PK/PD Modeling of Progranulin Elevation in Blood and CSF to Support AL101 Phase 2 Study

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Background

- Progranulin (PGRN) is a glycoprotein that is encoded by the *GRN* gene, regulated by sortilin-mediated endocytosis, and known to play a vital role in many cellular processes, such as inflammation, wound repair, lysosomal function, and neurodegeneration[1,2]
- *GRN* mutations resulting in downregulation of PGRN have been linked to the development of neurodegenerative disorders, such as Alzheimer's disease (AD)[3]
- Rare *GRN* loss of function mutations are reported in clinically diagnosed AD patients; the common variant rs5848 is associated with a ~15% decrease in plasma PGRN and has been identified as a genetic determinant of AD[2]
- Given the neurotrophic actions of PGRN, increasing PGRN levels may provide an appropriate therapeutic approach for individuals with neurodegenerative conditions such as AD[2,4]
- AL101 is a human immunoglobulin (Ig) G1 monoclonal antibody designed to bind to sortilin and inhibit interaction between PGRN and the sortilin receptor, thereby elevating PGRN levels in blood and cerebrospinal fluid (CSF) and slowing the rate of decline in individuals with AD[5]
- The safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and bioavailability of AL101, when administered as single or multiple intravenous (IV) or subcutaneous (SC) doses, were evaluated in healthy individuals in a phase 1 study[6]

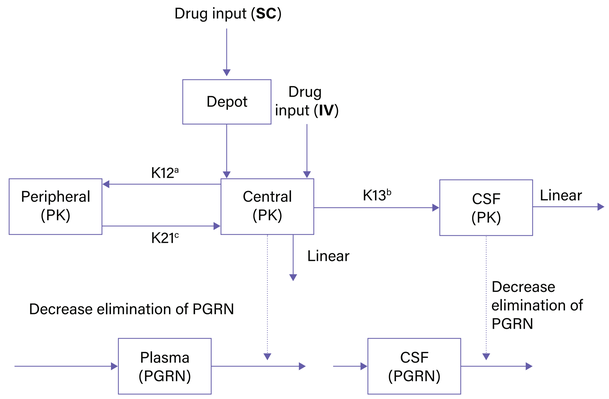
Objective

- To simulate a dose-response (in terms of average PGRN elevation during the dosing period in plasma and CSF) profile based on the phase 1 study results

Methods

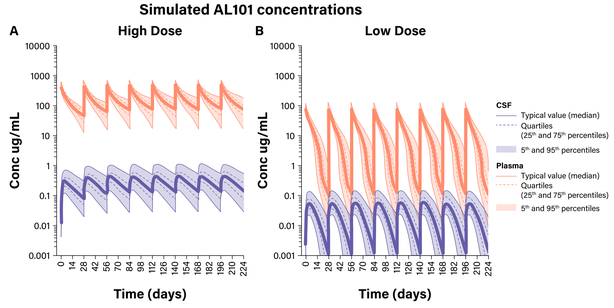
- The PK/PD model (**Figure 1**) was developed based on IV data from phase 1 study[5,6] and used to build a dose-response profile that tested the effects of AL101 while changing dose level and frequency
- Simulation studies establish a mathematical relationship between AL101 plasma and CSF concentrations and the expected change in PGRN plasma and CSF levels
- The final model included body weight (BW) as a covariate on clearance and volume of distribution in serum AL101, and baseline plasma PGRN as a covariate on the maximum effect term on plasma PGRN degradation. Once validated the model was used for simulating different clinical scenarios
- Simulations were performed considering the patient populations:
  - BW and baseline PGRN levels were extracted from a normal distribution from the phase 1 data, and the model assumed no difference in PK/PD between healthy volunteers (phase 1 study) and AD patients (simulated phase 2 study)
- 1000 simulations were conducted to estimate the effects of either a high dose administered every 4 weeks (q4w) IV (**Figure 2A**) or low dose administered q4w IV (**Figure 2B**) on AL101 concentrations in plasma and CSF and the corresponding percent change from baseline in PGRN levels in plasma and CSF (data not shown)
- The PK/PD profiles were simulated to build the dose-response curve in terms of average change from baseline of PGRN in CSF

Figure 1. PK/PD Model Structure and Parameterization



[a]K12 = transition rate from central compartment to peripheral compartment
[b]K13 = transition rate from central compartment to CSF compartment
[c]K21 = transition rate from peripheral compartment to central compartment
CSF, cerebrospinal fluid; IV, intravenous; PD, pharmacodynamics; PGRN, progranulin; PK, pharmacokinetics; SC, subcutaneous.

