Emmaus Life Sciences, Inc.
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Ticker (Exchange)	EMMA-OTCQX
Recent Price (01/24/2023)	$0.35
52-week Range	$0.0710 - 1.7000
Shares Outstanding	49.6 mm
Market Capitalization	$17.4 mm
Average 10-day volume	19,634
Insider Ownership +>5%	30%
Institutional Ownership	—
EPS (Qtr. ended 09/30/2022)	($0.01)
Employees	62

ENDARI ®

Source: Emmaus Life Sciences, Inc.

COMPANY DESCRIPTION

Emmaus Life Sciences, Inc. ("Emmaus" or "the Company") is a commercial-stage biopharmaceutical company engaged in the development and commercialization of therapies, primarily for rare and **orphan diseases†**, with an initial focus on **Sickle Cell Disease (SCD)**. Emmaus' lead commercial product is Endari® (**L-glutamine** oral powder), an oral treatment indicated to reduce acute complications of SCD in adult and pediatric patients. Emmaus' domestic operations are in addition to the Company's international business expansion, where Endari® received marketing approval in three Middle Eastern and North African countries during 2022 (United Arab Emirates, Qatar, and Kuwait). Emmaus is aggressively seeking additional marketing approval in geographic regions that account for a significant share of the world's SCD cases, with applications submitted in Saudi Arabia, Bahrain, and Oman, as well as expected additional approvals in this region, Europe, and Asia. Following its market introduction, Endari® achieved year-over-year revenue growth until it experienced negative impacts as a result of COVID-19. The Company has since regained its growth position in the second half of 2022, driven by the effective use of its in-house sales force and its newly launched direct-to-consumer programs, including an innovative full-service telehealth solution that provides online access to Endari®. Emmaus is also involved in assessing L-glutamine to treat **diverticulosis**, currently in a pilot trial, as well as pre-clinical programs for oncology and **regenerative medicine** with other compounds. The Company believes its Endari® commercial activities and pipeline of new products provide a sustainable business model, which could result in multiple future revenue sources.

KEY POINTS

- At the time of FDA approval (2017), Endari® was the first ever FDA-approved treatment for pediatric patients with SCD (5+ years old) and first new treatment for SCD in 20 years. Endari® has received **Orphan Drug designation** from the FDA and **Orphan Medicinal designation** from the European Commission.
- The global SCD treatment market was estimated at $3.4 billion in 2020, and is expected to reach $8.5 billion by 2026, behind an increasing prevalence of SCD and new innovative treatments.
- Results of Emmaus' Phase 3 trial have demonstrated that the use of Endari® led to a significant reduction in the number of **sickle cell crises**, a delay in median time to sickle cell crises, and a reduction in hospitalizations and cumulative days in hospital.
- Through its distribution agreements, the Company has accumulated a network of over 600 specialty and health system pharmacies distributing Endari®, with prescriptions having been filled in 46 states, Puerto Rico, and Washington D.C.
- Emmaus is led by a highly experienced management team with proven success in pharmaceutical research, development, and commercialization.
- The Company currently holds $1.1 million in cash and cash equivalents as of its most recent quarter.

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Executive Overview

Emmaus Life Sciences, Inc. ("Emmaus" or "the Company") is a commercial-stage biopharmaceutical company that seeks to improve the lives of people through the discovery, development, and commercialization of innovative treatments and therapies, primarily for rare and orphan diseases, with an initial focus on Sickle Cell Disease (SCD). Emmaus's lead commercial product, Endari® is an oral pharmaceutical-grade L-glutamine treatment indicated to reduce acute complications of SCD in adult and pediatric patients five years of age and older. Approved by the U.S. Food and Drug Administration (FDA) in 2017, Endari® has received Orphan Drug designation from the FDA and Orphan Medicinal designation from the European Commission. Emmaus' glutamine-based technology platform has also shown promise as an effective treatment for additional conditions beyond SCD, with the Company initially focused on using L-glutamine to treat diverticulosis, which is currently in a pilot trial. Emmaus' product pipeline also includes pre-clinical programs, involving anti-cancer treatments as well as regenerative medicine technologies for the treatment of bone related conditions and corneal disease, among others.

Sickle Cell Disease (SCD)

Sickle Cell Disease (SCD) is a term that defines a group of rare hereditary blood disorders characterized by the production of an altered form of **hemoglobin**, the protein in red blood cells (RBCs) that carries oxygen to the tissues. Normal RBCs are smooth, disk-shaped, and flexible. SCD causes hemoglobin to become fibrous, resulting in RBCs that are sickle-shaped, rigid, and adhesive. These cells stick together and cannot easily move through the blood vessels, blocking small blood vessels and interfering with the delivery of oxygen to the body.

Patients with SCD suffer from debilitating episodes of sickle cell crises, a broad term covering a range of disorders that are considered to be the most devastating complication of SCD, which occur when the sickle-shaped RBCs block blood vessels. Sickle cell crises cause excruciating musculoskeletal and visceral pain, increased risk of heart attacks and strokes, and frequent infections. These complications tend to progress at adolescence and worsen during early adulthood and often lead to early mortality, with life expectancy of people with SCD approximately 20 to 25 years shorter than for the non-SCD population.

SCD Market and Incidence

The global SCD treatment market was estimated at $3.4 billion in 2020, and is expected to reach $8.5 billion by 2026, being driven by an increasing prevalence of SCD, rising awareness of the disease, increased spending in healthcare infrastructure in developing countries, and innovative treatments (Source: Expert Market Research's *Global Sickle Cell Disease Treatment Market (2018-2028)*, 2022). The condition affects more than 100,000 people in the U.S. and an estimated 40 million to 50 million people worldwide, predominately in individuals with African, Middle Eastern, and Indian ancestry (Source: U.S. National Institutes of Health's National Heart, Lung, and Blood Institute).

