Recursion

REC-994: Phase 2 SYCAMORE Trial Results

FEBRUARY 2025

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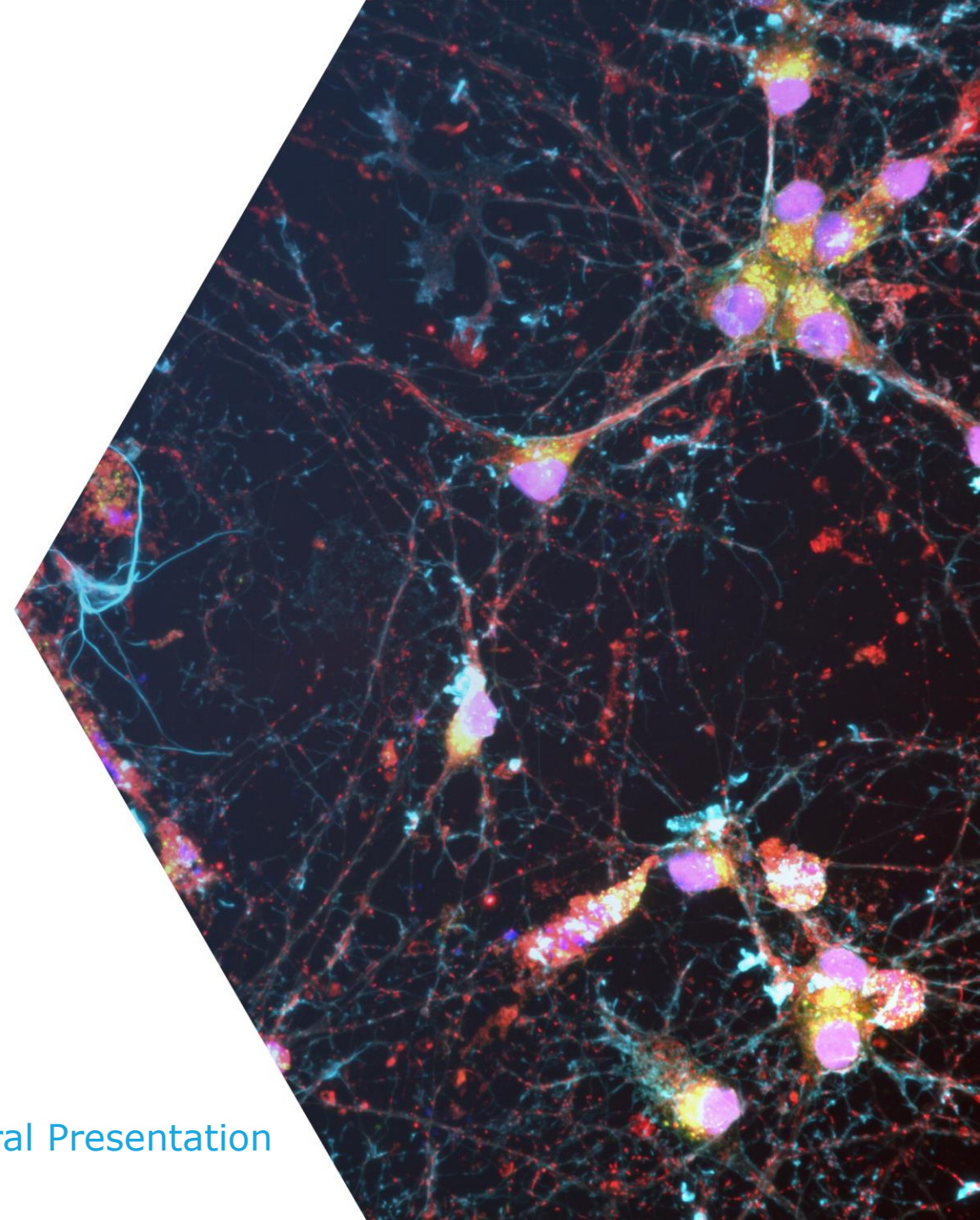
Recursion

A Phase 2, Randomized, Placebo-Controlled Trial Evaluating REC-994 in Patients with Symptomatic Cerebral Cavernous Malformations (CCM)



Dr. Jan Karl Burkhardt,
Division Head Cerebrovascular and Neurointerventional Surgery, Co-Director Neurointerventional Fellowship Program, The James and Agnes Kim Associate Professor of Neurosurgery

International Stroke Conference (2025) – Late-Breaking Oral Presentation

Cerebral Cavernous Malformations (CCM): A debilitating vascular genetic disorder with no approved therapies

Unmet Need

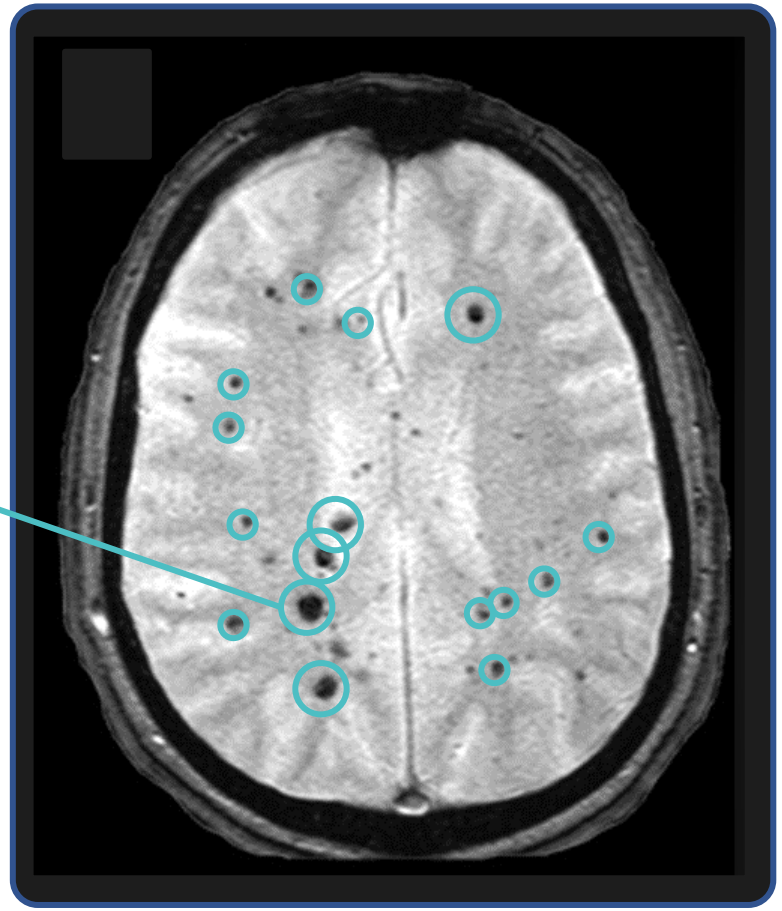
- **No approved therapy**
- **Surgical resection** or stereotactic radiosurgery is **non curative and not always feasible** because of location (e.g., brainstem lesions)

