Enhancing the Therapeutic Window of Everolimus in TSC-Associated Seizures: The Montara BrainOnly™ Platform

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Background on Montara Therapeutics

Montara Therapeutics is a precision medicine neuroscience biotech based in San Francisco, developing safer, more efficacious therapies for patients with neurological diseases. Many promising brain drug candidates fail because of serious side effects in the rest of the body. Our BrainOnly™ platform was developed to solve this. It pairs a brain-targeted treatment with a "blocker" drug that confines the therapy's activity to the brain; enhancing safety, expanding the therapeutic index, and unlocking targets previously considered out of reach. The science originated in the lab of Kevan Shokat at UCSF and has extended its application towards Tuberous Sclerosis Complex (TSC).

Team

Beyond its accomplished scientific founders, Montara Therapeutics has a management team and board of directors that bring proven biotech entrepreneurship with prior exits, deep expertise in CNS drug development, and a track record of platform execution.

Management Team

Board of Directors

Scientific Founders

- **Dr. Troy Wilson** — Successful serial biotech entrepreneur and current President and CEO of Kura Oncology.
- **Dr. Andrew Miller** — Founder and President of R&D at Karuna Therapeutics, led the development of KarXT from initial idea to the FDA approval of COBENFY for schizophrenia; Karuna was subsequently acquired by Bristol Myers Squibb.
- **Dr David Michelson** —Managed clinical research for neuroscience and ophthalmology, leading to numerous NDAs across organizations, including Merck and Lily. Served in executive and CMO roles at Proclara Biosciences and Regenacy Pharmaceuticals.
- **Dr. Hertz and Dr. Shokat** — Before Montara, Drs. Hertz and Shokat co-founded Mitokinin, which advanced a potential first-in-class, disease-modifying treatment for Parkinson's disease. In October 2023, Mitokinin was acquired by AbbVie - up to $655 million in total deal value.

TSC & Epilepsy Advisors

- **Dr. Chris Kingswood** — Consultant Nephrologist at St. George's University Hospital, TSC Clinic (UK)
- **Dr. Raj Rajaraman** — Associate Professor in Pediatric Neurology at UCLA
- **Dr. Martina Bebin** — Professor of Neurology and Pediatrics at the UAB Epilepsy Center
- **Dr. Steven Sparagana** — Previous TSC Clinic Director at Scottish Rite for Children
- **Dr. Jacqueline French** — Epileptologist at NYU Langone Comprehensive Epilepsy Center
- **Dr. Nadia Khan** — Current Senior Scientist with Montara Therapeutics with 10 years of TSC and temporal lobe epilepsy research experience

Financing Overview

Strong financial backing — Montara to date has raised **$28M** in seed funding from SV Health Investors' Dementia Discovery Fund, Two Bear Capital, Dolby Family Ventures, KdT Ventures, BEVC, and others, along with funding from the Michael J. Fox Foundation. Currently in the process of raising our Series A financing, expected to close by the end of Q3, 2026.

Seed Investors | **Research Foundation**

Montara Therapeutics BrainOnly Platform and its application to TSC

The Problem: Many neurological therapies are often dose-limited, due to the serious peripheral side effects, such as liver, lung and cardiovascular damage, gastrointestinal issues, anemia and infection.

Example in TSC: Everolimus (Afinitor)
Everolimus is an oral mTOR inhibitor that targets the overactive mTOR pathway in TSC. It was FDA approved (as Afinitor Disperz) in 2018 for the adjunctive treatment of TSC-associated partial-onset seizures in patients ≥2 years old.

In the phase 3 EXIST-3 trial, a ≥50% reduction in seizures was achieved by 40.0% (higher exposure) and 28.2% (lower exposure) of patients versus 15.1% on placebo ($p<0.0001$; $p=0.008$; Figure 1).

