



International Society for CNS Clinical Trials and Methodology

Impact of protocol decisions and modifications in RCT conduct

Steven T. Szabo, MD, PhD

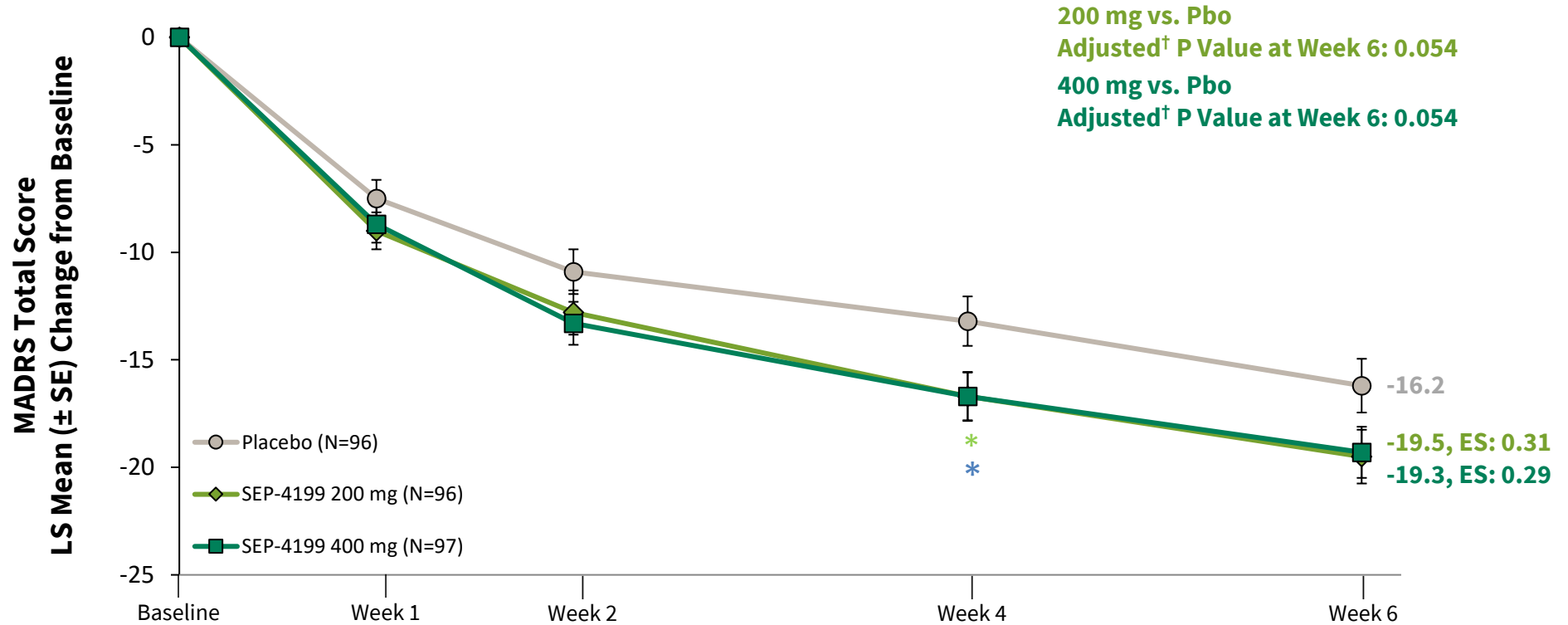
Senior Medical Director, Clinical Development, Neurocrine Biosciences, Inc.

Gerard Sanacora MD, PhD

George D. Gross and Esther S. Gross Professor of Psychiatry, Yale University School of Medicine

Director Yale Depression Research Program

MMRM Analysis of Change from Baseline in MADRS Total Score – Europe + US (mITT Population)

