2023 Shareholder Letter and Business Overview
A Letter from Our Co-Founder and CEO

Dear current or prospective shareholder,

Recursion celebrated its tenth anniversary in 2023, and as I reflect back on the past decade of building and look forward to the next decade, it feels increasingly clear that we are in the midst of a tremendous technology and AI-driven transition in our society.

Knowledge workers are on the precipice of a massive transformation in their work; much of the toil embedded into the processes, systems and delivery today will give way to higher efficiency, more creativity and smart risk-taking with new tools that will enable rapid and deep experimentation and fast failure. For many, embracing this evolving landscape of work will be tumultuous, but for those who are open to the possibilities technology brings, an exciting new future awaits.

Like all major past shifts in society, we will face many new challenges and obstacles as we come to terms with the risks and opportunities of the new tools that are becoming increasingly available at our fingertips.

The broad transformations in society will be mirrored in the life sciences with the evolution of BioTech into TechBio over the coming decade. The digitization of biology and chemistry will enable us to predict ways to map and navigate it, allowing us to design rather than discover better medicines faster with less failure. Advancements in laboratory automation, biological tools and quantified human health will allow for the emergence of massive datasets of human health and disease that will feed the AI-driven insights transforming life sciences.

Of course, the idea that an AI ‘black-box’ will pop out new cures at scale in the coming 12-24 months is a fallacy and we have to be careful not to be caught up in that sort of hype. Drug discovery is too complex, has too many steps and has too long of a feedback loop for that sort of ‘overnight’ shift. But looking back at how far we have come and the compounding improvements we see today, I believe that our industry will shift more in the coming decade than it ever has before.

A common argument from skeptics is that biology is too complex and healthcare too complicated for such a disruptive technological transformation to be possible. But like in prior industrial revolutions, a new technology (or technologies) has set in motion a current that will fundamentally reshape the forces and assumptions that drive various fields, including our own. Here are a few facts that signal this transformation is happening right now:

**Data & Compute:**
- The world has generated more data in the past 24 months than in all of human history before that
- The world has consumed more computational cycles in the last 12 months than in all of human history before that

**Biological Tools:**
- CRISPR-based gene editing has, in just the last five years, enabled for the first time arrayed genome-wide genetic screens
- Innovations in induced pluripotent stem cells allow us to generate high-quality, differentiated human cells at massive scale

**Automation and Reagents:**
- Robotic laboratory systems and software enable highly standardized and quality-controlled high-throughput screening to generate relatable data at scale
What's more, the signs of AI-enabled point-solutions are already plentiful across our industry:

- Protein folding
- Scaled protein-ligand interaction prediction
- Generative AI for chemistry for tractable targets
- The FDA is already discussing the use of LLMs for program review
- Major pharma companies are drafting regulatory filings like INDs by LLMs

These facts lay out a clear future where efficiencies and improvements across the many current AI-enabled point-solutions will begin to combine into integrated ‘tech-stacks’ and workflows that will result in compounding improvements in our ability to drug historically undruggable targets, understand the underlying networks of biology with increasing fidelity, fast-follow newly validated biology, characterize disease in increasingly robust ways and ultimately deliver more, better medicines to patients to alleviate suffering at scale. The question is no longer whether this sort of future is before us, but when and who will lead it.

**Looking Back at 2023 and Before**

Reflecting back on late 2013 when Recursion was founded and how far we have come, it is simultaneously incredible and unsurprising to see where we are today. Recursion was then a Utah-based startup founded by two graduate students and a professor. Our first office was a conference room in the nearby University Research Park and our first laboratory was a converted storage room. Today, Recursion is a multinational, clinical-stage company leading the transition of BioTech into TechBio. We have over 500 employees, five clinical stage programs, one of the world’s largest biological and chemical datasets and two of the largest discovery collaborations in the industry with Roche/Genentech and Bayer.

And in 2023, the opportunity ahead feels so much greater than it did in 2013, that in some ways it still feels like we are just getting started. In fact, from an internal perspective, 2023 felt like one of the best years in our history. In 2023 we achieved a lot of important milestones, and a lot of things we’ve been working to build, in some cases for years, really seemed to start hitting their stride, including:

**Pipeline**

- Five phase 2 clinical-stage programs with multiple upcoming data readouts expected, including REC-994 in cerebral cavernous malformation (CCM) in Q3 2024, REC-2282 in neurofibromatosis type 2 (NF2) in Q4 2024, REC-4881 in familial adenomatous polyposis (FAP) in H1 2025, and REC-4881 in AXIN1 or APC mutant solid tumors in H1 2025
- Completed a Phase 1 study for REC-3964 in healthy volunteers for the potential treatment of Clostridioides difficile (C. difficile) infection with a favorable safety and tolerability profile
- Advanced our RBM39 program in homologous recombination proficient ovarian cancer and other solid tumors to IND-enabling studies
- In-licensed a program (Target Epsilon) that emerged from our fibrosis collaboration with Bayer that represents a novel approach to treating fibrotic diseases with compelling early data
Our Collaborators

Roche and Genentech
Bayer
NVIDIA
Tempus
Enamine

Partnership

- Made significant progress against both the gastrointestinal-oncology and neuroscience portions of our collaboration with Roche and Genentech, including Roche exercising its Small Molecule Validated Hit Option to further advance our first partnership program in GI-oncology
- Updated our collaboration with Bayer to focus on challenging oncology indications with high unmet need, commensurate with higher per program milestone payments
- Entered into a collaboration with NVIDIA to accelerate the construction, optimization and deployment of foundation models for biology and chemistry as well as host Recursion-built computational and data tools on BioNeMo (NVIDIA’s drug discovery platform) – additionally, NVIDIA invested $50 million in Recursion via a private placement
- Entered into a collaboration with Tempus giving Recursion access to over 20 petabytes of proprietary de-identified, multimodal patient oncology data for the purpose of training causal AI models for the discovery of novel therapeutic hypotheses, biomarker strategies and patient cohort selection
- Entered into a partnership with Enamine to generate enriched screening libraries with insights from Recursion’s protein-ligand interaction predictions spanning across Enamine’s massive library of approximately 36 billion compounds

Recursion OS

- Built, scaled and industrialized multiple tools and technologies to heavily automate workflows across the drug discovery process, creating one of the most complete full-stack TechBio solutions
- Created LOWE (Large Language Model-Orchestrated Workflow Engine) connecting wet-lab and dry-lab components of the Recursion OS using a natural language interface to streamline complex drug discovery tasks
- Deployed large language models (LLMs) to map scientific literature in conjunction with our internally derived proprietary maps for the purpose of autonomously identifying novel opportunities in areas of unmet need
- Deployed Phenom-1, a vision transformer utilizing hundreds of millions of parameters trained on billions of biological images from our proprietary data, which we believe to be the world’s largest phenomics foundation model at this time
- Deployed new digital chemistry tools to predict the ligand-protein interactions for approximately 36 billion compounds in the Enamine REAL Space, reported to be the largest synthesizable chemical library
- Produced over 1 trillion human induced pluripotent stem cell (hiPSC)-derived neuronal cells since 2022, likely making Recursion one of the world’s largest producers of neuronal cells
- Began training causal AI models leveraging over 20 petabytes of multi-modal precision oncology patient data from Tempus to support the discovery of potential biomarker-enriched therapeutics at scale

LOWE (LARGE LANGUAGE MODEL-ORCHESTRATED WORKFLOW ENGINE) is connecting wet-lab and dry-lab components of the Recursion OS using a natural language interface to streamline complex drug discovery tasks

>1 Trillion

HUMAN INDUCED PLURIPOTENT STEM CELL (hiPSC)-derived neuronal cells produced since 2022
Company Building

- Acquired Cyclica and Valence Discovery to bolster digital chemistry and generative AI capabilities
- Expanded our operations in Salt Lake City and Montréal and opened our Canadian headquarters in Toronto with a focus on growing our machine learning and digital chemistry teams
- Committed to quadrupling the capacity of our supercomputer, BioHive-1, to support our pipeline, partnerships and the construction of foundation models across the multiple modalities of biology, chemistry and patient-centric data – we believe that this expansion should make our supercomputer a top 50 supercomputer across any industry according to the TOP500 list

As one of the leading TechBio companies, Recursion has played a critical role in driving the pace and scale of adoption of new TechBio tools across the industry. And while I am very proud of how our team delivered in 2023, the most important shift for our business happened outside our walls this year. We finally found the ideas embedded in TechBio, and in particular the belief in the utility of AI in our industry, finding mainstream support among some of the larger and more traditional companies in the space.

While there is no doubt there will be massive short-term volatility in the space, there is an increasing consensus among leaders in BioPharma that ML and AI are going to play a very important role over the coming decade. While we have incredible work before us, it feels as if we are no longer sailing into the wind, but now the wind is starting to shift to our backs. And I believe that there is no team in the world better prepared to sail fast in this new environment and continue to put deep blue water between us and many of our competitors as we look out over the coming years.

Looking Out at 2024 and Beyond

You could almost taste the shift in sentiment around TechBio at the J.P. Morgan Healthcare Conference at the beginning of this year when compared to years prior. While some skepticism still prevails, it no longer carries the room in most places as a shift towards cautious optimism permeates the executive teams and boards of the most powerful companies in our space.

Following the announcement of our partnership with NVIDIA in 2023, we co-hosted an event with them at the JP Morgan conference. We brought together members of the executive teams and boards of many of the largest biopharma companies in the world, many of the CEOs of leading TechBio companies, executives of leading tech companies, and investors and analysts who either already invest in or cover this convergence or are tempted to do so.

That evening, attendees heard from life science luminaries like Scott Gottlieb, Aviv Regev and Amy Abernethy as well as Jensen Huang, the CEO of NVIDIA. They heard conviction from those leaders about how clearly the trend of ML and AI will impact our industry going forward. What I found most interesting was how fluent the tech leaders among the group were in speaking the language of biopharma. Far more fluent, I would argue, than the leaders of biopharma are in speaking ‘tech.’ And that presents a risk for biopharma and an opportunity for companies like Recursion that are positioned as leaders in TechBio.
But despite all the excitement around our space, we are part of an industry with a mission to alleviate suffering by bringing new, better medicines to patients. That is how we ultimately measure our impact. And as I look ahead to the next 18 months, Recursion will take meaningful steps toward that goal as we read out our first four phase 2 studies.

This is incredibly exciting as it represents the first opportunity for us to demonstrate utility for the patients we aim to serve. But it is also important to come into these initial readouts with a focus on how they can help us learn and tune our platform.

The trials that will read out this year are from the earliest iterations of our Recursion OS. They represent repurposing opportunities in rare genetic diseases we modeled using challenging tools like siRNA. New generations of our operating system using more and more powerful biology tools, chemistry tools and AI tools are leading us to identify and advance more exciting programs with some even already moving to the clinic.

The industry average success rate for Phase 2 readouts is approximately 20-30%. This suggests that if even one of our upcoming four readouts demonstrates a useful signal, we are on the right track to developing meaningful potential treatments for patients. And while we hope to do better than that, for the good of all the patients we seek to treat, we are in this for the long-run and we will use every piece of data, positive or negative, to learn and feedback into the Recursion OS so that we can maximize our long term impact.

It is important to understand that we are not a company who built a platform to deliver a handful of medicines; we are a company who is building a platform to deliver many medicines over time. And if our thesis holds, our system should improve over time with decreasing rates of late-stage failures. We believe we have built an operating system capable of discovering and developing many medicines, both within our own pipeline and via partnerships with others in the industry.

And beyond the excitement we all have for all we will learn from our first generation of programs reading out in the near term, we are also tremendously excited to be helping the rest of the industry adopt tools and technologies that can help them put the power of our operating system at their fingertips.

We announced LOWE (Large Language Model Orchestrated Workflow Engine) at JP Morgan via a live software demonstration at the conference. Together with the audience we started a mock oncology program, from leveraging Recursion’s proprietary data to identify a target of interest in oncology, to designing and ordering potential small molecule modulators of the target, to scheduling follow-up experiments on our platform to evaluate the molecules in a first cycle of SAR. You can view a version of this demonstration and our software tool LOWE here: https://www.youtube.com/watch?v=Hf1bb9rPQtE

While this was a fun and exciting way to engage with the audience at JPM, we are actively discussing making LOWE available to various potential partners for deployment within their own R&D engine. While we don’t know exactly what the future holds for LOWE, this represents an exciting new opportunity for Recursion to help accelerate the industry and the broader adoption of TechBio by integrating portions of our RecursionOS into the engine of other companies in the space.
“From our perspective there are two key drivers that will determine the winners in this race: data and execution.”

**The Differentiator Will Be Data and Execution**

Extending our view out beyond the near term and over the next decade, it feels possible, and even probable, that there will be a small number of very powerful companies in TechBio who may supplant much of what we call BioTech today. Who will these companies be and how will they win?

While compute is supply-constrained right now, it has also never been anywhere near as abundant as it is today. Table-stakes in this race over the next few years will be access to dedicated compute and robust ML/AI and software engineering teams. That is why Recursion has continued investing in BioHive-1, our on-premise supercomputer. We announced in late 2023 an expansion of the computer with our partners at NVIDIA that is likely to make it the fastest supercomputer wholly owned and operated by any biopharma company on Earth, including all the big ones. We also have an incredible, talented and growing team of ML researchers and engineers working to leverage this compute to advance the OS. We've grown both organically on these teams and by acquisition when needed. But as I said, these are table stakes.

From our perspective there are two key drivers that will determine the winners in this race: data and execution.

There is a divergence of opinions on what sort of data to use. There are those who believe that much of the data needed to solve the biggest problems in drug discovery and development exist today, either publicly or in the hands of large pharmaceutical companies. There is some evidence to support this idea; for example, the incredible progress in protein folding has been driven by sophisticated compute applied to the Protein Data Bank (PDB), a publicly available dataset. But there are few other examples in our field of data as robustly and carefully annotated as in the PDB. In fact, it is well-understood that the majority of data in the published literature cannot be recapitulated by other laboratories.

Turning to large pharmaceutical companies, who obviously have large quantities of data from their longstanding operations in drug discovery and development, we find more headwinds. First, few if any of these large datasets were built for the purpose of machine-learning. And while that doesn’t mean machine learning and AI cannot be a useful tool, the unimodal nature of the data in these sources and the lack of inter-experiment controls, especially from preclinical and clinical sides, will make it challenging to extract enough value. Further, the success of large language models trained across the internet and the subsequent lawsuits we are beginning to see from content purveyors whose data was used to train these models (e.g., https://www.nytimes.com/2023/12/27/business/media/new-york-times-open-ai-microsoft-lawsuit.html) should be making it clear to large pharma companies that they must be cautious about sharing these data.

For all of the reasons above, at Recursion we have always believed that generating and aggregating large-scale, iterative many-modal data will be the fastest path to achieving our mission to decode biology. We have now done more than 200 million experiments across multiple -omics modalities. We have also signed our first data aggregation partnership with Tempus, where we now have access to the DNA and RNA-sequencing data of over 100K oncology patients on which we can train causal-AI models. And while each layer of our data is powerful, the true magic is found when we combine them together to train more general models of biology spanning massive cellular -omics data, animal omics data and human patient omics data. We believe this deeply enough that you can expect us to continue investing deeply in building data across new layers and partnering to aggregate the proprietary datasets we believe are key to our long-term ambition.
Finally, while it seems obvious to state that execution will be a differentiator in our space, the type of execution and the perspective from which decisions are made matters deeply here. The scale of the opportunity before us is so great that we are making decisions at Recursion which we believe are most likely to increase the probability of success that we are the first company to build a general utility AI model of biology. That is, to achieve our mission by decoding biology such that we can predict or simulate how any perturbation might affect not only a human cell, but a human patient. And while realization of that mission may take another decade or two, if a company were to achieve it well-ahead of other companies in the space or alongside a small set of other companies, there could be an opportunity to aggregate much of the multi-trillion dollar value of biopharma across one or a handful of companies, as opposed to the broad distribution of valuable companies we see in biopharma today (e.g. there are about a dozen public biopharma companies with market caps solidly above $100B as of writing this note). As such, we will make decisions that we believe increase the probability we will be one of a handful of big winners in this space versus decisions that increase the probability we achieve intermediate successes.

The next decade is going to be absolutely incredible for biopharma, where the pace of change will be much higher than at any point in our past. While there is much more work to do to best take advantage of the creative destruction that is ahead, I cannot imagine many other teams who are more ready to take this on and prepared to win.

Thank you,

Chris Gibson, Ph.D.
Co-Founder and Chief Executive Officer
ITEM 1.

Business
**Item 1. Business.**

**Business Overview**

Recursion is a leading clinical stage TechBio company decoding biology to industrialize drug discovery. Central to our mission is the Recursion Operating System (OS), a platform built across diverse technologies that enables us to map and navigate trillions of biological, chemical, and patient-centric relationships across over 50 petabytes of proprietary data. We frame this integration of the physical and digital components as iterative loops, where scaled 'wet-lab' biology, chemistry, and patient-centric experimental data are organized by ‘dry-lab’ computational tools in order to identify, validate, and translate therapeutic insights. We believe Recursion’s unbiased, data-driven approach to understanding biology will bring more, new, and better medicines at higher scale and lower cost to patients.

There are three key value-drivers at Recursion:

- An expansive **pipeline** of internally developed clinical and preclinical programs focused on precision oncology and genetically driven rare diseases with significant unmet need and market opportunities that could potentially exceed $1 billion in annual sales in some cases
- Transformational **partnerships** with leading biopharma and technology companies to map and navigate intractable areas of biology, identify novel targets, and develop potential new medicines by using advanced computational and data resources
- An industry-leading **dataset** intentionally designed to capitalize on computational tools and accelerate value created through our pipeline, partnerships and technology products

**Key Achievements in 2023**

**Pipeline**

- Five phase 2 clinical-stage programs with multiple upcoming data readouts expected, including REC-994 in cerebral cavernous malformation (CCM) in Q3 2024, REC-2282 in neurofibromatosis type 2 (NF2) in Q4 2024, REC-4881 in familial adenomatous polyposis (FAP) in H1 2025, and REC-4881 in *AXIN1* or *APC* mutant solid tumors in H1 2025
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**Partnership**

- Made significant progress against both the gastrointestinal-oncology and neuroscience portions of our collaboration with Roche and Genentech, including Roche exercising its Small Molecule Validated Hit Option to further advance our first partnership program in GI-oncology
- Updated our collaboration with Bayer to focus on challenging oncology indications with high unmet need, commensurate with higher per program milestone payments
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Recursion OS

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- Began training causal AI models leveraging over 20 petabytes of multimodal precision oncology patient data from Tempus to support the discovery of potential biomarker-enriched therapeutics at scale

Company Building

- Acquired Cyclica and Valence Discovery to bolster digital chemistry and generative AI capabilities
- Expanded our operations in Salt Lake City and Montréal and opened our Canadian headquarters in Toronto with a focus on growing our machine learning and digital chemistry teams
- Committed to quadrupling the capacity of our supercomputer, BioHive-1, to support our pipeline, partnerships and the construction of foundation models across the multiple modalities of biology, chemistry and patient-centric data – we believe that this expansion should make our supercomputer a top 50 supercomputer across any industry according to the TOP500 list

Vision, Mission, People and Culture

Human biology is an incredibly complex system for which human intelligence alone is insufficient to fully comprehend it. Our world is transiting its next industrial revolution based on extraordinary progress in automation, computation, machine learning (ML), and artificial intelligence (AI). This progress is apparent through the rapid rise of LLMs, generative AI, and accessible applications like ChatGPT. Undoubtedly, remarkable shifts in perception occurred in 2023 amongst technology and biopharma companies as well as among regulators and policymakers, who highlight the utility of AI/ML for broad drug discovery and development from novel target discovery through next-generation manufacturing.

However, a key lesson from numerous other industries is that computational sophistication alone is rarely sufficient to create disruptive change. It is when computational sophistication is paired with the right data, typically in an iterative process of ongoing learning, prediction, and refinement, that outsized change is created.
Figure 1. A simple formula is used across technology industries to map and navigate complex systems. First, high-dimensional data is generated, aggregated and organized to create digital representations. Then, AI/ML algorithms make predictions about that system that can be tested in reality. The result is a virtuous cycle of learning and iteration.

