ALKS 5461 in Major Depressive Disorder (MDD)

Investor Conference Call at
Society of Biological Psychiatry Annual Meeting

MAY 18, 2017

Forward-Looking Statements

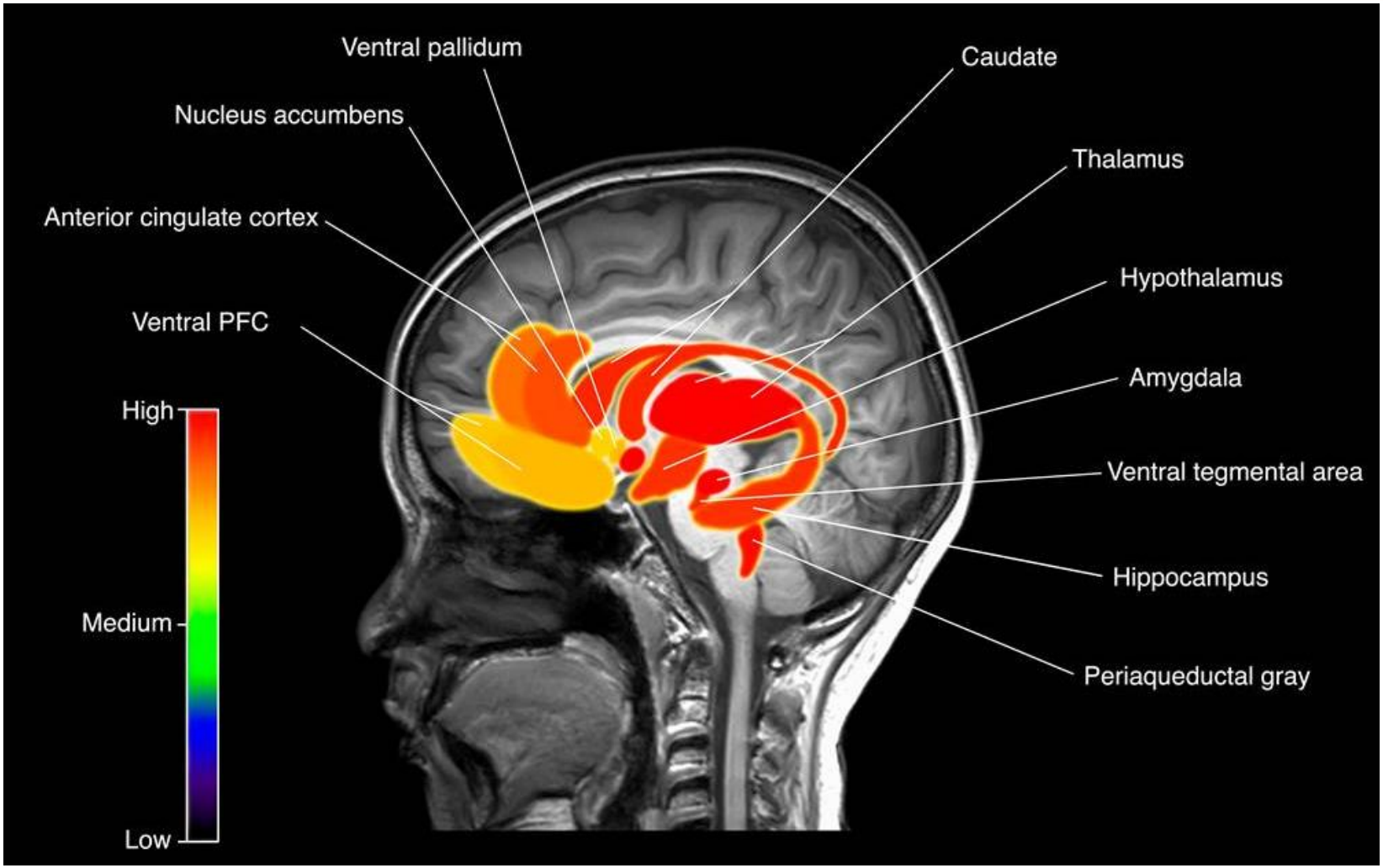
Certain statements in this presentation may constitute “forward-looking statements” within the meaning of the Private Securities Litigation Reform Act of 1995, as amended, including, but not limited to, statements concerning future business plans or prospects of Alkermes plc; the timing, funding and feasibility of product development and regulatory activities for ALKS 5461; whether the studies conducted for our ALKS 5461 development program will meet the U.S. Food and Drug Administration’s (“FDA”) requirements for filing and/or approval; and the therapeutic value and commercial potential of ALKS 5461. Although the company believes that such forward-looking statements are based on reasonable assumptions within the bounds of its knowledge of its business and operations, the forward-looking statements are neither promises nor guarantees and they are necessarily subject to a high degree of uncertainty and risk. Actual performance and results may differ materially from those expressed or implied in the forward-looking statements due to risks and uncertainties. The factors that could cause actual results to differ are described under the heading “Risk Factors” in the Alkermes plc Annual Report on Form 10-K for the fiscal year ended Dec. 31, 2016 and Quarterly Report on Form 10-Q for the quarter ended March 31, 2017, and in subsequent filings made by the company with the U.S. Securities and Exchange Commission (SEC), which are available on the SEC's website at www.sec.gov and on the company’s website at www.alkermes.com in the “Investors—SEC filings” section. Existing and perspective investors are cautioned not to place undue reliance on these forward-looking statements, which speak only as of the date they are made. Except as required by law, the company disclaims any intention or responsibility for updating or revising any forward-looking statements contained herein.

Agenda

- Role of Endogenous Opioid System in Emotional Regulation
- Introduction to ALKS 5461
- ALKS 5461: Data Update at Society of Biological Psychiatry
  - FORWARD-5 results
  - Pooled analysis of FORWARD-4 and FORWARD-5
- Summary of ALKS 5461 Development Program
- Future Areas of Development and Next Steps

Role of Endogenous Opioid System in Emotional Regulation

Core Brain Emotional Center: High Levels of Opioid Receptors



*For illustrative purposes only

References: Delay-Goyet, P, et al. *Brain Res.* 1987; 414(1), 8-14. Kuhar, MJ, et al. *Nature.* 1973; 245(5426), 447-450. Peckys, D & Landwehrmeyer, GB. *Neuroscience.* 1999; 88(4), 1093-1135. Peng, J, et al. *Drug and Alcohol Dependence.* 2012; 124(3), 223-228. Pilapil, C, et al. *NIDA Res Monogr.* 1986; 75, 319-322.

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Dysregulation of Endogenous Opioids and Their Receptors: A Key Underlying Abnormality in MDD

Kappa-opioid ligands in the study and treatment of mood disorders

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Molecular Psychiatry (2015) 20, 193–200

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IMMEDIATE COMMUNICATION

It still hurts: altered endogenous opioid activity in the brain during social rejection and acceptance in major depressive disorder

DT Hsu[1,2], BJ Sanford[2], KK Meyers[3], TM Love[2], KE Hazlett[4], SJ Walker[5], BJ Mickey[2], RA Koeppe[6], SA Langenecker[7] and J-K Zubieta[2,6]

Ultra-Low-Dose Buprenorphine as a Time-Limited Treatment for Severe Suicidal Ideation: A Randomized Controlled Trial

Yoram Yovell, M.D., Ph.D., Gali Bar, Ph.D., Moti Mashiah, M.D., Yehuda Baruch, M.D., Irina Briskman, M.D., Jack Asherov, M.D., Amit Lotan, M.D., Amihai Rigbi, Ph.D., Jaak Panksepp, Ph.D.
Am J Psychiatry 2016; 173:491–498; doi: 10.1176/appi.ajp.2015.15040535

J Clin Psychiatry. 2014 August ; 75(8): e785–e793. doi:10.4088/JCP.13m08725.

Safety, Tolerability, and Clinical Effect of Low-Dose Buprenorphine for Treatment-Resistant Depression in Mid-Life and Older Adults

Jordan F. Karp, Meryl A Butters, Amy Begley, Mark D. Miller, Eric J. Lenze, Daniel Blumberger, Benoit Mulsant, MD, and **Charles F. Reynolds III**

Introduction to ALKS 5461

ALKS 5461 in Major Depressive Disorder (MDD)

- Centrally acting opioid modulator with novel mechanism of action, designed to address dysregulation of endogenous endorphin and dynorphin neuropeptides

- Co-formulation of buprenorphine (partial mu agonist and kappa antagonist) and samidorphan (mu opioid antagonist) designed to normalize neurotransmission without addictive properties of classic opioids
  - Administered once daily as a single, sublingual tablet

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ALKS 5461 in Major Depressive Disorder (MDD)

- Comprehensive dataset from >1,500 patients demonstrates consistent antidepressive efficacy, safety and tolerability profile of ALKS 5461 in adjunctive treatment of MDD

- Designated Fast Track status by FDA;
  Regulatory submission planned for 2H 2017

FORWARD-5: Design and Results

FORWARD-5 Study Details

- Adjunctive treatment of MDD in patients with inadequate response to standard antidepressant treatment
  - Hamilton Depression Rating Scale (HAM-D) score ≥ 18, despite adequate trial of SSRI or SNRI
- Two dose levels tested: 1mg/1mg and 2mg/2mg ALKS 5461
  - Co-formulated sublingual tablet of buprenorphine and samidorphan
- All subjects remained on background antidepressant therapy
- Sequential Parallel Comparison Design (SPCD)
  - Same study design as FORWARD-4

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FORWARD-5 Statistical Analysis Plan Incorporated Learnings From FORWARD-3 and FORWARD-4

- Utilized multiple time points vs. single time point
  - Addresses week-to-week variation
  - Captures more information; reflective of therapeutic benefit over time
  - Improves precision

- Specified MADRS-6 as primary endpoint
  - Evaluates core symptoms of depression[1-3]
  - Appropriate for patients in adjunctive treatment setting
  - MADRS-10 additional endpoint in hierarchical primary analysis

[1]Bech, P. *Dialogues Clin Neurosci*. 2006 Jun; 8(2): 207–215.
[2]Bech, P., et al. *Nord J Psychiatry*. 2005; 59: 406-407.
[3]Thase, M., et al. *Int J Psychiatry Clin Pract*. 2012 Jun; 16(2): 121-31.

