# Update on the INFRONT-2 Phase 2 Study of AL001 in Frontotemporal Dementia Patients Carrying a Granulin Mutation (FTD-*GRN*)

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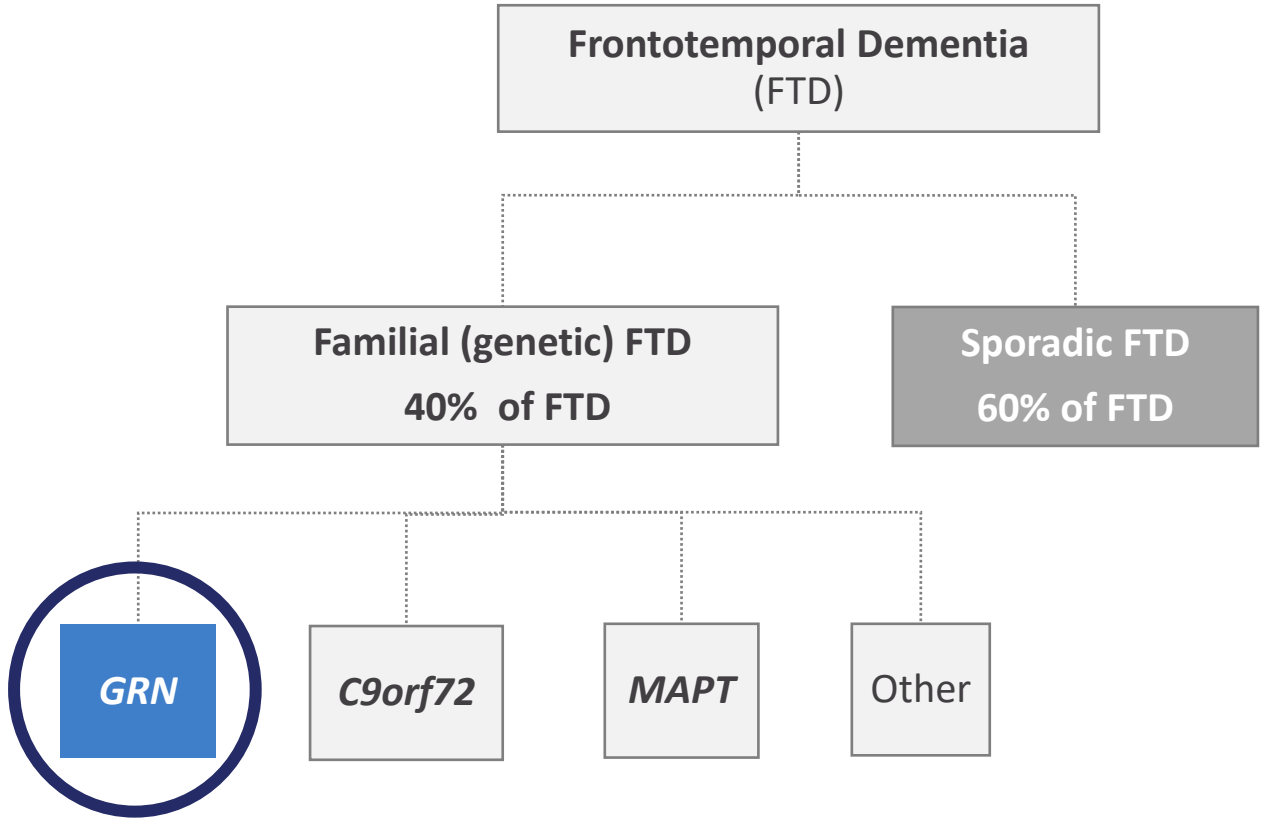
All authors are equity stakeholders in Alector, Inc and/or employees of Alector, LLC

# Frontotemporal dementia is a rapidly progressive form of dementia with no approved treatment

- Most common form of dementia under age 60
- Patients present with compulsive behavior, lack of restraint, apathy, anxiety, and aphasia
- Life expectancy after diagnosis is 7 - 10 years
- Estimated 170,000 FTD patients in U.S. and E.U
- 15,000 symptomatic patients with *GRN* mutations (FTD-*GRN*) in the U.S. and E.U.

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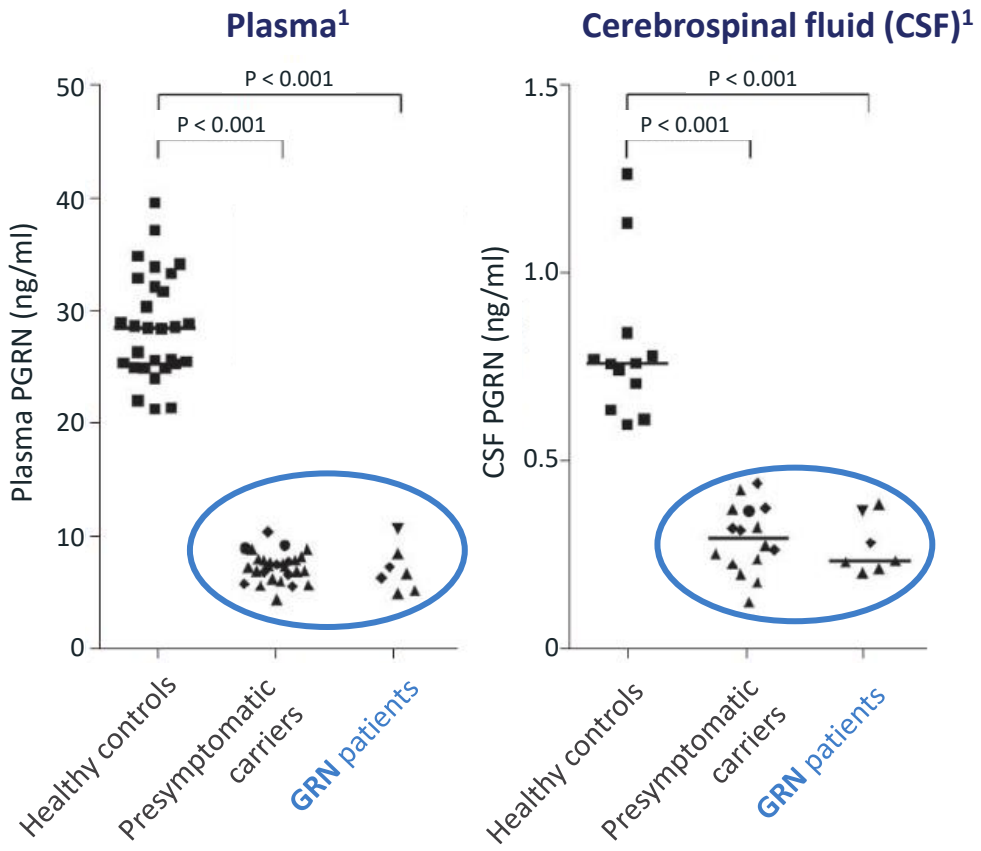
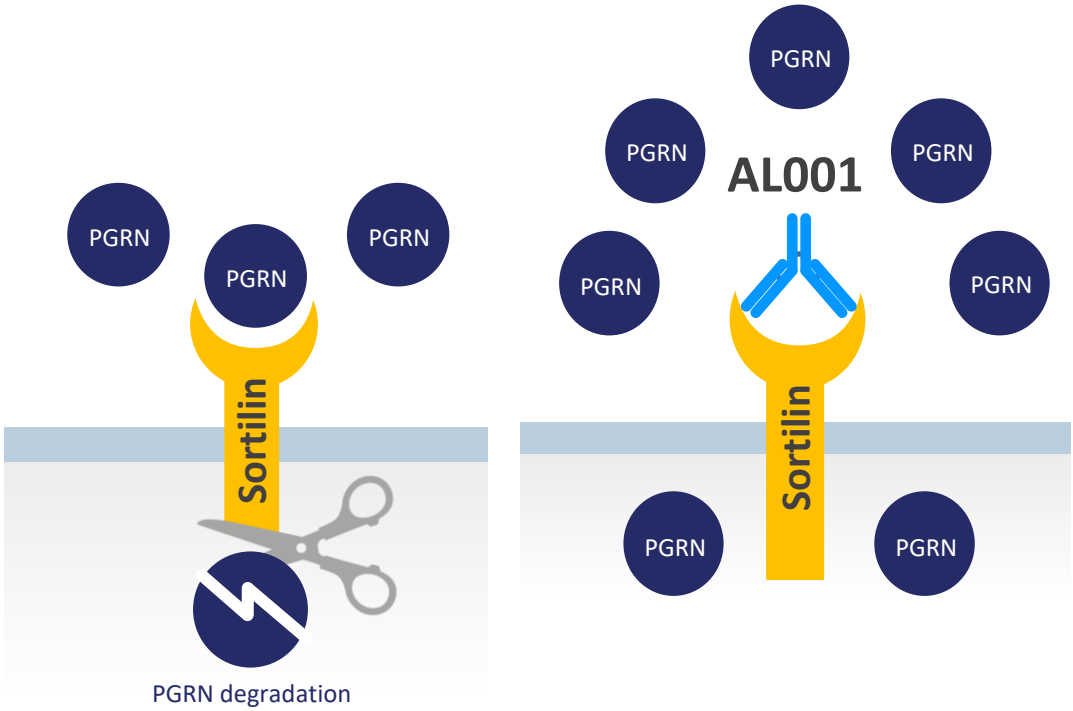
# AL001 increases PGRN levels by blocking sortilin-mediated PGRN degradation

