ALKS 5461: FORWARD-3 and FORWARD-4

American Society of Clinical Psychopharmacology Annual Meeting

JUNE 1, 2016
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ALKS 5461 in Major Depressive Disorder: Results From FORWARD Pivotal Program Being Presented at ASCP

Elliot Ehrich, M.D., Chief Medical Officer
ALKS 5461 in Major Depressive Disorder (MDD)

1. Centrally-acting opioid modulator with novel mechanism of action, addressing dysregulation of endogenous endorphin and dynorphin neuropeptides

2. Comprised of buprenorphine (partial opioid agonist) co-formulated with NME samidorphan (opioid antagonist) designed to normalize neurotransmission without addictive properties of classic opioids

3. Evidence from positive phase 2 clinical studies supporting anti-depressive effects and Fast Track status

4. 50% of placebo-controlled studies of FDA-approved MDD medicines failed\(^1\); Sequential Parallel Comparison Design (SPCD) studies are designed to address placebo response

\(^1\) Iovieno N. and Papakostas G. *J Clin Psych.* 2012; 73(10):1300-6
FORWARD Efficacy Studies Focus on Important Patient Population

- Confirmed diagnosis of Major Depressive Disorder
- Inadequate response to standard antidepressant treatment
  - Hamilton Depression Rating Scale (HAM-D) score ≥ 18, despite adequate trial of SSRI or SNRI
- Adjunctive therapy
  - Subjects remain on background antidepressant therapy
  - Randomized to receive ALKS 5461 or matching placebo
FORWARD-4: SPCD Stage 1 Subject Flow

Randomized
n=385

ALKS 5461
0.5/0.5
n=59

ALKS 5461
2/2
n=60

Placebo
n=265

5-Week Stage 1

Following randomization, one subject did not receive study drug and is excluded from the safety and efficacy analysis.
FORWARD-4: SPCD Stage 2 Subject Flow

Randomized
n=385

5-Week Stage 1

ALKS 5461 0.5/0.5 n=59
ALKS 5461 2/2 n=60
Placebo Responders n=83
Placebo Non-Responders n=168

6-Week Stage 2

ALKS 5461 0.5/0.5 n=56
ALKS 5461 2/2 n=56
Placebo n=56

14 subjects in the Stage 1 placebo group did not complete Stage 1. All efficacy analyses include subjects that received ≥ 1 dose of study drug and had ≥ 1 post-baseline Montgomery-Åsberg Depression Rating Scale (MADRS) assessment.
ALKS 5461 FORWARD-4 Primary Analysis: 0.5/0.5 Dose vs. Placebo by Stage Week

**MADRS Change From Baseline:**
Average Stage 1 and Stage 2

<table>
<thead>
<tr>
<th>Stage Week</th>
<th>Difference From Placebo (LS Mean Change From Baseline)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.1</td>
<td>NS</td>
</tr>
<tr>
<td>2</td>
<td>-0.6</td>
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</tr>
<tr>
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</tr>
<tr>
<td>5</td>
<td>0.4</td>
<td>NS</td>
</tr>
</tbody>
</table>

95% confidence interval
ALKS 5461 FORWARD-4 Primary Analysis: 2/2 Dose vs. Placebo by Stage Week

MADRS Change From Baseline:
Average Stage 1 and Stage 2

Stage Week

1 2 3 4 5 Last Visit

Difference From Placebo (LS Mean Change From Baseline)

-5 -4 -3 -2 -1 0 1 2 3

-1.0 -1.0 -2.2 * -1.8 * -1.7 * -2.4

p-value 0.16 0.25 0.02 0.05 0.10 0.02

95% confidence interval

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ALKS 5461 FORWARD-4 Stage 1: 2/2 Dose, MADRS Change From Baseline by Stage Week

Stage 1 “All-Comers”

MADRS Change From Initial Baseline (Mean)

Stage Week

FORWARD-4 PBO
FORWARD-4 2/2

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Subjects meeting placebo non-responder criteria at end of Stage 1 were re-randomized in Stage 2.
FORWARD-4 Summary

- Sequential Parallel Comparison Design (SPCD) performed as expected

- Clear evidence of efficacy
  - Primary analysis was not statistically significant at pre-specified Week 5 time point
  - Significant at other time points and over full study period
FORWARD-3 Design: HAM-D ≥ 20, Placebo Lead-in

Group 2
HAM-D = 18-19

Group 1
HAM-D ≥ 20

4-Week Lead-In

ALKS 5461 2/2

Placebo

Placebo
FORWARD-3: Efficacy Analysis

4-Week Lead-In

6-Week Efficacy Phase

All efficacy analyses include placebo non-responders from the 4-week lead-in who received ≥ 1 dose of study drug and had ≥ 1 post-baseline MADRS assessment during the efficacy phase.
FORWARD-3: Subject Flow

Group 2
HAM-D 18-19
N=30

Group 1
HAM-D ≥ 20
N=399

ALKS 5461
2/2
n=15

Placebo
n=15

Placebo Responders
n=77

Placebo Non-Responders
n=297

25 subjects in the Group 1 did not complete 4-week placebo lead-in period
FORWARD-3: Efficacy Analysis

4-Week Lead-In

6-Week Efficacy Phase

25 subjects in Group 1 did not complete 4-week placebo lead-in period
FORWARD-3: Efficacy Phase
Change in MADRS from Baseline

Six-Week Efficacy Phase

Week

MADRS Change From Initial Baseline (Mean)

FORWARD-3 PBO

FORWARD-3 2/2
ALKS 5461 2/2 Dose: FORWARD-3 Efficacy Phase vs. FORWARD-4 Stage 2

MADRS Change From Initial Baseline (Mean)

Week

FORWARD-4 2/2

FORWARD-3 2/2
Placebo Treatment: FORWARD-3 Efficacy Phase vs. FORWARD-4 Stage 2
FORWARD-3 Was Less Effective Than FORWARD-4 in Removing Placebo Responders

Placebo Responders Identified and Filtered

- FORWARD-3 Placebo Lead-In: 19%
- FORWARD-4 Stage 1: 31%
FORWARD-3: Subject Flow

Group 1
HAM-D ≥ 20
N=399

Group 2
HAM-D 18-19
N=30

ALKS 5461
2/2
n=15

Placebo
n=15

Placebo
N=399
FORWARD-3 and FORWARD 4: Safety and Tolerability

- High study retention rates

- Adverse events were generally mild, transient and occurred around time of treatment initiation
  - FORWARD-3: Nausea, headache and fatigue
  - FORWARD-4: Nausea, headache and dizziness

- Safety and tolerability profile consistent with that reported in phase 2 and FORWARD-1 studies

- Data reinforced non-addictive profile with no evidence of withdrawal or pattern of adverse events indicative of abuse potential
Key Learnings

- FORWARD-4 showed efficacy of ALKS 5461 2/2
  - Reinforces positive results from a previously reported phase 2 study

- FORWARD-4 design was superior to FORWARD-3 in identifying and filtering placebo responders

- ALKS 5461 2/2 had consistent safety, tolerability and efficacy profile in FORWARD-3 and FORWARD-4

- Learnings from FORWARD-3 and FORWARD-4 studies will be applied to ongoing FORWARD-5
FORWARD-5 Study Ongoing

- Applying key learnings from FORWARD-3 and FORWARD-4 to remaining portion of FORWARD-5
- SPCD consistent with FORWARD-4 design
- Evaluating 2mg/2mg and additional 1mg/1mg doses
- Expected enrollment: 400 subjects
- Topline data expected in Q4 2016
Conclusions

Richard Pops, Chief Executive Officer
Q&A