Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

Gingipain Inhibitors (COR338 / Atuzaginstat, COR588 / LHP588)

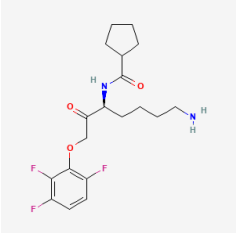
Evidence Summary

P. gingivalis is observationally associated with dementia. Small studies hinted at benefit of gingipain inhibitors in certain dementia patients but had serious hepatic safety concerns.

Neuroprotective Benefit: There is observational evidence of an association between periodontal infection and dementia, but there is little evidence that gingipain inhibitors are neuroprotective. Dental hygiene appears to be a modifiable dementia risk factor.

Aging and related health concerns: There is observational evidence of an association between periodontitis and cardiovascular disease, but gingipain inhibitors have not been tested in humans for these indications. Oral health is a modifiable risk factor.

Safety: There is limited in-human data, and a study of a first-generation gingipain inhibitor was placed on full clinical hold because of serious hepatic adverse effects. The second generation is reported to have a better safety profile, but more data is needed.

Availability: in clinical development	**Dose**: The planned dose for further COR388 studies was 40 mg twice daily. COR588 was tested from 20 mg to 200 mg.	**Chemical formula:** COR388: $C_{19}H_{25}F_3N_2O_3$ **MW**: 386.4  Source: PubChem
Half-life: COR388: 4.5 – 4.9 hours COR588/LHP588: 11-12 hours	**BBB**: Penetrant	
Clinical trials: COR388: 710 participants COR588: 64 participants	**Observational studies**: None	COR588: Not available

What is it?

As reviewed by Bostanci & Belibasakis and Olsen & Potempa (Bostanci & Belibasakis, 2012; Olsen & Potempa, 2014), *Porphyromonas gingivalis* (*P. gingivalis*) is a bacterial species that is commonly associated with chronic periodontitis. It is a Gram-negative anaerobe. *P. gingivalis* is an opportunistic, late colonizing pathogen that is rarely found at high levels in healthy tissue. Virulence factors are molecules that a bacterium produces to help colonize a host, and gingipains are one of the primary factors of *P. gingivalis*.

Gingipains are a group of cysteine proteinases that are often on the cell surface but can also be secreted in a soluble form. There are two classifications of gingipains, based on their substate: arginine-specific (Rgp) and lysine-specific (Kgp) gingipains. Cutting peptides or proteins allows the bacterium to promote their own survival in numerous ways. For instance, in order to help evade immune system detection, gingipains can cleave host immune cell receptors that are necessary for immune system activation; gingipains can stimulate or dampen different immune processes; they can digest host proteins to provide nutrients necessary for bacterial growth. Gingipains can also increase vascular permeability and

bleeding at sites of infection. The opposing effects of gingipains on immune processes help *P. gingivalis* adapt to the local microenvironment.

P. gingivalis is resistant to many antibiotics, calling for alternative approaches to managing this pathogen. Knocking out gingipains and/or immunizations against gingipains significantly reduce the virulence of *P. ginglivalis*. Inhibitors of gingipains are therefore of interest for periodontal disease, along with various health conditions that have been associated with periodontal disease such as cardiovascular disease, pre-term birth, and dementia. Inhibitors may be against either Rgp, Kgp, or both; it is not settled whether it is necessary to target both types of gingipains, or whether Rgp or Kgp is more useful to target clinically. There are a variety of types of gingipain inhibitors, such as synthetic inhibitors, antibiotics, and inhibitors from natural sources like plant polyphenols, though many of the inhibitor action has been shown in preclinical contexts rather than in humans. Many of these preclinical inhibitors are listed, in references, in the reviews by Olsen & Potempa, 2014 and Chow et al., 2022. A group of related small molecule gingipain inhibitors including KYT-1, KYT-36, and KYT-41 have been tested in animals. KYT-1 and KYT-36 both mitigated some of the effects of *P. gingivalis* infection after direct injection of the pathogen into the brain in mice (Liu et al., 2017). KYT-41 inhibits both Rgp and Kgp gingipains and appeared to be most advanced experimentally, having been tested in guinea pigs and dogs (Kataoka et al., 2014). Literature on these compounds is sparse.

