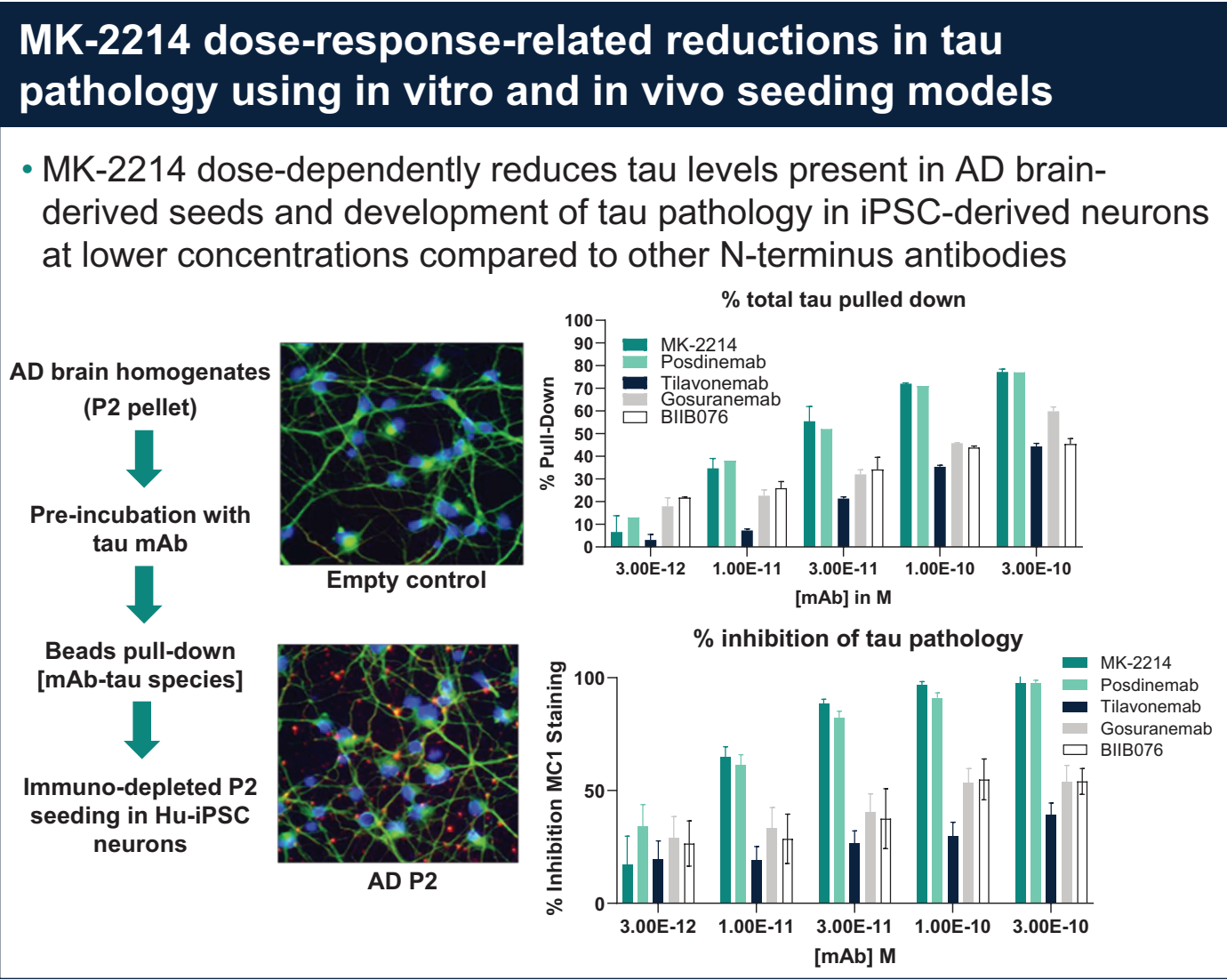


Phase 1 Studies of MK-2214, a Novel Antibody Targeting pS413 Tau, for the Treatment of Alzheimer’s Disease

