July 2021

# AAIC 2021 Reference Slides for AL001 Phase 2 INFRONT-2 study results

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# Results to be presented at AAIC on July 29, 2021

## 12-month data in up to 12 symptomatic FTD-*GRN* patients and 10 GENFI2-matched historical controls


**Primary endpoint**

- Safety and tolerability in symptomatic FTD-*GRN* patients

**Secondary endpoint**

- Progranulin level changes in plasma and cerebrospinal fluid (CSF)

**Exploratory endpoints**

- Changes in biomarkers of lysosomal dysfunction, complement activation and neuronal health at 12 months
  - PGRN levels, CTSD and LAMP1, C1QB, Nfl
- Changes in volumetric MRI
- Changes in CDR® plus NACC-FTD-SB cognitive scale at 12 months

# Creating a matched historical control cohort to contextualize clinical outcome assessments from the INFRONT-2 Phase 2 study in symptomatic FTD-*GRN* patients

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# Approximating the effects of randomization using propensity score matching

Propensity score matching is an established statistical technique to construct a synthetic control group by matching treated subjects with non-treated subjects of similar characteristics to more accurately estimate the effect of a treatment.

**Example use case: Assessing causal inference between taking aspirin and mortality benefit**

Before Matching: p values suggest marked imbalance between treated and untreated groups

Baseline Characteristics According to Aspirin Use (before matching)

| Variable | Aspirin* (n = 2310) | No Aspirin* (n = 3864) | P value |
|---|---|---|---|
| Age, years | 62 (11) | 56 (12) | < .001 |
| Body mass index, kg/m² | 29 (5) | 30 (7) | < .001 |
| Ejection fraction, % | 50 (9) | 53 (7) | < .001 |
| Resting heart rate, beats/min | 74 (13) | 79 (14) | < .001 |
| Resting systolic BP, mm Hg | 141 (21) | 138 (20) | < .001 |
| Resting diastolic BP, mm Hg | 85 (11) | 86 (11) | .04 |
| Heart rate recovery, beats/min | 28 (11) | 30 (12) | < .001 |
| Peak exercise cap., men (METs) | 8.6 (2.4) | 9.1 (2.6) | < .001 |
| Peak exercise capacity, women | 6.6 (2.0) | 7.3 (2.1) | < .001 |

*Cells contain mean (SD)

Baseline Characteristics By Aspirin Use (in %) (before matching)

| Variable | Aspirin (n = 2310) | No Aspirin (n = 3864) | P value |
|---|---|---|---|
| Men | 77.0 | 56.1 | < .001 |
| Clinical history: diabetes | 16.8 | 11.2 | < .001 |
| hypertension | 53.0 | 40.6 | < .001 |
| prior coronary artery disease | 69.7 | 20.1 | < .001 |
| congestive heart failure | 5.5 | 4.6 | .12 |
| Medication use: Beta-blocker | 35.1 | 14.2 | < .001 |
| ACE inhibitor | 13.0 | 11.4 | < .001 |

- Baseline characteristics appear very dissimilar: 25 of 31 covariates have p < .001, 28 of 31 have p < .05.
- Aspirin user covariates indicate higher mortality risk.

- Hazard Ratio (time to death) = 1.08 (95% CL: 0.85 – 1.39)
- Conclusion: aspirin **does not reduce** mortality risk

After Matching: *p* values suggest comparability between treated and untreated groups allowing a more accurate estimate of treatment benefit

Baseline Characteristics According to Aspirin Use (after matching)

| Variable | Aspirin* (n = 1351) | No Aspirin* (n = 1351) | P value |
|---|---|---|---|
| Age, years | 60 (11) | 61 (11) | .16 |
| Body mass index, kg/m² | 29 (6) | 29 (6) | .83 |
| Ejection fraction, % | 51 (8) | 51 (9) | .65 |
| Resting heart rate, beats/min | 77 (13) | 76 (14) | .13 |
| Resting systolic BP, mm Hg | 141 (21) | 141 (21) | .68 |
| Resting diastolic BP, mm Hg | 85 (11) | 86 (11) | .57 |
| Heart rate recovery, beats/min | 28 (12) | 28 (11) | .82 |
| Peak exercise cap., men (METs) | 8.7 (2.5) | 8.3 (2.5) | .01 |
| Peak exercise capacity, women | 6.5 (2.0) | 6.7 (2.0) | .13 |

*Cells contain mean (SD)

