



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

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- 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](https://www.recursion.bio) (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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Recursion Pharmaceuticals, Inc.

- 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.
- 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
- OBJECTIVES AND ENDPOINTS**

	Cohort A	Cohort B
Primary	Efficacy of REC-2282: PFS at 6 months	Efficacy of REC-2282: PFS (time from PFS)
Secondary	Efficacy of REC-2282: PFS12, PFS24	
Exploratory	Dose response: PFS12 and ORR	
Exploratory	Efficacy of REC-2282: ORR, TTR, and DOR	
Exploratory	Safety and tolerability of REC-2282: incidence of AEs, SAEs, and changes in laboratory parameters	
Exploratory	Effect of treatment with REC-2282: time to surgical resection for target tumor	
Exploratory	PK of REC-2282: C _{max} , T _{1/2} , AUC ₀₋₂₄ , C _{min} , and C _{24h}	
Exploratory	Effect of REC-2282 on CNS: Pharmacokinetic, meningioma-related symptoms, ophthalmologic findings	
Exploratory	Efficacy of REC-2282 in different <i>NF2</i> gene mutations as measured by PFS and ORR	
Exploratory	Efficacy of REC-2282 in adults and adolescents as measured by OS	
Exploratory	Tumor growth rate post-treatment compared to pre-treatment	
Exploratory	Correlation between meningioma-related biomarkers and effect of REC-2282	
Exploratory	Relationship between PK exposure, safety, and efficacy	
Exploratory	PK of the R-enantiomer of REC-2282 (REC-1157033) and PK of a REC-2282 metabolite (REC-1157384)	
- 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 sub-study.
 - 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.
- STUDY DESIGN**

COHORT A

FOOD EFFECT RUN-IN SUBSTUDY

Period 1: DAY 1 REC-2282 40 mg Single PO dose Fasted state; DAY 2 REC-2282 40 mg Single PO dose Fasted state

Period 2: DAY 5 REC-2282 40 mg Single PO dose Fasted state; DAY 6 REC-2282 40 mg Single PO dose Fasted state

Open-label Treatment duration: up to 28 cycles (2 years)

Adults (18 years) n = 20; Adolescents (12 to <17 years) n = 9

3 + 3 dose escalation 30 mg → 40 mg → 60 mg

COHORT B

Double-blind, placebo-controlled Treatment duration: up to 28 cycles (2 years) for best participant enrolled

Adults and adolescents n = 60; Randomized 2:1 1 dose REC-2282 or placebo
- ELIGIBILITY CRITERIA**

Key Inclusion Criteria

 - Adults and adolescents aged ≥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 molecular testing or having an *NF2*-related tumor and a pathogenic germline or proven mosaic *NF2* variant
 - MRIs (T1 and T2) and/or CT scan
 - Adequate bone marrow, renal, and liver function

Key Exclusion Criteria

 - Progressive disease associated with significant or disabling symptoms
 - Prior surgery, radiotherapy/steroid, radiotherapy or lower intensity thermal therapy to target tumor or adjacent within 6 months of study start
 - Received anti-tumor agent within prior 3 months
 - History of an active malignancy within the previous 3 years⁶
 - 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 CYP2C8 and P-gp, or substrates of CYP2C8 or BCRP for 2 weeks prior to first dose of study drug
 - Concomitant QT interval of >450 ms (men) and >470 ms (women)
- 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

United States, Europe

Additional information is available at ClinicalTrials.gov: <https://clinicaltrials.gov/ct2/show/NCT05130866>
- 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.
- REFERENCES**
 - Burns SS, et al. *Cancer Res*. 2013;73(2):760-803.
 - Lu Q, et al. *J Med Chem*. 2016;48(17):5530-5535.
 - Doni M, et al. *Nature Oncol*. 2011;1(9):983-999.
 - Jacob A, et al. *Lancet Oncol*. 2012;13(11):1114-19.
 - Collins KA, et al. *Cancer Chemother Pharmacol*. 2021;78(1):169-81.
- ACKNOWLEDGMENTS**

We extend our thanks to the patients, family, and caregivers, as well as the Recursion Pharmaceuticals, Inc.
- DISCLOSURES**

GM, LB, MB, KC, NK, DS, AW, and RC are employed by Recursion Pharmaceuticals, Inc.

1. >12 years of age and weighing at least 40 kg
2. Progressive meningioma that is amenable to volumetric analysis
3. 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

This document contains information that includes or is based upon "forward-looking statements" within the meaning of the Securities Litigation Reform Act of 1995, including, without limitation, those regarding early and late stage discovery, preclinical, and clinical programs; licenses and collaborations; prospective products and their potential future indications and market opportunities; Recursion OS and other technologies; business and financial plans and performance; and all other statements that are not historical facts. Forward-looking statements may or may not include identifying words such as "plan," "will," "expect," "anticipate," "intend," "believe," "potential," "continue," and similar terms. These statements are subject to known or unknown risks and uncertainties that could cause actual results to differ materially from those expressed or implied in such statements, including but not limited to: challenges inherent in pharmaceutical research and development, including the timing and results of preclinical and clinical programs, where the risk of failure is high and failure can occur at any stage prior to or after regulatory approval due to lack of sufficient efficacy, safety considerations, or other factors; our ability to leverage and enhance our drug discovery platform; our ability to obtain financing for development activities and other corporate purposes; the success of our collaboration activities; our ability to obtain regulatory approval of, and ultimately commercialize, drug candidates; the impact of the COVID-19 pandemic and force majeure events; our ability to obtain, maintain, and enforce intellectual property protections; cyberattacks or other disruptions to our technology systems; our ability to attract, motivate, and retain key employees and manage our growth; and other risks and uncertainties such as those described under the heading "Risk Factors" in our filings with the U.S. Securities and Exchange Commission, including our most recent Quarterly Report on Form 10-Q and our Annual Report on Form 10-K. All forward-looking statements are based on management's current estimates, projections, and assumptions, and Recursion undertakes no obligation to correct or update any such statements, whether as a result of new information, future developments, or otherwise, except to the extent required by applicable law.

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