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Augmentation Strategies – Focus on Depression Methodology and Regulatory Perspective

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Adjunctive vs. Augmentation Treatment

- The case for adjunctive therapy
  - Builds on partial success of first therapy
  - Avoiding washout is a pragmatic benefit for patients
  - When effective, benefits may be more rapid
  - Allows choice of treatment to target specific symptoms

- The term “adjunctive” is a strictly descriptive term
  - no assumption regarding mechanism

- The term “augmentation” suggests that the second medication enhances the pharmacological effect of the first treatment

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Adjunctive Treatment of MDD With Compound A: Target Population

- Patients who have had an inadequate response to antidepressant monotherapy (1-3 antidepressants)
  - Not intended as first-line treatment
  - Not intended for an indication of treatment-resistant depression
  - Inadequate response to tricyclics (TCAs) or MAOI antidepressants was not investigated

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Compound A as Adjunctive Treatment in MDD

- Indication in the US for 'Adjunctive treatment of major depressive disorder'
- 'Efficacy was established in two 6-week trials in patients with MDD who had an inadequate response to antidepressant therapy during the current episode'
- Studies conducted between June 2004 and September 2006
- A third double-blind study of the same design was also positive

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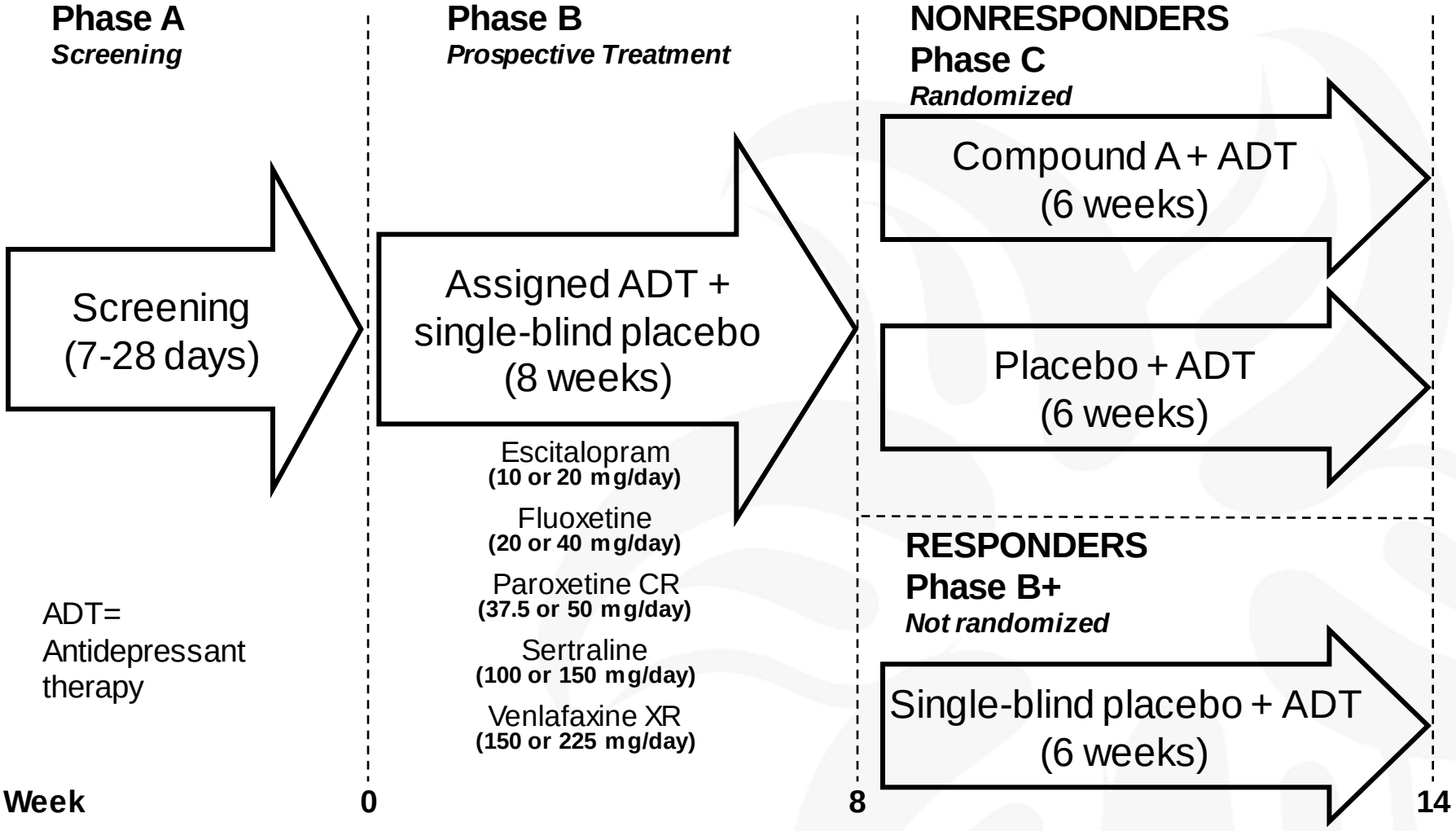
Overview of Study Design



