Baseline characteristics of INTERCEPT-AD: A phase 1 trial with ACU193 targeting soluble amyloid beta oligomers for the treatment of early Alzheimer's disease

Todd Feaster, PsyD
Acumen Pharmaceuticals, Inc

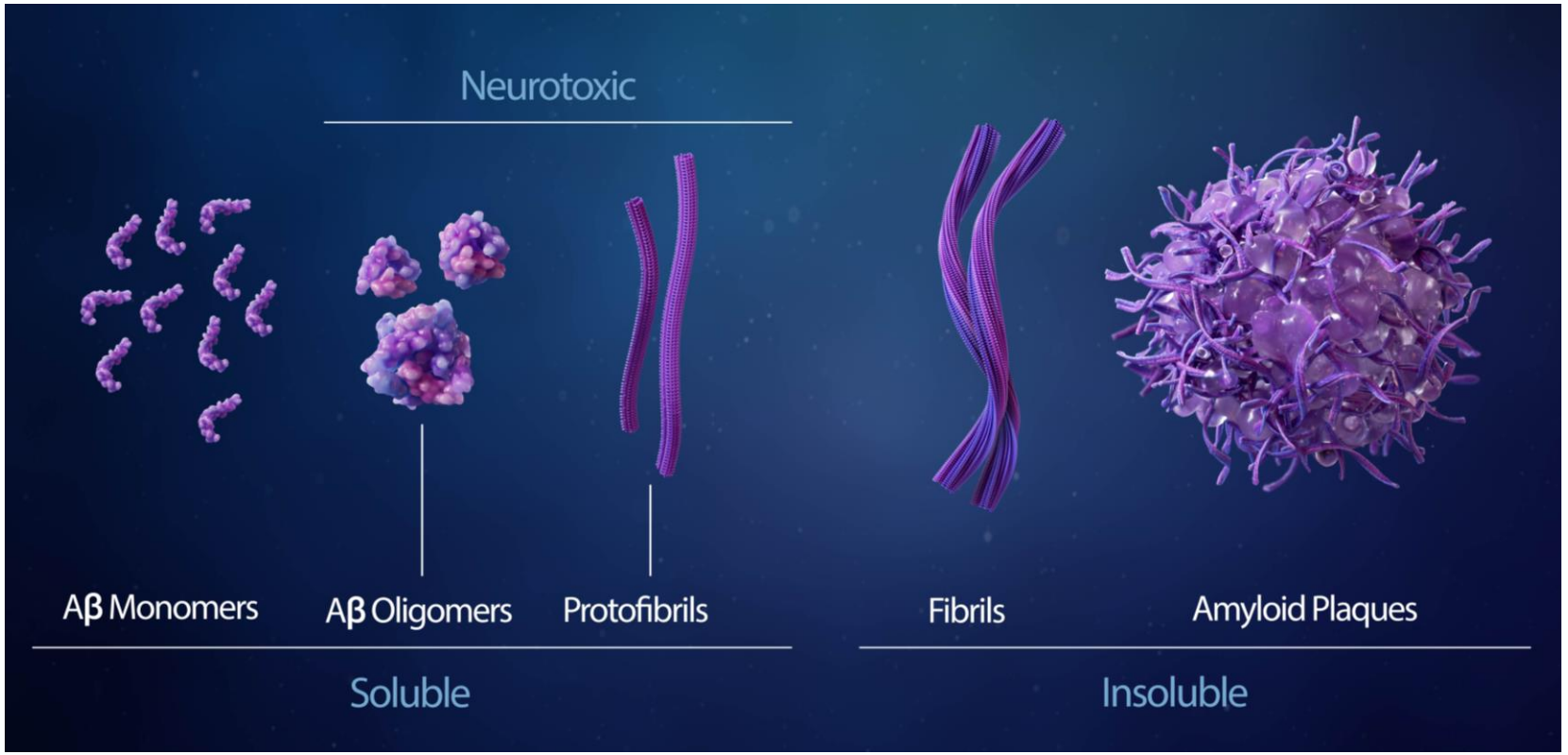
Disclosure

- Dr. Feaster is an employee shareholder at Acumen Pharmaceuticals, Inc.

Forward Looking Statement

This presentation contains forward-looking statements within the meaning of The Private Securities Litigation Reform Act of 1995. Any statement describing Acumen's goals, expectations, financial or other projections, intentions or beliefs is a forward-looking statement and should be considered an at-risk statement. Words such as "believes," "expects," "anticipates," "could," "should," "would," "seeks," "aims," "plans," "potential," "will," "milestone" and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. Forward-looking statements include statements concerning: Acumen's business; the safety, tolerability, pharmacokinetics, target engagement and other clinical measures associated with Acumen's product candidate, ACU193, including its performance against other antibodies; and the anticipated timeline for reporting topline data. These statements are based upon the current beliefs and expectations of Acumen management, and are subject to certain factors, risks and uncertainties, particularly those inherent in the process of discovering, developing and commercializing safe and effective human therapeutics. Such risks may be amplified by the impacts of geopolitical events and macroeconomic conditions, such as rising inflation and interest rates, supply disruptions and uncertainty of credit and financial markets. These and other risks concerning Acumen's programs are described in additional detail in Acumen's filings with the Securities and Exchange Commission ("SEC"), including in Acumen's most recent Annual Report on Form 10-K, and in subsequent filings with the SEC, including Acumen's most recent Quarterly Report on Form 10-Q. Copies of these and other documents are available from Acumen. Additional information will be made available in other filings that Acumen makes from time to time with the SEC. These forward-looking statements speak only as of the date hereof, and Acumen expressly disclaims any obligation to update or revise any forward-looking statement, except as otherwise required by law, whether, as a result of new information, future events or otherwise.

ACU193: A Monoclonal Antibody that Selectively Binds Soluble Aβ Oligomers



- ACU193 is a humanized, affinity-matured, IgG2 subclass monoclonal antibody targeting soluble amyloid beta oligomers (sAβOs)
- Considering the evidence, blocking the toxicity of sAβOs with ACU193 is a promising approach for treating AD

Study Population

- Diagnosis of MCI or Mild AD dementia (NIA-AA criteria)

- Key Inclusion criteria:
  - Age 55-90 years
  - MMSE total score 18-30 inclusive
  - CDR Global Score 0.5 or 1
  - Confirmation of amyloid pathology via Amyloid PET
  - Apolipoprotein E (*APOE*) genotype is recorded

- Measures of cognition, function, and behavior were obtained and include:
  - MMSE
  - CDR
  - ADAS-Cog_{13}
  - ADCS-ADL
  - iADRS
  - NPI-10
  - C-SSRS (children's version)
  - Brief computerized neuropsychological test battery

Study Objectives

Primary Objective:

- Determine the safety and tolerability of a single and multiple IV doses of ACU193

Secondary Objective:

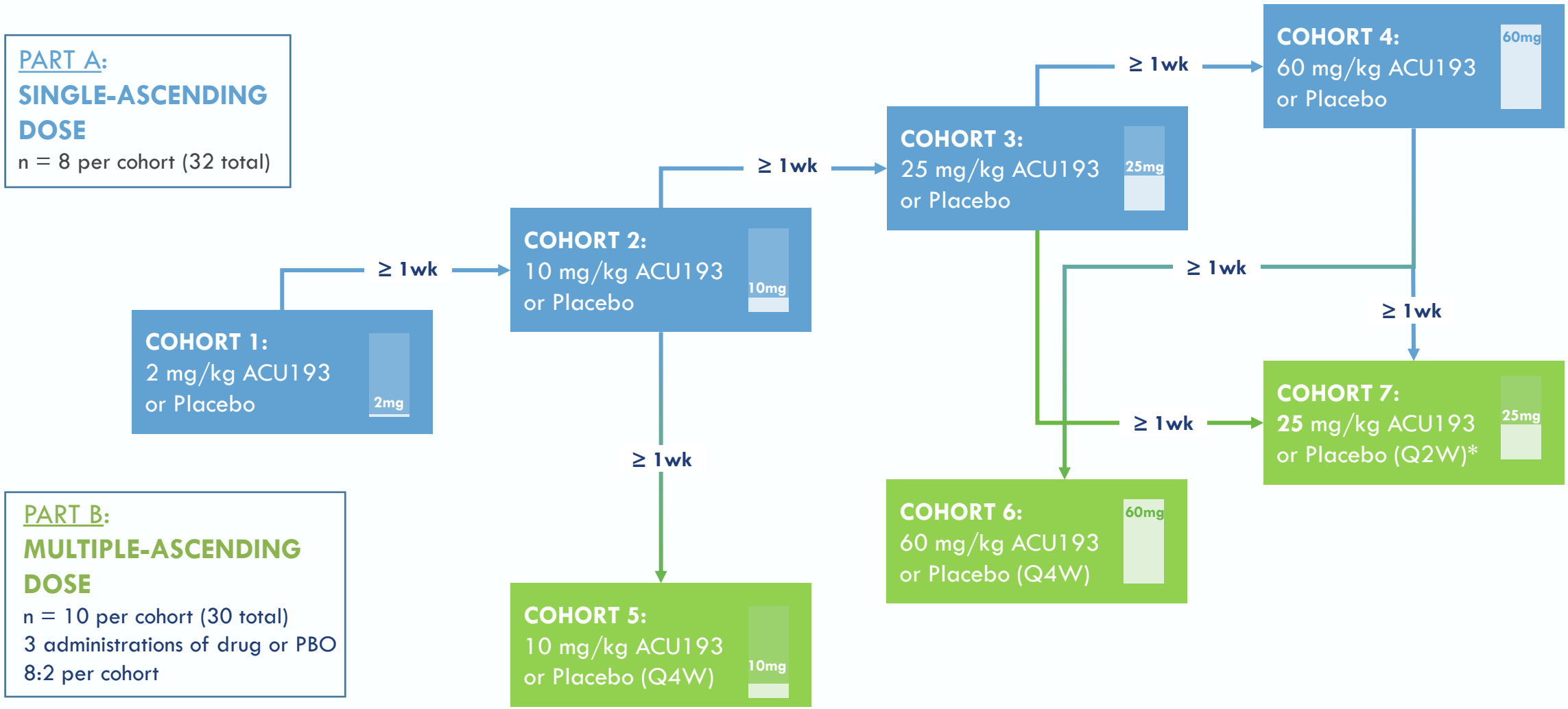
- Estimate serum PK of ACU193 following single and multiple IV doses of ACU193

Exploratory Objectives (following single and multiple IV doses of ACU193):

- Determine CSF concentrations of ACU193
- Evaluate central target engagement of ACU193 in CSF
- Evaluate changes in amyloid plaque load by PET
- Evaluate changes in CSF and blood-based concentrations of AD or other neurodegenerative disease biomarkers
- Evaluate changes in cognitive, functional, and behavioral measures
- Evaluate changes in cerebral blood flow by MRI, using Arterial Spin Labeling (ASL) pulse sequencing

