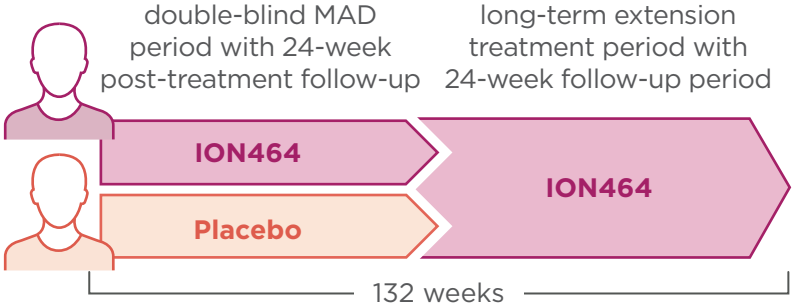
HORIZON Is a Phase 1 Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Intrathecally Administered ION464 in Adult Patients With Multiple System Atrophy (MSA)[1]

HORIZON

The Phase 1, multiple-ascending dose (MAD) clinical trial is currently underway[1]

Study objectives[1,2]:

To evaluate the safety and tolerability of an investigational RNA-targeted antisense medicine, ION464, in patients with MSA. This study will evaluate pharmacodynamics, pharmacokinetics, and biomarkers relevant to MSA.



This is a multicenter, multiple-ascending dose, two-part study of ION464. In **Part 1** participants will be randomized to receive a multidose regimen of ION464 or placebo for a period of 12 weeks, followed by a 24-week post-treatment follow-up period. Patients who are eligible[a] for **Part 2**, a long-term extension study, will receive ION464 for a period of 72 weeks with a 24-week post-treatment follow-up period.[1]

Select inclusion/exclusion criteria[1]:

- Patients aged 40 to 70 years
- Diagnosed with probable or possible MSA[b]
- SPECT consistent with neurodegenerative parkinsonism[c]
- Patients must be able to walk unassisted for ≥10 meters
- Patients with cognitive dysfunction are excluded[d]
- Patients with known family history of ataxia or parkinsonism and known genetic cause of ataxia or parkinsonism are excluded

Table: Key Clinical Endpoints[1]

Primary Endpoints	Number of Participants With Adverse Events
	Number of Participants With Serious Adverse Events
Secondary Endpoints	Changes From Baseline in Cerebrospinal Fluid Levels of Total α-Synuclein
	Serum Concentration of ION464
	Area Under the Concentration-Time Curve From Time Zero to Time of Last Measurable Concentration of ION464
	Maximum Observed Concentration of ION464
	Time to Reach Maximum Observed Concentration of ION464

For more study information scan here:

ION464 has not been evaluated for safety and efficacy by any regulatory authorities and is not indicated for the treatment of any disease.

[a]Participants who completed Part 1 of the study (including all planned doses of study drug, except those prematurely terminated from the study by the Sponsor due to tolerability or safety findings related to participation in the study) will be allowed to participate in Part 2 if they can provide consent or have a legally authorized representative, as appropriate and applicable, who can provide consent on their behalf to reconfirm their eligibility.[2] [b]Based on Gilman's criteria, of either parkinsonian or cerebellar type.[2] [c]Symmetric or asymmetric.[2] [d]Defined as having a Montreal Cognitive Assessment <25.[1]
SPECT, screening single-photon emissions computed tomography.

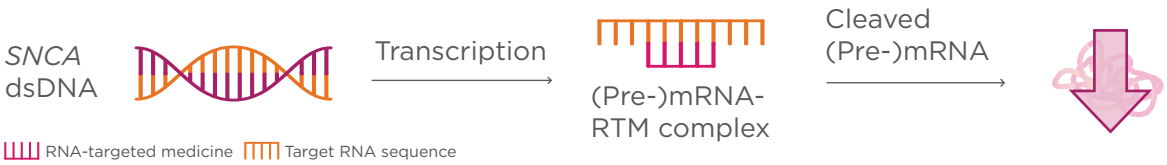
1. ClinicalTrials.gov. Accessed February 10, 2024. https://www.clinicaltrials.gov/study/NCT04165486/ 2. Ionis Pharmaceuticals. Data on file.

IONIS

ION464 Is an Investigational RNA-Targeted Medicine (RTM) That Has Been Designed to Reduce CNS Expression of α-Synuclein (α-Syn)[1-4]

HORIZON

Proposed ION464-Mediated Downregulation of α-Synuclein (*SNCA*)[1-4]



SNCA-targeting antisense RTM administration in animal models decreased *SNCA* mRNA and α-syn throughout the cortex and midbrain and prevented progression of α-syn–mediated pathology.[3]

Preclinical studies demonstrated *SNCA*-targeting antisense RTM administration restored striatal dopamine levels and dopaminergic cell function.[3]

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For more information or questions about participating sites, please contact us at **ionisHORIZONstudy@clinicaltrialmedia.com** or **(844) 748-5844.**[5]

LEADING THE RNA REVOLUTION

in the treatment of neurologic disease

With a history of major breakthroughs in RNA-targeted technology, Ionis' robust pipeline is filled with potential.

CNS, central nervous system; dsDNA, double-stranded DNA; mRNA, messenger RNA; *SNCA*, synuclein alpha.

1. Ionis Pharmaceuticals. The Ionis antisense pipeline. Accessed December 26, 2023. https://www.ionispharma.com/ionis-technology/antisense-pipeline/ 2. Dhuri K, et al. *J Clin Med.* 2020;9(6):2004. 3. Cole TA, et al. *JCI Insight.* 2021;6(5):e135633. 4. Bennett CF, et al. *Annu Rev Pharmacol Toxicol.* 2021; 61:831-852. 5. ClinicalTrials.gov. Accessed February 10, 2024. https://www.clinicaltrials.gov/study/NCT04165486/

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