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Phase A: Screening

- Inclusion criteria:
  - MDD patients who have a history of an inadequate response to 1-3 antidepressant trials in the current episode
  - HAMD-17 Total Score ≥ 18
  - No other significant psychiatric diagnoses
  - No prior atypical antipsychotic in current episode

HAMD-17 = 17-item Hamilton Depression Rating Scale

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Phase B: Prospective Antidepressant Treatment (ADT)

- 8-week single-blind placebo and open-label ADT treatment phase
  - Patients received a different ADT from previous treatments in the current episode
  - Choice of ADT was based on investigator judgment
  - ADTs administered:
    - Escitalopram 10 or 20 mg/day
    - Fluoxetine 20 or 40 mg/day
    - Paroxetine CR 37.5 or 50 mg/day
    - Sertraline 100 or 150 mg/day
    - Venlafaxine XR 150 or 225 mg/day

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End of Phase B: Randomization Criteria

- Patients with inadequate response to 8-week ADT monotherapy treatment were randomized to double-blind adjunctive treatment in Phase C
  - Inadequate response defined by all of the following:
    - <50% decrease on HAMD-17 Total Score versus end of Phase A
    - HAMD-17 Total Score ≥ 14
    - CGI-I ≥ 3 (minimally improved or worse)
- Open-label antidepressant from Phase B continued at same dose
- Double-blind Compound A started at 5 mg/day
  - Dose range 2 – 20 mg/day based on tolerability and efficacy
  - Target dose 10 mg/day if “well tolerated”

Study Endpoints

- Primary endpoint:
  - Mean change in Montgomery-Asberg Depression Rating Scale (MADRS) Total Score from end of prospective treatment phase to end of randomized treatment phase (LOCF)
- Key secondary endpoint:
  - Mean change in the Sheehan Disability Scale score from end of prospective treatment phase to end of randomized treatment phase (LOCF)
- Secondary efficacy measures:
  - Mean change in MADRS Total Score at each visit
  - Mean change in Clinical Global Impression-Severity of Illness (CGI-S) score
  - Mean change in Inventory of Depressive Symptomatology Self-Report Scale (IDS-SR) Total Score

LOCF = Last observation carried forward

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Subject Disposition

	Study 1	Study 2
Enrolled	1044	1151
Entered Phase B	781	830
Discontinued Phase B	159 (20.4 %)	179 (21.6 %)
Completed Phase B	622 (79.6 %)	651 (78.4 %)
Inadequate response to ADT in Phase B and randomized into Phase C	360 (57.9 %)	381 (58.5 %)
Completed Phase C	320 (88.9 %)	324 (85.0 %)

