Dravet Syndrome: Clinical Trials Overview

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Disclosure

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- The Epilepsy Study Consortium
- Pediatric Epilepsy Research Foundation
The Next Dravet Treatment...

- A product
  - Probably a medication
  - Maybe a device
- A sponsor
  - Probably a pharmaceutical company
  - Maybe an academic center or a non-profit
- Proof that the product is safe and effective in humans in short-term use
  - Successful navigation of the FDA regulatory process
Road Map

◆ Clinical trials process
◆ Recent Dravet clinical trials
◆ Future opportunities
“Science begins with counting.”
   - Siddhartha Mukherjee

“If you can’t measure it, you can’t improve it.”
   - Atul Gawande

“Everything that can be counted does not necessarily count; everything that counts cannot necessarily be counted.”
   - Albert Einstein
USA versus Europe

◆ FDA
  - New treatment must show it’s better than something (superiority)

◆ Europe
  - New treatment must show it’s not worse than an existing treatment (non-inferiority)

Figure 2 Results for seizure recurrence from a hypothetical placebo controlled trial demonstrating treatment effect for patients with increasing risk of seizure remissions.

Proportion with remission

- Standard AED
- Placebo

Increasing risk of remission
Typical road to FDA approval

- **Phase 1 studies**
  - 20-100 healthy volunteers
  - Safety and dosage
- **Phase 2 studies (70% of drugs make it here)**
  - A few hundred patients
  - Efficacy and side effects
- **Phase 3 studies (33% make it here)**
  - 300-3,000 patients
  - Efficacy and side effects
  - Control group
Orphan Diseases

- **US Orphan Drug Act (ODA) - 1983**
  - Disease affecting less than 200,000 persons in the US
  - About 6,000 orphan diseases
  - 25 million US residents affected
- **EU Orphan Medicinal Product Regulation (OMP) - 2000**
  - Life-threatening or chronically debilitating conditions affecting not more than 5 persons per 10,000 citizens in the European Community
  - 30 million European residents affected
Provisions of US ODA - 1983

- Federal tax credits for research done (up to 50% of costs) to develop a drug
- 7-year monopoly on drug sales
  - Applies only to approved use
- Waiver of drug approval application fees
  - About $1.5 million
- Waiver of annual FDA product fees
Orphan Drugs for Epilepsy

- Since 1993
  - LGS: Felbamate, Rufinamide, Clobazam
  - Infantile spasms: ACTH, Vigabatrin
  - Acute repetitive seizures (ARS): Rectal Diazepam
  - Short-term PHT replacement, Status: Fosphenytoin
  - Dravet syndrome: Stiripentol (EU only)

- More than 350 orphan drugs approved in US
  - About 1/3 of all FDA approvals
ODA - Limitations

- No approvals yet for very rare epilepsies
- None of the approved drugs for epilepsy are good enough
- Decreasing incentives to develop new treatments for common epilepsies
- Cost of approved products
Road Map

- Clinical trials process
- Recent Dravet clinical trials
- Future opportunities
Patient selection for a Dravet study

◆ Is the Dravet diagnosis accurate?
  ◆ Evolution of disease course over time
◆ Are the episodes seizures?
◆ Can the seizures be reliably counted?
◆ Do the seizures occur at regular intervals?

◆ How many errors and mistakes can the study tolerate?
◆ Some types of epilepsy are “easier” to study than others
Dravet syndrome – diagnosis

- Seizure onset 3-15 months of age
- Initial seizures
  - Hemi-clonic or GTC
  - Often triggered by fever
  - Often prolonged
- Other seizures emerge between 1-5 years
  - Myoclonic
  - Focal
  - Absence
  - Status
- Development
  - Normal in 1st year, then slows
- Genetics
  - SCN1A mutation in 70-80%
Dravet syndrome – red flags

- Development never normal
- Seizure onset outside of 3-15 months of age
- Single seizure type, other than hemi-clonic or GTC
- Atypical seizures before 12 months of age
- Infantile spasms
- Abnormal neuro-imaging
Accuracy by Seizure Type

Akman et al. Seizure 2009;18:524-529
Dravet syndrome – study challenges

- Infrequent prolonged seizures
- Variable seizure flurries
- Difficult-to-count seizures
- Length of pre-treatment baseline phase
  - 4, 6 or 8 weeks?
- Clinical or genetic diagnosis?
Potential Challenges in any Trial

- Non-seizure events called seizures
- Seizure events not identified
- Inconsistent counting between baseline and treatment phase
- Length of baseline phase
- Placebo response
- Drug unsafe, ineffective
Dravet syndrome – CBD