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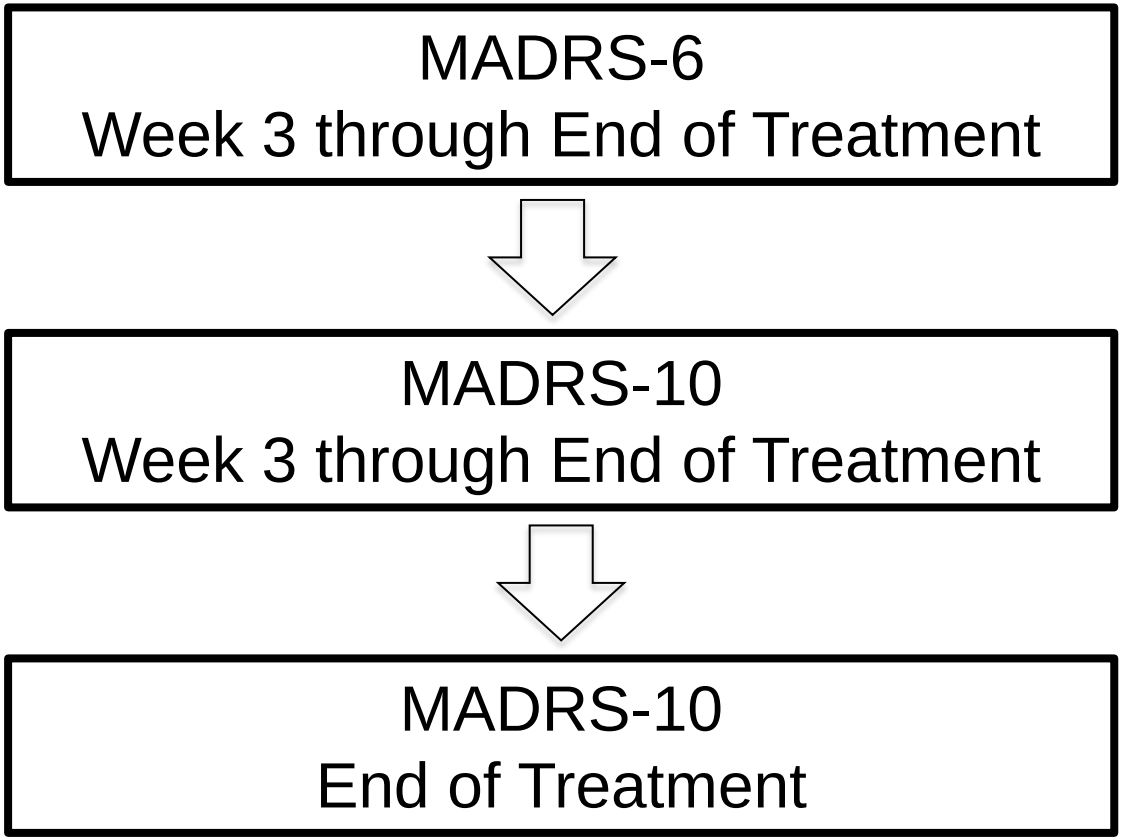
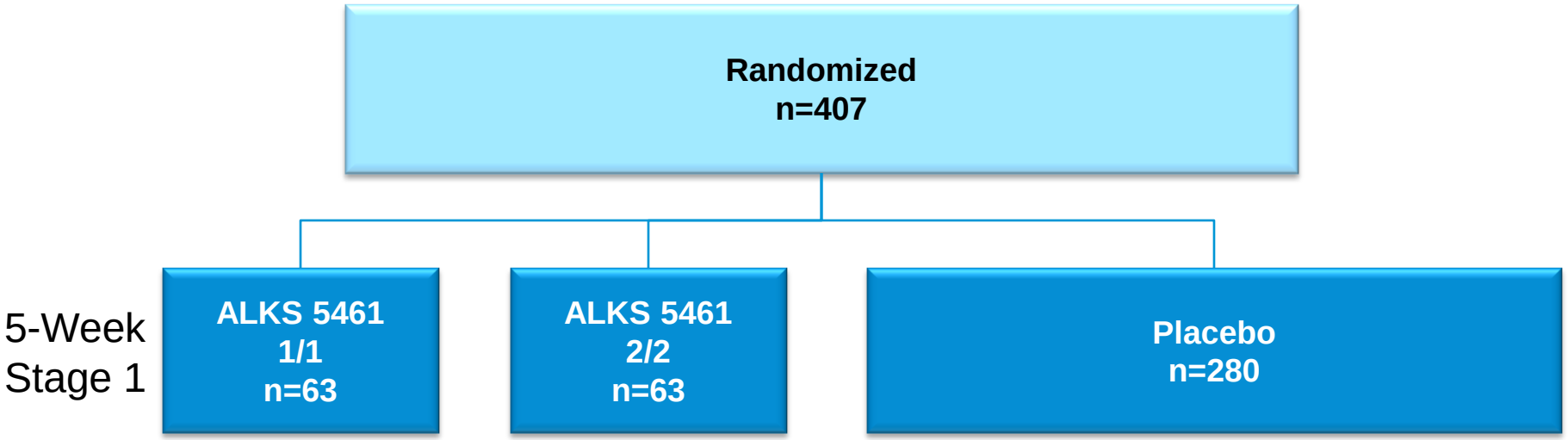
FORWARD-5 Primary Efficacy Endpoints: Fixed Sequence Hierarchical Testing



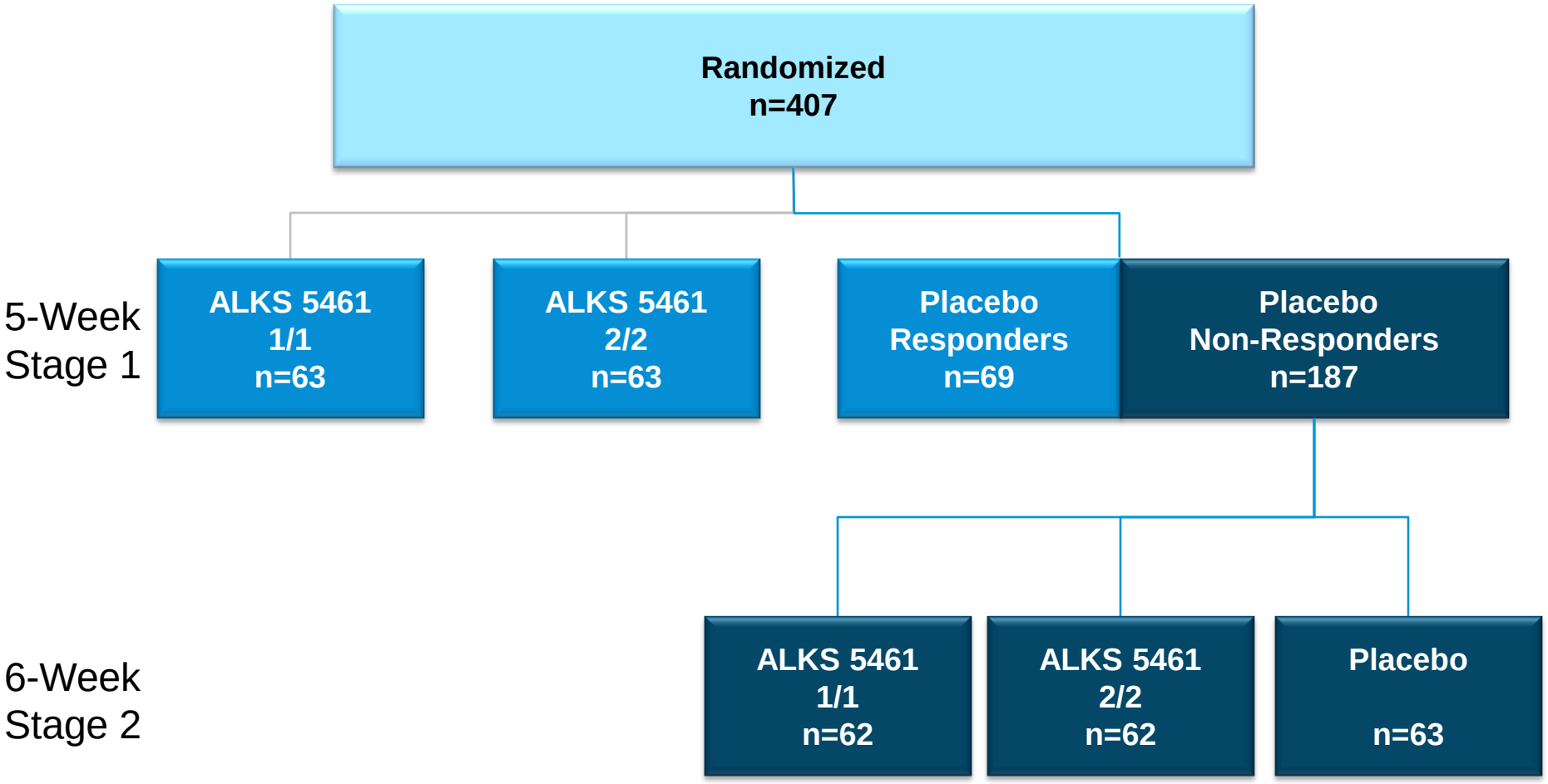
Multi-week Average: Stage 1 (Weeks 3,4,5); Stage 2 (Weeks 3,4,5,6)
End of Treatment: Stage 1 (Week 5); Stage 2 (Week 6)

FORWARD-5: SPCD Stage 1 Subject Flow



Following randomization, one subject did not receive study drug and is excluded from the safety and efficacy analysis

FORWARD-5: SPCD Stage 2 Subject Flow



22 subjects in the Stage 1 placebo group did not complete Stage 1 and two did not enter Stage 2. All efficacy analyses include subjects that received ≥ 1 dose of study drug and had ≥ 1 post-baseline Montgomery-Åsberg Depression Rating Scale (MADRS) assessment. One subject in Stage 1 did not receive study drug.

