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Intranasal Anti-CD3 mAb Therapy to Enable Breakthroughs in Neuroinflammatory and Neurodegenerative Diseases

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Investment Highlights

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

Intranasal foralumab Phase 2 study in non-active Secondary Progressive currently dosing

Phase 2 Alzheimer's Disease IND cleared for trial to start in 2024

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

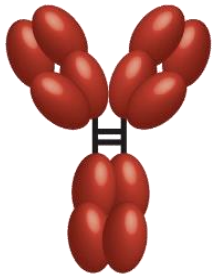
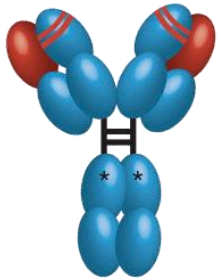
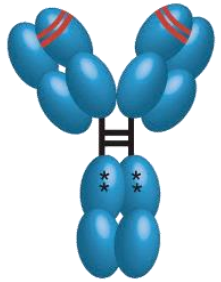
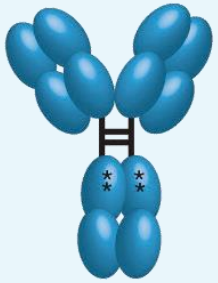
[2] https://www.pnas.org/doi/10.1073/pnas.2309221120

Lead Asset:
Intranasal Foralumab

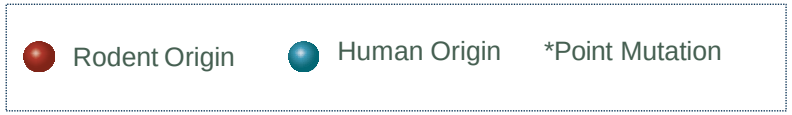
The only fully human anti-CD3 monoclonal antibody in clinical studies

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



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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.

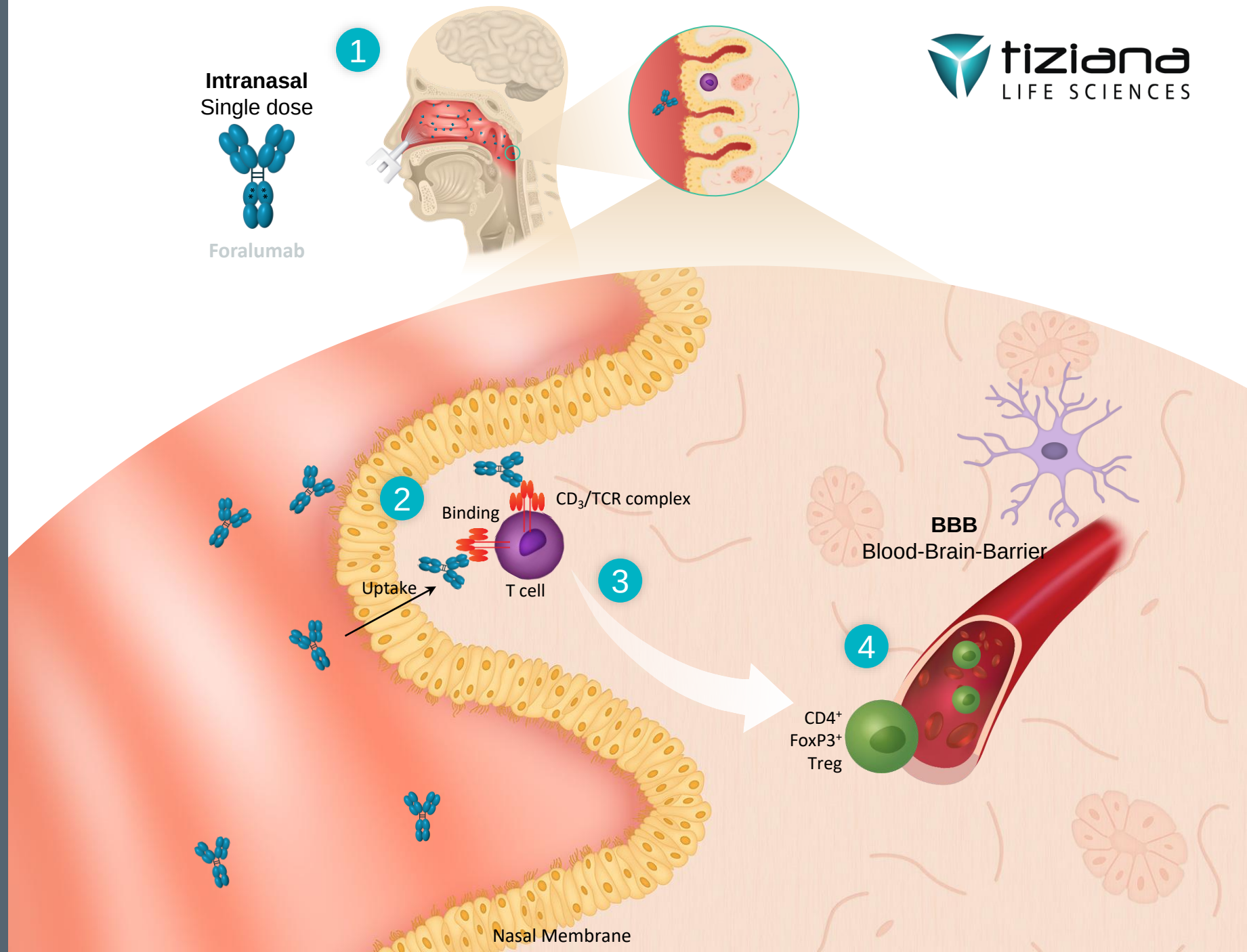
Foralumab: Mechanism of Action[1,2]

