Intranasal Foralumab Update

Enabling Breakthrough Immunomodulation Approaches to Enhance the Functionality of Treg-Based Therapies

NASDAQ: TLSA

tiziana LIFE SCIENCES

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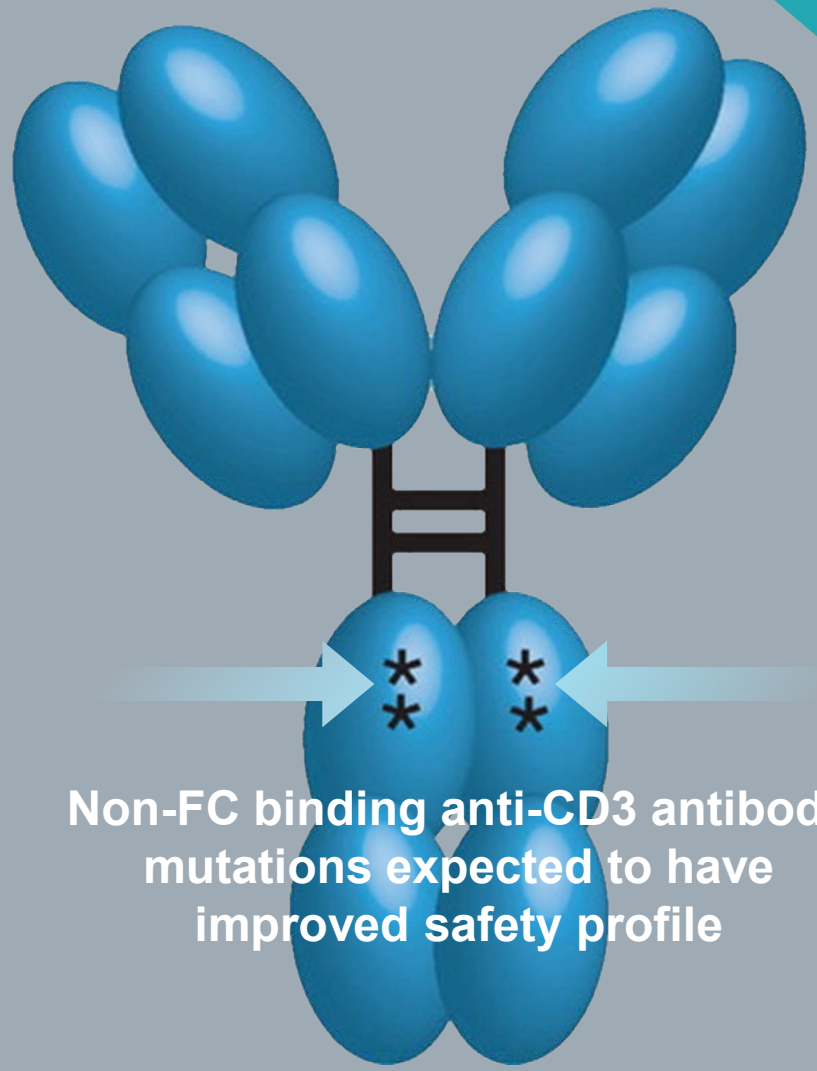
Lead Asset:
Foralumab

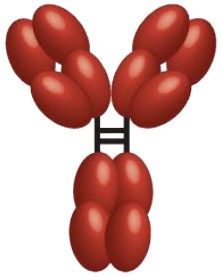
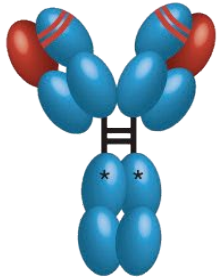
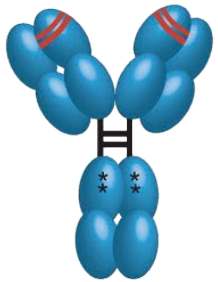
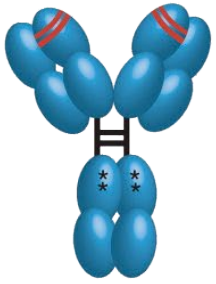
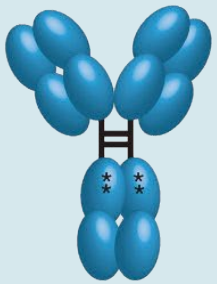
The only **fully human** anti-CD3 monoclonal antibody in clinical studies