Recursion was founded in 2013 with a vision to capitalize on the convergence of advancements in computation and machine learning to address the decreasing efficiency of drug discovery and development. We believe that this opportunity represents one of the most positively impactful applications of ML and AI. Our vision is to leverage technology to map and navigate biology, chemistry, and patient-centric outcomes in order to increasingly transition the process of developing medicines from discovery to design. We believe that neither advanced computational approaches, massive datasets, nor human intelligence alone can fundamentally shift the efficiency curve of drug discovery and development; instead, we believe that those companies that augment their teams with sophisticated computational tools and focus deeply on generating and aggregating the right datasets will have a significant advantage. Our success and the success of the burgeoning TechBio sector has the promise to drive more, new, and better medicines to patients at higher scale and lower prices in the coming decades. We are working to not only lead this space but define it.
Figure 2. Eroom’s Law observes that while technology advancements have made many processes faster and less expensive over the years, drug discovery is becoming slower and more expensive.¹ ² Recursion was created to take advantage of the discontinuity between these fields and harness the power of accelerating technological innovations to improve the efficiency of drug discovery and development.

Our mission at Recursion, **Decoding Biology to Radically Improve Lives**, flows naturally from our vision. We interpret our mission expansively and believe it to be a durable direction and source of inspiration for our team. We started pioneering, scaling, and industrializing phenomics (data based on images of cellular structures) over a decade ago, but we recognize that drug discovery is made up of many steps, and a point solution targeting one or two steps is insufficient to generate efficiencies across the entire process. To decode biology, we must construct a full-stack technology platform capable of integrating and industrializing many complex workflows. Success in decoding biology implies our ability to predict ways to navigate it. The ability to predictably navigate biology may enable us to build an expansive pipeline of medicines, either by ourselves, with partners, or both. As part of that work, we seek not only to radically improve the lives of patients who could benefit from the medicines we help to deliver, but the lives of those who care for those patients, the lives of our employees and their families, as well as the communities in which we operate our company.

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² Adapted from Roser, M et al. (2013). Technological Change. *OurWorldInData.org*. 
Our culture at Recursion is intentionally designed to fuel our mission. We believe culture drives delivery. Essential to decoding biology in our context is the Recursion Mindset, a deep commitment to achieving impact at unprecedented scale through pioneering new industrialized approaches. To decode biology, we intentionally source talent from an incredible breadth of fields from multiple industries. For all of our employees, Recursion is a new kind of company. The guideposts for teaching our people to successfully transition to TechBio and deliver our mission are our Founding Principles and Values. They are the essential shape of our culture. Our Founding Principles direct us in making scientific and technical decisions that further our mission. Our Values define the day-to-day behaviors that further our mission.

Figure 4. Recursion’s team requires operating at the interface of many diverse fields. Building a TechBio company requires fluency in operating at the interface of many disciplines and fields not previously attuned to working as closely in traditional biopharma.

How Recursion is Industrializing the Drug Discovery Process

The traditional drug discovery and development process is characterized by substantial financial risks, with increasing and long-term capital outlays for development programs that often fail to reach patients as marketed products. Historically, it has taken over ten years and an average capitalized R&D cost of approximately $2 billion per approved medicine to move a drug discovery project from early discovery to an approved therapeutic. Such productivity outcomes have culminated in a rapidly declining internal rate of return for the biopharma industry.
The primary driver of the cost to discover and develop a new medicine is clinical failure. Less than 4% of drug discovery programs that are initiated result in an approved therapeutic, resulting in a risk-adjusted cost of approximately $1.8 to $2.6 billion per new drug launched.\textsuperscript{3,4,5,6,7}

Despite significant investment and brilliant scientists, these metrics point to the need to evolve a more efficient drug discovery process and explore new tools. Traditional drug discovery relies on basic research discoveries from the scientific community to elucidate disease-relevant pathways and targets to interrogate. Coupled with biology's incredible complexity, this approach has forced the industry to rely on reductionist hypotheses of the critical drivers of complex diseases, which can create a 'herd mentality' as multiple parties chase a limited number of therapeutic targets. The situation has been exacerbated by human bias (e.g., confirmation bias and sunk-cost fallacy).

Accentuating this problem, the sequential nature of current drug discovery activities and the challenges with aggregation and relatability of data across projects, teams and departments lead to frequent replication of work and long timelines to discharge the scientific risk of such hypotheses. Despite decades of accumulated knowledge, the result is that drug discovery has unintentionally created hurdles for innovation.

Simultaneously, exponential improvements in computational speed and reductions in data storage costs driven by the technology industry, coupled with the rapid rise of large language models, generative AI and other ML tools, have transformed complex industries from media to transportation to e-commerce. Historically, the biopharma sector has been slow to embrace such innovations. Within the past 18 months, there have been remarkable shifts in perception among technology and biopharma companies as well as among regulators and policymakers, who highlight the utility of AI/ML for broad drug discovery and development from novel target discovery through next-generation manufacturing. We believe this rapid acceleration and adoption of these technologies demonstrates the growing consensus that AI/ML is a catalyst for substantial leaps in drug discovery.

At Recursion, we are pioneering the integration of innovations across biology, chemistry, automation, data science and engineering to industrialize drug discovery in a full-stack solution across dozens of key workflows and processes critical in discovering and developing a drug. For example, by combining advances in high content microscopy with arrayed CRISPR genome editing techniques, we can rigorously profile massive, high-dimensional biological and chemical perturbation libraries in multiple human cellular contexts to create digital 'maps' of human biology. Leveraging advances in scaled computation, we can conduct massive virtual screens to predict the protein targets for billions of chemical compounds. Similarly, data generated from our automated DMPK module and InVivomics platform enables us to predict ADME properties and identify toxicity signals, respectively, significantly faster than traditional methods. We believe that by harnessing advances in technology to industrialize drug discovery, we can derive novel biological insights not previously described by scientific researchers, reduce the effects of human bias inherent in discovery biology and reduce translational risk at the program outset.

\textsuperscript{7} Martin et al. (2017). Clinical trial cycle times continue to increase despite industry efforts. Nature Reviews Drug Discovery. 16, 157
Figure 6. Recursion’s approach to drug discovery. We utilize our Founding Principles on the right to build datasets which are scalable, reliable and relatable in order to elucidate novel biological and chemical insights and industrialize the drug discovery process.

We have used our approach to generate, aggregate, and integrate one of the largest biological, chemical, and patient-centric datasets in the world at over 50 petabytes at the end of 2023. This dataset includes proprietary phenomics, transcriptomics, predicted protein-ligand binding interactions, InVivomics, ADME data, and more across many biological and chemical contexts as well as preferred access to over 20 petabytes of multimodal oncology patient data from Tempus. Additionally, we have built a proprietary suite of software applications within the Recursion OS which has identified over 5 trillion predicted biological and chemical relationships. With our approach, we endeavor to turn drug discovery into a search problem where we map and navigate biology in an unbiased manner to discover new insights and translate them into potential new medicines at scale.

**Business Strategy and Value Drivers**

While most small to medium-sized biopharma companies are focused on a narrow slice of biology or a single therapeutic area, the Recursion OS allows us to discover and translate at scale across biology. However, we are cognizant that building disease-area expertise, especially in clinical development, is essential. We have developed a multi-pronged, capital-efficient business model focused on key value-drivers that enable us to demonstrate our progress over time while continuing to invest in the development of the Recursion OS, which we believe is the engine of value creation in the long-term. While our mapping and navigating tools have the plasticity to be applied across therapeutic areas and modalities, our business model is tailored to maximize value and advance programs cost-effectively based on the nature of market and regulatory dynamics associated with our three value drivers (internal pipeline, transformational partnerships, and fit-for-purpose proprietary biological, chemical, and patient-centric data).
Figure 7. We harness the value and scale of our Recursion OS using a capital efficient business strategy. Our business strategy is segmented into our following value-drivers: (i) internally developed programs in capital-efficient therapeutic areas; (ii) partnered programs in resource-intensive therapeutic areas; and (iii) proprietary, fit-for-purpose data and models. *Includes a single oncology indication from our Roche and Genentech collaboration.

Value Driver 1 - Internally Developed Programs in Capital Efficient Therapeutic Areas

We believe that the primary currency of any biotechnology company today is clinical-stage assets. These programs can be valued using a variety of models by stakeholders in the biopharma ecosystem and most importantly, present the potential to meet critical patient needs. For Recursion, these assets have a variety of additional benefits, including: (i) validation of key elements of the Recursion OS, (ii) growing our expertise in clinical development and (iii) building in-house processes to facilitate smooth interaction with regulatory agencies and advance medicines towards the market. If the Recursion OS evolves as designed, then it will continuously improve with more iterations such that future programs could be more novel and potentially more valuable than today’s programs. Operating as a vertically integrated TechBio company that leverages technology at every step from target discovery through clinical development (and even marketing and distribution) may be the long-term business model with the most upside for our stakeholders, including both investors and patients. We may be opportunistic about selling or licensing assets after they achieve key value-inflection milestones so that we can re-invest in our long-term strategy.

Value Driver 2 - Partnered Programs in Resource Intensive Therapeutic Areas

We believe that in its current form, our Recursion OS is already capable of delivering many more therapeutic insights than we would be able to shepherd alone today. As such, we have chosen to partner with experienced, top-tier biopharma companies like Bayer, Roche, and Genentech to explore intractable and resource-intensive areas of biology. The key advantages of these partnerships are that: (i) we are able to deploy the Recursion OS to turn latent value into tangible value in areas of biology where it would be challenging for us to do so alone; (ii) the clinical development paths for these large therapeutic areas are often resource-intensive and highly complex; and (iii) we are able to learn from our colleagues at these top-tier companies such that it could give us a competitive advantage in the industry over the longer term. This strategy also embeds us in the discovery process of large pharmaceutical companies and gives rise to an alternative long-term business model whereby we become a valued partner of many such companies. Based on how value is ascribed across our industry today, this model alone is not yet feasible to maximize our business impact. However, we feel that due to shifts within the biopharma industry there is some potential for this portion of our business model to accrete notable value over the long-term.
Value Driver 3 - Proprietary, Fit-for-Purpose Training Data and Models

As has been demonstrated in many other industries, a value driver and competitive advantage can be generated from the creation of a proprietary dataset. At Recursion, we have generated what we believe to be one of the largest fit-for-purpose, relatable biological, chemical, and patient-centric datasets on Earth. Spanning multiple omics technologies and more than 200 million unique experiments, the over 50 petabytes of data that Recursion generates, aggregates, and integrates has the fundamental purpose of being used to train machine learning models. Through intensive internal work, Recursion uses this data and our own models, algorithms, and software to advance our own internal pipeline of medicines (Value Driver 1) as well as in partnership with our collaborators to advance additional discovery programs (Value Driver 2). As our field increasingly recognizes the potential for a technology-driven revolution in drug discovery, our data has increasing potential to drive value directly. We increasingly see the potential to license select models and subsets of our data to a growing universe of collaborators for which internal efforts would be minimal, but value could be significant.

Competitive Landscape and Differentiation

There are a few key factors that differentiate Recursion from other technology-enabled drug discovery companies.

1. Recursion utilizes many biology, chemistry, and patient-centric proprietary datasets and modular tools to industrialize drug discovery, while most other competitor companies rely on a point solution to solve one important step in drug discovery. We recognize that drug discovery is made up of many steps, and a point solution is insufficient to generate efficiencies across the entire process. To decode biology, we must construct a full-stack technology platform capable of integrating and industrializing many complex workflows. In part, Recursion’s LOWE (LLM-Orchestrated Workflow Engine) is a natural progression of workflow automation. In the future, we believe the Recursion OS will also utilize large population genetics datasets and data from payer and healthcare systems to drive greater efficiencies and more precision medicine solutions for patients.

2. Recursion integrates wet-lab and dry-lab capabilities in-house to create a virtuous cycle of iteration. Fit-for-purpose wet-lab experimental data are translated by dry-lab digital tools into in silico hypotheses and testable predictions, which in turn generates more wet-lab data from which improved predictions can be made. Recursion is well positioned compared to companies of a similar stage either focused more specifically on the wet-lab only (traditional biotech or pharma companies) or dry-lab only (companies facing rapidly commoditized algorithms and a challenge differentiating on non-proprietary data).

3. Recursion has achieved a significant scale with respect to its scientific, technological, and business endeavors. With five clinical-stage programs, an exciting preclinical pipeline, two of the largest discovery partnerships in the biopharma industry with Roche/Genentech and Bayer, and three technology-focused partnerships, Recursion has achieved a scale, level of integration, and stage that few other TechBio companies have.

The Recursion OS

The creation of virtuous cycles of physical experiments and in silico models has been a competitive advantage for leaders in many industries outside of biopharma. In drug discovery, virtuous cycles of experimentation (wet-lab assays) and machine learning (dry-lab predictions) is an approach to efficiently mapping and navigating biology and chemistry at unparalleled scale and efficiency. Critically, by closely integrating the wet-lab and dry-lab in an iterative manner, one can create cycles of virtuous learning, where large fit-for-purpose wet-lab datasets support better in silico model generation and enable more focused future wet-lab experiments.
Figure 8. Recursion’s virtuous cycle of wet-lab and dry-lab. (1) Profile biological and chemical systems using automation to scale a small number of data-rich assays, including phenomics, transcriptomics, InVivomics, and ADME to generate massive, high quality empirical data; (2) aggregate and analyze the resultant data using a variety of in-house software tools; and (3) map and navigate leveraging proprietary software tools to infer relationships between biology and chemistry. These inferred relationships serve as the basis of our ability to predict how to navigate between biological states using chemical or biological perturbations, which we can then validate in our automated laboratories, completing a virtuous cycle of learning and iteration.

The Recursion OS is composed of many wet and dry-lab modules. Each module is both a capability as well as a set of standardized workflows that have been scaled and automated, in some cases, to a very high degree. In order to drive greater efficiency, these modules have been industrialized so that they can be plugged into drug discovery and development activities related to both our internal pipeline as well as large pharma partnerships. Connecting standardized workflows together can be thought of like modular programming but in a biological and chemical context. The general connected modular framework for carrying out industrialized, unbiased drug discovery and development is the Recursion OS.
Figure 9. The Recursion OS is composed of many wet- and dry-lab modules that can be connected to carry out industrialized, unbiased drug discovery and development. Each module is both a capability as well as a set of standardized workflows that have been scaled and automated, in some cases, to a very high degree.

Figure 10. The Recursion OS is meant to industrialize the drug discovery and development process through multiple cycles of learning and iteration. The Recursion OS is built on biologically native cycles of wet-lab and dry-lab modules leveraging phenomics, transcriptomics and InVivomics to drive discovery and validation of targets and compounds, while chemically native cycles of predictive ADME drive optimization of validated hits towards development candidates suitable for human clinical trials.

**Wet Lab (Physical)**

In order to create large and relatable datasets, standardization and scale are two critical requirements that can be best achieved through automation. Standardization means that the experiment is executed consistently every time, day after day, year after year - and that any deviations can be detected, tracked, and quantified. It involves meticulous metadata collection, prospective/retrospective experiment execution analysis, standard results storage, quantitative quality control and more. At the same time, massive scale, with millions of experiments executed per week, requires execution of multi-step assays processed rapidly and in a tightly orchestrated manner. This combination of precise repetition, high speed and massive volumes favors relying on robots over highly trained scientists, whose time is better spent on context-specific problems. In addition, automation of high-dimensional experiment readouts at scale enables cost reductions in the large high-dimensional digital datasets that can underpin today’s cutting-edge opportunities in machine learning.
Data utilized by the Recursion OS spans staining and multi-timepoint live-cell phenomics (brightfield), transcriptomics, proteomics, InVivomics, ADME assays, as well as predicted protein-ligand relationships. Recursion also has a physical library of over 1.7 million compounds, including over 1 million new chemical entity (NCE) starting point substances, a large library of known chemical entities which can serve as guideposts, and more than 500,000 compounds belonging to our collaborators. Further, Recursion has generated a custom whole-genome arrayed CRISPR guide library. Together, these tools allow Recursion to explore millions of different biological perturbations in our own wet labs. We have executed over 200 million phenomics and over 700,000 whole transcriptomics experiments across different biological and chemical contexts in multiple human cell types. In 2023, with the completion of our automated DMPK module, we have now conducted tens of thousands of ADME experiments. Our tissue culture facility has scaled the production of over 50 human cell types and has also enabled work at scale in co-cultures and complex iPSC-derived cell types. Since 2022, for example, Recursion generated more than 1 trillion hiPSC-derived neuronal cells for our partnered work with Roche and Genentech - a scale achieved by few other companies in the world.

Figure 11. Diverse datasets utilized by the Recursion OS are highly complementary and add useful context, like the different layers of digital maps of Earth. Multiple data modalities help identify connections within and between layers to enable decoding biology at scale.

**Automation**

While we do not consider ourselves to be hardware innovators, we have leveraged a significant team of automation scientists to assemble and synchronize advanced but widely-available robotic components, such as liquid dispensers, plate washers, incubation stations, automated HPLC, mass spectrometry and automated microscopy camera systems, to efficiently execute millions of experiments per week across a variety of data-rich outputs with only a small team overseeing the process at any given time. These robotic systems are modular by design and easily configurable to allow us to create complex and variable workflows. Furthermore, we have recently operationalized a fully integrated system that processes plates continuously through all steps in our primary experimental workflows. This fully integrated system is interoperable with the existing batch processing work cells but provides greater walk-away time for our operators and greater throughput in a smaller footprint.
Figure 12. Our high-throughput automation platforms make our labs look more like sophisticated manufacturing facilities than biology R&D laboratories. Our high throughput phenomics platform (top) can execute up to 2.2 million experiments each week with high quality to enable downstream analyses. We are increasingly automating many other of our assays at Recursion.

Cell Culture and Cell Differentiation Tools

We have built a state-of-the-art cell culture facility to consistently produce high-quality, primary mammalian cells, such as vein, kidney, lung, liver, skin and immune cell subsets, as well as stem cell-derived and cancer cell lines. In total, over 50 cell types have been onboarded to our high-throughput discovery systems. In 2022, we greatly expanded our cell culture facility footprint to perform work using human induced pluripotent stem cell (hiPSC) lines. Specifically, we have developed protocols using CRISPR genome editing technologies to generate knock-out or knock-in lines. We have developed protocols to differentiate hiPSCs into several distinct cell types using 3D and 2D differentiation methods. Furthermore, we have developed internal capabilities to characterize these cells using standardized and partly automated methods. Lastly, we have developed a scalable platform to produce 50-100 billion cells of interest per week and cryopreserve cells in assay-ready frozen format. Since 2022, our team produced over 1 trillion hiPSC-derived cells of interest to support various ongoing projects.
Figure 13. Various cells grown at scale for phenomics assays in-house by Recursion. These cells represent a variety of iPSC-derived neuronal cell types to support our neuroscience research.

**Phenomics**

Cellular morphology is a holistic measure of cellular state that integrates changes from underlying layers of cell biology, including gene expression, protein production and modification and cell signaling, into a single, powerful readout. Image-based -omics can be two to four orders of magnitude more data-dense per dollar than other -omics datasets that focus on these more proximal readouts, enabling us to generate far more data per dollar spent to inform our drug discovery efforts. We currently generate up to 13.2 million images or 110 terabytes of new data per week across up to 2.2 million experiments. Our phenomics approach builds on the recent explosion of powerful computer vision and ML approaches driven by the technology industry over the last decade. Modern ML tools can be trained to identify the most salient features of images without relying on any pre-selected, disease-specific subject matter expertise, even if these features are imperceptible to the human eye. Using these tools, we can capture the aggregate cellular response induced by a disease-causing perturbation or therapeutic and quantify these changes in an unbiased manner, freeing us from human bias. In contrast, traditional drug discovery relies on presumptive target hypotheses and bespoke biological signaling assays that only capture narrow, pre-determined biology and thus limit the scope of biological exploration.