## Heterozygous *GRN* mutations lead to >50% decrease in PGRN levels and is causal for FTD

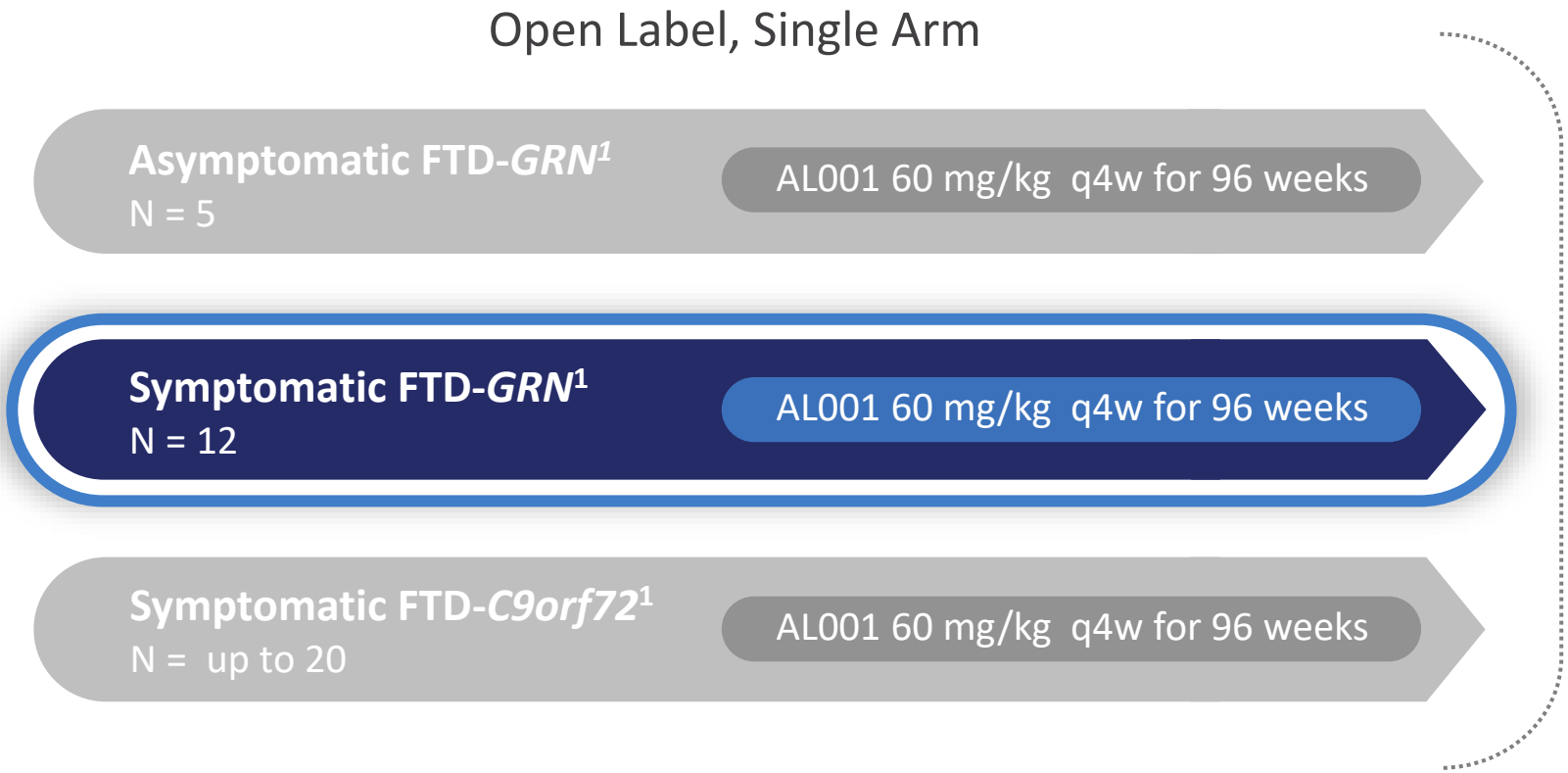



## AL001 increases the half-life of PGRN by blocking sortilin




1. Meeter et al. Dement Geriatr Cogn Disord Extra 2016;6:330-340

# INFRONT-2 Phase 2 is an open-label study evaluating three different FTD patient cohorts




**Primary Endpoint:**

- Safety and tolerability

**Secondary Endpoints:**

- PK, PD

**Exploratory Endpoints:**

- CSF and plasma biomarkers
- Volumetric MRI (vMRI)
- Clinical Outcome Assessment (CDR® plus NACC FTLD-SB[2])