Background

- Antibodies targeting extracellular tau have been proposed as a therapeutic strategy to reduce the spread of pathology and slow the progression of Alzheimer's disease^{1,2}
- MK-2214 is a novel, highly potent, antibody targeting phosphorylated serine 413 (pS413) containing tau which is present in pathological forms of tau³
- In vitro and in vivo seeding studies showed robust reductions in tau pathology with antibodies targeting pS413 tau, suggesting that reducing extracellular pS413 tau can reduce the extracellular spread of tau seeds³
- Studies in non-human primates demonstrated that MK-2214 has an extended half-life compared to traditional antibodies³



Objective

To evaluate the clinical pharmacology of MK-2214 in humans.

Results

Adverse events

- MK-2214 was generally well tolerated at all dose levels
- No dose limiting toxicity issues, no serious drug-related adverse events, and no pattern of drug-related events

Study 1: First-in-human, single dose

	MK-2214 IV Total		MK-2214 SC Total		MK-2214 Total		Placebo Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	36		12		48		16	
With one or more adverse events	23	(63.9)	10	(83.3)	33	(68.8)	15	(93.8)
With drug-related ^a adverse events	11	(30.6)	4	(33.3)	15	(31.3)	7	(43.8)
Discontinued drug due to an adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Drug-related ^a adverse events occurring in >1 participant in the MK-2214 total group								
Headache	11	(30.6)	3	(25.0)	14	(29.2)	6	(37.5)

Study 2: Japanese, single dose

	MK-2214 Total		Placebo Total	
	n	(%)	n	(%)
Participants in population	36		12	
With one or more adverse events	11	(30.6)	2	(16.7)
With drug-related ^a adverse events	4	(11.1)	0	(0.0)
Discontinued drug ^a due to an adverse event	0	(0.0)	0	(0.0)
Drug-related ^a adverse events occurring in >1 participant in the MK-2214 total group				
Orthostatic hypotension	2	(5.6)	0	(0.0)

Study 3: Cognitively impaired, multiple dose

	MK-2214 Total		Placebo Total	
	n	(%)	n	(%)
Participants in population	25		9	
With one or more adverse events	19	(76.0)	7	(77.8)
With drug-related ^a adverse events	6	(24.0)	1	(11.1)
Discontinued drug ^a due to an adverse event	0	(0.0)	1	(11.1)
Drug-related ^a adverse events occurring in >1 participant in the MK-2214 total group				
Headache	4	(16.0)	1	(11.1)

^aDetermined by the investigator to be related to the drug.

Disclosures

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Methods

- The safety, tolerability and serum pharmacokinetics of MK-2214 were evaluated in three randomized, double-blind, placebo-controlled studies
- Participants in each study were followed-up for between 139 (Study 1) to 239 (Studies 2 and 3) days after dosing based on the projected long half-life of MK-2214

