Top-line Results from the GAIN Trial: A Phase 2/3 Study of Atuzaginstat in Mild to Moderate Alzheimer's Disease

Predecessor company presentation at CTAD 2021

QUINCE THERAPEUTICS

Top-line Results from the GAIN Trial: A Phase 2/3 Study of Atuzaginstat in Mild to Moderate Alzheimer's Disease

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CTAD 2021

Speakers:

- **Dr. Michael Detke, MD, PhD; Chief Medical Officer, Cortexyme**
- **Dr. Marwan Sabbagh, MD; Professor of Neurology, Alzheimer's and Memory Disorders Division at the Barrow Neurological Institute**

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Disclosures

Dr. Detke is a full-time employee of Cortexyme and holds equity in the form of stock options.

Dr. Sabbagh is a consultant to Cortexyme who is compensated for his time. He is also a consultant to Alzheon, Biogen, Cognoptix, EIP Pharma, Eli Lilly, Eisai, Stage 2 Innovations, Acadia, Roche-Genentech; Brain Health Inc, Qynapse, NeuroReserve, NeuroTau, Optimal Cognitive Health Co., uMethod Health, Versanum Inc. and Athira. He receives research support from the NIH.

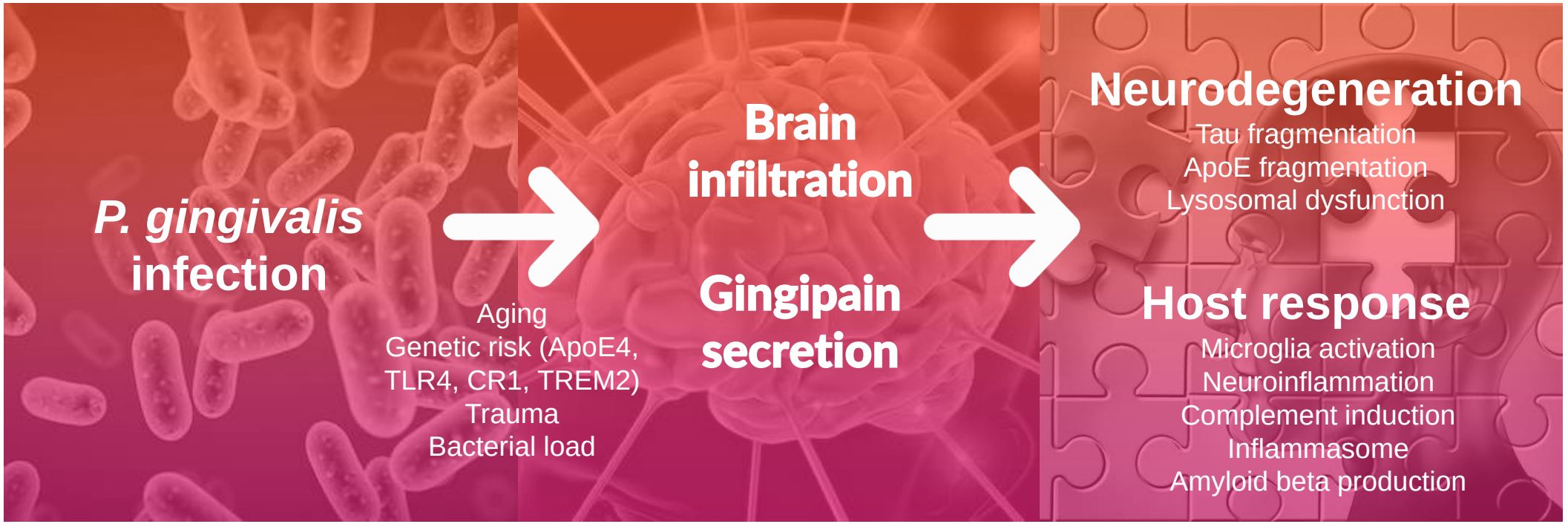
Overview – Key takeaways from the GAIN Trial

1. Clinical confirmation of *P. gingivalis* as an upstream driver of Alzheimer's, and a potential new target for treating AD

2. Identification of the patients for this therapeutic approach: mild-mod *Alzheimer's with Pg infection,* approximately 50% of mild-mod patients

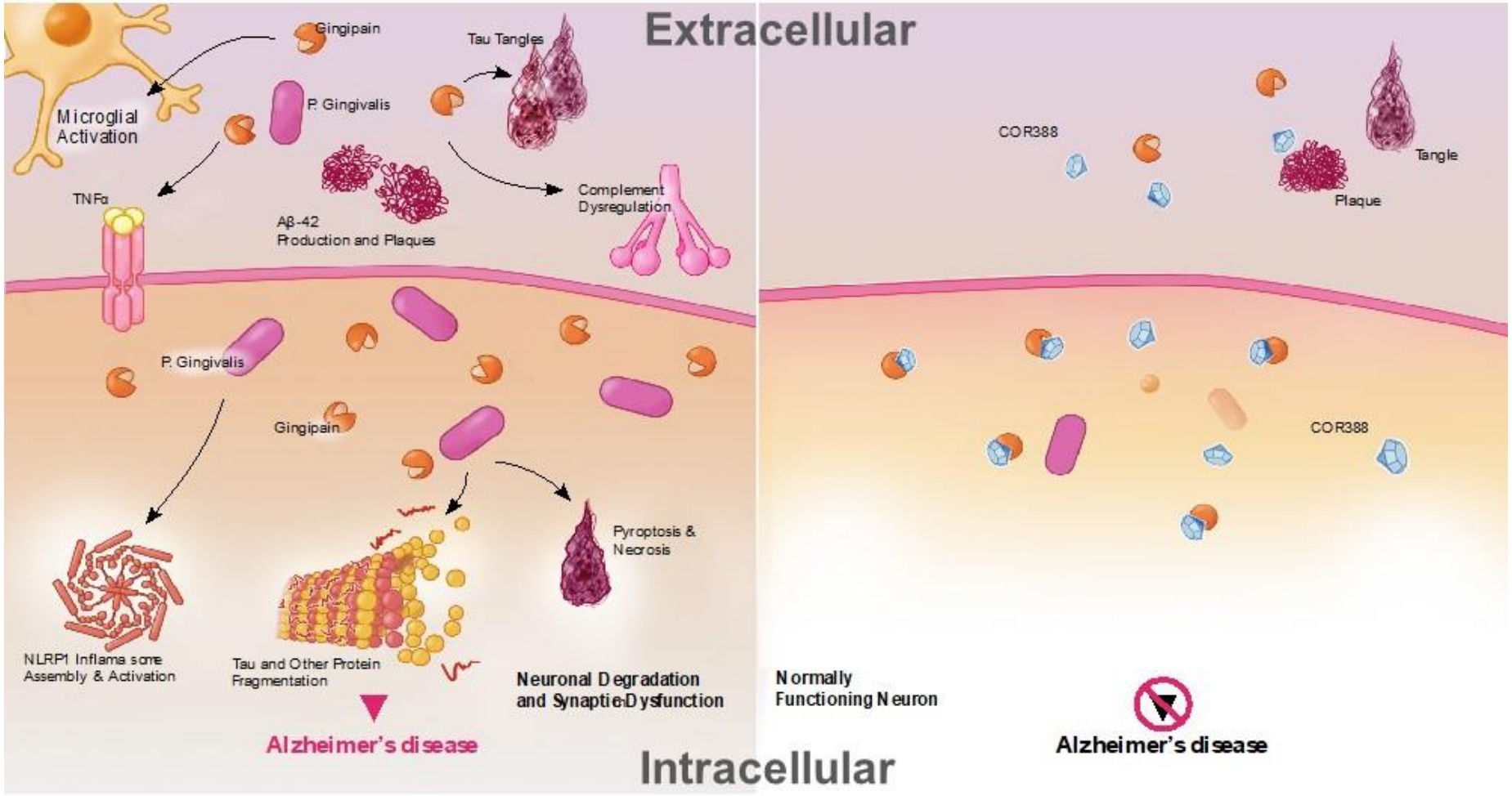
3. Characterization of the efficacy (30-50% slowing of decline) and safety profile of atuzaginstat, and a therapeutic dose

P. gingivalis infection upstream explains many features of Alzheimer's risk and pathology



See: www.cortexyme.com/science for literature; Foundational data published in Dominy et al 2019 Sciences Advances

P. gingivalis in Alzheimer's pathology and mechanism of action of atuzaginstat (COR388)



Converging evidence for *P. gingivalis* as a novel driver of Alzheimer's

Clinical Observational Studies

- AD patients with greater periodontal disease decline 6pts on ADAS-Cog in 6mo vs 1pt in mild/non-periodontal patients
- GAIN study participants identified 90% with periodontal disease despite no entry criteria
- 6x increased risk of AD in spouses of AD patients, consistent with infection