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FORWARD-5: Primary Efficacy Analysis

	ALKS 5461 1/1	ALKS 5461 2/2
MADRS-6 Average Change from Week 3 to EOT		
p-value	0.329	0.018
MADRS-10 Average Change from Week 3 to EOT		
p-value	0.277	0.026
MADRS-10 Change at EOT		
p-value	0.165	0.076

EOT = End of Treatment

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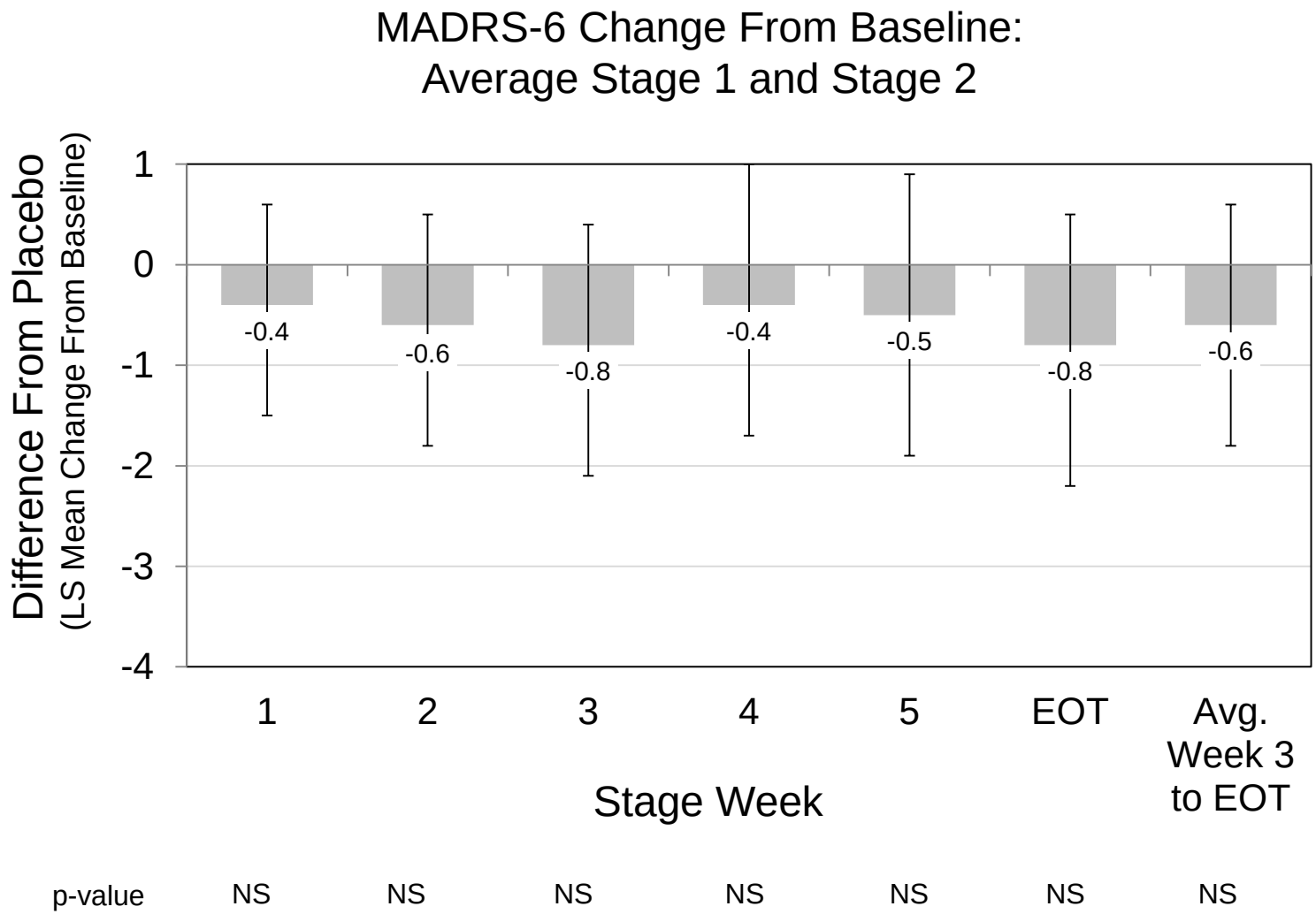
FORWARD-5 Primary Analysis: ALKS 5461 1/1 Dose vs. Placebo by Stage Week



95% confidence interval

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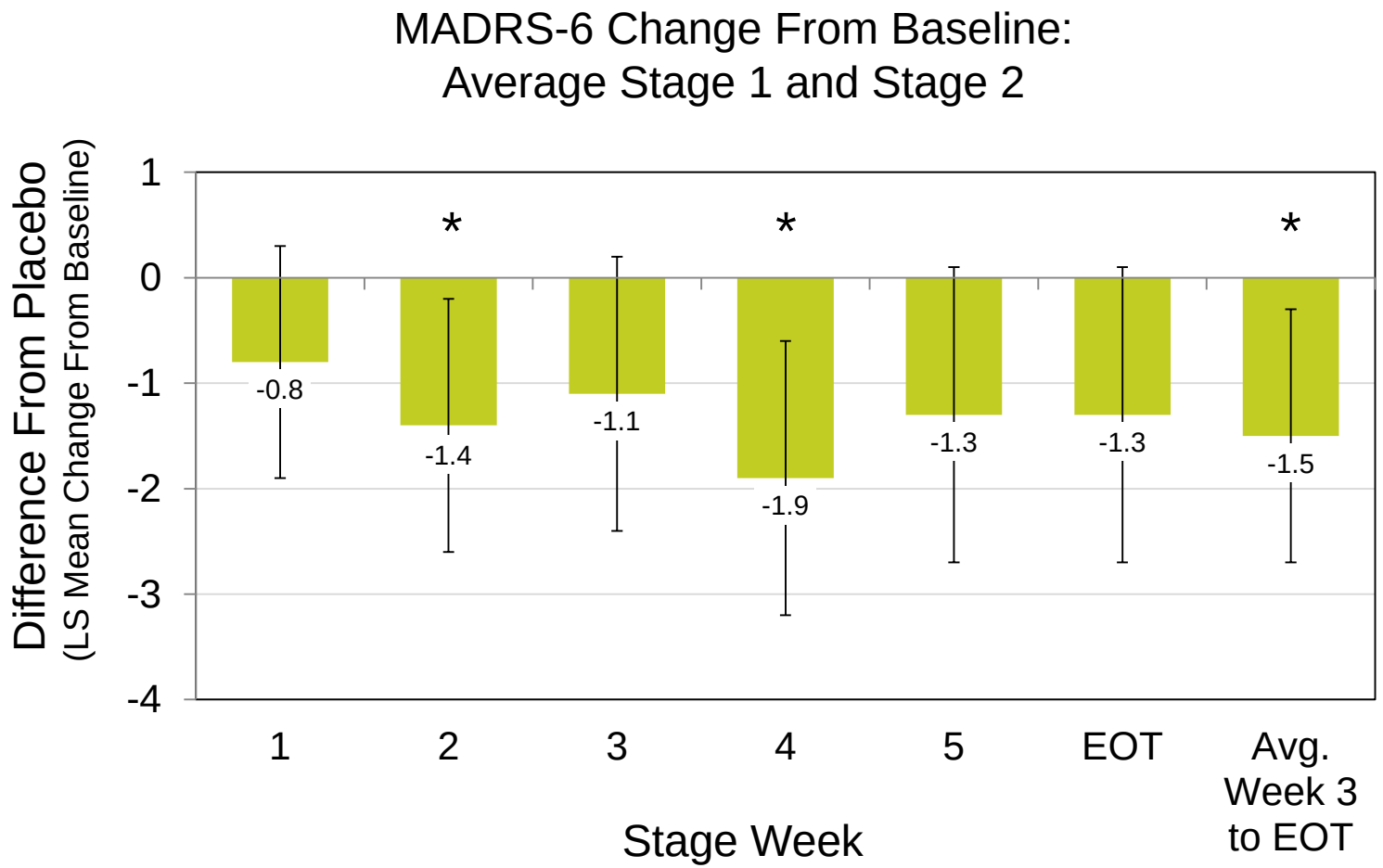
FORWARD-5 Primary Analysis: ALKS 5461 2/2 Dose vs. Placebo by Stage Week



95% confidence interval

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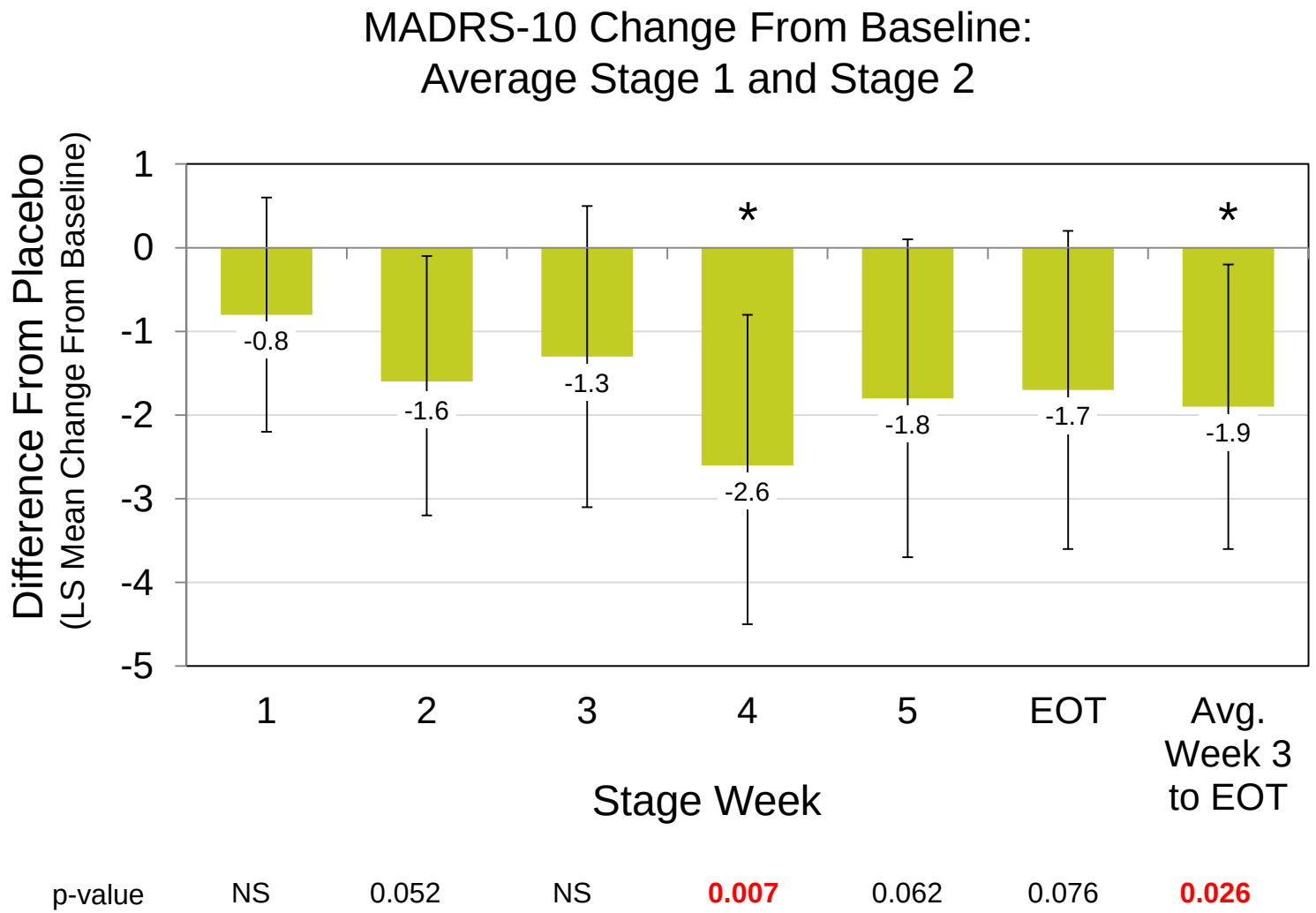
FORWARD-5 Primary Analysis: ALKS 5461 2/2 Dose vs. Placebo by Stage Week



