ISCTM
THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

Finding the Signal:

Case studies on how stakeholders (sponsors, sites, patients) influence risks

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Disclosures- S Brannan

- Current Employee at Karuna Pharmaceuticals
- Former employee at:
  - Forum
  - Takeda
  - Novartis
  - Cyberonics
  - Eli Lilly

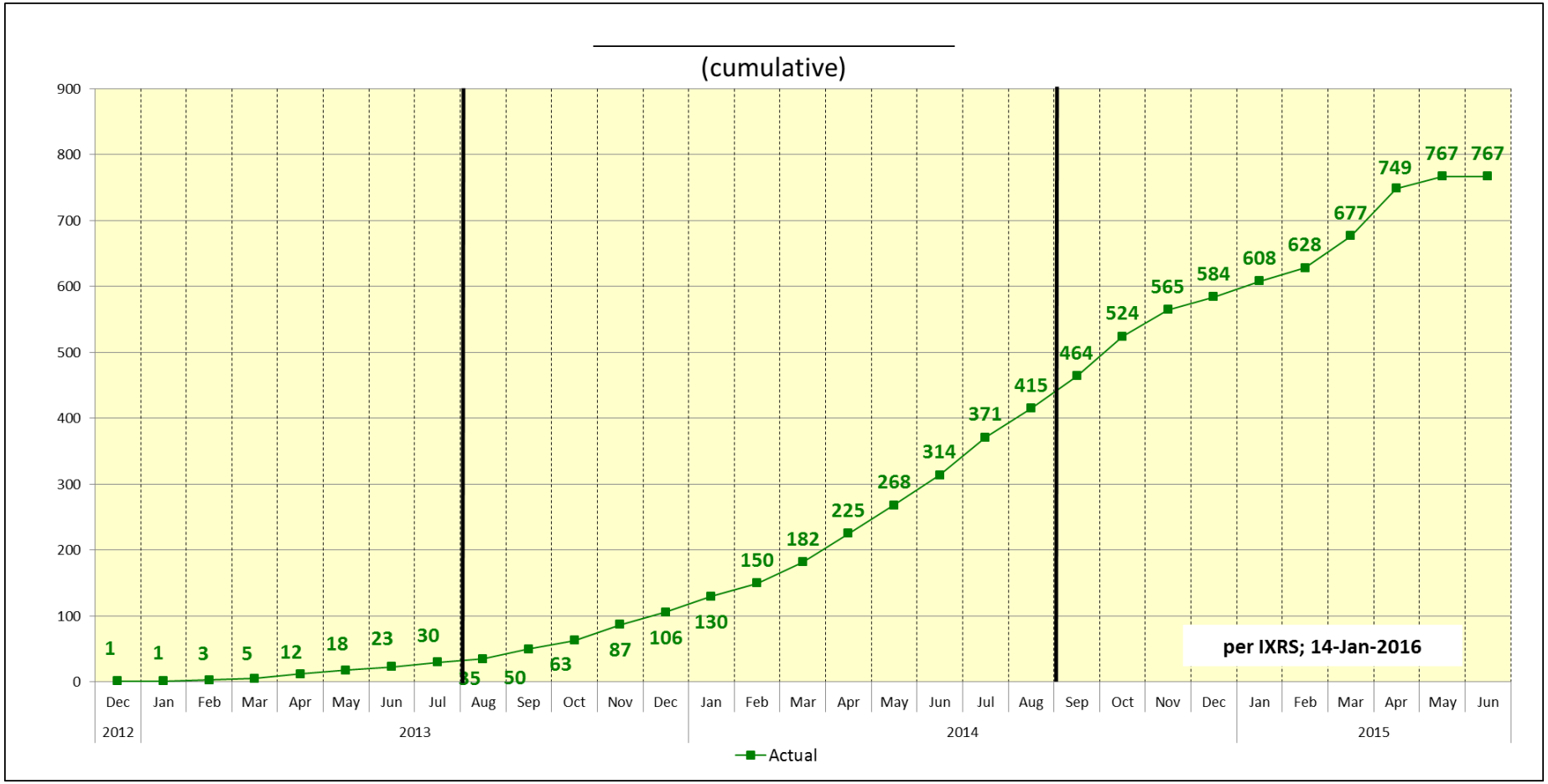
Some Negative Stakeholder Influence Risks for Clinical Trials

- Overly simplistic, inexperienced expectations for speed and broad geographic distribution of sites without regard to the unanticipated consequences
  - Unanticipated consequences of Speed
  - Potential consequences of broad Geographic distribution
- Other issues fraught with unanticipated consequences
  - Trial complexity
  - Frequency of rating scales

Consequences of Speed (in one program)

- I/E Changes to increase the pool of subjects can result in unintended consequences
- Enrollment pressure can have unintended consequences on quality

Randomization of a CNS trial



In an effort to accelerate enrollment, subjects could be enrolled if their regimen included 2 antipsychotics

