Intranasal Fully Human Anti-CD3 mAb (“FORALUMAB”) Therapy to Enable Breakthroughs in Neuroinflammatory and Neurodegenerative Diseases



Nasdaq: TLSA

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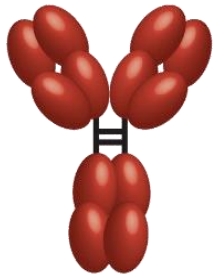
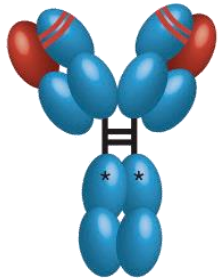
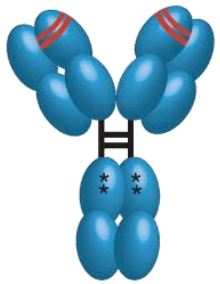
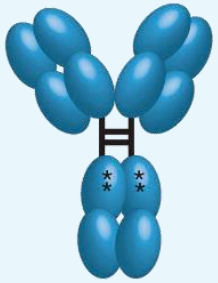
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Intranasal foralumab is investigational and is not approved for commercial use. Preliminary, early-stage and expanded-access findings may not predict results in larger or later-stage controlled trials. Any topline findings remain subject to completion of the full analysis. Open-label, uncontrolled and individual-patient observations do not establish efficacy. Cross-trial comparisons are subject to differences in study design, populations, endpoints and follow-up and do not establish comparative safety or efficacy. No assurance can be given that any product candidate will receive regulatory approval.

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The Evolution of CD3 Specific Monoclonal Antibodies

Foralumab is the Only Fully Human Anti-CD3 mAb in Clinical Trials

OKT3 / Muromonab	Otelixizumab	Teplizumab†	Foralumab
janssen | Johnson & Johnson	TOLERX Immune resolve. GSK	proventionbio sanofi	tiziana LIFE SCIENCES
			
Fully Murine	**Chimeric & Humanized**	**Humanized**	**Fully Human**
Solid organ transplantation immuno-suppression Via IV Delivery	Type 1 Diabetes, Psoriasis Via IV Delivery	Type 1 Diabetes (Stage 3) Via IV Delivery	MS, AD, MSA, ALS, TBI, SCI Via Intranasal Delivery
Withdrawn 2010 due to Cytokine Release Syndrome (CRS) & High immunogenicity	Not Approved, Side effects of Transient CRS & Lymphopenia	Approved 2022, Side effects of Leukopenia (21%), Lymphopenia (up to 73%)	No ADA or SAE seen to date (37.4 Patient Years of Dosing)

Rodent Origin Human Origin *Point Mutation

† Acquired by Sanofi for $2.9B

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Adapted from: Kuhn, Chantal, and Howard L. Weiner. "Therapeutic anti-CD3 monoclonal antibodies: from bench to bedside." Immunotherapy 8.8 (2016): 889-906.

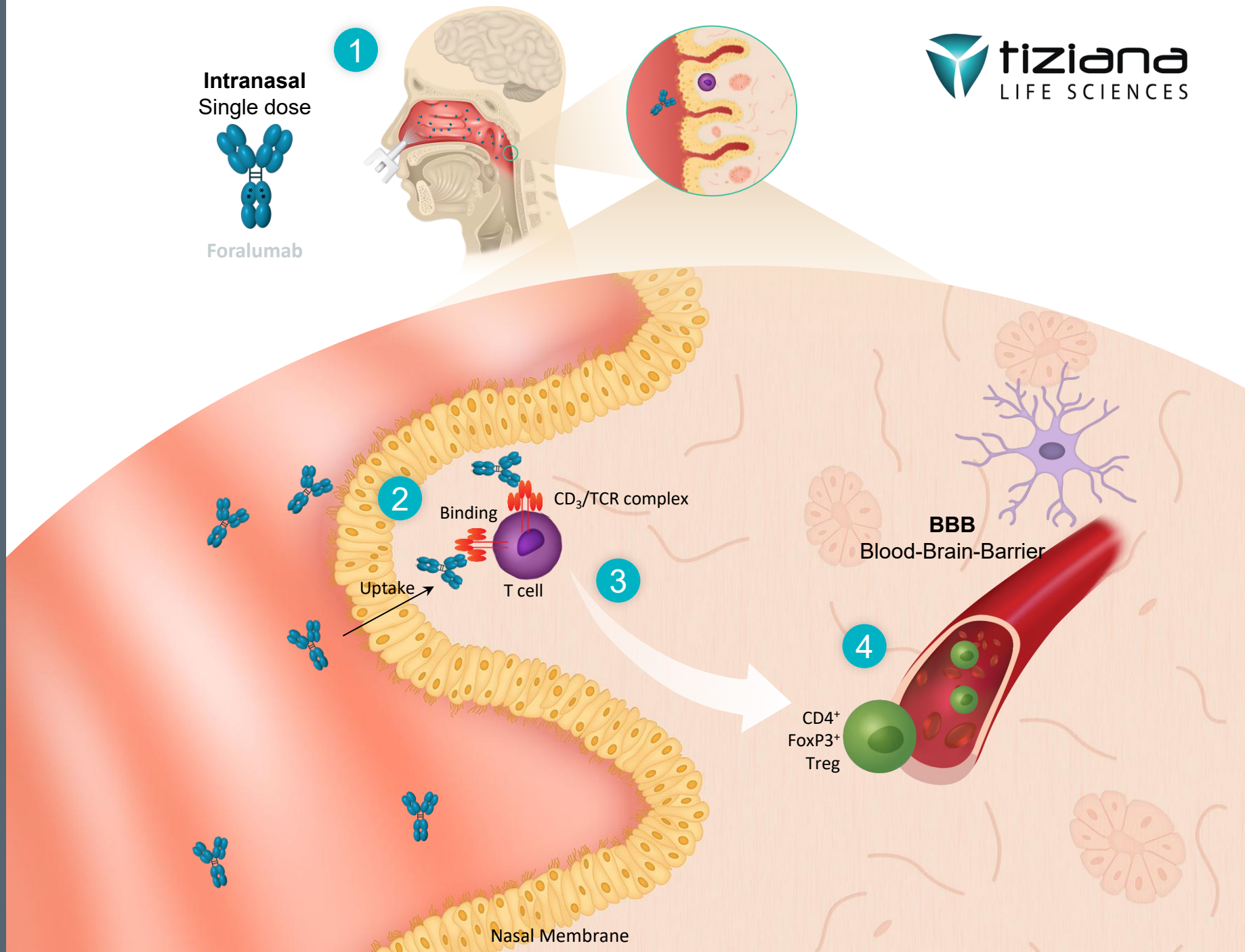
Foralumab: Mechanism of Action[1,2]

