BIPOLAR DEPRESSION: ACUTE STABLE RESPONSE TO MEDICATION AS A PREDICTOR OF LONG-TERM TREATMENT RESPONSE

D. V. Iosifescu, MD[1]; J. Tsai, PhD[2]; A. Pikalov, MD, PhD[2]; H. Kroger, MPH, MS[2]; A. Loebel, MD[2]

[1]Icahn School of Medicine at Mount Sinai, New York, NY; [2]Sunovion Pharmaceuticals Inc., Marlborough, MA and Fort Lee, NJ

INTRODUCTION

- Currently, olanazpine (alone, or in combination with fluoxetine), quetiapine, and lurasidone have demonstrated significant efficacy relative to placebo in the treatment of bipolar I depression on the basis of adequately powered, randomised, double-blind clinical trials[1-3]
- In patients with unipolar major depressive disorder, multiple studies have reported that early improvement at 2 weeks is significantly predictive of treatment response at 6-8 weeks.[4-7] The most common early improvement criterion is a 20-25% reduction in the Hamilton Depression Rating Scale (HAM-D) or the Montgomery-Asberg Depression Rating Scale (MADRS) scores[4-7]
- We have recently reported, for a bipolar depression population, that early improvement was a good predictor of acute (week 6) response, with positive predictive values in the range of 82-85%.[8] However, the absence of early improvement was not a reliable predictor of endpoint non-response. NPV was relatively low, ranging from 58-60% (ie, a relatively high proportion of patients went on to achieve clinical response despite lack of early improvement)
- We now examine the predictive value of achieving response criteria at 2 or more consecutive time points during acute treatment (acute stable response), on the ability to maintain response at month 3 or month 6 of extension treatment

OBJECTIVE

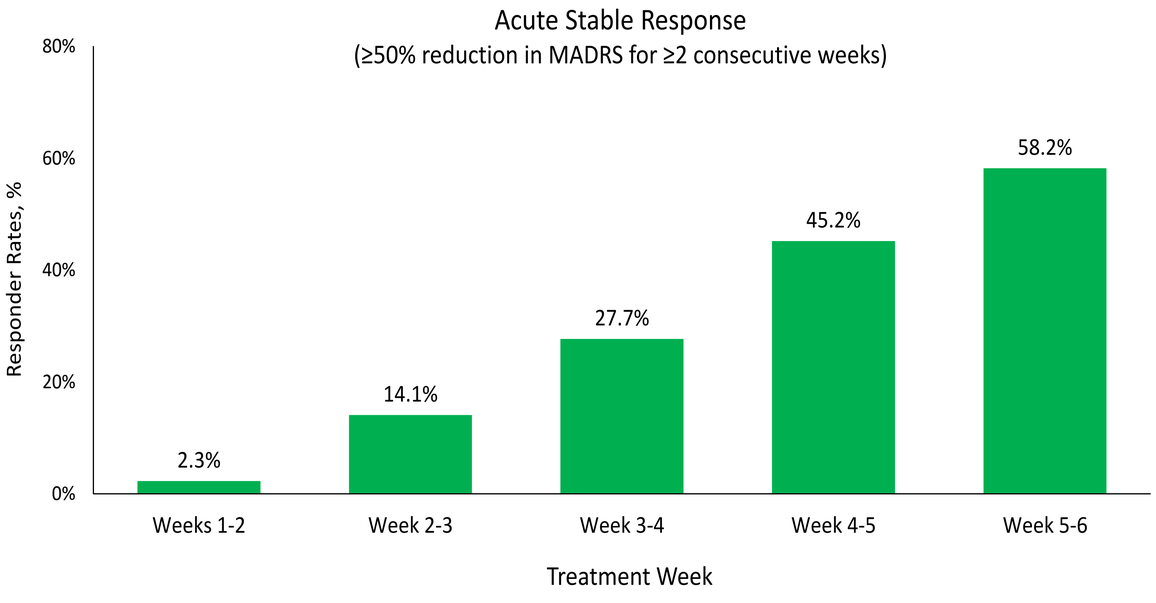
- The aim of the current post hoc analysis was to evaluate the predictive value of acute stable treatment response on long-term treatment response at 6 months, in patients receiving monotherapy medication for bipolar disorder

