Evaluation of the Efficacy and Safety of ALKS 5461 as Adjunctive Therapy in MDD: Results of FORWARD-3 and FORWARD-4 Studies

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INTRODUCTION

- Major depressive disorder (MDD) is associated with dysregulation of the endogenous opioid system[1].
- ALKS 5461 Sublingual tablet
  - Buprenorphine (BUP) a mu-opioid partial agonist (also blocks kappa-opioid activation), co-formulated with samidorphan (SAM), a potent mu-opioid antagonist
  - Combination binds with high affinity to opioid receptors with low net intrinsic signaling activity
- ALKS 5461 intended to support opioid tone in brain regions with impaired endogenous activity and dampen opioid tone in upregulated regions. SAM addresses abuse potential.
- Significant efficacy has been observed in two prior phase 2 studies[2,3].
- There is a high placebo response and high failure rate in clinical trials even with approved antidepressants[4].
- Objectives of FORWARD phase 3 program:
  - Evaluate efficacy and safety of ALKS 5461 as adjunctive treatment of MDD in subjects with inadequate response to standard antidepressants
  - Evaluate alternative study designs to address placebo response

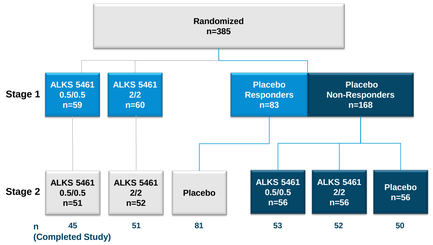
METHODS

- Study Population
  - Adults with confirmed diagnosis of MDD by DSM-IV-TR as assessed and confirmed by MINI
  - Inadequate response to standard antidepressant treatment (SSRI/SNRI/bupropriion) defined as HAMD-17 score ≥ 18
  - Background antidepressant treatment maintained throughout the study
- FORWARD-4 Study Design
  - Double-blind SPCD* comparing ALKS 5461 2 mg/2 mg and 0.5 mg/0.5 mg vs. placebo (Figure 1)
  - Subjects randomized to placebo or active treatment in Stage 1 (5 weeks)
  - Placebo non-responders from Stage 1 re-randomized to placebo or active treatment during Stage 2 (6 weeks)
- FORWARD-3 Study Design
  - Double-blind, active controlled 4-week placebo run-in phase followed by 6-week double-blind efficacy phase (Figure 4)
    - Group 1: Subjects with HAMD-17 score ≥ 20 at study initiation. Group 1 received placebo during run-in phase. Placebo non-responders during run-in randomized to ALKS 5461 2/2 vs. placebo for efficacy phase
    - Group 2: Subjects with HAMD-17 score of 18-19 at study initiation. Group 2 received either ALKS 5461 2/2 or placebo during run-in phase. Group 2 not included in efficacy analysis
- FORWARD-4 Primary Analysis
  - MADRS LS mean change from baseline difference from placebo; average of Stage 1 week 5 and Stage 2 week 5
- FORWARD-3 Primary Analysis
  - MADRS LS mean change from baseline difference from placebo
- Both Studies
  - MMRM for missing data
  - Variables for treatment group, visit, and a treatment group–by-visit interaction term as categorical fixed effects

*SPCD: Sequential Parallel Comparison Design

FORWARD-4 SPCD

FIGURE 1:



*Completion 86.2% (Stage 1: 91.9%; Stage 2: 93.8%)

BASELINE CHARACTERISTICS

Table 1: FORWARD-4 Demographic/Baseline Characteristics

	Stage 1			Stage 2		
	PBO (N=265)	0.5/0.5 (N=59)	2/2 (N=60)	PBO (N=56)	0.5/0.5 (N=56)	2/2 (N=56)
Age, Mean (SD)	45.8 (11.5)	45.0 (13.9)	46.2 (12.1)	45.8 (10.4)	45.5 (12.0)	49.1 (10.2)
Female, n (%)	182 (69)	38 (64)	40 (67)	40 (71)	33 (59)	42 (75)
Race, n (%)						
• White	182 (69)	42 (71)	42 (70)	35 (63)	35 (63)	41 (73)
• Black	77 (29)	16 (27)	16 (27)	20 (36)	19 (34)	15 (27)
• Other	6 (2)	1 (2)	2 (3)	1 (2)	2 (4)	0
MADRS Total Score Mean (SD)	31.9 (5.0)	32.7 (4.7)	32.0 (5.7)	27.5 (7.5)	26.6 (7.1)	26.2 (7.5)

