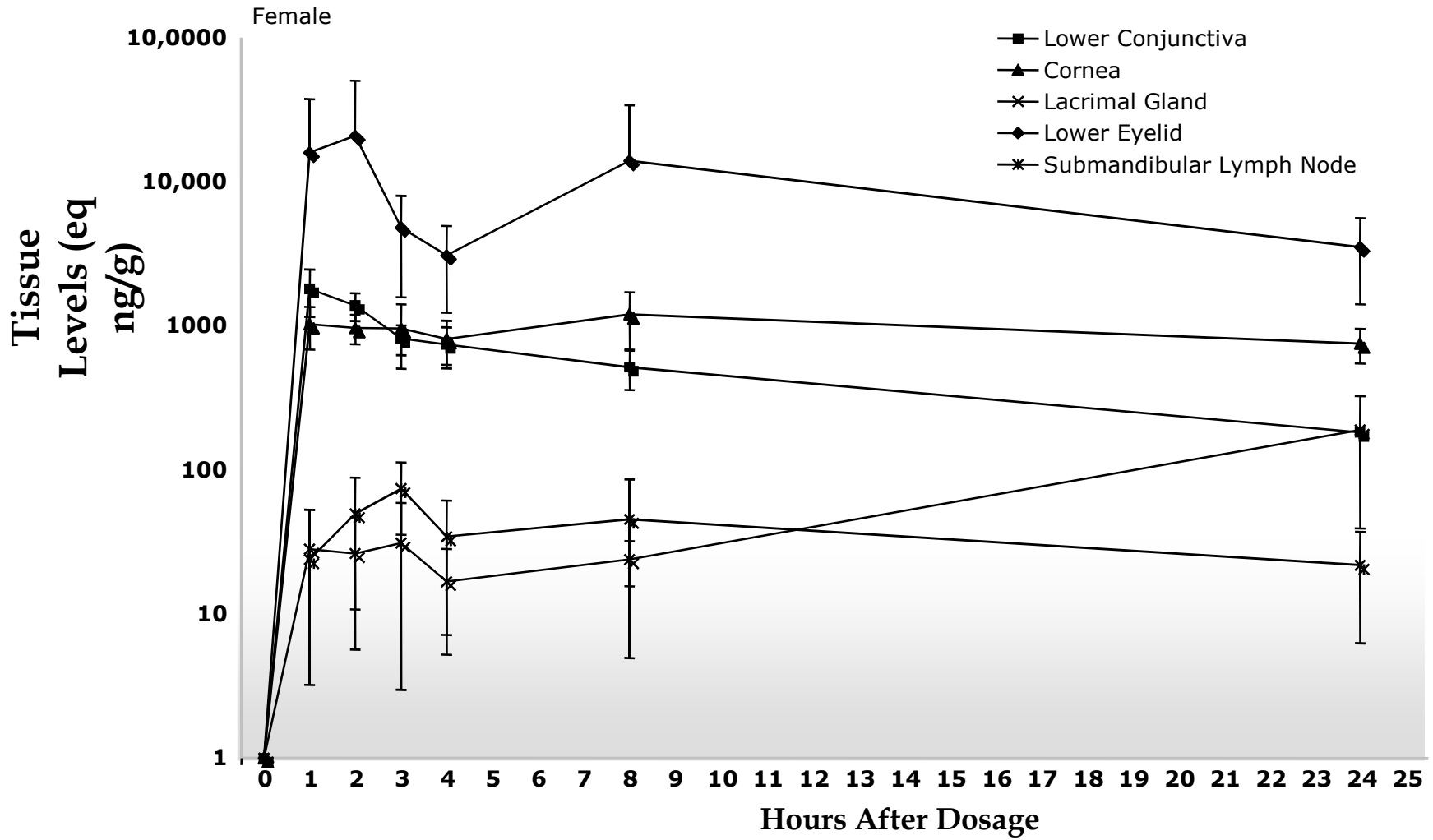


Voclosporin Pilot Efficacy Study Canine Keratoconjunctivitis Sicca

- 0.2% LX214 topically bid
  - No signs of irritation or ocular toxicity up to 30 days
  - No adverse reactions
- STT maintained at normal levels
  - Entire 30 days

