Effect of the *P. gingivalis* (Pg) gingipain inhibitor atuzaginstat on neuropsychiatric symptoms in Pg-positive mild-moderate AD patients

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Abstract

Background: In the phase 2/3 GAIN trial of the *P. gingivalis* (*Pg*) gingipain inhibitor atuzaginstat in mild-moderate AD dementia, the prespecified subgroup analysis demonstrated efficacy in patients with *Pg*-positive saliva (*Pg*+), slowing cognitive decline on the ADAS-Cog11 by 57% (p= 0.020, N=244) (**Figure 1**) [1].

The Neuropsychiatric Inventory (NPI) was also administered to understand if treatment could slow progression of troubling psychiatric/behavioral symptoms. In particular, agitation and aggression are a major cause of caregiver distress and patient long-term care placement, however, no disease-modifying treatment is available.

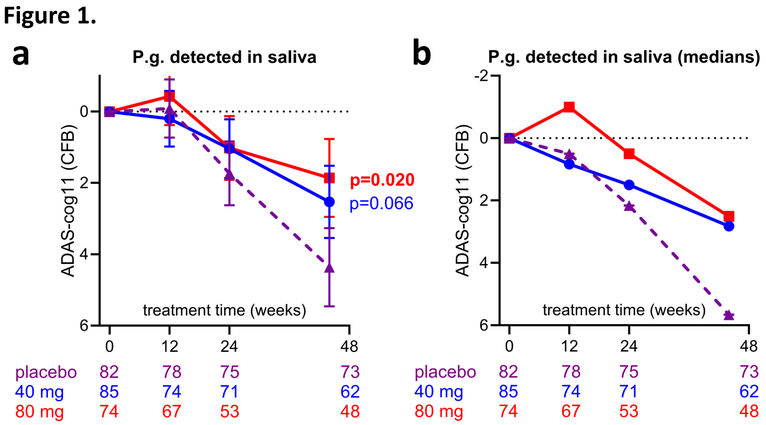
Methods: The Phase 2/3 GAIN study was a 3-arm RCT in 643 subjects with baseline MMSE scores of 12-24 who were randomized to one of two doses of atuzaginstat (40mg or 80mg BID) or placebo for 48 weeks. The NPI-12 was administered at baseline and weeks 24 and 48. New exploratory post-hoc analyses were conducted to evaluate the effect of both doses of atuzaginstat on the 12 NPI subdomains and Caregiver Distress using a covariate MMRM analysis. *Pg+* and *Pg-* groups were analyzed separately.

Results: At Week 48 a cluster of neuropsychiatric subdomains demonstrated nominally significant benefit (lower symptom scores) compared to placebo: Agitation/Aggression (40 mg p=0.001, 80 mg p=0.032); Disinhibition (40 mg p=0.011, 80 mg p=0.009); Elation/Euphoria (40 mg p<0.001, 80 mg p<0.001), and Apathy (40 mg p=0.041) (**Figure 2, Figure 3**). The Caregiver Distress scores in the *Pg+* group demonstrated a similar pattern, with nominally significant benefit at Week 48: Agitation/Aggression (40 mg p=0.002, 80 mg p=0.067); Disinhibition (40 mg p=0.004, 80 mg p=0.007); Elation/Euphoria (40 mg p<0.001, 80 mg p<0.001), and Apathy (40 mg p=0.014, 80 mg p=0.034) (**Figure 4, Figure 5**). In the *Pg-* cohort, there were no significant changes in any NPI-12 subdomains or Caregiver Distress items.

Conclusions: In addition to slowing cognitive decline, atuzaginstat demonstrated beneficial effects on a cluster of neuropsychiatric symptoms in *Pg+* AD patients that translated into less distress for caregivers in the GAIN trial. A phase-2 study of the second-generation gingipain inhibitor LHP588 in *Pg+* mild-moderate AD is currently underway (SPRING Trial NCT06847321) and will include assessment of benefit in Alzheimer's agitation and aggression, along with cognitive and functional endpoints.

Atuzaginstat slowed cognitive decline in prespecified Pg+ AD subgroup in the Phase 2/3 GAIN trial

Figure 1.