Current Therapeutic Options

The pharmacologic treatments currently available for SCD mainly focus on avoiding pain episodes, relieving symptoms, and preventing complications, while aiming to reduce the frequency of pain crises and the need for blood transfusions. Currently, only four therapeutic drugs have been approved by the FDA for the treatment of SCD: (1) hydroxyurea; (2) L-glutamine; (3) crizanlizumab; and (4) voxelotor. However, concerns about the safety and/or efficacy of some of these options are on-going. For example, hydroxyurea, approved by the FDA in 1998, contains a boxed warning (known as a **black-label warning**) highlighting the risk of severely low blood cell counts and cancer, the most stringent warning imposed by the FDA. And although voxelator was shown to reduce **hemolysis** and anemia in patients with SCD in clinical trials, it did not demonstrate a statistically significant improvement in preventing the occlusion of blood vessels. Voxelator's mechanism of action, increasing hemoglobin's oxygen affinity, presents some concerns of potential negative effects, as the bound oxygen might not be off loaded when needed, resulting in a potential risk for reduced oxygen delivery in tissues with high oxygen requirements, such as the brain and the heart.

ENDARI® (L-glutamine oral powder)

Endari® is a prescription oral treatment approved by the FDA to reduce the acute complications of SCD in adult and pediatric patients five years of age and older. Endari® was approved in July 2017 and, at the time, was the first ever FDA-approved treatment for pediatric patients with SCD (5+ years old) and the first new treatment for SCD in 20 years.

Phase 3 Clinical Trial

The FDA's approval of Endari® was based on the results of a 48-week placebo-controlled, multi-center Phase 3 clinical trial designed to evaluate the efficacy and safety of Endari® in 230 patients with SCD (5 to 58 years of age), with results published in *The New England Journal of Medicine* (Source: *New England Journal of Medicine, Vol. 379:226-235*, 2018).

Results of the trial demonstrated that the use of Endari® led to a reduction in the number of sickle cell crises by 25%, including a 63% reduction of **acute chest syndrome** occurrences, a potentially life-threatening obstruction of blood supply to the lungs characterized by fever, chest pain, cough, and lung infiltrates. Thirteen of 152 patients (8.6%) in the treated group had at least one episode of acute chest syndrome compared to 18 of 78 (23.1%) in the placebo group. Treatment with Endari® also resulted in a 56% delay in median time to first sickle cell crises (84 days vs. 54 days in the placebo group), as well as a significant reduction in median time to second sickle cell crises (212 days vs. 133 days in the placebo group).

Endari®'s use also resulted in fewer hospitalizations and fewer cumulative days in the hospital. Researchers found that Endari®'s positive effect on sickle cell crises resulted in a decrease of hospitalizations by 33% and a 41% decrease in cumulative hospital days (a median cumulative number of days in the hospital of 6.5 days vs. 11 days in the placebo group). These results were in line with a post-approval follow-up study assessing the use of Endari® in real world use. Compared to baseline, the use of Endari® resulted in significantly fewer **vascular occlusion crises (VOCs)**, fewer hospitalizations, fewer days in the hospital, and fewer blood transfusions *(Source: HemaSphere, Vol. 6 (Suppl):24-25,* 2022).

Endari®'s Commercialization

Endari®'s commercialization efforts rely on the following key marketing advantages compared to other therapeutic options:

- *Broad indication*: Approved for any complication of SCD.
- *Pediatric usage*: Approved for patients aged 5 and up.
- *Real-world data*: On the market for approximately five years.
- *Significantly lower cost than new competitors*: Annual list price of $40,500 in comparison to list prices of over $100,000 for both Adakveo® (crizanlizumab) and Oxbryta™ (voxelotor).
- *Positive safety profile*: No warnings, precautions, or drug interaction notices on label.
- *No labs required*: No requirement of blood testing before or during taking the medication.

Emmaus is expanding the reach of Endari® through the effective use of its in-house sales force, which targets pediatric and adult SCD hematologists, physicians, and treatment centers. Approximately 86% of SCD patients in the U.S. reside in major metropolitan areas in 18 states. This allows Emmaus to have a more targeted sales approach, as a highly concentrated market allows for a more effective and smaller sales force.

To support its sales and distribution efforts, Emmaus has agreements in place with leading distributors, as well as physician groups, purchasing organizations, and pharmacy benefits managers. The Company has agreements with three of the largest specialty distributors of prescription drugs in the U.S.: AmerisourceBergen Corporation, McKesson Corporation, and Cardinal Health Inc. The Company also has a network of over 600 specialty and health system pharmacies distributing Endari®, with prescriptions having been filled in 46 states, Puerto Rico, and Washington D.C. In addition, Endari® is well covered by various insurance programs, including Managed Medicare, the Children's Health Insurance Program (CHIP), commercial insurance, Medicare, and Medicaid.

Direct-to-Consumer Initiatives

The Company's U.S. marketing efforts include direct-to-consumer programs intended to reach individuals nationwide who lack information regarding available SCD treatment options, such as Endari®. An example of these initiatives is the collaboration between Emmaus and *The Steve Harvey Morning Show's* cast member Kier (Junior) Spates to share Mr. Spates' personal experience with the use of Endari® to treat his SCD during the show (link to interview https://bit.ly/3HhQtjS). *The Steve Harvey Morning Show* airs weekday mornings on more than 100 radio stations. The program is heard by nearly seven million weekly listeners and is the number one syndicated morning radio show in the U.S.

In addition, in April 2022, Emmaus launched an innovative full-service **telehealth** solution that provides online access to Endari®. The Company believes that of the approximately 100,000 sickle cell patients in the U.S., up to 75,000 can be accessed through telehealth, substantially more than the 25,000 accessible through traditional channels. Endari®'s telehealth program allows prospective patients to access a physician and perform an online appointment by phone or any device with internet access. The program allows for same day physician authorization and prescription, with medication sent to the patient's home within three business days.

The Company believes that Endari®'s safety profile and competitive advantage could result in the medication becoming the first choice SCD therapeutic candidate for patients using telemedicine services. In particular, the fact that Endari® does not require preliminary bloodwork to be prescribed or follow-up testing once it is administered, and the fact that Endari® has no FDA drug interaction limitations or warnings on its label, are key differentiators against competitive options that place Endari® in a better position to take advantage of the expansion of telemedicine in the U.S.

International Expansion

The Company believes that its international expansion is key to its future growth potential. Currently, Endari® is approved for use in the U.S. (2017), Israel (2020), United Arab Emirates (UAE) (March 2022), Qatar (November 2022), and Kuwait (December 2022). In addition, Emmaus is aggressively seeking additional marketing approvals for Endari® in geographic regions that account for a significant share of the world's SCD cases: the Middle East and North Africa (MENA), the Mediterranean (Europe), South America, and India.