◆ CBD versus placebo as add-on therapy
◆ 120 patients
  ◆ Mean age = 10 years
  ◆ Median convulsive seizures/month = 13
  ◆ Mean of 3 current AEDs, 4 past AEDs
  ◆ 4 week baseline, 14 week treatment period
  ◆ Central review of patient diagnosis and seizure types
◆ Results
  ◆ CBD – 39% convulsive seizure reduction
  ◆ Placebo – 13% convulsive seizure reduction (p = 0.01)

NEJM, May 25, 2017
## Table 2. Primary Efficacy End Point of Percentage Change in Convulsive-Seizure Frequency in Each Trial Group.*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cannabidiol</th>
<th>Placebo</th>
<th>Adjusted Median Difference (95% CI)</th>
<th>P Value †</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of convulsive seizures per mo — median (range)</td>
<td>12.4 (3.9 to 1717)</td>
<td>14.9 (3.7 to 718)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>12.4 (3.9 to 1717)</td>
<td>14.9 (3.7 to 718)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment period</td>
<td>5.9 (0.0 to 2159)</td>
<td>14.1 (0.9 to 709)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percentage change in seizure frequency — median (range)</td>
<td>-38.9 (-100 to 337)</td>
<td>-13.3 (-91.5 to 230)</td>
<td>-22.8 (-41.1 to -5.4)</td>
<td>0.01</td>
</tr>
</tbody>
</table>
## Cannabidiol – non-seizure outcomes

<table>
<thead>
<tr>
<th>End Point</th>
<th>Cannabidiol vs. Placebo</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change from baseline in CGIC score</td>
<td>-1.0 (-1.0 to 0.0)</td>
<td>0.02</td>
</tr>
<tr>
<td>Change from baseline in other variables*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleep-disruption score</td>
<td>-0.4 (-1.5 to 0.7)</td>
<td>0.45</td>
</tr>
<tr>
<td>Epworth Sleepiness Scale score</td>
<td>1.5 (-0.2 to 3.2)</td>
<td>0.08</td>
</tr>
<tr>
<td>Quality of Life in Childhood Epilepsy score</td>
<td>1.5 (-3.8 to 6.8)</td>
<td>0.58</td>
</tr>
<tr>
<td>Vineland-II score</td>
<td>-2.6 (-6.8 to 1.6)</td>
<td>0.21</td>
</tr>
<tr>
<td>Inpatient hospitalizations due to epilepsy</td>
<td>0.0 (0.0 to 0.1)</td>
<td>0.54</td>
</tr>
</tbody>
</table>

*Significant at the 0.05 level.

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NEJM, May 25, 2017
### Cannabidiol (CBD) side effects

#### Table 4. Adverse Events Occurring with a Frequency of Greater Than 10% in Either Trial Group, According to System Organ Class and Preferred Term.*

<table>
<thead>
<tr>
<th>System Organ Class and Preferred Term</th>
<th>Cannabidiol (N=61)</th>
<th>Placebo (N=59)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no. of patients (%)</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>19 (31)</td>
<td>6 (10)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>9 (15)</td>
<td>3 (5)</td>
</tr>
<tr>
<td>General</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>12 (20)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>9 (15)</td>
<td>5 (8)</td>
</tr>
<tr>
<td>Infections: upper respiratory tract infection</td>
<td>7 (11)</td>
<td>5 (8)</td>
</tr>
<tr>
<td>Metabolism: decreased appetite</td>
<td>17 (28)</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Nervous system</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Convulsion</td>
<td>7 (11)</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Lethargy</td>
<td>8 (13)</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Somnolence</td>
<td>22 (36)</td>
<td>6 (10)</td>
</tr>
</tbody>
</table>

NEJM, May 25, 2017
CBD Lessons

- Brisk enrollment
- Careful attention to:
  - Seizure classification and counting
  - Seizure clusters
- 4-week baseline OK
- Drug interactions
Many Clinical Trials are Copy Cats
Dravet syndrome - Fenfluramine

Screened for eligibility (N=173)

Screen failures (n=54)

Randomized to treatment (N=119)

Placebo (n=40)

Withdrawn (n=3)

ZX008 0.2 mg/kg/day (n=39)

ZX008 0.8 mg/kg/day (n=40)

Withdrawn (n=6)

Completed Study (n=110)

Placebo (n=37)

ZX008 0.2 mg/kg/day (n=39)

ZX008 0.8 mg/kg/day (n=34)

AES abstract, Dec 2017
Dravet syndrome - Fenfluramine

AES abstract, Dec 2017
Dravet syndrome - Fenfluramine

p-values are comparison vs placebo.