Despite these benefits, everolimus caused frequent, dose-related side effects because it acts on mTOR throughout the body. More than half of patients developed stomatitis (mouth sores), and about 85% developed high cholesterol, alongside high triglycerides, high blood sugar, and low white blood cell counts. Serious adverse events occurred in ~14% of treated patients versus 3% on placebo, often requiring dose reductions or interruptions (Table 1). These body-wide, dose-limiting toxicities are exactly what Montara's Brain-Only™ platform aims to overcome.

Citation: *French JA, et al. Lancet. 2016;388(10056):2153–2163 (EXIST-3).*

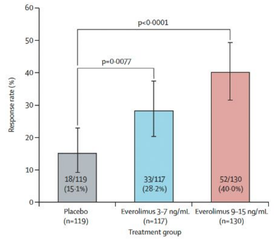

Figure 1. Everolimus reduces TSC seizures (EXIST-3). Proportion of patients with a ≥50% reduction in seizure frequency: 15.1% (placebo), 28.2% (everolimus 3–7 ng/mL; p=0.0077), and 40.0% (everolimus 9–15 ng/mL; p<0.0001 vs placebo). Error bars are 95% CIs. Represented from French et al., *Lancet* 2016.

Common Adverse Reactions with Everolimus (AFINITOR DISPERZ) in TSC Seizures

TSC-associated partial-onset seizures — EXIST-3 trial (adjunctive therapy, 18-week core phase)

Adverse Reaction	Low trough (3–7 ng/mL) N = 117		High trough (9–15 ng/mL) N = 130	
	Any %	Gr ≥ 3 %	Any %	Gr ≥ 3 %
Most common adverse reactions (≥ 10%)				
Stomatitis	55	3	64	4
Diarrhea	17	0	22	0
Vomiting	12	0	10	2
Nasopharyngitis	14	0	16	0
Upper respiratory tract infection	13	0	15	0
Pyrexia (fever)	20	0	14	0.8
Cough	11	0	10	0
Rash	6	0	10	0
Immune-related †				
Neutropenia	25	4	37	6
Metabolic ‡				
Hypercholesterolemia (high cholesterol)	86	0	85	0.8
Hypertriglyceridemia (high triglycerides)	43	2	39	2
Hyperglycemia (high blood sugar)	19	0	18	0
Hypophosphatemia (low phosphate)	9	0.9	16	2

Table 1. Common adverse reactions with everolimus (AFINITOR DISPERZ) in TSC-associated seizures (EXIST-3). Adverse reactions and laboratory abnormalities reported in ≥10% of everolimus-treated patients during the 18-week core phase of EXIST-3, by everolimus exposure target (low trough 3–7 ng/mL, N=117; high trough 9–15 ng/mL, N=130), shown as any-grade and Grade ≥3 (%). Placebo (N=119) not shown. Source: AFINITOR/AFINITOR DISPERZ U.S. Prescribing Information.

To overcome the peripheral limitations of existing and novel neurological drugs, Montara developed the BrainOnly™ platform

BrainOnly is designed to prevent on-target off-tissue peripheral side effects and increase the availability of drug to reach the brain.

Everolimus is a clear example: its adverse effects keep patients from reaching the dose needed for seizure control.
With BrainOnly, everolimus can stay active in the brain while the rest of the body is spared — preserving seizure control without the dose-limiting toxicity.

Applying this platform, **Montara developed MTX-E1 for TSC, a peripheral blocker that blocks everolimus's binding sites in the periphery to concentrate its activity in the brain.**

