ISCTM
THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

Long-Term Therapy in Psychiatry

Industry Perspective: Goals And Hurdles

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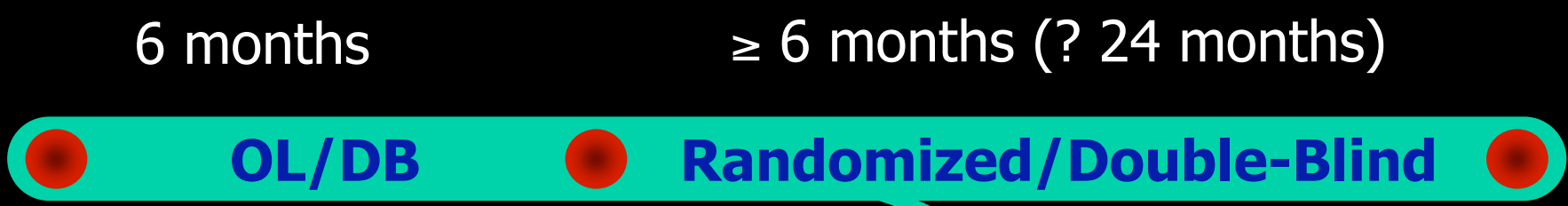
Potential Long-Term Efficacy Claims

- Prevention of relapse [within the index episode] (FDA, CPMP: not a claim in itself)
- Maintenance of effect
- Other:
  - Prevention of recurrence [of new episodes]
  - Effect on disease progression [reduction of intensity, frequency and duration of new episodes]

Relapse Prevention Design

- Prevention of relapse within the index episode
- May consist of multiple phases
  - Stabilization (open label or double-blind)
  - Continued stability (OL or double-blind)
  - Relapse prevention (double-blind)

Relapse Prevention Design



Baseline 1
- Acute treatment
- Stabilization

Baseline 2
- Randomization
  - Test drug
  - Comparator

- Relapse (time to and/or incidence)
- Retrieved Dropouts

Relapse Prevention Design

6 months ≥ 6 months (? 24 months)

Depression/Schizophrenia (symptomatic patients)
- Acute treatment 6 weeks
- Stabilization 6 months

Depression/Schizophrenia (stable patients)
- Historical documentation
- Cross titration and stabilization 6 months

