Moving towards a new psychiatry: targeting patient subtypes and symptom domains

an industry perspective of the current challenges

Giacomo Salvadore, MD
Neuroscience Experimental Medicine, Janssen R&D

Daniel Oravetz, *The Pearl*
Daniel Oravetz is a patient and artist from Hungary, living with schizophrenia.

Janssen Neuroscience
PHARMACEUTICAL COMPANIES OF Johnson & Johnson

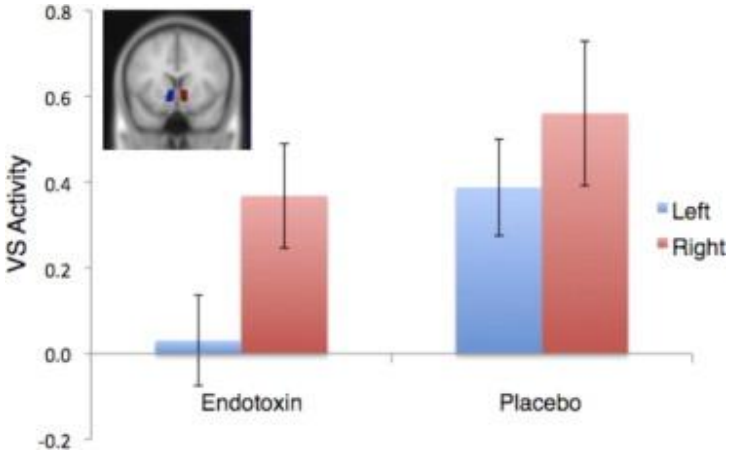
Disclosures

- Employee and shareholder of Johnson & Johnson, LLC

Peripheral immune dysregulation as a potential antidepressant target

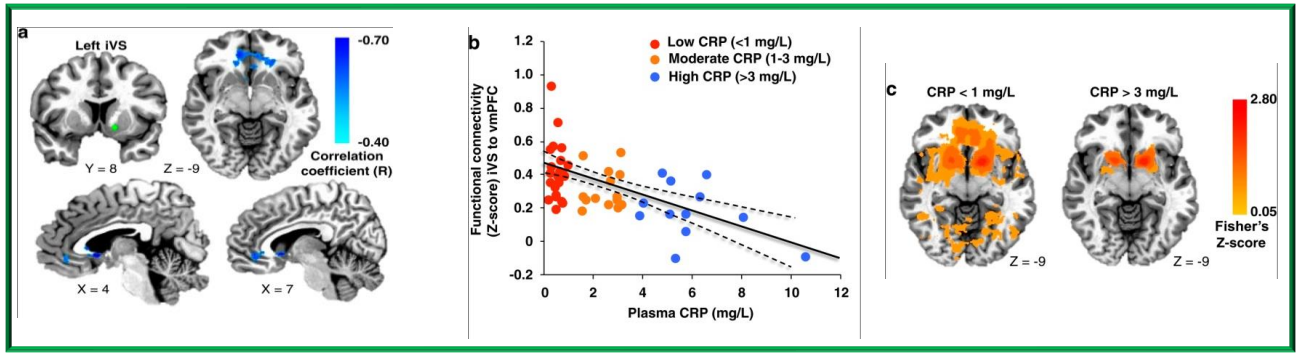
- Patients with depression show increased levels of peripheral inflammatory markers, including TNF-alpha, IL-6 and CRP
- Preclinical evidence that drugs which suppress peripheral inflammation (anti IL-6 antibodies) are able to trigger antidepressant-like response in susceptible animals
- Clinical evidence that antibodies which suppress peripheral inflammation improve depression symptoms in subjects with elevated peripheral inflammatory markers as well as subjects with primary inflammatory conditions
- PoC study to test the hypothesis that treatment with the anti-IL-6 antibody sirukumab improves depression symptoms in patients with MDD with increased CRP levels
- Investigation of the effects of sirukumab on anhedonia using the SHAPS scale