Patient inhales the antibody intranasally

Binding of foralumab to the T-cell receptor complex in cervical lymph node

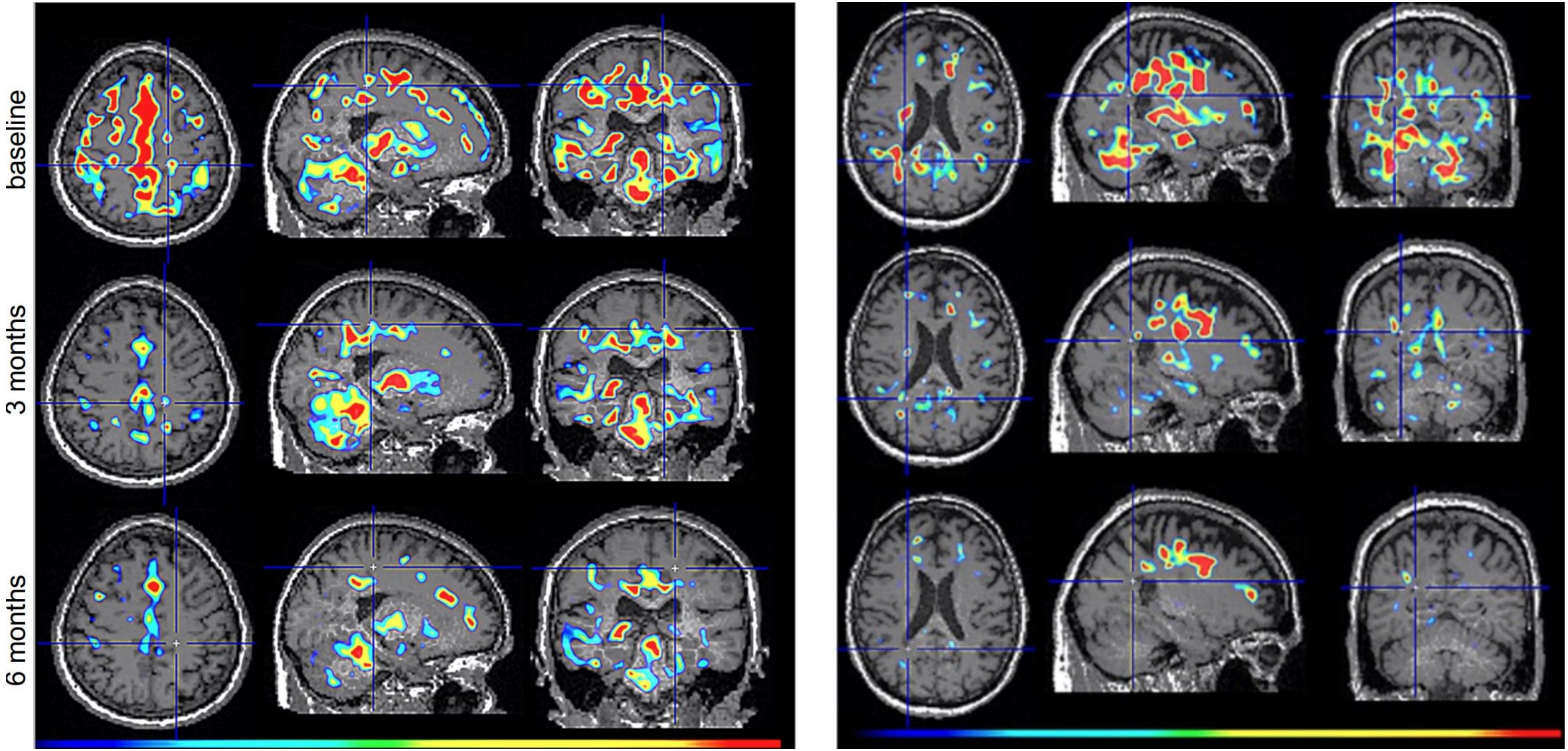
Tregs are then created and activated

These created Tregs then cross the blood brain barrier and regulate the activated innate immune system (microglia).



[1] https://www.pnas.org/doi/10.1073/pnas.2220272120
[2] https://www.pnas.org/doi/10.1073/pnas.2309221120

Intranasal Foralumab Reduces Neuroinflammation



Intranasal Foralumab Pipeline



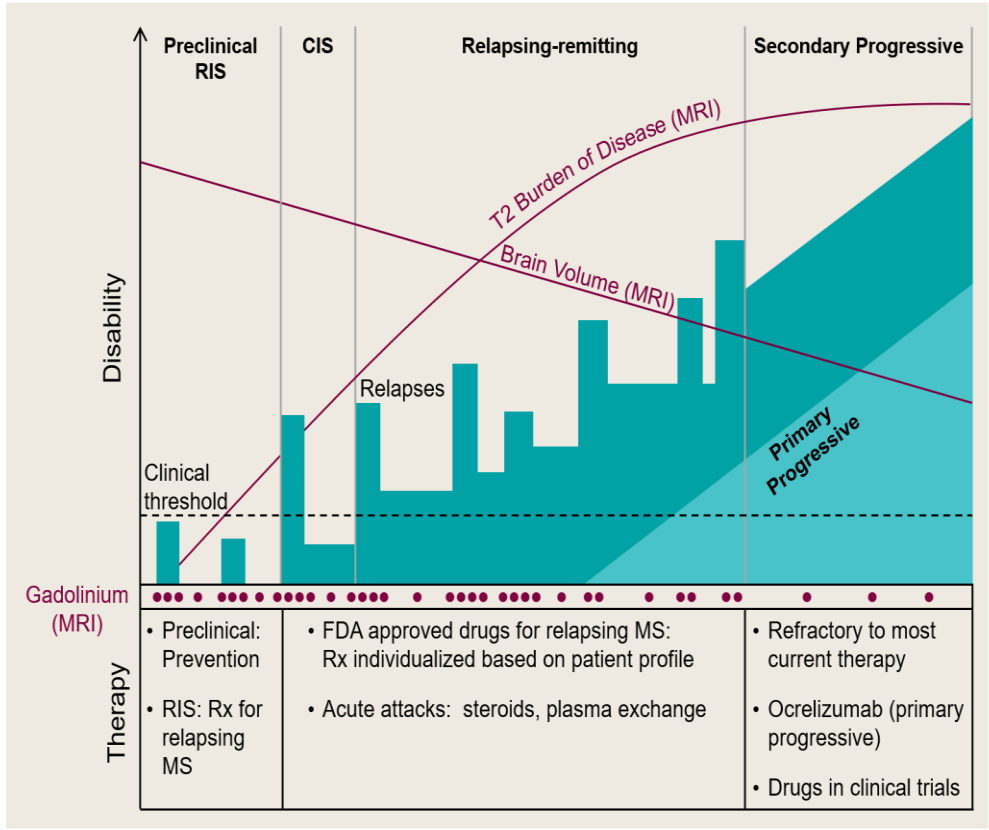
Non-active Secondary Progressive Multiple Sclerosis (na-SPMS)



Major Unmet Need in Non-Active Secondary Progressive Multiple Sclerosis

- No FDA-approved therapies specifically indicated for non-active SPMS
- Patients with progression independent of relapses (PIRA) remain in need of effective therapy
- ~25% of RRMS patients progress to SPMS; substantial portion become non-active
- Fatigue is a major symptom impacting quality of life and daily function
- Current treatments primarily target active/relapsing disease (e.g., Ocrelizumab)
- Intranasal foralumab uniquely targets microglial-driven neuroinflammation and PIRA