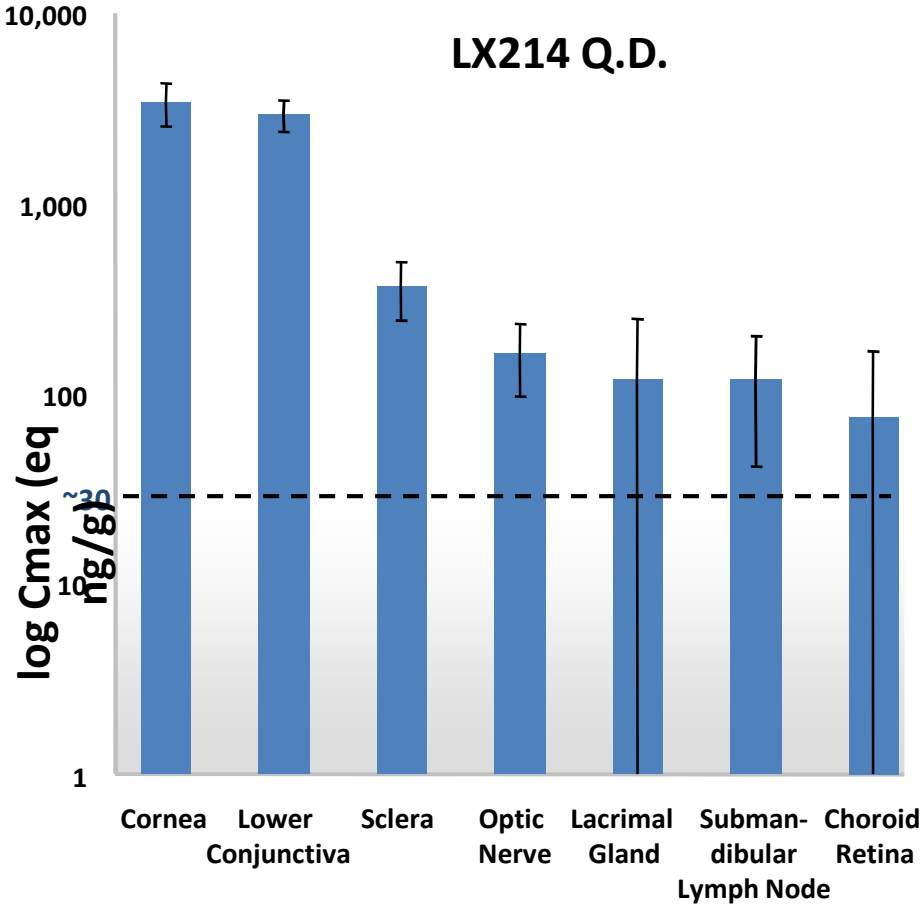
Ocular PK in Animals Supports Q.D. Dosing of Voclosporin

