Decisions, Decisions, Decisions:
Trying to find balance between speed, cost, and quality

ISCTM
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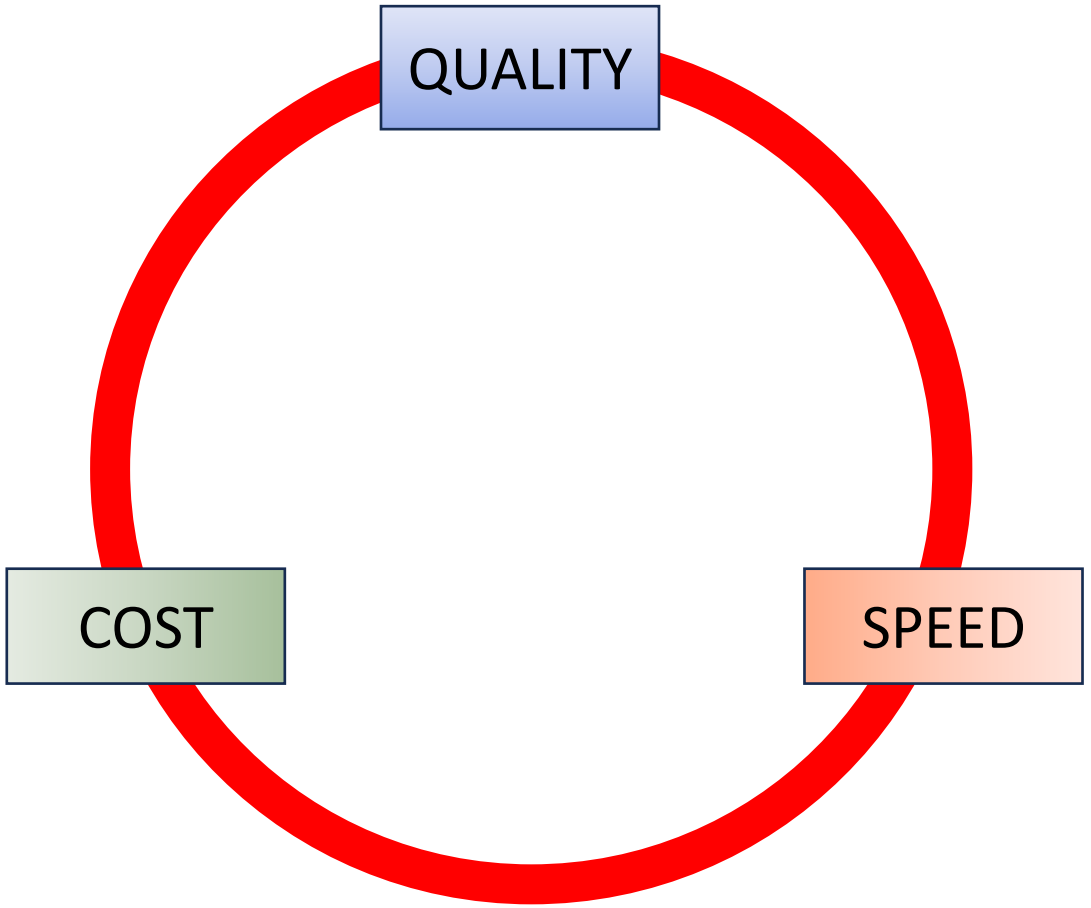

QUALITY
COST
SPEED

Background for the Study data (from several years ago) to be discussed

Two identical, global, placebo controlled, P3 studies for CIAS

Each study enrolled ~750 patients in 3 arms with stable schizophrenia
Treated with 1-2 atypical antipsychotics*

Co-primary endpoints:

- Neurocognitive component (NCC) of the MCCB (all the tests except for the MSCEIT)
- SCoRS (Clinical function related to cognition: Interviewer total score)

Baseline demographics were essentially evenly distributed across all treatment groups