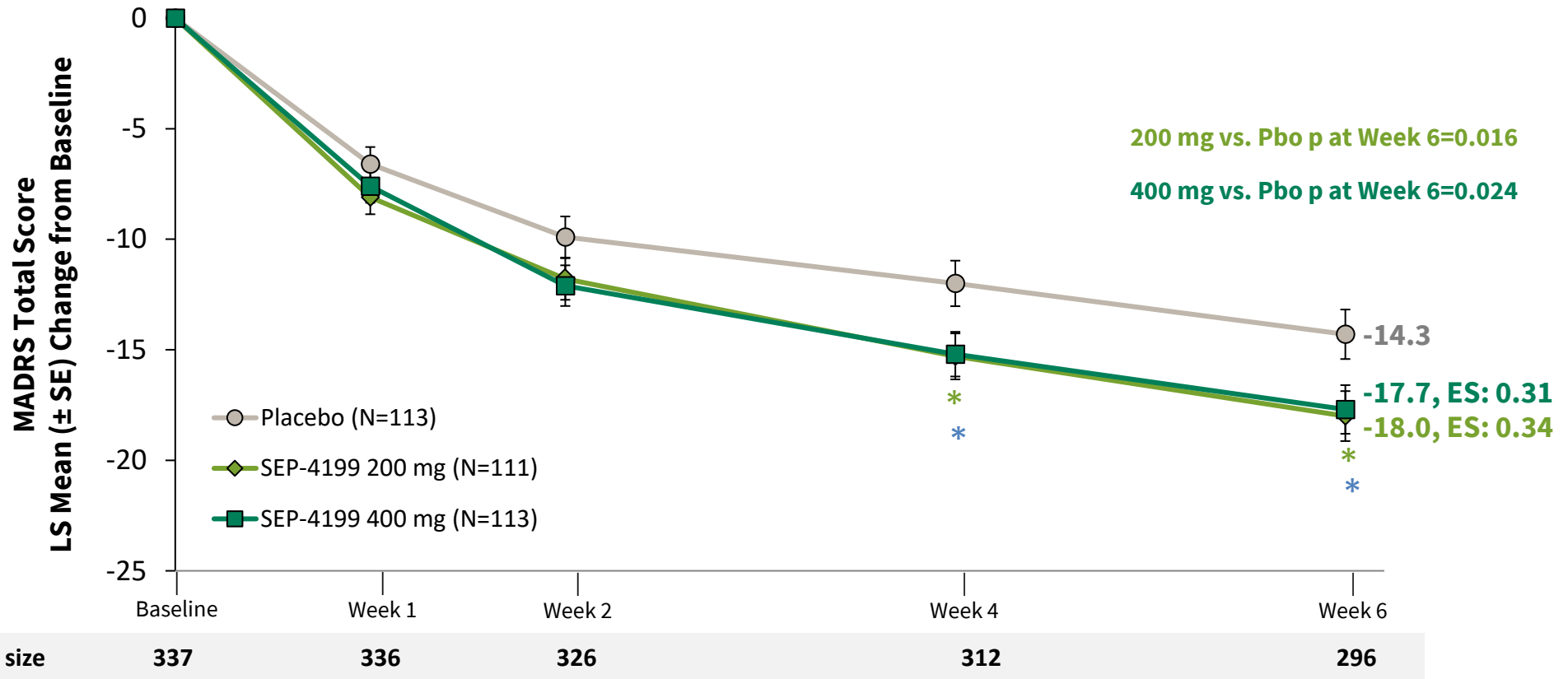


Total Sample size	289	288	280	269	253
-------------------	-----	-----	-----	-----	-----

Unadjusted p < 0.05

†Note: Adjusted P value indicates Truncated Hochberg Adjustment

MMRM Analysis of Change from Baseline in MADRS Total Score – Europe + US + Japan (mITT Population)



