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Intranasal Anti-CD3 mAb Therapy to Enable Breakthroughs in Neuroinflammatory Disease

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Investment Highlights

Targeting the U.S. market for neuroinflammatory anti-CD3 antibody treatments

Lead program is in non-active SPMS

IND cleared and “may proceed” to study foralumab in Alzheimer’s Disease

Validated MOA works across various neuroinflammatory applications

Recent $2.9B Sanofi acquisition of anti-CD3 molecule

MS Clinical data and publication in *PNAS*[1]

Alzheimer’s disease preclinical model data publication in *PNAS*[2]

Experienced scientific advisory board and management team that have brought multiple drugs to market

PNAS=Proceedings of the National Academy of Sciences journal

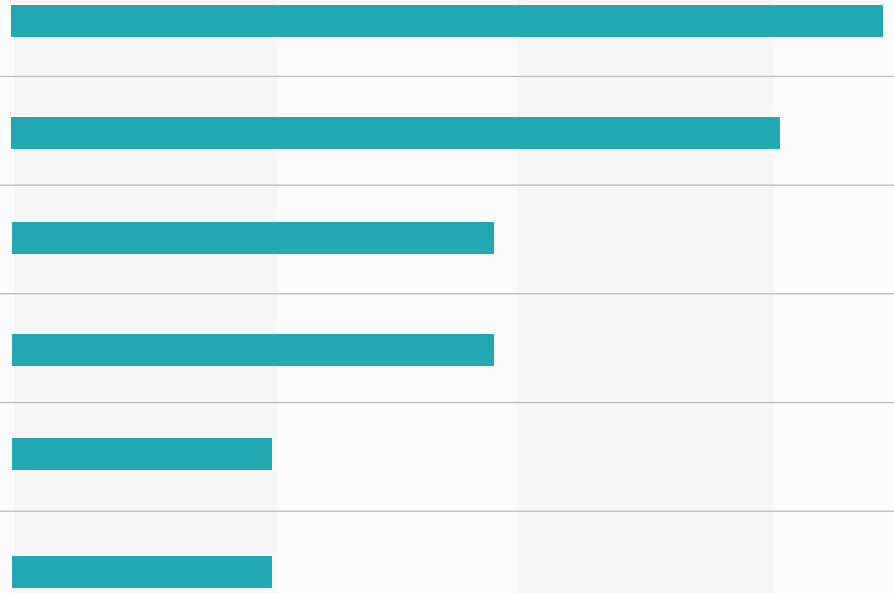
[1] https://www.pnas.org/doi/10.1073/pnas.2220272120

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

Lead Asset is Intranasal Foralumab

Multiple administration routes of a proven systemic anti-inflammatory, patent protected until 2040

	THERAPEUTIC AREA	PRECLINICAL	IND	PHASE 1	PHASE 2	PHASE 3	COMMENTS
FORALUMAB: NASAL (fully human anti-CD3 mAb)	Non-active SPMS*						Phase 2a expected to begin 3Q 2023
	Alzheimer's						IND clearance received 3Q 2023
	Long COVID						IND planned 4Q 2023
	Early Onset Type 1 DM						
	ALS**						
	Intracerebral Hemorrhage (ICH).						



* Non-Active Secondary Progressive Multiple Sclerosis (expanded program; n=6) ** Grant from Amyotrophic Lateral Sclerosis Association for development

