INTERCEPT-AD phase 1 insights and findings from the investigation of ACU193, a monoclonal antibody targeting soluble Aβ oligomers

Clinical Trials on Alzheimer's Disease
Boston, Massachusetts
October 27, 2023

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INTERCEPT-AD phase 1 insights and findings from the investigation of ACU193, a monoclonal antibody targeting soluble Aβ oligomers

Chair: Diana Kerwin, Kerwin Medical Center, Dallas, TX

Determination of target engagement at various doses of ACU193 in INTERCEPT-AD

Mirjam Trame, Certara, Boston, MA

Reduction in amyloid plaque load at higher doses of ACU193 in INTERCEPT-AD

Eric Siemers, Acumen Pharmaceuticals, Inc, Charlottesville, VA

Characteristics of participants in INTERCEPT-AD who did or did not develop ARIA with ACU193

Stephen Salloway, Alpert Medical School of Brown University, Providence, RI

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Acknowledgements

Participants and their Study Partners

- We acknowledge with thanks the individuals who enrolled in INTERCEPT-AD trial as well as their family, study partners, and friends who supported them.

Site Staff and Study Team Members

- We would also like to acknowledge the site staff, CRO, and all study team members who were vital to the successful completion of this trial.

Site Investigators

- Kimball Johnson (iResearch Atlanta), Diana Kerwin (Kerwin Research Center), Jeffrey Norton (Charter Research), Mohammad Reza Bolouri (Alzheimer's Memory Center), Alida Reinoso (Columbus Clinical Services), Shirley Valdez-Arroyo (Santos Research Center), Eric Carbonell (Combined Research), David Weisman (Abington Neurological), Alexander White (Progressive Medical Research), Beth Safirstein (MD Clinical), Lawrence Honig (Columbia University Hospital), Nelson Berrios (Clinical Trial Network), Steve Sitar (Orange County Research Institute), Nidia Laurin (Clinical Endpoints), Sanjiv Sharma (CenExel), Gustavo Alva (Hoag Memorial Hospital Presbyterian) and Maria Johnson (ACMR)

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Determination of Target Engagement at Various Doses of ACU193 in INTERCEPT-AD

Mirjam N Trame, PharmD, PhD
Vice President, Certara Drug Development Solutions

Clinical Trials on Alzheimer's Disease
Boston, Massachusetts
October 27, 2023

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Disclosure

- Dr. Trame is an employee of Certara and consulting for Acumen Pharmaceuticals.

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Forward Looking Statement

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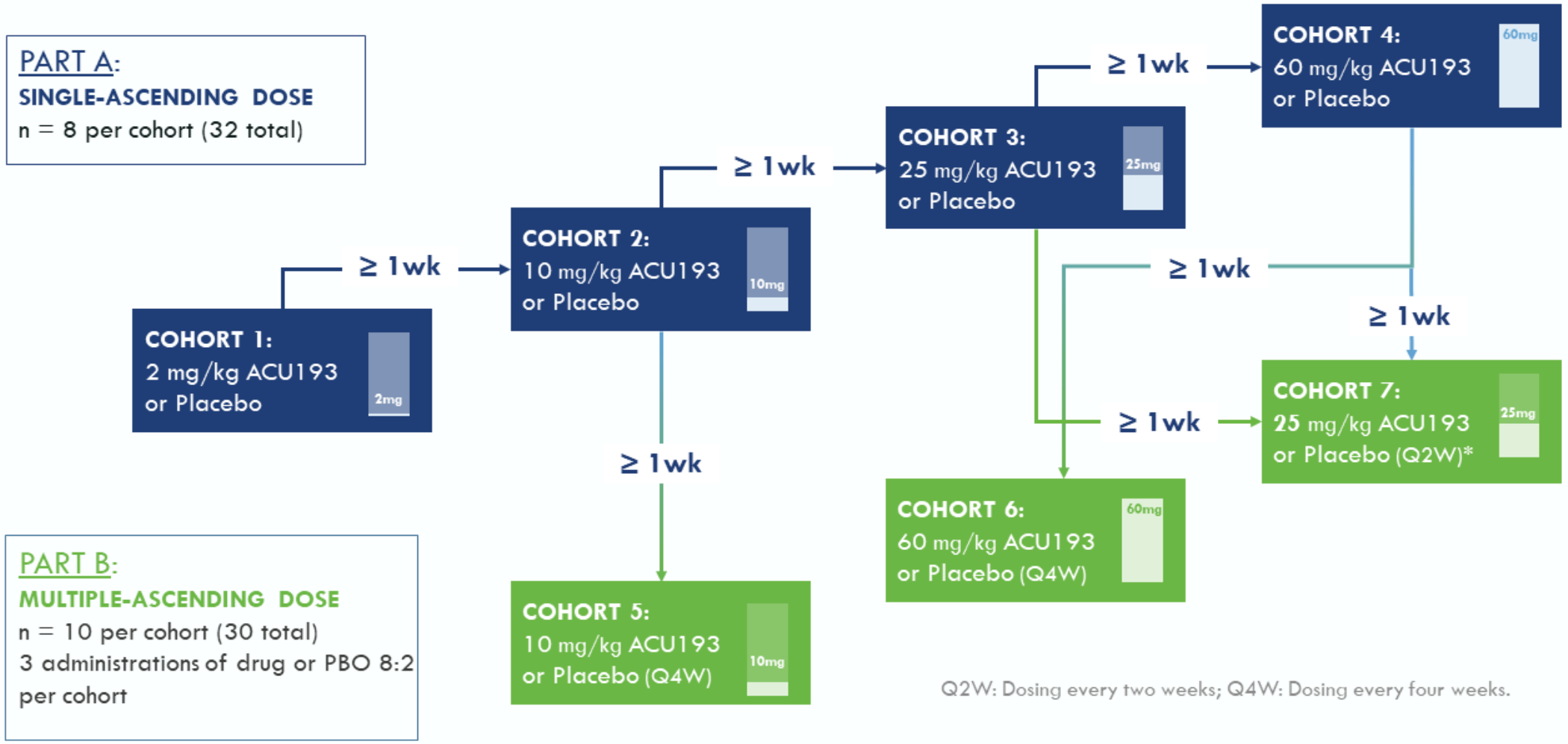
INTERCEPT-AD Phase 1 Study



Q2W: Dosing every two weeks; Q4W: Dosing every four weeks.

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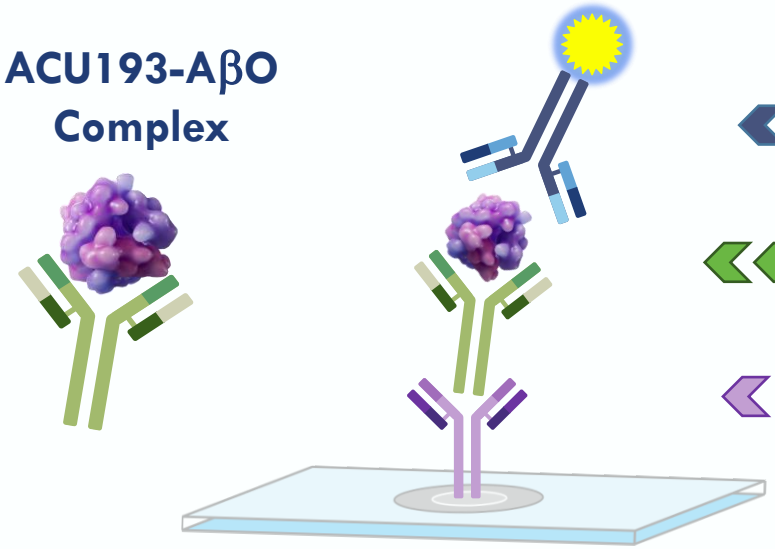
Target Engagement: Measuring ACU193-AβO Complex in CSF

MSD S-Plex (Turbo) Immunoassay

Virtual Poster #00312 presented by Erika Cline

ACU193-AβO Complex



- AβO selective detection (anti-AβO mAb)
- **Only drug/AβO complex is measurable**
- ACU193 drug specific capture (anti-ACU193 idiotype mAb)

Novel assay configuration tailored to selectively detect ACU193-AβO complex in CSF as direct measure of target engagement

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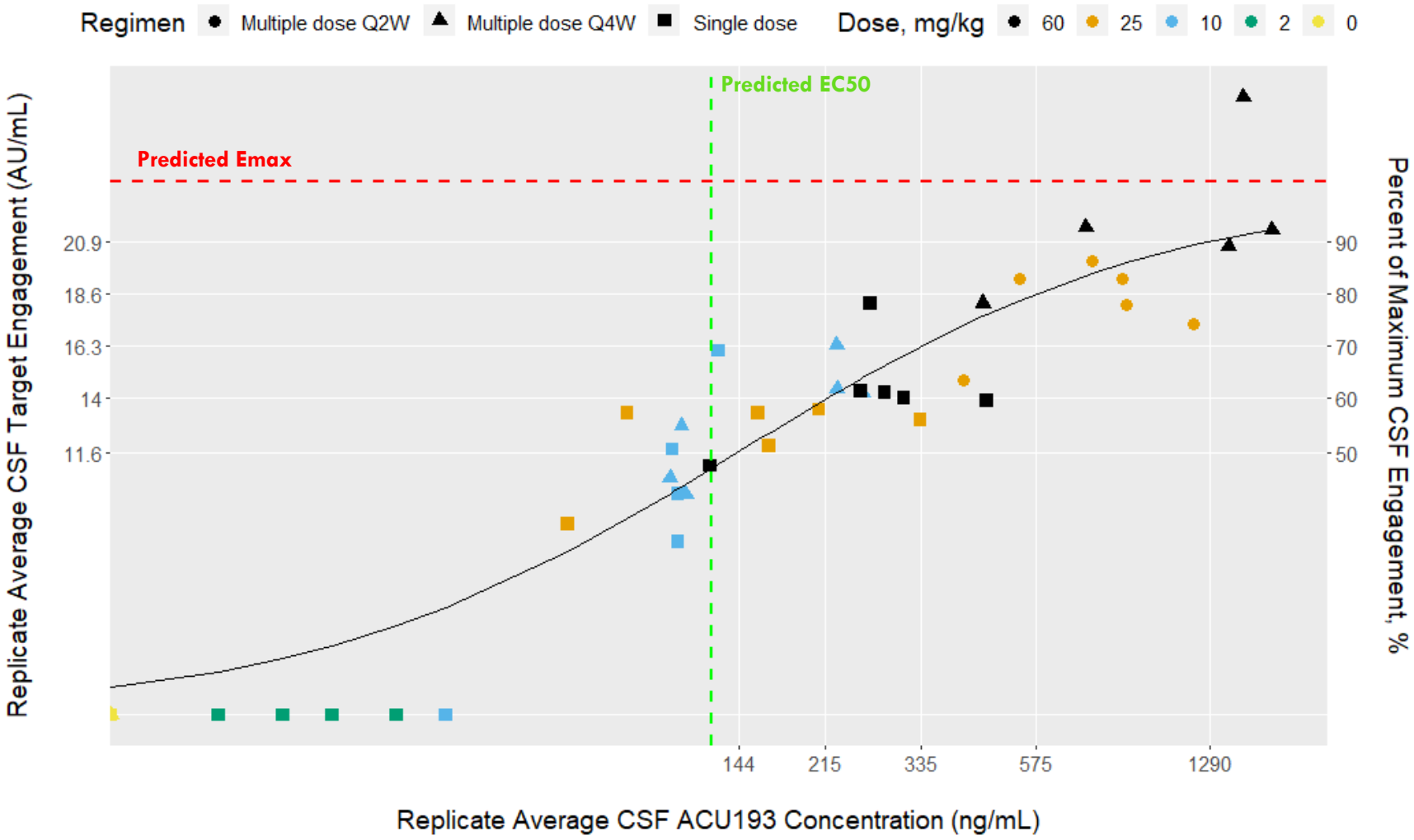
Clear ACU193 Concentration Target-Engagement Profile in the CSF

- Clear concentration-response profile in CSF
- These lumbar samples were taken while drug levels were falling, so they represent the *lowest* target engagement levels (something like "trough levels"); within dosing interval target engagement will be higher
- **These results motivated the development of a PK/PD model for ACU193 effect on target engagement in the CSF**



Red dashed line: predicted Emax from PKPD model; green dashed line: predicted EC50 from PKPD model

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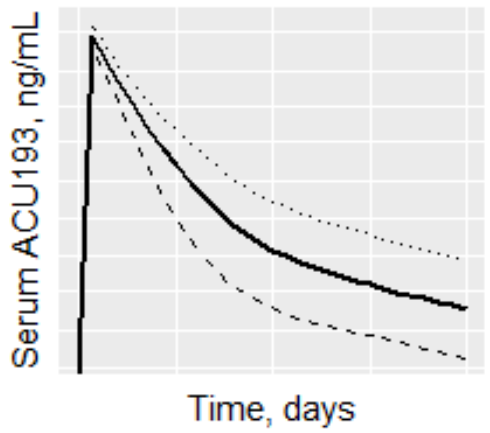
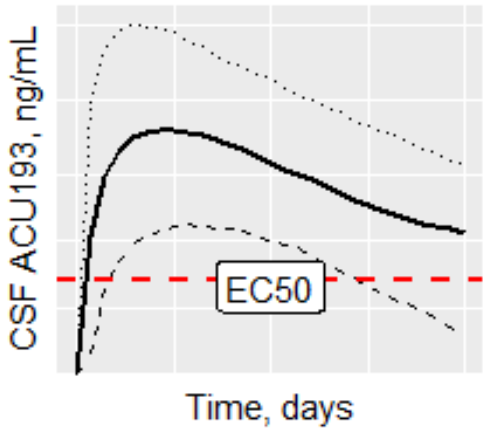
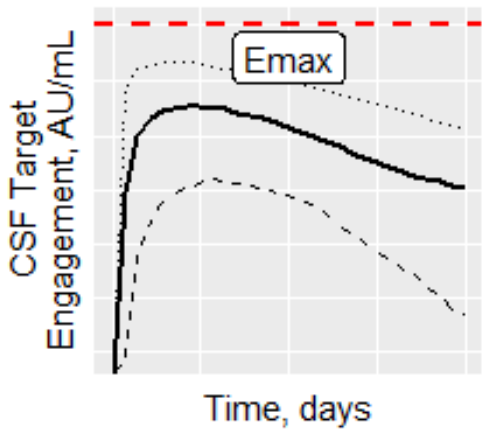
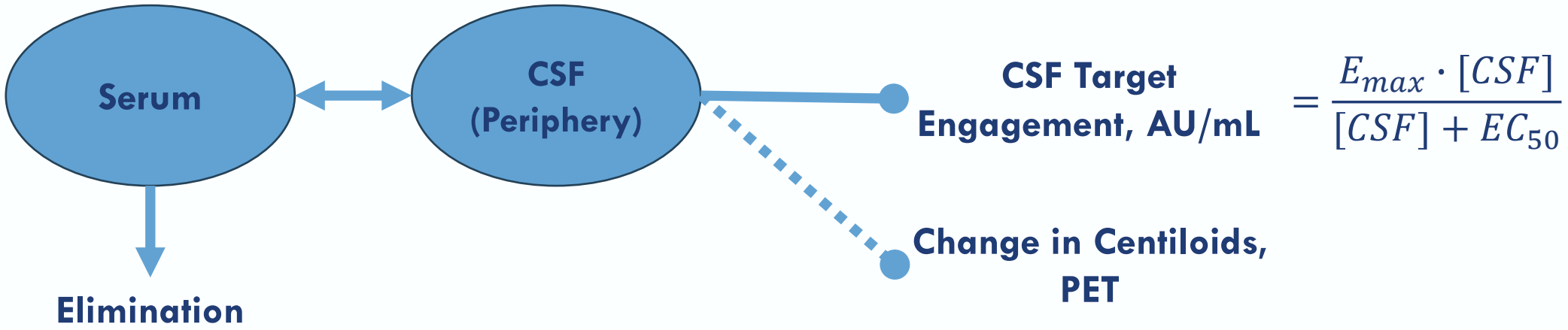
PK/PD Model for ACU193 Target Engagement