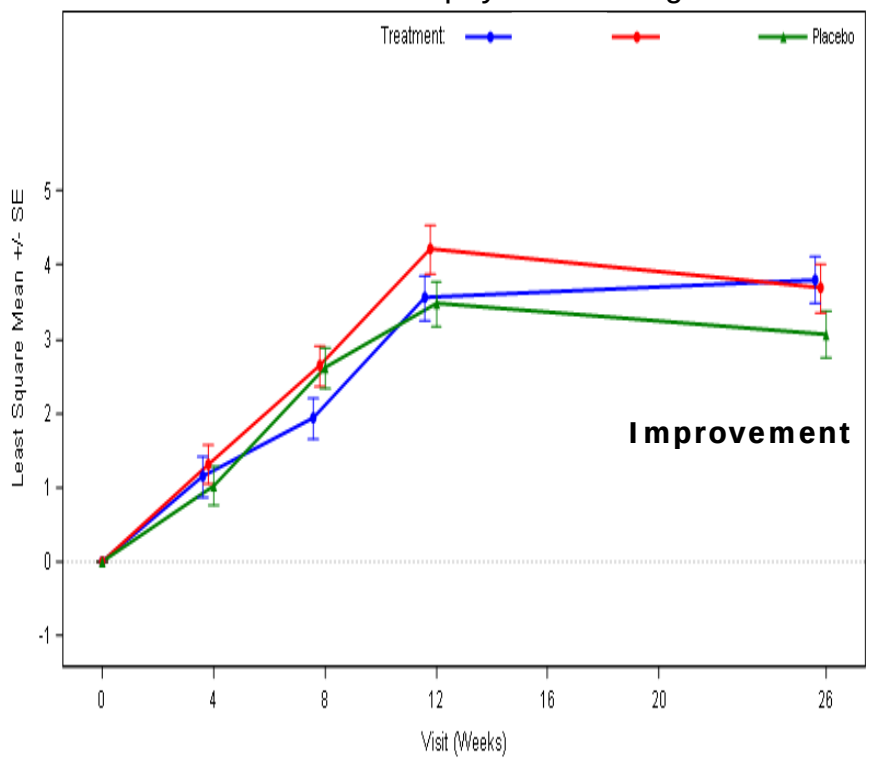
At the end of the trial, the breakdown of how many Antipsychotics subjects were on was:

- Stable on One Antipsychotic, N= 1343(90.55%)
- Stable on Two Antipsychotics, N= 140 (9.44%)

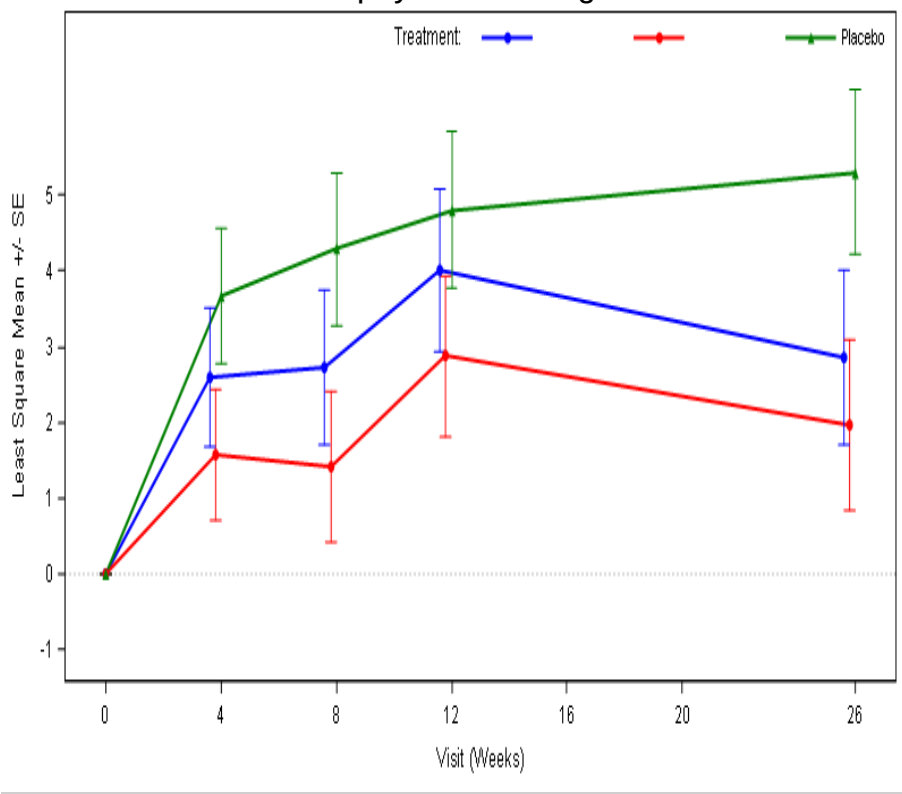
Despite the request from the sites to allow this, only a little less than 10% of subjects enrolled were actually stable on 2 antipsychotics; though there was no reason to believe this group would differ from those stable on 1 Antipsychotic, post hoc analysis showed this not to be the case.