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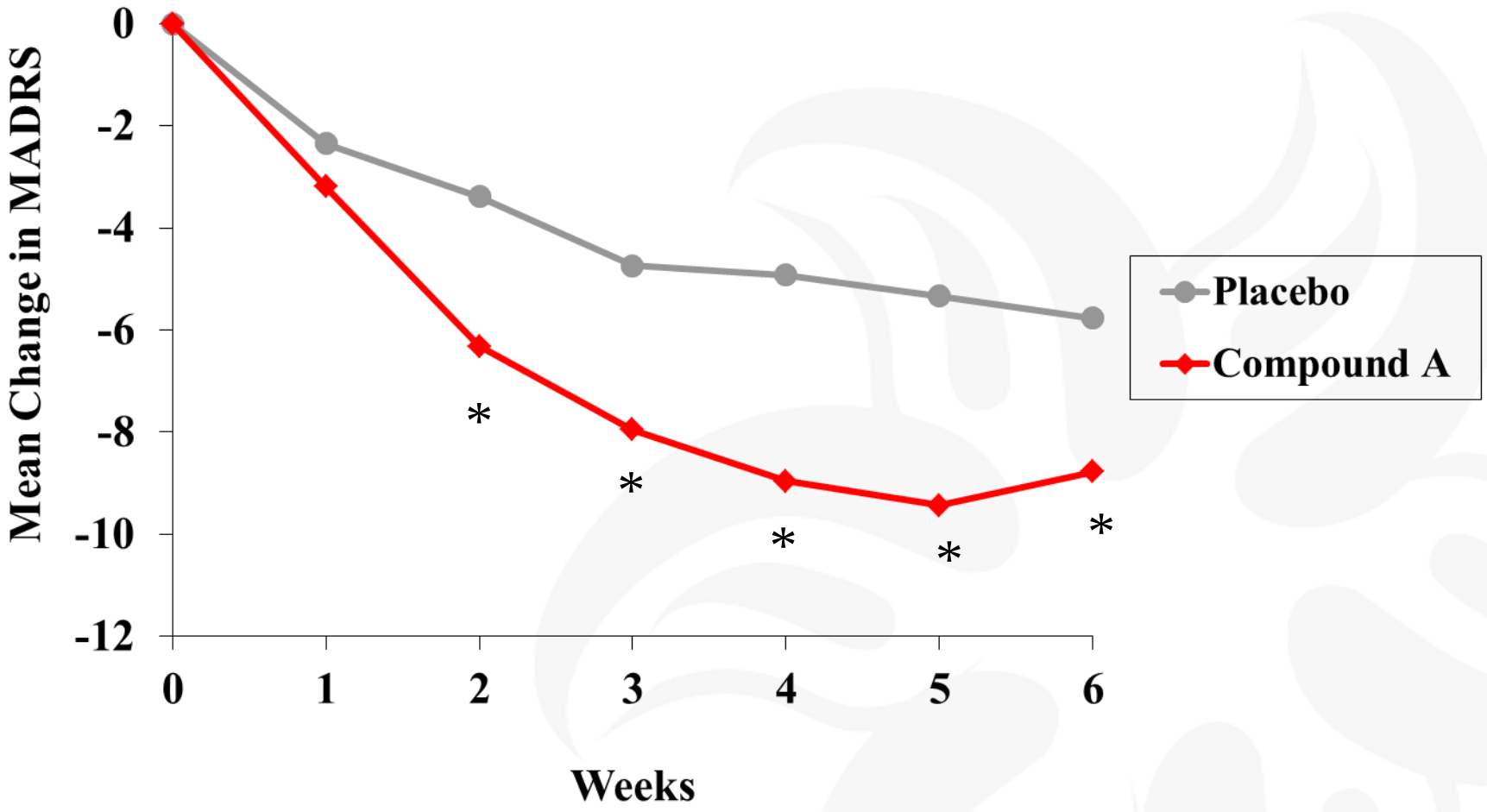
Effects of Compound A on MADRS Total Score (Study 1, LOCF)



Baseline MADRS: Placebo = 25.65, n=172; Compound A = 25.88, n=181
* $p < 0.001$, ANOVA/ANCOVA