* Unadjusted p < 0.05

more-strict eligibility

ARTIFICIAL INTELLIGENCE

*automatic,
algorithmic,
computer-
implemented*

HUMAN INTELLIGENCE

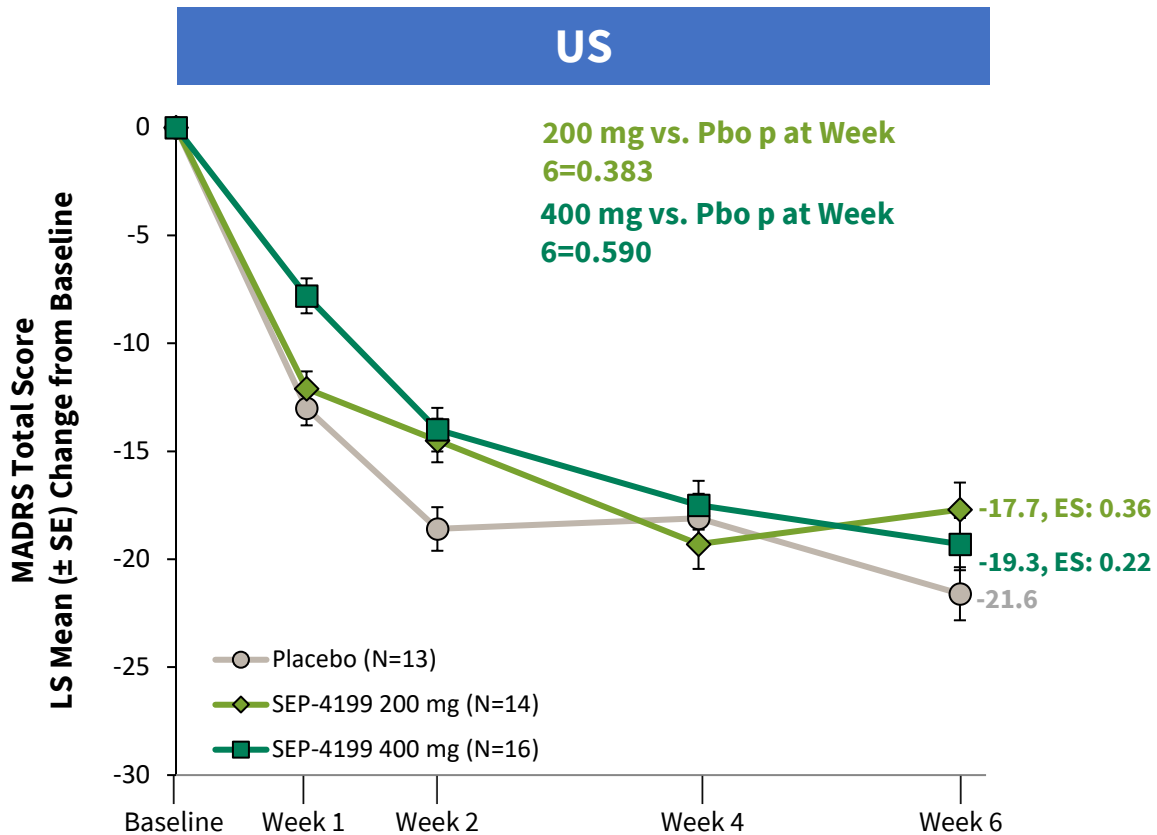
*human,
clinician-based
oversight and
judgement*