Patient inhales the antibody intranasally

Binding of foralumab to the T-cell receptor complex

Creation and activation of Tregs

Tregs will 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

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)

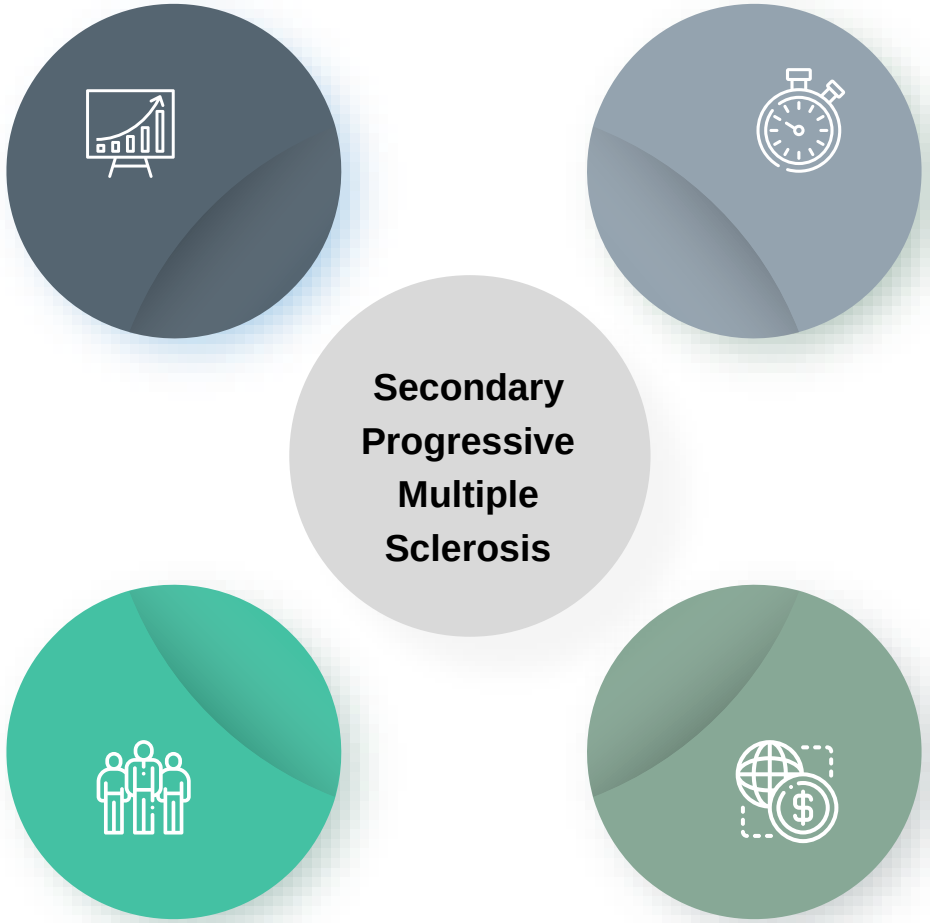
Non-active Secondary Progressive Multiple Sclerosis (na-SPMS)

