A Randomized Controlled Double-Blind Trial of Everolimus in Children and Adolescents with *PTEN* Mutations

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PTEN Clinical Trial Aim

Primary Objective

- To evaluate the **safety** of everolimus in patients with PTEN mutations

Secondary Objectives

- To evaluate the **efficacy** of everolimus on **neurocognition** and **behavior** in children and adolescents with PTEN mutations
  - This will be evaluated by assessing patients working memory, processing speed, and fine motor skills
- Will also assess the effects of everolimus on: overall global clinical improvement, autism symptoms, other behavioral problems, and adaptive abilities.
- We will also assess the effect of treatment on eye tracking tasks, resting state encephalogram (EEG), and task-related EEG through auditory evoked potentials (AEP).

Exploratory Objective

- To determine if PTEN-associated pathway molecules (PI3K/AKT, mTOR, MAPK), RNA levels, protein levels, and differences in the gut microbiome and mycobiome are affected by everolimus treatment and correlate with clinical improvements

Everolimus

- Oral derivative of rapamycin in clinical development since 1996
- Approved for several indications:
  - Renal cell carcinoma (2009)
  - Pancreatic neuroendocrine tumors (2011)
  - Hormone receptor-positive HER2-negative breast cancer (2012)
  - Immunosuppressant after organ transplantation (kidney 2010; liver 2013)
  - Subependymal giant cell astrocytoma (SEGA) in TSC (2010)
- In PTEN, mTOR pathway is abnormally upregulated and interferes with normal cell growth, proliferation, and function.
- Selectively inhibits mTOR pathway: Blocks the abnormal up-regulation of mTOR that occurs as a result of PTEN loss
- Binds FKB12 to inhibit mTORC1