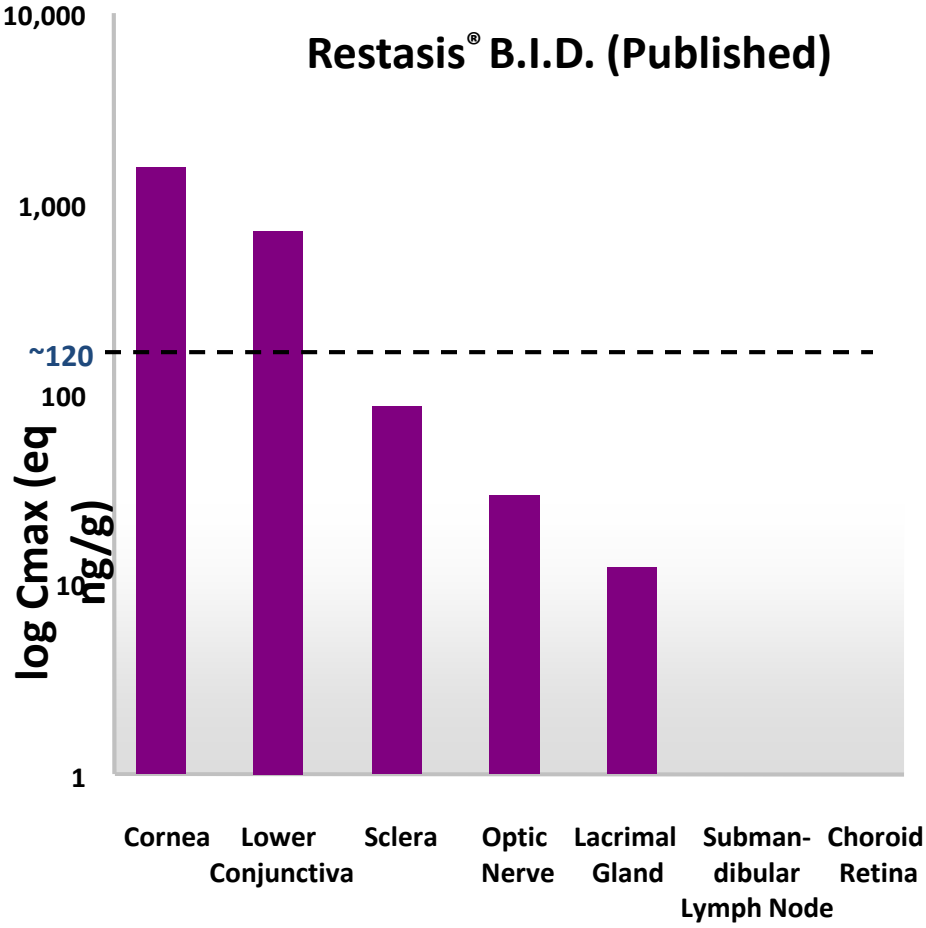
Tissue Levels After Single Dose in NZW Rabbits



Voclosporin Q.D. Produces Therapeutic Levels In Relevant Ocular Tissues

Cmax After Multiple Topical Dose (Day 7 or Day 9, Respectively) In Rabbits





Phase I Design

A Phase 1 Dose-Escalation Study to Assess the Safety and Tolerability of LX214 Ophthalmic Solution in Healthy Volunteers, Followed by an Open-Label Evaluation of LX214 Ophthalmic Solution in Subjects with keratoconjunctivitis sicca

- Primary Objective
  - Safety and Tolerability of LX214 in healthy volunteers and subjects with keratoconjunctivitis sicca (KCS)
- Secondary Objective
  - PK in healthy volunteers and subjects with KCS