Animal Models

- Oral *Pg* infection in wild-type mice and rats recreates AD pathology and behavior
- Atuzaginstat reverses *Pg*-induced AD pathology in mice

Disease Pathology

- Complement dysregulation by *Pg*
- Tau and ApoE cleavage by gingipains
- Compelling link to genetic risk: gingipain ApoE cleavage E4>E3>E4
- *Pg* infection induces brain p217tau, reversed by COR388 in mice

β-amyloid Antimicrobial Activity

- Amyloid is an antimicrobial peptide, consistent with infection as a causal mechanism

AD Brain Tissue Analysis

- *Pg* and gingipains found in AD brain through IHC and sequence analysis (0>0.0001 vs age-matched controls)
- Gingipain levels correlate with tau and ubiquitin, correlating with symptoms

Epidemiology

- Periodontal disease (*Pg* keystone cause) is a strong predictor of AD
- Serum Abs to perio pathogens are risk factor for AD
- Perio associates with higher brain amyloid

Inflammation

- Microglial and inflammasome activation consistent with chronic low-grade infection, both activated by *Pg*

Converging evidence for *P. gingivalis* as a novel driver of Alzheimer's

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Work published and/or replicated by independent 3rd party laboratories

Work done in collaboration with independent 3rd party laboratories

Cortexyme Data

β-amyloid Antimicrobial Activity

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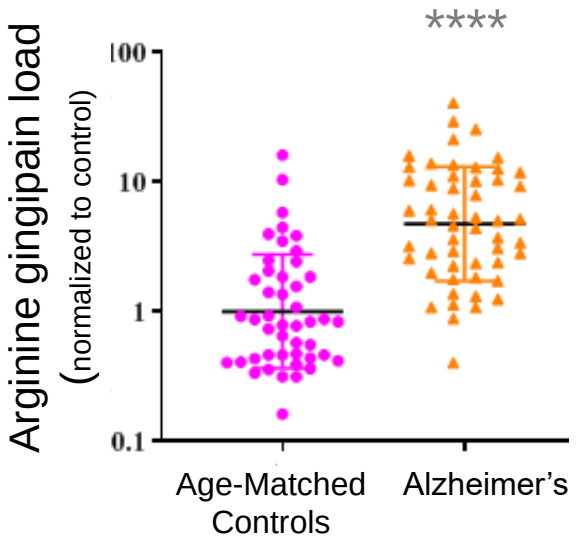
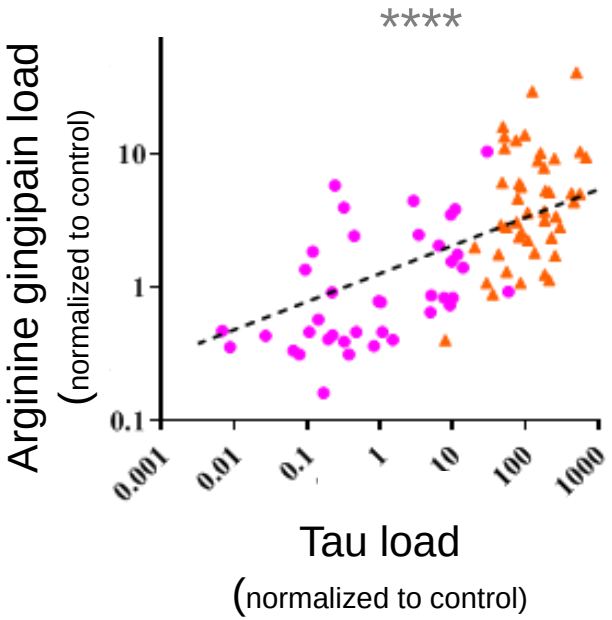
P. gingivalis brain infiltration precedes and is correlated with Alzheimer's symptoms and pathology





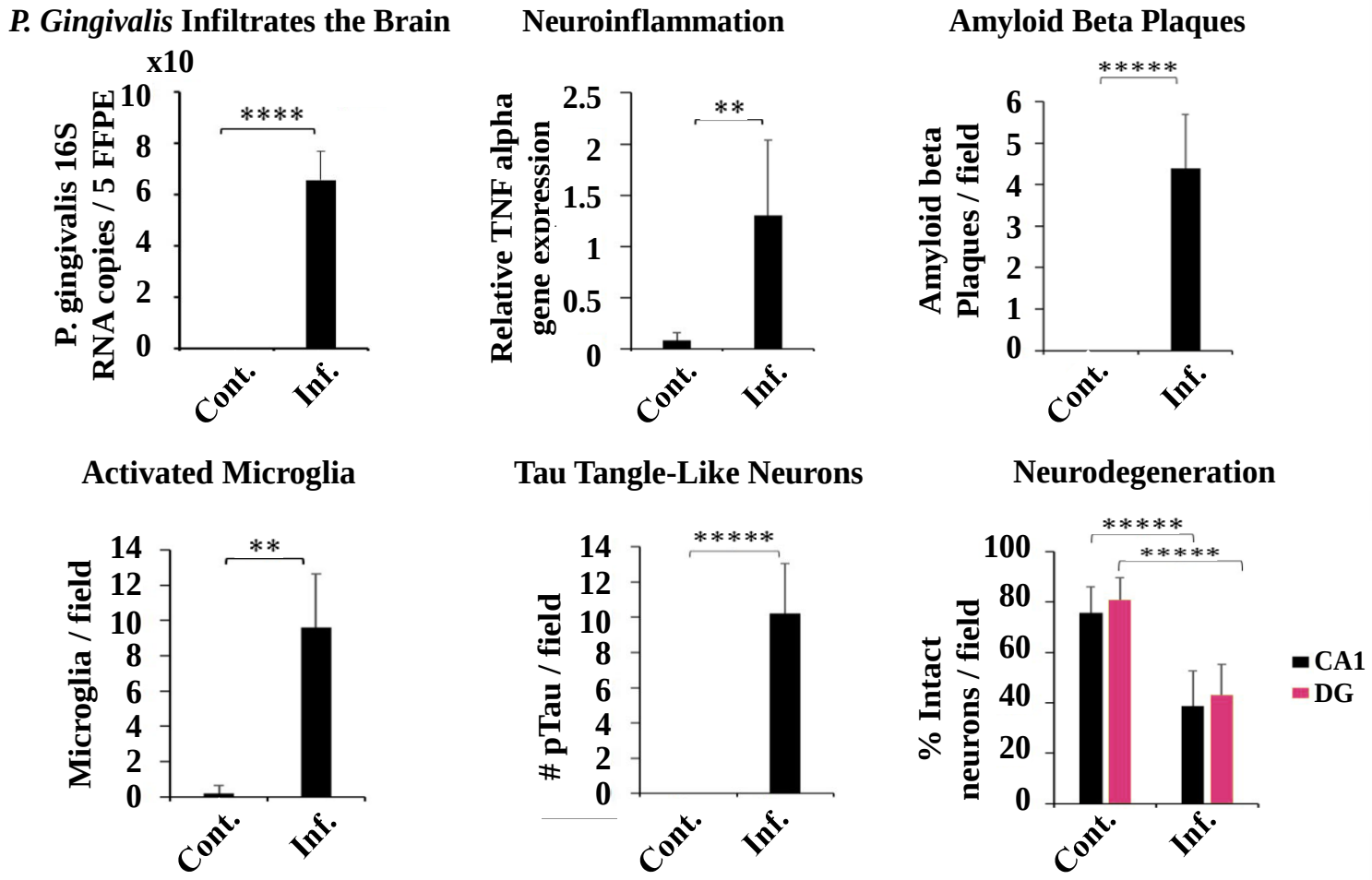
Immunohistochemistry of middle temporal gyrus microarray

Confirmed with multiple antibodies/antigens and PCR

Source: Collaboration with University of Auckland/ Neurovalida study ****p<0.0001; Dominy et al 2019 Sciences Advances

Evidence of causation:

Oral *Pg* infection of WT mice induces AD pathology after 22 weeks



Source: Adapted from Ilievski, et al. *Chronic oral application of a periodontal pathogen results in brain inflammation, neurodegeneration and amyloid beta production in wild type mice*. PLOS: One 2018

