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

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Abstract

Background: Gingipains, toxic protease virulence factors from the bacterial pathogen *P. gingivalis* (*Pg*), were discovered in postmortem brains of patients with Alzheimer's disease. Gingipain levels correlated with tau and ubiquitin pathology, and oral infection of wild-type mice with *Pg* resulted in brain inflammation and neurodegeneration that was blocked by gingipain inhibitors.

LHP588 is a second-generation orally bioavailable and brain-penetrant lysine gingipain inhibitor that reduces the toxicity of *Pg* and the bacterial load. A first-generation molecule (COR388/atuzaginstat) previously showed reduction of cognitive decline in prespecified cohorts defined by their infection load, but it was discontinued due to hepatic safety signal. We will review new data from the LHP588 SAD/MAD, and the design of the Phase 2b study planned for initiation later this year.

Method: The Phase 1 study of LHP588 enrolled 32 individuals in the SAD component with 4 cohorts and concurrent placebo (25 mg, 50 mg, 100 mg, 200 mg) and 24 healthy subjects in the 10-day MAD portion with 3 cohorts and concurrent placebo (50 mg, 100 mg and 200 mg).

Result: In the study of atuzaginstat, significance was not observed in the full intent-to-treat population, however, prespecified subgroup analyses indicated efficacy in the patients with *Pg*-positive saliva (*Pg*+), slowing cognitive decline compared with placebo on the ADAS-Cog11 by approximately 50% (p= 0.02). Changes in *Pg* DNA in saliva correlated significantly with changes on the ADAS-Cog, CDR-SB, and MMSE.

The second-generation lysine gingipain inhibitor LHP588 was well-tolerated in the SAD and 10-day MAD study; adverse events in the active arms were mild and sporadic. PK with once-daily dosing achieved target concentrations 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.

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 proposed to start in 2024 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

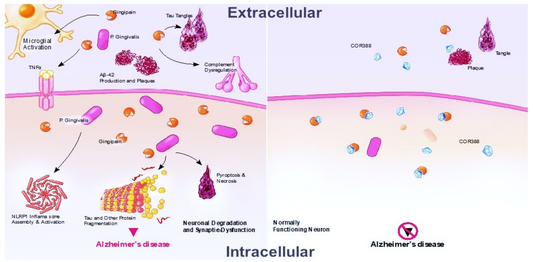
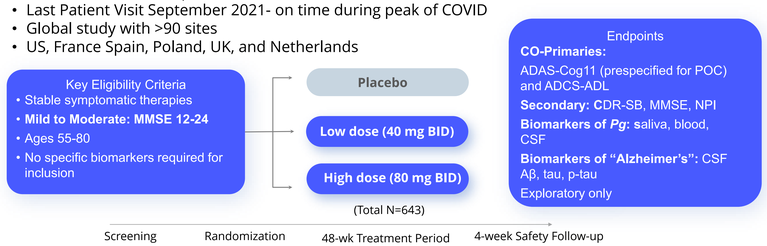


Figure 2. Completed Phase 2/3 GAIN Trial

- 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



Disclosures & Acknowledgements:
Dr. Detke is a co-founder of Lighthouse Pharma and holds equity in the form of stock.
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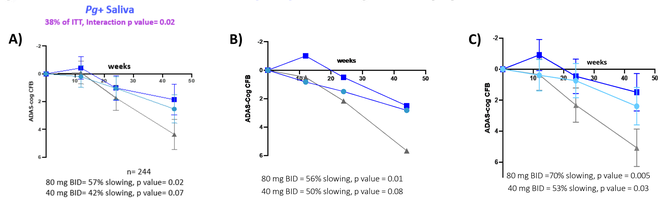
Atuzaginstat Phase 2/3: Efficacy

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

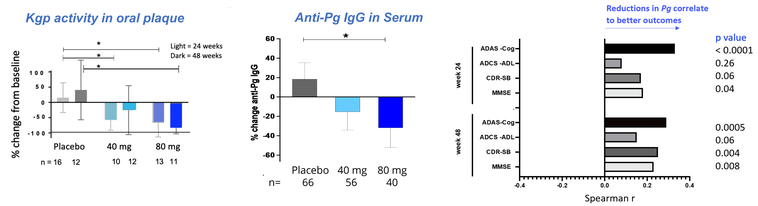
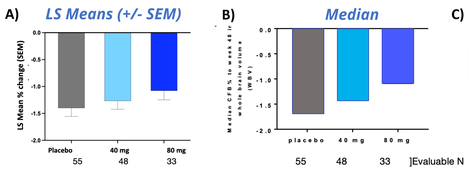


Figure 5. MRI Whole Brain Volume (WBV) Atrophy from Baseline to 48 weeks



	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

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. FDA placed COR388 on full clinical hold.
- **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.
- COR388 metabolite M9 is at high levels in liver at levels that could inhibit BSEP and cause subsequent hepatic signals; **LHP588 de-risked for this.**

Table 1. Comparison of COR388 (atuzaginstat) and LHP588

Table 1	COR388	LHP588	LHP588 Improvements
Bile salt exporter pump (BSEP)	M9, IC50 = 50 uM	M5, IC50 > 300 uM	Potential >> 60x increased safety window based on this mechanism
Projected peak liver levels of major reductive (inactive) liver metabolite	M9, Cmax = 50 uM	M5 Cmax = 5 uM	

Statistically significant relationship between the major liver metabolite of COR388, M9, and maximum AST (p-value= 0.0005) and maximum ALT (p-value= 0.0013).

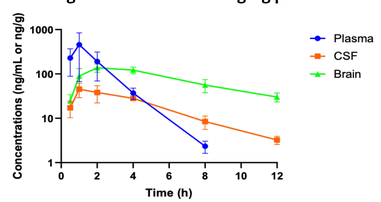
Next Generation Small Molecule: LHP588

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)

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

Figure 6. Mouse PK 10 mg/kg po



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 and CSF levels, 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

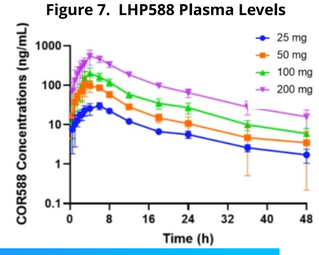


Table 3. Potentially Drug-Related Adverse Events in MAD

	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. g**ING**ivalis* associated dementia with gingipain inhibition
- PIND with FDA completed May 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**
- Primarily in US, Australia, Poland