# 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.

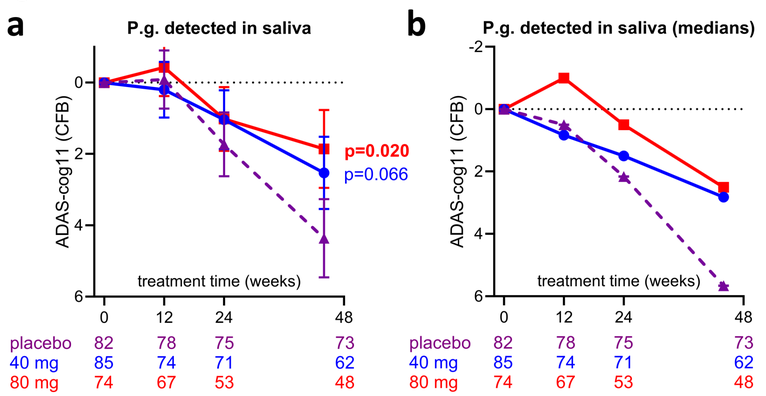
**Methods:** The Phase 2/3 GAIN study was a 3-arm RCT in 643 subjects with baseline MMSE scores of 12-24 who were randomized to one of two doses of atuzaginstat (40mg or 80mg BID) or placebo for 48 weeks. The NPI-12 was administered at baseline and weeks 24 and 48. New exploratory post-hoc analyses were 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.

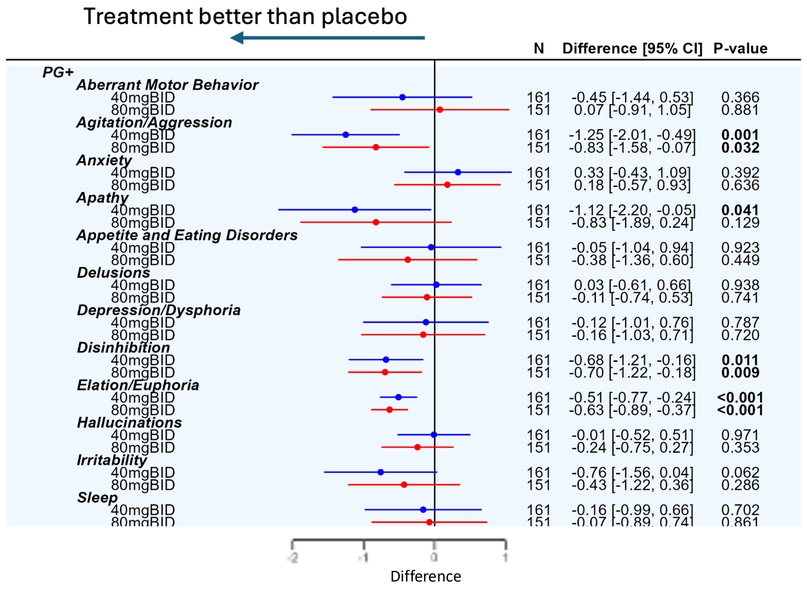
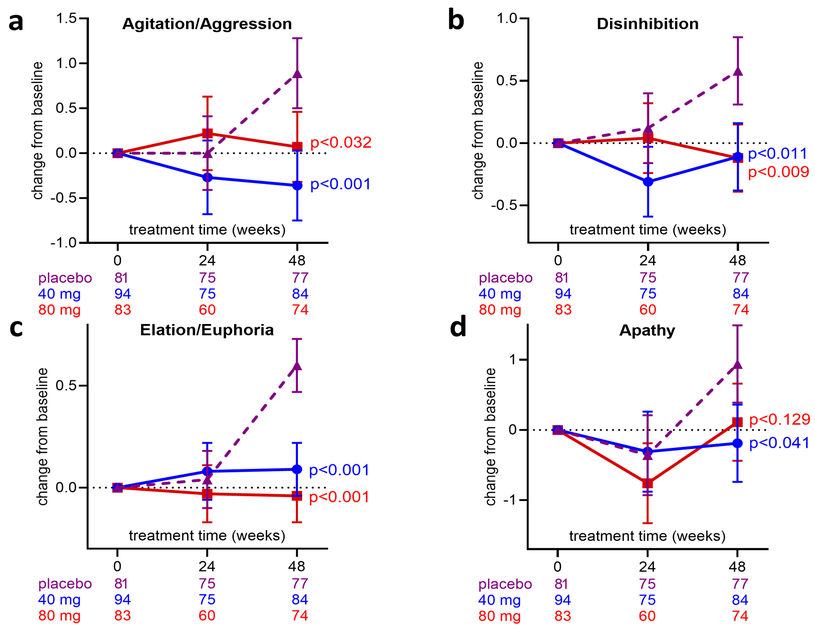