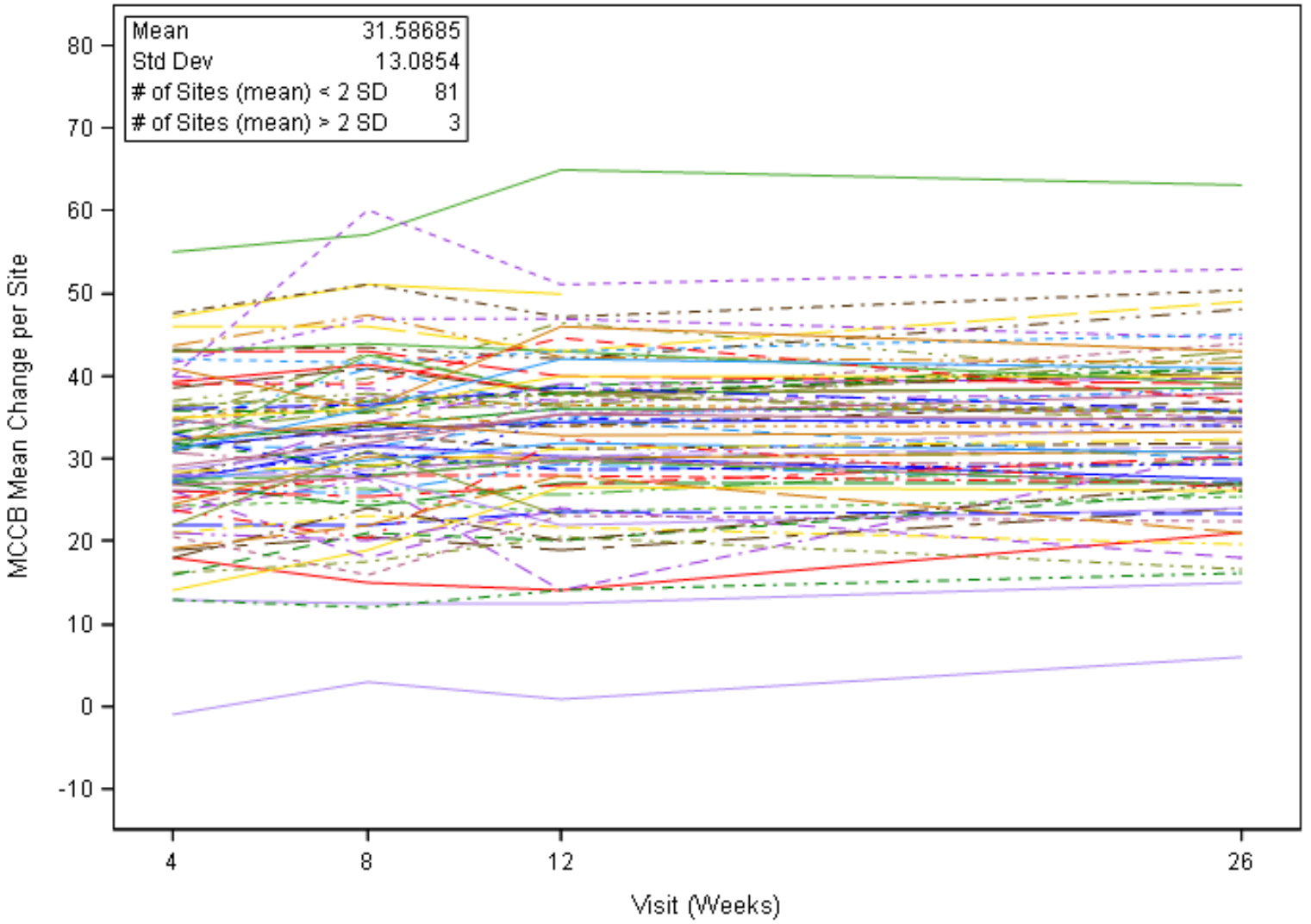
Strong baseline (and pre-baseline) to endpoint cognitive effects were seen – unfortunately across all three dosing groups.