- CSF concentrations defined by a two-compartment model, then linked to target engagement in the CSF and Amyloid PET Centiloid reduction using a Michaelis-Menten (Emax) model









$$= \frac{E_{max} \cdot [CSF]}{[CSF] + EC_{50}}$$

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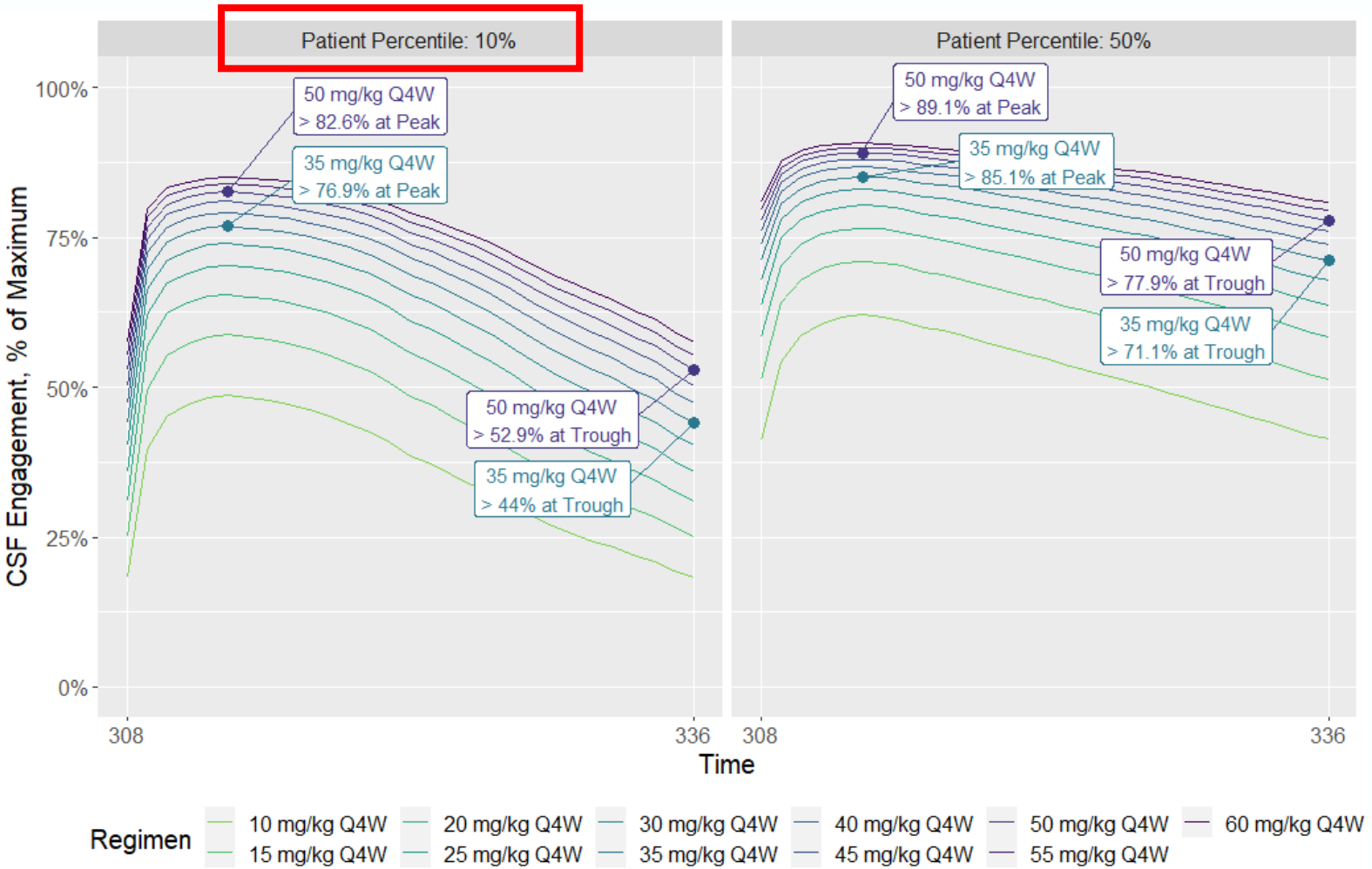
Simulated CSF Target Engagement at Steady-State

CSF target engagement was simulated at a candidate list of doses given Q4W at steady-state



Ph2/3 Dosing Strategy (ALTITUDE-AD)

lower dose: 35 mg/kg Q4W

upper dose: 50 mg/kg Q4W

- Notable **diminishing differentiation** as dose increases
- Doses were selected with **variation** in patient PK/PD in mind: select doses based on patients with the **lowest** (10th percentile) CSF target engagement
- Doses were selected with **peak-trough** variation in mind: select doses based on trough (end of dosing interval) CSF engagement

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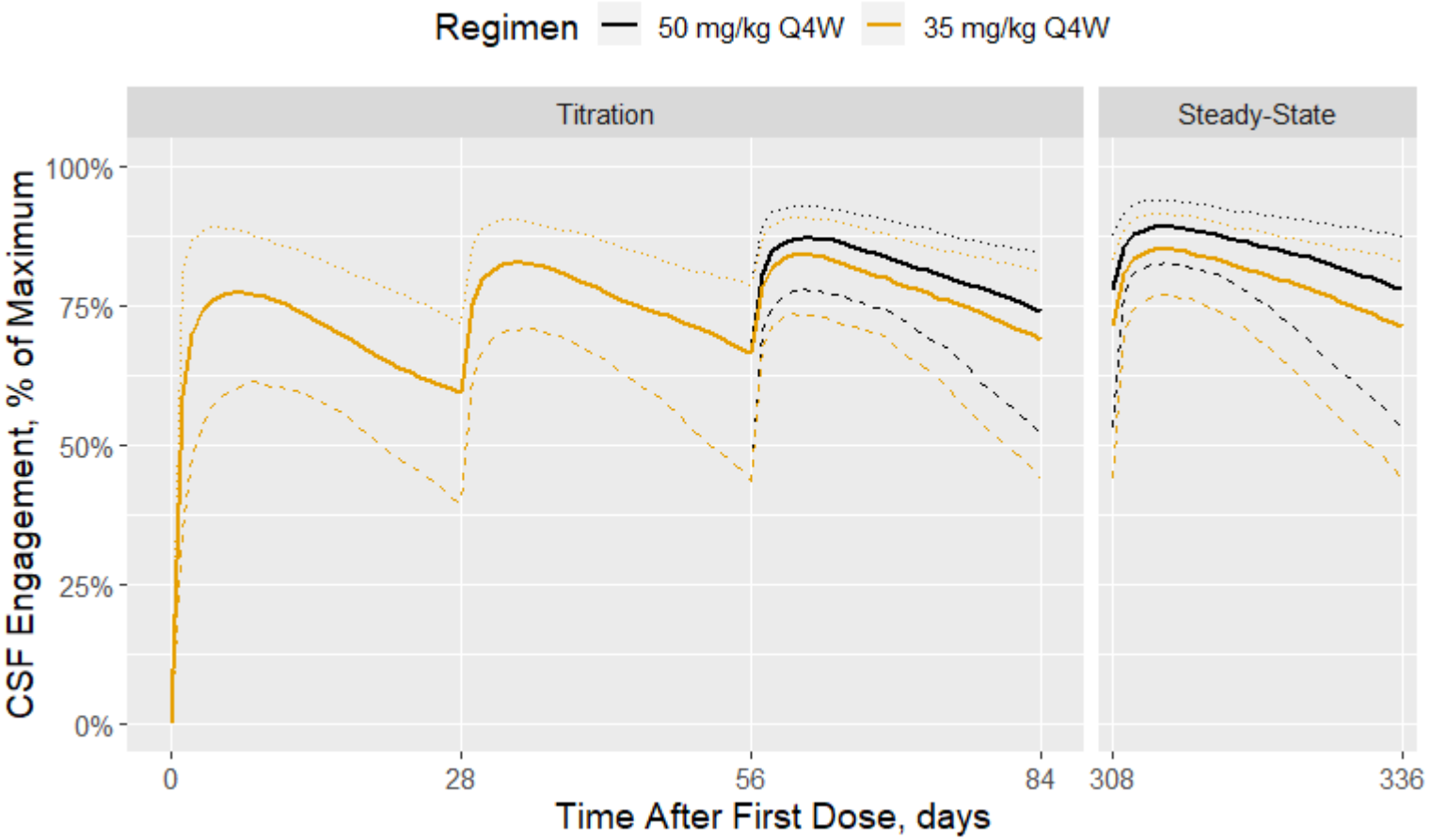
Simulated CSF Target Engagement for Doses Chosen for ALTITUDE-AD

CSF target engagement was simulated for doses chosen for the subsequent Phase 2/3 study



Solid lines: median patient; dashed and dotted lines are the 10th and 90th percentile patient

Ph2/3 Dosing Strategy (ALTITUDE-AD)

lower dose: 35 mg/kg Q4W

upper dose: 50 mg/kg Q4W

- Doses were selected with **accumulation** in mind: ACU193 concentrations build with repeated dosing, increasing target engagement
- To mitigate ARIA incidence, titration will be used for the 50 mg/kg dose starting at 35 mg/kg for the first two doses

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Positive Effect and Significant Reduction in Amyloid PET Centiloids

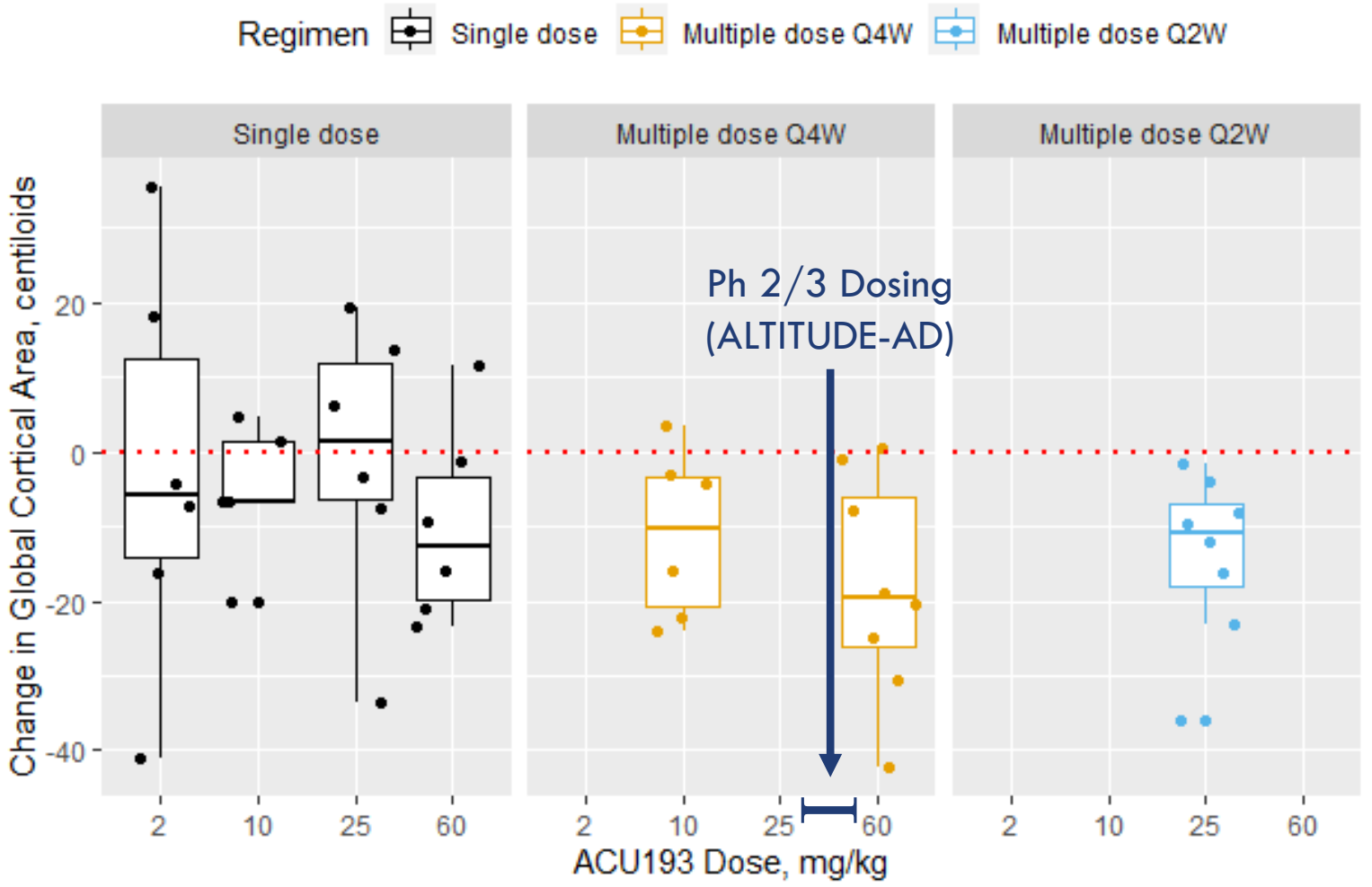
The PET data signal-to-noise is challenging, but dose and schedule dependence is evident in plaque reduction

Ph2/3 Dosing Strategy (ALTITUDE-AD)

lower dose: 35 mg/kg Q4W

upper dose: 50 mg/kg Q4W

- **Centiloid** data **supports** the **doses** selected by target engagement in the CSF
- No change: 2, 10, 25 mg/kg single dose
- **Plaque reduction**: 60 mg/kg single dose, 10 mg/kg Q4W, 25 mg/kg Q2W, 60 mg/kg Q4W



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Summary and Conclusions

- A CSF measure of target engagement (ACU193-Aβ-oligomer complex) was developed showing clear dose-related increases in target engagement across all cohorts
- A PK/PD model was utilized and demonstrated that the highest doses used in INTERCEPT-AD (60 mg/kg Q4W and 25 mg/kg Q2W) approached target engagement at Emax
- Significant reduction in Amyloid PET Centiloids was observed with the highest two doses in INTERCEPT-AD
- PK/PD simulations were used to assess CSF target engagement at various doses to guide study design for upcoming Phase 2/3 study
- ALTITUDE-AD (Phase 2/3 study) will study three arms at the following dose levels:
  - Placebo
  - 35 mg/kg Q4W
  - 50 mg/kg Q4W (with titration from 35 mg/kg)

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Thank you!

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Reduction in amyloid plaque load using higher doses of ACU193 in INTERCEPT-AD

Eric R Siemers, MD
Chief Medical Officer, Acumen Pharmaceuticals

Clinical Trials on Alzheimer's Disease
Boston, Massachusetts
October 27, 2023

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Disclosures

Dr. Siemers is an employee and shareholder at Acumen Pharmaceuticals.

Consulting Agreements (2021 or later)

- Cogstate Ltd.
- Gates Ventures LLC
- Hoffman La-Roche Ltd.
- Vaccinex, Inc.

