Sequential Parallel Comparison Design (SPCD)

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History of SPCD

- SPCD was invented in 2003 at MGH by Drs. Fava and Schoenfeld (M Fava, AE Evins, DJ Dorer, DA Schoenfeld. Psychotherapy and psychosomatics 2003; 72 (3), 115-127; original article cited >300 times in the literature)
- Six patents on SPCD (System and method for reducing the placebo effect in controlled clinical trials; Patent numbers: 8219419, 8145505, 8145504, 7983936, 7840419, and 7647235)
- The first multi-center trial using SPCD completed enrollment in September 2009 (NCT00683852) (Fava et al, Psychother Psychosom. 2012;81(2):87-97)

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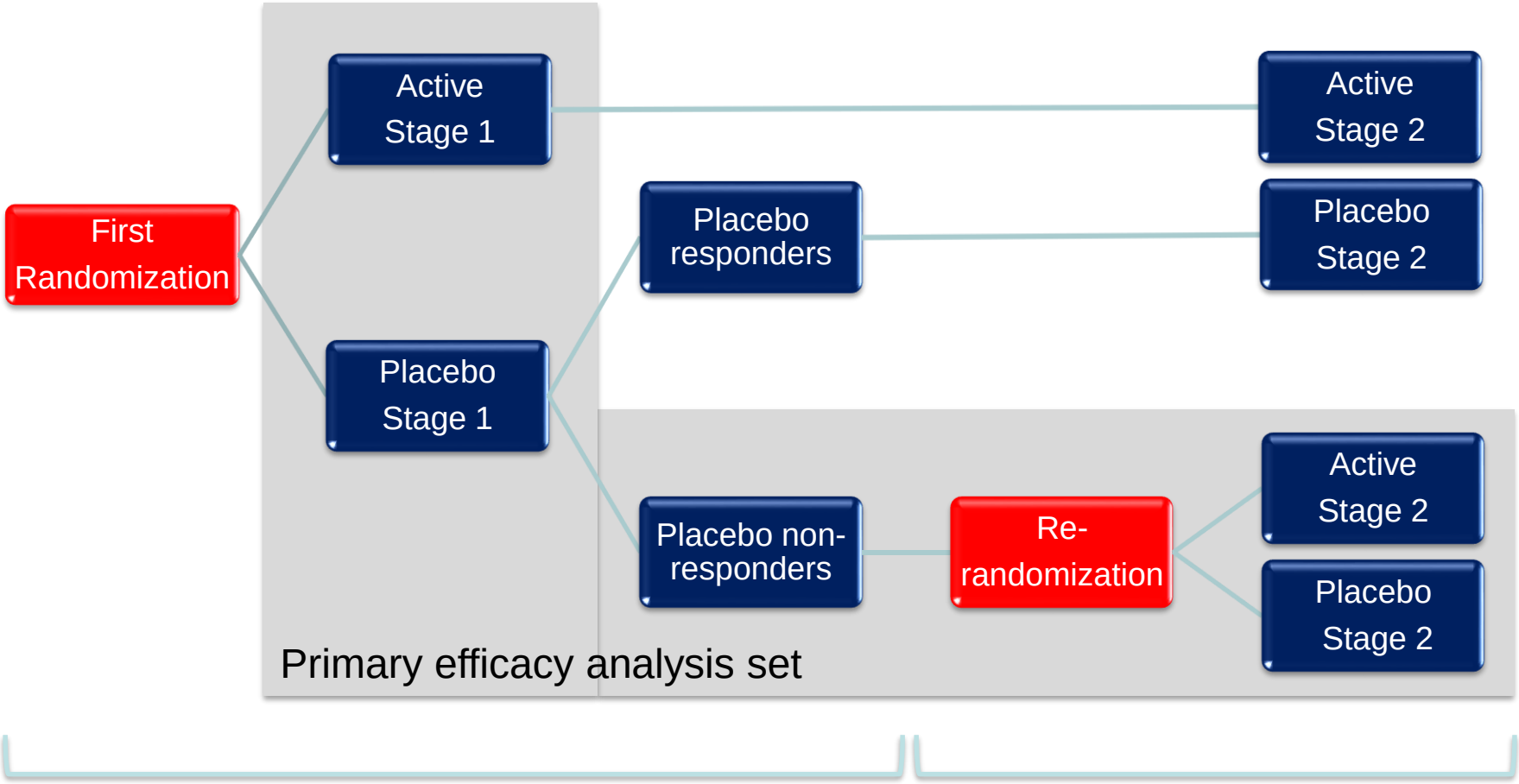
Sequential Parallel Comparison Design (SPCD) Structure



