December 7, 2022

The Promise of FTD Research Trials: What Should I Know About Current Drug Studies?

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BLUEFIELD
PROJECT

Current interventional trials in genetic & sporadic FTD

FTD-GRN (Progranulin)

- Latozinemab (AL001), Phase 3, Alector/GSK
- PR006, Phase 1/2, Prevail Therapeutics/Eli Lilly
- PBFT02, Phase 1/2, Passage Bio
- TAK-459/DNL359, Phase 1/2, Denali Therapeutics/Takeda
- AVB-101, Phase 1/2, AviadoBio *(not yet recruiting)*

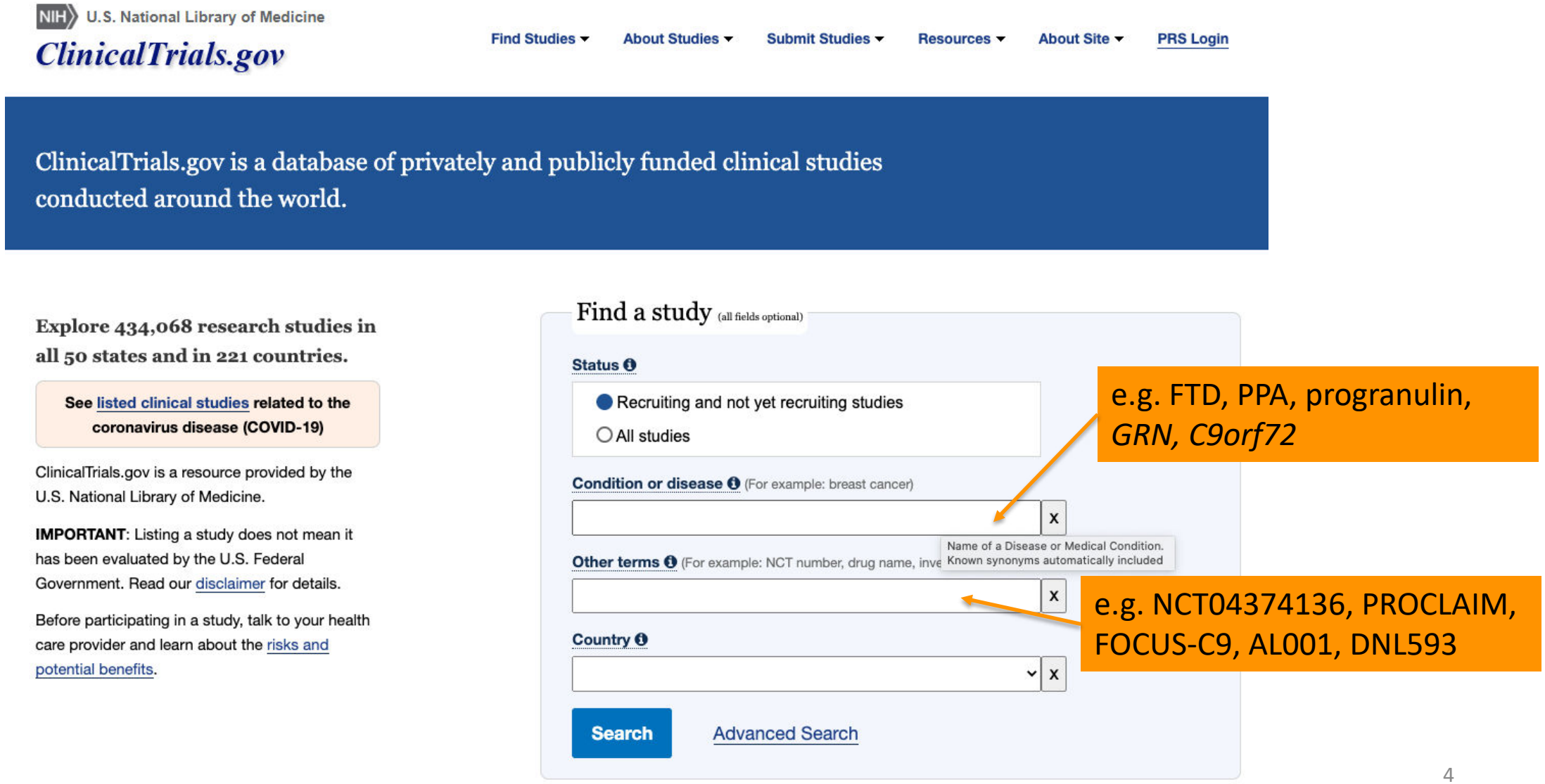
FTD-C9orf72

- WVE-004, Phase 1/2, Wave Life Sciences
- TPN-101, Phase 2, Transposon Therapeutics

