# Plasma Drug Exposure-response Relationship Of Neflamapimod In The Rewind-LB Trial In Patients With Dementia With Lewy Bodies

Monday
#1219

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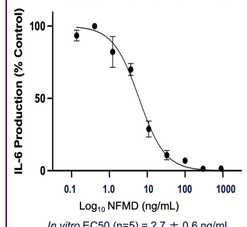
A consistent pharmacokinetic-pharmacodynamic relationship was observed across studies, with a $C_{trough}$ threshold (~4 ng/mL) associated with biomarker and clinical effects in AD and DLB. The findings support the mechanism of action, strengthen RewinD-LB efficacy results, and inform on dose selection for future trials.

## INTRODUCTION

**Background:** Neflamapimod, a selective p38α kinase inhibitor, has demonstrated potential to slow clinical progression (CDR-SB,ADCS-CGIC) and reduce disease activity (plasma GFAP) in the RewinD-LB clinical trial in patients with dementia with Lewy bodies (DLB). Herein, we establish the *in vitro* concentration-response relationship for neflamapimod's primary pharmacologic effect— inhibition of interleukin (IL)-1β signaling— and related this to pharmacokinetic-pharmacodynamic (PK-PD) relationships observed in RewinD-LB and prior studies in early Alzheimer's disease (AD).

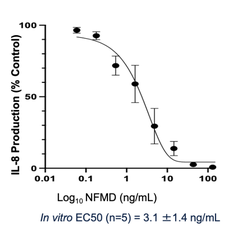
### In Vitro Potency for IL-1β Signaling

In Vitro: IL-1β stimulated IL-6 Production from huma PBMCs




*In vitro* EC50 (n=5) = 2.7 ± 0.6 ng/mL

In Vitro: IL-1β stimulated IL-8 Production from human PBMCs




*In vitro* EC50 (n=5) = 3.1 ±1.4 ng/mL

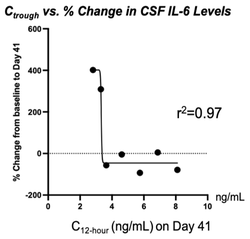
IC50 for inhibition of LPS stimulated IL-1β production = 14.4 ± 5.7 ng/mL

## RESULTS

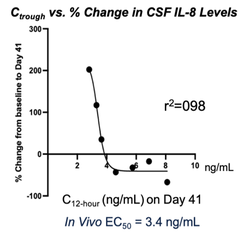
### Clinical Studies in Early AD

**PK-PD Relationship in 6-Week Clinical Pharmacology Study of Neflampimod 40mg BID**

In Patients with Early Alzheimer's Disease: Change in CSF IL-6 After 6 Weeks of Neflamapimod Treatment



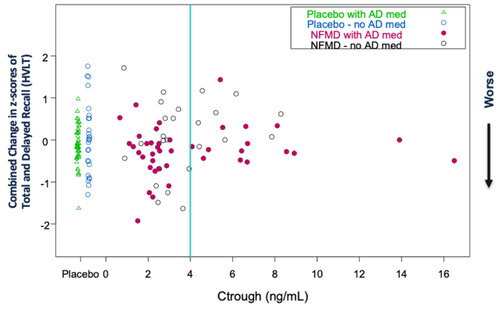

In Patients with Early Alzheimer's Disease: Change in CSF IL-8 After 6 Weeks of Neflamapimod Treatment




*In Vivo* $EC_{50}$ = 3.4 ng/mL

Maximal pharmacodynamic effect achieved at trough plasma drug concentration ($C_{trough}$) ~4 ng/mL, i.e. when EC50 is exceeded in plasma (~EC80 in the brain)

**PK-PD Relationship in a 24-Week Placebo-Controlled Study of Nelfmapimod 40mg BID in Patients with Early AD**

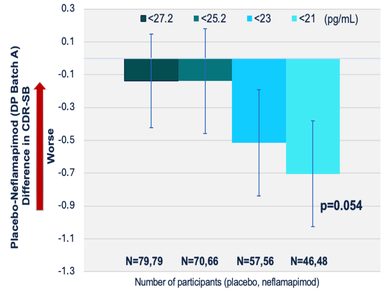



Adapted from Prins et al. Alzheimer's Research & Therapy (2021) 13:106

### Phase 2b ("RewinD-LB") Clinical Trial in Patients with DLB

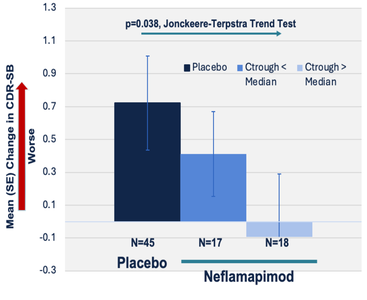
- PK-PD relationship established in most responsive patient subset – those with low likelihood of AD Co-pathology, as defined by plasma ptau181 < 21 pg/mL. Neflamapimod dose: 40mg TID x 16 Weeks

Neflamapimod Effect on Change in CDR-SB vs. Placebo During Randomized Phase by Plasma pTau181 Cutoff



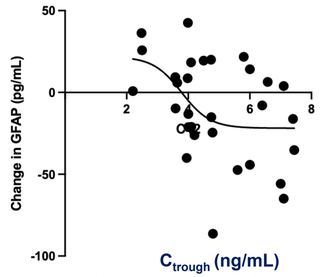

Output from Mixed-Effects Model for Repeated Measures (MMRM) with baseline CDR-SB, Sex, Age and Mini-Mental State Examination (MMSE) as covariates

Change in CDR-SB During Placebo Controlled Phase by Trough Plasma Drug Concentration in <21 pTau181 Subset




Median Observed $C_{trough}$ = 3.64 in < 21 pg/mL subset

$C_{trough}$ vs. change in plasma GFAP during 32-week Extension Phase




GFAP: glial fibrillary acidic protein

| | % of patients with $C_{trough}$ ≥ 4 ng/mL | Clinical Activity |
|---|---|---|
| 40mg BID (Phase 2a only) | 25% | No discernible activity |
| 40mg TID Batch A (Phase 2b) | 50% | Marginal clinical activity, except potentially in those who achieve $C_{trough}$ target |
| 40mg TID Batch B (Phase 2b) | 75% | Demonstrated improvement on CDR-SB, CGIC and plasma GFAP |
| 50mg TID (Dose regimen going forward) | *~90% (Estimated)* | TBD |

## CONCLUSIONS

- A consistent pharmacokinetic-pharmacodynamic relationship was observed across studies, with a $C_{trough}$ threshold(~4 ng/mL) associated with biomarker and clinical effects.
- This threshold exceeds in plasma the EC50 for inhibition of IL-1β signaling and approximates the EC80 in the brain (brain drug concentrations with neflamapimod are ~ two-fold higher than in plasma).
- These findings support the mechanism of action, strengthen RewinD-LB efficacy results, and support use of 50mg TID for future clinical trials, a dosing regimen expected to achieve mean $C_{trough}$ of ~6 ng/mL and $C_{trough}$ ≥ 4ng/mL in approximately 90% of participants.

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