BioMarin Pharmaceutical Inc.
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BioMarin—transformative medicines through genomic and development expertise

Global biotechnology company BioMarin focuses on developing and commercializing innovative therapies through a range of modalities. The company's diverse pipeline, spanning exploratory to marketed programs, relies heavily on its genetic and genomic expertise, manufacturing capabilities, and long-term partnering models.

With a global footprint in over 75 countries, a portfolio of seven approved products, and an extensive roster of clinical and preclinical product candidates, BioMarin has set an ambitious goal of becoming the world leader in genetic medicines. For almost 25 years, the mid-sized Bay Area biotech has been developing and commercializing therapies for rare genetic diseases, harnessing multiple modalities to optimally treat each individual condition. Over the years, BioMarin's science and expertise have yielded some of the most complex therapies in the world to address rare genetic diseases. With the goal of translating genetic discoveries into transformative medicines, the company leverages its foundation in genetics, genomics, and rare diseases to apply principles of drug development to larger indications, sharpening its foci on genetic, metabolic, cardiac, neurological/neuromuscular, hematologic, and skeletal disorders across multiple modalities, including gene, oligonucleotide, peptide, biologic, and small-molecule therapies.

More than two decades ago, BioMarin's scientific foundation was built upon the research and development of enzyme-replacement therapies for five rare genetic conditions. The company's approvals yielded the first therapies for these serious and life-threatening conditions. An increased understanding of genetic diseases and how to treat them is described by BioMarin in terms of four core attributes: genetic, targeted, assessable, and transformational. In approaching its discovery and development through that lens, the company (1) leverages genetic discoveries and tools to ensure a clear understanding of the underlying disease mechanisms; (2) develops targeted therapies that directly or proximally address the fundamental drivers of the diseases; (3) defines readily assessable biomarkers or endpoints that yield clear efficacy signals that reliably translate into clinical benefit; and (4) ensures products have a transformational impact on patients' lives by profoundly improving the way they feel, function, and survive (Fig. 1). "Rigorous adherence to these principles of drug development has enabled success early in BioMarin's development and will sustain us in the future," said Hank Fuchs, President of Worldwide Research and Development (WWRD) at BioMarin.

Leveraging genetic discoveries and tools, BioMarin has a clear understanding of the underlying disease mechanism

BioMarin can develop a targeted therapy that directly or proximally addresses the fundamental defect of the disease

Study designs use readily assessable biomarkers/endpoints that yield clear efficacy signals and reliably translate into clinical benefit

The medicine has a transformational impact on patients' lives by profoundly improving the way they feel, function, and survive

Fig. 1 | BioMarin is committed to the translation of genetic discoveries into transformative medicines. The company does this by focusing on diseases with precisely understood mechanisms that are rooted in genetics, developing targeted therapeutic interventions that address the underlying cause of disease, utilizing readily assessable endpoints that are proximal to the disease pathway, and enabling transformational changes to the way patients feel, function, and survive. This approach, which BioMarin calls its four core attributes, underlies the company's scientific strategy, and allows BioMarin to approach treatments for a range of diseases.

> **"BioMarin's scientists are driven to discover and develop therapies to treat some of the most complex diseases with unmet medical needs**
>
> Hank Fuchs, President of Worldwide Research and Development, BioMarin

Today, BioMarin remains at the forefront of scientific discovery, following a modality-agnostic approach to drug development. Combining the four core attributes with recent advances in genomic analysis and genetic understanding, the company has made it a strength to harness therapeutic modalities—small molecules, biologics, or gene therapies—that provide optimal solutions for the conditions and biological mechanisms being targeted. The principal driver of this flexibility has been fluency in genomic analysis, backed by a global network of expanding partnerships. Creative collaboration arrangements focusing on top science that best meets patients' needs have resulted in a winning strategy for patients, the partners, and BioMarin.

"BioMarin's scientists are driven to discover and develop therapies to treat some of the most complex diseases with unmet medical needs," said Fuchs. "We strive to explore avenues not traditionally taken by drug developers. And our experience over the past almost 25 years has taught us that this journey can be significantly enhanced through collaboration with partners that are equally committed to fundamentally improving the lives of patients."