NPI Subdomain Analysis in Pg+ at 48 Weeks

Figure 2. Benefit shown for the PG+ group in agitation/aggression, apathy, disinhibition and elation/euphoria.

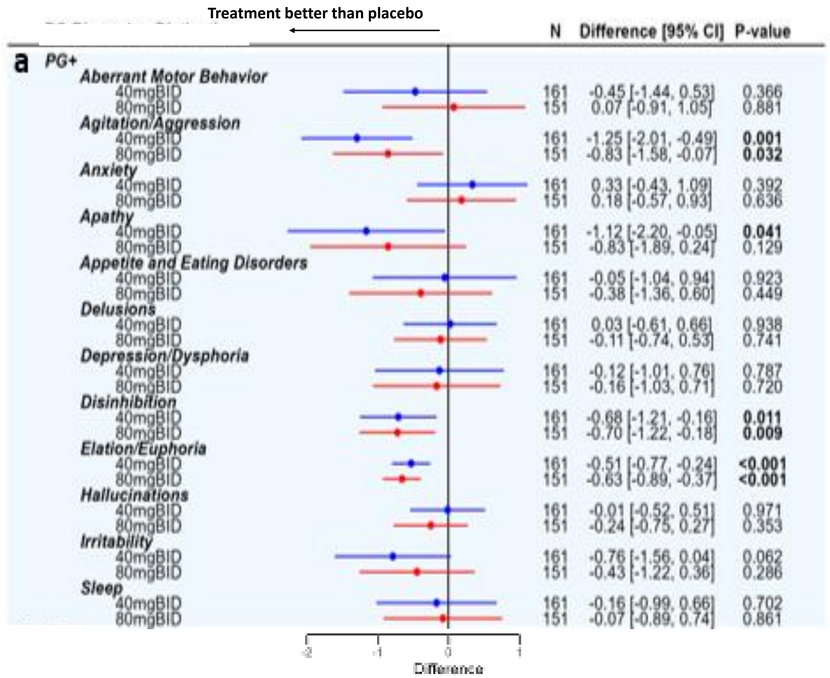
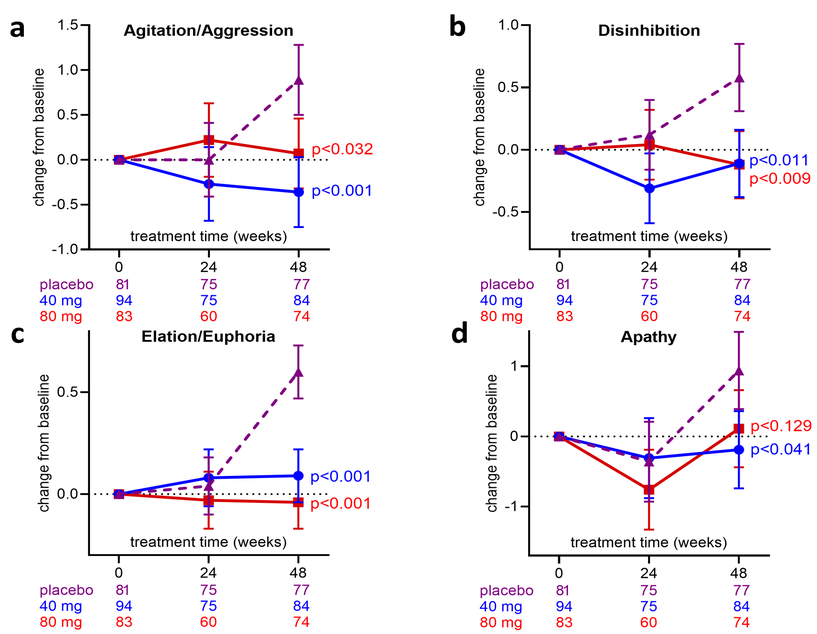


Figure 3. Analysis of atuzaginstat treatment effect reveals a cluster of neuropsychiatric symptoms including agitation.