BPD-Frequently Relapsing
- Stabilization 4-6 months

Schizophrenia with suicidality
- No stabilization needed

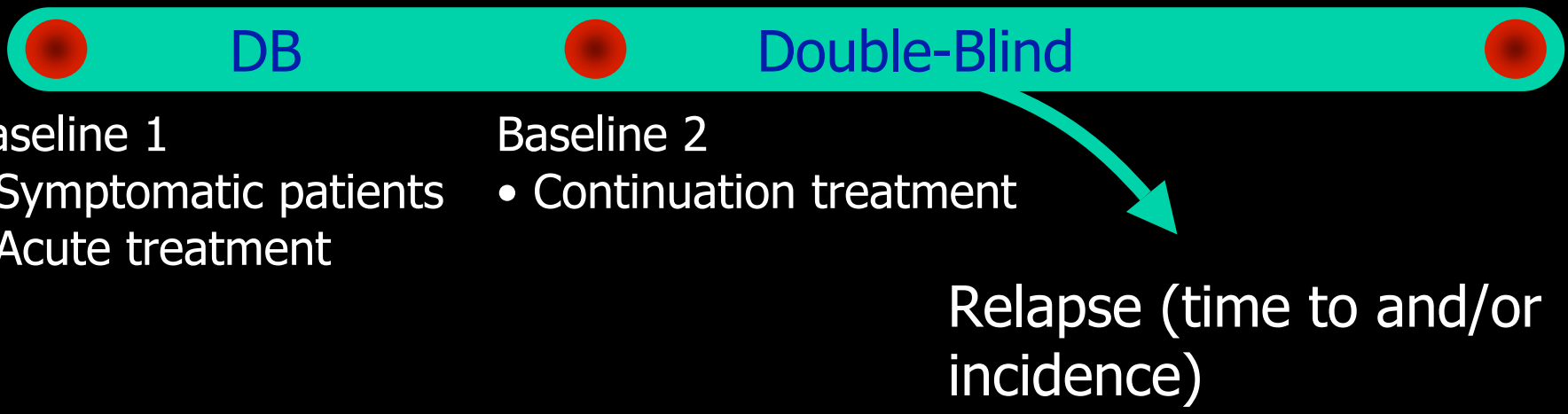
Relapse Prevention Design

6 months ≥ 6 months (? 24 months)

Depression ≥ 6 months
Schizophrenia ≥ 12 months
BPD ≥ 18-24 months
Schizophrenia suicidal ≥ 24 months

Relapse Prevention Design

Alternative Design



This design although not favored has led to relapse prevention labeling by CPMP

Relapse Prevention Design

At study entry: patients

- Acutely ill or symptomatically stable
  - Acutely ill
    - More likely to relapse within a shorter period
    - Ziprasidone in schizophrenia, lamotrigine in BPD
    - InterSept → patients with active suicidality
  - Symptomatically stable
    - Less likely to relapse, may need longer study duration
    - Risperidone versus haloperidol in schizophrenia