Baseline Characteristics By Aspirin Use [%] (after matching)

| Variable | Aspirin (n = 1351) | No Aspirin (n = 1351) | P value |
|---|---|---|---|
| Men | 70.4 | 72.1 | .33 |
| Clinical history: diabetes | 15.0 | 15.3 | .83 |
| hypertension | 50.3 | 51.7 | .46 |
| prior coronary artery disease | 48.3 | 48.8 | .79 |
| congestive heart failure | 5.8 | 6.6 | .43 |
| Medication use: Beta-blocker | 26.1 | 26.5 | .79 |
| ACE inhibitor | 15.5 | 15.8 | .79 |

- Baseline characteristics similar in matched users and non-users.
- 30 of 31 covariates show NS difference between matched users and non-users. [Peak exercise capacity for men is p = .01]

- Hazard Ratio (time to death) = 0.67 (95% CL: 0.51 – 0.87)
- Conclusion: aspirin **reduces** mortality risk



Reference: Love, T.E. Reducing the Impact of Selection Bias with Propensity Scores. 7th 26 International Conference on Health Policy Statistics [ICHPS], 18 January 2008. Cleveland, Ohio, USA: Center for Health Care Research and Policy, Case Western University at MetroHealth Medical Center.

# Objective: Create a matched historical control for the Phase 2 INFRONT-2 study of AL001

Using the GENFI2 FTD registry, we set out to create a cohort of untreated participants ("GENFI2 matched historical control") that is comparable, based on prospectively identified observed covariates, to a cohort of treated patients that participated in the Phase 2 INFRONT-2 study of AL001.

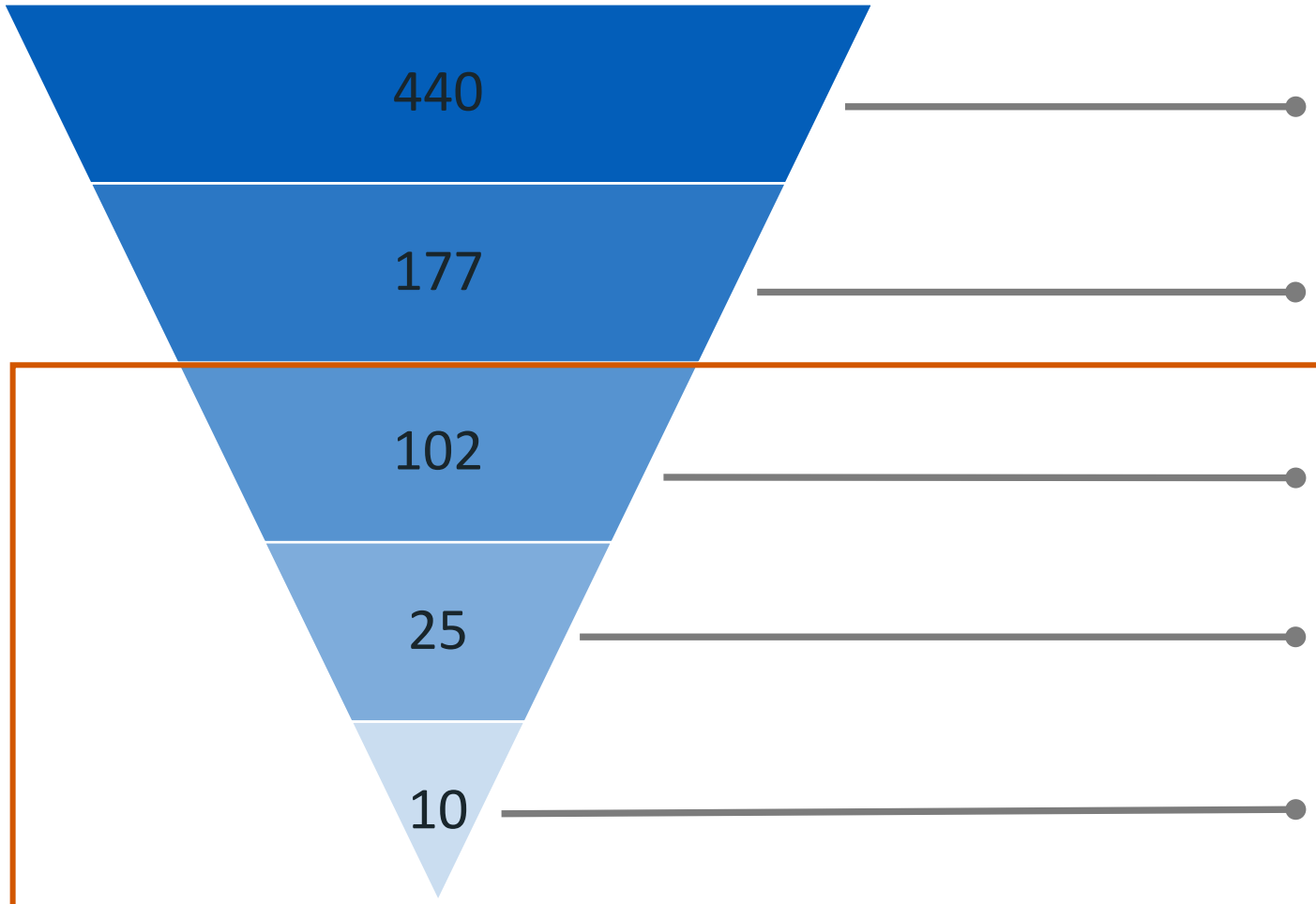
- Genetic Frontotemporal Dementia Initiative (GENFI) is a group of research centers across Europe and Canada focused on familial FTD