**Twelve-month biomarker and clinical data presented today is from symptomatic FTD-*GRN* cohort**

1. Asymptomatic and Symptomatic FTD-*GRN* enrollment closed; FTD-*C9orf72* cohort currently enrolling
2. CDR® plus NACC FTLD-SB: Clinical Dementia Rating (CDR) dementia staging instrument plus National Alzheimer's Coordinating Center (NACC) behavior and language domains frontotemporal lobar degeneration (FTLD) sum of boxes (SB)

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# AL001 is well tolerated in INFRONT-2 FTD patients treated for a median duration of 12 months

| | aFTD-*GRN* (N=5) n (%) | FTD-*GRN* (N=12) n (%) | FTD-*C9orf72* (N=10) n (%) | Total (N=27) n (%) |
|---|---|---|---|---|
| Any TEAE | 5 (100) | 11 (92) | 9 (90) | 25 (93) |
| Any treatment-related TEAE | 1 (20) | 2 (17) | 8 (80) | 11 (41) |
| Any SAE[1] | 0 | 3 (25) | 0 | 3 (11) |
| Any treatment-related SAE | 0 | 0 | 0 | 0 |
| Any TEAE leading to study drug discontinuation | 0 | 0 | 0 | 0 |

1. SAEs observed in study: Deep venous thrombosis, syncope, pneumothorax
Data cut: Electronic data capture extraction Sep 2, 2021
TEAE = treatment emergent adverse event; SAE = serious adverse event

# AL001 impacts key markers of the disease cascade in symptomatic FTD-*GRN* patients

## Key biomarkers and clinical outcome assessments reflect underlying disease activity in FTD-*GRN* patients

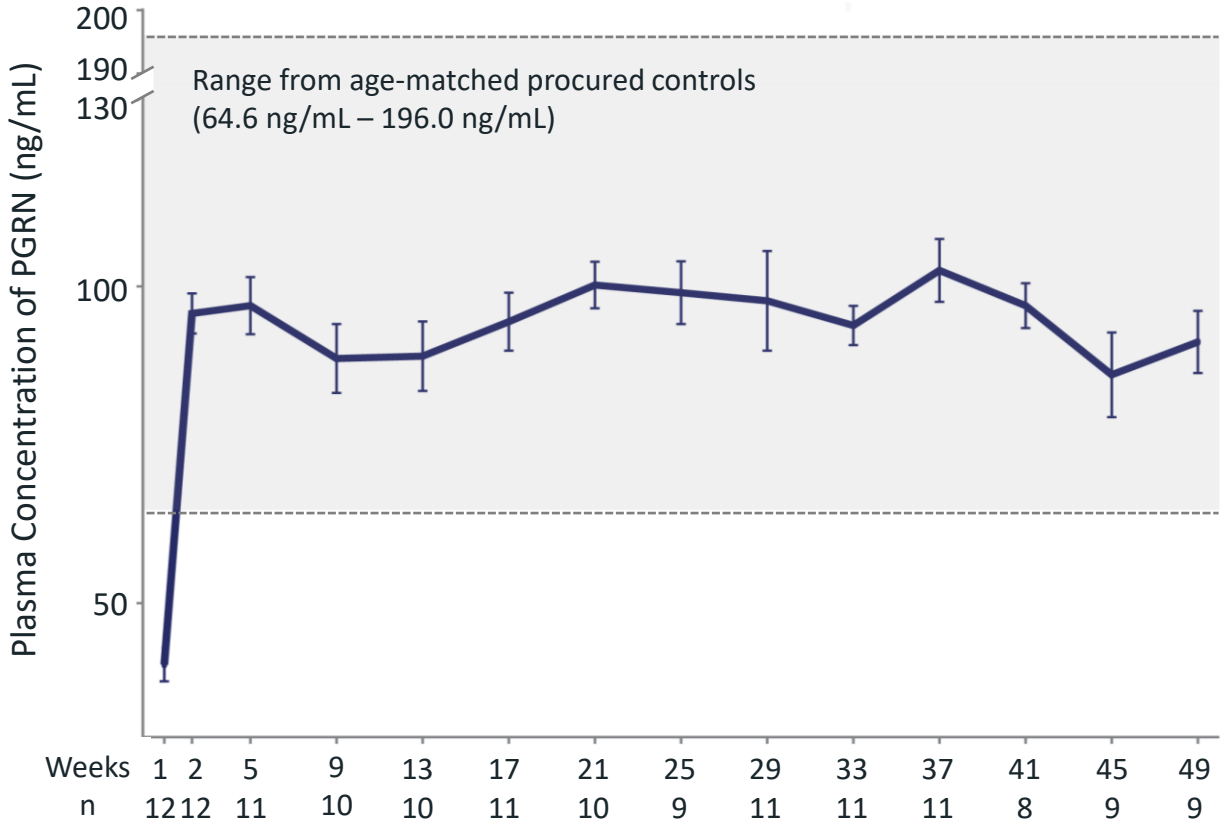
| TARGET ENGAGEMENT | BIOMARKERS OF DISEASE ACTIVITY | | | | CLINICAL BENEFIT |
|---|---|---|---|---|---|
| PGRN (plasma and CSF) | Lysosomal dysfunction | Complement activation | Astrogliosis | Neuronal health | Clinical Outcome Assessments |
| **PGRN** | **e.g. CTSD, LAMP1** | **e.g. C1QB** | **GFAP** | **NfL** | **CDR® plus NACC FTLD-SB** |
| > 50% reduction in PGRN levels causal for FTD | Dysfunctional lysosomes are hallmark of FTD-*GRN* | Pathological increases in complement proteins in FTD correlate with cognitive decline | GFAP is increased in conditions characterized by astrogliosis | NfL is a measure of axonal damage | FDA approvable endpoint for measuring clinical decline in FTD |

CTSD = cathepsin D; LAMP1 = lysosomal associated membrane protein 1; C1QB = complement C1q B chain; GFAP = glial fibrillary acidic protein NfL = neurofilament light chain; CDR® plus NACC FTLD-SB: Clinical Dementia Rating (CDR) dementia staging instrument plus National Alzheimer's Coordinating Center (NACC) behavior and language domains frontotemporal lobar degeneration (FTLD) sum of boxes (SB)