Figure 14. AI/ML models can detect cellular phenotypes that are indistinguishable to the human eye. Most morphological differences within our images are too subtle for the human eye to detect, but AI models like Phenom-1 deployed in our Recursion OS can readily distinguish between them. The heatmap of similarities shown here between learned embeddings of these images shows clear separation where even well-trained cell biologists or pathologists would be hard-pressed to describe consistent differences.

Imaging data that we generate can be broadly and consistently used across various biological and chemical contexts to create vast, relatable datasets rather than creating data islands of custom one-off imaging readouts. Previously, most of our phenomics data consisted of fluorescent microscopy images that capture composite
changes in cellular morphology. This protocol, consisting of six subcellular dyes imaged in six different channels, has been optimized to capture a wide array of biology across nearly any adherent human cell type that can be cultured and perturbed in laboratory conditions. In 2023, we expanded how we gather phenomics data and started capturing dynamic timepoint information from our cells throughout an assay using brightfield imaging. This technique offers the benefit of being able to capture data within the same well over time and across assays (e.g., we can capture a transcriptomic endpoint from the same experimental well in which we imaged cells over time after a perturbation of interest). Brightfield imaging, which increasingly comprises our phenomics experiments, enables faster, more cost-effective image analysis across multiple timepoints and modalities. With these broadly applicable approaches, we can capture the effects of a wide range of biological and pharmacological phenomena of interest, including phenotypic changes induced by small molecules, genetic gain- and loss-of-function, toxins, secreted factors, cytokines, infectious agents, or any combination of the above.

Figure 15. A cellular image leveraging our fluorescent staining protocol (left) compared to a brightfield cellular image (right), both of which capture multiple levels of information about the cellular state. Brightfield imaging, which increasingly comprises our phenomics experiments, enables faster, more cost-effective image analysis across multiple timepoints and modalities.

Figure 16. Maps made with phenomics data from both Cell Paint and Brightfield techniques demonstrate highly similar results. Heatmaps reveal relationships between genes that span a wide variety of well-documented cellular systems.
**Transcriptomics**

We have developed an in-house transcriptomics laboratory platform, complete with walk up automation and push button digital data processing, capable of profiling up to 25,000 samples per week covering expression of nearly 20,000 genes from samples drawn from any of our biological modules. At the end of 2023, we had leveraged our transcriptomics platform to sequence over 700,000 individual transcriptome samples to improve our biological understanding of many of our programs and to begin to create another layer of orthogonal biological mapping data to complement our phenomics mapping data. In 2024, we intend to further scale and automate this capacity to enable more hits identified from our phenomics platform to be confirmed using an orthogonal, transcriptomic readout as part of our industrialized program generation workflows and we expect to be able to approach whole-genome scale mapping in this data-layer as well. This approach of combining high dimensional, large scale data layers from the Recursion OS, across phenomics and transcriptomics allows us to increase our confidence around which insights to prioritize for scientist follow-up, while at the same time minimizing cost and human effort. Similar to how we scaled transcriptomics to complement phenomics, we expect to scale additional data types like proteomics, metabolomics, lipidomics, and others.

![Transcriptomics Image](image1)

**InVivomics**

*In vivo* studies are an important tool for assessing efficacy and safety of a compound within the context of a complete, complex whole-organism system. Like other steps in the drug discovery and development process, conventional *in vivo* studies are fraught with human bias and limited in the post-study endpoints that they measure. Using our In Vivo Data Collection Infrastructure (which we call InVivomics), we can collect more holistic measurements of an individual animal’s behavior and physiological state using continuous video feeds and sensor technology (e.g., temperature), surveilling animals uninterrupted in their home environment and analyzing readouts live throughout studies in progress across days, weeks, or even months.

In 2023, our Digital Vivarium consisted of over one-thousand digital mouse cage units. These support digital tolerability studies, which allow us to identify phenotypic responses unique to different modes of toxicity and prioritize which compounds and doses should be used in efficacy studies. We also conduct InVivomic efficacy studies to evaluate treatment effects early based on whole-animal digital observations. We have also initiated the expansion of our InVivomics tolerability studies into rats to leverage the advantages of whole-animal digital observations for exploratory non-GLP toxicology studies.

![InVivomics Image](image2)
Figure 18. Our proprietary, scalable Smart Housing System for in vivo studies automatically collects and analyzes video and sensor data from all cages continuously.

**ADME Data**

In 2023 Recursion’s custom-built high-throughput robotic ADME experimentation platform entered production. High quality, reproducible data is evaluated against a rigorously designed set of standard controls and QC metrics to ensure data quality. This data is included in our warehousing system that connects experimental data. We will be deploying this fast-growing dataset to build predictive models for the microsomal stability, plasma protein binding, microsomal protein binding and passive permeability outcomes. These predictive models aim to ultimately prioritize the acquisition of high-quality compounds into the Recursion collection to accelerate our programs. We have also built an analytical laboratory equipped with state-of-the-art liquid chromatography-mass spectrometry equipment. Our analytical chemistry team supports work throughout the lifecycle of our programs, including assessing compound identity and purity for quality control, bioanalysis of compound concentration in plasma and tissue samples from in vivo studies, and biomarker identification and validation activities in support of preclinical and clinical translational efforts.

Figure 19. Recursion’s automated DMPK module allows for automated assay execution across plasma protein binding, microsomal stability and cell permeability studies at scale and in both human and rodent cells to advance programs while generating state-of-the-art training data for ML and AI algorithm development. The system has been designed to potentially add new modules into the automated workflow, such as additional in vitro absorption, distribution, metabolism, excretion, and toxicity (ADMET) testing.
Our in-house chemistry tools include physical compound collections, state-of-the-art compound storage and handling infrastructure and high-precision analytical equipment. The physical capabilities paired with our cutting-edge computational and digital chemistry platforms combine to accelerate hit identification and progression through virtuous cycles of potency and property optimization to deliver differentiated drug candidates. We have a total in-house chemical library of over 1.7 million small molecules from a combination of commercial, semi-proprietary, proprietary, and partner sources and use this library to identify chemical starting points for discovery campaigns. Over 1 million of these compounds reside within the Recursion’s novel chemical entity library curated by our computational and medicinal chemists and designed for highly druggable chemical properties while avoiding undesirable chemical properties, such as poor solubility and permeability. While this library has been constructed to maximize chemical diversity, we have ensured that several analogs of many compound cores are included to help identify emergent SAR for early hits and to enable rapid hit expansion into readily available analogs. Additionally, we have curated a selection of approximately 10,000 clinical-stage and preclinical compounds from public forums or filings, covering approximately 1,000 unique mechanisms of action, for which an abundance of existing data and annotations currently exist. These well-characterized molecules are frequently used as tool compounds within our work and may be advanced as therapeutic programs if the Recursion OS reveals unique and previously undisclosed biological activity.

Figure 20. Our state-of-the-art compound storage and handling infrastructure. These tools provide the potential to store up to more than 60 million compounds (in plated formats) onsite.

In December 2023, we entered into a collaboration with Enamine to generate and design enriched compound libraries for the global drug discovery industry. By leveraging Recursion’s MatchMaker AI model, a product added to Recursion after the acquisition of Cyclica in 2023, to identify compounds in the Enamine REAL Space predicted to bind to high-value targets, we believe we can generate more powerful compound libraries for drug discovery purposes. Recursion is expanding our chemical libraries by leveraging MatchMaker and other Recursion-developed predictive ML models to select compounds that represent tractable starting points and have an increased probability of exhibiting biological activity on our phenomics platform. We believe that the scale of our total in-house chemical library is comparable to the scale of chemical libraries curated by some large pharmaceutical companies. We plan to substantially increase the size and diversity of our NCE library over the coming years through a combination of partnerships and investments in automated chemical microsynthesis in order to more fully understand novel biological and chemical relationships. With the completion of our recent wet-laboratory expansion, we now have the potential capability to store up to more than 60 million compounds (in plated formats) onsite.
Figure 21. Our MatchMaker technology predicted the protein target(s) for ~36 billion chemical compounds in the Enamine REAL Space, reported to be the world’s largest searchable chemical library. We use the predicted interactions as a complementary data layer in our multiomics dataset for honing mechanistic predictions from our wet-labs and for accelerating SAR cycles through better predictions for our internal pipeline and within our partnerships.

**Patient-Centric Genomics Data**

In 2023, we entered into a collaboration with Tempus giving Recursion access to over 20 petabytes of proprietary deidentified, multimodal patient oncology data, spanning DNA and RNA tumor sequencing data, imaging, and health records collected from the diagnostic profiling of hundreds of thousands of cancer patients. We believe this data gives Recursion a unique opportunity to fuse the “reverse genetics” approach of our wet-lab platform (identifying cellular phenotypes associated with particular genetic perturbations) with a patient-centric “forward genetics” dataset (identifying genotypes associated with disease-related phenotypes including but not limited to cancer type, progression, response, and survival). In particular, we intend to use this dataset to train causal AI models making use of both patient data and Recursion-proprietary experimental data to go beyond mere correlations or associations in patient data to improve the speed, precision, and scale of therapeutic development in oncology by identifying superior therapeutic targets and well-calibrated populations to accelerate our oncology clinical trials.

Figure 22. Integration of Recursion reverse-genetics and Tempus forward-genetics data. New potential causal nodes beyond known drivers in lung cancer. At top right, a distribution of potential genetic targets in lung cancer prioritized based on literature-derived evidence. At bottom right, re-ranking of these genes making use of joint Recursion-Tempus evidence using our causal discovery workflow discovers several novel targets with therapeutic impact potentially comparable to known non-small-cell lung cancer drivers.
Dry Lab

Processing and Data Storage Infrastructure

The Recursion OS is built on top of a core technology stack that is highly scalable and flexible. We have adopted a hybrid-cloud strategy, leveraging the benefits of both public and private cloud infrastructure depending on the context and our needs.

Public Cloud. The public cloud is our default choice for production workloads and applications. The scale, elasticity of compute and storage, and economies of scale offered by public cloud computing providers enable us to cost-effectively execute our strategy. We benefit from large capital and investments from cloud service providers to utilize at-scale technologies that would otherwise be cost-prohibitive to build on our own.

Private Cloud. We make use of owned infrastructure to orchestrate the activities in our labs and transfer the data to the public cloud. We also own and operate GPU-based high-performance computing to train our state-of-the-art machine learning models. Owning this infrastructure is critical both for resiliency (on-premises laboratories) and for availability (GPUs) at a time when GPU availability continues to be at a premium.

BioHive-1 and High-Performance Computing in a Private Cloud. Much of our deep learning model training and research happens with our world-class supercomputer named BioHive-1. BioHive-1 is built on NVIDIA’s DGX SuperPod architecture and as of November 2023 is ranked #157 on the TOP500 list of the world’s most powerful supercomputers. In November 2023, we committed to working with NVIDIA to expand BioHive-1 to increase the computational capacity by over 4X. We project that upon completion and benchmarking, BioHive-1 will be in the top 50 most powerful supercomputers in the world across any industry (according to the TOP500 list) and will be the most powerful supercomputer owned and operated by any biopharma company. We believe that a combination of compute, data and talent will enable us to train industry leading AI/ML foundation models.

![Figure 23. We believe BioHive-1 is one of the most powerful supercomputers dedicated to drug discovery.](image)

In November 2023, we committed to adding over 500 NVIDIA H100 Tensor Core GPUs to the more than 300 NVIDIA A100 Tensor Core GPUs already in place, which will increase our computational capacity by more than 4X.
Modern approaches to drug discovery are built on significant datasets, in both structured and unstructured forms, as well as from various sources, proprietary, licensed, and public. Recursion enables access to the Data Universe through a combination of modern Data Lake / Warehouse tools for our structured data, and proprietary tools for managing our large volume of unstructured data. Recursion combines these data sources as part of The Recursion Data Universe, which compromises the following data sets, among others:

- **Proprietary, Unstructured**: This represents the data we generate from our scientific platforms, and consists of high-resolution images from our phenomics assays, sequence readouts from our transcriptomics assays, mass spectrometry data from our DMPK module, and video data from our InVivomics assays.

- **Proprietary, Structured**: To enable access to all this data, Recursion keeps significant metadata and structured data related to the outcomes from our experiments. This includes the embeddings output from our deep learning models, as well as various analyses of the data from our assays. Our unique use of high dimensional readouts from our assays enables comparison over time in ways not otherwise possible in industry.

- **Licensed, Structured and Unstructured**: In 2023, we entered into a collaboration with Tempus giving Recursion access to over 20 petabytes of proprietary deidentified, patient-centric, multimodal oncology data for the purpose of training causal AI models. We are adding this data to our Data Universe and enabling further data layers to our drug discovery workflows.

- **Public, Structured**: We regularly make use of public datasets as part of the Recursion Data Universe to expand our understanding of biology and chemistry. Sources include the UK Biobank, TCGA and DepMap from the Broad Institute of MIT and Harvard.

### Mapping and Navigating to Drive Insights and Outcomes

The Recursion Data Universe spans many petabytes of biological, chemical, and patient-centric data, relatable across years of experiment execution and data types. We have also built a rapidly growing suite of in-house software applications designed to process and translate this data into rapidly actionable insights. Increasingly, these tools and data are joined in automated workflows to rapidly prosecute drug discovery programs.

A core part of the Recursion Data Universe is our maps of biology and chemistry: massive in silico datasets created from our physical assays (e.g., phenomics) as well as in silico models (e.g., MatchMaker). Our maps predict relationships and interactions and allow Recursion to be extremely efficient in what studies to prioritize for a given drug discovery opportunity. By layering different maps from different technical modalities or from different biological or chemical spaces, we create a drug discovery "atlas" in which insights are further strengthened and understood by looking across map layers in an unbiased manner (e.g., characterizing a compound across phenomics, transcriptomics, ligand-target binding, in vitro and in vivo ADMET, etc.).

Collectively, our phenotypic maps contain over 5 trillion inferred relationships generated by ML tools without human bias, spanning across genetic perturbations as well as a large number of small- and large-molecule perturbations. Our ability to query the relationships between any perturbations in our phenotypic maps changes drug discovery from an iterative trial-and-error process into a computationally driven search problem. Unlike a traditional high-throughput screen, in which many compounds are profiled for their activity against a single target at a time, our mapping and navigating approach enables every compound we profile to be analyzed not just for its activity against a single target, but for its inferred activity against all possible targets in our arrayed CRISPR library, as well as its similarity to every compound we have previously analyzed – producing a super-linear growth in biological and chemical relationships.
**Figure 24. Mapping and navigating enable simultaneous genome-wide screening.** Traditional pharma high-throughput screening methods (left) screen thousands to millions of compounds simultaneously against single targets, but little or no information about other targets. Recursion’s mapping and navigating approach (right) enables us, in a single experiment, to infer the activity of a compound against all potential targets in our arrayed CRISPR knockout screen.

**LOWE: Large-Language Model (LLM) Orchestrated Workflow Engine**

The growing number of AI tools and datasets at Recursion – comprised of many wet-lab and dry-lab modules that can be connected – increases the complexity of our early drug discovery workflows. Moreover, each module often requires specific expertise to operate and is only accessible to highly trained data scientists or machine learning engineers. LOWE is an LLM agent designed to orchestrate complex drug discovery workflows using a natural language interface. These workflows chain together a variety of steps and tools, from finding significant relationships within Recursion’s maps of biology and chemistry to generating novel compounds and scheduling them for synthesis and experimentation. Through its natural language interface and interactive graphics, LOWE puts state-of-the-art AI tools into the hands of every drug discovery scientist at Recursion in a simple and scalable way.

LOWE not only represents the next evolution of the Recursion OS, but also how we believe drug discovery will be done at every company in the next 5 to 10 years. Today, LOWE is directed by scientists who formulate hypotheses and ask questions. In the future, we believe LOWE could be combined with additional AI agents capable of formulating hypotheses and learning from results, effectively thinking like a biologist or chemist. LOWE is a first step towards the development of autonomous ‘AI scientists’ for therapeutic discovery.
Figure 25. LOWE can orchestrate both wet-lab and dry-lab complex drug discovery tasks using natural language. In the examples above, LOWE has i) identified a list of targets involved in non-small cell lung cancer, ii) identified the top 50 commercially available compounds that have a similar structure to an initial hit, and iii) designed a phenomics experiment to test the compounds for phenosimilarity to a given target.

Because LOWE deploys via a web-based application, the most up to date versions of data and modules are automatically propagated for usage so that version control is not an issue. At Recursion, we are working on an autonomous agent that interfaces with a set of drug discovery modules, whereby a human scientist would review a set of potential programs for further advancement. Whether running via human prompts or autonomously, LOWE maintains a precise record of the commands being made, versions of the data and modules being called, and results being relayed so that workflows could be replicated in the future and computational and experimental results can be collected as evidence for the progression of programs for our internal pipeline, external partners, or regulatory groups.

**Other Enabling Software Tools and LLMs**

Additional internal software tools drive efficiency by enabling us to map and navigate data spanning more than 5 trillion predicted biological and chemical relationships, prioritize disease, target, and compound opportunities, design large experimental layouts, and automatically execute and continuously monitor experimental protocols. For example, MapApp enables scientists to explore relationships using several visualizations, statistical measurements and data layers including known information about compounds or known relationships between genes and diseases to rapidly distinguish novel insights. Other tools monitor real-time onsite reagent supplies, enable consistent control strategies, and design standards that make each week’s data relatable across time. Additionally, these tools automatically flag experiments or processes which miss quality requirements or stall at some point in the process and notify the appropriate personnel.
Figure 26. Our MapApp tool allows scientists to simultaneously view multiple relationships between genes and compounds.

**Large Language Model (LLM) Cataloging of Scientific Literature.** To efficiently initiate programs from our maps of biology, we use a proprietary in-house workflow that incorporates LLMs. This automated approach allows us to rapidly search for and prioritize the most promising opportunities from the large number of insights in our maps. In service to this process, we deploy LLMs to map the corpus of scientific literature against our internally derived proprietary maps in order to automatically surface critical data arbitrages. By layering these LLM-derived maps of scientific literature onto our proprietary maps, we can focus our work on novel and emerging biological, chemical, and patient-centric opportunities rather than the well-trodden and highly competitive diseases and targets the rest of the industry are focused on.

**Computational Tools and Foundation Models in Biology**

To understand, explore and relate new or existing data, we must normalize, transform and analyze that data. Our tools in this layer manage the streaming of our data at scale to the appropriate public and private cloud, the transformation of data into mathematical representations through our in-house proprietary foundation models, and the analyses performed on our data as parameterized and requested by users. Anomalies are flagged to the team for fast resolution.

**Phenom-1.** Our phenomics-based foundation model, Phenom-1, is a large vision transformer utilizing hundreds of millions of parameters trained on billions of cellular images from our proprietary phenomics library. Phenom-1 demonstrated the scaling hypothesis within a biological context, namely that larger models trained on larger datasets lead to improved performance. Also, Phenom-1 performed up to 28% better at recapitulating known biological relationships.

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8 Kraus, O et al. (2023). Masked Autoencoders are Scalable Learners of Cellular Morphology. NeurIPS 2023 Generative AI and Biology (GenBio) Workshop
Figure 27. Image reconstruction tasks demonstrate impressive visual results of Phenom-1, our phenomics foundation model. Reconstructing partially masked images was the training task which has enabled emergent capabilities of the model in drug discovery tasks such as detecting biological relationships.

Forward- and Reverse-Genetics Causal AI Models. We invested in deepening the translational potential of the Recursion OS by incorporating patient-relevant, forward-genetics data through our collaboration with Tempus. Recursion’s maps of biology represent a “reverse genetics” strategy, in which we identify and relate to each other the cellular phenotypes induced by genetic and chemical perturbations. Patient genomic datasets like those from Tempus represent a “forward genetics” strategy, cataloging genetic factors associating with patient phenotypes, including cancer type, progression, and more factors ascertainable from the health record. We seek to combine these forward genetics datasets with Recursion’s experimental capabilities to build causal AI models that may better predict which programs are likely to translate therapeutic benefits for patients and which patients are more likely to benefit from such treatments.

