

Miglustat: Overview of Endpoints

Ronald Farkas, M.D., Ph.D.
Division of Neurology Products
Office of New Drugs, CDER

Neurology Division Assessment

Would the endpoints, if positive, represent clinical benefit?

Clinical Benefit:

- Improve patient's symptoms (how patient feels) and/or prolong survival

Clinical Benefit

- Even a small improvement in a symptom relevant to a disease, or in survival, *if true*, can support efficacy

However

- If an aspect of disease is not bothersome, treating that aspect, by definition, cannot be of direct clinical benefit

Prospective Study Endpoints

Primary

- Horizontal Saccadic Eye Movement Velocity

Secondary

- Swallowing
- Walking
 - Hauser Standard Ambulation Index
- Cognitive
 - Folstein Mini-Mental State Examination
- Ataxia/spasticity/dystonia observations

Retrospective Survey

- NP-C Disability Scale (Iturriaga 2006)
 - Ambulation
 - Language
 - Swallowing
 - Manipulation

Saccadic Eye Movement Velocity

Neurology Division Assessment

- *HSEM is not a symptom*
- Visual symptoms of *any* kind not prominent in NP-C

Conclusion

HSEM-alpha fundamentally incapable of showing direct clinical benefit to NP-C patients

Could HSEM-alpha provide *indirect* evidence of clinical benefit?

Conclusion

FDA not aware of evidence that preserved eye movement would decrease any symptom of NP-C

In fact, some data from other diseases suggests horizontal gaze not correlated with reading, intelligence, manual dexterity, or ability to perform visual tasks

Chronic progressive external ophthalmoplegia (Man 2006)

Horizontal gaze palsy of ROBO3/E319K mutation (Amoiridis 2006)

Secondary endpoints

Endpoint

- Swallowing
- Walking
- Cognitive

Measured by

- Observation
- Hauser Ambulation Index
- Folstein Mini-Mental
 - *Small changes not clearly meaningful*

Conclusion

- Endpoints are symptoms in NP-C
- Above could have been acceptable *if had been analyzed in a statistically sound way*

Secondary Endpoints

- Ataxia/spasticity/dystonia
- Non-standardized clinical observations
- Relative severity of observations not clear

Conclusion

- Not useful as an endpoint

Retrospective Study

- NP-C Disability Scale

- Walking
- Talking/Communicating
- Swallowing
- Manipulating



**poorly defined, may
decrease reliability**

Conclusion

- Would have been acceptable (nearly) in a *placebo-controlled prospective* study, but...

...As used, not considered reliable

- Retrospective, no concurrent control
- The hope that drug works is a powerful potential bias
- Endpoints measured by NP-C disability scale are susceptible to this and other forms of bias