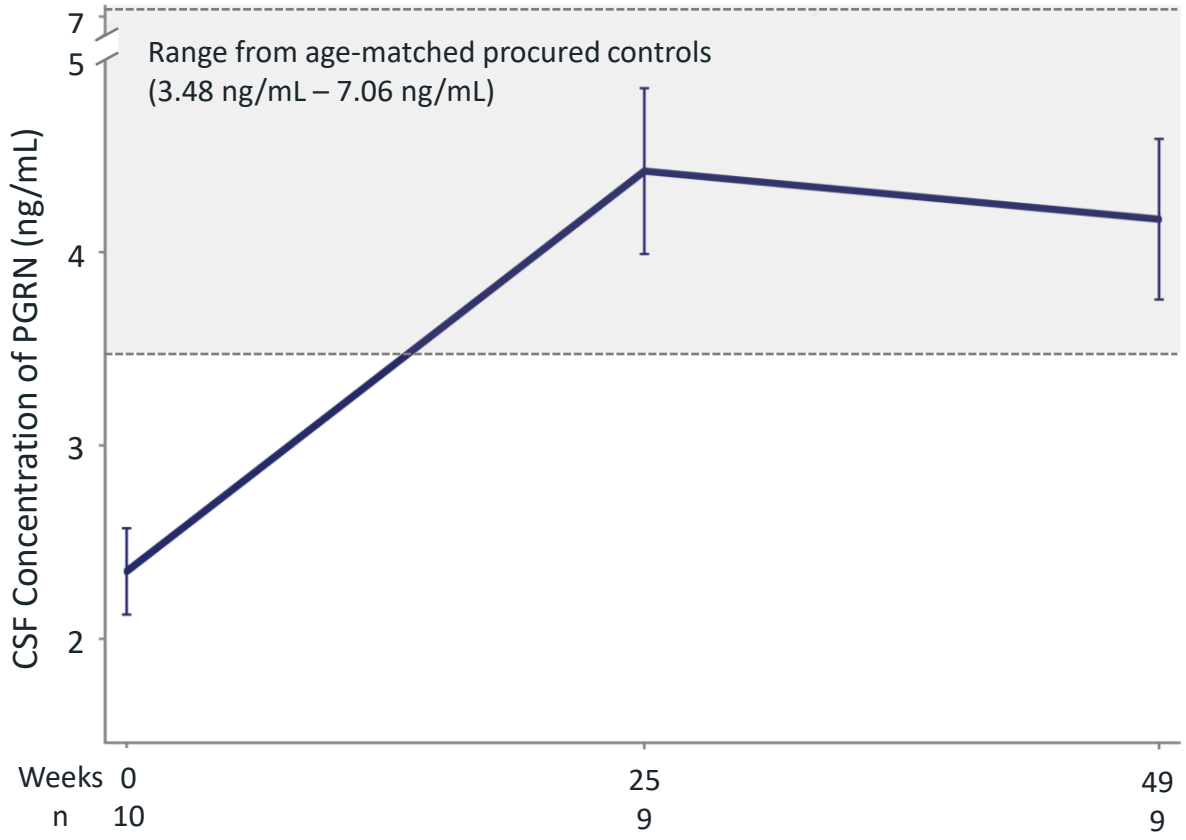
# INFRONT-2: AL001 restores PGRN in plasma and CSF to normal levels throughout 12 months of treatment

## TARGET ENGAGEMENT

### PGRN plasma concentration




### PGRN CSF concentration

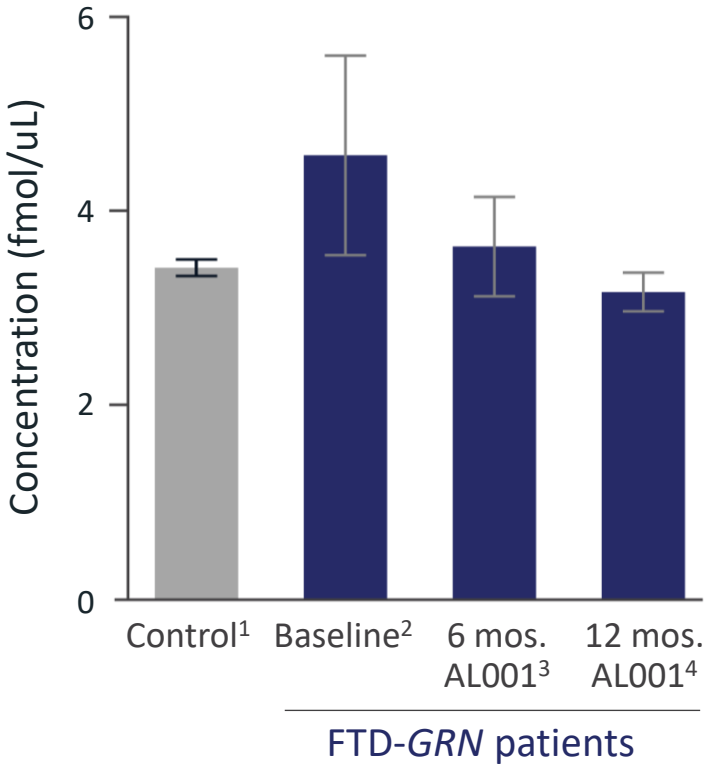



Data cut-off June 15, 2021
Mean +/- SEM

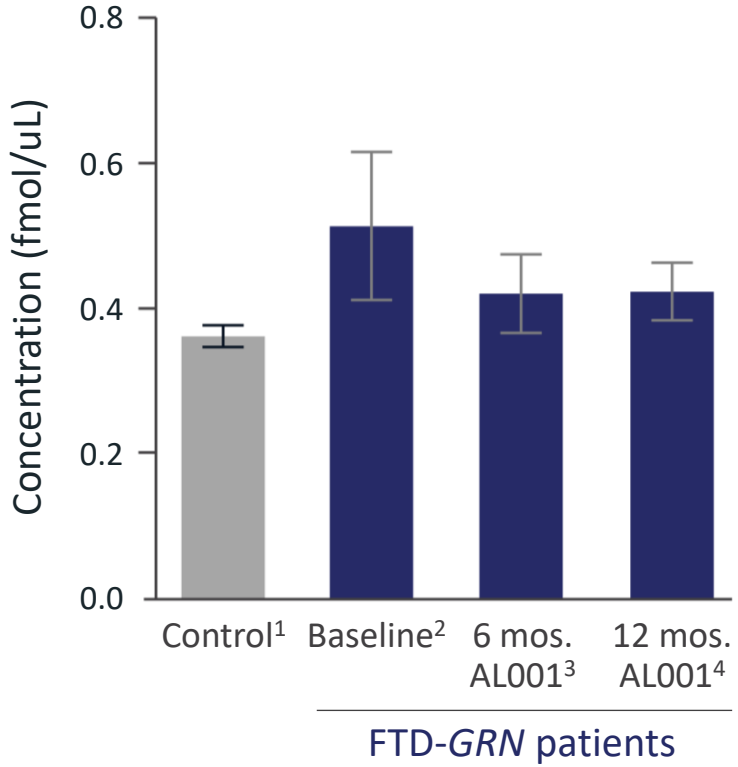
# INFRONT-2: AL001 treatment normalizes lysosomal and complement biomarkers in CSF