MADRS baseline score for Stage 2 population reflects score at Stage 2 randomization

Table 2: FORWARD-3 Demographic/Baseline Characteristics

	Group 1		Group 2	
	PBO (N=148)	2/2 (N=147)	PBO (N=15)	2/2 (N=15)
Age, Mean (SD)	48.1 (12.51)	47.4 (12.31)	45.9 (11.44)	47.5 (12.63)
Female, n (%)	94 (63.5)	88 (59.9)	7 (46.7)	8 (53.3)
Race, n (%)				
• White	115 (77.7)	106 (72.1)	13 (86.7)	12 (80.0)
• Black	33 (22.3)	33 (22.4)	2 (13.3)	3 (20.0)
• Other	0	8 (5.4)	0	0
MADRS Total Score Mean (SD)	27.4 (6.56)	27.7 (6.33)	27.7 (3.97)	28.2 (4.5)

MADRS baseline score for Group 1 population reflects score at end of placebo run-in

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3. Fava M, Memisoglu A, Thase ME, Bodkin JA, de Somer M, Du Y, Leigh-Pemberton R, DiPetrillo L, Silverman B, Ehrich E. Opioid Modulation with ALKS 5461 as Adjunctive Treatment for Inadequate Responders to Antidepressants: A Randomized, Double-blind, Placebo-controlled Trial. Am.J.Psych. In Press. 2016.
4. Khin NA, Chen YF, Yang Y, Yang P, Laughren TP. Exploratory analyses of efficacy data from major depressive disorder trials submitted to the US Food and Drug Administration in support of new drug applications. J Clin Psychiatry. Apr;72(4):464-72. 2011.

DISCLOSURES

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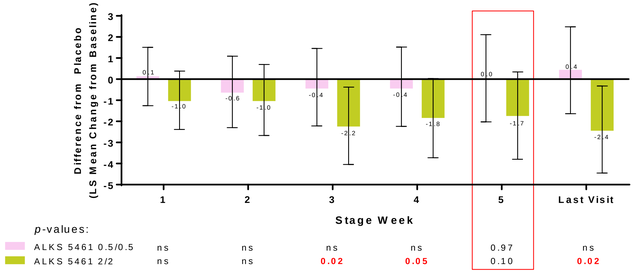
E.Ehrich, W.Martin, A.Memisoglu, S.Pathak, A.D. Stanford, I.Webster, L. DiPetrillo and Y.Jiang are full-time employees of Alkermes, Inc.
Drs.Thase and Fava are paid consultants to Alkermes.
Dr. Fava is an inventor on the patent for the SPCD, which is licensed by MGH to Pharmaceutical Product Development, LLC.

FORWARD-4 RESULTS

FIGURE 2: FORWARD-4: Primary Analysis MADRS* ALKS 5461 vs. Placebo by Stage Week

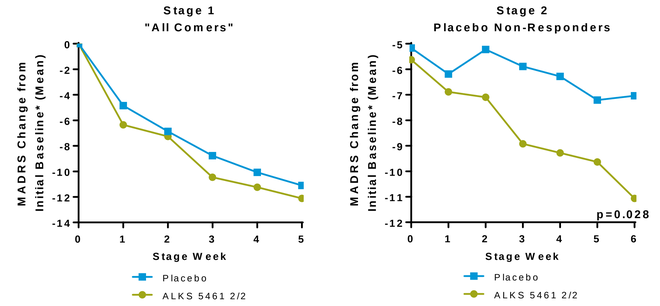


p-values:

ALKS 5461 0.5/0.5	ns	ns	ns	ns	0.97	ns
ALKS 5461 2/2	ns	ns	0.02	0.05	0.10	0.02

* Average Stage 1 and Stage 2 change from baseline-difference from placebo (± 95% CI)

FIGURE 3: FORWARD-4 MADRS Change from Baseline*



* Baseline is defined as MADRS score at Stage 1 randomization

Table 3: FORWARD-4 Summary of AEs

Stage 1

Event/Preferred Term, n(%)	PBO (N=265)	0.5/0.5 (N=59)	2/2 (N=60)
Any AE	142 (53.6)	34 (57.6)	41 (68.3)
SAE	1 (0.4)	0	0
Nausea	17 (6.4)	14 (23.7)	17 (28.3)
Constipation	4 (1.5)	4 (6.8)	10 (16.7)
Dizziness	9 (3.4)	4 (6.8)	8 (13.3)
Somnolence	7 (2.6)	5 (8.5)	6 (10.0)
Vomiting	4 (1.5)	4 (6.8)	6 (10.0)
Headache	22 (8.3)	7 (11.9)	5 (8.3)

