Additional Data from the Phase 2/3 GAIN Trial of COR388 (Atuzaginstat) for the Treatment of Mild to Moderate Alzheimer's Disease

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AD/PD 2022

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Disclosures

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

Overview

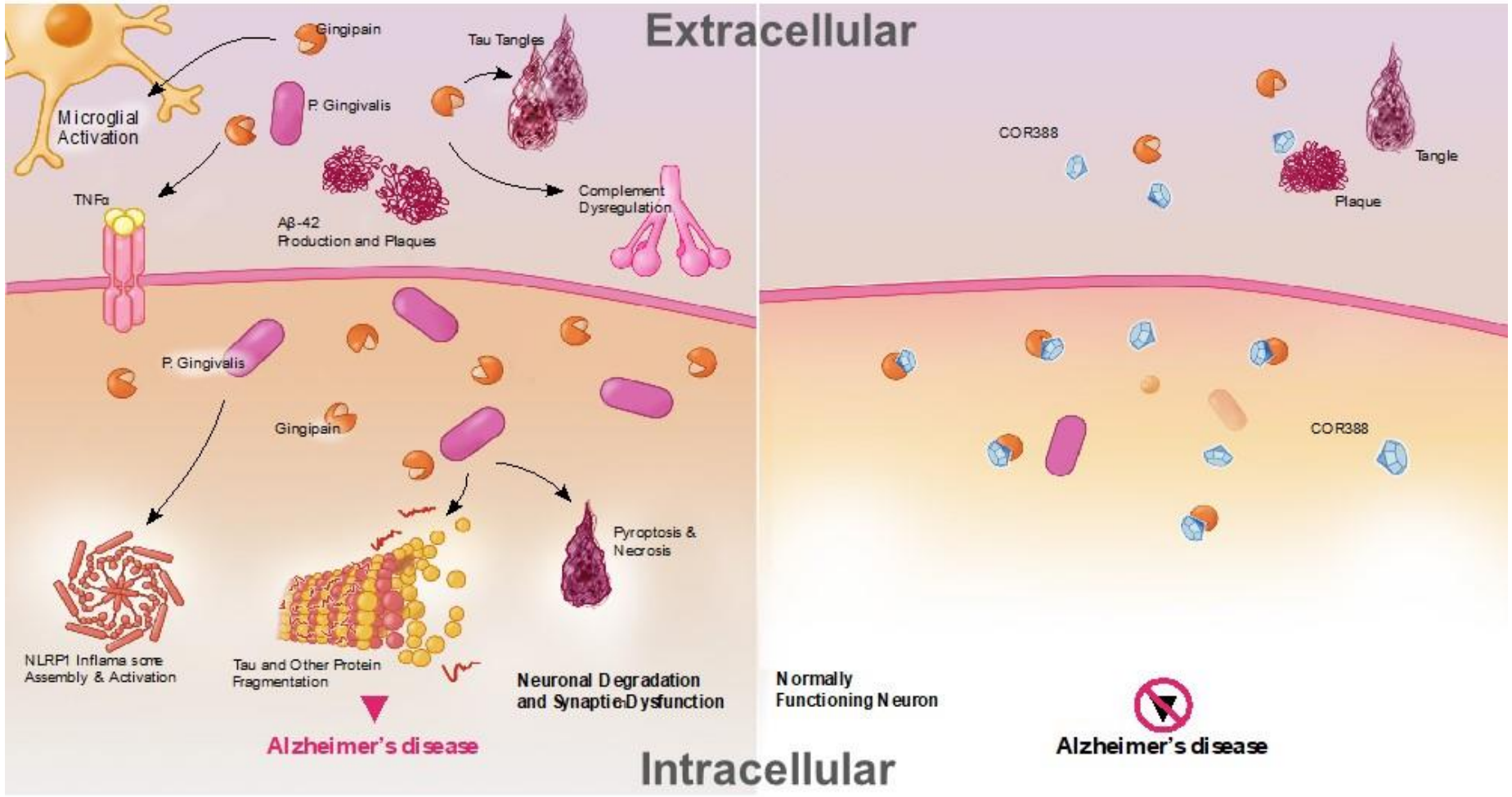
1. Extensive preclinical, epidemiological, clinical, and other data support the role of *P. gingivalis* (Pg) as an upstream driver of Alzheimer's Disease (AD) and as a potential new target for treating AD and other neurodegenerative diseases

2. GAIN Trial clinical results provided clinical confirmation of Pg as an upstream driver of Alzheimer's, and a new target for treating AD, with a 30-50% slowing of decline in mild-moderate AD patients with evidence of high Pg infection

3. NEW biomarker data and biomarker/clinical correlations presented today further support the role played by Pg as an upstream driver of AD pathology and atuzaginstat as an effective treatment

4. This presentation is the first of multiple presentations this year which are expected to include incremental analysis and biomarker data from the GAIN Trial

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

Published and/or replicated by independent 3rd parties

Collaborations with independent 3rd parties

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 ($p<0.0001$ vs age-matched controls)
- Gingipain levels correlate with tau and ubiquitin, correlating with symptoms

Epidemiology

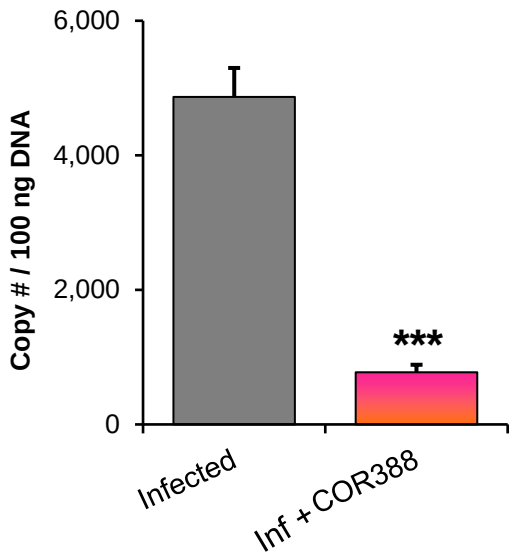
- Periodontal disease (*Pg* keystone cause) is a strong predictor of AD
- Serum Abs to perio pathogens are risk factor for AD
- Perio associates with higher brain amyloid

Inflammation

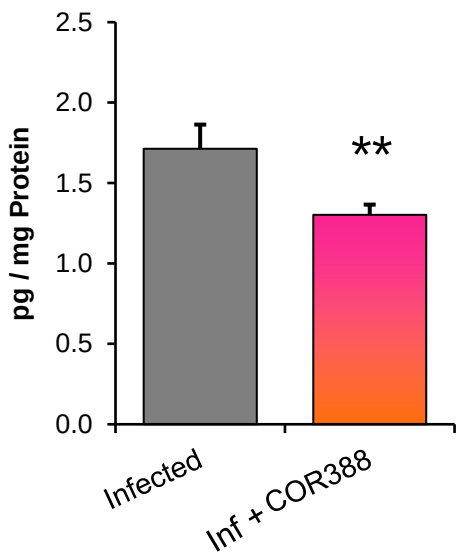
- Microglial and inflammasome activation consistent with chronic low-grade infection, both activated by *Pg*

Pg oral infection in wild type mouse recreates extensive AD pathology – and atuzaginstat reverses

