Study Design of a Multiple Ascending Intravenous Dose Study Evaluating the Safety, Tolerability, and Pharmacokinetics of VY7523 in Participants with Early Alzheimer's Disease

Monroe Butler, Naomi Muse, Sarah Piantedosi, Thrusha Chauhan, Beth Mellen, Charlotte Chung, Raj Rajagovindan, Vik Arora, Albena Patroneva, Maurice Emery, Alfred Sandrock, Toby A. Ferguson and Elena Ratti

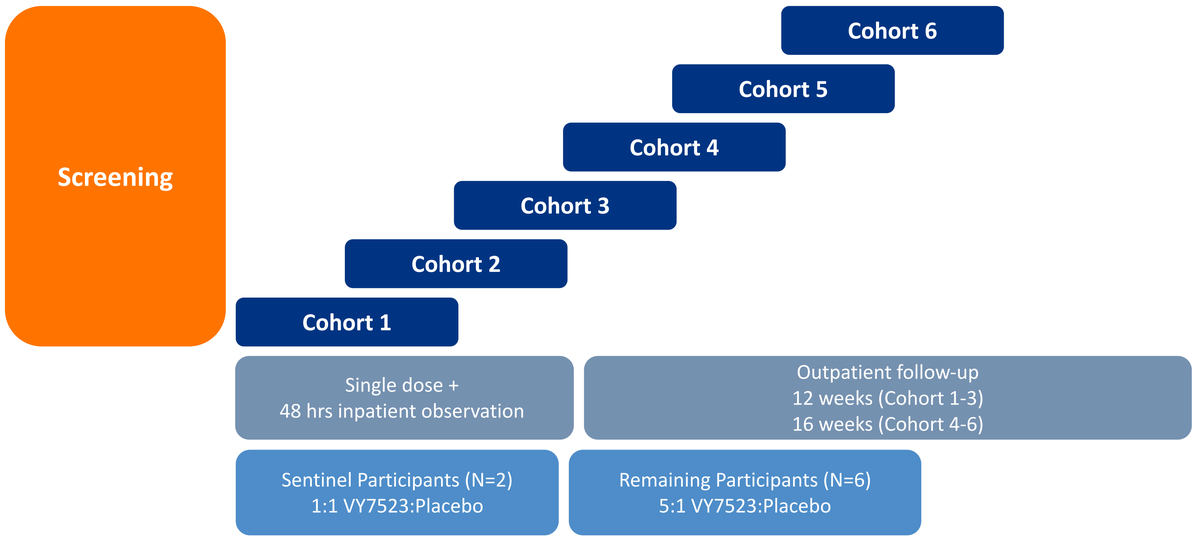
Voyager Therapeutics Inc., Lexington, MA, USA

BACKGROUND

- Alzheimer's disease (AD) is a neurodegenerative disease characterized by progressive cognitive and functional decline and accumulation of brain amyloid and pathological tau
- Tau spreading across brain regions correlates with cognitive decline and disease progression
- No tau targeting therapies are currently approved
- VY7523 is a C-terminal targeting humanized immunoglobulin gamma 4 (IgG4) monoclonal antibody designed to inhibit the spread of human pathological tau protein, potentially leading to the prevention of AD progression
- A single ascending dose (SAD) study in healthy adult participants was recently completed and supports continued development of VY7523

FIRST-IN-HUMAN STUDY OF VY7523

Single Ascending Dose (SAD) Study in Healthy Adult Participants



Population

- Up to 48 healthy adult participants
- BMI 18-32 kg/m2
- Age 18-75 years

Objectives

- Safety, tolerability, and pharmacokinetics (PK) of 6 single IV ascending doses of VY7523

Primary Endpoints

- Incidence of treatment-emergent adverse events (TEAEs)
- Incidence of clinically relevant changes from baseline in vital signs, electrocardiograms (ECGs) and clinical laboratory parameters

Secondary Endpoints

- Serum VY7523 PK parameters
- Cerebrospinal fluid (CSF) concentration of VY7523
- Incidence of treatment emergent anti-drug antibodies (ADAs)

Administration

- Intravenous (IV), single dose, 6 dose levels

Sites

- 1 site (Clinical Pharmacology Phase 1 Unit)

SAD SAFETY SUMMARY

- No deaths, SAEs or severe AEs; no infusion related reactions (IRRs)
- All TEAEs were mild to moderate in severity; no trends in AE severity across the ascending doses
- No clinically significant changes in Labs (chemistry, hematology, coagulation), vital signs (including orthostatic testing), ECG and urinalysis
- No TEAEs leading to treatment discontinuation
- 55 TEAEs overall reported by 17 (35%) participants [11 (31%) treated; 6 (50%) placebo]
- Most frequent TEAE overall was headache, experienced by 4 (8%) participants [2 (6%) treated; 2 (17%) placebo]
- 5 TEAEs in treated participants (dizziness, nausea, headache and 2 events of chest pain) considered related to study product by Investigator