Emmaus obtained marketing approval for Endari® in UAE, Qatar, and Kuwait; with submission for approval already filed in Saudi Arabia, Bahrain, and Oman. Emmaus opened an office in Dubai in 2020 and entered into exclusive distribution agreements with strategic partners to register, commercialize, and distribute Endari® in the **Gulf Cooperation Council** countries and other countries throughout the MENA region. In November 2022, the Company announced that it had received the first major purchase order from its distributor in Saudi Arabia, where Endari® is available on an early access basis only.

The Company is also working to obtain marketing approval in EU and non-EU countries, with an initial focus on **Early Access programs** currently underway or planned in the UK, France, and Turkey. In addition, Emmaus is actively looking for distribution partners in Africa, Asia (with a focus on India), and Latin America (with a focus on Brazil and Colombia).

Historical Business Results

The Company launched Endari® in 2018, which resulted in approximately $16.5 million in revenue for the fiscal year. Following its launch, acceptance of Endari® continued to increase, resulting in revenues of $22.8 million in 2019. According to the Company, the COVID pandemic significantly affected its sales and marketing efforts, resulting in limited growth. However, despite this and the FDA approval of Adakveo® and Oxbryta™ in 2019, revenues in 2020 of $23.2 million were in line with the previous year. Fiscal year 2021 resulted in a slight decrease in revenue ($20.6 million) as a result of distributor overstocking of the medication as they accumulated inventory in line with pre-COVID sales expectations. This effect continued into the early part of 2022.

However, revenue numbers from the second half of 2022 show a steady growth once more. Weekly sales have continued to increase, reaching steady levels of $500,000 to $600,000 per week during the latter part of the year (equivalent to expected annualized sales of between $26 million to $31 million). The Company believes that this growth is due to a post-COVID shutdown recovery to normal business levels, coupled with the initial effects of its direct-to-consumer marketing initiatives that started in 2022. Emmaus believes that this domestic growth can continue behind the effect of its direct-to-consumer marketing programs, including expansion of its telehealth initiative.

This growth is in addition to the Company's international business expansion, where Endari® has received marketing approval in three Middle Eastern and North African (MENA) countries during 2022, with expectations for additional approvals in this region as well as in Europe and Asia.

Manufacturing Operations

Endari® uses prescription grade L-glutamine (PGLG), which differs from non-prescription grade L-glutamine widely available as a nutritional supplement in terms of purity and manufacturing oversight. There are limited global suppliers of PGLG. Currently, Emmaus obtains all of its PGLG needs through a sourcing partnership with Ajinomoto Health and Nutrition North America, Inc. (Ajinomoto), a subsidiary of Ajinomoto North American Holdings, Inc. By securing a source of PGLG, Emmaus overcomes one of the biggest barriers to entry for companies intending to use L-glutamine for the treatment of SCD or other conditions due to its limited availability.

In December 2019, EJ Holdings, Inc., a Japanese corporation established as a joint venture between Emmaus (40% ownership) and Japan Industrial Partners, Inc. (60% ownership), purchased a phased-out active pharmaceutical ingredient manufacturing facility in Ube, Japan for the manufacture of L-glutamine and other amino acids. EJ Holdings is in the process of retrofitting the plant to prepare it for regulatory recertification for the manufacture of PGLG. Emmaus currently anticipates the process to be completed and test production runs to take place during the 4Q 2023/1Q 2024, with regulatory approval following shortly thereafter.

The joint venture between Emmaus and Japan Industrial Partners was established as a variable interest entity. The agreement established that Emmaus would be the principal source of funding for EJ Holdings' ownership and operation of the plant, including the refurbishment process, and as a result, the ownership interest of Emmaus would increase accordingly. The Company expects to start the ownership transfer process during the 1Q 2023/2Q 2023, resulting in an ownership position by the Company of at least 95%.

Emmaus Clinical and Pre-Clinical Programs

L-glutamine has also shown promise in combating other conditions. The most promising development involving L-glutamine beyond SCD is in the treatment of diverticulosis, currently in a pilot trial. In addition, the Company's pipeline includes two pre-clinical programs: (1) a regenerative medicine program based on **cell sheet technology**; and (2) an oncology program for solid cancers, blood-cancers, and lymphoma. The Company's technologies are also being investigated by third parties for the use of burn injuries (Phase 3) and pancreatic cancer (Phase 1), with study product provided by Emmaus. The Company believes that the combination of the commercially available Endari® in addition to its clinical and pre-clinical programs provide Emmaus with a sustainable business model and developing pipeline of new products, resulting in multiple potential future sources or revenue.

Headquarters, Corporate History, and Employees

Emmaus was incorporated in Delaware on March 20, 1987, under the name Age Research, Inc. Prior to January 16, 2007, it existed as a shell company with nominal assets. On January 16, 2007, the Company entered into an Agreement and Plan of Merger with CNS Response, Inc., and CNS Merger Corporation, its wholly owned subsidiary, pursuant to which CNS Merger Corporation merged with and into CNS Response, Inc. On November 2, 2015, the Company changed its corporate name to MYnd Analytics, Inc. On July 17, 2019, it completed a merger transaction with EMI Holding, Inc., formerly known as Emmaus Life Sciences, Inc. and changed its name to Emmaus Life Sciences, Inc. As of December 31, 2021, the Company had 62 employees, 58 of whom were full time. Emmaus' corporate offices are located in Torrance, California.

Intellectual Property

The Company depends on licenses of certain patents to develop some of its product candidates. If any of these licenses terminate, or if any of the licensed patents is successfully challenged, Emmaus may be unable to continue to develop its product candidates. While Emmaus does not currently own any issued patents directed to the treatment of sickle cell anemia, there is an exclusive marketing privilege provided by the Orphan Drug Designation. The Company also owns patent applications within that area, as well as issued patents and patent applications directed at the treatment of diverticulosis, diabetes, and hypertriglyceridemia.

Endari®

Emmaus' success with respect to Endari® will depend, in part, on its ability to preserve its trade secrets and to prevent third parties from infringing upon its proprietary rights since the Company does not have (and does not expect to be able to obtain) composition of matter patents or methods of use patents that cover Endari®. In particular, the patent for the use of L-glutamine to treat SCD expired in May 2016 and the Company's license to the patent terminated. However, there is exclusivity protection facilitated by Orphan Drug Designation until July of 2024.