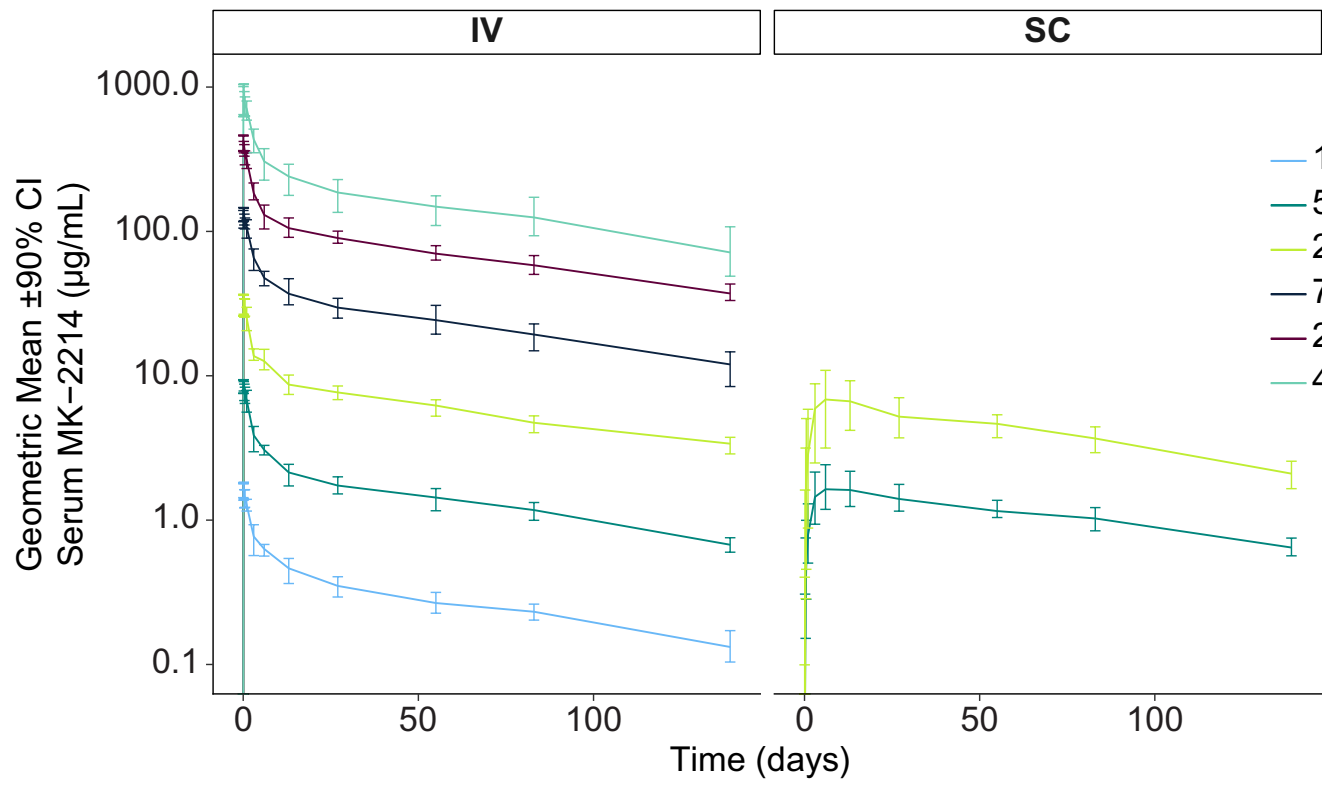
Study	Population	Eligible age range (actual mean)	Doses and route	Dosing regimen	Sample size
1. First-in-human, single dose (EUDRACT 2021-003581-12)	Healthy non-Japanese men and women	18-55 y (mean, 36 y)	IV: 10, 50, 200, 700, 2100, 4200 mg SC: 50, 200 mg	Single ascending dose	Total N=64 IV: 36 MK-2214/12 pbo SC: 12 MK-2214/4 pbo
2. Japanese, single dose (JRCT 2031220627)	Healthy Japanese men	Younger: 18-55 y (mean, 42 y) Older: 56-75 y (mean, 62 y)	IV: 700, 2100, 4200 mg IV: 4200 mg	Single ascending dose	Total N=48 Younger: 27 MK-2214/9 pbo Older: 9 MK-2214/3 pbo
3. Cognitively impaired, multiple dose (NCT05466422)	Men and women with mild-to-moderate cognitive impairment ^a	50-80 y (mean, 71 y)	IV: 4, 20, 100, 500 mg	Multiple ascending dose: 1 dose per month for 3 months	Total N=34 25 MK-2214/9 pbo

^aDefined as a history of cognitive and functional decline with gradual onset and slow progression for at least 1 year, and MMSE >12; could include those with Mild Cognitive Impairment and mild-to-moderate Alzheimer's disease, but those with other neurological disorders were excluded. IV, intravenous; SC, subcutaneous; pbo, placebo.

