

# Performance of automated hyperemia assessment in allergic conjunctivitis interventional study

Michael J Wald (michael.wald@novartis.com)<sup>1</sup>, Bruno Lay<sup>2</sup>, Ronan Danno<sup>2</sup>, Cynthia L Grosskreutz<sup>1</sup>, Sudeep Chandra<sup>1</sup>

<sup>1</sup>Translational Medicine; Novartis Institutes for BioMedical Research, Inc., Cambridge, Massachusetts, USA

<sup>2</sup>ADCIS, Saint-Contest, France

## Introduction

- Ocular hyperemia is an important efficacy<sup>1</sup>, safety<sup>2</sup>, and tolerability<sup>3</sup> endpoint in ophthalmic clinical trials.
- Validated subjective standardized scales, e.g. the validated bulbar redness scale<sup>4</sup> and McMonnies/Chapman-Davies scale<sup>5</sup>, suffer from intra- and inter-grader variability necessitating large study populations.
- Objective methods of assessing ocular hyperemia offer the potential to reduce the length and/or size of clinical trials.
- A novel automated approach called Imaging System for Ocular Surface (ISOS)<sup>6</sup> may offer a robust method to measure hyperemia grade with the added detail of vessel morphology.

## Objective

Explore the reproducibility and sensitivity of automated ocular hyperemia efficacy readout in a double-blind interventional study in allergic conjunctivitis

## Methods

- Twenty three subjects were randomly assigned to receive two slit lamp photographs of their right temporal conjunctiva after seven days of either 0.1% Dexamethasone (Maxidex®) ophthalmic solution or vehicle control BID in a double blinded fashion as part of NCT02079649.
- Between slit lamp photographs, subjects were dosed with study medication just before spending 3 hours in an **environmental exposure chamber (EEC)** in which ragweed pollen was circulated at 3500 ± 500 particles per m<sup>3</sup>.

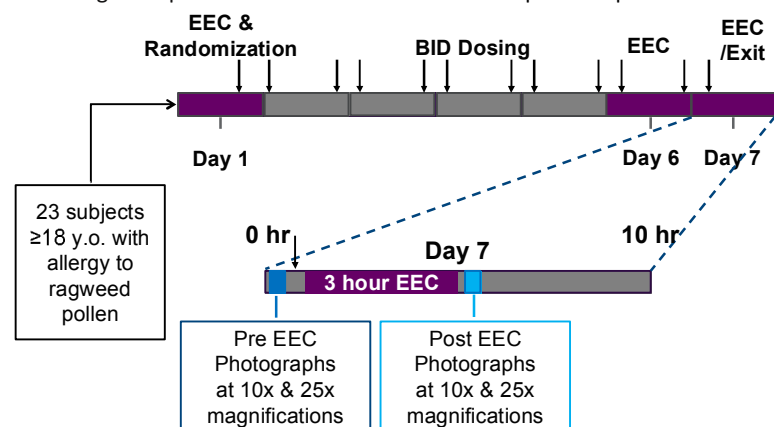


Figure 1. Study Design of Ocular Hyperemia Sub-study

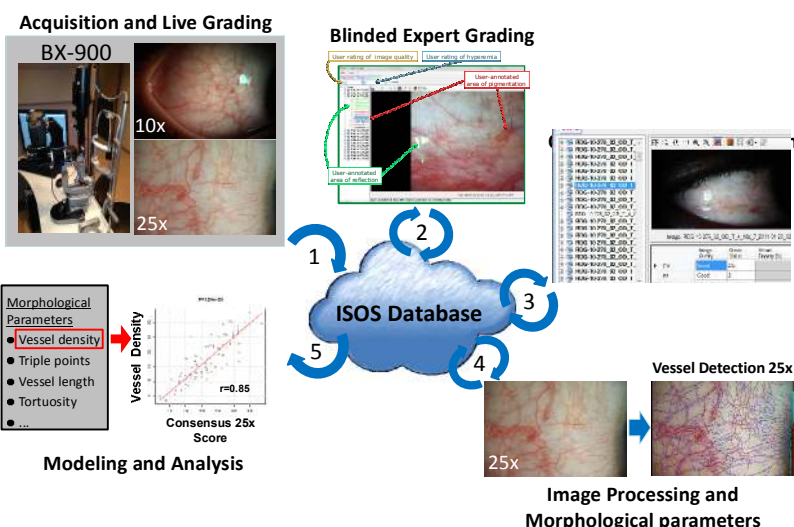


Figure 2. Steps in Data Generation and Analysis

## Methods (cont.):

- Photographs were immediately scored using the validated bulbar redness scale from 0 to 4 in 0.5 increments by one of two ophthalmologists (live scoring) and later by three fully-blinded expert graders.
- A consensus expert score was calculated for each 25x photo to minimize grader variability which was estimated by repeated scorings and modeling.
- 35 morphological parameters (e.g. vessel density, length and width, # triple points, etc.) of the conjunctival vasculature were calculated using an automatic vessel segmentation algorithm from each 25x photograph.
- Multivariate linear regression models were used to predict live and expert consensus scores from the morphological parameters.
- The Maxidex® effect was explored via a linear mixed model of change from Pre-EEC relative to vehicle group for hyperemia scores and image descriptors.
- Estimated N-sizes were made based on observed mean change and standard deviation within the Maxidex® treatment group using a paired T-test model.