Sporadic FTD

- NIO752, Phase 1, Novartis
- Verdiperstat, Phase 1, Investigator-sponsored
- Oxytocin, Phase 2, Lawson Health Research Institute
- Low-dose lithium, Phase 2, Columbia University

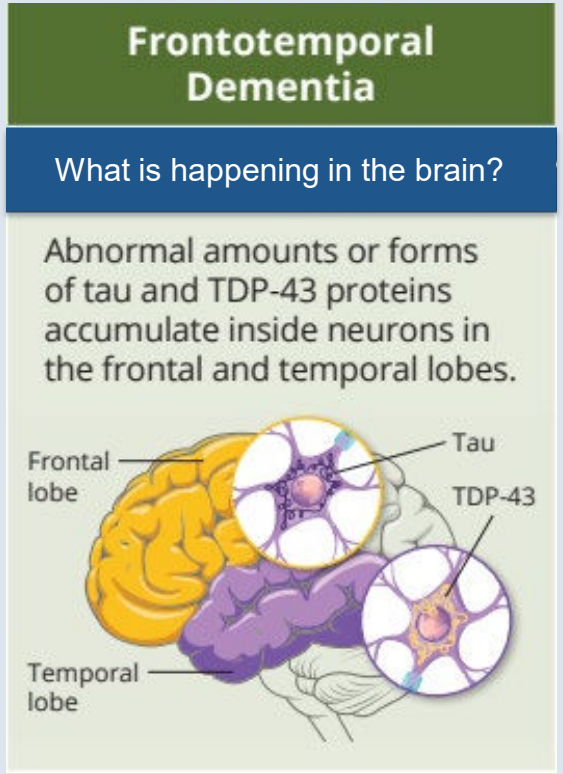
ClinicalTrials.gov is a searchable database of clinical studies conducted in the US and around the world



Explanation of the template to describe each clinical trial:

Sponsor:	**The entity running the trial, usually a company or a university**
Development Stage	Phase 1, 2 or 3 in the process for FDA approval (+ trial name)
ClinicalTrials.gov identifier:	Enter this number at **www.clinicaltrials.gov** to see the specific details of the trial
Enrollment criteria:	Criteria that interested individuals must meet in order to qualify to participate in the trial
Experimental drug:	The name of the experimental drug
Delivery method:	How the experimental drug will be administered to the participant (by mouth, injection, infusion, etc.)
Placebo-controlled?:	Will some participants receive a placebo instead of the experimental drug?
Length of trial:	How long participants will be monitored
Locations:	Countries where clinical trial sites are planned or actively recruiting participants
How to contact:	Phone number and website to contact the sponsor

