Prospective Multicenter Trial of a Compounded Fixed Combination of Timolol Maleate 0.5%, Brimonidine Tartrate 0.2%,Dorzolamide Hydrochloride 2%, Latanoprost 0.005%, for Glaucoma

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Financial Disclosures

- Aeire (DG:S)
- Alcon (NR:C)(DG:C,S)
- Allergan (NR:C,S)((DG:C,S)
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- Iridex (NR:C)
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- Kala (DG:S)
- New World Medical(NR:C)(DG:C)
- Ocular Science (NR:C)(DG:O)
- Ocular Therapeutix (DG:S)
- Shire (DG:S)
- Tear Solution (DG:S)
- Valeant (G:S)
- Ziess (NR:C)(DG:S)

Introduction

- In the United States, glaucoma is primarily controlled with topical eye drop therapy with the goal of reducing intraocular pressure (IOP) by 30%. To achieve this goal up to 40% of patients will require more than one topical eye drop medication .[1]

- A single bottle of compounded combination glaucoma medication containing multiple molecules could accomplish the necessary 30% IOP reduction while improving compliance, simplifying dose schedule, reducing preservatives, and providing potential cost savings.

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- The purpose of this investigation is to demonstrate non-inferiority as well as the safety and efficacy of a compounded combination IOP lowering medication in the treatment of glaucoma in patients using 3 or more medications who exhibit difficulty with compliance or elevated intraocular pressure.

Method

- This was a Prospective, Randomized Multi-center, Observer Masked Investigation of Parallel-Group with primary open-angle glaucoma. Inclusion criteria required patients to be currently taking at least 3 IOP lowering medications.
- Study Design: Randomized 1:1, double masked, prospective, multi-center study of 53 subjects with POAG

Multiple Drops Group (Control)
Continue current multiple drop therapy of 3 commercially-available medications.

Compounded Drops Group (IP)
- 1. Timolol maleate 0.5%, brimonidine tartrate 0.2%,dorzolamide hydrochloride 2%, with BAK 0.001% qAM
- 2. timolol maleate 0.5%, brimonidine tartrate 0.2%, dorzolamide hydrochloride 2%, latanoprost 0.005%, with BAK 0.001% qhs

Subjects were seen for evaluation at Baseline and on Days 7±2, 30±7, 60±7, and 90±7 following the initial visit and randomization arm was masked.

Method

- The primary outcome measurement was IOP change, and secondary measurements included corneal staining, patient-reported symptoms, and visual acuity.
- Study eye was defined as the eye with the highest morning IOP score at the screening visit (baseline) and was the primary eye used for analyses. Patients without baseline or any post baseline IOP data were excluded from analyses
- Primary Outcome: Non-inferiority as assessed by upper bound of 2-sided 95% confidence interval for the between-group difference in mean change from baseline at all time point
- Analysis of covariance, ANCOVA, was used to analyze continuous measures, with fixed effects for treatment and investigative site, and baseline as a continuous covariate