Secondary Progressive Multiple Sclerosis Represents an Attractive Market

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

Based on population prevalence data of SPMS patients in the U.S, we have submitted to the FDA for Orphan Designation**

Patients who have progression independent of relapses are underserved



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

Global Ocrevus sales estimated to be over $9.1 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 8.4 billion CHF in 2023

SPMS Development Program History and Next Steps

Gathered 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	Microglial activation reduced (improved) in 5 out of 6 patients Fatigue improved in 70% of patients Clinical improvement or stabilization seen in all 10 expanded access patients FDA permitted enrollment of an additional 20 patients into EAP
Phase 2a	Started enrollment in November 2023

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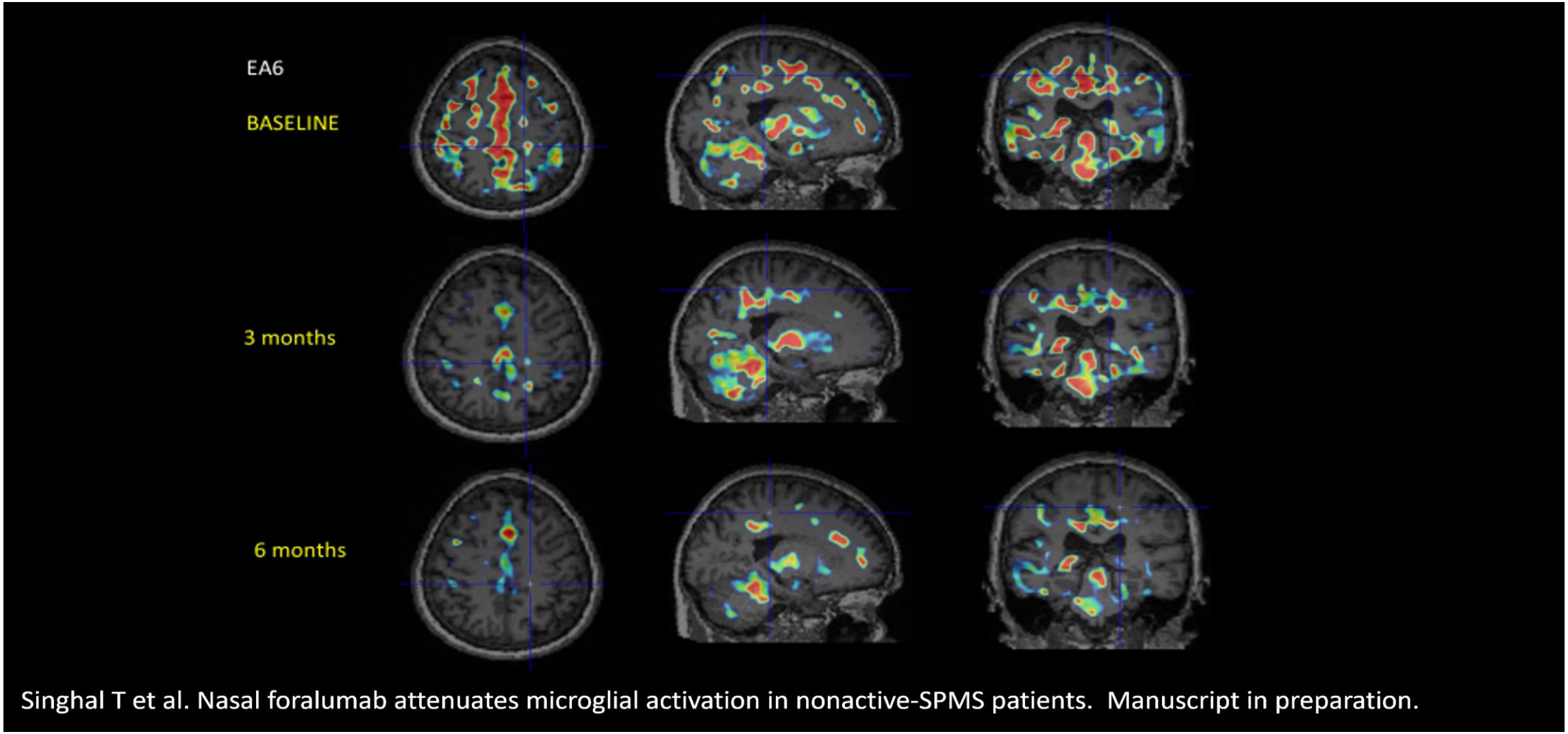
https://www.frontiersin.org/articles/10.3389/fimmu.2022.956907/full

