Effect of the *P. gingivalis* (*Pg*) gingipain inhibitor atuzaginstat on neuropsychiatric symptoms in *Pg*-positive mild-moderate AD patients and distress in their caregivers: Analysis of the NPI-12 in the Phase 2/3 GAIN trial

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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% in the high-dose arm (p=0.020, N=242).

The Neuropsychiatric Inventory (NPI-12) 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 only two drugs have been approved by the FDA for this indication, the antipsychotic brexpiprazole, and most recently the antidepressant combination dextromethorphan/bupropion.

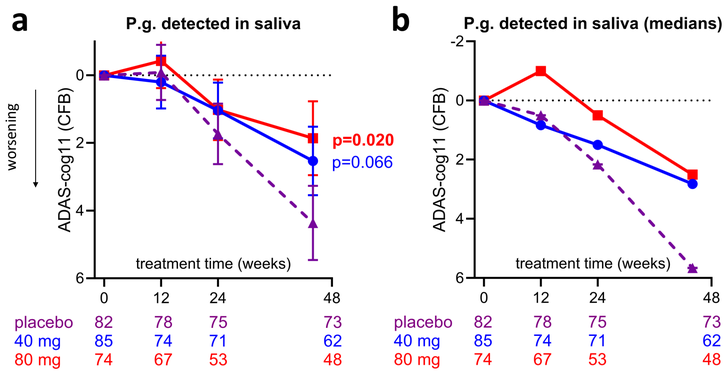
Methods: The Phase 2/3 GAIN study was a 3-arm RCT in 643 subjects with baseline MMSE scores of 12-24 who were randomized to one of two doses of atuzaginstat (40mg or 80mg BID) or placebo for 48 weeks. The NPI-12 was administered at baseline and weeks 24 and 48. New exploratory post-hoc analyses were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

Results: At Week 48, in *Pg*+ participants a cluster of NPI-12 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). There was no significant effect on the overall/total NPI-12 score. 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). Furthermore, the overall/total Caregiver Distress score was nominally significant (40 mg p<0.001, 80 mg p<0.001). In the *Pg*- cohort, there were no significant changes in any NPI-12 subdomains or Caregiver Distress items consistent with the mechanism of action.

Conclusions: In addition to slowing cognitive decline, atuzaginstat demonstrated beneficial effects on a cluster of neuropsychiatric symptoms in *Pg*+ AD patients, that also translated into less distress for caregivers in the GAIN trial. The NPI-12 domain findings showing emergence of certain neuropsychiatric symptoms at 48 weeks in the placebo group and prevention of this emergence in the treatment group is compatible with a disease-modifying effect of atuzaginstat. Other currently approved symptomatic treatments for Alzheimer's disease agitation, such as dextromethorphan/bupropion and brexpiprazole, could be used in combination with atuzaginstat. A phase-2 study of the second-generation gingipain inhibitor LHP588 in *Pg*+ mild-moderate AD is currently underway (SPRING Trial) and will include assessment of benefit in Alzheimer's agitation and aggression using the Cohen-Mansfield Agitation Inventory (CMAI), along with cognitive (ADAS-Cog) and functional endpoints (CDR-SB and ADCS-ADL).

Atuzaginstat slowed cognitive decline in prespecified Pg+ group 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.