Stages of Multiple Sclerosis



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INFORM-MS TOPLINE DATA

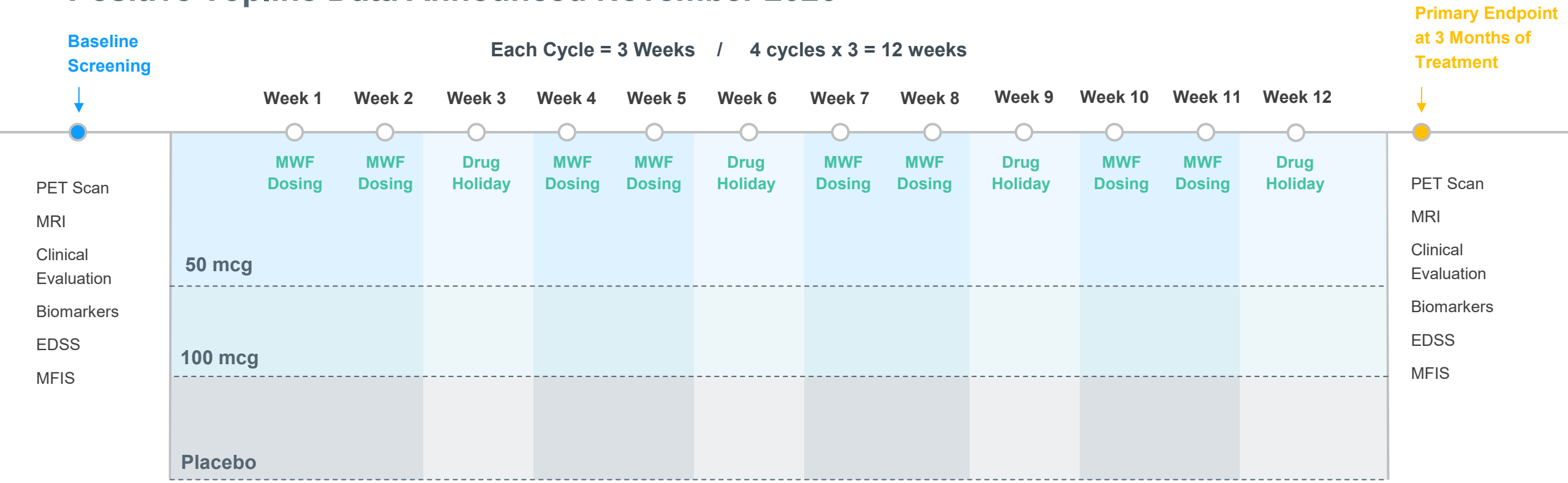
Phase 2 Placebo Controlled, Double Blind Trial of Intranasal Foralumab Confirms Results of EA Program

Non-active Secondary Progressive Multiple Sclerosis (na-SPMS)



Non-Active Secondary Progressive MS: Phase 2a:

Intranasal Foralumab Dosing (n=48); Double-Blind, Placebo-Controlled
Positive Topline Data Announced November 2026

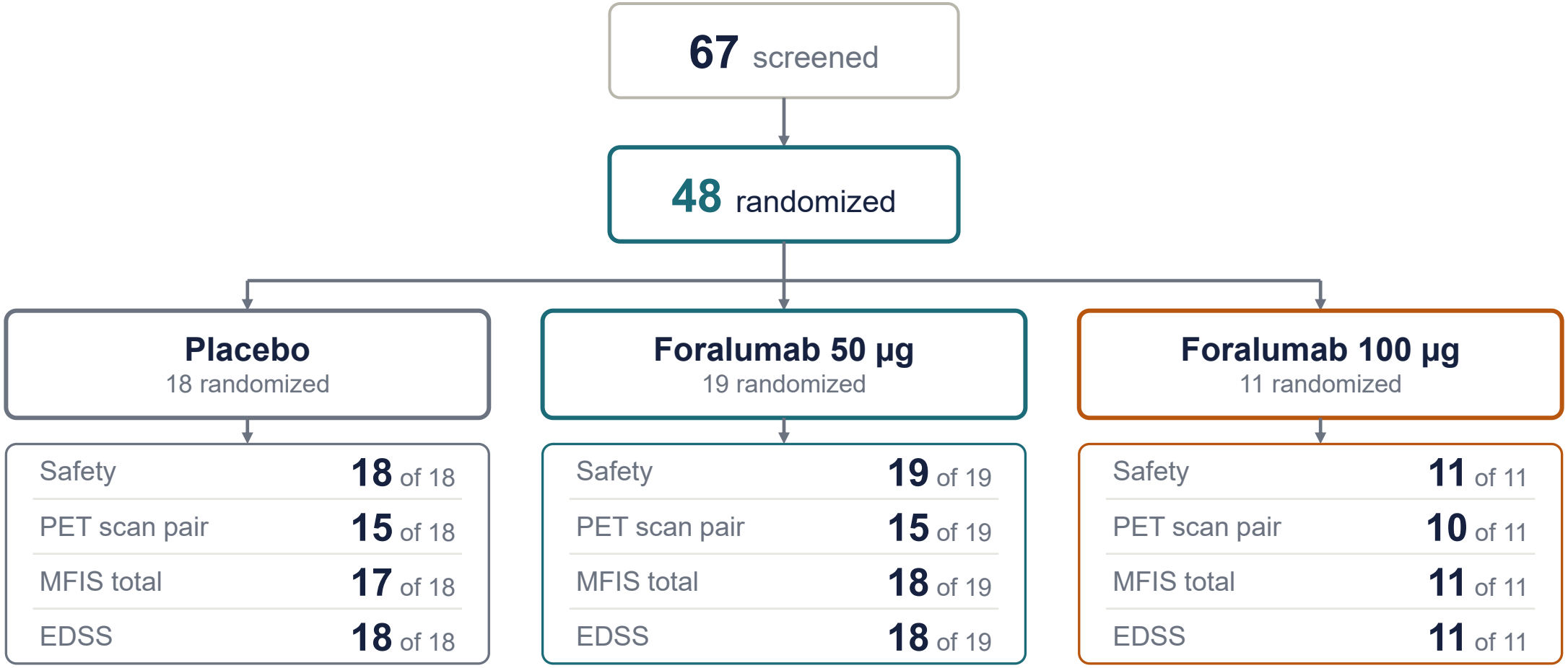


Sites Enrolled:

HARVARD MEDICAL SCHOOL
BRIGHAM AND WOMEN'S HOSPITAL
Jefferson Thomas Jefferson University
Yale UNIVERSITY
UNIVERSITY OF MASSACHUSETTS AMHERST 1863
JOHNS HOPKINS UNIVERSITY
University at Buffalo
Cornell University

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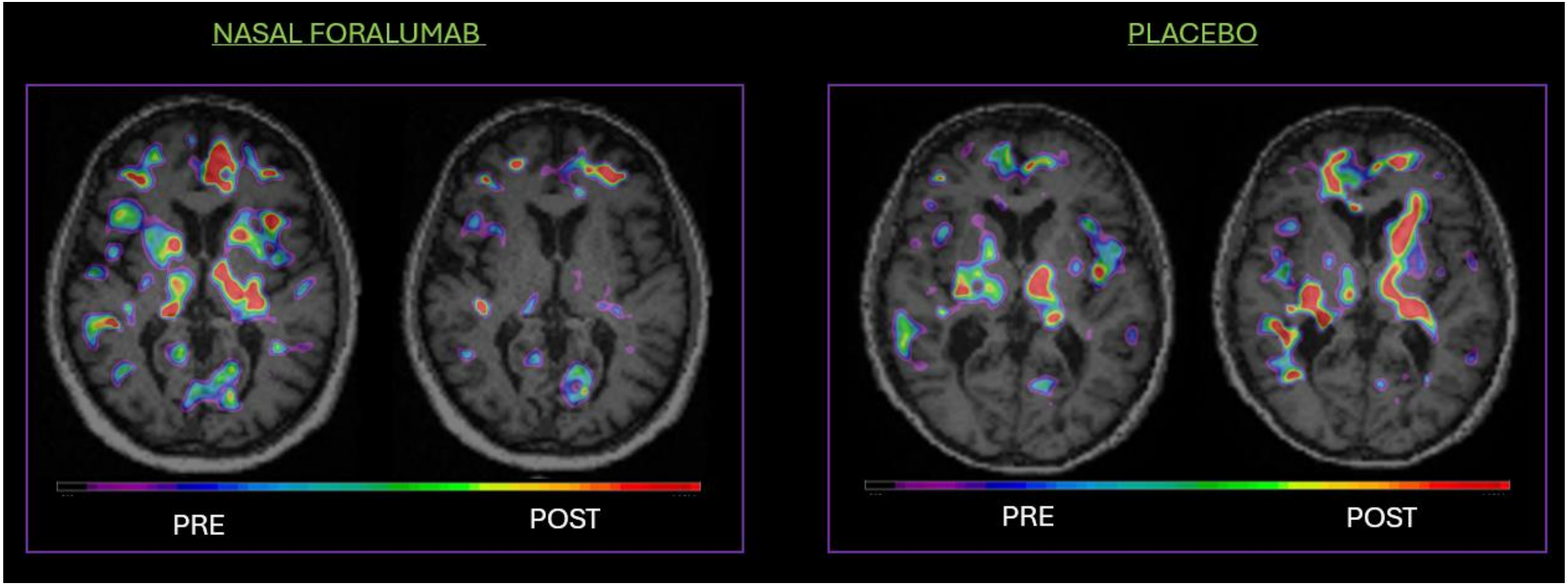
INFORM-MS: Participant Flow and Evaluable Data