Explanation of how the experimental drug targets processes that have led to FTD



Adapted from the National Institute on Aging

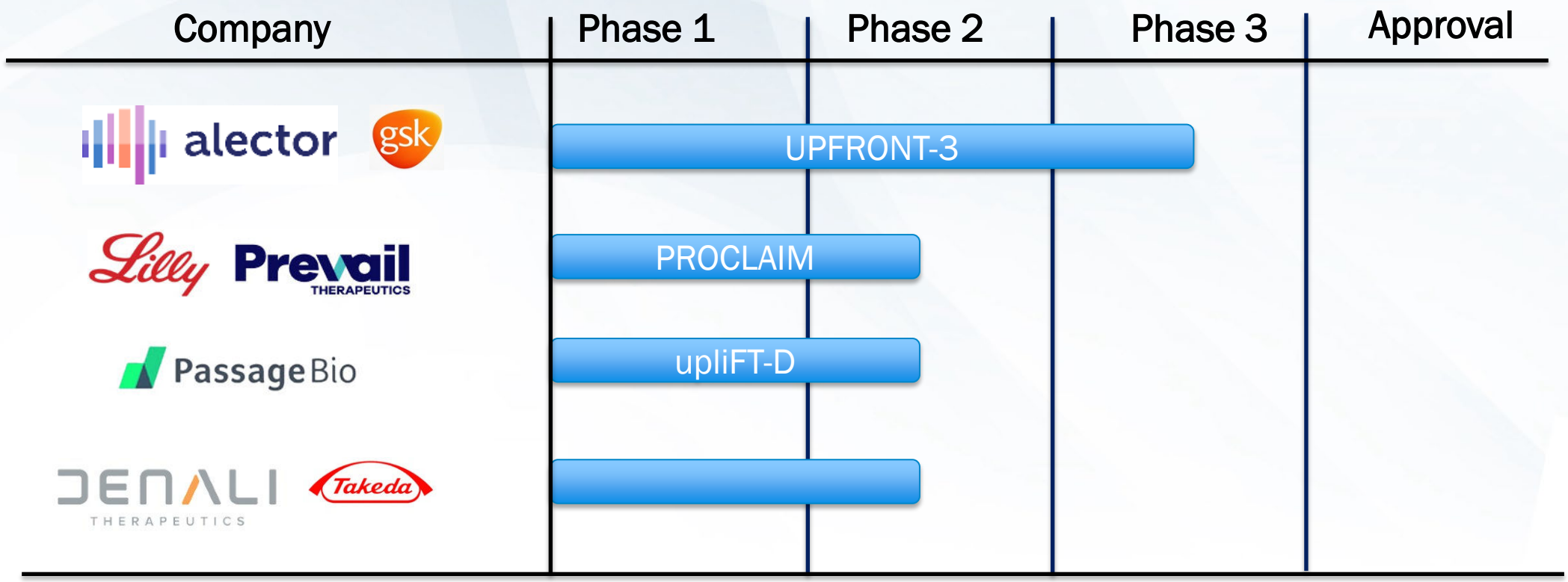
All of these trials require participants to know they carry a mutation in progranulin in order to enroll

Current clinical trials for FTD caused by mutations in progranulin (*GRN*)

- **INFRONT-3**
  - Latozinemab (AL001), Phase 3, Alector/GSK (Antibody)
- **PROCLAIM**
  - PR006, Phase 1/2, Prevail Therapeutics/Eli Lilly (Gene replacement)
- **upliFT-D**
  - PBFT02, Phase 1/2, Passage Bio (Gene replacement)
- **TAK-594/DNL593**, Phase 1/2, Denali Therapeutics/Takeda (Protein replacement)

- **AVB-101**, Phase 1/2, AviadoBio *(not yet recruiting)* (Gene replacement)

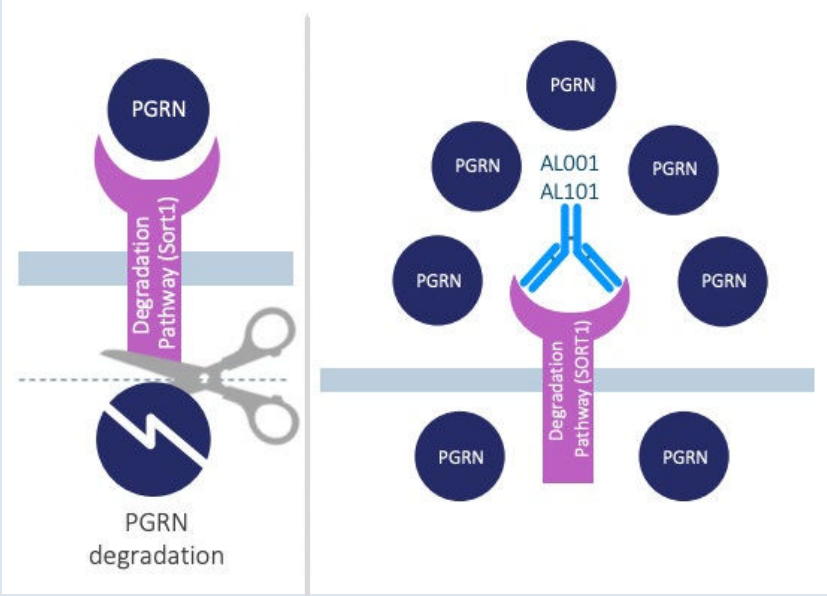
Four experimental therapies for FTD-GRN are currently in clinical trials



Not listed above: A Phase 1/2 trial of AVB-101 from AviadoBio is expected to start soon