Association between peripheral inflammation and activity in the reward circuitry



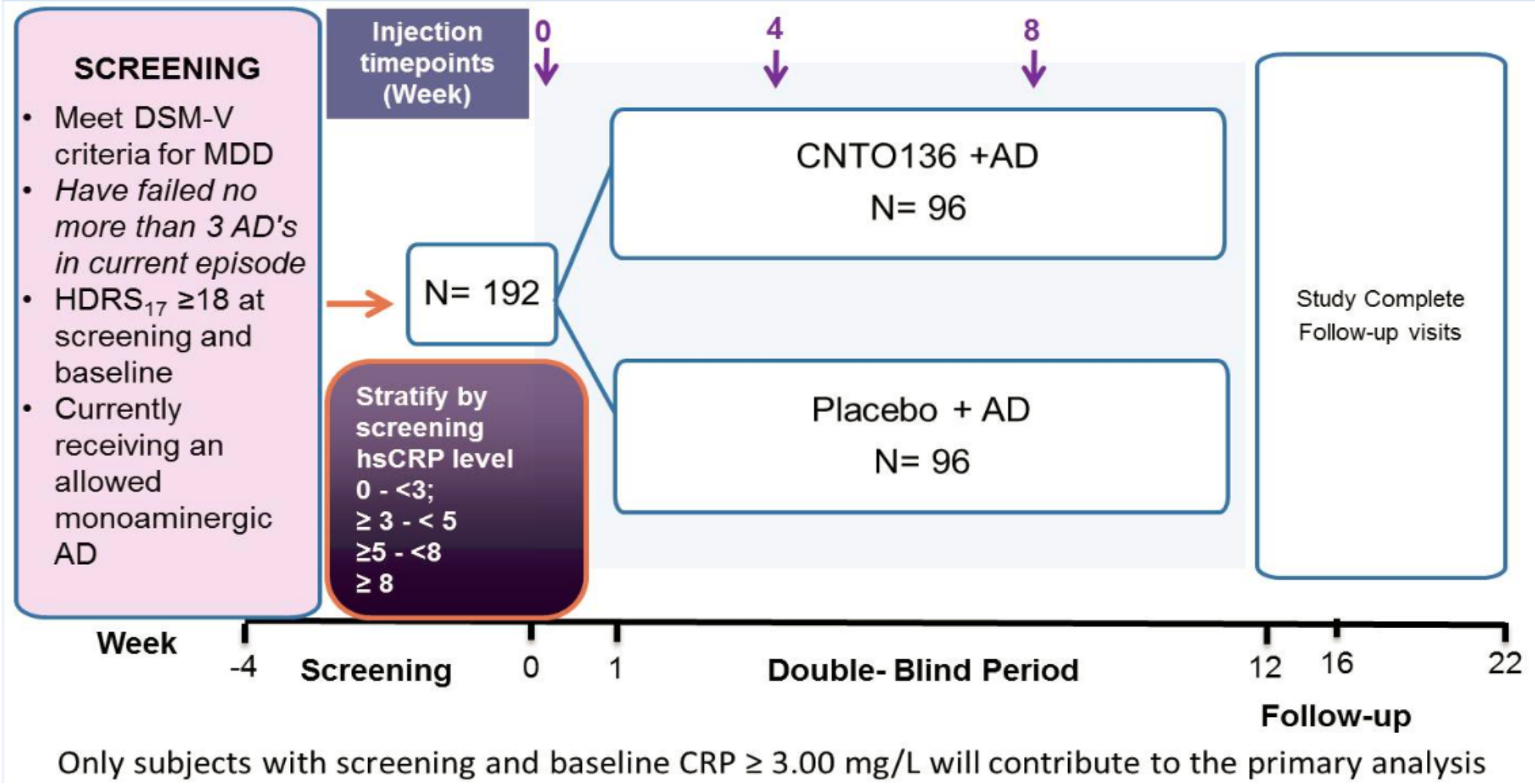
- Elevation of peripheral cytokines through LPS challenge blunts ventral striatal activity
- Decreased activity in the reward circuitry might mediate depressive symptoms post-LPS challenge

- Increased CRP correlates with decreased FC between the ventral striatum and the vmPFC
- This association mediates the relationship between CRP and anhedonia