While Emmaus has an Orphan Drug designation for the use of L-glutamine for the treatment of SCD in the U.S., the Company's Orphan Drug exclusivity will expire in July 2024 and may be lost sooner if another L-glutamine product for the same indication demonstrates clinical superiority. If approved in the EU, this exclusivity is for ten years from the approval date for sickle cell anemia. If the Company's competitors develop alternative L-glutamine products, it may have a material, adverse effect on Emmaus' business and results of operations. Emmaus may seek to pursue improvements and reformulations of Endari® to preserve its intellectual property rights in Endari® following the expiration of its Orphan Drug designation.

Other Intellectual Property

The Company's **chondrocyte** cell sheet technology is supported by the U.S. patent application No.: 63/360,710, filed on October 21, 2021, entitled "Engineering of Different Stratified Cell Sheets Using Human Adipose Stromal Cells," filed on October 21, 2021.

Emmaus' device measuring cell sheets transparency technology is supported by the Patent Cooperation Treaty (PCT) patent application No. PCT/US2022/011267, entitled "System and Method of Evaluating Cell Culture," filed on January 5, 2022.

Emmaus has issued patents related to compositions, including PGLG and methods involving administration of PGLG for the treatment of diverticulosis in the U.S., Europe, Japan, Australia, India, Mexico, China, Indonesia, Korea, and Russia. Associated patent applications are currently pending in the U.S., the EU, Brazil, Korea, and Russia.

Patents directed to compositions for decreasing **HbA1C** levels in individuals who are shown to have average blood sugar levels in the diabetic range have issued in Japan, Indonesia, and the Philippines. Associated applications are currently pending in the U.S., Europe, Brazil, India, China, the Philippines, and Japan.

The Company has issued patents directed to the treatment of **hypertriglyceridemia** in Japan and the Philippines. A corresponding European patent application has been granted and is currently the subject of an Opposition proceeding. Associated applications are pending in the U.S., Brazil, India, China, and the Philippines.

A patent application directed to the treatment of sickle cell using a multi-component composition is pending in the U.S. and Europe. An international application directed to the same invention has been filed under the Patent Cooperation Treaty.

Trademarks

Emmaus holds U.S. trademark registrations for “Emmaus Medical” and “Endari” and a trademark registration for “Xyndari” (as Endari® will be marketed if approved) in the EU.

Company Leadership

Emmaus is led by a highly experienced management team with proven success in pharmaceutical research, development, and commercialization. Biographies of its management team and Board of Directors are provided in the accompanying section.

Management

Yutaka Niihara, MD, MPH, Chief Executive Officer, Chairman of the Board

Dr. Niihara has been involved in patient care and research for sickle cell disease (SCD) for most of his career and is the principal inventor of the patented L-glutamine therapy to treat SCD. He is a cofounder of Emmaus, principal investigator for LABioMed at Harbor-UCLA Medical Center, and Clinical Professor of Medicine at the David Geffen School of Medicine at UCLA. His experience includes serving as President, Chief Executive Officer, and Medical Director of Hope International Hospice. Board-certified by the American Board of Internal Medicine, the American Board of Internal Medicine/Hematology. He is American Board of Internal Medicine/Oncology. Dr. Niihara is licensed to practice medicine in both the U.S. and Japan. His honors include the Lifetime Achievement Award from the Sickle Cell Disease Foundation of California and the Abigail Kawananako Award. Dr. Niihara received his B.A. in Religion from Loma Linda University, obtained his M.D. from Loma Linda University School of Medicine in 1986, and received his MPH from Harvard School of Public Health in 2006.

Willis C. Lee, MS, Chief Operating Officer, Vice-Chairman of the Board

Mr. Lee has more than 30 years of management and consulting experience with influential companies in the semiconductor and healthcare industries. Prior to joining Emmaus, Mr. Lee led worldwide sales and business development of Yield Dynamics' product group at MKS Instruments. He joined the Company in 2009 and has served as Chief Operating Officer since May 2011. He has held various managerial and senior positions at companies, including HPL, Syntricity, and Reden & Anders, a subsidiary of United Healthcare that provides actuarial services, including capitation and risk assessment analyses for healthcare insurance carriers. Mr. Lee received his B.S. and M.S. in Physics from University of Hawaii and University of South Carolina, respectively. He was a member of the American Physical Society, completed TQM/SPC programs, and has published papers in Nuclear Instruments and Methods.

Yasushi Nagasaki, CPA, Chief Financial Officer

Mr. Nagasaki joined Emmaus in 2011 and is the Senior Vice President, Finance of the Company. Prior to joining Emmaus, Mr. Nagasaki was the Chief Financial Officer and served on the board of directors at Hexadyne Corporation, an aerospace and defense supplier. Previously, he was the Controller at Upsilon Intertech Corporation, an international distributor of defense and aerospace parts and subsystems. Mr. Nagasaki is a Certified Public Accountant and received a B.A. in Commerce from Waseda University and an M.A. in International Policy Studies from the Monterey Institute of International Studies, and is a graduate school of Middlebury College.

Charles W. Stark, Pharm.D., Senior Vice President of Medical Affairs, Clinical, Regulatory

Dr. Stark has served as Emmaus' Senior Vice President of Research and Development since 2013, bringing more than 30 years of experience in medical affairs, research, and academia. Previously, Dr. Stark was Director of Clinical Development at Bavarian Nordic, an immunotherapeutic company, and prior to that Associate Director of Medical Affairs for the Dendreon Corporation, an immunotherapeutic company. He has served as Director, Medical Science Liaisons (cardiovascular, metabolic, and oncology) at Pfizer, Inc. Dr. Stark has served as the Director of Investigational Drug Services and Clinical Research at LABioMed at Harbor UCLA and at the Health Research Association at USC Medical Center. He has also served as a faculty member at the University of Southern California School of Pharmacy. Dr. Stark received his Pharm.D. from the University of Southern California and completed his residency at the Veteran's Affairs Medical Center in West Los Angeles.