All participants (48) Safety 48 · PET scan pair 40 · MFIS total 46 · EDSS 47

INFORM-MS: Neuroinflammation Was Statistically Significantly Reduced

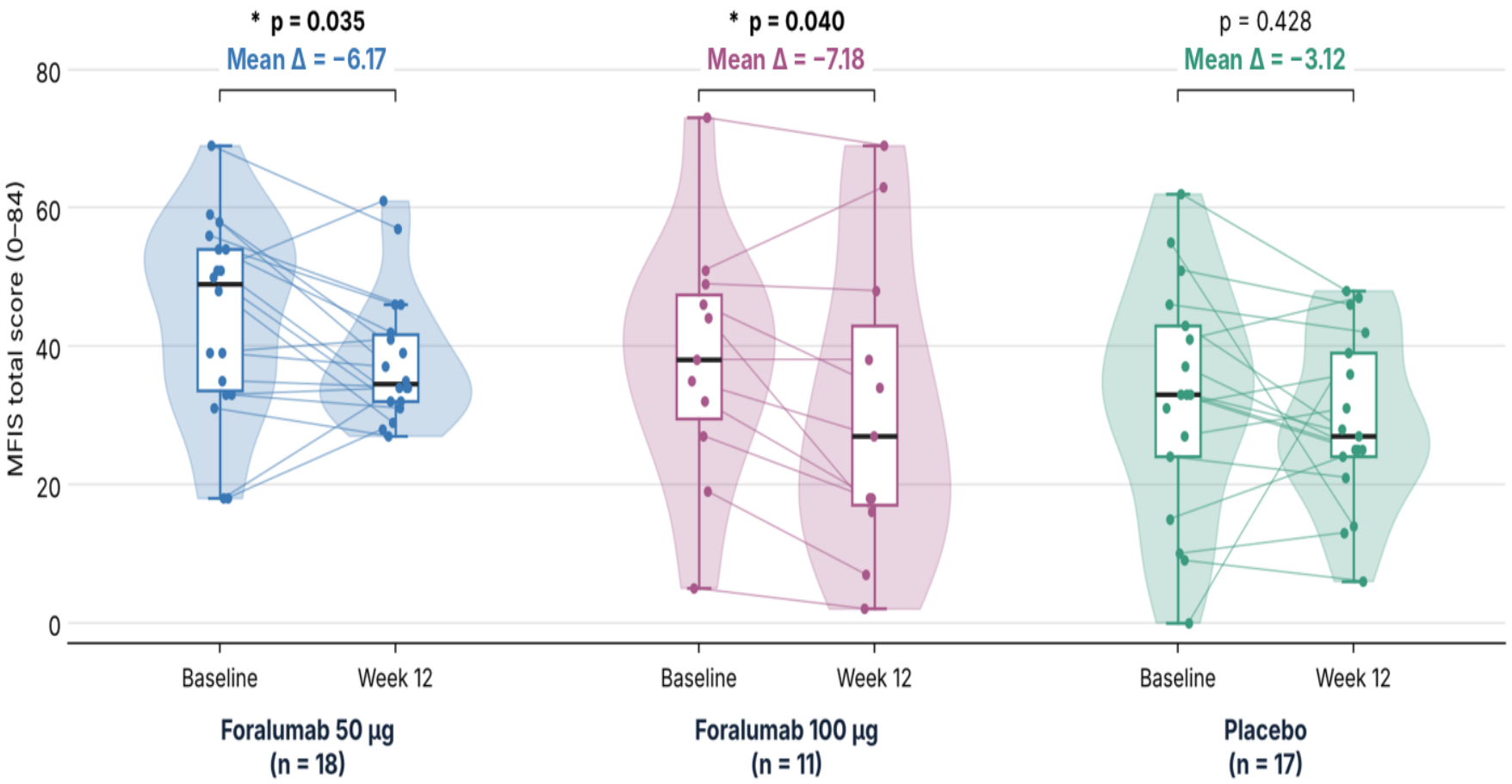
On ANCOVA analysis, [^{18}F]PBR06-TSPO PET demonstrated a significant reduction in globally normalized White Matter SUVR (p=0.0168) after 12 weeks of treatment between the 50 ug nasal foralumab treatment arm and placebo.



Examples of individualized patient mGALP z-score maps following treatment with 50mcg of nasal foralumab and with placebo

INFORM-MS: Nasal Foralumab Reduced Fatigue (Lowered Modified Fatigue Impact Scores; “MFIS”)

MFIS total score, baseline to Week 12





Multiple Sclerosis and Related Disorders 35 (2019) 158–163

Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

journal homepage: www.elsevier.com/locate/msard

Clinical trial

Minimally important difference of the fatigue severity scale and modified fatigue impact scale in people with multiple sclerosis

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ARTICLE INFO

Key words:
Multiple Sclerosis
Fatigue
Minimally important difference
Fatigue Severity Scale
Modified Fatigue Impact Scale

ABSTRACT

Background: Fatigue is a common and debilitating symptom of Multiple Sclerosis (MS); however, it is unknown what constitutes a clinically significant change in fatigue. Establishing the minimally important difference (MID) of fatigue outcome measures can inform the interpretation of changes in fatigue by estimating the level of change that is considered clinically relevant.
Aim: Determine the MID for the Fatigue Severity Scale (FSS) and Modified Fatigue Impact Scale (MFIS) in people with MS.
Methods: This cross-sectional study collected information on self-reported fatigue (FSS and MFIS) and quality of life (EQ-5D and MS Impact Scale 29) through an online survey. Anchor-based methods were used to estimate MID, and ordinal logistic regression models were used to determine the difference in fatigue that would predict a significant effect on quality of life.
Results: 365 people with MS (81.9% female, 69.3% relapsing-remitting MS, mean age 46.2 ± 11.6 years, mean time since diagnosis 9.6 ± 8.7 years) responded to the survey. MID estimates for the FSS and MFIS ranged from 0.45–0.88 and 3.86–8.11 respectively, accounting for 6.4–12.6% of maximum FSS score and 4.6–9.7% of maximum MFIS score.
Conclusions: MID estimates derived from this study indicate that a difference of at least 0.45 points on the FSS or 4 points on the MFIS constitutes a clinically significant difference in fatigue. Therefore, these estimates represent a threshold value which can be used to interpret changes in the FSS and MFIS over time or in response to an intervention.