*p< 0.05,**p<0.01, ***p<0.001, ****p<0.001

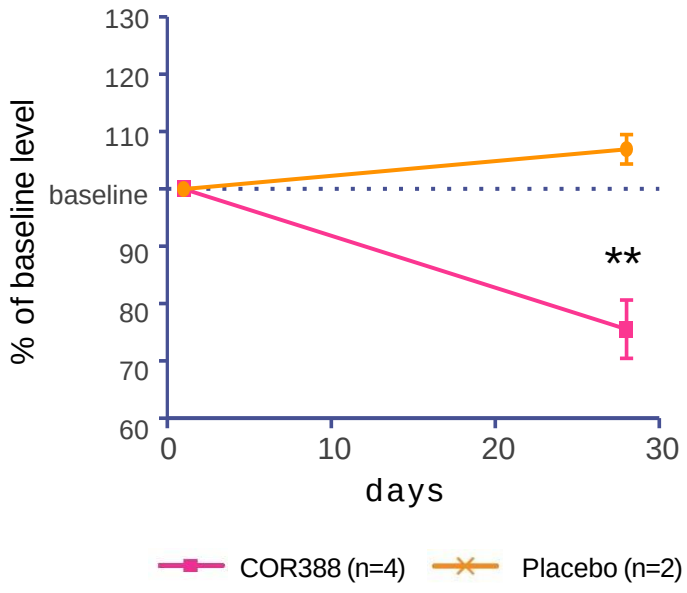
Atuzaginstat (COR388) lysine gingipain inhibitor

Small molecule optimized from proprietary protease inhibitor library

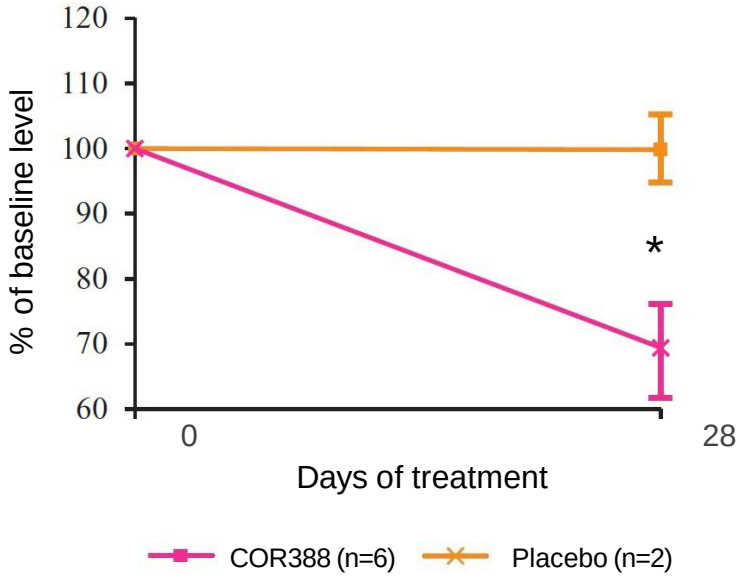
- Novel & proprietary small molecule
- Potent: Target IC50 < 50pM
- Selective over 800 human anti-targets, including other cellular proteases
- Orally available, brain penetrant
- Large therapeutic window in toxicology studies

Phase 1b MAD 28-day study of 50 mg BID in AD patient cohort

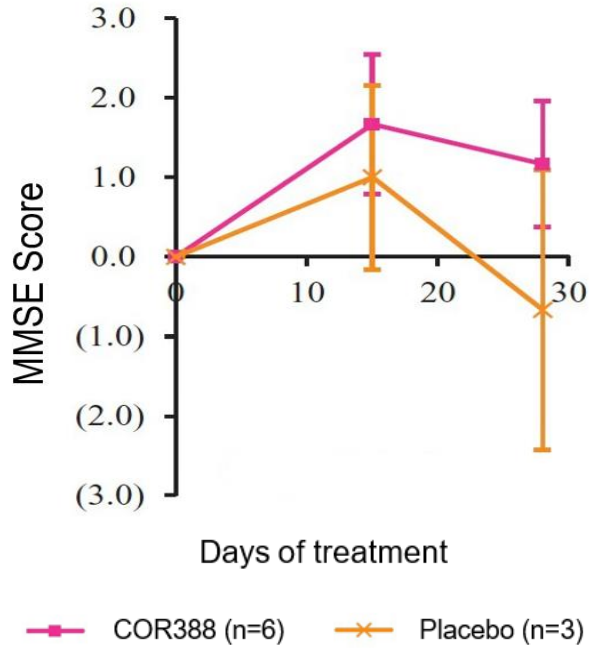
Plasma RANTES (CCL5) is reduced in Atuzaginstat treated subjects



CSF ApoE fragments are reduced in Atuzaginstat treated subjects



MMSE

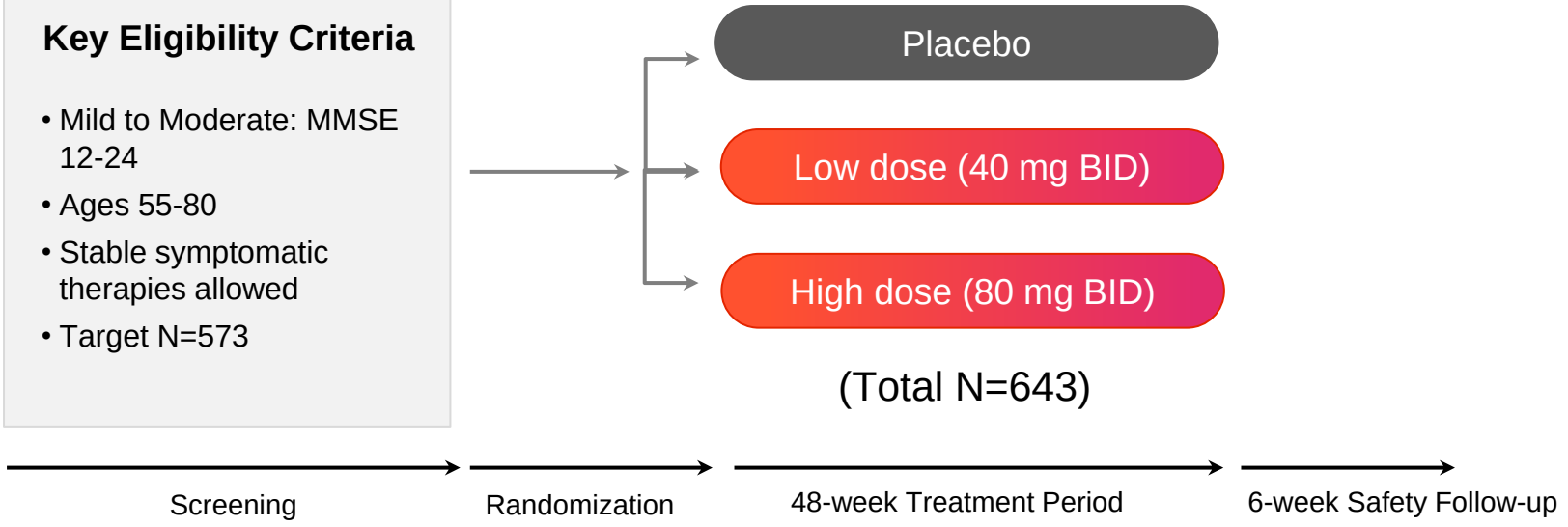


Source: Cortexyme ApoE and MAD study: *p< 0.05, ** p< 0.01

Phase 2/3 GAIN Trial: Atuzaginstat in mild to moderate Alzheimer's disease

Key Eligibility Criteria

- Mild to Moderate: MMSE 12-24
- Ages 55-80
- Stable symptomatic therapies allowed
- Target N=573



Timelines

- Enrollment initiated Apr. 2019; completed Sept. 2020
- Global study with >90 sites
- US, France, Spain, Poland, UK, and Netherlands

Endpoints

Co-Primaries:
ADAS-Cog11 and ADCS-ADL

Secondary:
CDR-SB, MMSE, NPI

Biomarkers of Pg: saliva, blood, CSF

Primary Biomarker: MRI - hippocampal volume

Biomarkers of Alzheimer's: CSF Aβ, tau, p-tau (results pending)

More information: www.gaintrial.com

GAIN baseline demographics

Parameter	Placebo	40 mg BID	80 mg BID
Mean Age at Informed Consent, years (SD)	69.5 (6.9)	68.6 (6.9)	69.3 (6.9)
Sex			
Male	92 (42%)	89 (42%)	97 (45%)
Female	125 (58%)	123 (58%)	117 (55%)
Race and Ethnicity			
Black or African American	17 (8%)	12 (6%)	13 (6%)
White, Hispanic or Latino	21 (10%)	16 (8%)	32 (15%)
White, Not Hispanic/Latino	171 (79%)	172 (81%)	162 (76%)
Other or Unknown	8 (4%)	12 (6%)	7 (3%)

Parameter	Placebo	40 mg BID	80 mg BID
MMSE			
Moderate >=12 to <=18	110 (51%)	107 (51%)	107 (50%)
Mild >=19 to <=24	107 (49%)	105 (50%)	107 (50%)
ApoE4 Carriers	140 (65%)	137 (65%)	137 (64%)
Non-Carriers	77 (36%)	75 (35%)	77 (36%)
ADAS-Cog Mean (SD)	23.9 (8.7)	23.5 (8.1)	23.7 (8.3)
ADCS-ADL Mean (SD)	60.4 (11.3)	60.0 (11.3)	59.9 (11.2)

Eight Black participants and one Other participant also identified as Hispanic/Latino.
Randomization was stratified by mild vs. moderate and ApoE4 carriers positive vs. negative.