Non-FC binding anti-CD3 antibody mutations expected to have improved safety profile

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

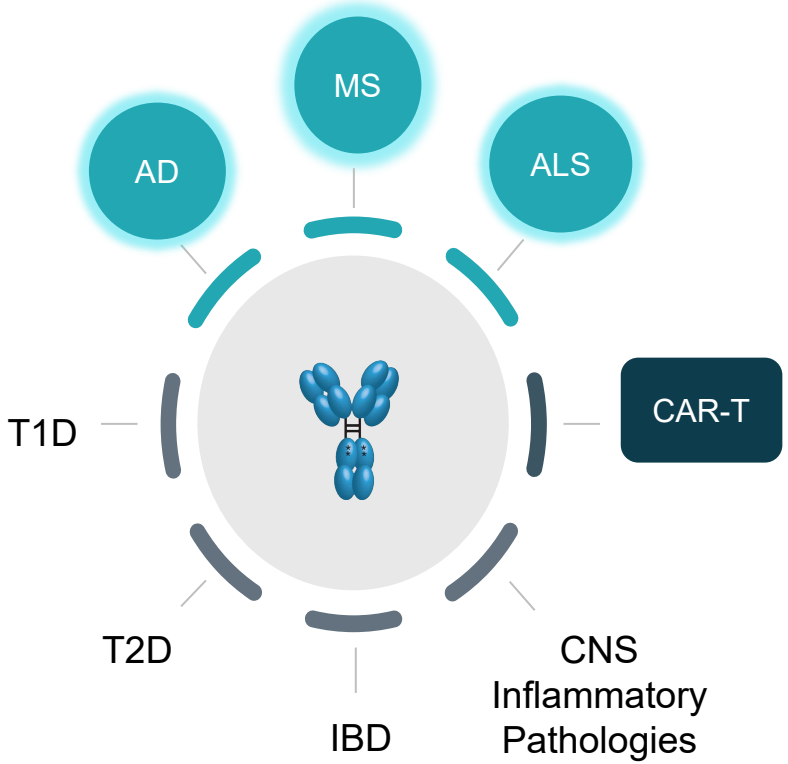
CD3-specific Monoclonal Antibodies in Clinical Development

OKT3	ChAglyCD3	(Ala-Ala) hOKT3γ1	Nuvion	Foralumab
Muromonab*	Otelixizumab	Teplizumab	Visilizumab	
				
IgG2a	IgG1 N297/A	IgG2 L234/A, L235A	IgG2 L234/A, V237/A	IgG1 L234/A, V335E
Fully Murine	Chimeric & Humanized	Humanized	Humanized	**Fully Human**

*Approved by the FDA for solid organ transplantation immuno-suppression

Rodent Origin

Human Origin * Point Mutation



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

Foralumab Facilitates Locally Targeted Immunomodulation to Improve Tregs Production and Enhance their Functionality