Stage 2

Event/Preferred Term, n (%)	PBO (N=56)	0.5/0.5 (N=56)	2/2 (N=56)
Any AE	29 (51.8)	27 (48.2)	29 (51.8)
SAE	0	0	0
Nausea	1 (1.8)	5 (8.9)	8 (14.3)

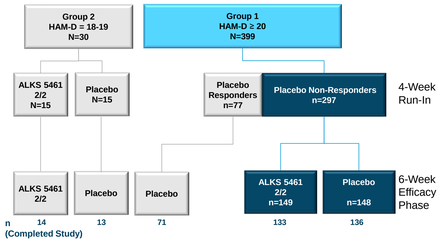
- There were no SAEs with ALKS 5461.
- There was no evidence of withdrawal.
- No pattern of AEs indicative of abuse potential.

ACKNOWLEDGEMENTS

The authors would like to thank the ALKS FORWARD-3 and FORWARD-4 Study Group, investigators, study coordinators and raters.

FORWARD-3 Double-Blind Run-in

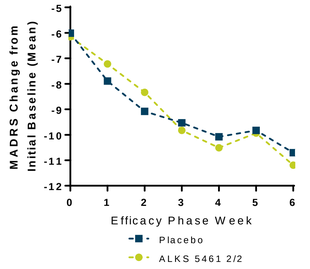
FIGURE 4:



*Completion Rate ~90% (Group 1: 90.6%; Group 2: 90%)

FORWARD-3 RESULTS

FIGURE 5: FORWARD-3 MADRS Change from Baseline*



* Baseline defined as MADRS score at start of placebo run-in

Table 4: FORWARD-3 Summary of AEs

Event/Preferred Term, n(%)	Group 1		Group 2	
	PBO (N=148)	2/2 (N=147)	PBO (N=15)	2/2 (N=15)
Any AE	51 (34.5)	63 (42.9)	8 (53.3)	11 (73.3)
SAE	1 (0.4)	0	0	0
Nausea	1 (0.7)	13 (8.8)	2 (13.3)	4 (26.7)
Headache	5 (3.4)	6 (4.1)	1 (6.7)	4 (26.7)
Constipation	1 (0.7)	3 (2.0)	0	3 (20.0)
Dry mouth	2 (1.4)	3 (2.0)	1 (6.7)	2 (13.3)

- There were no SAEs with ALKS 5461.
- There was no evidence of withdrawal.
- No pattern of AEs indicative of abuse potential.

CONCLUSIONS

- FORWARD-4 showed efficacy of ALKS 5461 2/2 in adjunctive treatment of MDD.
  - Reinforces positive results from previously reported phase 2 studies.
- Study design matters:
  - FORWARD-4 was superior to FORWARD-3 in identifying/filtering placebo responders.
  - Both studies demonstrated similar reductions in MADRS for ALKS 5461 2/2; the difference between studies was placebo response rate.
- ALKS 5461 2/2 was safe and generally well tolerated without evidence of abuse potential.
- Learnings from FORWARD-3 and FORWARD-4 studies will be applied to ongoing FORWARD-5.

FORWARD-3 VS. FORWARD-4

FIGURE 6: FORWARD-4 Stage 2 vs. FORWARD-3 Efficacy Phase

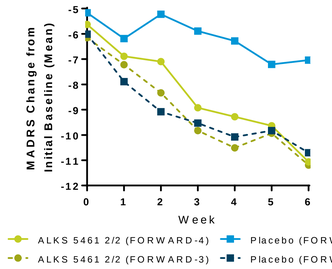
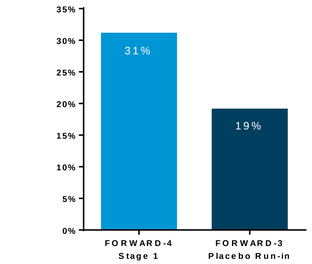


FIGURE 7: FORWARD-4 vs. FORWARD-3: Placebo Responders Identified and Filtered



- FORWARD-4 was more effective than FORWARD-3 at identifying and filtering placebo responders.