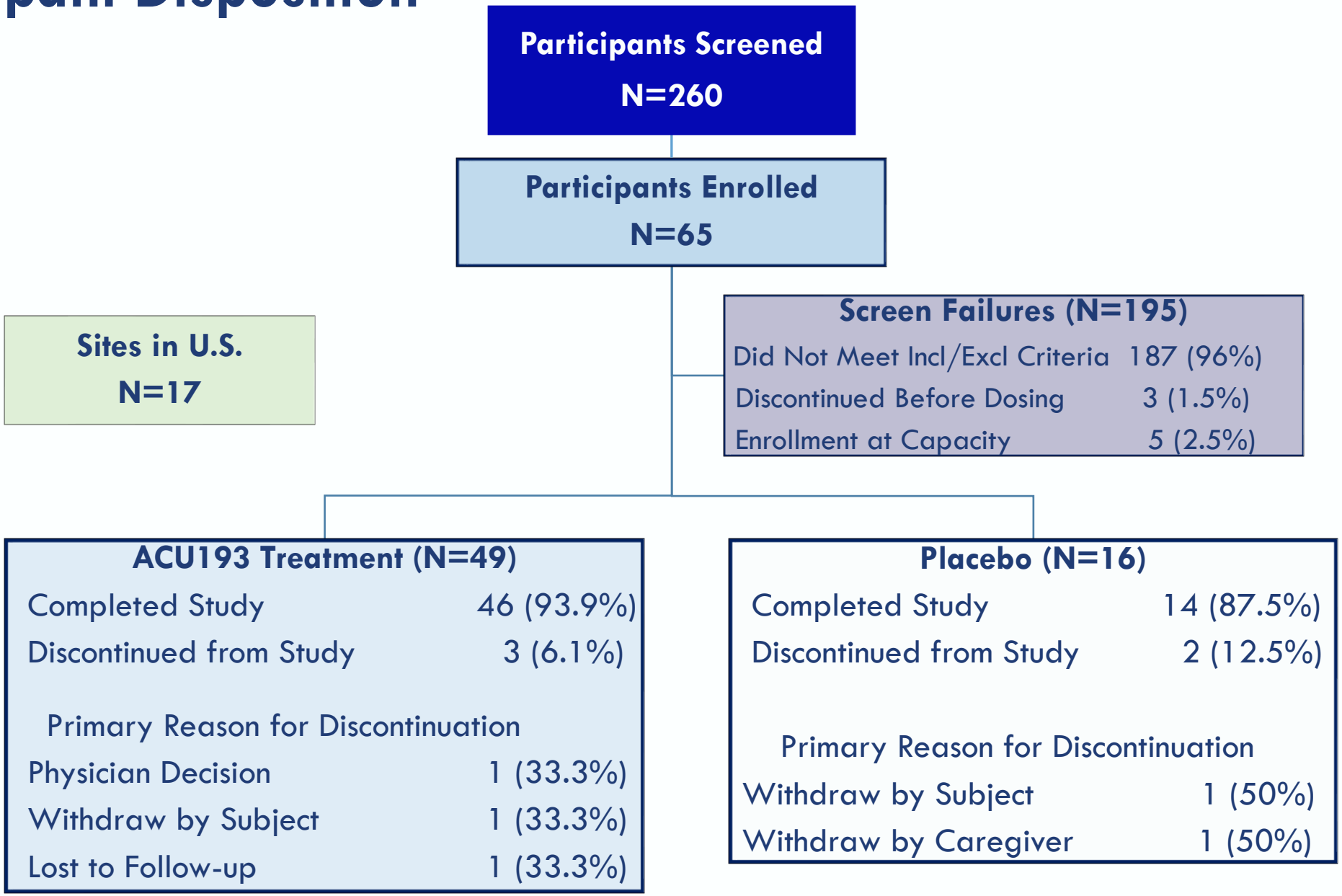
- Participant and Study Partner exit interviews (optional) to assess study experience, burden, perceptions of meaningful change, and treatment expectations

Study Design

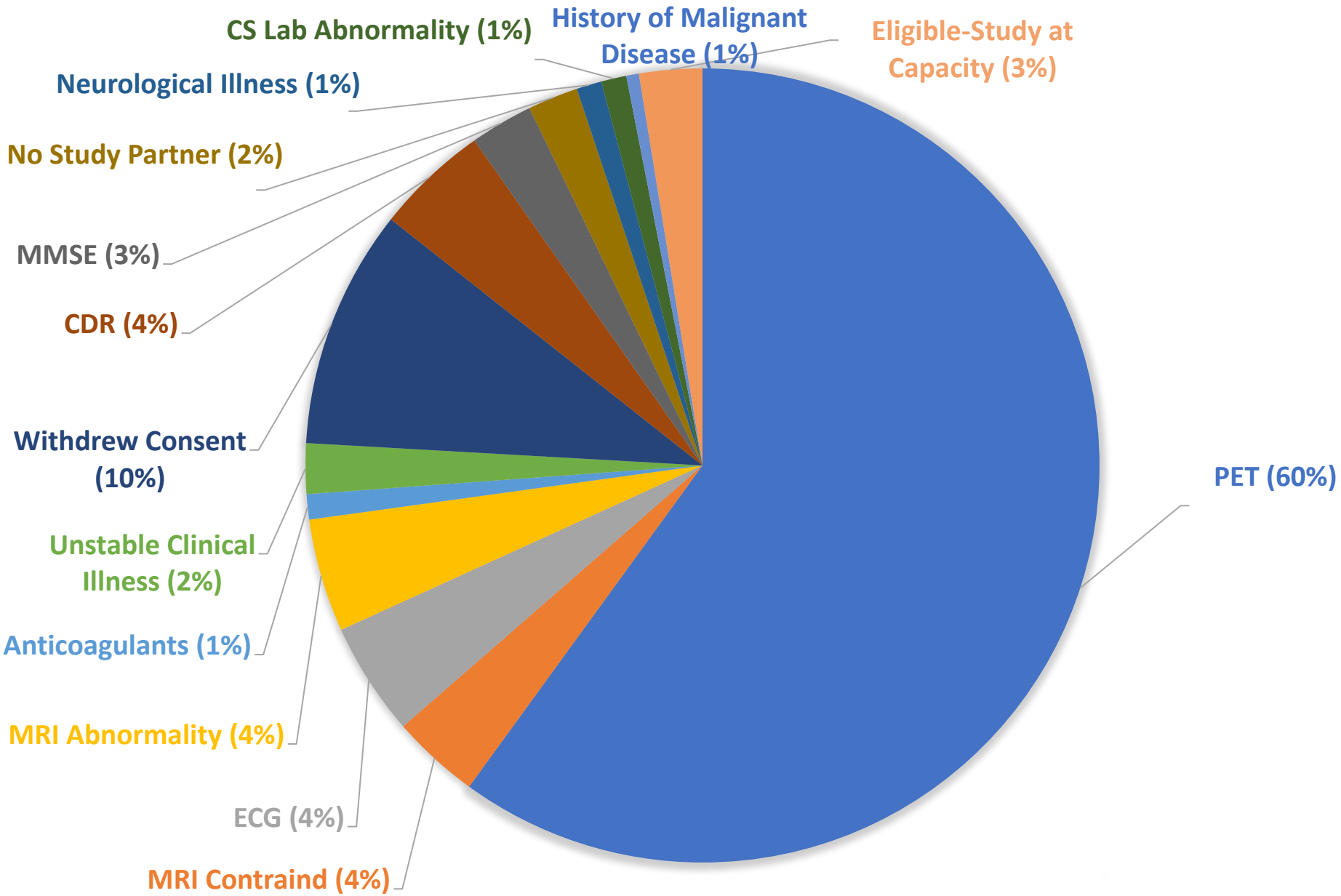


Q2W: Dosing every two weeks; Q4W: Dosing every four weeks.

Participant Disposition



Primary Reasons for Screen Failures



Baseline Demographics

Characteristic	ACU193 (N=49)	Placebo (N=16)
Age, median (range), years	72.3 (56,85)	71.3 (59,83)
Female, n (%)	27 (55.1)	8 (50.0)
Race, n (%)		
Asian	0 (0)	0 (0)
Black/African American	2 (4.1)	1 (6.3)
Caucasian	46 (93.9)	15 (93.7)
American Indian/Alaskan	1(2.0)	0 (0)
Ethnicity, n (%)		
Hispanic or Latino	8 (16.3)	2 (12.5)
Not Hispanic or Latino	41 (83.7)	14 (87.5)
Height in centimeters, n (%)	168.7 (8.7)	166.6 (9.3)
Weight in kilograms, n (%)	80.1 (16.6)	79.9 (13.8)
BMI in kg/m^2 , n (%)	28.0 (5.4)	28.9 (5.7)

Baseline Clinical Characteristics

Characteristic	ACU193 (N=49)	Placebo (N=15)
APOE4 Status, n (%)		
Noncarrier	21 (43.75)	4 (28.6)
Heterozygous Carrier	21 (43.75)	8 (57.1)
Homozygous Carrier	6 (12.5)	2 (14.3)
CDR-GS, mean (SD)	0.6 (0.3)	0.6 (0.2)
CDR-SB, mean (SD)	3.6 (1.9)	3.2 (1.8)
MMSE, mean (SD)	24.1 (3.7)	24.8 (3.6)
iADRS, mean	111.5	110.6
PET SUVr, mean (SD)	1.42 (0.25)	1.33 (0.19)
PET Centiloids, mean (SD)	64.8 (42.8)	48.5 (33.4)

Summary

- Screen failure rates are similar to other studies requiring amyloid positivity
- The amyloid plaque load in INTERCEPT-AD tends to be lower compared to other studies in this population
- Sites can successfully recruit patients with MCI and early AD into a Phase 1 trial that incorporates many measures found in larger Phase 2 or 3 trials

Thank you!

Recruitment strategies and tactics for INTERCEPT-AD: A phase I trial of Aβ oligomer-targeting ACU193 in early Alzheimer's disease

Robyn Moxon
Acumen Pharmaceuticals, Inc

Author Disclosures

Robyn Moxon is an employee of Acumen Pharmaceuticals.

Forward Looking Statements

This presentation contains forward-looking statements within the meaning of The Private Securities Litigation Reform Act of 1995. Any statement describing Acumen's goals, expectations, financial or other projections, intentions or beliefs is a forward-looking statement and should be considered an at-risk statement. Words such as "believes," "expects," "anticipates," "could," "should," "would," "seeks," "aims," "plans," "potential," "will," "milestone" and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. Forward-looking statements include statements concerning: Acumen's business; the safety, tolerability, pharmacokinetics, target engagement and other clinical measures associated with Acumen's product candidate, ACU193, including its performance against other antibodies; and the anticipated timeline for reporting topline data. These statements are based upon the current beliefs and expectations of Acumen management, and are subject to certain factors, risks and uncertainties, particularly those inherent in the process of discovering, developing and commercializing safe and effective human therapeutics. Such risks may be amplified by the impacts of geopolitical events and macroeconomic conditions, such as rising inflation and interest rates, supply disruptions and uncertainty of credit and financial markets. These and other risks concerning Acumen's programs are described in additional detail in Acumen's filings with the Securities and Exchange Commission ("SEC"), including in Acumen's most recent Annual Report on Form 10-K, and in subsequent filings with the SEC, including Acumen's most recent Quarterly Report on Form 10-Q. Copies of these and other documents are available from Acumen. Additional information will be made available in other filings that Acumen makes from time to time with the SEC. These forward-looking statements speak only as of the date hereof, and Acumen expressly disclaims any obligation to update or revise any forward-looking statement, except as otherwise required by law, whether, as a result of new information, future events or otherwise.

Recruitment for AD Trials

- Clinical trials are essential but recruitment is often difficult

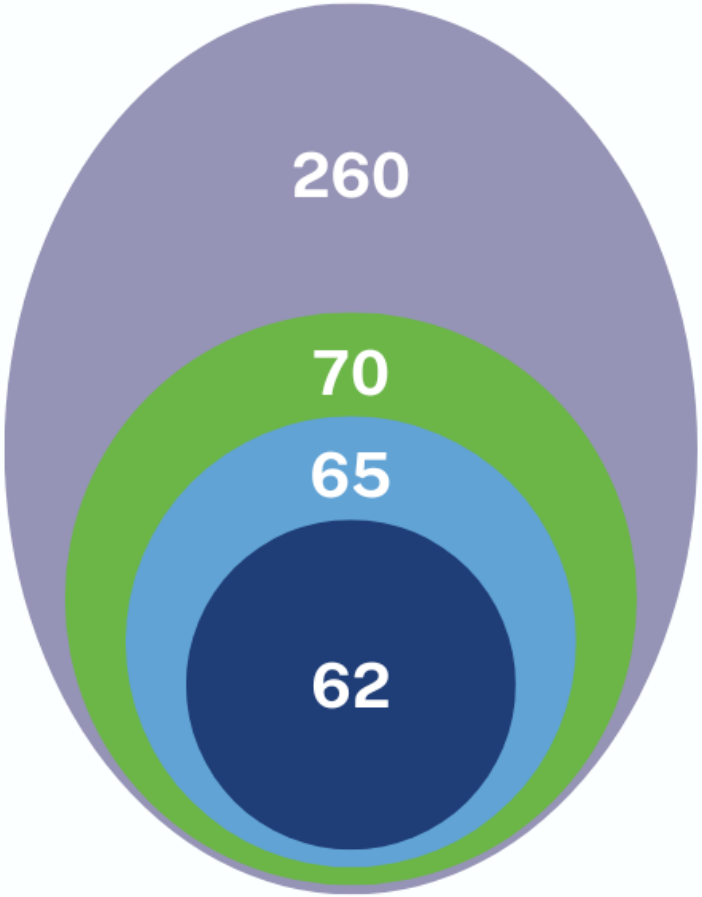
- Recruitment tactics often include:
  - Media advertising
  - Physician referrals
  - Patient registries
  - Referral campaigns
  - Social media/digital ads
  - Targeted community outreach

- Not all recruitment tactics are successful for every site

- Recognize and overcome site-specific recruitment obstacles

INTERCEPT-AD Participants

- INTERCEPT-AD is a phase 1 randomized, placebo-controlled, double-blind study of ACU193 in mild cognitive impairment or mild dementia due to AD
- Seventeen study sites in the U.S.
- Eligible vs Randomized Participants



