# Meta-Analysis of Five Adult Environmental Trials Evaluating the Efficacy of Azelastine Eye Drops, 0.05% in Symptomatic Patients with Seasonal Allergic Conjunctivitis

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An ASTA Medica company

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# INTRODUCTION

- Developed by ASTA Medica AG
- Azelastine hydrochloride is available as a tablet outside US for allergic rhinitis and asthma
- Azelastine hydrochloride is available globally as a nasal spray (Astelin®) for allergic rhinitis
- Optivar™(azelastine 0.05% aqueous solution) was approved by the FDA in May 2000 for the treatment of itching associated with allergic conjunctivitis in patients ≥3 years old
- Optivar™ launched globally in over 40 countries

# INTRODUCTION (Cont'd)

- Co-promotion agreement with Bausch & Lomb (ophthalmologists & optometrists)-launched August 2000

- Optivar™ will be launched to non-eye care specialists (PCP's, IM's and Allergists) in April 2001 by Muro Pharmaceutical Inc.

# INTRODUCTION (Cont'd)

- The efficacy of Optivar™ was evaluated in 14 clinical trials
  - one placebo controlled pivotal allergen challenge study conducted in the U.S. and a number of European allergen challenge and environmental studies

- We will present a meta analysis of the results from the five adult environmental efficacy trials conducted in Europe

# META-ANALYSIS

- Meta Analytic methods are statistical methods used to combine results of similarly designed studies in order to test a common hypothesis.

- The statistical literature of recent years contains many examples of meta analytic methods. The approach used for the current presentation is due to D'Agostino et al.

# Meta Analysis: (Cont'd)

When is it appropriate to use meta analyses in combining results of clinical trials?

- Meta analyses can only be done on studies with similar design features.
- Meta analyses are utilized in combining studies when differences between active and placebo are generally in the same direction, but are not all statistically significant.
  - A formal test of homogeneity is required

# OVERVIEW OF STUDIES

- The five adult environmental efficacy trials conducted in Europe for Optivar™ (Azelastine Eye Drops 0.05%) are included in the meta analysis:

**The Common Study Design:**

. Environmental, Multi-center

. Parallel Group, Placebo Controlled, Randomized, Double Blind

. Adult Patients w/ History of Seasonal Allergic Conjunctivitis & Symptomatic at Baseline

# OVERVIEW OF STUDIES (Cont'd)

- Treatments of interest: One drop of Optivar™or placebo per eye bid (patients were allowed to increase to 3 or 4 applications per day when necessary to control severe symptoms)

- Study visits at Day 3, Day 7 (3 of 5 studies), and Day 14

- Efficacy Variables: Itching and Redness Assessed by the Investigator at each Visit

- Symptom Severity Scale:0=none; 1=mild; 2=moderate; 3=severe

# RESULTS OF INDIVIDUAL STUDIES

| Study | Mean Itching Severity | Day 3 | Day 7 | Day 14 |
|---|---|---|---|---|
| 2981 | Placebo (n=94) | 1.56 | 1.33 | 1.09 |
| | AZE 0.050 (n=91) | 1.20 | 1.07 | 0.88 |
| | p-value | 0.005 | 0.058 | 0.127 |
| 2982 | Placebo (n=49) | 1.55 | 1.20 | 1.20 |
| | AZE 0.050 (n=43) | 0.85 | 0.77 | 0.81 |
| | p-value | 0.001 | 0.031 | 0.066 |
| 2983 | Placebo (n=70) | 1.43 | ♦ | 1.39 |
| | AZE 0.050 (n=206) | 1.32 | | 1.04 |
| | p-value | 0.311 | | 0.010 |
| 2984 | Placebo (n=76) | 1.18 | ♦ | 0.96 |
| | AZE 0.050 (n=75) | 1.15 | | 0.97 |
| | p-value | 0.797 | | 0.935 |
| 2985 | Placebo (n=143) | 1.60 | 1.20 | 0.84 |
| | AZE 0.050 (n=141) | 1.40 | 1.02 | 0.64 |
| | p-value | 0.039 | 0.084 | 0.053 |