Sponsor:	**Alector Therapeutics** alector.com / Partnered with Glaxo Smith Kline
Development Stage	Phase 3 (INFRONT-3)
ClinicalTrials.gov identifier:	NCT04374136
Enrollment criteria:	Known *GRN* mutation carrier • May be **asymptomatic** • If **symptomatic**, must have one or more of the criteria for the diagnosis of possible behavioral variant FTD, or a diagnosis of Primary Progressive Aphasia
Experimental drug:	Latozinemab (AL001)
Delivery method:	Intravenous (IV) infusion every 4 weeks
Placebo-controlled:	Yes
Length of trial:	Up to 96 weeks, with optional open label extension
Locations:	54 sites in the US, Canada, Australia, Argentina, Europe and Western Asia
How to contact:	650-826-2454; clinicaltrials@alector.com

Latozinemab (AL001) increases progranulin levels by blocking progranulin degradation



Progranulin is degraded in cells as part of its life cycle

Latozinemab increases the half-life of progranulin by blocking sortilin, a degradation receptor, in order to restore progranulin to normal levels

From Alector's November 2022 corporate presentation

Sponsor: **Prevail Therapeutics**
prevailtherapeutics.com / A subsidiary of Eli Lilly and Co.

Development Stage Phase 1/2 (PROCLAIM)

ClinicalTrials.gov identifier: NCT04408625

Enrollment criteria: Known *GRN* mutation carrier
- Must have a clinical diagnosis of FTD

Experimental drug: PR006

Delivery method: Single intra-cisterna magna injection

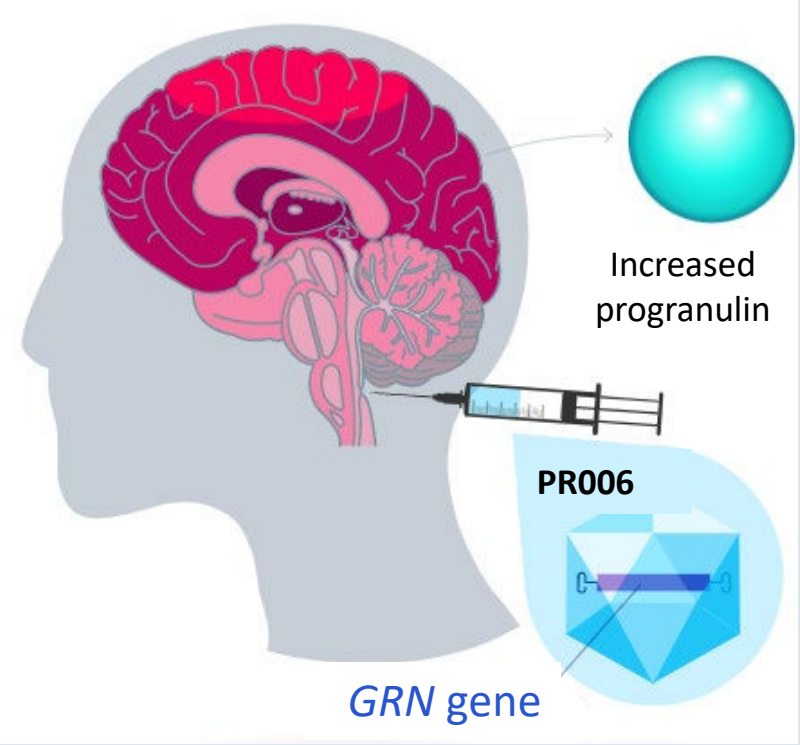
Placebo-controlled: No

Length of trial: 12 months plus 4 years long term follow-up (5 years total)