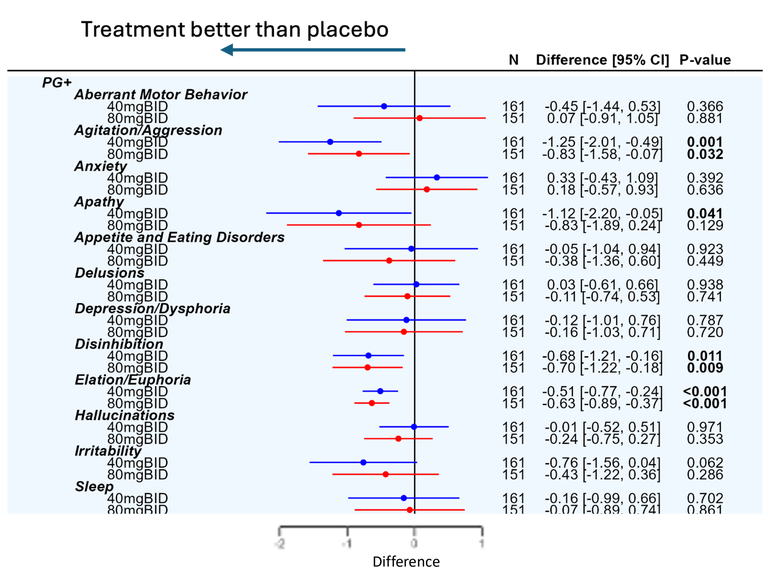
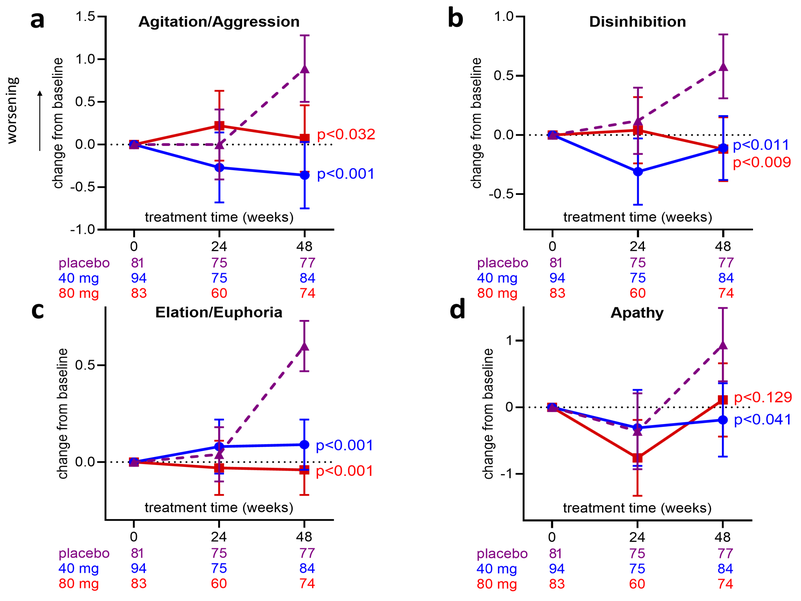


Figure 3. Analysis of atuzaginstat treatment effect reveals benefit on a cluster of neuropsychiatric symptoms including agitation.



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.

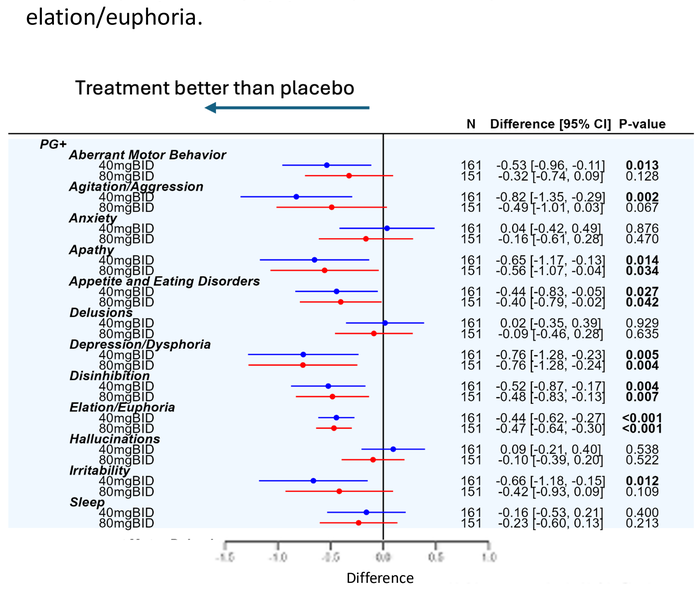
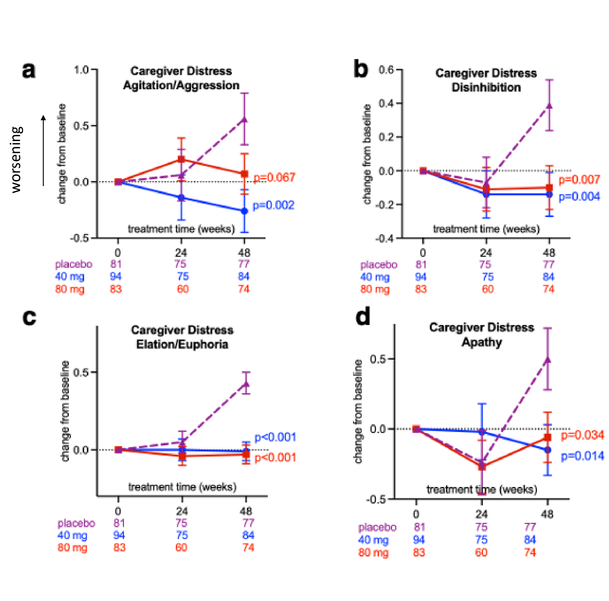


Figure 5. Analysis of atuzaginstat treatment effect reveals benefit on a cluster of neuropsychiatric subdomains demonstrated nominally significant benefit (lower symptom scores) compared to placebo.



Ongoing: SPRING Trial: 300 patients with Pg+ AD

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

www.springclinicaltrial.com