95% confidence interval

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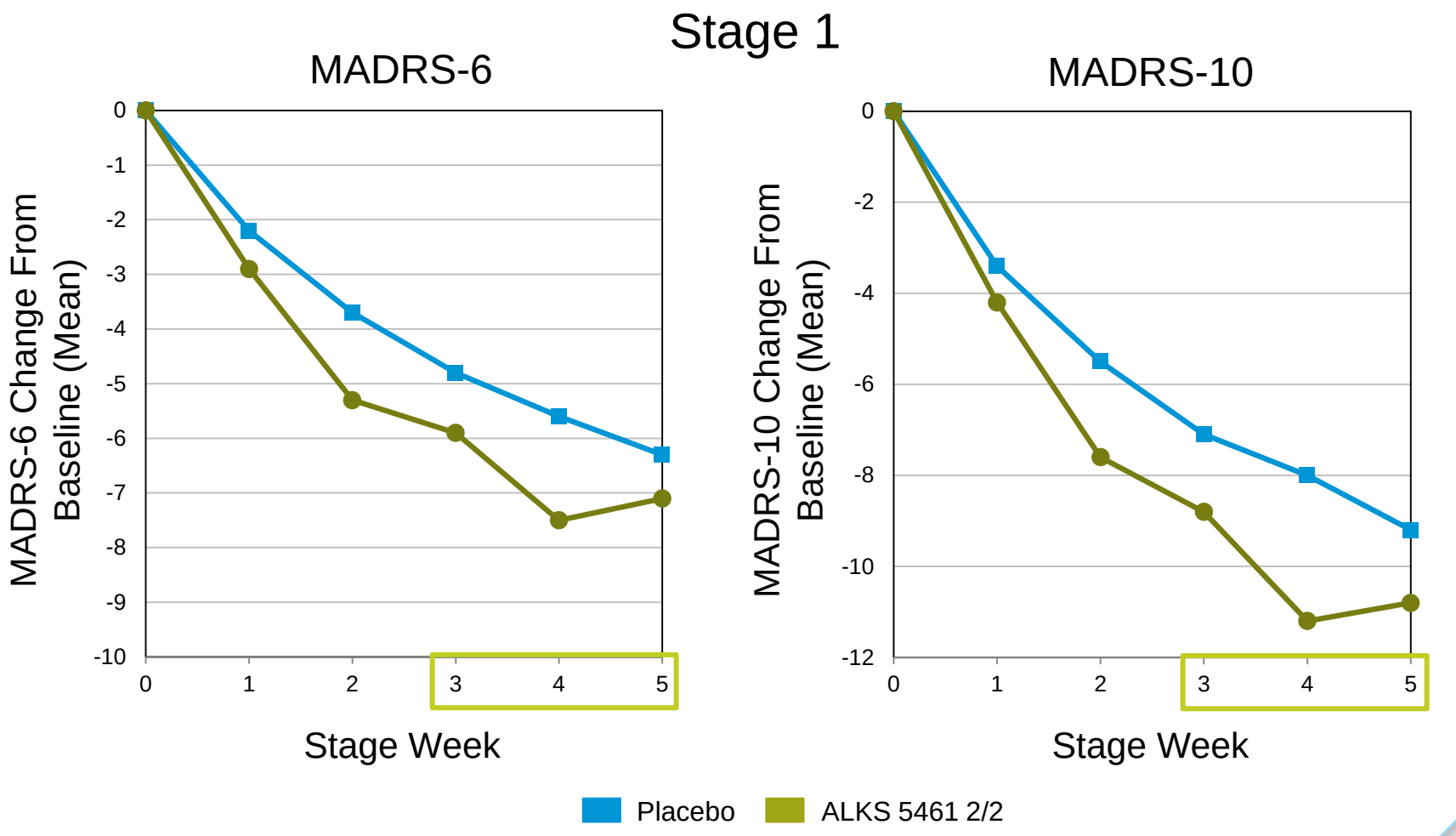
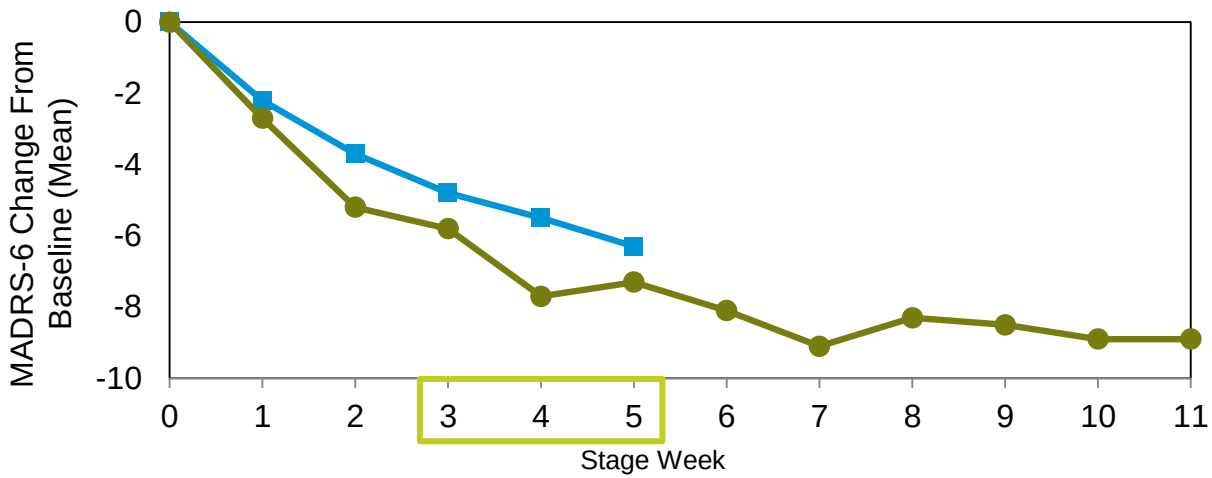
FORWARD-5 Stage 1: 2/2 Dose MADRS-6 and MADRS-10



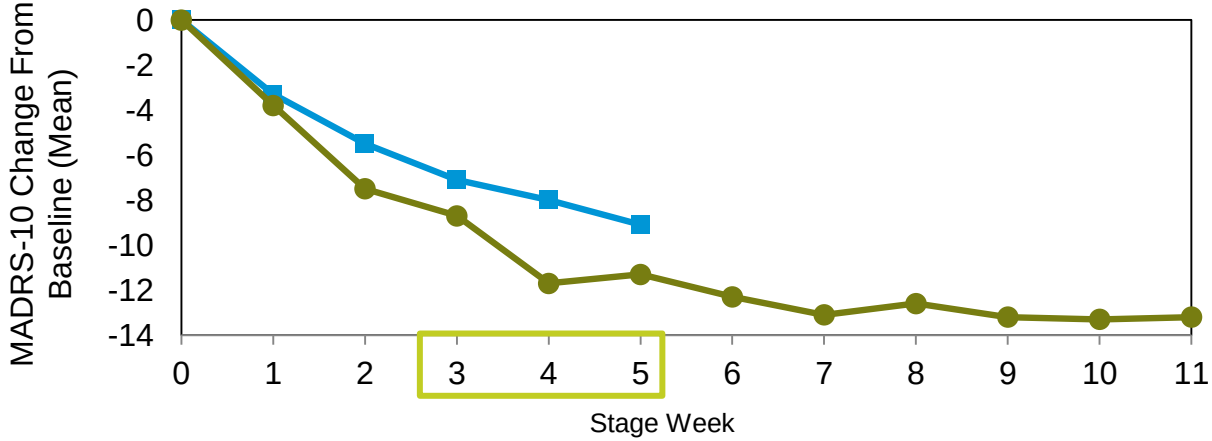
Green boxes represent weeks averaged in Stage 1 as part of primary efficacy analysis

