Evaluation of the effects of repeated lumbar punctures on Alzheimer's Disease CSF and blood biomarkers

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What does this mean for the AD community?

- Our data inform the design of future studies that rely on multiple CSF sampling timepoints to measure fluid pharmacodynamic biomarkers.
- Reducing the confounding impact of lumbar punctures on fluid pharmacodynamic biomarkers may increase the robustness of such biomarker data and improve decision making in early clinical development.

Conclusions

- Prior CSF sampling can impact assessments of CSF AD biomarkers when samples are collected by repeated LPs separated by less than 7 days.
- This effect may be due to a change in intracranial pressure the days following the LP, which normalizes in 7 days.
- Inter-LP intervals should be carefully considered in both the design and interpretation of trials focused on longitudinal CSF pharmacodynamic endpoints.

Background

Cerebrospinal fluid (CSF) and blood biomarker measurements are critical early indicators of central nervous system (CNS) pharmacodynamic activity in Phase I studies, which are most frequently conducted in healthy volunteers. However, repeated sampling of CSF through lumbar punctures (LP) may cause fluid biomarker levels to transiently deviate from baseline[1], which can complicate the evaluation of pharmacodynamic effects of investigational products. We sought to characterize the impact of different LP intervals on CSF and blood biomarkers.

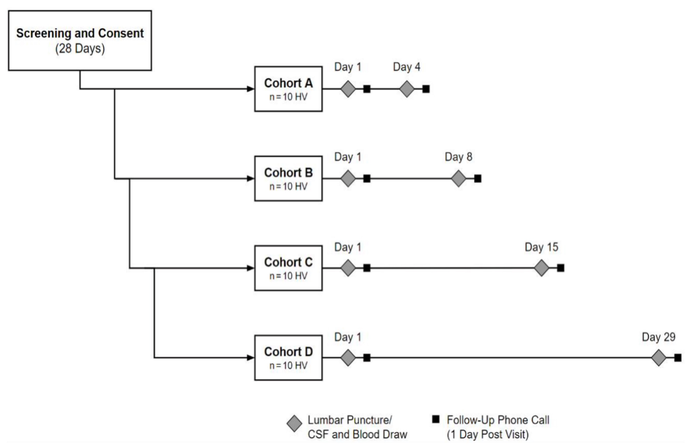
Objectives

- To determine the effect of inter-LP duration on CSF and blood biomarkers of neurodegeneration and neuroinflammation.
- To evaluate adverse events (AE) related to repeated LPs across different LP intervals.

Methodology

Study design

Healthy volunteers (HV) underwent two LPs separated by either 3, 7, 14, or 28 days. CSF and blood were collected at baseline day 1 and follow-up days 4, 8, 15 or 29.



NeuroToolKit CSF and blood biomarker measurements

The NeuroToolKit, a panel of exploratory robust prototype assays (Roche Diagnostics International Ltd, Rotkreuz, Switzerland) was applied to measure:

- **CSF:** Aβ42, Aβ40, tTau, pTau181, neurogranin, GFAP, IL-6, YKL-40, sTREM2, NFL, S100B, aSyn, NPTX2 and SNAP-25.
- **Plasma:** Aβ42, Aβ40, tTau, pTau181, NFL, sTREM2, YKL-40, S100B (serum), IGFBP7, NSE (serum), APOE4, NPTX2 and SNAP-25.

Aβ, beta-amyloid; aSyn, alpha synuclein; GFAP, glial fibrillary acidic protein; IL-6, interleukin 6; NFL, neurofilament light chain; pTau, tau phosphorylated at threonine 181; S100b, S100 calcium-binding protein B; sTREM2, soluble triggering receptor expressed on myeloid cells 2; tTau, total tau; YKL-40, chitinase-3-like protein; NSE, neuron-specific enolase; NTPX2, neuronal pentraxin; IGFBP7, insulin growth factor binding protein 7; APOE4, apolipoprotein E4; SNAP-25, synaptosomal-associated protein 25kDa

Results

Table 1. Study demographics

	Cohort A (n=11)	Cohort B (n=11)	Cohort C (n=11)	Cohort D (n=11)
Age, years				
Mean (SD)	30.6 (11.1)	30.1 (6.7)	33.5 (9.5)	33.1 (9.7)
Median (Range)	26.6 (20.6-47.6)	32.5 (19.6-41.5)	35.4 (22.4-50.4)	29.4 (23.4-49.3)
Sex, n (%)				
Male	10 (91)	5 (46)	5 (46)	8 (73)
Female	1 (9)	6 (55)	6 (55)	3 (27)