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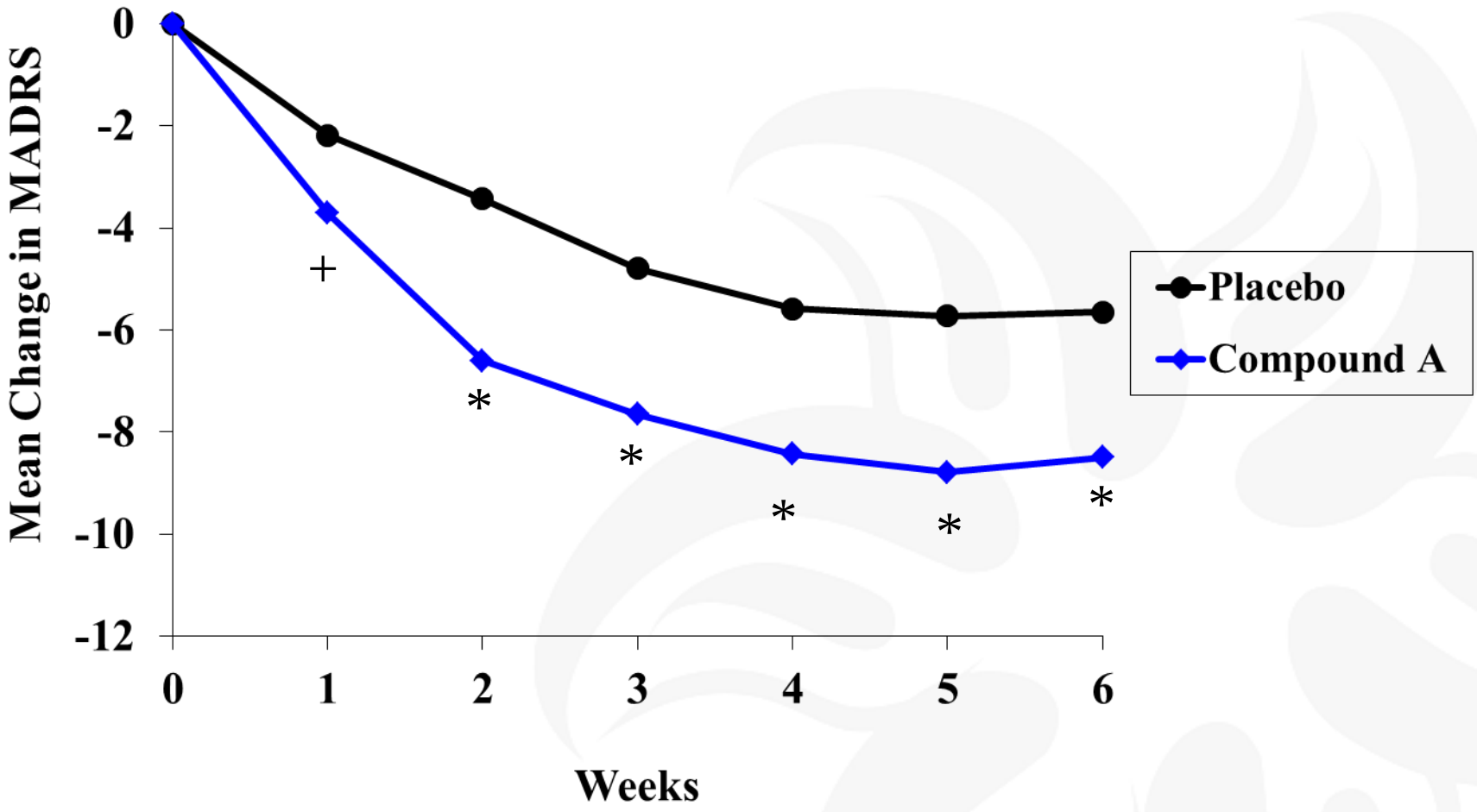
Effects of Compound A on MADRS Total Score (Study 2, LOCF)



Baseline MADRS: Placebo = 26.55, n=184; Compound A = 24.59, n=185
+ $p < 0.01$* $p < 0.001$, ANOVA/ANCOVA