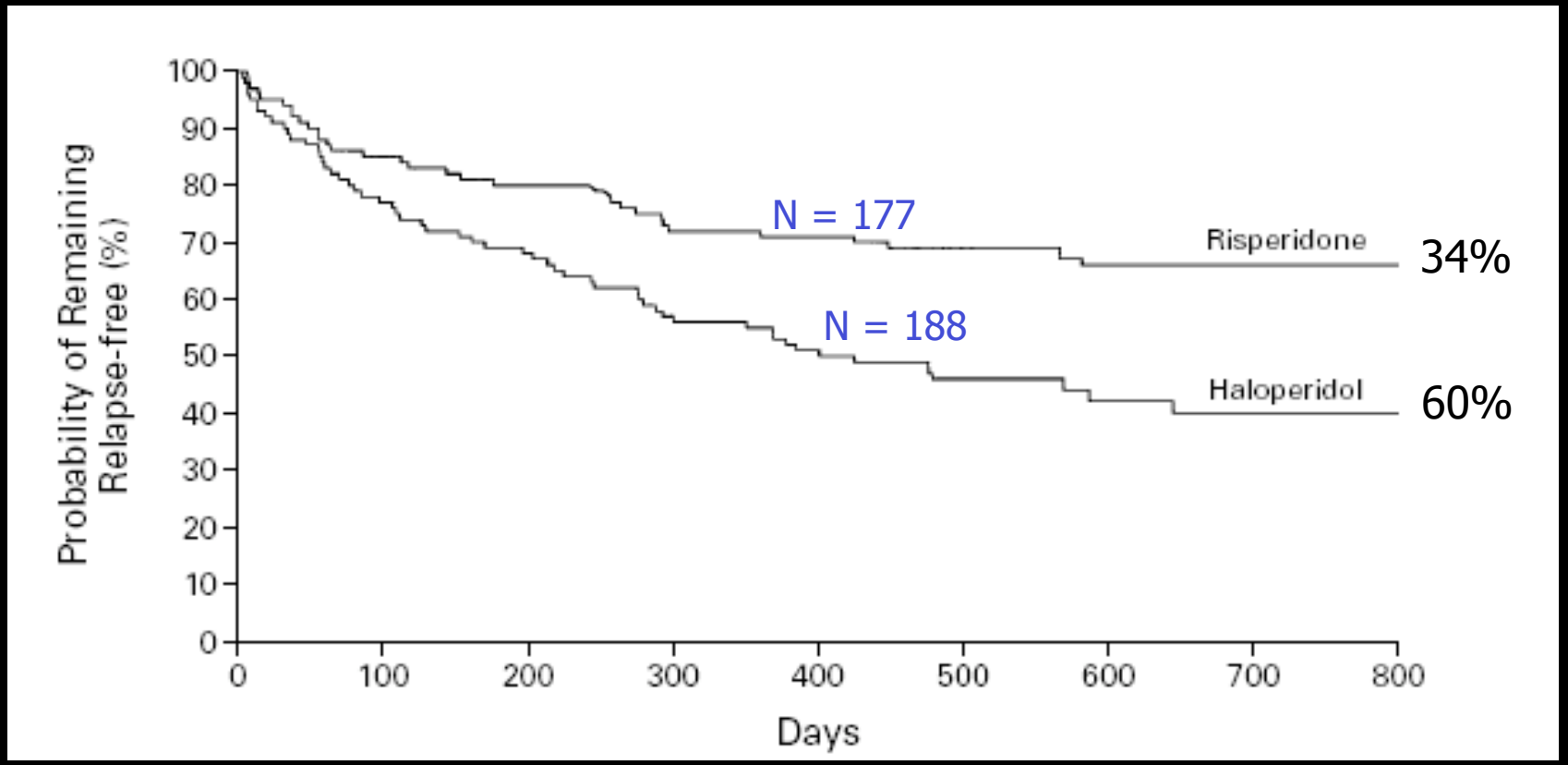
Relapse Prevention Design

- Stabilization period
  - Criteria for stability
  - Extended stability needed? Why? Consistency with relapse within the index episode?
  - Visit frequency
  - Score deflation
  - Patients who fail to meet stability criteria

Relapse Prevention Design

- Randomized treatment
  - Use of placebo versus active comparator
  - Active comparator: superiority versus non-inferiority
    - NCE (AP) versus haloperidol: non-inferiority design
    - 600 patients per group: adequate to show non-inferiority based on <4 points difference on the PANSS total
  - Abrupt withdrawal versus tapering
  - Visit frequency
    - Frequent visits→ versus clinical practice
    - Infrequent visits→ may miss symptom fluctuations
  - Drug effect versus drug regimen effect

Relapse Prevention: Stable Patients with Schizophrenia at Baseline



Median duration of treatment RIS 364 (3-799) versus HAL 238 (4-794)