~360,000
Symptomatic CCM
US + EU5[1]

~90,000
Brainstem lesions
US + EU5[1]

Disease Overview

- **Vascular malformations** (cavernomas) in the brain and spinal cord
- **Debilitating symptoms**, including intractable seizure, intracerebral hemorrhage, focal neurological deficits
- **Progressive increase in CCM size** and number over time **worsens symptoms**[2]
- **CCM lesion volume** and **CCM at brainstem** are among the **top predictors of re-hemorrhage risk**[3]
- **Two forms of the disease:** Sporadic (1 lesion), Familial (>1 lesion)



1. Prevalence for hereditary and sporadic symptomatic population; Internal company estimates.
2. Smith ER. N Engl J Med (2024).
3. Zhao M. Nature (2024).

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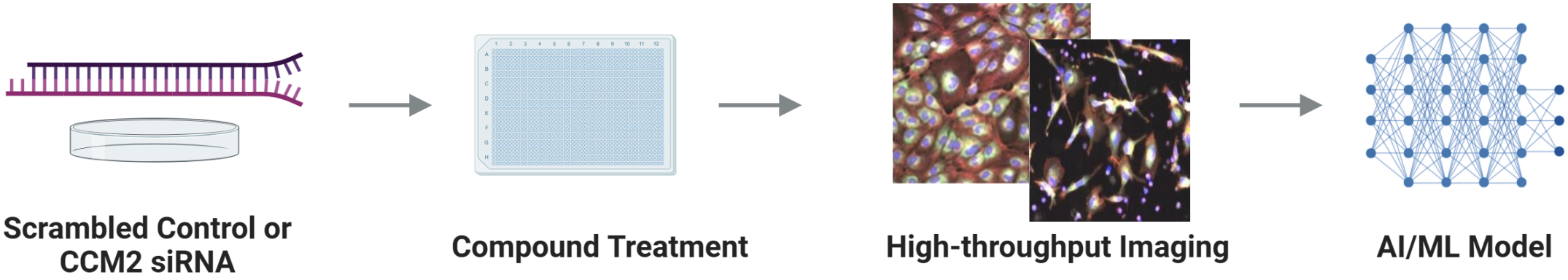
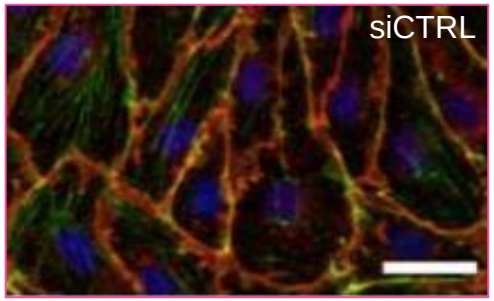
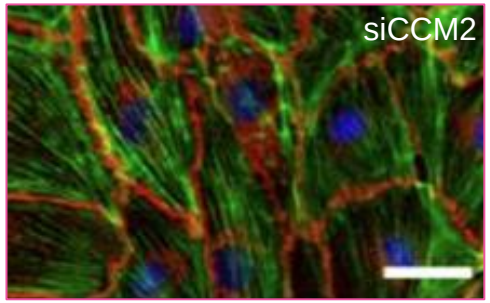
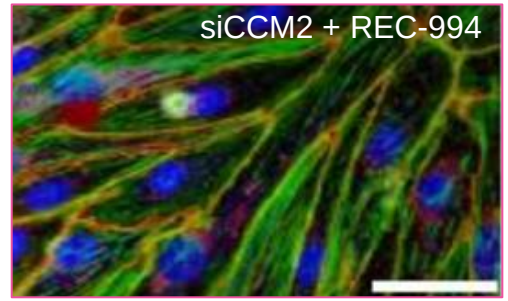
REC-994 was identified using the Recursion OS platform to rescue a CCM2 loss-of-function phenotype





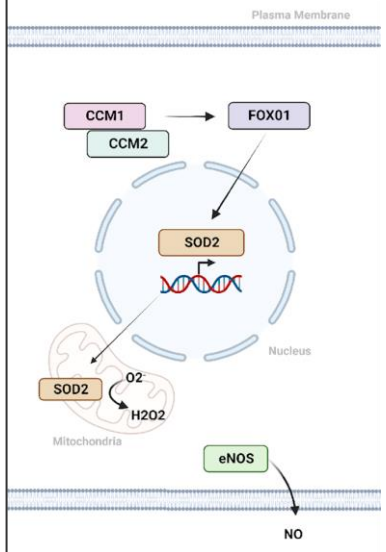




Source: Gibson et al, Circulation (2015)

Mechanism of Action: REC-994 works to restore oxidative stress balance and endothelial function

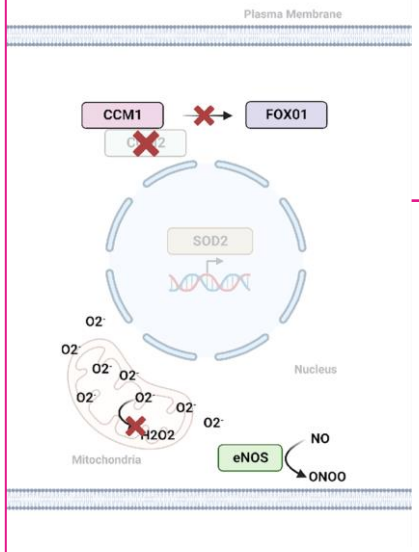
HEALTHY



By regulating SOD2, CCM1 (KRIT1) & CCM2 suppress:

- Endothelial cell activation
- Smooth muscle proliferation
- Leukocyte adhesion
- Platelet aggregation

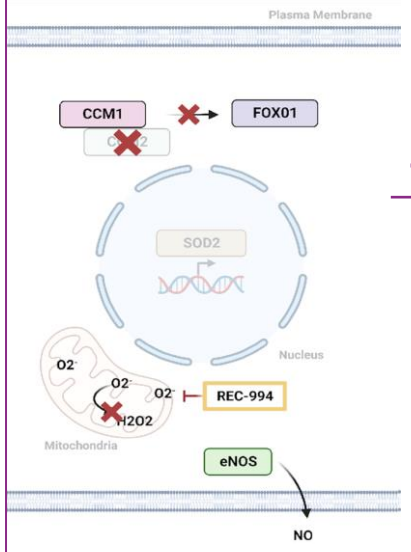
CCM



CCM1 or CCM2 loss of function leads to activated endothelium:

