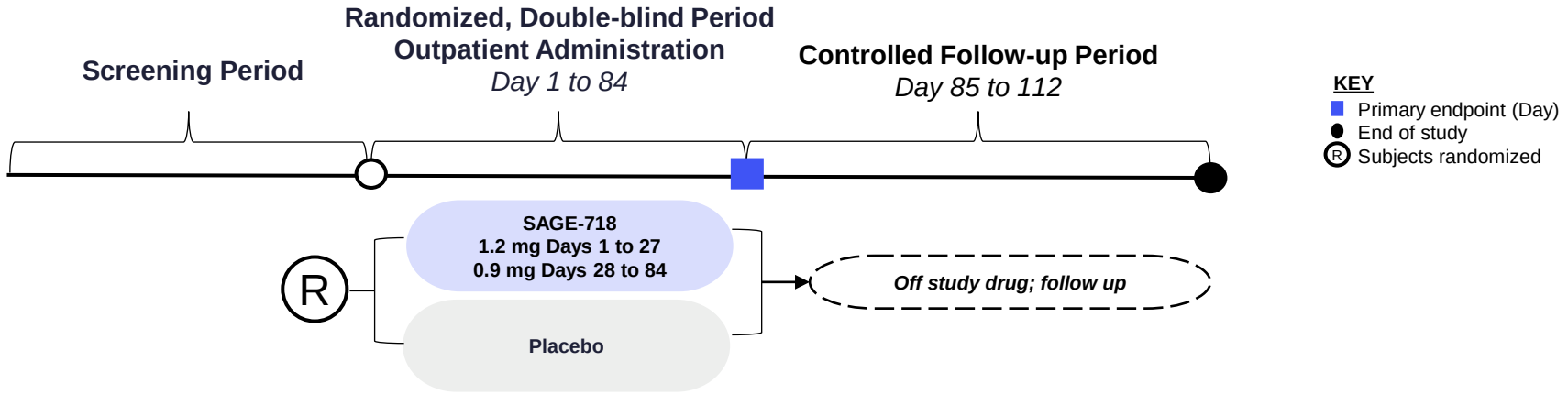
Sage Therapeutics®

SAGE-718 Ongoing Study Designs

March 2022

DIMENSION Study - SAGE-718

Placebo-controlled study in patients with early Huntington's disease



STUDY OVERVIEW

Status	Enrolling
Indication	Huntington's Disease Cognitive Impairment
Phase	Phase 2
Arms	Double-blind, randomized: 1:1 • SAGE-718, placebo
Dosing Regimen	1.2 mg oral daily from days 1 to 27; 0.9 mg oral daily from days 28 to 84

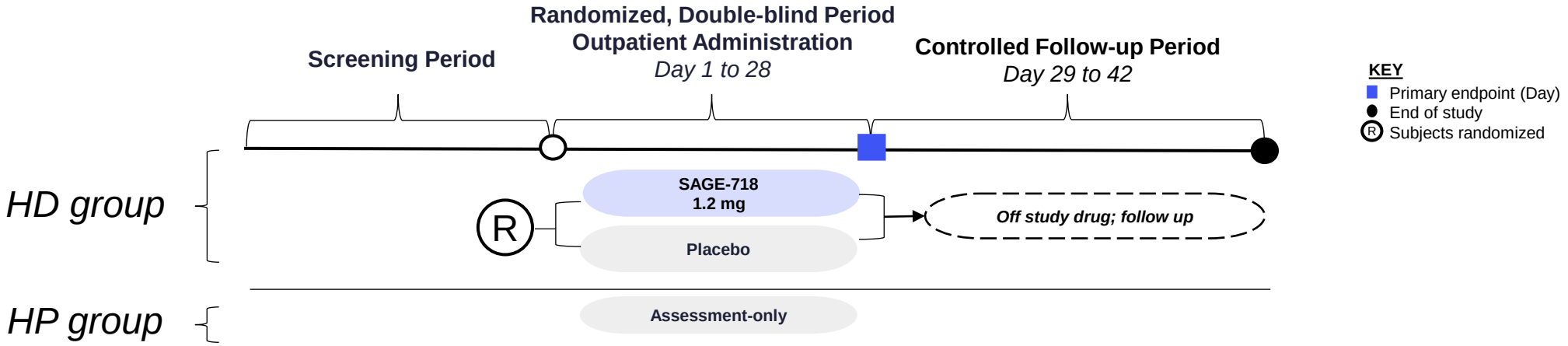
Objectives	• To evaluate the effect of SAGE-718 on cognitive performance in participants with HD • To evaluate the effect of SAGE-718 on daily function in participants with HD
Primary Endpoint	• Change from baseline in Composite score of the Huntington's Disease Cognitive Assessment Battery (HD-CAB)
Key Secondary Endpoint	• UHDRS Independence Scale