260 Screened
70 eligible participants and 190 Screen Failed participants

70 Eligible
62 dosed, 3 discontinued and 5 eligible participants

65 Randomized
62 dosed and 3 discontinued participants

62 Dosed
62 Dosed patients in INTERCEPT-AD

Recruitment Categories

SITE DATABASE

Patients in site's database or referred by clinic staff

EXTERNAL REFERRAL

Patients referred by friends, family, or self-referrals

PHYSICIAN REFERRAL

Patients referred by physicians not affiliated with study site

SITE CAMPAIGN

Site-led ads, events, and databases not study specific

CAMPAIGN A

Vendor used digital ads linking to a study website with a pre-screening questionnaire

CAMPAIGN B

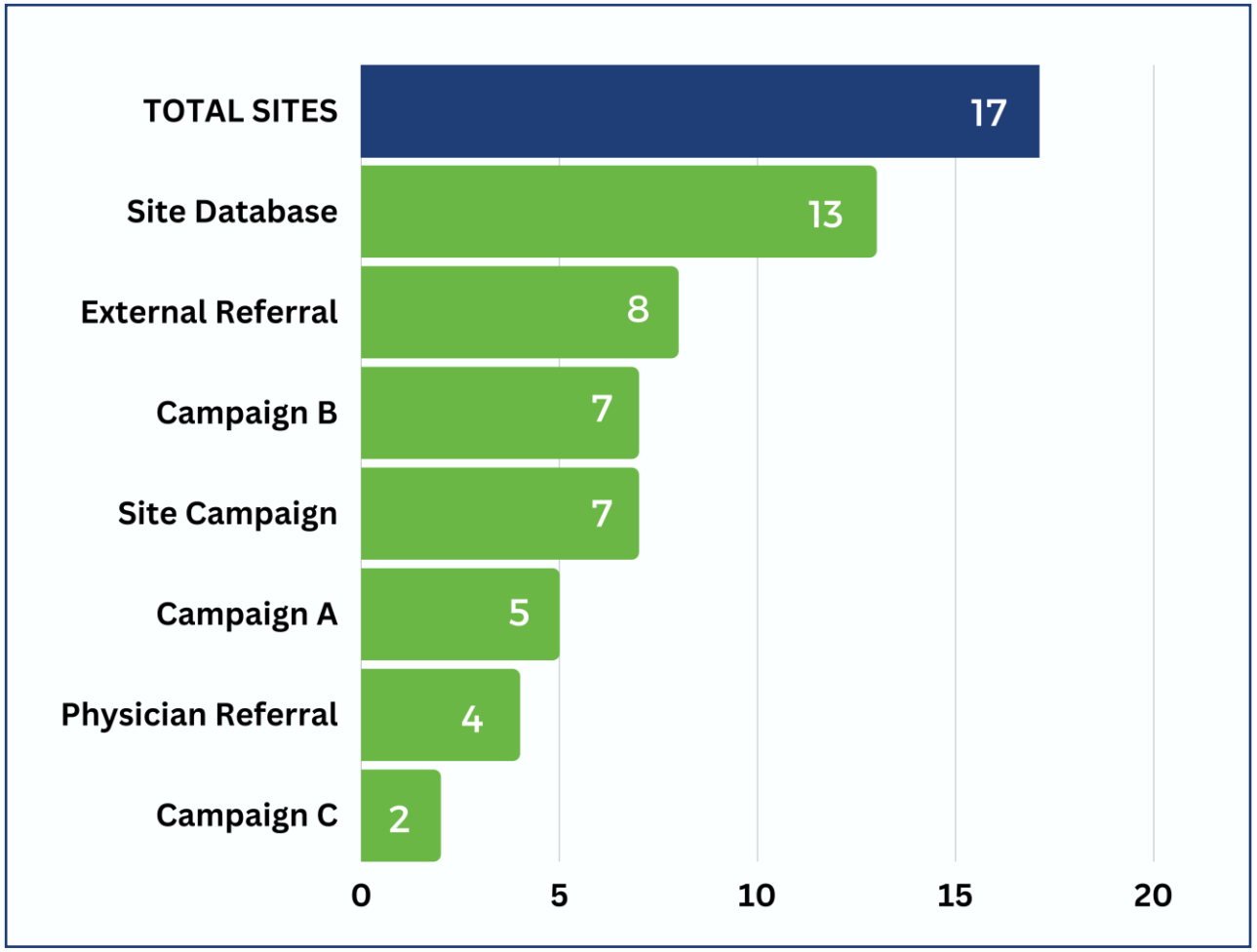
Vendor used their own patient identification system to pre-screen and refer participants to site

CAMPAIGN C

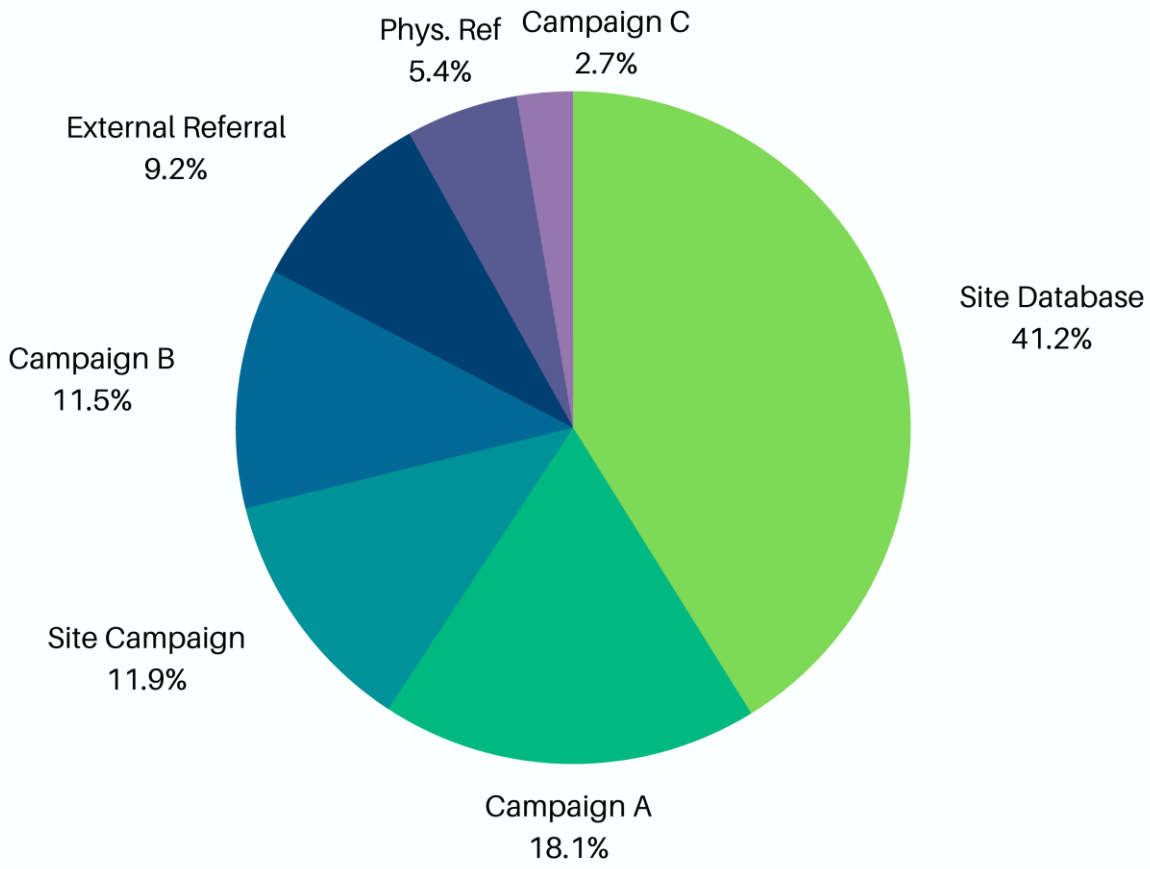
Vendor used social media interest groups to recruit, generic ads with INTERCEPT-AD pre-screener

Referral Source Use by Sites for Screening

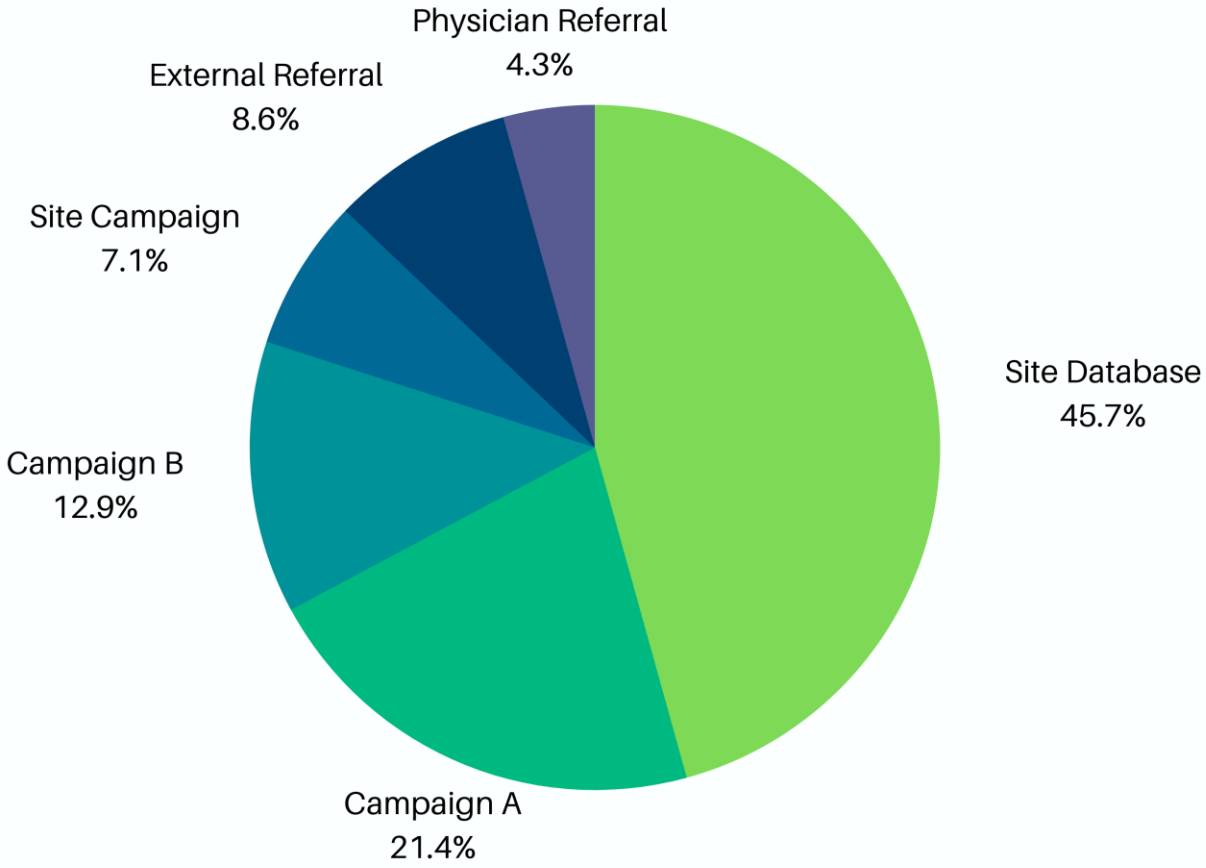
- Site databases
  - Used by most sites 13 (76%)
  - Accounted for most screenings 107 (41%)
  - Identified more eligible participants 32 (46%)
- Recruitment tactics customized for successful site enrollment
- Selection was based on site-specific needs