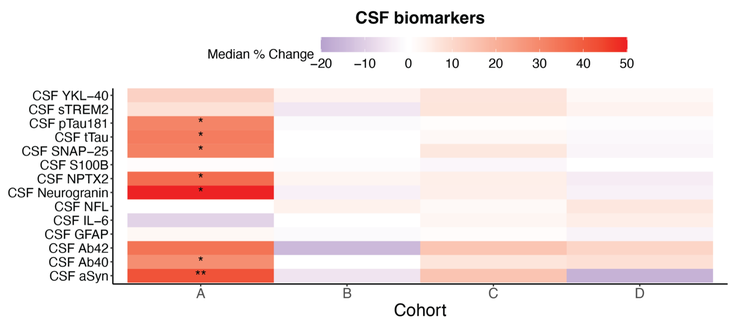
SD, standard deviation.

Table 2. Summary of AEs related to study procedure

Characteristic	Cohort A (n=11)	Cohort B (n=11)	Cohort C (n=11)	Cohort D (n=11)
Total no. patients with ≥ 1 AE	6 (54.5%)	10 (90.9%)	8 (72.7%)	7 (53.6%)
Total no. AEs	13	23	12	13
Total no. deaths	0	0	0	0
Discontinuation due to AE	1 (9.1%)	1 (9.1%)	1 (9.1%)	1 (9.1%)
AEs between 1st and 2nd LP	5 (45.5%)	8 (72.7%)	6 (54.5%)	6 (54.5%)
AEs after 2nd LP	1 (9.1%)	5 (45.5%)	1 (9.1%)	2 (18.2 %)
AEs reported in ≥ 10%				
Post LP syndrome	2 (18.2%)	4 (36.4%)	3 (27.3%)	3 (27.3%)
Procedural Pain	3 (27.3%)	4 (36.4%)	3 (27.3%)	1 (9.1%)

Figure 1. CSF biomarker changes between 1st and 2nd LPs

- 29-50% median increases from baseline were observed in CSF Aβ40, Aβ42, tTau, pTau181, aSyn, SNAP-25, Neurogranin, and NPTX2 levels on day 4 (2nd LP) in Cohort A.



*p < 0.05; ** p < 0.01, Wilcoxon test followed by Bonferroni adjustment.

Figure 3. Absolute CSF concentrations of select biomarkers at the 1st and 2nd LP across cohorts

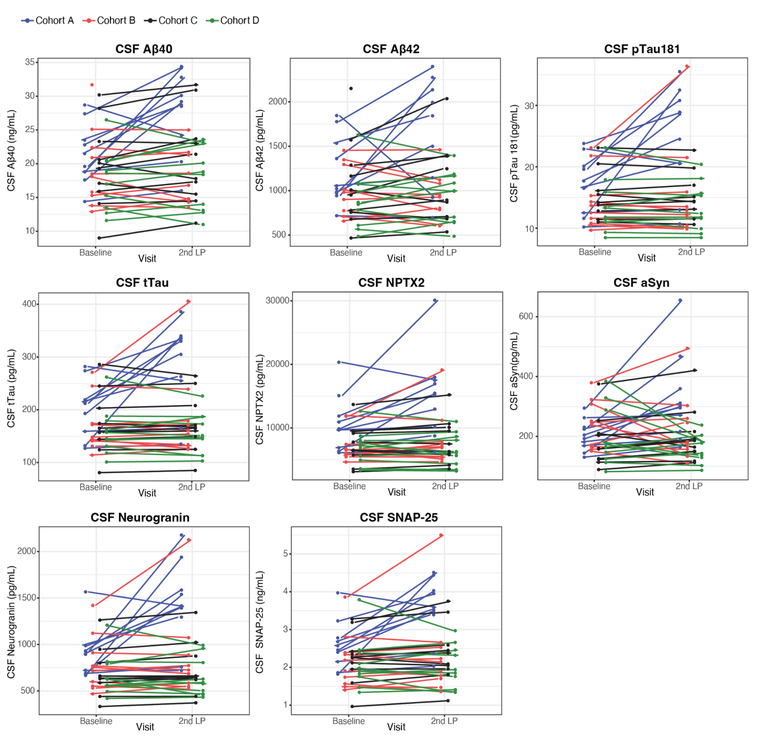


Figure 3. Plasma/serum biomarker changes between 1st and 2nd LPs

- No significant changes in blood biomarkers between 1st and 2nd LP in any cohort.