**Figure 3.** Analysis of atuzaginstat treatment effect reveals a cluster of neuropsychiatric symptoms including agitation.




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.

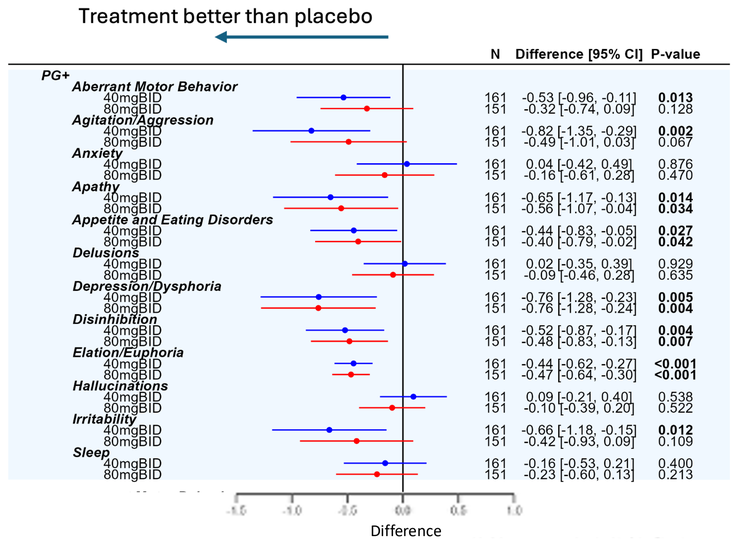
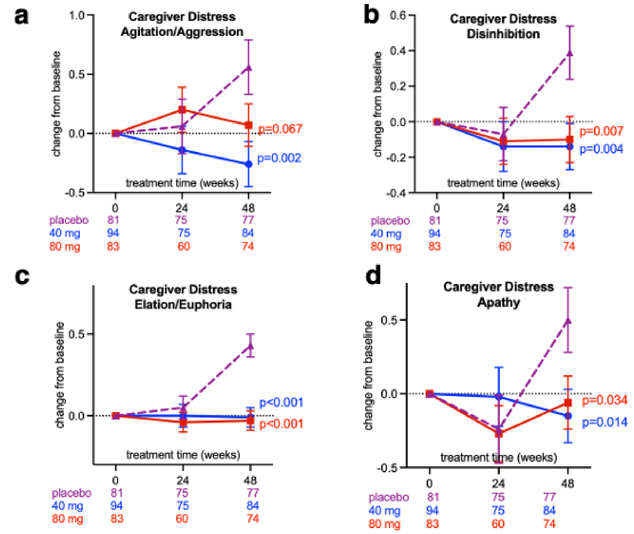



**Figure 5.** Analysis of atuzaginstat treatment effect reveals a cluster of neuropsychiatric subdomains demonstrated nominally significant benefit (lower symptom scores) compared to placebo.




## 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.

**www.springclinicaltrial.com**

**Key Eligibility Criteria**
- **Pg+ saliva test**
- Mild to Moderate: MMSE 12-24
- **Plasma p-tau 217**
- Ages 55-80
- Stable symptomatic therapies

**Placebo**

**Low dose (25mg QD)**

**High dose (50mg QD)**

**Endpoints**
- **Primary:** ADAS-Cog11
- **Secondaries:** CDR-SB, ADCS-ADL, MMSE, **CMAI to measure agitation for Regulatory pathway**
- **Primary disease biomarker:** Whole brain volume MRI
- **Biomarkers:** *Pg* in Saliva, Anti-*Pg* IgG in serum, plasma p-tau 217

Screening → Randomization → 48-week Treatment Period → 4-week Safety Follow-up