## BIOMARKERS OF DISEASE ACTIVITY

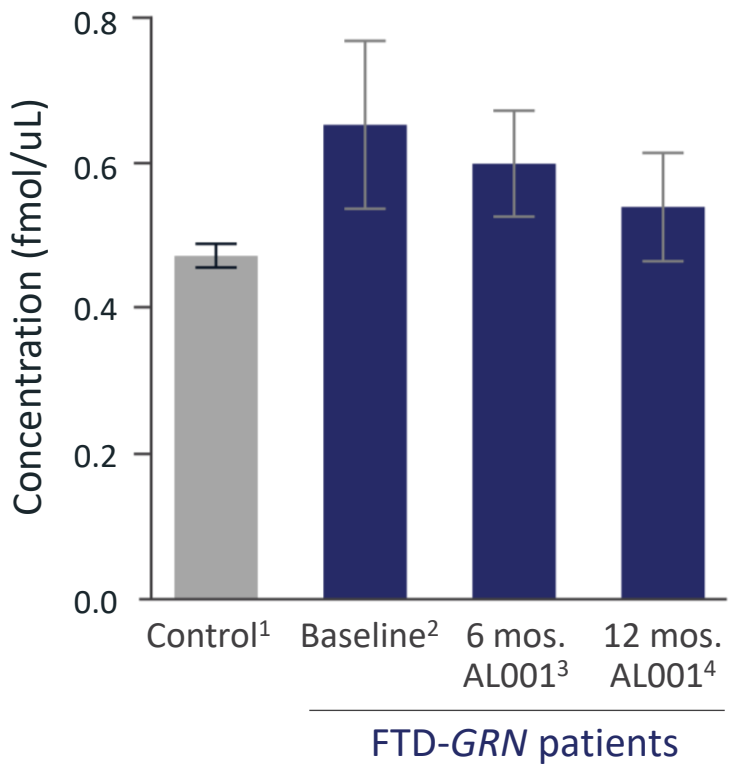
### Lysosomal dysfunction - CTSD




### Lysosomal dysfunction - LAMP1




### Complement activation - C1QB




CTSD = cathepsin D; LAMP1 = lysosomal associated membrane protein 1; C1QB = complement C1q B chain
Mean +/- SEM; Data cut-off June 15, 2021 Only FTD-*GRN* participants with baseline and post-treatment data are included

1. Age-matched procured control samples (N = 44)
2. N = 11
3. N = 9
4. N = 10

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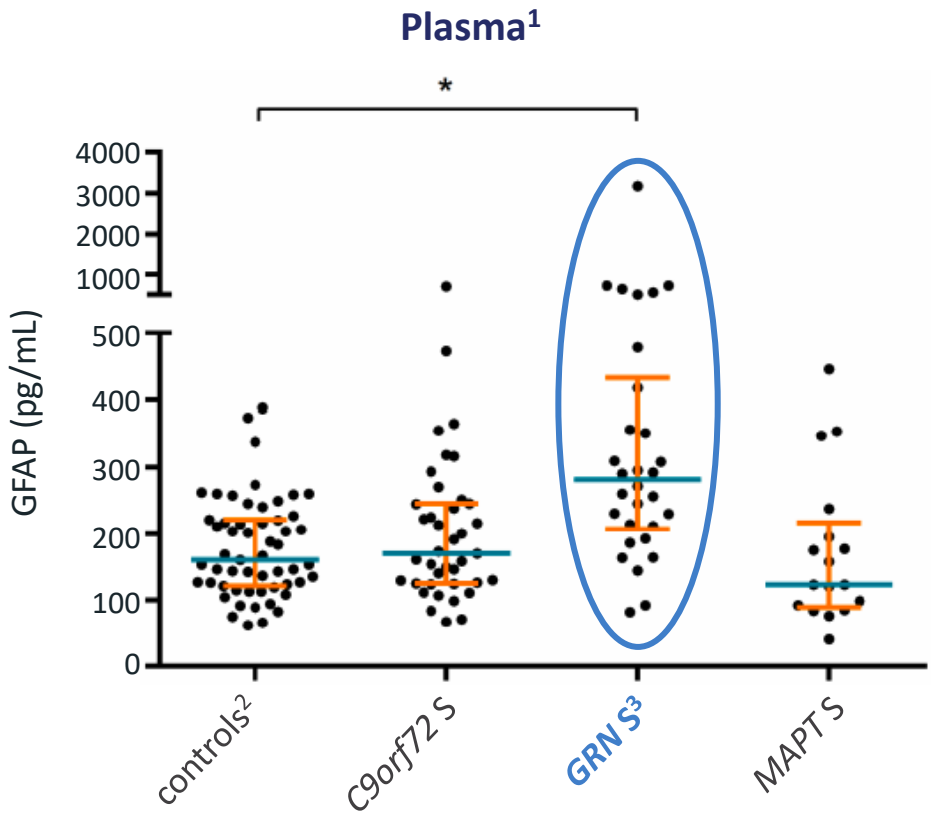
# GFAP is a marker of astrogliosis and is elevated in symptomatic FTD-*GRN* patients



- Astrocytes are the most abundant cell type in the adult CNS and execute vital functions in the maintenance and homeostasis of the CNS
- GFAP is a major component of the astrocytic cytoskeleton and serves as a marker of astrogliosis
- GFAP is elevated in symptomatic FTD-*GRN* patients compared to age-matched controls[1]
- Higher levels of GFAP at baseline are correlated with faster rates of atrophy in the temporal lobe of symptomatic FTD-*GRN* patients[1]