George Sekulich, Senior Vice President of Global Commercialization and Chief Information Officer

During the last two years, Mr. Sekulich has overseen the commercial launch of Endari® in the U.S. and more recently has been engaged in laying the groundwork for the launch of Endari® and Xyndari® in overseas markets, with a special emphasis on the Saudi Arabia market as well as Europe and Latin America. Additionally, Mr. Sekulich brings considerable experience and training in computer information services to designing and supporting Emmaus's computer information systems. Prior to Emmaus, Mr. Sekulich was the owner and operator of Magellan Net, a software provider services company.

Dale E. Short, JD, Legal Consultant and Corporate Secretary

Mr. Short joined Emmaus in September 2018 as the Company's first General Counsel and currently serves as a legal consultant and Corporate Secretary.

Board of Directors

Yutaka Niihara, MD, MPH, Chief Executive Officer, Chairman of the Board

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Willis C. Lee, MS, Chief Operating Officer, Vice-Chairman of the Board

Biography on page 10.

Wei Peu (Derek) Zen, MBA, Director

Mr. Zen is Vice Chairman and Chief Executive Officer of Wai Kee Holdings Limited., a Hong Kong-based construction and infrastructure company whose shares are listed on the Main Board of the Hong Kong Stock Exchange Limited. He is also the Chairman of Build King Holdings Limited and Chairman of Road King Infrastructure Limited, both of which are subsidiaries of Wai Kee Holdings Limited. Mr. Zen has over 45 years of experience in civil engineering, and is responsible for the overall management of the Wai Kee Holdings Limited group of companies and oversees the operations of the group's construction, quarry, and concrete divisions. Mr. Zen holds a B.Sc. degree in Engineering from The University of Hong Kong and an MBA from The Chinese University of Hong Kong and is a member of both the Institution of Civil Engineers and fellow member of the Hong Kong Institution of Engineers and the Institute of Quarrying, UK respectively. He is a past Honorary Treasurer of Hong Kong Construction Association and a member of HKTDC Infrastructure Development Advisory Committee. He is also the President of Hong Kong Contract Bridge Association.

Seah H. Lim, M.D., Ph.D., Director

Dr. Lim was appointed as a director on October 4, 2022 and has more than 25 years of experience working in academia and with pharmaceutical companies in the clinical development of products in hematology, oncology, and transplantation. He is board-certified in Internal Medicine, Hematology, and Medical Oncology and is an internationally recognized physician-investigator with extensive leadership experience and a track record of success in clinical and research and development. Most recently, since June 2021, he has served as Chief Executive Officer of Medicovestor Bio PLC, Kuala Lumpur, Malaysia, a privately-held development-stage biotechnology company. From January 2017 to December 2021, he served as a consultant to Salix Pharmaceuticals/Bausch Healthcare, where he was instrumental in obtaining FDA designation of rifaximin as an orphan drug for the treatment of sickle cell disease (SCD). He also has served as a consultant to numerous "big pharma" companies, including Genzyme, USA, Burroughs Wellcome, and Amgen Corporation. Since October 2021, he has served as Associate Director, Allogenic Stem Cell Transplant and Director of the Adult Sickle Cell Program at Upstate State University of New York Medical Center, Syracuse, New York. Dr. Lim has authored or co-authored numerous peer-reviewed publications and has served as Section Editor, *Journal of Translational Medicine* since 2016. He received his MB ChB and MD degrees from Aberdeen University School of Medicine, Aberdeen, Scotland, and Ph.D. from University of Wales College of Medicine, Cardiff, Wales. Emmaus believes Dr. Lim is well-qualified to serve as a

director based on his expertise and experience in the treatment of sickle cell disease (SCD) and extensive background as a researcher and executive officer and consultant in the pharmaceutical industry both in the U.S. and abroad.

Ian Zwicker, Director

Mr. Zwicker was appointed as a director on October 4, 2022. He previously served as a director, Chair of the Compensation Committee, and member of the Governance and Nominations Committee of the Company's Board of Directors from the completion of the Company's merger transaction with EMI Holding, Inc. on July 17, 2019, until his retirement as a director in conjunction with Emmaus' Annual Meeting of Stockholders held on November 23, 2021. He had served as a director of EMI Holding, Inc. since December 7, 2015. Mr. Zwicker is the founder of Zwicker Advisory Group, an independent financial advisory consulting firm, and has been its Chief Executive Officer since 2014. From 1981 to 1990, Mr. Zwicker served as Managing Director and held a variety of management positions at the investment banking firms of SG Cowen and Hambrecht & Quist. From 1990 to 1999, Mr. Zwicker served as Managing Director and head of worldwide technology investment banking for Donaldson, Lufkin & Jenrette Securities Corporation, and from 2000 to 2001 as the President of WR Hambrecht + Co (WRH). He was a Director of Stirling Energy Systems, Inc. from 2006 to 2012. Mr. Zwicker was a Partner at WRH and was also Head of Capital Markets from 2013 to 2014. Emmaus believes Mr. Zwicker is qualified to serve as a director due to his prior service on the Board of Directors and standing Board committees and his extensive investment banking and financial expertise and experience.