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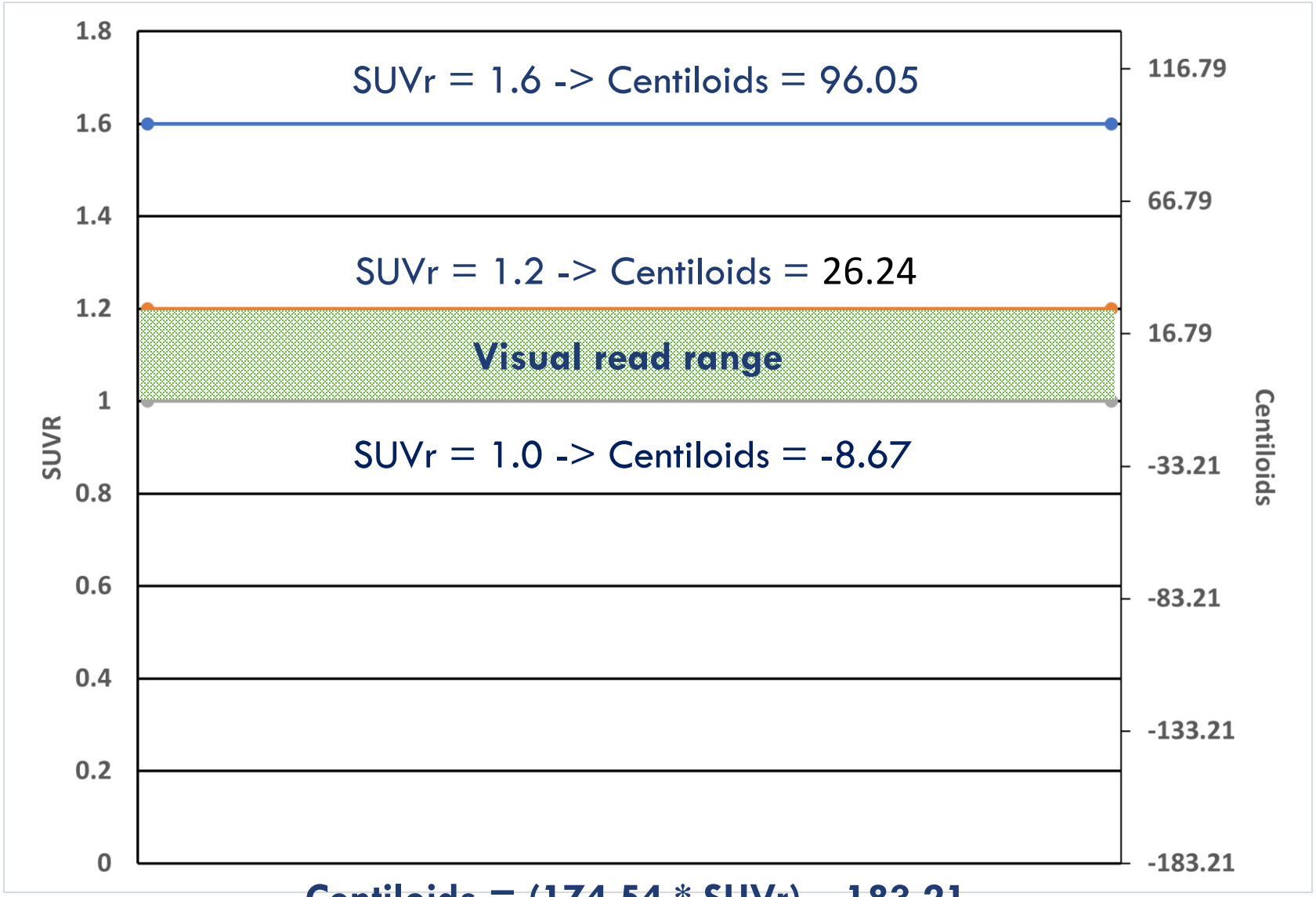
Relationship between florbetapir SUVr and Centiloids



Centiloids = (174.54 * SUVr) – 183.21

Results from hybrid SUVr/visual read assessments

- **Of 194 amyloid PET scans obtained during screening:**
  - 49 (25%) had a global cortical SUVr of <1.0
  - **81 (42%) had a global cortical SUVr of 1.0 – 1.2**
  - 64 (33%) had a global cortical SUVr of >1.2
- **Of the 81 scans with a global SUVR of 1.0 – 1.2, 14 (17%) were read visually as amyloid positive**
  - For the 14 scans with positive visual reads, Centiloid values ranged from -6.7 to 21.0
- **Of the 65 randomized patients, 11 (17%) entered the study with an intermediate global cortical SUVr and a positive visual read**

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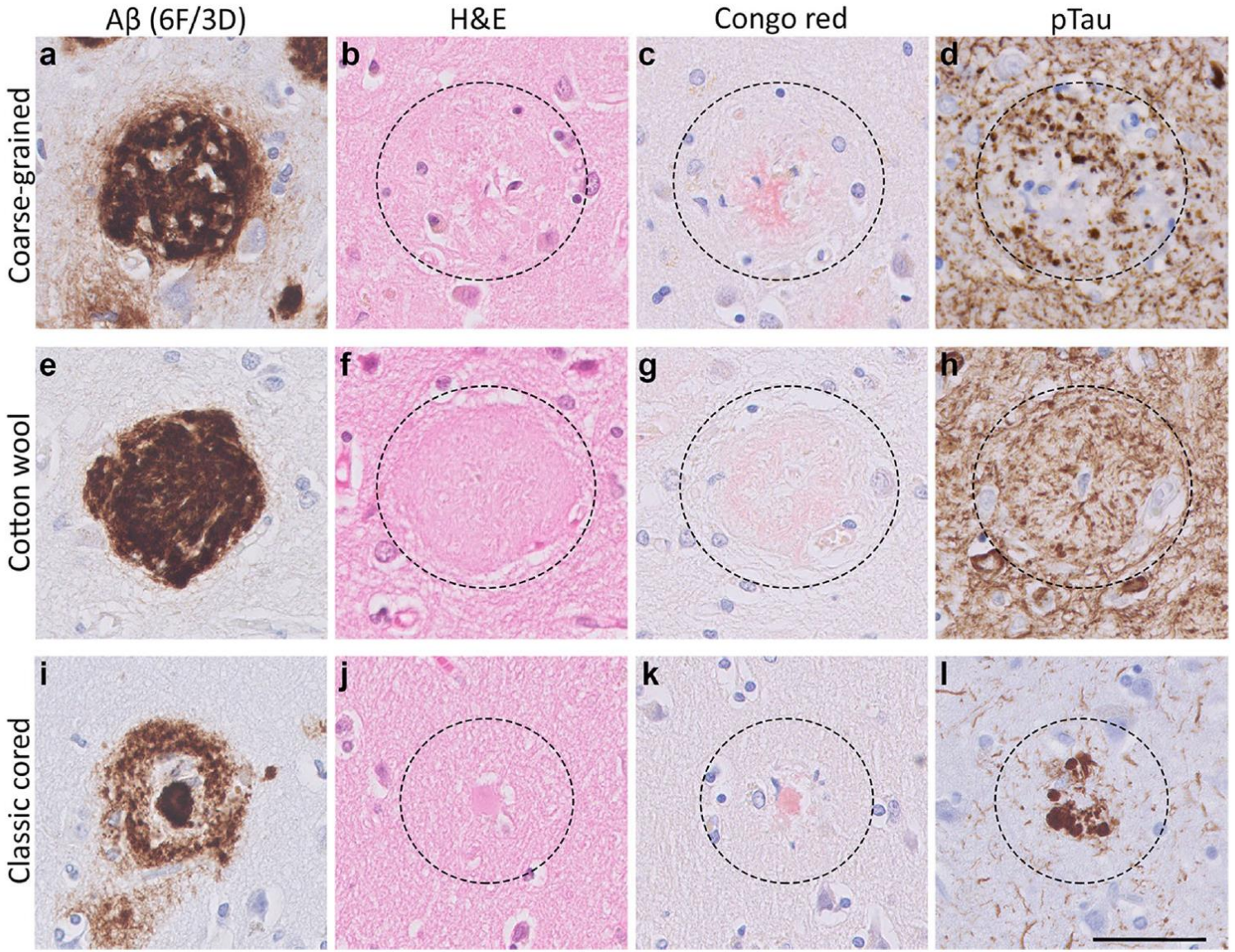
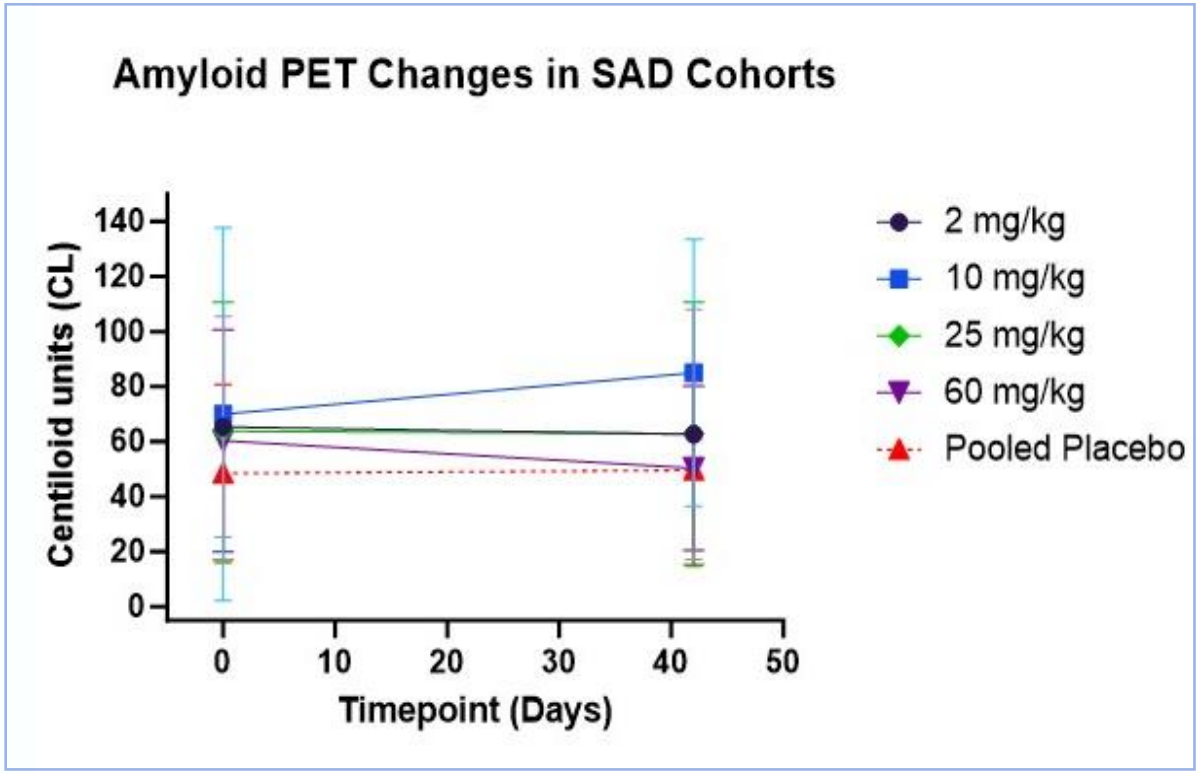
All amyloid plaques are not created equal

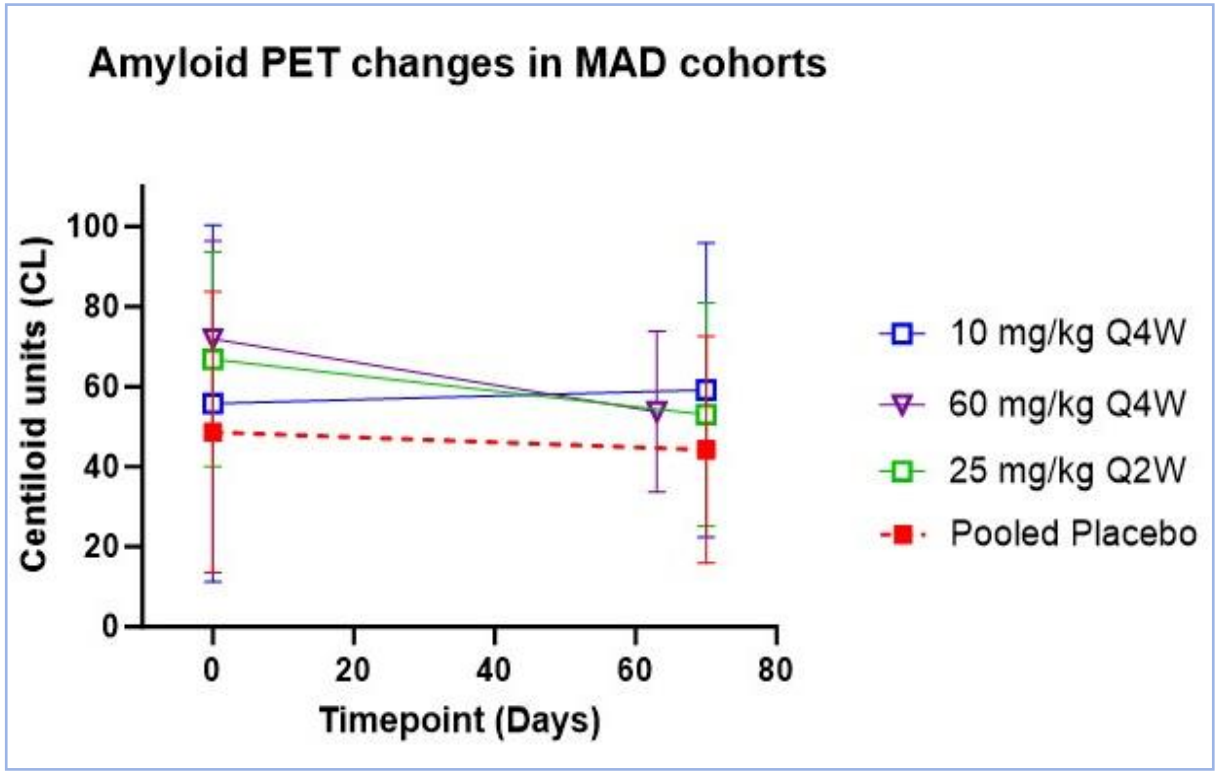


Boon et al. Acta Neuropathologica (2020) 140:811-830 https://doi.org/10/1007/s00401-020-02198-8