PHARMACOKINETICS SUMMARY

- VY7523 demonstrated dose proportional, linear and predictable pharmacokinetics (PK)
  - Clearance and volume of distribution typical of monoclonal IgG4 antibodies
  - Proportional increases in exposure over the range of doses assessed
  - Mean half-life ranged between 22 to 29 days which supports monthly dosing
  - Demonstrated CNS penetrance with %CSF-to-serum of approx. 0.3% typical of IgGs
- Unremarkable immunogenicity profile following single dose
  - One possible treatment emergent ADA observed – not associated with neutralizing antibody formation or with impact on PK or safety

MAD STUDY OBJECTIVES AND ENDPOINTS (NCT06874621)

Multiple Ascending Dose (MAD) Study of VY7523 in Early Alzheimer's Disease (AD)

	OBJECTIVES	ENDPOINTS
1	**Primary**	
	To characterize VY7523 safety and tolerability	• Incidence of treatment-emergent adverse events (TEAEs) • Clinically significant changes from baseline vital signs, electrocardiograms (ECGs) and clinical and laboratory parameters
2	**Secondary**	
	To characterize VY7523 pharmacokinetics (PK) in serum and determine cerebrospinal fluid (CSF) concentrations	• Serum concentrations at specified timepoints • PK parameters • CSF concentrations
	To evaluate VY7523 ability to prevent the spread of pathologic tau	• Changes from baseline in the standardized uptake value ration (SUVR) using tau-positron emission tomography (PET)
	To evaluate VY7523 immunogenicity	• Incidence of treatment emergent anti-drug antibodies (ADAs)

MAD STUDY OUTLINE

- Multicenter, randomized, placebo-controlled, double-blind with 3 sequential cohorts (N~52):

Cohort 1 and Cohort 2

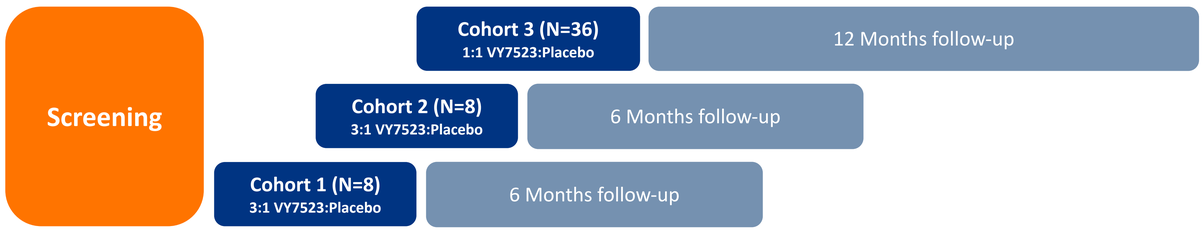
- 8 participants each
- Treatment-to-placebo randomization of 3:1
- 6 months duration post-randomization

Cohort 3

- 36 participants
- Treatment-to-placebo randomization of 1:1
- 12 months duration post-randomization

- Cohort 3 designed to assess preliminary efficacy based on effect on tau PET
- Administration: monthly intravenous (IV) infusions; conducted in US and Canada

MAD STUDY DESIGN



MAD STUDY POPULATION

- Age: 50-90 years
- Early AD:
  - Mild cognitive impairment (MCI) due to AD or mild AD defined by:
    - NIA-AA core clinical criteria
    - Global Clinical Dementia Rating (CDR) score of 0.5 or 1
    - CDR Memory Box sub-score ≥ 0.5
    - Mini-Mental State Examination (MMSE) range 18-30 in Cohort 1-2 and 22-30 in Cohort 3
    - History of memory decline with gradual onset and slow progression over at least 6 months before Screening
  - Evidence of pathology consistent with AD:
    - Amyloid positivity in all participants
    - Tau-positron emission tomography (PET) positivity in Cohort 3
- Presence of reliable informant/caregiver
- Concomitant medications:
  - AD treatment naïve or on stable dose of AD medications (except approved AD disease-modifying or anti-amyloid therapies) for at least 8 weeks before Screening
- Previous participation in clinical trials:
  - If study blind has been broken and the participant was known to be on placebo
  - Participation in a clinical drug trial or device prior to 30 days (or 5 half-lives, whichever is longer and 3 months for a biologic) of Screening
    - Cohort 1 and 2: participants could have received AD disease-modifying therapies (except gene therapies) 6 months to 1 year before Screening
    - Cohort 3: participants naïve to AD disease modifying therapies

23 study locations in:

- California
- Connecticut
- Florida
- Georgia
- New Jersey
- North Carolina
- Pennsylvania
- Ontario
- Quebec

Detailed list available at clinical trials.gov

SUMMARY AND CONCLUSIONS

- The MAD Study is ongoing; enrollment is complete
- This study will inform on the preliminary safety profile, PK, immunogenicity and tau PET data related to the ability of VY7523 to prevent the spread of pathological tau in MCI-AD and mild AD dementia