- MCCB not significantly different from placebo in the ITT population

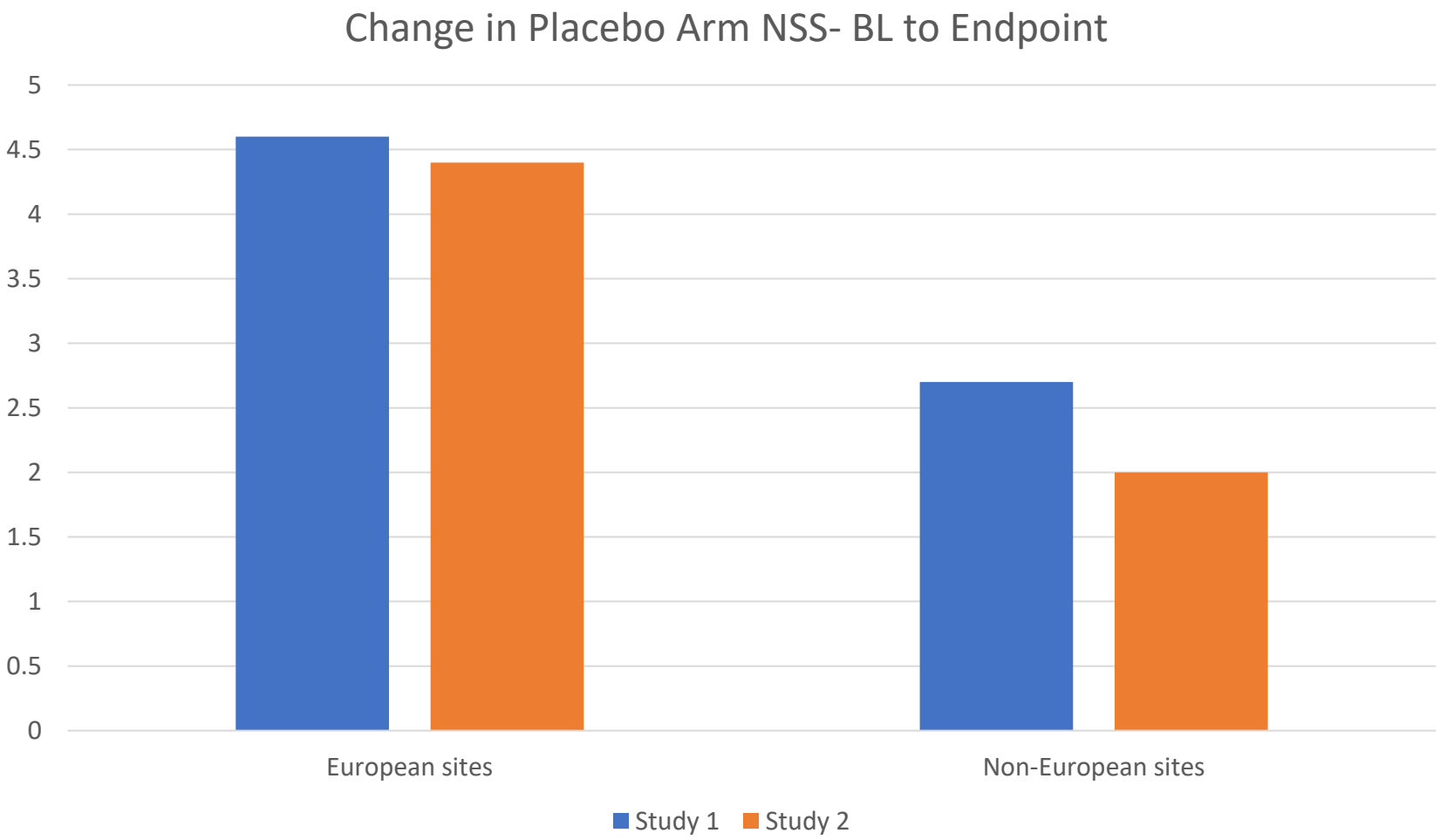
Examples of Trial Variance and Placebo

Mean Per Site: Placebo MCCB Score Over time

- *An extensive range of placebo responses, most of which are flat after the first 4 weeks*
- *Not easy to explain how there can be such differences between the sites*