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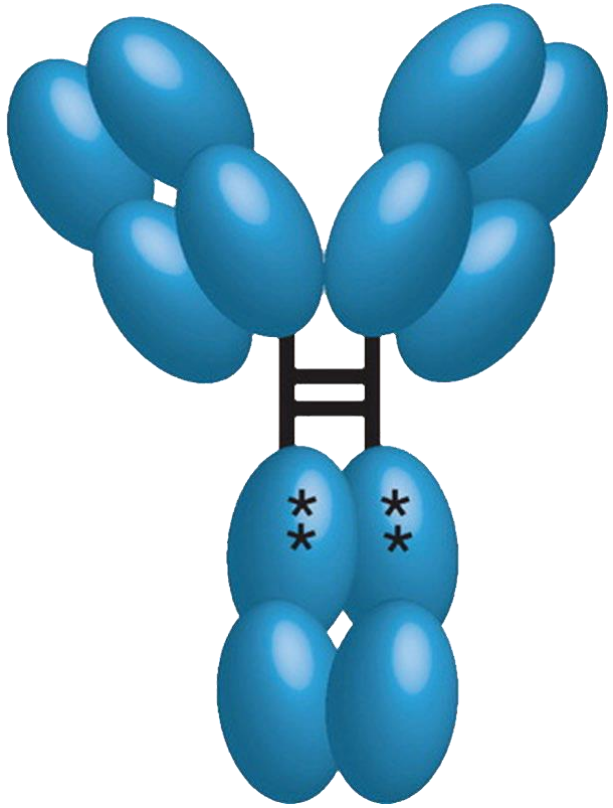
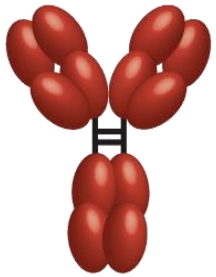
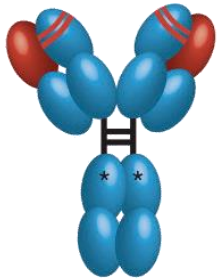
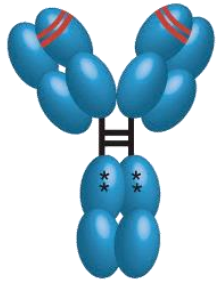
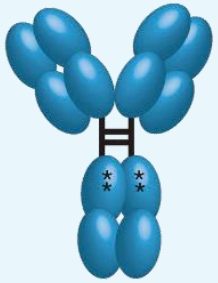
Lead Asset:
Intranasal Foralumab

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



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

Approved and Investigational CD3-specific Monoclonal Antibodies

OKT3 Muromonab†	Otelixizumab	Teplizumab††	Foralumab
			
IgG2a	IgG1	IgG2	IgG1
Fully Murine	Chimeric & Humanized	Humanized	Fully Human

† Approved by the FDA for solid organ transplantation immuno-suppression
†† Acquired by Sanofi for $2.9B

Rodent Origin

Human Origin *Point Mutation

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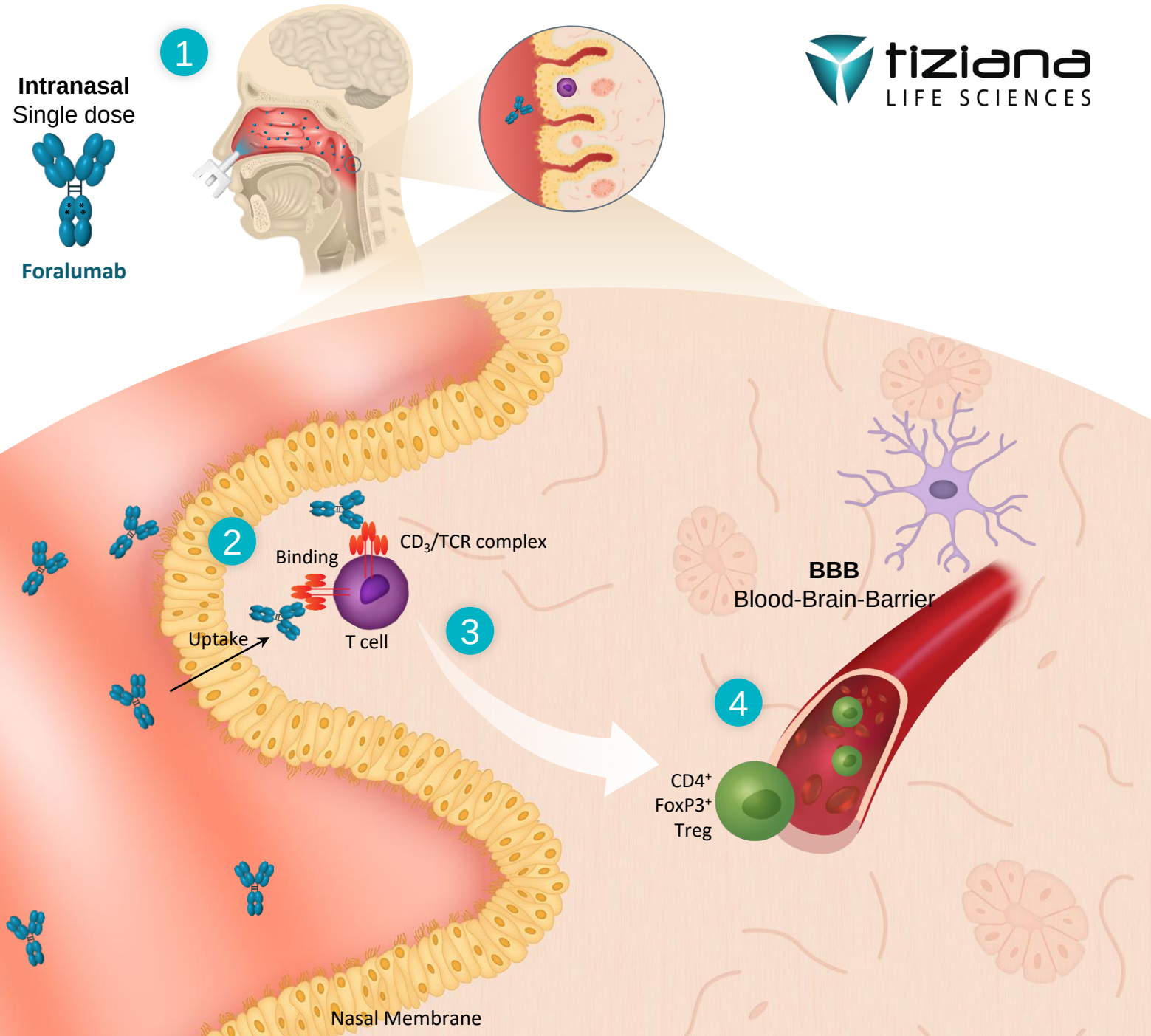
Adapted from: Kuhn, Chantal, and Howard L. Weiner. "Therapeutic anti-CD3 monoclonal antibodies: from bench to bedside." Immunotherapy 8.8 (2016): 889-906.