- The aim of the group is to understand more about genetic FTD, particularly in those who have mutations in the progranulin (GRN), microtubule-associated protein tau (MAPT) and chromosome 9 open reading frame 72 (C9orf72) genes

- GENFI investigates both people who have developed symptoms of FTD and also people who have a risk of developing symptoms in the future because they carry an abnormal genetic mutation

- The organization follows carriers and tracks their disease progression over time using a number of markers including clinical outcome assessments, neuropsychology, imaging, biomarkers and genetics

# GENFI2 matched cohort selection overview




We started with a pool of 440 GENFI2 subjects as of May 2019

Of those, 177 were FTD-GRN mutation carriers

Subjects with at least one post-baseline CDR® plus NACC FTLD-SB

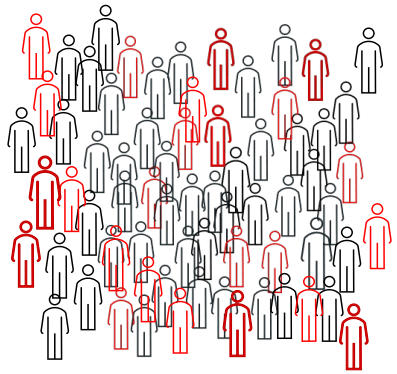
Potential GENFI2 matches based on Propensity Score Matching using CDR® plus NACC FTLD-SB

Matched historical control based on blinded clinical adjudication

# A two-step matching strategy to eliminate potential confounding factors was used to construct the GENFI2 matched historical control cohort

**Step 1**

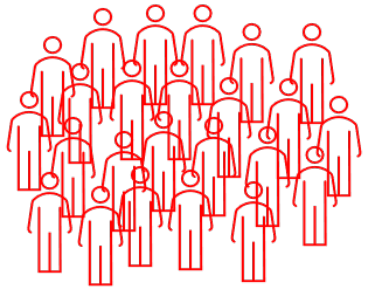
GENFI2 FTD-GRN participants with at least one post-baseline CDR® plus NACC FTLD-SB (n=102)



Propensity score matching by baseline CDR®-SB

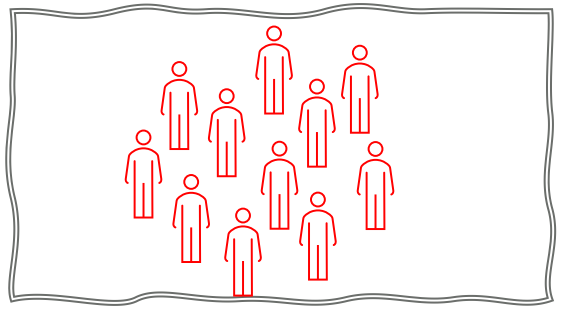
**Step 2**

Potential GENFI2 matches using propensity score matching based on CDR® plus NACC FTLD-SB (n=25)



Blinded clinical adjudication matching by NfL at baseline, age, diagnosis and gender

GENFI2 matched historical control cohort (n=10)



- Propensity scores were computed using a logistic regression including the most important covariate, cognition, measured at baseline using the CDR® plus NACC FTLD-SB
- Matching was done by comparing the logit propensity score

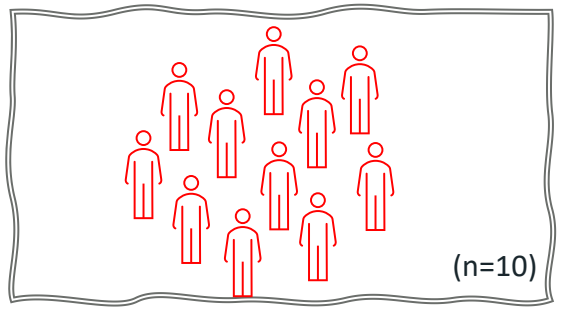
- To further increase the chances that the matched historical control cohort would mimic a placebo group in a randomized experiment, clinical adjudication of secondary covariates, including NfL at baseline, age, diagnosis and gender were used to refine and construct the final matched historical control cohort
- This step was done on a blinded basis