Csernansky et al, NEJM Jan 2002

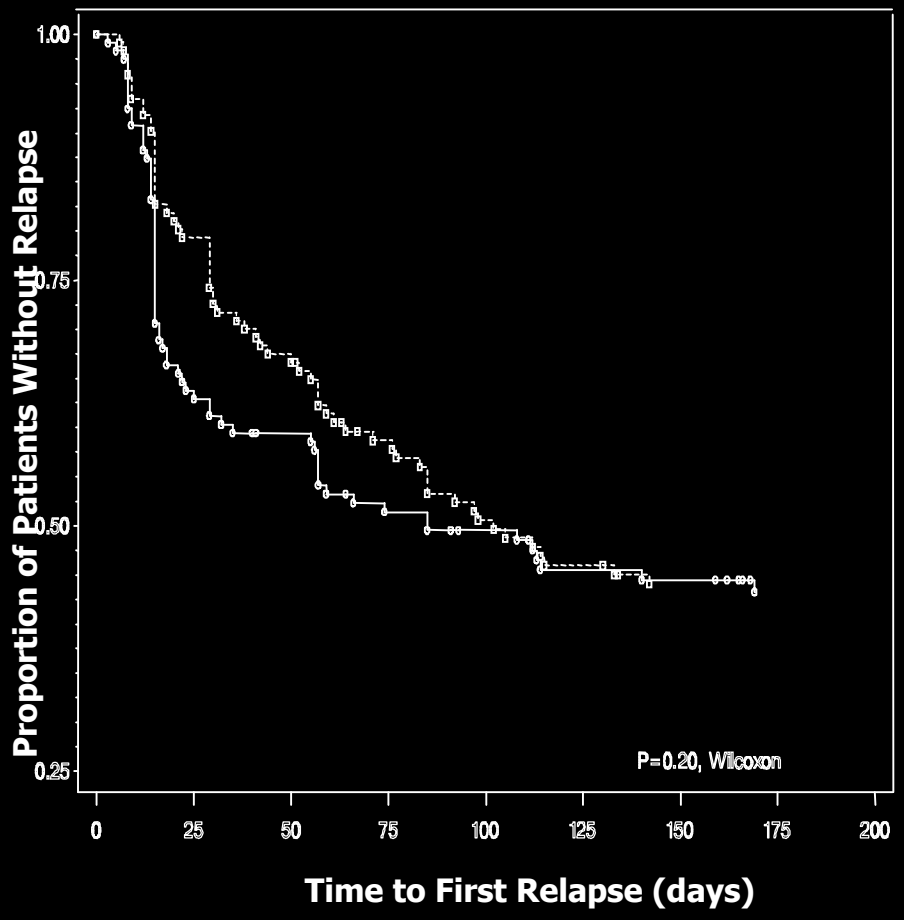
Relapse Prevention Design

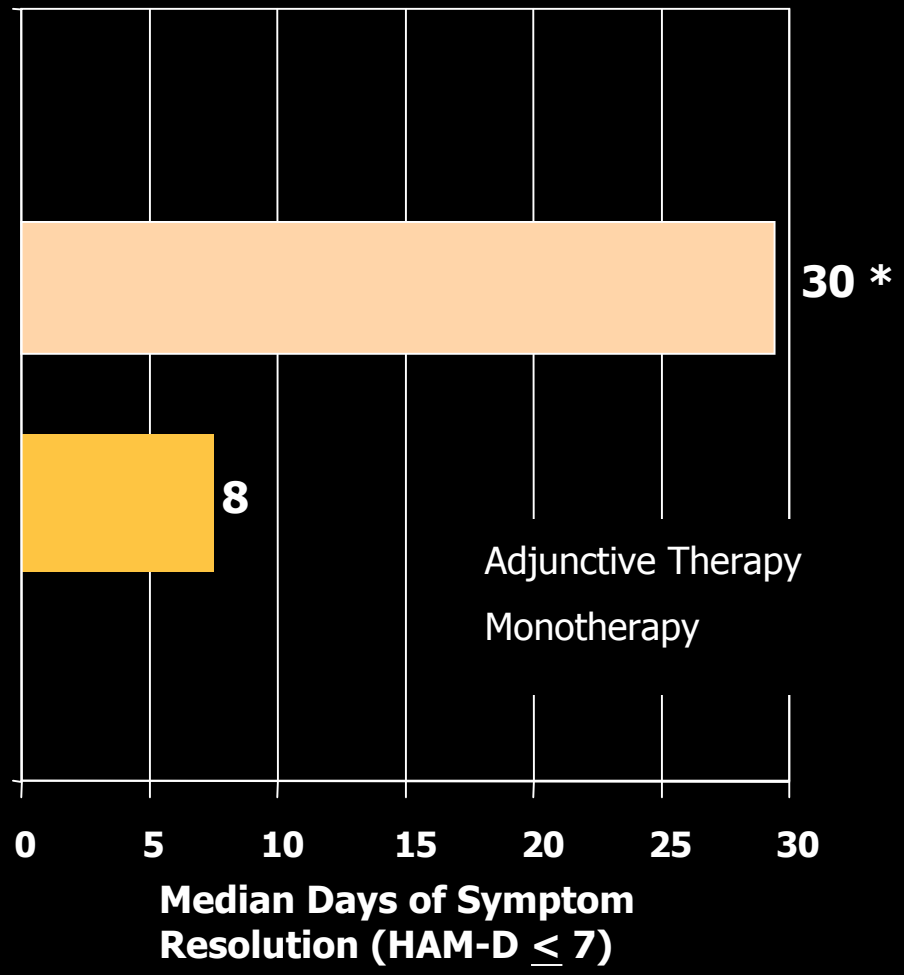
- Randomized treatment
  - Definition of relapse (diagnosis specific)
    - Combination of hard and soft criteria
      - Total scores and CGI
      - Hospitalization
      - Event under study e.g., suicidal event, substance use
      - Use of rescue medication
    - Short-lived event in chronic illnesses
    - Need for confirmation of relapse
  - Use of independent monitoring boards