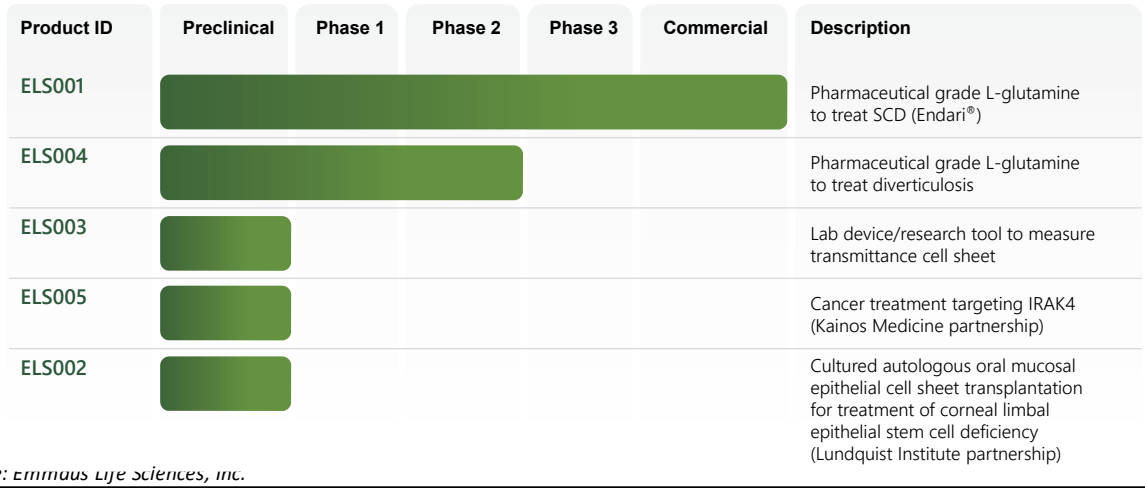
Core Story

Emmaus Life Sciences, Inc. ("Emmaus" or "the Company") is a commercial-stage biopharmaceutical company engaged in the discovery, development, and commercialization of innovative treatments and therapies, primarily for rare and orphan diseases, with an initial focus on Sickle Cell Disease (SCD). The Company's lead commercial product, Endari®, is an oral pharmaceutical-grade L-glutamine treatment indicated to reduce acute complications of SCD in adult and pediatric patients five years of age and older. Endari®, approved by the U.S. Food and Drug Administration (FDA) in 2017, has received Orphan Drug designation from the FDA and Orphan Medicinal designation from the European Commission.

Emmaus' glutamine-based technology platform has also shown promise as an effective treatment for additional conditions beyond SCD, with the Company initially focused on the use of glutamine to treat diverticulosis, currently in a pilot trial. Emmaus product pipeline further includes pre-clinical programs, involving anti-cancer treatments as well as regenerative medicine technologies for treating bone related conditions and corneal disease, among others. Figure 1 provides an overview of the Company's products and product candidates. The Company's technologies are additionally being investigated by third parties for the use of burn injuries (Phase 3) and pancreatic cancer (Phase 1), with study product provided by Emmaus.

Figure 1

PRODUCT PIPELINE



Source: Emmaus Life Sciences, Inc.

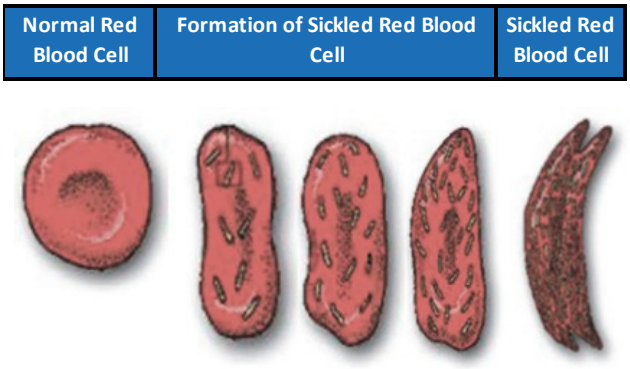
SICKLE CELL DISEASE BACKGROUND

Sickle cell disease (SCD) is a term that defines a group of rare hereditary blood disorder characterized by the production of an altered form of hemoglobin, the protein in red blood cells (RBCs) that carries oxygen to the tissues. Normal RBCs are smooth, disk-shaped, and flexible. SCD causes hemoglobin to become fibrous, resulting in RBCs that are sickle-shaped, rigid, and adhesive, as shown in Figure 2 and Figure 3 (page 14).

After sickle hemoglobin releases oxygen, it clumps together turning RBCs into a sickle or crescent shape. These sickle cells stick together and cannot easily move through the blood vessels, blocking them and interfering with the delivery of oxygen to the body. This problem gets compounded by the fact that sickle cells only live for about 10 to 20 days, compared with normal RBCs, which can live up to 120 days. Furthermore, the shape and stiffness of sickle cells causes these RBCs to get eliminated by the spleen at a higher rate than normal RBCs. The combination of lower RBC count and lack of oxygen delivery capabilities not only can cause chronic anemia, but sickled cells can also damage the spleen, increasing the risk for infections. As the spleen filters the sickle-shaped RBCs, it can become overworked and eventually start to fail (Source: John Hopkins Medicine).

Figure 2

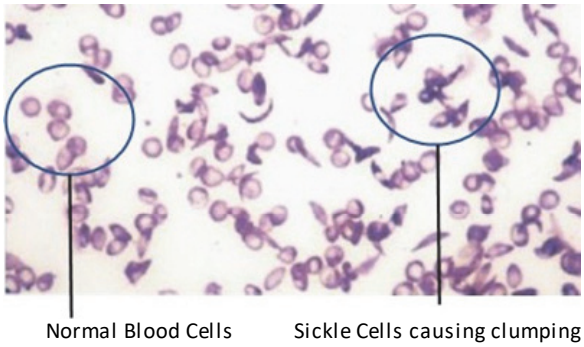
FORMATION OF SICKLE CELLS



Source: Emmaus Life Sciences, Inc.

Figure 3

SICKLE CELL COMPARISON

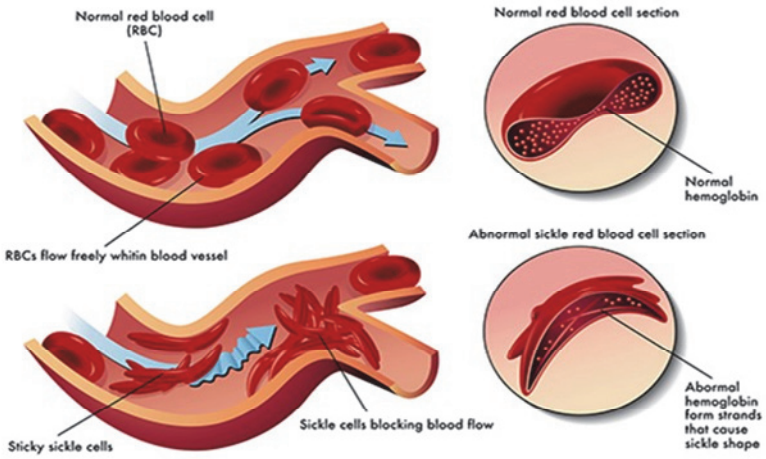


Source: Emmaus Life Sciences, Inc.