1. Background

Fatigue is a complex symptom of Multiple Sclerosis (MS) that is reported in 70% of the population (Lerdal et al., 2007; Hadjimichael et al., 2008; Rooney et al., 2019), and is often perceived as the most debilitating symptom which significantly impacts upon quality of life (QoL) (Bakshi, 2003). Fatigue may be described as exhaustion, a lack of energy, or overwhelming tiredness which can occur at rest (Mills and Young, 2008), and is commonly defined as “a subjective lack of physical and/or mental energy that is perceived by the individual or caregiver to interfere with usual and desired activities” (Multiple Sclerosis Council for Clinical Practice Guidelines, 1998). Due to the subjective nature of fatigue, patient reported outcome measures (PROMs) are commonly used to assess the severity and impact of fatigue, and two of the most frequently used in studies involving people with MS are the Fatigue Severity Scale (FSS) and the Modified Fatigue Impact Scale (MFIS) (Blikman et al., 2013; Heine et al., 2015; van den Akker et al., 2016).

Interpreting changes in PROMs is important when evaluating the effectiveness of interventions, and it is recognised that conventional statistical analysis provides little information regarding the clinical significance of changes observed following an intervention (Goodman, 1999). However, the interpretation of meaningful changes in fatigue can be enhanced by establishing the minimally important difference (MID) for fatigue PROMs (Revicki et al., 2006). MID, which is defined as “the smallest difference in the outcome of interest which patients perceive as beneficial” (Jaeschke et al., 1989), is a threshold value used to interpret whether a change in an outcome is important from the patient's perspective (Guyatt et al., 2002). MID can be determined using anchor-based or distribution-based methods – the

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https://doi.org/10.1016/j.msard.2019.07.028
Received 26 February 2019; Received in revised form 29 June 2019; Accepted 27 July 2019
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MFIS: * p < 0.05 is a within-arm paired t-test; no treatment-versus-placebo comparison is implied (n = 18, 11, 17 with a complete pair).
https://www.msard-journal.com/article/S2211-0348(19)30319-0/fulltext Rooney et al. 2019

INFORM-MS: Topline Results Overview

Both primary endpoints were met (TSPO-PET Neuroinflammation and safety). Secondary MFIS endpoint also met.

PET

Microglial Activation

50 µg vs Placebo

p = 0.0168

Statistically significant reduction in TSPO-PET signal demonstrating decreased microglial activation.

In an exploratory dose arm (100 µg) no significant change in PET signal. Fewer patients enrolled in this arm. Prior data with 250 µg also showed less immunomodulatory effects than the 50 µg dose.

FATIGUE (MFIS)

Clinically Meaningful

Change from baseline → Week 12

−6.17 / −7.18

50 µg (p=0.035) · 100 µg (p=0.040)

Within-arm paired improvements at both doses.

Fatigue is a key driver of quality of life in progressive MS.

SAFETY

Clean Profile

Both doses

No Drug Related SAEs

The first non-invasive anti-CD3 therapy shown to be safe and well tolerated

No study-drug related serious adverse events.

All 48 participants completed treatment

No discontinuations due to AEs.

All 48 participants completed the 12-week treatment period · Both doses safe and well-tolerated · Supports advancement toward registrational path

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Positive Results With Nasal Foralumab in Expanded Access Program

No Toxicities

No treatment-related toxicities observed

No anti-drug antibodies (ADAs) detected in serum

TSPO PET

8 / 10

Patients Showed Reduced Neuroinflammation After 3 Months Treatment

Fatigue

6 / 10 Patients Improved After 6 Months Treatment

4 / 4 Patients Improved After 12 Months Treatment

EDSS

10 / 10 Patients Stabilized After 6 Months Treatment

3 / 4 Patients Improved After 12 Months Treatment



RESEARCH ARTICLE OPEN ACCESS

Nasal Foralumab for the Treatment of Progression Independent of Relapses in Patients With Nonactive Secondary Progressive Multiple Sclerosis

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Neurol Neuroimmunol Neuroinflamm 2026;13:e200543. doi:10.1212/NXI.0000000000200543

MORE ONLINE

Class of Evidence
Criteria for rating therapeutic and diagnostic studies
NPub.org/coe

Supplementary Material

Abstract

Background and Objectives

Progression independent of relapses (PIRA) is a major therapeutic challenge in multiple sclerosis (MS). Nasal anti-CD3 treats animal models of progressive MS by inducing regulatory T cells (Tregs) that suppress CNS inflammation and lessen clinical disease.

Methods

Ten patients with nonactive secondary progressive MS (naSPMS) that continued to progress on B-cell therapy were treated with nasal anti-CD3 (foralumab) for a minimum of 6 months in an open-label study. Safety monitoring included otolaryngology evaluation and neurologic assessments including Expanded Disability Status Scale (EDSS), MS Functional Composite, Modified Fatigue Impact Scale (MFIS), California Verbal Learning Test, and Low Contract Visual Acuity. MRI and microglial translocator protein (TSPO)-PET imaging with [F-18] PBR06 were conducted. Serum and CSF proteomic biomarkers and single-cell RNA sequencing of blood were performed to evaluate foralumab-induced immunomodulation. The end points of our study were safety, clinical effects, microglial signal, and immune measures.

Results

Our clinical observations were that all patients stabilized on EDSS scores and 3 of 4 patients treated continuously for 12 months had improvement on EDSS. Six of 10 patients had improvement in fatigue on the MFIS scale. There were no treatment-related serious adverse events or severe AEs, and no new T2 lesions were observed on MRI. There was a reduction in TSPO-PET signal over 6 months ($p < 0.05$). Changes in peripheral blood gene expression occurred as early as 3 months and affected antigen presentation, interferon responses, and regulatory pathways in multiple cell types including FoxP3+ Tregs, $CD4^+$ Tcm cells, $CD8^+$ Tem cells, $CD14^+$ and $CD16^+$ monocytes, and B cells. TGFβ expression was increased across multiple cell subsets.

Discussion

These findings identify a novel, nontoxic immune based therapy for the treatment for PIRA that acts by the induction of a regulatory immune responses and dampens microglial inflammation. Double-blind placebo-controlled trials are warranted to explore nasal foralumab for the treatment of naSPMS.

*These authors contributed equally to this work as co-first authors.

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The Article Processing Charge was funded by the authors.