Foralumab:
Mechanism of Action

1. Patient inhales the antibody intranasally
2. Binding of foralumab to the T-cell receptor complex
3. Creation and activation of Tregs
4. Tregs will cross the blood brain barrier and regulate the activated innate immune system (microglia).



Publication in Proceedings of National Academy of Sciences Characterized the Anti-Inflammatory Properties of Foralumab in MS and COVID-19 Patients

PNAS RESEARCH ARTICLE | IMMUNOLOGY AND INFLAMMATION OPEN ACCESS

Nasal administration of anti-CD3 mAb (Foralumab) downregulates *NKG7* and increases *TGFB1* and *GIMAP7* expression in T cells in subjects with COVID-19

Thais G. Moreira[a,1], Christian D. Gauthier[a], Liam Murphy[a], Toby B. Lanser[a], Anu Paul[a], Kimble T. F. Matos[b], Davide Mangani[a], Saef Izzy[a], Rafael M. Rezende[a], Brian C. Healy[a], Clare M. Baecher-Allan[a], Tanuja Chitnis[a], Vijay Kuchroo[a], and Howard L. Weiner[a,1]

Edited by Lawrence Steinman, Stanford University, Stanford, CA; received November 28, 2022; accepted January 30, 2023

Illustrates that the immunological basis of the mechanism of action for intranasal foralumab is based on increasing production of naïve-like T cells and Tregs, while simultaneously decreasing the production of effector T cells

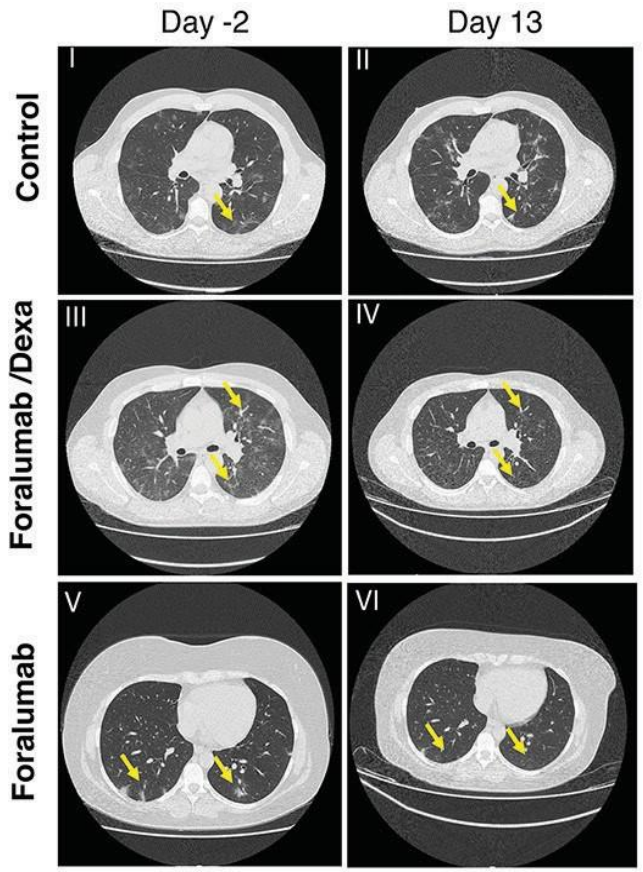
Further, highlights how intranasal foralumab has similar immune gene expression effects in COVID patients, Multiple Sclerosis patients and in heathy volunteers