Criteria for Evaluation of Safety and Tolerability

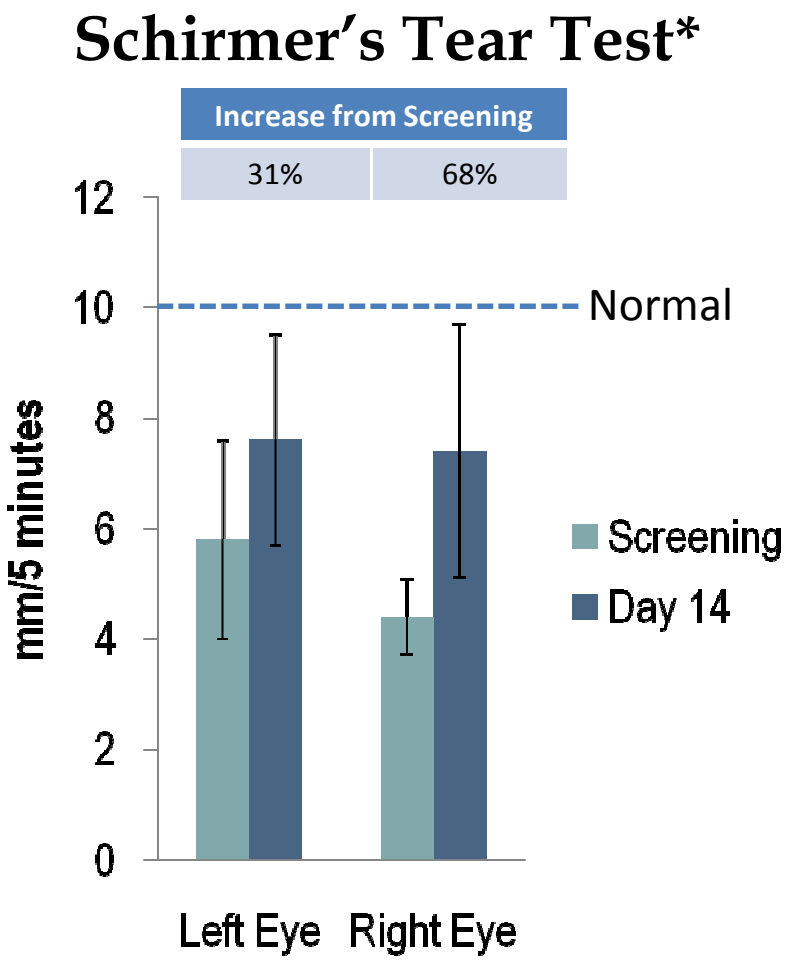
Tolerability

- Treatment-Emergent Ocular Symptomatology

Safety

- Adverse Events
- Treatment-Emergent Adverse Events
  - Biomicroscopy findings
  - Ophthalmoscopy findings
