Clinical Studies in Infantile Spasms

Peripheral and Central Nervous System Drugs Advisory Committee

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Day 2

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Center for Drug Evaluation and Research
Clinical Studies in Infantile Spasms

- Three Phase 3 Efficacy Studies
  Study 1A Elterman and Shields
  Study W019 Appleton
  Study FR03 Chiron

- Assessment of Intramyelonic Edema (IME) and MRI Abnormalities
Clinical Review of New Drug Application (NDA)

Evaluates whether the design, conduct, data, and analyses of clinical studies are adequate to demonstrate that the drug is safe and effective in its proposed indication and that the drug’s benefits outweigh its risks.
Criteria for Adequacy of Pivotal Studies Include

• Placebo or active control with adequate randomization procedure
• Adequate blinding procedure (double blind)
• Prospective choice of primary endpoint
• Validated method to assess primary endpoint
• Prospective **Statistical Analysis Plan**
  - Prespecified analysis method
  - Prespecified interim analyses
  - Multiplicity adjustment to p value
  - Protection of blinding after interim analysis
• Adequate planned study size (adequate power)
• Adequate patient enrollment (minimal drop-outs)
• Adequate treatment period length
Three Phase 3 Efficacy Studies

Study 1A Elterman and Shields
Study W019 Appleton
Study FR03 Chiron
Three Phase 3 Efficacy Studies

- Study 1A is single-blind, W019 is double-blind, FR03 is open-label
- All studies were investigator-initiated and not intended to support a new drug application
- There are shortcomings in conduct and analysis of the studies
Study Design:

- Multicenter, randomized, single-blind (investigators knew randomization to which study arm; caregiver only knew the dose but not the study arm)

- Two doses:
  - high dose (100 to 148 mg/kg/day)
  - low dose (18 to 36 mg/kg/day)

- Study population: younger than 2 years with new onset IS
Study 1A

Study Design (cont.):

- Study Phase:
  - Phase 1: Single-blind phase, 14-21 days
  - Phase 2: Open-label follow-up, up to 3 years

- Study sites: 9 sites in US
Study 1A

**Primary efficacy endpoint:** the proportion of subjects achieving spasm cessation for 7 consecutive days beginning within the first 14 days of therapy as determined by caregiver assessment and then confirmed by an 8 hour CCTV EEG monitoring session within 3 days of the seventh day of spasm freedom

**CCTV EEG interpreter** was blinded

**Statistical method:** Pearson Chi-square test
Primary Efficacy Result:
- 227 subjects were enrolled into the study and 221 subjects were analyzed for primary efficacy

Spasm free:
- High dose group: 16% (17/107)
- Low-dose group: 7% (8/114)

p=0.0375 (Pearson Chi-square test, nominal p-value)

However, there are a series of concerns that may impact the validity of this conclusion
Concerns with Study 1A Efficacy

Concerns with Statistical Analysis Plan

• Aventis (previous sponsor) did not develop an SAP for Study 1A although Drs. Elterman and Shields included statistical methods in both the first and second interim Clinical Study Reports.

• The final Statistical Analysis Plan was not signed-off until October 2004; last patient completed in April 2002.
Study 1A

Issues in Sample Size Increase:

- History of sample size increase
  37-40 subjects → 44 subjects → 150 subjects → 250 subjects

There was no additional power analysis conducted to determine the final two increases in sample size; the adjustment was made to allow physicians to continue to administer drug while awaiting FDA approval.