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.

6 Month Clinical Update Demonstrates Improvements or Stabilization in all Patients

70% of patients demonstrated improved fatigue scores

	EDSS	Pyramidal score	T25FW	MFIS
EA1	–	↓	–	–
EA2	↓	–	↓	↓
EA3	–	–	↓	–
EA4	↓	–	–	↓
EA5	–	↓	↓	↓
EA6	–	–	–	↓
EA7	–	–	↓	↓
EA8	↓	↓	–	↓
EA9	↓	–	–	↓
EA10	–	↓	–	–

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– Denotes stabilization

↓ Denotes improvement

Patient EA2 Clinical Snapshot

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

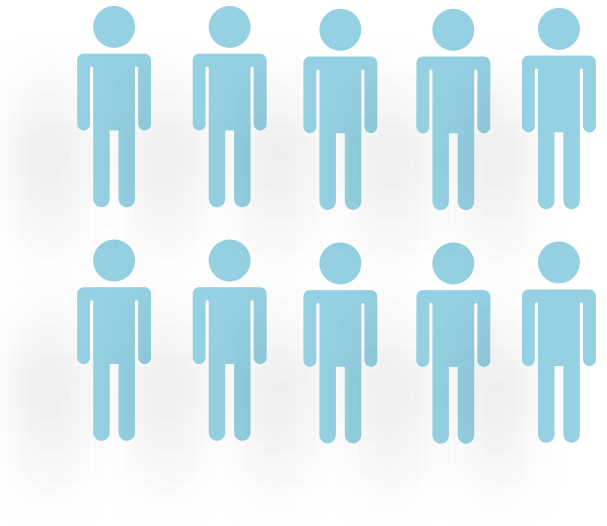
- EA2 returned to work and has been working since January, now full-time

Expanded Access (EA) Non-Active MS Program Summary

Patient Progress

First Ten Patients

- All patients received at least 6-months of treatment
- Clinical improvements or stabilization was reported across the entire group
- Median reduction of 36% in White Matter Z-scores
- Fatigue scores as measured by MFIS improved in 7/10 patients