# RESULTS OF INDIVIDUAL STUDIES (Cont'd)

| Study | Mean Redness Severity | Day 3 | Day 7 | Day 14 |
|---|---|---|---|---|
| 2981 | Placebo (n=94) | 1.34 | 1.12 | 0.87 |
| | AZE 0.050 (n=91) | 1.09 | 0.97 | 0.76 |
| | p-value | 0.047 | 0.236 | 0.349 |
| 2982 | Placebo (n=49) | 1.10 | 0.90 | 0.73 |
| | AZE 0.050 (n=43) | 0.61 | 0.72 | 0.70 |
| | p-value | 0.010 | 0.343 | 0.846 |
| 2983 | Placebo (n=70) | 1.50 | ♦ | 1.23 |
| | AZE 0.050 (n=206) | 1.24 | | 0.88 |
| | p-value | 0.024 | | 0.021 |
| 2984 | Placebo (n=76) | 0.92 | ♦ | 0.84 |
| | AZE 0.050 (n=75) | 0.97 | | 0.84 |
| | p-value | 0.708 | | 0.989 |
| 2985 | Placebo (n=143) | 1.66 | 1.31 | 0.98 |
| | AZE 0.050 (n=141) | 1.37 | 1.11 | 0.65 |
| | p-value | 0.003 | 0.056 | 0.002 |

# Meta Analysis of Five European Studies

## Methodology

- Six separate meta analyses were performed:
  - Itching Assessed on Days 3, 7, and 14
  - Redness Assessed on Days 3, 7, and 14

- Each meta analysis was initiated with a formal test of homogeneity to evaluate the validity of combining the studies

# Meta Analysis of Five European Studies (Cont'd)

- Effect sizes were calculated for each individual study:

  Effect size= (Mean for Optivar ™ – Mean for placebo) / pooled standard deviation

- An overall effect size was computed as a weighted average of the individual effect sizes.

- A significance test, based on the overall effect size, was performed.

- For graphical presentations, 95% confidence intervals were calculated for the effect sizes.