Patient disposition

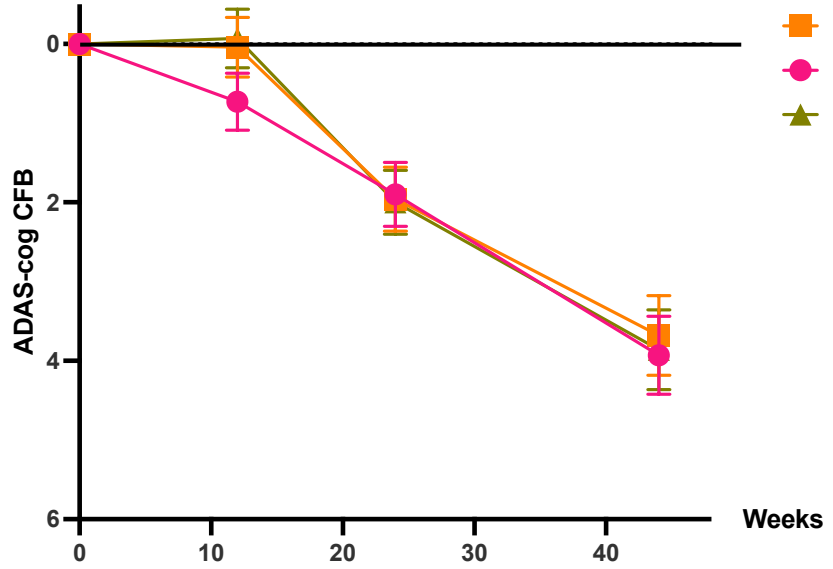
	Randomized (N=643)		
	Placebo BID	40 mg BID	80 mg BID
Randomized	217	212	214
Discontinued	55	86	86
Lost to follow-up	3	2	1
Protocol violation	2	0	2
Adverse events	8	39	35
Withdrawal of consent	36	40	38
Death	0	0	4
Other	6	5	6
Completed double-blind treatment period	181	140	138

- AE discontinuations per protocol requirements related to transaminase elevations: 1 (placebo), 5 (40mg BID) and 17 (80mg BID); virtually all were completely asymptomatic.
- Discontinuations include the 6-week safety follow-up whereas completed double-blind phase is only 48 weeks.
- Deaths are more comprehensively reviewed in the adverse events slide.

Overall co-primary endpoints in the intent-to-treat (ITT) population

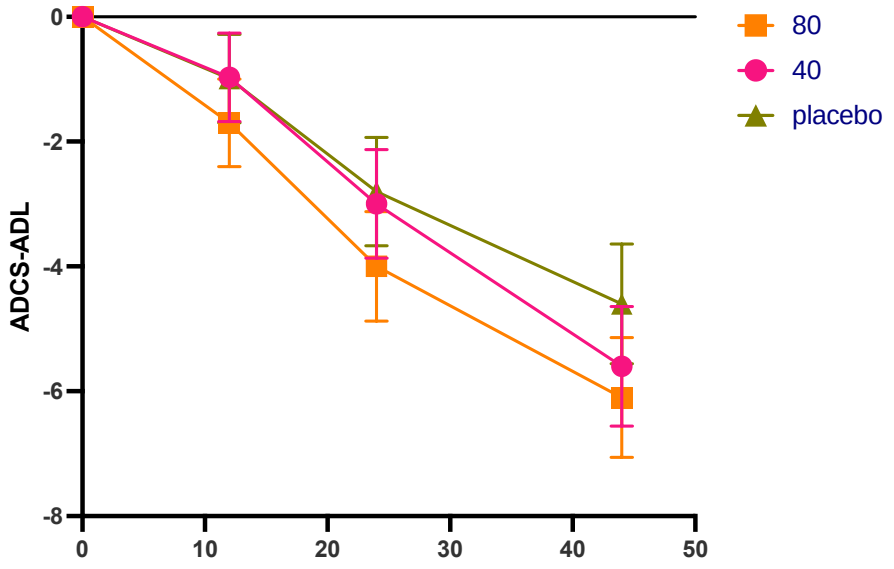
Primary analysis
MMRM

ADAS-Cog



n	Baseline	12 weeks	24 weeks	40/48 weeks
80	214	198	166	146
40	212	185	172	148
Placebo	217	205	197	187

ADCS-ADL



n	Baseline	12 weeks	24 weeks	40/48 weeks
80	214	198	169	149
40	211	189	175	150
Placebo	216	206	200	187

Improvement is up on all scales

Analyses prespecified in GAIN Statistical Analysis Plan as most likely to identify responders to atuzaginstat

Key goals of the study were to test which population(s) would be responsive, and to test potential companion diagnostics. It was important to determine whether one was needed at all (thus the overall cohort was primary) and if so, to understand which one was most accurate and least invasive.

- The following were subgroup or cohort analyses for biomarkers of Pg infection at baseline:
  - *P. gingivalis* DNA status (PG-DS) from oral rinse (Detected vs. Not) – 38% detected*
  - Anti- *P. gingivalis* antibody levels in serum (High vs Low) – median split
  - Anti- *P. gingivalis* antibody levels in cerebrospinal fluid (High vs Low) – median split

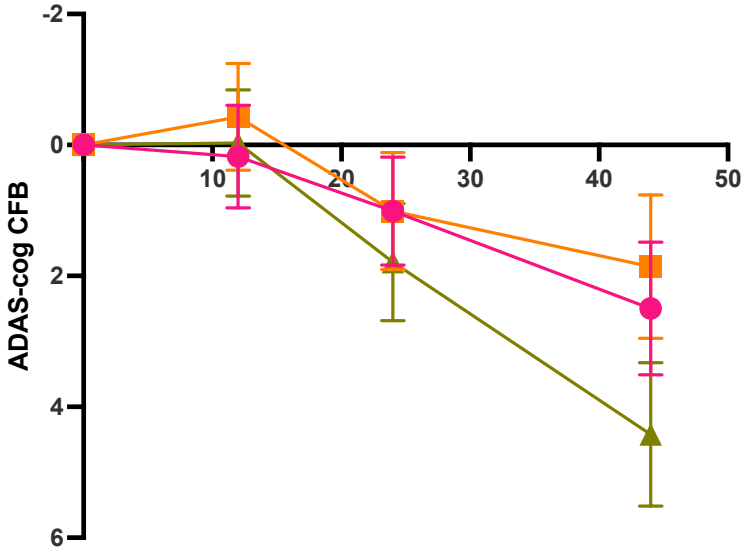
- Correlations between biomarkers of *P gingivalis* infection with clinical endpoints were also prespecified

*In neat saliva, *Pg* DNA is detected in 56% of well-characterized (ATN) Alzheimer's patients and this method will be used for future studies.

Consistent effects in all 3 prespecified *P. gingivalis* infection cohorts on ADAS-Cog: MMRM analysis

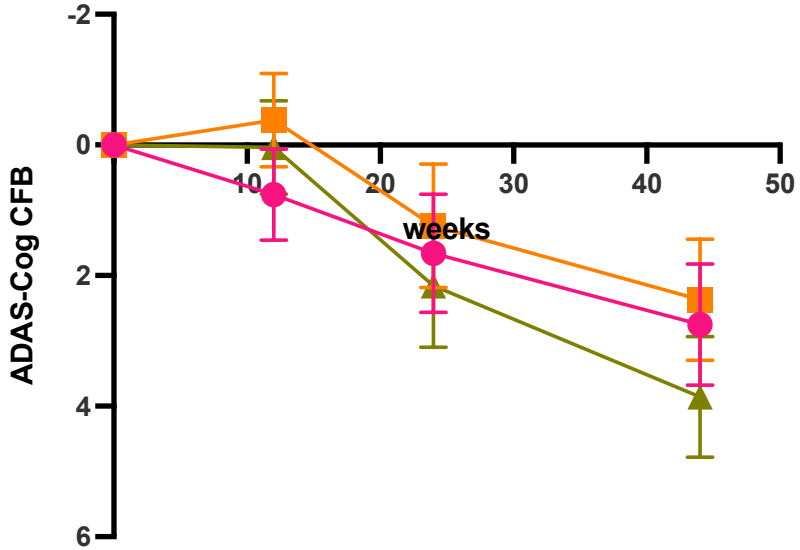
80
40
placebo

Pg Detected in Saliva (PG-DS; 38%)