INFRASTRUCTURE

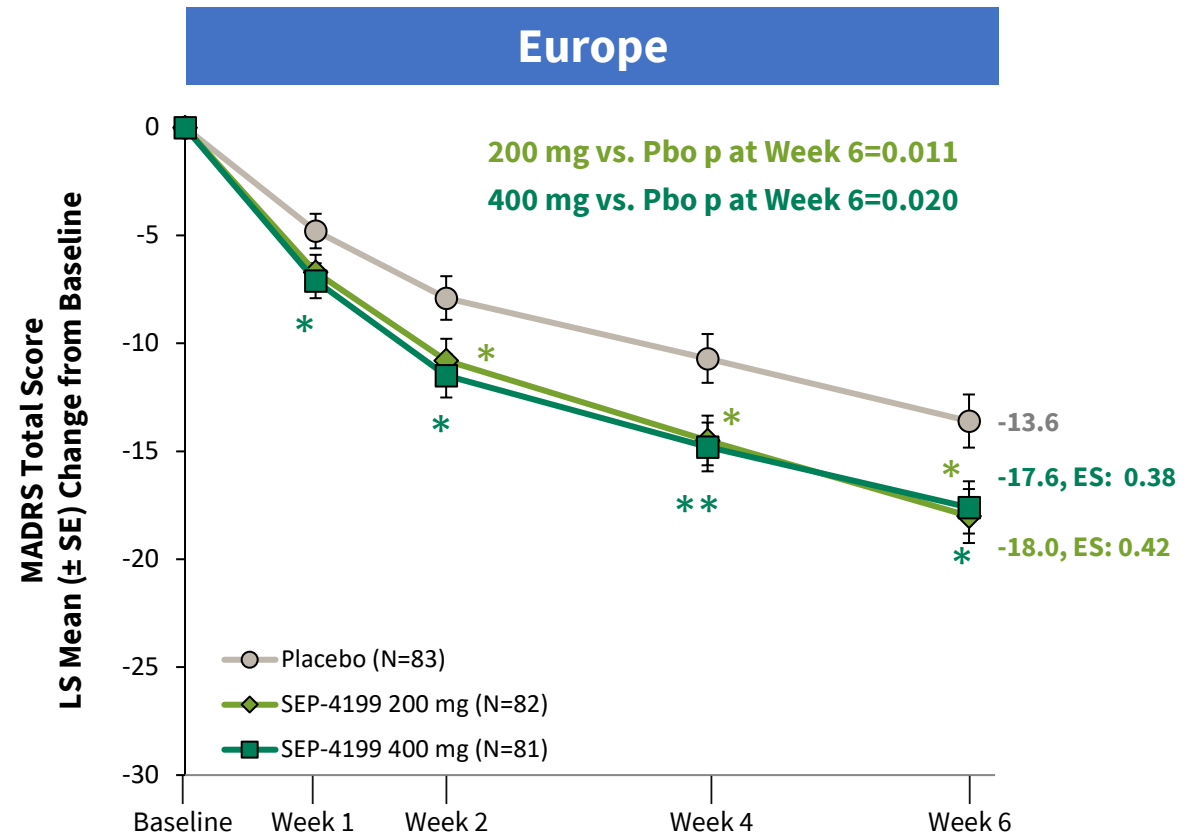
*impact of business incentives on
the study population, role for
academic medical centers*

TO ADDRESS EROSION OF DRUG SIGNAL IN USA STUDIES...
3 DOMAINS OF INNOVATION

MMRM Analysis of Change from Baseline in MADRS Total Score – US vs. Europe (mITT Population)



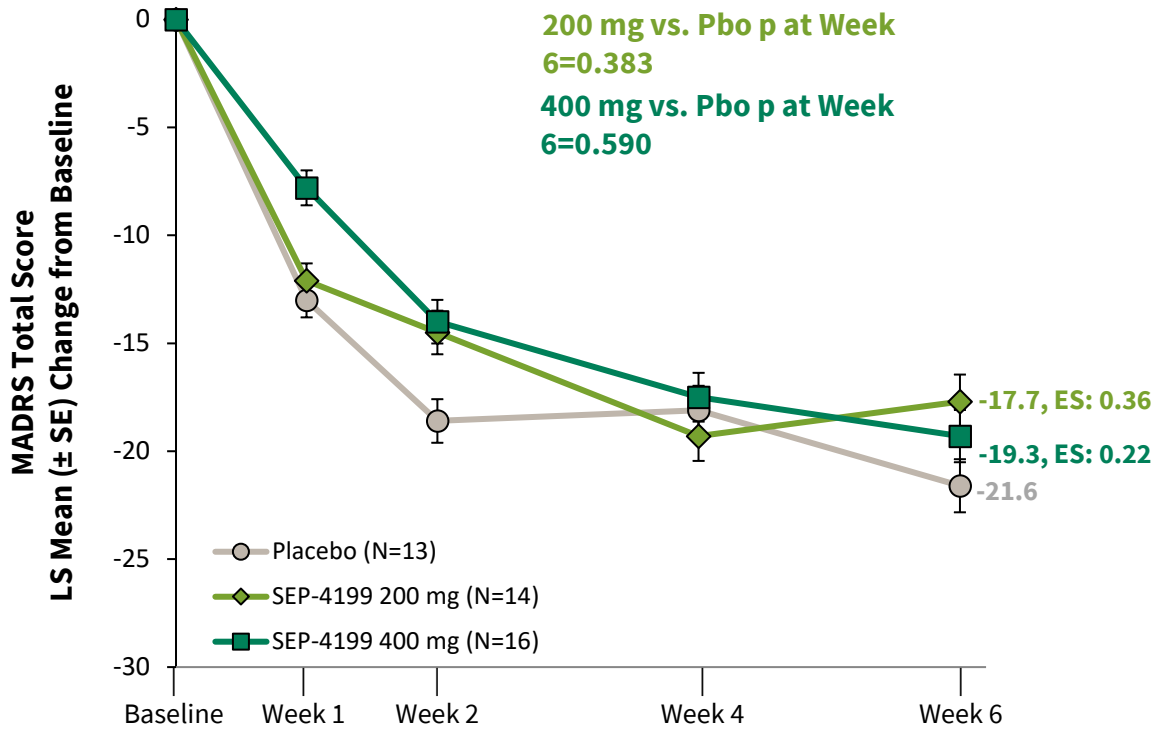
Total Sample size	43	43	41	39	35
-------------------	----	----	----	----	----