Results

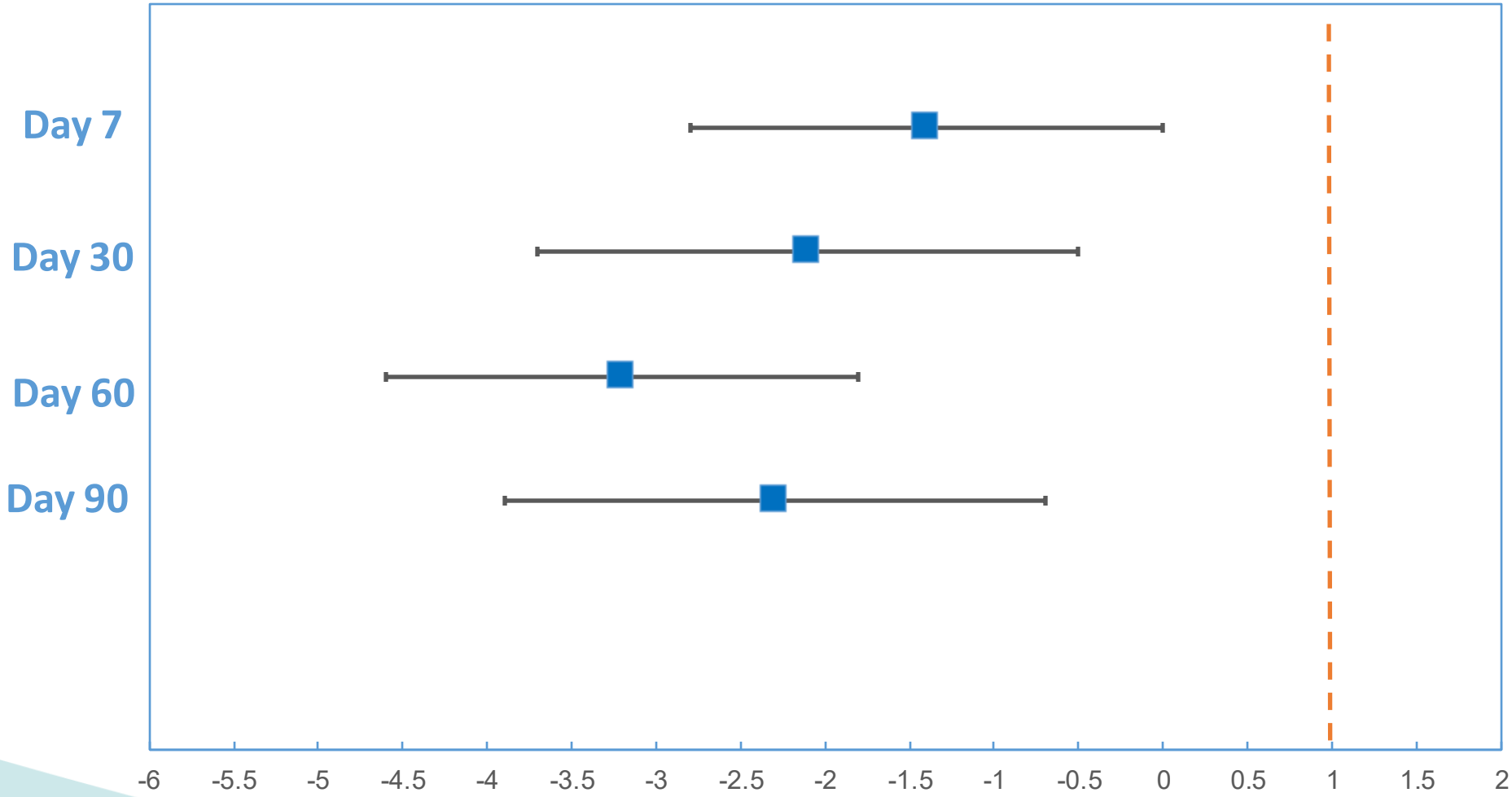
- 29 patients randomized to IP and 31 to Control
- 2 patients (one in Control and one in IP group) withdrew consent and discontinued early; 2 with no post-baseline data
- Morning IOP study eye: upper limit of 95% CI was <1.0 mmHg at all time points (days 7, 30, 60 and 90) demonstrating non-inferiority of IP to Control
  - Upper limit of 95% CI <0 at days 7, 30, 60 and 90 indicating superiority of IP
  - Additionally, upper limit <1 for morning fellow eye IOP and both eyes for afternoon IOP at all time points
- Mean decreases from baseline in Total CFS were greater in the IP group and significantly so at days 7, 30, 60 and 90 (study eye and fellow eye)
- Changes from baseline in visual acuity were similar between IP and Control (study eye)

IP = Compounded Drops Group
Control = Multiple Commercial Drops Groups

Baseline Characteristics

		Control (N=30)	IP (N=28)
Female **Male**	N (%)	23 (77%) 7 (23%)	14 (50%) 14 (50%)
Age	N Mean (SD) Min, Max	30 76.5 (11.29) 52, 98	28 74.8 (11.20) 43, 94
Morning IOP	N Mean (SD) Min, Max	30 18.2 (4.61) 11, 28	28 19.5 (6.59) 13, 47
Pachymetry	N Mean (SD) Min, Max	30 556.6 (24.53) 515, 614	28 549.1 (86.45) 415, 953
ON Ratio	N Mean (SD) Min, Max	29 0.66 (0.199) 0.1, 0.9	28 0.70 (0.177) 0.3, 0.9