Other Foundation Models. With the vast patient-centric data from Tempus and our own growing proprietary multimomics datasets, we anticipate the construction and application of more foundation models, including large language models, across biology, chemistry and translation. When specific foundation models are combined, we believe that a grand canonical foundation model which incorporates in-cellular insights through in-patient causal outcomes could drive a more deterministic and holistic understanding of biology, chemistry, and patient-centric care. We believe these increasingly sophisticated models will enable us to develop more, new, and better medicines at higher scale and lower cost to patients.
Figure 28. Phenom-1 demonstrates that the scaling hypothesis holds within a biological system. This scaling plot illustrates how increasing the compute power (X-axis), which is required for dataset size and model complexity, improved the model’s ability to recapitulate known biological relationships (Y-axis). This observed improvement was not directed as part of the training, but rather emerged as a result of scaling the model.

**Computational Tools and Foundation Models in Chemistry**

The acquisitions of Cyclica and Valence in May 2023 added industry-leading capabilities in digital chemistry, machine learning, and artificial intelligence to Recursion’s existing small molecule drug discovery capabilities. We are leveraging these capabilities to advance our internal and partnership drug discovery programs.

*MatchMaker*, a tool acquired during the Cyclica acquisition, is an AI-enabled deep learning engine that uses both AlphaFold2 structures and homology models to predict the polypharmacology of small molecules across the proteome. We utilized MatchMaker to successfully predict the protein target interactions of several commercially available libraries, including the 36 billion compound Enamine REAL Space collection. Predicting the proteome profiling of 36 billion molecules was a massive computational exercise involving the *in-silico* evaluation of over 2.8 quadrillion molecule-target pairs. Achieving this exercise was an important step in bridging the gap between the protein universe and the chemical universe and enabling us to intelligently search vast chemical libraries to identify molecules for profiling in our wet-lab platforms.

*MolE*, developed in-house by Recursion, is a self-supervised foundation model for chemistry. MolE learns generalizable, graph-based representations of compounds and transforms them into robust, task-specific ML models via fine-tuning. Fine-tuned MolE models span endpoints related to drug efficacy and safety. MolE models are trained across a wide array of public and private datasets, including the massive-scale data generated by Recursion’s phenomics and DMPK platforms.9

Our digital chemistry platform is a core part of Recursion’s software ecosystem, comprising an integrated suite of proprietary and commercial tools, enabling our medicinal and computational chemistry team to scale and advance programs from hit to candidate. Key aspects of this platform include: (i) unified access to and visualization of chemical structures and assay data, including internally generated high or low-dimensional assay data, externally generated *in vitro* or *in vivo* data, and ADME data; (ii) integrated predictive modeling, chemical search and computational chemistry capabilities; and (iii) molecular design and collaboration. We intend to further invest in predictive and digital chemistry capabilities across three domains: (i) chemistry-centric ML model development, (ii) chemistry-centric data generation and (iii) digital and physical chemistry process development to drive the Design-Make-Test-Analyze cycle of chemistry optimization more efficiently, including the roll-out of industrialized workflows that integrate chemistry and biological assay steps autonomously.

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Bridging Insights to Program Advancement with the Recursion OS

The Recursion OS is an integrated, multi-faceted system for iteratively mapping and navigating massive biological and chemical datasets that contain trillions of inferred relationships between disease-causative perturbations and potentially therapeutic compounds. Collectively, the components of the Recursion OS can be joined together in a modular way to identify, validate and advance a broad portfolio of novel therapeutic programs quickly, cost-effectively and with minimal human intervention and bias - industrializing drug discovery. We use standardized, automated workflows to identify programs and advance them through key stages of the drug discovery and development process which includes:

- Patient Connectivity and Novelty (i.e., program initiation)
- Hit and Target Validation
- Compound Optimization
- Translation
- IND Enabling Studies
- Clinical Development

Late-stage clinical failures are the primary driver of costs in today’s pharmaceutical R&D model. Reducing the rate of costly, late-stage failures and accelerating the timeline from hit to a clinical candidate would create a more sustainable R&D model. To achieve this more sustainable model, we believe that in its ideal state, a drug discovery funnel would morph from the being shaped like the letter ‘V’ to being shaped like the letter ‘T,’ where a broad set of possible therapeutics could be narrowed rapidly to the best candidate, which would advance through subsequent steps of the process quickly and with no attrition. Recursion’s goal is to leverage technology to reshape the typical drug discovery funnel towards its ideal state by moving failure as early as possible to rapidly narrowing the funnel into programs with the highest probability of success.

Our goal is to leverage technology to reshape the typical drug discovery funnel by:

1. Broadening the funnel of potential therapeutic starting points beyond hypothesized and human-biased targets
2. Rapidly narrowing the funnel by identifying failures earlier in the research cycle when they are relatively inexpensive
3. Accelerating development of high potential drug candidates

Figure 29. Reshaping the drug discovery funnel. Recursion’s goal is to leverage technology to reshape the typical drug discovery funnel towards its ideal state by moving failure as early as possible to rapidly narrowing the funnel into programs with the highest probability of success.
We believe we have made progress in reshaping the traditional drug discovery funnel in the following ways:

- **Broaden the funnel of therapeutic starting points.** Our flexible and scalable mapping tools and infrastructure enable us to infer trillions of relationships between human cellular disease models and therapeutic candidates based on real empirical data from our own wet labs.

- **Identify failures earlier when they are relatively inexpensive.** Our proprietary navigation tools enable us to explore our massive biological, chemical, and patient-centric datasets to validate more and varied hypotheses rapidly. While this strategy results in an increase in early-stage attrition, the system is designed to rapidly prioritize programs with a higher likelihood of downstream success because they have been explored in the context of high-dimensional, systems-biology data. Over time, and as our OS improves, we expect that moving failure earlier in the pipeline will result in an overall lower cost of drug development.

- **Accelerate delivery of high-potential drug candidates to the clinic.** The Recursion OS contains chemistry tools that enable highly efficient exploration of chemical space as well as translational tools that improve the robustness and utility of *in vivo* studies.

By leveraging our Recursion OS to explore and advance our programs, we have shown leading indicators of improvement when compared to the traditional drug discovery process, particularly with respect to cost and time. Across all Recursion programs from late 2017 through 2023, the average amount of time to reach the validated lead stage is approximately 11 months. By the end of 2024, we believe that Recursion programs could reach the validated lead stage in about half that time or less. Ultimately, we believe that future iterations of the Recursion OS will enable even greater improvements minimizing the total dollar-weighted failure and maximizing the likelihood of success.

![Figure 30. The trajectory of our drug discovery funnel mirrors the ‘ideal’ pharmaceutical drug discovery funnel.](image)

We believe that, compared to industry averages, our approach enables us to: (i) identify low-viability programs earlier in the research cycle, (ii) spend less per program and (iii) rapidly advance programs to a validated lead candidate. All industry data has been adapted from Paul, et al. *Nature Reviews Drug Discovery*. (2010) 9, 203–214. The cost to IND has been inflation-adjusted using the US Consumer Price Index (CPI). The Recursion data shown for the transition stages and time to validated lead is the average of all Recursion programs since late 2017 through 2023. The Recursion data shown for cost to IND pertains to the actual and projected costs for a novel chemical entity to reach IND.

The Recursion OS has not only improved speed and cost, but also led us to explore novel targets which could give us a competitive advantage where multiple parties often simultaneously pursue a limited number of similar target hypotheses. Below one can see quantitative measures for how we prioritize programs characterized by (i) strong genetically driven biological evidence and (ii) differentiated novel biology.
Our method uncovers innovative targets that we believe provide a differentiated therapeutic potential for oncology R&D.

LLMs harness Public Datasets such as:
- Cancer Dependency Map
- Open Targets
- TCGA
- CLE
- COSMIC

LLMs harness RXRX Proprietary Datasets such as:
- Phenopix inferences
- Matchmaker assessments
- InvivoX experiments
- ADME predictions
- Compound promiscuities

We expect to initiate 300 exploratory programs in 2024 from this space, where our proprietary data provides a distinct arbitrage, with significant human effort reserved for novel relationships that confirmed and validated on our platform. Previously, over 40 FTEs were deployed to explore our maps and public data manually to initiate programs.

Figure 31. We use LLMs to organize relationships within public data as well as our own proprietary data and software tools to identify starting points for all of our internal programs. We prioritize programs at scale by focusing on targets where our proprietary data provides a distinct arbitrage that suggests we can drive towards novel target identification and selection in oncology. Each circle represents a gene that can be searched by the Recursion OS across a number of biological and pharmacological factors. Circles in green reflect targets for drugs that have obtained regulatory approval for the treatment of specific diseases and are adapted from Ochoa, D. et al. Nucleic Acids Research. (2023).

Our Pipeline

All of the programs in our internal pipeline are built on unique biological insights surfaced through the Recursion OS where: (i) the etiology of the disease is well defined but the subsequent impacts of the disease are generally obscure, the primary targets are typically considered undruggable, or the primary targets are extensively recognized in association with a particular disease and (ii) there is a high unmet medical need, no approved therapies, or significant limitations to existing treatments. Several of our internal pipeline programs could have potential market opportunities of more than $1 billion in annual sales. We currently have five programs in or planning to initiate Phase 2 clinical studies and we are preparing to submit an IND for a sixth program in H2 2024. In addition to our clinical stage programs, we are actively developing dozens of preclinical and discovery programs.

Clinical Programs

- REC-994 for the potential treatment of cerebral cavernous malformation, or CCM — SYCAMORE, a Phase 2, randomized, double-blind, placebo-controlled, safety, tolerability and exploratory efficacy study is underway. Orphan Drug Designation has been granted in the US and EU. We expect to share Phase 2 data in Q3 2024. This trial was fully enrolled in June 2023 and the vast majority of participants who completed 12 months of treatment continue to elect to enter the long-term extension study.

- REC-2282 for the potential treatment of neurofibromatosis type 2, or NF2 — POPLAR, an adaptive, Phase 2/3, randomized, multicenter study is underway. Enrollment of Phase 2 is expected to complete in H1 2024. Orphan Drug Designation in the US and EU as well as Fast Track Designation in the US have been granted. We expect to share Phase 2 safety and preliminary efficacy data in Q4 2024.

- REC-4881 for the potential treatment of familial adenomatous polyposis, or FAP — TUPELO, a Phase 1b/2, open label, multicenter study is underway with Part 1 complete. FPI for Part 2 is anticipated in H1 2024.
Orphan Drug Designation in the US and EU as well as Fast Track Designation in the US have been granted. We expect to share Phase 2 safety and preliminary efficacy data in H1 2025.

- REC-4881 for the potential treatment of AXIN1 or APC mutant cancers — LILAC, a Phase 2 open label, multicenter study in solid tumors initiated at the end of 2023 with FPI anticipated in Q1 2024. We expect to share Phase 2 safety and preliminary efficacy data in H1 2025.

- REC-3964 for the prevention of recurrent Clostridioides difficile infection — a Phase 1 study in healthy volunteers completed in Q3 of 2023. REC-3964 was well tolerated with no serious adverse events (SAEs) reported. We expect to initiate a Phase 2 study in 2024.

We believe that the number of potential programs we can generate with our Recursion OS is key to the future of our company, as a greater volume of validated programs has a higher likelihood of creating value. Additionally, we believe that our large number of potential programs makes us an attractive partner for larger pharmaceutical companies. The static or declining level of R&D output at several large pharmaceutical companies indicates an ongoing requirement for new projects to sustain their product pipelines.

<table>
<thead>
<tr>
<th>Program</th>
<th>Indication</th>
<th>Target</th>
<th>Patient Population</th>
<th>Preclinical</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
</tr>
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<tbody>
<tr>
<td>REC-994</td>
<td>Cerebral Cavernous Malformation</td>
<td>Superoxide</td>
<td>~ 360K</td>
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<tr>
<td>REC-2282</td>
<td>Neurofibromatosis Type 2</td>
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<td>~ 33K</td>
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<td>~730K</td>
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<tr>
<td>REC-4881</td>
<td>AXIN1 or APC Mutant Cancers</td>
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<td>~ 65K</td>
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<td>HR-Profluent Ovarian &amp; Solid Tumors</td>
<td>RBM39</td>
<td>~ 200K</td>
<td></td>
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</tr>
</tbody>
</table>

Figure 32. The power of our Recursion OS as exemplified by our expansive therapeutic pipeline. All populations defined above are US and EU5 incidence unless otherwise noted. EU5 is defined as France, Germany, Italy, Spain and UK. Prevalence for hereditary and sporadic symptomatic population Annual US and EU5 incidence for all NF2-driven meningiomas. Prevalence for adult and pediatric population. Our program has the potential to address several indications. We have not finalized a target product profile for a specific indication. Incidence for US only. 2L drug-treatable population. 2L drug-treatable population comprising ovarian, prostate, breast and pancreatic cancers with no HRR mutations.

**REC-994 for Cerebral Cavernous Malformation – Phase 2**

REC-994 is an orally bioavailable, superoxide scavenger small molecule currently under development for the treatment of symptomatic CCM. CCM is among the largest rare disease opportunities and has no approved therapies to date. REC-994 demonstrated excellent tolerability and suitability for chronic dosing in Phase 1 SAD and MAD trials in healthy volunteers directed and executed by Recursion. SYCAMORE, a Phase 2 randomized, double-blind, placebo-controlled, safety, tolerability and exploratory efficacy study is underway, and Orphan Drug Designation has been granted in the US and EU. We expect to share Phase 2 data in Q3 2024. This trial was fully enrolled in June 2023, with the vast majority of participants who completed 12 months of treatment electing to enter the long-term extension portion of the study.

**Disease Overview**

CCM is a neurovascular condition that impacts approximately 360,000 symptomatic individuals in the US and EU5. Yet, with only around 30% of patients exhibiting noticeable symptoms, the disease is severely underdiagnosed, potentially affecting over 1 million patients. CCM originates from genetic mutations in any of three genes involved in endothelial function: CCM1, CCM2, or CCM3 and approximately 20% of patients inherit a familial form of CCM in an autosomal dominant pattern. Sporadic disease in the remaining population is caused by somatic mutations that arise in the same genes. CCM manifests as vascular malformations of the spinal cord and brain characterized by abnormally enlarged capillary cavities without intervening brain parenchyma. Patients with CCM lesions are at
substantial risk for seizures, headaches, progressive neurological deficits, and potentially fatal hemorrhagic stroke. Current non-pharmacologic treatments include microsurgical resection and stereotactic radiosurgery. Given the invasive and risky nature of these interventions, these options are reserved for a subset of patients with significant symptomatology and/or easily accessible lesions. Rebleeds and other negative sequelae of treatment further limit the effectiveness of these interventions. There is no approved pharmacological treatment that affects the rate of growth of CCM lesions or their propensity to bleed or otherwise induce symptoms. Hence, CCM remains a serious health condition resulting in progressive neurologic impairment and a high risk of death due to hemorrhagic stroke.

![Figure 33. Vascular malformations (cavernomas) in the brain of a CCM patient.](image)

**Insight from Recursion OS**

*CCM2* knock-down in human endothelial cells revealed pronounced structural and functional phenotypes that are distinct from healthy cells. We hypothesized that these observed structural changes could be used to enable unbiased drug discovery. Fluorescent microscopy and automated cellular quantification and profiling software enabled high throughput analysis. More than 2,000 commercially available and known chemical entities were rapidly evaluated with this strategy based on the hypothesis that hits from this library could be more quickly translated to the clinic. The novel use of REC-994 for CCM was discovered leveraging this early form of the Recursion OS. The exciting aspect of this novel, unbiased approach was that the drug candidates chosen using automated software analysis outperformed those chosen by human analysis in subsequent orthogonal screens.

![Figure 34: Rescue of structural phenotypes associated with loss of *CCM2*.](image)

(green) and VE-cadherin (red). According to a machine learning classifier trained on images, REC-994 shows image-based rescue.

REC-994 is a small molecule therapeutic designed to alleviate neurological symptoms associated with CCM and potentially reduce the accumulation of new lesions. REC-994 is an orally bioavailable superoxide scavenger with pharmacokinetics supporting once-daily dosing in humans. The putative mechanism of action of REC-994 is through reduction of reactive oxygen species and decreased oxidative stress that leads to stabilization of endothelial barrier function. In addition, REC-994 exhibits anti-inflammatory properties which could be beneficial in reducing disease-associated pathology.

Figure 35. REC-994 mechanism of action and proposed potential therapeutic impact.

Preclinical

The activity of REC-994 as a potential treatment for CCM was further confirmed in orthogonal functional assays and in acute and chronic in vivo models. REC-994 demonstrated benefit on acute to subacute disease-relevant hemodynamic parameters such as vascular dynamics and vascular permeability. Chronic administration of REC-994 was also tested in two endothelial-specific knockout mouse models for the two most prevalent genetic causes, CCM1 and CCM2. These mouse models faithfully recapitulate the CNS cavernous malformations of the human disease. Mice treated with REC-994 demonstrated a decrease in lesion number and/or size compared to vehicle treated controls. Notably, 24-hour circulating plasma levels of REC-994 in this in vivo experiment were consistent with exposures seen in humans at a 200 mg daily dose.
Figure 36. REC-994 rescues acetylcholine-induced vasodilation defect and dermal permeability defect in Ccm2 endothelial specific knockout mice.  

Figure 37. REC-994 reduces lesion severity in chronic mouse models of CCM Disease. Mice treated with REC-994 demonstrated a statistically significant decrease in the number of small-size lesions, with a trend toward a decrease in the number of mid-size lesions.

**Clinical**

We conducted a Phase 1 Single Ascending Dose (SAD) study in 32 healthy human volunteers using active pharmaceutical ingredients with no excipients in a powder-in-bottle (PIB) dosage form. Results showed that systemic exposure ($C_{max}$ and AUC) generally increased in proportion to REC-994 dose after both single and multiple doses. Median $T_{max}$ and $t_{1/2}$ appeared to be independent of dose. There were no deaths or SAEs reported during this study and no TEAEs that led to the withdrawal of subjects from the study. These data supported a MAD study in healthy human volunteers.

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A subsequent Phase 1 Multiple Ascending Dose (MAD) study was conducted in 52 healthy human volunteers and was designed to investigate the safety, tolerability, and PK of multiple oral doses of REC-994, to bridge from the PIB dosage form to a tablet dosage form, as well as to assess the effect of food on PK following a single oral dose. Overall, multiple oral doses of REC-994 were well tolerated in healthy male and female subjects at each dose level administered in this study. There appeared to be no dose-related trends in TEAEs, vital signs, ECGs, pulse oximetry, physical examination findings, or neurological examination findings. Pharmacokinetic results support once-daily oral dosing with tablet formulation.

<table>
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<th>MAD Study</th>
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<tr>
<td>Total Number of TEAEs</td>
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<td>0</td>
<td>10</td>
<td>4</td>
<td>15</td>
</tr>
<tr>
<td>Total Subjects with ≥ one TEAE</td>
<td>4</td>
<td>0</td>
<td>3</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

Table 1. Summary of Adverse Events from Phase 1 Multiple Ascending Dose Study. AE=adverse event; MAD=multiple ascending dose; SAE=serious adverse event; TEAE=treatment-emergent adverse event.

Recursion initiated the SYCAMORE study, a two-part Phase 2 trial in CCM patients in Q1 2022. Part 1 is a randomized, double-blind, placebo-controlled trial to investigate the safety, efficacy, and PK of daily doses of REC-994 (200 mg and 400 mg) compared to placebo in participants with symptomatic CCM over a treatment period of 12 months. Part 2 is an optional, double-blind, long-term extension (LTE) study of daily doses of REC-994 (200 mg and 400 mg) for participants completing Part 1 of the study. Currently, there is no regulatory precedent or registrational pathway for CCM drug development. Results from the ongoing Phase 2 study are expected to inform a pivotal trial design with guidance from the FDA.
Phase 2 trial design to assess the efficacy and safety of REC-994 in patients with symptomatic CCM. Enrollment criteria includes MRI-confirmed lesion(s), diagnosis of familial or sporadic CCM, and having symptoms directly related to CCM. Primary outcome measures are safety and tolerability. Secondary measures are focused on efficacy, including clinician-measured outcomes, imaging of CCM lesions, acute stroke scales and patient reported outcomes. This trial was fully enrolled in June 2023 and the vast majority of participants who completed 12 months of treatment continue to enter the long-term extension study.