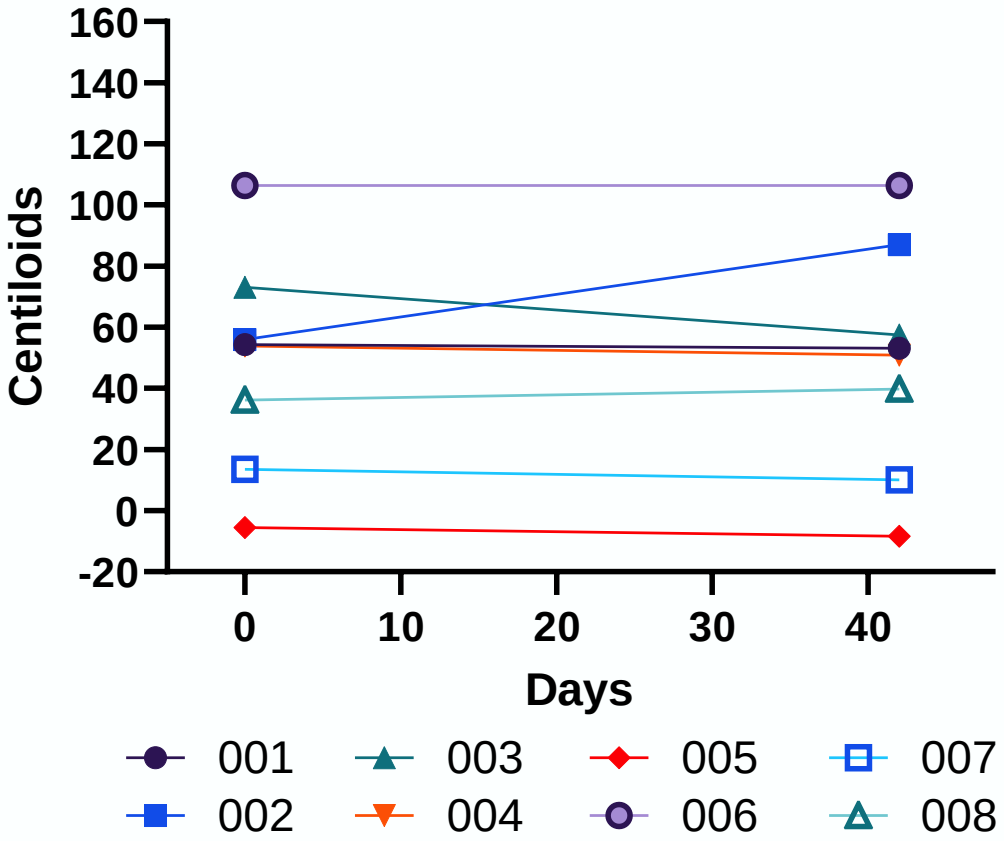
INTERCEPT-AD Individual Cohort Results

Mean Centiloid changes by cohort





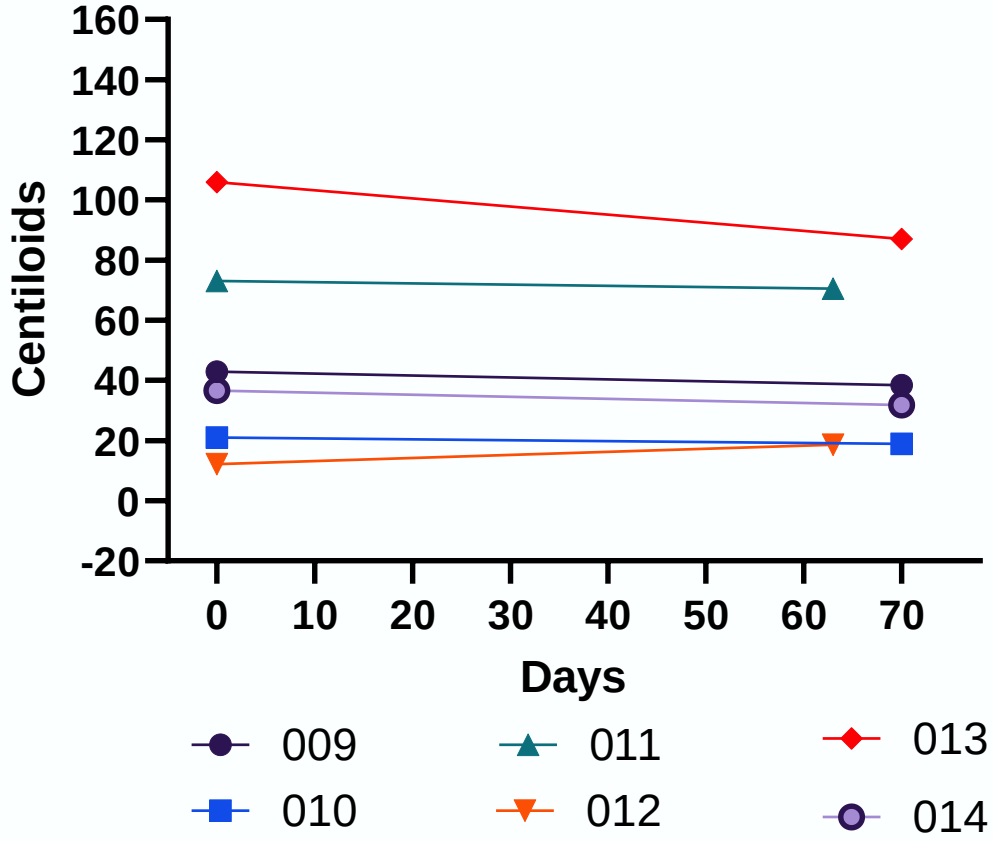
SAD placebo



Baseline mean = 48.5 Centiloids

Endpoint mean = 50.0 Centiloids

MAD placebo



Baseline mean = 48.6 Centiloids

Endpoint mean = 44.2 Centiloids

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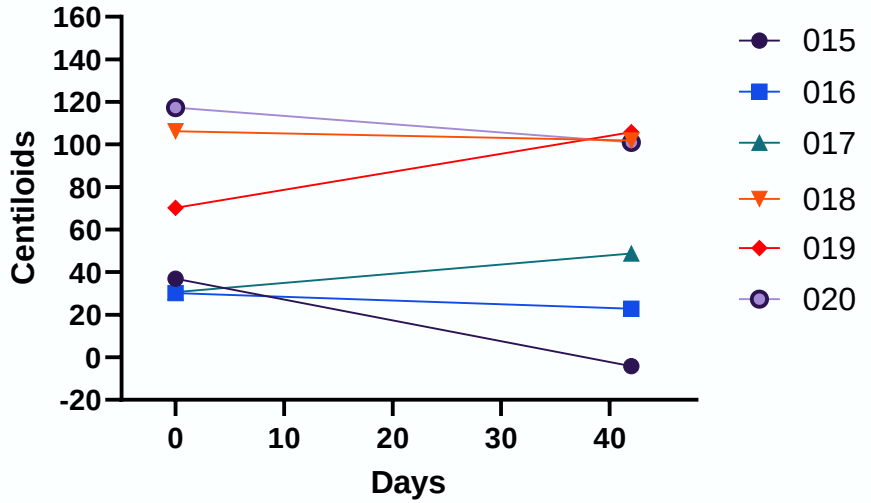
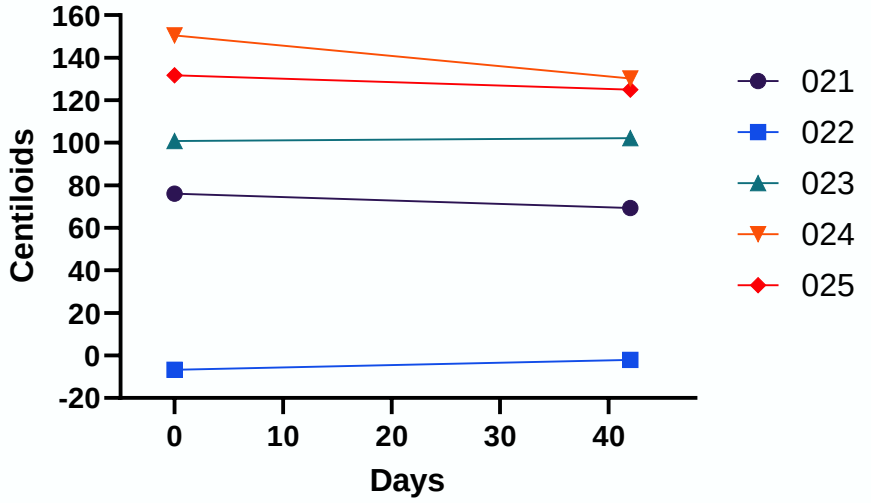
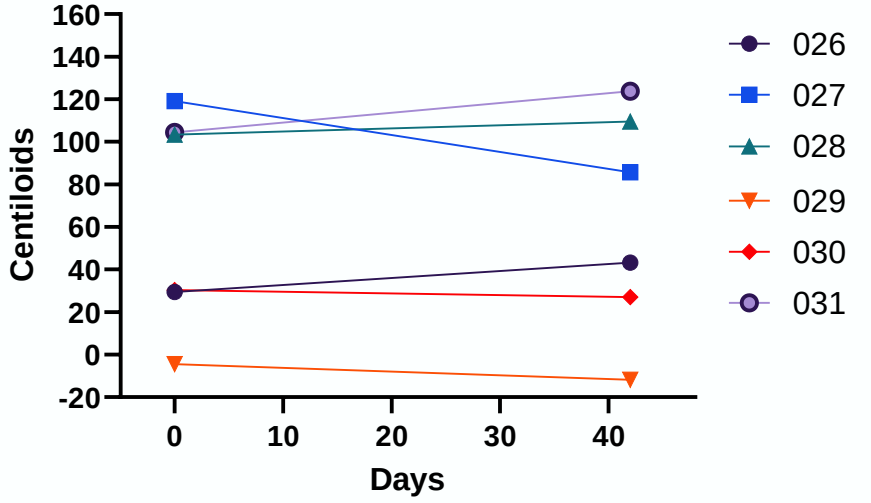
Cohort 1
2 mg/kg SAD



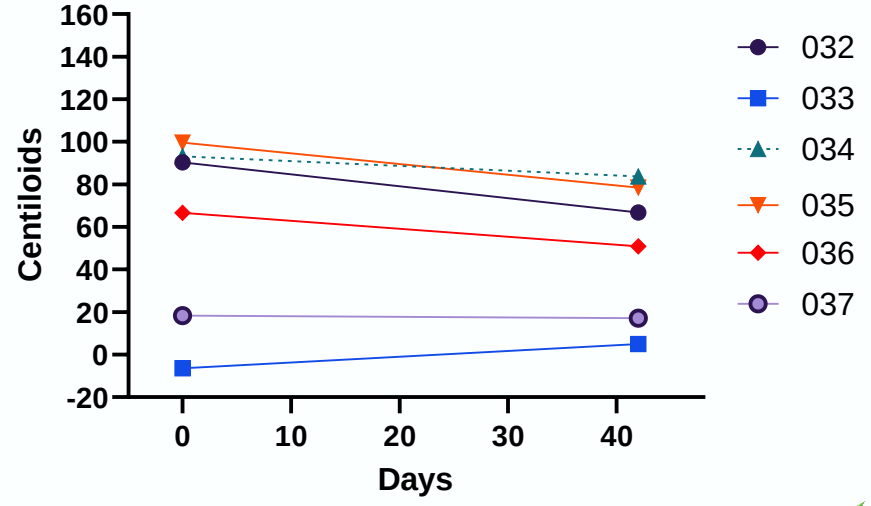
Cohort 2
10 mg/kg SAD



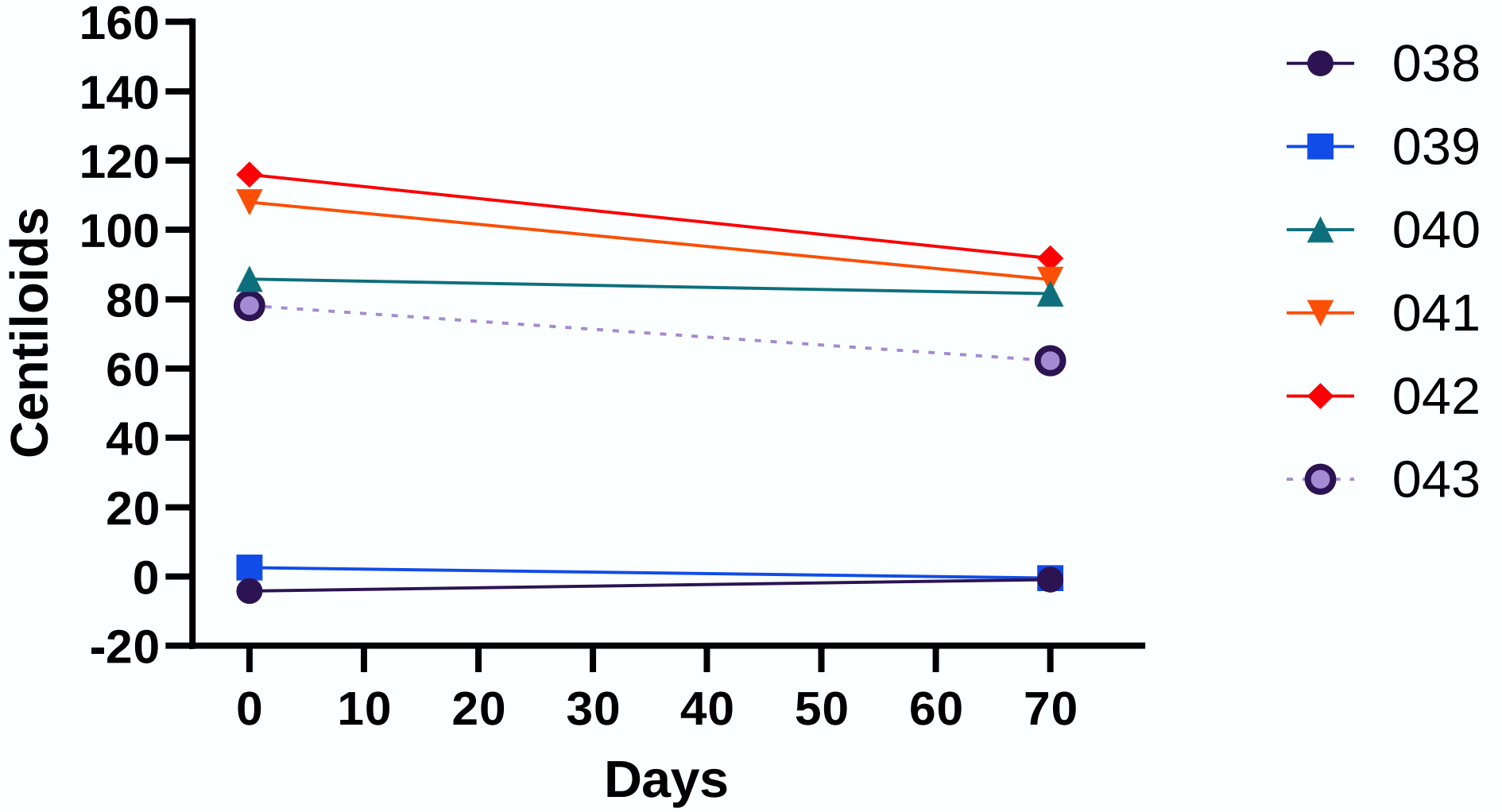
Cohort 3
25 mg/kg SAD



Cohort 4
60 mg/kg SAD



Cohort 5: 10 mg/kg Q4W MAD



Baseline mean = 55.8 Centiloids

Endpoint mean = 53.4 Centiloids

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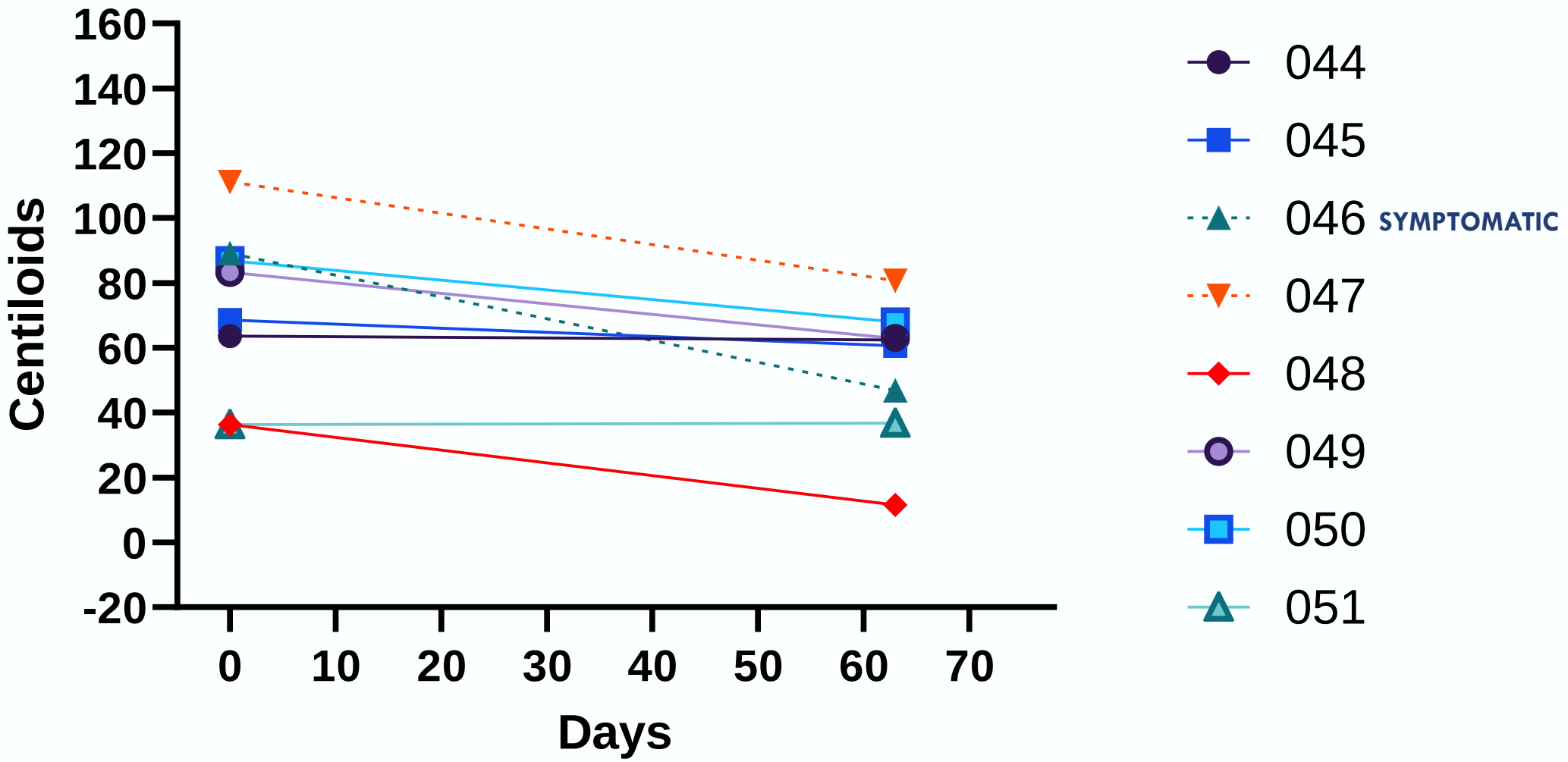
Cohort 6: 60 mg/kg Q4W MAD



