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Table 15 Summary of Primary Efficacy Endpoints (Full Analysis Set)

Visit		Pro-ocular 0.5% (N=29) n (%)	Pro-ocular 1% (N=30) n (%)	Placebo (N=30) n (%)	Overall (N=89) n (%)
Corneal Fluorescein Staining by NEI Scale at Week 12 (with LOCF)					
Baseline	n (missing)	29 (0)	30 (0)	30 (0)	89 (0)
	Mean (SD)	7.4 (3.00)	7.7 (2.88)	8.2 (3.47)	7.8 (3.11)
	Median	7.0	7.0	8.0	7.0
	Q1, Q3	5.0, 9.0	5.0, 10.0	5.0, 11.0	5.0, 10.0
	Min, Max	4, 15	4, 13	4, 15	4, 15
Week 12	n (missing)	29 (0)	30 (0)	30 (0)	89 (0)
	Mean (SD)	4.5 (2.92)	5.7 (3.85)	4.4 (3.20)	4.9 (3.37)
	Median	4.0	4.5	4.0	4.0
	Q1, Q3	2.0, 6.0	3.0, 9.0	1.0, 7.0	2.0, 7.0
	Min, Max	0, 11	0, 13	0, 11	0, 13

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Visit		Pro-ocular 0.5% (N=29) n (%)	Pro-ocular 1% (N=30) n (%)	Placebo (N=30) n (%)	Overall (N=89) n (%)
Week 12 change from Baseline	n (missing)	29 (0)	30 (0)	30 (0)	89 (0)
	Mean (SD)	-2.9 (3.67)	-2.0 (2.33)	-3.8 (3.31)	-2.9 (3.21)
	Median	-1.0	-1.5	-3.0	-2.0
	Q1, Q3	-4.0, 0.0	-4.0, 0.0	-5.0, -2.0	-4.0, -1.0
	Min, Max	-12, 1	-7, 2	-12, 1	-12, 2
Intensity of Dryness / Irritation Patient Feeling assessed by SANDE at Week 12 (with LOCF)					
Baseline	n (missing)	29 (0)	30 (0)	30 (0)	89 (0)
	Mean (SD)	70.2 (26.01)	63.9 (29.25)	74.7 (22.97)	69.6 (26.29)
	Median	77.0	68.2	73.2	73.0
	Q1, Q3	54.4, 93.5	43.9, 87.5	58.7, 97.0	53.5, 94.0
	Min, Max	20, 100	0, 100	28, 100	0, 100
Week 12	n (missing)	29 (0)	30 (0)	30 (0)	89 (0)
	Mean (SD)	48.4 (28.23)	44.1 (32.25)	45.1 (25.62)	45.8 (28.57)
	Median	43.1	35.2	49.3	47.4
	Q1, Q3	30.0, 70.4	11.2, 74.6	25.5, 61.5	20.8, 68.5
	Min, Max	0, 100	2, 98	2, 100	0, 100
Week 12 change from Baseline	n (missing)	29 (0)	30 (0)	30 (0)	89 (0)
	Mean (SD)	-21.8 (30.07)	-19.9 (22.66)	-29.7 (26.89)	-23.8 (26.71)
	Median	-17.5	-18.6	-24.8	-19.2
	Q1, Q3	-42.5, -5.0	-37.1, -1.5	-49.6, -4.5	-44.6, -4.3
	Min, Max	-83, 54	-69, 21	-91, 5	-91, 54

Source: Table 14.2.1.1, Statistical Output in Appendix 16.2.
Intensity of Dryness / Irritation Patient Feeling assessed by SANDE at Week 12 (with LOCF): Combined analyses of the Frequency and Severity scale.
Abbreviations: N, total number of patients per group; n, number of non-missing observations; SD, standard deviation; Q1 / Q3, first and third quartile.

Table 16 Analysis of Primary Efficacy Endpoints (Full Analysis Set)

	Pro-ocular 0.5% (N=29) n (%)	Pro-ocular 1% (N=30) n (%)	Placebo (N=30) n (%)	Overall (N=89) n (%)
Corneal Fluorescein Staining by NEI Scale at Week 12 with LOCF				
LS Mean (95% CI)	-3.09 (-4.31;-1.87)	-2.09 (-3.30;-0.88)	-3.73 (-4.98;-2.48)	-
LS Mean Difference, 1% Pro-ocular – Placebo (95% CI)	-	-	-	1.64 (0.15;3.14)
LS Mean Difference, 0.5% Pro-ocular – Placebo (95% CI)	-	-	-	0.64 (-0.87;2.16)

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	Pro-ocular 0.5% (N=29) n (%)	Pro-ocular 1% (N=30) n (%)	Placebo (N=30) n (%)	Overall (N=89) n (%)
p-value, 1% Pro-ocular – Placebo (HB rank, HB criteria)	-	-	-	0.032 (1; 0.025)
p-value, 0.5% Pro-ocular – Placebo (HB rank, HB criteria)	-	-	-	0.400 (3;0.05)
Intensity of Dryness / Irritation Patient Feeling assessed by SANDE at Week 12 with LOCF				
LS Mean (95% CI)	-18.97 (-29.32;-8.62)	-19.66 (-29.97;-9.34)	-24.84 (-35.49;-14.19)	-
LS Mean Difference, 1% Pro-ocular – Placebo (95% CI)	-	-	-	5.19 (-7.67;18.04)
LS Mean Difference, 0.5% Pro-ocular – Placebo (95% CI)	-	-	-	5.87 (-6.95;18.70)
p-value, 1% Pro-ocular – Placebo (HB rank;HB criteria)	-	-	-	0.425 (4;0.1)
p-value, 0.5% Pro-ocular – Placebo (HB rank;HB criteria)	-	-	-	0.365 (2;0.03)

Source: Table 14.2.1.2, Statistical Output in Appendix 16.2.
Intensity of Dryness / Irritation Patient Feeling assessed by SANDE at Week 12 (with LOCF): Combined analyses of the Frequency and Severity scale.
Abbreviations: N, total number of patients per group; n, number of non-missing observations; CI, confidence interval; HB; Holm-Bonferroni.
The change from Baseline is analysed by means of an ANCOVA model with treatment, visit and visit*treatment as fixed effects and baseline measure and stratification factor (male, female: menopausal) as covariates.
* = significant result after adjustment for multiplicity using Holm-Bonferroni method.

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