Pre-Clinical Candidate for Orphan Genetically-defined Seizure Disorders

- Orphan pediatric indication with life-long chronic (1-100) daily seizures
- Standard of care (SOC) is inadequate
- Novel mechanism of action for first-in-class small molecule NT-125
- NT-125 reduces seizures by 60-70% in animal proof-of-concept
- Lead optimization is gating to pre-IND meeting
TEAM

Science

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Liaison between TSA and the 68 TSC Clinics, Project leader of the TSC natural history database (2000 participants)

Business

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Tuberous Sclerosis Complex, a genetically-defined (TSC1/TSC2) life-long epilepsy disorder

**TSC diagnosis**: First by pediatricians, referred to specialists based upon presentation

- 1-100 Daily Seizures: 85% of all patients
- Median age of seizure onset: 3 months
- Skin patches: dermatologist, then neurologist

**Characteristics**

- Brain Malformations
- Childhood onset seizures
- Life-long
- AED resistant

**Current SOC**

- Brain surgery
- Everolimus

**Efficacy**

- Limited efficacy
- Side-effects

**Comorbidities**

- Insomnia
- Learning disabilities
- Behavior issues (e.g., anxiety)

- High burden on care givers and patients: We need new drugs to treat seizures and comorbidities
- Our small molecule rescues brain malformations leading to seizure reduction in preclinical studies
TSC is an orphan disorder with a high societal cost

- Incidence: 1.6 million worldwide
  1/6,000 new births
  50,000 TSC pts with epilepsy in the US
  30,000-40,000 TSC pts with drug-resistant epilepsy (60-80% all pts)

- Cost of the SOC, Everolimus (Afinitor): $16K/mo/pt, $192K/year/pt
  For 30,000 patients this represents a potential US market opportunity of $5-6B/year
Inadequate SOC - Established clinical trial design

**Brain surgery:** Only possible in 10-15% of pts
  - Seizures remain in ~40% of operated pts
  - Seizures return in 50% of seizure-free pts post-op

**Everolimus:** Limited efficacy (40% of pts respond at high dose)
  (Afinitor) Major side-effects

We will use everolimus trial’s design and clinical endpoints

**Primary endpoint Phase III:** Percent change in seizure frequency from baseline
  (Time Frame: Baseline (8 wks), Core phase (18 wks))

**Secondary endpoints:** Impact on behavior and quality of life (and more)
Filamin A (FLNA) is increased in TSC patients and mouse models

TSC patients

Our mouse model:
Definitive and only model for TSC seizures
• Hsieh, Bordey 2016
• Validated through collaborations with Biotechs

Our mouse model:
Zhang, Bordey, 2014, 2020
Targeting FLNA offers a novel mechanism of action

- FLNA is an actin-binding molecule with 24 Ig domains that has dozens of binding partners
- Normalizing or blocking FLNA shrinks brain malformations.

![Diagram showing the mechanism of action involving FLNA and its effect on brain malformations and seizures.]

- Mutant TSC1/TSC2 leads to increased Rheb, which in turn increases mTOR and Filamin A.
- Increased cell size and brain malformations are inhibited by Everolimus, acting here.
- NT-125 acts here to prevent seizures.

Seizures
FLNA Target validation in our mouse model: *Flna* shRNA in utero prevents brain malformations and seizures

Abnormal cell growth reduced

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>TSC disease</th>
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<tbody>
<tr>
<td>Control</td>
<td>Control shRNA</td>
<td>Control shRNA</td>
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</table>

Seizure activity decreased

Mean seizure number/day

![Seizure activity decreased graph](image)
Animal proof-of-concept
FLNA modulator NT-125 reduces seizures and abnormal cell growth

Neonatal treatment

Seizures reduced

![Graph showing reduced seizures with NT-125 compared to Vehicle](image)

Adult treatment

Seizures reduced

![Graph showing reduced seizures with NT-125 compared to Vehicle](image)

Abnormal cell growth reduced

![Comparison of abnormal cell growth](image)

NT-125 Room for improvement

- PK properties: 80% BBB permeability, high solubility, but short half-life (2 hrs)
- Goal: improved half-life once daily injection, liquid formulation for pediatric administration
Lead optimization: Synthesis of new FLNA modulators, NT-210 series