Baseline mean = 71.9 Centiloids

Endpoint mean = 53.7 Centiloids

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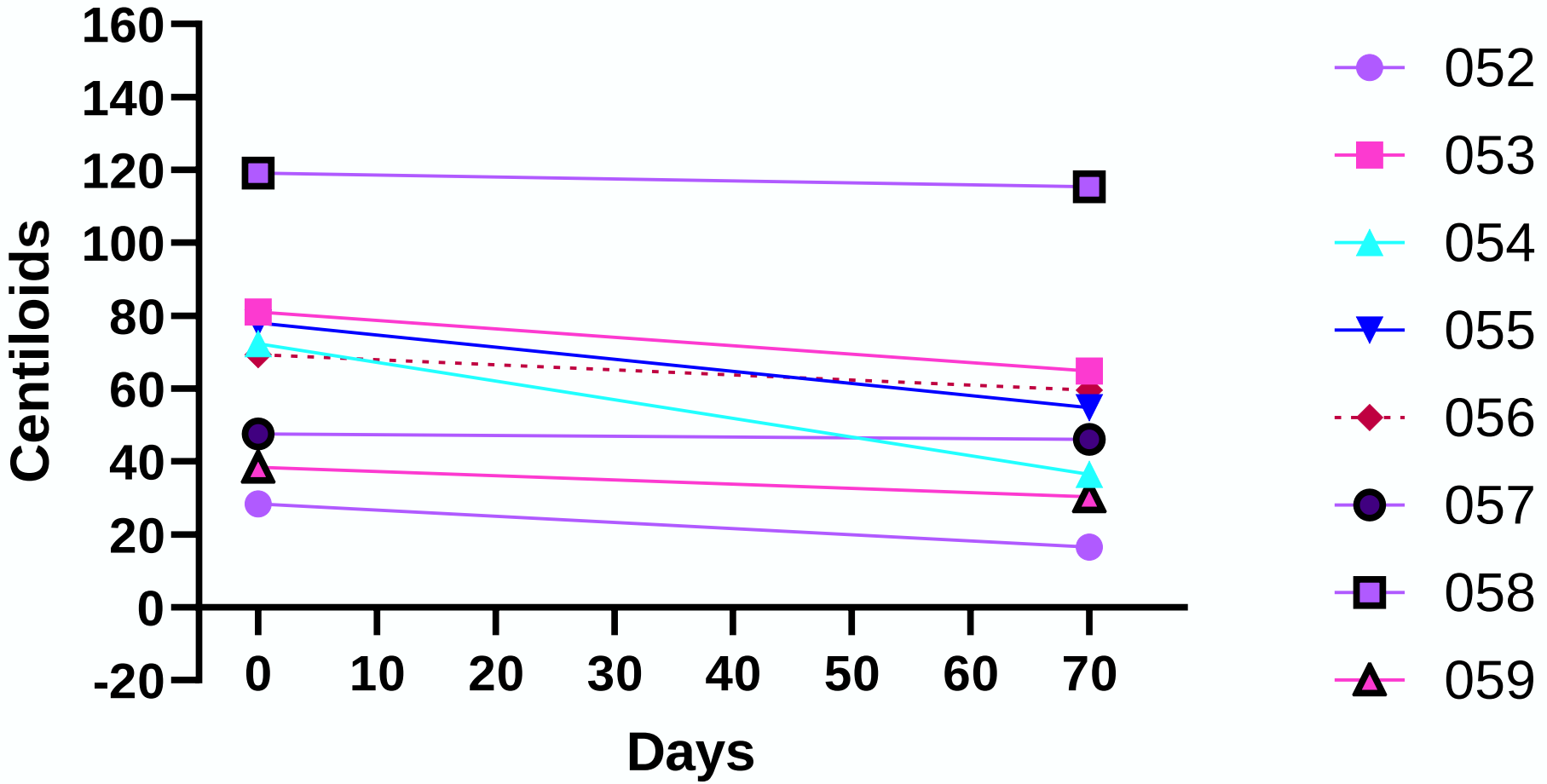
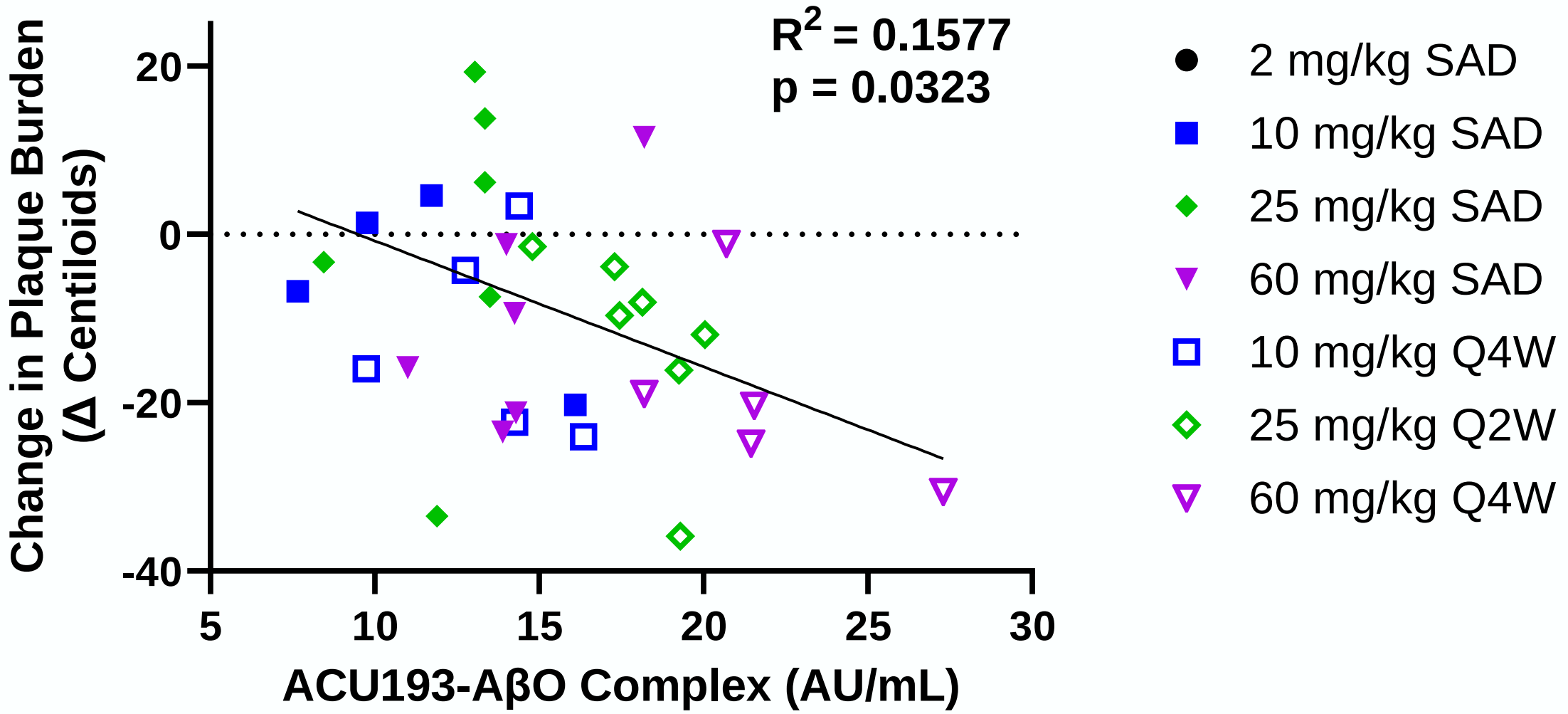
Cohort 7: 25 mg/kg Q2W MAD



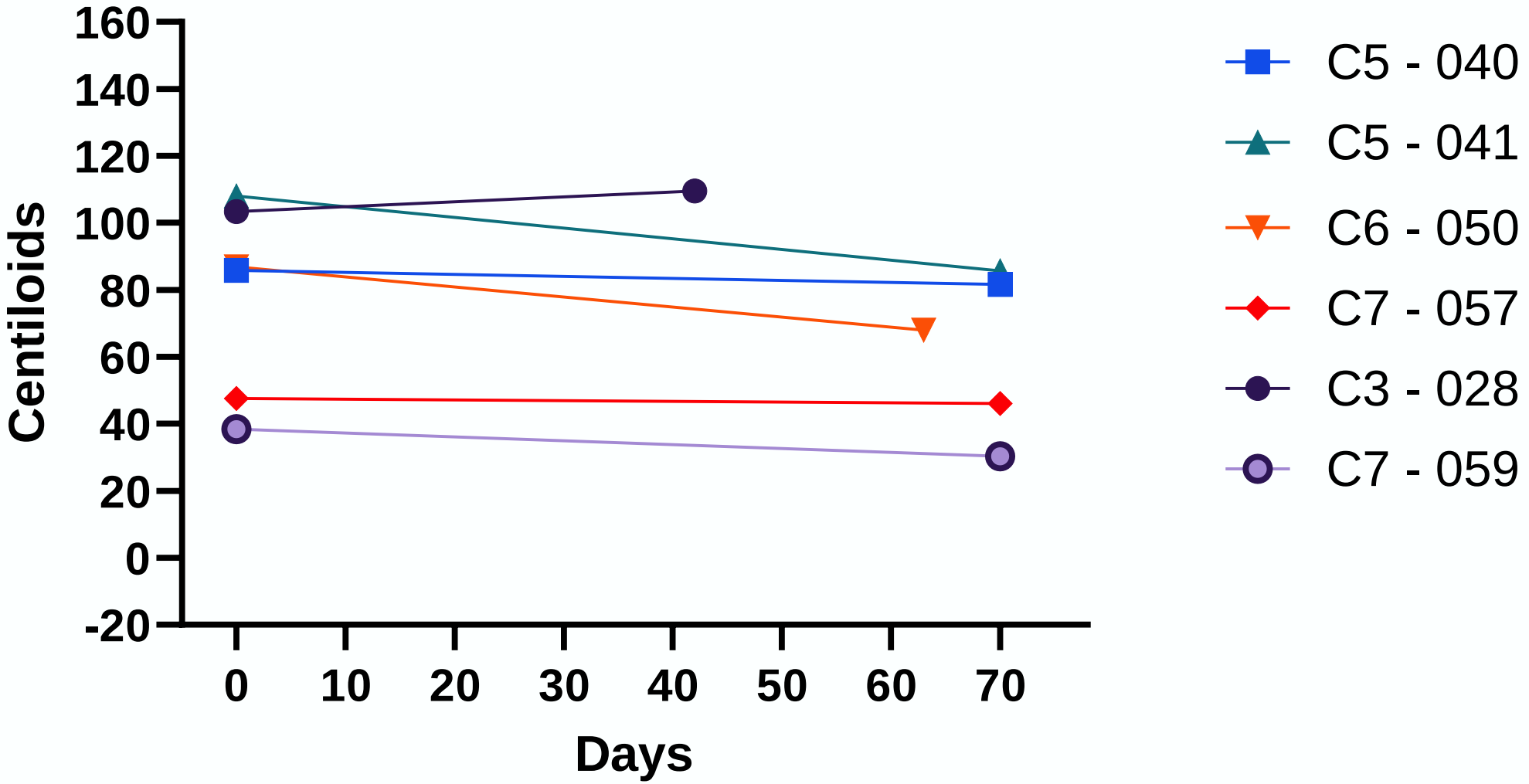
Baseline mean = 66.8 Centiloids

Endpoint mean = 53.0 Centiloids

All cohorts: Plaque reduction vs target engagement



ApoE4 homozygotes



Baseline mean = 78.3 Centiloids

Endpoint mean = 70.2 Centiloids

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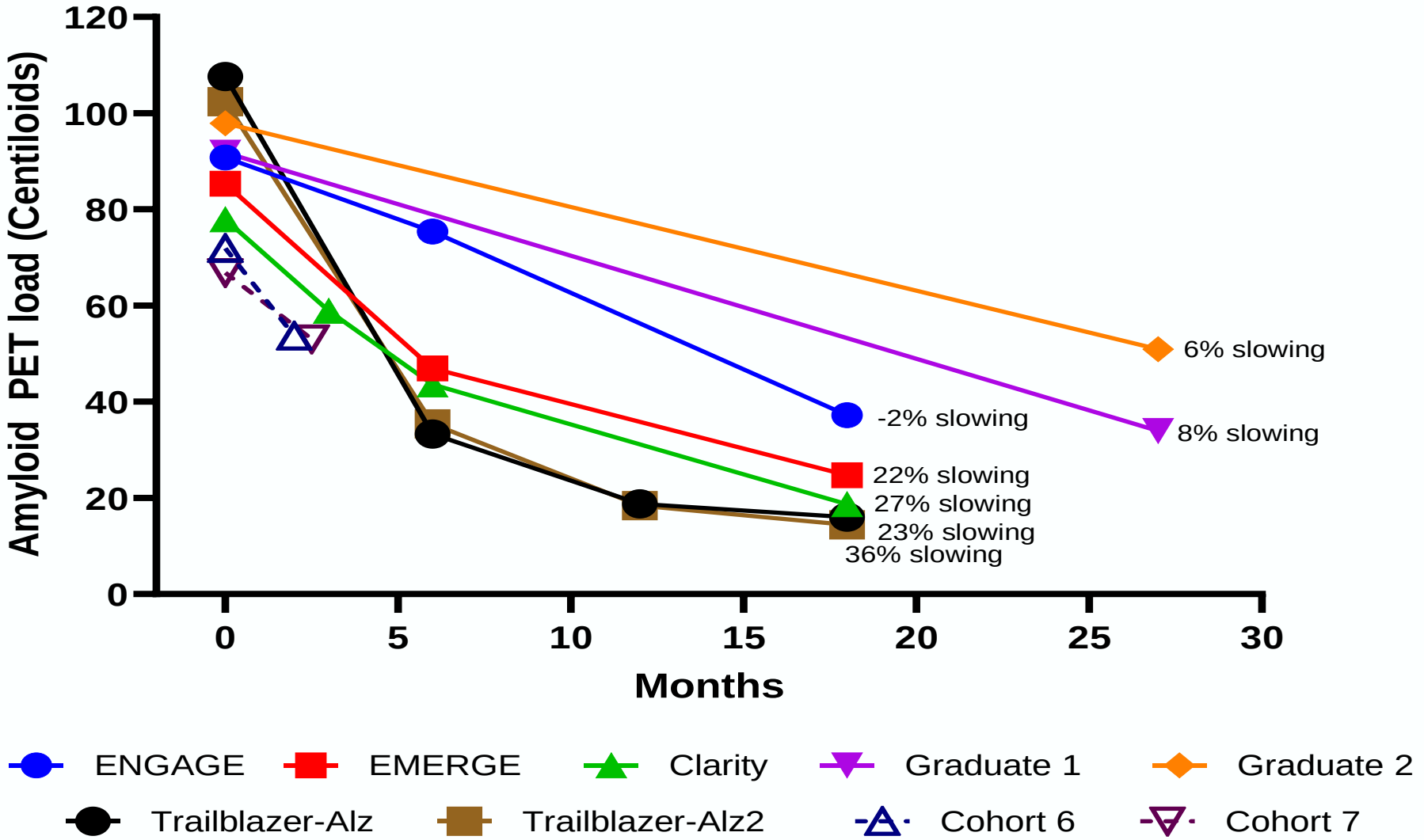
Slowing of CDR-SB progression versus reduction in plaque load



Summary and conclusions

- **Hybrid quantification/visual read system was used in Phase 1 trial of early AD**
  - Relatively few patients entered the trial on the basis of the visual read
  - Given the SUVr cut-off used in this study, somewhat lower baseline Centiloid values were seen compared to other studies of early AD

- **Plaque reductions in cohorts using the highest 2 doses of ACU193 (60 mg/kg Q4W and 25 mg/kg Q2W)**

- **Low baseline Centiloid values had little or no decrease in plaque load; however, reduction in plaque load not clearly related to baseline**

- **While reduction in plaque load modest compared to longer trials, at similar early timepoints plaque reduction seen in INTERCEPT-AD similar to plaque reduction seen with other antibodies**

- **Mechanism of reduction in plaque load unclear: possibly due to direct binding of ACU193 to plaque, shifts in equilibria, or combination of both**

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Thank you!