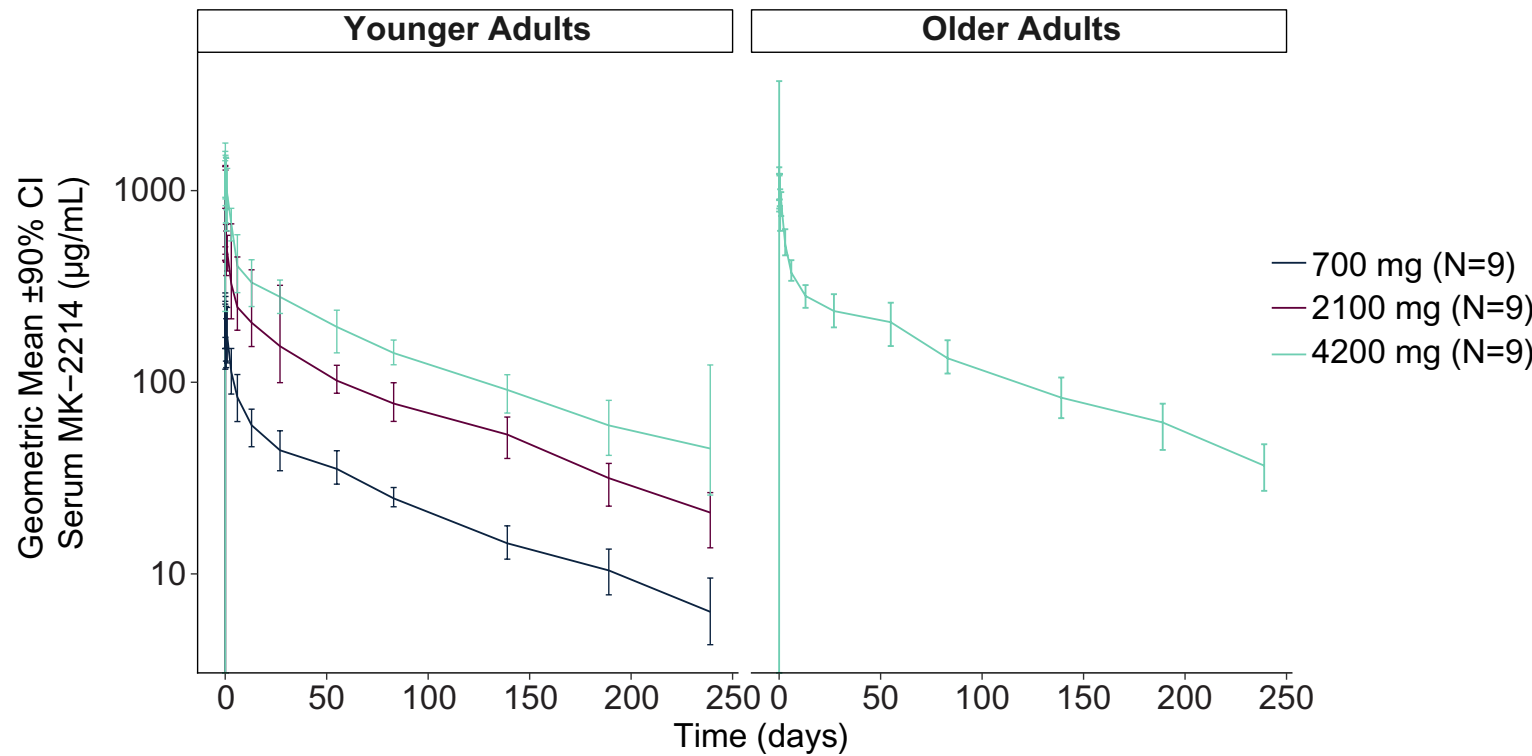
Serum pharmacokinetics

- The half-life of MK-2214 was approximately 80 days across the 3 studies
- Exposures and C_{max} were approximately dose proportional in each study
- The bioavailability of the SC injection versus the IV infusion in Study 1 (geometric mean ratio for AUC_{0-inf}) was 0.63 combined across the 50 mg and 200 mg doses
- The pharmacokinetics of MK-2214 in Japanese participants in Study 2 were generally similar to non-Japanese participants in Study 1
- The pharmacokinetics of the 4200 mg IV dose in healthy older Japanese men were comparable to those in healthy younger Japanese men
- The pharmacokinetics in cognitively impaired older adults in Study 3 were comparable to those in healthy young adults in Study 1