Trial Overview

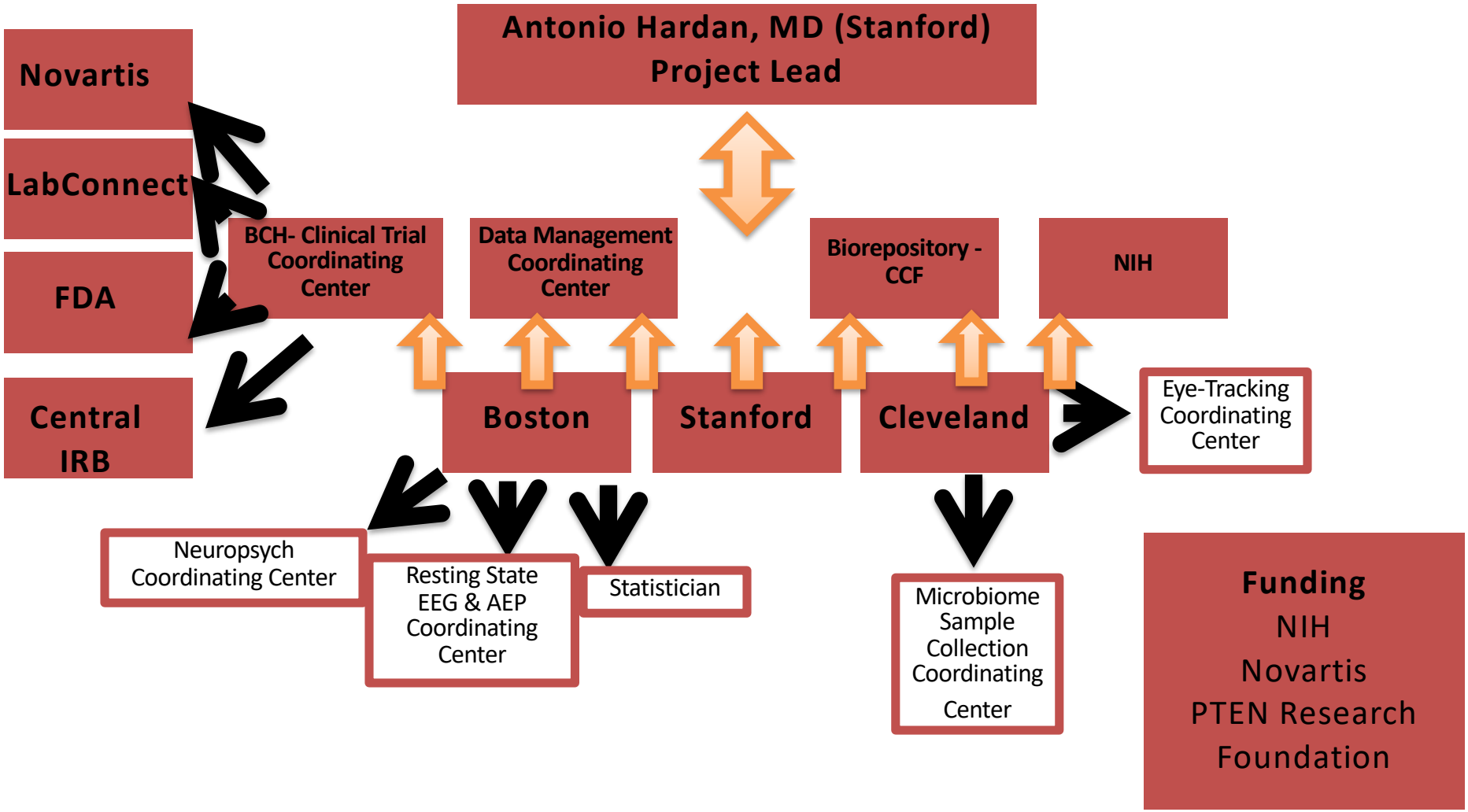
Developmental Synaptopathies Consortium

- Phase I/II Trial
- Double-Blind
- Placebo-Controlled
- Multi-Center: 3 sites
- Primary Endpoint:
  - Safety & efficacy of everolimus in individuals with PTEN mutations.
  - Effect on neurocognition at 3 month and 6 month

Clinical Trial Sites

Developmental Synaptopathies Consortium

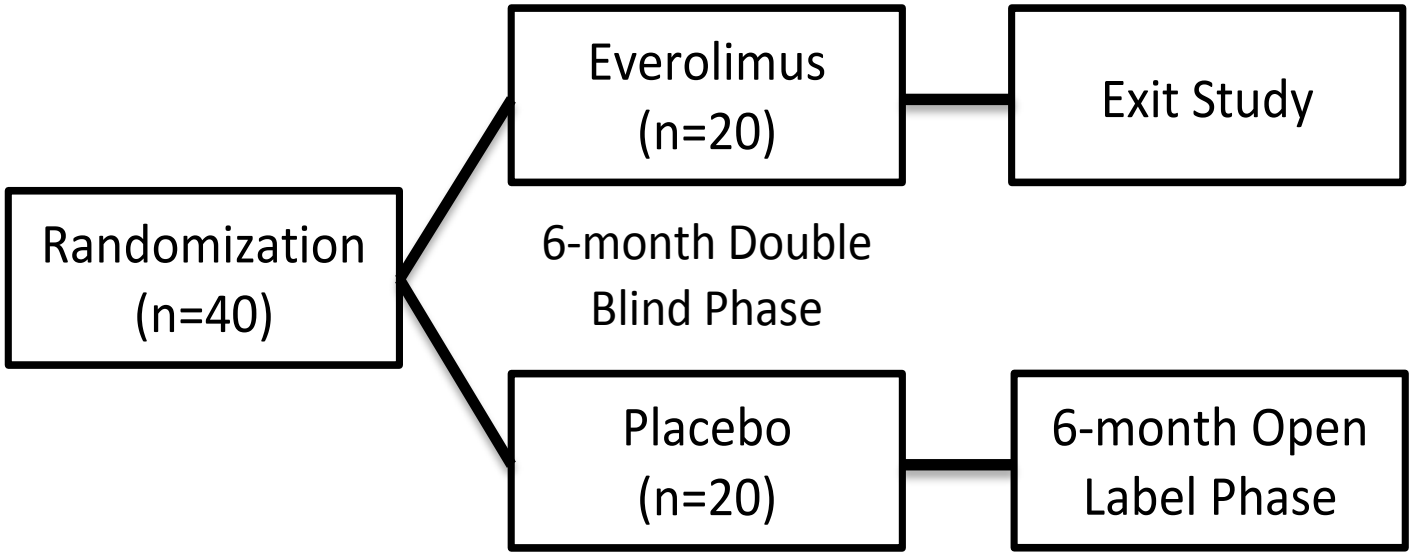
Clinical Trial Organization



Overview of Trial Desi

- Participant Flow
- Inclusion/Exclusion Criteria
- Study Design
- Endpoints
- Efficacy Composite
- Other

Participants Flow



- Multi-site trial:
  - Stanford University (PI: Antonio Hardan): 10
  - Cleveland Clinic (PI: Charis Eng, MD, PhD): 20
  - Boston Children's Hospital (PI: Mustafa Sahin, MD, PhD): 10