Referral Sources for Screened and Eligible Participants



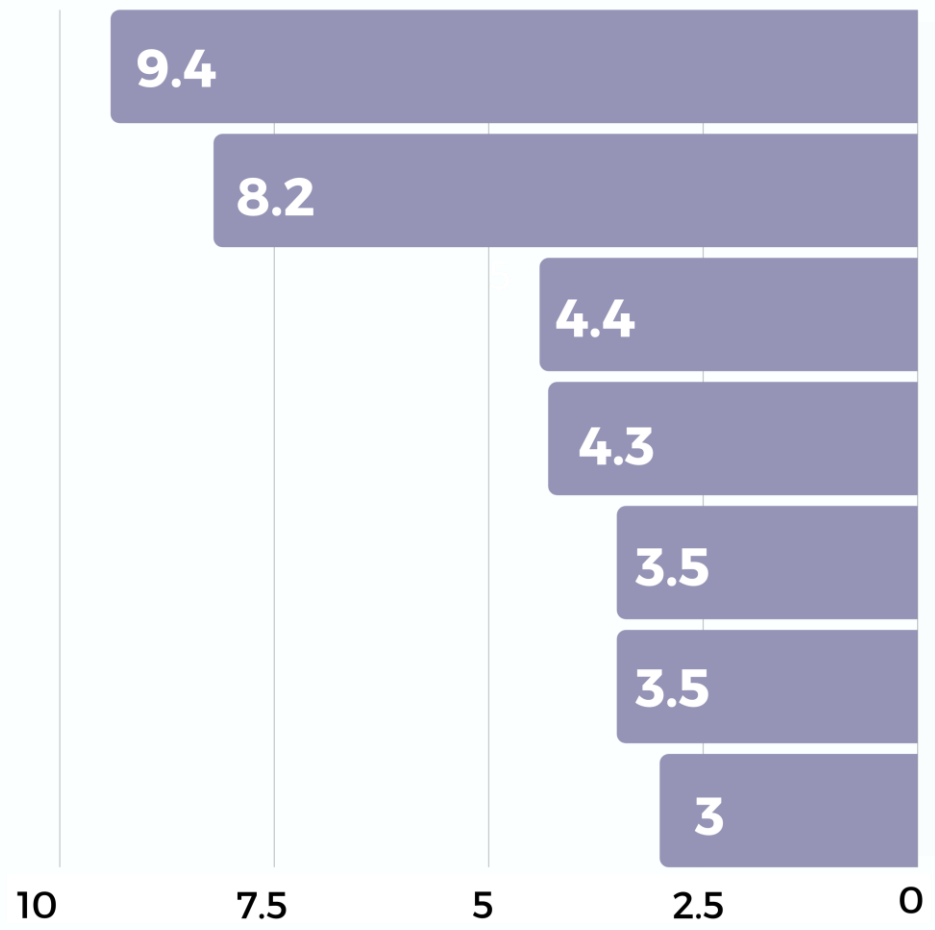
Screened Participants (n=260)



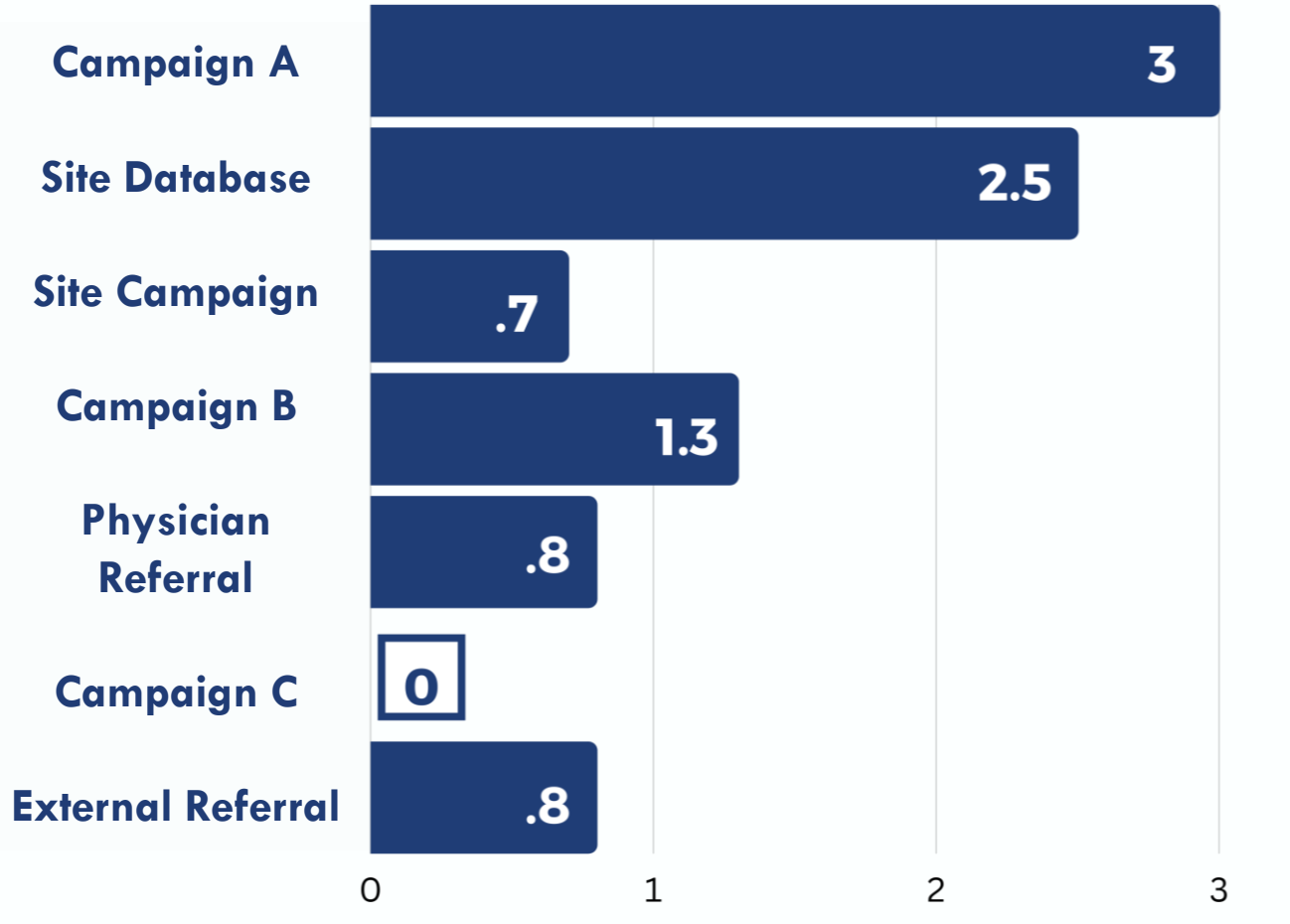
Eligible Participants (n=70)

*Campaign C had 0 Eligible Participants

INTERCEPT-AD Screening and Eligibility Rate by Referral Source

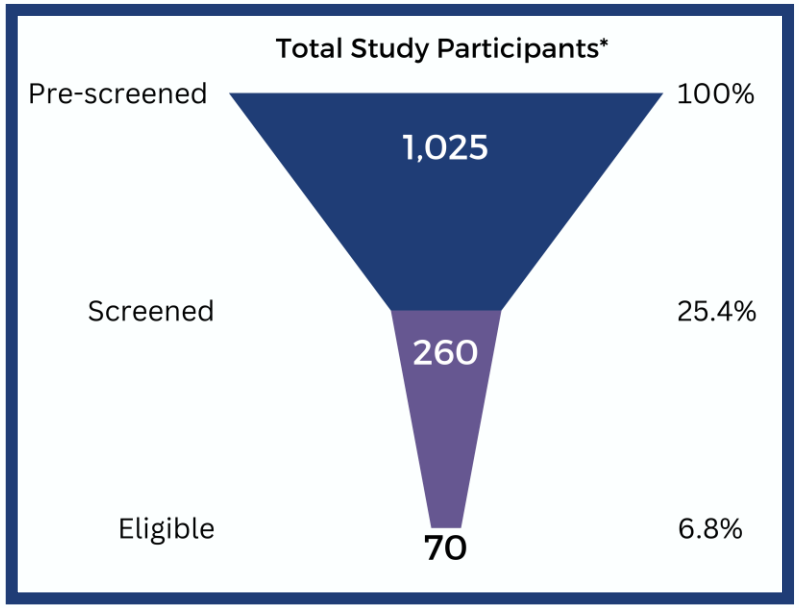


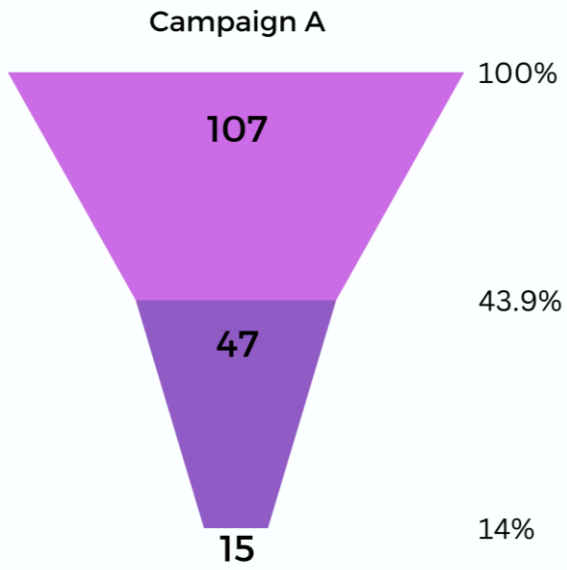
Screening Rate per Site by Referral Source

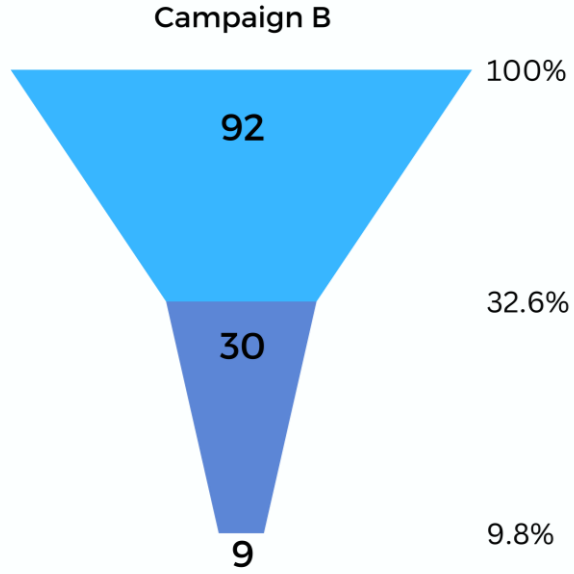


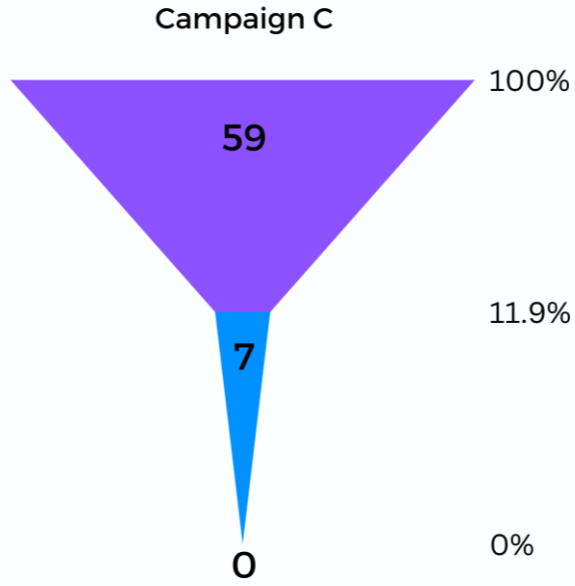
Eligibility Rate per Site by Referral Source