Our Therapeutic Approach

Site targeted local immunomodulation

Augment Tregs production

1

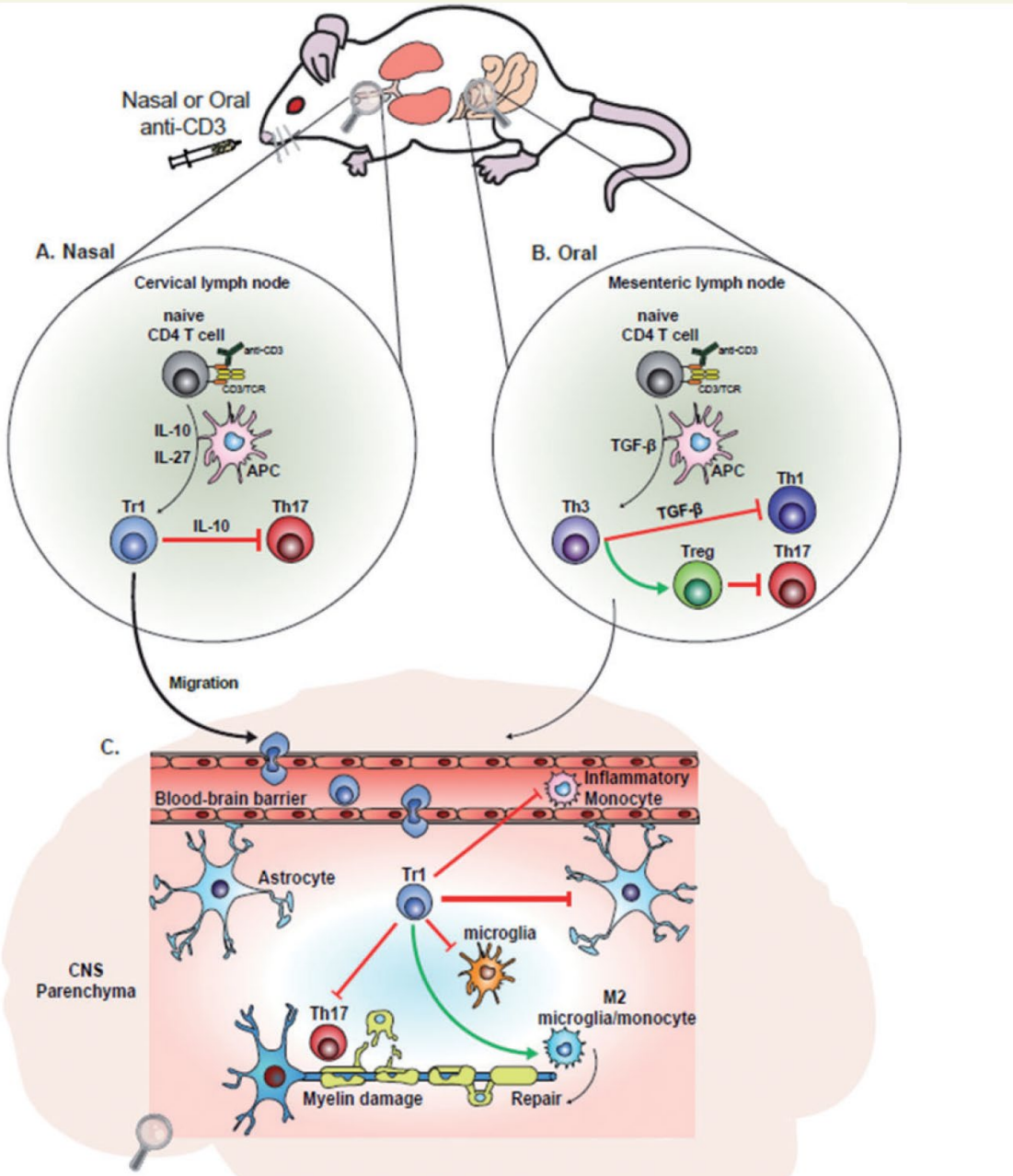
Enhance Tregs Functionality

2

Foralumab intranasal administration to facilitate local activity

3

The binding of foralumab to the T-cell receptor complex, through either the nasal or oral route, results in suppression of effector T-cells involved in various inflammatory and autoimmune diseases along with a reduction in inflammatory cytokines and increase in Tregs anti-inflammatory cytokines.



BRAIN 2016: 139; 1866–1876

Intranasal Foralumab

Safety Profile

- 13-week toxicology showed ample safety margin
- 26-month toxicology has begun with unaudited data expected Dec 2023
- No significant adverse events have been reported to date in preclinical or human studies

Pharmacology

- Phase 1 study (healthy subjects) - saw an inverted U-shaped dose effect curve
  - Mid-range dose with greatest pharmacologic response
- Additional clinical support
  - Foralumab demonstrated clinical proof of concept for intranasal delivery in mild-to-moderate COVID-19 patients

Intranasal Foralumab for Treatment of Neurodegenerative Diseases (Multiple Sclerosis)

