Issues and Analyses on Missing X-ray Scores

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Outline

- X-ray Results and Concern for Missing X-ray Scores
- Characteristics of X-ray Missing Cohort
- Correlation Between X-ray Score and Clinical Measurements
- Sensitivity Analysis

X-ray Assessment

- Placebo Controlled Phase III Studies
  - US301: 1 year
  - MN301: 6 months
- X-Ray Schedule
  - Baseline
  - End of Study

X-ray (Non-missing) Results

Treatment Group	N (%)	Change from Baseline	Difference LEF vs. PLB	P-value LEF vs. PLB
US301 (12 Mo)				
Leflunomide	131 (73%)	0.53	-1.63	0.0007
Placebo	83 (70%)	2.16		

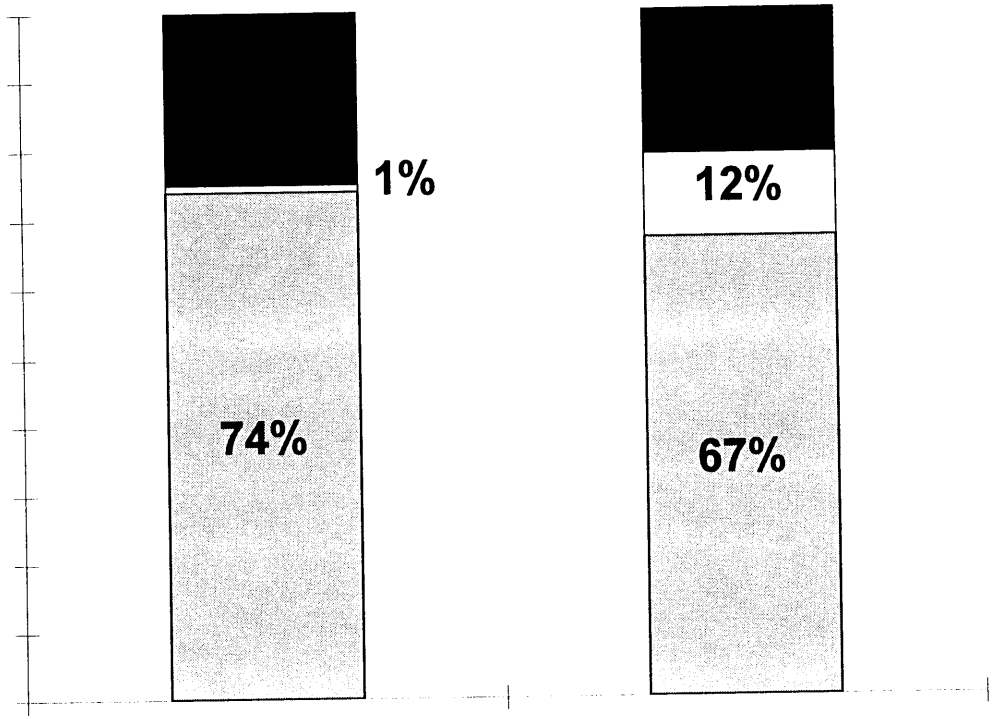
X-ray (Non-missing) Results

Treatment Group	N (%)	Change from Baseline	Difference LEF vs. PLB	P-value LEF vs. PLB
MN301 (6 Mo)				
Leflunomide	89 (68%)	-0.06	-5.66	0.0081
Placebo	62 (68%)	5.60		

Causes for Missing X-rays

- Lost to Follow-up
- Unreadable X-ray

Patient Distribution



Distribution of the Missing Cohort Among Treatment Groups

The Distribution of Missing X-ray Was Similar Among Treatment Groups in Both Studies

Baseline X-ray Score

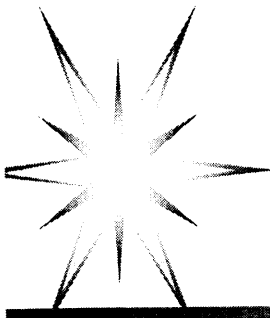
- US301
  - Baseline X-rays in the Lost to Follow-up Cohort Were Not Read by Dr. Sharp.
- MN301
  - Baseline Scores Were Not Available in the Unreadable Cohort.
  - No Statistical Significance Was Found in Baseline X-ray Scores Between the Lost to Follow-up Cohort And Non-missing Cohort.