Surprisingly, the 10% of study subjects who were stabilized on 2 Antipsychotics showed a very different placebo response than those on only one antipsychotic

One Antipsychotic Drug

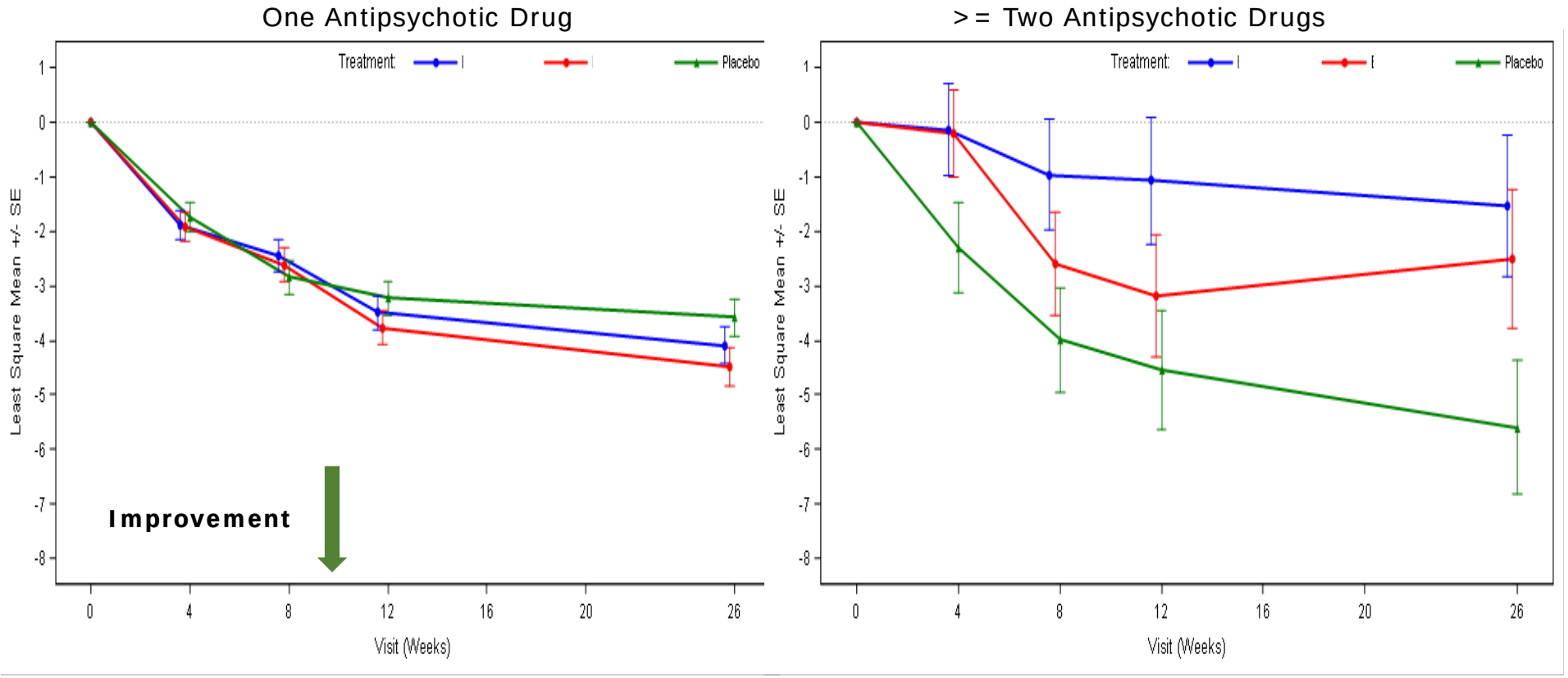


>=Two Antipsychotic Drugs



Least Squares Means (+/-SE) of Change from Baseline Overtime in NCC Scores by Treatment Group

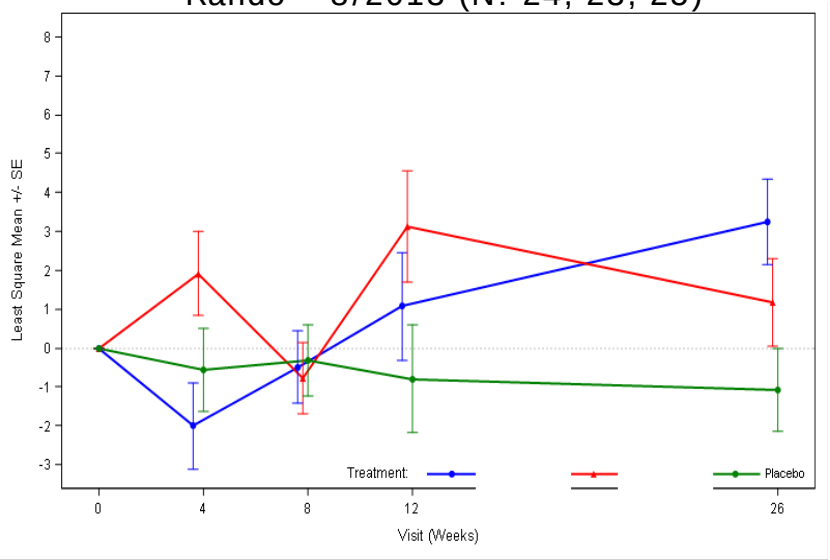
A similar pattern is seen in the functional co-primary with the placebo arm doing markedly better than the drug arms