  - External handlight examination findings
- Snellen Visual Acuity
- Intraocular Pressure
- Vital Signs
- Clinical Laboratory Evaluations

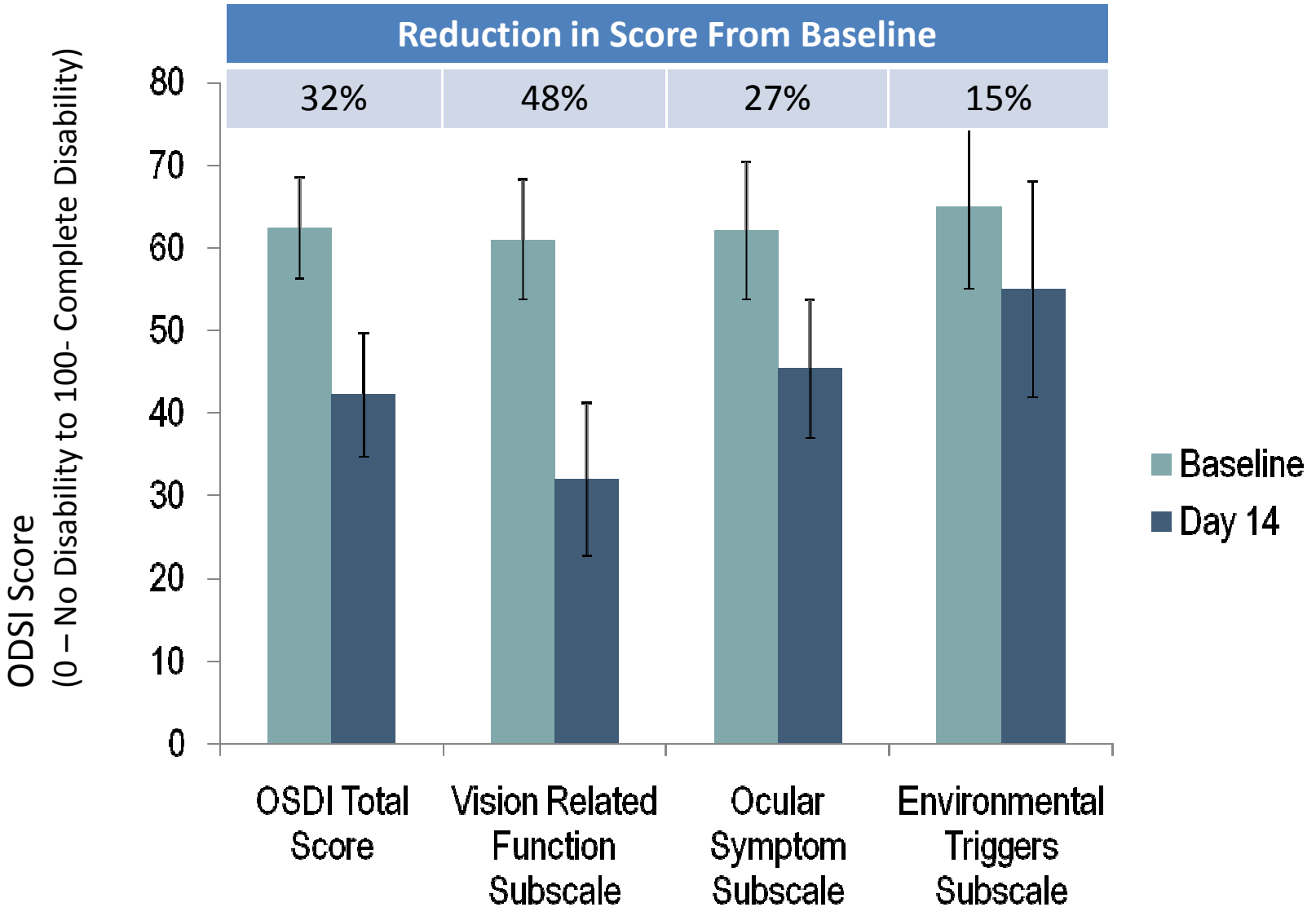
LX214 (0.2% bid) - Promising Early Signs of Efficacy at 2 Weeks (Signs)