Relapse Prevention Design

- Outcomes
  - Incidence versus time to relapse
  - Alternative outcomes
    - Number of "days well"
      - Diagnosis specific
      - Investigator versus patient/informant reported
    - Frequency, severity and duration of symptom fluctuations
      - Cyclical disorders

Relapse Prevention Design





Relapse Prevention Design

- Following relapse or dropout
  - Retrieved dropouts (RDO)
    - Visit frequency
    - What treatment? Test drug versus treatment as usual
    - How to integrate data from RDO patients
      - Time to event [re-remission]/second event following remission
      - True ITT

Relapse Prevention Design

- RPT measure failure rate in patients who initially responded to treatment
  - Trial duration is becoming prohibitive
  - Placebo rejected by most IRBs/ECs in the USA/W-EU
- Most frequently asked question, i.e., "will continuing medication that induced benefit (e.g., remission) maintain this benefit for long-term use", is not answered by the RPT design
- Maintenance of effect trials would answer this question

Maintenance of Effect Design

- Concept:
  - Achieve predefined therapeutically relevant response (response/remission)
  - Maintenance of the achieved benefit during the extended treatment
- Consists of multiple phases
  - Symptom control: double blind
  - Maintenance of effect: double blind

Maintenance of Effect Design

Baseline 1
- Acute treatment
- Control:
  - Placebo
  - Active comparator

Baseline 2
- Continue all patients on current medication
- Benefit definition applied

Maintenance of Effect Design

- At study entry: patients
  - Symptomatically unstable
  - Criteria
    - Criteria for severity DSM, core symptoms, proxy symptoms (aggression or agitation)
    - Duration of symptom exacerbation (recency) versus chronicity or symptom resistance

Maintenance of Effect Design

- At the end of stabilization
  - Definition of stability/benefit
    - symptom control or remission
    - Composite criteria e.g., PANSS + CGI
  - Criteria for continuation therapy
  - Patients who do not meet criteria for stability
    - Follow up? For how long?