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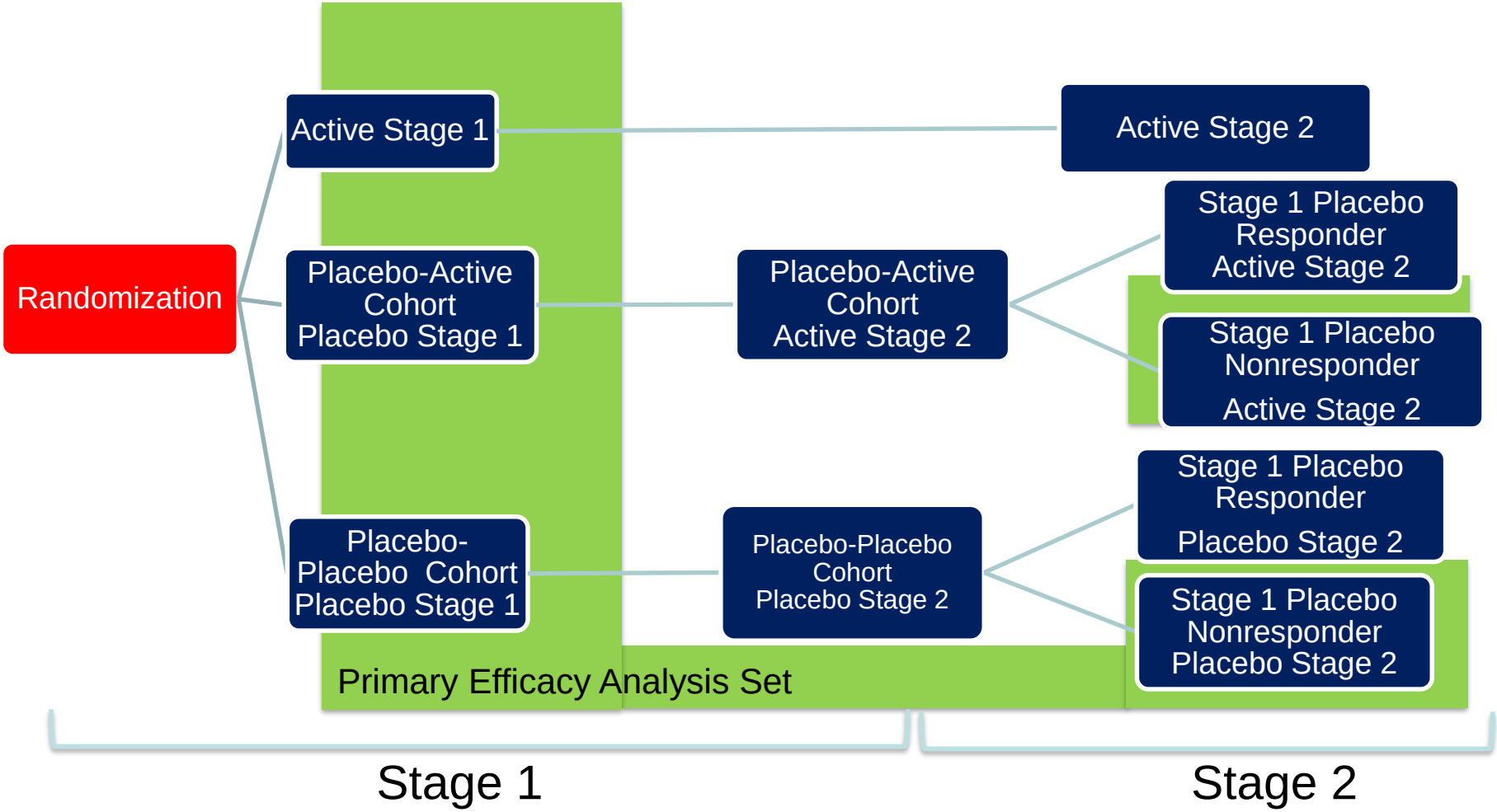
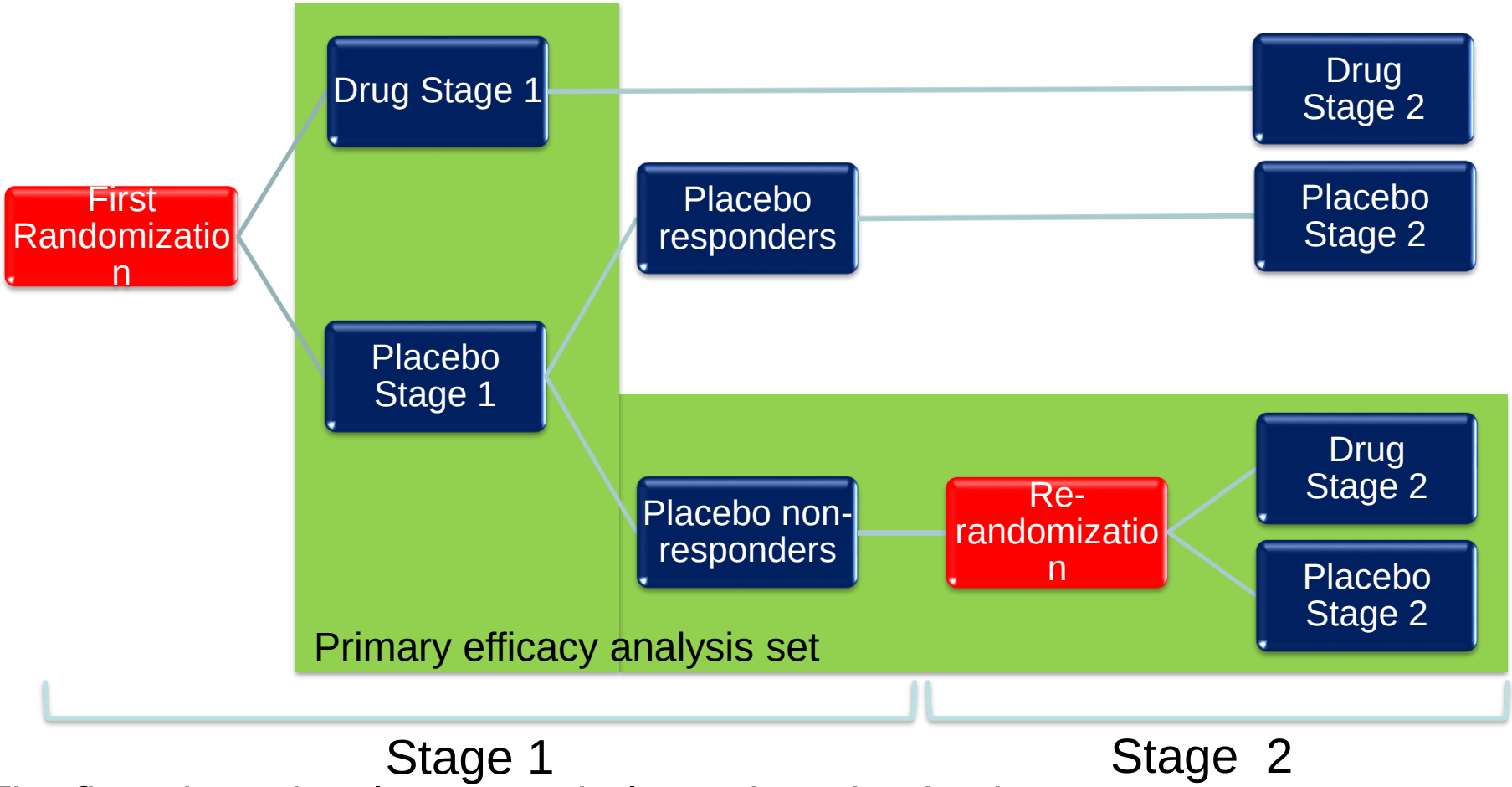
Fava et al, Psychother Psychosom. 2003; 72(3): 115-27

SPCD - Pre-Randomization



"Eligible subjects are then randomized to one of three treatment groups: drug alone (DD), placebo then drug (PD) and placebo then placebo (PP)." *Fava et al Psychother Psychosom 2003;72:115–127*

SPCD - Re-Randomization



"The first phase involves an unbalanced randomization between placebo and active treatment with more patients randomized to placebo. In the **second** phase, non-responders treated with placebo are **randomized** to either active treatment or placebo." *Fava et al, Psychother Psychosom 2003;72:115–127*

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Why Two Phases of Treatment?

