



Recursion Announces Initiation of Phase 2/3 Trial for the Treatment of NF2-Mutated Meningiomas at Children's Tumor Foundation NF Conference

June 20, 2022

- If successful, REC-2282 could be the first approved treatment for *NF2*-mutated meningiomas, which are debilitating lesions that occur in approximately 33,000 patients per year
- REC-2282 has been granted Fast Track and Orphan Drug designations for *NF2* meningiomas by the U.S. Food and Drug Administration, as well as Orphan Drug designation for *NF2* meningiomas by the European Commission

SALT LAKE CITY, June 20, 2022 /PRNewswire/ -- [Recursion](#) (NASDAQ: RXXR), the clinical-stage biotechnology company industrializing drug discovery by decoding biology, today announced the initiation of its Phase 2/3 POPLAR-NF2 clinical trial during the Children's Tumor Foundation NF Conference. The trial will evaluate REC-2282: a potentially first-in-disease, orally bioavailable, central nervous system (CNS) penetrant small molecule histone deacetylase (HDAC) inhibitor, for the treatment of progressive neurofibromatosis type 2 (*NF2*)-mutated meningiomas.

The study is actively enrolling patients who meet criteria including the following:

POPLAR-NF2: A Parallel-Group, Two-Staged, Phase 2/3, Randomized, Multicenter Study to Evaluate the Efficacy and Safety of REC-2282 in Participants With Progressive *NF2*-Mutated Meningiomas

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1 BACKGROUND

- Recursion is a clinical-stage biotechnology company decoding biology by integrating technological innovations across biology, chemistry, automation, machine learning, and engineering to industrialize drug discovery.
- REC-2282 is an orally bioavailable, small-molecule, broad-spectrum inhibitor of histone deacetylase (HDAC) enzymes.^{1,2}
- In studies of meningioma and schwannoma cell lines and mouse xenograft models, treatment with REC-2282 inhibited growth of primary cultures of human cell lines, inhibited tumor growth, decreased tumor volume, and induced apoptosis.^{3,4}
- The first-in-human clinical trial of REC-2282 resulted in median progression-free survival (PFS) of 1.7 and 9.1 months in patients with non-CNS solid tumors or CNS solid tumors, respectively,⁵ suggesting the potential benefit of REC-2282 in schwannoma and meningioma.
- POPLAR-NF2 (NCT05130866) is a Phase 2/3, randomized, multicenter trial to investigate the efficacy and safety of REC-2282 in patients with progressive meningiomas who have either neurofibromatosis type 2 (*NF2*) disease-related meningioma or sporadic meningiomas that have *NF2* mutations.

2 KEY ELEMENTS

- Being developed for the treatment of progressive *NF2*-mutated meningiomas
- Adult and adolescent patients with familial *NF2* meningiomas or sporadic meningiomas with *NF2* mutation
- Oral bioavailability and CNS exposure together are unique among clinical-stage HDAC inhibitors
- Potentially reduced cardiac toxicity compared to class

3 OBJECTIVES AND ENDPOINTS

	Cohort A	Cohort B
Primary	Efficacy of REC-2282: PFS at 6 months; Efficacy of REC-2282: PFS (time from PFS)	Efficacy of REC-2282: ORR, TTR, and DOR
Secondary	Efficacy of REC-2282: PFS12, PFS24	Safety and tolerability of REC-2282: Incidence of AEs, SAEs, and changes in laboratory parameters
Exploratory	Dose response: PFS3 and ORR at each dose level	Effect of treatment with REC-2282: time to surgery/radiation for target tumor
		PK of REC-2282: C _{max} , T _{1/2} , AUC ₀₋₂₄ , t _{1/2} , C _{min} , and C _{trough}
		Effect of REC-2282 on CNS: physical findings, meningioma-related symptoms, ophthalmologic findings
		Efficacy of REC-2282 in different <i>NF2</i> gene mutations as measured by PFS and ORR
		Correlation between meningioma-related biomarkers and effect of REC-2282
		Relationship between PK exposure, safety, and efficacy
		PK of the <i>R</i> -enantiomer of REC-2282 (REC-1157033) and PK of the REC-2282 metabolite, REC-1157034, and its <i>R</i> -enantiomer (REC-1157941)

4 METHODS

- Approximately 20 adult and 9 adolescent participants will be randomized to 1 of 2 dose levels of REC-2282 in Cohort A.
- The first 8 adults enrolled in Cohort A will complete a food effect run-in substudy.
- Adolescents will participate in a 3 + 3 dose escalation study.
- In Cohort B, approximately 60 adult and adolescent participants will be randomized to a single dose of REC-2282 or placebo in a 2:1 ratio to assess the efficacy and safety of REC-2282 compared with placebo.
- Both cohorts include screening (up to 8 weeks), treatment, a 4-week safety follow-up, and a 6-month follow-up.
- Participants may be eligible for an open-label extension.

5 STUDY DESIGN

6 ELIGIBILITY CRITERIA

Key Inclusion Criteria:

- Adolescents and adults ≥ 12 years of age weighing ≥ 40 kg
- Progressive meningioma* that is ≤ 1 cm³ and amenable to volumetric analysis with no intervention or systemic therapy since last progression
- Has either sporadic meningioma with prior tumor analysis demonstrating *NF2* mutation or a confirmed diagnosis of *NF2* disease by Manchester criteria or having an *NF2*-related tumor and a pathogenic germline or proven mosaic *NF2* variant
- KPS of ≥ 1 at screening
- Adequate bone marrow, renal, and liver function

Key Exclusion Criteria:

- Progressive disease associated with significant or disabling symptoms
- Prior surgery, radiotherapy/stereotactic radiosurgery or laser interstitial thermal therapy in target tumor (or adjacent) within 6 months of screening
- Received anti-tumor agent within prior 3 months
- History of an active malignancy within the previous 3 years[†]
- Other investigational drug within 30 days or prior treatment with REC-2282 or another HDAC inhibitor within prior 3 years
- Use of drugs or supplements that are inhibitors of BCRP and P-gp, or substrates of CYP3C4 or CYP3A4 for ≥ 2 weeks prior to first dose of study drug
- Corrected QT interval of >450 ms (men) and >470 ms (women)

7 ENROLLMENT

- Approximately 89 participants will be enrolled across 25 centers
- Cohort A: 29 participants in ~12 sites (10 US, 2 UK)
- Cohort B: 60 participants in ~25 global sites

8 SUMMARY

POPLAR-NF2 is designed to investigate the efficacy and safety of REC-2282, representing a potential new pharmacologic treatment for patients with progressive *NF2*-mutated meningiomas. Enrollment is ongoing.

9 REFERENCES

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10 ACKNOWLEDGMENTS

We extend our thanks to the patients, family, and caregivers, as well as to the study staff. This study was funded by Recursion Pharmaceuticals, Inc.

11 DISCLOSURES

GM, LB, MB, TC, KC, KK, DS, HW, and RD are employed by Recursion Pharmaceuticals, Inc.

- >12 years of age and weighing at least 40 kg
- Progressive meningioma that is amenable to volumetric analysis
- Has either 1) sporadic meningioma with confirmed *NF2* mutation; or, 2) confirmed diagnosis of *NF2* disease (revised Manchester criteria); or, 3) at least one *NF2*-related tumor (with pathogenic germline or proven mosaic *NF2* variant)

There are currently no FDA-approved drugs for the treatment of patients with *NF2*, an inherited genetic syndrome that can cause a variety of benign tumors in the central nervous system, including meningiomas. Recursion discovered REC-2282 as a potential candidate for treatment of disease resulting from mutation in the *NF2* gene by leveraging its proprietary AI-powered drug discovery platform, the Recursion OS. We believe this approach, in which machine learning is used to identify relationships between biological contexts and chemical entities, will enable Recursion to accelerate the drug discovery process and expand the scope of potential therapeutic candidates for numerous diseases.

"We are currently crying out for a therapy for inoperable meningiomas and in particular the multiple meningiomas that we see in neurofibromatosis type 2 that cause so much morbidity and ultimately mortality," said Professor Gareth Evans, Manchester University NHS Foundation Trust, St. Mary's Hospital. "An efficacious drug that reduces meningioma size or at least stabilizes tumor growth would be highly impactful for neurofibromatosis type 2 patients, with 60% of even isolated meningiomas in these patients being associated with loss of *NF2* gene function."

"Initiating patient enrollment in our Phase 2/3 POPLAR-NF2 clinical trial marks a significant moment for patients with neurofibromatosis type 2 and

sporadic meningiomas driven by mutations in the *NF2* gene," said Glenn Morrison, M.Sc., Ph.D., Vice President of Clinical Development at Recursion.

The Phase 2/3 trial is designed as a randomized, multi-center, double-blind, placebo-controlled study to investigate the safety, efficacy and pharmacokinetics of REC-2282. The study is expected to enroll approximately 90 participants.

For more information about enrollment, please visit [this link](#) or reach out to clinicaltrials@recursion.com.

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About REC-2282

REC-2282 is a CNS-penetrant, orally bioavailable, small molecule pan-HDAC inhibitor being developed for the treatment of *NF2*-mutated meningiomas. This molecule appears to be well tolerated, including in patients dosed for multiple years, and potentially has reduced cardiac toxicity that would differentiate it from other HDAC inhibitors. Its oral bioavailability and CNS penetrance distinguish it from currently-approved HDAC inhibitors. REC-2282 has been granted Fast Track and Orphan Drug designations for *NF2*-mutated meningiomas by the U.S. Food and Drug Administration, as well as Orphan Drug designation for *NF2*-mutated meningiomas by the European Commission.

About Neurofibromatosis Type 2

NF2 is an autosomal dominant, inherited, rare tumor syndrome caused by loss-of-function mutations in the *NF2* tumor suppressor gene, which encodes the cell signaling regulator protein 'merlin.' Loss of *NF2* function results in growth of the hallmark tumors that characterize this disease: vestibular schwannomas (VS) and meningiomas. The VS and meningioma tumor types seen in *NF2* are among the most common in neuro-oncology. In addition, *NF2* mutations give rise to mesotheliomas and underlie subsets of additional tumor types. *NF2*-mutated meningiomas occur in approximately 33,000 patients per year. The large numbers of these lesions that frequently occur in *NF2* patients lead to significant morbidity, including hearing, vision, and mobility impairment, and mortality.

About Recursion

[Recursion](#) is the clinical-stage biotechnology company industrializing drug discovery by decoding biology. Enabling its mission is the Recursion Operating System, a platform built across diverse technologies that continuously expands one of the world's largest proprietary biological and chemical datasets, the Recursion Data Universe. Recursion leverages sophisticated machine-learning algorithms to distill from its dataset the Recursion Map, a collection of hundreds of billions of searchable relationships across biology and chemistry unconstrained by human bias. By commanding massive experimental scale — up to millions of wet lab experiments weekly — and massive computational scale — owning an operating one of the most powerful supercomputers in the world, Recursion is uniting technology, biology and chemistry to advance the future of medicine.

The Company is headquartered in Salt Lake City, where it is a founding member of [BioHive](#), the Utah life sciences industry collective. Recursion also has offices in Toronto, Montréal and the San Francisco Bay Area. Learn more at www.Recursion.com, or connect on [Twitter](#) and [LinkedIn](#).

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Forward-Looking Statements

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