An update and baseline data from the Phase 2/3 GAIN trial of COR388 (atuzaginstat) a novel bacterial virulence factor inhibitor for the treatment of Alzheimer's Disease

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Abstract

Background: The novel mechanism of action of atuzaginstat is based on the discovery of gingipains, toxic protease virulence factors from the bacterial pathogen *Porphyromonas gingivalis* (Pg), in >90% of Alzheimer's disease (AD) brains (ref 1). Gingipain levels correlated with AD diagnosis and tau and ubiquitin pathology, and oral infection of mice with Pg results in classic AD pathology that can be blocked by atuzaginstat, an irreversible lysine-gingipain inhibitor (ref 1 and ref 2). Pg is best known for its role in periodontal disease. Atuzaginstat was well tolerated in phase 1, including trends of efficacy on clinical scales, and significant improvement on a computerized speech assessment and two relevant biomarkers.

Methods: The Phase 2/3 GAIN trial, designed to be potentially pivotal, completed enrollment in November 2020. 643 subjects (aged 55-80; mild-moderate AD with MMSE 12-24) were randomized to one of two doses of atuzaginstat (40mg or 80mg BID) or placebo. The co-primary endpoints are mean change in ADAS-Cog 11 and ADCS-ADL from baseline to 48 weeks. Additional endpoints include change in CDR-SB, MMSE, NPI, Winterlight Speech Assessment, CSF and oral biomarkers, MRI and other measures.

Results: Baseline data show that the 643 randomized subjects are: 57% female, 64% ApoE4 positive, 50% mild (MMSE = 19-24) and 50% moderate (12-18). 74% of subjects received symptomatic AD co-medications. New baseline biomarker data from the full set of subjects in the study will be shared, including anti-Pg IgG, amyloid-β peptide ratio 42/40, and phospho tau. 233 GAIN trial patients are also participating in a dental sub-study, and while not selected for periodontal disease, approximately 90% have moderate - severe periodontitis.

Conclusions: Enrollment of the GAIN trial was completed in November 2020, and top-line efficacy data are expected December Q4 2021. An interim analysis in December 2020 indicated that the study should continue as planned without sample size adjustment. Subjects enrolled exhibit baseline characteristics consistent with AD and with Pg infection, indicating an appropriate population to test the efficacy and safety of atuzaginstat in mild-moderate AD. The high correlations of AD, periodontal disease, and Pg infections observed in GAIN replicates findings by others and supports a causal role of Pg in AD.

GAIN Rationale and Trial Design

Figure 1. Schematic for Gingipain hypothesis of Alzheimer's

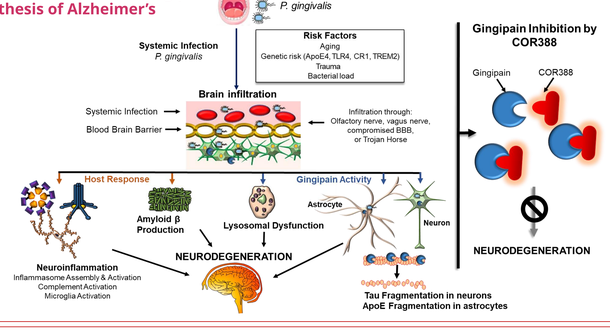
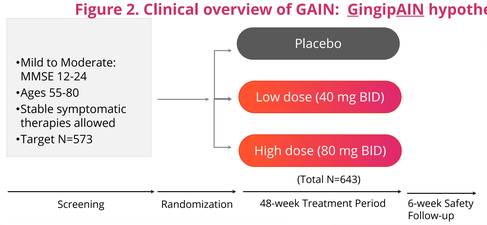


Figure 2. Clinical overview of GAIN: GingipAIN hypothesis of Alzheimer's



Endpoints

Co-Primary:
ADAS-Cog11 and ADCS-ADL

Secondary:
CDR-SB, MMSE and NPI

Exploratory:
Winterlight, MRI (hippocampal volume and cortical thickness)

Biomarkers of Pg and gingipain activity: blood, saliva

Biomarkers of Alzheimer's: CSF Aβ, tau, p-tau

Markers of disease modification: MRI volumetric measures

Timelines

- Enrollment initiated Apr. 2019; completed Sept. 2020
- Interim analysis in December 2020 successfully completed with no sample size adjustment
- Top-line data expected on time Q4 2021

Periodontal REPAIR sub-study

- 233 subjects
- Assessment of pocket depth and clinical attachment level at 6 and 12 months