Totally 227 subjects were enrolled to Study 1A.
<table>
<thead>
<tr>
<th>Description</th>
<th>5/31/1997 (Cut-off date)</th>
<th>2/28/1999 (Cut-off date)</th>
<th>4/2/2002 (Cut-off date)</th>
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<tbody>
<tr>
<td>Description</td>
<td>First analysis</td>
<td>Second analysis and Neurology article</td>
<td>Final analysis</td>
</tr>
<tr>
<td>N randomized</td>
<td>89</td>
<td>179</td>
<td>227</td>
</tr>
<tr>
<td>N analyzed</td>
<td>62</td>
<td>142</td>
<td>221</td>
</tr>
<tr>
<td>Responders Low Dose</td>
<td>15% (5/33)</td>
<td>11% (8/75)</td>
<td>7% (8/114)</td>
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<tr>
<td>Responders High Dose</td>
<td>28% (8/29)</td>
<td>36% (24/67)</td>
<td>16% (17/107)</td>
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<tr>
<td>P-value</td>
<td>.35 Fisher’s Exact</td>
<td>&lt;.001 Mntl Hszl Chi Sqr</td>
<td>.0375 Pearson Chi Sqr</td>
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<tr>
<td>Date</td>
<td>Description</td>
<td>Comments</td>
<td>N randomized</td>
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</tr>
<tr>
<td>9/27/1996 (Cut-off Date)</td>
<td>FDA post-hoc analysis</td>
<td>First 44 Infants (original minimal number to be recruited)</td>
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<tr>
<td>1/1997 (Cut-off date)</td>
<td>Amendment 4</td>
<td>Increase to 150 Infants</td>
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<tr>
<td>5/31/1997 (Cut-off date)</td>
<td>First analysis</td>
<td>This analysis used in Feb 2000 report &amp; Neurology article</td>
<td>179</td>
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<tr>
<td>2/28/1999 (Cut-off date)</td>
<td>Second analysis</td>
<td>This FDA analysis uses same primary outcome as the final analysis</td>
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<td>2/28/1999 (Cut-off date)</td>
<td>Second analysis Revised (FDA post-hoc)</td>
<td>Increase to 250 Infants</td>
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<tr>
<td>10/2000</td>
<td>Amendment 5</td>
<td>Based upon the SAP of 10/2004; no correction for interim analyses</td>
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<tr>
<td>4/2/2002 (Cut-off date)</td>
<td>Final analysis</td>
<td>Using Fisher’s Exact; no correction for interim analyses</td>
<td>227</td>
</tr>
<tr>
<td>4/2/2002 (Cut-off date)</td>
<td>Final Analysis (FDA post-hoc)</td>
<td></td>
<td>227</td>
</tr>
</tbody>
</table>
Study 1A

- It seems that the two “interim” analyses were not pre-specified and the p-value for the final analysis was not adjusted for these first two analyses.

- The results of the second “interim” analysis were formulated for February 2000 study report (published in *Neurology* in October of 2001) and the last subject completed the study in April, 2002. The impact of this “interim analysis” and its publication on the single-blind trial conduct and final analysis is unknown.
Study 1A Elterman and Shields: Limitations

- Originated as compassionate use IND
- Many changes in statistical analysis plan
- Only partially single blind since care-givers knew dosage and might deduce which arm (low vs high dose) that their infant was in
- Unprespecified multiple “interim” analyses with no p value adjustment and with a potential threat to blinding
Study W019 Appleton

- Double-blind placebo-control parallel group monotherapy trial
- Randomized to VGB 50 mg/day or placebo
- As-needed dose increase to a maximum of 150 mg/kg/day during 5 day double-blind treatment period
Study W019 Appleton

Primary endpoint: percent change in the average frequency of spasms, assessed during a predefined two-hour window, from baseline to the end of the double-blind study period, where end of the double-blind study period is defined as the final two days of the period.
## Study W019 Appleton

Percent Change in Mean Spasm Frequency

<table>
<thead>
<tr>
<th></th>
<th>2 Hrs</th>
<th>24 Hrs</th>
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</thead>
<tbody>
<tr>
<td>Vigabatrin</td>
<td>54.4%</td>
<td>68.9%</td>
</tr>
<tr>
<td>Placebo</td>
<td>41.5%</td>
<td>17%</td>
</tr>
<tr>
<td>P-Value</td>
<td>0.56</td>
<td>0.030</td>
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</table>
Study W019 did not demonstrate an effect of vigabatrin on infantile spasms, based on the pre-specified primary endpoint, the average percent change in daily spasm frequency, assessed during a predefined two-hour CCTV-EEG window. When this efficacy variable was based on data collected over the 24-hour window, there appears to be a treatment difference in favor of vigabatrin, but this is a post hoc outcome measure and this 24-hour data is not verified by CCTV-EEG.
Study W019 Appleton
Limitations