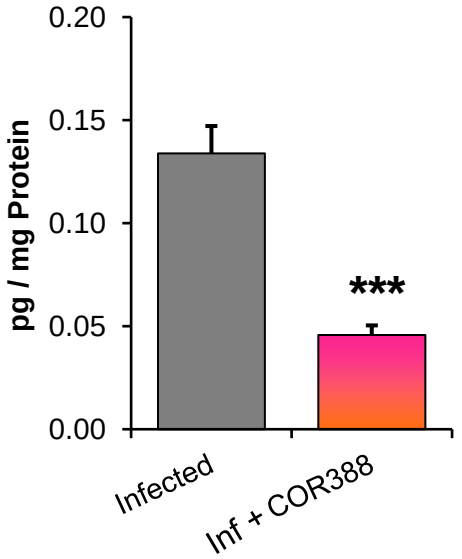
P gingivalis PCR in the brain



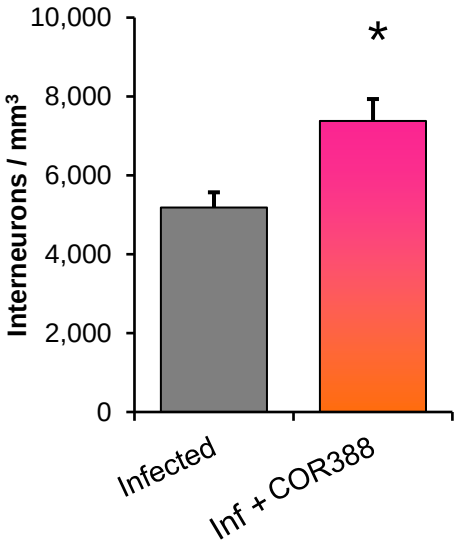
Amyloid beta in the brain

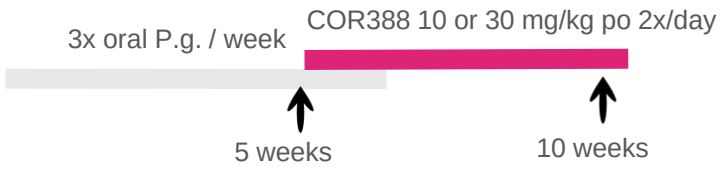


TNFalpha in the brain



Hippocampal interneurons



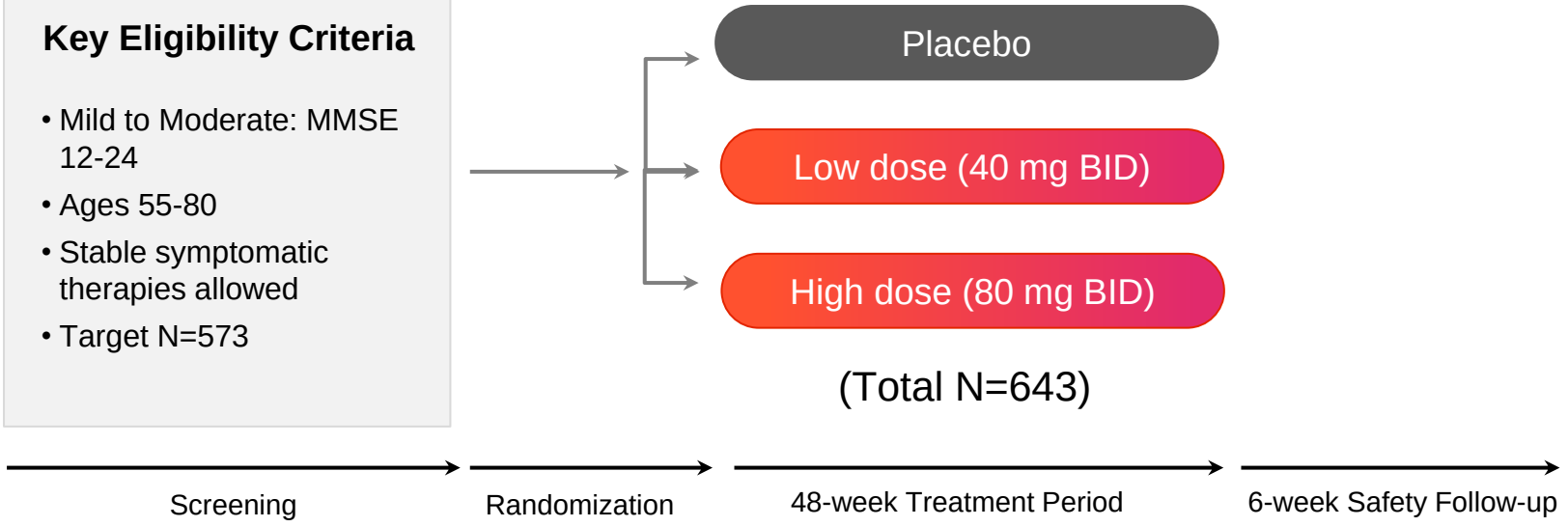


Source: Cortexyme COR388 dose response study, Mean +/- SEM *p< 0.05,**p<0.01, ***p<0.001

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

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%)

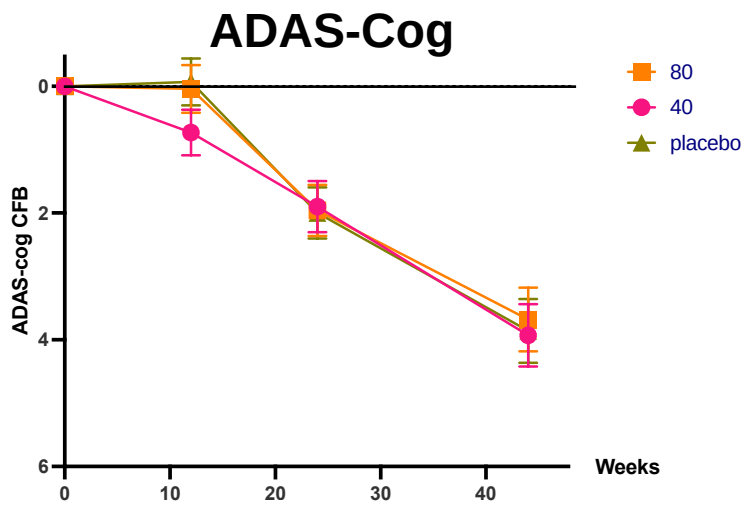
Parameter	Placebo	40 mg BID	80 mg BID
MMSE			
Moderate >=12 to <=18	110 (51%)	107 (51%)	107 (50%)
Mild >=19 to <=24	107 (49%)	105 (50%)	107 (50%)
ApoE4 Carriers	140 (65%)	137 (65%)	137 (64%)
Non-Carriers	77 (36%)	75 (35%)	77 (36%)
ADAS-Cog Mean (SD)	23.9 (8.7)	23.5 (8.1)	23.7 (8.3)
ADCS-ADL Mean (SD)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

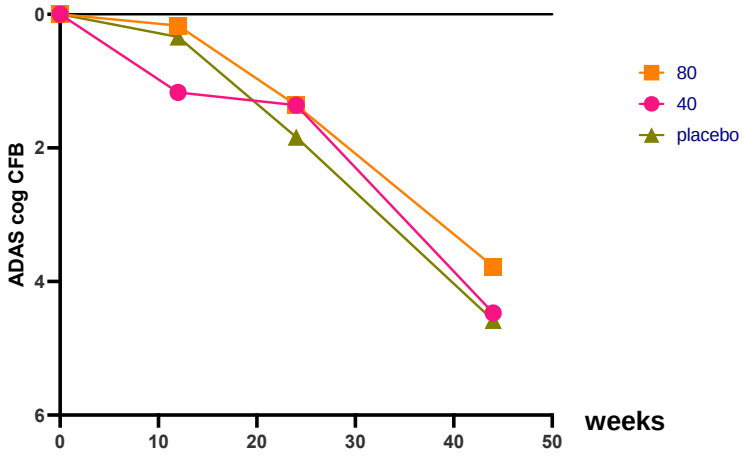
Eight Black participants and one Other participant also identified as Hispanic/Latino.
Randomization was stratified by mild vs. moderate and ApoE4 carriers positive vs. negative.