- The first phase is aimed at:
  - Comparing drug and placebo in a standard parallel comparison design fashion – drug-placebo differences are expected to be smaller
  - Generating a large cohort of placebo non-responders – single-blind placebo lead-ins do not work as well as double-blind placebo lead-ins
- The second phase is aimed at:
  - Comparing drug and placebo in a standard parallel comparison design fashion in placebo non-responders – drug-placebo differences are expected to be greater

Completed SPCD Studies Funded by NIH

- Adjunctive Isradipine for the Treatment of Bipolar Depression (Isradipine) (NCT01784666)
- Efficacy and Tolerability of Riluzole in Treatment Resistant Depression (NCT01204918)
- Trial of Low Field Magnetic Stimulation Augmentation of Antidepressant Therapy in Treatment-Resistant Depression (RAPID) (NCT01654796)

Completed SPCD Studies Funded by Industry

- Alkermes (NCT01500200)
- Alkermes (NCT02158533)
- Alkermes (NCT02218008)
- Avanir (NCT01584440)
- Avanir (NCT02153502)
- BMS (NCT00683852)
- Cerecor (NCT01941043)
- Euthymics (NCT01318434)
- Janssen (NCT01998958)
- Neuralstem (NCT02695472)
- Pamlab (NCT00321152)
- Pamlab (NCT00955955)
- Pfizer (NCT02310568)

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Over 15 Ongoing SPCD Studies Funded by Industry and NIH

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Why Use SPCD In Clinical Trials?

- SPCD reduces the chance of a failed trial due to (a) lack of separation from placebo or (b) insufficient power, even when placebo response is low
- SPCD is a cost-efficient design which enhances signal detection, and therefore:
  - For any given “n”, greater power can result
  - For any given power, a smaller “n” can be used
- SPCD de-risk trials as its benefits apply whether placebo response is high or low

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How Can SPCD Improve Signal Detection and Reduce P-Value?

- Because of several features, SPCD can, over a wide range of treatment responses, reduce p-value if the treatment being tested does have therapeutic benefit
  - Data from both stages are utilized
  - Data from all eligible subjects randomized in Stage 1 are utilized at least once
  - Data from placebo non-responders are utilized twice
  - Placebo response can be significantly reduced in the second stage

Planning a Clinical Trial…Expecting High Placebo Response

	Assumed Response Rate		
	Drug	Placebo	Difference
Single Stage Design or SPCD Stage 1	60%	45%	15%
SPCD Stage 2	50%	25%	25%

1.6X

	Total *n*	
Power	Single Stage Design	SPCD
70%	274	156
80%	346	199
90%	462	266

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SPCD Analysis

Validity of Analytical Methods

- Over the past 10 years, many biostatisticians have reviewed SPCD and have recognized that:
  - There are a number of efficient methods of aggregating the outcome data that take into account the potential correlation of observations from subjects included in more than one stage
  - There are a number of valid test statistics that preserve the type 1 error rate

SPCD Analyses
Validity of Analytical Methods

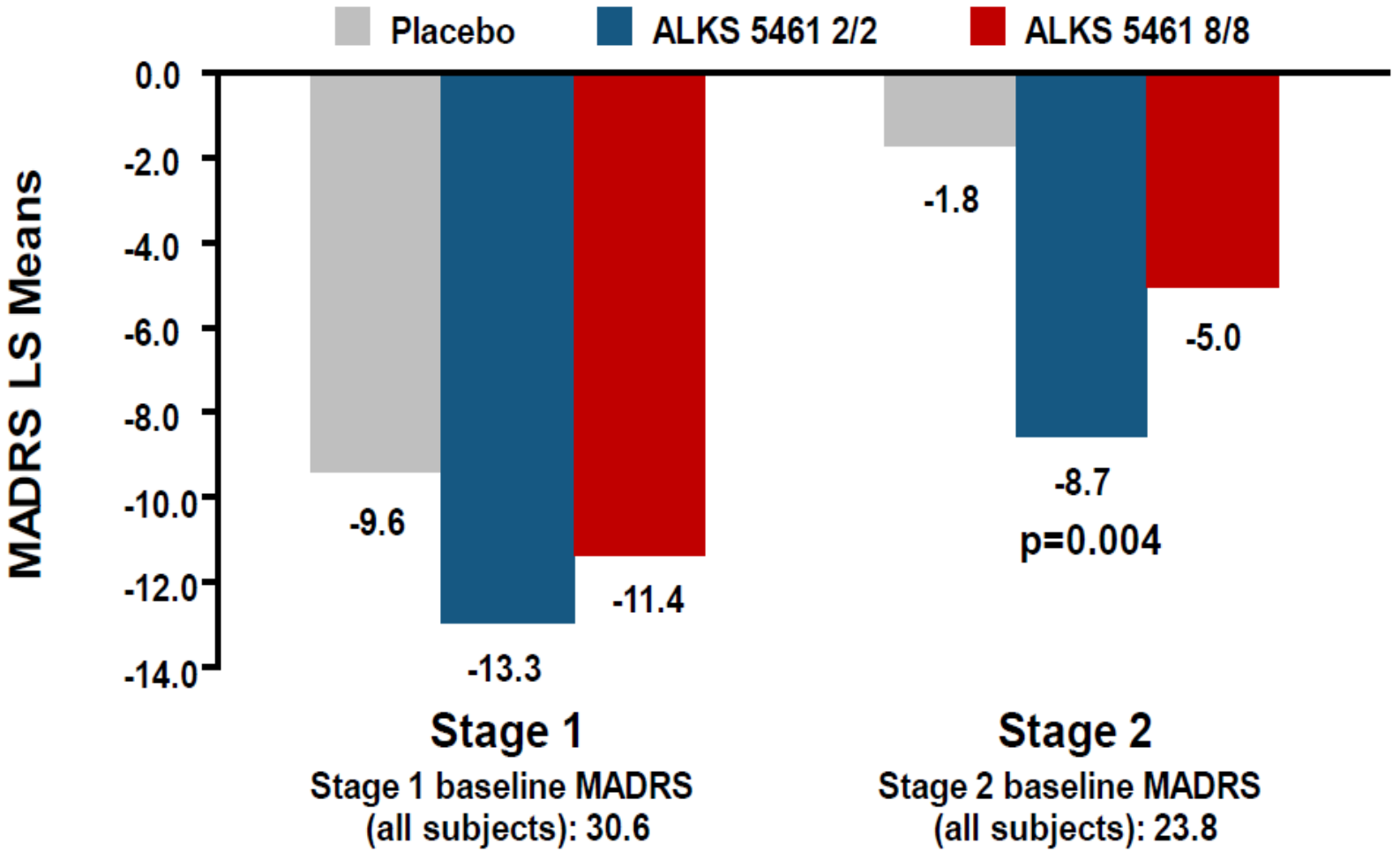
- Six Examples of Analytical Methods Proposed by Authors from Academia, Industry and FDA:
  - **Categorical data**
    - **Fava M., Evins A., Dorer D., Schoenfeld D.**: The Problem of the Placebo Response in Clinical Trials for Psychiatric Disorders: Culprits, Possible Remedies, and a Novel Study Design Approach; Psychotherapy and Psychosomatics 2003; 72:115-127; and Erratum 2004; 73:123.
    - **Ivanova A., Qaqish B., Schoenfeld D.**: Optimality, sample size and power calculations for the sequential parallel comparison design; Statistics in Medicine 2011; 30: 2793-2803.
  - **Continuous data**
    - **Tamura R., Huang X.:** An examination of the efficiency of the sequential parallel design in psychiatric clinical trials; Clinical Trials 2007; 4:309-317.
    - **Chen Y., Yang Y., Hung H., Wang S.:** Evaluation of performance of some enrichment designs dealing with high placebo response in psychiatric clinical trials; Contemporary Clinical Trials 32 2011; 592-604.
    - **Liu Q., Lim P., Singh J., Lewin D., Schwab B. & Kent J.:** Doubly Randomized Delayed-Start Design for Enrichment Studies with Responders or Nonresponders; Journal of Biopharmaceutical Statistics 2012, 22:4, 737-757.
    - **Doros G., Pencina M., Rybin D., Meisner A., Fava M.:** A Repeated Measures Model for Analysis of Continuous Outcomes in Sequential Parallel Comparison Design Studies; Statistics in Medicine 2013 DOI 10.1002/sim.5728.