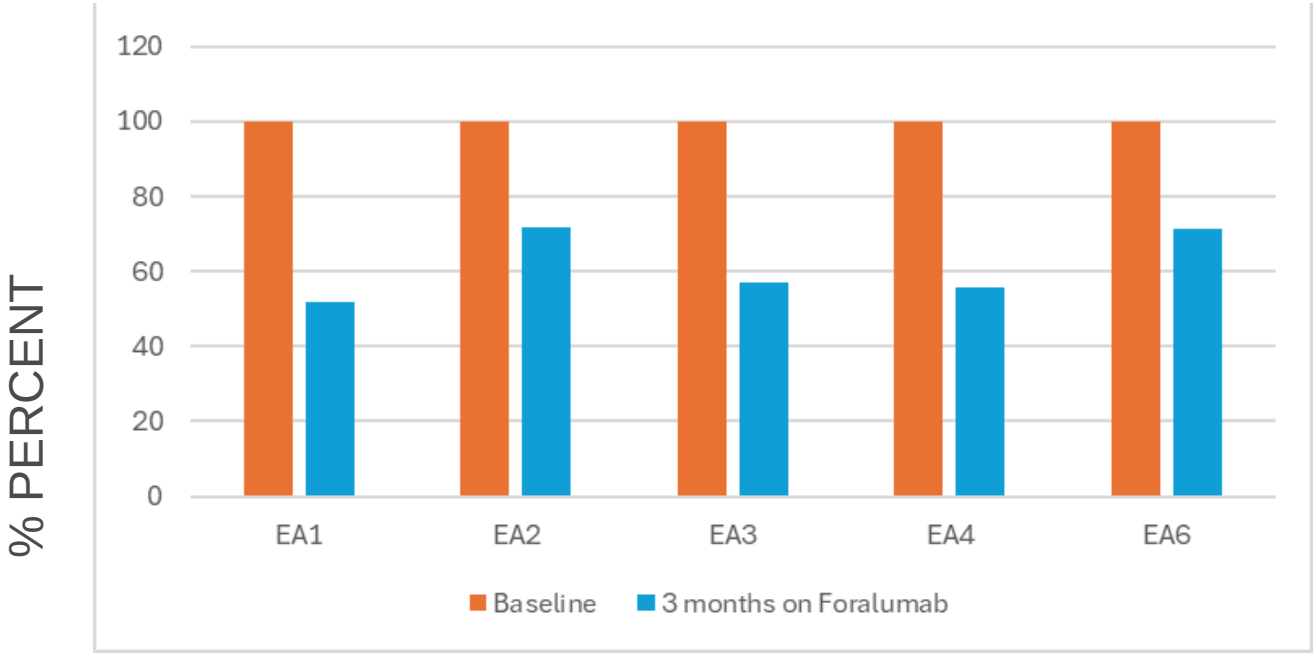


Data was presented at AAN 2024

Microglial Activation Dampened as Measured by White Matter Z-scores

Data from Expanded Access program: Quantitative [F18]PBR06-PET data showed the dampening of microglial activation, an indicator of brain inflammation. Reductions of 28% to 48% were seen, indicating improvement in 5 out of 6 patients, and a 36% median reduction in White Matter Z-scores compared to baseline

Figure 1*



White Matter Z-scores were used to measure the effect of intranasal foralumab on microglial activation at baseline and then after foralumab treatment for three months.

Foralumab na-SPMS: Phase 2a Program Ongoing

Design	Endpoints
✓ Placebo-controlled	☐ PET Scan
✓ Multi-center	☐ Expanded Disability Status Scale (EDSS)
✓ Dose-ranging	☐ Multiple Sclerosis Functional Composite
✓ Established outcome measures	