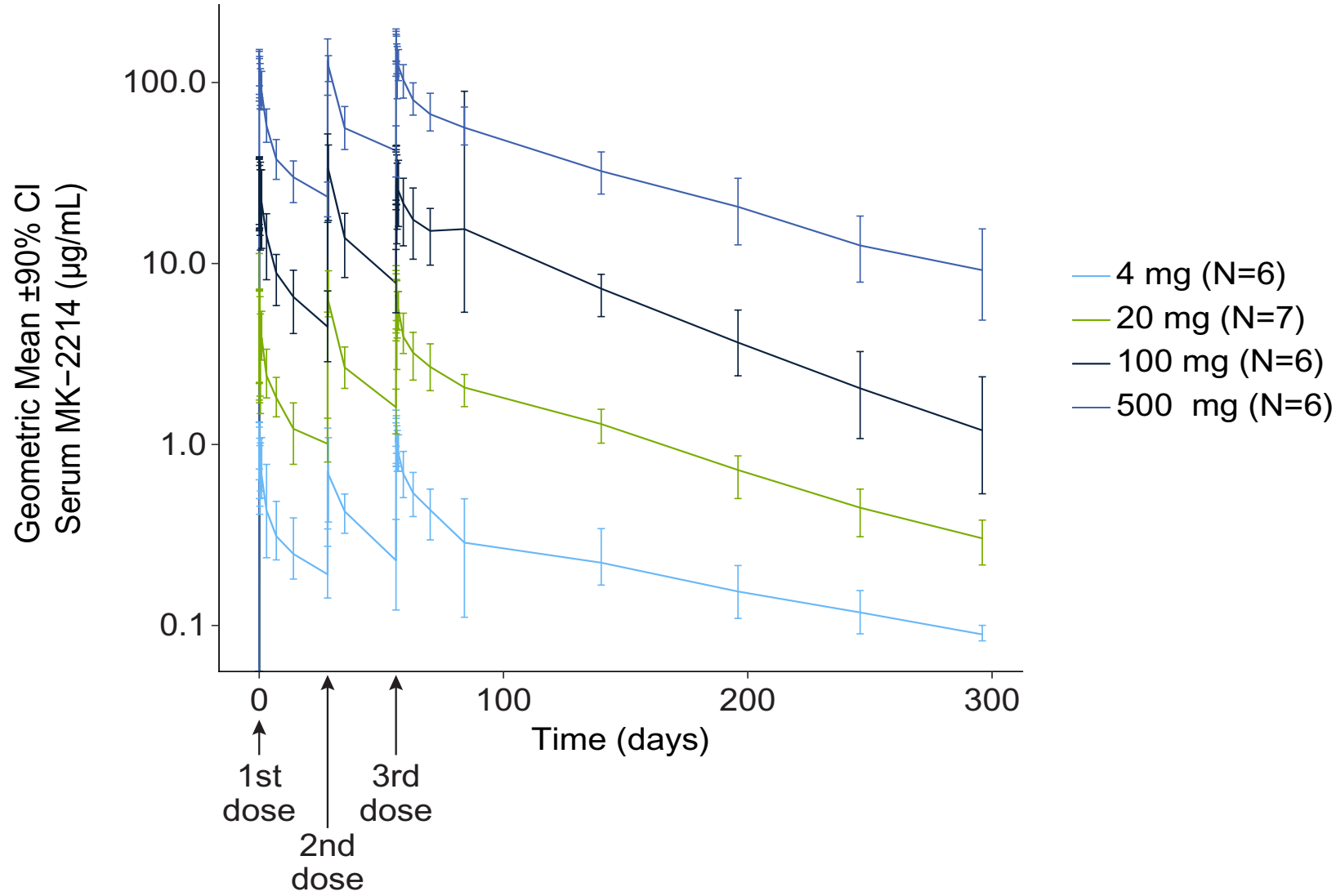
Study 1: First-in-human, single dose



Study 2: Japanese, single dose



Study 3: Cognitively impaired, multiple dose

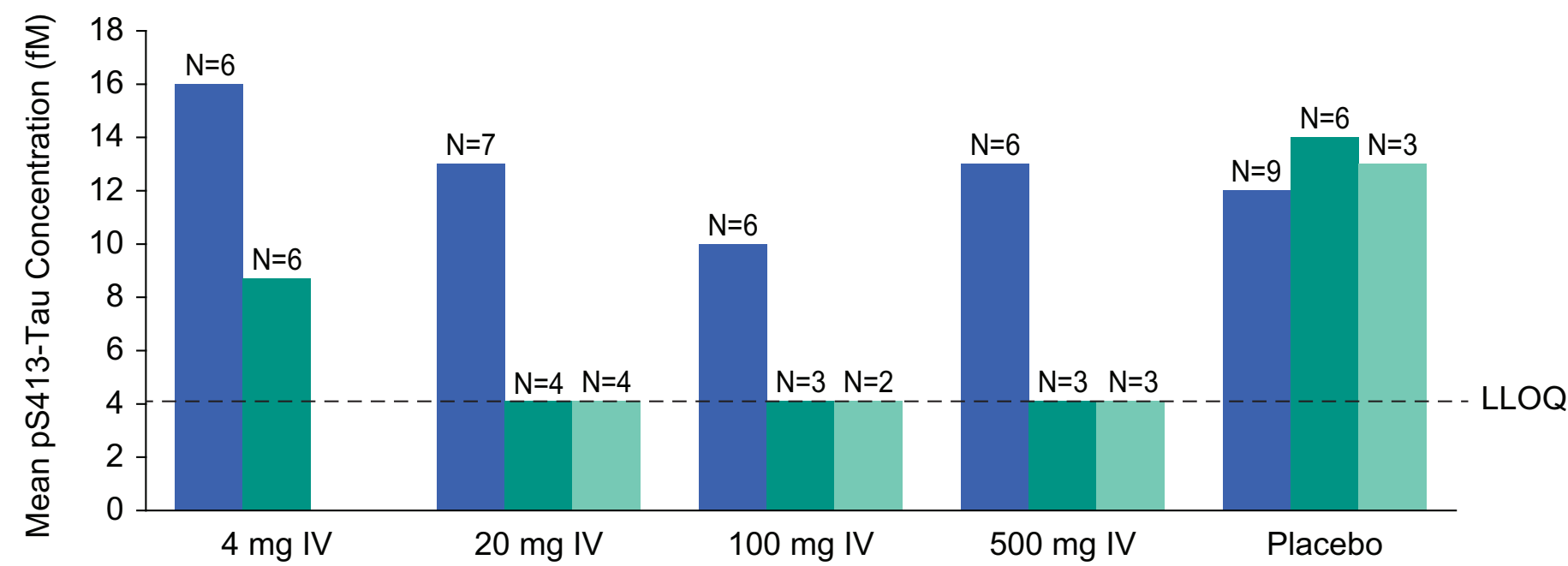


CSF vs serum concentrations

- In Study 1, the geometric mean CSF-to-serum MK-2214 concentration percentages were 0.26% on Day 28 after a single dose of 200 mg IV and 0.31% on Day 28 after a single dose of 200 mg SC
- In Study 3, the geometric mean CSF-to-serum MK-2214 concentration percentages ranged from 0.29% to 0.45% on Day 28 after single IV doses from 4 mg to 500 mg

CSF pS413 tau concentrations in Study 3

- Reductions in CSF pS413 tau concentrations were consistent with high potency and near-saturating levels of target engagement



Conclusions

- MK-2214 has a favorable pharmacological profile as an antibody to slow the progression of Alzheimer's disease
 - Long half-life of approximately 80 days
 - Single dose administration in healthy participants, and multiple dose administration in participants with mild-to-moderate cognitive impairment, well-tolerated at doses that produced near-saturating binding of free pS413 tau
- An ongoing phase 2 trial is evaluating MK-2214 for slowing the progression of tau spreading in people with early Alzheimer’s disease (NCT07033494)

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