Concludes that immunomodulation by nasal anti-CD3 mAb represents a novel avenue for treatment of inflammatory human diseases

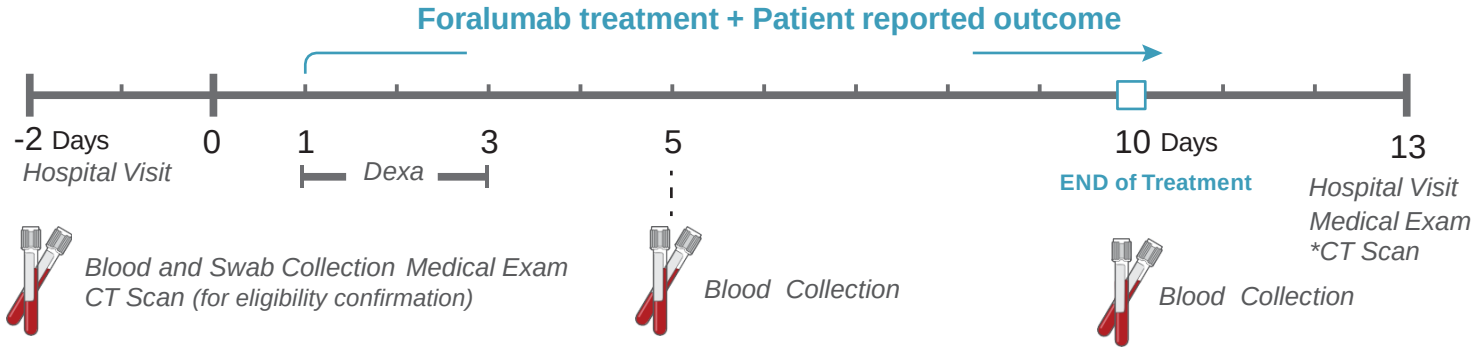
Having an intranasal fully human monoclonal antibody that positively modulates the immune system allows Tiziana to explore multiple inflammatory disease indications in addition to multiple sclerosis (MS)

Foralumab: Clinical Proof of Concept for Intranasal Delivery First Demonstrated in Mild-to-Moderate COVID-19

CT Scan of Patients' Lungs



The First Validation That Intranasally Administered Foralumab is Well-tolerated and the Treatment Provides Clinical Benefits



Results: Biomarkers measured via cytokines and C-reactive proteins

Cohort	Lung CT Scan	Cytokine IL-6	C-Reactive Protein
Evaluable patients	% Improvement	% Reduction	% Reduction
Control, n=14	43	37	40
Foralumab + Dexa, n=12	75	41	55
Foralumab, n=10	**80**	**69**	**85**