Line plot of SCoRS score over time by treatment group

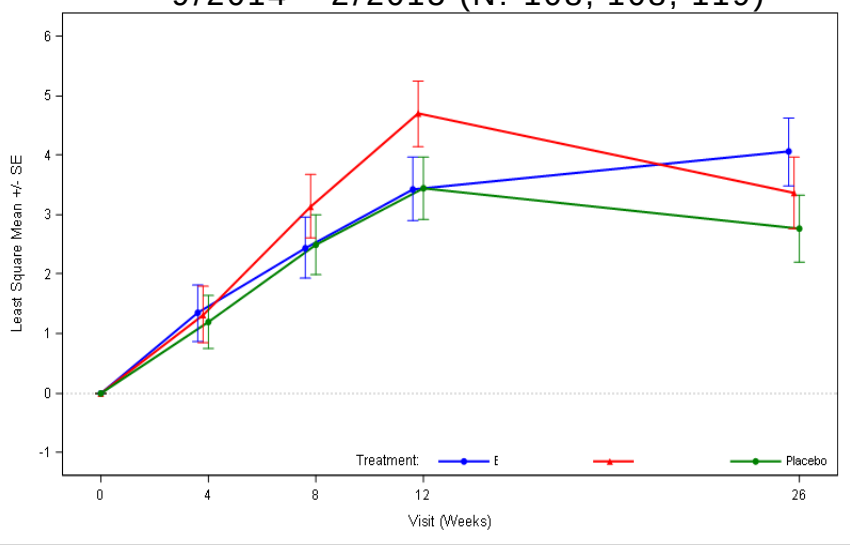
Notable differences, particularly in the placebo arm, in the time windows;

Rando – 8/2013 (N: 24, 23, 25)

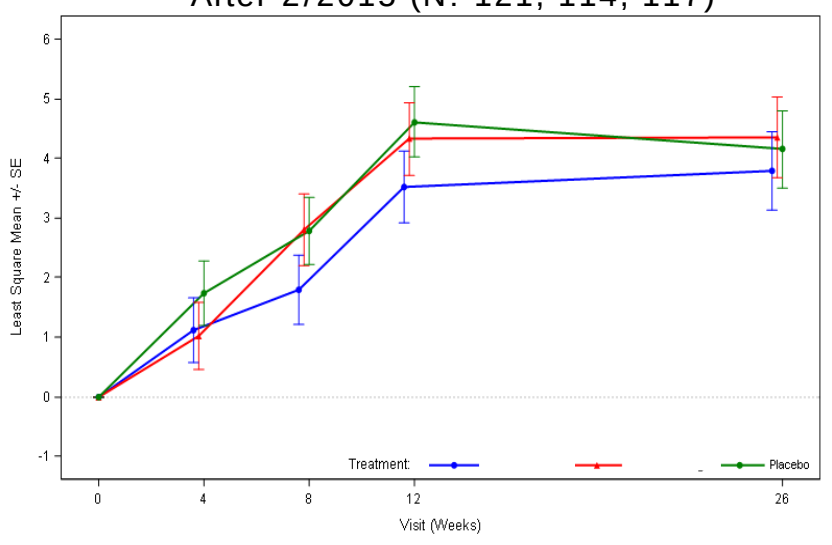


8/2013 - 8/2014 (N: 249, 244 235)

9/2014 – 2/2015 (N: 108, 108, 119)

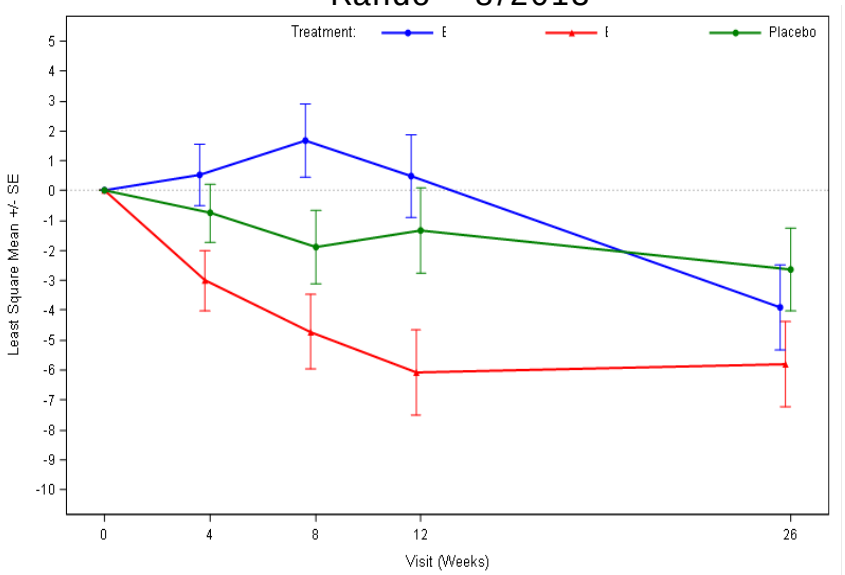


After 2/2015 (N: 121, 114, 117)