METHODS

- Patients with bipolar depression were randomised to 6 weeks of once-daily, double-blind treatment, in a monotherapy study, with fixed-flexible doses of lurasidone 18.5-55.5 mg/d, lurasidone 74-111 mg/d, or placebo
- Patients completing 6 weeks of acute double-blind treatment were continued for 6 months of open-label extension treatment with flexible doses of lurasidone, 18.5-111 mg/d
- Response was defined as ≥50% reduction from double-blind baseline on the Montgomery-Asberg Depression Rating Scale (MADRS) total score, and partial response was defined as ≥25% but <50% reduction on the MADRS
- Acute stable response was defined as ≥2 consecutive weeks of meeting response criteria during the initial 6 week double-blind treatment
  - Early acute stable response criterion: ≥50% reduction in MADRS total score at weeks 1 and 2
  - Overall acute stable response criterion: ≥50% reduction in MADRS total score for ≥2 consecutive weeks by week 6
- The predictive value of early acute stable response and overall acute stable response for long-term response at 3 and 6 months, was evaluated with sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV)
- Receiver operating characteristic (ROC) curves were used to evaluate the performance characteristics of early improvement criteria for the prediction of endpoint response, reported as the area under the ROC curve (AUC_{ROC})
- The proportion of responders for the completer sample at month 3 (N=177) and month 6 (N=154) was determined among patients who were non-responders, partial responders, and responders at each week during the 6 weeks of acute double-blind treatment
- We determined the proportion of responders at 6 months who had clinically meaningful improvement (≥1-point) during 6 weeks of acute treatment on the CGI-BP-S (Clinical Global Impression of Severity, Bipolar Depression scale)

RESULTS

Figure 1. Acute Stable Response During 6 Weeks of Double-blind Treatment



- During extension phase treatment, responder rates were 79.7% at Month 3 and 90.3% at Month 6

RESULTS

Table 1. Acute Stable Response and Prediction of Response at Month 3 and Month 6

	Response at Month 3		Response at Month 6	
	Early Acute Stable Response	Overall Acute Stable Response	Early Acute Stable Response	Overall Acute Stable Response
Sensitivity	2.13%	65.25%	2.16%	61.15%
Specificity	97.22%	69.44%	100.00%	80.00%
PPV	75.00%	89.32%	100.00%	96.59%
NPV	20.23%	33.78%	9.93%	18.18%
AUC_{ROC}	0.56	0.71	0.66	0.78

- Absence of early or overall acute stable response was not a reliable predictor of non-response at month 3 or month 6. NPV rates ranged from 10-34% (ie, false negative rate was high, and a relatively high proportion of patients went on to achieve clinical response at months 3-6 despite the absence of acute stable response.
- Consistent with this, 77% of patients with only a partial response at week 6 (25% to <50% reduction in MADRS total score) achieved a full response at month 3, and 79% at month 6

Figure 2. ROC Curves for Early Acute Stable Response: Prediction of Response at Month 3 and Month 6