2-Sided 95% CI for Between-Group Difference in Mean Change from Baseline in IOP

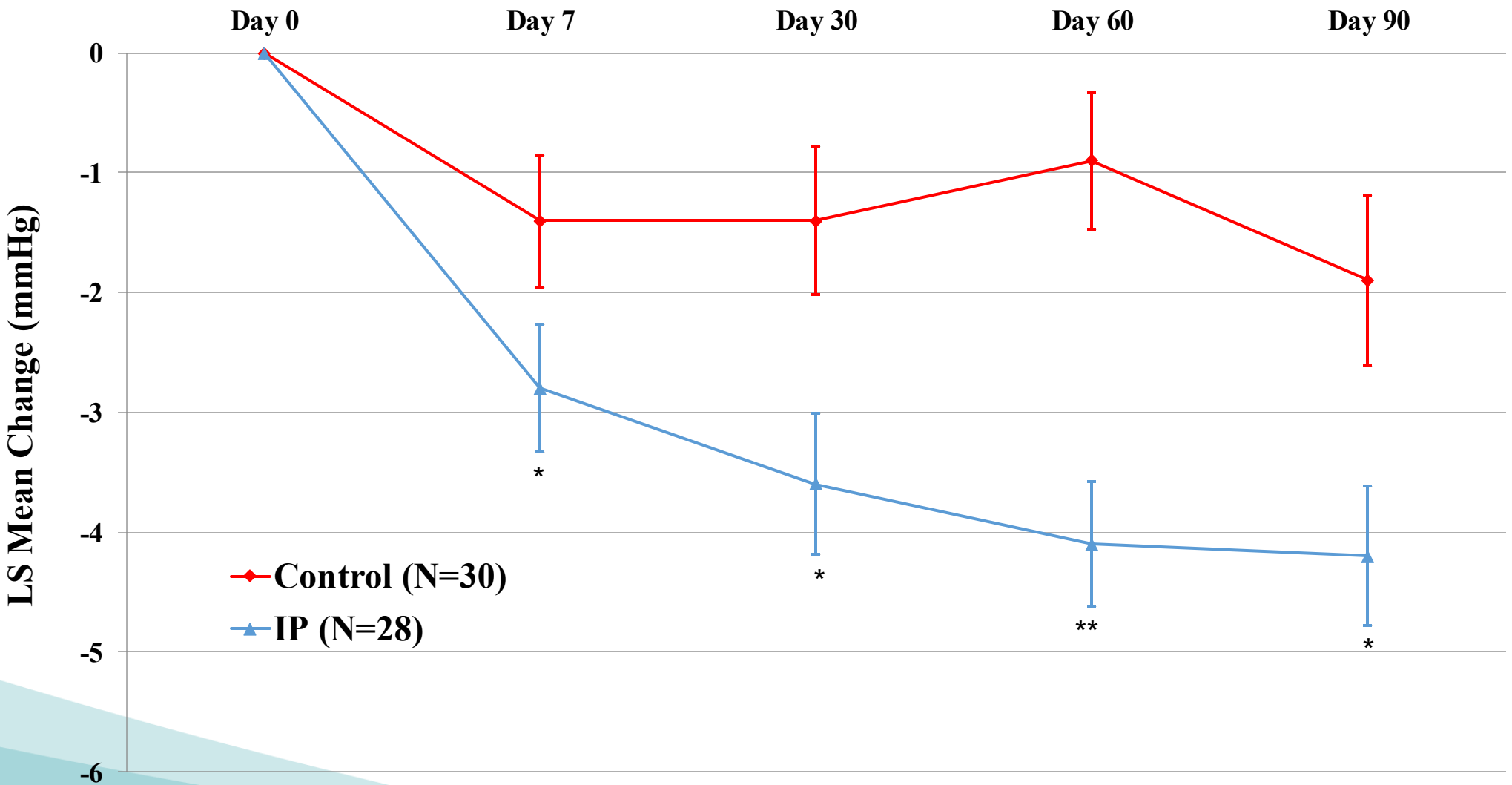


Morning IOP Change From Baseline

		Control	IP	IP minus Control	P-value*
Day 7	N LS Mean (SE) 95% CI LS Mean (95% CI)	30 -1.4 (0.55) (-2.5, -0.3)	28 -2.8 (0.53) (-3.9, -1.8)	-1.4 (-2.8, 0.0)	0.049
Day 30	N LS Mean (SE) 95% CI LS Mean (95% CI)	29 -1.4 (0.62) (-2.7, -0.2)	28 -3.6 (0.59) (-4.8, -2.4)	-2.1 (-3.7, -0.6)	0.009
Day 60	N LS Mean (SE) 95% CI LS Mean (95% CI)	28 -0.9 (0.57) (-2.0, 0.3)	28 -4.1 (0.52) (-5.1, -3.1)	-3.2 (-4.6, -1.8)	<0.001
Day 90	N LS Mean (SE) 95% CI LS Mean (95% CI)	26 -1.9 (0.71) (-3.4, -0.5)	28 -4.2 (0.58) (-5.4, -3.1)	-2.3 (-3.9, -0.7)	0.006