Placebo response in the European sites (4.5) was higher than Non-European sites (2.4)

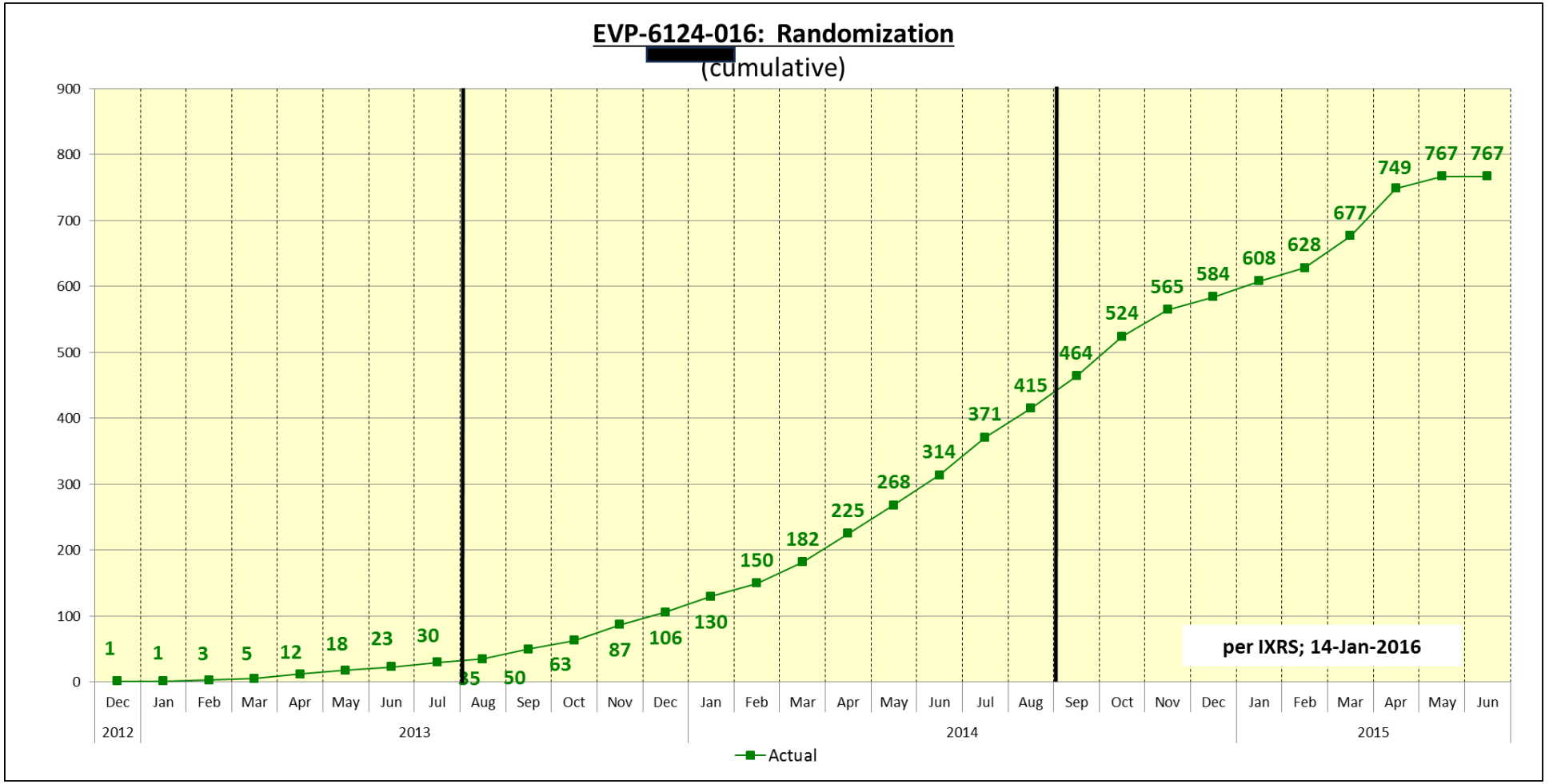


Other Issues that Occurred in this Program

Effects of low **n** at a site and treatment adherence

- Sites that Recruited less than 6 subjects showed almost no differences between Treatment Groups (with large standard deviations)
  - This is a phenomena seen in many types of studies
- Subjects who do not take the study medication tend to have very little beneficial effects
  - In the 2 studies, 17 & 18% of the subjects taking the study med had at least one PK level of 0 (on a drug with a long half life)
  - And 4% & 5% respectively had levels of 0 throughout the trial
  - This also is a phenomena seen in many types of studies

016 Randomization: one of the 2 CIS trials, both with essentially the same pattern



To accelerate enrollment, after Aug 2013, the protocols were changed so that subjects could be enrolled if their regimen included 2 antipsychotics (prior to that they had to be stable on 1 Antipsychotic)

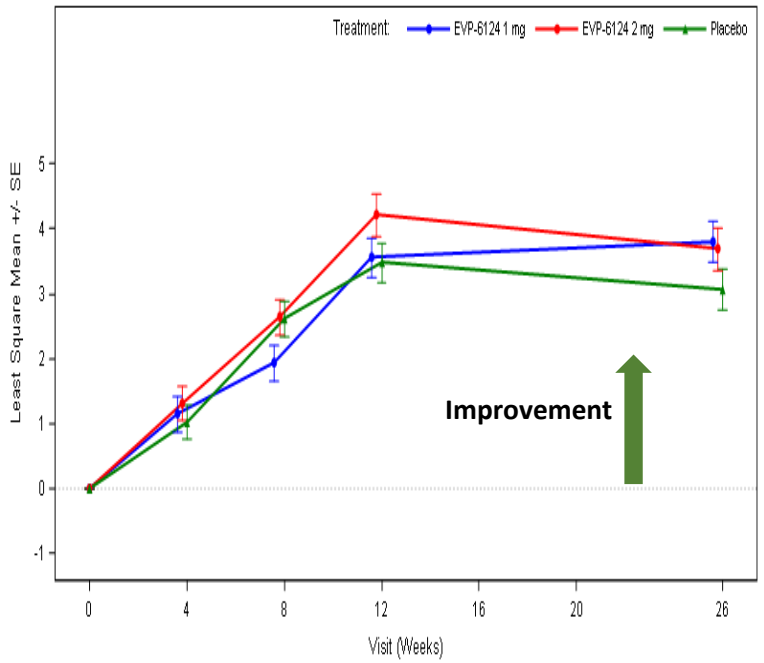
- Sites had complained that they would not be able to reach their enrollment targets without such an amendment

- 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%)