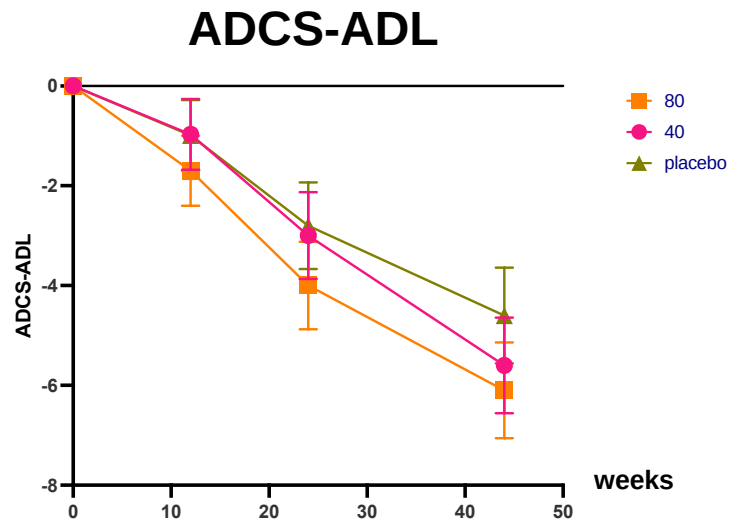
Overall co-primary endpoints in the intent-to-treat (ITT) population

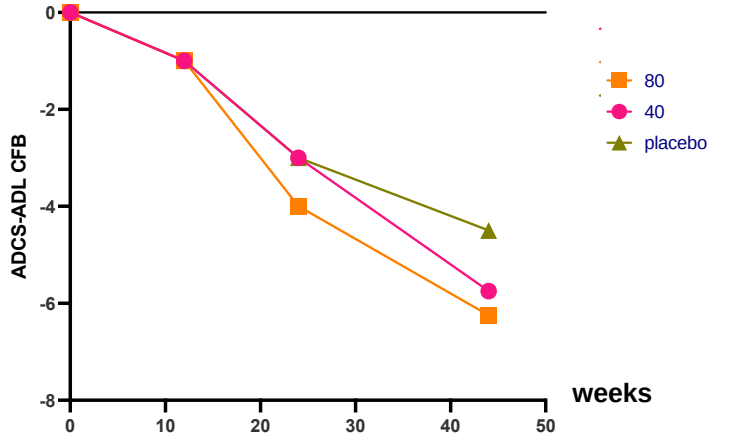
Parametric
Primary analysis
MMRM

Nonparametric
Prespecified sensitivity analysis









Improvement is up on all scales

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

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

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

- The following were prespecified cohort analyses:
  - *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

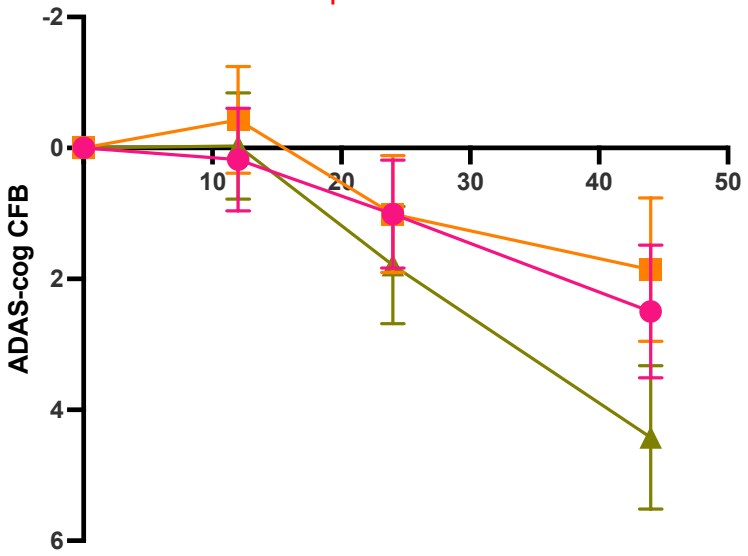
- Correlations between biomarkers of *P. gingivalis* infection with clinical endpoints were also prespecified

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%)

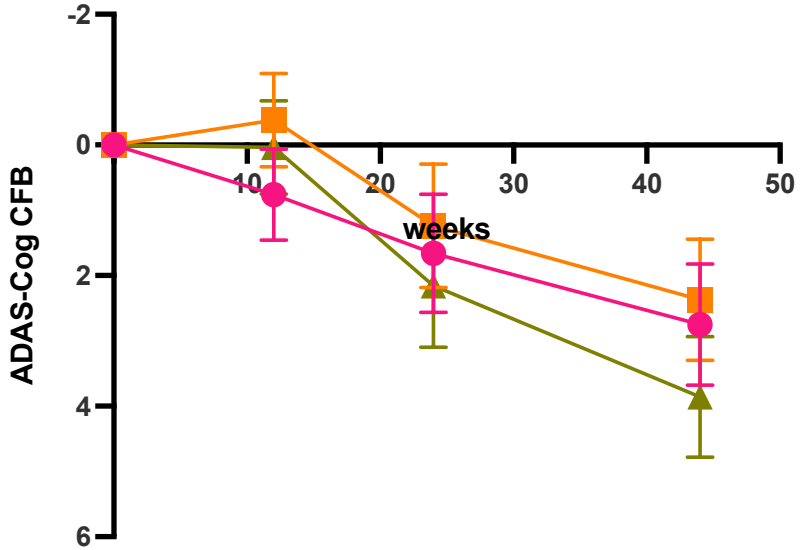
Interaction p value = 0.02



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

High IgG Serum (50%)

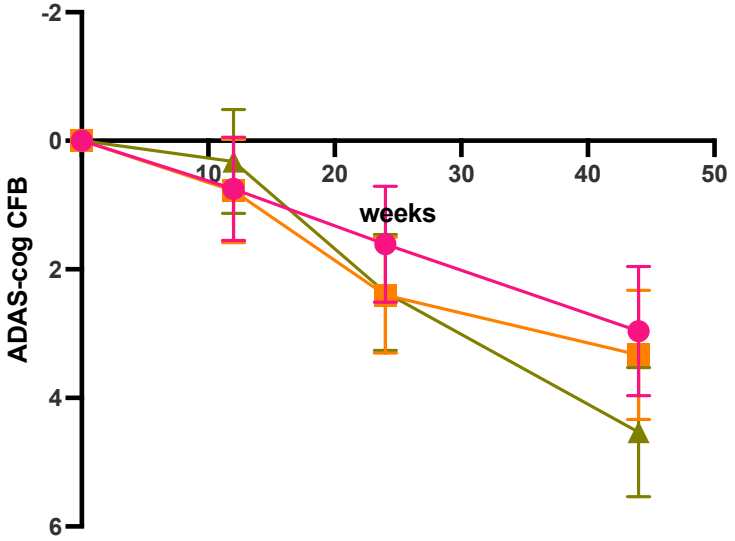
Interaction p value = 0.03



80 mg BID = 39% slowing
40 mg BID = 29% slowing

High IgG CSF (50%)