FORWARD-5: Durability of Effect Throughout Entire 11-Week Study

MADRS-6

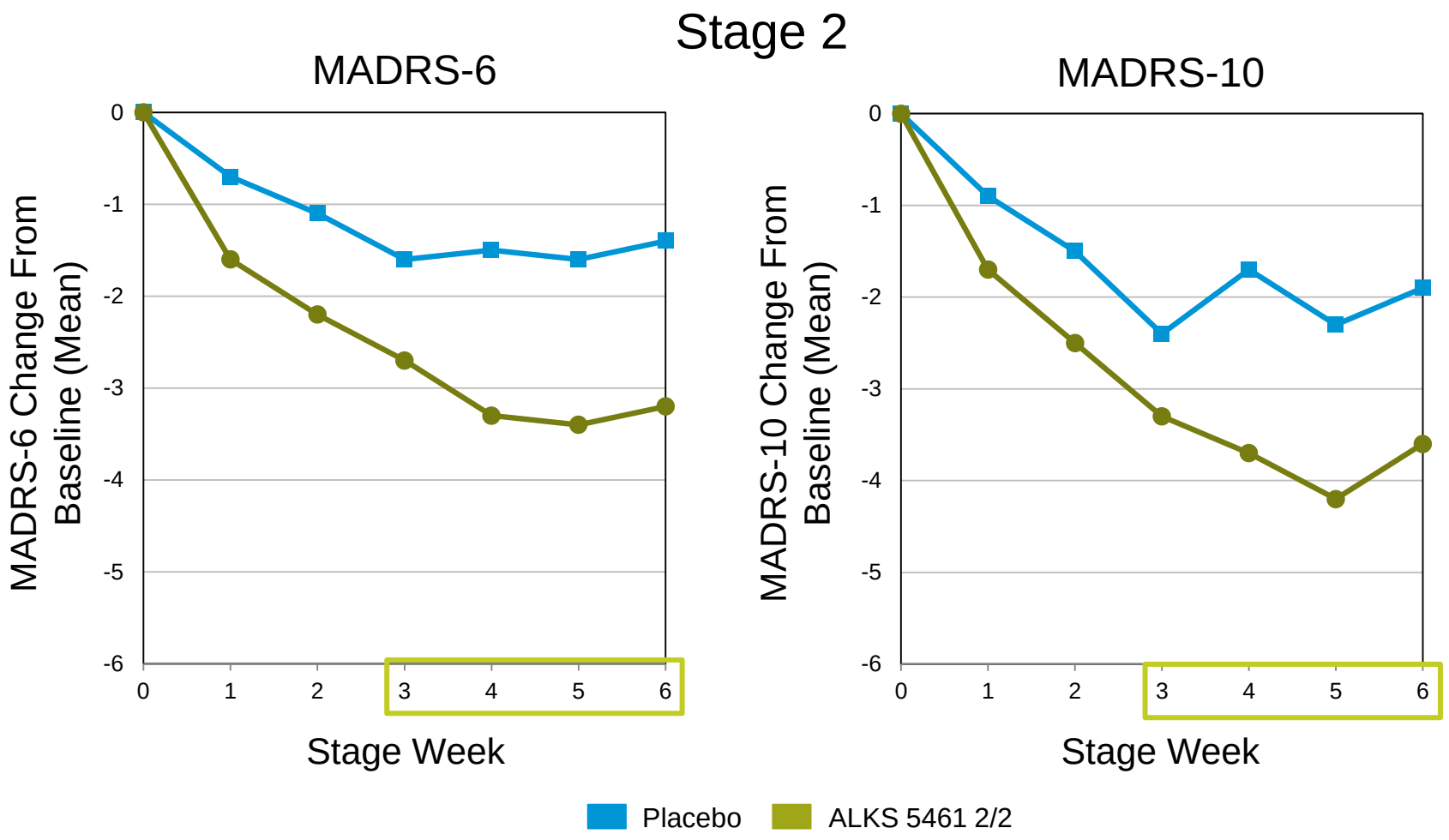


MADRS-10



Green boxes represent weeks averaged in Stage 1 as part of primary efficacy analysis

FORWARD-5 Stage 2: 2/2 Dose MADRS-6 and MADRS-10



Green boxes represent weeks averaged in Stage 2 as part of primary efficacy analysis
Subjects meeting placebo non-responder criteria at end of Stage 1 were re-randomized in Stage 2

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FORWARD-5: Robust Efficacy in U.S.

82.5% of Overall Study Population

	ALKS 5461 2/2 Overall study	ALKS 5461 2/2 U.S. only
MADRS-6 Average Change from Week 3 to EOT		
p-value	0.018	0.006
MADRS-10 Average Change from Week 3 to EOT		
p-value	0.026	0.005
MADRS-10 Change at EOT		
p-value	0.076	0.028

EOT = End of Treatment

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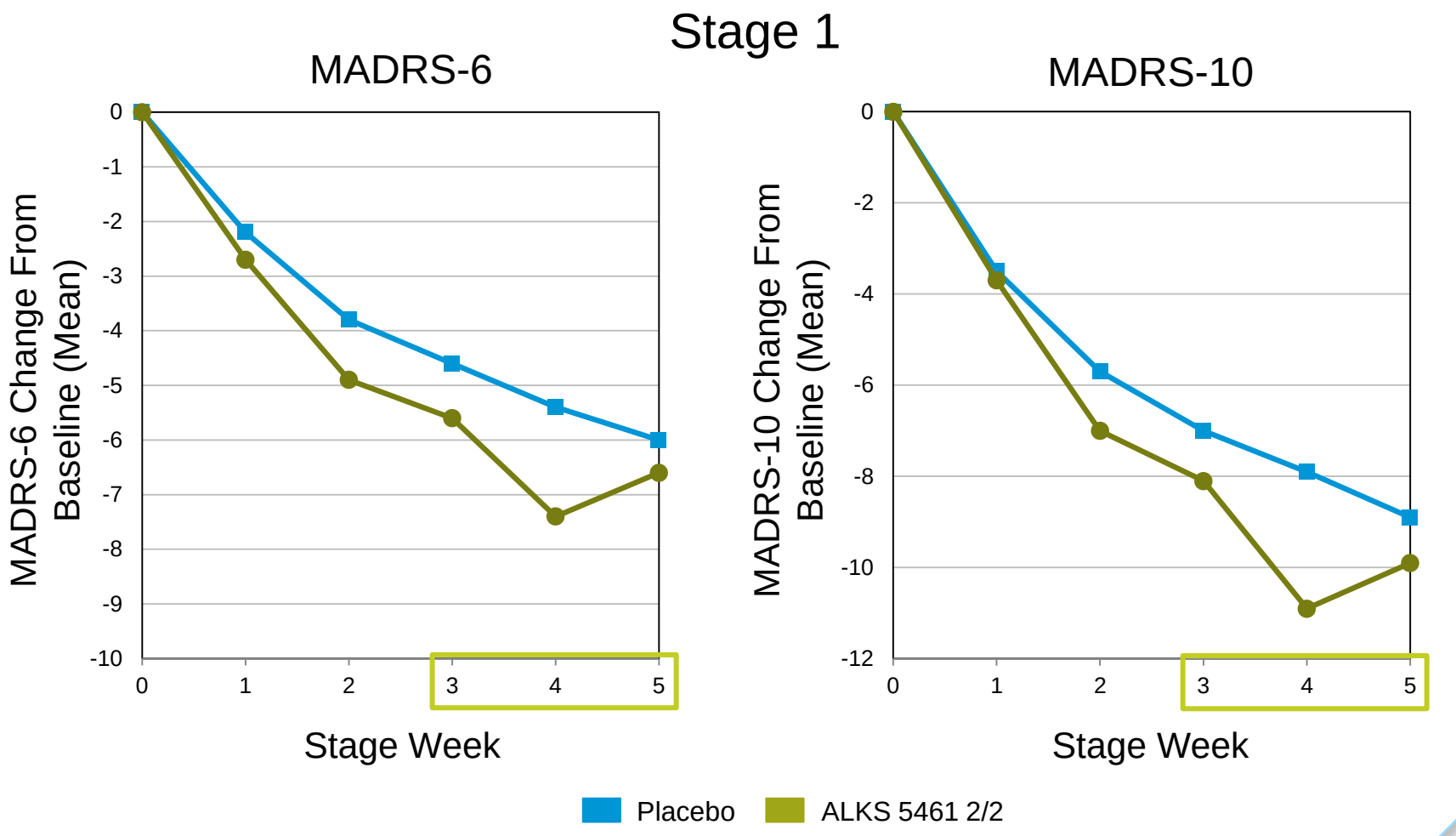
FORWARD-5: Robust Efficacy in U.S. Subjects



Green boxes represent weeks averaged in Stage 1 as part of primary efficacy analysis

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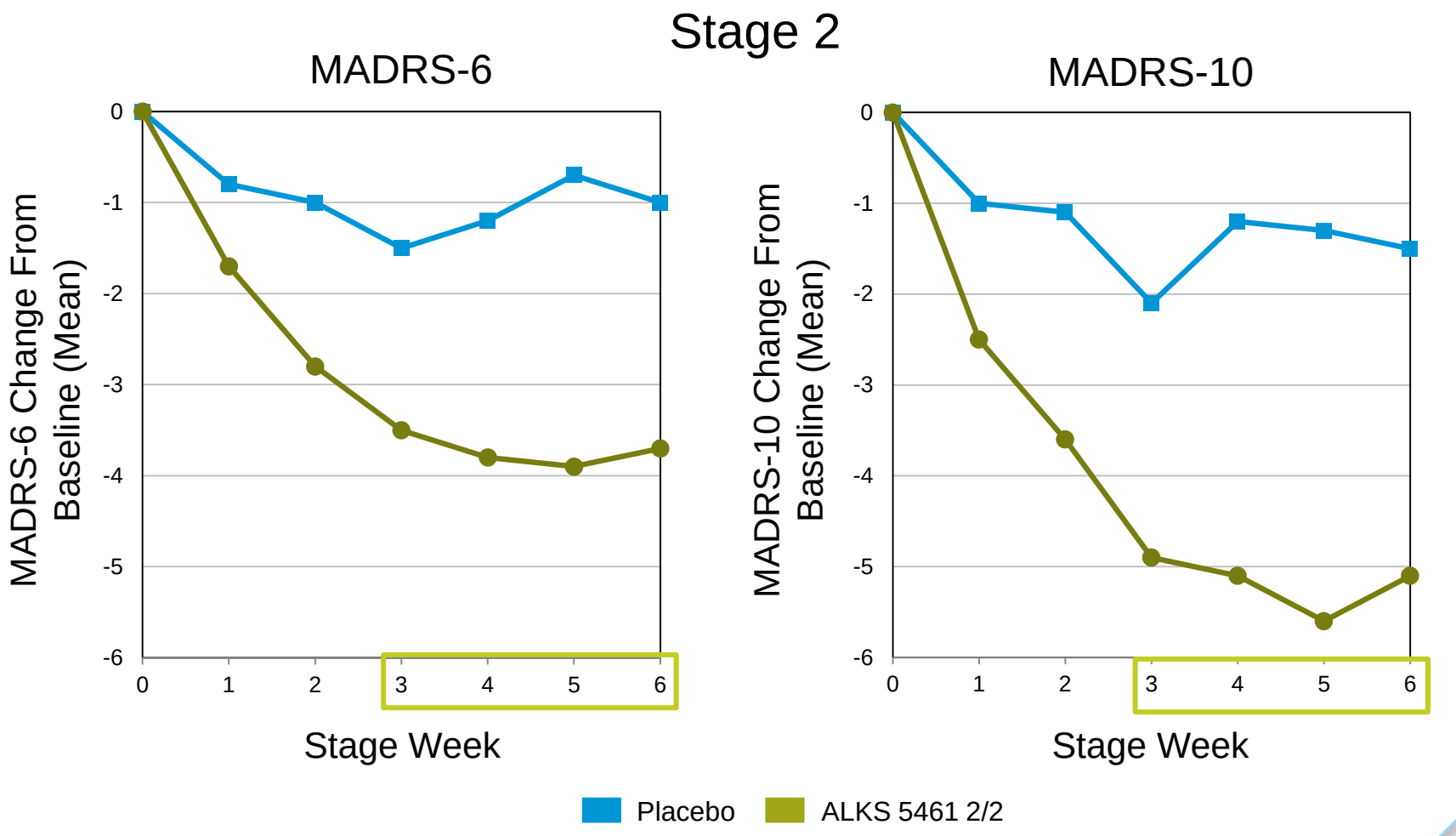
FORWARD-5: Robust Efficacy in U.S. Subjects