*with anesthesia

**4th Protocol amendment removed requirement for fluorescein staining

LX214 (0.2% bid) - Promising Early Signs of Efficacy at 2 Weeks (Symptoms)



LX214 - Efficacy Comparison to Restasis®

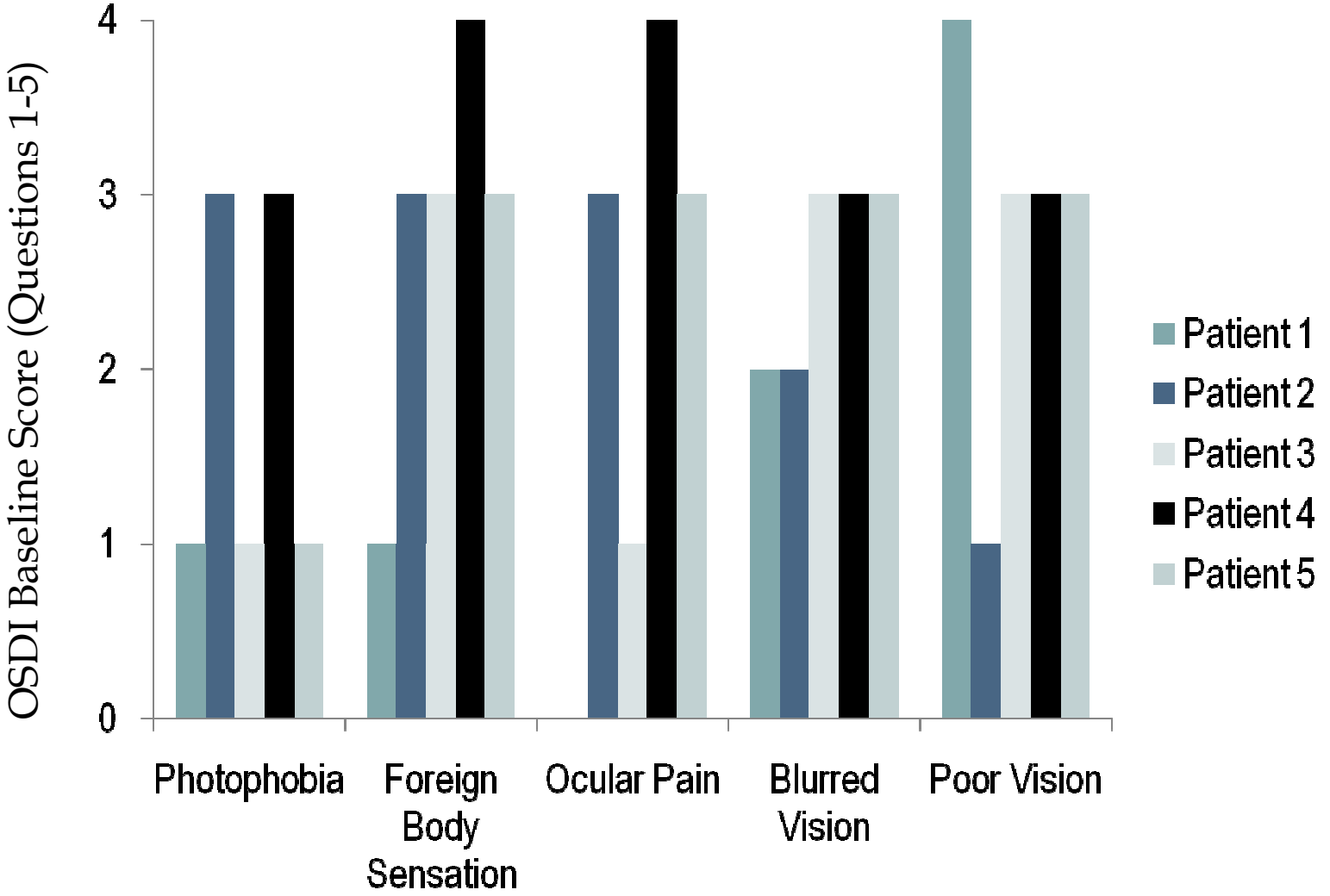
Restasis – Schirmer's

- Phase II (12 weeks)
  - Mean Baseline 2.4 – 3.1 mm/5min
  - 0.1% concentration - mean increase 4.3 (week 8) 2.8 mm (week 12)
- Phase III (6 months)
  - Categorized improvements
  - 0.05% (Restasis), +0.9 and +0.4 (month 3 and 6)
  - 0.1% concentration, -0.1 and +0.3 (month 3 and 6)
- Safety Extension (1 year)
  - Mean Baseline 5.8mm/5min
  - 0.1% concentration - mean improvement 0.4mm/5min (n=278)