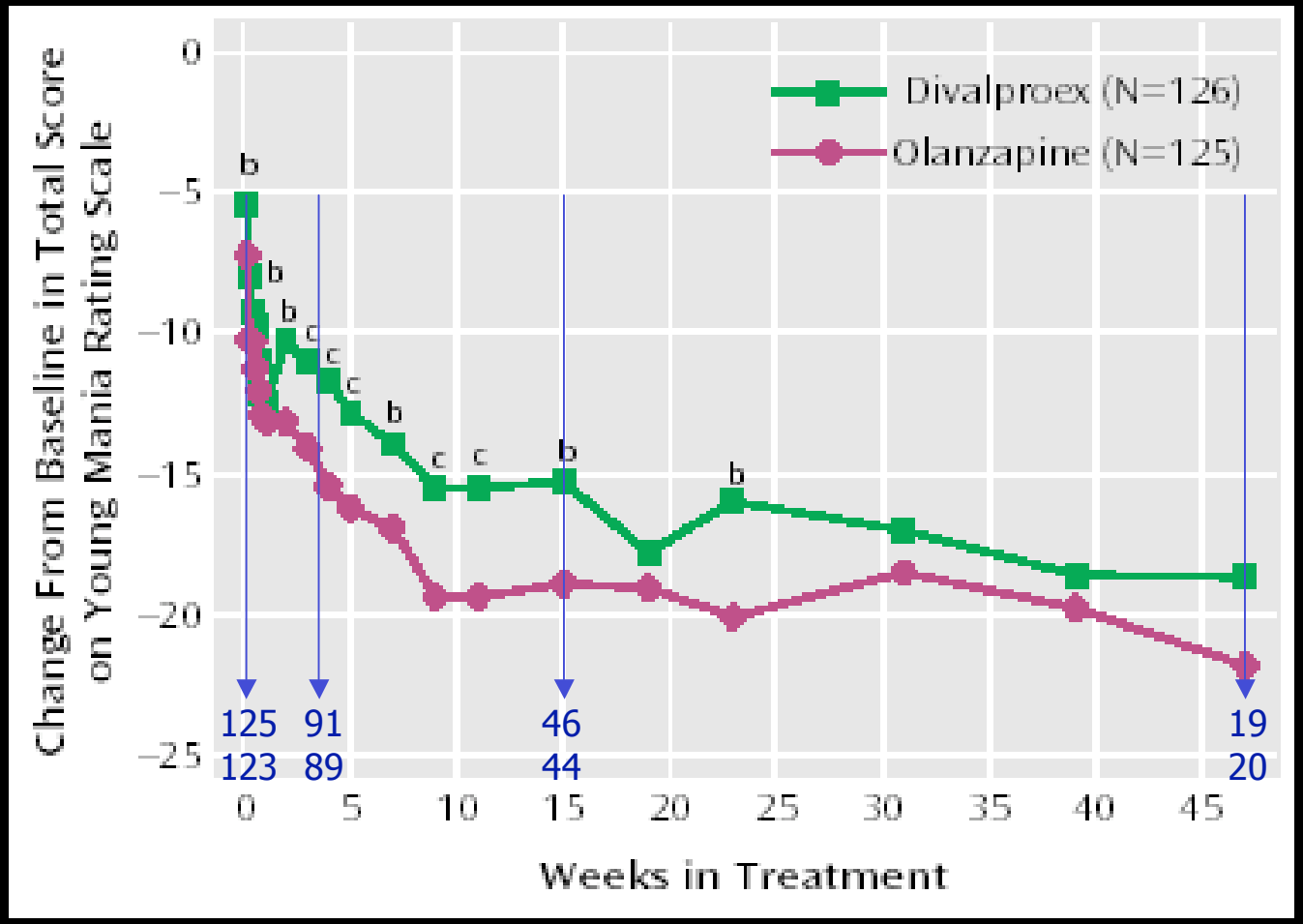
Maintenance of Effect Design

- Continuation therapy:
  - Maintenance of placebo?
  - Superiority versus non-inferiority
  - Duration of treatment
  - Visit frequency
  - Use of rescue medication
  - Issue of dropouts