Inclusion Criteria	• Be at least 25 years old but no older than 65 years of age at Screening
	• Meet all the following criteria for HD:
	  • Genetically confirmed disease with huntingtin gene CAG expansion ≥36
	  • UHDRS-Total Functional Capacity (TFC) score >6 and <13
	  • No features of juvenile HD
	• Score <26 on the Montreal Cognitive Assessment (MoCA) at screening
	• Be willing to invite a study partner, if available, who is reliable, competent, and at least 18 years of age to participate in the study

Exclusion Criteria	• Have participated in a previous clinical study of SAGE-718, have participated in a previous gene therapy study, or have received study treatment in any other drug, biologic, or device trial within 180 days or 5 half-lives (whichever is longer), unless the patient participated solely in the placebo arm of the study • Have a diagnosis of an ongoing neurodegenerative condition other than HD, including but not limited to, Alzheimer's Disease, vascular dementia, dementia with Lewy bodies, or Parkinson's Disease

SURVEYOR Study - SAGE-718

PBO-controlled study in patients with early HD, with Healthy Participant (HP) Comparator Arm



STUDY OVERVIEW

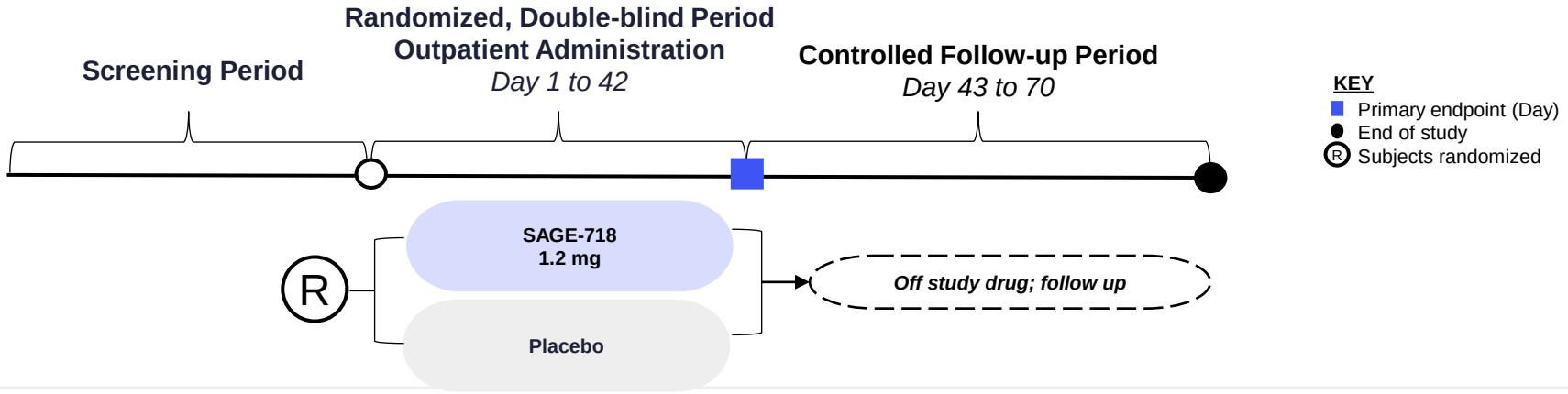
Status	Start-up	**Objectives**	• To assess the magnitude of the baseline difference between participants with early Huntington's Disease (HD) and healthy participants (HP) with respect to measures of cognitive performance. • To evaluate the effect of SAGE-718 on cognition and functioning outcomes in participants with HD
Indication	Huntington's Disease Cognitive Impairment	**Primary Endpoint**	• Baseline measures of the Huntington's Disease Cognitive Assessment Battery (HD-CAB) cognitive composite score.
Phase	Phase 2	**Secondary Endpoints**	• Change from Baseline to Day 28 on HD-CAB, VRFCAT, other endpoints. • Safety and tolerability of SAGE-718