- Decreased cell-cell junctional integrity and increased monolayer permeability
- Impaired vasodilation
- Cavernous angioma formation

REC-994 IMPACT



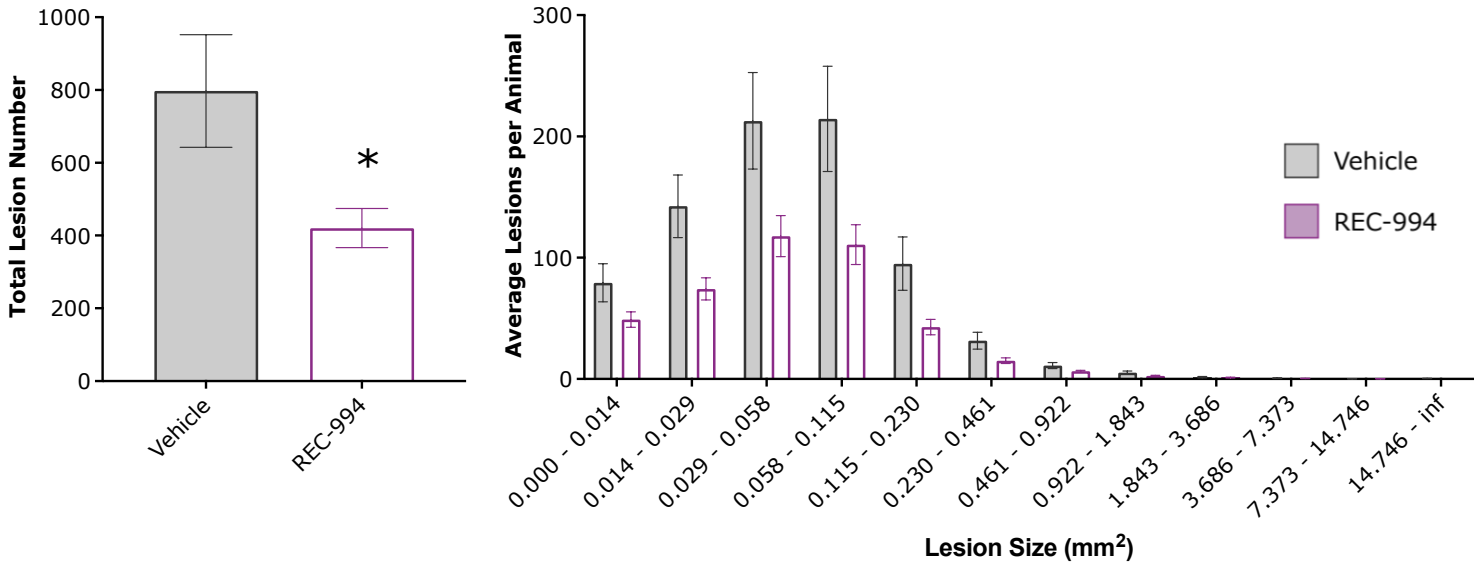
Dosing of REC-994 restores normal function:

- Normalized Reactive Oxygen Species balance
- Restores quiescent endothelial cell state
- Stabilizes endothelial barrier function

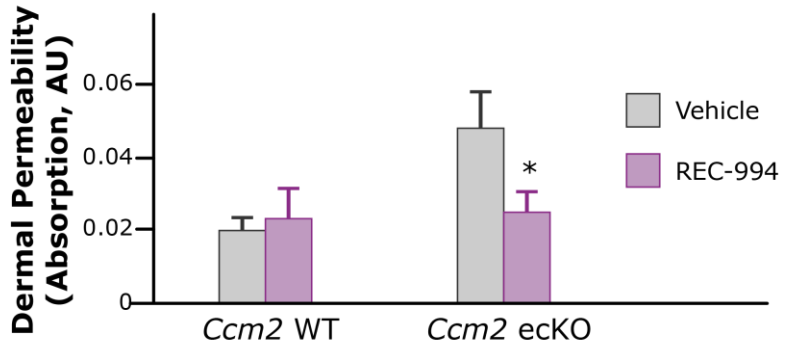
Source: Alfa et al, Pharmacology, Res Perspec (2024)

Preclinical Models: REC-994 reduces CCM lesion size, number, and rescues endothelial permeability

