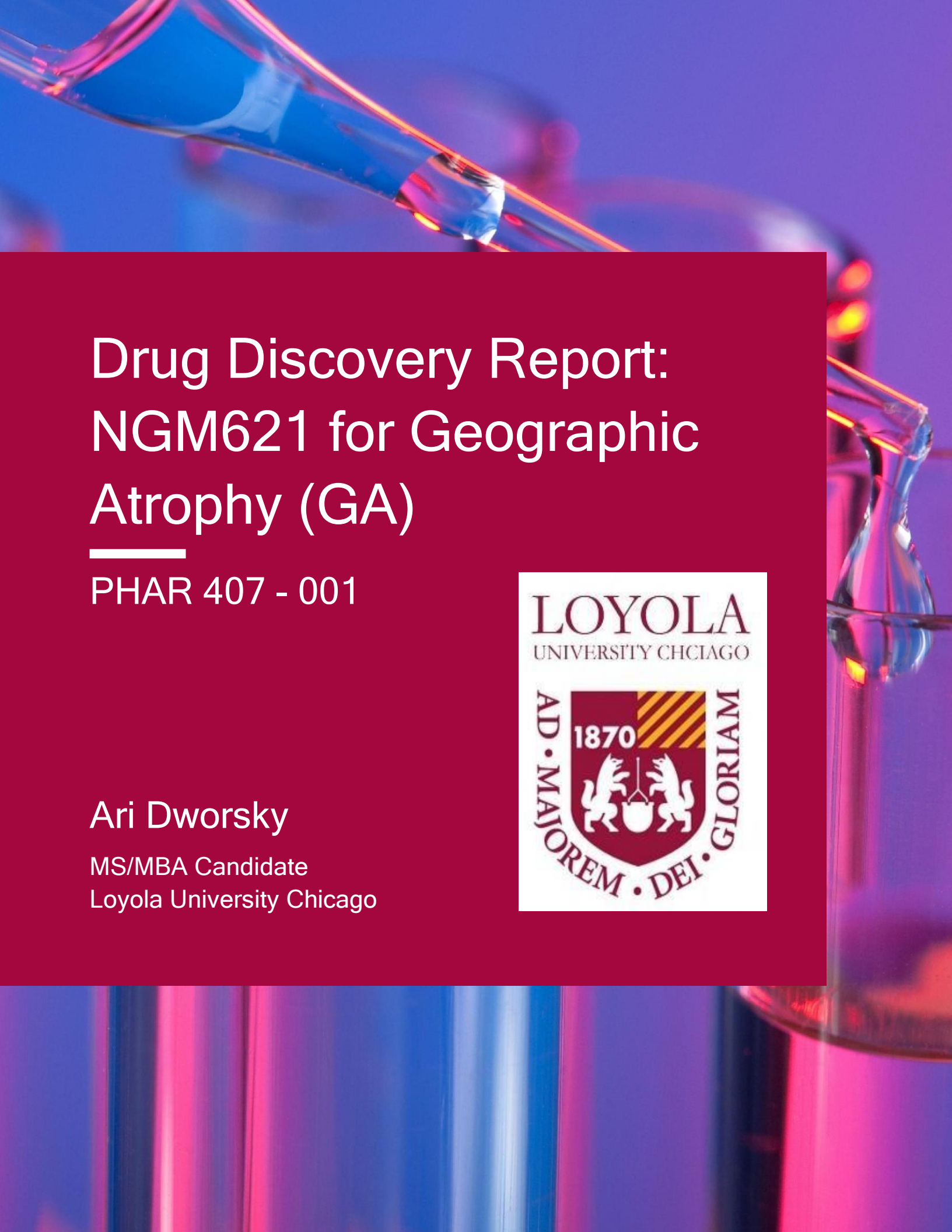

Drug Discovery Report: NGM621 for Geographic Atrophy (GA)

PHAR 407 - 001

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Drug Profile

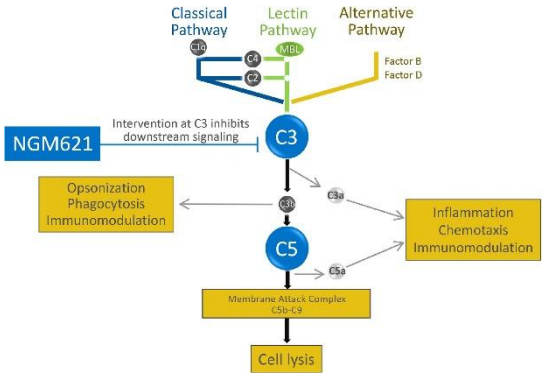
Drug: NGM621
Class: Biologic
Indication: Geographic Atrophy (GA) / Age-Related Macular Degeneration (AMD)
Sponsors: NGM Biopharmaceuticals and Merck & Co.