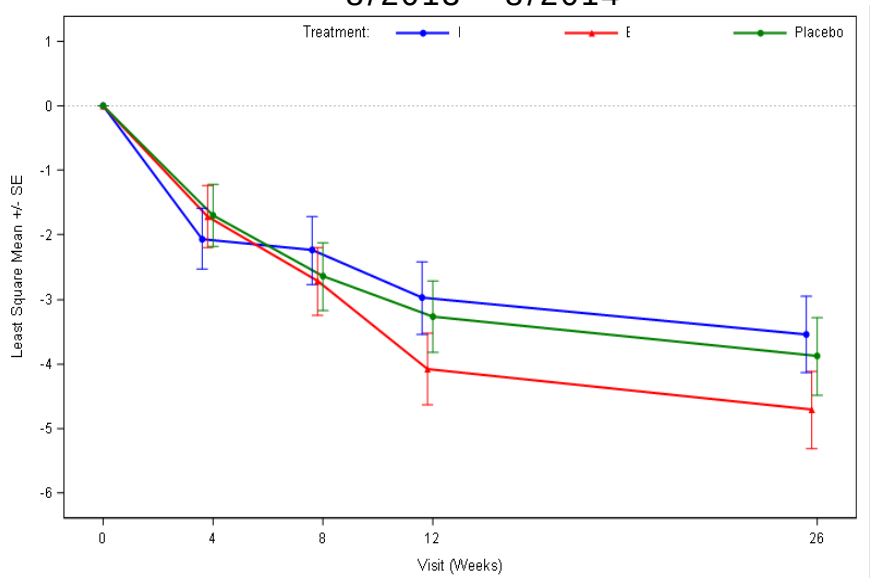


Similar findings are also seen in the functional co-primary

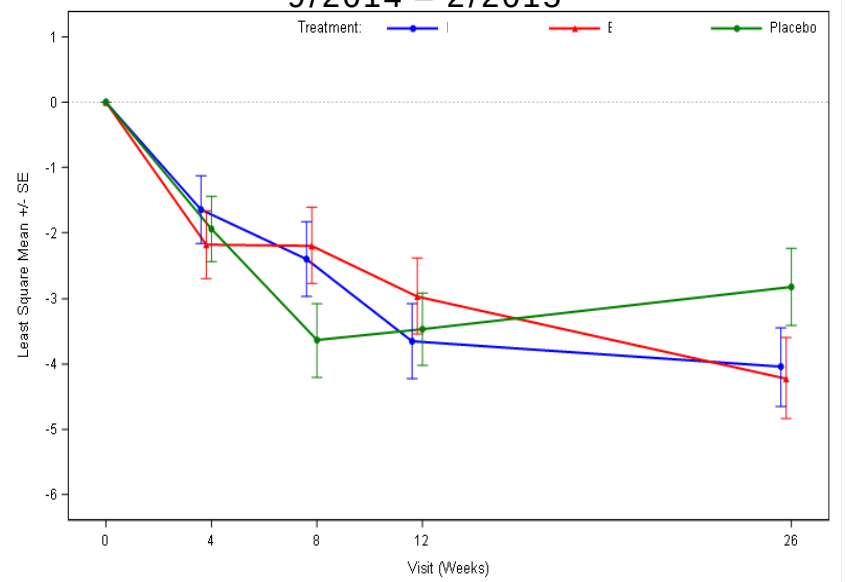
Rando – 8/2013



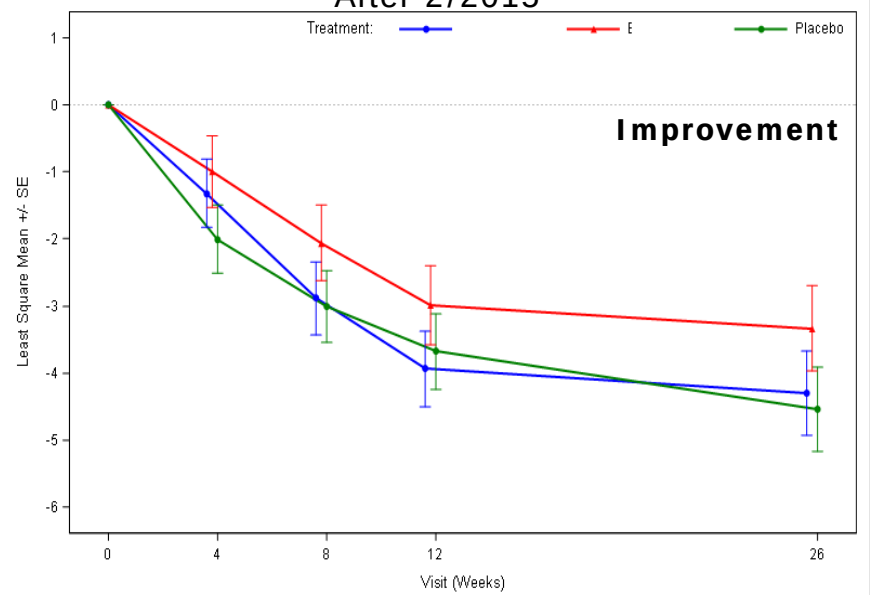
8/2013 – 8/2014