Pre-clinical target validation and Phase 1 highlights of Atuzaginstat

Figure 3. Atuzaginstat acts upstream of AD pathology

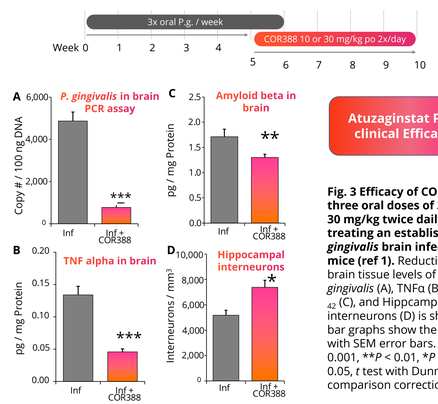


Fig. 3 Efficacy of COR388 at three oral doses of 3, 10, and 30 mg/kg twice daily in treating an established *P. gingivalis* brain infection in mice (ref 1). Reduction of brain tissue levels of *P. gingivalis* (A), TNFα (B), $A\beta_{1-42}$ (C), and Hippcampal interneurons (D) is shown. The bar graphs show the means with SEM error bars. ***$P < 0.001$, **$P < 0.01$, *$P < 0.05$, *t* test with Dunn's multiple comparison correction; *n* = 39.

Figure 4. Cognition and Biomarker Readouts from Phase 1 MAD

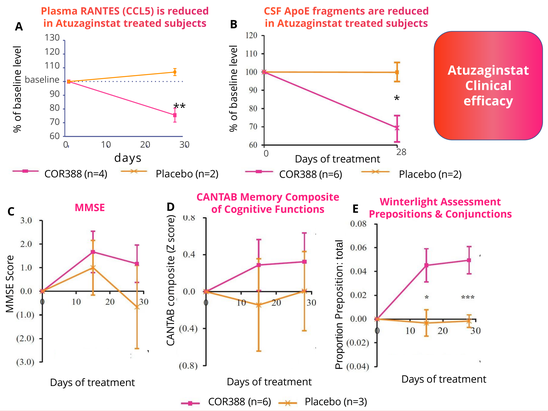


Fig. 4 Effect of 28 days of atuzaginstat (COR388) dosing on ApoE LMW fragments in CSF, peripheral pro-inflammatory mediators, and speech in AD patients compared to placebo. (A) Plasma level of RANTES (CCL5) is significantly reduced by atuzaginstat compared to placebo. (B) CSF ApoE LMW protein fragment level is significantly reduced by atuzaginstat compared to placebo. (C to E) Improvement in three Winterlight speech assessment measures with atuzaginstat dosing relative to baseline and placebo, with (E) remaining significant after a Bonferroni correction for multiple comparisons. ****p<0.0001, ***p<0.001, **p<0.01, *p<0.05.

GAIN Demographics

Table 1. GAIN baseline demographics

Parameter	Overall (N=643)
Age at Informed Consent in years (range)	69.1 (55 – 80)
Sex	
Male	278 (43%)
Female	365 (57%)
Race and Ethnicity	
Black or African American	42 (7%)
White, Hispanic or Latino	68 (11%)
White, Not Hispanic/Latino	505 (79%)
Other	10 (2%)
Missing	18 (3%)
Region	
North America	447 (70%)
Europe	196 (30%)
MMSE, n (%)	
Moderate >=12 to <=18	324 (50%)
Mild >=19 to <=24	319 (50%)
ApoE4 (Stratum), n (%)	
ApoE4 Positive	414 (64%)
non-ApoE4	229 (36%)
Cholinesterase Inhibitor/Memantine Use	
Yes	476 (74%)
No	167 (26%)

GAIN Baseline Biomarkers

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Figure 5. Baseline characterization of AD CSF markers

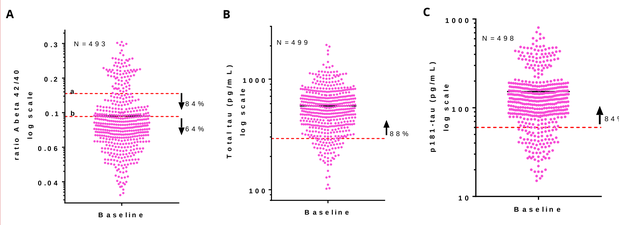


Fig. 5 Cerebral spinal fluid neurodegeneration markers at baseline. Abeta 40, Abeta 42, total tau, and p181-tau were measured using kits from Euroimmune. (A) Ratio of Abeta 42/40 cutoff b is reported by Euroimmune at 0.095 where subjects below this cutoff have clinical Alzheimer's disease diagnosis. Ratio of Abeta 42/40 cutoff is reported by Euroimmune at 0.129 where subjects below this cutoff are predicted to be amyloid PET positive. These cutoffs have a positive predictive value (ppv) of 88.5% and negative predictive value (npv) of 87.8%. (B) Total tau cutoff is reported by Euroimmune at 290 pg/mL where subjects above this cutoff have clinical diagnosis of neurodegeneration and overlap with Alzheimer's disease clinical diagnosis with a ppv of 89% and npv of 78%. (C) Phospho181-tau cutoff is reported by Euroimmune at 60 pg/mL where subjects above this cutoff have clinical diagnosis of Alzheimer's disease with a ppv of 79% and npv of 93%. Data shown for consenting subjects with evaluable CSF.