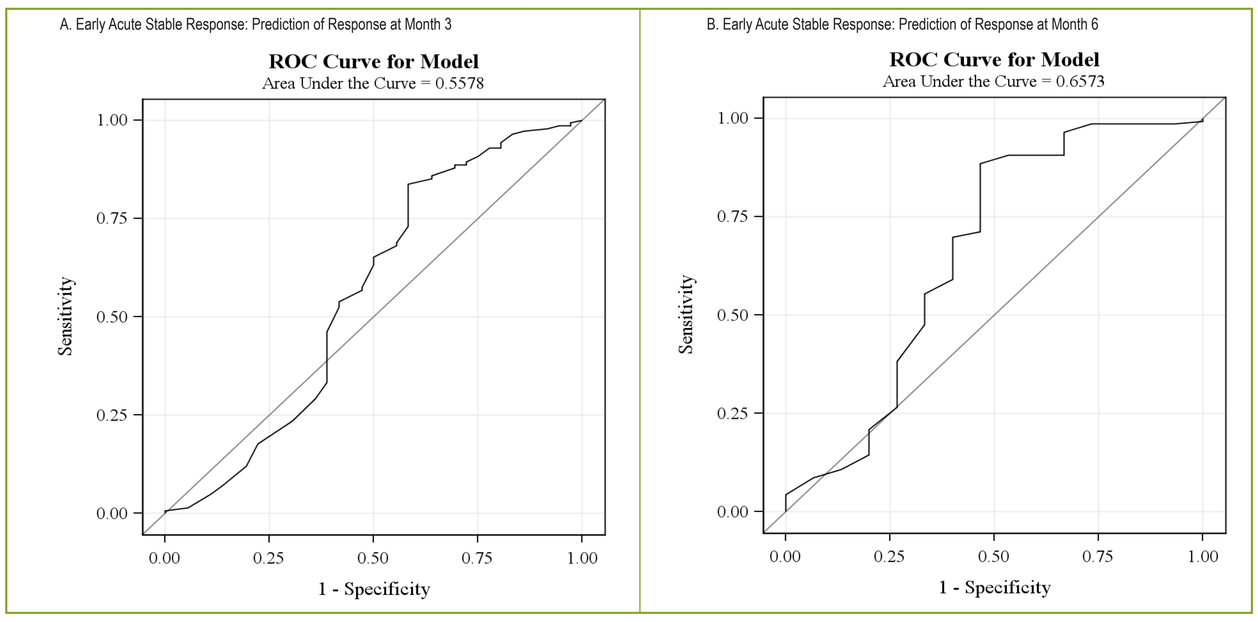


Figure 3. ROC Curves for Overall Acute Stable Response at Prediction of Response at Month 3 and Month 6

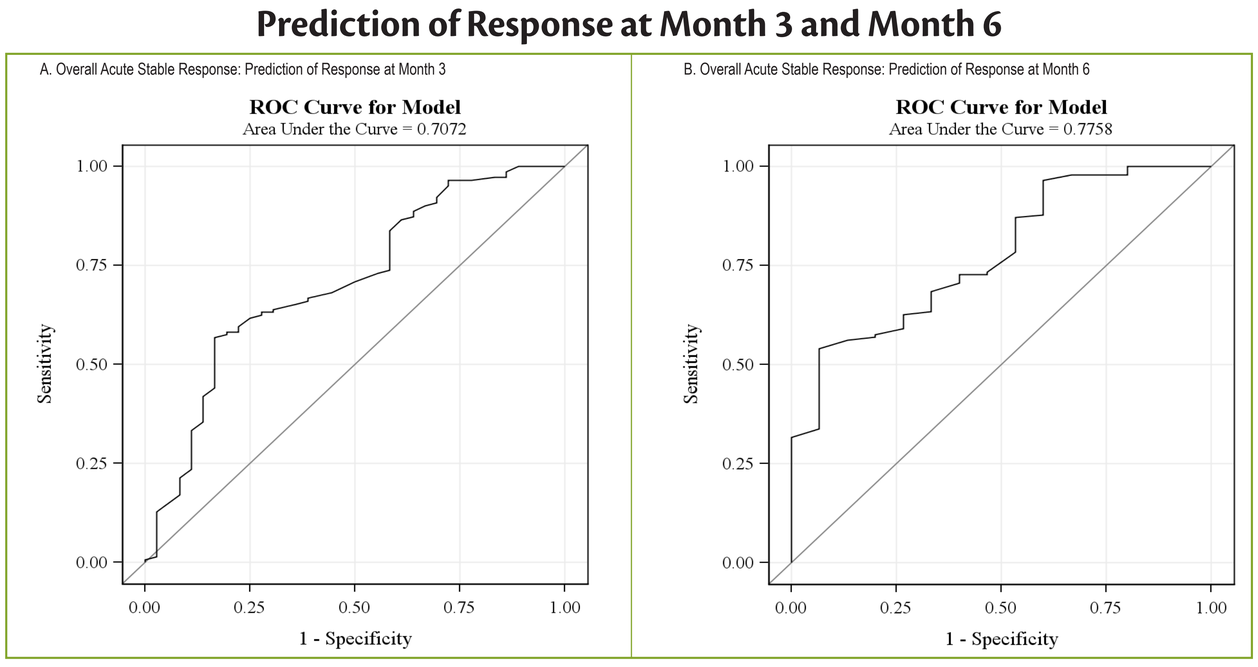
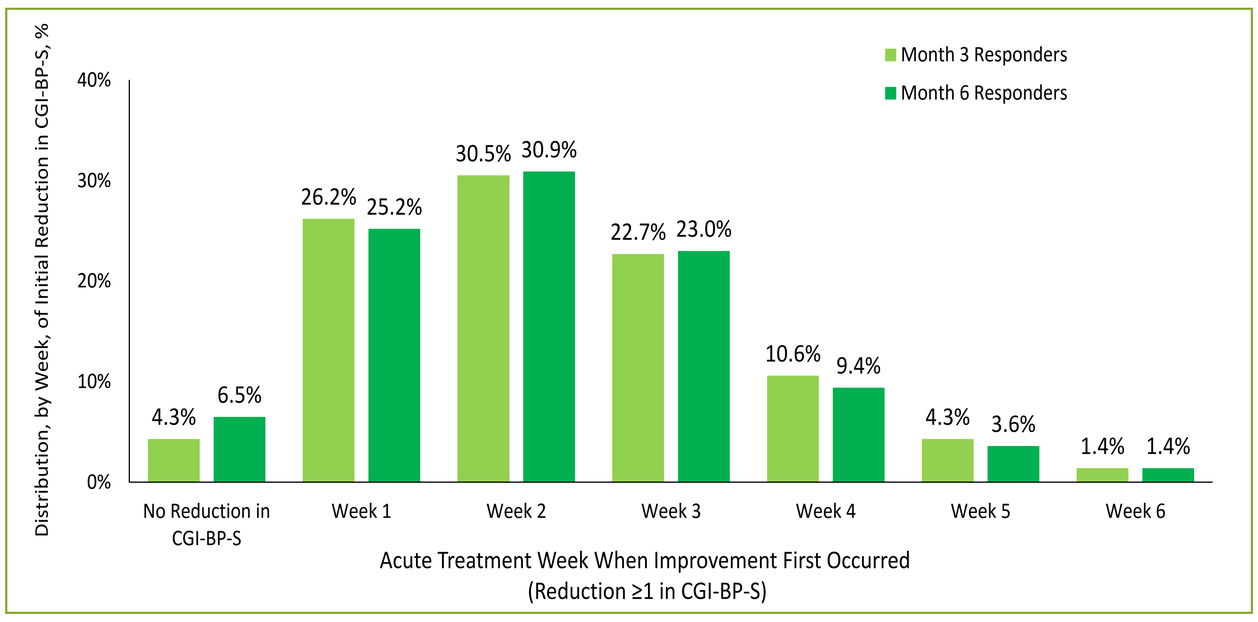