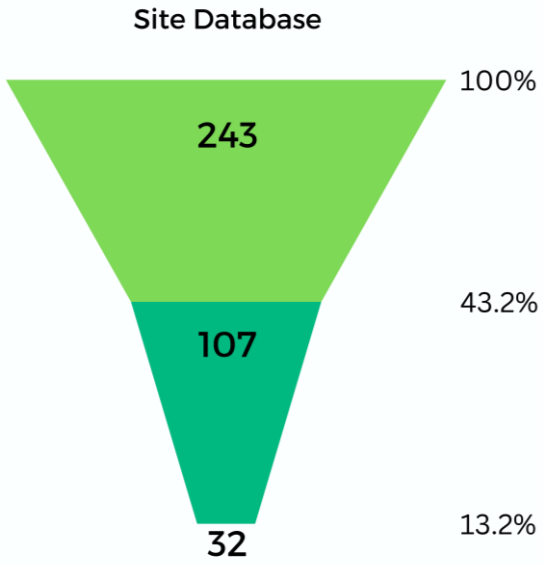
Participant Funnels by Source

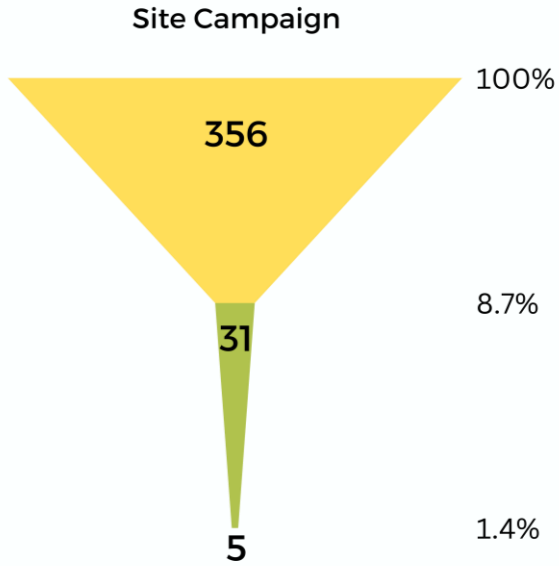


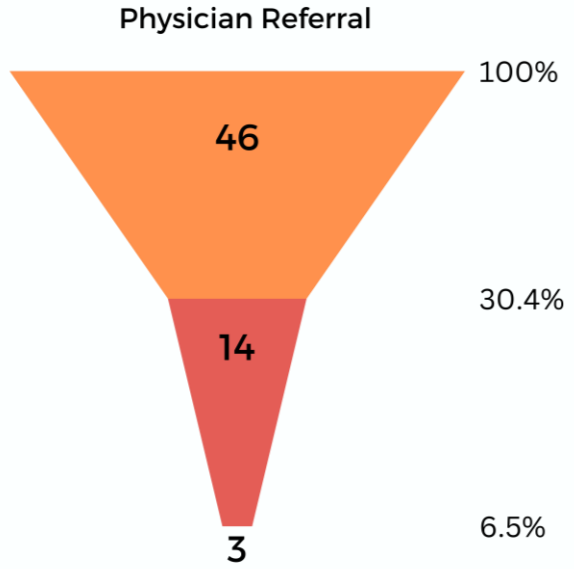


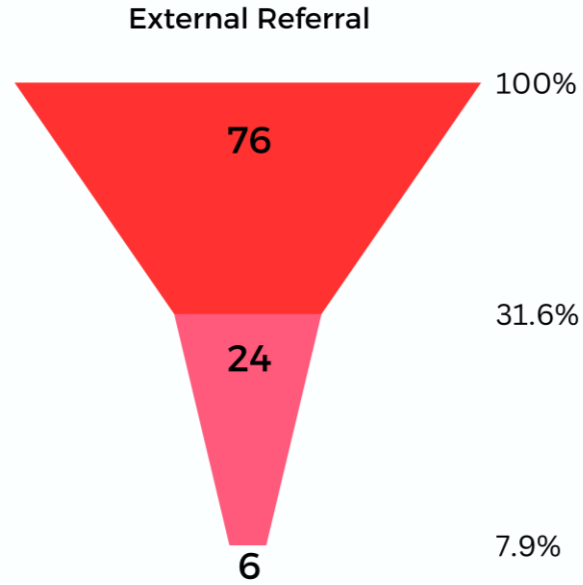












** Includes 43 Pre-screened patients with unknown referral source*

Summary

- Sites with robust internal patient databases contributed higher numbers of screening and eligibility
- Digital advertising can be a successful source for recruiting for Alzheimer's trials
- Recruitment strategies may find success with a customized approach addressing unique capabilities of individual sites

We want to thank all INTERCEPT-AD PIs and site staff as well as the participants and their study partners for their contributions to this study.

Topline results of INTERCEPT-AD: A phase I trial of Aβ oligomer-targeting ACU193 in early Alzheimer's disease

Eric Siemers, MD
Chief Medical Officer
Acumen Pharmaceuticals, Inc

Disclosures

Chief Medical Officer
- Acumen Pharmaceuticals Inc.

Consulting Agreements (2021 or later)
- Cogstate Ltd.
- Cortexyme Inc.
- Gates Ventures LLC
- Hoffman La-Roche Ltd.
- Indiana University
- LuMind Research Down Syndrome Foundation
- Partner Therapeutics Inc.
- Vaccinex, Inc.

Stock positions
- Shareholder: Eli Lilly and Company
- Stock options: Acumen Pharmaceuticals Inc.

Forward-Looking Statements

This presentation contains forward-looking statements within the meaning of The Private Securities Litigation Reform Act of 1995. Any statement describing Acumen's goals, expectations, financial or other projections, intentions or beliefs is a forward-looking statement and should be considered an at-risk statement. Words such as "believes," "expects," "anticipates," "could," "should," "would," "seeks," "aims," "plans," "potential," "will," "milestone" and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. Forward-looking statements include statements concerning: Acumen's business; the safety, tolerability, pharmacokinetics, target engagement and other clinical measures associated with Acumen's product candidate, ACU193, including its performance against other antibodies; and the anticipated timeline for reporting topline data. These statements are based upon the current beliefs and expectations of Acumen management, and are subject to certain factors, risks and uncertainties, particularly those inherent in the process of discovering, developing and commercializing safe and effective human therapeutics. Such risks may be amplified by the impacts of geopolitical events and macroeconomic conditions, such as rising inflation and interest rates, supply disruptions and uncertainty of credit and financial markets. These and other risks concerning Acumen's programs are described in additional detail in Acumen's filings with the Securities and Exchange Commission ("SEC"), including in Acumen's most recent Annual Report on Form 10-K, and in subsequent filings with the SEC, including Acumen's most recent Quarterly Report on Form 10-Q. Copies of these and other documents are available from Acumen. Additional information will be made available in other filings that Acumen makes from time to time with the SEC. These forward-looking statements speak only as of the date hereof, and Acumen expressly disclaims any obligation to update or revise any forward-looking statement, except as otherwise required by law, whether, as a result of new information, future events or otherwise.

Treatment Emergent SAEs: Participants dosed with ACU193

Subject ID	Treatment Assignment	SAE Verbatim	Severity	Relationship	Action Taken	Outcome
112-1002	10mg/kg (Cohort 5, MAD)	Ovarian Fibroma	3	Not Related	Dose Not Changed	Resolved
112-1004	10mg/kg (Cohort 5, MAD)	Pneumonia	3	Unlikely Related	Dose Not Changed	Resolved
	10mg/kg (Cohort 5, MAD)	Altered Mental Status	2	Not Related	Dose Not Changed	Resolved

All SAEs for patients taking ACU193 were deemed not related or unlikely related by the site Principal Investigator

TEAEs >3% and ACU193>Placebo

TEAE	ACU193 (N=48) n (%)	Placebo (N=14) n (%)
≥ 1 TEAE	27 (56.3)	6 (42.9)
COVID-19	3 (6.3)	0
Bronchitis	2 (4.2)	0
Headache	2 (4.2)	0
ARIA-H	4 (8.3)	1 (7.1)
ARIA-E	5 (10.4)	0
Hypersensitivity	3 (6.3)	0
Fall	2 (4.2)	0
Post LP syndrome	2 (4.2)	0

ARIA-E Summary for INTERCEPT-AD

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

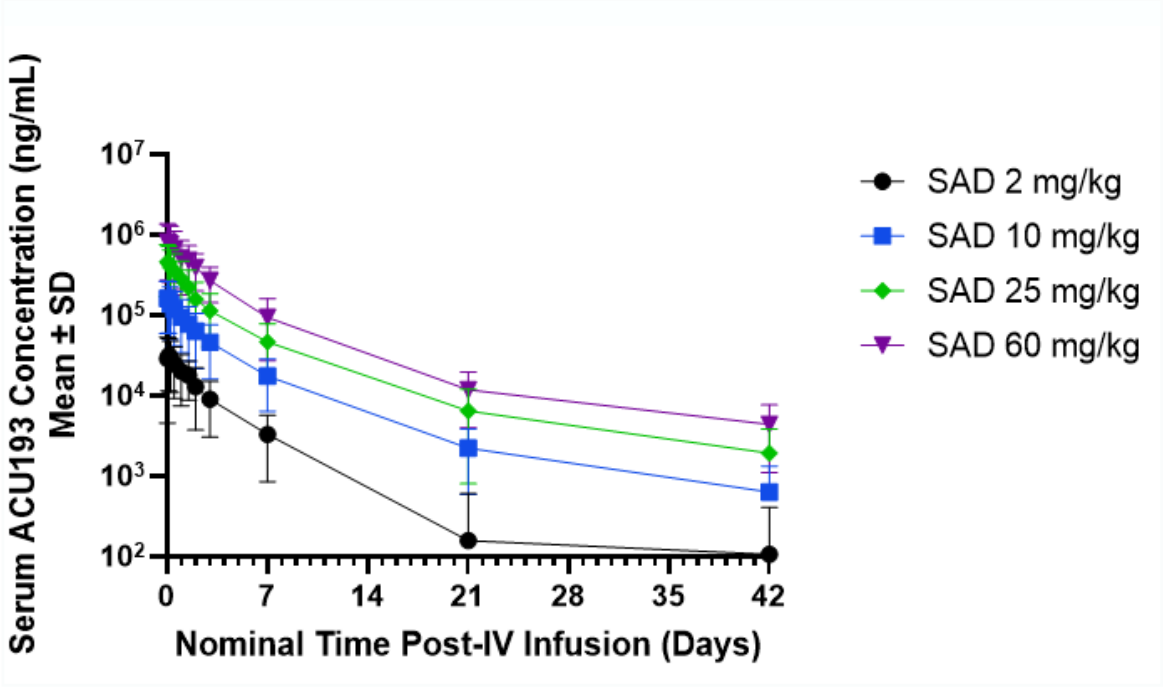
ARIA-E: Patient Details

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

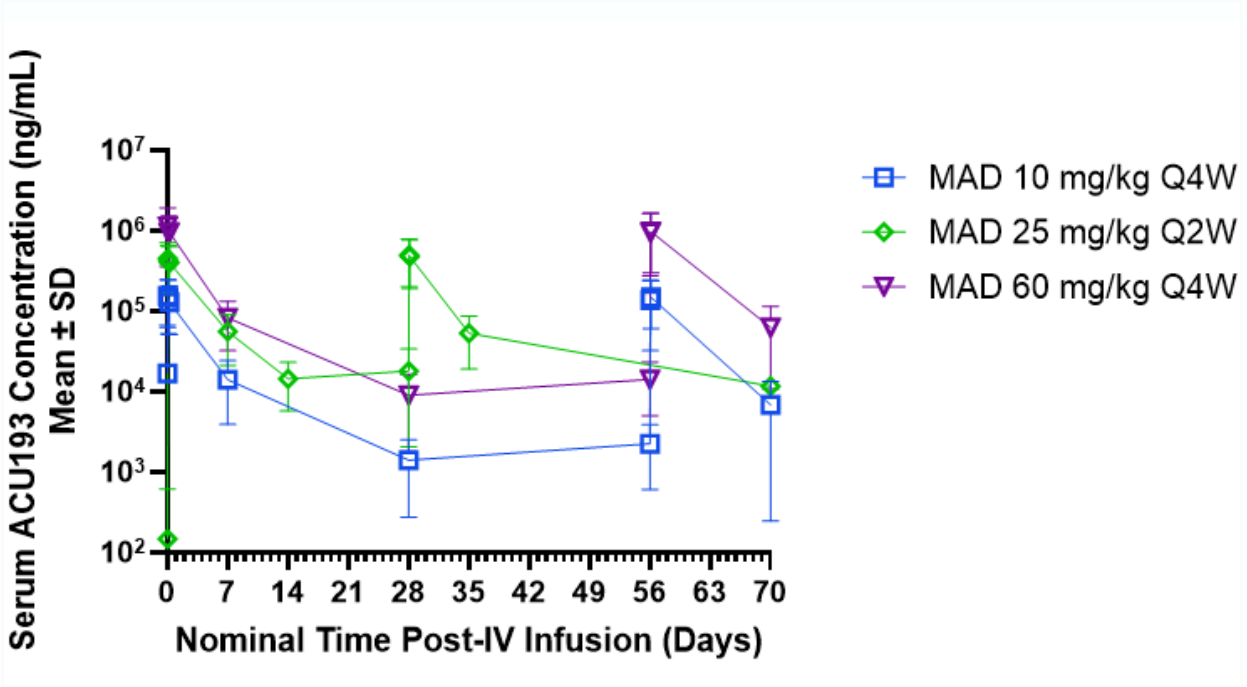
Of 5 total ARIA-E cases, 1 was symptomatic (20%) and symptoms resolved with resolution of radiographic ARIA-E. All cases showed radiographic resolution or improvement.

