Randomized, double-blind, placebo-controlled trial of asenapine maintenance therapy in adults with an acute manic or mixed episode associated with bipolar I disorder

BACKGROUND

- Asenapine is FDA indicated for acute treatment of adult and pediatric patients with bipolar mania and for acute and maintenance treatment of adults with schizophrenia
- Most current atypical antipsychotics may be more effective in controlling one polarity's symptoms (better at mania than depression, or vice versa)

OBJECTIVE: *"…to investigate asenapine in preventing the recurrence of any mood episode in subjects with bipolar I disorder…"*

METHODS

STUDY DESIGN

- Inclusion Criteria:
  - 18 years or older
  - Diagnosis of bipolar I disorder and current manic or mixed episode
- Exclusion Criteria:
  - Clinically significant medical or psychiatric conditions
  - Abnormal laboratory or physical examination findings
  - BMI <18.5 or >40.0
  - Risk of self-harm or harm to others
  - Substance abuse or dependence (in the prior 6 months)
  - History of rapid cycling
- Subjects from 87 centers in Bulgaria, Croatia, Romania, Russian Federation, Serbia, Turkey, Ukraine, Philippines, India [open label: 58.3%, DBP: 70.6%] , and the United States [open label: 41.7%, DBP: 29.4%]
- Open-Label Treatment (n=549):
  - Received on placebo tablet and one asenapine tablet (5 mg or 10 mg) at the same time twice daily
  - Subjects not blind to asenapine dose
  - 12-16 weeks
- Double-Blind Period (DBP) (n=253):
  - Subjects who met stabilization/stable-responder criteria were randomized to continue treatment with *only* asenapine or placebo (only one tablet unlike open-label)
  - 26 weeks
- Power of 85% reached at n=250 during DBP

OUTCOMES

- Primary efficacy outcome was time to recurrence of any mood event during double-blind treatment
  - Recurrence- requirement or initiation of non-study medication to treat manic, depressive, or mixed symptoms, need for psychiatric hospitalization, study discontinuation because of mood event, or a total YMRS or MADRS score $\geq$ 16
- Secondary outcomes of interest were rate of recurrence for manic, mixed, and depressive mood episodes and time to discontinuation for any reason

STATISTICS

- Kaplan-Meier used to estimate time to first recurrence of any, manic, mixed, and depressive episodes
- Difference in survival curves evaluated using two-sided log rank test
- Cox proportional hazard models used to estimate hazard ratios

RESULTS

- 171 (67.9%) completed double-blind treatment (highest in asenapine group)

- Reasons for discontinuation
    - Placebo: adverse events (19.8%) and recurrence (14.3%)
    - Asenapine: adverse events (7.1%) and withdrawn consent (5.6%)
- Compliance
    - Placebo: 101.02%
    - Asenapine: 99.58%
- Primary outcome
    - Time to recurrence of any mood episode was significantly longer in asenapine-treated subjects relative to placebo-treated subjects (log-rank test p <.0001; hazard ratio: 0.22, 95% CI= 0.11-0.43; NNT=5)
- Secondary outcomes of interest
    - Time to recurrence of manic episode was significantly longer in asenapine group (p <0.001; hazard ratio: 0.16, 95% CI= 0.06-0.43; NNT=7)
    - Time to recurrence of depressive episode was significantly longer in asenapine group (p=0.0452; hazard ratio: 0.35, 95% CI= 0.12-1.02; NNT = 16)
    - Time to recurrence of mixed episode was longer in asenapine group but not statistically significant (p=0.0739; hazard ratio: 0.10, 95% CI = 0.01-1.06; NNT= 32)
    - Time to early discontinuation for any reason was significantly longer in asenapine group (p<0.0001; hazard ratio: 0.34, 95% CI= 0.21-0.55)

STRENGTHS

- Double-blind, control trial design
- Used acceptable strengths and lengths of treatments for asenapine

LIMITATIONS

- Authors of the trial have many connections to drug companies affiliated with Saphris (asenapine)
- Bias may have affected the design and interpretations of the results of this trial
- Adherence values were reported, but details surrounding this issue are questionable
- Potential for un-blinding in taste differences in placebo and control
- Used a placebo instead of another atypical antipsychotic
- Strict exclusion criteria that may be seen in clinical practice
- Adverse events reported are misleading in nature of reporting style

CONCLUSION

- In patients with acute bipolar I manic or mixed episode who were stable responders to asenapine 5 mg BID or 10 mg BID over 12-16 weeks, asenapine was found to be statistically superior to placebo in preventing recurrences over 26 weeks of double-blind randomized withdrawal treatment.
- Approximately fourfold higher risk of recurrence with placebo relative to asenapine treatment
- Asenapine may be a good first line option choice for patients with bipolar I disorder who need effective short-term and long-term treatment and may be helpful in preventing recurrence of manic or depressive episodes
- A future trial should be conducted comparing asenapine to another atypical antipsychotic (i.e. lurasidone, aripiprazole) and time to recurrence

Reference: Szegedi A, Durgam S, Mackle M, Yun Yu S, Wu X, Matthew M, Landbloom RP. Randomized, double-blind, placebo-controlled trial of asenapine maintenance therapy in adults with an acute manic or mixed episode associated with bipolar I disorder. Am J Psychiatry. 2018: 175(1); 71-79.