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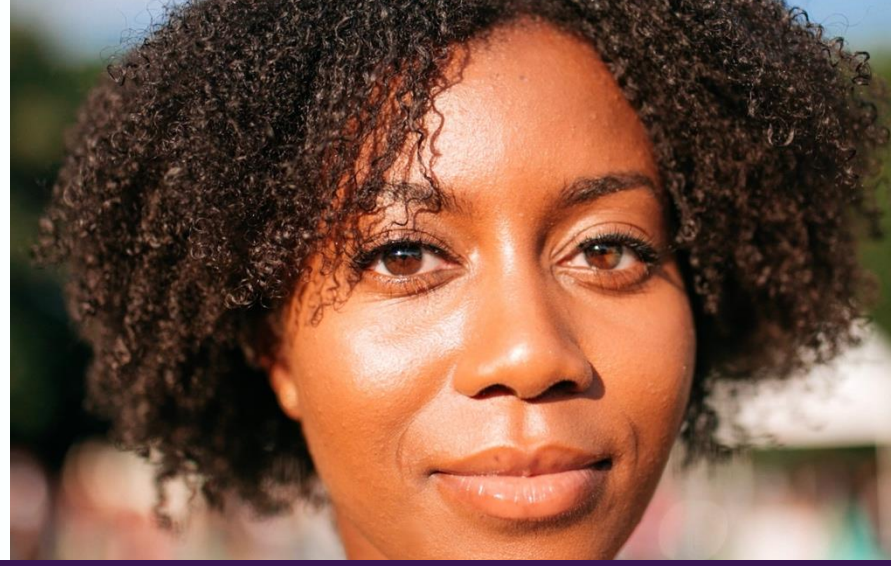
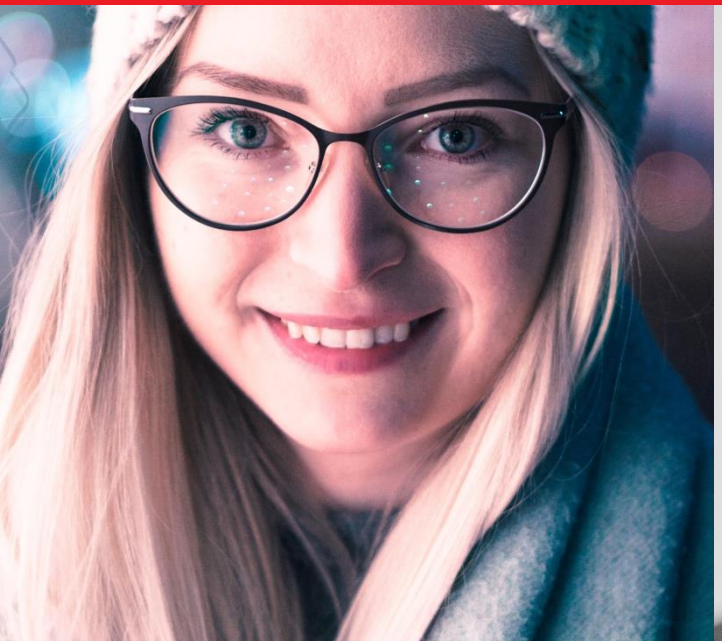
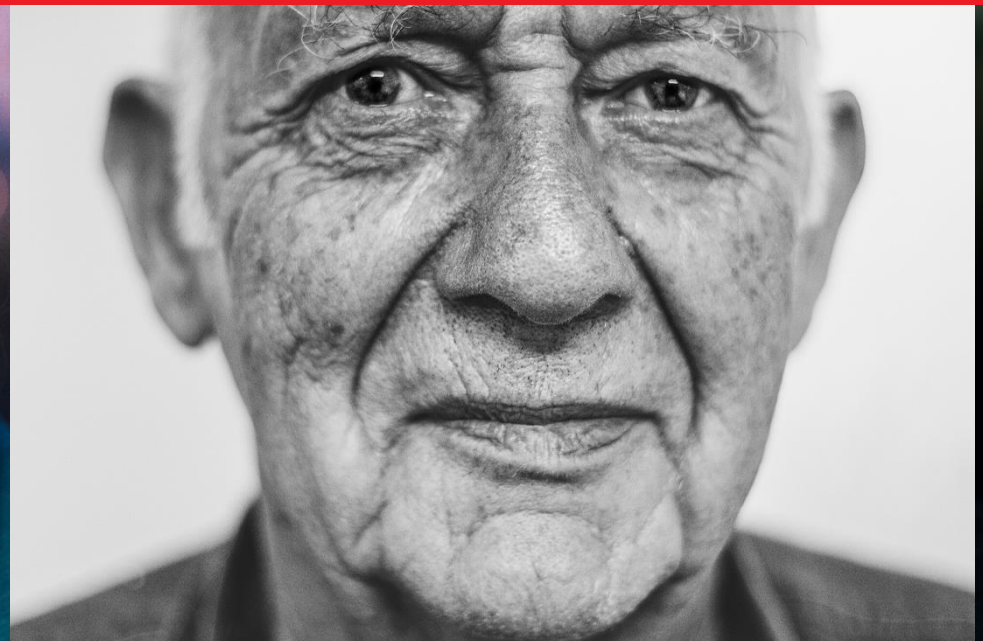
BROWN



Characteristics of participants in INTERCEPT-AD who did or did not develop ARIA





Disclosures

Stephen Salloway, MD, MS

- Butler Hospital receives research support for clinical trials from Janssen, Lilly, Eisai, Genentech, Roche, and Biogen
- Dr. Salloway has provided consultation to Eisai, Biogen, Lilly, Roche, Genentech, Bolden, Novo Nordisk, Prothena, Acumen, Labcorp, Alector, Corium, Kisbee and AbbVie
- Dr. Salloway is a member of the ADRD Therapeutic Working Group and an author on the Appropriate Use Recommendations for lecanemab and aducanumab. He is also a member of the Editorial Board of the Journal of Alzheimer's Disease Prevention and Alzheimer's and Dementia: Diagnosis, Assessment and Disease Monitoring
- Dr. Salloway owns no stocks or equity in any pharmaceutical company and has no patents or royalties

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INTERCEPT-AD: MRI-related protocol information

- **Exclusion Criteria: MRI at screening has more than four ARIA-H, presence of ARIA-E, or superficial siderosis**

- **The investigator may request a safety MRI at any time based on clinical findings or suspicion**
  - Medical management will be determined by local reading of the images; however, the readings from the central imaging vendor will be used for the final determination for the clinical safety data base

- **If a participant is found to have ARIA-E, administration of study drug will be withheld, and he/she will have approximately monthly MRI examinations until ARIA-E findings are resolved**
  - Management of treatment-emergent ARIA-H will be as determined by the investigator

- **Medical management of the study participants based on MRI findings (e.g., presence of ARIA-E) will be determined by the site principal investigator**

MRI and ACU193 dosing schedule

SAD Cohorts 1-4 (2,10, 25 and 60 mg/kg)			
	Day 1	Day 21	Day 140
ACU193 (or placebo)	X		
MRI		X	X

MAD Cohort 5 (25 mg/kg Q4W) MAD Cohort 6 (60 mg/kg Q4W)							
	Baseline	Day 28	Day 56	Day 63	Day 70	Day 126	Day 196
ACU193 (or placebo)	X	X	X				
MRI – cohort 5		X			X		X
MRI – cohort 6		X		X		X	

MAD Cohort 7 (25 mg/kg Q2W)					
	Baseline	Day 14	Day 28	Day 70	Day 98
ACU193 (or placebo)	X	X	X		
MRI			X	X	X

MRI results for cohorts 6 and 7 were to be read prior to dosing

INTERCEPT-AD: ARIA-E summary

SAD

2 mg/kg
Cohort 1

ApoE	D21	D140
3,4		
3,3	PBO	PBO
3,4		
2,3		
3,4	PBO	PBO
3,3		
3,3		
3,3		

10 mg/kg
Cohorts 2, 5

ApoE	D21	D140
3,4	PBO	PBO
3,3		
3,3		
3,4		
3,4	PBO	PBO
3,4		
3,4		
3,4		

25 mg/kg
Cohorts 3, 7

ApoE	D21	D140
3,3		
3,3	PBO	PBO
4,4		
3,3		
2,4		
3,3	PBO	PBO
3,4		
3,3		

60 mg/kg
Cohorts 4, 6

ApoE	D21	D140
4,4	PBO	PBO
3,4		
3,4	PBO	PBO
3,3		
3,3		
3,4		
2,4		
3,4		

MAD

ApoE	D28	D70	D196
2,3			
3,3			
3,3			
4,4			
3,3	PBO	PBO	PBO
3,4			
4,4			
3,4			
3,3			
3,4	PBO	PBO	PBO

ApoE	D28	D70	D98
3,3			
3,4			
3,4			
3,4			
3,4			
3,4	PBO	PBO	PBO
3,3			
3,4	PBO	PBO	PBO
4,4			
4,4			

ApoE	D28	D63	D126
3,4			
3,3			
3,3			
4,4			
4,4	PBO	PBO	PBO
3,3			
3,4			
3,4			
3,4	PBO	PBO	PBO
3,3			

NO ARIA-E
Asymptomatic ARIA-E
Symptomatic ARIA-E
Discontinued

PBO: Patient on placebo

No ε4 homozygotes developed ARIA-E despite comprising 13% in study;
4/5 ARIA-E cases are ε4 heterozygotes which comprise 47% of the population

ARIA-E: Patient details

Cohort	ApoE4	Gender	Age	Baseline/Endpoint Plaque Load (Centiloids)	Severity by FDA Criteria
C4 SAD 60 mg/kg	**Heterozygote**	**F**	**58**	93.1/83.8	Moderate - Asymptomatic
C5 10 mg/kg Q4W	**Heterozygote**	**F**	**72**	78.2/62.2	Mild - Asymptomatic 3rd/final dose on D56
C6 60 mg/kg Q4W	**Heterozygote**	**F**	**80**	89.1/46.9	Moderate - **Symptomatic** (R leg dysfunction) 1 dose at BL; 2 remaining doses withheld
C6 60 mg/kg Q4W	**NonCarrier**	**F**	**56**	111.2/80.7	Mild - Asymptomatic 3rd/final dose on D56
C7 25 mg/kg Q2W	**Heterozygote**	**F**	**70**	69.3/59.6	Moderate - Asymptomatic 3rd/final dose on D28 D28 ARIA-E (mild) noted in retrospective review

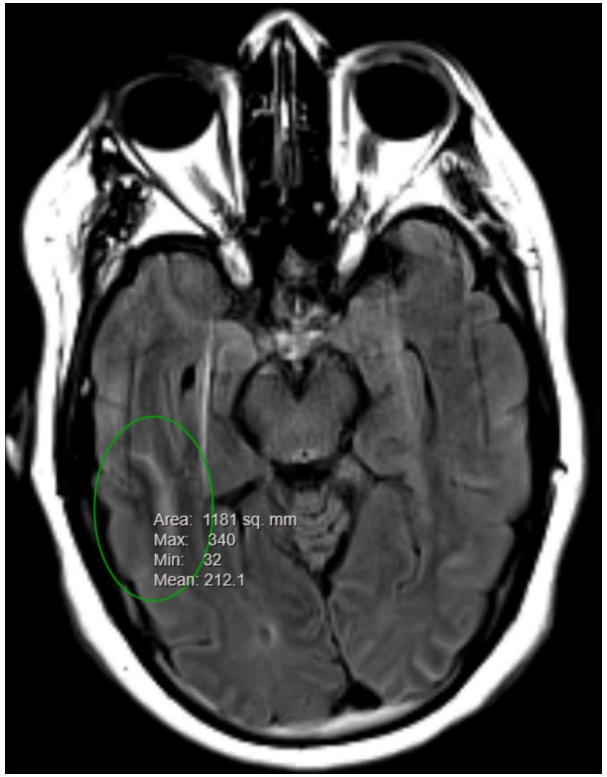
Of 5 total ARIA-E cases, 1 was symptomatic (2.1% overall) and symptoms resolved with resolution of radiographic ARIA-E. All cases showed radiographic resolution.