Reduces lesion number and size in Ccm2 LOF mouse models

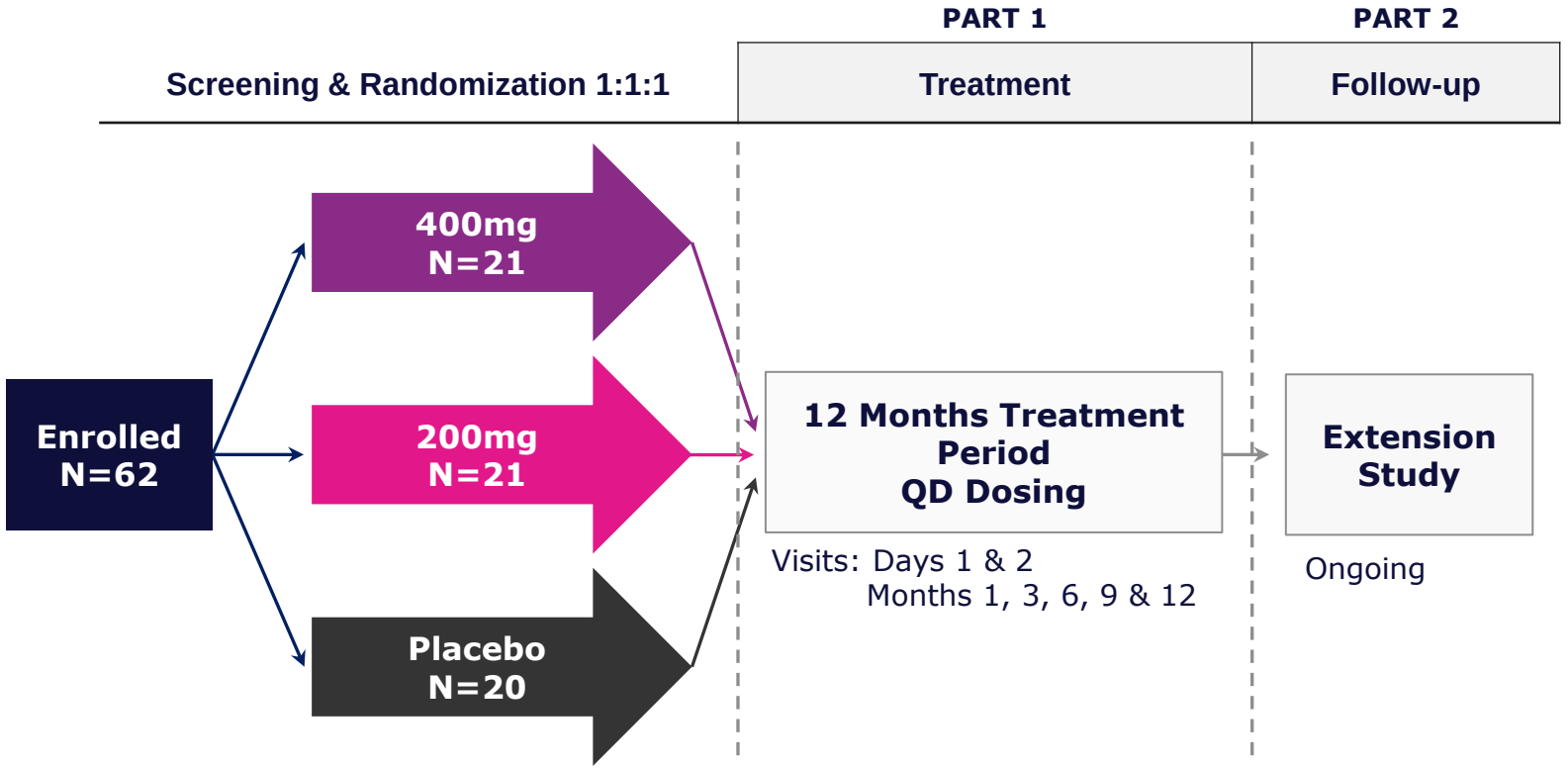


Rescues dermal permeability defect in Ccm2 mice



Source: Gibson et al, Circulation (2015) and unpublished data

Sycamore REC-994-201: A randomized, double-blind, placebo-controlled phase 2 trial in symptomatic CCM patients



Enrollment Criteria

- MRI-confirmed CCM lesion(s)
- Familial or sporadic
- Symptoms directly related to CCM
- Modified Rankin score ≥1

Study Objectives

- **Primary:** Safety and tolerability
- **Secondary:** neurologic disability (mRS), Patient-reported outcomes, disease-associated symptoms, MRI-or CT-related hemorrhagic events, pharmacokinetics
- **Exploratory:** Lesion volume change, Hemosiderin ring changes, and Biomarkers

Note: No patient enrichment by symptom; No stratification; 13 US sites enrolled in 18 months
Secondary and exploratory endpoints not statistically powered

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Patient Demographics: Baseline characteristics were generally balanced between treatment arms

Characteristic	Placebo (N=20)	REC-994 200 mg (N=21)	REC-994 400 mg (N=21)	Total (N=62)
Age, years	47.1 (15.8)	46.6 (14.5)	48.9 (10.8)	47.5 (13.6)
At time of diagnosis, years	37.1 (15.2)	36.7 (20)	40.6 (14.6)	38.1 (16.6)
Sex, n (%)				
Female	14 (70.0)	9 (42.9)	16 (76.2)	39 (62.9)
Male	6 (30.0)	12 (57.1)	5 (23.8)	23 (37.1)
White race, n (%)	17 (85.0)	18 (85.7)	17 (81.0)	52 (83.9)
BMI, kg/m^2	28.1 (7.8)	27.6 (5.7)	27.1 (5.7)	27.6 (6.3)
CCM Disease Etiology, n (%)				
Familial	12 (60.0)	13 (61.9)	9 (42.9)	34 (54.8)
Sporadic	8 (40.0)	7 (33.3)	12 (57.1)	27 (43.5)
Unknown	-	-	-	1 (1.61)
Previous symptom related to CCM, n (%)				
Focal neurological deficit	15 (75.0)	15 (71.4)	13 (61.9)	43 (69.4)
Intracerebral hemorrhage	11 (55.0)	14 (66.7)	16 (76.2)	41 (66.1)
Headache	12 (60.0)	16 (76.2)	12 (57.1)	40 (64.5)
Epileptic seizure	5 (25.0)	4 (19.0)	6 (28.6)	15 (24.2)
Genetic mutations, n (%)				
CCM1 (KRIT1)	6 (30)	7 (33.3)	3 (14.3)	16 (25.8)
CCM2	3 (15)	5 (23.8)	5 (23.8)	13 (21)
CCM3 (*PDCD10*)	0	0	2 (9.5)	2 (3.2)

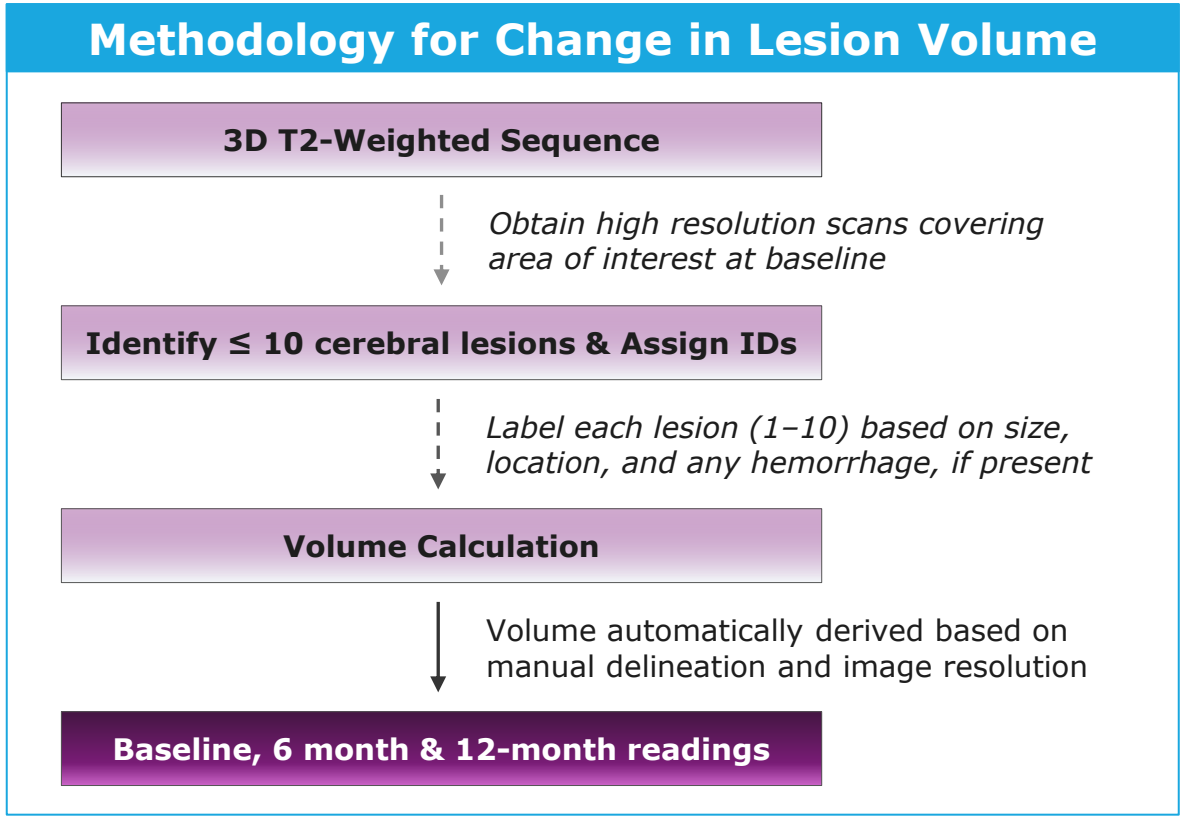
Ph 2 Safety: No new safety signals observed, with incidence of adverse events comparable across arms