Competitors

To our knowledge, the REC-994 program is the first industry sponsored therapeutic program in clinical trials for CCM. If approved, REC-994 would be the first pharmacologic disease-modifying treatment for CCM, one of the largest areas of unmet need in the rare disease space. There are currently three other active programs in clinical development for CCM.

- OV-888, a ROCK2 inhibitor from Ovid Therapeutics, is currently in Phase 1, with a signal-finding trial expected to initiate in H2 2024.
- NRL-1049, a ROCK inhibitor from Neurelis in-licensed from BioAxone BioSciences, is currently in Phase 1.
- Atorvastatin, a competitive HMG-CoA reductase inhibitor, is being studied in an investigator sponsored Phase 1/2 study in CCM patients with a recent history of symptomatic bleeds.

**REC-2282 for Neurofibromatosis Type 2 - Phase 2/3**

REC-2282 is a small molecule HDAC inhibitor currently under development for the treatment of NF2-mutant meningiomas. In prior clinical trials, the molecule was well tolerated, including in patients dosed for multiple years. In contrast to approved HDAC inhibitors, REC-2282 is both CNS-penetrant and orally bioavailable. An adaptive, Phase 2/3, randomized, multicenter study is underway with enrollment of Phase 2 expected to complete in H1 2024. Orphan Drug Designation in the US and EU as well as Fast Track Designation in the US have been granted. We expect to share Phase 2 safety and preliminary efficacy data in Q4 2024.

**Disease Overview**

Neurofibromatosis type 2 (NF2) is an autosomal dominant, inherited, rare, tumor syndrome that predisposes affected individuals to multiple nervous system tumors, the most common of which are bilateral vestibular schwannomas, intracranial meningiomas, spinal meningiomas and other spine tumors such as ependymomas.
Approximately one-half of individuals with NF2 have meningiomas and most of these individuals will have multiple meningiomas. In patients with NF2 the incidence of meningiomas increases with age, and lifetime risk may be as high as 75%. Combined, we believe NF2-driven meningiomas occur in approximately 33,000 patients per year in the US and EU5. Patients with NF2 are diagnosed typically in their late teens or early 20s and present with hearing loss which is usually unilateral at the time of onset, focal neurological deficits, and symptoms relating to increasing intracranial pressure.

Although most meningiomas are benign, their location often makes complete resection untenable, and subsequently patients with NF2 experience loss of hearing, facial paralysis, poor balance, and visual difficulty. Spinal tumors can result in weakness and disability and some patients become wheelchair bound. Many patients with multi-tumor disease die in early adulthood. Due to the catastrophic nature of the disease and lack of non-surgical options for management, new approaches to treatment are needed, particularly those directed toward shrinking tumor burden.

**Insight from Recursion OS**

We selected REC-2282 for our NF2 program through the application of a brute-force approach by developing a high content phenotypic screen to identify cellular and structural changes associated with the genetic knockdown of NF2 by siRNA in HUVEC cells. Transfected NF2-deficient cells were treated with thousands of compounds to discover molecules that restored the structural defects associated with loss of NF2. REC-2282 reversed this complex cellular phenotype back to a healthy state (wildtype) in four independent screens at concentrations between 0.1 to 1 μM, in line with efficacious concentration levels in our preclinical experiments. Additionally, REC-2282 failed to exhibit the same level of dose dependent rescue in the evaluation of hundreds of other tumor suppressor or oncogene knockdown models, providing further evidence of a selective effect in the specific context of NF2 loss of function. Together, these experiments demonstrated robust and reproducible activity in disease relevant settings suggesting the therapeutic potential of REC-2282 in treating NF2-mutant tumors.

**Figure 39.** REC-2282 rescued the loss of NF2. A) Immunofluorescent images of human endothelial cells treated with siRNA control or siRNA NF2. B) REC-2282 rescued the high-dimensional disease phenotype as evidenced with a left shift from the disease to the healthy state. HUVEC, human umbilical vein endothelial cells; NF2, neurofibromatosis type 2; siRNA, small interfering RNA.
REC-2282 is an orally bioavailable, CNS-penetrating, pan-histone deacetylase, or HDAC, inhibitor with PI3K/AKT/mTOR pathway modulatory activity. By comparison to marketed HDAC inhibitors, REC-2282 is uniquely suited for patients with NF2 and NF2-mutant CNS tumors, due to its oral bioavailability, CNS-exposure, and as of yet undocumented cardiovascular liabilities.

Figure 40. REC-2282 would be a first-in-class HDAC inhibitor for the potential treatment of NF2 meningiomas. We believe REC-2282 is well suited for NF2 vs other HDAC inhibitors due to its oral bioavailability and CNS-exposure.¹³,¹⁴,¹⁵

NF2 disease is driven by mutations in the NF2 gene, which encodes an important cell signaling modulator, merlin. Loss of merlin results in the activation of multiple signaling pathways converging on PI3K/AKT/mTOR among others and results in enhanced cell proliferation. Anti-neoplastic effects of HDAC inhibitors, like REC-2282, are thought to derive primarily via disruption of the protein phosphatase 1 (PP1)-HDAC interaction, and the subsequent inhibition of PI3K/AKT signaling leading to growth arrest and apoptosis of cancer cells.

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¹⁵ Prescribing Information of Vorinostat/Belinostat/Romidepsin respectively.
Figure 41. REC-2282 acts on an important pathway in tumor development to inhibit the growth of tumor cells. A potential mechanism of action of REC-2282 in NF2.\textsuperscript{16}

**Preclinical**

After we discovered the novel use of REC-2282 for NF2 using our platform, we performed a literature search to better understand the molecule and validate its activity in disease relevant preclinical models. REC-2282 has been shown to be pharmacologically active in various human cancer cell lines and human cancer xenograft models. REC-2282 had been shown to inhibit \textit{in vitro} proliferation of vestibular schwannoma, or VS, and meningioma cells by inducing cell cycle arrest and apoptosis at doses that correlate with AKT inactivation. In preclinical models, REC-2282 inhibited the growth of primary human VS and \textit{Nf2}-deficient mouse schwannoma cells, as well as primary patient-derived meningioma cells and the benign meningioma cell line, Ben-Men-1.

In animal models of NF2, REC-2282 suppressed \textit{in vivo} tumor growth of an \textit{Nf2}-deficient mouse vestibular schwannoma allograft. In addition, REC-2282 suppressed \textit{in vivo} tumor growth of human vestibular schwannoma xenograft models in mice fed chow formulated to deliver 25 mg/kg/day REC-2282 for 45 days. REC-2282 also suppressed the growth of meningioma cells in an orthotopic mouse model of \textit{Nf2}-deficient meningioma that contained luciferase-expressing Ben-Men-1 meningioma cells. These animal data served as a functional and orthogonal validation of our platform findings.

Figure 42. REC-2282 shrinks vestibular schwannoma xenografts in SCID-ICR mice and prevents growth & regrowth of tumors in the NF2-deficient meningioma mouse model. (A) Change in VS tumor volume for each control mouse, demonstrating a mean 6% increase. (B) REC-2282 significantly reduces the mean size of VS tumor volume by ~28% across SCID-ICR mice implanted with VS xenografts. Error bars shown are the 95% CI. P=0.006. C) REC-2282 also suppressed the growth of Ben-Men-1-LucB tumor xenografts as measured by tumor bioluminescence. 17, 18

Clinical

Four Investigator-Sponsored Trials (ISTs) of REC-2282 (previously referred to as AR-42) have been completed. In study AR-42-001, REC-2282 was administered as monotherapy. In the other 3 trials, REC-2282 was administered in combination with anti-neoplastic agents: decitabine (AR-42-002), pazopanib (AR-42-003) and pomalidomide (AR-42-004), respectively. In these studies, REC-2282 was given to 77 patients with solid or hematological malignancies in doses ranging from 20 mg to 80 mg three times a week for three weeks followed by one week off-treatment in four-week cycles. Multiple patients were treated for multiple years using this dosing regimen at the 60 mg dose and the longest recorded treatment duration is 4.4 years at the 40 mg dose. The majority of adverse events were transient cytopenia that did not result in dose reduction or stoppage. The MTD in patients with solid tumors was determined to be 60 mg. The REC-2282 plasma exposure in patients with hematological malignancies and solid tumors generally increased with increasing doses. There were no consistent signs of plasma REC-2282 accumulation across a 19-day administration period nor obvious differences in PK between hematologic and solid tumor patients.

In another early Phase 1 pharmacodynamic IST conducted by Ohio State University, it appeared that REC-2282 suppressed aberrant activation of ERK, AKT and S6 pathways in vestibular schwannomas from adult patients undergoing tumor resection. These results may be difficult to achieve with single pathway inhibitors of ALK or MEK.

Recursion is currently enrolling patients in POPLAR, an adaptive, Phase 2/3, randomized, multicenter study to evaluate the efficacy and safety of REC-2282 in patients with progressive NF2-mutated meningiomas with underlying NF2 disease and sporadic meningiomas with documented NF2 mutations. The study is designed to accelerate the path to potential product registration by allowing for initiation of a confirmatory Phase 3 study prior to full completion of Phase 2. This is a two-staged Phase 2/3 with enrollment done in two parts. Cohort A is a signal seeking Phase 2 in which 20 adult subjects and up to nine adolescent subjects will begin treatment on two active dose arms. Subject safety will be monitored by an independent Data Monitoring Committee, which will apply dose modification and stopping rules as indicated. After all 20 adult subjects have completed six months of treatment, an interim analysis will be performed for the purpose of 1) determination of go/no-go criteria for Cohort B, or the Phase 3 portion of the study, 2) selection of the dose(s) to carry forward, 3) re-estimation of sample size for the planned Phase 3 and 4) agreement from FDA to initiate the Phase 3. Subjects in the Phase 2 portion will continue treatment for up to 26 months total and then have the option to enroll in an Extension study. The Phase 3 portion currently requires recruitment of an additional 60 subjects (adult and potentially adolescent subjects), who will receive treatment for up to 26 months. The planned primary endpoint is Progression-Free Survival (PFS).

Phase 2/3 two-staged study design to assess the safety, tolerability, and preliminary efficacy of REC-2282 in patients with progressive NF2-mutated meningiomas. Enrollment criteria include MRI-confirmed progressive meningioma and either (1) sporadic meningiomas with confirmed NF2 mutation or (2) confirmed diagnosis of NF2 disease. The primary outcome measure for the Phase 2 portion of the study is progression-free survival (PFS) rate at 6 months.

Competitors

There are currently eight active programs in clinical development targeting NF2-driven brain tumors.

- Brigatinib, an approved ALK inhibitor for NSCLC from Takeda Pharmaceuticals, is in Phase 2 for NF2 disease meningioma, vestibular schwannoma, and ependymoma.

- Neratinib, an approved HER2 inhibitor for HER2+ breast cancer after trastuzumab-based therapy from Puma Biotechnology, is in Phase 2 for NF2 disease meningioma, vestibular schwannoma, and ependymoma.

- Crizotinib, an ALK/ROS1 inhibitor, is being studied in an investigator sponsored Phase 2 study in progressive vestibular schwannoma in NF2 patients.

- Selumetinib, a MEK inhibitor from AstraZeneca, is being studied in a Phase 2 study for NF2 related tumors.

- GSK2256098, a FAK inhibitor from GlaxoSmithKline, is being studied in a basket Phase 2 for meningiomas with a variety of targeted therapies and genetic alterations, including NF2 mutation.

- IK-930, a TEAD inhibitor from Ikena Oncology, is being studied in a basket Phase 1 for advanced solid tumors driven by hippo signaling, including patients with NF2 mutations.

- VT-3989, a TEAD inhibitor from Vivace Therapeutics, is being studied in a basket Phase 1 for advanced malignant mesothelioma and other tumors with NF2 mutations, including meningiomas.

- IAG933, a TEAD inhibitor from Novartis, is being studied in a basket Phase 1 for advanced malignant mesothelioma and other tumors with NF2 mutations, including meningiomas.
**REC-4881 for Familial Adenomatous Polyposis (FAP) - Phase 1b/2**

REC-4881 is an orally bioavailable, non-ATP-competitive, allosteric small molecule inhibitor of MEK1 and MEK2 currently under development to reduce polyp burden and progression to adenocarcinoma in FAP patients. REC-4881 was well tolerated in prior clinical studies, demonstrating dose dependent increases in exposure and pharmacological activity. Recursion is currently enrolling patients in TUPELO, a Phase 1b/2, open label, multicenter study with FPI in the Part 2 portion anticipated in H1 2024. Orphan Drug Designation in the US and EU as well as Fast Track Designation in the US have been granted. We expect to share Phase 2 safety and preliminary efficacy data in H1 2025.

**Disease Overview**

FAP is a rare tumor predisposition syndrome affecting approximately 50,000 patients in the US and EU with no approved therapies. FAP is a genetic disorder resulting from a heterogeneous spectrum of point mutations in the adenomatous polyposis coli (APC) gene. The APC gene is a tumor suppressor gene which encodes a negative regulator of the Wnt signaling pathway.

FAP is characterized by progressive development of hundreds to thousands of adenomatous polyps in the lower gastrointestinal tract, mainly in the colon and rectum, and is associated with up to a 100% lifetime risk of colorectal cancer before age 40 if left untreated. The standard of care for patients with FAP is colectomy in late teenage years. Without surgical intervention, affected patients will progress to colorectal cancer by early adulthood. Post-colectomy, patients receive endoscopic surveillance every 6-12 months to monitor disease progression given the ongoing risk of malignant transformation.

Despite removing the main at-risk organ, approximately 50% of patients will develop adenomatous lesions in the neo-rectum. Once endoscopic management is no longer sufficient, additional surgical procedures are required. Similarly, these patients also develop duodenal (particularly ampullary) adenomas which also require endoscopic management. In the presence of larger adenomas and evidence of carcinoma, patients require additional localized surgery, including radical Whipple procedures. There are currently no approved therapies for FAP.

**Insights from Recursion OS**

The novel use of REC-4881 for FAP was discovered by leveraging knock-down of the FAP disease gene APC in human cells using the Recursion OS. To select REC-4881 as a potential therapeutic for FAP, Recursion developed a high content phenotypic screen to identify cellular and structural changes associated with knockdown of APC using small interfering RNA (siRNA) in osteosarcoma U2OS cells. Using machine vision and automated analysis software, Recursion quantified hundreds of cellular parameters associated with APC knockdown. This complex phenotype was used as the basis for a chemical screen of more than 3,000 known drugs and bioactive compounds, revealing several RAF and MEK inhibitors, including REC-4881, which reversed the structural defects associated with loss of APC. REC-4881 exhibited highly specific and potent reversal of cellular phenotypes when compared to the MEK inhibitors selumetinib and binimetinib.
Figure 44. REC-4881 rescued phenotypic defects of cells with APC knockdown. Compared to thousands of other molecules tested, REC-4881 rescued phenotypic defects substantially better (including better rescue than other MEK inhibitors) for APC-specific knockdown.

REC-4881 is an orally bioavailable, non-ATP-competitive, allosteric small molecule inhibitor of MEK1 and MEK2 (IC50 2-3 nM and 3-5 nM, respectively) that is being developed to reduce polyp burden and progression to adenocarcinoma in FAP patients.

FAP is driven by loss of function of APC, which is a critical component of the β-catenin destruction complex, leading to aberrant activation of the Wnt pathway. This Wnt-on state can lead to RAS stabilization, activation of the RAS/ERK pathway and the activation of MYC, leading to cell proliferation and survival - including the growth of adenomas seen in FAP. REC-4881 inhibits MEK1/2 thereby inhibiting ERK activation, decreasing MYC activity, restoring cells back to a Wnt-off state and inhibiting cell proliferation.

Lending further support for the use of MEK inhibitors in FAP, studies have shown that ERK signaling is activated in adenoma epithelial cells and tumor stromal cells, including fibroblasts and vascular endothelial cells. In addition, genomic events resulting in alteration of mitogen-activated protein kinase signaling, such as activating mutations in KRAS, are frequent somatic events that promote the growth of adenomas in FAP. Overall, suppression of aberrant MAPK signaling in adenomas of FAP with REC-4881 has the potential to regress or slow the growth of these tumors by acting on core pathways driving their growth.
Figure 45. REC-4881 inhibits *APC*-mutation induced MAPK signaling to block cell proliferation in the context of FAP. A potential mechanism of action of REC-4881 in cells with loss of function mutations in *APC*.\textsuperscript{19}

**Preclinical**

We validated the findings from the initial phenotypic screens using tumor cell lines and spheroids grown from human epithelial tumor cells with a mutation in *APC*. REC-4881 inhibited both the growth and organization of spheroids in these models and, in tumor cell lines, had well over a 1,000-fold selectivity range in cells harboring *APC* mutations.

We subsequently evaluated REC-4881 in a disease relevant preclinical model of FAP. Mice harboring truncated *Apc*, or *Apc\textsuperscript{Min}*\textsuperscript{a}, were treated with multiple oral daily doses of REC-4881 or celecoxib (as a comparator) over an eight-week period. Mice treated with celecoxib had approximately 30% fewer polyps than did those treated with vehicle, whereas mice treated with 1 mg/kg or 3 mg/kg REC-4881 exhibited approximately 50% fewer polyps than vehicle-treated mice. Mice that were treated with 10 mg/kg REC-4881, the highest dose tested, exhibited an approximately 70% reduction in total polyps.

In FAP, polyps arising from mutations in *APC* may progress to high-grade adenomas through accumulation of additional mutations and eventually to malignant cancers. To evaluate the activity of REC-4881 on both benign polyps and advanced adenomas, gastrointestinal tissues from mice treated with REC-4881 were histologically evaluated and polyps were classified as either benign or high-grade adenomas. While celecoxib reduced the growth of benign polyps in the model, a large proportion of polyps that remained were dysplastic. By contrast, treatment with REC-4881 specifically reduced not only benign polyps, but also precancerous high-grade adenomas, a finding with the potential for translational significance.

\textsuperscript{19} Jeon, WJ, et al. (2018). Interaction between Wnt/\beta-catenin and RAS-ERK pathways and an anti-cancer strategy via degradations of \beta-catenin and RAS by targeting the Wnt/\beta-catenin pathway. npj Precision Oncology, 2(5).
Figure 46. REC-4881 reduces GI polyp count and high-grade adenomas in the Apc\textsuperscript{Min} mouse model of FAP. GI polyp count (left panel) and the percent of high-grade adenomas (right panel) after oral administration of indicated dose of REC-4881, celecoxib, or vehicle control for 8 weeks. Polyp count at the start of dosing reflects animals sacrificed at the start of study (15 weeks of age). \( P \leq 0.001 \) for all REC-4881 treatment groups versus vehicle control. Quantification of high-grade adenomas versus total polyps was based on blinded histological review by a pathologist. While celecoxib reduces benign polyps, the majority of remaining lesions are high grade adenomas. By contrast, REC-4881 reduces both polyps and high-grade adenomas.

Clinical

In the Phase 1 dose escalation study previously conducted by Millenium Pharmaceuticals in 51 participants with non-hematologic malignancies (Study C20001), TAK-733 (REC-4881) was administered in the dose range of 0.2 mg QD to 22 mg QD for 21 days. The maximum tolerated dose (MTD) was determined to be 16 mg QD in this study. In this study, REC 4881 exposures increased in a less than dose-proportional manner.

The most commonly reported AEs were rashes, with rash of any type reported in 34 participants (67%); 4 of the 7 participants who discontinued study drug treatment due to an AE discontinued for rash or some type of skin condition. Fourteen (27%) participants experienced at least 1 treatment-emergent SAE; the only SAEs that occurred in more than 1 participant were metastatic melanoma (3 participants; 6%), pulmonary embolism (2; 4%) and anemia (2; 4%). Five participants died during the study; all deaths were due to disease progression.

REC-4881-101 was a safety and PK study conducted by Recursion in healthy volunteers to confirm comparability of REC-4881 with TAK-733. Twenty-five (25) healthy participants, separated into 2 cohorts, were exposed to single doses of REC-4881 4 mg and 8 mg (under fed and fasting conditions) and single doses of REC-4881 12 mg (under fasting conditions). Each cohort received single doses of study drug across 3 study periods with each period separated by 14 days.