# Meta Analysis of Five European Studies: (Cont'd)

## Results

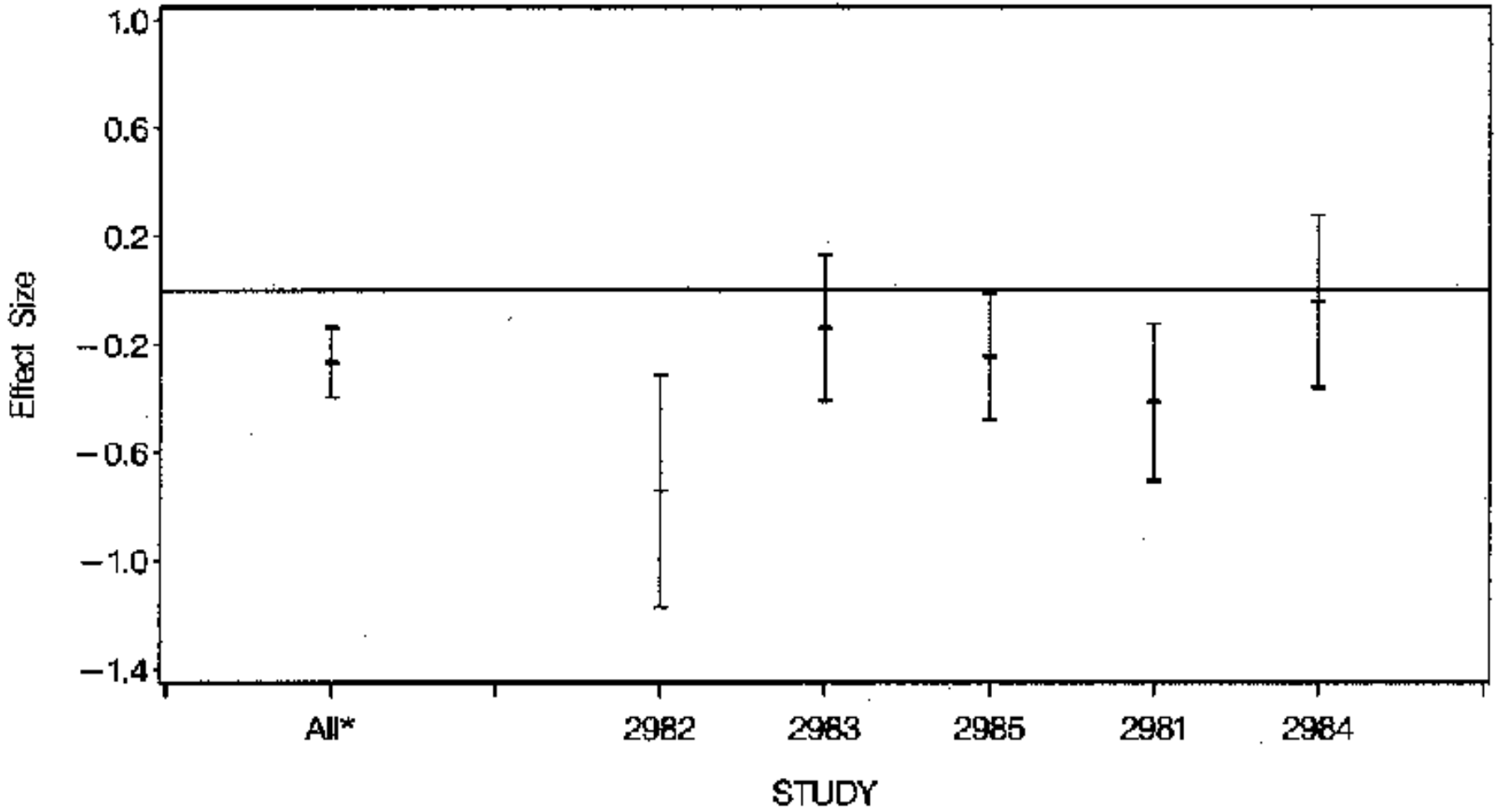
- For all six meta analyses the test of homogeneity confirmed the appropriateness of combining the study results
- The meta analysis showed statistically significant differences between the mean itching severity scores of Optivar ™ (n=556) and placebo (n=435) treatment groups for all assessment days (Days 3, 7, and 14).
- Similarly, the meta analysis showed statistically significant differences between the mean redness severity scores of Optivar ™ and placebo treatment groups for all assessment days (Days 3, 7, and 14).

# Conclusion

- The meta analysis results from the five environmental studies provide further evidence of the efficacy of Optivar ™ already established in individual challenge and environmental studies.