Too small (20 pts on VGB, 20 pts on PBO)

Treatment period too short (ascending as needed from 50 mg/kg/day to 150 mg/kg/day over 5 days)

2-hour CCTV-EEG window too short given spasm variability

Wrong endpoint: Cessation of spasms rather than spasm frequency would have been a more clinically meaningful outcome measure

Post Hoc 24-hour endpoint is not verified by CCTV EEG
Study FR03 Chiron

Multicenter, open-label, 2-month cross-over study of 23 infants with tuberous sclerosis and IS
Crossover after 1 month
Vigabatrin (150 mg/kg/day)
Active control: hydrocortisone (15 mg/kg/day)
Study FR03

Primary efficacy endpoint: Proportion of infants with total cessation of spasms (no CCTV EEG confirmation) as determined by caregiver

No formal statistical analysis plan
Study FR03

22 infants in efficacy analysis:
11/11 of infants on vigabatrin first had elimination of spasms (no crossover)
4/11 of infants on hydrocortisone first had elimination of spasms
7/11 of infants on hydrocortisone first did not respond and crossed over to VGB; all 7 responded to vigabatrin
Limitations of Study FR03

Limited to infants with tuberous sclerosis

No CCTV EEG confirmation of spasm cessation determined by unblinded caregiver-observer

Open label
Study FR03

Impressive supportive evidence of efficacy

Open label study that provides supportive evidence but is not a pivotal study
Efficacy Studies

Follow-on studies are uncontrolled, open-label studies.

The question of whether treatment could be short-term (weeks to months) rather than long-term (months to years) is not addressed.
Summary of Concerns about Efficacy Studies

None designed as pivotal trials.

1A (single blind) had multiple analyses, ongoing changes in statistical analysis plan, and possible breach of single blind.

W019 (double-blind placebo-control) had too few infants, was too brief, had wrong primary outcome, and was negative.

FR03 (open label) is supportive evidence.
Summary of Concerns: Efficacy Studies

Although the outcomes of these three studies are suggestive of efficacy, by the usual criteria we cannot conclude that these are positive pivotal studies.
Safety Concern

Assessment of Intramyelinic Edema (IME) and MRI Abnormalities
IME

- Animal toxicology studies (rat and dog) demonstrated vacuolization of cells in specific brain regions after chronic or subchronic VGB
- Regions: brainstem, cerebellum, basal ganglia, and anterior commissure
- Vacuoles within the myelin laminae (intramyelinic edema or IME)
IME in Rat and Dog

- Appeared within 4 weeks of dosing
- Progressed to a plateau despite continued dosing
- Resolved within 3 months of discontinuation of dosing
- Residual astrocytosis and mineralization seen in some rodents but not in dogs
IME in Rat and Dog

• IME in rat and dog correlated in onset and resolution with prolongation of evoked potential (EP) latencies and with high T2 signal on MRI in these animals
• Therefore clinical trials of VGB for CPS in 400 adults and 200 children included prospective monitoring with EP and MRI; no evidence of EP and MRI abnormalities in these patients
IME and MRI

- Report of 3 infants treated with VGB who developed MRI lesions which author linked to preclinical IME (Pearl, 2006)
- Ten more cases from postmarketing safety surveillance
- Six more cases in draft manuscript
IME and MRI

These lesions were in the deep grey matter rather than in the white matter.

The IME seen in animal models was in the white matter.

Do the MRI lesions represent IME?
IME and MRI

- Ovation expert review panel (pediatric epileptologists and neuroradiologists) in February 2007
  - MRI lesions not definitely due to VGB
  - Unlikely to have clinical sequelae
  - Recommended retrospective study to define incidence and prevalence
IME and MRI

Ovation Retrospective Study of 5 Centers found 204 infants with MRI reports of which 23 infants had T2 MRI findings suggesting a VGB-associated lesion

- 12/23 had complete or partial resolution of the MRI lesions
  - 7/12 had continued treatment
  - 5/12 had discontinued treatment
- Remaining 11/23 did not have repeat MRIs so could not document resolution of the T2 lesion
IME and MRI: Study OV-1019