Introduction

NGM621 is a biologic therapeutic produced between the partnership of NGM Biopharmaceuticals and Merck & Co. for the treatment of Age-Related Macular Degeneration (AMD) and Geographic Atrophy (GA) (Heier, 2023). The humanized monoclonal IgG1 antibody targets the complement system, specifically C3 and C3b, inhibiting the upstream elements that lead to the progression of GA and AMD through the complement system, upregulating inflammation, cell lysis, and phagocytosis (Wykoff, 2022). With promising preclinical results, NGM Biopharmaceuticals and Merck & Co.'s goal was to market a competitive treatment that would be given through a one-time intravitreal injection treating blindness and loss of sight caused by AMD and GA.

Background of NGM Biopharmaceuticals

NGM Biopharmaceuticals is a biology-centered drug discovery company that primarily focuses on novel discovery of biological mechanisms to provide drug candidates for patients that currently do not have existing treatment options. Their values described in their mission and vision statement are, “Our mission is to translate complex, powerful biology with rigor and urgency into life-changing medicines. Our vision is to make lasting scientific contributions that improve human life” (NGM Bio, 2024). The company was founded by Doctor Jin-Long Chen in San Francisco in 2007 (Crunchbase, 2024). Since then, they have had notable impacts on the biotech sector through their diverse pipeline of innovative biologics, strategic partnerships, and collaborations to accelerate their drug development, and they have conducted numerous clinical trials for conditions ranging from cancer to rare diseases. As of today, NGM Biopharmaceuticals most-used products include Aldfermin for the treatment of primary sclerosing cholangitis (PSC), NGM120 antibody to treat hyperemesis gravidarum, NGM707 daval antagonist antibody inhibiting interleukin response to tumors, and NGM831 antibody for the treatment of solid tumors used in combination with pembrolizumab (NGM Bio, 2024).

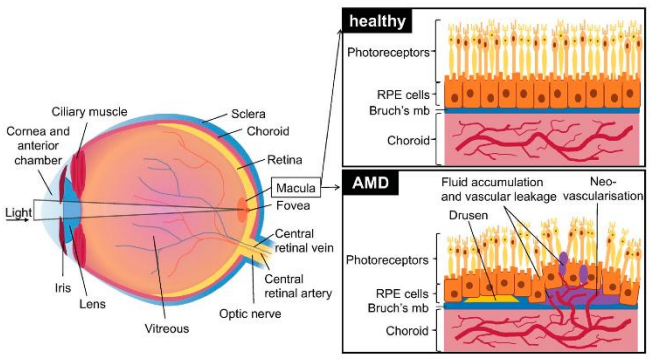


Background of Merck & Co.

Merck & Co. is a well-established international pharmaceutical company that has been operating for over 130 years. George Merck, on January 1, 1891, was originally founded as a chemical distributor in New York (History - Merck.com, 2024). Today, Merck operates in a highly competitive pharmaceutical industry on a global scale. The companies actively competing with their market space include notable companies such as Eli Lilly, Johnson & Johnson, AbbVie, and Bristol-Myers Squibb (MarketBeat, 2024). Merck has developed and distributed medicines and vaccines, including their notable examples of pembrolizumab for cancer treatment and Gardasil for HPV (Merck.com, 2024). Merck is actively seeking public health opportunities and exploring ways to continue driving science to improve patient lives and remain one of the best biopharmaceutical companies.

Age-Related Macular Degeneration (AMD)

Vision is one of the most vital senses that has played a profound role in human evolution and survival. Many patients struggle with vision problems late in life, as loss of eyesight and deterioration are common among adults and elderly patients. One of the leading causes of vision loss is macular degeneration. It is the medical term for deterioration of light-sensitive photoreceptors at the back of the retina that begin to deteriorate or become damaged (AMDF, 2024). Like many other neuronal cells, damage to these areas can be critical, leading to permanent loss of eyesight, blurry vision, inability to detect color, and reduction in the central visual field (AMDF, 2024). Patients that experience visual impairment may struggle to participate in usual daily routines and lifestyles such as reading, operating machinery, exercise, working, and more. A study published by The Vision and Eye Health Surveillance System (VEHSS) estimates that 19.8 million Americans live with AMD and is growing at a fast rate (CDC, 2024). Macular degeneration may come in either dry or wet forms based upon the disease progression. Approximately 80% of AMD patients have dry AMD, which does not include vascularization of the eye. However, up to 20% of dry AMD patients may progress to wet AMD, which is characterized by the increased growth of blood vessels in the macula of the eye (Everyday Health, 2023). Treatment and management for AMD often involves consistent monitoring of symptoms with an ophthalmologist over time to track the progression of the disease and related symptoms. If the condition transitions to wet AMD, medical intervention may be necessary with regular treatment of an injection of anti-VEGF, an anti-vascular endothelial growth factor that is designed to reduce the vascularization and leakage caused by the condition (Everyday Health, 2024).