Inclusion Criteria I

- 6 and 21 years of age with a PTEN mutation
- Pathogenic PTEN mutation confirmed by clinical testing
  - Report reviewed at screening visit
- NVIQ or IQ ≥ 50 and ability to participate in testing procedures to the extent that valid standard scores can be obtained
  - Report reviewed by Neuropsychologist at/following screening
- Performance below the age-adjusted population mean on at least one standardized measure such as the CPT (mean reaction time) or Working memory (SB5) or Purdue Pegboard fine motor assessment (both hands);
  - Report reviewed by Neuropsychologist at/following screening
- Stable psychotropic and anti-epileptic medications for ≥ 2months
- Adequate bone marrow function
  - As measured by screening safety labs

Inclusion Criteria II

- Adequate liver function
  - As measured by screening safety labs
- Adequate renal function: serum
  - As measured by screening safety labs
- Negative urine pregnancy test for females and no plans to become pregnant
- Medically stable with no active medical problem
- No anticipated changes in existing interventions or school placement
- Availability of a caregiver who can reliably bring subject to clinic visits
- Fluent in English

Exclusion Criteria I

- Known intolerance or hypersensitivity to everolimus or other rapamycin analogs (e.g. sirolimus, temsirolimus)
- Known impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of oral everolimus
- Pregnancy, planned pregnancy, or unwillingness to use adequate contraception
- Planned changes to concomitant medications
- Patients currently receiving anticancer therapies or who have received anticancer therapies within 4 weeks of the start of everolimus (including chemotherapy, radiation therapy, antibody based therapy, etc.)
  - Prior or concomitant therapy with known or possible anti-mTOR activity, including rapamycin (sirolimus)
- Concomitant therapy with strong inhibitor (e.g., cyclosporine and ketoconazole) or inducer of CYP3A
- Active infection at time of enrollment

Exclusion Criteria II

- Significant medical illness, such as endocrinopathies or cardiovascular disease:
  - Uncontrolled diabetes mellitus
  - Patient with uncontrolled hyperlipidemia
  - Chronic treatment with corticosteroids or other immunosuppressive agents; topical or inhaled corticosteroids are allowed
- Known history of HIV seropositivity
- Participation in a clinical trial in the 30 days prior to study entry
- Patients who have received live attenuated vaccines within 1 week of start of everolimus and during the study
- Patients who have a history of another primary cancer
- Major surgery, radiation therapy or stereotactic radio-surgery within previous 4 weeks of enrollment
- Neurosurgery within prior 6 months of enrollment
- Male patients whose sexual partner(s) are WOCBP who are not willing to use adequate contraception, during the study and for 8 weeks after the end of the trial

Study Design & Safety Measu

Measurement	Performed by:	Rationale:	Screening	Baseline	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	PRN
Medical History	Clinician	Eligibility	X								
Psychiatric History	Clinician	Eligibility	X								
Clinical Interview	Clinician	Eligibility/Safety	X	X	X	X	X	X	X	X	
Inclusion/Exclusion Criteria	Clinician	Eligibility	X	X							
CGI-Severity&Improvement	Clinician	Efficacy		X	X	X	X	X	X	X	
Vital Signs	Clinician	Safety	X	X	X		X		X	X	
Physical & Neurological Exam	Clinician	Safety	X							X	X
Dermatology Exam	Clinician	Efficacy		X			X			X	
Neuropsychology Assessments	Clinician	Eligibilty/Efficacy	X	X			X			X	
Developmental Milestones	Clinician	Safety		X						X	
DOTES	Clinician	Safety	X	X	X	X	X	X	X	X	
Concomitant Medication Log	Clinician	Safety/Efficacy	X	X	X	X	X	X	X	X	
Optional EEG&AEP	Clinician	Efficacy		X			X			X	
Laboratory Tests	Laboratory	Safety	X	X	X		X		X	X	X
Everolimus Level	Laboratory	Safety			X						X
Optional Biomarker Tests	Laboratory	Efficacy		X			X			X	
Optional Microbiome/Mycobiome	Laboratory	Efficacy		X			X			X	

Primary efficacy Measu

- Composite index score of neurocognitive function:
  - Average of measures evaluating :
    - working memory: SB-5 working memory
    - processing speed: CPT mean reaction time
    - fine motor skills: Purdue Pegboard-average of both hands

- Additional approach for assessing effectiveness on neurocognition:
  - the above average weighted by 2/3
  - an average of the remaining standardized, norm-referenced neurocognitive measures: non-verbal ability, visuomotor skills, verbal learning, receptive and expressive language
    - weighted by 1/3.