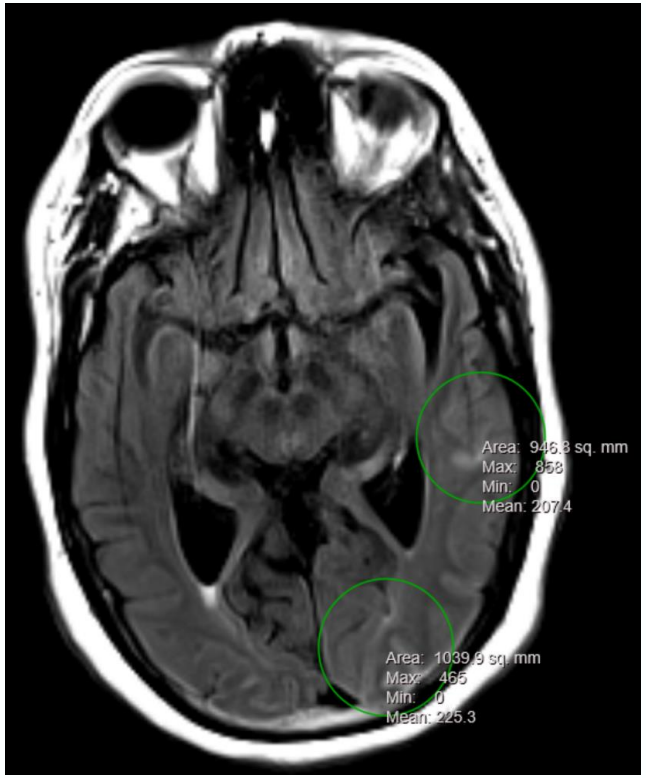
Cohort 4 participant (asymptomatic ARIA-E)

- **58-year-old white female**
  - History of hypothyroidism, diverticulum, diabetes mellitus, depression, and menopause
- **SAD Cohort 4 (ACU193 60 mg/kg)**
- **ARIA-E found on Day 21 MRI**
  - Asymptomatic
  - One infusion of ACU193
  - Extensive ARIA-E leptomeningeal parieto-occipital left and bilateral temporal
  - The investigator considered the event of ARIA-E severe (Grade 3) in severity.
- **ARIA-E resolved 81 days after onset**

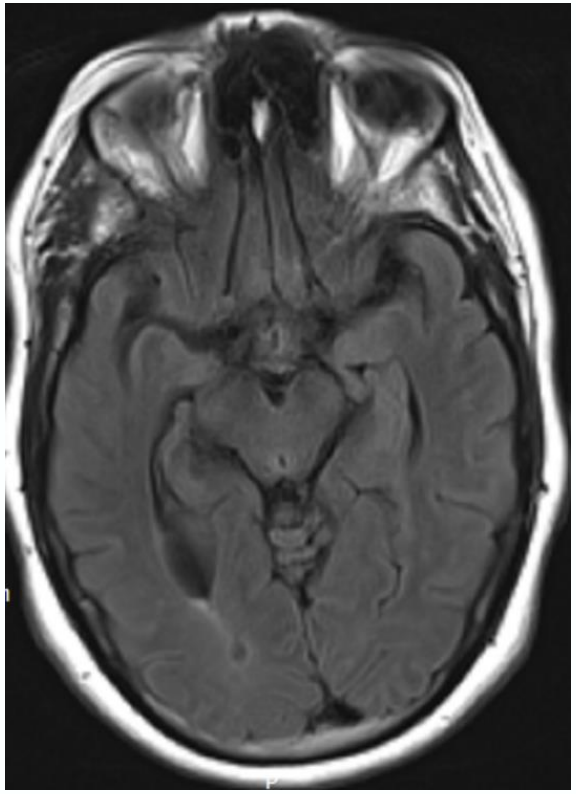
Cohort 4 participant (asymptomatic ARIA-E) images

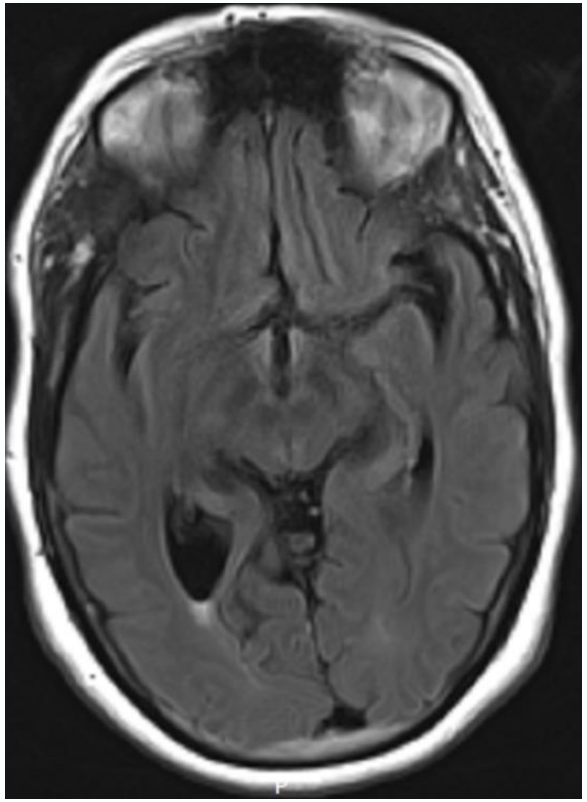
Day 21





Day 140 (EOS)





Cohort 6 participant (symptomatic ARIA-E)

- **80-year-old white female subject**
  - History of ventricular extrasystoles, essential tremor, arthritis, scoliosis, spinal osteoarthritis, rotator cuff syndrome, skin cancer, pollakiuria, allergy to arthropod sting, and drug hypersensitivity (penicillin)

- **MAD Cohort 6 (60 mg/kg Q4W)**

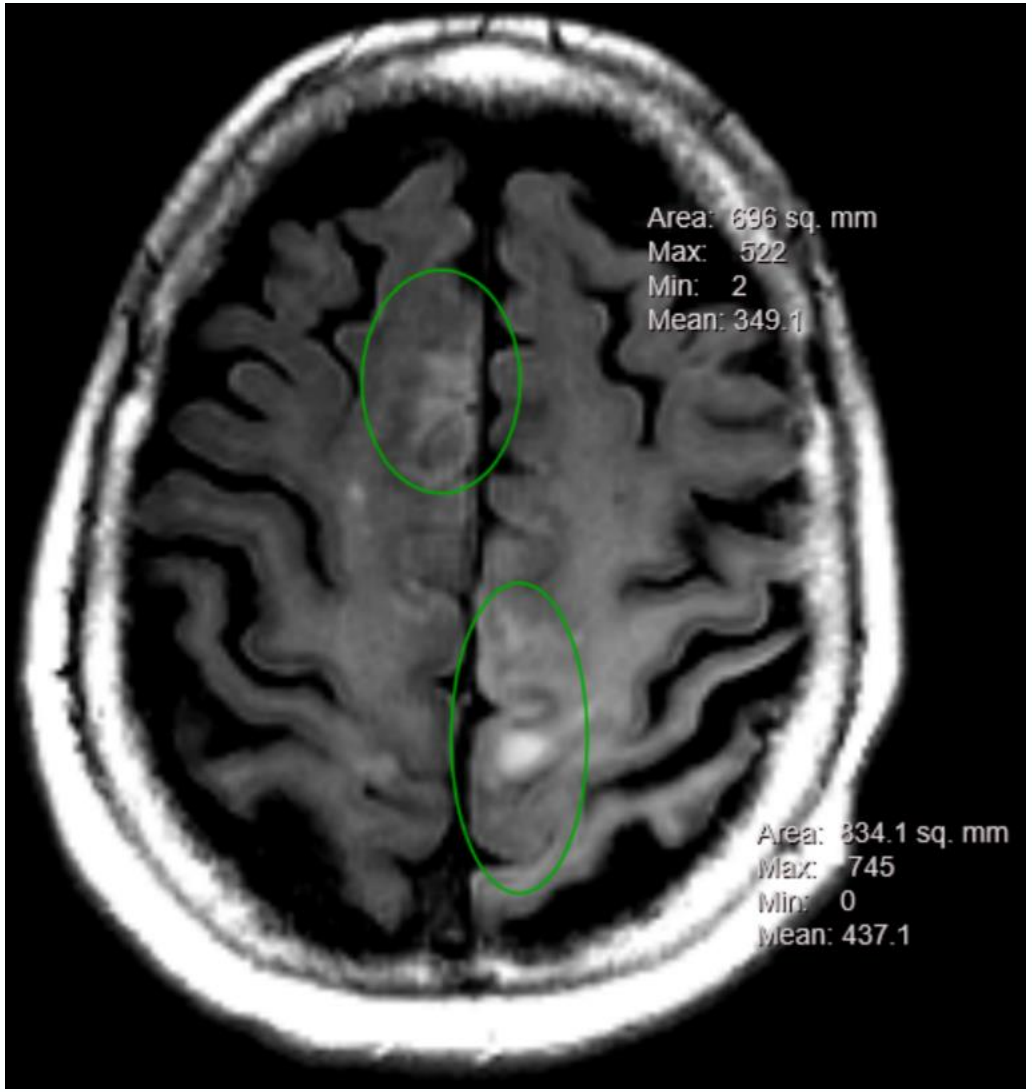
- **ARIA-E found on Day 28 MRI**
  - Symptomatic (right leg dysfunction)
  - One of three infusions of ACU193; study drug stopped
  - Multifocal ARIA-E bifrontal (L>R) and R parieto-occipital, mostly consisting of FLAIR parenchymal hyperintensities with some sulcal hyperintensity in R parietal region
  - The investigator considered the event of ARIA-E moderate (Grade 2) in severity.

- **ARIA-H**
  - Two microhemorrhages (MH) at screening
  - One new MH identified (L frontal) on UNSCHEDULED follow-up MRI for the initial ARIA-E
  - The investigator considered the event of ARIA-H mild (Grade 1) in severity.

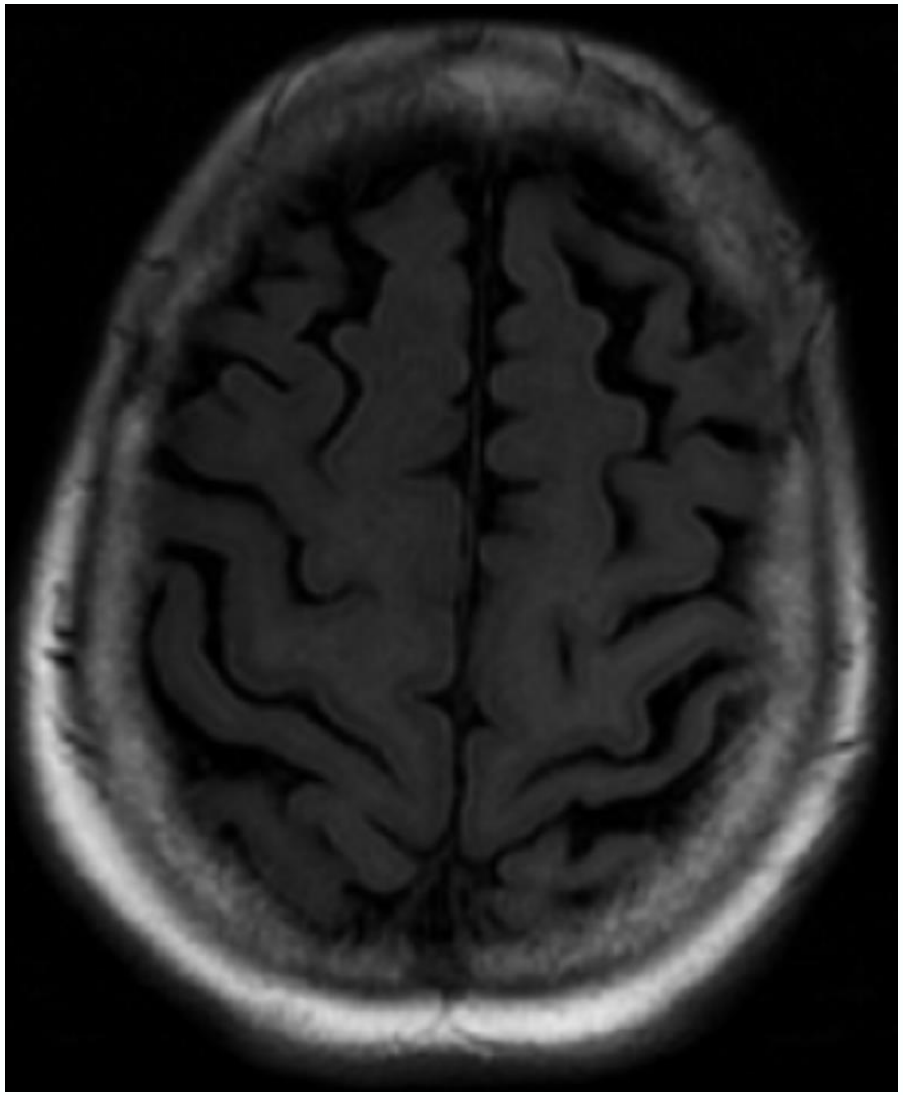
- **ARIA-E resolved 69 days after onset**

Cohort 6 participant (symptomatic ARIA-E) images

Day 28



Day 126 (EOS)

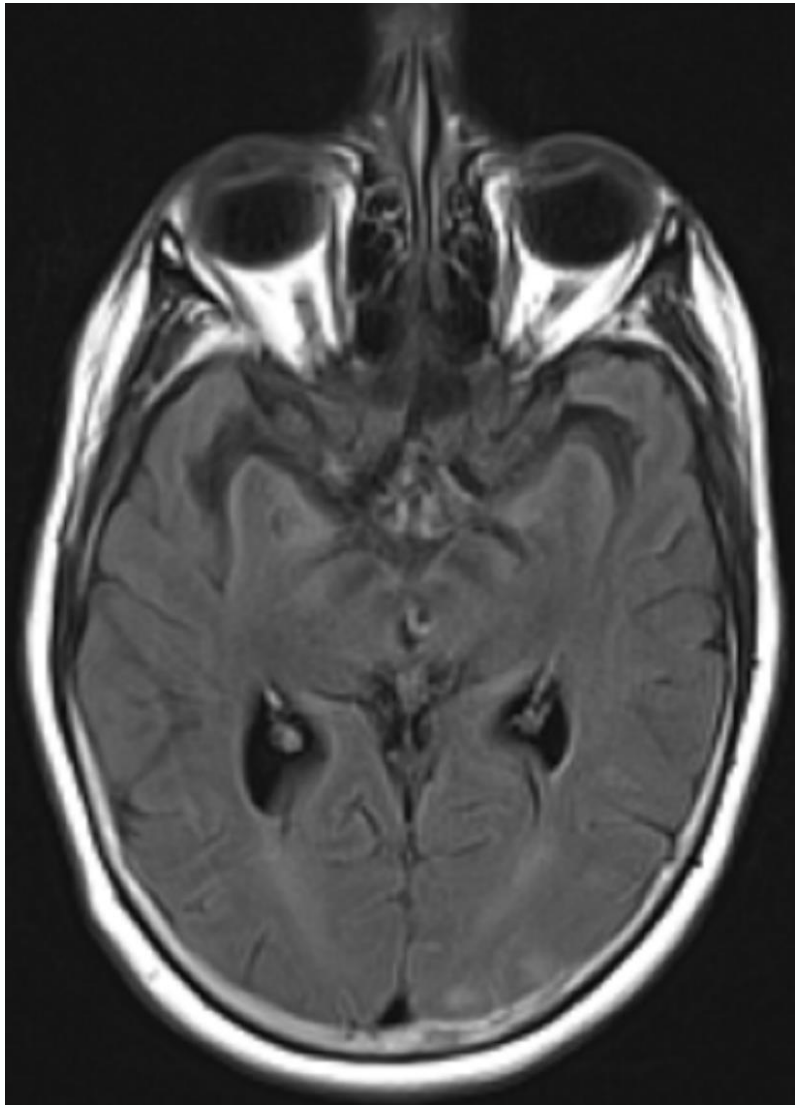


Cohort 7 participant (asymptomatic ARIA-E and superficial siderosis)

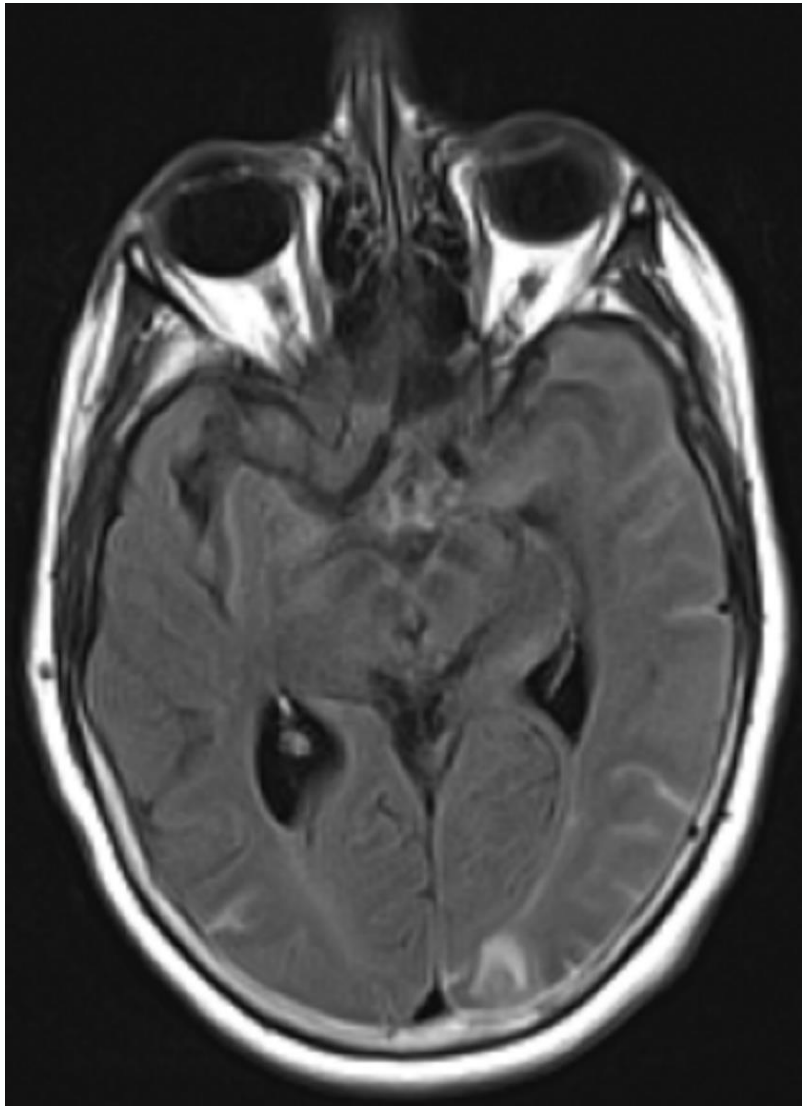
- **70-year-old white female**
  - History of GERD, osteoporosis, hyperlipidemia, urinary tract infection, and hypertension
- **MAD Cohort 7 (ACU193 25 mg/kg Q2W)**
- **ARIA-E and superficial siderosis found on Day 70 MRI**
  - Asymptomatic
  - All three infusions of ACU193
  - Extensive multifocal ARIA-E increased compared to previous scan (Note: previous scan originally read no findings)
    - Leptomeningeal most of the left hemisphere except frontal lobe; increase multifocal sulcal right hemisphere; extensive parenchymal involvement left
  - Multifocal small deposits of superficial siderosis (L parietal, L temporal)
  - At Day 70 MRI, ARIA-E was retrospectively identified on the Day 28 MRI
- **The investigator considered the events of ARIA-E and superficial siderosis moderate (Grade 2) in severity.**
- **ARIA-E resolved 135 days after onset**