SPCD Analyses

Validity of Analytical Methods

- With respect to the type 1 error rate:
  - **Ivanova et al. (2011)**: "All tests preserve the type 1 error rate rather well…"
  - **Chen et al. (2011)**: "…the weighted test statistic based on MMRM estimates appears to be the most robust test statistic for SPD-ReR in terms of type 1 error control, power performance, and estimation accuracy."
  - **Liu et al. (2012)**: "From Table 2, it is seen that the simulated type 1 error rates are very close to the theoretical value a = .025".
  - **Doros et al. (2012)**: "Our extensive simulations show that when compared with the other methods, our approach preserves the type 1 error even for small sample sizes and offers adequate power and the smallest mean squared error under a wide variety of assumptions."

Figure 4: MADRS Change from Baseline at Week 4



Fava et al, Am J Psychiatry. 2016 May 1;173(5):499-508

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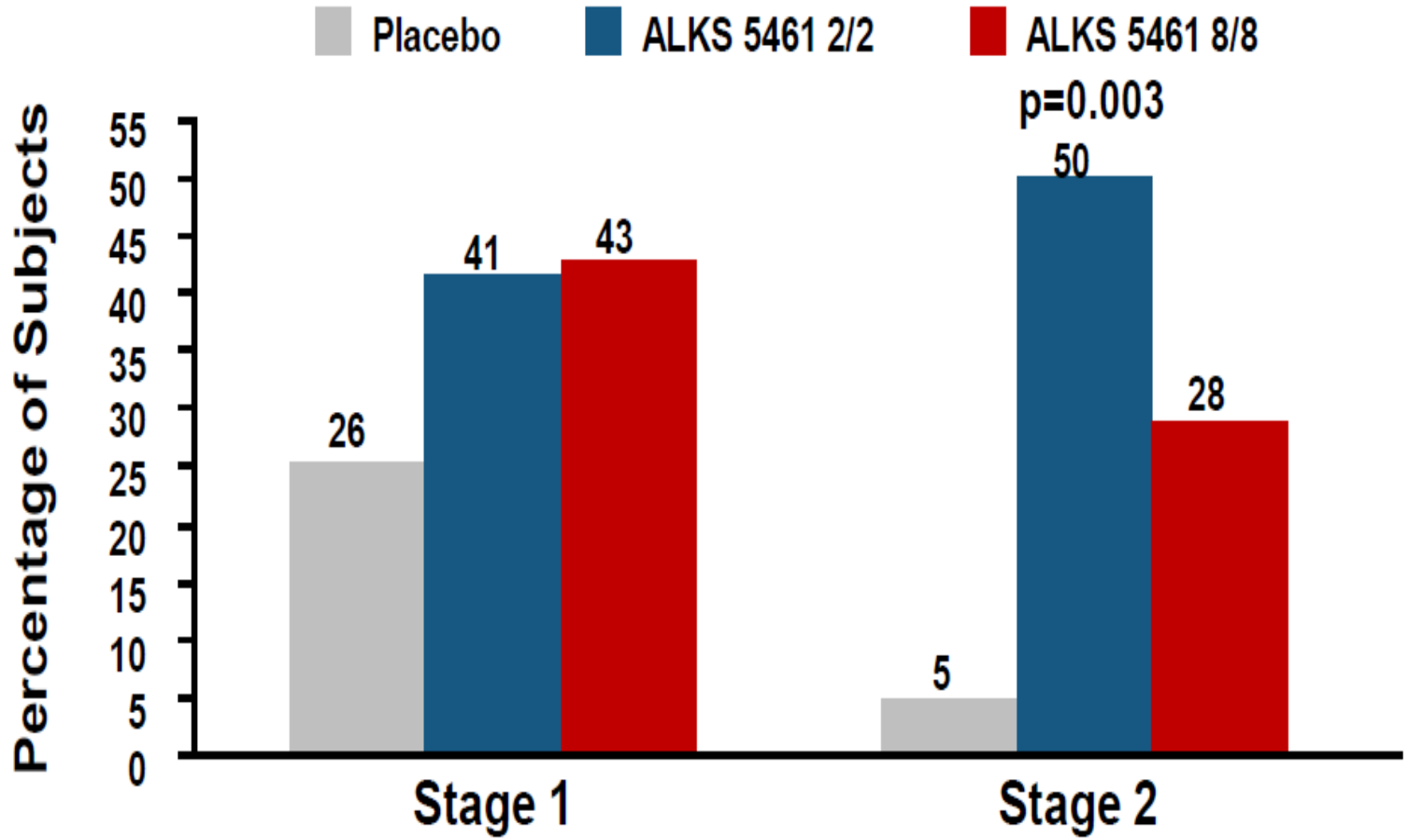
Figure 5: Responder Analysis: Subjects with ≥50% Reduction in MADRS Compared to Baseline