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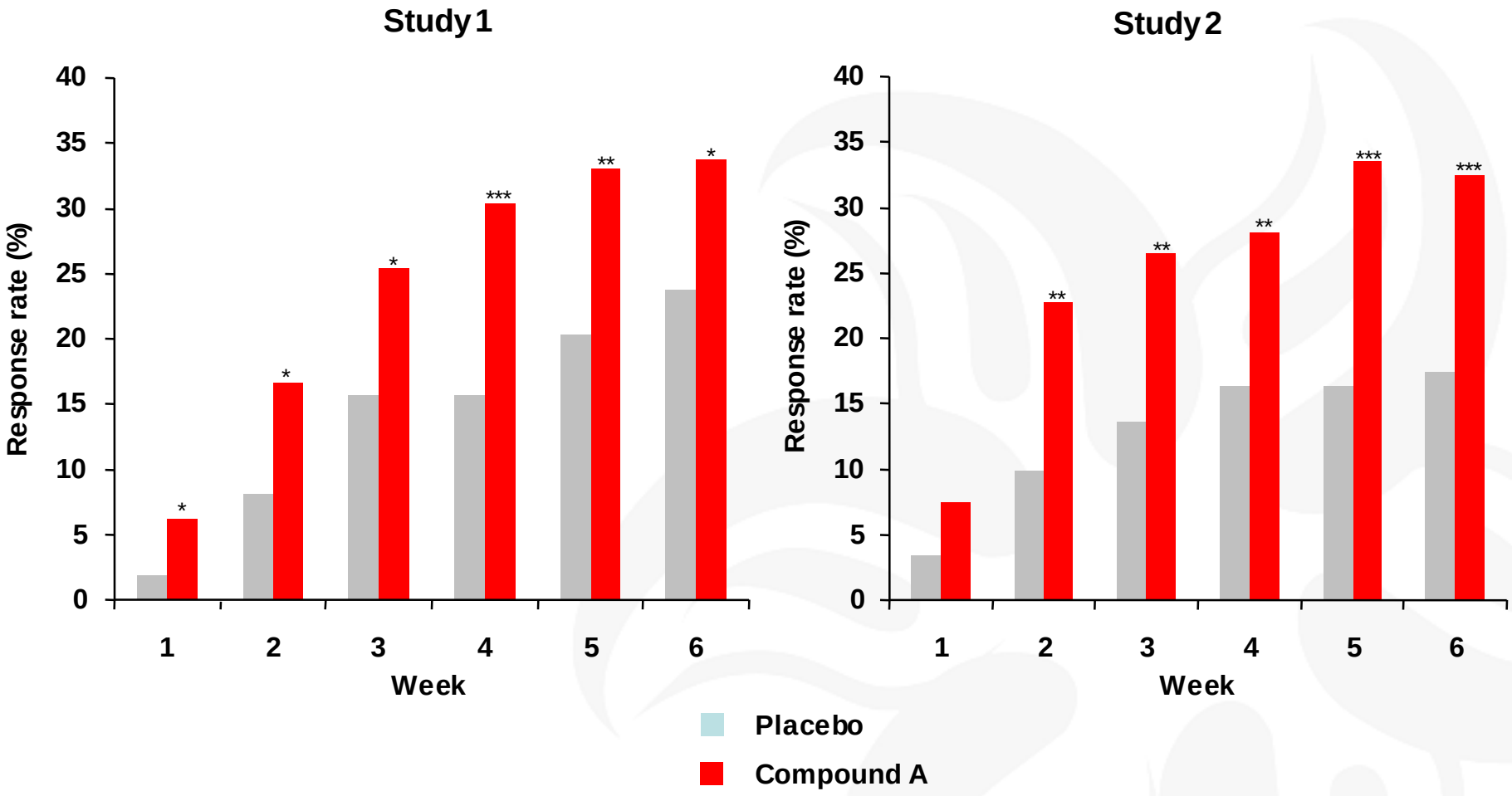
MADRS Response Rates



*p≤0.05 vs placebo; **p≤0.01 vs placebo; ***p≤0.001 vs placebo; Response = Patient with ≥50% decrease from baseline on MADRS score; MADRS = Montgomery-Asberg Depression Rating Scale