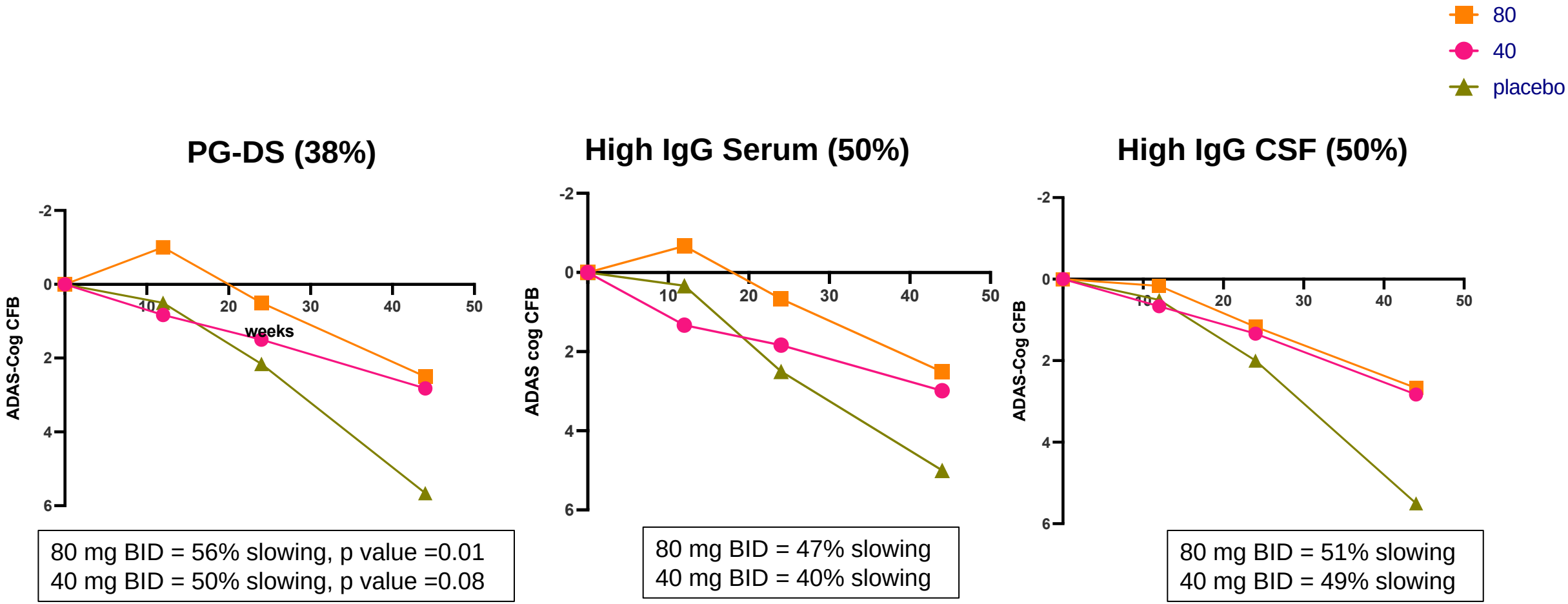
Interaction p value = 0.33



80 mg BID = 26% slowing
40 mg BID = 35% 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

	ADAS-Cog11	ADCS-ADL	CDR-SB	MMSE
Spearman's Rho (CFB to week 24)	**.33**	**.09**	**.16**	**.17**
P-value	**<.0001**	**.26**	**.06**	**.04**
Spearman's Rho (CFB to week 48)	**.30**	**.16**	**.25**	**.23**
P-value	**.0005**	**.06**	**.004**	**.008**

All correlations listed as positive indicate greater reduction in *Pg* is associated with better clinical outcomes, and increases in *Pg* are associated with worse clinical outcomes.

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

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%)

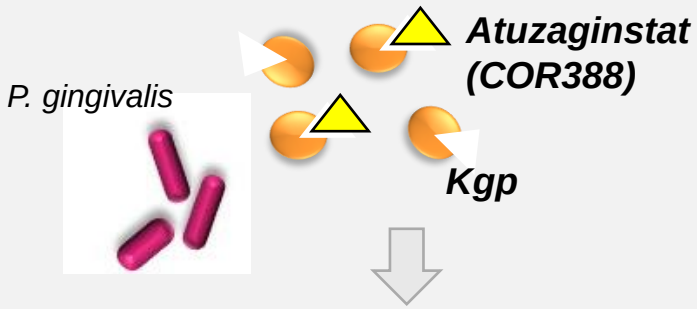
FINDINGS

- 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 AEs are GI related.
- 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*

GAIN biomarker analysis – New data March 2022

Target Engagement and Inhibition



- Kgp inhibition

Target Mechanism of Action

Host Response

- Anti-Pg IgG
- Inflammation

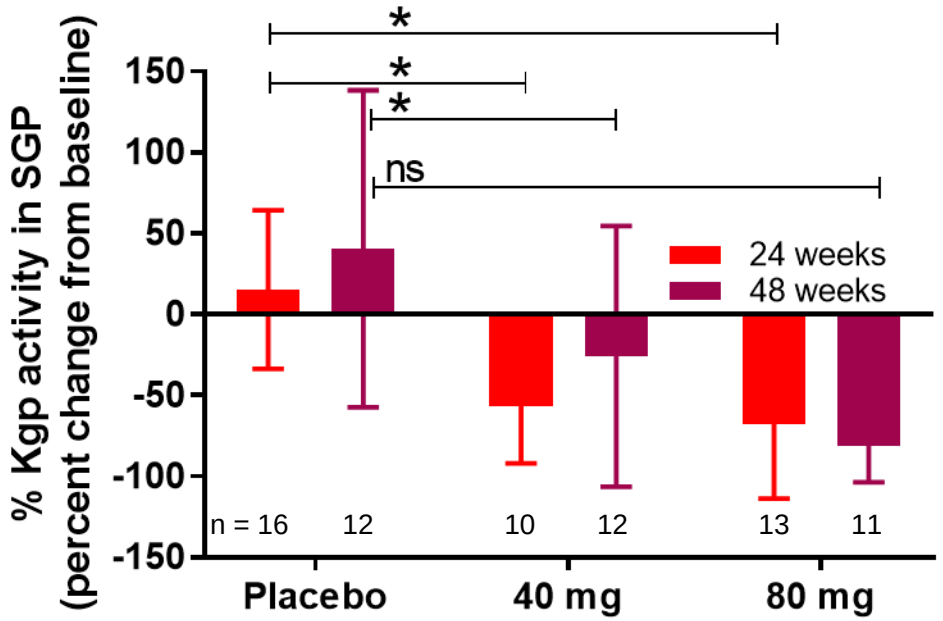
Target Activity

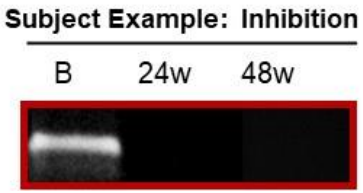
- ptau/t-tau
- Abeta 42/40
- ApoE
- Neuro-degeneration