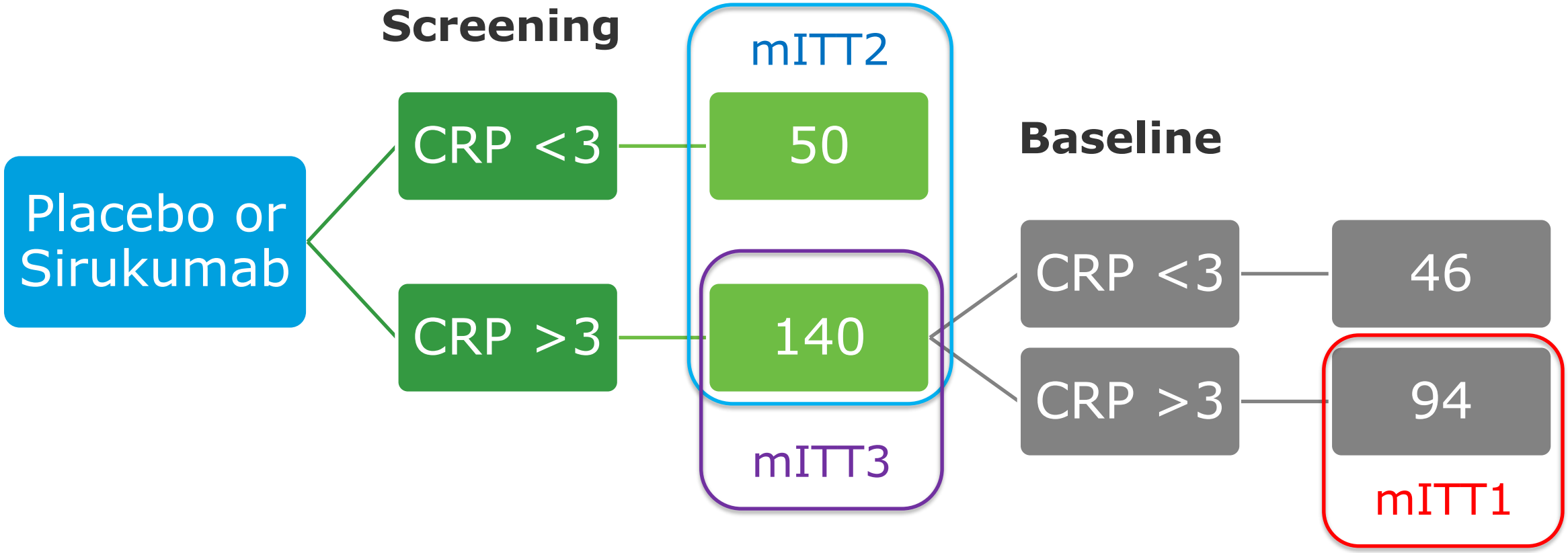


Eisenberger et al., 2010. Biol Psychiatry 68: 748-54;
Felger et al., in press. Mol Psychiatry