Event, n (%)	Placebo (N=20)	REC-994 200 mg (N=21)	REC-994 400 mg (N=21)	Total (N=62)
Any Treatment Emergent Adverse Event (TEAE)	**17 (85.0)**	**18 (85.7)**	**15 (71.4)**	**50 (80.6)**
TEAEs Grade ≥3	4 (20.0)	7 (33.3)	3 (14.3)	14 (22.6)
Any TEAE related to study drug[1]	**2 (10.0)**	**0**	**5 (23.8)**	**7 (11.3)**
Grade ≥3 TEAE	0	0	0	0
Discontinuation due to TEAE	0	0	0	0
Dose interruption due to TEAE	0	0	0	0

- **Most common adverse** events reported in at least 10% of participants included:
  - Covid-19
  - Dizziness
  - Headache
  - Back pain
  - Constipation
- **No SAEs related** to study drug
- Majority of TEAEs were **Grade 1-2**
- **No treatment-related** adverse events that led to discontinuations

1. In the REC-400 mg arm these consisted of dizziness, rash, anemia, nausea and peripheral edema. In the placebo arm these consisted of dizziness and erythema multiforme. Across both arms, TEAEs related to study drug were Grade 1 or 2.

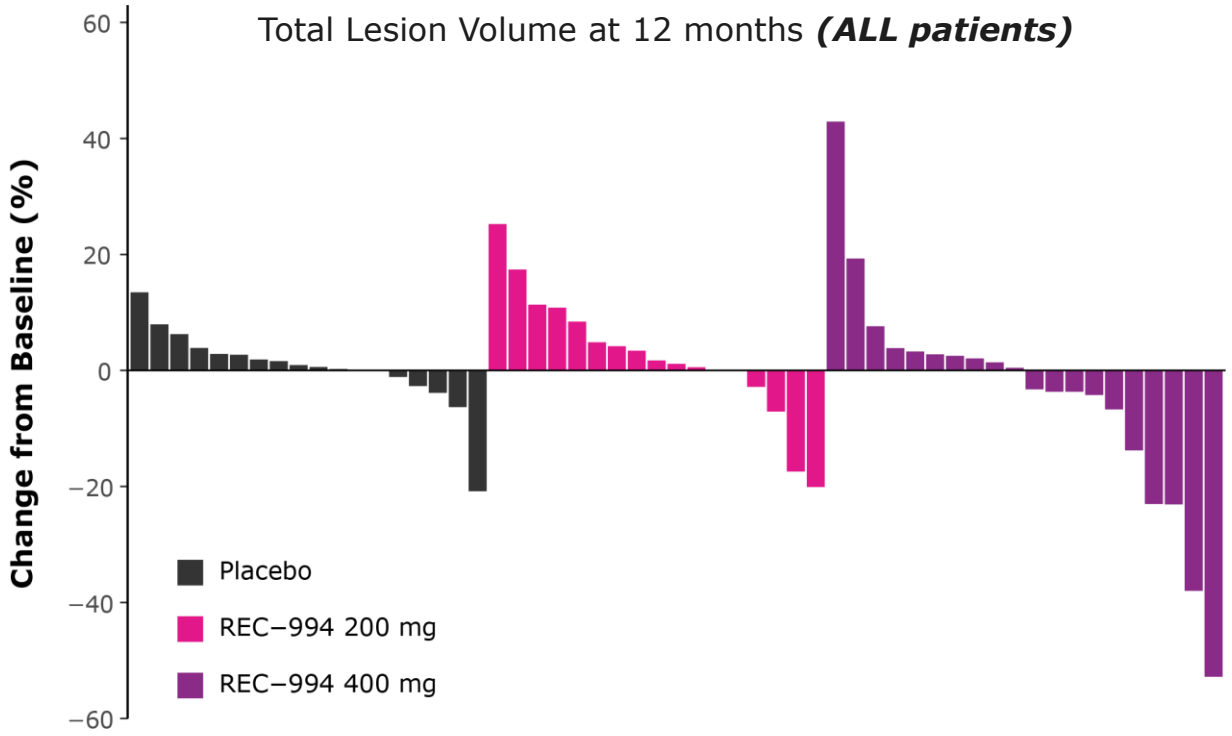
MRI assessments of cerebral lesions were conducted at baseline, 6 months, and 12 months



- 3D T2-weighted sequence is the primary MRI sequence used for delineation of each lesion
- CCM lesion details were captured and **up to 10 most relevant CCM** lesions followed longitudinally through the treatment period
- **A single, blinded, central neuroradiologist** performed all MRI readings per study specified protocol

Recursion

Exploratory Analysis: 50% of patients on 400 mg achieved a reduction in total lesion volume (LV)