With its core scientific capabilities and its global footprint, BioMarin has put in place a uniquely efficient and effective R&D organization, an innovative regulatory capability and the operation and continuous expansion of its own commercial manufacturing facilities (Fig. 2). As a result, the majority of BioMarin's therapeutic development programs have a shorter than average timeline from investigational new drug (IND) filing to approval, and the company's two current good manufacturing practice (cGMP) biologics facilities and its award-winning gene therapy manufacturing facility are considered best in class globally.

Partnering on foundational research

From its inception, BioMarin has thrived by developing therapies based on the most precise science available on the root causes of a disease. Based on this approach, the company has amassed a robust pipeline of marketed products, products in clinical trials, and exploratory

candidates developed in-house and as part of external collaborations across genetic, metabolic, cardiac, neurological/neuromuscular, hematologic, and skeletal disorders.

BioMarin's strategy is based on establishing collaborations in foundational research to help establish the root causes of genetic diseases and identify treatment targets to address them. Recently, for example, BioMarin initiated a collaboration with the Seattle-based Allen Institute for Brain Science to enable the creation of a new class of gene therapies displaying a higher level of precision to treat diseases of the central nervous system (CNS). While gene therapies are a promising approach to treat patients with such conditions, a key hurdle for the development of novel techniques has been the need to target specific cells to improve safety and efficacy.

Together with researchers at the Allen Institute, BioMarin is developing modified adeno-associated viruses (AAVs) engineered to impact specific classes of cells in the brain by means of unique molecular enhancers that restrict viral gene expression to only those cell types relevant to a particular disease. The researchers at the Allen Institute originally developed the technology to study the behavior of individual brain cell types by differentially labeling them and allowing their observation in vivo[1,2].

"This collaborative effort to enhance the precision of AAVs for therapeutic purposes exemplifies BioMarin's quest to bring novel therapies to patients with significant unmet medical needs," said Brinda Balakrishnan, Group VP, Business and Corporate Development. "Combining our experience in developing transformational therapies for rare genetic diseases with the Allen Institute's intimate knowledge of the CNS lays the foundation for delivering multiple targeted investigational gene therapies to the clinic." Another potential outcome of the work, Balakrishnan added, is that improved precision could reduce the development risk of gene-therapy candidates. The structure of the partnership includes exclusive licenses to BioMarin to each program for research, development, and commercialization.

Paving the path to the clinic

BioMarin's extensive experience and proven record in bringing therapies for rare genetic diseases from bench to bedside makes it the partner of choice for researchers and companies looking to translate their early-stage discoveries into candidates for clinical trials. By combining its R&D, regulatory, manufacturing, and commercial capabilities, BioMarin offers an incubator-like setting for advancing a drug candidate through to an IND filing and beyond. Importantly, BioMarin has demonstrated the experience and capabilities to conduct clinical trials almost anywhere in the world, invaluable assets it has leveraged in developing targeting treatments for rare diseases.

A collaborative agreement between BioMarin and Toronto-based Deep Genomics to develop oligonucleotide drug candidates in four indications is a recent example of BioMarin's partnerships. Through this collaboration, BioMarin will advance lead compounds identified and validated using Deep Genomics' artificial intelligence (AI) drug-discovery platform into preclinical and clinical development leveraging BioMarin's experience translating early therapeutic candidates into lead clinical compounds. The AI drug-discovery platform uses deep-learning techniques to analyze massive amounts of in vitro and in vivo data to identify targetable molecular mechanisms for oligonucleotide-based therapeutics. BioMarin has successfully applied such analytic approaches to narrow down biological targets for potential interventions for genetic short stature and skeletal dysplasia[3].

"At BioMarin, we believe these translational collaborations will help unlock critical therapeutic potential more effectively and efficiently," noted Balakrishnan. "Using our experience and technical capabilities to pave the path to the clinic for companies is a win–win scenario not only for our partners, but also our key stakeholders, and primarily the patients in need of novel therapies." As part of this collaboration, BioMarin receives an exclusive option to each of the four disease programs for development and commercialization, while Deep Genomics receives payment upfront and at defined development milestones.