Maintenance of Effect Design

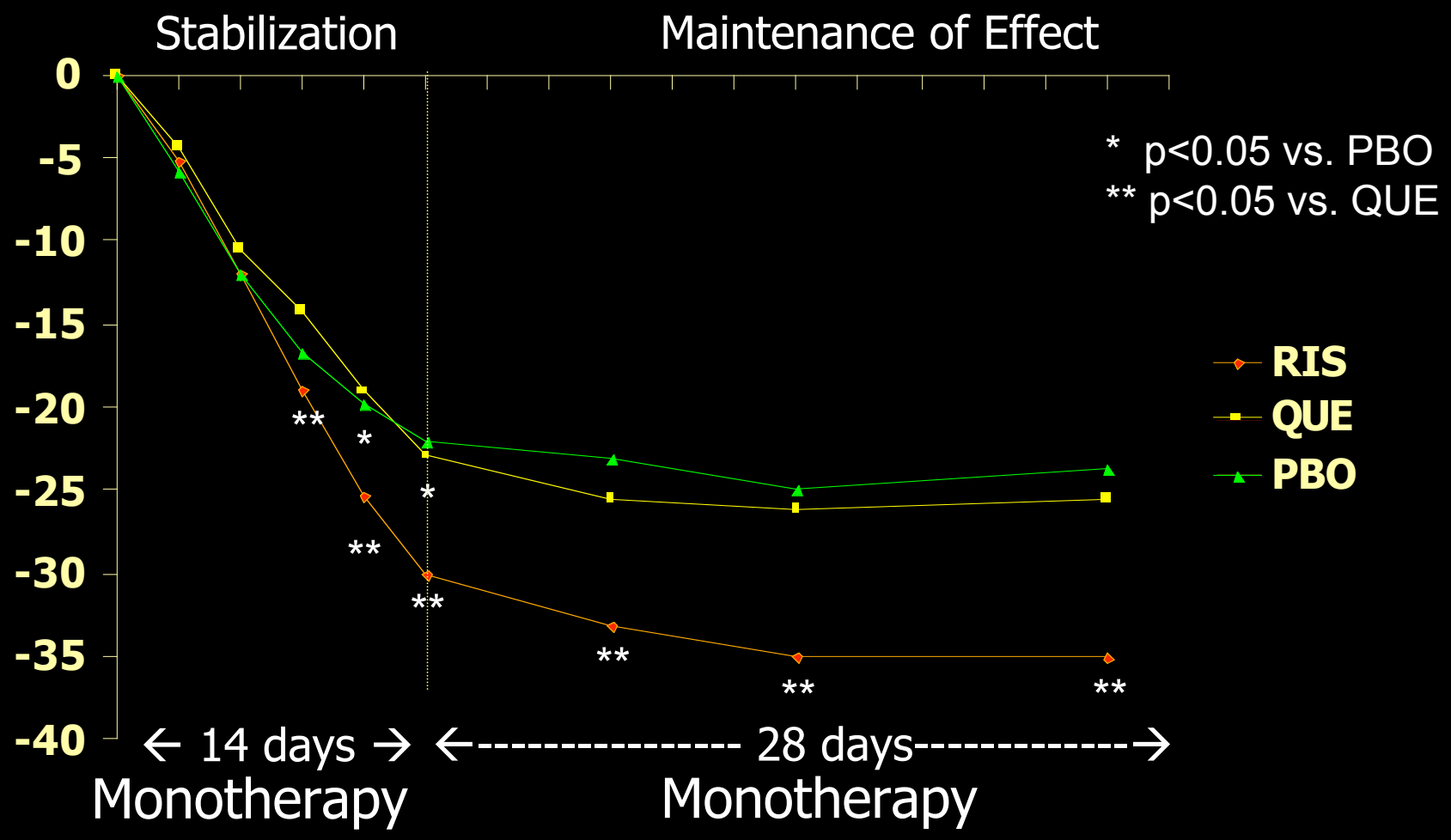
- Outcome
  - Percent of patients at week 52 maintaining benefit seen at 6 week endpoint
    - Compare to active control (non-inferiority – CPMP)
    - Mean change from week 6 to week 52 in responders (statistical issues)
    - Lack of use of rescue medication
  - Area under the curve
    - Number of days well or in remission
      - MDD, anxiety disorders
      - Schizophrenia, BPD
      - Substance abuse disorders
    - Investigator versus patient reported outcomes