Locations: 7 sites in the US, Australia, Belgium, Spain and the United Kingdom

How to contact: 917-336-9310; prevail_patients@lilly.com

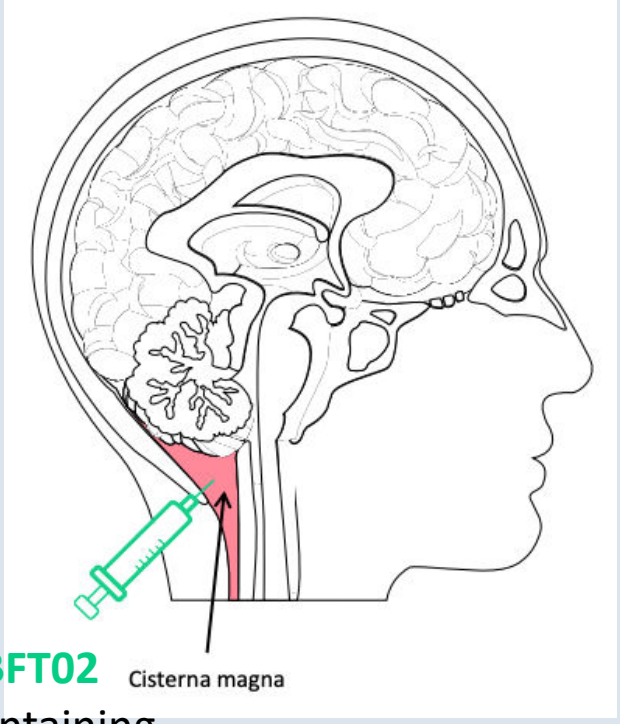
PR006 increases progranulin levels by delivering a healthy *GRN* gene into the brain



Adapted from prevailtherapeutics.com

Sponsor:	**Passage Bio** passagebio.com
Development Stage	Phase 1/2 (upliFT-D)
ClinicalTrials.gov identifier:	NCT04747431
Enrollment criteria:	Known *GRN* mutation carrier • Must have a clinical diagnosis of FTD
Experimental drug:	PBFT02
Delivery method:	Single intra-cisterna magna injection
Placebo-controlled:	No
Length of trial:	24 months plus 4 years long-term follow-up (5 years total)
Locations:	9 sites in the US, Canada, Brazil, Italy, Portugal and the United Kingdom
How to contact:	267-866-0113; patientservices@passagebio.com

PBFT02 increases progranulin levels by delivering a healthy *GRN* gene into the brain



PBFT02 containing healthy *GRN* gene

From Passage's November 2022 corporate presentation

Sponsor: **Denali Therapeutics**
denalitherapeutics.com /partnered with Takeda

Development Stage Phase 1/2

ClinicalTrials.gov identifier: NCT05262023

Enrollment criteria: Known *GRN* mutation carrier
- Must have a clinical diagnosis of FTD

Experimental drug: TAK-594/DNL593

Delivery method: Intravenous (IV) infusion

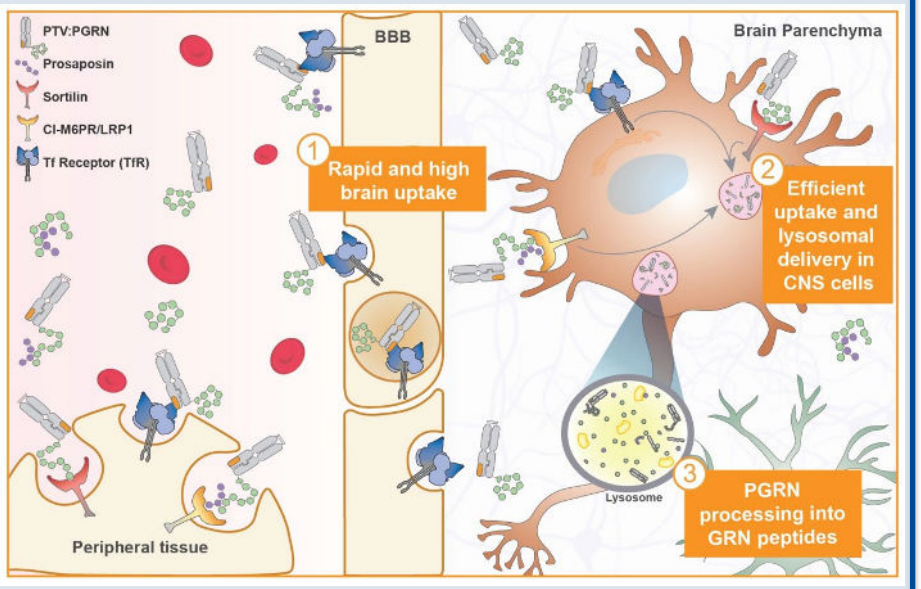
Placebo-controlled: Yes

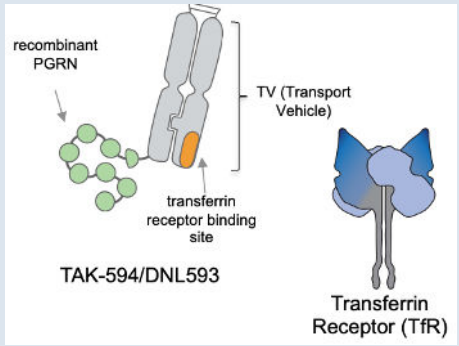
Length of trial: 6 months, with optional 18 month open-label extension