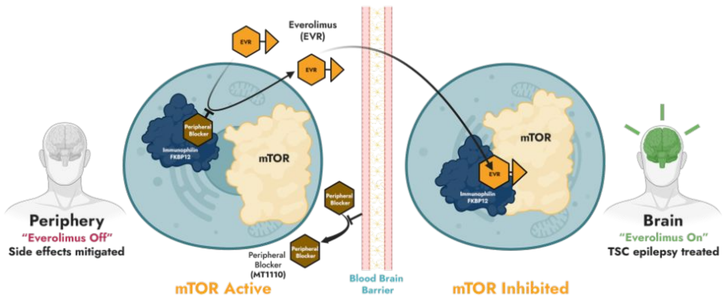

Figure 2. The Brain-Only™ platform confines everolimus activity to the brain. Everolimus (EVR) is paired with a peripheral blocker that cannot cross the blood–brain barrier. In the periphery (left), the blocker occupies FKBP12 — everolimus's binding partner — so mTOR stays active ("Everolimus Off") and side effects are reduced. In the brain (right), where the blocker cannot reach, everolimus inhibits mTOR normally ("Everolimus On"), treating TSC epilepsy. The result is brain-selective mTOR inhibition — seizure control with less peripheral toxicity.

Montara Therapeutics Clinical Plan for Treating TSC

A phased path from first-in-human testing to a registrational Phase 2 trial

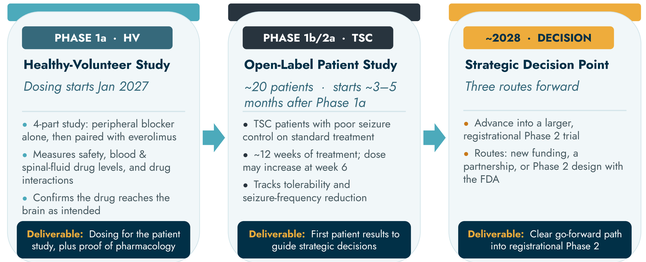

Figure 3. Montara's phased clinical plan for treating TSC-associated seizures. A three-stage path from first-in-human testing to a registrational Phase 2 trial: a Phase 1a healthy-volunteer study (2027) establishing dosing and proof of pharmacology, a Phase 1b/2a open-label study in ~20 TSC patients assessing tolerability and seizure reduction, and a ~2028 strategic decision point defining the route into registrational Phase 2.

Preclinical Data- Seizure Suppression with AE mitigation using BrainOnly

In collaboration with PsychoGenics, we tested the BrainOnly™ combination — everolimus plus the Montara peripheral blocker — in a genetic mouse model of TSC. Compared with everolimus alone, the combination further reduced seizure frequency and duration while also lowering elevated blood glucose and restoring activated T-cell levels — enhancing seizure control while mitigating peripheral toxicity.

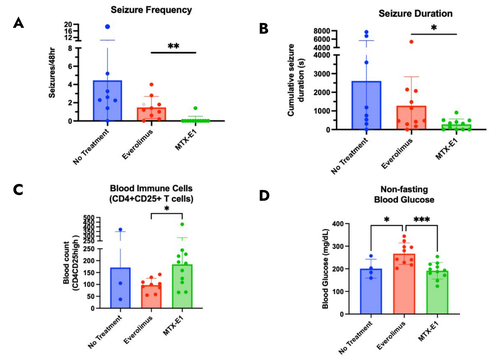

Figure 4. MTX-E1 potentiates seizure suppression while reversing everolimus's peripheral side effects (TSC mouse model). Mice received no treatment, everolimus alone, or MTX-E1 (everolimus + Montara peripheral blocker). **(A)** Seizure frequency and **(B)** seizure duration were reduced more by MTX-E1 than by everolimus alone. **(C)** Activated T cells ($CD4^+CD25^+$), suppressed by everolimus, were restored by MTX-E1; **(D)** everolimus-elevated non-fasting blood glucose was normalized by MTX-E1. Mean ± SD; *p<0.05, **p<0.01, ***p<0.001.

Contact Information

Patients & Caregivers: If you or someone you care for lives with TSC-associated seizures, we want to hear from you. We're especially interested in the experiences of people who are currently taking everolimus, or who have taken it in the past — what has it been like for you? We'd also welcome the chance to connect with anyone interested in learning about recruitment for future clinical trials.

Physicians: We'd love to connect with clinicians who are interested in the BrainOnly platform or who care for patients who may be interested in enrolling in a future trial.

For more information or to get in touch, please contact Max Lebovitz, VP of Business Operations: mlebovitz@montaratx.com