Total Sample size	246	245	239	230	218
-------------------	-----	-----	-----	-----	-----

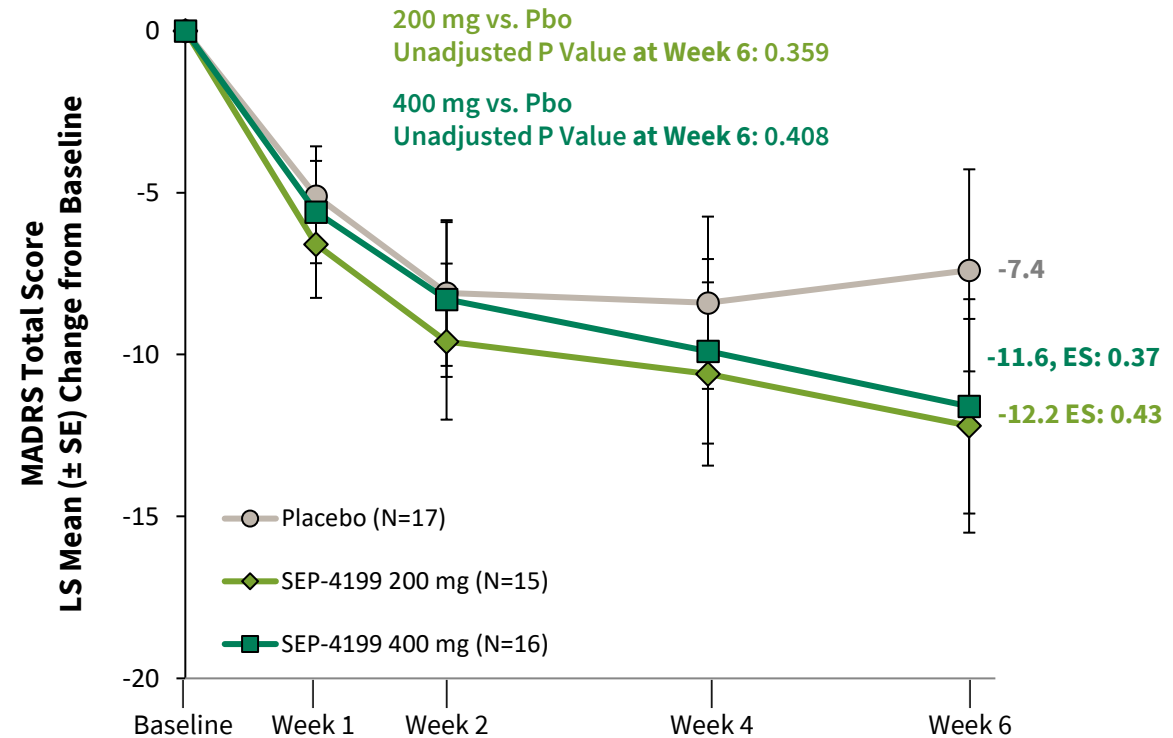
MMRM Analysis of Change from Baseline in MADRS Total Score – US vs. Japan (mITT Population)