Locations: 4 sites in Spain, with more to be added (not yet in US)

How to contact: patients@dnli.com

TAK-594/DNL593 increases progranulin levels by delivering the progranulin protein across the blood brain barrier





From Denali's November 2022 FPI presentation

Both of these trials require participants to know they carry a *C9orf72* expansion in order to enroll

Current clinical trials for FTD and ALS caused by expansions in *C9orf72*

- **FOCUS-C9**
  - WVE-004, Phase 1/2, Wave Life Sciences (Antisense oligonucleotide)
- **TPN-101**, Phase 2, Transposon Therapeutics (Small molecule)

- **Latozinemab (AL001),** Phase 2, Alector/GSK *(no longer recruiting)*
- **LAM-002A**, Phase 2 , AI Therapeutics (*no longer recruiting*)

Sponsor: **Wave Life Sciences**
wavelifesciences.com

Development Stage Phase 1/2 (FOCUS-C9)

ClinicalTrials.gov identifier: NCT04931862

Enrollment criteria: Must have GGGGCC [G4C2] repeat expansion in the first intronic region of the *C9orf72* gene and be:

- Diagnosed with FTD, or
- Diagnosed with ALS, or
- Diagnosed with mixed phenotype (FTD and ALS)

Experimental drug: WVE-004

Delivery method: Intrathecal (IT) infusion every 4 weeks

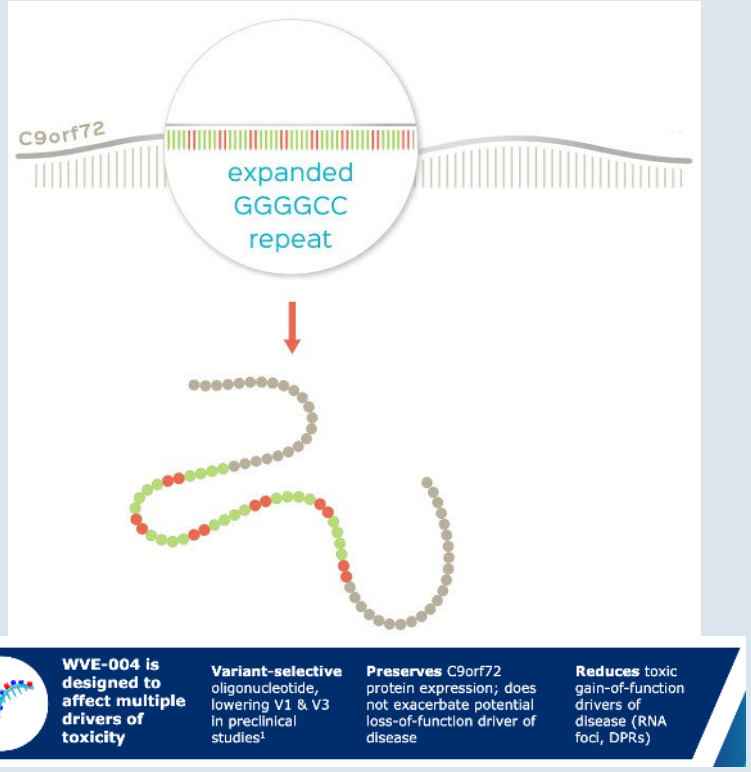
Placebo-controlled: Yes

Length of trial: 24 weeks

Locations: 17 sites in Canada, Australia, New Zealand and Europe (not yet in US)

How to contact: 855-215-4687; clinicaltrials@wavelifesci.com

WVE-004 selectively blocks the mutant *C9orf72* gene from making harmful proteins



From wavelifesciences.com

Sponsor: **Transposon Therapeutics**
transposonrx.com

Development Stage Phase 2

ClinicalTrials.gov identifier: NCT04993755

Enrollment criteria: Hexanucleotide repeat expansion in *C9orf72* gene, and

- Diagnosed with FTD, or
- Diagnosed with ALS, or
- Diagnosed with mixed phenotype (FTD and ALS)