# Figure 1a

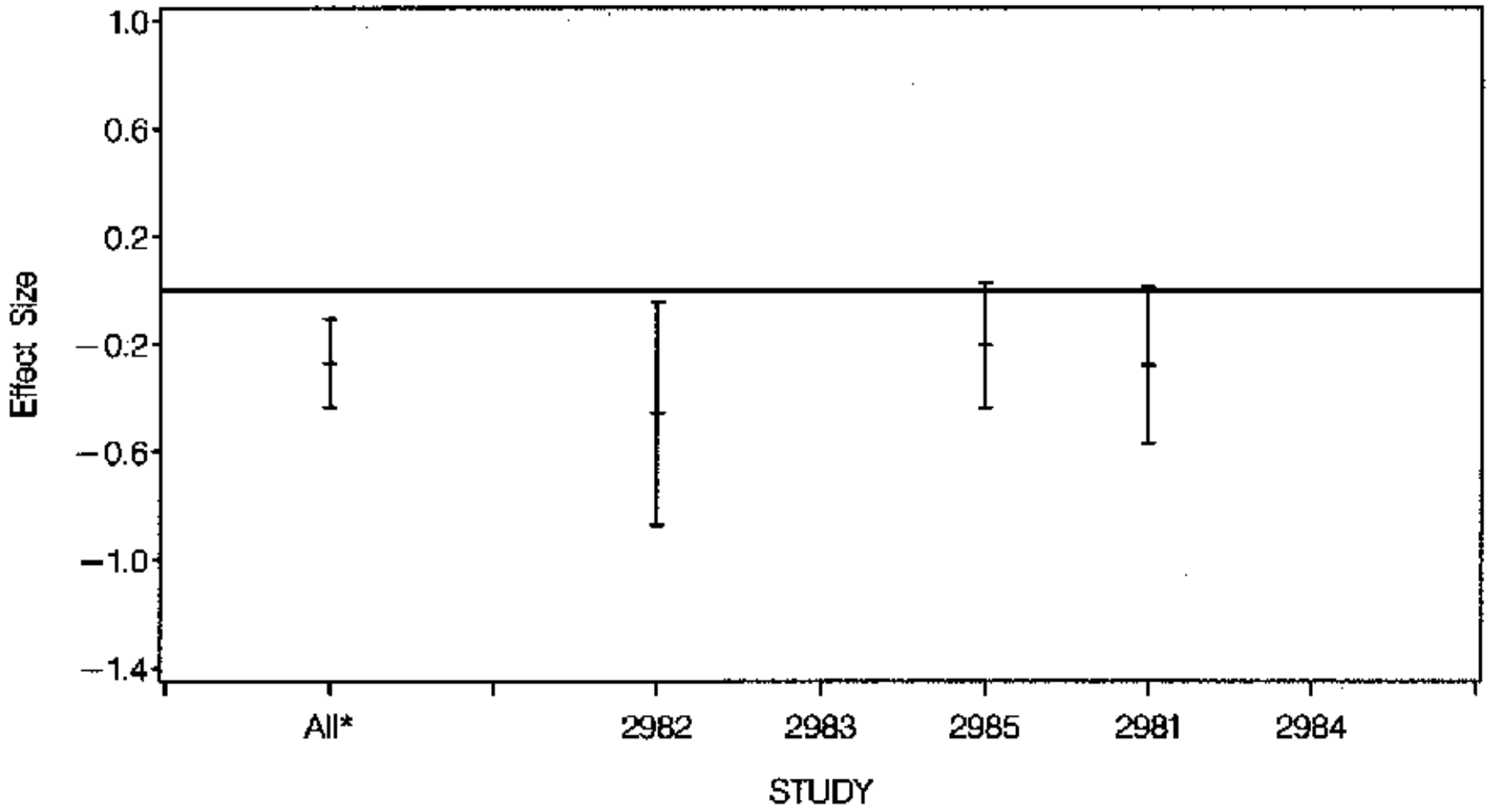
## Meta Analysis Results for Day 3 Evaluation of Itching




* represents the result of meta analysis which combines all the studies involved, $p < 0.0001$