Green boxes represent weeks averaged in Stage 2 as part of primary efficacy analysis
Subjects meeting placebo non-responder criteria at end of Stage 1 were re-randomized in Stage 2

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FORWARD-5: Most Common Adverse Events

	Preferred Term n(%)	PBO (N=280)	1/1 (N=63)	2/2 (N=63)
Stage 1	Nausea	20 (7.1)	9 (14.3)	17 (27.0)
	Dizziness	12 (4.3)	6 (9.5)	7 (11.1)
	Fatigue	1 (0.4)	5 (7.9)	7 (11.1)
	Vomiting	7 (2.5)	3 (4.8)	6 (9.5)
	Constipation	9 (3.2)	9 (14.3)	5 (7.9)
	Headache	22 (7.9)	4 (6.3)	5 (7.9)
	Preferred Term n(%)	**PBO (N=62)**	**1/1 (N=62)**	**2/2 (N=63)**
Stage 2	Nausea	1 (1.6)	2 (3.2)	5 (7.9)
	Constipation	0	2 (3.2)	4 (6.3)

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FORWARD-5 Safety and Tolerability

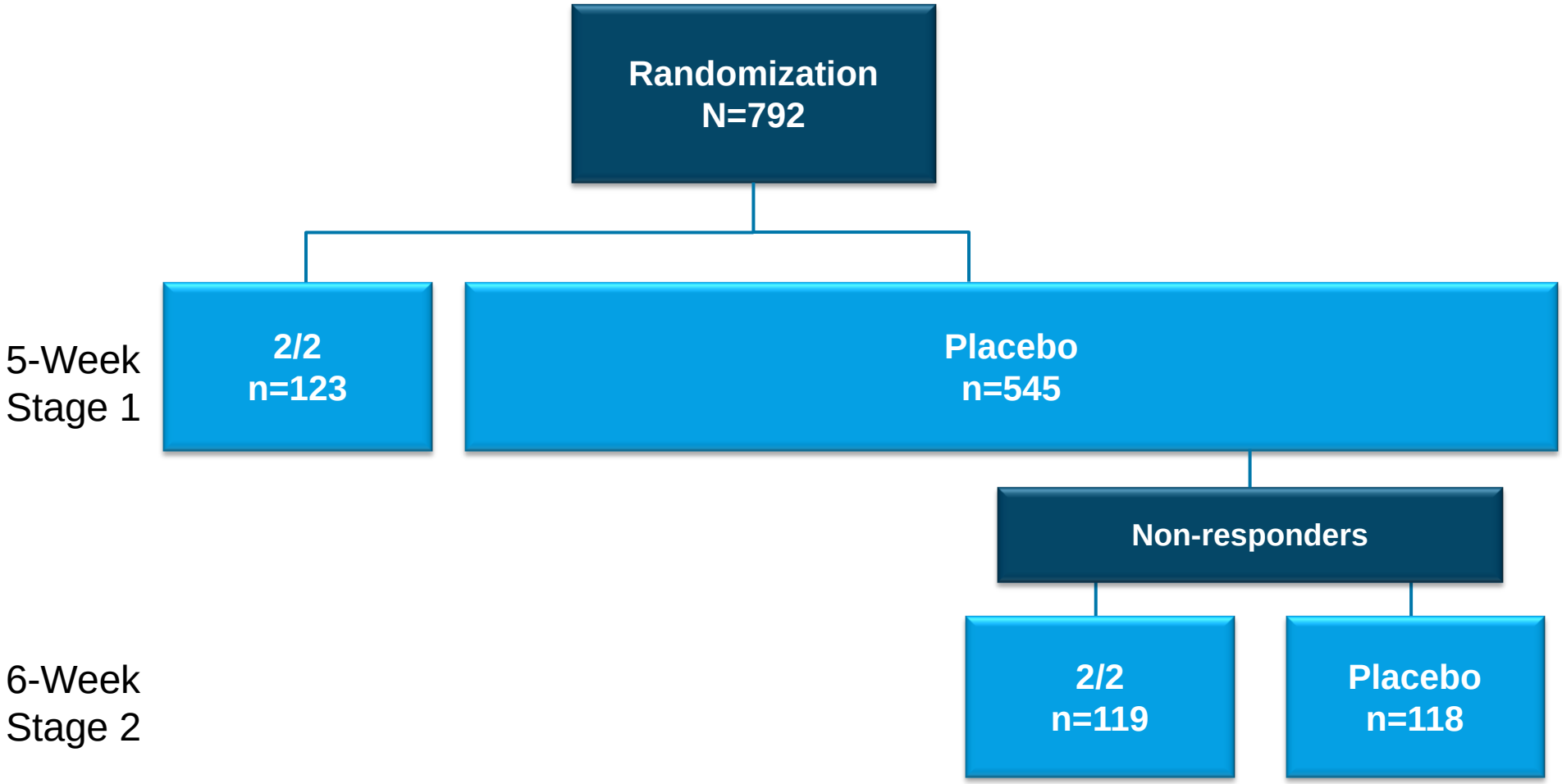
- Most common adverse events included nausea, dizziness and fatigue
  - Generally mild, transient and occurring around treatment initiation
  - Lower incidence of AEs with blinded initiation of treatment
- No evidence of withdrawal following end of treatment
- No pattern of AEs suggestive of abuse potential

FORWARD-5 Summary

- ALKS 5461 2/2 dose demonstrated statistically significant reductions in depressive symptoms, as measured by MADRS-6 and MADRS-10
- Clinical benefit maintained throughout 11-week study
- Efficacy results pronounced in U.S. patient population
- Safety and tolerability profile consistent with that reported previously for ALKS 5461
- Consistent evidence of lack of abuse potential

FORWARD-4 and FORWARD-5 Pooled Analysis

Pooled FORWARD-4 and FORWARD-5: Subject Flow



36 subjects in the Stage 1 placebo group did not complete Stage 1 and two did not enter Stage 2. 118 placebo non-responders were randomized to ALKS 5461 doses other than ALKS 5461 2/2 in Stage 2 and are not shown. All efficacy analyses include subjects that received ≥ 1 dose of study drug and had ≥ 1 post-baseline Montgomery-Åsberg Depression Rating Scale (MADRS) assessment. Two subjects in Stage 1 did not receive study drug.

Prespecified Pooled Efficacy Analysis: ALKS 5461 2/2 vs. Placebo

	FORWARD-4*	FORWARD-5	Pooled FORWARD-4 and -5
MADRS-6			
Average Change from Week 3 to EOT			
p-value	0.005	0.018	<0.001
MADRS-10			
Average Change from Week 3 to EOT			
p-value	0.018	0.026	0.004
MADRS-10			
Change at EOT			
p-value	0.023	0.076	0.010

EOT = End of Treatment; *Re-analyzed using the same hierarchical statistical analysis plan as FORWARD-5

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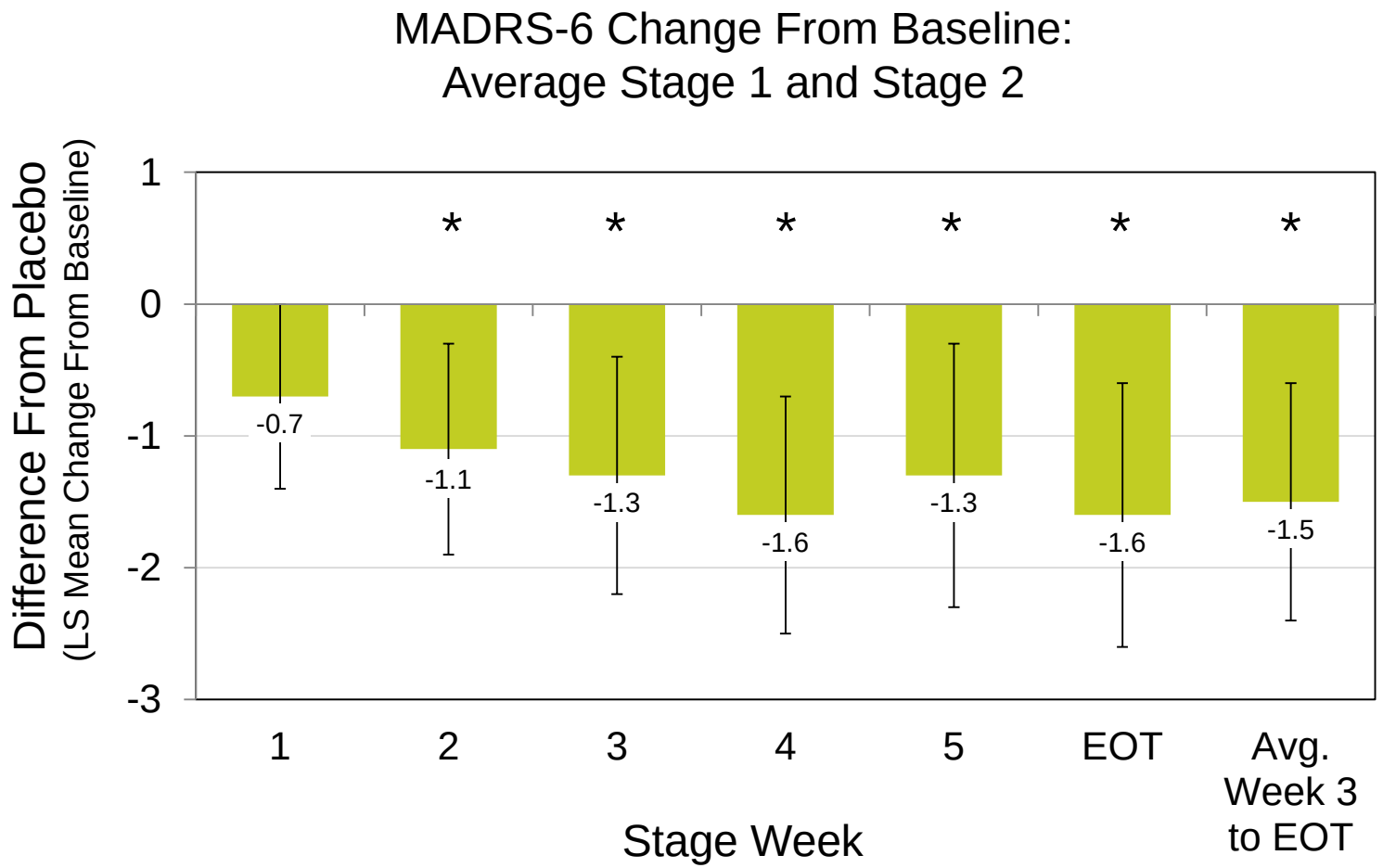
FORWARD-4 and FORWARD-5 Pooled Analysis: ALKS 5461 2/2 Dose vs. Placebo by Stage Week