Fava et al, Am J Psychiatry. 2016 May 1;173(5):499-508

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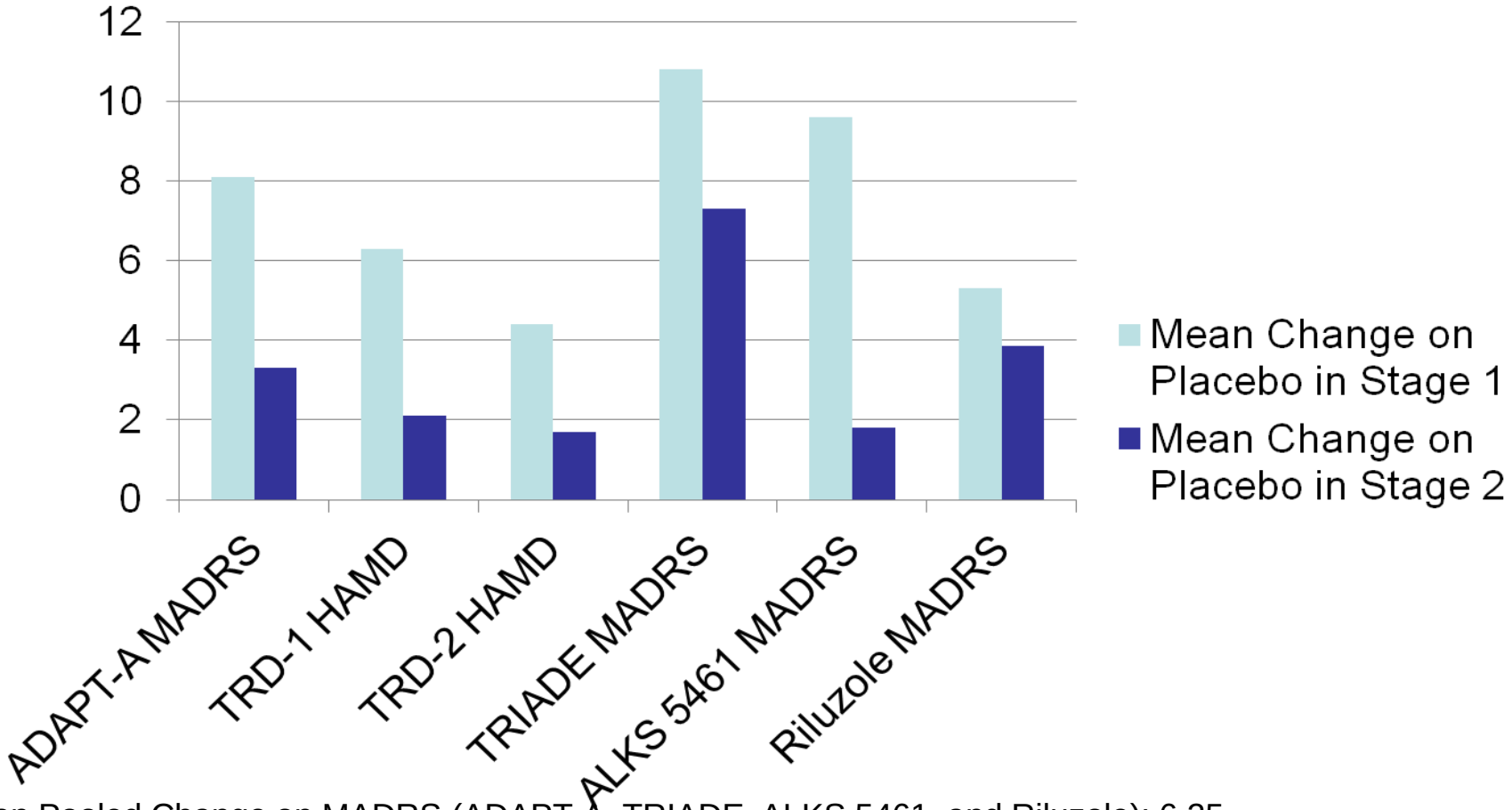
Stage 1 and Stage 2 Mean Changes on Placebo in Completed Multicenter SPCD TRD Trials



- Mean Pooled Change on MADRS (ADAPT-A, TRIADE, ALKS 5461, and Riluzole): 6.25
- Mean Pooled Change on HAMD (TRD-1 and TRD-2): 3.63

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ADAPT-A (Fava et al, Psychoth Psychosom. 2012 81(2):87-97), TRD-1 and TRD-2 (Papakostas et al, Am J Psychiatry. 2012;169(12):1267-74), TRIADE (Freeman et al, ACNP Meeting, 2013), ALKS 5461 (Fava et al, Am J Psychiatry. 2016 May 1;173(5):499-508), and Riluzole (Mathew et al, Neuropsychopharmacology. 2017 Dec;42(13):2567-2574)