COR388 and COR588, two small molecule inhibitors of Kgp gingipains, are some of the only gingipain inhibitors tested in humans for the purpose of gingipain inhibition.

This report will therefore focus on COR388 (Atuzaginstat) and a second-generation inhibitor LHP588 (also named COR588). Both COR388 and COR588 were originally developed by Cortexyme. COR388 advanced to Phase 2/3 trial in patients with mild to moderate AD but missed its two primary endpoints assessing cognitive function. Cortexyme reported a potential benefit in patients who had *P. gingivalis* DNA detectable in their oral cavity (Press release).

Cortexyme began and successfully completed a Phase 1 trial of COR588, another gingipain inhibitor. COR588 demonstrated a half-life that allowed once daily dosing instead of the twice daily dosing called for with COR388 (Press release). They also planned to test COR388 in patients with evidence of *P. gingivalis* infection, as assessed by oral swab, and also test in patients with Parkinson's disease, based on their Phase 2/3 results.

However, a full clinical hold was placed on COR388 due to concerns about liver toxicity before they could begin further trials of COR388. Cortexyme subsequently changed their name to Quince and discontinued the gingipain inhibitor program. In January 2023, Quince announced they had sold the small molecule protease inhibitor portfolio to Lighthouse Pharmaceuticals, which is co-founded by a former CEO of Cortexyme.

Neuroprotective Benefit: There is observational evidence of an association between periodontal infection and dementia, but there is no evidence that gingipain inhibitors are neuroprotective. Dental hygiene appears to be a modifiable dementia risk factor.

Types of evidence:

- 1 meta-analysis
- 2 clinical trials
- 11 observational studies
- 6 reviews
- 7 laboratory studies

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function:

No in-human studies were found that tested or explored the use of any gingipain inhibitors for prevention of dementia, decline, or on improved cognitive function.

There is epidemiological evidence from several studies that periodontitis - and thus *P. gingivalis* infection- and concomitant gingipain activity may increase risk of dementia or cognitive impairment, and some evidence that dental treatment may be protective, thus providing a theoretical rationale for testing gingipain inhibitors for dementia prevention and/or treatment. It should be noted that there are other possibilities, including that (1) dementia is a risk factor for periodontal disease, whether through malnutrition or poor oral hygiene or (2) that periodontal disease and dementia have risk factors in common, such as education levels, so controlling for different variables and/or assessing incidence of dementia in populations that have already been diagnosed with periodontitis can be particularly useful.

A 2020 systematic review and meta-analysis assessed for possible association between periodontal disease and increased risk of dementia in cohort and case-control studies. The paper included 12 total studies, though data was only available from 7 of those studies for statistical analysis in the meta-analysis. The studies either compared dementia patients to cognitively intact patients and assess for periodontal disease, or followed patients with diagnoses of periodontitis and assessed incidence of subsequent dementia diagnosis. Those 7 studies included 226,628 patients, and the cohort studies all had follow-up periods of at least 8 years. The authors found that periodontal disease was significantly associated with dementia (RR=1.38; 95%CI 1.01 – 1.90) (Nadim et al., 2020).

A 2015 study examined the association between periodontal disease and Aβ load as measured by ^{11}C-Pittsburgh compound B (PIB) PET scan in 38 cognitively intact elderly people, all of whom had at least 12 years and a mean of 17.6 years of education. They found that dental measures associated with periodontal inflammation and/or infectious burden were associated with increased PIB uptake in regions vulnerable to Aβ accumulation such as the prefrontal cortex (p=0.002) (Kamer et al 2015).

While the above studies look at periodontitis rather than *P. gingivalis* specifically, a 2009 paper looked at 2,355 participants 60 years or older in the Third National Health and Nutrition Examination Survey (NHANES-III). NHANES-III was a cross-sectional nationwide health survey performed between 1988 and 1994. The researchers looked at the level of serum antibodies against *P. gingivalis* and sought to determine whether there was an association between the level and cognitive performance. After adjusting for vascular and socioeconomic factors, they found that people with the highest levels of antibodies against *P. gingivalis* were more likely to have impaired delay recall (OR 3.01; 95% CI 1.06 – 8.53) and difficulty with serial subtraction (OR 2.00; 95% CI 1.19 – 3.36) (Noble et al 2009).