REC-4881 was generally well tolerated. No deaths or SAEs were reported during the study. For both cohorts, the percentage of participants reporting TEAEs was comparable between participants who received REC-4881 and placebo. No apparent relationship with the dose of REC-4881 or food conditions was observed. All TEAEs were assessed by the Investigator as being of Grade 1 severity except 1 (blurred vision reported with 4 mg REC-4881/ fed). Two additional participants reported treatment-related eye disorders (blurred vision in both eyes in 1 participant with 8 mg REC-4881/fasted and vitreous floaters in 1 participant with 12 mg REC-4881/fasted). In all instances, the symptoms resolved. Notably, no instance of QTcF abnormality (change from baseline or prolongation) was noted in these healthy participants.

Recursion is currently enrolling patients in TUPELO, a Phase 1b/2, open label, multicenter study to evaluate efficacy, safety, pharmacokinetics, and pharmacodynamics of REC-4881 in patients with FAP. The study is being conducted in two parts. Part 1 evaluated the PK, safety, tolerability, and PD in participants with FAP following administration of REC-4881 in single and multiple doses. Five FAP patients received single dose and 14 days of
REC-4881 treatment at 4 mg QD. 4 mg QD was generally well tolerated with a safety profile consistent with other MEK inhibitors. Preliminary PD data suggests the 4 mg dose may be pharmacologically active in FAP patients. Part 2 will assess the efficacy, safety, PK, and PD following administration of once daily doses of REC-4881 to participants with FAP who have previously undergone a colectomy/proctocolectomy and have a confirmed germline APC mutation. Study drug will be administered orally for 3 months.

**Screening & Treatment**

**Part 2**

- **Single agent REC-4881 Dose Escalation**
  - Safety
  - Tolerability
  - PK/PD

- **Recommended Phase 2 Dose**
  - 12 mg QD
  - 8 mg QD
  - 4 mg QD

- **Dose Expansion at RP2D**
  - Futility Assessment
  - Go/No-Go

**Trial Update**

- 5 FAP patients treated in Part 1
- 4mg dose appears pharmacologically active
- Phase 2 initial readout expected H1 2025

*Figure 47. Phase 1b/2 study schema for REC-4881 in FAP.* Phase 1b/2 clinical study to assess the efficacy, safety, and pharmacokinetics of REC-4881 in patients with classical FAP. Enrollment criteria include (1) Confirmed APC mutation; (2) ≥ 55 years of age; (3) Post-colectomy/proctocolectomy; (4) No GI cancer; (5) Polyps in duodenum (including ampulla of Vater and/or rectum/pouch). Outcome measures: PK, safety, tolerability, preliminary efficacy (change from baseline in polyp burden, histological grade, extent of desmoid disease).

**Competitors**

There are currently three active programs in clinical development for FAP.

- ALFA, also known as eicosapentaenoic acid from SLA Pharma, is currently in Phase 3 for FAP patients that harbor a pathogenic APC mutation and have had a previous colectomy.

- Flynovi, a combination of CPP-1X and sulindac from Panbela, is currently in Phase 3 for FAP patients with a focus on lower GI disease. Further guidance on a regulatory path forward is expected in H2 2024.

- eRapa, an mTORC1 inhibitor also known as encapsulated rapamycin from Emtora Biosciences, is currently in Phase 2 for FAP patients.

**REC-4881 for AXIN1 or APC Mutant Cancers - Phase 2**

REC-4881 is an orally bioavailable, non-ATP competitive, allosteric small molecule inhibitor of MEK1 and MEK2 being developed for the treatment of AXIN1 or APC mutant cancers. REC-4881 was well tolerated in prior clinical studies, demonstrating dose dependent increases in exposure and pharmacological activity. Recursion initiated LILAC, a Phase 2 study in AXIN1 or APC mutant cancers at the end of 2023, and FPI is anticipated in Q1 2024. We expect to share safety and preliminary efficacy data in H1 2025.
**Disease Overview**

AXIN1 and APC function as critical tumor suppressors that form part of the beta-catenin destruction complex, directly and indirectly regulating beta-catenin and RAS levels, respectively, in the cell. Aberrant activation of the Wnt and RAS pathways through inactivating mutations in *AXIN1* or *APC* appear frequently across a wide variety of human cancers with an estimated 65,000 patients in the US and EU5 eligible for treatment in the second line. These tumors are often considered clinically aggressive and less sensitive to treatments with chemotherapies and/or immunotherapies, representing a heavily refractory population. Accordingly, there is a substantial need for developing therapeutics for patients harboring mutations in *AXIN1* or *APC*, as these mutations are considered undruggable. There are no treatments specifically approved for *AXIN1* or *APC* mutant cancers.

**Insight from Recursion OS**

The REC-4881 program for *AXIN1* or *APC* mutant cancers is our first program nominated solely based on our inferential search approach. In our HUVEC map, we discovered that REC-4881 exhibited a phenotypically opposite relationship across clinically relevant doses to the gene knockout of *AXIN1*, in addition to the previously uncovered relationship with *APC*. We interpreted this relationship as a second novel insight around this molecule and that the use of REC-4881 could potentially restore the biological consequences driven by *AXIN1* or *APC* loss, found in many cancers.

Two additional insights provided us with conviction in this interpretation:

- AXIN1 and APC are central components of the beta-catenin destruction complex. This destruction complex physiologically regulates the levels of beta-catenin and RAS in cells. As AXIN1 and APC exist together in a complex, they are considered functionally related. Our map revealed a strong degree of phenotypic similarity between the gene knockout of *AXIN1* and *APC*, suggesting that this axis of biology is recapitulated in our high dimensional embedding space.

- Our Phase 1b/2 program for REC-4881 in FAP was initiated using our brute-force screen approach where we discovered a concentration dependent cellular restoration from a modeled disease state (APC gene knockdown by siRNA) to a modeled healthy state (wildtype) in the U2OS cell type. Our map imputed a similar phenotypic effect with REC-4881 across concentrations in HUVEC, suggesting alignment between the brute-force approach and the inferential search approach. These discoveries arose from two different cell contexts, were conducted at different points in time, and under different conditions, robustly validating our interpretation.

**Figure 48. Insights from Recursion OS.** REC-4881 displays a phenotypic opposite relationship across clinically relevant doses to genetic knockout of *AXIN1* and *APC* in HUVEC.
**Preclinical**

On the basis of our inference generation from our Recursion OS, we advanced REC-4881 into two PDX mouse studies, focusing on HCC and Ovarian tumors. A PDX clinical trial (PCT) is a population study with PDX models that can be used to assess efficacy and predict responders to treatment in the preclinical setting. Across 29 total PDX models, treatment with single-agent REC-4881 resulted in a significantly better response in *AXIN1* or *APC* mutant models versus wildtype models. These responses led to a significant benefit in PFS (modeled as the time of tumor doubling from baseline), observed specifically in *AXIN1* or *APC* mutant models, providing further evidence of a biomarker driven effect.

![Tumor Growth Inhibition and PFS across 29 PDX mouse models](image)

Figure 49. Tumor growth inhibition and PFS across 29 PDX mouse models. REC-4881 shows enhanced activity in mouse models with *AXIN1* or *APC* mutant tumors. Tumor volumes were measured three per week after randomization in two dimensions using a caliper, and the volume was expressed in mm3 using the formula: $V = (L \times W \times W)/2$, where $V$ is tumor volume, $L$ is tumor length (the longest tumor dimension), and $W$ is tumor width (the longest tumor dimension perpendicular to $L$). %TGI was calculated using the formula %TGI = (TV vehicle - TV treatment) / (TV vehicle – TV initial) *100 for all mice (Wong, H, et al. Clin Cancer Res., 2012, 18(14): 3846-3855).

**Clinical**

LILAC, a Phase 2 open label, multicenter study in select tumor types initiated towards the end of 2023 with FPI anticipated in Q1 2024. This phase 2, open label, multicenter study is designed to evaluate the safety, tolerability, PK, PD, and preliminary anti-tumor activity of REC-4881 administered orally (PO) at an initial dose of 12 mg on a once daily (QD) schedule in participants with unresectable locally advanced or metastatic cancer harboring *AXIN1* or *APC* mutations. Participants must have progressed on at least one prior line of therapy in order to be eligible for the trial.

The study will consist of two arms – an AXIN1 cohort and an APC cohort and two parts. In Part 1, a maximum of 20 participants will be enrolled in a 1:1 allocation across each arm. In Part 2, up to 20 additional patients may be enrolled in each arm. Once the first six cumulative participants have enrolled in Part 1, enrollment will be briefly paused, and a safety assessment will be conducted by a Safety Review Committee to review the completion of the first four weeks of study drug. The study will follow a Bayesian design with futility analysis after the first 10 participants have been enrolled in each arm of the trial. Study drug may be administered for up to 2 years. Disease status will be evaluated every eight weeks, for the first 24 weeks, and then every 12 weeks, until treatment discontinuation or withdrawal. The primary endpoints for this study are safety, tolerability, and preliminary anti-tumor activity as measured by Objective Response Rate (ORR). We expect to share safety and preliminary efficacy data in H1 2025.
Figure 50. Phase 2 study schema for REC-4881 in AXIN1 or APC mutant cancers. Phase 2 open label, multicenter clinical study to assess the efficacy, safety, and pharmacokinetics of REC-4881 in patients with AXIN1 or APC mutant cancers. Enrollment criteria include (1) unresectable, locally advanced, or metastatic cancers; (2) ≥ 55 years of age; (3) confirmed AXIN1 or APC mutation by NGS (tissue or blood); (4) no MEK inhibitor treatment within 2 months of initial dose; (5) ≥ 1 prior line of therapy; and (6) ECOG PS 0-1. The primary endpoints are safety, tolerability, and preliminary anti-tumor activity as measured by Objective Response Rate (ORR).

Competitors

There are currently 3 active programs in clinical development for AXIN1 or APC mutant cancers.

- FOG-001, a TCF-blocking β-catenin inhibitor from FogPharma, is being studied in a Phase 1/2 trial in patients with locally advanced or metastatic solid tumors with Wnt activating mutations, including AXIN1 or APC.

- Tegavivint, a TBL1 inhibitor from Iterion Therapeutics, is being studied in a Phase 1/2 trial in combination with pembrolizumab in patients with advanced hepatocellular carcinoma harboring mutations in either CTNNB1 or AXIN1.

- DKN-01, an anti-DKK1 monoclonal antibody from Leap Therapeutics, is being studied in a Phase 2 trial in combination with pembrolizumab in patients with advanced or recurrent endometrial cancer harboring Wnt activating mutations, including AXIN1 or APC.

REC-3964 for Clostridioides difficile Infection - Phase 2

REC-3964 is an orally bioavailable, small molecule inhibitor of C. difficile glucosyltransferase. This molecule has the potential to prevent recurrent disease and be used as secondary prophylaxis therapy in high-risk patients with C. difficile infections, a leading cause of antibiotic-induced diarrhea and a major cause of morbidity and mortality. A Phase 1 study in healthy volunteers completed in Q3 2023 and demonstrated that REC-3964 was well tolerated with no serious adverse events (SAEs) reported. We expect to initiate a Phase 2 study in 2024.
**Disease Overview**

*C. difficile*-induced diarrhea is a leading cause of antibiotic-induced diarrhea and arises from the disruption of normal bacterial flora in the colon. Toxins A, or TcdA, and B, or TcdB, secreted by the bacterium are responsible for considerable morbidity, including severe diarrhea, colitis, toxic megacolon, sepsis, extended hospital stays and potentially, death. More than 730,000 patients are diagnosed in the US and EU5 each year. Recurrence of disease occurs in 20-30% of patients treated with standard of care. Standard of care includes antibiotic therapies which can further impair gut flora and lead to relapse.

**Insight Recursion OS**

REC-3964 is a new chemical entity that was identified with our brute-force approach which utilized phenomics to identify cellular and structural changes in epithelial cells associated with the pathological changes resulting from exposure to *C. difficile* toxins. Structure-activity-relationship (SAR) was driven through the Recursion OS to identify structural series that restored structural defects resulting from *C. difficile* toxins’ effects. REC-3964 was identified from a lead benzodiazepinedione structural series that confers selective antagonism against the *C. difficile* toxins’ effects with nanomolar potency on our platform, and dose dependent cellular restoration to a modeled healthy state in human endothelial cells.

![Figure 51. REC-3964 rescued the phenotype of human epithelial cells treated with C. difficile toxin. REC-3964 was identified as demonstrating concentration-responsive rescue in HUVEC cells treated with C. difficile toxin B on Recursion's phenomics platform.](image)

**Preclinical**

REC-3964 was validated in orthogonal functional assays including the Electrical Cell-substrate Impedance Sensing (ECIS) assay where it demonstrated concentration-dependent activity in blocking toxin-mediated barrier disruption.
We have shown in a target-based validation assay that REC-3964 selectively inhibits the toxin’s innate glucosyltransferase (IC50 = 4.7-9 nM), suggesting suppression of toxin-induced glycosylation of Rho-GTPases in host cells as the most likely mode of action. REC-3964 has negligible off-target activity, does not target the host’s glucosyltransferases, produces favorable gut and plasma exposure levels following oral dosing, and is non-mutagenic. Further, in an in vivo hamster model of C. difficile infection, treatment with REC-3964 significantly prolonged the survival of animals relative to bezlotoxumab and vehicle treated controls.

Figure 52. REC-3964 blocks C. difficile Toxin B-mediated endothelial barrier disruption. Transendothelial resistance was quantified with ECIS after incubation of HUVEC cells with 10ng/mL TcdB from C. difficile in the presence of REC-3964. Barrier resistance is shown on a normalized scale with 0% representing the resistance in the absence of REC-3964, and 100% representing the resistance of healthy monolayers that were not exposed to toxin B. Data are presented as Mean ± SEM, N≥3 independent experiments.

Figure 53. C. difficile infected model hamsters treated with REC-3964 survive longer than vehicle treated animals. REC-3964 was administered by oral gavage twice daily for 5 consecutive days along with groups for vehicle and vancomycin (50 mg/kg, QD). N=5 in untreated and vancomycin treated animals and N=10 in vehicle and REC-3964 treated animals.
**Figure 54. REC-3964 selectively inhibits the toxin’s innate UDP-glucose glucosyltransferase.** (A) Autocatalytic event releases *C. difficile* toxin’s glucosyltransferase enzymatic domain into the infected cell, which locks Rho family GTPases in the inactive state. Inactivation of Rho GTPases alters cytoskeletal dynamics, induces apoptosis and impairs barrier function which drives the pathological effects of *C. difficile* infection. (B) REC-3964 binds and blocks catalytic activity of the toxin’s innate glucosyltransferase with no effect on the host protein. 20

**Figure 55. REC-3964 significantly extended survival over the standard of care, bezlotoxumab, in a human disease relevant CDI hamster model.** REC-3964 was administered at 200 mg/kg by oral gavage twice daily for 7 consecutive days along with groups for vehicle and vancomycin (50 mg/kg, QD). Bezlotoxumab was administered at 10 mg/kg BID 2 days prior to inoculation with *C. difficile* (strain 630). N=10 hamsters per group. Clinical observations were conducted from Day 0 to Day 7, with surviving animals monitored until Day 14. REC-3964 demonstrated a significant difference in the probability of survival vs bezlotoxumab at the end of treatment (p<0.001, log-rank test).

Clinical

We conducted a Phase 1 healthy volunteer study to evaluate the safety, tolerability, and PK of REC-3964 at increasing oral doses in comparison with placebo. A total of 90 healthy subjects participated in this study with 48 subjects in the Single Ascending Dose (SAD) study and 42 subjects in the Multiple Ascending Dose (MAD) study. The SAD study included a cohort of healthy elderly subjects (age > 65 years). REC-3964 monotherapy was safe and well tolerated at single doses up to 1200 mg (SAD) and multiple doses (MAD) up to 900 mg.

In the SAD study, the most frequently reported TEAE with REC-3964 was contact dermatitis (4 subjects, 11.1%). All TEAEs were mild in severity and the only TEAE that was considered related to REC-3964 was a single TEAE of fatigue. There were no serious adverse events (SAEs), deaths, or TEAEs that led to discontinuation. In the MAD study, the most frequently reported TEAEs with REC-3964 were fatigue and headache (6 subjects each, 17.6%). All TEAEs were mild in severity. For subjects receiving REC-3964, 11.8% (n=4) had TEAEs considered to be related to treatment, consisting of abdominal distension (3 subjects) and flatulence (1 subject). Abdominal distension was also considered to be related to the study drug for 25% (n=2) of subjects who received placebo. There were no serious adverse events (SAEs), deaths, or TEAEs that led to discontinuation.

PK analysis demonstrated that exposures (AUC) increased approximately dose-proportionally across the dose ranges tested and the half-life ranged from approximately 7 to 10 hours. The peak and systemic exposure to REC-3964 was comparable between healthy elderly subjects and subjects aged ≤ 65 years. As a result, BID dosing is expected to reach targeted trough concentrations.

There were no clinically meaningful trends or clinically significant abnormalities in hematology and chemistry and no clinically relevant effects on ECG parameters (including QTcF) or vital signs after administration of single or multiple doses of REC-3964.

We plan to initiate a Phase 2 open label, multicenter study in 2024 to evaluate the safety, tolerability, efficacy, and PK of REC-3964 at doses of either 250 mg or 500 mg both administered orally (PO) twice a day (BID) over a 28-day period compared to an observational cohort after an initial cure with vancomycin. The primary endpoints for this study will be safety, tolerability, and preliminary efficacy as assessed by the rate of recurrent Clostridioides difficile infection (rCDI).

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<td>6 (60.0)</td>
<td>3 (37.5)</td>
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<td>3 (8.8)</td>
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<tr>
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<td>0</td>
<td>0</td>
<td>1 (2.9)</td>
<td>1 (2.4)</td>
</tr>
</tbody>
</table>

| Severity |
| Grade 1 | 6 (75.0) | 8 (80.0) | 4 (50.0) | 5 (62.5) | 4 (50.0) | 21 (61.8) | 27 (64.3) |
| Grade 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Grade ≥ 3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Total Number of SAEs | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Discontinued Study Drug Due to AE | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

Table 2. Summary of Adverse Events from Phase 1 Multiple Ascending Dose Study. AE=adverse event; MAD=multiple ascending dose; SAE=serious adverse event; TEAE=treatment-emergent adverse event.
Figure 56. Planned Phase 2 study schema of REC-3964 for prevention of rCDI. Phase 2 open-label, multicenter clinical study to assess the safety, tolerability, PK, and efficacy of REC-3964 at two dose levels. Enrollment criteria include (1) High risk for rCDI; (2) *C. difficile* associated diarrhea with confirmation of toxin positivity (3) No fulminant CDI; (4) No history of chronic diarrheal illness due to other causes. The primary endpoints are safety, tolerability, and efficacy as determined by the rate of reduction of rCDI after initial clinical cure with vancomycin.

Competitors

There are a number of approved drugs for the treatment and prevention of *C. difficile* infection.

- Antibiotics are the main treatment for *C. difficile* infection with vancomycin and fidaxomicin as the two most commonly prescribed. Metronidazole may also be prescribed for severe cases. However, the efficacy of antibiotic therapy decreases with each recurrence.

- Bezlotoxumab is a human monoclonal antibody against *C. difficile* toxin B approved for reducing CDI recurrence in patients receiving antibiotics who are at high-risk for CDI recurrence.

- Stool derived microbiome products are used to prevent recurrent *C. difficile* infection with RBX2660 and SER-109 approved for this indication, following antibiotic treatment for recurrent CDI.

There are currently 2 active programs in clinical development for the prevention of recurrent *C. difficile* infection.

- VE303, an oral microbiome therapeutic from Vedanta Biosciences, is being studied in a Phase 3 trial in patients with ≥ 1 prior occurrence of CDI, including a high-risk for recurrence population.