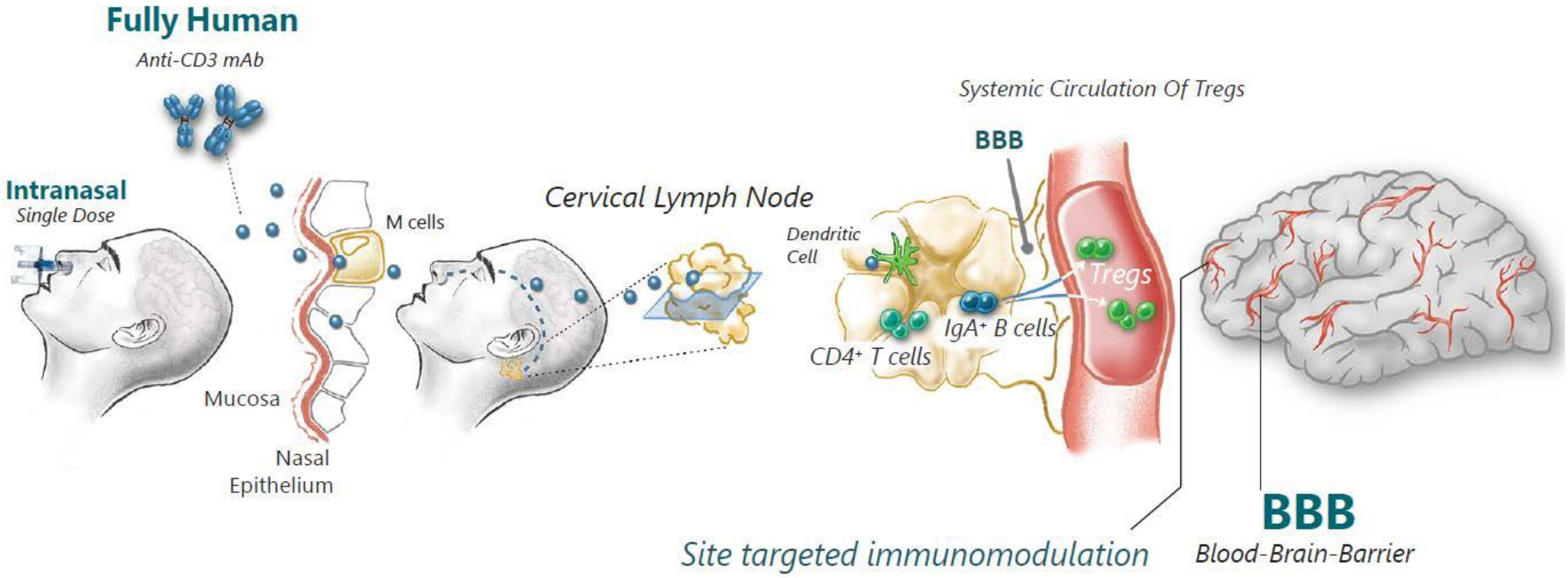
Local action with improved safety and lowered dosing