AES abstract, Dec 2017
### Dravet syndrome - Fenfluramine

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Placebo (n=40)</th>
<th>ZX008 0.2 mg/kg/day (n=39)</th>
<th>ZX008 0.8 mg/kg/day (n=40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects with ≥1 TEAE</td>
<td>26 (65.0%)</td>
<td>37 (94.9%)</td>
<td>38 (95.0%)</td>
</tr>
<tr>
<td>Subjects with ≥1 serious TEAE</td>
<td>4 (10.0%)</td>
<td>4 (10.3%)</td>
<td>5 (12.5%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3 (7.5%)</td>
<td>12 (30.8%)</td>
<td>7 (17.5%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>4 (10.0%)</td>
<td>4 (10.3%)</td>
<td>3 (7.5%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>1 (2.5%)</td>
<td>4 (10.3%)</td>
<td>4 (10.0%)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>8 (20.0%)</td>
<td>7 (17.9%)</td>
<td>2 (5.0%)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>5 (12.5%)</td>
<td>4 (10.3%)</td>
<td>7 (17.5%)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>5 (12.5%)</td>
<td>8 (20.5%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Fall</td>
<td>2 (5.0%)</td>
<td>4 (10.3%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Weight decreased</td>
<td>0 (0.0%)</td>
<td>5 (12.8%)</td>
<td>2 (5.0%)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>2 (5.0%)</td>
<td>8 (20.5%)</td>
<td>15 (37.5%)</td>
</tr>
<tr>
<td>Lethargy</td>
<td>2 (5.0%)</td>
<td>4 (10.3%)</td>
<td>7 (17.5%)</td>
</tr>
<tr>
<td>Seizure</td>
<td>5 (12.5%)</td>
<td>4 (10.3%)</td>
<td>3 (7.5%)</td>
</tr>
<tr>
<td>Somnolence</td>
<td>3 (7.5%)</td>
<td>6 (15.4%)</td>
<td>4 (10.0%)</td>
</tr>
</tbody>
</table>

AES abstract, Dec 2017
Fenfluramine Lessons

◆ Brisk enrollment
◆ Careful attention to:
  ◆ Seizure classification and counting
  ◆ Seizure clusters
◆ 6-week baseline OK
◆ No clinically significant cardiac valve toxicity detected
Fenfluramine + Stirapentol

% DIFFERENCE FROM PLACEBO IN REDUCTION IN MEAN MONTHLY CONVULSIVE SEIZURES
(3 WK TITRATION + 12 WK MAINTENANCE PERIOD = TREATMENT PERIOD)

p<0.001

54.7%

0.5 mg/kg/day

p-value is treatment compared with placebo group

PROPORTION OF PATIENTS WHO ACHIEVED ≥50% AND ≥75%
REDUCTION IN MEAN MONTHLY CONVULSIVE SEIZURES
(3 WK TITRATION + 12 WK MAINTENANCE PERIOD = TREATMENT PERIOD)

p<0.001

53.5%

6.8%

32.6%

2.3%

≥ 50% Reduction

≥ 75% Reduction

0.5 mg/kg/day

Placebo

Zogenix, unpublished, July 2018
Road Map

- Clinical trials process
- Recent Dravet clinical trials
- Future opportunities
Future Dravet Syndrome Studies

- Better understanding of placebo effect
- Reducing placebo exposure with novel study designs
  - More patients receive active drug
  - Active or placebo lead-in, then randomize
  - Crossover
  - Time to event
- Non-seizure outcome measures
- Increased recognition of caregiver burden during studies
Placebo response

Meta-analysis of pediatric focal epilepsy trials

- 20% of pediatric patients in placebo arm were 50% responders

Placebo response – why?

Meta-analysis of pediatric (6-18 years) antidepressant trials

Number of study sites, less severe disease

Bridge J al. Am J Psych 2009;166:42
Effect size by region

Median percentage reductions in seizure frequency per 28 days in the Full ITT – Double-blind Phase versus Baseline

French et al, AAN 2011
Non-seizure Outcomes

◆ Behavior
◆ Sleep
◆ Attention
◆ Gait
◆ Abnormal movements (not seizures)
◆ Quality of Life

◆ Valid and usable instruments to measure non-seizure outcomes are needed
Conclusions

- Careful diagnosis and seizure counting are always important
- Central review of study subjects is now commonly used
- Dravet syndrome clinical trials can be successful
- Placebo response has many facets and is poorly understood
- Reducing placebo exposure is a goal
  - Control groups do matter
- Valid and usable instruments to measure non-seizure outcomes are needed