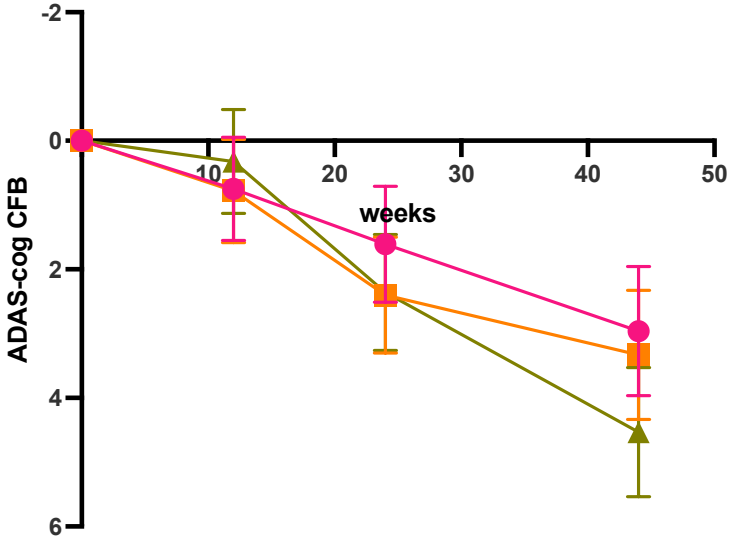
80 mg BID = 57% slowing, p value = 0.02
40 mg BID = 42% slowing, p value = 0.07

High IgG Serum (50%)



80 mg BID = 48% slowing, p value = 0.04
40 mg BID = 28% slowing

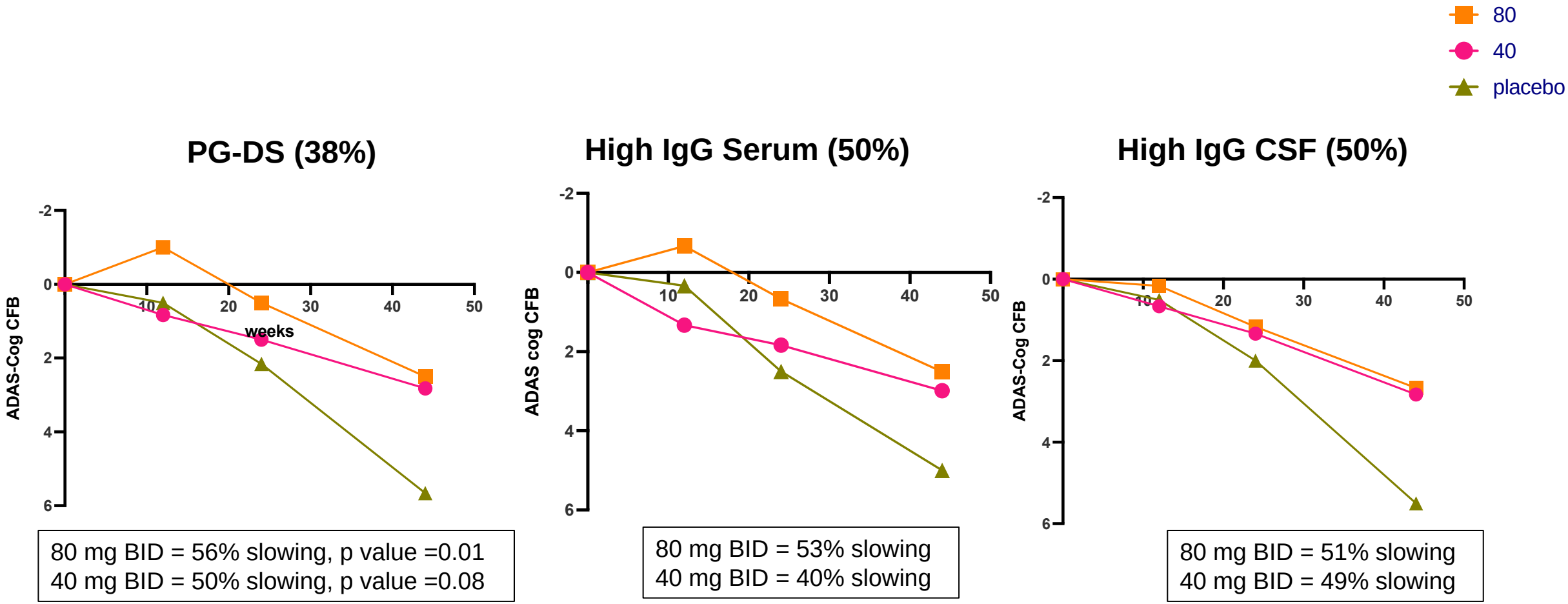
High IgG CSF (50%)



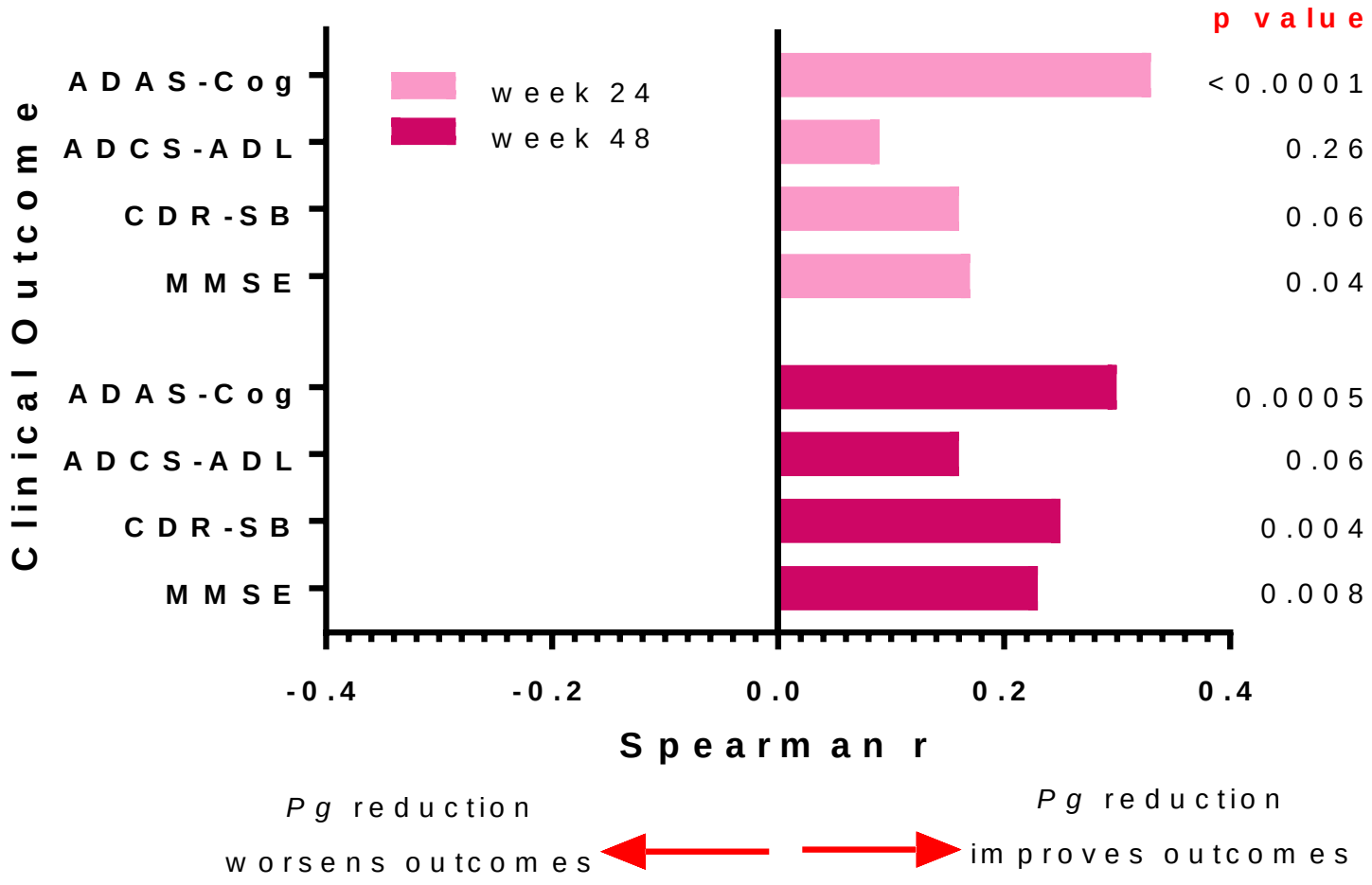
80 mg BID = 24% slowing
40 mg BID = 37% slowing

All subgroups were balanced for ApoE4 carriers and average MMSE at baseline across arms.

