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TITLE: Treatment of Fragile X Syndrome with a Neuroactive Steroid

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This study is a Phase II trial to assess the safety, tolerability, and efficacy of ganaxolone, a GABAA agonist, for the treatment of behavioral problems, including anxiety and inattention in children with FXS. It has been demonstrated in the fragile X mouse model and the Drosophila (fruit fly) models of FXS that the GABAA system, including multiple receptors, is dramatically down-regulated. Ganaxolone is a drug that enhances GABAA activity. We hypothesized that ganaxolone will significantly improve behavioral problems such as anxiety, inattention, and impulsivity problems in children with fragile X syndrome. We planned to enroll 60 children, ages 6-17 years, with fragile X syndrome over a 4-year period and they would be randomized to receive either ganaxolone or a placebo initially and then crossed over after 6 weeks. We have used innovative outcome measures in addition to standard outcome measures that have been successful in previous treatment trials in fragile X syndrome at baseline and follow-up visits.
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1. INTRODUCTION
This study is a Phase II trial to assess the safety, tolerability, and efficacy of ganaxolone, a GABAA agonist, for the treatment of behavioral problems, including anxiety and inattention in children with FXS. It has been demonstrated in the fragile X mouse model and the Drosophila (fruit fly) models of FXS that the GABAA system, including multiple receptors, is dramatically down-regulated. Ganaxolone is a drug that enhances GABAA activity. We hypothesized that ganaxolone will significantly improve behavioral problems such as anxiety, inattention, and impulsivity problems in children with fragile X syndrome. We planned to enroll 60 children, ages 6–17 years, with fragile X syndrome over a 4-year period and they would be randomized to receive either ganaxolone or a placebo initially and then crossed over after 6 weeks. We have used innovative outcome measures in addition to standard outcome measures that have been successful in previous treatment trials in fragile X syndrome at baseline and follow-up visits.

2. KEYWORDS: fragile X syndrome, targeted treatments, ganaxolone, GABAA agonist, controlled treatment trial.

3. OVERALL PROJECT SUMMARY
TASKS 1, 2 and 3 were completed in the beginning of Year 2. Regarding TASK 4, we are actively recruiting subjects at a rate of 3–4 individuals per month to meet the enrollment goal of sixty. From Jul 15, 2014 to Jul 14, 2015, 14 subjects were enrolled, screened, and randomized, bringing the total enrollment to 50. Thirty-five have completed; there have been eight early terminations and two screen failures. We currently have 5 patients in the active protocol and they will finish in the fall of 2015. No serious adverse events have occurred. Data-entry is being completed on a regular basis. At the end of the last patient completion, we will start the statistical analysis with Dr. Danh Nguyen. We have been in active communication with him and have put through a mock data set; he is ready to analyze the data once we have finalized all of the data. The second Data Safety Monitoring Board (DSMB) meeting took place in January 2015, and the trial was allowed to proceed.

Work on TASK 5, data-analysis and report writing, is in the preliminary stages. We are currently preparing for data-analysis using test data in anticipation of study close. We plan on having data-analysis and report writing completed by the end of Year 5.

4. KEY RESEARCH ACCOMPLISHMENTS
* We have studied 50 patients with fragile X syndrome in a controlled trial, and they have tolerated ganaxolone well without significant adverse effects.
* Ganaxolone is safe in children with FXS between the ages of 6 to 17yo.
* We do not yet know the efficacy of ganaxolone in FXS, but we hope to have this data by early 2016 once our analysis is complete.

5. CONCLUSION
Ganaxolone is a targeted treatment in fragile X syndrome that is safe in children 6 to 17yo. Our research will demonstrate whether this treatment is efficacious in children with FXS for treatment of anxiety or other behavioral problems. We will soon have our efficacy data. If this medication is efficacious, we will work with Marinus Pharmaceuticals, who makes ganaxolone, to get it FDA approved. If it does not demonstrate efficacy, we may consider further trials where ganaxolone is combined with other targeted treatments.
6. PUBLICATIONS, ABSTRACTS, AND PRESENTATIONS:
   a. List all manuscripts submitted for publication during the period covered by this report resulting from this project. Include those in the categories of lay press, peer-reviewed scientific journals, invited articles, and abstracts.
      1. Lay Press:
         https://books.google.com/books?id=HT3LAwAAQBAJ&lpg=PA183&ots=0CvsBgBixj&dq=Rosenberg%E2%80%99s%20Molecular%20and%20Genetic%20Basis%20lozano&pg=PA183#v=onepage&q=Rosenberg%E2%80%99s%20Molecular%20and%20Genetic%20Basis%20lozano&f=false

      2. Peer-Reviewed Scientific Journals:


      3. Invited Articles: N/A
      4. Abstracts: N/A

   b. List presentations made during the last year (international, national, local societies, military meetings, etc.). Use an asterisk (*) if presentation produced a manuscript.

      New treatments for fragile X syndrome and autism, Seminar, Hautepierre Hospital, Strasbourg, France, 3/9/2015
      Targeted treatments for fragile X syndrome, Fragile X Conference, Karolinska University Hospital, Stockholm, Sweden, 5/7/2015.
      New treatments for fragile X and autism, Conference on Rare Diseases, Frambu Centre for Rare Disorders, Siggerud, Norway, 5/29/2015.

7. INVENTIONS, PATENTS AND LICENSES: N/A

8. REPORTABLE OUTCOMES
   We have discussed ganaxolone as a targeted treatment for FXS in many papers and reviews. Ganaxolone represents a group of GABAA agonists that are likely to be efficacious in FXS, and we have shown that it is safe in children 6 to 17 yo.

9. OTHER ACHIEVEMENTS
We are also assessing the biomarkers that may improve with ganaxolone; this will be part of the trial results that will be analyzed in the fall of 2015 once all of the data is obtained.

10. REFERENCES
N/A

11. APPENDICES
N/A