Geographic Atrophy (GA)

Geographic atrophy is an advanced stage of dry macular degeneration that also affects central vision caused by the development of blind spots in the macula of the retina. According to the Cleveland Clinic, over 8 million patients in the United States suffer from geographic atrophy, which has a 20% rate of affecting those already diagnosed with AMD (Cleveland Clinic, 2023). Ophthalmology research suggests that the onset of geographic atrophy is part of an immune response with the complement cascade, an endogenous immune reaction to protect against pathogens. The complement system utilizes a number of protein and biological pathways to identify bacteria or viruses and activate an inflammatory response to remove them from the body (Cleveland Clinic, 2022). The FDA has approved Pegcetacoplan and IZERVAY, which are the first pharmaceutical treatments for geographic atrophy. Similar to AMD treatment, it requires injections to the eye on a monthly or bimonthly basis (Cleveland Clinic, 2023).

Investigational Biologic NGM621

NGM621 is under the biological classification of pharmaceutical treatment and is a humanized immune globulin G1 (IgG1) monoclonal antibody. The molecule was designed to act as an anti-complement C3 antibody, preventing the immune response activated by the complement system from destroying the macula of the retina (Heier, 2023). The pharmaceutical properties of the biologic antibody include its molecular weight of approximately 150 kD and an affinity of 340 pm (Heier, 2023). The ADMET data indicated that the drug would achieve over 90% C3 binding over a 7-week period. The drug would be distributed across the vitreous humor and would be excreted by the reticuloendothelial system after 8 weeks (NGM Bio, 2020). The monoclonal antibody is primarily metabolized by proteolytic degradation, and toxicity reports from the phase 1 study did not report any serious adverse events, inflammation, neovascularization of the eye, or drug-related adverse events. Within the phase 1 study, NGM Biopharmaceuticals experimented with doses of 2 mg, 7.5 mg, and up to 15 mg injection in the 15 patient sample (NGM Bio, 2020).

Discovery and Mechanism of Action

NGM Biopharmaceuticals designed a targeted-discovery route to unveil their clinical trial drug, NGM621. Their research focused on the complement cascade system that promotes an immune response known to play a significant role in the onset of cell damage to the macula of the retina, leading to impairment of vision (NGM Biopharmaceuticals, 2020). NGM Biopharmaceuticals discovered that NGM621 is an effective inhibitor that potently downregulates C3, the upstream element, preventing membrane-attacking complexes from forming and destroying photoreceptors leading to blindness (Wykoff, 2022).

Clinical Development

The clinical trial design for NGM621 in phase 2 was a randomized double-masked sham-controlled study with a patient population meeting the inclusion criteria for AMD and GA (Heier, 2023). The purpose of the study was to identify if NGM621 was a suitable treatment option for GA and AMD by measuring the change in GA lesion over the duration of the study. Additionally, they also measured the rate of incidence for both ocular and systemic adverse events that were paired within the treatment group (Heier, 2023). The phase 2 CATALINA study concluded that NGM621 did not meet its efficacy endpoint; however, it did not produce severe adverse effects within the treated population.

Clinical Trial Conclusion

NGM621 was a promising biological candidate for the treatment of AMD and GA produced through the strategic partnership between NGM Biopharmaceutical and Merck & Co. Although early clinical trials showed some insight for the IgG1 monoclonal antibody being effective, the trials were discontinued after its phase 2 CATALINA study when it did not meet the efficacy conditions for being a marketable treatment option. Similar to many other investigational studies and early clinical trials, many drugs' candidates are rejected after studies fail to provide evidence of efficacy and safety for human patient populations. Although this trial was not successful, there are still other targets amongst the complement cascade system that could prevail for treating patients with conditions such as AMD/GA. The strategic collaboration between NGM Biopharmaceuticals and Merck & Co. provides yet another case study of the challenging regulatory landscape in drug development and the opportunity for research development and innovation in the field of ophthalmology.

Market Analysis

The current retinal biologic market size is approximately $7.3 billion and is forecasted to rise to nearly $20 billion by 2032 (Market Research Future, 2024). The market's estimated annual growth rate (CAGR) from 2023-2032 is projected to be 13.2% for retinal biologics and 7.01% for the entire retinal health market globally (Market Research Future, 2024). Factors that contribute to the sharp market growth are the increased number of patients with age-related macular degeneration and geographic atrophy observed in the population (Market Research Future, 2024). The competitive landscape for GA treatment includes Genentech's RG6147 (Phase 2), Apellis' pegcetacoplan (Phase 3), and Iveric Bio's Zimura (Phase 3) (Retina Today, 2022/2021). Within the competition, the average cost of similar monoclonal antibody therapies in the United States was approximately $96,731 (Innovations Journals, 2024). The high cost for monoclonal antibody treatment is caused by several factors, including intellectual patents, market demand for optimized treatment, lack of current medical care for indications, and the cost of manufacturing and research.