Approximately 84% of GAIN subjects have the traditional CSF markers characterized for Alzheimer's Disease diagnosis

Figure 6. Highlights from baseline characterization of AD exploratory serum analytes

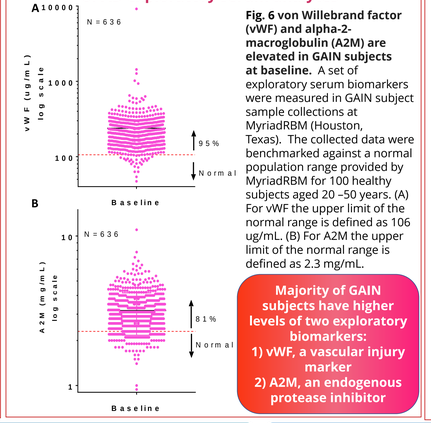


Fig. 6 von Willebrand factor (vWF) and alpha-2-macroglobulin (A2M) are elevated in GAIN subjects at baseline. A set of exploratory serum biomarkers were measured in GAIN subject sample collections at MyriadRBM (Houston, Texas). The collected data were benchmarked against a normal population range provided by MyriadRBM for 100 healthy subjects aged 20 –50 years. (A) For vWF the upper limit of the normal range is defined as 106 ug/mL. (B) For A2M the upper limit of the normal range is defined as 2.3 mg/mL.

Majority of GAIN subjects have higher levels of two exploratory biomarkers:
1) vWF, a vascular injury marker
2) A2M, an endogenous protease inhibitor

Figure 7. REPAIR - Periodontal disease sub-study

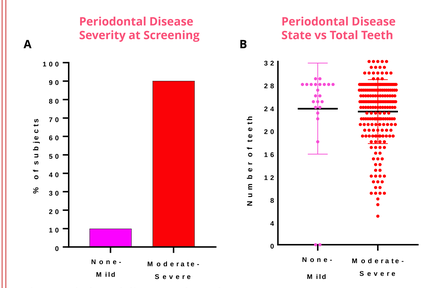
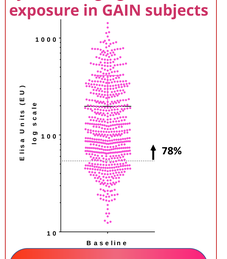


Fig. 7 Periodontal disease sub-study baseline summary. (A and B) Measurements of pocket depth and gingival margin were used to calculate attachment levels. These parameters were used to determine the presence of periodontitis according to the centers for disease control / American academy of periodontology criteria. N= 233 subjects

90% of REPAIR subjects have moderate – severe periodontal disease

Figure 8. Evidence of systemic *P. gingivalis* exposure in GAIN subjects



100% of GAIN subjects have evidence of systemic *P. gingivalis* exposure and 78% have IgG antibody titers that correlate with periodontal disease

Fig. 8 Serum anti-Pg antibodies demonstrate systemic exposure of *P. gingivalis* Anti-Pg IgG antibodies were measured in serum from GAIN subjects against a reference pool created with sera from Alzheimer's subjects with similar age and MMSE as GAIN. The data are reported in Elisa Units which are translated from test sample readings at OD_{450} arbitrarily by defining OD for the 1:8000 dilution of the reference pool = 100 EU. Serum was collected from all enrolled subjects and N = 638 for these data. A previously defined cutoff of 54 EU was applied to these data to identify active periodontal disease subjects (ref 3).

Summary

- Data continue to accumulate supporting the gingipain hypothesis of Alzheimer's
- The GAIN trial, designed to be a key clinical proof of concept and potentially pivotal trial, is fully enrolled. Topline data expected Q4 2021.
- Baseline data support that this is an appropriate population for testing atuzaginstat for AD
  - Demographics
  - Traditional AD CSF biomarkers: Aβ, Total tau and p-Tau 181
  - Pg antibodies and exploratory biomarkers in serum
  - Periodontal disease data in a sub study

References, Disclosures and Acknowledgements

References:
1. Dominy et al, Sci Advances 2019; 5(1): 1-21
2. Ilievski, et al, PLoS ONE 2018; 13(10): 1-24
3. Offenbacher et al, J Periodontology 2007 Oct; 78(10):1911-25

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