Human research to suggest benefits to patients with dementia:

Some studies have found associations between periodontal infection and rate of decline. A 2016 study enrolled 60 patients with mild to moderate dementia. The researchers assessed their cognitive function and dental health at baseline and then again 6 months later. The authors did not find a differences in cognitive function between patients with and without periodontitis at baseline, but did find that patients with periodontitis at baseline had a faster rate of decline as measured by ADAS-cog as compared to patients who did not have periodontitis at baseline (mean difference=4.9; 95% CI 1.2 – 8.6, p=0.01) (Ide et al., 2016).

A randomized trial of 417 patients in nursing homes in Japan examined the impact of regular oral care from staff and a dental hygienist versus no given oral care over the course of 2 years on pneumonia, death from pneumonia, activities of daily living (ADL), and cognitive function as measured by MMSE. The authors found that patients not given care were more likely to develop pneumonia (RR=1.67; 95% CI 1.0 1– 2.75, P < .05) and die from pneumonia (RR=2.40; 95% CI 1.54 – 3.74, P < .01). Patients in the non-oral care group had a higher rate of mortality (RR=3.20; 95% CI 1.34 – 7.64, P < .05). Excluding the data from patients who died from pneumonia, the authors found that both ADL and MMSE scores trended towards improvements with oral care, but only the MMSE was significantly improved in the oral care group as compared to the no-oral care group at 24 months (P < .05) (Yoneyama et al 2002).

A 2019 paper from Dominy and colleagues reported on rationale for and development of COR388, a small molecule inhibitor of lysine-specific gingipains. The group first examined tissue samples from 29 AD patients and 29 age- and sex-matched controls and reported that the gingipain load was significantly higher in AD patients, and that gingipain load correlated significantly with tau load. As a control, they also probed brain tissue from patients with other neurodegenerative diseases (Parkinson's disease, Huntington's disease, and ALS) and did not identify differences between the gingipain load in patients with those neurodegenerative diseases and that of controls.

The authors then reported on their developments of small molecule inhibitors of gingipains, all named COR with number identifiers. Using a variety of dosing strategies, they report that their inhibitors COR119, COR271, COR286, and COR388 – all oral or subcutaneous formulations – protect against neurodegeneration caused by direct gingipain injection into the brain of mice and reduce brain *P. ginglivalis* load, Aβ42 levels, and TNFα levels after oral infection with *P. ginglivalis* compared to mice given vehicle control. The authors reported that COR388 had superior pharmacokinetic properties and moved on to clinical trials using COR388 (Dominy et al., 2019).

COR388 completed Phase 2/3 trial (the GAIN study) before COR388 was placed under a full clinical hold. GAIN randomized 643 patients with mild to moderate AD to placebo, 40 mg COR388 twice daily, or 80 mg of COR388 twice daily. The co-primary endpoints were ADAS-Cog11 and ADCS-ADL, and secondary endpoints were the CDR, MMSE, and Neuropsychiatric Inventory. Biomarker data including CSF levels of Aβ, tau, and p-tau, and volumetric changes by MRI were also collected. The study also prespecified subgroups of markers of *P. gingivalis* infection for analysis, such as salivary *P. gingivalis* DNA and antibodies against *P. gingivalis* in serum and CSF.

The results of GAIN were presented at and ahead of CTAD 2021. The study investigators did not see any cognitive benefit of COR388 in their overall patient population. In their prespecified subgroup analyses they found that in patients who had detectable *P. gingivalis* DNA in their saliva, there was a consistent 30 – 50% slowing of cognitive decline as measured by ADAS-Cog in the 40 mg BID and the 80 mg BID group. When they performed a pre-specific correlation between reduction in salivary *P. gingivalis* DNA and cognitive measures, they found significant correlations between reduction of salivary *P. gingivalis* DNA and improvement in ADAS-Cog, CDR-SB, and MMSE.