- LMN-201, an oral biologic from Lumen Bioscience, is being studied in a Phase 2 trial in patients newly diagnosed with CDI planning to receive antibiotic treatment.

To our knowledge, REC-3964 is the first orally bioavailable, non-antibiotic, *C. difficile* toxin inhibitor that selectively targets bacterial toxin while sparing the host.
Selected Preclinical Programs

- Novel CDK12-adjacent target, RBM39, for the potential treatment of HR-proficient ovarian cancers and other Solid Tumors (previously identified as Target Gamma).

- Potential first-in-class novel chemical entity for the treatment of an undisclosed indication in Fibrosis (Target Epsilon)

HR-Proficient Ovarian Cancers and other Solid Tumors (Previously Identified as Target Gamma)

Using inferential search, we identified compounds that inhibit RBM39 and phenocopy the loss of CDK12, but not CDK13. We further optimized these molecules to generate lead candidates with oral bioavailability capable of single agent activity in homologous recombination proficient (HR-proficient) ovarian cancers and other solid tumors. There are approximately 200,000 drug-treatable patients per year in the US and EU5 whose tumors lack mutations in the homologous recombination repair (HRR) pathway and who have progressed on frontline therapies. While PARP inhibitors have significantly improved outcomes for patients with HR-deficient cancers, patients with HR-proficient tumors have poorer prognosis and unfavorable outcomes. We expect to submit an IND for this program in H2 2024.

Disease Overview

Mutations in DNA repair pathways and genomic instability are a fundamental hallmark of cancer. Large-scale genomic datasets highlight cancers such as ovarian, breast, prostate, pancreatic, non-small cell lung, and small-cell lung cancers harboring molecular alterations within the DDR repair network. Cancers with genetic alterations in the DDR pathway such as homologous recombination (HR) can often be treated with DDR inhibitors, such as PARP inhibitors. However, patients with HR-proficient tumors do not derive significant clinical benefit from PARP inhibitors. Accordingly, there is a high unmet need for developing therapeutics that can regulate DNA repair mechanisms for the treatment of HR-proficient cancers, including ovarian cancer.

Insight from Recursion OS

Reports suggest that genetic or pharmacologic depletion of CDK12 can reduce the expression of several genes involved in the homologous recombination repair pathway such as BRCA1 and BRCA2, inducing a BRCA-like phenotype and DDR response. Thus, CDK12 has received considerable interest as a therapeutic target and tumor biomarker for HR-proficient cancers. Despite reports of functional redundancy, we observed that the genetic knockout of CDK12 could be clearly distinguished phenotypically from that of CDK13. Using map-based inference to characterize and relate cellular phenotypes, we identified RBM39 as an alternative target that selectively mimics CDK12 loss, but not CDK13, providing a novel approach for targeting CDK12 biology while circumventing any toxicities that may arise due to CDK13. We subsequently discovered REC-1170204 as an RBM39 molecular glue degrader that closely mimics the phenotypic loss of CDK12 and RBM39, but not CDK13. Functionally, REC-1170204 treatment globally impacts the expression of many DDR genes but does so in a CDK12 independent manner.
Product Concept

We aim to discover and develop novel, orally bioavailable, small molecules that drive de novo sensitivity in HR-proficient tumors. While the biological and clinical evidence supporting CDK12 as a therapeutic target is promising, the high homology of CDKs makes targeting a single homolog difficult and prone to off-target toxicity. Mimicking the effects of CDK12 inhibition via alternative novel targets could be a route to treating HR-proficient tumors. We intend to position our lead candidate as a single agent for the potential treatment of HR-proficient ovarian cancers and other HR-proficient solid tumors.

Preclinical

In vivo efficacy studies evaluated REC-1170204 as a single agent and in combination with niraparib in OV0273, an ovarian BRCA proficient patient derived xenograft (PDX) model. We observed statistically significant responses in both single agent REC-1170204 and combination versus either niraparib or vehicle arms. REC-1170204 also demonstrated a significant survival benefit as a monotherapy, or in combination with niraparib at >30 days post final dose. As a result of our strategic collaboration with Tempus, we are leveraging genomic data across all tumor types to identify clinical biomarkers for patient expansion. We are advancing our lead candidate through IND-enabling studies with IND submission expected in H2 2024.

![Figure 58: REC-1170204 ± niraparib inhibits tumor growth in the OV0273 PDX mouse model.](image) In the OV0273 PDX model, mice were treated with a representative lead molecule REC-1170204 (100 mg/kg, BID, PO) ± niraparib (40 mg/kg, QD, PO) for 28 days. Single agent REC-1170204 or in combination with niraparib resulted in a statistically significant response vs either
niraparib or vehicle arms, where the reduction in tumor volume is plotted using a logarithmic scale (y-axis). In addition, there was a statistically significant improvement in survival > 30 days post final dose. *p<0.05, ** p<0.01, **** p<0.0001.

Undisclosed Indication in Fibrosis – Target Epsilon

Phenotypic screening of human PBMCs was used to identify novel and structurally diverse small molecules that reverse the phenotypic features of disease-state fibrocyte cells into those of healthy-state cells. The power of the Recursion OS revealed a relationship between the small molecule hits and a novel target that could impact fibrotic diseases. The most promising hit compounds were confirmed as potent inhibitors of this novel target (Target Epsilon) in validation experiments. Optimized hit compounds were found to be effective in an in vivo mouse model of fibrosis. This program is now entering IND-enabling studies.

Disease Overview

Fibrotic diseases carry a high, mostly unmet clinical need and can afflict all major organs. Patients across fibrotic disease indications may benefit from the modulation of common pathways and cells involved in driving pathogenesis of fibrosis. Immune cells, particularly monocyte-derived cell populations including fibrocytes closely associated with collagen producing myofibroblasts, can drive a fibrotic response exceeding what is necessary for injury repair. Monocyte-derived cells produce growth factors that promote the continued activation of mesenchymal populations. Molecules that modulate this immuno-mesenchymal interface may enable a shift towards a pro-resolution and tissue repair response. Despite the important role these cell types play in fibrotic processes there are no current therapies to effectively target the accumulation and differentiation of these pathogenic cell populations. With limited treatment options, two approved anti-fibrotics, patients need greater therapeutic efficacy to address this burden.

Insight from Recursion OS

With the critical role that monocyte-derived immune cells play in fibrotic disease, we developed a phenotypic screening assay from hPBMC-derived fibrocytes that could capture key features of disease in this important cell type. Human recombinant pentraxin-2 (PTX-2) is a constitutive, anti-inflammatory, innate immune plasma protein whose circulating level is decreased in chronic human fibrotic diseases. PTX-2 has an impact on monocyte differentiation to fibrocytes and macrophage polarization state, which elicit tissue repair and reduce fibrosis. Leveraging Recursion’s phenotypic screening platform, we identified multiple structurally diverse and novel small molecules that were able to phenotypically mimic the morphological effects of PTX-2 on hPBMC-derived fibrocytes and macrophages. The hPBMC-fibrocyte reversal assay was also leveraged for optimization of the identified compounds. Using inferential search of Recursion’s HUVEC phenomap, we identified a putative binding target (Epsilon) for the small molecules which was later confirmed through biochemical binding assays with the isolated protein. The identified target represents a novel approach to modulating immuno-mesenchymal cell populations in fibrosis.

Reversal of Fibrocyte Differentiation Assay

Figure 59: Phenotypic screening assay. Differentiation of human PBMCs into fibrocytes can be reversed by Pentraxin-2, a tissue repair protein, to mimic a healthy state. Small molecules are identified which rescue disease state to healthy state.
**Product Concept**

We aim to discover and develop an orally bioavailable immuno-mesenchymal modulator offering a novel mechanism of action designed to treat fibro-inflammatory diseases. We are targeting a small molecule with single agent efficacy that reverses fibrosis by modulating fibrocytes, fibrotic macrophages, and adaptive immune cells. Discovered using Recursion’s phenomics platform, our lead molecule has shown promise in both *in vitro* and *in vivo* models of fibrosis, suggesting that it might restore immuno-mesenchymal homeostasis and tissue integrity by targeting immune and mesenchymal cell populations. It exhibits a unique profile with immunomodulatory effects on multiple cell types and shows anti-fibrotic effects, with the possibility of differentiating from current treatment options.

**Preclinical**

We identified multiple structurally distinct small molecules capable of imparting the desired phenotypic rescue of the fibrocyte disease model. REC-1169575, a representative lead molecule, is a potent compound with an EC\textsubscript{50} of 0.40 µM in the fibrocyte reversal assay and an IC\textsubscript{50} of 12nM at target Epsilon. In digital tolerability, REC-1169575 was well-tolerated in C57BL/6 mice at all doses (30, 200, and 300 mg/kg/day, PO x 6 days). REC-1169575 did not significantly affect the body weight, breathing rate, motion, or body temperature of the mice. In a rodent in vivo efficacy model of fibrosis, REC-1169575 significantly reduced collagen, an important histological marker of fibrosis.
Figure 61: REC-1169575 reduces collagen in a mouse model of fibrosis. There was a statistically significant reduction in collagen ratio, a marker of fibrosis, in both our representative lead molecule REC-1169575 (50 mg/kg BID, PO) and a control molecule known to inhibit fibrosis, SB525334, a selective inhibitor of TGF-beta receptor type 1 compared to fibrosis-induced vehicle treated mice. *p<0.05 (Kruskal-Wallis test)

**Therapeutics Partnerships**

We have and in the future may collaborate with third parties to broadly explore diverse disease domains (such as fibrosis, neuroscience, oncology, immunology and inflammation) in order to identify novel target insights and potential therapeutics that may include small molecules, large molecules, gene therapies and cell therapies. We may also explore a communal asset-type strategy where we license search results from our phenomaps to partners.

The goal of every partnership is to create therapeutics, yet the approach may take multiple forms:

- **Novel Therapeutics.** Without any presumptive target hypothesis, we can identify differentiated therapeutics by rapidly evaluating large compound libraries within our maps of human cellular biology.

- **Novel Targets.** By profiling diverse biological perturbations (such as genetic factors) on our platform, we may be able to identify novel druggable targets that we can then exploit with partners to generate therapeutic candidates.

**Roche & Genentech Collaboration and License Agreement**

On December 5, 2021, we entered into a Collaboration and License Agreement with Genentech, Inc. and F. Hoffmann-La Roche Ltd, pursuant to which we will construct, using our imaging technology and proprietary machine learning algorithms, unique maps of the inferred relationships amongst perturbation phenotypes in a given cellular context and together with Roche and Genentech will create multimodal models and maps to further expand and refine such inferred relationships, in both cases with the goal to discover and develop therapeutic small molecule programs in a gastrointestinal cancer indication and in key areas of neuroscience.

**Upfront Payment.** In January 2022, Roche paid us an upfront cash payment of $150.0 million.

**Phenomap Creation, Acceptance and Access.** Under the Collaboration Agreement, we are responsible for creating a certain number of phenomaps in each of the Exclusive Fields. We will also provide Roche with limited access to our pre-existing human umbilical vein endothelial cells (HUVEC) phenomap. Roche will have specified rights to query or access the phenomaps to generate novel inferences that may lead to the discovery or development of therapeutic products.
Phenomap-Related Options. Each of the phenomaps requested by Roche and created by Recursion may be subject to either an initiation fee, acceptance fee or both. Such fees could exceed $250.0 million for sixteen (16) accepted phenomaps. In addition, for a period of time after Roche’s acceptance of certain phenomaps, Roche will have the option to obtain, subject to payment of an exercise fee, rights to use outside the collaboration the raw images generated in the course of creating those phenomaps. If Roche exercises its External Use Option for all twelve (12) eligible phenomaps, Roche’s associated exercise fee payments to Recursion could exceed $250.0 million.

Collaboration Programs and Roche Options. Roche and Recursion will collaborate to select certain novel inferences with respect to small molecules or targets generated from the phenomaps for further validation and optimization as collaboration programs. Roche and Recursion may also combine sequencing datasets from Roche with Recursion’s phenomaps and collaborate to generate new algorithms to produce multimodal maps from which additional collaboration programs may be initiated. For every collaboration program that successfully identifies potential therapeutic small molecules or validates a target, Roche will have an option to obtain an exclusive license to develop and commercialize such potential therapeutic small molecules or to exploit such target in the applicable Exclusive Field. In October 2023, Roche exercised its Small Molecule Validated Hit Option to further advance our first partnership program in GI-oncology.

Payments if Roche Exercises Option for a Collaboration Program. Under the collaboration, Roche may initiate up to forty (40) small molecule collaboration programs. Each small molecule collaboration program, if optioned and successfully developed and commercialized by Roche, could yield more than $300.0 million in research, development, commercialization and net sales milestones for Recursion, as well as mid- to high-single digit tiered royalties on net sales. Recursion is also eligible for research, development, commercialization and net sales milestones for target collaboration programs optioned by Roche.

Recursion Programs. If Roche does not exercise its options in the Collaboration Agreement for certain collaboration programs, we may, with Roche’s prior consent, choose to independently validate, develop and commercialize products in a limited number of such programs, subject to agreed milestones and royalties to Roche. Roche will have rights to obtain an exclusive license to exploit such products by providing notice and paying us an opt-in fee and economics exceeding those that would otherwise be applicable if Roche had exercised its option for such program.

Exclusivity. During an agreed period of time after the Collaboration Agreement’s effective date, we are subject to certain exclusivities that limit our ability to conduct certain research and development activities with respect to compounds and targets in the Exclusive Fields, other than pursuant to the collaboration with Roche. However, we may continue pursuing products that we are researching and developing in the Exclusive Fields as of the effective date of the Collaboration Agreement.

Termination. The Collaboration Agreement includes standard termination provisions, including for material breach or insolvency and for Roche’s convenience. Certain of these termination rights can be exercised with respect to a particular Exclusive Field or exclusive license, as well as with respect to the entire Collaboration Agreement.

Figure 62. Under our collaboration with Roche & Genentech, we are creating multimodal maps of cellular biology to elucidate novel targets and starting points.
Bayer AG Amended and Restated Research Collaboration and Option Agreement

On August 28, 2020, Recursion and Bayer entered into a Research Collaboration and Option Agreement, which was subsequently expanded on December 1, 2021, for research and collaboration on a certain number of projects related to fibrosis. On November 8, 2023, the parties amended and restated the original Bayer Agreement to realign the collaboration with Bayer’s strategic shift in focus to oncology. As a result, the parties wound down their joint work in fibrosis and the exclusivities with respect to the field of fibrosis were terminated.

Under the Restated Agreement, Recursion will collaborate with Bayer for the remainder of the five-year period under the original Agreement (extendable by up to 2 years to enable completion of certain research activities), to initiate up to seven programs in oncology. During certain agreed time periods within the collaboration term, Recursion is prohibited from conducting certain research and development activities with respect to certain identified genes of relevance in oncology outside of the collaboration, either by itself or together with third parties. However, Recursion may continue research and development activities for any such identified genes that it has initiated prior to the date of identification of such gene.

Under each oncology project, Recursion will work with Bayer to identify potential lead candidates for development. Under the Restated Agreement, Bayer has the first option to license potential candidates; each such license could potentially result in option exercise fees and development and commercial milestones paid to Recursion with an aggregate value of up to approximately $210.0 million for one license and up to approximately $1.5 billion if each program is licensed, as well as tiered royalties for each such license, ranging from low- to mid-single digit percentages of sales, depending on commercial success. Royalty periods for each license are on a country-by-country basis, and the duration of each such period is tied to the duration of patent or regulatory exclusivity in each country (with a minimum term of 10 years each).

If Bayer does not exercise its option with respect to a lead candidate or otherwise discontinues a project prior to completion, within a specified period of time, Recursion may exercise an option to negotiate with Bayer in good faith to obtain an exclusive license under Bayer’s interest in any lead series developed pursuant to the project and backup compounds related thereto, as well as a non-exclusive license under Bayer’s background intellectual property necessary for Recursion’s use of the project results related to such compounds.

Bayer may terminate the collaboration at any time without cause. Either party may terminate the agreement for a material breach by the other party. The term of each license agreement continues on a product-by-product and country-by-country basis until the later of (a) the expiration of the last to expire valid claim of the licensed patents covering such product in such country, (b) the expiration of any applicable regulatory exclusivity period for such product in such country and (c) ten years after the first commercial sale of such product in such country. Bayer may terminate each such license agreement at any time without cause. Either party may terminate each such license agreement for the other party’s uncured material breach.

Technology Partnerships

While we focus on the generation and utilization of the Recursion Data Universe to maximize our pipeline and partnership value-drivers, we are exploring ways to make small, select data layers and foundation models externally available to drive additional value and technology and data collaborations that strengthen our platform. Large datasets generated for training AI models are rare and valuable, especially with respect to biology and chemistry, where most data generated is siloed and not relatable across experimental contexts. The Recursion OS has generated, and continues to generate, highly relatable and reliable datasets used to train foundation models. Our collaborations with NVIDIA, Tempus and Enamine highlight how data, foundation models and compute are integral value drivers in the TechBio space and for Recursion.

NVIDIA

In July 2023, we entered a strategic collaboration with NVIDIA to accelerate the development of our groundbreaking AI foundation models for biology and chemistry using our supercomputer, BioHive-1, and priority access on NVIDIA DGX™ Cloud. We intend to optimize and distribute these models for internal use in addition to possible commercial license or release on BioNeMo, NVIDIA’s cloud service for generative AI in drug discovery. During the JP Morgan
Healthcare Conference in 2024 we released, with NVIDIA, Phenom-Beta on the BioNeMo platform. Phenom-Beta is a smaller, yet still powerful, version of the Phenom-1 model discussed above. In November 2023, we committed to working with NVIDIA to expand BioHive-1, increasing the computational capacity by over 4X. We project that upon completion and benchmarking, BioHive-1 will be in the top 50 most powerful supercomputers in the world across any industry (according to the TOP500 list) and will be the most powerful supercomputer owned and operated by any biopharma company.

**Tempus**

In November 2023, we entered a collaboration with Tempus to gain preferred access to one of the world’s largest proprietary, de-identified, patient-centric oncology datasets, spanning DNA, RNA, health records and more to support the discovery of potential biomarker-enriched therapeutics at scale through the training of causal AI models. By combining the forward genetics approach of Tempus with the reverse genetics approach at Recursion, we believe we have an opportunity to improve the speed, precision, and scale of therapeutic development in oncology.

**Enamine**

In December 2023, we entered a collaboration with Enamine to generate and design enriched compound libraries for the global drug discovery industry. By leveraging Recursion’s MatchMaker, an AI model, to identify compounds in the Enamine REAL Space predicted to bind to high-value targets, we believe we can generate more powerful compound libraries for drug discovery purposes. Enamine may offer the resulting libraries to customers for purchase and will co-brand any libraries under both the Enamine and Recursion’s MatchMaker trademarks. This collaboration is an example of how select data layers can drive value in novel ways.

**People and Culture**

Essential to leading and defining TechBio is our team of over 500 Recursionauts, balanced between life scientists such as chemists and biologists (approximately 35% of employees) and computational and technical experts such as data scientists and software engineers (approximately 40% of employees). This kind of functional balance intentionally stands in contrast to traditional biotechnology companies. Together our team creates an environment where empirical data, statistical rigor and creative thinking is brought to bear on the problems we address. While we are united in a common mission, *Decoding Biology to Radically Improve Lives*, our strength lies in our differences: expertise, gender, race, disciplines, experience and perspectives. Deliberately building and cultivating this culture is critical to achieving our audacious goals.
One of the most critical elements supporting Recursion’s leadership in TechBio is what we call the Recursion Mindset – a deep belief and commitment to industrialization through automation, systems-thinking, algorithms and data to deliver our mission. Broadly at the company we apply this mindset to eliminate toil and inefficiency creating space for our creative energy to be pointed at Recursion’s hardest problems. The Recursion Mindset is made manifest through our Founding Principles and supported by our Culture and Values. Our Founding Principles are the guideposts to our approach to technical and scientific decision-making. Our Values are the core behaviors that define our Culture and are the simplest definition of how we will achieve our mission. Combined they are the shape of our culture and guide us to reimagine how medicines are made on the path to delivering our mission.
Figure 64. Recursion’s Founding Principles. These six founding principles differentiate our approach from nearly every other biopharma company, enable us to lead TechBio and form the foundation for a mindset we teach and enrich for at Recursion.