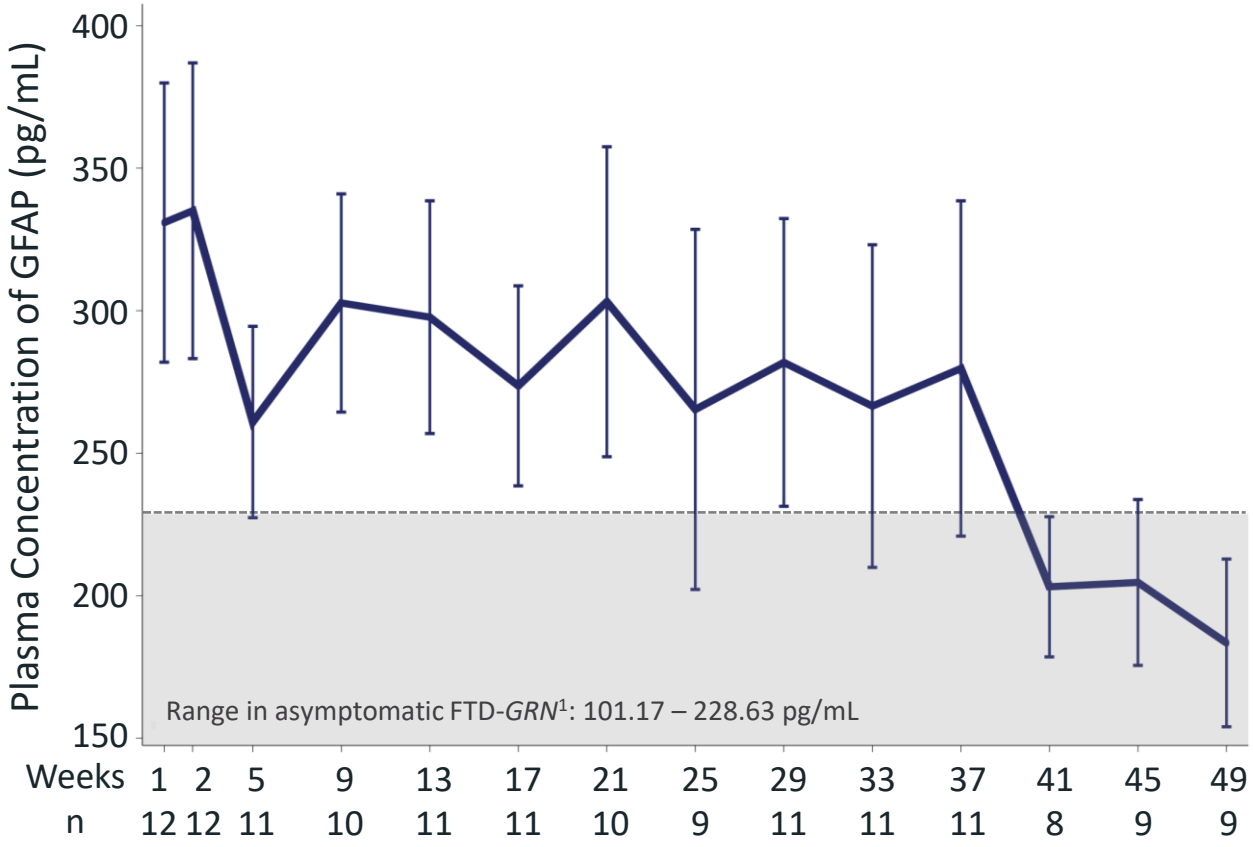

1. Heller et al. J. Neurol Neurosurg Psychiatry 2020; 91:263-270
2. Age-matched controls median GFAP (interquartile range): 160.4 (121.5 - 221.3) pg/mL
3. GRN S median GFAP (interquartile range): 281.2 (211.5 - 417.8) pg/mL

CNS = central nervous system; S = symptomatic; * = significant differences

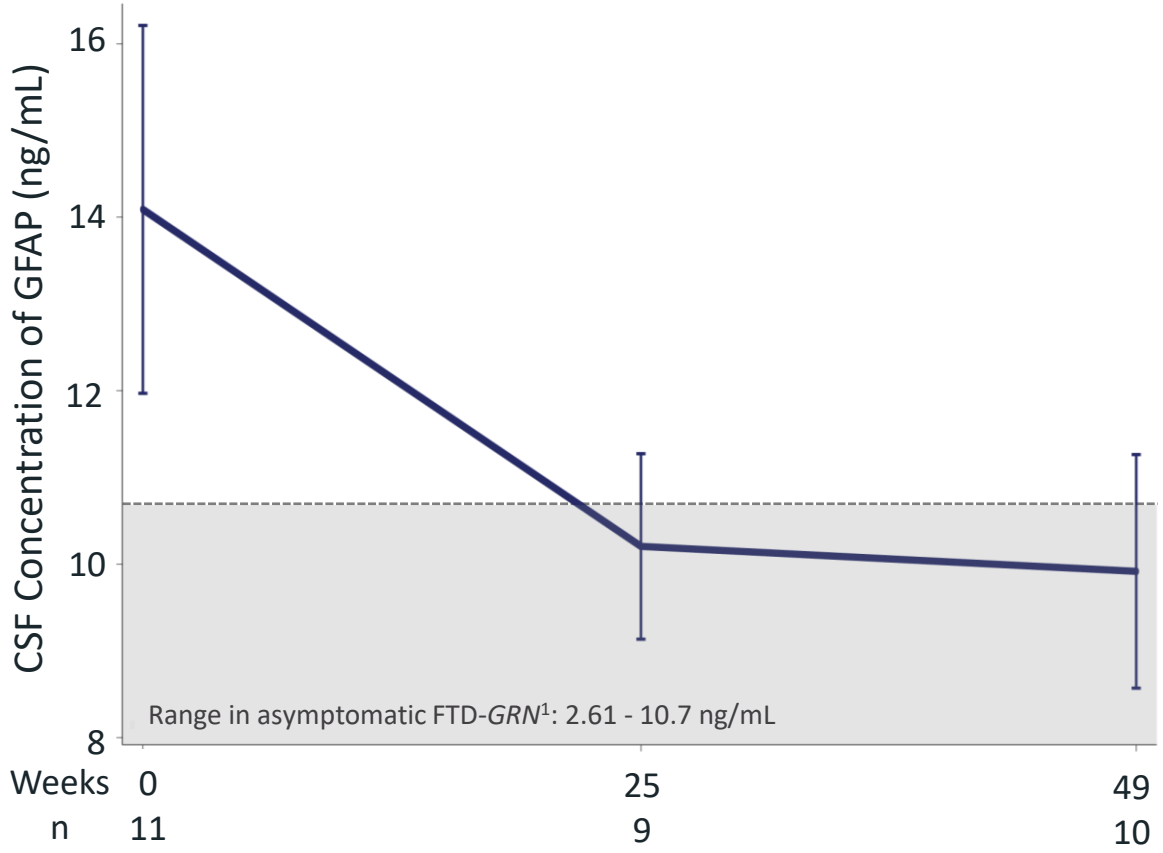
# INFRONT-2: AL001 treatment decreases GFAP levels towards normal levels in plasma and CSF of FTD-*GRN* patients suggesting a reduction in astrogliosis