Mechanisms of action for neuroprotection identified from laboratory and clinical research:

There are a number of potential mechanisms of action for neuroprotection of gingipain inhibitors. Some mechanisms may be indirect. Periodontitis involves chronic inflammation, which can impact the brain. As gingipains are a virulence factor of *P. gingivalis* – that is, that gingipains help *P. gingivalis* colonize hosts – gingipain inhibitors can treat periodontitis and the concomitant systemic inflammation. Periodontitis is also linked to cardiovascular risk factors such as stroke that can then impact neuronal health; therefore, gingipain inhibitors could indirectly improve cardiovascular health, and thus brain health.

Gingipain inhibitors may also exert more directly neuroprotective effects. One experimental study infected wild-type mice with *P. gingivalis* and found that infected mice had impairments in learning and memory, and also increased levels of inflammatory cytokines in the brain (Ding et al., 2018). Another experimental study detected *P. gingivalis* and gingipains in the brains of wild-type mice infected with *P. gingivalis*, and also found Aβ plaques, neurofibrillary tangle (NFT) pathology mice, increased levels of inflammatory cytokines, increased expression of genes associated with increases in amyloid (APP and BACE1), and neurodegeneration in the hippocampi of these wild-type mice. They did not see any of these signs in the brains of control mice (Ilievski et al., 2018). Treating mice with the gingipain inhibitor COR388 after oral infection with *P. gingivalis* led to reduction in brain amyloid load and TNFα levels, and mitigated neural loss (reviewed in Sabbagh and Decourt 2022).

As reviewed in Kanagasingam et al., 2020, gingipains may be detrimental to neuronal health through cleaving APP to produce Aβ fragments. Gingipains may also cleave tau. Cleavage products from both of these proteins may be toxic. While *P. gingivalis* may access the brain through a blood-brain barrier already compromised by other disease processes or peripheral inflammation, it is also possible that gingipains themselves could damage the blood-brain barrier. Gingipains also activate inflammatory

signaling that can lead to downstream consequences such as tau hyperphosphorylation. Effective gingipain inhibition would decrease or eliminate these effects as mediated by gingipains.

APOE4 interactions:

Gingipains may cleave ApoE and demonstrate an isoform preference, cleaving ApoE4 > ApoE3 > ApoE2. This cleavage difference appears to be because of the three-dimensional structure of the proteins (Sabbagh & Decourt, 2022).

Raha and colleagues reported that they observed more low molecular weight ApoE fragments in the CSF of AD patients than in non-AD patients. The authors also reported that after 28 days of treatment with COR388, that they detected significantly less ApoE fragments in AD patients treated with COR388 compared to AD patients who received placebo. The brief did not include figures or other statistical information (Raha et al., 2020).

Aging and related health concerns: There is observational evidence of an association between periodontitis and cardiovascular disease, but gingipain inhibitors have not been tested in humans for these indications. Oral health is a modifiable risk factor.

Types of evidence:

- 2 meta-analyses
- 2 observational studies
- 1 laboratory studies

As reviewed by Chow et al., 2022 and Breigant et al., 2022, among others, *P. gingivalis* and its gingipains may play a role in a variety of conditions including diabetes, aspiration pneumonia, and cardiovascular disease through degradation or dysregulation of proteins and immune system components. While there is therefore mechanistic basis for theoretical benefit of gingipain inhibitors, these inhibitors have largely not been tested in these conditions and so remain only a theoretical benefit rather than even a potential one. The strongest evidence thus far appears to be in plaque formation, through mechanisms such as platelet aggregation induced by gingipains.

CARDIOVASCULAR AND CEREBROVASCULAR DISEASE: POTENTIAL BENEFIT

Observational studies have found a potential link between periodontitis and atherosclerosis.

A study of subjects nested in a random population-based sample followed 986 patients over 15 years. The authors found that in the 893 patients who did not have cardiovascular disease at baseline, patients who had antibodies against *P. gingivalis* also had a higher odds of stroke as compared to those who were seronegative (OR=1.63; 95% CI 1.0 6– 2.50 for men; OR=2.30; 95% CI 1.39 – 3.78 for women) (Pussinen et al., 2007).

Two recent meta-analyses examined the association of periodontitis and stroke and found a significant association, though also found heterogeneity and/or methodological issues depending upon the type of study included.