ACU193 Serum PK

Single Dose Cohorts



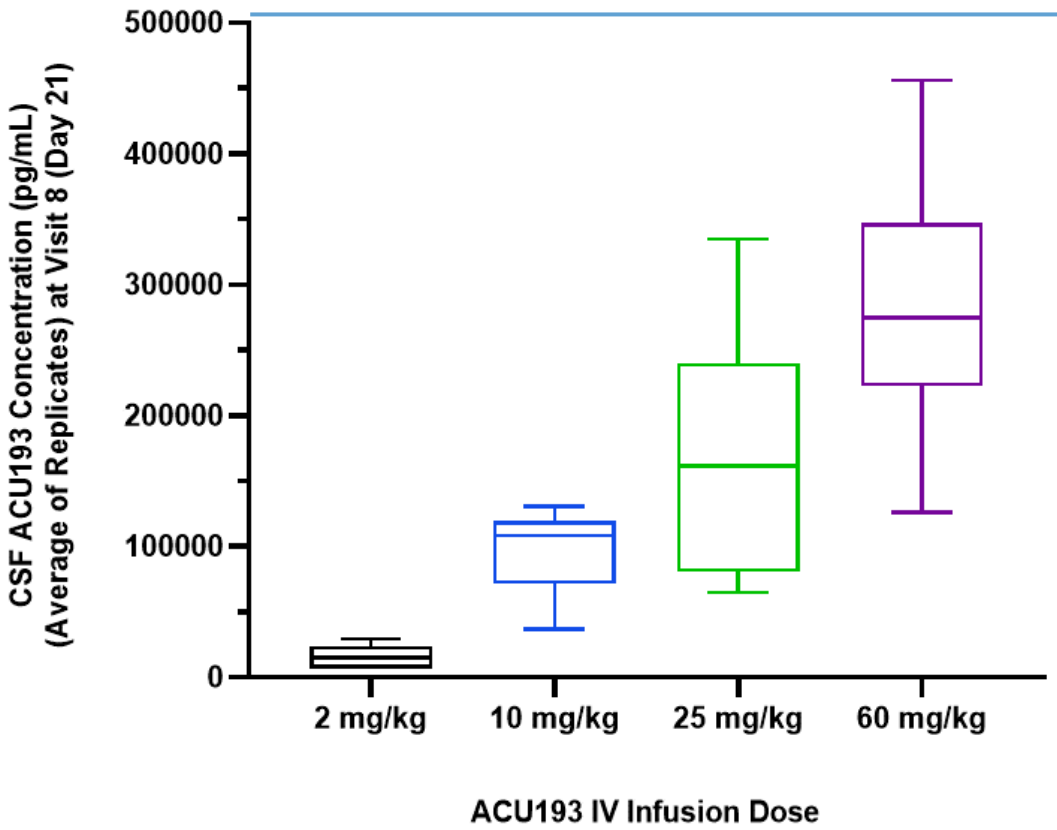
Multiple Dose Cohorts



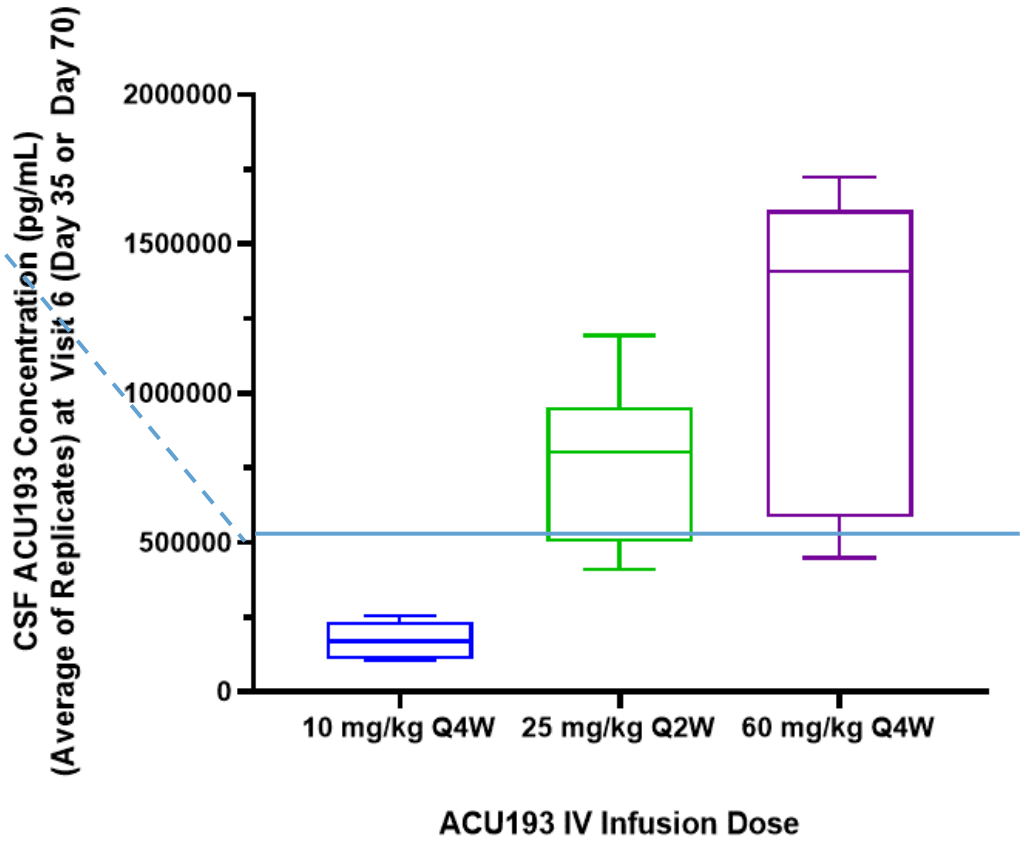
Serum exposure is dose proportional without accumulation

ACU193 CSF PK

Single Dose Cohorts



Multiple Dose Cohorts*



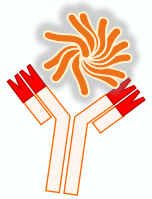
CSF exposure is dose & dose-regimen proportional

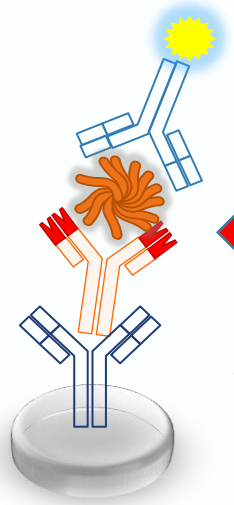
*One patient from Cohort 5 (10 mg/kg Q4W) excluded because only received one administration of drug (discontinued after lacunar infarct)

Target Engagement Assessed by Measuring ACU193-AβO Complex in CSF

MSD S-Plex (Turbo) Immunoassay

ACU193-AβO Complex





AβO selective detection
(anti-AβO mAb)

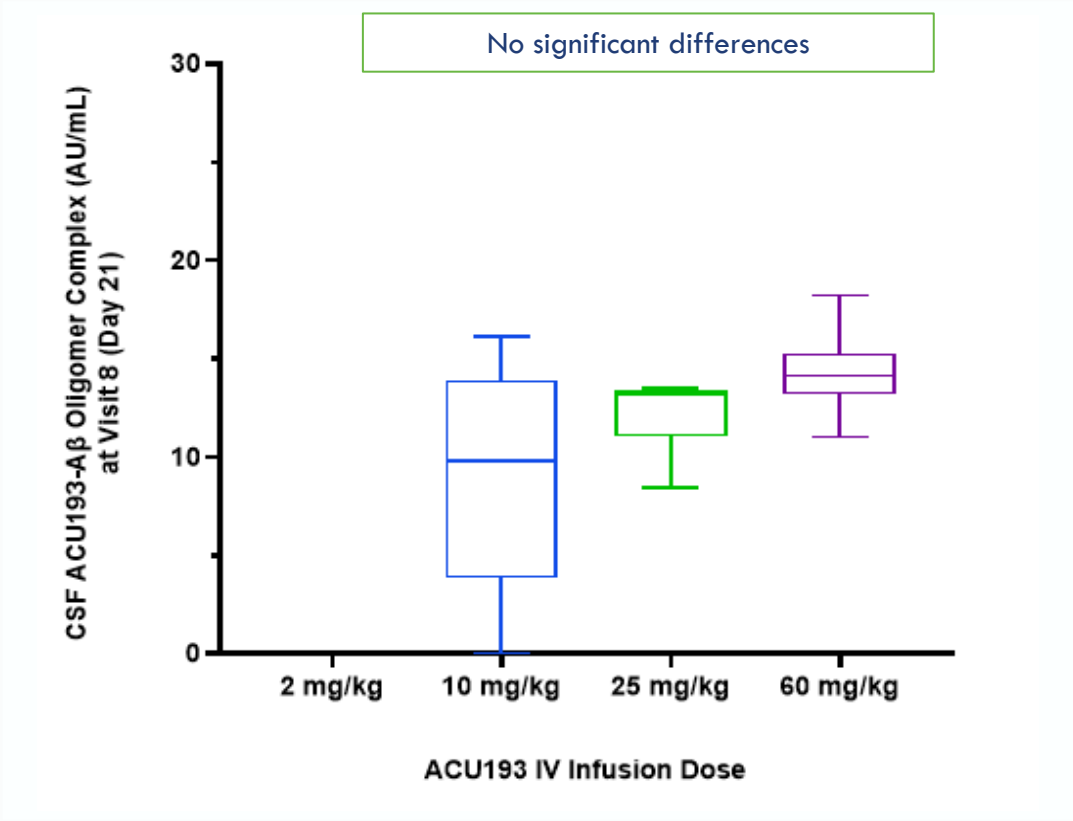
Only drug/oligomer complex is measurable

ACU193 drug specific capture
(anti-ACU193 idiotype mAb)

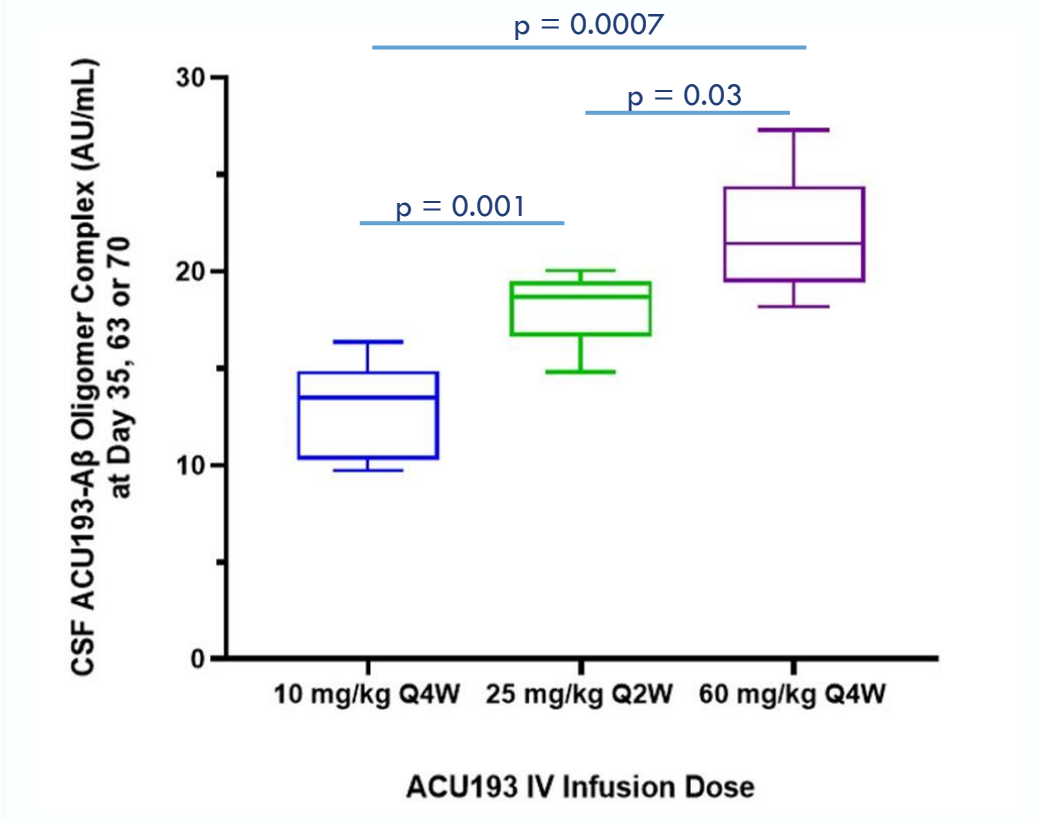
Novel assay configuration tailored to selectively detect ACU193-AβO complex in CSF as direct measure of target engagement