# Figure 1b

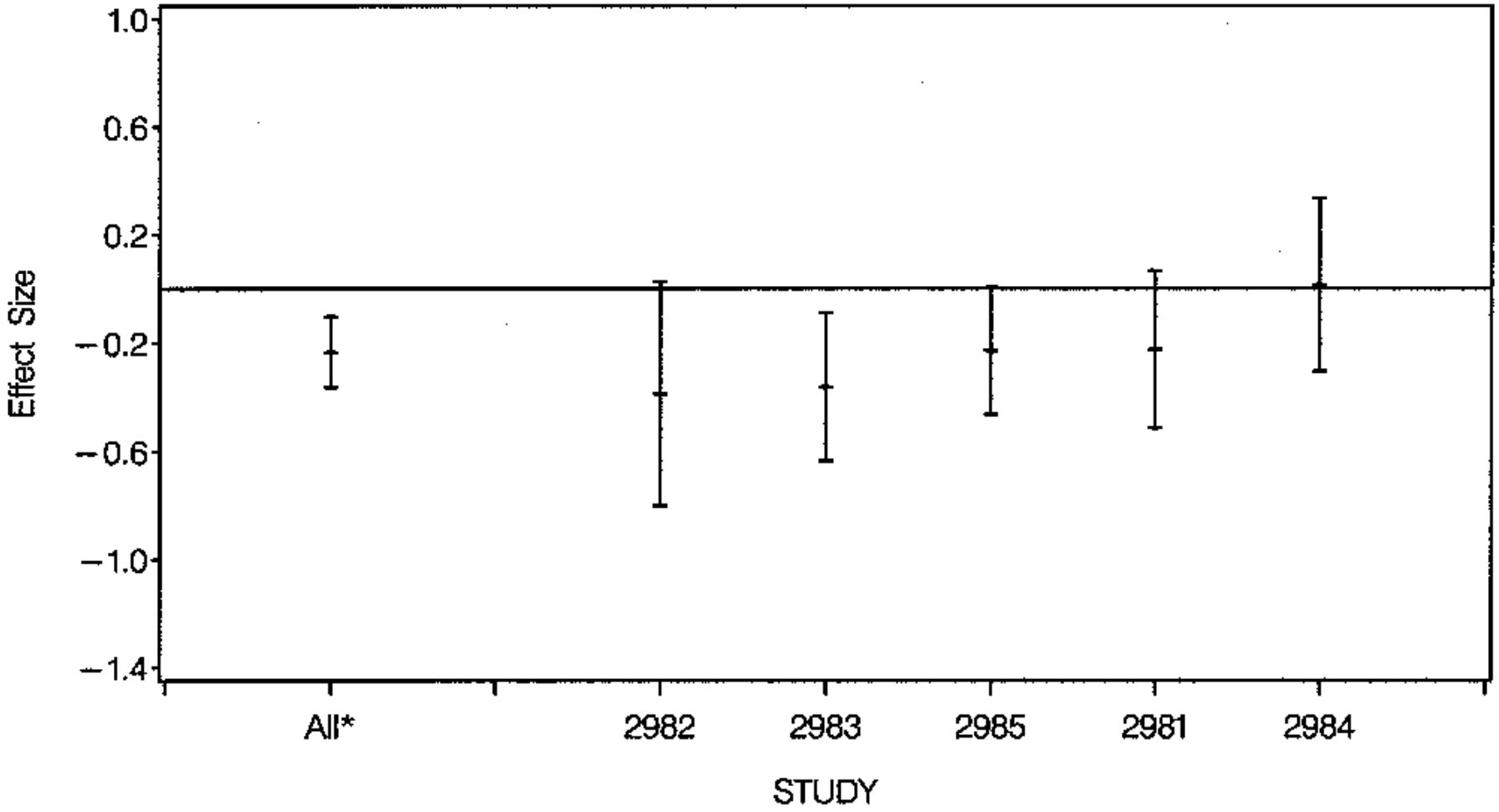
## Meta Analysis Results for Day 7 Evaluation of Itching




* represents the result of meta analysis which combines all the studies involved, $p < 0.01$