US



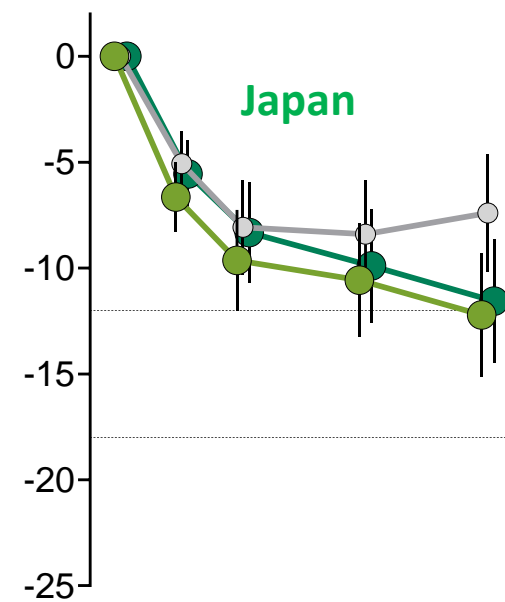
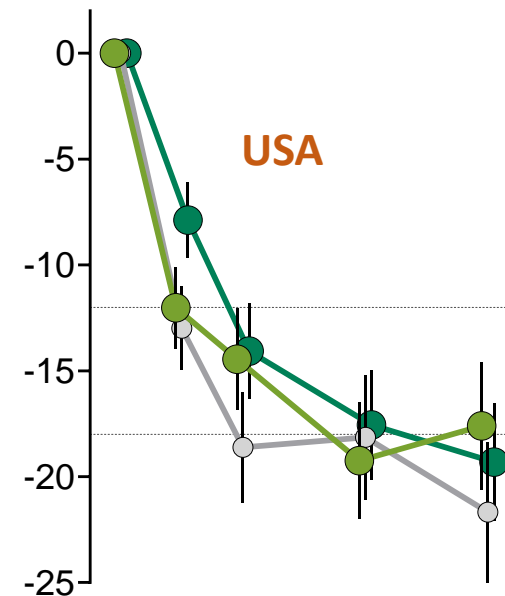
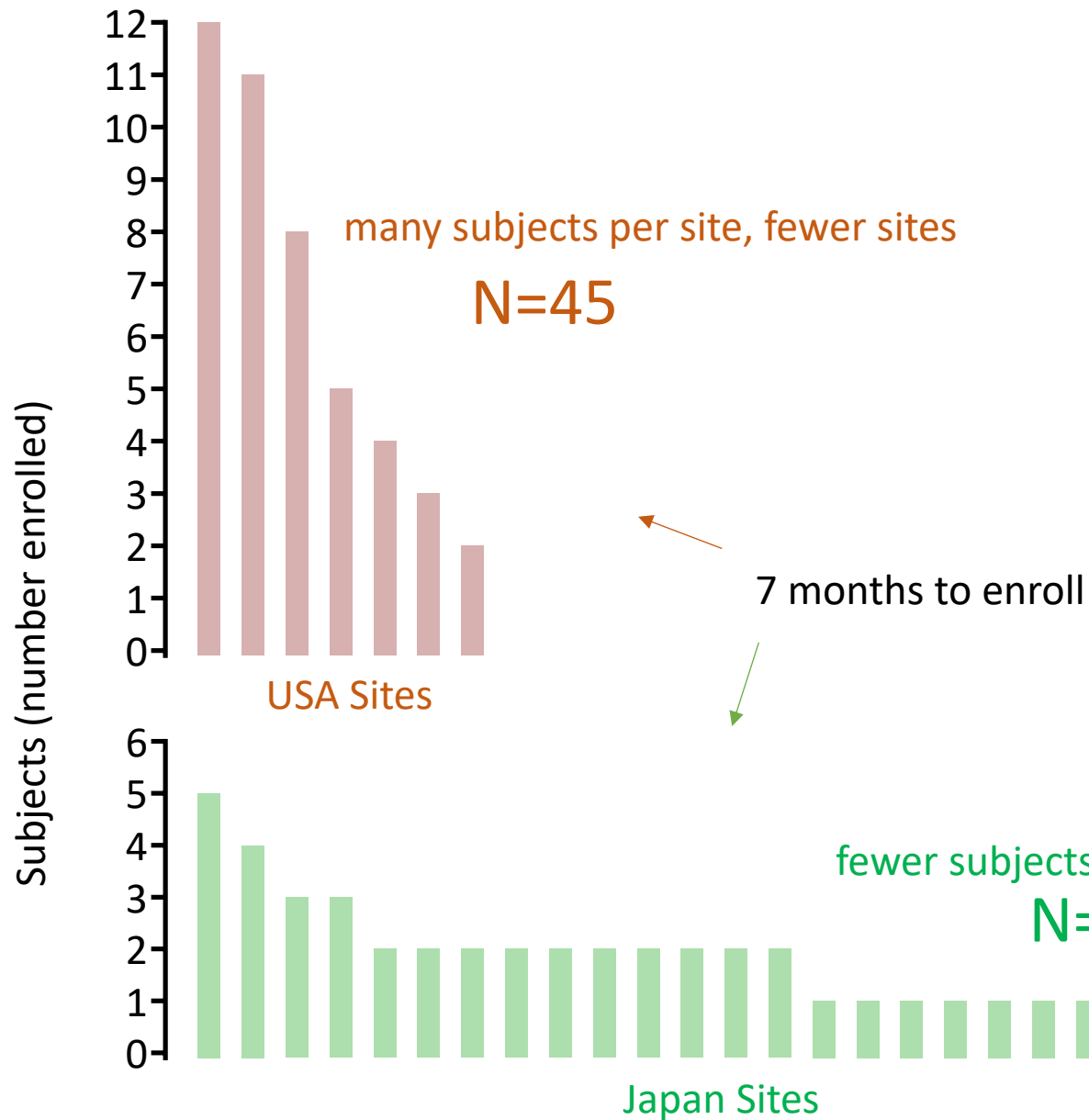
Total Sample size	43	43	41	39	35
-------------------	----	----	----	----	----