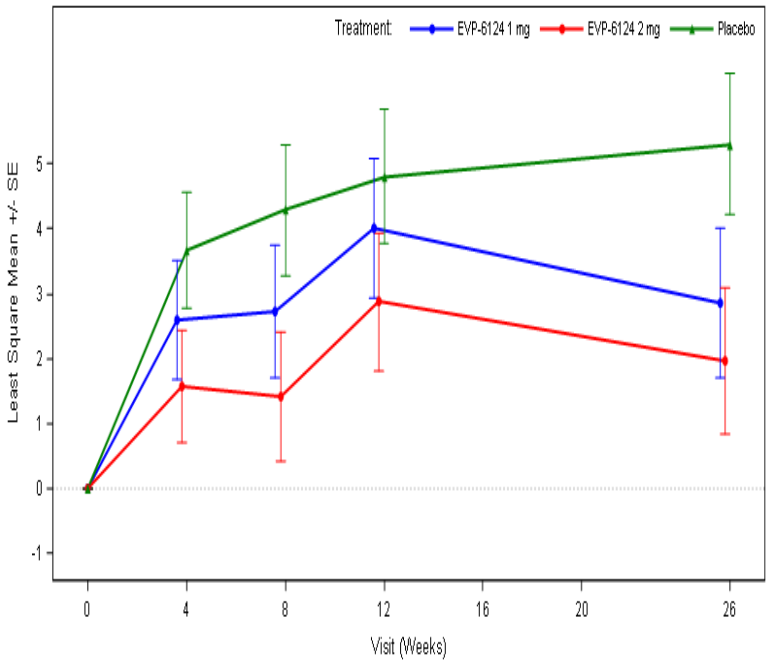
- Despite the request from the sites to allow this, only a little less than 10% of subjects enrolled were actually stable on 2 antipsychotics; though there was no reason to believe this group would differ from those stable on 1 Antipsychotic, post hoc analysis showed this not to be the case.