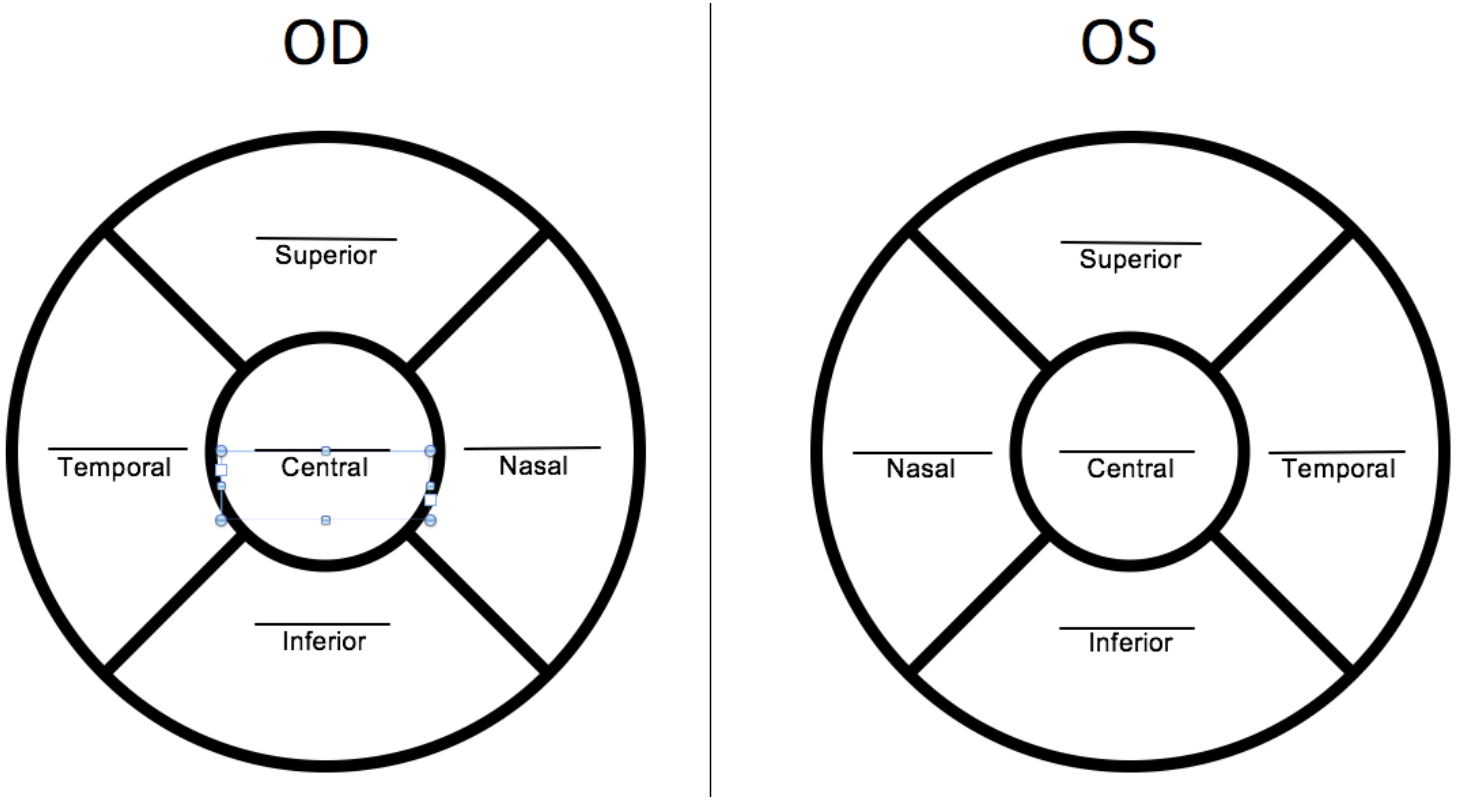
* ANCOVA

Mean (SE) Change from Baseline in IOP over Time



* p<0.05 and **p<0.001, ANCOVA

Total Corneal Staining Scale

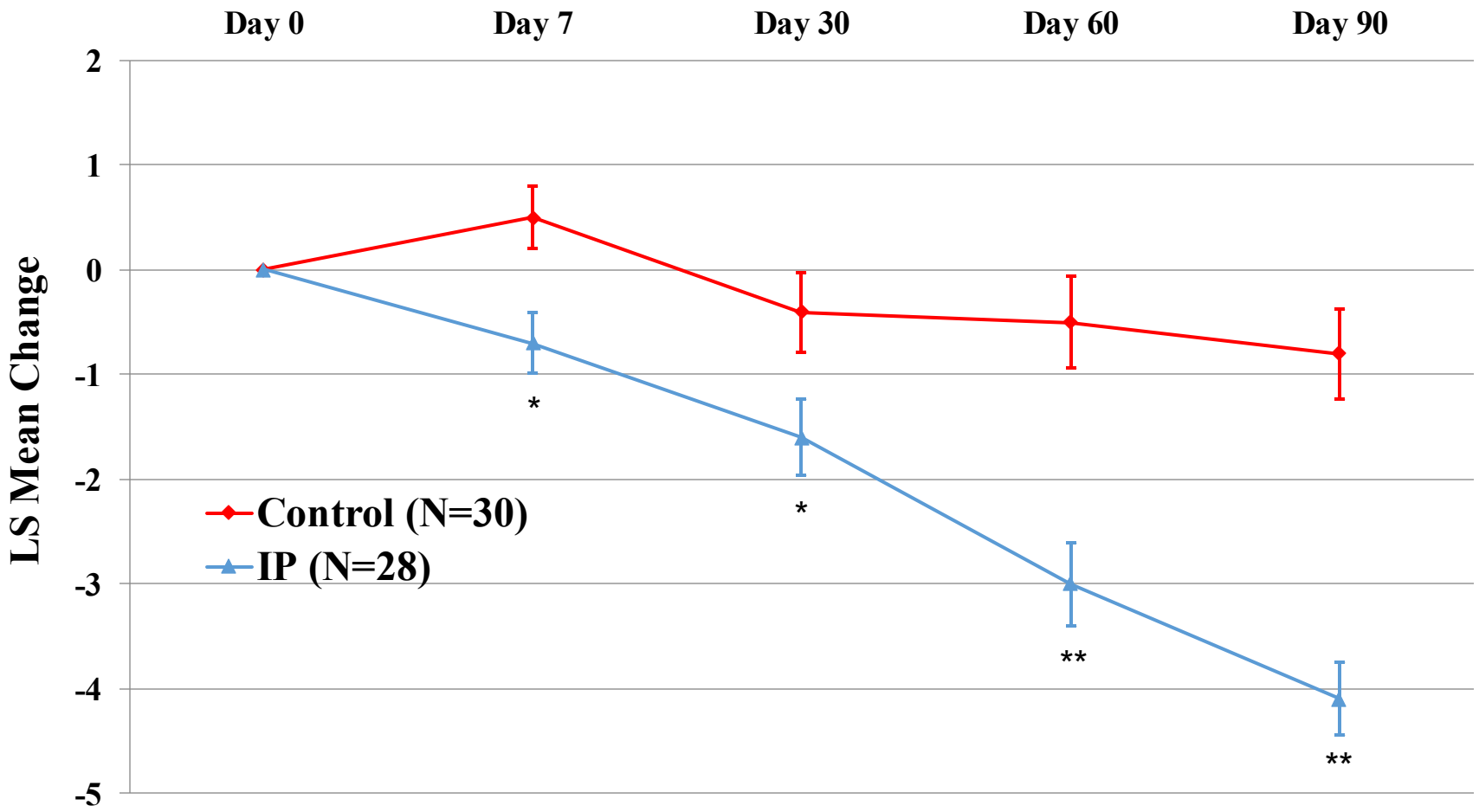


Grading Method for Corneal Defects. Corneal fluorescein staining is a proven method of assessing the presence and magnitude of superficial punctate keratopathy, a common side effect of preservatives such as benzalkonium chloride[1,2]. The density of staining is measured in each indicated area on a scale of 0-3. A maximum score of 15 per eye indicates an extreme level of corneal surface erosion

Total Corneal Staining

- 82% of subjects assigned to IP and 36% of control subjects showed an improvement from baseline to Day 60
- 89% of subjects assigned to IP and 54% of control subjects showed an improvement from baseline to Day 90
- 54% of subjects assigned to IP and 4% of control subjects improved at least 4 points from baseline to Day 90
- 2 subjects assigned to IP had a 10 point improvement from baseline by Day 90

Mean (SE) Change from Baseline in CFS over Time



* p<0.05 and **p<0.001, ANCOVA

Visual Acuity (logMar) Change From Baseline

		Treatment		
		Control	IP	P-value*