Consistent benefits of atuzaginstat in all 3 prespecified *P. gingivalis* infected cohorts on ADAS cog: Multiple imputation nonparametric analysis



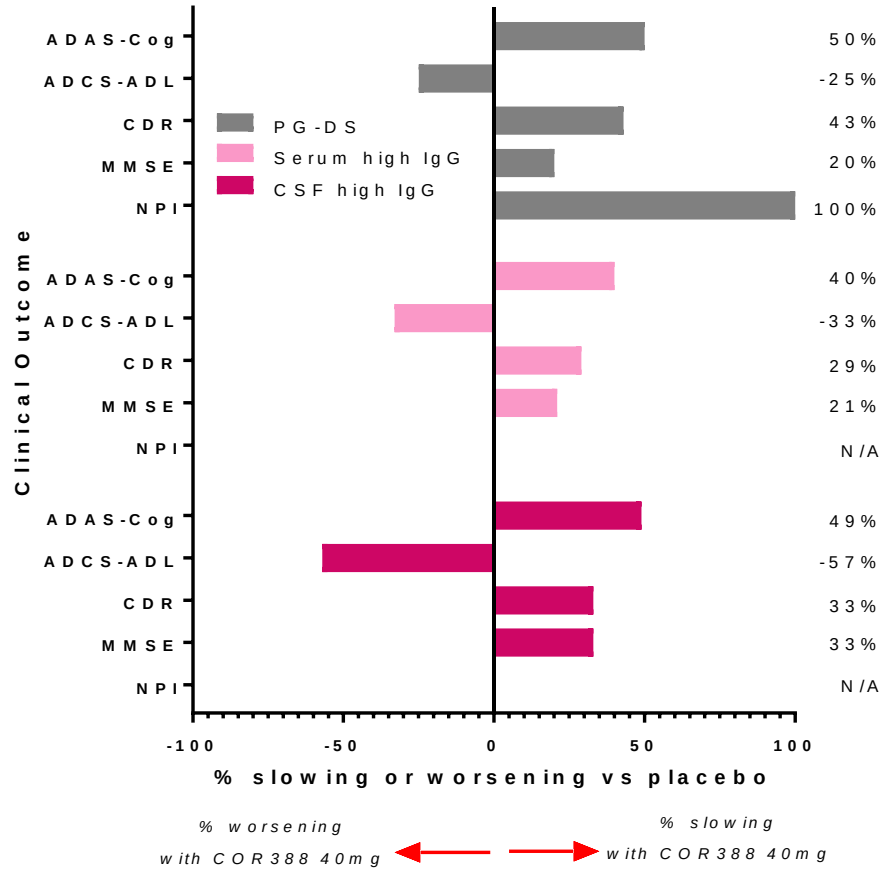
Prespecified correlations between *P. gingivalis* DNA change in saliva at 24 weeks and clinical outcomes at both 24 and 48 weeks



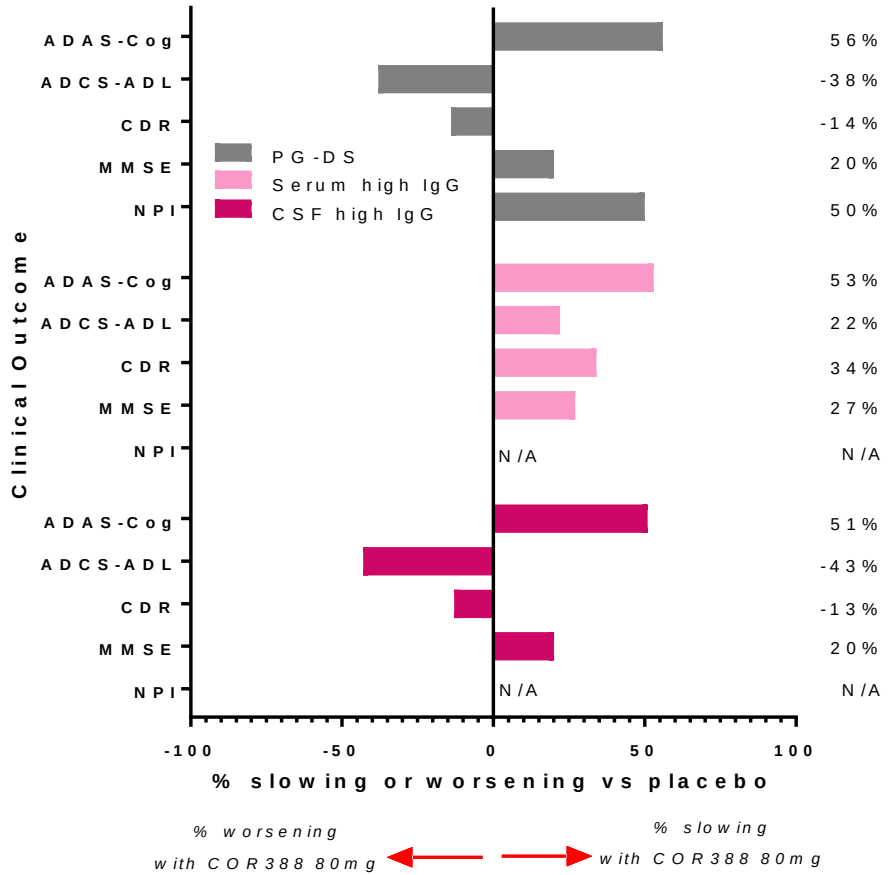
Analysis includes all three study arms and participants positive for Pg DNA in saliva at any point in the study.

Efficacy of 40 mg BID across secondary endpoints in all prespecified *P. gingivalis* infected cohorts at end of treatment

Atuzaginstat 40mg vs Placebo

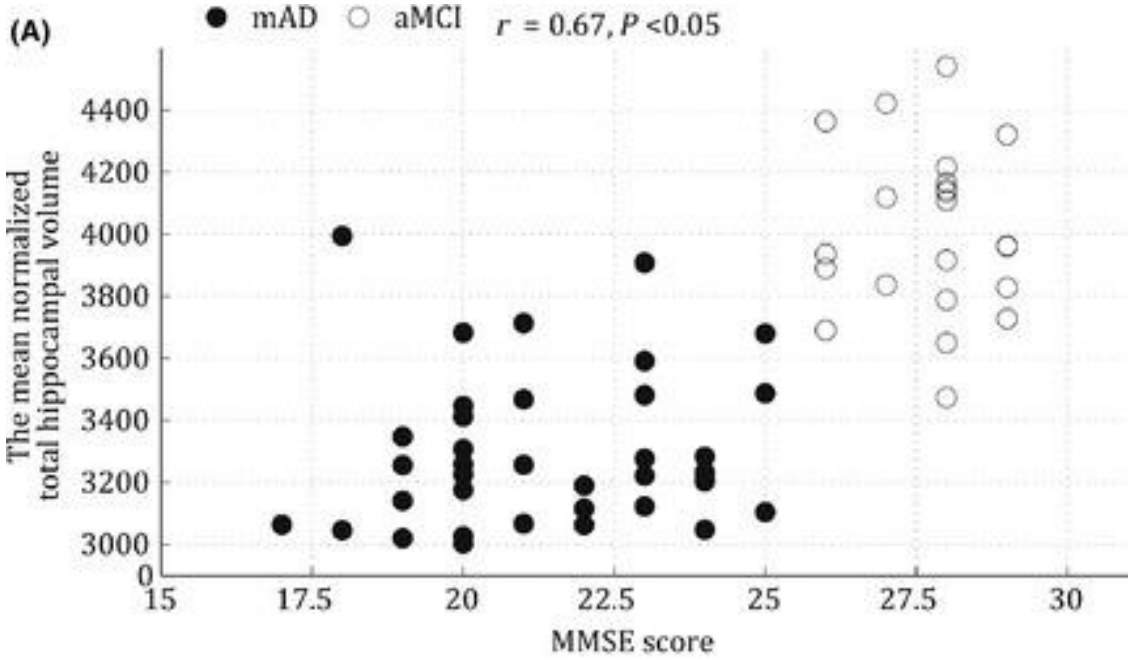


Atuzaginstat 80mg vs Placebo



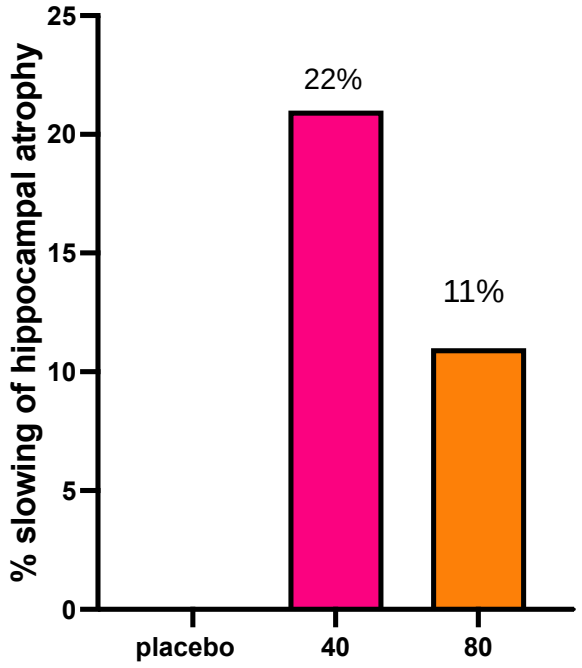
Prespecified primary biomarker: Hippocampal atrophy