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



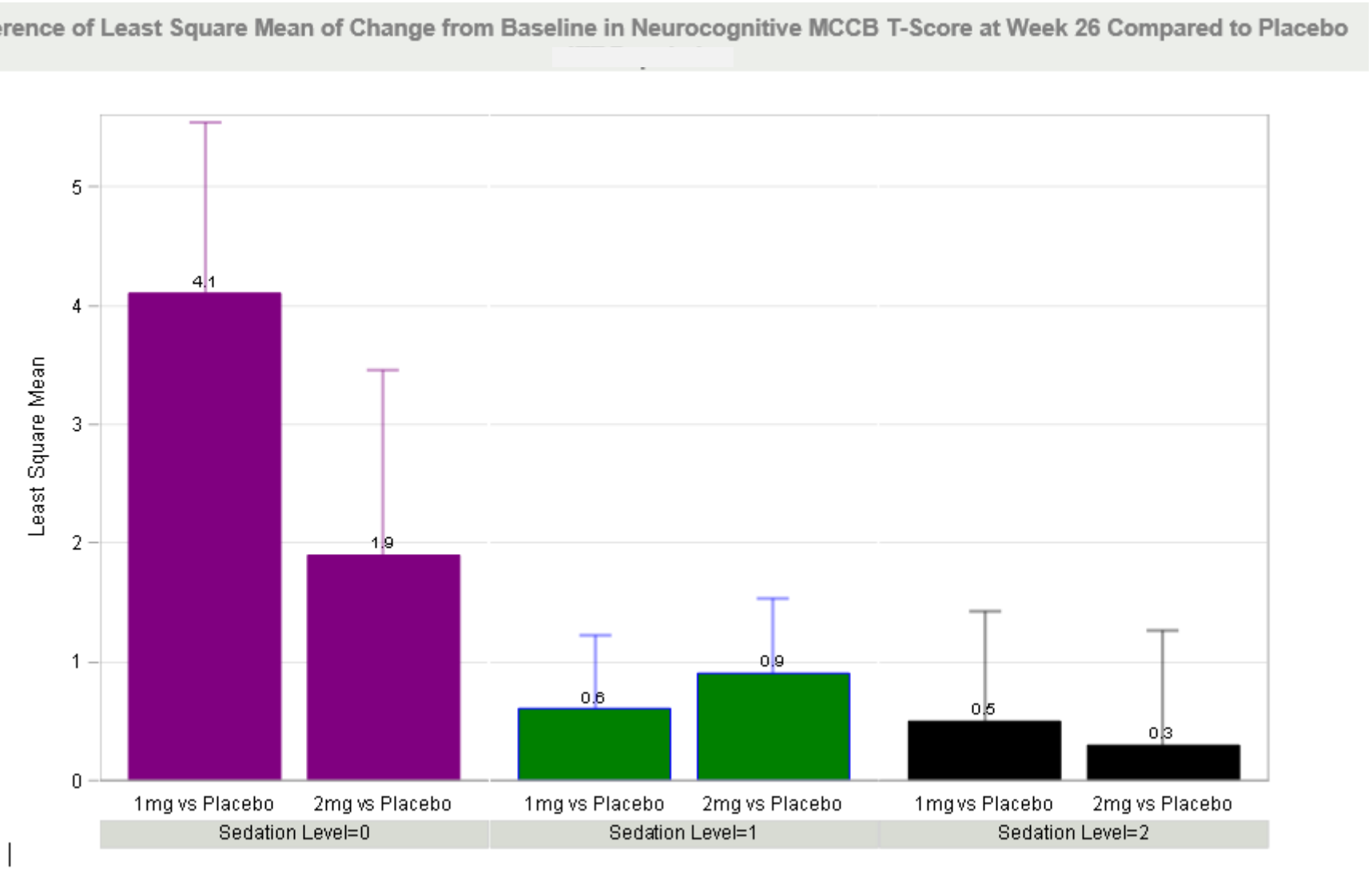
>=Two Antipsychotic Drugs



A similar pattern is seen in the functional co-primary with the placebo arm doing markedly better than the drug arms in those on 2 Antipsychotics

Least Squares Means (+/-SE) of Change from Baseline Overtime in NCC Scores by Treatment Group- EVP-6124-015+016

Sedating Antipsychotics blunt the Response of Study drug to the MCCB*



Analysis done on the “Cleanest” population
Sedation of antipsychotics determined by staff using Stahl’s ranking

Summary of post-hoc analysis findings (1)

Significant separation can be seen in the pooled (n=1515) data when removing:

- Subjects on second antipsychotic (n=142) & Subjects who were rarely compliant [define with no plasma exposure] (n=272) or Subjects showing high variability from screening to baseline (n=125, 175, 240)
- Doing all three above exclusions results in a data set shows the greatest separation (and the placebo arm behaves more as expected)

Substantial difference in pooled data (n=1,515) between patients enrolled early in the trial and later

- Partly confirmed with Baseline differences seen between the 1st time cohort and the rest of the study

Some regional variation

- Europe has higher response to drug and a quite robust response to placebo
  - Russia & the Ukraine were specifically looked at, but do not explain the overall differences seen
- North America has lower drug response and much lower placebo/learning response
- No specific country created havoc

No one medication or combination of medications appears to be “toxic” or helpful