95% confidence interval

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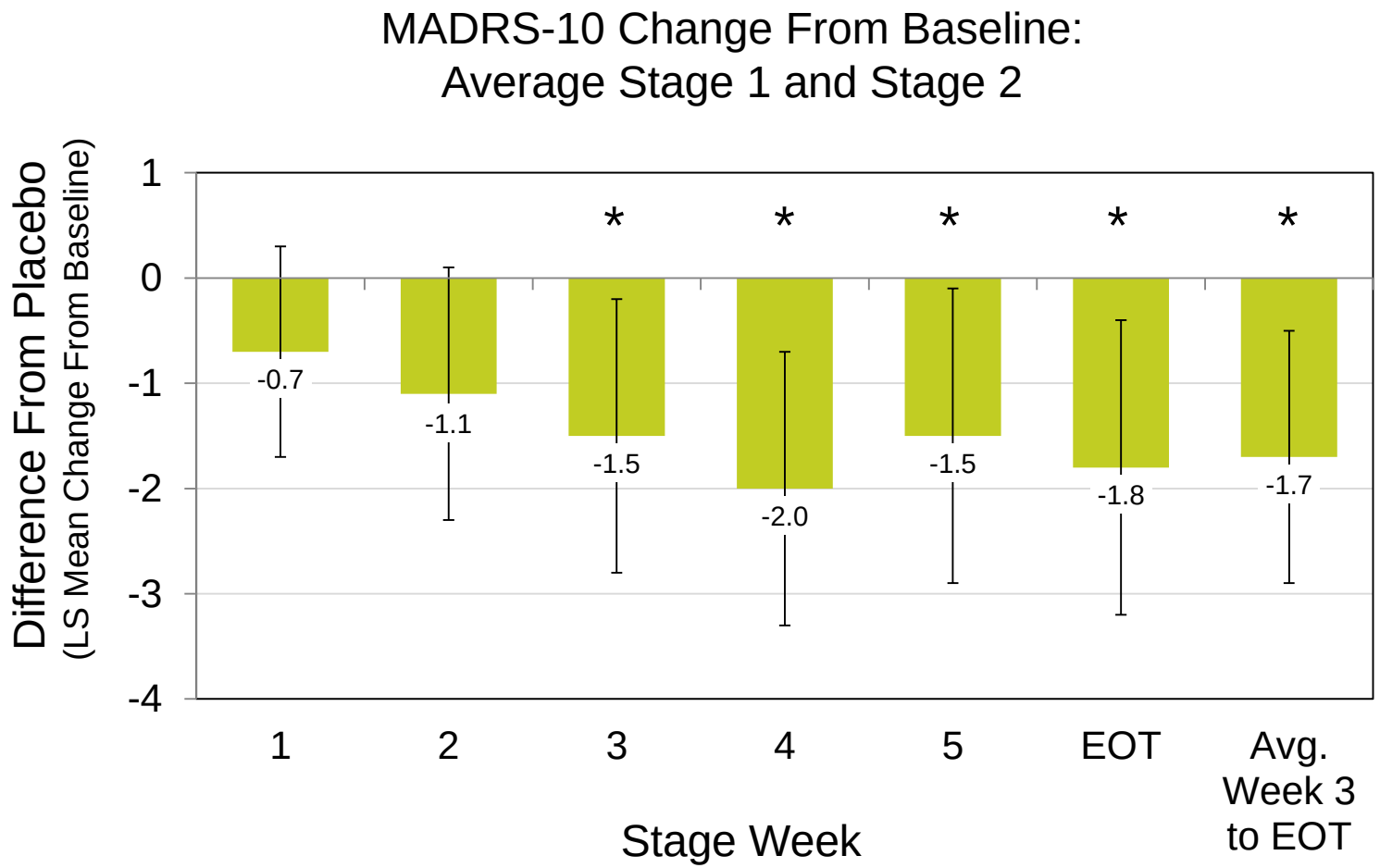
FORWARD-4 and FORWARD-5 Pooled Analysis: ALKS 5461 2/2 Dose vs. Placebo by Stage Week



95% confidence interval

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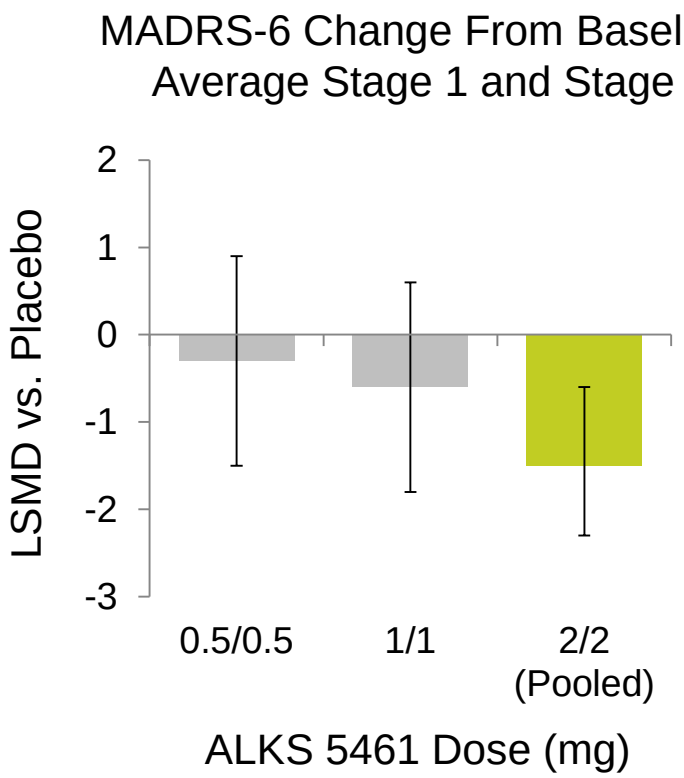
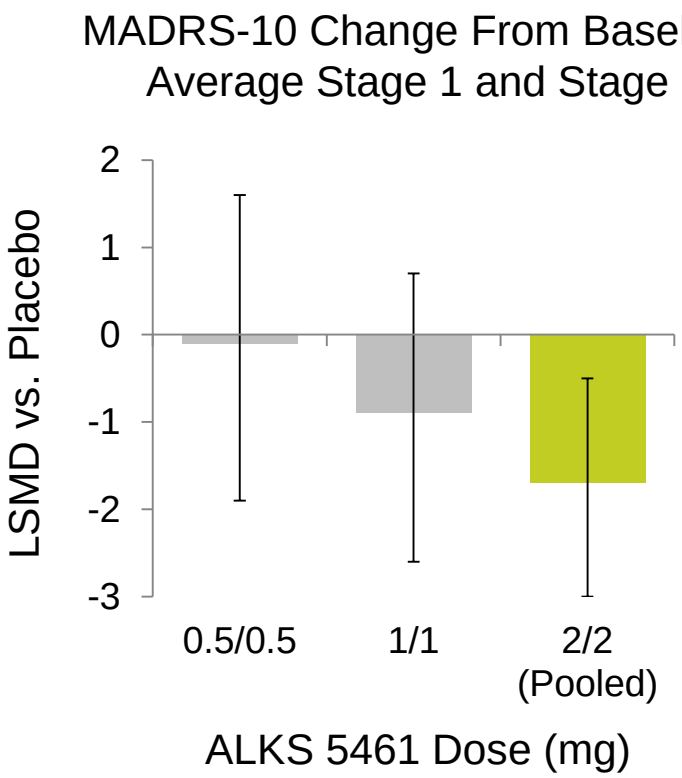
ALKS 5461: Dose-Response Relationship





ALKS 5461 0.5/0.5 dose from FORWARD-4; ALKS 5461 1/1 dose from FORWARD-5; ALKS 5461 2/2 dose from pooled FORWARD-4 and -5.

Error bars represent 95% confidence intervals.