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Multiple System Atrophy (MSA)



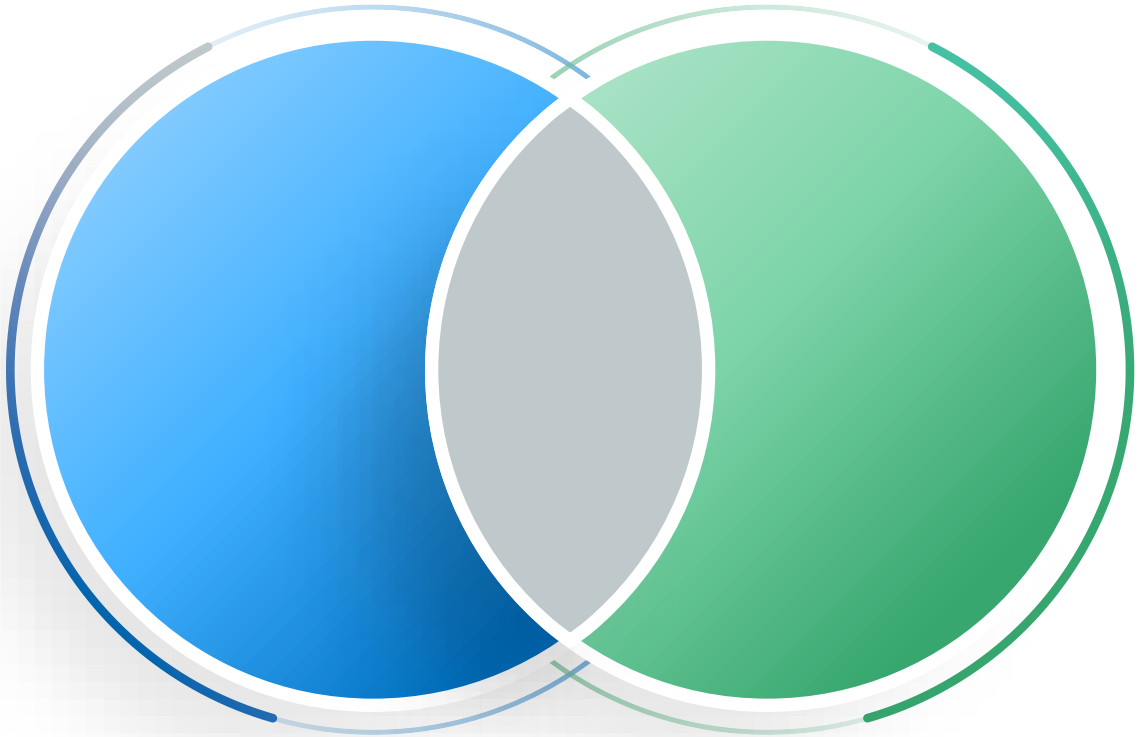
Multiple System Atrophy (MSA) Phase 2a Clinical Trial

MSA is a rapidly progressive neurological disorder. It is caused by degeneration or atrophy (shrinking) of nerve cells in several (or multiple) areas of the brain.

Classified as Orphan disease by the FDA

No FDA approved treatments available

Similar symptoms to Parkinson's disease so often misdiagnosed



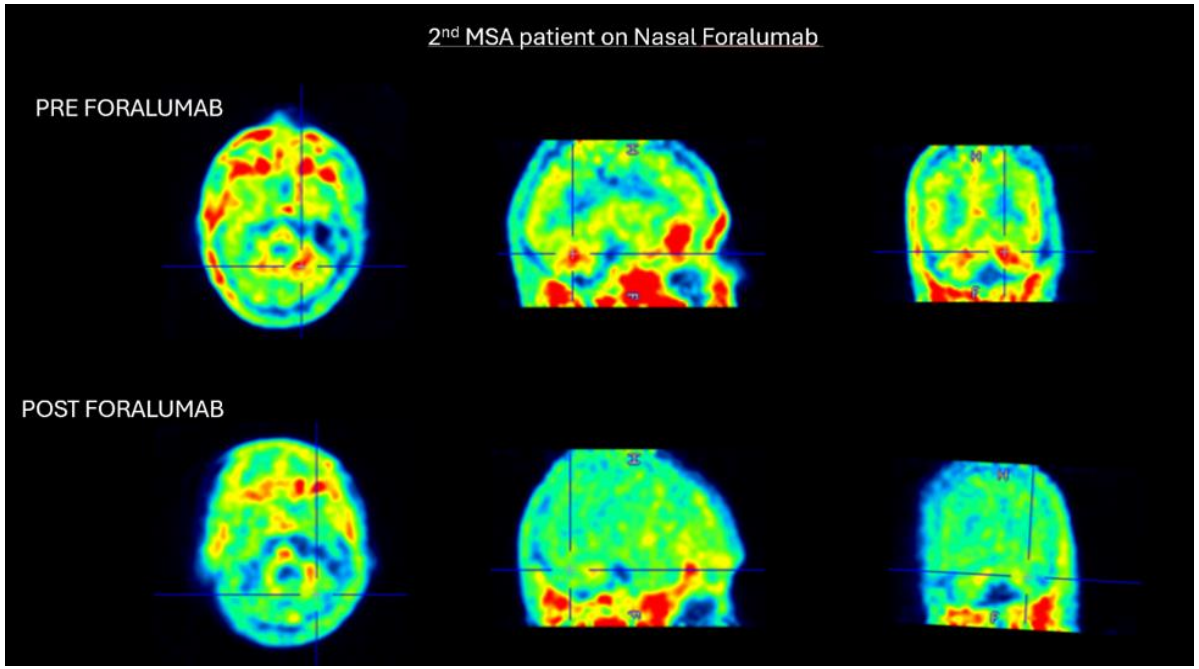
FDA Approved IND Q3 2025

3 Patients completed Phase 2 study

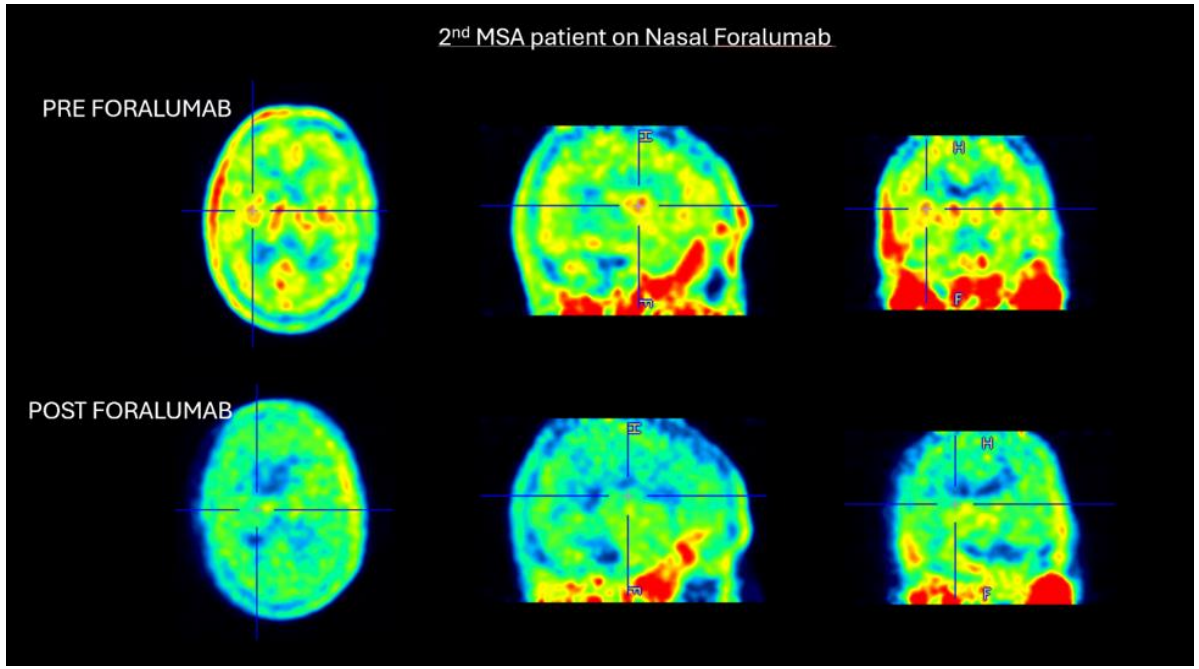
Trial will assess microglial activation and MSA clinical outcome measures

Multiple System Atrophy (MSA) Phase 2a Clinical Trial Ongoing Results

All Patients have shown similar quantitative reductions of approximately 35% in standardized uptake value (SUV) and 24% reduction in standardized uptake value ratio (SUVR)