OLZ versus Divalproate BP Mania



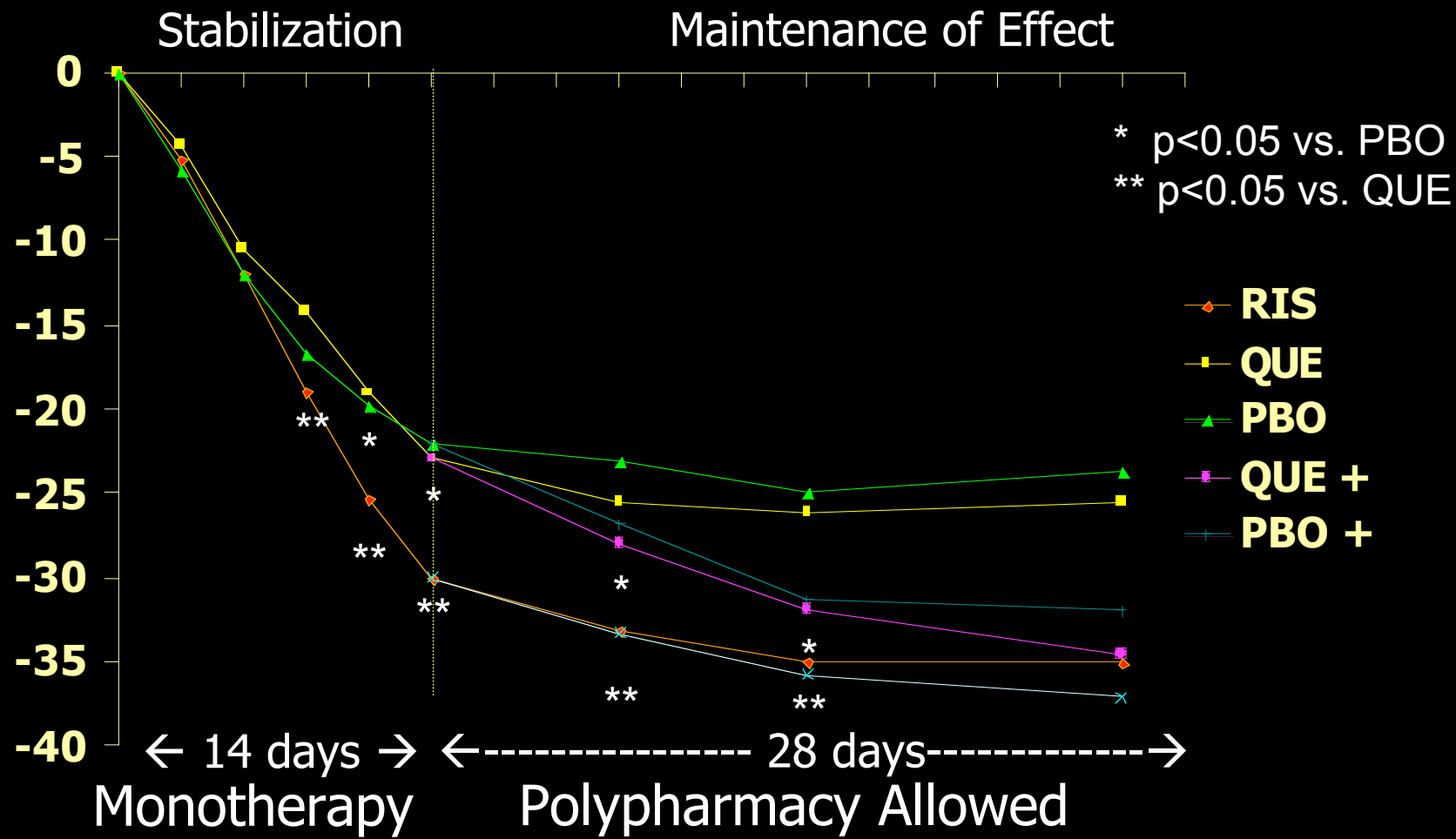
Tohen et al, AJP July 2003

Maintenance of Effect Design



Potkin et al, CINP 2004

Maintenance of Effect Design



Potkin et al, CINP 2004

Maintenance of Effect Design

- Statistical analyses
  - Mixed model, repeated measures
  - LOCF → last observation will tend to reflect worsening
  - OC → impact of attrition rate
  - RDO → how to integrate the data? True ITT

Maintenance of Effect Design

- Provides useful information to clinicians and patients on benefit of continuing treatment
- Shorter duration and easier to conduct
- Less of an issue for IRBs/ECs, clinicians and caregivers

Additional Designs

- Prevention of recurrence
  - Recurrence: "a reemergence of symptoms [new episode] after a time of no or minimal symptoms"
- Adjunctive treatment designs
  - Treatment as usual ± test drug

Relapse Prevention Design

- Other practical issues
  - Number of patients per site
    - Limit by the number of screened patients (forced randomization)
    - Limit by the number of randomized patients (ratio of screened versus randomized patients)
  - Structure of research grants
    - Load in OL → ↑ ratio screened versus randomized patients
    - Load in DB → ↑ number of ineligible patients