# Figure 1c

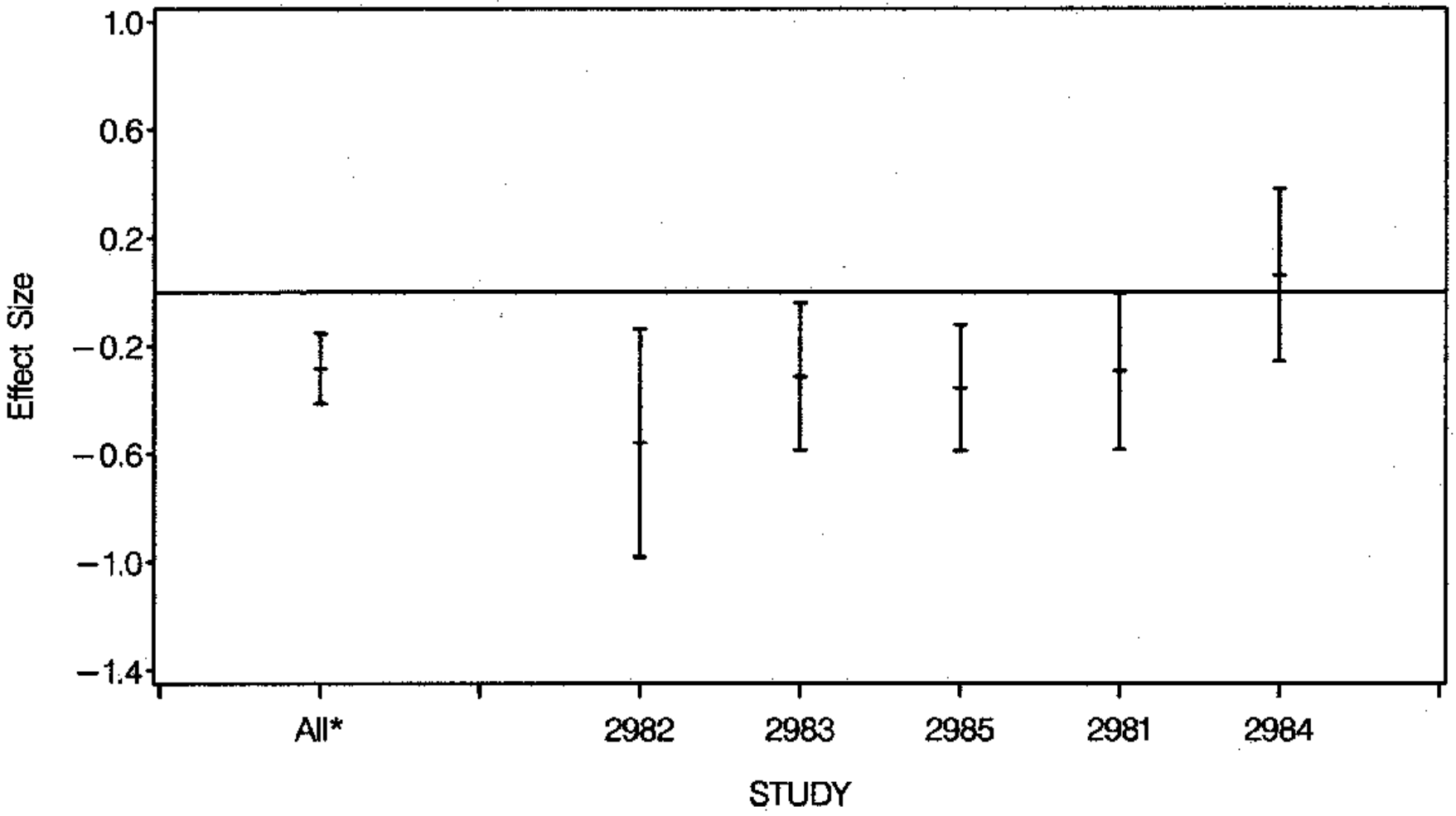
## Meta Analysis Results for Day 14 Evaluation of Itching




* represents the result of meta analysis which combines all the studies involved, $p < 0.001$