- Though differences, nothing substantial seen overall in the study that seemed to sway the data
- Though differences, nothing substantial seen in the subgroup that was stable on 2 antipsychotics

When Antipsychotics were looked at regarding how sedating or anticholinergic they were, a signal emerged that the more sedating or anticholinergic they were, they less likely they were to show a separation from placebo

Outlier values were apparent when looking at scatterplots; much of our interest has focused on the pre-baseline changes (e.g. an improvement of 24 points on the SCoRS)

- When cutoffs were established for the top 10% of pre-baseline changes for each outcome measure, eliminating those subjects from the analysis decreased variance and enhanced the separation of drug over placebo for all outcomes in the combined data sets, equivalent to eliminating those subjects who rarely took the drug

Summary

- Care/caution should be exercised in one's choices during protocol creation and especially in making adjustments after the study has started given the "unintended consequences" that can occur
  - Remember the likelihood of site and Regional differences even when making initial protocol choices
  - Remember that nonadherent subjects and poorly enrolling sites have big impact during study execution
  - Loosening I/E criteria can often speed up trials, but unfortunately can harm the trial outcomes
  - Think carefully about how one's choice of allowable medicines might impact trial outcomes
- I have concentrated primarily on the efficacy examples and considerations, I will now turn it over to my colleague to focus on the safety/tolerability side