9/2014 – 2/2015



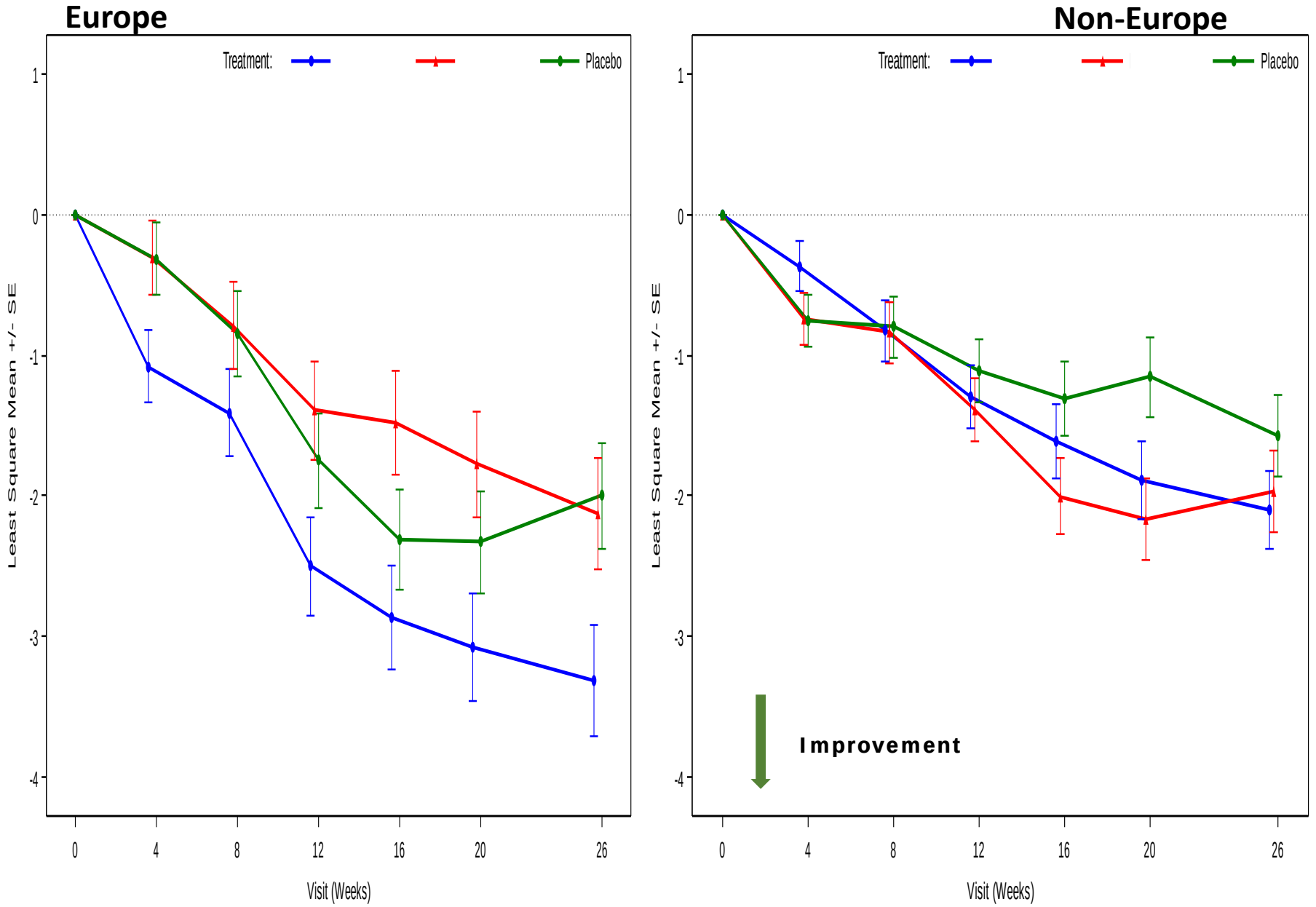
After 2/2015



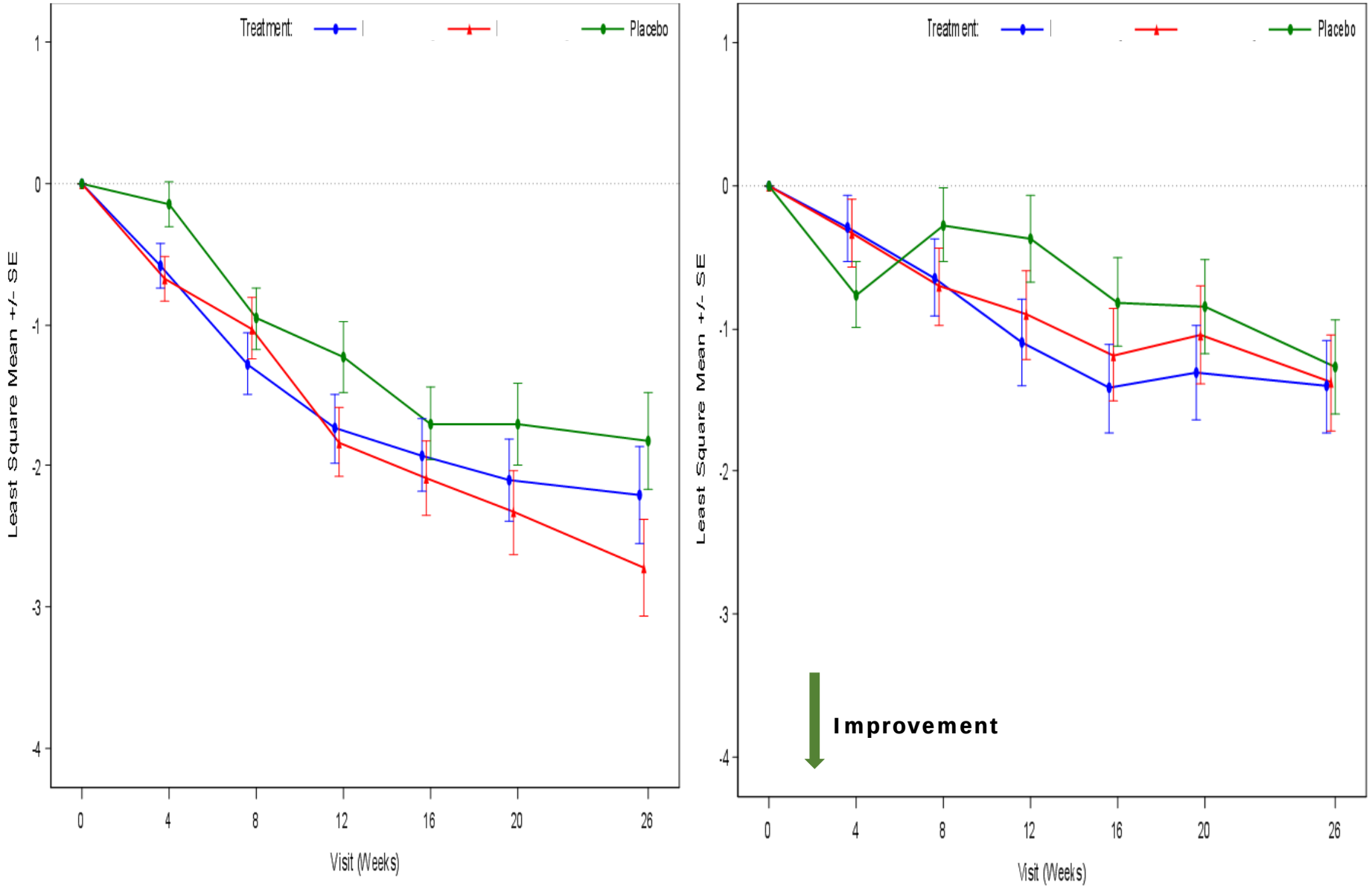
Broad Geographic Distribution

- Not uncommonly associated with increased variance