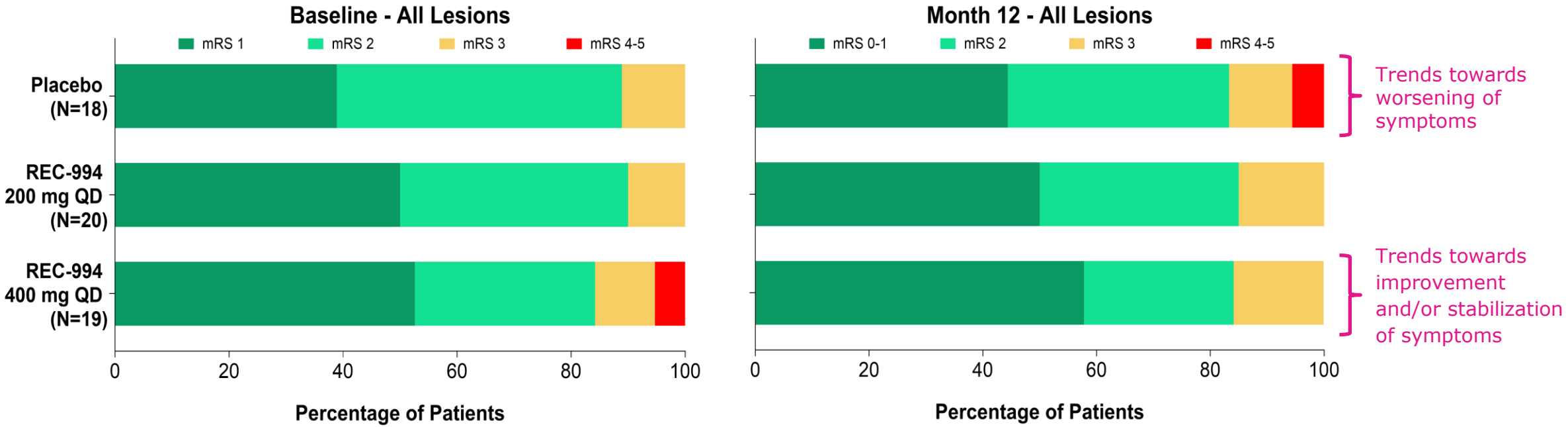


All Patients with Baseline and 12-month Scans	Placebo (N=18)	REC-994 200 mg (N=17)	REC-994 400 mg (N=20)
Absolute mean change in LV[1] per patient	53 mm^3	61 mm^3	**– 457 mm^3**
Percent change in LV from baseline per cohort	1%	1%	**– 10%**
Percent of patients with any reduction in LV	28%	24%	**50%**

1. Analysis of change from baseline between treatment and placebo for change in lesion volume (LV) at month 12 for REC-994 200 mg (p=0.912) and REC-994 400 mg (p=0.089) assessed by mixed model for repeated measures(MMRM) analysis

Recursion

Exploratory Analysis: Modified Rankin scale (mRS) suggests potential REC-994 improved clinical function in CCM patients

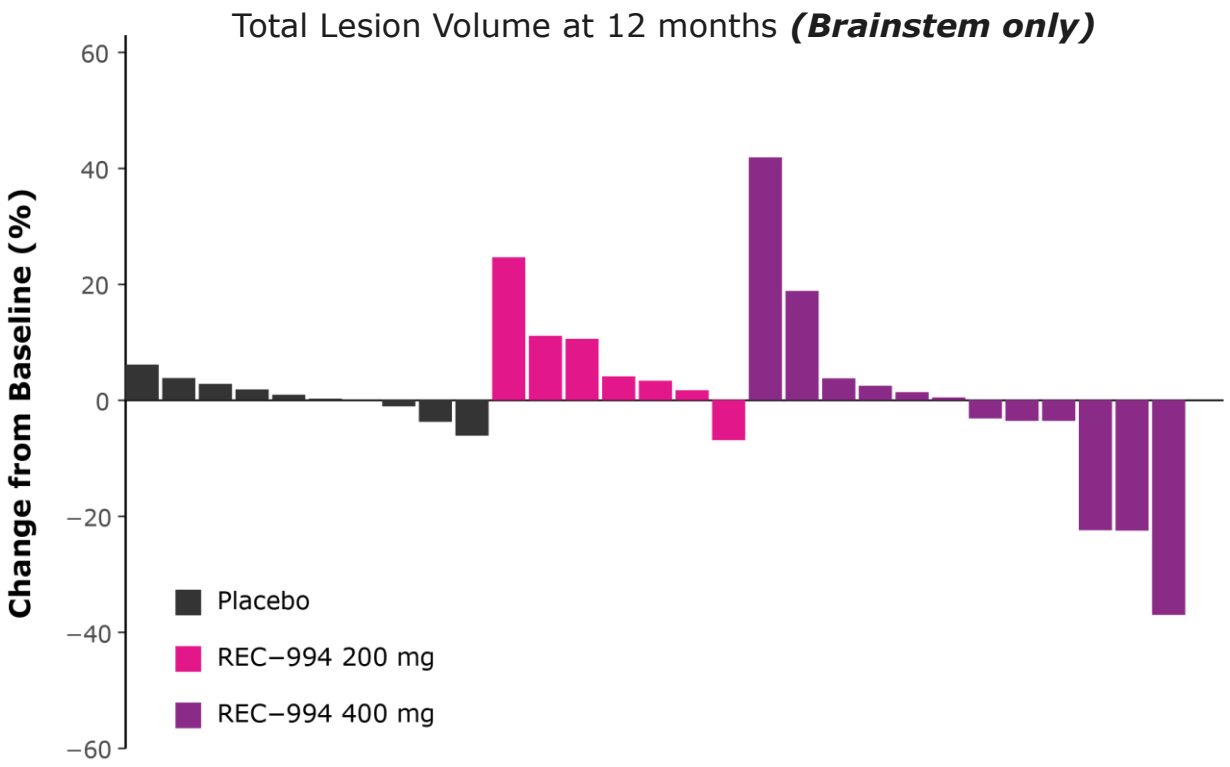


- The modified Rankin Scale (mRS) is widely recognized and approved by the FDA as a clinically meaningful endpoint for assessing functional outcomes in acute stroke trials[1]
- A single point change on the mRS is clinically relevant, with the FDA accepting dichotomous approaches using mRS cutoffs[1]

1. Broderick et al, Stroke (2017)

Recursion

Exploratory Analysis: 50% of patients on 400 mg achieved a reduction in total lesion volume (LV)



Brainstem only patients with Baseline and 12-month Scans	Placebo (N=10)	REC-994 200 mg (N=7)	REC-994 400 mg (N=12)
Absolute mean change in LV[1] per patient	-23 mm^3	123 mm^3	**– 256 mm^3**
Percent change in LV from baseline per cohort	-0.4%	7.5%	**-5.6%**
Percent of patients with any reduction in LV	27%	13%	**50%**

1. Analysis of change from baseline between treatment and placebo for change in lesion volume (LV) at month 12 for REC-994 200 mg (p=0.987) and REC-994 400 mg (p=0.449) assessed by mixed model for repeated measures(MMRM) analysis