Patients with SCD suffer from debilitating episodes of sickle cell crises, which occur when these rigid and adhesive RBCs block, or occlude, small blood vessels (Figure 4). Sickle cell crises causes severe and chronic pain throughout the body due to insufficient oxygen being delivered to tissue (tissue ischemia) and inflammation. These events may lead to a variety of other adverse outcomes, such as acute chest syndrome, that requires hospitalization. These complications tend to progress at adolescence and worsen during early adulthood and often lead to early mortality.

Figure 4

SICKLE CELL BLOOD FLOW



Source: The Scientist.

Sickle Cell Disease Market and Incidence

The global SCD treatment market was estimated at $3.4 billion in 2020 and is expected to reach $8.5 billion by 2026, behind an increasing prevalence of SCD, rising awareness of the disease, increased spending in healthcare infrastructure in developing countries, and innovative treatments (Source: Expert Market Research's *Global Sickle Cell Disease Treatment Market (2018-2028)*, 2022).

The condition affects more than 100,000 people in the U.S. and an estimated 20 million to 25 million people worldwide, predominately in people with African, Middle Eastern, and Indian ancestry (Source: U.S. National Institutes of Health (NIH)'s National Heart, Lung, and Blood Institute). However, the global incidence estimates are not considered reliable, as many of the new cases come from regions where medical care is not readily available, leaving many people undiagnosed (Source: Sickle-Cell.com).

For perspective, in countries such as Cameroon, the Republic of Congo, Gabon, Ghana, and Nigeria, the prevalence of sickle cell trait can be as high as 20% to 30%, and even reach 45% in some parts of Uganda. Due to the poor access to medical resources, over 90% of children with SCD in some of these areas do not survive to adulthood, with the majority of children who have the most severe form of the disease dying prior to the age of five, usually from an infection or severe blood loss. Because of this, the World Health Organization and the United Nations recognize SCD as a global health issue (Source: World Health Organization). Many advances made in treating SCD have not yet reached countries with high poverty levels. Thus, the growing awareness about SCD treatments and the expected improvement in healthcare facilities in Africa are expected to provide lucrative growth opportunities to the market (Source: Sickle-Cell.com).

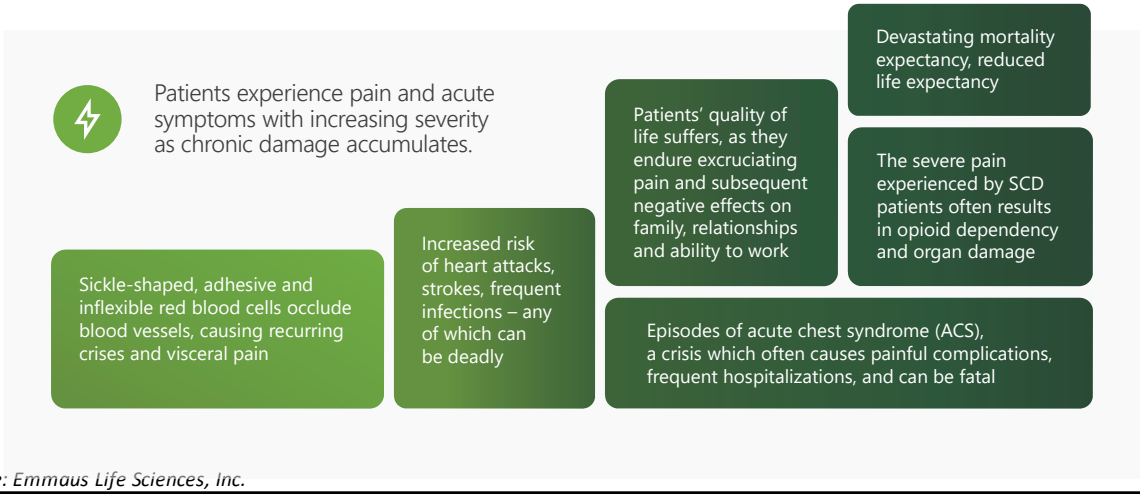
Complications and Symptoms of SCD

Sickle cell crisis (also known as acute pain crisis), a broad term covering a range of disorders, is considered to be the most devastating complication of SCD. Sickle cell crisis occurs when the sickle-shaped RBCs occlude blood vessels, blocking blood flow and causing excruciating musculoskeletal and visceral pain, increased risk of heart attacks and strokes, and frequent infections. The severe pain experienced, which in most cases requires medical care and administration of pain medication, can also lead to opioid dependency and increased hospitalizations, with 30-day and 14-day rehospitalization rates of 33.4% and 22.1% in U.S, respectively (Source*: JAMA, Vol. 303(13):1288-94*, 2010), leading to a significant decrease of a patient's quality of life.

These chronic complications can result in increased **morbidity**, early mortality, or both. Despite tremendous strides in treating and preventing the complications of SCD that have extended life expectancy, with nearly 95% of individuals born with SCD in the U.S. reaching 18 years of age, life expectancy is approximately 20 to 25 years shorter than for the non-SCD population. When the quality-of-life decrement is considered, SCD patients have a quality-adjusted life expectancy of 33 years, compared with 69 years for the U.S. general population (Source: *JAMA Network Open*, Vol. 2(11):e191537, 2019). Figure 5 provides an overview of the prognosis of patients with SCD.

Figure 5

SICKLE CELL DISEASE PROGNOSIS



Source: Emmaus Life Sciences, Inc.

Sickle cell crises can happen without warning and occur periodically throughout the life of a person with SCD. In adults, the acute pain typically persists for five days or longer, followed by a dull, aching pain generally ending only after several weeks and sometimes persisting between crises. Common areas affected by pain include the abdomen, chest, lower back, or arms and legs. (Source: U.S. NIH National Heart, Lung, and Blood Institute). The most common and severe types of sickle cell crisis include:

- Vaso-occlusive crisis (VOCs), characterized by obstructed blood flow to bones and organs such as the liver, kidneys, eyes, or the central nervous system. When the blockage occurs at the major blood vessels that supply the brain with oxygen, a stroke can occur, resulting in severe brain damage. Patients who have one stroke from sickle cell anemia are more likely to have recurrent ones.

- Aplastic crisis and hemolytic crisis, characterized by acute anemia typically due to viral infection or reduced RBC count, respectively. The latter is caused by the accelerated death of sickle RBC, resulting in less RBCs available.