Study design

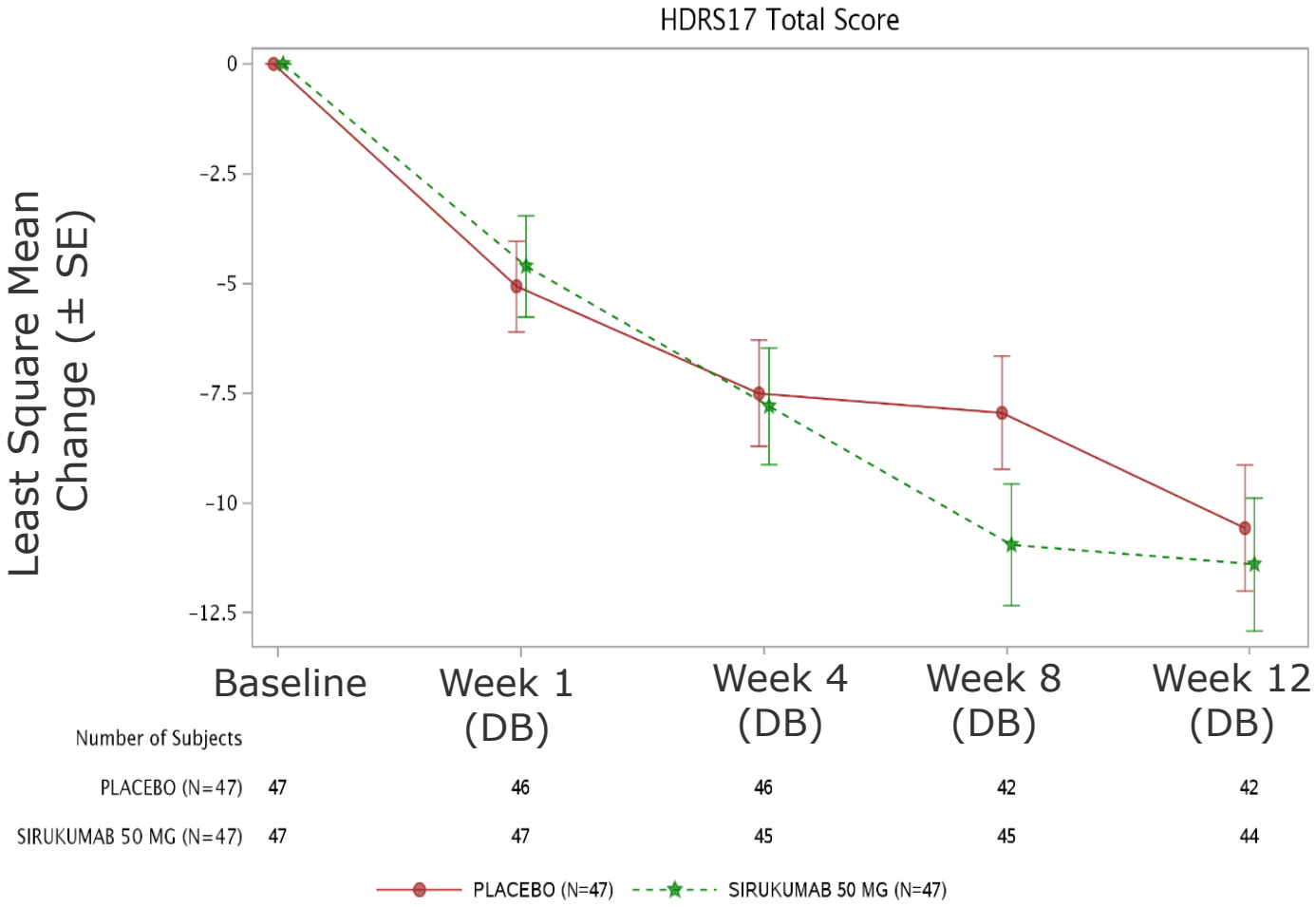


Study Subjects Info in Each Analysis Set