Long COVID IND planned Q4 2023

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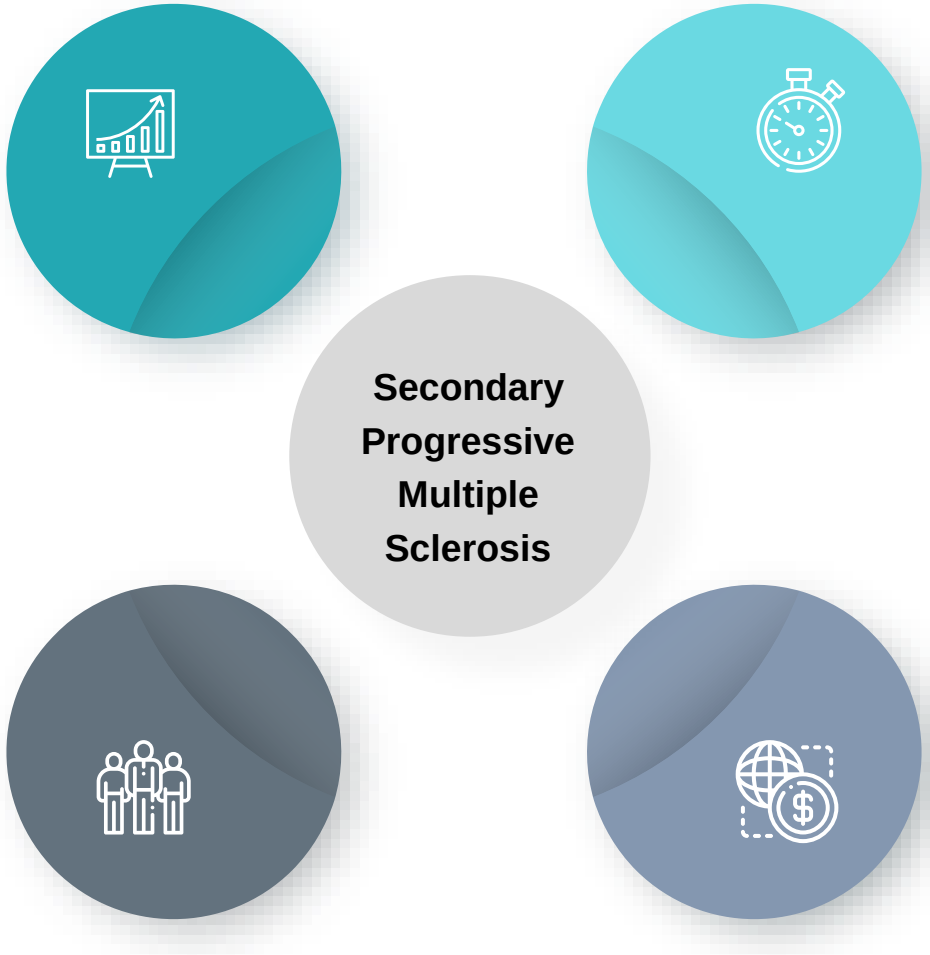
Non-active Secondary Progressive Multiple Sclerosis (na-SPMS)

Fully Human
Anti-CD3 mAb

Secondary Progressive Multiple Sclerosis Represents an Attractive Market

Approximately 25% of Relapsing Remitting MS (RRMS) patients are estimated to progress to SPMS*

Patients are treated with disease-modifying standard of care for RRMS before running out of options



Based on population prevalence data, we estimate 94,000 SPMS patients in the U.S. and 155,000 SPMS patients in EU**

Global Ocrevus sales estimated to be over $7.4 billion#

Sources: *Vasanthaprasad et al. BMC Neurology (2022) 22:301 **Tjalf Ziemssen, et. al Neurol Neuroimmunol Neuroinflamm. 2023 Jan; 10(1): e200064; #Ocrevus global sales reported by Roche as CHF 3.2 billion in 1H 2023

SPMS Development Program History and Next Steps

Gathering safety & efficacy evidence via Expanded Access Program before advancing to Phase 2a

Phase 1

- 27 healthy volunteers
- 10ug, 50ug, or 250ug studied
- Desired immune effects of nasal foralumab occur at the 50ug dose
- No safety concerns