BIOMARKERS OF DISEASE ACTIVITY – ASTROGLIOSIS

## GFAP Plasma Concentration




## GFAP CSF Concentration



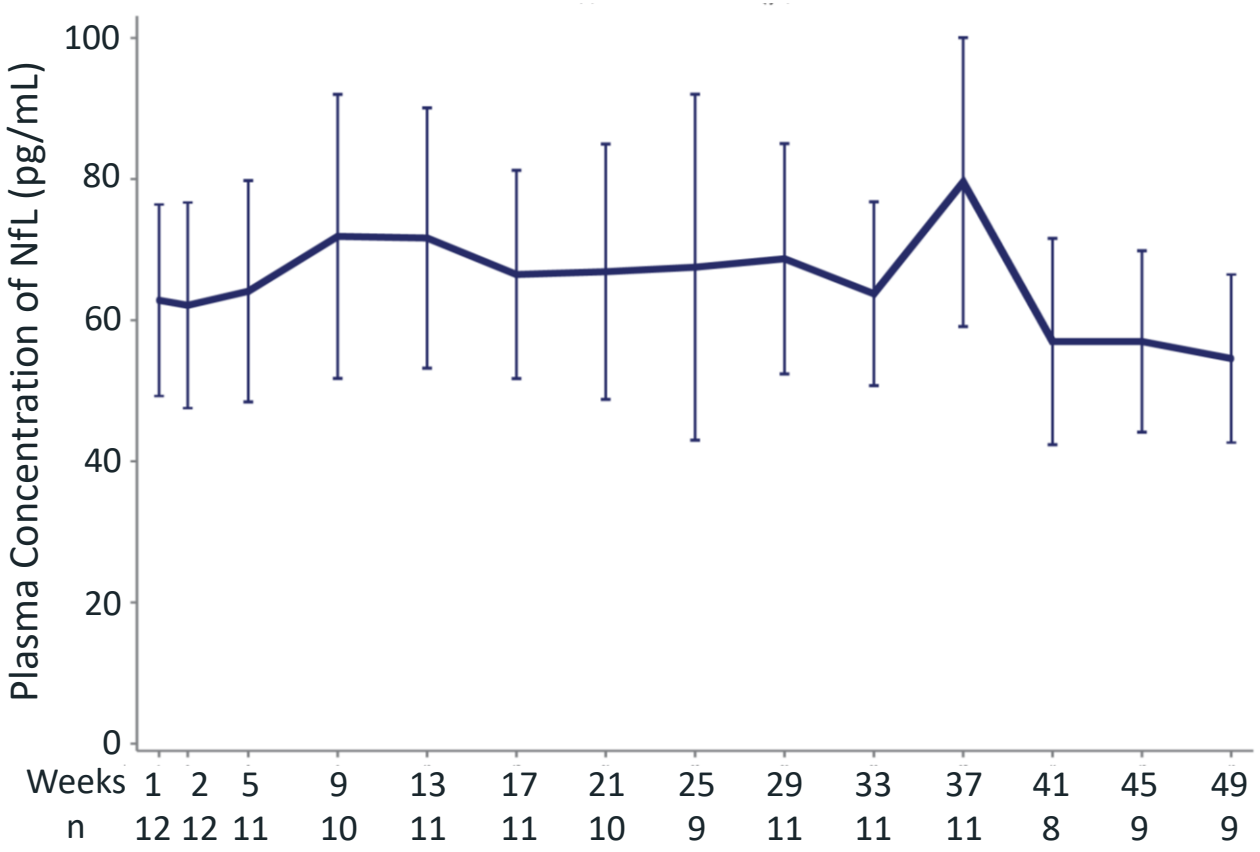

Data cut-off June 15, 2021
Mean +/- SEM

1. Range is of baseline GFAP levels in asymptomatic FTD-*GRN* patients enrolled in INFRONT-2

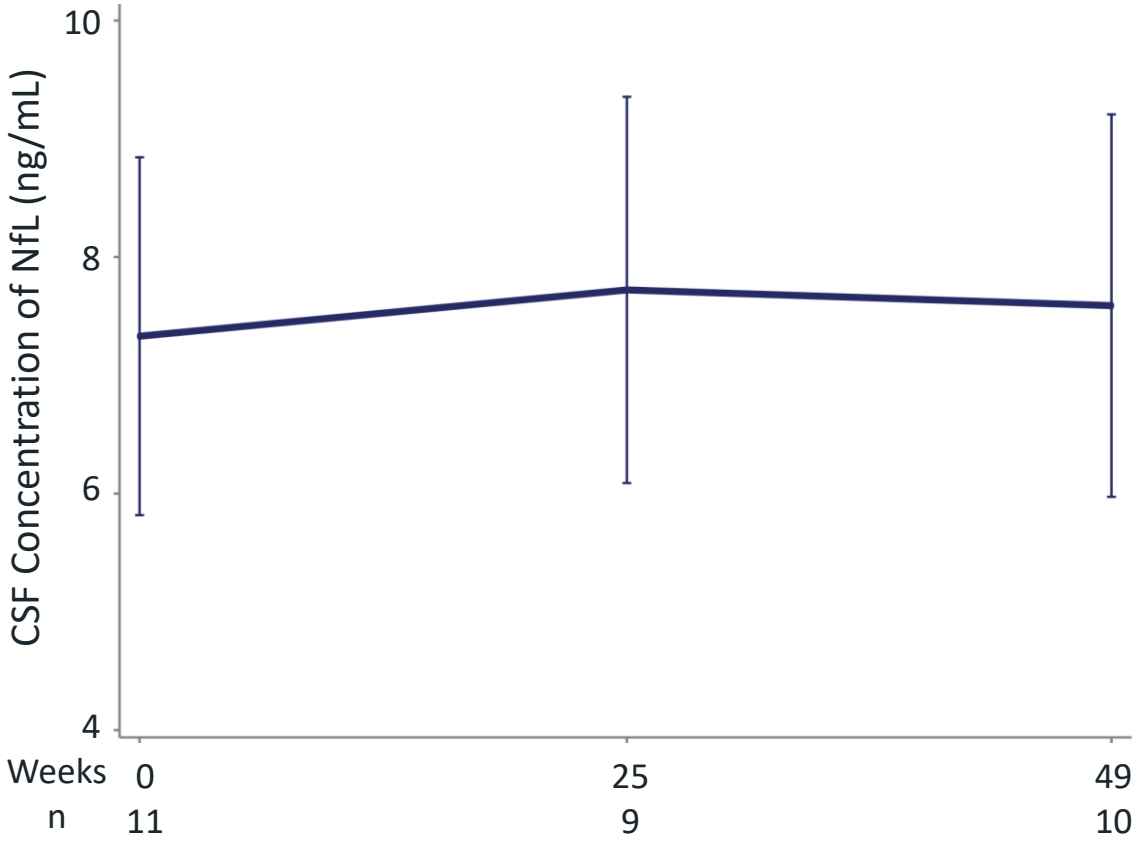
# INFRONT-2: NfL levels in plasma and CSF are stable over 12 months in AL001-treated FTD-*GRN* patients

BIOMARKERS OF DISEASE ACTIVITY – NEURONAL HEALTH

## NfL Plasma Concentration




## NfL CSF Concentration

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Data cut-off June 15, 2021
Mean +/- SEM

