Pre-Clinical Candidate NT-001 for Tuberous Sclerosis Complex Seizures

- Orphan pediatric indication with life-long chronic (1-100) daily seizures
- Genetically-defined patient populations
- No effective therapeutic standard of care (SOC)
- Novel mechanism of action for first-in-class small molecule NT-001
- Animal proof-of-concept (POC) is gating to pre-IND meeting
- Clinical trial for NT-001 possible within 24 months of POC
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Tuberous Sclerosis Complex (TSC), a Life-long Epilepsy

**TSC diagnosis:** First by pediatricians, referred to specialists based upon presentation
- 1-100 Daily Seizures: pediatric neurologist sends for MRI scan (brain tubers) and confirms
- Skin patches: dermatologist, then neurologist

**Incidence:** ~1/6000 new births in US, **55,000** patients in US
Estimated societal costs are **$2B/year in US** (~$40,000/pt/year)
Current Therapy: Limited Efficacy

**Surgery:** 10-15% of the pts
- Seizures remain in ~60% of the operated pts
- Seizures come back in 50% of the operated pts

**Everolimus:** Limited efficacy (40% decrease seizure in 40% of the pts)
- Major side-effects limit increasing the treatment dose

✓ Completed Everolimus trials validate clinical endpoints and design

- **Primary endpoints of Phase III:** Percentage change from baseline in seizure frequency [Time Frame: Baseline (8-week period before randomization), maintenance period (week 7 to 18) of the core phase (18 weeks)]
  - Response rate (% pts with ≥50% of reduction from baseline in weekly seizure frequency)
  - Median percentage reduction in seizure frequency during maintenance period
- **Secondary endpoints:** % of seizure-free pts, response rate at ≥ 25% of reduction, impact on behavior and quality of life (and more).
Filamin A (FLNA) upregulation in patients and mouse models

Humans

- Enlarged diseased cells

Our mouse model

- Zhang, Bordey, 2014, 2020
Target validation:
*Flna* shRNA in utero prevents brain malformations and seizures

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

Mean seizure number/day

![Graph showing mean seizure number/day](image-url)
Animal POC in Yale Model
Small molecule FLNA modulator reduces seizures and cell enlargement

**Neonatal treatment**

Mean seizure number/day

- Vehicle
- Drug 12mg/kg

**Adult treatment**

Mean seizure number/day

- Vehicle
- Drug 12mg/kg

Seizure number (week3) /Mouse /day

1 mouse per row

5 consecutive days

Zhang, Bordey, 2020
NT-001: clinical candidate binds FLNA and rescues cell morphology

- Predictions of NT-001 (yellow) docking sites on FLNA Ig24 (dimer, purple).
- The green outlines represents the amino acids (VAKGL) where the validated FLNA modulator binds.
- MW: 317 g/mol

IP Status: Yale patent appl. filed for targeting FLNA for epilepsy treatment by NT-001
Proposed NT-001 mouse in vivo efficacy studies will enable our IND application

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

Clinical endpoints
- 4 months dosing safety
- MRI
- Monitor daily seizures
- Change in seizure frequency

Genetically-Defined Patient Population
$210K to Confirm Clinical Candidate → ~18 months to pre-IND Meeting

Now

- Target validation
  - shRNA
  - Small Molecule
- IP & Oral/BBB (in progress)
- Clinical collaboration
- Animal model in place
- Clinical endpoints established

15-20 months

Blavatnik Support Deliverables Part 2:
- Preliminary Formulation
- Preliminary PK/BBB ($60K)

20-22 months

File IND for Dr. Anderson led Phase 1b/2a of NT-001

34 months

Analysis of clinical response to NT-001

26 months

Interim indication of efficacy

Blavatnik Support Deliverables Part 1:
- PK data in mouse oral delivery ($30K)
- Confirmation of BBB via oral route ($30K)
- PanLabs preliminary tox microsomal stability mouse and human ($30K)
- 2x CRO reproduction via oral delivery using Yale Model ($120K; 8-10wks)

✓ Commercial Interest:
  - Numerous confidential meetings with biotechs and several VC’s
    - All satisfied with Yale model
    - All waiting for in vivo results with NT-001

Partnering

Interim indication of efficacy
Back-ups/References/links
Filamin A (FLNA) upregulation in patients and mouse models

Humans
Diseased cells  FLNA  Nuclei

Our mouse model

![FLNA and GAPDH Western Blots](image)

- Relative FLNA
  - Contra
  - Ipsilateral

- Pairwise comparison
  - Contra vs. Ipsilateral
  - P-value: 0.0377
Animal POC Yale Model
Small molecule FLNA modulator reduces seizures and cell enlargement

Neonatal treatment P8-61
Seizures/day

Adult treatment P29-54
Seizures/day

Zhang, Bordey, 2020

Animal model: generated by the Bordey lab (Hsieh, Bordey, 2016; Nguyen, Bordey, 2019)