Marked reduction in Cerebellar white matter uptake following nasal foralumab

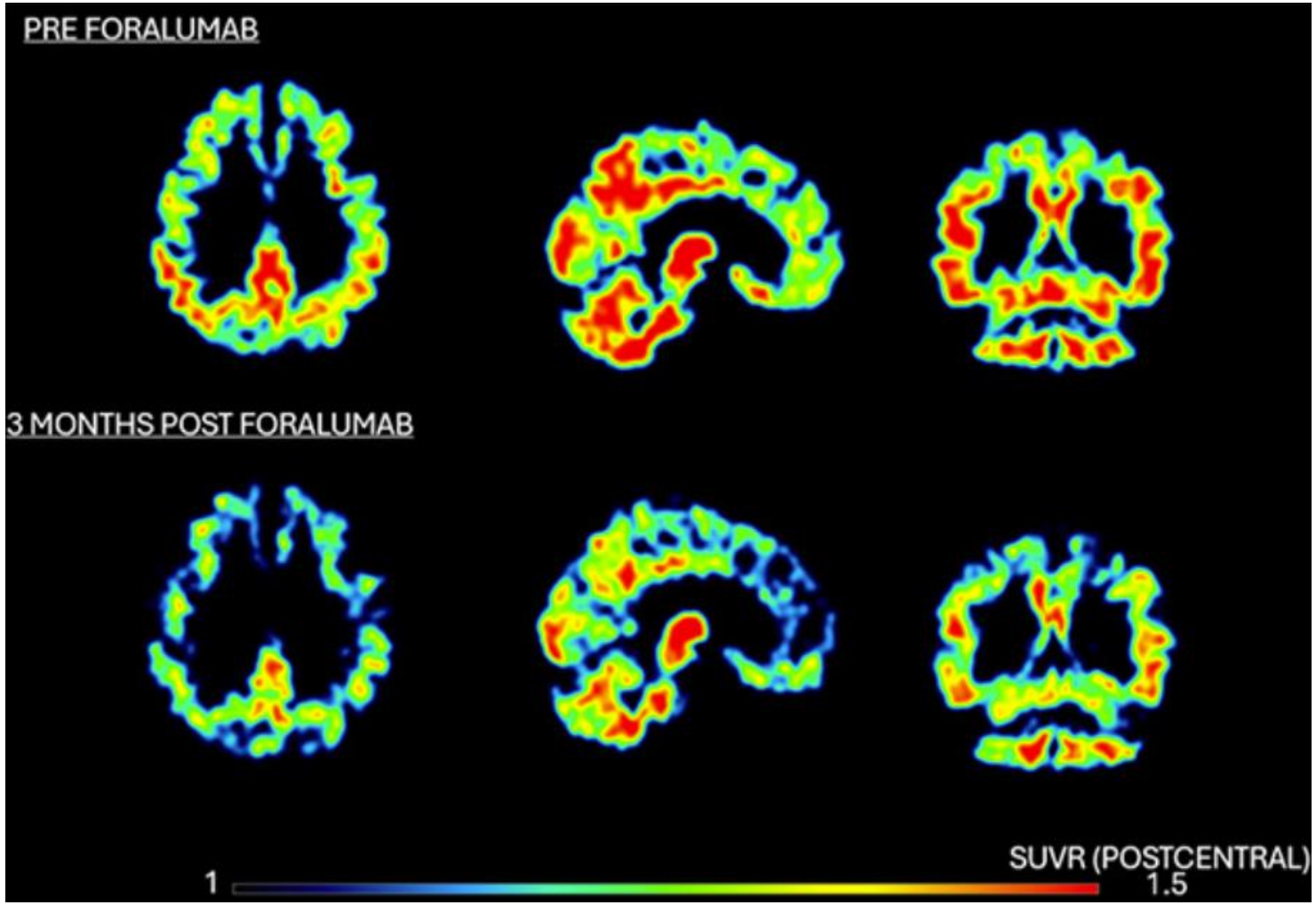


Significant reduction in basal ganglia and thalamic uptake following nasal foralumab

Early Symptomatic & Moderate Alzheimer's Disease (AD)



Moderate Alzheimer's Disease Expanded Access Study



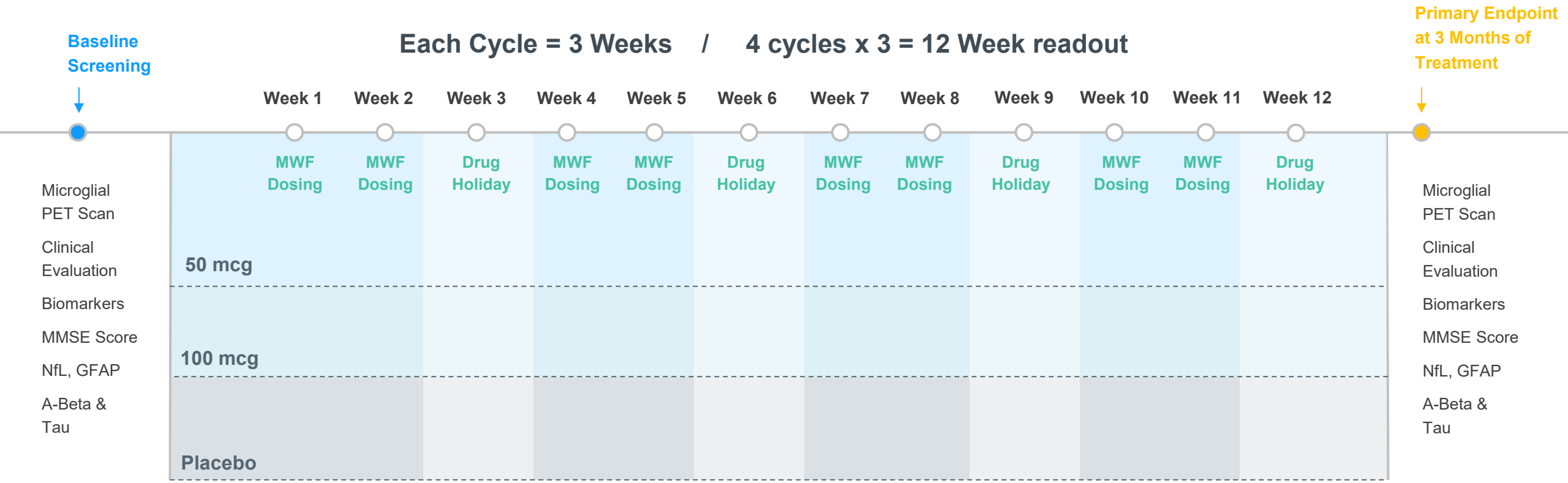
- 78-Year-Old Moderate Alzheimer's patient treated for 3 months with intranasal foralumab
- PET Scan shows significant reduction of microglia activity following 3 months of treatment

- Data presented at AD/PD in April 2025
- Data Published in the Journal of Clinical Nuclear Medicine in May 2025

https://journals.lww.com/nuclearmed/Fulltext/9900/dampening_of_microglial_activation_with_nasal.1721.aspx

Early Symptomatic Alzheimer's Disease: Phase 2a Study Design:

Intranasal Foralumab Dosing (n=32); Double-Blind, Placebo-Controlled, 2 Treatment Arms: 12 x 50mcg, 12 x 100mcg, 8 x Placebo.