Correlations Between Changes in X-ray Score and Clinical Measurements

US301:

	R	P-value
Change in SJC	.13	.03
AUC	.15	.01

MN301: None



Question

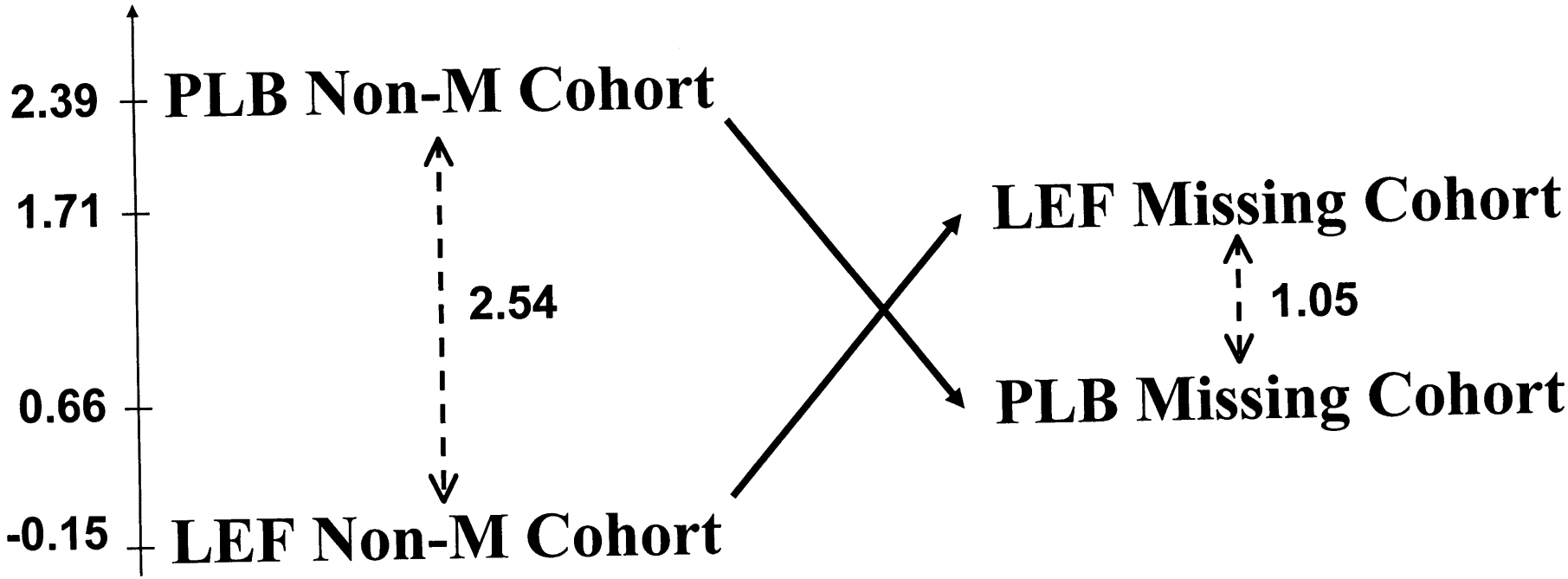
How Different Would the Missing Cohort Have to Be From the Non-missing Cohort to Nullify the Statistical Significance in the Non-missing Cohort?