COVID Trial

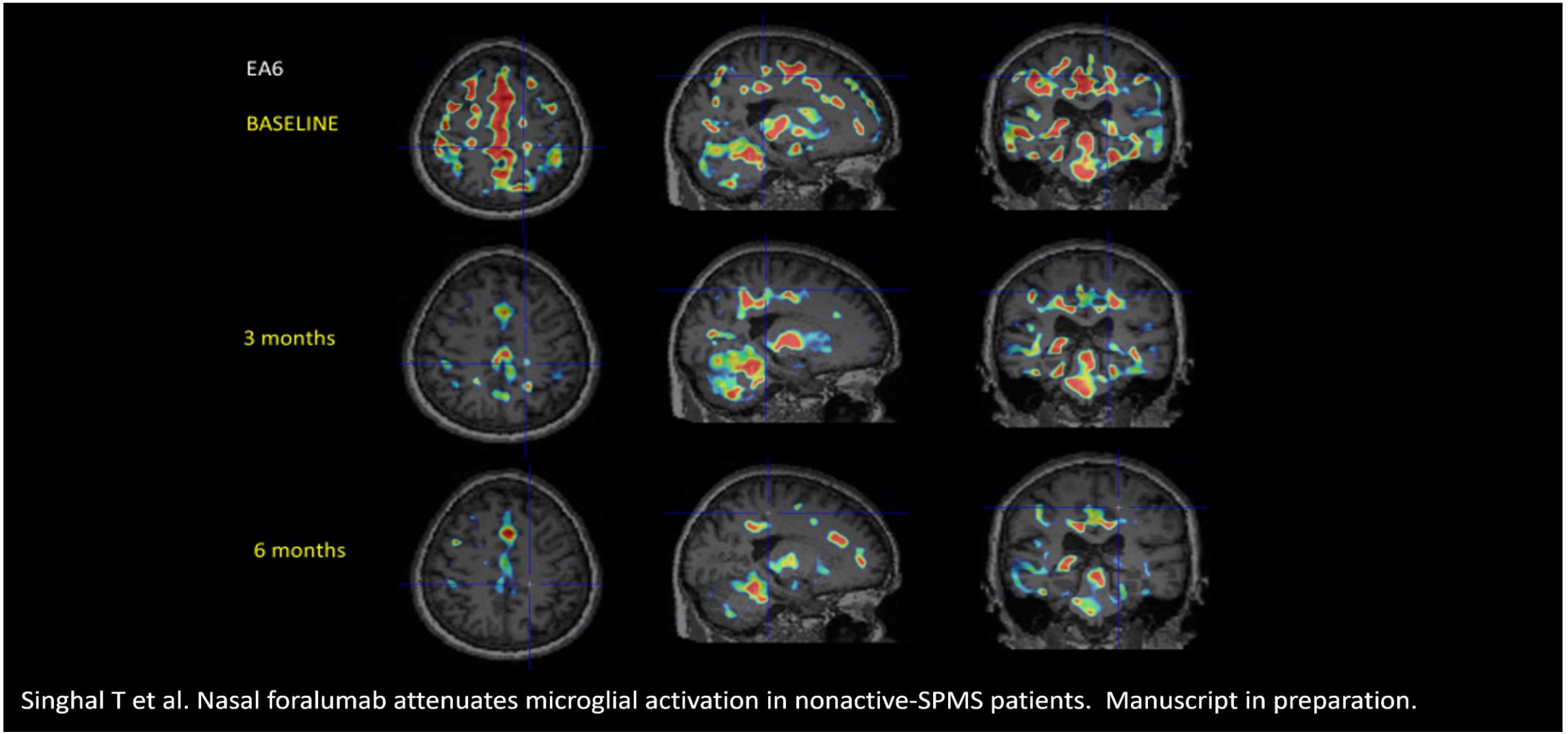
- Thirty-nine with mild to moderate COVID-19 patients
- Control (n=16), foralumab with 6 mg dexamethasone and foralumab alone (100ug/day)
- Well-tolerated and provided clinical benefit

na-SPMS expanded access program (n=10 patients) underway

- Demonstrating improvements in brain inflammation in 5/6 patients (4 additional patients being enrolled)

Phase 2a to begin 3Q 2023

EA1-6 Update: 5 out of 6 Dosed Showing Reduction in Microglia Activation



Singhal T et al. Nasal foralumab attenuates microglial activation in nonactive-SPMS patients. Manuscript in preparation.

Clinical Update on Patient 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 feet.

2022

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

2023

- EA2 returned to work and has been working since January, now full-time

EA1-6: 6 Month clinical update

	EDSS	Pyramidal score	T25FW	MFIS
EA1	–	↓	–	–
EA2	↓	–	↓	↓
EA3	–	–	↓	–
EA4	↓	–	–	↓
EA5	–	↓	↓	↓
EA6	–	–	–	↓

- Denotes stabilization ↓ Denotes improvement

Expanded Access (EA) Non-Active MS Program Expanded to 6 Total na-SPMS Patients with the Aim of Enrolling a Total of 10

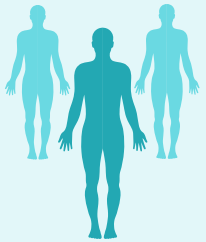
Patient Progress

EA3 THROUGH EA6
(4 patients)

- All patients enrolled and received 6-month dose
- 3-month PET scans completed (3 of 4 with lower inflammation)
- Improvement in fatigue scores (MFIS) reported

Data was presented at ECTRIMS October 2023

EA7 THROUGH EA10
(additional 4 patients)