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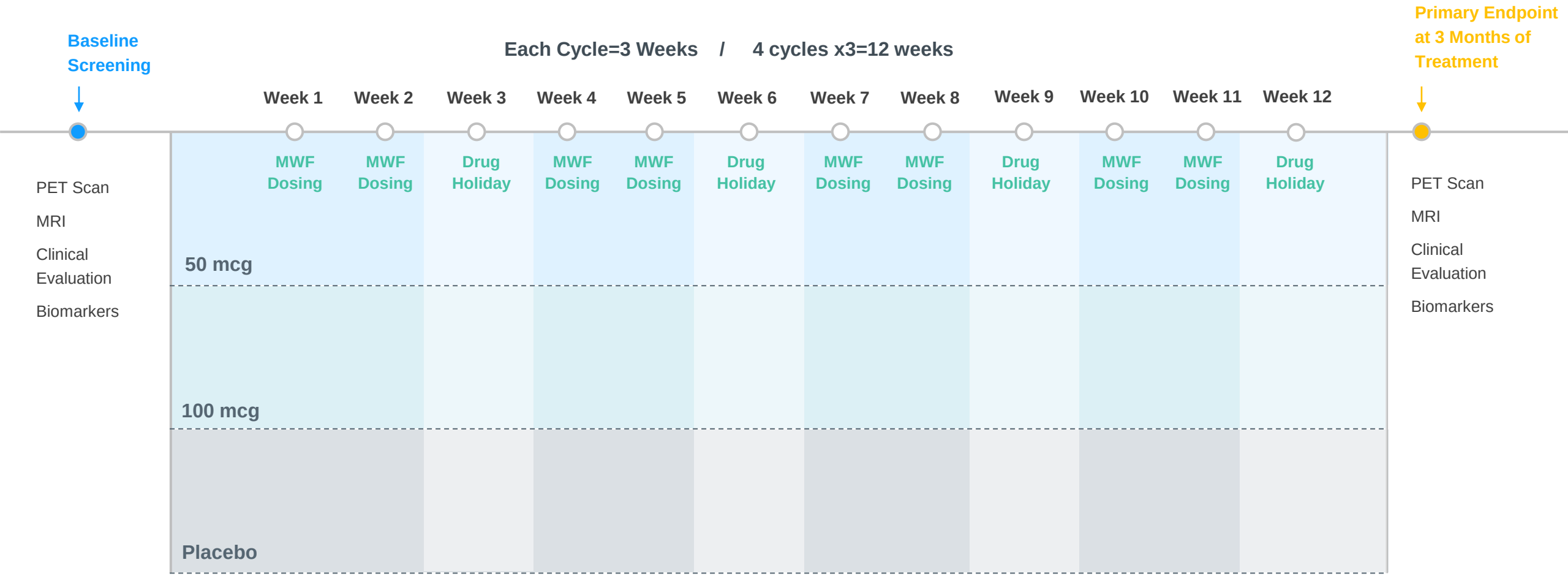
Phase 2a Study Design in na-SPMS: Double-Blind, Placebo-Controlled

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



Alzheimer’s Disease
Amyloid-Related Imaging Abnormalities (ARIA)

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*
Intranasal Foralumab as a Potential 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

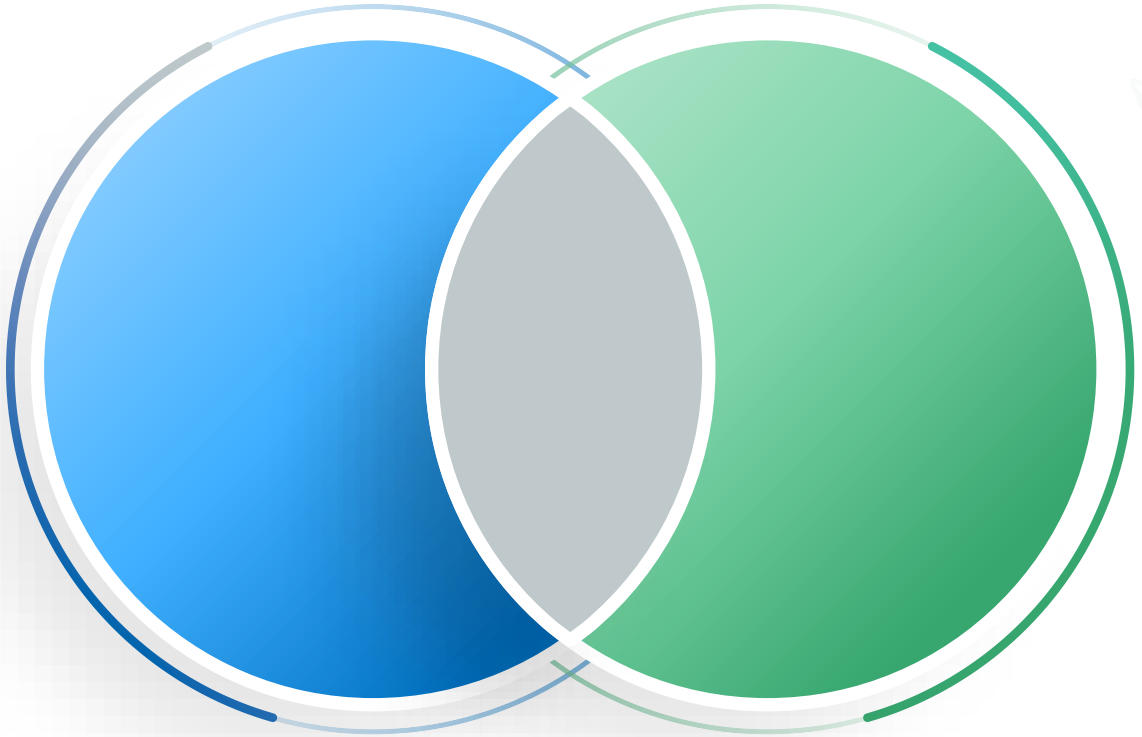
Alzheimer's disease (AD) is a neurodegenerative disease characterized by amyloid plaques, neurofibrillary tangles, and microglial activation. Therapies targeting amyloid beta have shown positive effects in subjects with AD. Nasal anti-CD3 has been shown to treat animals with a progressive form of experimental 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.