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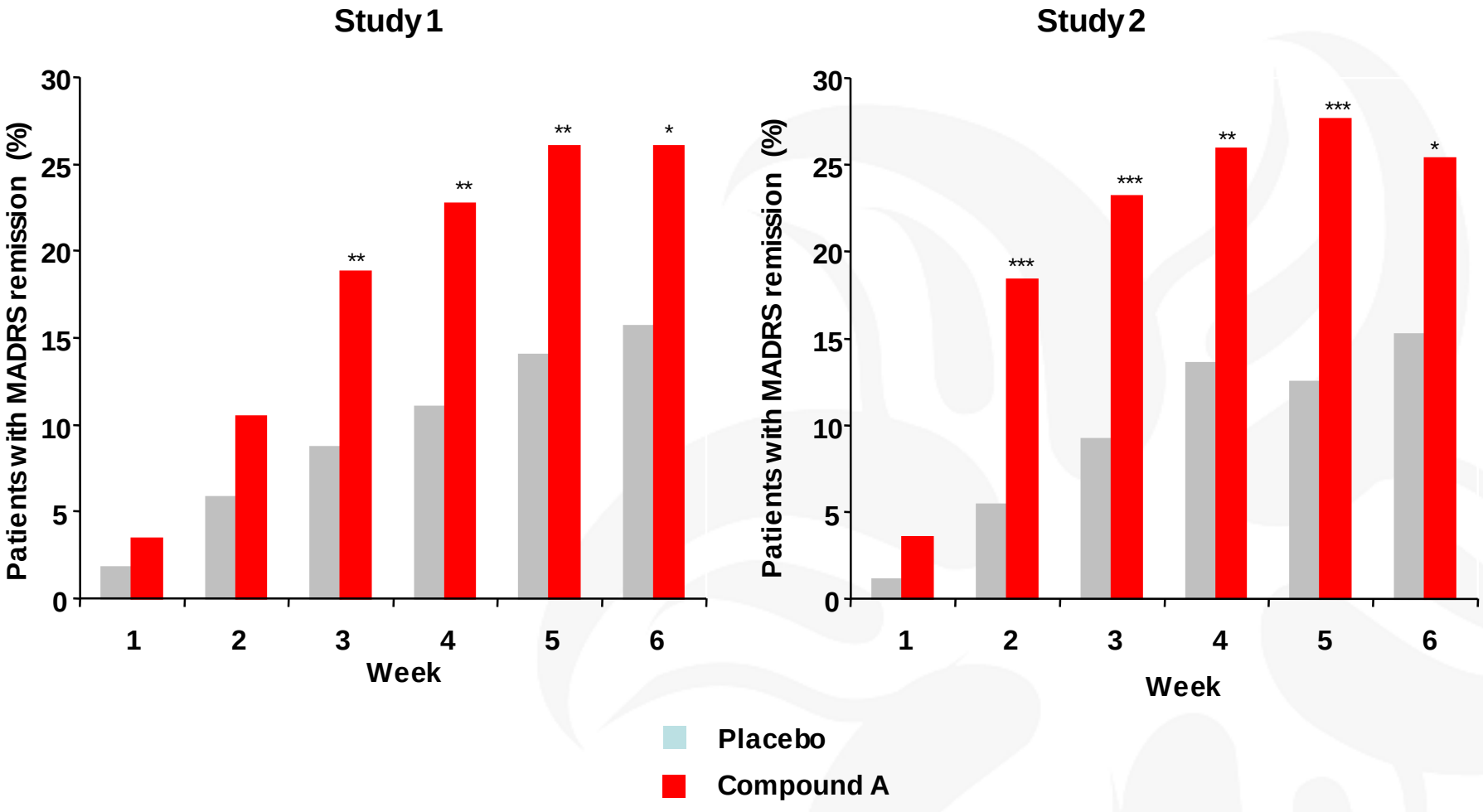
MADRS Remission Rates



*p≤0.05 vs placebo; **p≤0.01 vs placebo; ***p≤0.01 vs placebo; Remission = MADRS Total score of ≤10 and ≥50% reduction in MADRS Total score from end of prospective treatment; MADRS = Montgomery-Asberg Depression Rating Scale