## Results

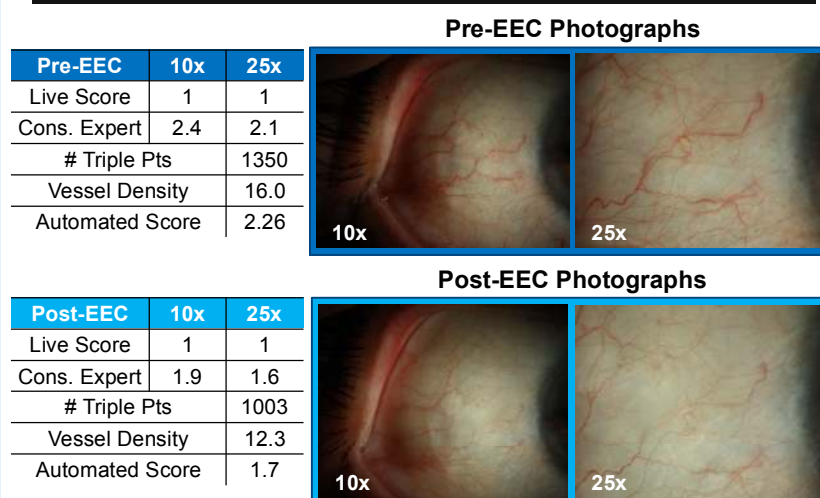


Figure 3. Slit lamp photographs and hyperemia assessments in an example vehicle treated subject

- 13 subjects were randomized to Maxidex® and 10 to vehicle control.
- Intrinsic variability of automated score was similar to consensus expert score and better than that of live and individual expert scorings (Figure 4).
- Live hyperemia score was best predicted by vessel density alone (r=0.68) while consensus expert score was best fit by a linear model (r=0.93) of 14 morphological descriptors (e.g. vessel density, vessel length, # triple points).

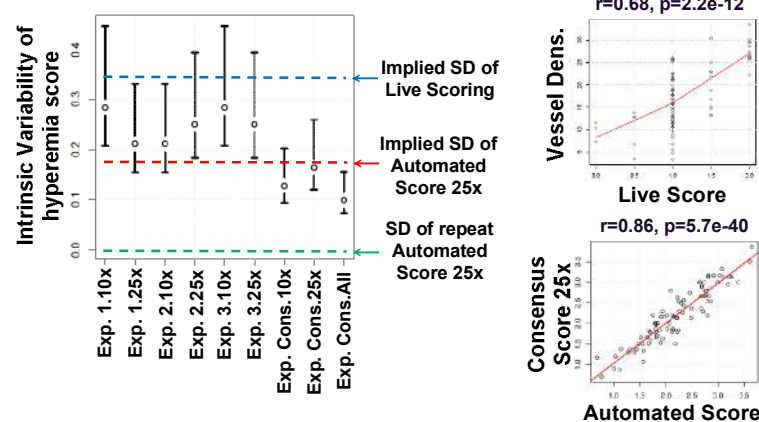


Figure 4. Intrinsic variability of hyperemia scores and best-fit morphological predictions of live and expert consensus scores

## Results (cont.):

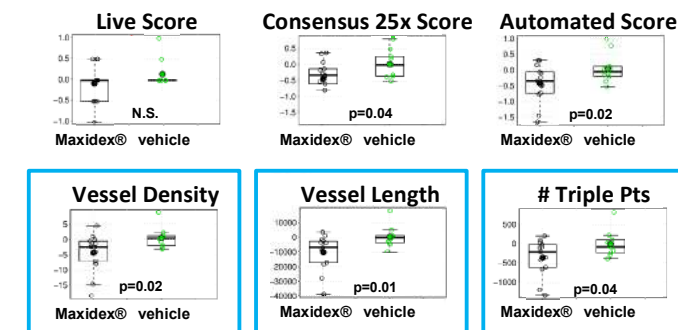


Figure 5. Changes from Pre-EEC in hyperemia scores and vessel morphology for Maxidex® and vehicle treated groups

- A significant Maxidex® response (p<0.05) relative to vehicle was observed in consensus expert and automated scores with further characterization of the response offered by vessel density, vessel length, and # triple points (Figure 5).
- Improved reliability of automated hyperemia readouts offer the potential for reduced study sizes (Table 1).

Measure	Maxidex® Effect (Post-Pre EEC)	N estimate (p<0.05, 80%)
Live Score	-0.077±0.45	270
Expert Cons. Score 25x	-0.44±0.65	19
Automatic Score	-0.40±0.56	18
Vessel density	-4.32±6.35	19
Triple Pts	-351±477	17
Vessel Length	-10048±12341	14

Table 1. N-size estimates based on Maxidex® effect between Post- and Pre-EEC evaluations

## Conclusions

- ISOS-based hyperemia assessment offers a deeper understanding of the hyperemia response with a high degree of reliability.
- Its application in additional indications and further implementation enhancements could dramatically improve the efficiency for future clinical trials.

## References

- Nazarov O et al., *Arzneim.-Forsch./Drug Res.* 2003; 53(3).
- Alagoz G et al., *Ophthalmologica* 2008; 222.
- Dumbleton K et al., *Optom Vis Sci* 2006; 83(10).
- Schulze MM et al., *Optom. Vis Sci.* 2007; 84(10).
- McMonnies CW, Chapman-Davies A, *Am J Optom Physiol Opt* 1987; 64.
- Tort M et al., *Poster #41, 27<sup>th</sup> Biennial Cornea Conf. in Boston, MA 2011.*

## Acknowledgements

The authors would like to acknowledge Kay Fisk of Alcon for operational support and Jean-Philippe Vert of Mines ParisTech for performing the statistical analysis.

## Disclosures

- Data was collected as part of NCT02079649, a clinical trial sponsored by Alcon Labs, a Novartis company.
- MJW, CLG, and SC are employees (E) of Novartis Institutes of Biomedical Research.
- BL and RD are employees (E) of ADCIS and consult (C) for Novartis.