Fully Human
Anti-CD3 mAb

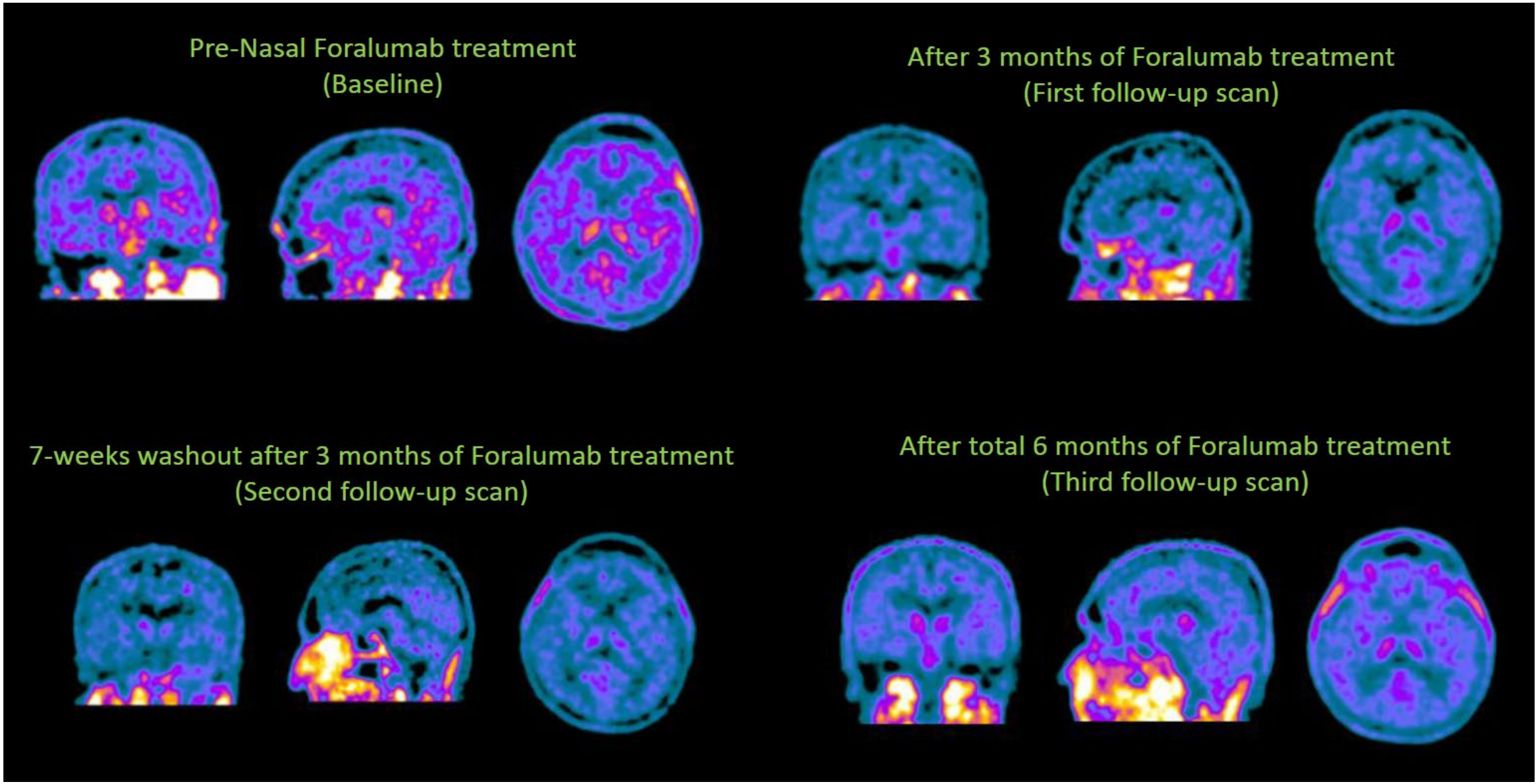
Intranasal

Intranasally-Administered Foralumab for Neurodegenerative Diseases

An Innovative Approach to Penetrate the Blood Brain Barrier (BBB)



Assessment of Inhibition of Microglial Activation by PET Imaging Following Treatment with Nasally Administered Foralumab in First Non- Active SPMS Patient (EA1)



Intranasally Administered Foralumab in Non-Active SPMS Patients

Two patients were dosed with intranasal foralumab M-W-F for two weeks with a subsequent 1-week washout period (regimen then repeated).

Positive Results: The regimen was well-tolerated with associated beneficial clinical and biomarker changes

Clinical Results

PET imaging data

- Indicated continued inhibition of microglial cell activation
- The reduction in microglial activation was seen in all parts of brain
- Suppression of microglial activation further increased after six months of treatment

Clinical Test Evaluation

- 9-Hole Peg Test (9HPT)
- Expanded Disability Status Scale (EDSS)
- Improvement in Timed 25-Foot Walk Test (T25FW)
- Symbol Digit Modality Test (SDMT)

Biologic Response

Biomarker changes

Downregulated serum levels of pro-inflammatory cytokines*, including:

- Interferon-gamma (IFN-g)
- Interleukin (IL)-18
- IL-1b
- IL-6

**These biomarkers are known to be associated with multiple sclerosis pathogenesis and progression*

Clinical Update on EA2

2018 – 2021

- Patient's non-active SPMS disability progressed
  - EDSS worsened from 3.5 to 6.0 despite ocrelizumab therapy
- Ocrelizumab was discontinued in 2021
- **At this time, EA2 required a cane to walk 100 meters.**

2022

- Enrolled in the intranasal foralumab Expanded Access Program (EAP) in January 2022
- **EA2 able to walk 100 meters without a cane in September 2022**
  - EDSS score improved from 6.0 to 5.5
- **EA2 able to walk 200 meters without a cane in December 2022**
  - EDSS score improved from 5.5 to 5.0
- Pyramidal score continued to remain stable

Expanded Access (EA) Non-Active MS Program Expanded to 8 Total Non-Active SPMS Patients

Patient Progress

EA3 through EA6
(4 patients)

✓All patients enrolled
✓Baseline PET scans finished

All patients scheduled to receive first dose Jan 2023

EA7 through EA10
(additional 4 patients)

Enrollment scheduled for Q2 2023

Phase 2 Planning and Design

TYPE C FDA meeting request for a Phase 2 study in Non-Active Secondary Progressive MS Submitted Jan 2023