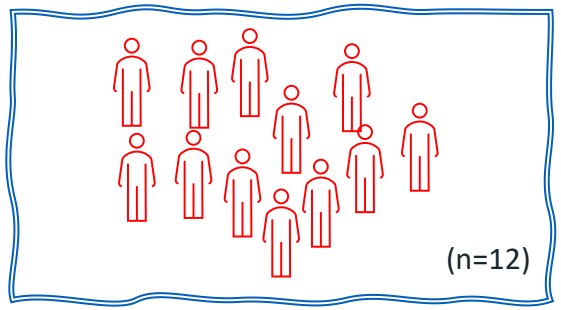
Note: Figures are illustrative - do not correspond to exact patient numbers.

# Creating a relevant context for the 12-month AL001 Phase 2 INFRONT-2 results

GENFI2 matched historical control cohort




AL001 INFRONT-2 FTD-GRN cohort




- Through the two-step matching process, the resulting **GENFI2 matched historical control** cohort has comparable baseline characteristics to the **Phase 2 INFRONT-2 study** participants
- Thus, similar to the Aspirin example (see Slide 4), a comparable control group allows us to make meaningful comparisons and more accurately estimate any treatment benefit associated with AL001



Note: Figures are illustrative - do not correspond to exact patient numbers.

# Selection of biomarkers

# Measuring the effects of AL001 on FTD-*GRN* disease cascade

Target engagement (Proof of mechanism)

Biomarkers of activity

Clinical benefit (Proof of efficacy)


| **PGRN in plasma and CSF** | **CTSD<br>LAMP1** | **C1QB** | **NfL<br>Volumetric MRI (vMRI)** | **CDR® plus NACC FTLD-SB** |
|---|---|---|---|---|
| Direct measure of target. In FTD, PGRN levels are diminished, correlating with symptom onset | Lysosomal proteins and dysfunctional lysosomes are a hallmark of FTD-*GRN* brains | Complement proteins in FTD are known to correlate with cognitive decline | Neurofilament light chain is a measure of axonal damage<br><br>vMRI is a measurement of brain atrophy | FDA agreed-upon primary endpoint for measuring clinical decline in FTD |



CTSD = Cathepsin D; LAMP1 = Lysosomal associated membrane protein 1; C1QB = Complement C1q B chain; NfL = Neurofilament light chain; vMRI = volumetric MRI.

# Publication references

## Progranulin in FTD / FTD disease cascade

**The lysosomal function of progranulin, a guardian against neurodegeneration**

- https://pubmed.ncbi.nlm.nih.gov/29744576/

**Progranulin in neurodegenerative disease**

- https://pubmed.ncbi.nlm.nih.gov/24800652/

**Progranulin, lysosomal regulation and neurodegenerative disease**

- https://pubmed.ncbi.nlm.nih.gov/28435163/

**New directions in clinical trials for frontotemporal lobar degeneration: Methods and outcome measures**

- https://pubmed.ncbi.nlm.nih.gov/31668596/

**Progranulin as a therapeutic target for dementia**

- https://pubmed.ncbi.nlm.nih.gov/29889573/

## CDR® plus NACC FTLD-SB

**Background on the CDR plus NACC FTLD-SB scale from a study done by UCSF to examine if memantine could slow down decline in cognition**

- https://pubmed.ncbi.nlm.nih.gov/23290598/

## Biomarkers of activity

**CTSD, LAMP1, C1QB levels are elevated in GRN knock-out mice (Huang et al. 2020)**

- https://actaneurocomms.biomedcentral.com/articles/10.1186/s40478-020-01037-x

**CTSD, LAMP1 levels are elevated in post-mortem brains of FTD-GRN mutation carriers (Gotzl et al. 2014 )**

- https://link.springer.com/article/10.1007%2Fs00401-014-1262-6

**Complement protein C1Q (of which C1QB is a subunit) promotes TDP-43 granule development in GRN knock-out mice (Zhang et al. 2020)**

- https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7746606/

**Increasing complement protein C1QA (another subunit of C1Q) levels correlate with cognitive function decline in FTD-GRN mutation carriers (Liu et al. 2016)**

- https://www.cell.com/cell/fulltext/S0092-8674(16)30392-0?_returnURL=https%3A%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS0092867416303920%3Fshowall%3Dtrue

**Neurofilament light chain (NfL) (Van der Ende et al. 2019; Rojas et al. 2021)**

- https://www.thelancet.com/journals/laneur/article/PIIS1474-4422(19)30354-0/fulltext
- https://n.neurology.org/content/96/18/e2296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