Cohort 7 participant (asymptomatic ARIA-E) images

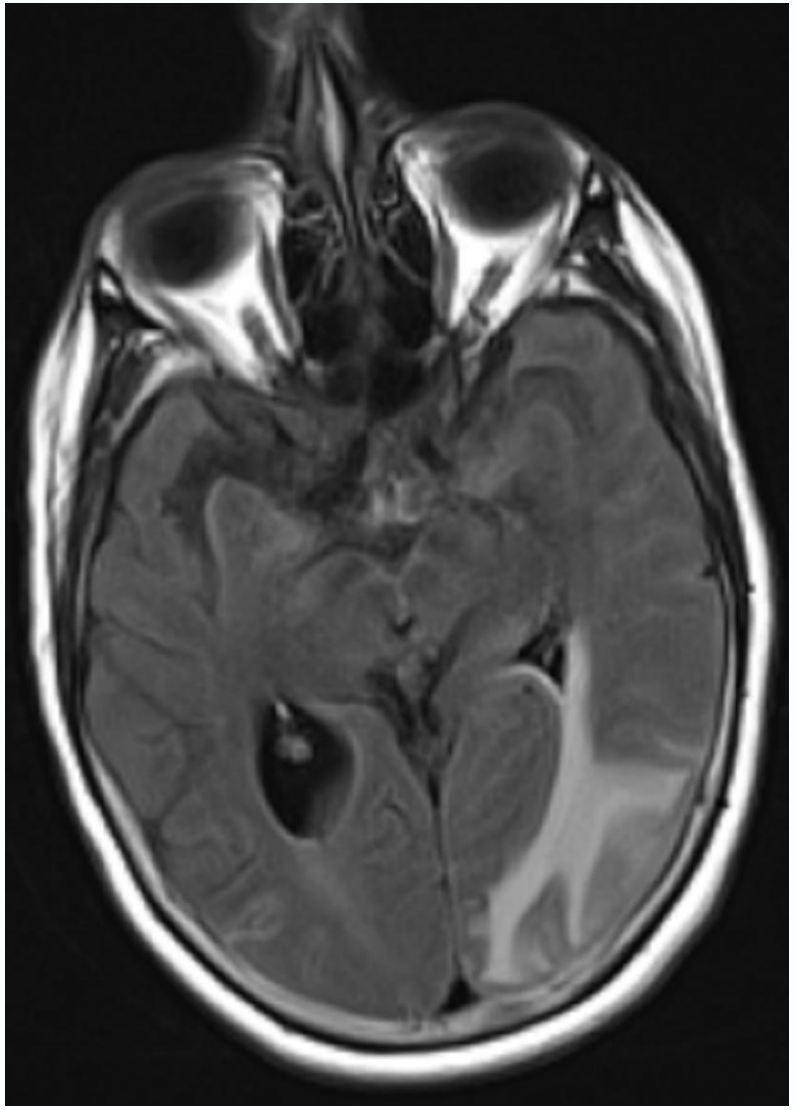
Day 28
ARIA-E noted in retrospect at D70



Day 70
ARIA-E first identified

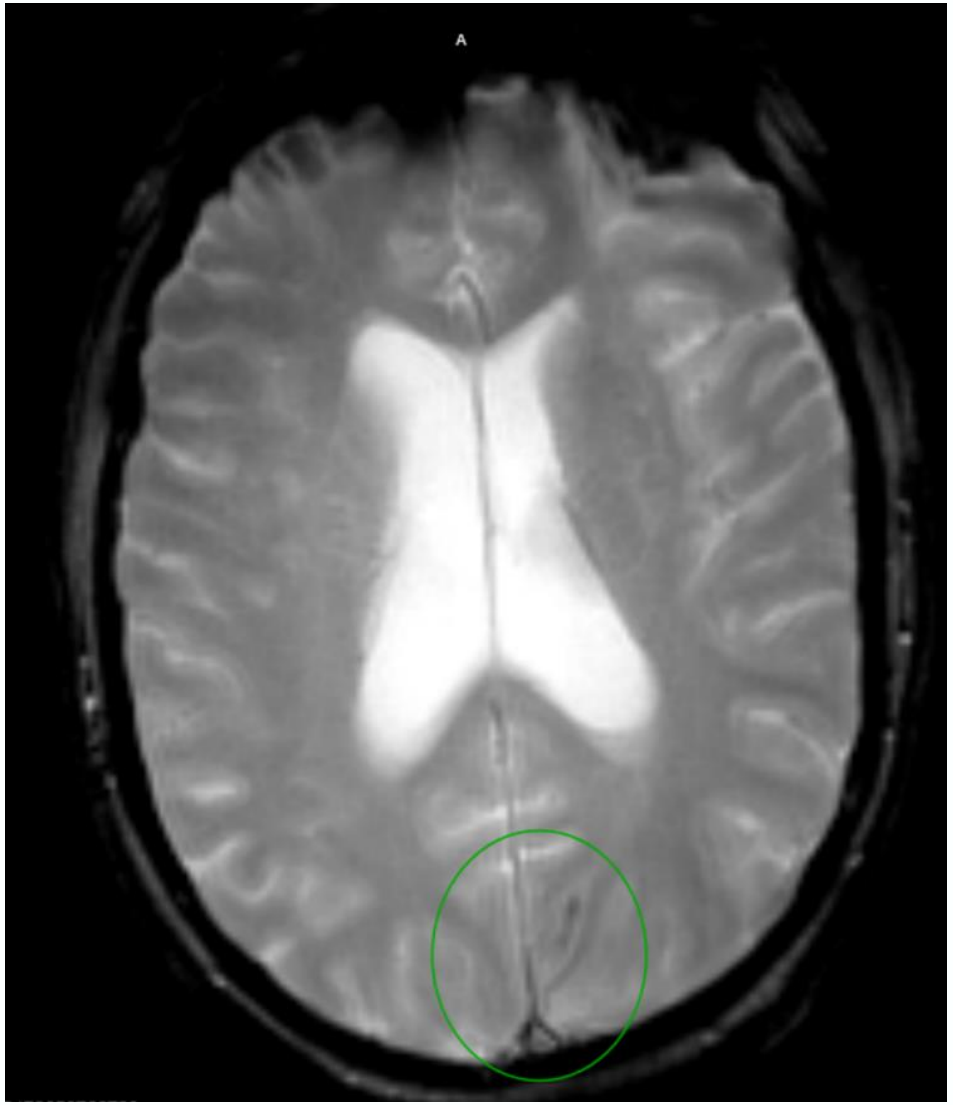


Day 98 (EOS)
Resolution occurred D135 - post DBL

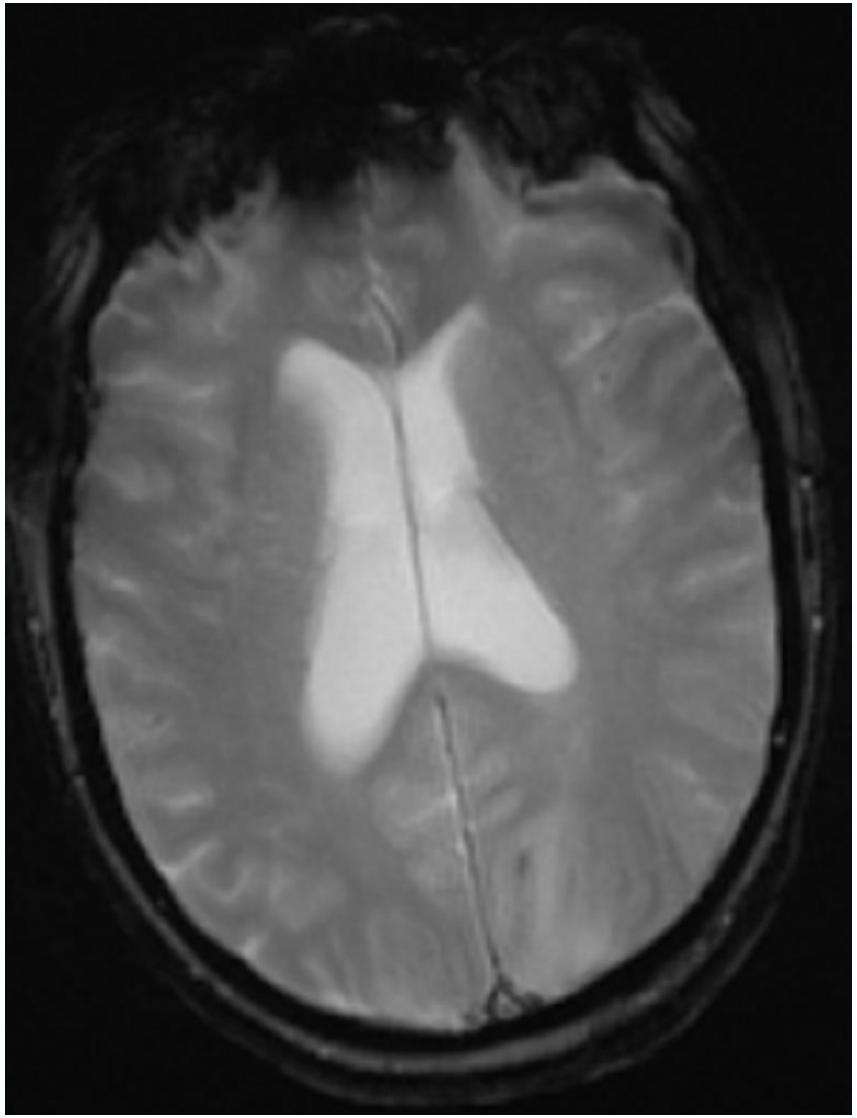


Cohort 7 participant (superficial siderosis) images

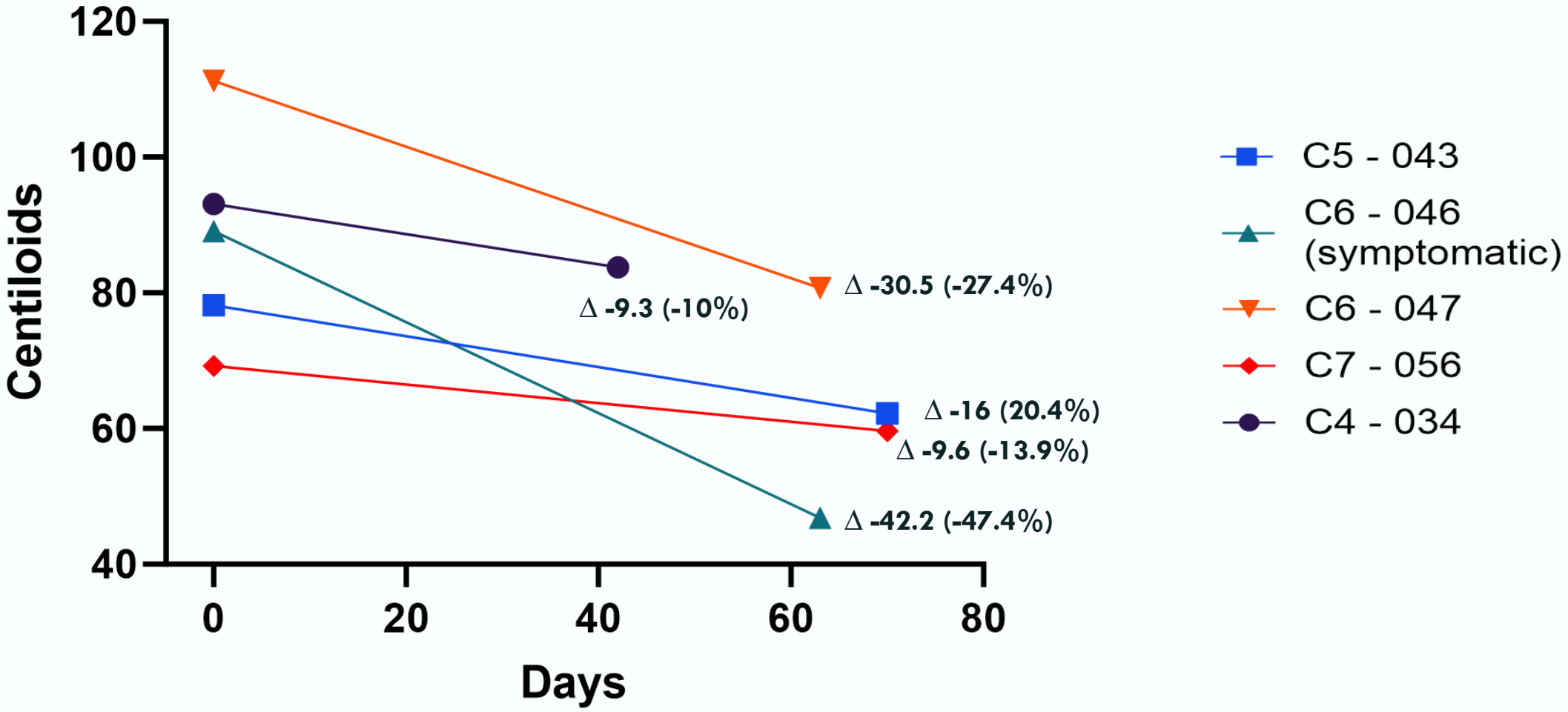
Day 70



Day 98 (EOS)



Change in amyloid burden in participants with ARIA-E



Baseline mean = 88.2 Centiloids

Endpoint mean = 66.6 Centiloids

Summary

- **Differentiated rate of ARIA-E**
  - 5 cases of ARIA-E; 1 symptomatic from 48 on drug
    - No cases of symptomatic ARIA-E at 2, 10, or 25 mg/kg doses
  - 4 of 5 ARIA-E cases in ApoE4 heterozygotes
  - No ARIA-E observed in ApoE4 homozygotes (n=6)

- **All treatment-emergent ARIA-E showed radiographic resolution**

- **Phase 2/3 trial (ALTITUDE-AD) scheduled to start next year**
  - Doses selected (35 and 50 mg/kg Q4W)
  - Careful monitoring of ARIA

Frequency of ARIA-E in combined SAD/MAD groups			
	10 mg/kg	25 mg/kg	60 mg/kg
Any ARIA-E	1/14 (7.1%)	1/14 (7.1%)	3/14 (21.40%)
Symptomatic ARIA-E	0/14 (0.0%)	0/14 (0.0%)	1/14 (7.1%)

Thank you!