Arms	Double-blind, randomized: 1:1 (HD)
	• SAGE-718, placebo
	Assessment-only comparator arm (HP)
		Inclusion Criteria (HD Participants)	• Be at least 25 years old but no older than 65 years of age at Screening
			• Meet all the following criteria for HD:
			  • Genetically confirmed disease with huntingtin gene CAG expansion ≥36
			  • UHDRS-Total Functional Capacity (TFC) score >6 and <13
			  • No features of juvenile HD
			• Score <26 on the Montreal Cognitive Assessment (MoCA) at screening
			• Be willing to invite a study partner, if available, who is reliable, competent, and able to participate in the study

Dosing Regimen	1.2 mg oral daily	**Exclusion Criteria (HD Participants)**	• Have participated in a previous clinical study of SAGE-718, have participated in a previous gene therapy study, or have received study treatment in any other drug, biologic, or device trial within 90 days or 5 half-lives (whichever is longer), unless the patient participated solely in the placebo arm of the study • Have a diagnosis of an ongoing neurodegenerative condition other than HD, including but not limited to, Alzheimer's Disease, vascular dementia, dementia with Lewy bodies, or Parkinson's Disease

PRECEDENT Study - SAGE-718

Placebo-controlled study in patients with MCI due to Parkinson's Disease



STUDY OVERVIEW

Status	Start-up
Indication	Mild Cognitive Impairment (MCI) due to Parkinson's Disease
Phase	Phase 2
Arms	Double-blind, randomized: 1:1 • SAGE-718, placebo
Dosing Regimen	1.2 mg oral daily
Objectives	• To evaluate the effect of SAGE-718 on cognitive performance in participants with Parkinson's Disease (PD) Mild Cognitive Impairment (MCI) • To evaluate the safety and tolerability of SAGE-718 oral capsule in participants with PD-MCI
Primary Endpoint	• Change from Baseline to Day 42 in the Wechsler Adult Intelligence Scale-IV (WAIS-IV) Coding test
Key Secondary Endpoint	• Proportion of participants experiencing treatment emergent adverse events (TEAEs) and severity of TEAEs. • Number of participants who withdraw due to adverse events (AEs).

Inclusion Criteria	• Be between the ages of 50 and 75 at Screening
	• Meet all the following criteria for PD-MCI:
	  • Have a confirmed diagnosis of idiopathic PD according to 2015 MDS clinical diagnostic criteria, and
	  • Meet MDS Task Force Criteria for MCI in PD (excluding requirement for UK PD Brain Bank diagnostic criteria).
	• For participants meeting Level 1 PD-MCI criteria, have a MoCA score of 20 to 25 (inclusive) at Screening
	• For participants meeting Level 2 PD-MCI criteria, have a MoCA score of 18 to 25 (inclusive) at Screening
	• Meet criteria for modified Hoehn and Yahr Stage I to III (mild to moderate motor severity) at Screening
	• Have stable motor symptoms for at least 4 weeks prior to Screening, in the opinion of the investigator

Exclusion Criteria	• Have participated in a previous clinical study of SAGE-718, have participated in a previous gene therapy study, or have received study treatment in any other drug, biologic, or device trial within 180 days or 5 half-lives (whichever is longer), unless the patient participated solely in the placebo arm of the study • Have a diagnosis of dementia of any etiology, including but not limited to: Dementia associated with PD (probable or possible), Dementia with Lewy Bodies, Alzheimer's Dementia, and Vascular Dementia • Have any parkinsonism other than PD, including secondary parkinsonism or atypical parkinsonism