PHASE 1 SAD/MAD DATA AND PHASE 2 STUDY DESIGN FOR LHP588, A NEXT-GENERATION GINGIPAIN INHIBITOR FOR THE TREATMENT OF *P. GINGIVALIS*-POSITIVE ALZHEIMER'S DEMENTIA

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Abstract

Background: Gingipains are toxic protease virulence factors from the bacterial pathogen *P. gingivalis* (*Pg*) that were discovered in postmortem brains of patients with Alzheimer's disease (AD). Gingipain levels correlated with AD diagnosis and tau pathology, and oral infection of wild-type mice with *Pg* resulted in brain inflammation, neurodegeneration, and Aβ42 production that was blocked by gingipain inhibitors [1]. LHP588 is a second-generation orally bioavailable and brain-penetrant lysine-gingipain inhibitor that reduces the toxicity of *Pg* and the bacterial load. In a prior Phase 2/3 study of COR388 (atuzaginstat) (NCT03823404), a first-generation lysine-gingipain inhibitor, the primary intent-to-treat prespecified endpoint was not met. However, prespecified subgroup analyses indicated efficacy in patients with *Pg*-positive saliva (*Pg*+) (N = 244), slowing cognitive decline compared with placebo on the ADAS-Cog11 by 57% in the high-dose group (p =0.02) [2]. Changes in *Pg* DNA in saliva correlated significantly with changes on the ADAS-Cog, CDR-SB, and MMSE. Atuzaginstat was generally well tolerated but development was discontinued because of liver transaminase elevations that demonstrated significant correlations with high levels of an inactive metabolite, M9. The supportive data from the atuzaginstat clinical trial informed the development of the approach, target, and population for clinical testing of LHP588 in mild-to-moderate AD with biomarker evidence of *Pg* infection. We will review new data from the LHP588 SAD/MAD, and the design of the Phase 2b study.

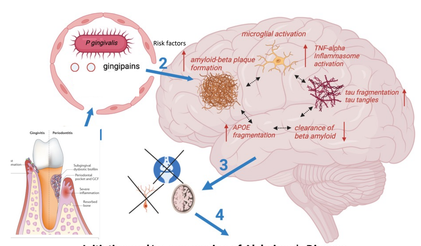
Methods: The Phase 1 study of LHP588 enrolled 32 healthy volunteers in the SAD component with 4 cohorts and concurrent placebo (25 mg, 50 mg, 100 mg, 200 mg) and 24 healthy volunteers in the 10-day MAD portion, with 3 cohorts and concurrent placebo (50, 100 mg, and 200 mg). There were also tests of the effect of food on the PK, and of brain penetrance by assessment of LHP588 exposure in CSF.

Results: The second-generation lysine gingipain inhibitor LHP588, which doesn't create the M9 metabolite produced by atuzaginstat, was well-tolerated in the SAD and 10-day MAD study. Adverse events in the active arms were mild and sporadic and fewer than the placebo arm. PK with once-daily dosing achieved target concentrations predicted to be sufficient for reduction of systemic *Pg* infection at doses >25 mg of LHP588, and exposures equivalent or greater than those achieved with the high dose of atuzaginstat. LHP588 was also detected in the CSF. The dose of 200mg, 4x the highest dose planned for further development (50mg), achieved approximately 7x the exposure of the 50 mg dose, further supporting the overall safety index.

Conclusion: LHP588 was well-tolerated in healthy volunteers without evidence of hepatic safety signals to date, and its PK profile was supportive of once daily dosing. The Phase 2 trial of LHP588 will be similar in design to the prior atuzaginstat study but will be restricted to subjects with *Pg*+ saliva.

Atuzaginstat Ph 2/3 GAIN Trial: Rationale & Trial Design

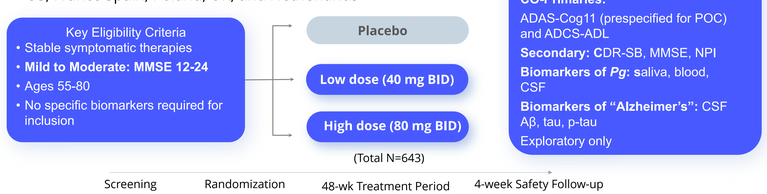
Figure 1. *P. gingivalis* Mechanism of Action in Alzheimer's disease



Ryder et al. 2022

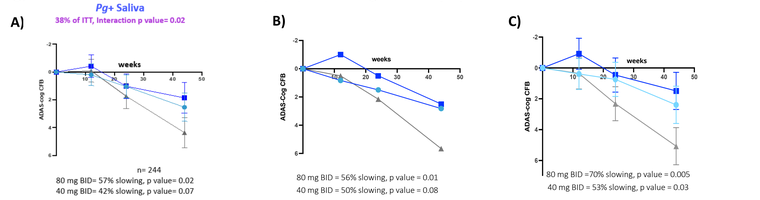
Figure 2. Completed Phase 2/3 GAIN Trial

- Enrollment initiated April 2019
- Last Patient Visit September 2021- on time during peak of COVID
- Global study with >90 sites
- US, France Spain, Poland, UK, and Netherlands



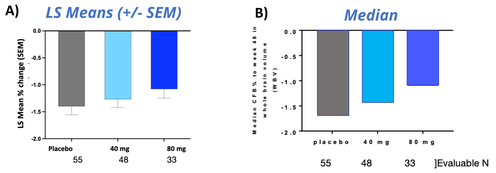
Atuzaginstat Phase 2/3: Efficacy

Figure 3. Efficacy demonstrated in prespecified *Pg*+ saliva population



A) Prespecified Analysis ADAS-Cog, MMRM *LSMeans (+/- SEM)
B) Prespecified Nonparametric sensitivity analysis
C) Post hoc inclusive covariate model