Leira et al., 2017 included cohort, case-control, and cross-sectional studies that assessed periodontitis in ischemic stroke patients. They found significant results but high heterogeneity when combining all study types and when looking just at case-control studies. When looking just at cohort studies (total n=12,246), they found less heterogeneity but significant association between periodontitis and stroke as compared to no periodontitis (cohort pooled RR=2.52; 95% CI 1.77 - 3.58) (Leira et al., 2017).

Fernandes Fagundes et al., 2019, included observational studies where patients with periodontitis were compared to patients without, and the primary outcome was risk of cerebrovascular event. They included 10 studies in their analysis. They found a higher incidence of stroke in patients with periodontitis as compared to those without periodontitis in cohort studies (RR=1.88; 95% CI 1.55 - 2.29, n=28,900) The authors also found a higher incidence of ischemic stroke events in patients with periodontitis compared to those without periodontitis in case–control studies (RR=2.72; 95% CI 2.00 - 3.71, n=1,015) (Fernandes Fagundes et al., 2019).

A study examined the effects of COR388 on atherosclerotic plaques and systemic inflammation as assessed by C-reactive protein (CRP) in rabbits. The researchers induced atherosclerosis through diet high in cholesterol in the rabbits, then compared a group that was sham infected vs. a group infected with *P. gingivalis* and vehicle treatment vs. a group infected with *P. gingivalis* and treatment with COR388. The authors report that the rabbits infected with *P. gingivalis* had more severe atherosclerosis as compared to sham-infected animals, but that COR388 treatment reduced arterial plaques and

systemic levels of CRP. The brief did not include figures or other statistical information (Ermini et al., 2020).

Safety: There is limited in-human data, and a study of a first-generation gingipain inhibitor was placed on full clinical hold because of serious hepatic adverse effects. The second generation is reported to have a better safety profile, but more data is needed.

Types of evidence:

- 1 Phase 2/3 trial
- 2 Phase 1 trials

COR388 has been tested in a Phase 1 and a Phase2/3 trial. COR588/LHP588 has been tested in a Phase 1 trial. All clinical results have been reported as press releases or posters or talks at conferences rather than as peer-reviewed publications.

The Phase I study tested a range of doses in healthy adults, cognitively intact older adults, and in AD patients (AlzForum). They tested doses of 5 to 250 mg of COR388 or placebo in 34 healthy adults. They then tested 25, 50, and 100 mg doses of COR388 or placebo every 12 hours for 10 days in 24 healthy older adults, and 50 mg or placebo every 12 hours for 28 days in 9 AD patients.

In a single-dose study of 5 to 250 mg capsules in 34 healthy adults, the compound was safe and well-tolerated. A multiple-dose study assessed safety and tolerability in 24 healthy older adults (mean age of 60 years) and nine with AD (mean age 72). According to a company press release and a poster presentation at the 2018 CTAD conference (lead author Mark Ryder), healthy adults received 25, 50, or 100 mg COR388 or placebo every 12 hours for 10 days; AD patients took 50 mg or placebo every 12 hours for 28 days. The pharmacokinetic profiles of COR388 in AD and controls were reported to be similar.

The Phase 2 study of COR388, named GAIN, randomized 643 patients with mild to moderate AD to placebo, 40 mg COR388 twice daily, or 80 mg of COR388 twice daily. The co-primary endpoints were ADAS-Cog11 and ADCS-ADL, and secondary endpoints were the CDR, MMSE, and Neuropsychiatric Inventory. They collected biomarker data including CSF levels of Aβ, tau, and p-tau, and volumetric

changes by MRI. The study also prespecified subgroups of markers of *P. gingivalis* infection for analysis, such as salivary *P. gingivalis* DNA and antibodies against *P. gingivalis* in serum and CSF (AlzForum).

In February 2021, the FDA placed a partial hold on COR388 due to concerns about liver adverse effects. In line with this hold, Cortexyme discontinued dosing in the open label extension, but continued the placebo-controlled portion of their trial.