Strengths, Weakness, Opportunity, and Threats Analysis (SWOT)

NGM621 offers many strengths within the current market of AMD/GA, starting with their innovative mechanism. NGM621 targeting the complement system was a novel approach to treating geographic atrophy and age-related macular degeneration. The biological therapeutic also offered a very safe pharmacological profile. The phase 1 studies indicated that NGM621 was sufficiently safe with no serious adverse events occurring. Moreover, the strategic partnership between Merck & Co. and NGM Biopharmaceuticals expands the research capabilities and financing opportunity of this business opportunity. These initial strengths provided a strong foundation to enter clinical trials with adequate funding, research resources, and market opportunities to treat the unmet needs of GA/AMD patients.

The weakness of NGM621 was primarily derived from the phase 2 CATALINA study results. Not meeting the primary efficacy endpoint was a major concern for investors and researchers. It is unknown whether the partnership was aware of preliminary data that could have predicted the results would not meet regulatory requirements or speculated from preclinical data if uncertainty was higher than anticipated for this particular biological candidate. Another key business area in which NGM Biopharmaceutical and Merk & Co. could have struggled would be in the heavy competition that already exists in the market. FDA-approved drugs such as Pegcetacoplan and IZERVAY may have a high level of efficacy in comparison to NGM621. Finally, with a high focus on this project, the partnership may have pulled financial and research resources away from other business opportunities that could have prevailed during this project. Business strategy and effective communication between the organization regarding preclinical speculation and relative position to market competition are the keys to mitigating the financial risk in which the project does not provide a financial return.

The retinal biologic market offers many opportunities seen within the compound annual growth rate and future projections indicating significant growth of the prevalence for AMD and GA. Although medications exist on the market, post-marketing surveillance and FDA monitoring may provide insights into the effectiveness of currently approved AMD/GA treatments. Additionally, NGM Biopharmaceuticals and Merk & Co. acquiring fast-track designation for this investigational biologic shows effectiveness in regulatory affairs and working with federal agencies. These are opportunities the partnership can carry into the future as they continue to tackle the future challenges that may arise within patients suffering from ocular conditions.

An optimistic view for future business opportunities for NGM Biopharmaceutical can only be as strong as its preparation for upcoming threats to the retinal biologic market. With a change in presidential candidates, the regulatory landscape may change drastically, creating new challenges with dealing with the FDA. The strict regulatory requirements may require robust efficacy to gain IND approval to initiate a clinical trial. Along with the political change, economic factors and market fluctuations may pose a significant risk. With the treatment and

R&D costs rising, it could limit the ability to execute a discovery and clinical trial as effectively. Moreover, the investing environment could change drastically, making it more difficult to acquire financing for the business opportunity if inflation and interest rates change investor portfolios to invest in the pharmaceutical sector. Lastly, NGM Biopharmaceutical pivoting into a new direction and studying another component of the complement cascade system could result in another unsuccessful drug candidate. There is still lots of research and area for discovery to further understand the biological system that makes up both GA and AMD. Placing high financial position in another project with current market treatments poses a threat to stakeholders if continuous business projects in the retinal market default.

Projected Revenues

The projected revenues for NGM biopharmaceuticals and Merck & Co. are based upon a model assumption that treating 10% of the global AMD and GA population by year 10 using the CAGR of 7.01% would estimate a total of 920,003 patients. With the average cost of treatment starting with a soft estimate of $2,000 and growing at 8% per year, it produces an estimated $2.04 billion in revenue in year 10. This analysis is a preliminary overview of projected sales and does not include factors of actual market volatility, OPEX, CAPEX, or free cash flows.

Financing and Risk Analysis

Common risk factors for pharmaceutical development include significant challenges and events occurring throughout the research and clinical trials for NGM621. Some of the serious drivers of risk in this sector include clinical trial failure, federal regulations of biologics, market competition with candidates in existing trials, and standardization of manufacturing processes. In the United States, the average cost for clinical trials was approximately $13.8 million for Phase 2 and $30.7 million for Phase 3 trials (Sofpromed, 2024). Finally, the expenditures in OPEX and CAPEX for manufacturing and marketing NGM621 could be substantial, affecting the financial runway for the development of the business project. To support the project, NGM Biopharmaceuticals and Merck & Co. created a financial agreement of a $450 million option deal to support the research and development over a 5-year period (Fierce Biotech, 2023). After the failure of the phase 2 CATALINA study not meeting its efficacy target, Merck did not choose to exercise the option, closing the partnership between the two firms.

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