Figure 65. Recursion’s Values. These five values support our founding principles and guide our culture at Recursion.

Diversity, Equity, Inclusion and Belonging

At Recursion, we believe in the moral and business case for diversity. The research-based evidence is unequivocal that diverse perspectives support better complex decision-making, foster greater innovation and ultimately result in greater company performance and success. We seek the best talent by maximizing diversity at the top of the recruiting funnel and then mitigating bias through objective decision-making throughout the hiring process. We foster an environment of inclusion for candidates and employees to unleash the strength of our differences. Lastly, acknowledging the breadth of societal injustice and inequities we pursue fair and equitable outcomes across all people-decisions through process design and supported by analytics.

Employee Recruitment, Development and Training

We take a design-thinking approach to building the employee experience at Recursion. It is a fit-for-purpose system that finds, grows and retains top talent to deliver our mission. Our people are mission-driven, humble, bright, generous of spirit and constructively dissatisfied with the status quo. We employ a targeted approach to identify, attract and hire diverse employees across highly technical scientific disciplines including: biology, chemistry, data science, machine learning, engineering, robotics, clinical development and more. We seek people that are a fit for our commitment to industrialization as defined by our Recursion Mindset, which is manifested in our Founding Principles and Values.

Culturally, we instill an expectation to be constantly learning and teaching in pursuit of growing ourselves as fast as Recursion. Most notable is a 2-day experience offered year-round to all employees called Decoding Recursion. It is an opportunity for close interaction with senior leaders who teach the Recursion Mindset through stories. The need to learn is reinforced throughout our performance system which creates accountability for our learning, delivery and impact on others.

People stay at Recursion because of the opportunity to impact the world and grow in a place where they feel challenged, supported and connected. Throughout the employee experience we create moments, rituals, programs and spaces that inspire ambition, reward contributions and growth and foster belonging.
Employee Health and Safety

We have dedicated Standard Operating Procedures to manage occupational health and safety, safety training and injury and illness and incident reporting. Every employee is responsible to ensure these procedures and policies are followed. We offer extensive training to ensure understanding and compliance. Compliance is mandatory for all laboratory employees per requirements of the Occupational Safety and Health Administration standard on Hazardous Chemicals in Laboratories. Our Co-Founder and CEO is the Director of Public Safety at the company and has the ultimate responsibility for chemical hygiene within the organization. Our Chemical Hygiene Officer and Lab Manager oversees the day-to-day management of institutional chemical hygiene.

Read more about how we invest in and motivate our people to achieve our mission in Recursion’s latest Environmental, Social and Governance Report, available at our corporate website.

Facilities

Headquarters

Our United States headquarters is in downtown Salt Lake City, Utah where we lease 105,419 square feet of office and laboratory space. The lease for this space expires in May 2028. In November 2022, we expanded into 103,634 square feet of office and laboratory space adjacent to our headquarters under a lease that expires in May 2032. Our modern headquarters is a draw for local, national and international talent.
Figure 66. Our headquarters is centrally located in downtown Salt Lake City, Utah. We are a proud founding member of BioHive, the branding effort of the life science hub of Utah. Working with state and local government, we are helping to create a burgeoning life science ecosystem around a downtown cluster of companies centered around our headquarters.

**Satellite Offices and Facilities**

*Toronto and Montréal.* In June 2023, we celebrated the opening of our 28,110 square foot Toronto site, which serves as the headquarters for Recursion Canada. The lease for this space expires in November 2032. The new site represents Recursion’s significant growth in Canada and our continued investment in the local economy. Following the acquisition of Cyclica, we consolidated our Toronto based teams into our new headquarters. In addition to our Recursion Canada headquarters we have a site in Montréal that houses our semi-autonomous artificial intelligence research engine, Valence Labs, which is located in the world-renowned artificial intelligence and machine learning hub MILA.
Figure 67. Recursion’s satellite offices and facilities. Left panel: Mila, the Quebec Artificial Intelligence Institute, is recognized worldwide for its major contributions to AI. Right panel: Government and biotech leaders celebrate the opening of our Toronto office, home to Recursion’s Canadian headquarters and our largest site outside of our global headquarters in Salt Lake City, Utah. This site, along with the Mila Montreal office, serves as multidisciplinary hubs across data science and machine learning.

Digital Vivarium. We lease a property that serves as a rodent vivarium. This lease expires in May 2028. We use this facility to conduct drug-discovery enabling pharmacokinetic, pharmacodynamic and exploratory safety studies. The facility is equipped with proprietary, digitally enabled cage technology.

Corporate Social Responsibility

We believe that to achieve our mission, we must act like the company we aim to be, which means we must be a good corporate citizen. In recognition of our commitment to excellence in environmental, social and governance stewardship, Recursion received a Prime Rating in 2023 for ESG performance from Institutional Shareholder Services (ISS). The ISS ESG Corporate Rating provides an assessment of a company's environmental, social and governance activity. A Prime Rating is awarded to companies with ESG performance above a sector-specific threshold and is defined by ISS as “absolute best in class”. Additionally, as of January 2024, Recursion was ranked 16 out of over 900 companies (approximately top 2%) in the pharmaceutical category by Morningstar Sustainalytics21 which gives an in-depth analysis of a company’s ESG performance and compares it to industry peers. This ranking places Recursion in Sustainalytics’ 2024 Top-Rated ESG Companies List.

To date, we have focused our community efforts in areas of impact that are aligned with our Values and our strengths, including: (i) diversity, equity and inclusion in technology and biotechnology (e.g., in 2020 the Recursion Foundation launched Altitude Lab, a life science incubator and accelerator for diverse health care entrepreneurs); (ii) the growth and sustainability of our local life science and technology ecosystems (e.g., Recursion is a founding member of BioHive, a Utah life science collective); and (iii) the promotion of sustainable environmental practices (e.g., Recursion aims to achieve net-zero greenhouse gas emissions across our operations by the year 2030). We believe that through these principles of community engagement, we can extend our mission of radically improving lives to those in our communities.

Read more about how we are delivering on that belief in Recursion’s Environmental, Social and Governance Report.

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Commercialization

We may retain significant development and commercial rights to some of our drug candidates. If marketing approval is obtained, we may commercialize our drug candidates on our own, or potentially with a partner, in the United States and other geographies. We currently have no sales, marketing, or commercial product distribution capabilities. Decisions to create this infrastructure and capability will be made following further advancement of our drug candidates and based on our assessment of our ability to build the necessary capabilities and infrastructure with competitive advantage. Clinical data, the size of the addressable patient population, the size of the commercial infrastructure, manufacturing needs and major trends as to how value is accrued in the industry may all influence or alter our commercialization plans.

Manufacturing

We currently utilize contract development and manufacturing organizations to produce drug substance and investigational drug product in support of the assets within our pipeline. To date, we have obtained drug substance and drug product for our drug candidates from third party contract manufacturers. We are in the process of developing our supply chain for each of our drug candidates on a project-by-project basis based on our development needs.

Strategic Agreements

To achieve our mission, we may partner with leading biotechnology companies, pharmaceutical companies and academic research institutions to access datasets, molecules, or other intellectual property.

Tempus Master Agreement

On November 3, 2023, Recursion Pharmaceuticals, Inc., or the Company, and Tempus Labs, Inc., or Tempus entered into a Master Agreement, or the Tempus Agreement pursuant to which Tempus may provide certain services and deliverables to the Company and/or license certain data to the Company. The term of the Tempus Agreement is five years from the effective date of the Tempus Agreement, or the Term.

Under the terms of the Tempus Agreement, the Company is granted a limited right to access Tempus’s proprietary database of de-identified clinical and molecular data for certain therapeutic product development purposes, including to develop, train, improve, modify, and create derivative works of the Company’s machine learning/artificial intelligence models for the purposes of therapeutic product development. The Company is permitted to download a maximum number of de-identified records at any one time, subject to an aggregate cap in the total unique records that can be downloaded over the course of the Term, and to retain each downloaded record for a period of 180 days from the date of download. After such 180-day period, The Company may elect to license such downloaded records for a longer period subject to additional terms and the payment of additional fees.

In exchange for these rights, the Company will pay Tempus an initial license fee in an amount equal to $22.0 million, or the Initial License Fee and annual license fees during the Term ranging between $22.0 million and $42.0 million, which, together with the Initial License Fee, totals up to $160.0 million over the Term, subject to the Company’s early termination, which may be triggered only following the third anniversary of the Master Agreement’s effective date, and payment by the Company of an early termination fee (as further discussed below). The Initial License Fee and each annual license fee shall be payable at the Company’s option either in the form of (x) cash, (y) shares of Class A Common Stock of the Company or (z) a combination of cash and shares of Class A Common Stock in such proportion as is determined by the Company in its sole discretion; provided that (a) the aggregate number of shares of Class A Common Stock that the Company may issue in connection with all payments under this Agreement shall not exceed 19.9% of the aggregate total of shares of Class A Common Stock and the Company’s Class B Common Stock outstanding on November 2, 2023 or the date immediately preceding the date of any shares of Class A Common Stock issued pursuant to the Tempus Agreement, whichever is less (the “Share Maximum”).

In the event that all or any portion of the Initial License Fee or any annual license fee is payable in the form of shares of Class A Common Stock, the Company shall, subject to the Share Maximum, issue to Tempus a number of
shares of Class A Common Stock equal to (1) the amount of such fee divided by (2) the volume weighted average price of Class A Common Stock for the seven trading day period ending on the trading day immediately preceding (and including) the date that is five business days before the date on which such fee is paid (any shares so issued, the "Tempus Shares").

The Company has agreed to use commercially reasonable efforts to prepare and file a registration statement (or a prospectus supplement to an effective registration statement on Form S-3ASR that will become automatically effective upon filing with the SEC pursuant to Rule 462(e)) with the Securities and Exchange Commission as soon as practicable but in no event later than 30 days after each issuance of Tempus Shares under the Tempus Agreement, and to use its commercially reasonable efforts to have the registration statement declared effective as promptly as possible but in any event within 30 days following initially filing (or up to 90 days in the event of full SEC review). After such registration, the Company has agreed to use commercially reasonable efforts to keep such registration statement effective until such date that all Tempus Shares covered by such registration statement have been sold thereunder or may be sold without restriction or volume limitation under Rule 144 as promulgated by the SEC under the Securities Act of 1933, as amended.

The Tempus Agreement also grants the Company the right to access and use Tempus’ LENS software that permits the viewing and analysis of clinical, molecular, and other health data maintained by Tempus. Company will pay Tempus a six-figure annual license fee for the duration of the Term for the use of such software.

In addition to mutual rights to terminate for an uncured breach of the Tempus Agreement, the Company may terminate the Tempus Agreement for convenience after three years upon 90 days prior notice, subject to payment by the Company of an early termination fee equal to (a) an amount per unique record that Company has downloaded prior to termination less (b) the sum of any annual license fees paid prior to termination, which could result in early payment of the aggregate annual license fees contemplated by the Tempus Agreement to the extent all records made available under the Tempus Agreement have been downloaded.

Either party may assign its rights under the Tempus Agreement subject to limited restrictions, but the Company may not assign the Tempus Agreement without Tempus’s consent if the proposed assignee is a large pharmaceutical company.

**REC-994: University of Utah Research Foundation Agreements**

In February 2016, we entered into an Amended and Restated License Agreement with the University of Utah Research Foundation, or UURF, pursuant to which we obtained an exclusive license under certain patents and a non-exclusive license under certain know-how, in each case controlled by UURF and related to the drug tempol, or REC-994, to make, have made, use, offer to sell, sell, import and distribute products incorporating REC-994 worldwide for the treatment of cerebral cavernous malformation, or CCM. In partial consideration for the license rights, we issued UURF equity in our company. In addition, we agreed to reimburse UURF for a specified portion of costs associated with the filing, maintenance and prosecution of the licensed patent rights. The Amended and Restated License Agreement will expire on a country-by-country basis upon the expiration of the last-to-expire patent within the patent rights in the applicable country. UURF may terminate the agreement for an uncured material breach, if we cease commercially diligent efforts to develop or commercialize a licensed product or service, or our bankruptcy or insolvency.

**REC-2282: Ohio State Innovation Foundation In-License**

In December 2018, we entered into an Exclusive License Agreement with the Ohio State Innovation Foundation, or OSIF, pursuant to which we obtained an exclusive, sublicensable, non-transferable, royalty-bearing license under certain patents and a non-exclusive license under certain know-how, in each case controlled by OSIF and related to the pan-histone deacetylase inhibitor, OSU-HDAC42, or REC-2282, to develop, make, have made, use, sell, offer for sale and import products incorporating OSU-HDAC42 worldwide. OSIF also assigned certain assets to us, relating to the pharmaceutical composition known as AR-42. OSIF retains the right to use and allow other academic, nonprofit and government institutions to use the licensed intellectual property for research, non-commercial and educational purposes. OSIF shall not practice, have practiced, or transfer such reserved rights for any clinical purpose other than completion of the existing clinical trials at the time of the license agreement without our prior written consent. We are developing REC-2282 for the treatment of NF2 and are evaluating the utility of the compound in additional disease states using our platform.
Pursuant to the agreement, we must use commercially reasonable efforts to commercialize licensed products and are required to meet certain diligence milestones within two years following the execution of the agreement, including the initiation of clinical trials. The license agreement is also limited by and made subject to certain rights and regulations of the government, including the Bayh-Dole Act.

In consideration for the license, we paid OSIF an upfront payment of $2.0 million dollars and are obligated to pay OSIF certain milestones, totaling up to $20.0 million dollars, as well as mid-single digit royalties on net sales of the licensed products. In addition, we owe 25% of any non-royalty sublicensing consideration prior to a Phase II clinical trial or 15% of such sublicensing consideration after initiation of a Phase II clinical trial, provided that milestone payments are creditable against these sublicensing fees. In 2022 we paid OSIF $1.0 million dollars upon dosing of the first patient in the Phase 2 study of REC-2282 for the treatment of NF2.

The agreement expires on the expiration of the last valid claim within the licensed patents. We may terminate this agreement on 90 days prior written notice to OSIF. Either party may terminate the agreement on 60 days prior written notice for an uncured, material breach by the other party, or bankruptcy or insolvency of the other party.

**REC-4881: Takeda License Agreement**

In May 2020, we entered into a License Agreement, or the Takeda In-License, with Takeda Pharmaceutical Company Limited, or Takeda, pursuant to which we obtained an exclusive (even as to Takeda and its affiliates), worldwide, sublicensable under certain conditions, transferable, royalty-bearing license to certain Takeda patents, know-how and materials related to develop, manufacture and commercialize Takeda's clinical-stage compound known as TAK-733, a non-ATP-competitive allosteric inhibitor of MEK1 and MEK2, subject to a non-exclusive, royalty-free, irrevocable, fully paid up, license back to Takeda to use the licensed compounds for non-clinical research purposes. We are currently developing the compound REC-4881 for the treatment of FAP, and patients with spontaneous APC-mutant tumors. We are also evaluating the utility of the compound in additional disease states using our platform.

We are required to use commercially reasonable efforts to develop and commercialize at least one licensed product in each of (a) the US, (b) at least three of the following European countries: the United Kingdom, France, Germany, Italy and Spain and (c) Japan.

Upon execution of the agreement, we paid an upfront fee of $1.5 million to Takeda. Under the Takeda In-License, we are obligated to pay Takeda milestones amounts totaling up to $39.5 million upon achievement of specified development and regulatory milestone events. In addition, we are obligated to pay Takeda low-to-mid single-digit royalties based on net sales of products containing the licensed compounds by us, our affiliates or sublicensees, subject to specified reductions. Our obligation to pay royalties continues on a country-by-country basis until the latest of expiration of the last to expire patent licensed by Takeda that covers the product, expiration of any regulatory exclusivity period for the product and ten years after the first commercial sale of the product, in such country. As of the date of this filing, we have not made any milestone or royalty payments to Takeda.

Each party has the right to terminate the license agreement for the other party's material uncured breach, insolvency or bankruptcy. In addition, we may terminate the agreement without cause any time after May 2023, and Takeda may terminate the agreement if we have not conducted any material activities in support of the development or commercialization of the licensed compounds or any product containing a licensed compound and have not demonstrated that we used commercially reasonable efforts towards the development of such compounds or products for a period of 12 consecutive months and such failure is not due to events beyond our reasonable control. Further, Takeda may terminate the license agreement if we challenge the validity or enforceability of a licensed patent. Upon termination for any reason other than for Takeda’s breach of the license agreement, upon Takeda’s request we are obligated to negotiate in good faith, for a period of 120 days, terms and conditions of a license to Takeda under certain technology developed by us during the term of the agreement for the purpose of developing, commercializing and otherwise exploiting the licensed compounds and products containing the licensed compounds.
In December 2023, we entered into a License Agreement with Bayer, the Bayer License Agreement, pursuant to which we obtained (a) an assignment of certain compounds, know-how and inventions related primarily to fibrosis, and (b) an exclusive, sublicensable and royalty-bearing license under certain project know-how related to fibrosis to research, develop, manufacture and commercialize products as independent research tools in all fields worldwide, subject to a non-exclusive, royalty-free license back to Bayer to use such licensed project know-how solely for internal research and development purposes.

We are required to use commercially reasonable efforts to develop and commercialize at least one product in one of the following countries: (a) the US, (b) Japan, or (c) a country of the European Union.

Under the Bayer License Agreement, we are obligated to pay Bayer milestone amounts totaling up to approximately $34 million upon achievement of specified development, regulatory and sales milestones. In addition, we are obligated to pay Bayer low single-digit royalties based on net sales of products containing certain compounds by us, our affiliates, or sublicensees, subject to specified reductions. Our obligation to pay royalties continues on a product-by-product and country-by-country basis until the latest of: (a) expiration of the last to expire patent filed by us, our affiliates or sublicensees that covers the product, and (b) ten years after the first commercial sale of the product in such country. As of the date of this filing, we have not made any milestone or royalty payments to Bayer.

Each party has the right to terminate the license agreement for the other party's material uncured breach. In addition, we may terminate the agreement without cause. Upon termination by us without cause or by Bayer for our breach, Bayer would have the right to use, practice, develop and exploit (including the right to sublicense) certain assigned know-how solely for Bayer’s internal research and development purposes.

**Competition**

Our efforts to date have resulted in several clinical-stage programs, an expansive pipeline of differentiated programs in early discovery and preclinical development, several partnerships with large pharma and technology companies, as well as an intellectual property portfolio comprising patents, trademarks, software and trade secrets. We believe that our differentiated approach provides us with a significant competitive advantage. We are a hybrid company, competing within multiple categories of the pharmaceutical, biotechnology, and technology industries where companies are similarly working to integrate rapidly advancing technologies into their drug discovery and development activities and/or are creating scalable scientific platforms. Notable competitors include:

- **TechBio Companies.** Such companies apply computational tools to unlock novel insights or accelerate drug discovery and development across different points in the value chain. Representative examples include Relay Therapeutics, Exscientia, Isomorphic Labs, Schrodinger, and AbCellera.

- **Scalable Platform Companies.** Such companies are applying novel scientific approaches or engineering novel therapeutic modalities with the potential to seed large numbers of therapeutic candidates. These companies may compete directly with our pipeline of predominantly small molecule therapeutics. Representative companies include Moderna, BioNTech, and Roivant Sciences.

- **Traditional Biopharma Companies.** Such companies, while primarily engaged in late-stage clinical development and product commercialization, are increasingly making their own investments in the application of ML and advanced computational tools across the drug discovery and development value chain. Such investments may include partnerships with other biotechnology companies (including Recursion) from which we may benefit. Representative companies include Janssen (a subsidiary of Johnson & Johnson), Merck, and Pfizer.

- **Large Technology Companies.** Large technology companies constantly seek growth opportunities. Technology-enabled drug discovery may represent a compelling opportunity for these companies, some of which have research groups or subsidiaries focused on drug discovery and others of which have signed large technology partnerships with biopharma companies. Representative companies include Alphabet, Microsoft, and Amazon.