Double-Blind Study of LFMS in MDD

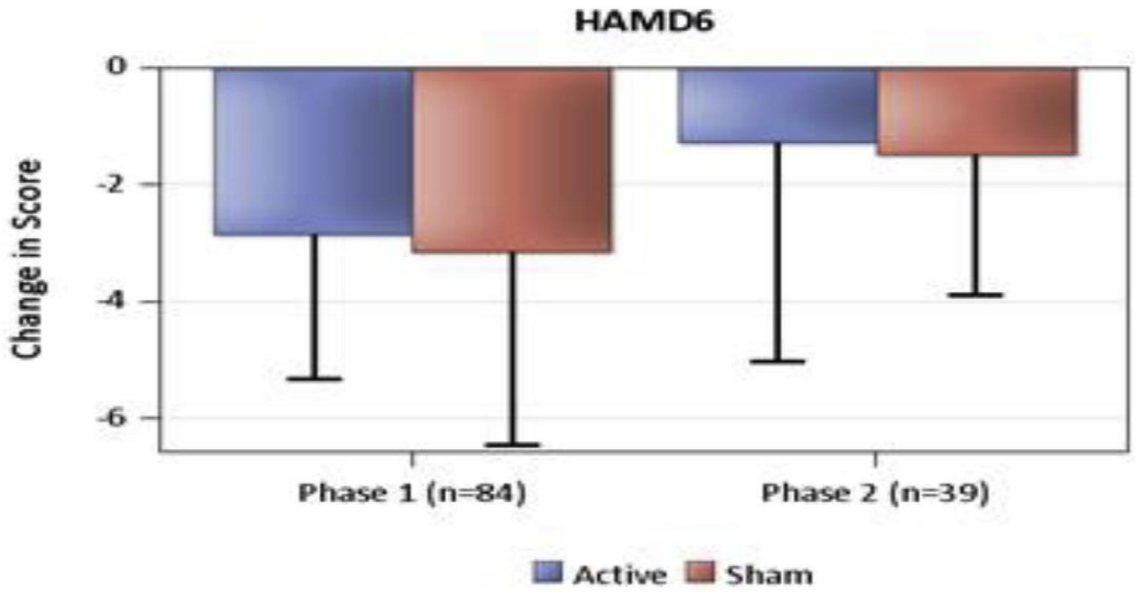

Fig. 1. Change in HAM-D-6 scores during phases 1 and 2 of the SPCD trial. Average change scores per treatment group per phase are shown. Each phase consisted of 2 treatments, one per day, on two consecutive days, so that the phase 1 treatment was delivered on days 0 and 1, and phase 2 treatment was delivered on days 2 and 3. Phase 1 change scores reflect HAM-D-6 scores assessed on day 2, the day after phase 1 treatment ended, minus HAMD6 scores on day 0, as assessed right before the start of the phase 1 treatment. Phase 2 change scores reflect HAM-D-6 scores assessed on day 4, the day after phase 2 treatment ended, minus HAM-D-6 scores on day 2, as assessed right before the start of the phase 2 treatment. Note that, as per the SPCD design, only scores of participants who were randomized to sham in phase 1, and who were non-responders to this sham treatment, are relevant to phase 2 outcomes. Thus, sample sizes are different for the effects shown for phase 1 (n = 84) and phase 2 (n = 39).

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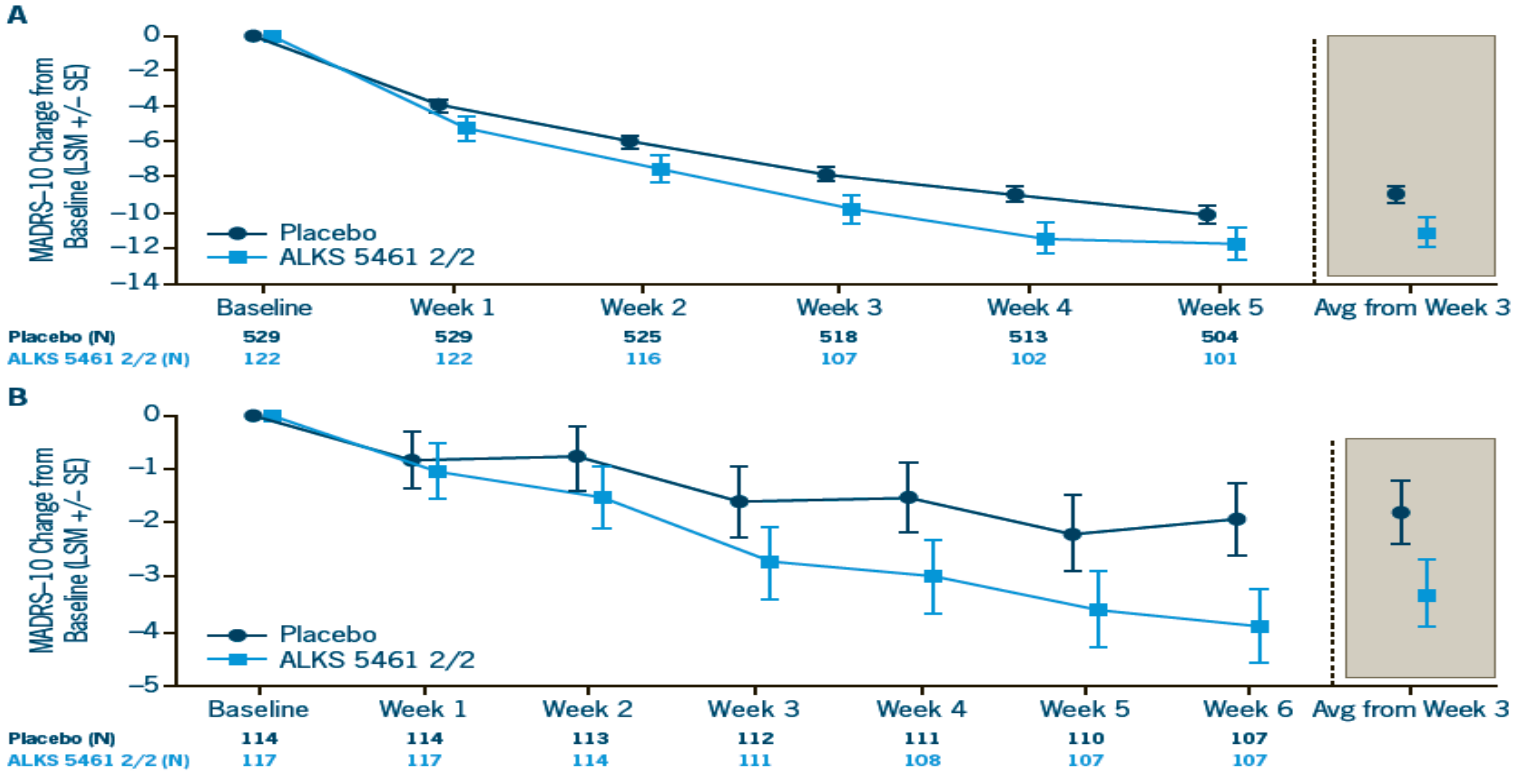
Fava et al, Brain Stimul. 2018 Jan - Feb;11(1):75-84

Forward 4 and Forward 5 Studies

Figure 6: LSM (±SE) Change From Baseline in MADRS-10 by Visit During Each Efficacy Period—Stage 1 (A) and Stage 2 (B) FAS



Note: Numbers under the X-axis are patient counts for the placebo and ALKS 5461 2/2 groups at each study week. Avg from Week 3 (displayed in the line plot) includes data from Weeks 3, 4, and 5. Baseline is the randomization baseline at Visit 2.