Efficacy Outcome Measu

Measurement	Performed by:	Rationale:	Screening	Baseline	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6
SB-5/Mullen Scales of Learning	Clinician	Efficacy	X	X			X			X
Conners' Continuous Performance Tasks	Clinician	Efficacy	X	X			X			X
Wechsler Processing Speed Index	Clinician	Efficacy		X			X			X
Wide Range Assessment of Memory and Learning-2	Clinician	Efficacy		X			X			X
Peabody Picture Vocabulary Test- 4th Edition	Clinician	Efficacy		X			X			X
Expressive Vocabulary Test- 2nd Edition	Clinician	Efficacy		X			X			X
Purdue Pegboard Test	Clinician	Efficacy	X	X			X			X
ADOS-2	Clinician	Efficacy		X			X			X
SRS-2	Parent	Efficacy		X			X			X
RBS-R	Parent	Efficacy		X			X			X
Developmental Coordination Disorder Questionnaire	Parent	Efficacy		X			X			X
BRIEF	Parent	Efficacy		X			X			X
Adult/Child Behavior Checklist	Parent	Efficacy		X			X			X
SSP	Parent	Efficacy		X			X			X
VABS-3	Parent	Efficacy		X			X			X
CGI-Severity&Improvement	Clinician	Efficacy		X	X	X	X	X	X	X
Dermatology Exam	Clinician	Efficacy		X			X			X
Optional Resting State EEG	Clinician	Efficacy		X			X			X
Optional Auditory Evoked Potential	Clinician	Efficacy		X			X			X
Optional Biomarker Tests	Laboratory	Efficacy		X			X			X
Optional Microbiome/Mycobiome	Laboratory	Efficacy		X			X			X

Everolimus Administration

Participants should be advised to take the dose as follows:

1. Same time every morning
2. After a low fat meal
3. With a glass of water
4. Pills should not be crushed or dissolved

Missed doses: A missed dose should be taken as soon as possible (within 2 hours of the typical dosing time). **DO NOT** take 2 doses on same day (even if vomiting occurs).

Concomitant Medicatic Considerations

- **Avoid concomitant use with strong CYP3A4/PgP inhibitors.**
  - e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, nefazodone, saquinavir, telithromycin, ritonavir, indinavir, nelfinavir, voriconazole
- **Avoid concomitant use with strong CYP3A4/PgP inducers.** If combination cannot be avoided, increase dose of everolimus.
  - e.g., phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital
  - preparations with St. John's Wort should be avoided
- **Avoid**: Grapefruits, grapefruit juice, and other foods that are known to inhibit cytochrome P450 and PgP activity

Everolimus Side Effects: Clir

- The majority of AE are mild to moderate
- Mild transitory adverse effects:
  - fatigue, headache, gastrointestinal events (aphthous stomatitis, and mouth ulceration, diarrhea, anorexia, nausea, vomiting), peripheral edema, headache, epistaxis, mucosal inflammation, weight loss, respiratory symptoms (cough, dyspnea), infections (mild-moderate common infectious events), sexual dysfunction, and skin disorders (acne, rash, pruritis, dry skin, erythema, and exanthema)
- Allergic interstitial pneumonitis
- Psychiatric disorders
  - Common: Insomnia; Uncommon: aggression

Everolimus Side Effects Laboratory Abnormaliti

- Decrease hematology parameters:
  - hemoglobin, lymphocytes, platelets and neutrophils
- Increased levels of:
  - cholesterol, triglycerides, glucose, AST, ALT, creatinine, bilirubin
- Decreased levels of:
  - phosphate and potassium
- Renal dysfunction:
  - Proteinuria

Additional Study Informat

- Screening for hepatitis B and C if needed
- Visit Window is +/- 14 days
- Randomization: 1:1
  - Directly communicated to the sites (pharmacies)
- Dosing: 5 mg QD or QOD (starting dose is 4.5 mg/m^2)
  - 2.5 mg for dose adjustments
- Everolimus blood level: 5-15 ng/ml
- Dose adjustment may also be made based on side effects
- Training and Reliability of Independent Evaluators:
  - CGI-S; CGI-I; and ADOS-2

PTEN Clinical Trial Regulatory Pr

- All sites have enrolled patients
  - >9 participants

Questions?