Day 7	N LS Mean (SE) 95% CI	30 -0.02 (0.01) (-0.04, 0.01)	28 -0.02 (0.01) (-0.04, 0.01)	0.963
Day 30	N LS Mean (SE) 95% CI	29 -0.02 (0.01) (-0.04, 0.00)	28 -0.01 (0.01) (-0.03, 0.01)	0.458
Day 60	N LS Mean (SE) 95% CI	28 -0.04 (0.03) (-0.10, 0.02)	28 -0.01 (0.02) (-0.06, 0.04)	0.309
Day 90	N LS Mean (SE) 95% CI	26 0.02 (0.02) (-0.02, 0.06)	28 -0.01 (0.02) (-0.04, 0.02)	0.246

* ANCOVA

Discussion

- In this study, we evaluated a compounded medication containing 4 topical intraocular pressure-lowering molecules (timolol, brimonidine, dorzolamide and latanoprost) and found that it was not inferior compared to the standard regimen.
- At Days 30, 60, and 90 of the trial, the IP group showed a greater absolute intraocular pressure reduction than the control.
- We found no evidence of additional safety problems associated with the use of IP vs. the standard regimen (control).
- Mean differences in corneal fluorescein staining showed that, compared with the standard regiment, the IP was associated with lower levels of corneal surface lesions. These differences were significant at Days 7, 60, and 90. This can potentially be explained by the lower levels of preservatives in the IP compared to the standard regimen.[3-4]
- Inherently there are many benefits to combining four medications into a single bottle. These benefits include a lower amount of preservative exposure to patient, the use of fewer bottles, an easier dosing schedule, and potential cost savings.
- Potential future areas for investigation include the safety and efficacy of the PGA-containing 4-drop therapy used twice daily, as this would further reduce the number of bottles required.

Conclusions

- In this study, the IP was not inferior to standard multiple commercially-available medication regimen.
- There was no evidence of additional safety problems from the compounded IP compared to the standard regimen.
- Corneal fluorescein staining showed improvement in the IP group compared to the group on the standard regimen.
- The potential benefits of compounded combination medications warrant further investigation.

Citations

1. Kass MA, Heuer DK, Higginbotham EJ, et al. Arch Ophthalmol. 2002 Jun;120:701-13.
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3. Aihara, Makoto MD, et al. *Journal of Glaucoma.* 2016;25:e610-e614.
4. Pauly A, Roubeix C, Liang H, et al. Invest Ophthalmol Vis Sci. 2012 Dec 13;53:8172-80.

Thank You