Experimental drug: TPN-101

Delivery method: Capsule, taken once daily by mouth

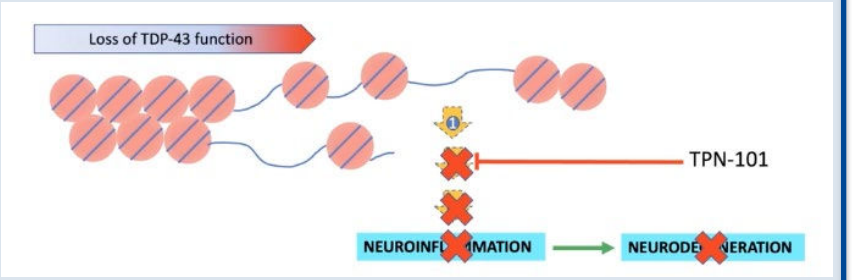
Placebo-controlled: Yes

Length of trial: 24 weeks, with a 24 wk open label extension

Locations: 19 sites in US and Europe

How to contact: 310-261-5312; clinicaltrials@transposonrx.com

TPN-101 blocks disease-causing production of the LINE-1 gene



Loss of nuclear TDP-43 during FTD leads to **harmful LINE-1 expression**.

Preclinical evidence shows blocking LINE-1 production with **TPN-101 mitigates neurotoxic pathology.**

From May 6, 2022 NEALS webinar, "A Phase 2a Study of TPN-101 in Patients with C9ORF72 ALS/FTD"

There are currently no treatment trials **specifically for FTD caused by mutations in *MAPT***, but efforts for future trials are in development

Current clinical trials for sporadic (i.e. non-genetic) FTD

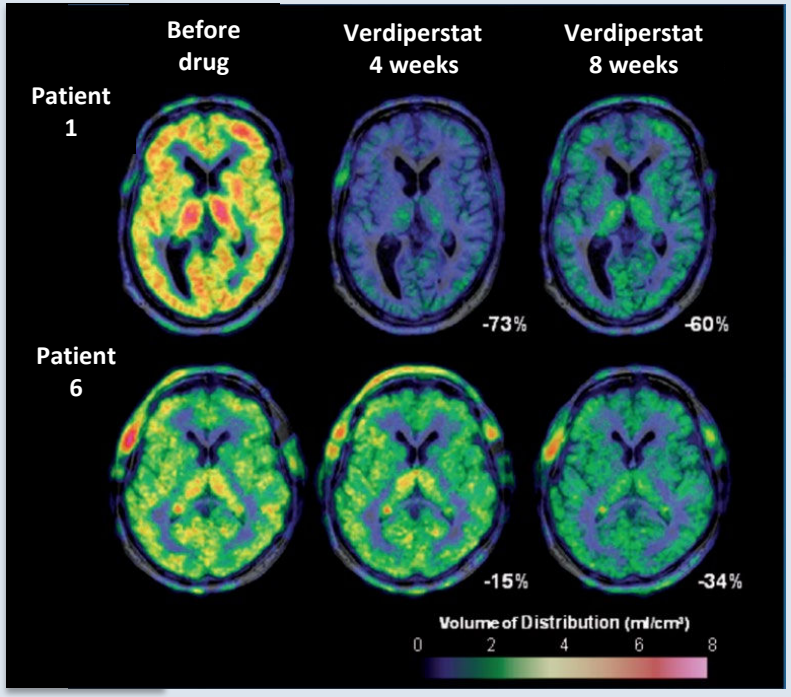
- **PSP**
  - NIO752, Phase 1, Novartis (Antisense oligonucleotide)
- **Semantic dementia**
  - Verdiperstat, Phase 1, Investigator-sponsored (Small molecule)
- **FTD**
  - Oxytocin, Phase 2, Lawson Health Research Institute (Hormone nasal spray)
- **bvFTD or sv-PPA or nfv-PPA with behavior**
  - Low-dose lithium, Phase 2, Columbia University (Small molecule)

Sponsor:	**Novartis** https://www.recruiting-trials.novartis.com/clinicaltrials/study/nct04539041
Development Stage	Phase 1
ClinicalTrials.gov identifier:	NCT04539041
Enrollment criteria:	PSP diagnosed for less than 5 years with a current classification of probable PSP Richardson syndrome, a progressive supranuclear palsy rating scale (PSPRS) score < 40 and MOCA score >17 at screening
Experimental drug:	NIO752
Delivery method:	Intrathecal (IT) infusion 4x over 3 months
Placebo-controlled:	Yes
Length of trial:	12 months
Locations:	12 sites in the US, Canada, Germany and the UK
How to contact:	888-669-6682; novartis.email@novartis.com

NIO752 is an antisense oligonucleotide that reduces production of tau (*MAPT*) protein.