Japan



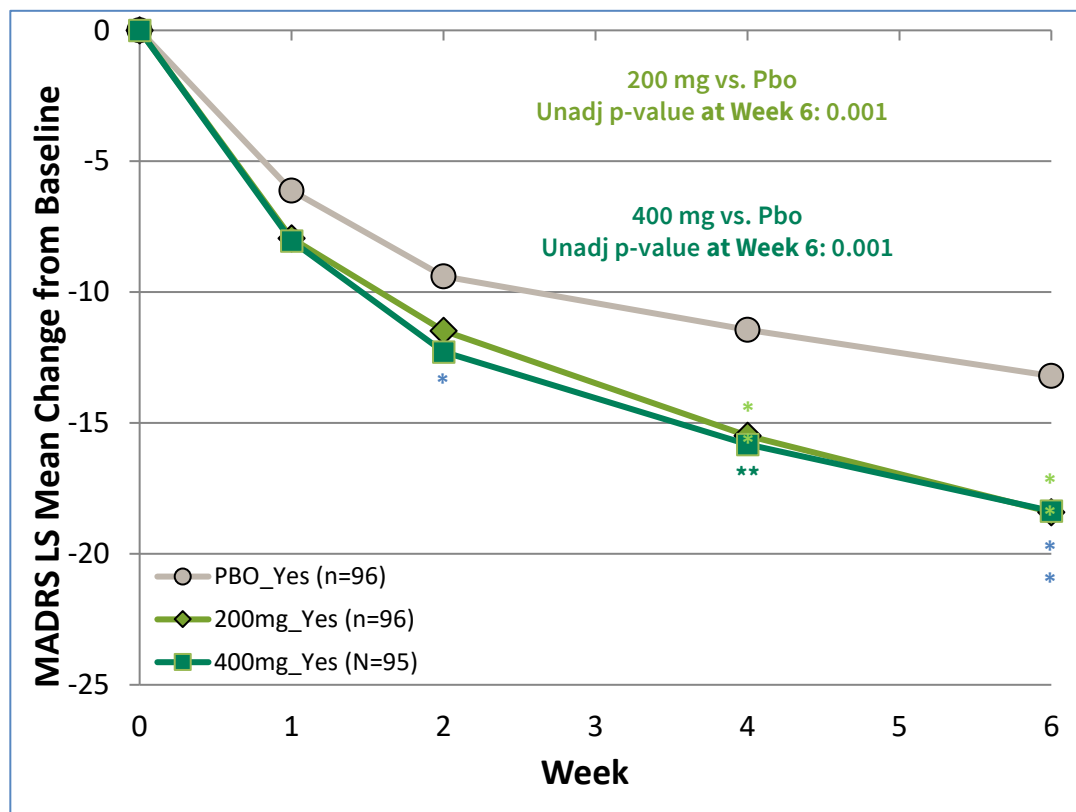
Total Sample size	48	48	46	43	43
-------------------	----	----	----	----	----

Which approach yielded better-quality data?