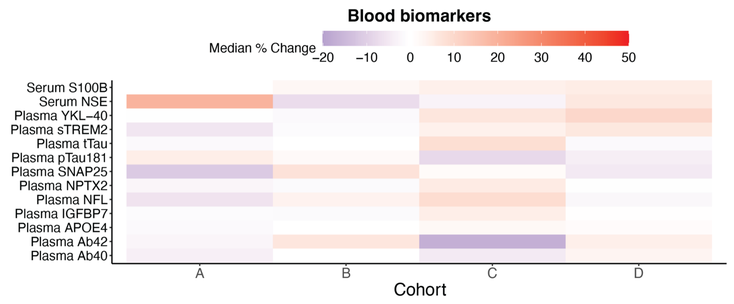
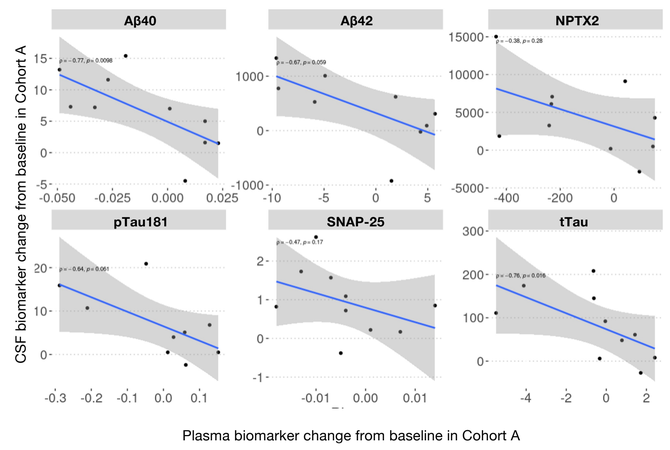


Figure 4. Change from baseline correlations across CSF and plasma for select biomarkers (Cohort A only)



p, Spearman Rho; *p*, p-value.

Discussion

- Significant increases in CSF Aβ40, Neurogranin, tTau, pTau181, aSyn, SNAP-25, and NPTX2 were observed in the 3-day inter-LP interval cohort but not the 7-,14- ,and 28-day inter-LP interval cohorts.
- Plasma/serum biomarkers did not significantly change from baseline across 3-,7-,14- and 28-day inter-LP interval cohorts.
- Negative correlations between plasma and CSF Aβ40 and tTau changes from baseline were observed in the 7-day cohort, possibly due to reduced biomarker drainage from CSF into the blood as a result of decreased intracranial pressure[2,3].
- Further studies are needed to understand the mechanisms underlying the LP-induced changes in fluid biomarkers.
- Consistent with the prior literature[4], the most common LP-related AEs were headache, back pain/discomfort, and pain at the LP site.
- No consistent relationships between AE frequency and inter-LP interval were observed. Fewer AEs were associated with the second LP than with the first.

References

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- The NeuroToolKit is a panel of exploratory prototype assays designed to robustly evaluate biomarkers associated with key pathologic events characteristic of AD and other neurological disorders, used for research purposes only and not approved for clinical use (Roche Diagnostics International Ltd, Rotkreuz, Switzerland).

Disclosures

AB, YZ, CA, SS, EC, LZ, VM, BZ, RC, TK, PT, LJ, and ET are full-time employees of Genentech/Roche. TB is a full-time employee of F. Hoffmann-La Roche and Genentech. AB, YZ, CA, SS, EC, LZ, VM, BZ, RC, TK, PT, LJ, TB and ET are shareholders in F. Hoffmann-La Roche. GK is a full-time employee of Roche Diagnostics GmbH. KB has served as a consultant and at advisory boards for Abbvie, AC Immune, ALZPath, AriBio, BioArctic, Biogen, Eisai, Lilly, Neurimmune, Novartis, Ono Pharma, Prothena, Roche Diagnostics, and Siemens Healthineers, and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program.