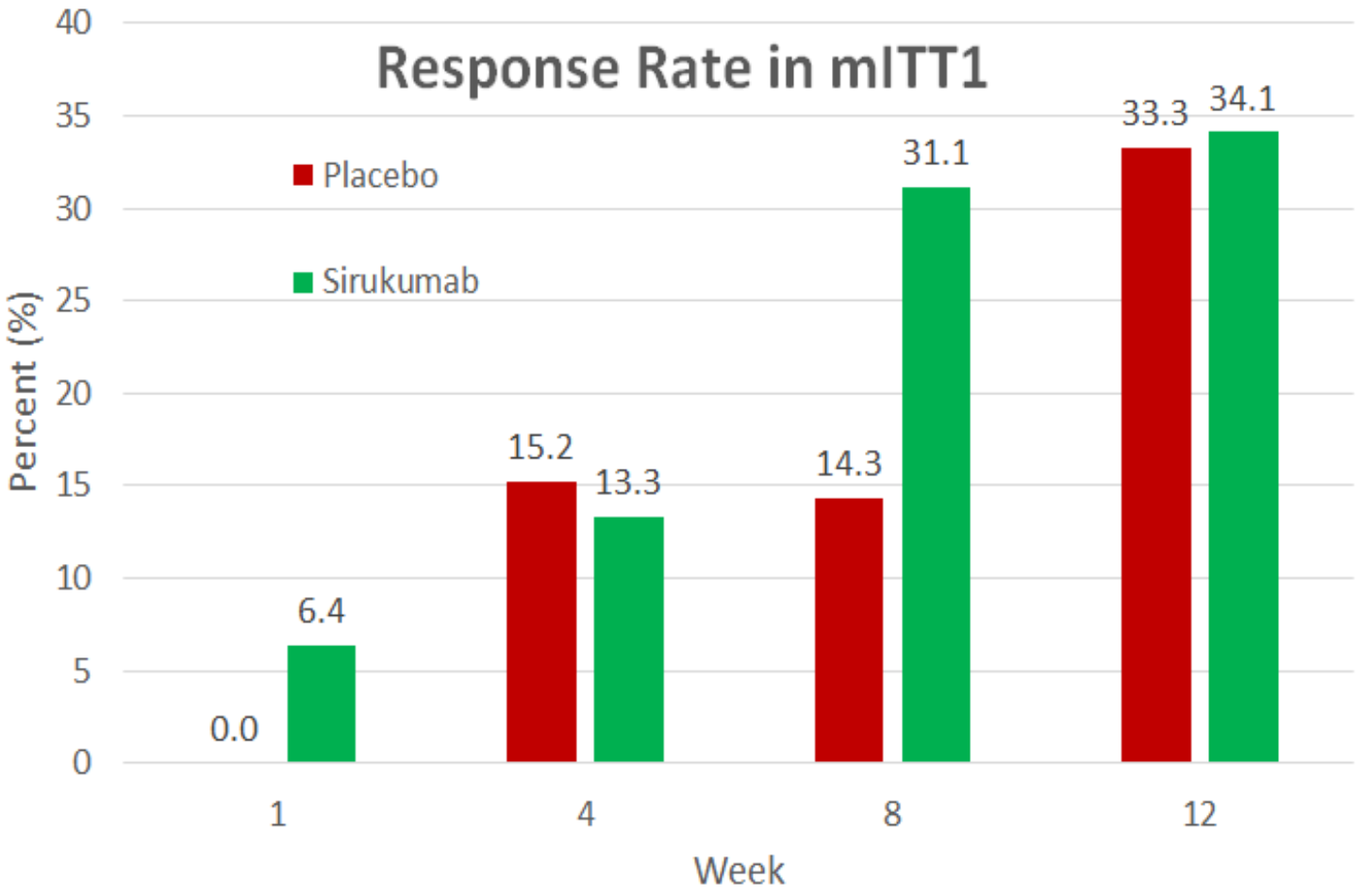
Depressed subjects showed elevation of CRP at screening: average CRP 4.2 mg/L (N=931)