# Figure 2a

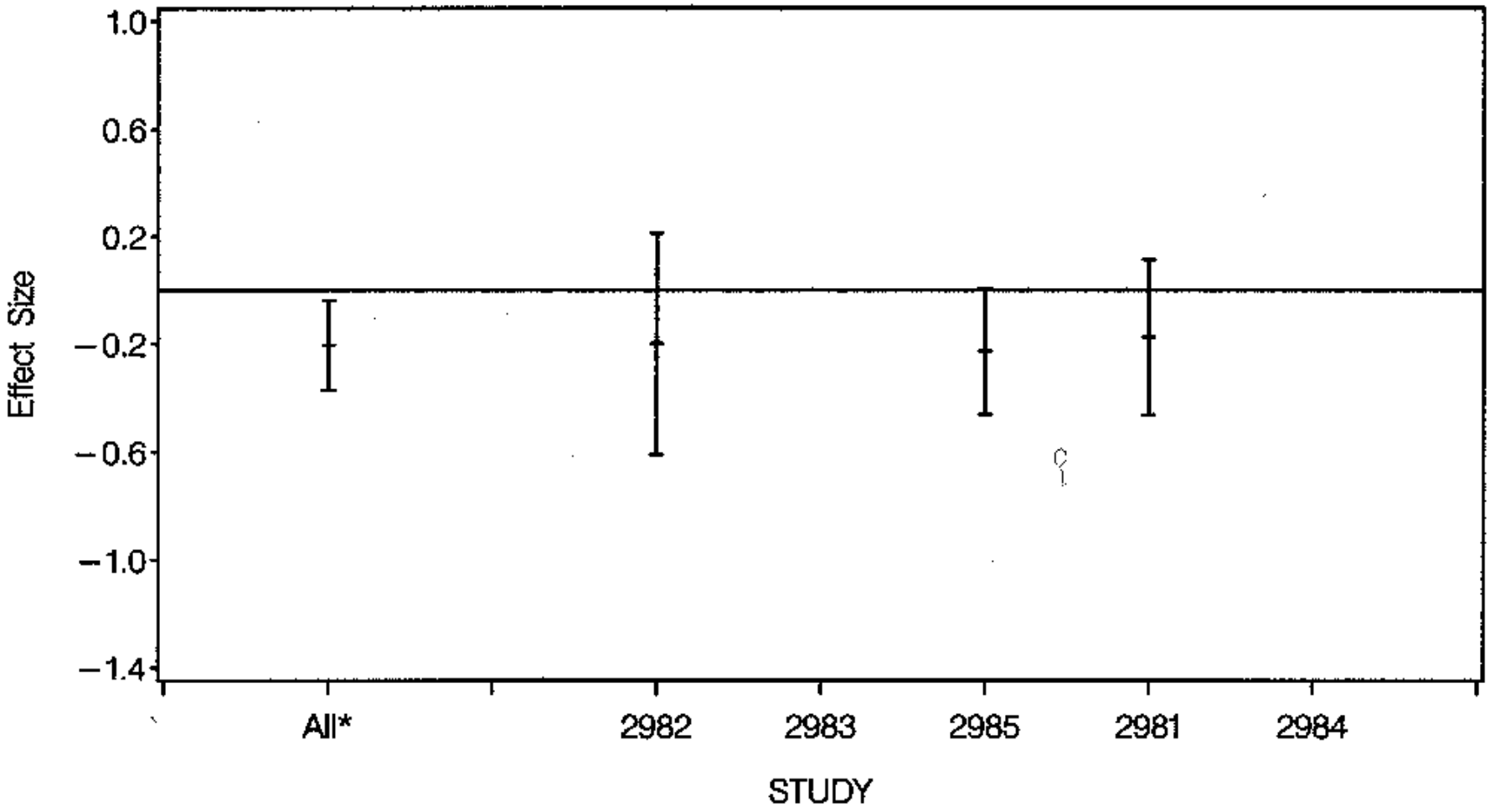
## Meta Analysis Results for Day 3 Evaluation of Redness




* represents the result of meta analysis which combines all the studies involved, $p < 0.0001$