Enrollment scheduled for Q3 2023

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Foralumab Next Steps in na-SPMS: Phase 2a Plan and Read-Out Timing

First investigator meeting to start Q3 2023 and first patient to be enrolled Q4 2023

Design

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

Endpoints

- ☐ PET Scan
- ☐ Expanded Disability Status Scale (EDSS)
- ☐ Improvement in Timed 25-Foot Walk Test (T25FW)

Topline results expected Q4 2024

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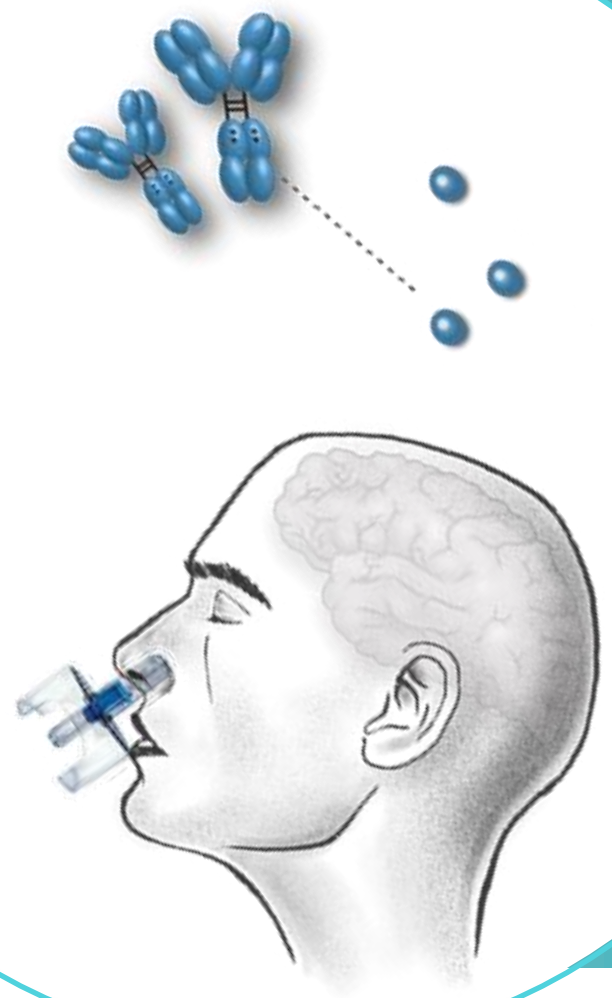
Phase 2a Study Design in SPMS: Double-Blind, Placebo-Controlled

Intranasal foralumab dosing (n=54); 18 patients per treatment arm

Other Potential CNS-related Indications (Alzheimer’s, ALS, Long COVID and Intracerebral Hemorrhage)

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.



Second Publication in Proceedings of National Academy of Sciences now Validates Intranasal Foralumab MoA for Treatment of Alzheimer's Disease

RESEARCH ARTICLE | IMMUNOLOGY AND INFLAMMATION |

Nasal administration of anti-CD3 monoclonal antibody ameliorates disease in a mouse model of Alzheimer's disease

Juliana R. Lopes, Xiaoming Zhang, Julia Mayrink, +11, and Howard L. Weiner Authors Info & Affiliations

Edited by Lawrence Steinman, Stanford University, Stanford, CA; received June 4, 2023; accepted July 31, 2023

September 5, 2023 | 120 (37) e2309221120 | https://doi.org/10.1073/pnas.2309221120

Alzheimer's disease (AD) is a neurodegenerative disease characterized by amyloid plaques, neurofibrillary tangles, and microglial activation. Therapies targeting amyloid beta have shown positive effects in subjects with AD. Nasal anti-CD3 has been shown to treat animals with a progressive form of experimental autoimmune encephalomyelitis, a model for multiple sclerosis, by inducing regulatory T cells that dampen microglial inflammation in the brain. Here, we show that nasal anti-CD3 also ameliorates disease in a murine model of AD by targeting microglial activation in the brain independent of amyloid beta deposition. These studies identify a unique approach to treat Alzheimer's disease that could also be given in combination with anti-amyloid therapy.