Target Engagement of ACU193 with AβOs is Dose Proportional

Single Dose Cohorts



Multiple Dose Cohorts*

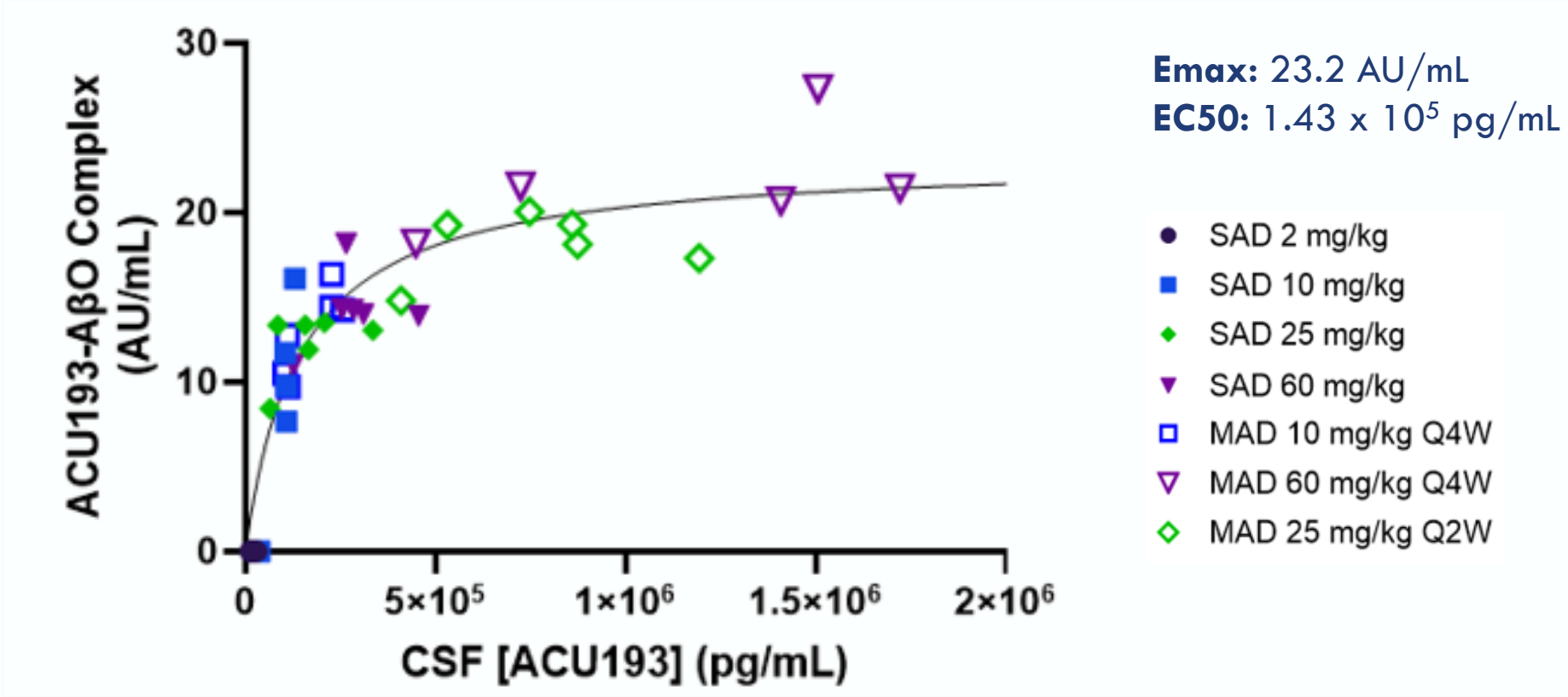


Dose-related target engagement

*One patient from Cohort 5 (10 mg/kg Q4W) excluded because only received one administration of drug (discontinued after lacunar infarct)

ACU193 CSF Target Engagement vs. Drug Exposure, Emax Model

Single & Multiple Dose Cohorts - Exposure Response Relationship (Emax Model)

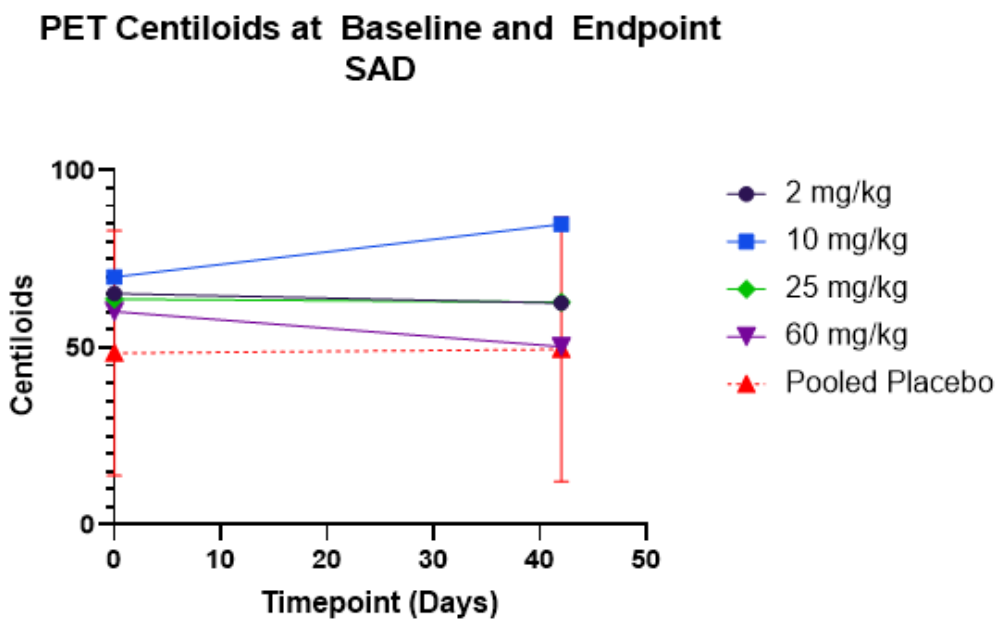


Approaching maximal TE response at doses of 25 mg/kg Q2W and 60 mg/kg Q4W

*One patient from Cohort 5 (10 mg/kg Q4W) excluded because only received one administration of drug (study drug discontinued after lacunar infarct)

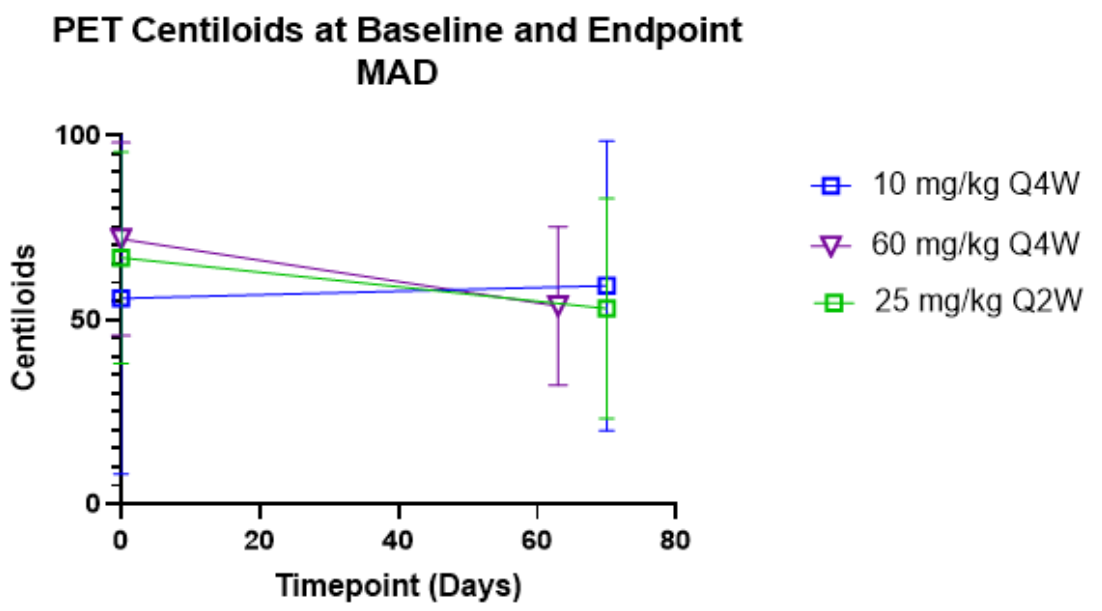
Aβ PET: Mean Changes in Amyloid Plaque in SAD and MAD Cohorts

Single Dose Cohorts



Mean ± SD Error bars shown only for pooled placebo group.

Multiple Dose Cohorts

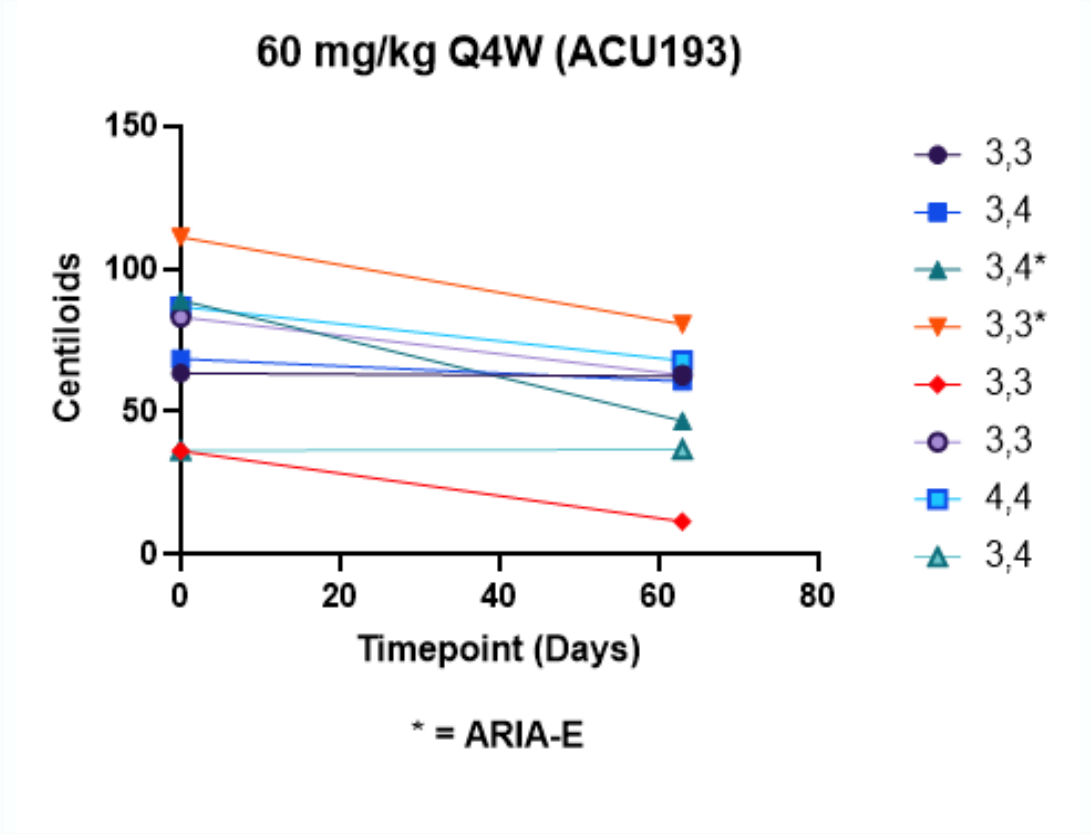


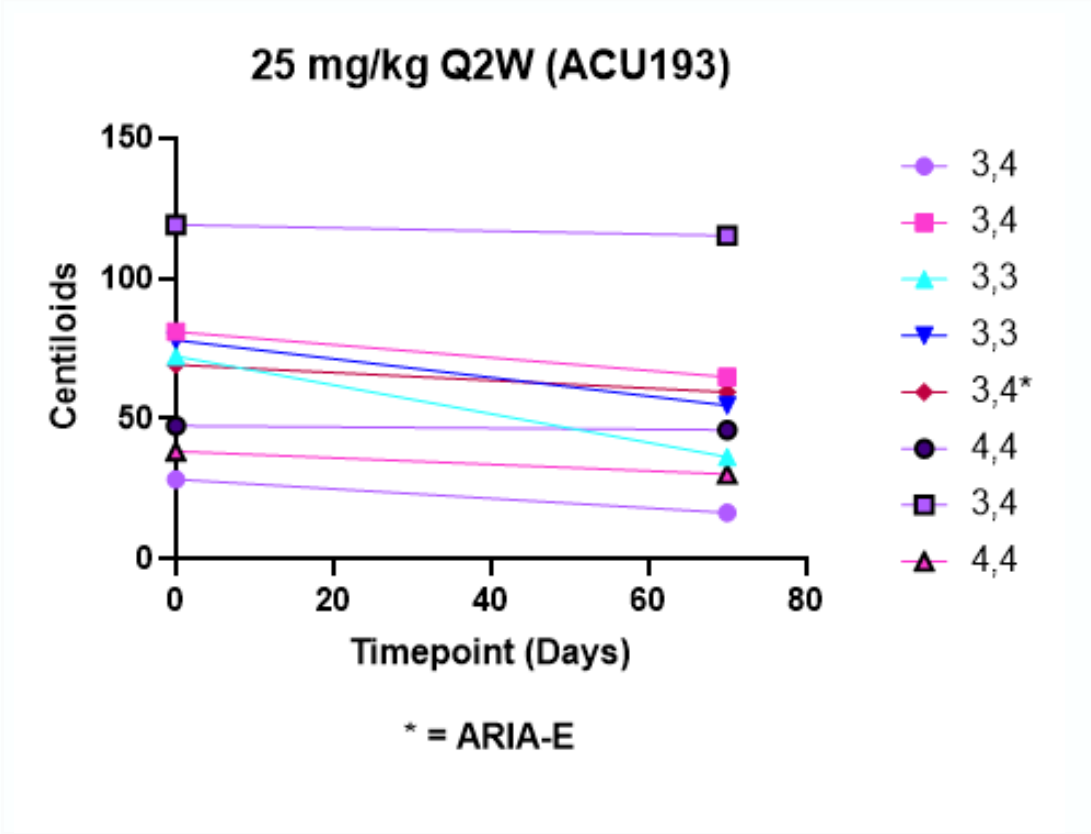
Mean ± SD

Small changes in plaque load based on florbetapir PET appeared to be present in 60 mg/kg Q4W and 25 mg/kg Q2W cohorts

Note: Placebo patients not included in MAD due to limited numbers and varying timepoints.