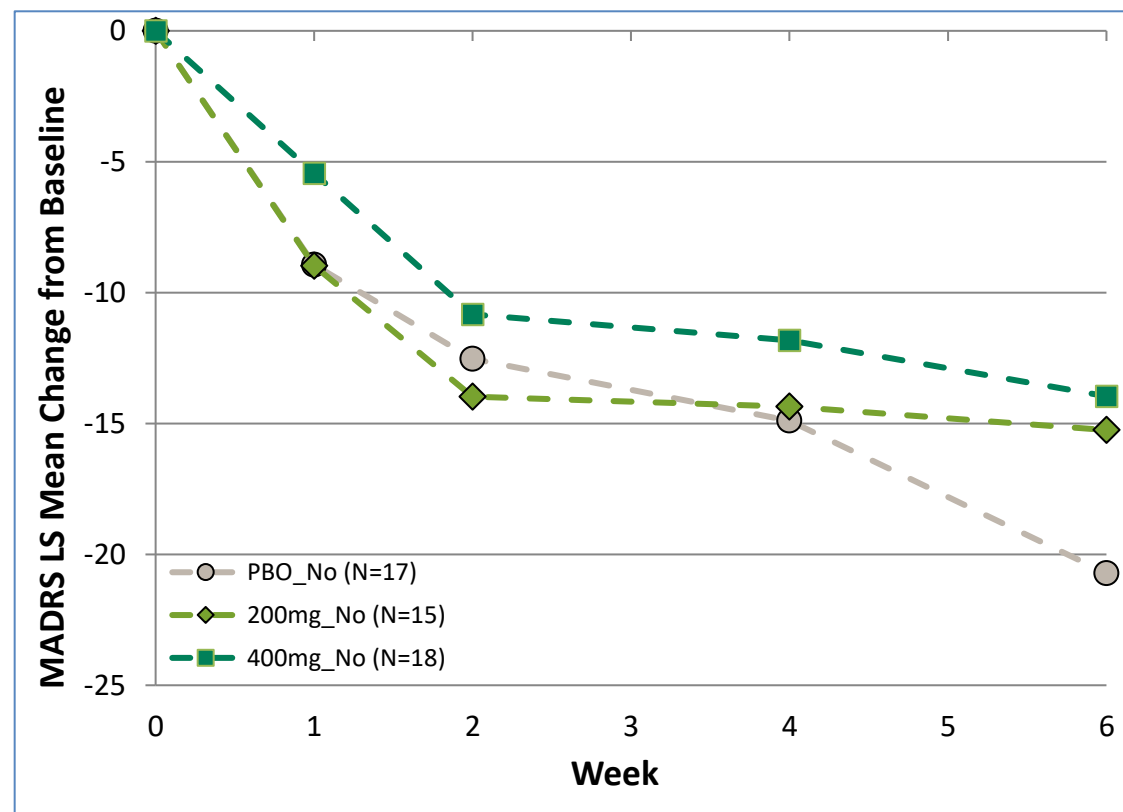


CFB in MADRS Total Score Across Time, by Medical Records Presence - MMRM (ITT) — Europe + US + Japan

Med Records Present



Med Records Not Present



ES (200 mg vs PBO)	-0.25	-0.23	-0.4 **	-0.49 **
ES (400 mg vs PBO)	-0.27	-0.32 *	-0.44 **	-0.48 **

ES (200 mg vs PBO)	-0.01	-0.16	0.05	0.51
ES (400 mg vs PBO)	0.49	0.19	0.3	0.63

- * Unadj p < 0.05
- ** Unadj p < 0.01
- *** Unadj p < 0.001

more-strict eligibility

ARTIFICIAL INTELLIGENCE

*automatic,
algorithmic,
computer-
implemented*

HUMAN INTELLIGENCE

*human,
clinician-based
oversight and
judgement*

INFRASTRUCTURE

*impact of business incentives on
the study population, role for
academic medical centers*

TO ADDRESS EROSION OF DRUG SIGNAL IN USA STUDIES...
3 DOMAINS OF INNOVATION