# Figure 2b

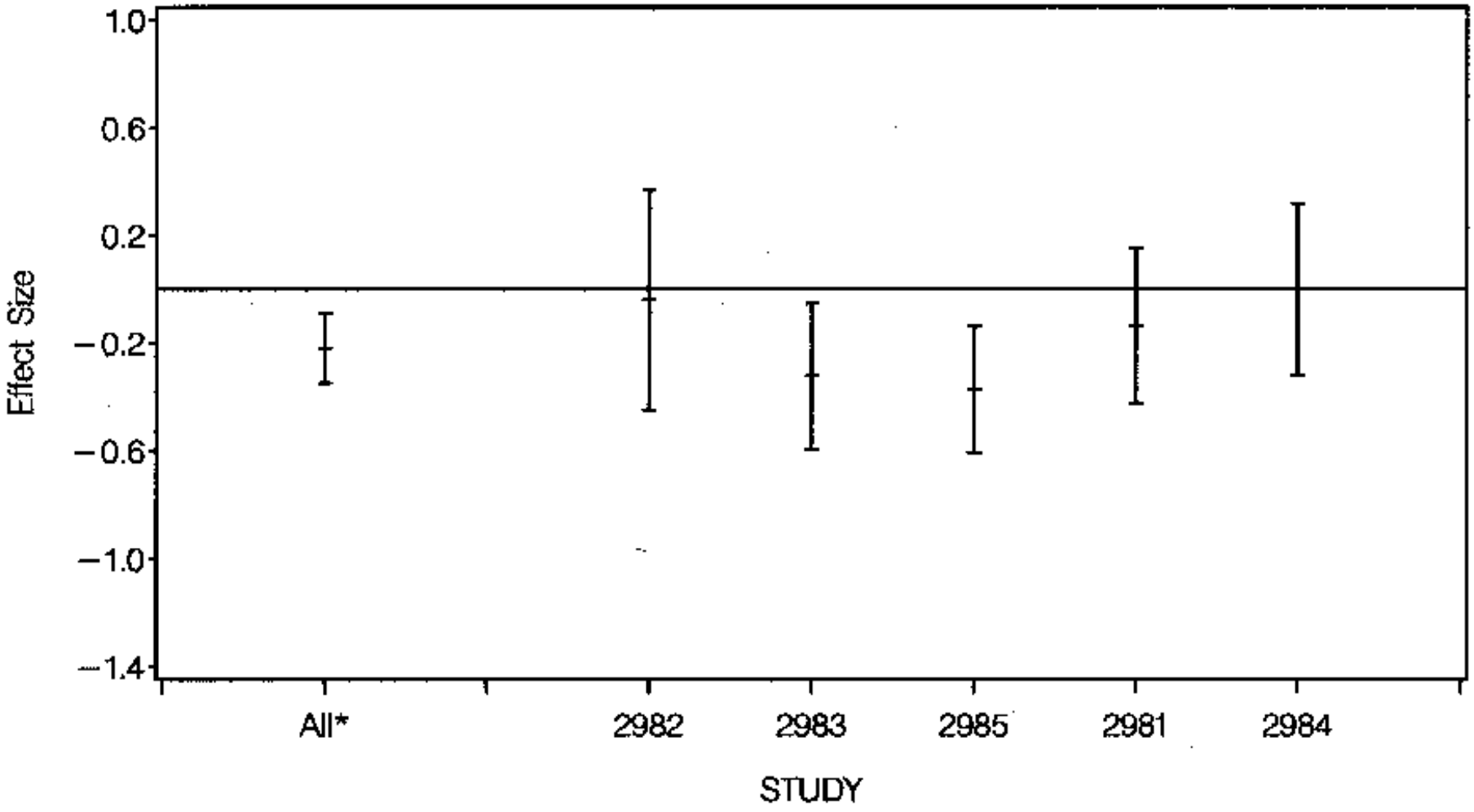
## Meta Analysis Results for Day 7 Evaluation of Redness




* represents the result of meta analysis which combines all the studies involved, $p < 0.05$

# Figure 2c

## Meta Analysis Results for Day 14 Evaluation of Redness




* represents the result of meta analysis which combines all the studies involved, $p < 0.001$

# REFERENCES


D'Agostino RB, Weintraub M. Meta-analysis: A Method for Synthesizing Research. *Clinical Pharmacology and Therapeutics*. December 1995: 605-616.

Friedlaender M, Harris J, LaVallee N, Russell H, Shilstone J. Evaluation of the Onset and Duration of Effect of Azelastine Eye Drops (0.05%) Versus Placebo in Patients with Allergic Conjunctivitis Using an Allergen Challenge Model. *Ophthalmology*. December 2000: 2152-2157.