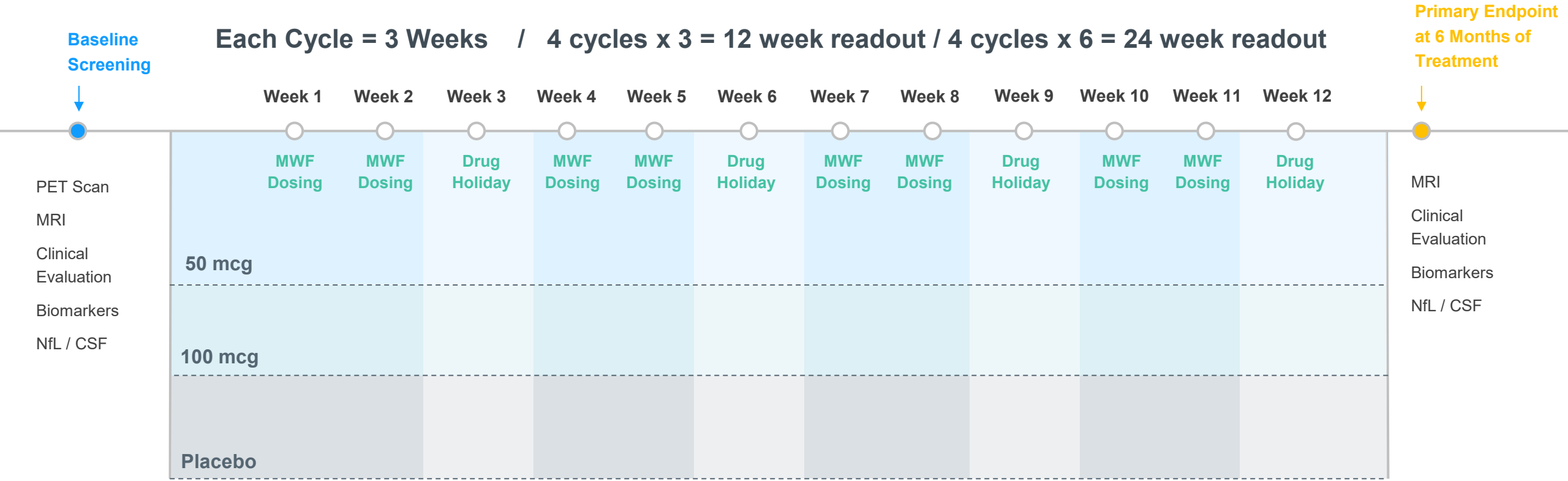


Amyotrophic Lateral Sclerosis (ALS)



ALS: Phase 2a Study Design:

Intranasal Foralumab Dosing (n=44); 3:1 Randomized, Placebo Controlled Trial



Intranasal Foralumab Pipeline

	Preclinical	IND	Phase 1	Expanded Access Program	Phase 2	Phase 3	
Non-Active Secondary Progressive Multiple Sclerosis Phase 2 Study							Positive Topline Data November 2026
Multiple System Atrophy (MSA) Phase 2 Study							Expecting Topline Data Q1 2027
Alzheimer's Disease (Mild) Phase 2 Study							Expecting Topline Data Q1 2027
ALS Phase 2 Study							First Patients Dosed Sept 2026
Non-Active Secondary Progressive Multiple Sclerosis (EA Program)							Ongoing Expanded Access Program
Moderate Alzheimer's Disease (EA Program)							Ongoing Expanded Access Program

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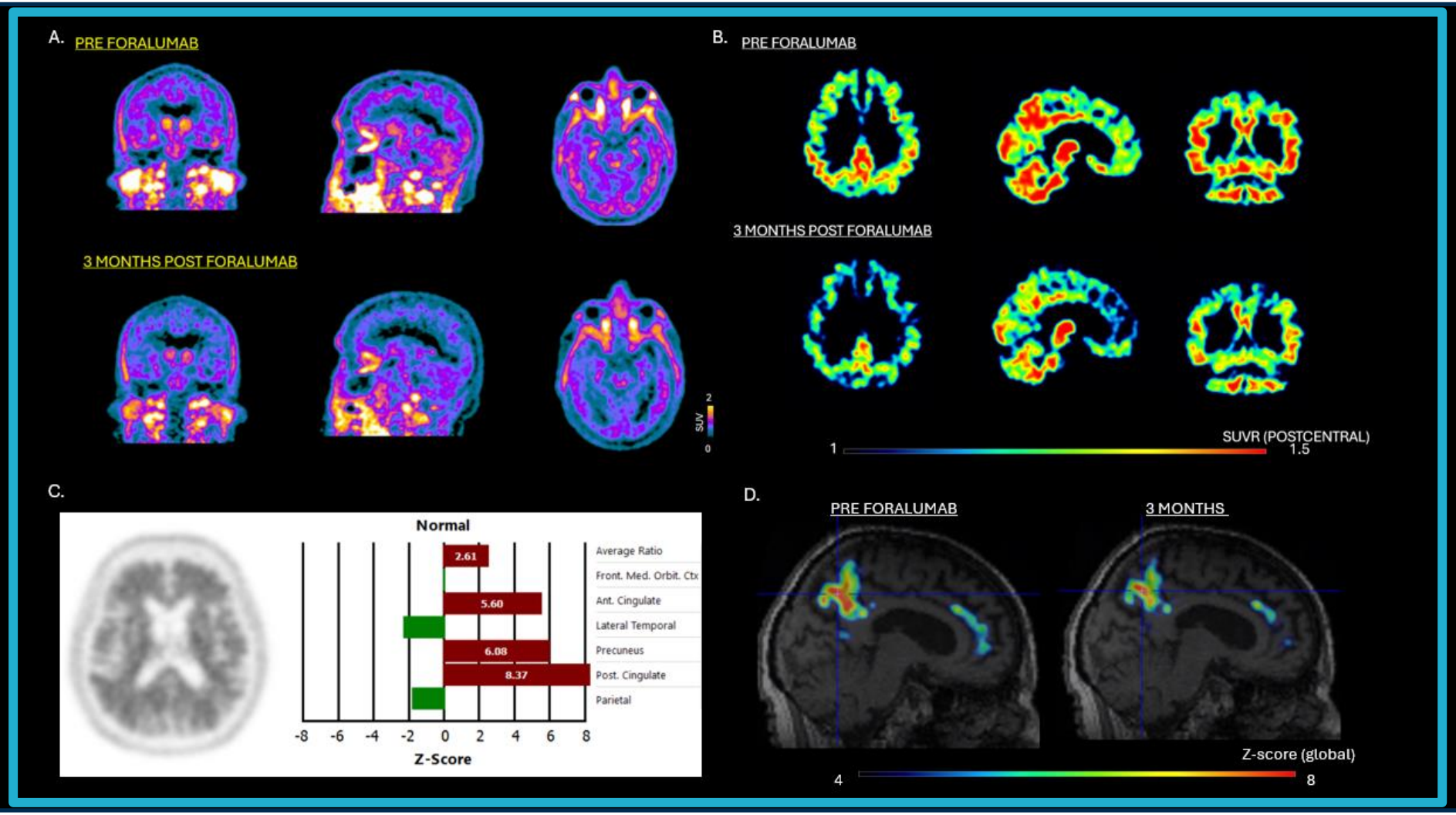
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Nasdaq: TLSA

Nasal foralumab dampens microglial activation in Alzheimer's Disease



Singhal T, Cicero S, Gale SA, Horan N, Dubey S, Marshall GA, Weiner HL. Dampening of Microglial Activation With Nasal Foralumab Administration in Moderate Alzheimer's Disease Dementia Clin Nucl Med. 2025 Aug 1;50(8):756-757