Nasal administration of anti-CD3 monoclonal antibody ameliorates disease in a mouse model of Alzheimer's disease.
A copy of the article can be found at pnas.org.

Alzheimer’s Disease Program is Advancing and Equally Exciting

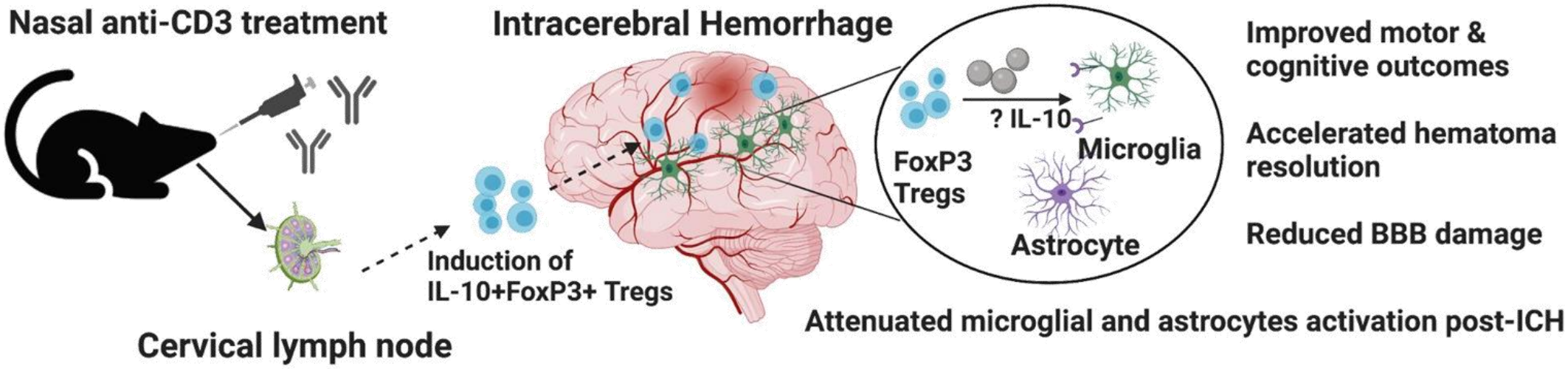
Phase 2 Alzheimer’s Disease IND cleared for trial to start in 2024

Letter to Proceed received for IND to conduct a Phase 2 study of intranasal foralumab in Alzheimer’s disease patients



Phase 2 trial planned to start 2024 and will assess microglial activation as part of combination therapy with recently approved drugs

Preclinical Studies Suggest Possible Benefit in Preventing and Treating Amyloid-Related Imaging Abnormalities (ARIA)



Nasal anti-CD3 represents a novel therapeutic approach for treating ICH and potentially other types of acute brain injury

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 neuroinflammatory and neurodegenerative diseases
- Mechanism of action published in prestigious *Proceedings of National Academy of Sciences* (PNAS)
- Phase 2a in na-SPMS ongoing
- Phase 2a in Alzheimer's Disease to start 2024

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.

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.

US Headquarters (New York)
Tiziana Life Science Ltd.
420 Lexington Avenue, Suite 2525
New York, NY 10170

UK Headquarters (London)
Tiziana Life Sciences plc
14-15 Conduit Street
London
W1D 2XJ

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