HDRS-17 primary efficacy results in mITT1 population



No effect of sirukumab at Week 12 on HDRS-17 scores (independent raters) in mITT1 population

Response Rate is comparable between sirukumab and placebo at Week 12

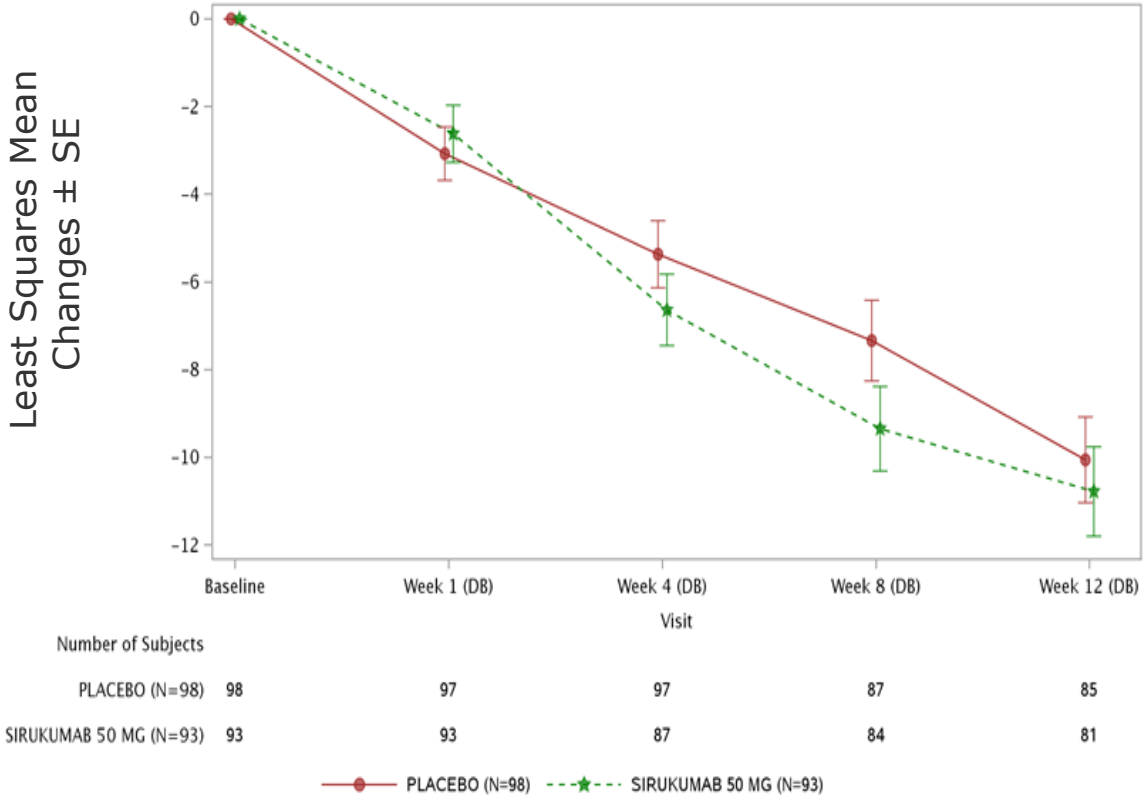


Response defined as ≥ 50% improvement in HDRS-17 total score from baseline

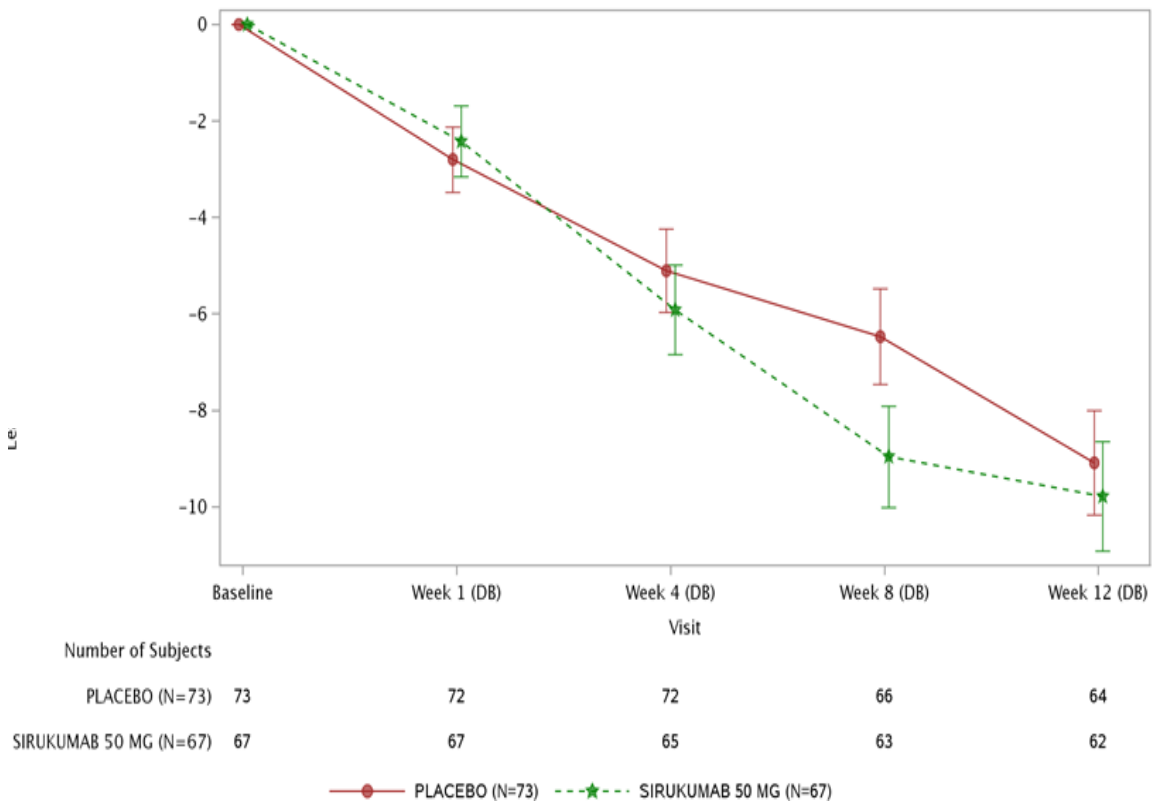
Week 12 response rate didn't favor sirukumab over placebo

HDRS-17: Sirukumab Fails to Differentiate from Placebo at 12 weeks Regardless of Screening CRP levels