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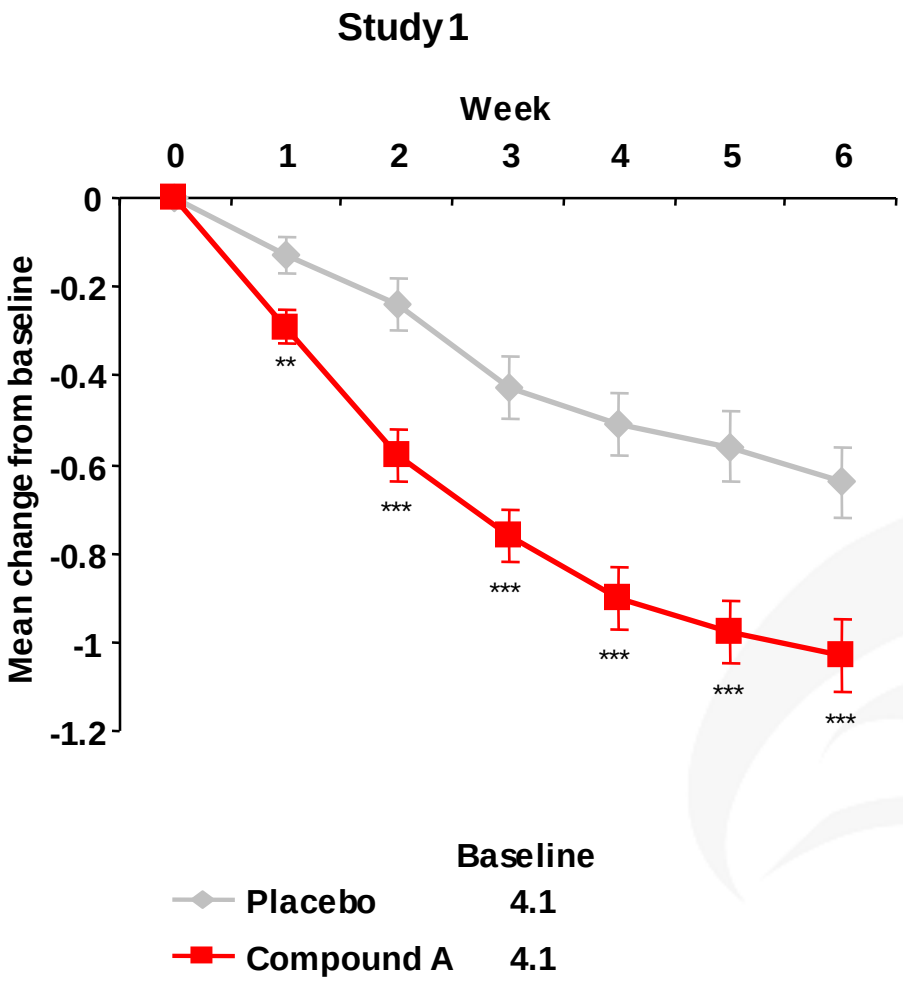
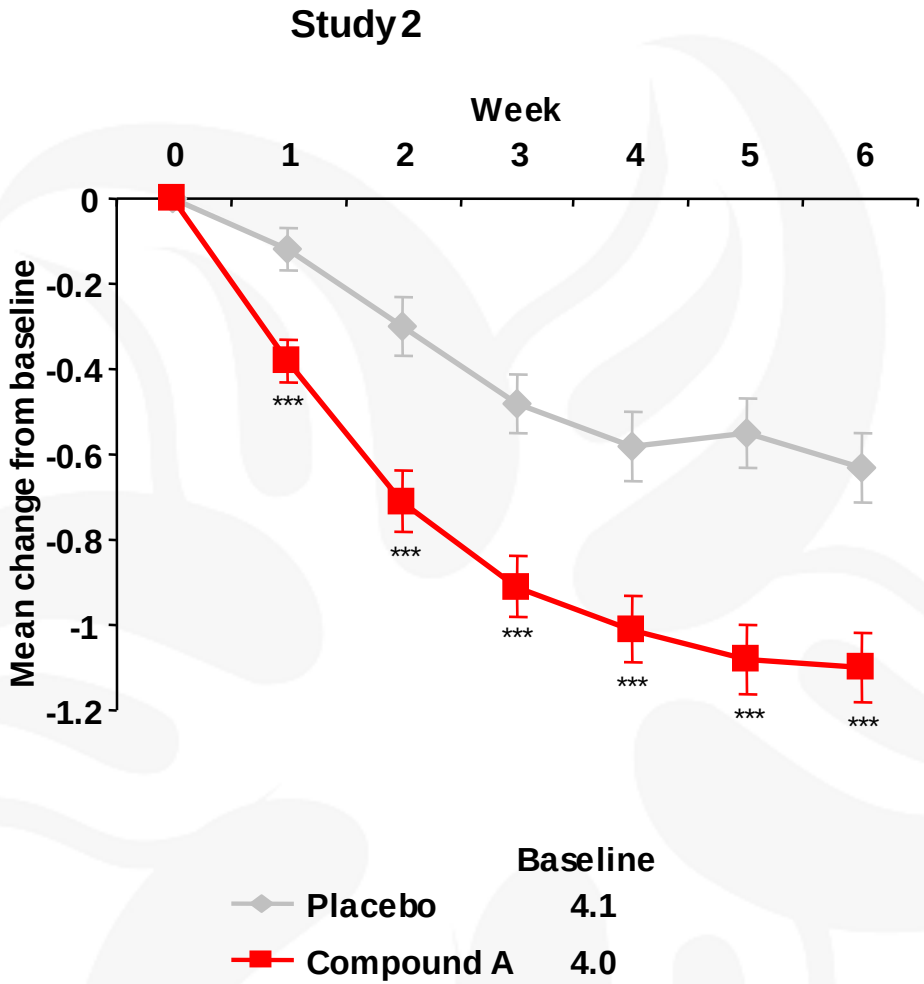
CGI-Severity Scores (LOCF)





*p<0.05 vs placebo; **p<0.01 vs placebo; ***p<0.001 vs placebo; LOCF = Last observation carried forward

- This study design was innovative at the time but is now widely used
- Placebo responses have been rising in MDD studies
- What changes, if any, should be made to this design to study a new drug in 2012?