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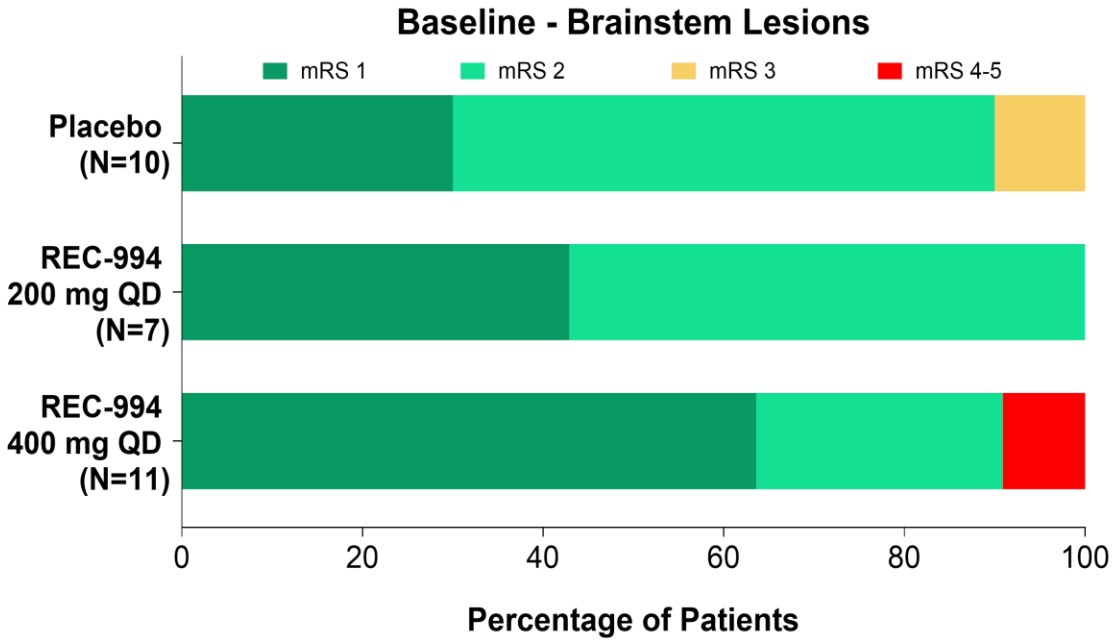
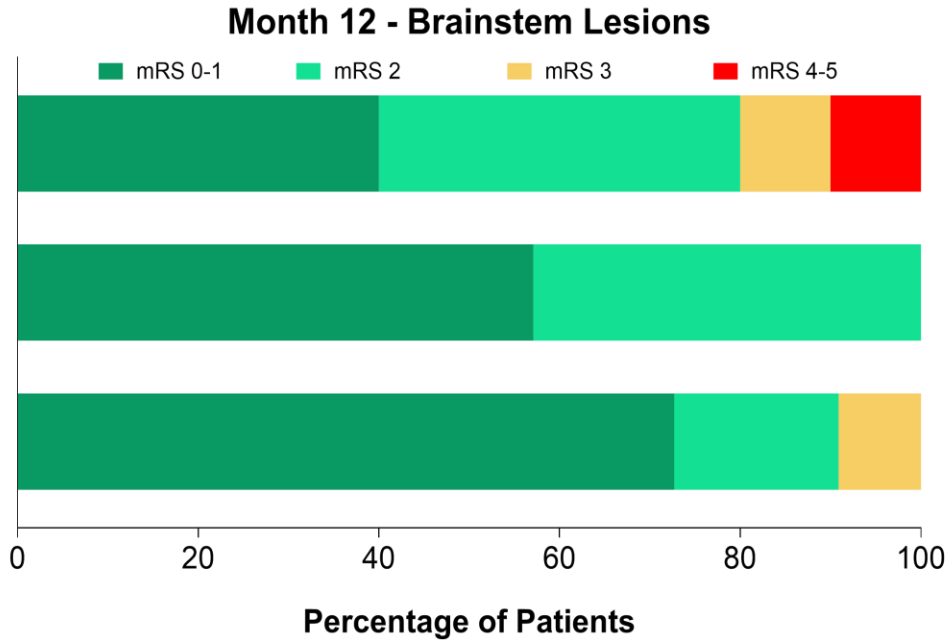
Exploratory Analysis: Signals of symptom improvement in brainstem lesions supports further investigation





- Similar trends in improvement or stabilization as assessed by mRS in the 400mg REC-994 arm was seen in the cohort of patients with brainstem lesions
- These observations support further investigation in a population of high unmet need, as cavernomas located in the brainstem are not amenable to surgical intervention

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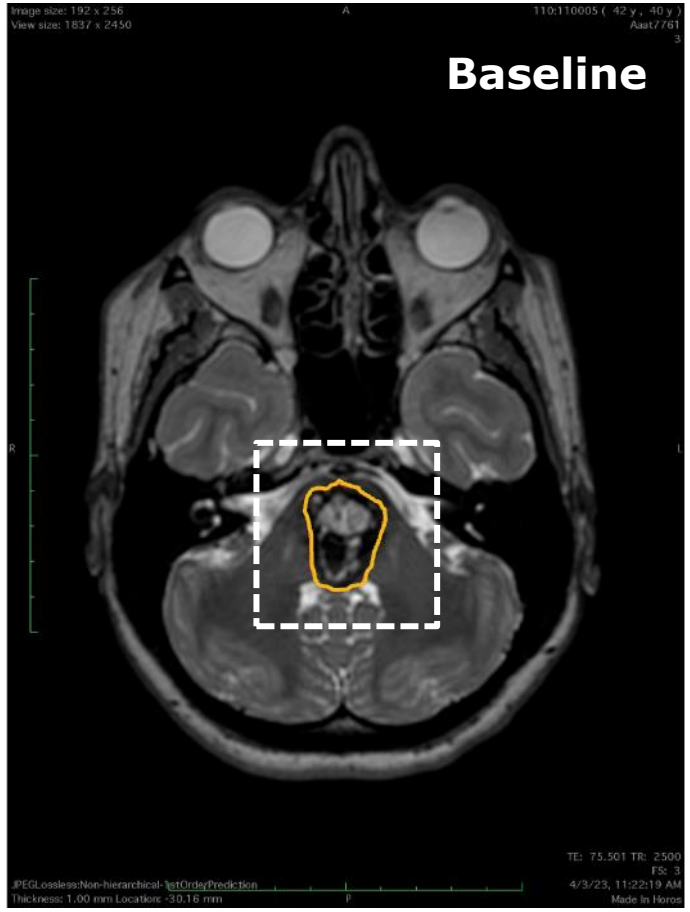
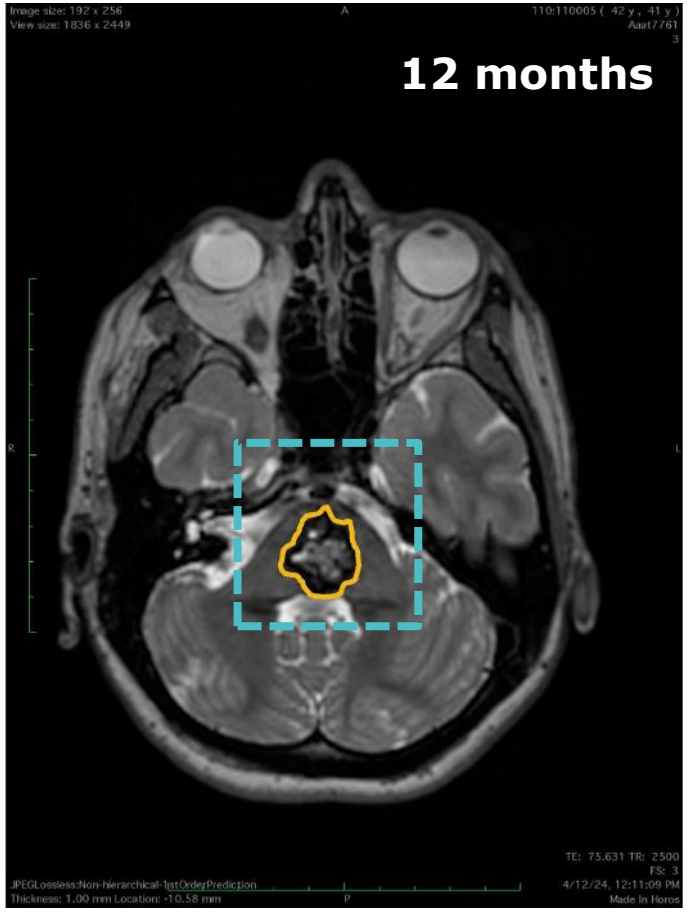
Case Study: Reductions in brainstem lesion volume and resolution in CCM-associated symptoms