Figure 4. Among Month 3 and Month 6 Responders, When Did Improvement First Occur? (≥1-point improvement in the CGI-BP-S During Acute Treatment)



DISCUSSION

- More than 80% of patients who were responders at months 3 or 6 showed clinically meaningful improvement by week 4 of acute treatment
- Based on the AUC_{ROC}, the value of overall acute stable response for predicting longer-term response at months 3 and 6 was moderate; while the predictive value of early stable response was fair-to-poor[9]
- NPV for early and overall acute stable response were relatively low (18-34%) suggesting that a significant proportion of patients who were not responders at those time points nonetheless achieved response at months 3 and 6. Thus, the absence of week 6 improvement was not found to be a reliable predictor of non-response during 3-6 months of continued treatment with lurasidone
- Further analyses are needed to determine the clinical utility of early treatment response for clinical decision-making regarding long-term treatment

REFERENCES

1. Vieta & Valentí. CNS Drugs 2013;27:515–529.
2. Loebel et al. Am J Psychiatry. 2014;171:169-77.
3. Loebel et al. Am J Psychiatry. 2014;171(2):160-8.
4. Szegedi et al. J Clin Psychiatry. 2009;70:344-53.
5. van Calker et al. J Affect Disord. 2009;114:243-53.
6. Henkel V et al. J Affect Disord. 2009;115:439-49.
7. Kim et al. J Affect Disord. 2011;129:183–90.
8. Iosifescu et al, Poster presentation, ISBD, June 3-6, 2015, Toronto.
9. El Khouli et al. J Magn Reson Imaging. 2009;30:999-1004.

DISCLOSURES

Over the past 3 years Dr. Iosifescu has received research funding through the Icahn School of Medicine at Mount Sinai from NIMH, AstraZeneca, Brainsway, Euthymics, Neosync, and Roche; he has received consulting fees from Avanir, CNS Response, Otsuka, Lundbeck, Servier, and Sunovion.

Drs. Tsai, Pikalov, Kroger, and Loebel are employees of Sunovion Pharmaceuticals Inc.

Sponsored by Sunovion Pharmaceuticals Inc.

International Society for CNS Clinical Trials & Methodology (ISCTM); Aug 27 to Aug 29, 2015; Amsterdam