Sensitivity Analysis

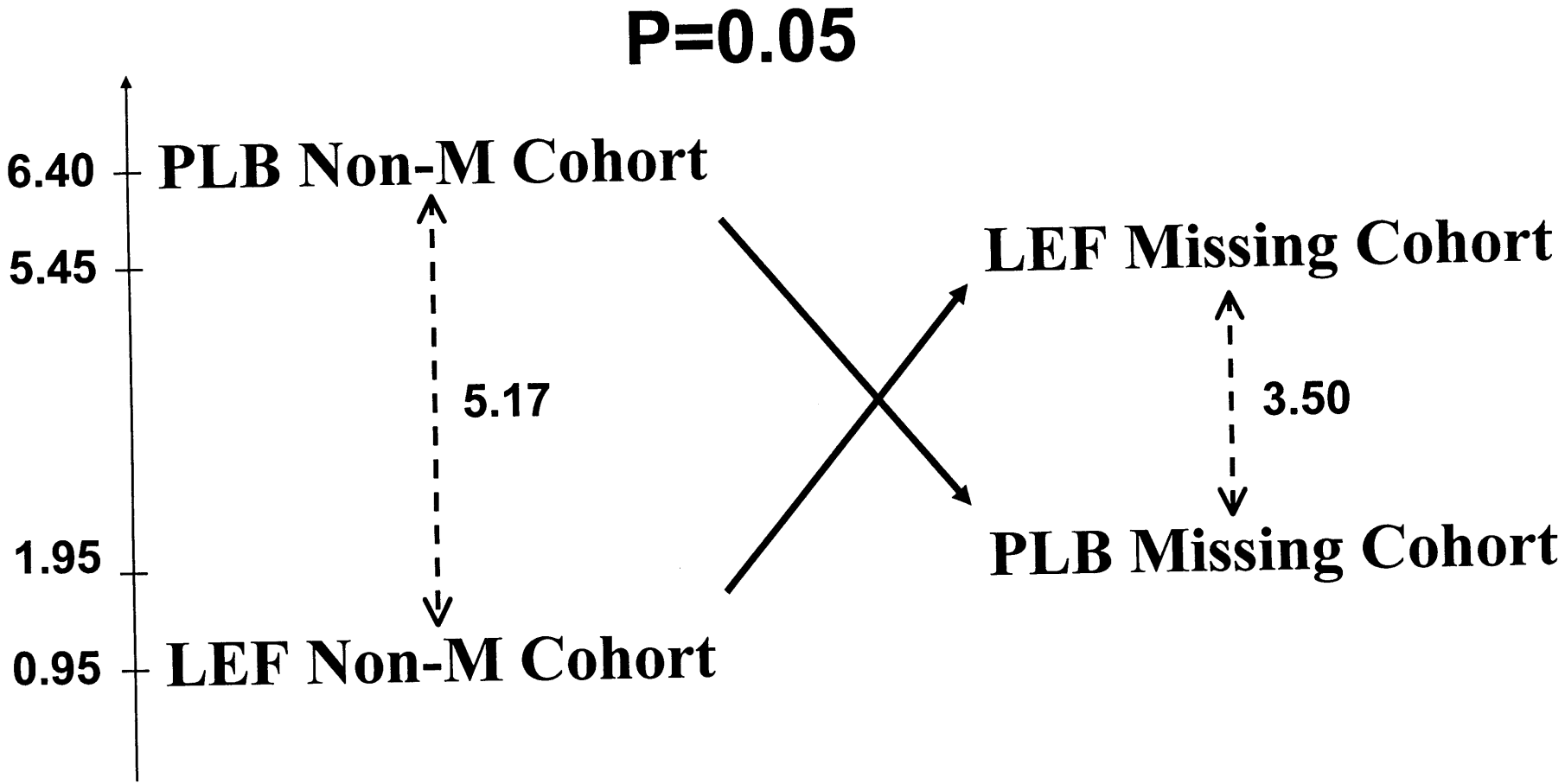
- Randomly Select X-ray Scores From the Non-missing Cohort and Assign Them to the Corresponding Treatment in the Missing Cohort.
- In the Missing Cohort, Raise the Scores in the LEF Group and Lower the Scores in the PLB Group by the Same Size, Until the Overall P-value Reaches .05.

Results (US301)

P=0.05



Results (MN301)



Summary

- To Nullify the Statistical Significance, PLB Would Have to Be Better Than LEF in the Missing Cohort (US301:1.05, MN301:3.50)

- Validation of Sponsor's Results?