Figure 4. MRI Whole Brain Volume (WBV) Atrophy from Baseline to 48 weeks

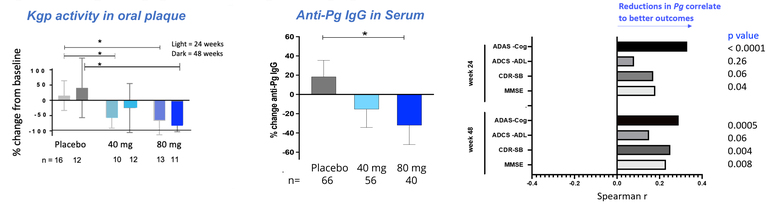


C)

	ADAS-Cog11	ADCS-ADL
Spearman's rho (CFB to Week 48)	0.58	0.44
P-value	<0.0001	<0.0001

A) LS Means +/- SEM
B) Medians
C) Correlations in WBV at Week 48 with Week 48 clinical outcomes

Figure 5. Target engagement: Changes in *P. gingivalis* infection correlate to improved outcomes



Atuzaginstat Phase 2/3: Safety

- Hepatic safety signal: Liver transaminase (ALT, AST) elevations >3X ULN were observed in 2% of participants on placebo, 7% on 40 mg BID, 15% on 80 mg BID. Two cases also had bilirubin elevations >2X ULN without a definitive alternative cause; both cases were in the 80 mg BID arm.
- **No evidence of ARIA, microhemorrhages, superficial siderosis or any other imaging safety signals.**
- Otherwise well-tolerated with diarrhea (14%), headache (8%), nausea (6%) as the most common AEs reported by participants.
- **Statistically significant relationship was found between the major liver metabolite of COR388, M9, and maximum AST (p-value= 0.0005) and maximum ALT (p-value= 0.0013).**
- COR388 metabolite M9 is at high levels in liver at levels (Cmax= 50 uM) that could inhibit BSEP (IC50 = 50 uM) and cause subsequent hepatic signals;
- **LHP588 does not make the M9 metabolite.** LHP588 has only two known human metabolites present at lower levels that do not inhibit BSEP or other transporters up to tested concentrations of 300 uM.

Disclosures: MD, MS, JB, JW, MR, LJH, CL, SD own Lighthouse Pharmaceuticals stock. The other authors declared no competing interests.

References:
1. Dominy SS, et al. Sci Adv 2019; Jan 23;5(1):eaau3333. doi: 10.1126/sciadv.aau3333
2. Detke MJ, et al. AD/PD Conference 2022; Mar 23: https://www.vjdementia.com/video/tjympcjxwx0

Next Generation Small Molecule: LHP588

Novel & proprietary small molecule → New structure, same therapeutic mechanism of action as COR388; covalent binding to active site

Potent→ Target IC50 = 0.32 nM, 90% free drug in plasma

Designed for improved selectivity / safety→ Selectivity vs. known COR388 anti-targets: cathepsins, BSEP, ion channels

Designed for improved PK→
- **Once a day vs. twice a day dosing demonstrated in human Phase 1**
- High brain tissue levels and increased free CSF levels
- Rapid clearance of major liver metabolite (10x reduced liver levels)

Figure 6. Mouse PK 10 mg/kg po

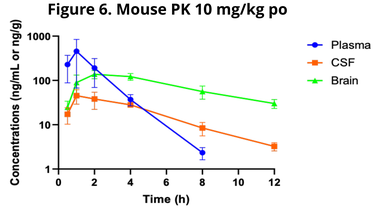


Table 2. Mouse PK: Comparison of COR388 (atuzaginstat) and LHP588

	COR388	LHP588
% unbound drug in plasma (range across species)	15 - 30%	70 - 90%
Human ½ life	1.8 - 4.5 hrs	8 -12 hrs
Brain: plasma ratio AUC	1.04	1.20
CSF: plasma ratio AUC	0.03	0.28

LHP588 Phase 1: MAD/SAD Safety & Outcome

- **Study enrolled:**
  - 32 subjects in the SAD component (placebo, 25 mg, 50 mg, 100 mg, 200 mg)
  - 24 subjects in the 10 day MAD component (placebo, 50 mg, 100 mg, 200 mg)
- **Well tolerated, supporting safety and once-daily oral dosing**
  - No moderate or severe AEs; no SAEs; no clinically significant safety findings
  - No evidence of abnormal liver enzyme elevations at any dose
  - **Excellent PK, T1/2 = 10 hrs**
  - Consistent with once a day dosing 25-50 mg (>80 mg BID COR388 AUC equivalent)
  - Ratio Parent: major metabolite = 0.5
  - **Exposures in CSF in all subjects tested**

Figure 7. LHP588 Plasma Levels

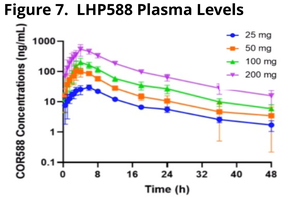


Table 3. Potentially Drug-Related Adverse Events in MAD

	Placebo	50 mg	100 mg	200 mg
Subjects (n)	6	6	6	6
ECG findings	2 (33%)	1 (17%)	0	0
Headache	1 (17%)	0	2 (33%)	0
Visual Impairment	1 (17%)	0	0	0

LHP588 Phase 2b: SPRING Trial

- **SPRING trial: S**topping **PR**ogression of *P. gING**ivalis*** associated dementia with gingipain inhibition
- PIND with FDA completed May 2023, IND submitted Oct 2023
- Doses selected provide ≥ 80 mg BID free drug exposure (AUC) in COR388 study
- Simplified trial design and improved SAP based on learnings
- **De-risked execution based on learnings from GAIN trial**
- To be conducted in US, Australia, Poland