Aβ PET: Individual Patient Changes in Amyloid Plaque in Cohort 6 at 60 mg/kg Q4W and Cohort 7 at 25 mg/kg Q2W

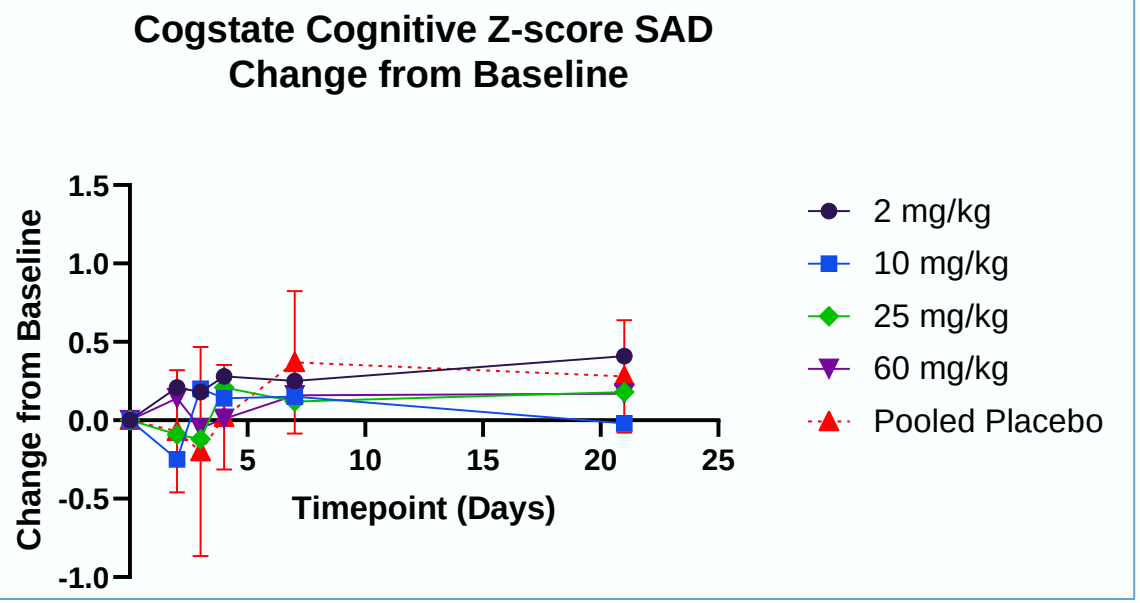




Some but not all individual participants in 60 mg/kg Q4W and 25 mg/kg Q2W cohorts showed small reductions in plaque load after 63 or 70 days

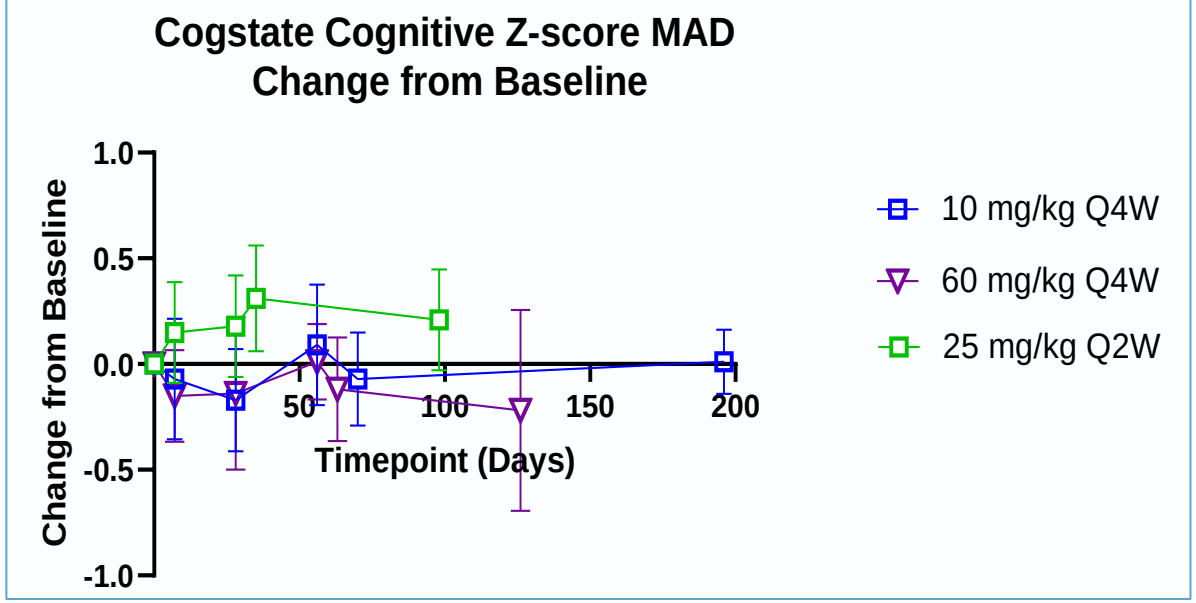
Exploratory Computerized Cognitive Testing

Single Dose Cohorts



Means ± SD. Error bars shown only for pooled placebo group.

Multiple Dose Cohorts



Means ± SD.

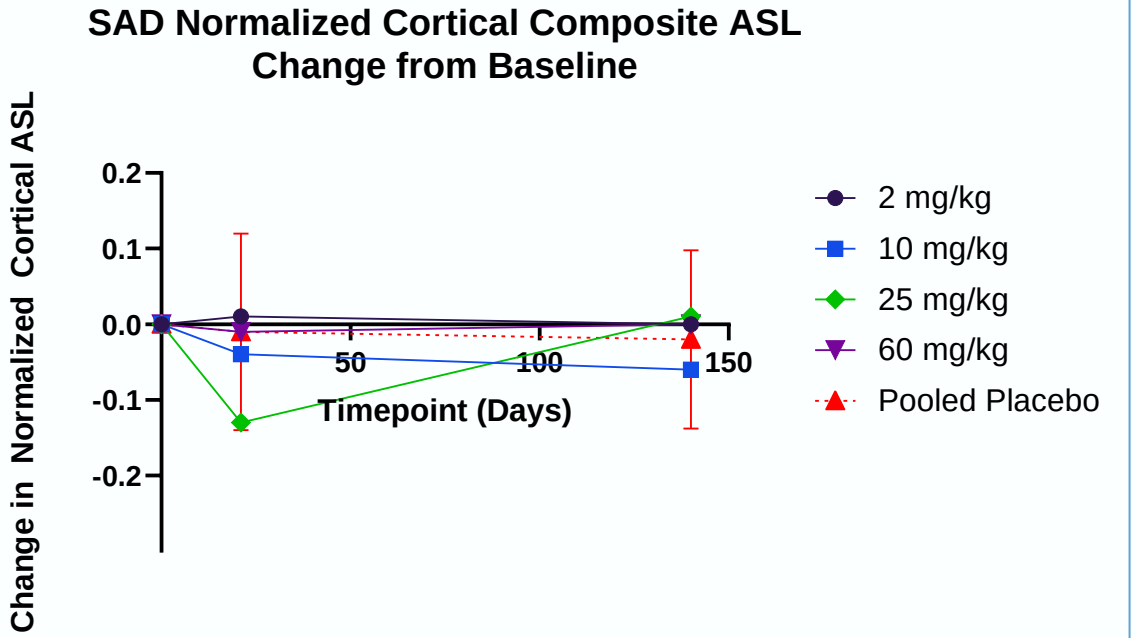
Computerized cognitive testing was feasible, did not show training effects, and variability was reasonable. No clear effect of ACU193 could be demonstrated.

Note: Placebo patients not included in MAD due to limited numbers and varying timepoints.

Exploratory Arterial Spin Labeling

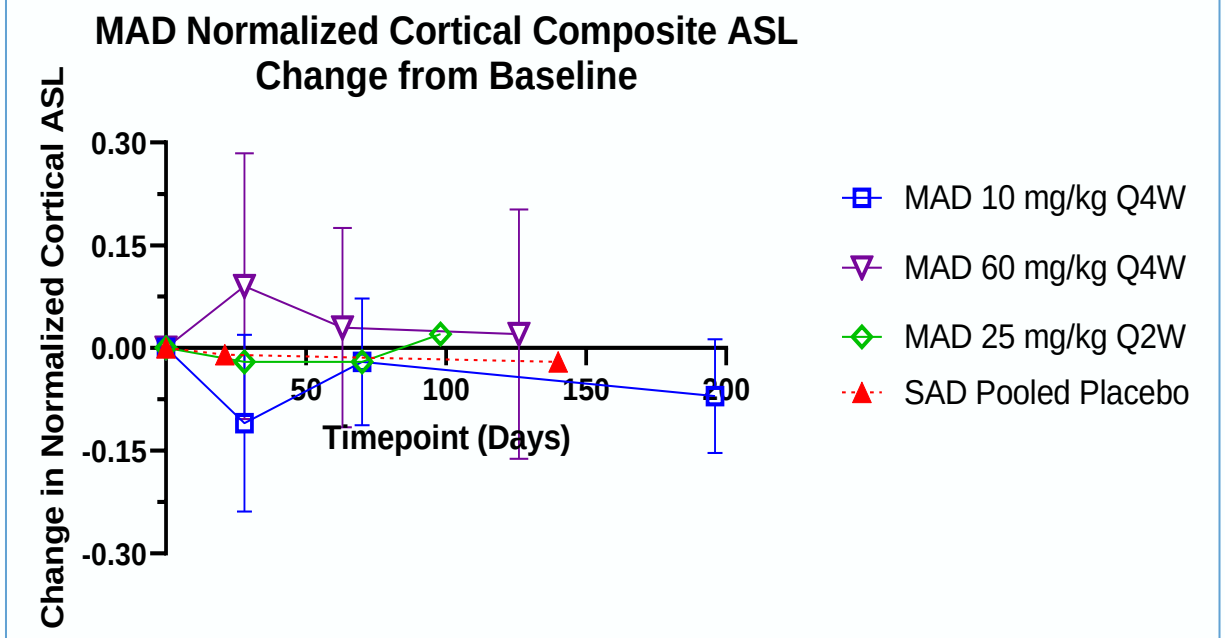
(Siemens MRI scanners only)

Single Dose Cohorts



Means ± SD. Error bars shown only for pooled placebo group.

Multiple Dose Cohorts



Means ± SD.

Cerebral blood flow (CBF) as determined by ASL could be quantified and showed reasonable variability. No clear effect of ACU193 on CBF could be demonstrated.

Note: Placebo patients not included in MAD due to limited numbers and varying timepoints.

Conclusions

- **No unexpected safety signals found; rates of ARIA-E appear to be manageable and no cases of ARIA-E occurred in 6 participants who were ApoE e4 homozygotes and received ACU193**

- **PK is generally consistent with Q4W dosing; INTERCEPT-AD provides data that will inform doses for the subsequent Phase 2/3 study**
  - For 25 mg/kg Q4W, CSF PK will need to be modeled

- **Target engagement is clearly demonstrated in INTERCEPT-AD**
  - Dose response and PK/PD modeling suggest that an Emax is nearly achieved with 60 mg/kg Q4W or 25 mg/kg Q2W dosing
  - These findings suggest that dosing above 60 mg/kg Q4W would have limited additional target engagement

- **In addition to target engagement, reduction in plaque based on florbetapir PET was seen in the highest doses of the MAD cohorts**

- **Exploratory analyses do not support an immediate symptomatic effect of ACU193, but do show that applications in larger Phase 2 studies may provide important information regarding dose response**
  - Computerized cognitive testing showed little if any training effects and reasonable variability. Optimization of these tests and use in typical Phase 2 trials may provide important insights into pharmacodynamic effects of treatments for AD
  - Use of ASL pulse sequences to assess CBF can be implemented in clinical trials and could provide important information regarding central pharmacology, especially for drugs with novel mechanisms for AD

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)

Thank you!