- An example of different “placebo” responses across different geographies

Least Squares Means (+/-SE) of Change from Baseline (MCCB*)



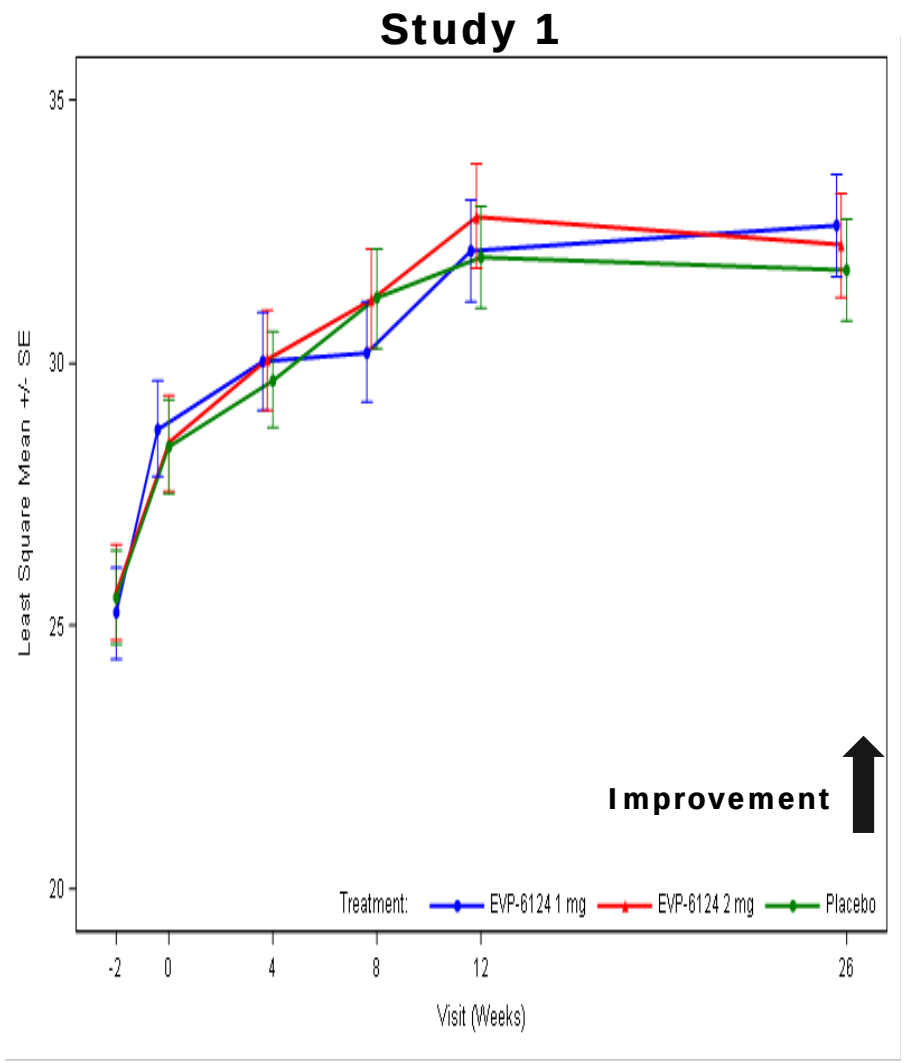
Least Squares Means (+/-SE) of Change from Baseline (SCORS)