LX214 - Schirmer's

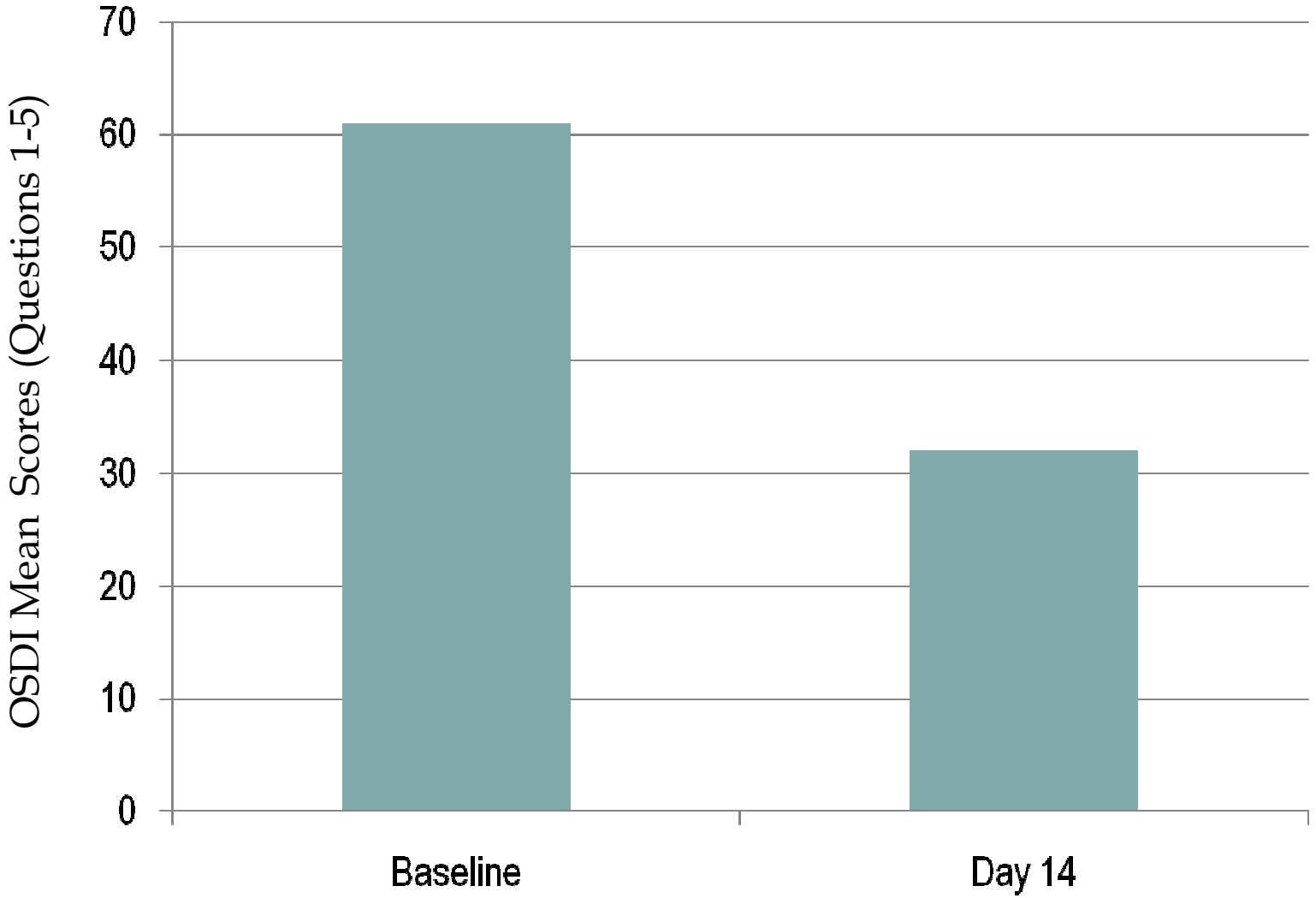
- Phase I (2 weeks)
  - Mean Baseline 5.8mm/5min (left eye) and 4.4mm/5min (right eye)
  - Mean improvement 1.8mm/5min (left eye) and 3mm/min (right eye)
  - Categorized improvements, worse eye +5