Thase et al, US Psych Congress, 2017

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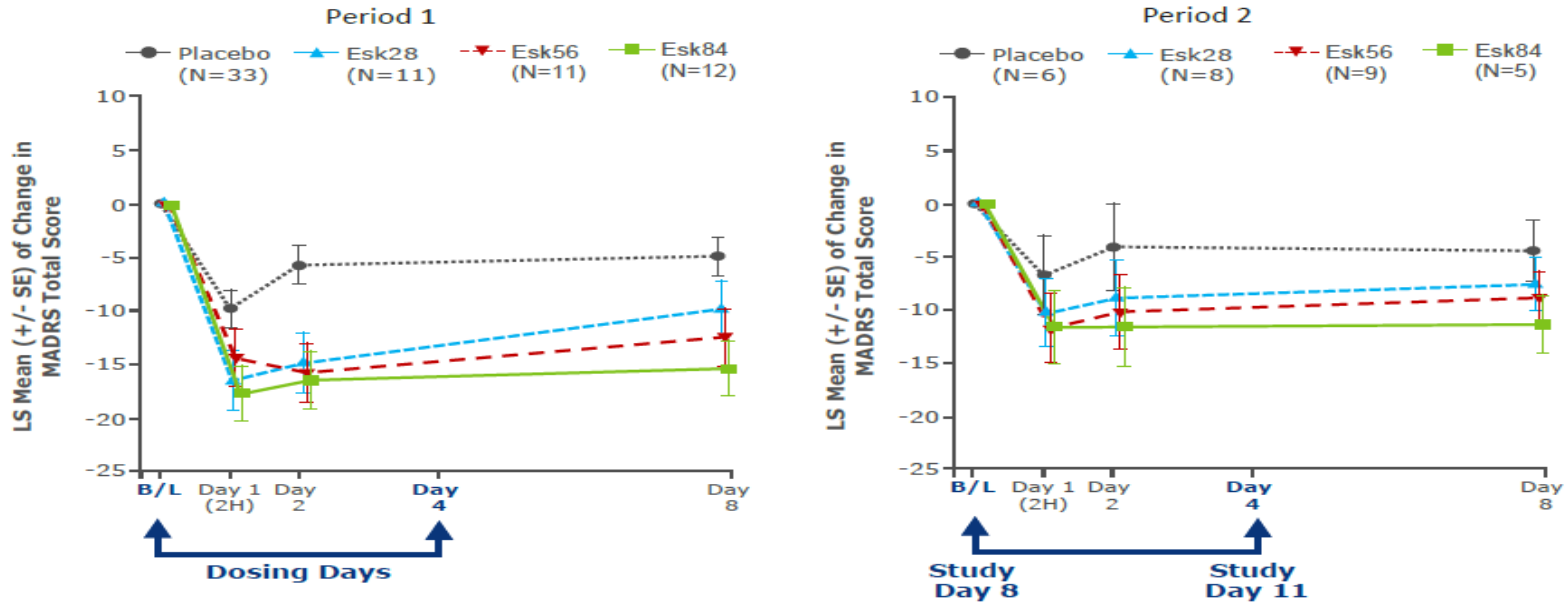
A Double-Blind, Doubly-Randomized, Placebo-Controlled Study of Intranasal Esketamine in TRD*

Figure 2: MADRS Total Score LS Mean Change from Baseline to End Point – ANCOVA LOCF Analysis (Intent-to-Treat Analysis Set-DB)



	Esk 28	Esk 56	Esk 84
Period 1 and Period 2 Combined			
Mean (SE) differences from placebo	−4.2 (2.09)	−6.3 (2.07)	−9.0 (2.13)
90% CI	−7.67, −0.79	−9.71, −2.88	−12.53, −5.52
One sided p-value	0.021	0.001	<0.001

CI: confidence interval; DB: double-blind; Esk: esketamine; MADRS: Montgomery-Asberg Depression Rating Scale; SE: standard error

- Assuming equal variance across treatments and periods, the effect size combining both periods ranged from 0.52 for 28 mg, 0.92 for 56 mg, and 1.20 for 84 mg esketamine

*TRD assessed with the ATRQ

Daly et al, JAMA Psychiatry. 2018 Feb 1;75(2):139-148.

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SPCD Published Literature

Boessen R., Knol M., Groenwold R., Grobbee D., Roes K.: Increasing trial efficiency by early reallocation of placebo nonresponders in sequential parallel comparison designs: Application to antidepressant trials; Clin Trials 2012 9:578 DOI: 10.1177/1740774512456454 http://ctj.sagepub.com/content/9/5/578

The authors refer to SPCD as "SPC".

Chen Y., Yang Y., Hung H., Wang S.: Evaluation of performance of some enrichment designs dealing with high placebo response in psychiatric clinical trials; Contemporary Clinical Trials 32 2011; 592-604. http://www.ncbi.nlm.nih.gov/pubmed/21540126

The authors refer to SPCD Format 1 as the "SPD-ReR" and refer to SPCD Format 2 as the "SPD".

Doros G., Pencina M., Rybin D., Meisner A., Fava M.: A Repeated Measures Model for Analysis of Continuous Outcomes in Sequential Parallel Comparison Design Studies; Statistics in Medicine 2013 DOI 10.1002/sim.5728. http://onlinelibrary.wiley.com/doi/10.1002/sim.5728/abstract

Fava M., Schoenfeld D.: Several issued U.S. patents including Nos. 7,647,235; 7,840,419; 7,983,936; 8,145,504; 8,145,505, and 8,219,419, each with a priority date of March 31, 2003.