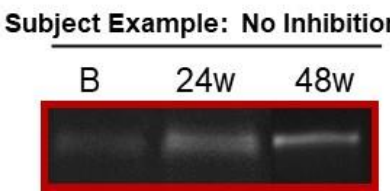
Disease

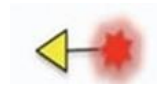
- Brain atrophy (MRI measures)
- ADAS-Cog11, ADL
- Neurodegeneration markers

Kgp target engagement and inhibition – New data March 2022









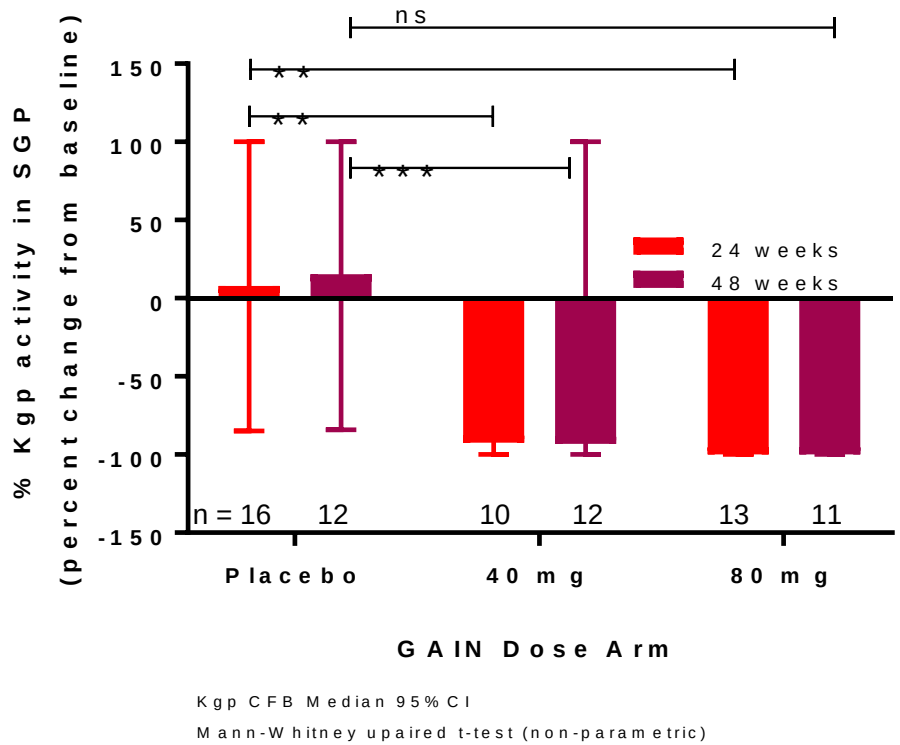
Gingipain Active Site probe

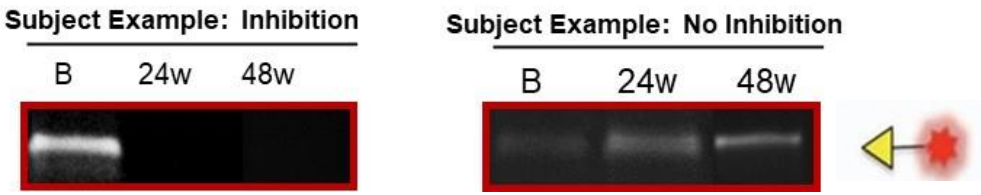
% CFB Mean, 95% CI
Unpaired t-test with Welch's correction (parametric)

ns	P > 0.05
*	P ≤ 0.05

Analysis of subgingival plaque (SGP) in a subset of subjects demonstrates atuzaginstat target engagement and inhibition of Kgp

Kgp target engagement and inhibition – New data March 2022





Gingipain Active Site probe

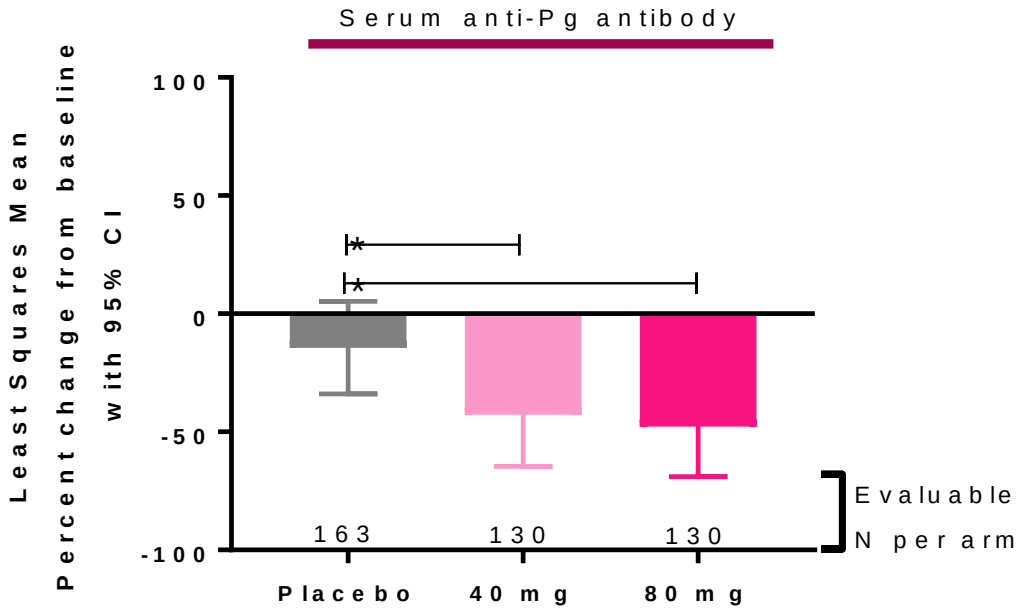
ns	P > 0.05
**	P ≤ 0.01
***	P ≤ 0.001

Median 95% CI
/hitney unpaired t-test (non-parametric)

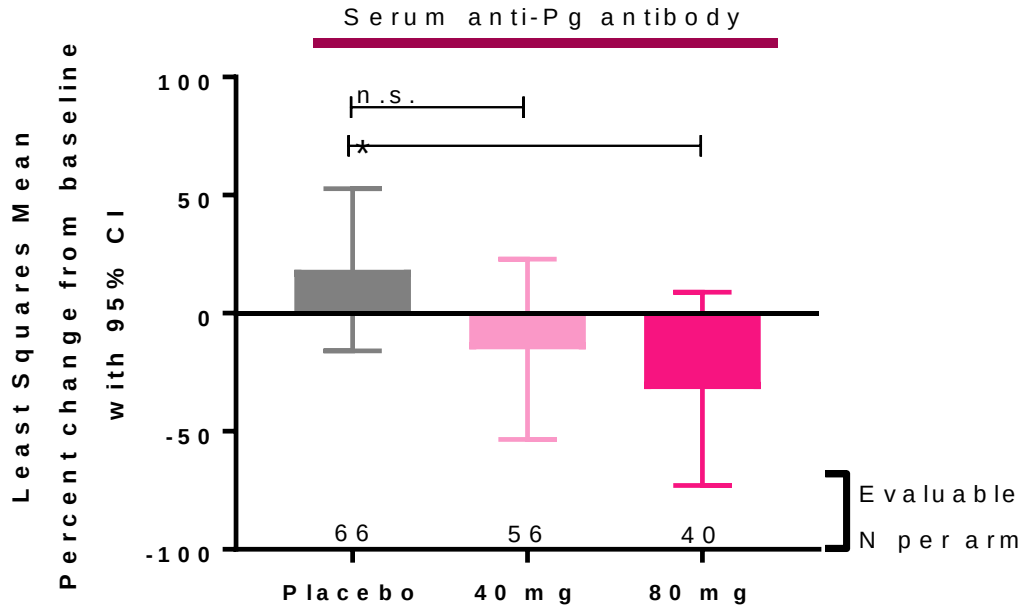
Analysis of subgingival plaque (SGP) in a subset of subjects demonstrates atuzaginstat target engagement and inhibition of Kgp