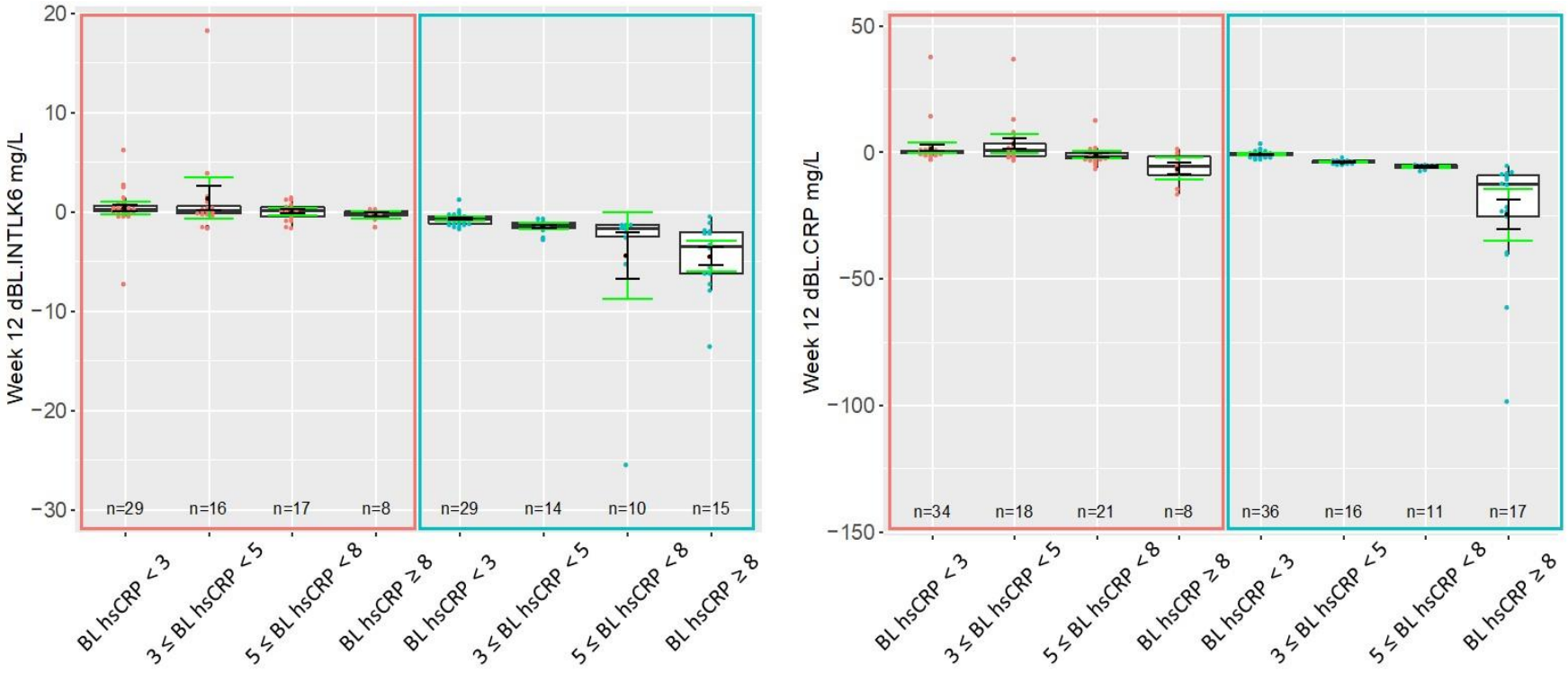
mITT2



mITT3

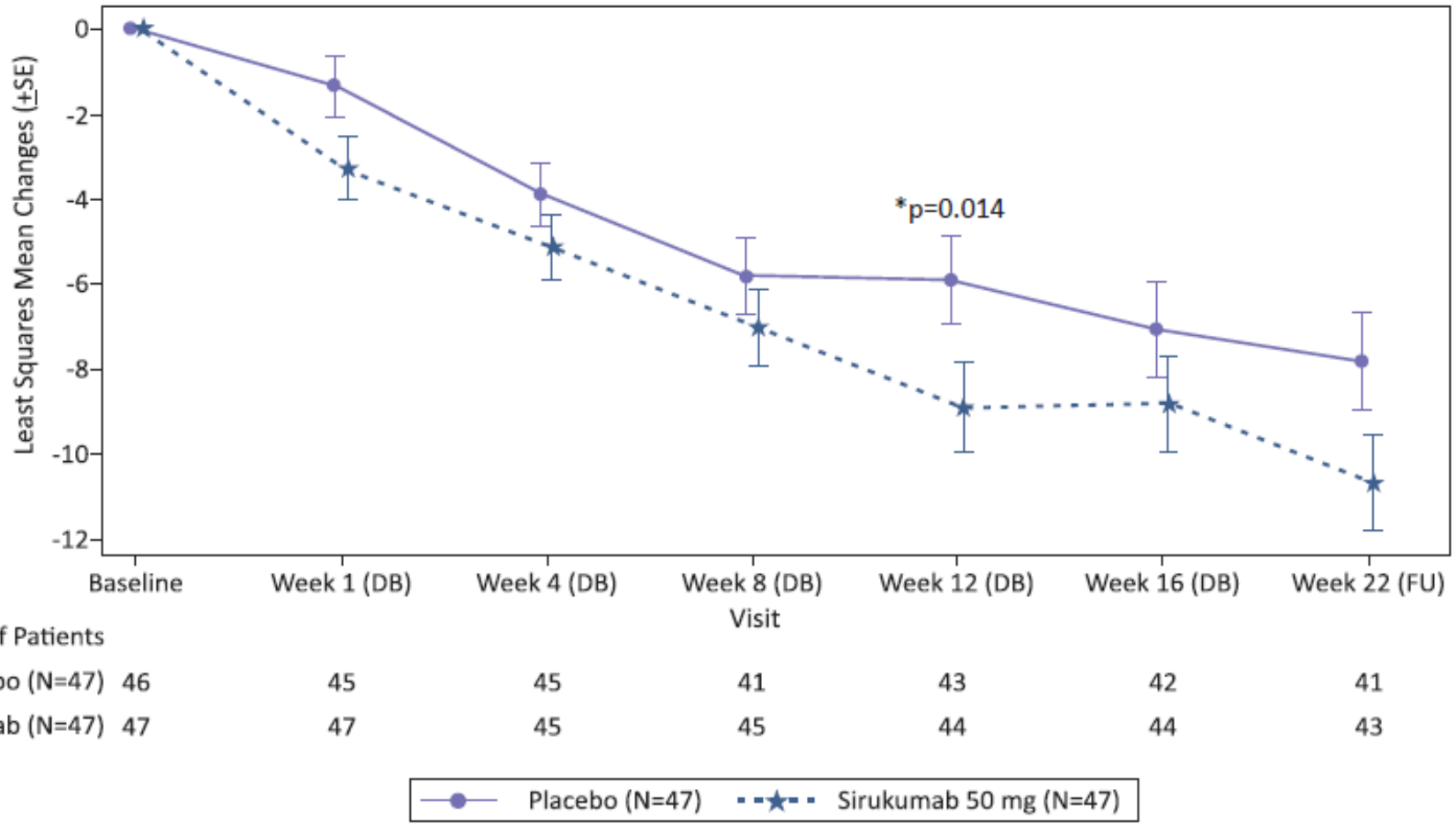


Sirukumab treatment is associated with decreased peripheral inflammatory biomarkers



Changes from baseline to week 12 in IL-6 (Left) and hsCRP (Right) stratified by baseline hsCRP levels

SHAPS: Sirukumab improves anhedonia symptoms in MDD subjects



Study results summary

- Lack of efficacy using a “general” depression scale despite adequate suppression of peripheral inflammatory biomarkers
- Lack of an enrichment biomarker to identify responders
- Promising signal on an anhedonia scale
- Positive effect on anhedonia is plausible from a biological standpoint
- Previous positive studies with monoclonal antibodies used depression rating scales that emphasize anhedonia, such as the HADS

Is there a path forward for drugs which target anhedonia?

- Regulatory hurdles: showing that anti-anhedonic effects are not part of a general antidepressant effect to avoid pseudo-specificity

- Development hurdles: does a drug improve anhedonia in subjects with MDD only or improve anhedonia across different diagnosis?

- Payers hurdles: how do we show quantifiable value for anhedonia to payers?
  - What is the burden of untreated anhedonia?

- Prescribers hurdles: do they see anhedonia as an area of unmet need? How do they identify subjects with anhedonia?