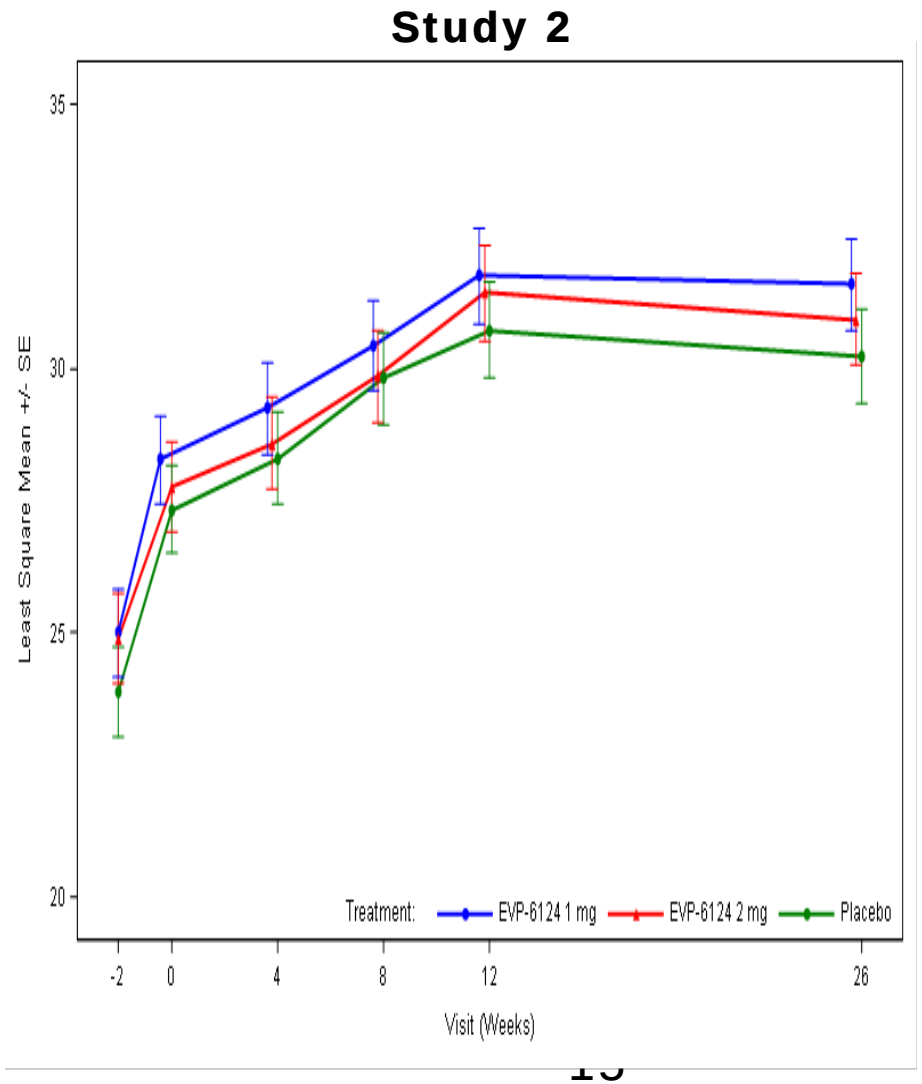


Frequency of a rating scale

- More is not necessarily better
  - Not just a “placebo” type effect
  - Did not manage the “learning effect” in the anticipated way

Large changes in the NCC in all arms from baseline (and pre-baseline) to endpoint with little differentiation





Trial Complexity

- More is not better
  - Can tire subjects
  - Can increase placebo effect