Sponsor:	**University of California, San Francisco** Dr. Peter Ljubenkov
Development Stage	Phase 1
ClinicalTrials.gov identifier:	NCT05184569
Enrollment criteria:	Diagnosed with semantic dementia (semantic variant primary progressive aphasia, svPPA)
Experimental drug:	Verdiperstat
Delivery method:	Tablet, taken twice daily by mouth
Placebo-controlled:	Yes
Length of trial:	24 weeks
Locations:	1 site at University of California, San Francisco (additional sites in US to open shortly)
How to contact:	415-514-5745; taylor.sulse@ucsf.edu 415-476-0661; mary.koestler@ucsf.edu

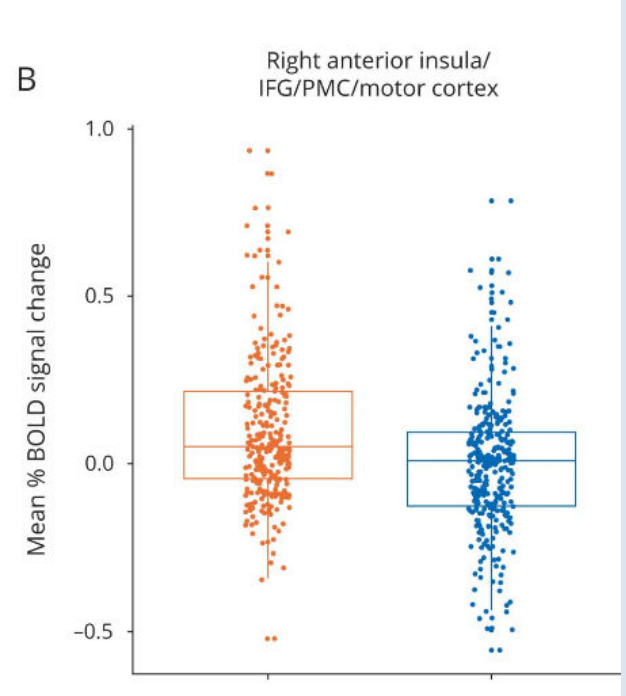
Verdiperstat irreversibly inhibits myeloperoxidase to reduce neuroinflammation



Jucaite, A. *et al.* Effect of the myeloperoxidase inhibitor AZD3241 on microglia: a PET study in Parkinson's disease. *Brain* **138**, 2687–2700 (2015).

Sponsor:	**Lawson Health Research Institute** Dr. Elizabeth Finger
Development Stage	Phase 2
ClinicalTrials.gov identifier:	NCT03260920
Enrollment criteria:	Diagnosis of FTD
Drug:	Syntocinon (Oxytocin)
Delivery method:	Intranasal spray
Placebo-controlled:	Yes
Length of trial:	20 weeks
Locations:	11 sites in Canada and the US
How to contact:	Contact individual sites as listed on clinicaltrials.gov or on ftdregistry.org

Oxytocin increases neural activity in brain areas associated with emotions and empathy



Oliver, L. D. *et al.* Neural effects of oxytocin and mimicry in frontotemporal dementia: A randomized crossover study. *Neurology* **95**, e2635–e2647 (2020).

Sponsor:	**Columbia University** Dr. Ted Huey
Development Stage	Phase 2
ClinicalTrials.gov identifier:	NCT02862210
Enrollment criteria:	Diagnosed with bvFTD or sv-PPA or nfv-PPA with behavior
Drug:	Low-dose lithium
Delivery method:	Tablet, taken 1-4x daily depending on dose
Placebo-controlled:	Yes
Length of trial:	12 weeks
Locations:	1 site at Columbia University
How to contact:	212-304-7943; cs4125@cumc.columbia.edu 212-305-1134; edh2126@columbia.edu

Lithium carbonate will be compared to placebo in the treatment of agitation, aggression, and inappropriate repetitive behaviors in people diagnosed with FTD.

Stay informed about clinical research via the FTD Disorders Registry

www.ftdregistry.org

Thank you!

Contact me at laura.mitic@bluefieldproject.org

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