Figure 2. PK/PD Simulations: Estimated Concentrations of AL101 in Plasma and CSF of AD Patients in Response to High (A) or Low (B) Doses Based on q4w IV Dosing

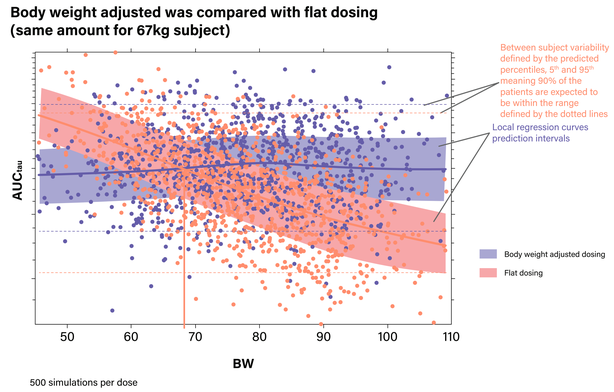


AD, Alzheimer's disease; CSF, cerebrospinal fluid; IV, intravenous; PD, pharmacodynamics; PK, pharmacokinetics; q4w, every 4 weeks.

Results

- Providing the estimated parameters, variability in model parameters, residual errors, and random extracted covariates (ie, BW and PGRN baseline values), the PK/PD model was used to simulate AL101 (**Figure 2**) concentrations in plasma (red) and CSF (blue)
- BW was detected as a statistically significant covariate in the PK/PD model. However, its impact on area under the curve at steady state (AUC_{ss}), over the dosing interval (AUC_{tau}), and maximum concentration at steady state (C_{max}) [data shown in log-scale] suggested mostly similar exposure-distribution between flat and weight-based dosing and minimal or no impact on the safety margin (**Figure 3**)

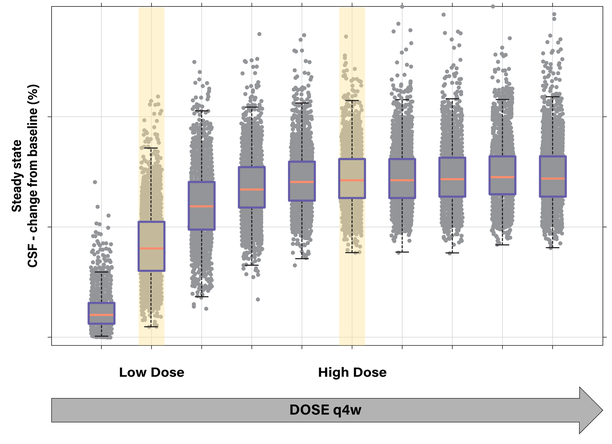
Figure 3. Estimated Effect of BW on AUC_{tau} in Response to Weight-Adjusted vs Flat Dosing Regimens



AUC_{tau}, area under the curve at over the dosing interval; BW, body weight.

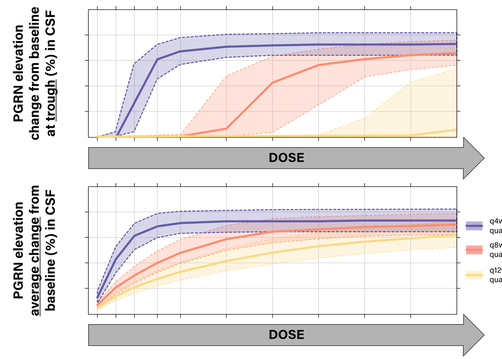
- **Figure 4** shows the relationship between dose (AL101 q4w IV) and response (steady-state baseline-corrected CSF PGRN concentrations) and **Figure 5** demonstrates the impact of changing the dosing frequency considering q4w, q8w, and q12w
- Two IV dose levels will be considered for the phase 2 study. A high dose q4w IV is proposed as the top dosing regimen to reach and maintain the maximum expected PGRN elevation in CSF
  - A dose that exceeds the high dose proposed here would not be expected to yield an improved PD effect
  - Increasing the dosing interval from q4w would impact the PGRN concentration profile and lead to lower CSF PGRN levels with major impact at the end of the dosing period

Figure 4. AL101 Average Expected Dose Response Based on Varying Dose Levels Administered q4w IV (2000 simulations per dose level)



CSF, cerebrospinal fluid; q4w, every 4 weeks.

Figure 5. PGRN Elevation in CSF From Baseline at Trough (A) and as an Overall Average (B)



CSF, cerebrospinal fluid; PGRN, progranulin; q4w, every 4 weeks; q8w, every 8 weeks; q12w, every 12 weeks.

Conclusions

- PK/PD characterization and simulations supported the transition to flat dosing compared to weight-based dosing and justified the administration of two dose levels at q4w intervals
- The high dose q4w is expected to be the minimal dose which would allow obtaining the maximum PGRN elevation in CSF and maintain it for the entire dosing period, whilst the lower dose level is expected to be the median effective dose (ED50) in terms of average PGRN elevation from baseline in CSF
- Additional simulation testing could allow for further investigation regarding the effects of dosing frequency and the impact of utilizing different routes of administration
- The PK/PD model will be integrated with emerging data to increase the confidence in parameter estimation and confirm and inform potential covariate effects

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Disclosures

Massimiliano Germani, Robert Lai, David Roth are all employees and shareholders of GSK. Lovingly Park and Balasubrahmanyam Budda are employees and shareholders of Alector, Inc. Mike Ward is an independent consultant of Alector, Inc. and Athena Bioscience, LLC, and a shareholder of Alector, Inc. Carey Hines and Amitkumar Joshi are employees of PPD and may hold equity in PPD.

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