Alzheimer’s Disease Program is Advancing and Equally Exciting

Start Phase 2 program in 1H of 2024

- Letter to Proceed received for IND to conduct a Phase 2 study of intranasal foralumab in Alzheimer’s disease patients
- Phase 2 trial to assess microglial activation after 3 months of treatment of mild-to-moderate patients as part of combination therapy with recently approved drugs and monotherapy

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Intranasal Foralumab in Amyotrophic Lateral Sclerosis (ALS)

ALS patients have limited therapeutic options and a high unmet need

In September 2022, a Lawrence & Isabel Barnett Drug Development Program Grant was awarded to the Ann Romney Center for Neurologic Diseases at Brigham and Women's Hospital 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.

– Dr. Howard Weiner

Tiziana Life Sciences Ltd. Management

Seasoned leaders at multiple biotechnology and pharmaceutical companies

Gabriele Cerrone, Founder, Executive Chairman and Acting Chief Executive Officer has founded ten biotechnology companies in oncology, infectious diseases and molecular diagnostics. Mr. Cerrone co-founded Cardiff Oncology, Inc., an oncology company and served as its Co-Chairman; he was a co-founder and served as Chairman of Synergy Pharmaceuticals, Inc. and was a Director of and led the restructuring of Siga Technologies, Inc. Mr. Cerrone also co-founded FermaVir Pharmaceuticals, Inc. and served as Chairman of the Board until its merger in September 2007 with Inhibitex, Inc. Mr. Cerrone served as a director of Inhibitex, Inc. until its US$2.5B sale to Bristol Myers Squibb Co in 2012.

Matthew W. Davis, M.D., Chief Medical Officer and Chief Operating Officer has extensive regulatory experience filing new drug applications (NDA) and biologic license applications (BLA), as well as with FDA approvals and device clearances. He has worked on several important approved brands, including Lidoderm®, Sculptra®, Colcrys® and most recently QWO®. Dr. Davis previously served as Chief Scientific Officer and Chief Medical Officer at Endo Pharmaceuticals. Additionally, Dr. Davis was Chief Medical Officer for Lupin Inc. and URL Pharma, Inc. where he spearheaded three NDA approvals and was the inventor on all 17 Orange Book listed patents for Colcrys®. He also was on the executive team that sold URL Pharma to Takeda Pharmaceutical Company for approximately $800M combined with over $1B in performance-based contingent earn out payments.

William Clementi, Pharm. D., FCP, Chief Development Officer is responsible for overseeing the Company's development strategies and advancing its portfolio of therapeutic product candidates. Dr. Clementi completed his NIH Training Fellowship in drug metabolism and vascular smooth muscle relaxation research under John L. McNay, M.D. and Thomas M. Ludden, Ph.D. Thereafter, he led innovative programs in teaching, research and therapeutic drug monitoring in acute care wards within the University of Texas, College of Pharmacy. He held joint appointments in the School of Medicine and Graduate School of Biomedical Sciences. Prior to launching his own regulatory consulting company, Clementi & Associates, Ltd., he held positions at Synthelabo's U.S. affiliate, Lorex Pharmaceuticals where he directed and designed pivotal studies in cardiovascular drug development and was Worldwide Director of Market Development.

Keeren Shah, Chief Financial Officer Ms. Shah currently also serves as the CFO of Accustem Sciences Inc, OKYO Pharma Ltd and Rasna Therapeutics Inc., Prior to these companies, Ms. Shah was at Visa Inc. where she led and participated in key transformation programs and Visa Inc.'s initial public offering. Before this, Ms. Shah held a variety of finance positions at other leading companies including Arthur Andersen and BBC Worldwide. Ms. Shah received a Bachelor of arts with honors in Economics and is a member of the Chartered Institute of Management Accountants.

In Summary…

An exciting and innovative platform focused in areas of high unmet need, with significant momentum ahead

- Novel, fully human anti-CD3 intranasal mAb for potential treatment of multiple inflammatory diseases
- Mechanism of action validated in prestigious *Proceedings of National Academy of Sciences* (PNAS)
- Formulation IP - protected until 2040

Q3 2023
IND clearance in Alzheimer's Disease

Q3 2023
First investigator meeting for Phase 2 in non-active SPMS to begin

Q4 2023
Data presentation at ECTRIMS

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US Headquarters (Pennsylvania)

Tiziana Life Science Ltd.
601 New Britain Road
Building 100, Suite 102
Doylestown PA 18901

UK Headquarters (London)

Tiziana Life Sciences plc
14-15 Conduit Street
London
W1D 2XJ

Investors:
+44 7769 88 4020
info@tizianalifesciences.com