Fava M., Evins A., Dorer D., Schoenfeld D.: The Problem of the Placebo Response in Clinical Trials for Psychiatric Disorders: Culprits, Possible Remedies, and a Novel Study Design Approach; Psychotherapy and Psychosomatics 2003; 72:115-127; and Erratum 2004; 73: 123. http://www.ncbi.nlm.nih.gov/pubmed/12707478 http://content.karger.com/Erratum

Fava M., Mischoulon D., Iosifescu D., Witte J., Pencina M., Flynn M., Harper L., Levy M., Rickels K., Pollack M.: A Double-Blind, Placebo-Controlled Study of Aripiprazole Adjunctive to Antidepressant Therapy (ADT) Among Depressed Outpatients with Inadequate Response to Prior ADT (ADAPT-A Study); Psychotherapy and Psychosomatics 2012;81:87-97. http://content.karger.com/ProduktDB/produkte.asp?Doi=332050

Grandi: The Sequential Parallel Comparison Model: A Revolution in the Design of Clinical Trials; Psychotherapy and Psychosomatics 2003; 72:113-114. http://www.ncbi.nlm.nih.gov/pubmed/12707477

Huang X., Tamura R.: Comparison of Test Statistics for the Sequential Parallel Design; Statistics in Biopharmaceutical Research 2010; Vol.2, No. 1. http://pubs.amstat.org/doi/abs/10.1198/sbr.2010.08015

The authors refer to SPCD as the "Sequential Parallel Design".

Ivanova A., Qaqish B., Schoenfeld D.: Optimality, sample size and power calculations for the sequential parallel comparison design; Statistics in Medicine 2011; 30: 2793-2803. http://onlinelibrary.wiley.com/doi/10.1002/sim.4292/abstract

SPCD Published Literature

Liu Q., Lim P., Singh J., Lewin D., Schwab B. & Kent J.: Doubly Randomized Delayed-Start Design for Enrichment Studies with Responders or Nonresponders; Journal of Biopharmaceutical Statistics 2012, 22:4, 737-757. http://dx.doi.org/10.1080/10543406.2012.678234

The authors refer to SPCD Format 1 as "Doubly Randomized Delayed-Start Design" and refer to SPCD Format 2 as the "Sequential Parallel Design".

Mi M.Y., Betensky R.A.: An analysis of adaptive design variations on the sequential parallel comparison design for clinical trials; Clinical Trials 2012; 0:1-9. http://ctj.sagepub.com/content/early/2013/01/02/1740774512468806

Mischoulon D., Witte J., Levy M., Papakostas G., Pet L., Hsieh W., Pencina M., Ward S., Pollack M., Fava M.: Efficacy of dose increase among nonresponders to low-dose aripiprazole augmentation in patients with inadequate response to antidepressant treatment: a randomized, double-blind, placebo-controlled, efficacy trial; J Clin Psychiatry 2012 Mar; 73 (3): 353-7. http://www.ncbi.nlm.nih.gov/pubmed/21939613

Papakostas G., Shelton R., Zajecka J., Etemad B., Rickels K., Clain A., Baer L., Dalton E., Sacco G., Schoenfeld D., Pencina M., Meisner A., Bottiglieri T., Nelson E., Mischoulon D., Alpert J., Barbee, J., Zisook S., Fava M.: L-Methylfolate as Adjunctive Therapy for SSRI-Resistant Major Depression: Results of Two Randomized, Double-Blind, Parallel-Sequential Trials; Am J Psychiatry 2012; 169: 1267 - 1274.

http://ajp.psychiatryonline.org/article.aspx?articleid=1461102

Papakostas G., Vitolo O., IsHak W., Rapaport M., Zajecka J., Kinrys G., Mischoulon D., Lipkin S., Hails K., Abrams J., Ward S., Meisner A., Schoenfeld D., Shelton R., Winokur A., Okasha M., Bari M., Fava M.: A 12-Week Randomized Double-Blind, Placebo Controlled, Sequential Parallel Comparison Trial of Ziprasidone as Monotherapy for Major Depressive Disorder; J Clin Psychiatry 2012 Dec; 73(12):1541-7 doi: 10.4088/JCP.12m07670.

http://www.ncbi.nlm.nih.gov/pubmed/23290327

Tamura R., Huang X.: An examination of the efficiency of the sequential parallel design in psychiatric clinical trials; Clinical Trials 2007; 4:309-317. http://ctj.sagepub.com/content/4/4/309.abstract

The authors refer to SPCD as the "Sequential Parallel Design".

Tamura R., Xuang X., Boos D.: Estimation of Treatment Effect for the Sequential Parallel Design; Statistics in Medicine 2011; 30:3496-3506. http://onlinelibrary.wiley.com/doi/10.1002/sim.4412/abstract

The authors refer to SPCD as the "Sequential Parallel Design".

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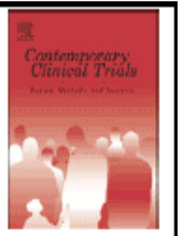

Evaluation of performance of some enrichment designs dealing with high placebo response in psychiatric clinical trials ☆

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ABSTRACT

Dealing with high placebo response remains a big challenge to conventional clinical trials for psychiatric disorders. A widely-used design strategy is to implement a placebo lead-in phase prior to randomization. The sequentially parallel design (SPD) proposed by Fava et al., which contains two consecutive double-blind treatment stages, has recently been promoted to reduce both the high placebo response and the required sample size in clinical trials for psychiatric disorders. Our work aims to study these two design strategies and evaluate the relevant statistical approaches for continuous measures under SPD in the presence of missing data. Based on the FDA archived database, we found that a longer placebo lead-in period seemed to help in identifying more placebo responders and thus increase the chance to detect a drug–placebo difference on continuous efficacy endpoint. Using a simple weighted ordinary least square test statistic Z_{OLS}, we analytically showed that, under the SPD with re-randomization of placebo non-responders at the second stage (SPD-ReR), Z_{OLS} can be used as a viable alternative to the weighted test statistic based on seemingly unrelated regression estimate Z_{SUR} proposed by Tamura and Huang to assess treatment efficacy. Results from simulation study comparing three imputation methods (last-observation-carried-forward approach, multiple imputation, and mixed-effects model for repeated measures (MMRM)) demonstrate that, when data are missing-at-random under SPD-ReR and the dropout rate is moderate, the weighted test statistic based on MMRM estimates appears to be the most robust test statistic for SPD-ReR in terms of type I error control, power performance, and estimation accuracy.

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A Conference summary of a workshop on SPCD with the FDA is available at:

http://mghcme.org/academy-uploads/SPCD_MGH_FDA_workshop_draft_summary_9.24.2016.pdf

Conclusion

- There has been a progressive increase over time in placebo response rates in drug trials
- Improving efficiency of study design among the most promising strategy to reduce the placebo response
  - SPCD is a clear example of a novel approach with a consistent track record

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