Serum biomarker: anti-Pg antibody – New data March 2022

ITT

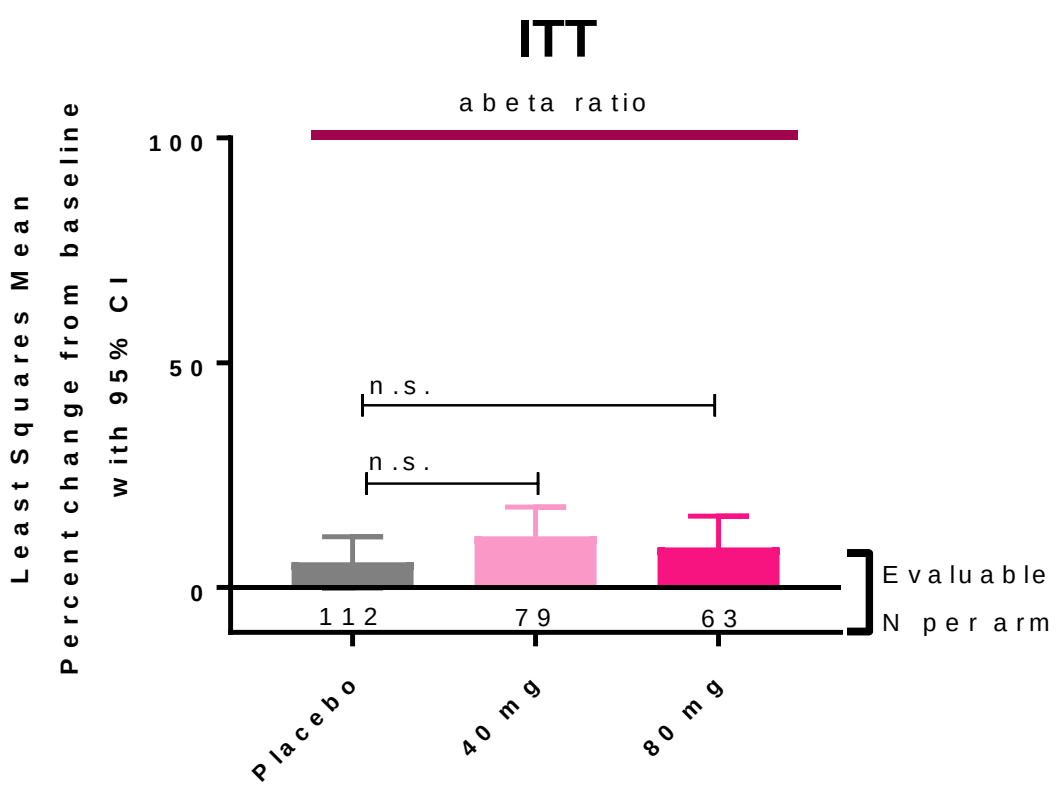


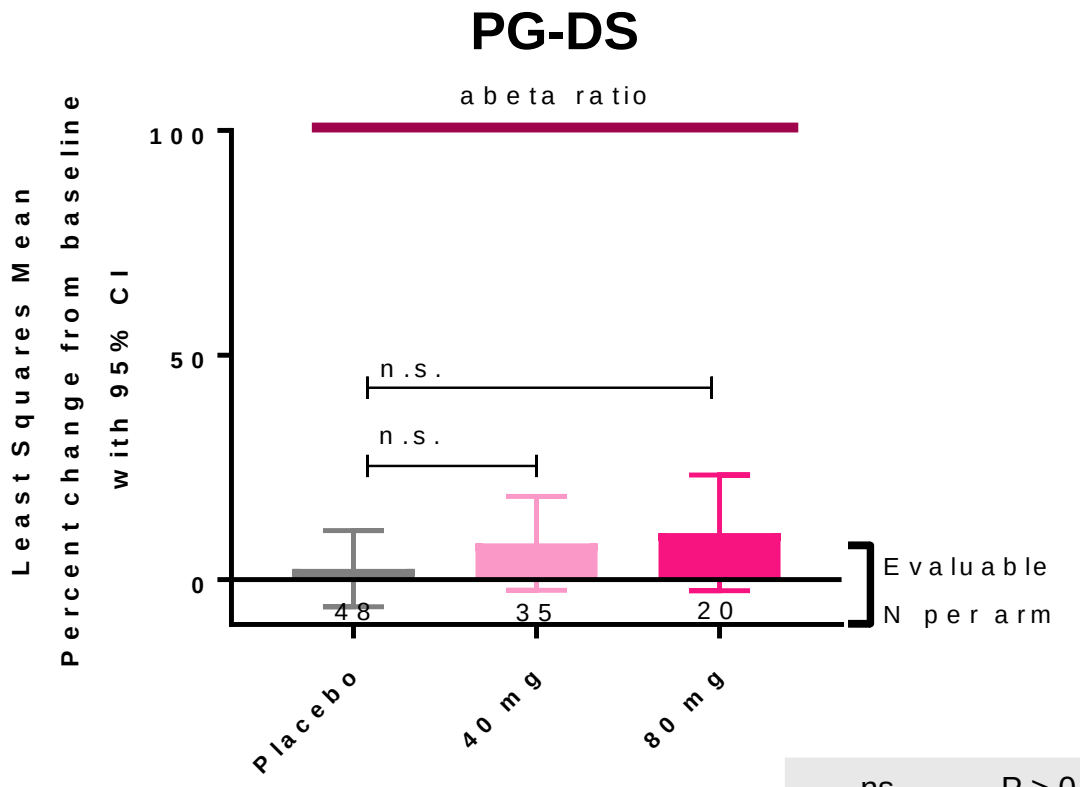
PG-DS



ns	P > 0.05
*	P ≤ 0.05

CSF biomarker: Abeta 42/40 ratio – New data March 2022

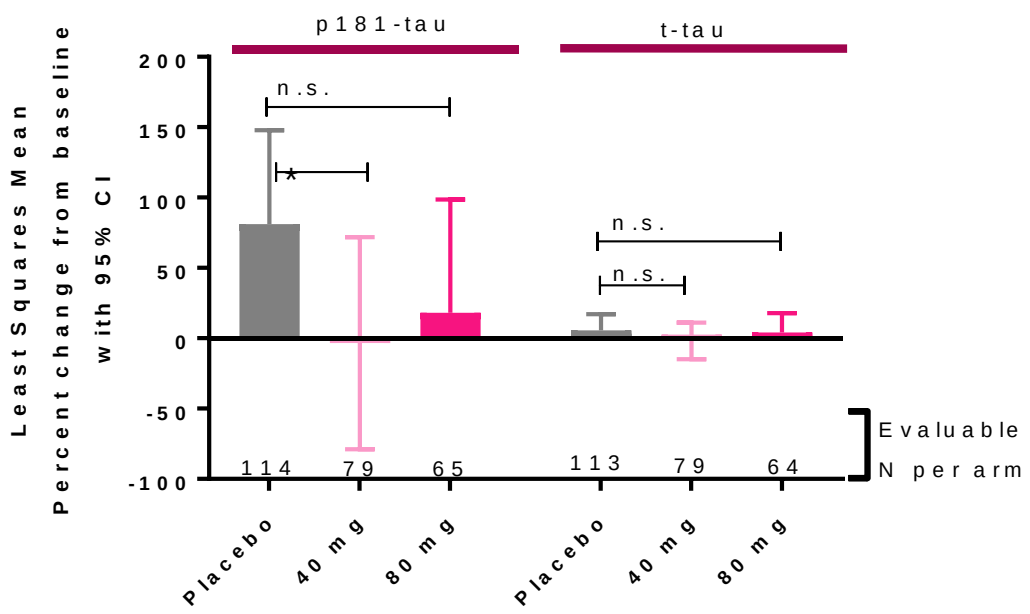




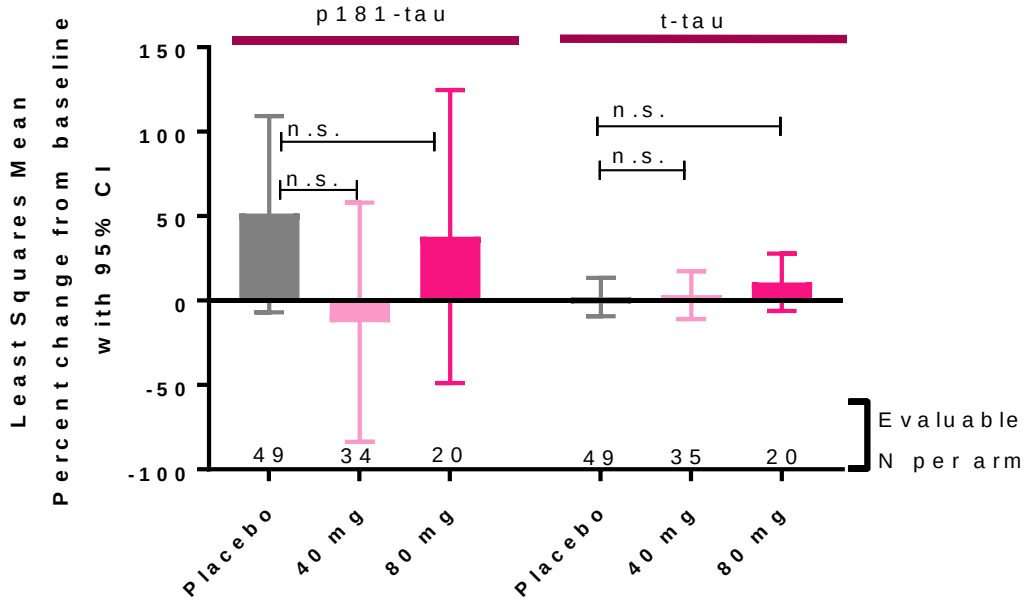
ns P > 0.05

CSF biomarkers: p181-tau and t-tau – New data March 2022

ITT

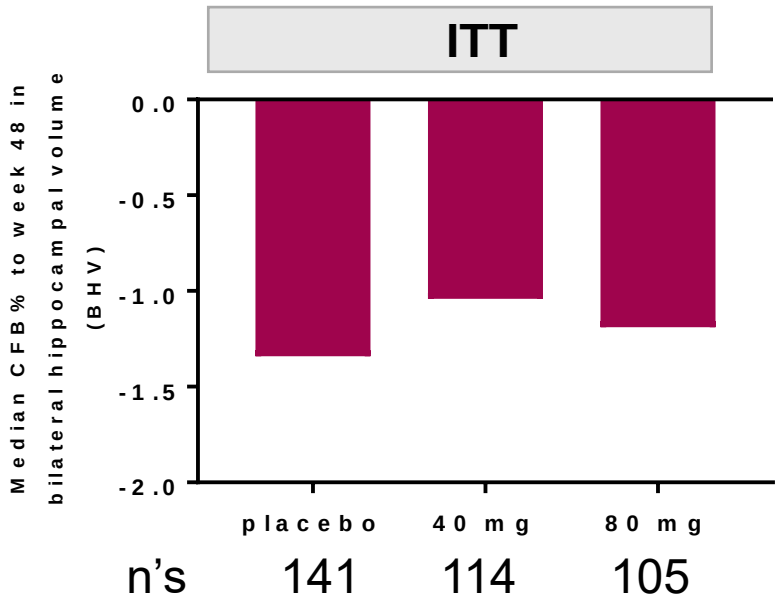


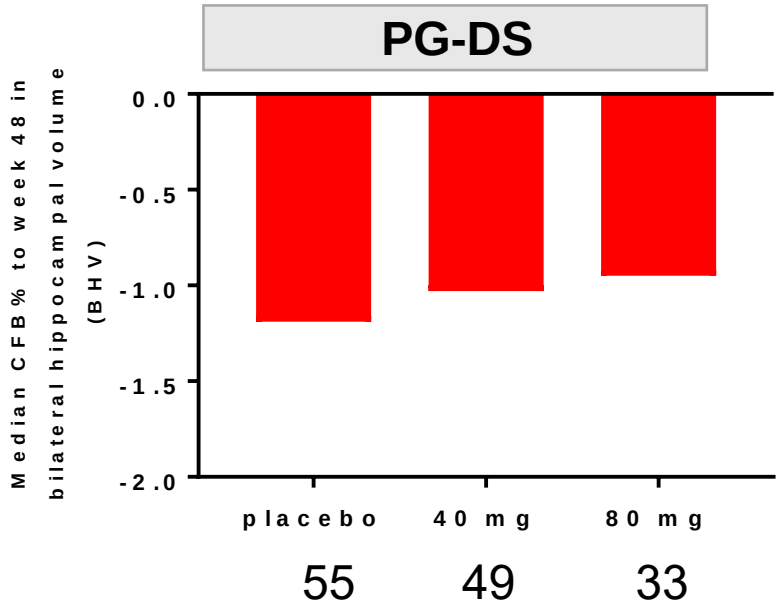
PG-DS



ns	P > 0.05
*	P ≤ 0.05

Bilateral hippocampal volume – New data March 2022

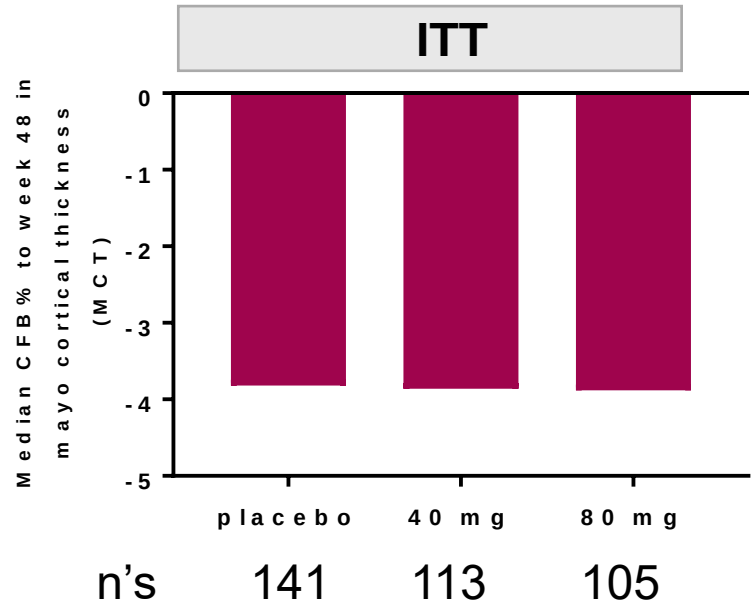


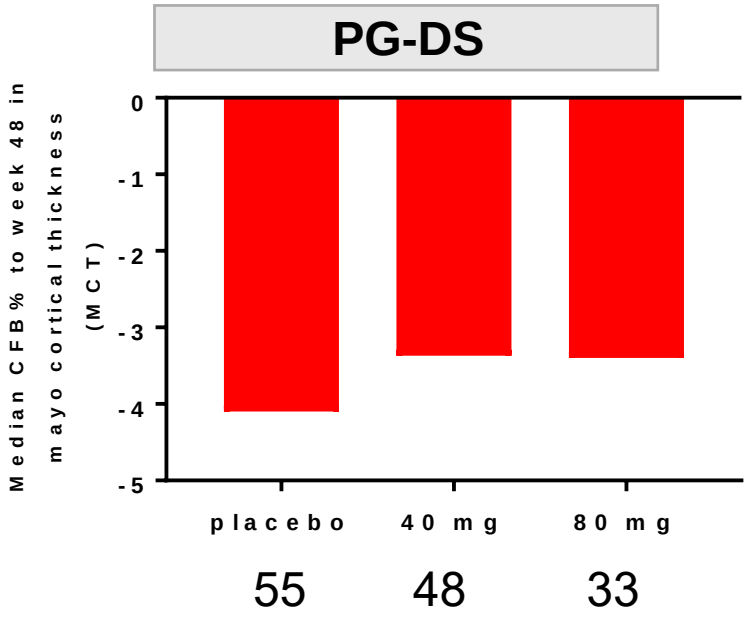


Correlations in BHV at Week 48 with Week 48 clinical outcomes

		ADAS-Cog11	ADCS-ADL
ITT	**rho (CFB to week 48)**	0.05	0.15