Design

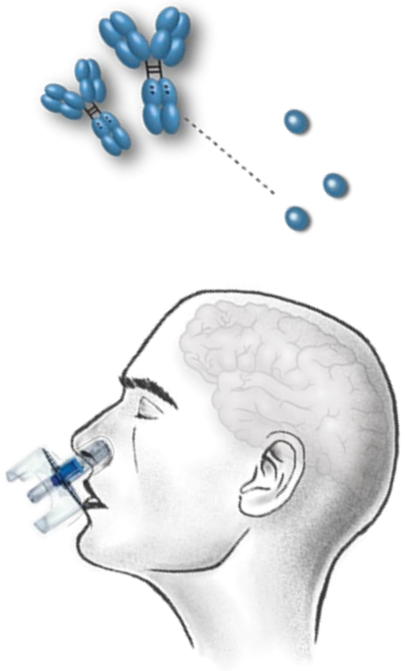
- ✓ Placebo-controlled
- ✓ Multi-center
- ✓ Dose-ranging
- ✓ Established outcome measures

Endpoints

- ❑ 9-Hole Peg Test (9HPT)
- ❑ Expanded Disability Status Scale (EDSS)
- ❑ Improvement in Timed 25-Foot Walk Test (T25FW)

First patient expected to enroll Q3 2023

Other Potential CNS-related Indications (Alzheimer's and ALS)



Intranasal anti-CD3 provides a unique approach for treating progressive neurologic diseases by modulating microglial cells. The intranasal route of immunotherapy has minimal toxicity and induces regulatory T cells locally, that then migrate to the brain to dampen brain inflammation.

Proof-of-Concept Demonstrated in Alzheimer's Disease

Study Presented at the Alzheimer's Association International Conference® (AAIC®)

"Treatment of Alzheimer's disease by modulation of microglial neuroinflammation by nasal anti-CD3 mAb" (presented by Weiner, M.D., Co-Director of the Ann Romney Center for Neurologic Disease at the Brigham and Women's Hospital (BWH) and Chairman of Tiziana's Scientific Advisory Board)

In this study animal models of Alzheimer's disease (AD) demonstrated that microglia activity was restored and cognition was improved following the dosing of intranasal anti-CD3 monoclonal antibody.

- Clinical measures were assessed in the mouse models using the Y-maze and Morris water maze tests which showed improvements in cognition. Biological improvements were also observed based on restoration of genetic phenotypes as measured by the presence of homeostatic microglia genes detected by Nanostring. In addition, it was found that intranasal anti-CD3 induced the migration of regulatory T cells (Tregs) to the brain which then interacted with microglia.
- Alzheimer's is another potentially valuable application of anti-CD3 based on its ability to stimulate the immune system to promote homeostatic microglial cells while decreasing degenerative microglial cells in the brain.

Alzheimer's Disease Plan is Underway

Received (August 2022) an affirmative written response from the FDA on a Pre-Investigational New Drug Application (PIND)

Submit an Investigational New Drug Application (IND) to conduct a Phase 2 study intranasal foralumab in Alzheimer's disease patients Q2 2023

Requested 13-Week toxicology studies completed

Requested 6-Month toxicology studies ongoing

Start Phase 2 program in 2H of 2023

Intranasal Foralumab in Amyotrophic Lateral Sclerosis (ALS)

ALS patients have limited therapeutic options and high unmet need

- In September, a Lawrence & Isabel Barnett Drug Development Program Grant was awarded to the Ann Romney Center for Neurologic Diseases at Brigham and Women's Hospital (BWH) by the ALS Association.
- This prestigious research grant supports the study of an intranasal anti-CD3 monoclonal antibody (mAb) in an animal model of Amyotrophic Lateral Sclerosis (ALS).
- The grant will allow further study the role of intranasal anti-CD3 mAb in dampening the microglial activation which amplifies ALS disease progression.

"We have now seen the potential of intranasal foralumab to dampen microglial activation in three major neuroinflammatory-related diseases, which creates significant optionality for exploring its benefits in some of the most important and burdensome medical conditions of our time."

Tiziana Life Sciences Announced Near-Term Strategic Focus on Intranasal Foralumab for Diseases of the Central Nervous System (CNS)

Focus on intranasal foralumab allows for efficient use of funds and staff

Sufficient cash reserves to perform Phase 2 MS trial
- Plan to use **non-dilutive** funding for Alzheimer's Disease, ALS, and T1D studies
- No anticipated requirement to raise capital in 2023

Deprioritized program development in oral foralumab, milciclib, and our fully human anti IL-6 receptor inhaled antibody

We believe this decision is the most pragmatic and value creating path forward for the near-term

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