Hippocampal atrophy correlates to cognitive decline



From Peng et al. 2014, see also Sabuncu et al, 2011

Bilateral hippocampal volume % slowing of atrophy



n=	148	114	105

Safety summary: most common treatment-emergent adverse events (TEAEs)

	Placebo (n= 217)	40 mg BID (n= 212)	80 mg BID (n= 214)
Deaths*	0 (0.0%)	1 (0.5%)	5 (2.3%)
SAE's	19 (8.8%)	20 (9.4%)	25 (11.7%)
Any TEAE	147(67.7%)	170 (80.2%)	164 (76.6%)
Diarrhea	7 (3.2%)	34 (16.0%)	27 (12.6%)
ALT increased	4 (1.8%)	20 (9.4%)	37 (17.3%)
AST increased	3 (1.4%)	20 (9.4%)	34 (15.9%)
Urinary tract infection	21 (9.7%)	16 (7.5%)	28 (13.1%)
Lipase increased	11 (5.1%)	13 (6.1%)	20 (9.3%)
Headache	14 (6.5%)	18 (8.5%)	15 (7.0%)
Amylase increased	8 (3.7%)	12 (5.7%)	16 (7.5%)
Nausea	4 (1.8%)	13 (6.1%)	13 (6.1%)
Agitation	7 (3.2%)	9 (4.2%)	10 (4.7%)
Decreased appetite	2 (0.9%)	9 (4.2%)	10 (4.7%)
Fall	5 (2.3%)	7 (3.3%)	11 (5.1%)
Abdominal pain	3 (1.4%)	7 (3.3%)	11 (5.1%)
TEAEs potentially of interest with incidence lower than 5%:			
COVID-19	5 (2.3%)	7 (3.3%)	1 (0.5%)

FINDINGS

- Overall, rates of SAE's are comparable to those seen in similar AD trials and are too few to draw firm conclusions.
- Most common treatment-associated AE is diarrhea.
- Virtually all cases of laboratory abnormalities were not clinically significant and asymptomatic, but there were 2 cases of Hy's Law in the 80 mg BID treatment arm.
- Rates of AEs in the PG-DS subgroup were comparable to or lower than those in the overall cohort.
- No increase in ARIA or brain SAE's

Deaths were determined as not related to study drug by investigator: COVID-19 (40 mg BID), Worsening AD (2), presumed cardiac arrest, urosepsis*, lung cancer: 2 occurred outside the treatment period*

Safety: Measures of interest - Hepatic enzyme elevations

- Liver transaminase (ALT, AST) elevations >3X ULN were observed in 2% of participants on placebo, 7% on 40 mg BID and 15% on 80 mg BID.
  - Hepatic experts consider these not clinically significant (NCS) in isolation.
  - Virtually all patients were completely asymptomatic (verbatim quotation from expert hepatic assessment committee report).
  - Most commonly observed 6 weeks after starting drug; incidence of elevations decreases significantly thereafter.
- Two of the above cases also had bilirubin elevations >2X ULN without a definitive alternative cause; both cases were in the 80mg BID arm.
- All enzyme elevations resolved while remaining on drug or after withdrawal and without any long-term adverse effects.
- An independent expert hepatic assessment committee believes dose titration upon treatment initiation may mitigate these transaminase elevations significantly.
  - Data from this trial and from other drugs support titration.

Safety: Measures of interest - treatment-emergent ARIA and superficial siderosis

MRI assessment	Placebo (n= 217)	40 mg BID (n=212)	80 mg BID (n=214)
Microhemorrhage (Mild)	6 (2.8%)	7 (3.3%)	4 (1.9%)
Microhemorrhage (Moderate)	1 (0.5%)	0 (0.0%)	0 (0.0%)
Microhemorrhage (Severe)	0 (0.0%)	1 (0.5%)	0 (0.0%)
ARIA-E (Edema)	1 (0.5%)	0 (0.0%)	0 (0.0%)
Superficial Siderosis	0 (0.0%)	1 (0.5%)	0 (0.0%)
Other Abnormality	2 (0.9%)	0 (0.0%)	1 (0.5%)

Summary

- Extensive literature supports the role of *P. gingivalis* as a driver of Alzheimer's.

- In this trial, efficacy of atuzaginstat was not observed in the overall intent-to-treat cohort.

- This study, the first ever large clinical trial of this mechanism, reinforces *P. gingivalis* as an important driver of Alzheimer's disease and empirically advances development of atuzaginstat.
  - Efficacy signals were seen across 3 pre-specified cohorts identifying the infection with diverse methods.
  - Efficacy magnitudes were consistent across sensitivity analyses.
  - Benefits were seen across multiple clinical endpoints.
  - Significant correlations were shown between change in *Pg* load and multiple clinical outcomes.

- Atuzaginstat is highly differentiated from amyloid-targeting therapies:
  - Patient population (both disease severity and *Pg* infection)
  - Safety and monitoring profile (no need for PET or MRI imaging)
  - Route of administration (oral)

Conclusions from the GAIN trial & next steps

1. Clinical confirmation of *P. gingivalis* as an upstream driver of Alzheimer's, and a potential new target for treating AD.

2. Identification of the patients for this therapeutic approach: mild-mod *Alzheimer's with Pg infection,* approximately 50% of mild-mod patients

3. Characterization of the efficacy and safety profile of atuzaginstat, and the therapeutic dose.

Planning is underway for a confirmatory trial, pending discussions with global regulators:

- In mild to moderate *Alzheimer's with P. gingivalis,* diagnosed by the best empirical method
- Based on approximately 30-50% slowing of decline on ADAS-Cog11 and CDR-SB
- Dosing at 40 mg BID with titration

Acknowledgements

THANK YOU!!

- Patients and caregivers who participated in the GAIN Trial
- Dedicated site investigators and staff
- Key business partners, including Bioclinica, MedAvante-Prophase, Winterlight, ERT, WCT and more
- Clinical Advisory Board, Data Monitoring Committee, and Hepatic Advisory Committee
- Cortexyme team

Dr. Marwan Sabbagh, MD; Professor of Neurology, Alzheimer's and Memory Disorders Division at the Barrow Neurological Institute

Converging evidence for *P. gingivalis* as a novel driver of Alzheimer's

Clinical Observational Studies

- AD patients with greater periodontal disease decline 6pts on ADAS-Cog in 6mo vs 1pt in mild/non-periodontal patients
- GAIN study participants identified 90% with periodontal disease despite no entry criteria
- 6x increased risk of AD in spouses of AD patients, consistent with infection

Animal Models

- Oral *Pg* infection in wild-type mice and rats recreates AD pathology and behavior
- Atuzaginstat reverses *Pg*-induced AD pathology in mice

Disease Pathology

- Complement dysregulation by *Pg*
- Tau and ApoE cleavage by gingipains
- Compelling link to genetic risk: gingipain ApoE cleavage E4>E3>E4
- *Pg* infection induces brain p217tau, reversed by COR388 in mice

Work published and/or replicated by independent 3rd party laboratories

Work done in collaboration with independent 3rd party laboratories

Cortexyme Data

β-amyloid Antimicrobial Activity

- Amyloid is an antimicrobial peptide, consistent with infection as a causal mechanism

AD Brain Tissue Analysis

- *Pg* and gingipains found in AD brain through IHC and sequence analysis (0>0.0001 vs age-matched controls)
- Gingipain levels correlate with tau and ubiquitin, correlating with symptoms