# Contextualizing INFRONT-2 clinical results with GENFI2 matched controls

- INFRONT-2 clinical results compared against comparable, GENFI2 matched controls
- Comparable baseline characteristics established between INFRONT-2 FTD-*GRN* symptomatic cohort and GENFI2 controls in two-steps:
  - Propensity score matching[1] based on CDR® plus NACC FTLD-SB at baseline
  - Matching refined by age, gender, baseline plasma NfL levels, and FTD disease variant at baseline[2]

| Baseline characteristics | | INFRONT-2 (N=12) | GENFI2 Matched Controls (N=10) |
|---|---|---|---|
| **CDR® plus NACC FTLD-SB** | **Mean (SD)** | **5.9 (3.74)** | **5.2 (3.60)** |
| | **Min, Max** | **0.5, 11** | **0.5, 11.5** |
| **AGE (Years)** | Mean (SD) | 63.2 (9.71) | 62.1 (6.74) |
| | Min, Max | 49, 79 | 52, 72 |
| **GENDER** | Male | 8 (67%) | 3 (30%) |
| **PLASMA NfL (pg/mL)** | N | 12 | 9 |
| | Mean (SD) | 62.8 (47.00) | 40.3 (27.28) |
| | Min, Max | 11.2, 148.8 | 9.3, 99.9 |
| **FTD DISEASE VARIANT** | bvFTD | 5 (42%) | 5 (50%) |
| | PPA | 3 (25%) | 3 (30%) |
| | Both | 3 (25%) | 0 |
| | Other | 1 (8%) | 1 (10%) |

GENFI = The Genetic Frontotemporal Initiative
GENFI2 refers to the longitudinal FTD registry dataset
1. Propensity score matching is a well-established statistical method intended to mimic randomization
2. Clinical reviewers blinded to outcome data

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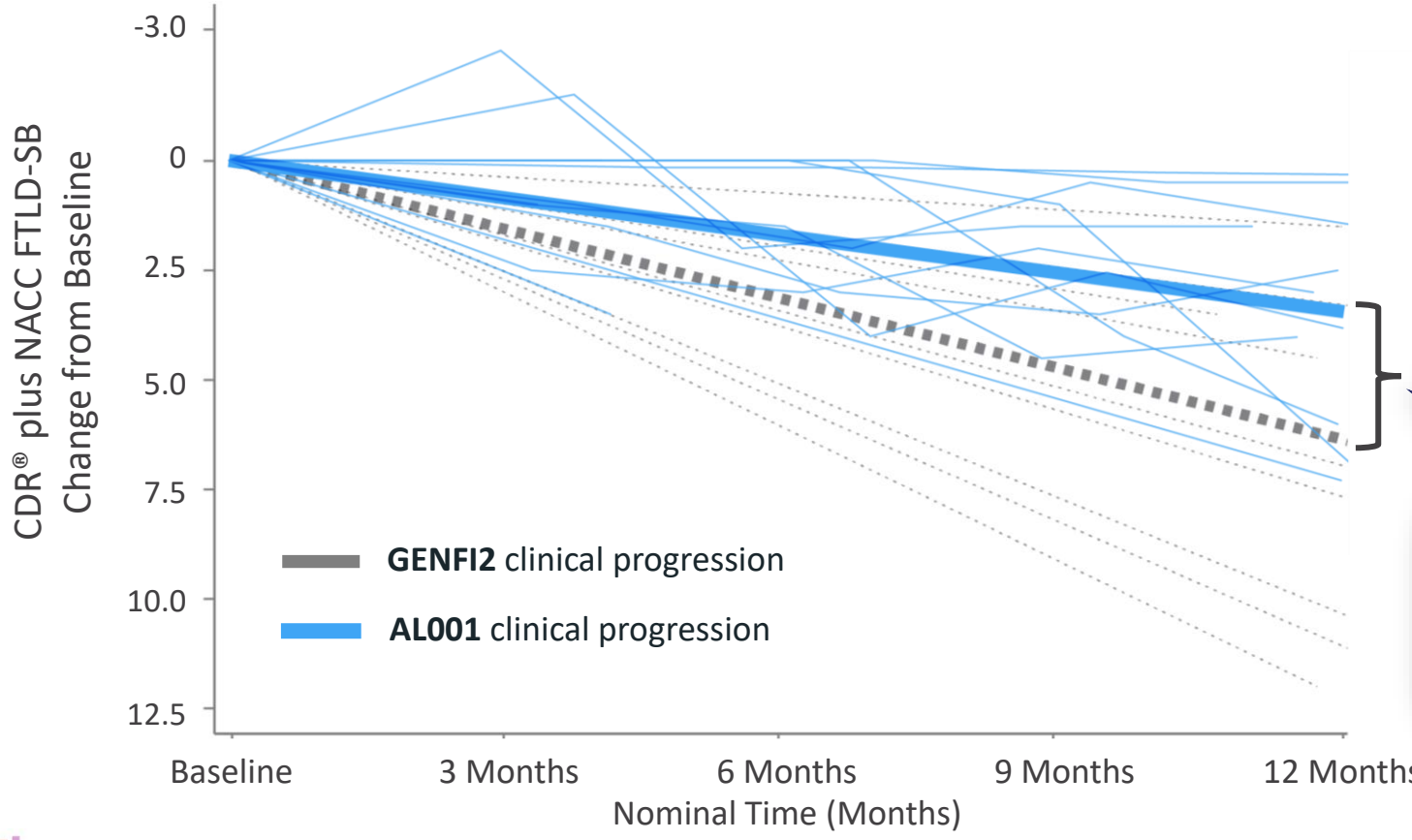
# Treatment with AL001 showed a slowing of clinical progression in AL001-treated patients relative to matched GENFI2 controls

## CLINICAL BENEFIT

**CDR® plus NACC FTLD-SB**




| Parameter | Estimate[1] | 95% CI |
|---|---|---|
| Annual Change in **GENFI2** (n=10) | 6.4 | [4.35,8.42] |
| Annual Change in **AL001** (n=12) | 3.3 | [1.38,5.28] |
| **Difference in Annual Change (GENFI2 – AL001)** | **3.1** | **[0.24,5.88]** |

**~48%**
slowing of clinical progression
(3.1 point change)

1. Random Coefficient Model with Repeated Measurements including baseline & all available post-baseline measurements up to 12 months
Data cut-off Sep 8, 2021

# Summary

- AL001 treatment is well tolerated in FTD-*GRN* patients treated for a median duration of 12 months
- AL001 treatment rapidly restored PGRN to normal levels in FTD-*GRN* patients for the entire duration of treatment
- AL001 treatment demonstrated consistent effects on disease biomarkers in FTD-*GRN* patients over 12 months including:
  - Persistent trends toward normalization of lysosomal and complement biomarkers
  - Decreased GFAP levels towards normal levels in plasma and CSF
  - Stable NfL levels in plasma and CSF
- AL001 treatment in FTD-*GRN* patients slowed clinical progression by ~48% as measured by CDR® plus NACC FTLD-SB compared with GENFI2 matched controls
- A global, randomized Phase 3 pivotal clinical trial of AL001 in FTD-*GRN* using CDR® plus NACC FTLD-SB as a primary endpoint is actively enrolling (NCT04374136)

# Acknowledgements

We thank all participants and their families without whom this and future studies would not be possible, and the INFRONT investigators and sites

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GENFI | ALLFTD | Bluefield Project | UCSF

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# Thank you