Retrospective blinded review of 205 infants treated at 10 US or Canadian sites for IS (VGB vs Other Rx)
Incidence of VGB-associated MRI lesions was 36%
Incidence of MRI lesions with other therapy was 6%
IME and MRI: Study OV-1019

Retrospective blinded review of 205 infants treated at 10 US or Canadian sites for IS (VGB vs Other Rx)

- Prevalence of VGB-associated MRI lesions was 21.5%
- Prevalence of MRI lesions with other therapy was 4%
IME and MRI: Study OV-1019

Retrospective blinded review of 205 infants treated for IS (VGB vs Other Rx)

- VGB was discontinued in most infants as soon as lesion detected
- Suggestion of dose response
- No characteristic clinical signs or symptoms associated with MRI lesion
IME and MRI: Repeat Review

Retrospective Examination of 400 adults and 200 older children treated for CPS
*Prevalence: 14% in VGB treated pts
  13% in Other Rx treated pts
*Incidence: 11% in VGB treated pts
  8% in Other Rx treated pts
No VGB MRI changes in age > 3 years??
IME and MRI: Conclusions

- **Sponsor:** There is a causal relationship between VGB treatment of infants for IS and the occurrence of MRI signal changes (abnormal T2 and FLAIR signal).
- **Agency:** Concur
IME and MRI: Clinical correlate?

No evidence for clinical sequelae in Pearl abstract, the prepublication paper, or the Ovation retrospective reviews.
IME and MRI: Clinical Correlate?

However, 3 Finnish infants receiving VGB for IS reported to have abnormal motor movements coincident with MRI abnormalities and resolving after discontinuation of VGB.

EMEA review concluded that risk-benefit balance was unchanged for VGB as initial therapy for IS.
IME and MRI: Conclusions

• Sponsor: The MRI changes occur in a characteristic anatomical distribution with symmetric involvement of globus pallidus, thalamus, brainstem and deep cerebellar nuclei.

• Agency: Concur
IME and MRI: Conclusions

- Sponsor: There is likely a dose relationship of VGB-induced MRI changes in infants. Infants taking higher doses are likely at greater risk for the development of MRI changes than those patients treated with lower doses (<125 mg/kg/day).
IME and MRI: Conclusions

Agency:

• Dose relationship is plausible but not statistically significant.

• In any case, the “higher doses” are in the dose range used for the treatment of Infantile Spasms.
IME and MRI

• Sponsor: The MRI abnormalities are generally transient, whether or not VGB is continued.

• Agency: Conclusion is uncertain given limited data from two retrospective studies in which not all patients had baseline or follow-up MRI scans.
IME and MRI

No VGB MRI changes in children of ages > 3 years??

Not clear that age 3 is an absolute cutoff beyond which there is no risk of MRI signal abnormalities with whatever pathologic and clinical correlations exist.
IME and MRI: Conclusions

These MRI changes seen in children are presumed by the Sponsor to represent the IME observed in the white matter of multiple animal species.

However, the MRI lesions may instead correlate with a juvenile rat grey matter lesion that differs from IME.
IME and MRI

Dr Schmued: the juvenile rat lesion

- Seen in same deep grey nuclei as the lesions in the pediatric MRIs
- Appear not to be reversible IME (white matter) but rather irreversible neuronal degeneration in grey matter
- Might explain why MRI lesion in human infants occurs in first 3 years of life
IME and MRI Lesion

The MRI lesion remains a problematic consideration in weighing benefit-to-risk for VGB as IS therapy.
Overall Summary of Clinical Concerns: Efficacy and Safety

- **Efficacy**: Two pivotal studies (1A and W019) and supportive study (FR03) do not meet usual criteria for efficacy demonstration
- **Efficacy**: Need for short-term vs long-term vigabatrin therapy has not been studied
- **Safety**: The MRI changes seen in 20% of infants are not definitely IME, may not always be transient, may not be dose dependent, and may have clinical sequelae
- **Safety**: Retinal toxicity (as discussed by Dr. Farkas)