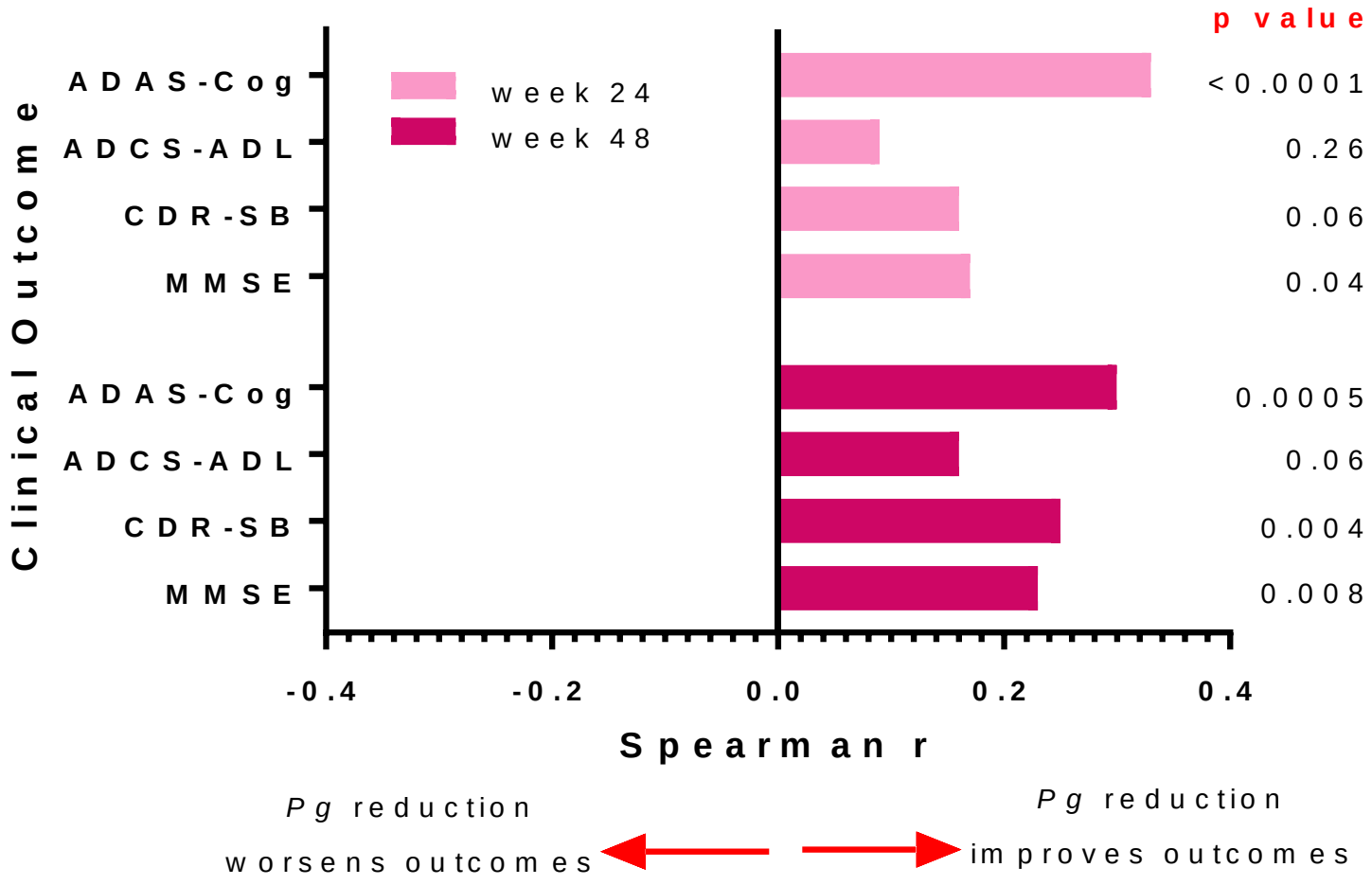
Epidemiology

- Periodontal disease (*Pg* keystone cause) is a strong predictor of AD
- Serum Abs to perio pathogens are risk factor for AD
- Perio associates with higher brain amyloid

Inflammation

- Microglial and inflammasome activation consistent with chronic low-grade infection, both activated by *Pg*

Prespecified correlations between *P. gingivalis* DNA change in saliva at 24 weeks and clinical outcomes at both 24 and 48 weeks



Analysis includes all three study arms and participants positive for Pg DNA in saliva at any point in the study.

Subgroup Analysis: Common practice in Phase 2 designs to identify target populations likely to benefit in confirmatory studies

Features that provide greater confidence that the signal may be a true positive:

- Biological/mechanistic plausibility
- Pre-specification of cohort analysis
- Reliability of findings across different statistical analysis techniques (sensitivity analyses)
- Consistent findings across different measures
- Corollary evidence both narrow (e.g., correlations of biomarkers and clinical outcomes) and broad (other supportive mechanistic evidence)

Selecting a group likely to benefit is common practice and considered reasonable and appropriate:

Indication	Therapeutic	Responsive Cohort
Cardiovascular	BiDil	Heart Failure in self-identified black patients (per FDA label)
Oncology	Herceptin	HER2+ metastatic breast cancer
	Keytruda	Bladder cancer with high PD-L1 expression
Alzheimer's Disease and Dementia	Aduhelm	Amyloid PET+, early disease subgroups (established across trials of similar agents)
	ALZ801	ApoE 4/4 carriers
	Donanemab	Subjects with intermediate tau
	Azeliragon	Signal in subjects with elevated HgbA1C
	TMS	Signal in mild AD, no signal in moderate

Therefore, the GAIN Findings support the hypothesis and identify a group likely to show clinical benefit (mild-moderate AD with *P. gingivalis* infection)

Summary

- The GAIN Trial clinically confirms the Pg/gingipain hypothesis of Alzheimer's.
- The GAIN study confirms a target population can be identified. Specifically, mild to moderate subjects with high *P. gingivalis* loads are much more likely to benefit from treatment with atuzaginstat.
- Another success of the trial is the identification of an therapeutic dose.
- Benefits of atuzaginstat include twice a day oral dosing, no requirement for MRI monitoring or PET imaging. Atuzaginstat has a good safety profile and is well tolerated.
- The GAIN trial has been rigorously designed and implemented to be a key clinical proof of concept.
- Mild-moderate AD is a population that has unmet needs not likely to be treated with mABs.

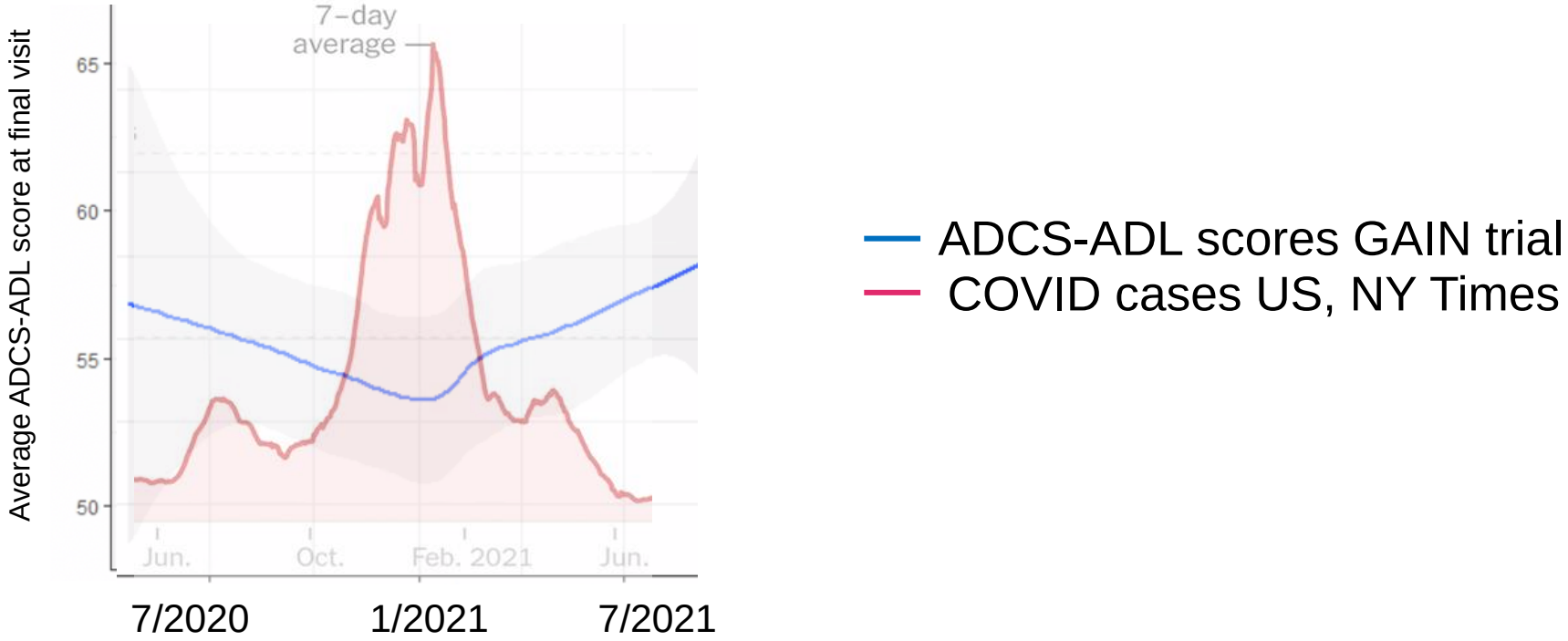
CORTEXYME

Thank you!

Important consideration for the field: Already heterogeneous functional outcome scores are being more severely impacted by the pandemic

- Caregivers are instructed not to consider if disease was the cause of functional change
  - Unrelated events have major impact on scores that drive mean changes (eg: car crash, -60 points change ADL)

- Many questions on ADCS-ADL, especially, and CDR are directly impacted by quarantine
  - Go grocery shopping? Keep appointments (hairdresser)? Travel outside home? hobbies (eg: bingo)?



Major dip in week 48 ADCS-ADL scores around Nov -January 2021 compared to higher scores July – Aug 2021 when many quarantines were lifted. Time of year had as much impact on scores as 48 weeks in the study