1. Detke MJ, et al., AD/PD Conference 2022; Mar 23: https://youtu.be/TjYmPcJxWx0?si=-2WAJpd5voqap4bb

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NPI Caregiver Distress in Pg+ population

Figure 4. Benefit shown in Caregiver Distress Perception for the PG+ group in agitation/aggression, apathy, appetite and eating disorders, depression/dysphoria, disinhibition, and elation/euphoria.

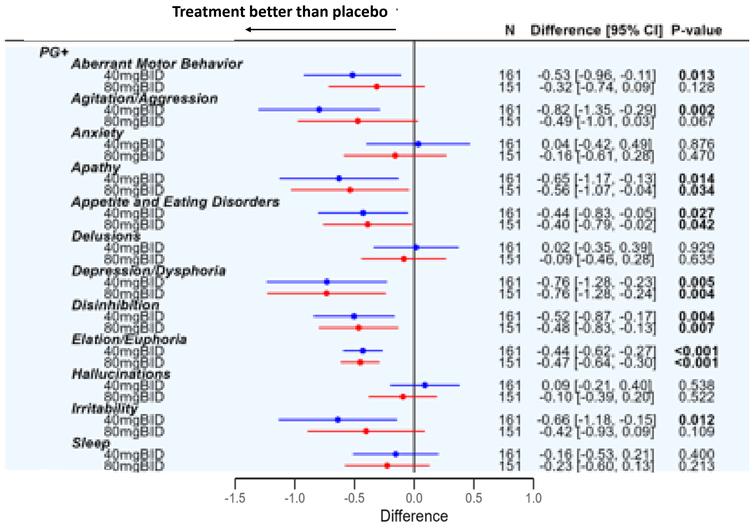
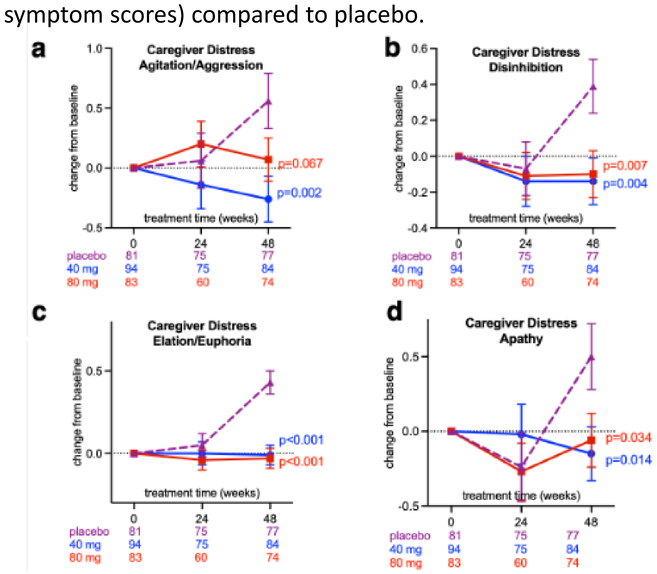
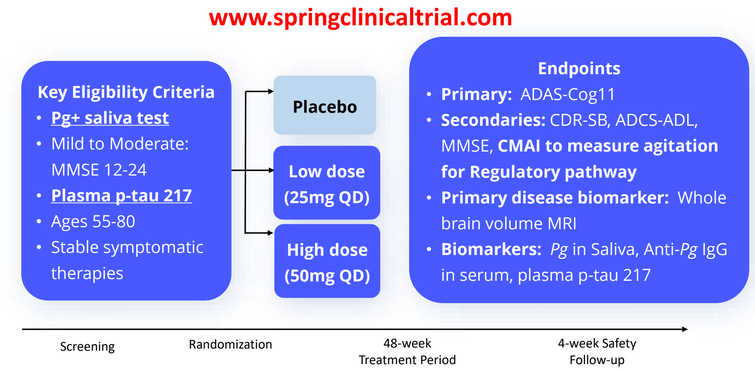


Figure 5. Analysis of atuzaginstat treatment effect reveals a cluster of neuropsychiatric subdomains demonstrated nominally significant benefit (lower symptom scores) compared to placebo.



Ongoing: SPRING Trial: 300 patients with Pg+ AD

LHP588: New structure, same MOA as atuzaginstat. Potent, once daily dosing, well tolerated in Phase 1 supporting safety.

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