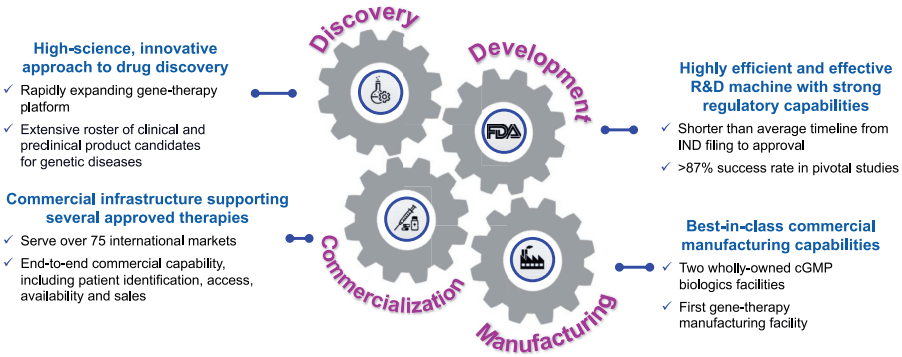

Fig. 2 | BioMarin—an end-to-end fully integrated biotechnology company. BioMarin seamlessly integrates (1) innovative drug discovery approaches based on the best available science, (2) a highly efficient and effective R&D machine with strong regulatory capabilities, (3) best-in-class commercial manufacturing capabilities, and (4) a global commercial infrastructure covering the range from patient identification to sales in over 75 countries. cGMP, current good manufacturing practice; IND, investigational new drug; R&D, research and development.

Getting to the heart of translation

Also in 2020, BioMarin finalized a licensing agreement with Swiss gene-therapy company DiNAQOR. The collaboration will focus on the rapid advancement of DiNAQOR's lead program in one of the most prevalent genetic heart diseases, hypertrophic cardiomyopathy (HCM), caused by mutations in myosin-binding protein C3 (*MYBPC3*)—the gene that encodes cardiac myosin-binding protein C (MyBP-C).

BioMarin is poised to bring its experience in gene therapy development to jointly advance DiNAQOR's lead HCM therapy through clinical trials. BioMarin's manufacturing capabilities and global footprint will be invaluable factors in maximizing the likelihood of success for this novel therapeutic approach.

"Our extensive experience with gene therapy development was one of the principal triggers for establishing this partnership with DiNAQOR to develop new solutions for adults and children affected by major genetic cardiomyopathies," said Balakrishnan. "While we are initially focusing on *MYBPC3* HCM, we entered this partnership with a long-term commitment to provide the opportunity for tackling additional cardiomyopathies in the future, leveraging DiNAQOR's deep expertise in genetic cardiomyopathies and relevant model systems."

In it for the long haul

One of BioMarin's hallmarks is the company's long-term commitment to patients and partners alike. This is embodied in the company's program to develop potentially the first gene therapy for hemophilia A. This genetic disease is caused by a missing or defective gene that codes for factor VIII, an essential blood-clotting protein. The path to the clinic for BioMarin's investigational factor VIII gene therapy showcases the company's philosophy and enabling capabilities not only in drug development, but also in manufacturing. Licensed in 2013 from University College London and St. Jude Children's Research Hospital, the early-stage factor VIII gene therapy program for hemophilia A was rapidly advanced through comprehensive preclinical research and the IND regulatory process to allow the first patients to be treated in a phase 1/2 clinical trial at the end of 2015. BioMarin now has multiple clinical studies underway for the treatment of hemophilia A, including an ongoing phase 3 global study. According to Balakrishnan, "BioMarin entered this preclinical partnership with the goal of advancing the program all the way to regulatory approval and commercialization. This long-term vision helps us build trust and maximize the chances of success by navigating any challenges encountered along the way as a team with a common goal. This ethos applies across the board to all our partnerships."

1. Graybuck, L. T. et al. *Neuron* **109**, 1449–1464.e13 (2021).
2. Mich, J. K. et al. *Cell Rep.* **34**, 108754 (2021).
3. Estrada, K. et al. *Nat. Commun.* **12**, 2224 (2021).

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