CRO: Dr. Van Zandt at NEDP (New England Discovery Partners)

**High- to medium-throughout assays to test:**

**FLNA binding:**
- Competitive assay
  - (Click chemistry with NT-125)

**Effect on ribosome biogenesis:**
- Western blot in cell lines for ribosome protein
  - S6 reduced by Flna shRNA and NT-125

**Effect on cell growth:**
- In our mouse model

**IP Status:** Yale patents filed for
- Use of NT-125 and analogs to treat epilepsy
Mouse *in vivo* efficacy studies of NT-210 series will enable our IND application

### Mouse in vivo studies
- Dosing range in animal
- MRI
- Monitor daily seizures
- Change in seizure frequency

### Translate well into clinical studies

### Genetically-Defined Patient Population

### Clinical endpoints
- 4 months dosing safety
- MRI
- Monitor daily seizures
- Change in seizure frequency
Lead optimization plan is gating to pre-IND meeting

Completed
- Target validation
  - shRNA
  - Small Molecule
- Preliminary PK data
- Clinical collaboration
- Animal model in place
- Clinical endpoints established

**Commercial Interest:**
- Numerous confidential meetings with biotechs and several VC’s
  - all satisfied with Yale model
  - all aware of published NT-125 findings
  - all interested in vivo results with NT-210 series

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**Months 1-12**

**Deliverables Part 1 – $200K**
- MedChem with NEDP ($110K)
- PK/BBB data in mouse oral delivery ($20K)
- Preliminary tox microsomal stability ($10K)
- Efficacy of 2 analogs on seizures via oral delivery via CRO using Yale Model ($60K)

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**Months 12-24**

**Deliverables Part 2 – $100K**
- Pre-clinical Formulation
- Confirm PK/BBB

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**Months 24-36**

**Partnering After Blavatnik**
- Final Tox study
- Pre-IND package for Dr. Anderson (led Phase 1b/2a of NT-210 lead compound)

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**Deliverables**
- Pre-IND Formulation
- Clinical collaboration
- Animal model
- Clinical endpoints

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**Deliverables**
- Pre-IND Formulation
- Clinical collaboration
- Animal model
- Clinical endpoints
Back-ups/References/links
# Competition

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Efficacy</th>
<th>Formulation</th>
<th>Side-effects</th>
<th>Mode of action</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conventional AED</td>
<td>Seizure reduction in 30-40% pts</td>
<td>Liquid, pill,</td>
<td>e.g., Sleepiness, nausea depending on the drug</td>
<td></td>
<td>several</td>
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<td></td>
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<td>suppository</td>
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<tr>
<td>Everolimus (SOC) (Afinitor)</td>
<td>40% pts with &gt;50% seizures</td>
<td>Liquid suspension</td>
<td>Many and serious: e.g., stomatitis, diarrhea, infections (bone loss)</td>
<td>mTOR inhibitor</td>
<td>Novartis</td>
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<td></td>
<td>reductions</td>
<td></td>
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<tr>
<td>Under development</td>
<td>Unknown</td>
<td>unknown</td>
<td>Unknown but widespread expression</td>
<td>mGluR5 antagonist</td>
<td>Noema Pharma</td>
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<td>Previously developed by Roche,</td>
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<td>but failed phase II for Fragile</td>
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<td>X syndrome</td>
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<td>Epidiolex (cannabidiol)</td>
<td>Age 1-57 years, 201 pts</td>
<td>Liquid solution,</td>
<td>serious: e.g. diarrhea, suicidal thoughts, elevated liver enzymes, sleepiness, fever, vomiting, rash</td>
<td>Cannabinoid</td>
<td>Greenwich</td>
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<tr>
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<td>48% reduction (low dose)</td>
<td>twice daily</td>
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<td>receptor</td>
<td>Biosciences Inc.</td>
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<td>47% reduction (high dose)</td>
<td></td>
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<td>mTOR inhibition</td>
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<td>30% reduction (placebo)</td>
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<td>NT-125 analogs</td>
<td>To be tested</td>
<td>To be determined</td>
<td>None based on NT-125 (Alzheimer’s disease trial)</td>
<td>FLNA modulator</td>
<td>Yale</td>
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- **Mode of action**
- **Company**

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