	P-value	0.37	0.006
PG-DS	**rho (CFB to week 48)**	-	-
	P-value	-	-

Mayo cortical thickness – New data March 2022

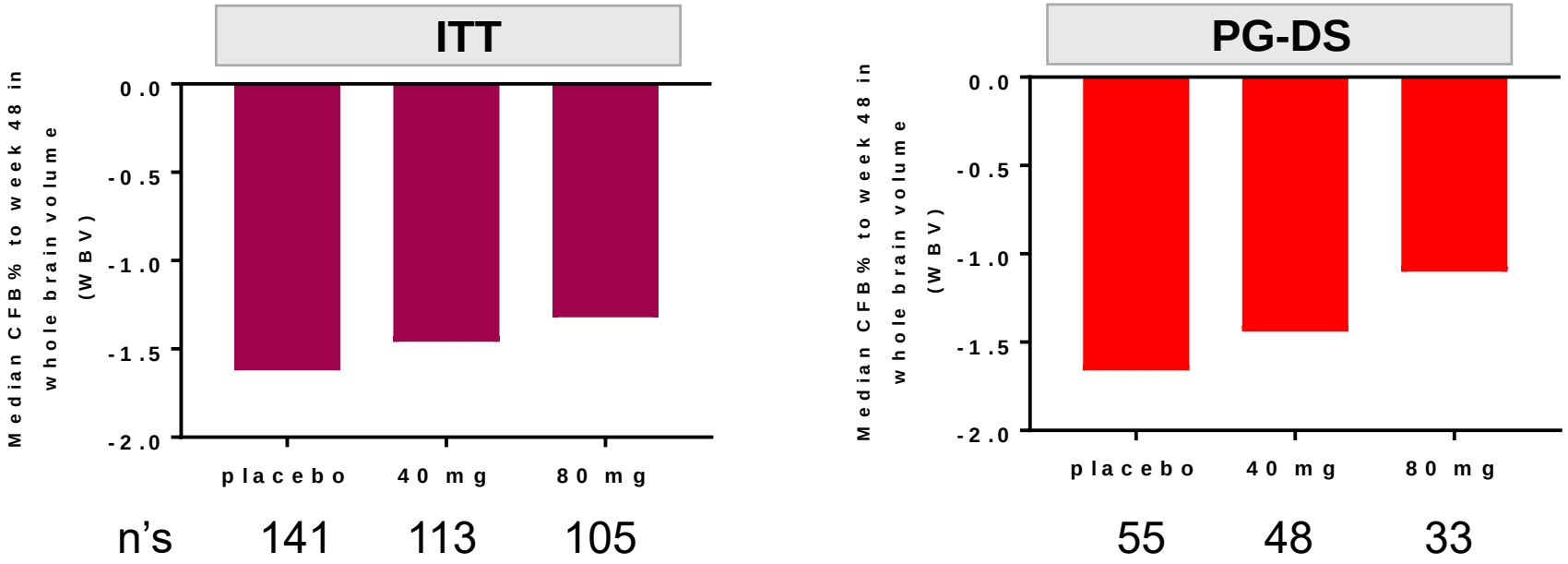




Correlations in MCT at Week 48 with Week 48 clinical outcomes

		ADAS-Cog11	ADCS-ADL
ITT	**rho (CFB to week 48)**	0.49	0.39
	P-value	<0.0001	<0.0001
PG-DS	**rho (CFB to week 48)**	-	-
	P-value	-	-

Whole brain volume – New data March 2022



Correlations in WBV at Week 48 with Week 48 clinical outcomes

		ADAS-Cog11	ADCS-ADL
ITT	**rho (CFB to week 48)**	0.50	0.42
	P-value	<0.0001	<0.0001
PG-DS	**rho (CFB to week 48)**	0.58	0.44
	P-value	<0.0001	<0.0001

Summary

- Extensive convergent data support the role of Pg as an upstream driver of AD prior to the GAIN Trial

- The clinical results of the GAIN Trial confirmed the Pg/gingipain hypothesis of Alzheimer's, showing 30-50% slowing of decline in patients with mild-moderate AD and markers of high Pg infection

- The overall weight of the evidence from the NEW biomarkers presented today reinforce the above findings:
  - Atuzaginstat showed evidence of direct target engagement (Kgp activity)
  - Atuzaginstat impacted multiple additional downstream biomarkers
  - All markers were at least numerically supportive of the mechanism of action
  - Biomarker – clinical correlations were among the highest ever reported in the AD literature

- More to come with multiple presentations this year which are expected to include incremental analysis and biomarker data from the GAIN Trial

Thank you!