- 39-year-old female diagnosed with a **sporadic CCM brainstem lesion**
- After 12 months of REC-994 400 mg treatment:
  - **~38% reduction** in baseline lesion volume (-2,630 mm^3 absolute lesion volume change)
  - **Complete resolution** of moderate/severe CCM symptoms incl. impaired mobility, headaches, hearing, and blurry vision symptoms





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Additional Analyses

Additional Secondary and Exploratory Analyses[1]

- Time-dependent reductions in hemosiderin ring size observed in the 400 mg arm as compared to 200 mg and placebo
- Seizure frequency appeared to be reduced in the 400 mg arm as compared to 200 mg and placebo however, there was imbalance with respect to seizure history and frequency across the arms
- Incidence of new symptomatic hemorrhage events were comparable across arms and in line with natural history studies
- Other PROs including PROMIS29, CCM-HI, NIHSS, SMSS, CGI, and PGI did not demonstrate differences between the treatment arms of the study nor placebo

1. These analyses were not statistically powered to detect changes from Placebo

Conclusions

- **Phase 2 Results:**
  - REC-994 was observed to be **safe and well tolerated** with no treatment related ≥ Grade 3 adverse events
  - **REC-994 400 mg treatment reduced lesion size and volume** in CCM patients, including those with brainstem lesions
  - **REC-994 400 mg improved clinical function** as seen by **modified Rankin score (mRS),** in CCM patients, including those with brainstem lesions

- **REC-994 identified using Recursion OS platform** to rescue a *Ccm2* loss-of-function phenotype by **restoring oxidative stress balance and endothelial function**

Next Steps:

- Long-Term Extension Part 2 is ongoing
- Interactions with Health Authorities planned to discuss potential clinical development

Sycamore Investigators & Clinical Sites

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Thank you

To all the Sycamore trial patients and their families

To the Alliance to Cure for their support

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Q&A


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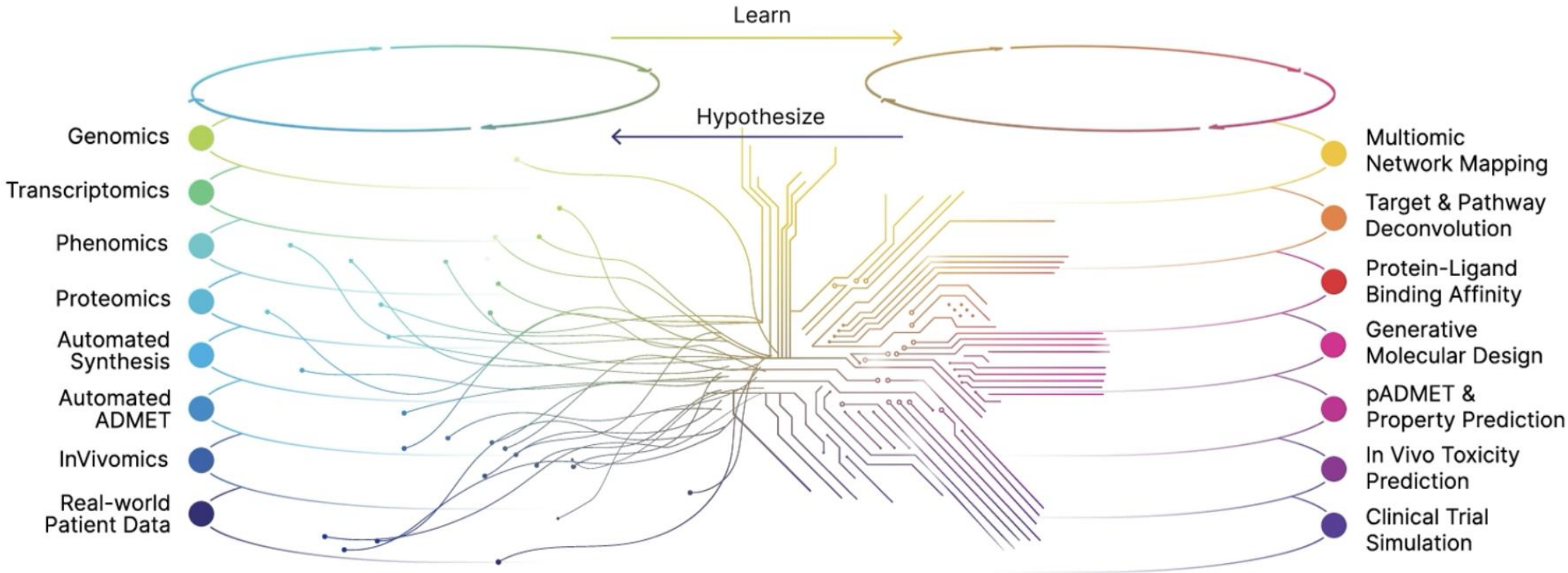

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