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Summary of ALKS 5461 Development Program: Consistent Efficacy and Safety Profile

Strong Foundation of Placebo-Controlled Studies Supporting Efficacy of ALKS 5461

	Study Name/Phase	Design/Size	Summary Results
1	**-201** Phase 2a	Parallel n=32	Preliminary efficacy for 2mg/2mg dose
2	**-202** Phase 2b	SPCD n=142	Met primary endpoint for 2mg/2mg dose
3	**FORWARD-5** Phase 3	SPCD n=407	Met primary endpoint for 2mg/2mg dose
4	**FORWARD-4** Phase 3	SPCD n=385	Missed primary endpoint at single time point. Post-hoc analyses show statistical efficacy for 2mg/2mg dose.
5	**FORWARD-3** Phase 3	Placebo run-in n=329	Negative study due to high placebo response

Pooled Analysis

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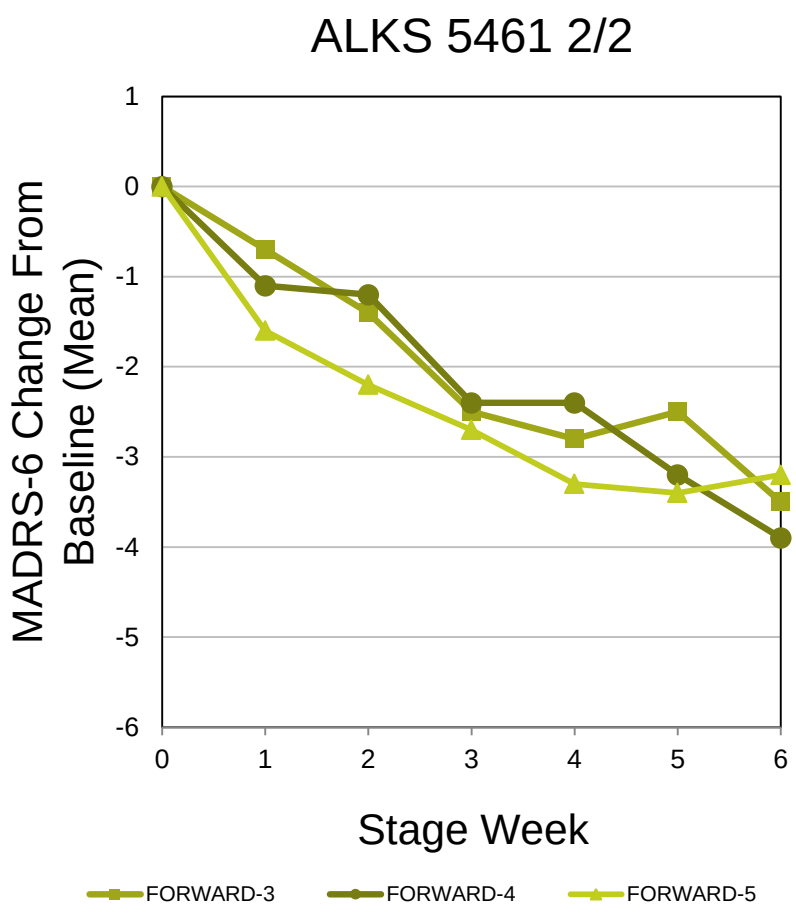
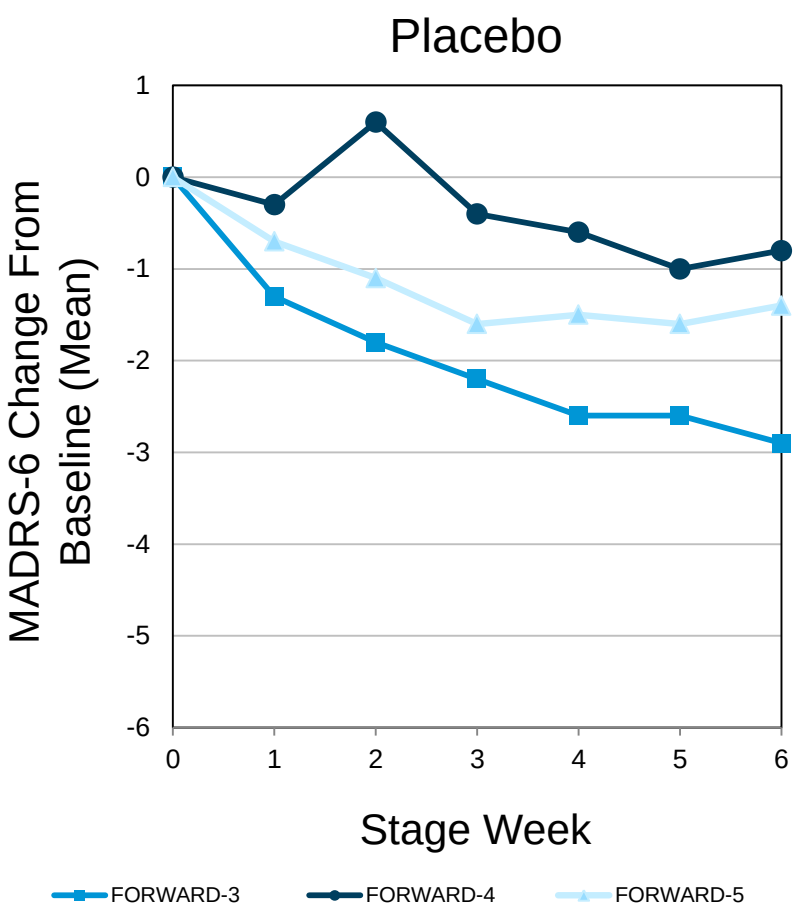
FORWARD Efficacy Studies: 2/2 vs. Placebo MADRS-6

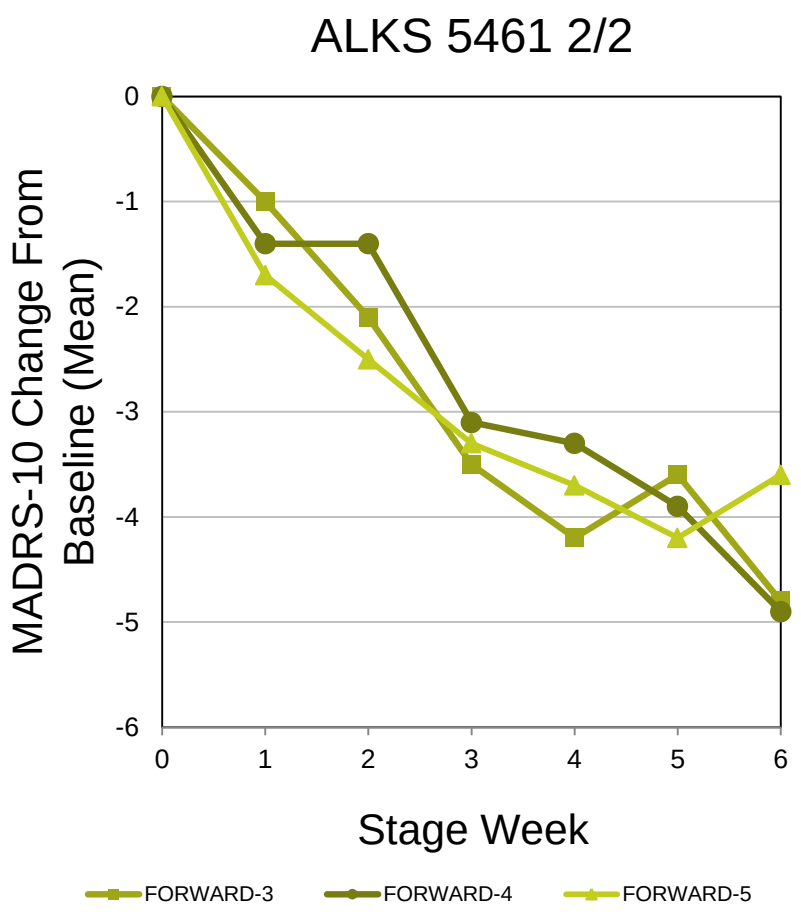
Stage 2 FORWARD-4 and FORWARD-5 vs. FORWARD-3 Efficacy Phase

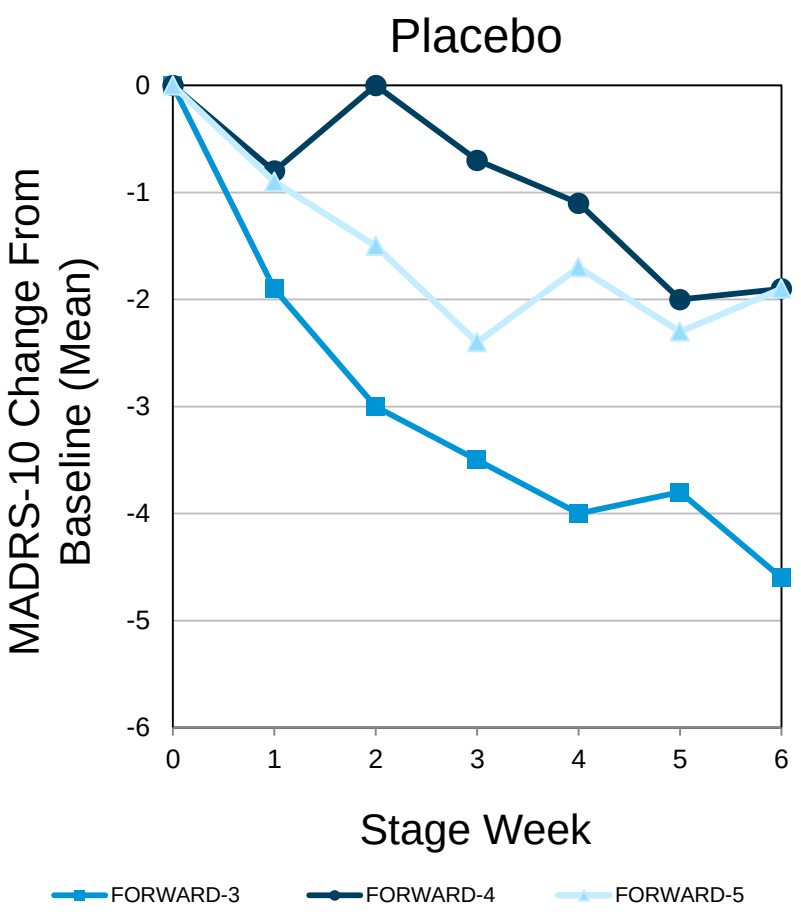




FORWARD Efficacy Studies: 2/2 vs. Placebo MADRS-10

Stage 2 FORWARD-4 and FORWARD-5 vs. FORWARD-3 Efficacy Phase





Future Areas of Development and Next Steps

ALKS 5461: Expanding Development Program for First-in-Class Candidate

FORWARD Pivotal Program Objectives for First Approval

- ✓ Establish antidepressive activity in adjunctive setting
- ✓ Demonstrate safety and satisfy exposure requirements

Future Areas of Focus/ Label Expansion

- ❑ Identify patient populations with greatest potential response to ALKS 5461
- ❑ Assess domains regulated by opioid modulation (e.g., social connection, resilience)
- ❑ Investigate additional indications (PTSD, bipolar depression, psychic pain, atypical depression)
- ❑ Evaluate monotherapy

Conclusions

- ALKS 5461 demonstrated consistent safety, tolerability and efficacy in adjunctive treatment of MDD
  - Pre-NDA meeting with FDA scheduled for July 2017
  - NDA submission planned for 2H 2017
- New mechanism of action targeting endogenous opioid system may provide distinct clinical benefit for patients
  - Additional studies planned to further elaborate full potential of this medicine

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