Patients Entered Study with a High Degree Of Symptomatology

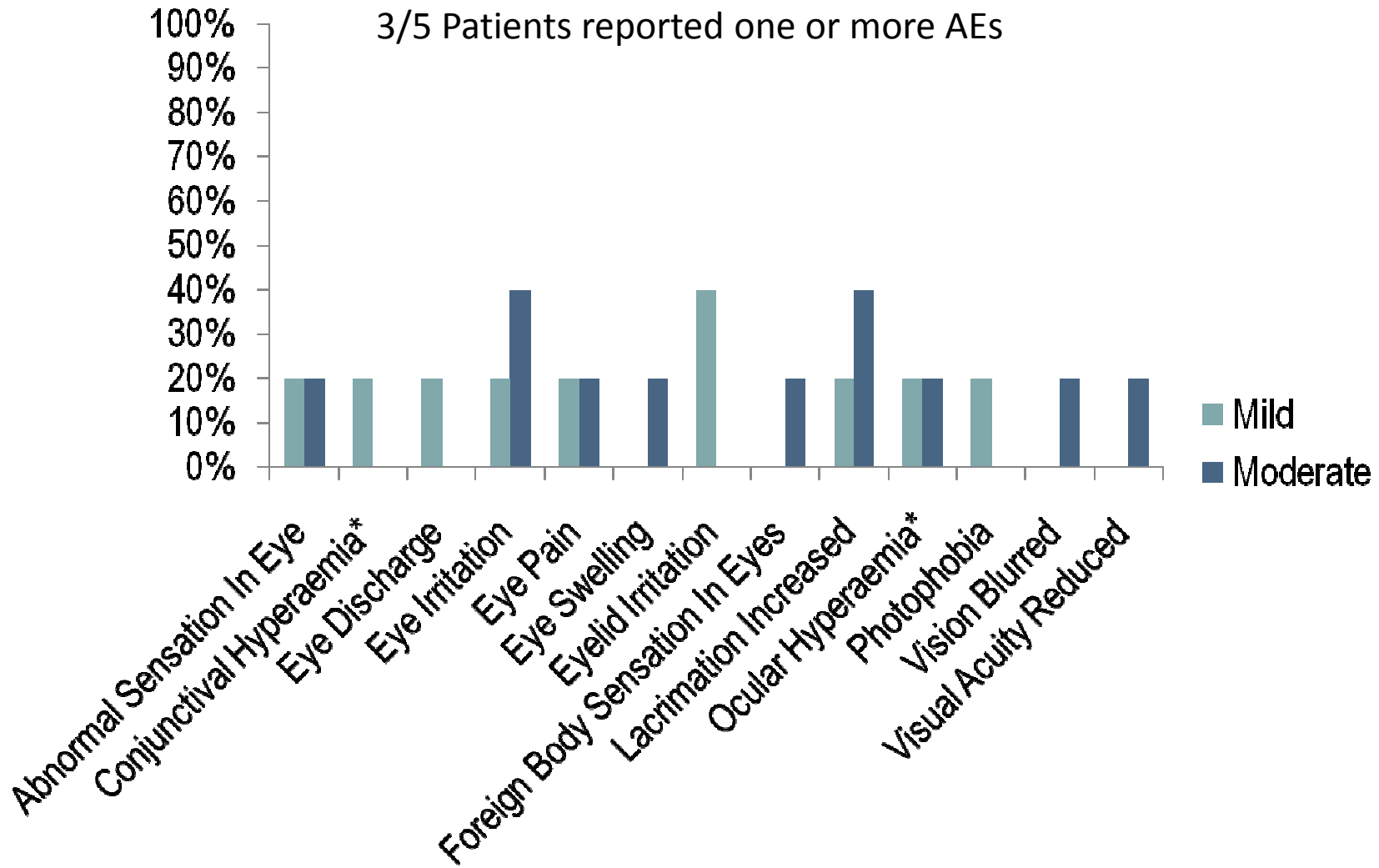


0= None of the time, 1= Some of the time, 2= Half the time, 3= Most of the time, 4= All of the time

Patients Experienced a Decease In Symptomatology with LX214



Low Rate of Ocular Treatment Related Side Effects in A Highly Symptomatic Disease



* One patient entered the trial with pre-existing hyperemia

LX214 Phase I Conclusions

In short-term exposure

- Tolerability in healthy volunteers similar to placebo
- No apparent effect on intraocular pressure
- Blood levels well below threshold level defined by FDA (not requiring sampling in future studies)
- Intriguing hint of efficacy in the small patient population

Acknowledgments

- Lux Biosciences:
  - Dr. Ulrich Grau
  - Clarke Atwell
  - Dr. Eddy Anglade
  - Sidney Weiss
  - Dr. Poonam Velagaleti
  - Dr. Brian Gilger
  - Dr. Cecil Moore
  - Daniel Haders
- University of Missouri-Kansas City:
  - Dr. Subramanian Natesan
  - Sudharshan Hariharan
  - Mukul Minocha
  - Kishore Cholkar