In the fall of 2021, Cortexyme announced that they had missed both of the co-primary endpoints, though subgroup analysis indicated that patients with certain indicators of *P. gingivalis* infection benefitted (See "Human research to suggest benefits to patients with dementia" section for more details; a news release also covers some details). They presented results at CTAD 2021. These are the most detailed clinical data available about gingipain inhibitors. Eight of 217 placebo patients (3.7%) experienced adverse events that led to discontinuation in the study, in comparison to 38 of 212 (17.9%) in the 40 mg BID COR388 group, and 35 of 214 (16.4%) in the 80 mg BID COR388 group (clinicaltrials.gov results).

The news release also noted that '[the liver enzyme] elevations alone were not clinically significant and virtually all participants were asymptomatic' (Press release).

Liver enzyme elevations more than 3 times the upper limit of normal were seen in 2% of placebo patients, 7% of 40 mg BID COR388 patients, and 15% of 80 mg BID COR388 patients. Cortexyme reported that hepatic experts consider these elevations to be not significant in isolation. Two of these patients additionally had bilirubin elevations more than 2 times the upper limit of normal; both were in the 80 mg BID COR388 group. If the patient experienced these elevations, they were typically seen around 6 weeks after start of treatment. Cortexyme also reported that these elevations resolved without any long-term adverse effects while on the study drug or after discontinuation (Press release). In light of these data, they planned to do a confirmatory trial in a subgroup of patients with *P. gingivalis* infection, dosing at 40 mg BID with titration.

However, in January 2022, the FDA placed a full clinical hold on COR388 because of hepatic adverse effects. This may be in accordance with FDA guidelines on avoiding drug-induced liver injury based on what's known as 'Hy's Law'. If a drug causes (1) elevations of more than 3 times the upper limit of normal in the liver enzymes ALT or AST, and (2) elevation of bilirubin more than 2 times the upper limit of normal, in the absence of (3) any other explanation, such as alcohol abuse or viral hepatitis, that

patients experiencing these conditions has a 10-50% chance of a liver transplant. The official guidance is that finding one patient who meets Hy's Law is concerning, but finding two is 'highly predictive that the drug has potential to cause severe drug induced liver damage' in a larger population.

At the time of the full clinical hold, Cortexyme had an ongoing Phase I trial of COR588. Cortexyme announced that they would prioritize development of COR588, pending the results of the Phase I trial.

In July 2022, Cortexyme announced the results of the Phase I trial of COR588. The trial enrolled 64 healthy adults and tested both a single ascending dose and a multiple ascending dose. The single ascending dose included doses between 25 and 200 mg. The multiple ascending dose included once daily doses of between 50 and 200 mg for 10 days. No serious adverse events were reported. The company also stated that no 'clinically significant findings' were observed on safety measures, which included vital signs, ECG, laboratory findings, and telemetry. Cortexyme stated that 'no clinical chemistry or hematology safety concerns were reported at any dose'.

Drug interactions: Drug interactions have not been reported for either COR388 or COR588.

Research underway:

There are currently no ongoing registered trials on COR588; the Phase 1 study has been completed. There is a full clinical hold on COR388 that was placed after the Phase 2/3 trial was completed. There are four ongoing or soon-to-start studies investigating possible links between dementia and periodontitis and/or *P. gingivalis*.

NCT05557617 is examining CSF and medical records, including dental records, from patients with and without dementia in a Swedish memory clinic, to assess if there is any association between periodontitis, *P. gingivalis* DNA, gingipain protein, gingipain enzyme activity, or antibodies against *P. gingivalis* and dementia diagnosis or cognitive function.

NCT04869904 and NCT05077618 are two trials for the same overall study in France that seeks to characterize and compare the oral bacterial and viral species in patients with dementia and those without dementia.

NCT05189132 is a study in Portugal that will examine the association between periodontitis and AD, and/or severity of AD, by performing dental examinations and cognitive assessments on both dementia patients and healthy controls. The researchers will also compare inflammatory and microbiological measures between groups.

Search terms:

Pubmed, Google: gingipain inhibitors, COR388, COR588, LHP388, LHP588

- +dementia, +Alzheimer's, +APOE

Websites visited for COR388 & COR588

- Clinicaltrials.gov: COR388, COR588
- PubChem
- Cafepharma