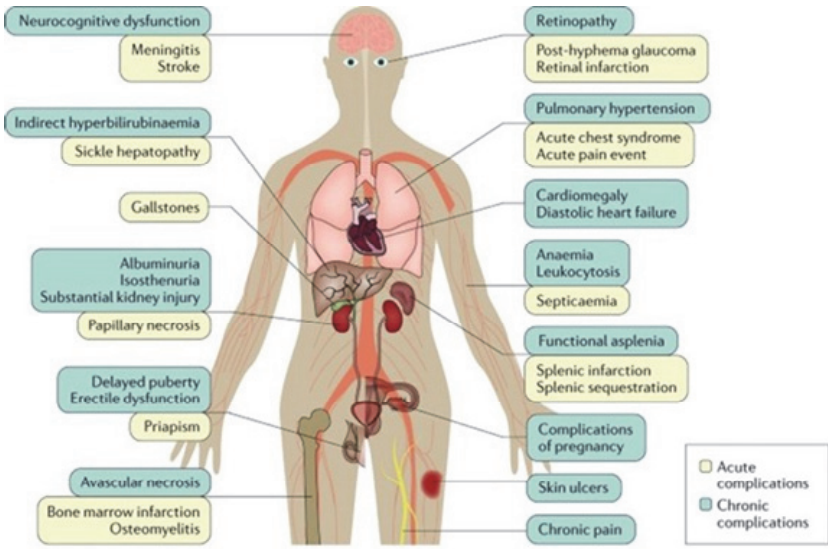
- Splenic sequestration crisis, a result of sickle cells pooling in the spleen leading to a painful enlargement of the spleen due to trapped RBCs. This can cause a sudden drop in hemoglobin and can be life-threatening if not treated promptly. After repeated episodes, the spleen becomes scarred and permanently damaged. Most children with SCD, by age eight, do not have a working spleen either from surgical removal or from repeated episodes of splenic sequestration, which increases the risk of infection, one of the major causes of death in children younger than age five in this population.

- Acute chest syndrome, a potentially life-threatening obstruction of blood supply to the lungs characterized by fever, chest pain, cough, and lung infiltrates. Acute chest syndrome often occurs suddenly, when the body is under stress from infection, fever, or dehydration, and can result in lung injury, breathing difficulty, and low oxygen to the rest of the body. Acute chest syndrome is a medical emergency and should be treated in the hospital right away (Source: U.S. NIH National Heart, Lung, and Blood Institute).

Figure 6 provides an overview of the most common clinical complications in patients with SCD.

Figure 6

SICKLE CELL DISEASE CLINICAL COMPLICATIONS



Source: Nature Review.

Limitations of the Current Standard of Care

Currently, **bone marrow transplantation (BMT)**, also called hematopoietic stem cell transplantation (HSCT), is the only curative option to treat SCD. In HSCT, a patient receives healthy blood-forming cells (stem cells) from a donor to replace their own cells. However, since it requires a match donor, availability remains limited, with less than 15% of patients with SCD in the U.S. having a matched donor. In addition, due to treatment-related mortality that can increase with age, guidelines recommend that young patients with SCD who have a donor should be transplanted as early as possible (Source: ChangeforSCD.com).

Upon the onset of sickle cell crisis, the current standard of care is focused on pain management, often with prescription narcotics or non-prescription oral medications taken at home. If the pain is not relieved, patients may seek medical attention, including hospitalization for more potent pain medications, typically opioids administered intravenously. Other supportive measures during hospitalization may include hydration, supplemental oxygen, and treatment of any concurrent infections or other conditions.

However, sickle cell crisis episodes almost always result in tissue damage at the affected site in the body, increasing the importance of preventative measures. While pain medications can be effective in managing pain during sickle cell crisis, they do not affect or resolve the underlying vascular occlusion, tissue ischemia, or potential tissue damage. Additionally, opioid narcotics that are generally prescribed to treat pain can also lead to tissue or organ damage and result in complications and morbidities. Given the duration and frequency of sickle cell crises, addiction to these opioid narcotics is also a significant concern.

The pharmacologic treatments currently available for SCD mainly focus on avoiding pain episodes, relieving symptoms, and preventing complications, while aiming to reduce the frequency of pain crises and the need for blood transfusions. Currently, only four therapeutic drugs have been approved by the FDA to treat SCD: (1) hydroxyurea; (2) L-glutamine; (3) crizanlizumab; and (4) voxelotor.

Hydroxyurea (Droxia®, Siklos®)

Hydroxyurea is an oral therapy, available in both generic and branded formulations, initially approved for several types of cancer and later developed and used for SCD. The therapy, marketed as Droxia by Bristol-Myers Squibb, was approved by the FDA in 1998 to help reduce the frequency of vaso-occlusive crisis (VOCs) and the need for blood transfusions in adults with SCD. In December 2017, the FDA approved Siklos to reduce VOCs and lower the need for blood transfusions in children ages two and older with SCD and recurrent moderate-to-severe VOCs. The therapy's use was extended to adult patients in February 2022.

Trials and real-life data suggest that people with SCD who take hydroxyurea have fewer pain crises, episodes of acute chest syndrome, blood transfusions, and hospital stays. Based on over 30 years of use, hydroxyurea used at therapeutic doses is generally well-tolerated, with a safety profile consistent with that reported in previous trials. However, since it can reduce the levels of certain blood cells in a patient's bone marrow, Hydroxyurea may increase the risk of a serious infection, bleeding, and certain types of cancers. As such, the therapy's label contains a boxed warning highlighting the risk of severely low blood cell counts and cancer, referred to as a black-label warning, the most stringent warning imposed by the FDA. Because of this, patients taking hydroxyurea must be monitored monthly with blood tests.

Endari® (L-glutamine oral powder)

Endari®, an oral L-glutamine powder, was approved in July 2017 to reduce severe complications associated with SCD in adult and pediatric patients five years and older. Endari® works by increasing the amount of free glutamine circulating in the blood to create **antioxidant** molecules that are taken up by sickle cells. The presence of the newly created antioxidants helps neutralize the sickled RBCs so they can regain flexibility and properly travel through vessels without slowing blood flow and successfully carry oxygen throughout the body.

Endari®'s Phase 3 clinical trial demonstrated that it reduced the frequency of sickle cell crises, hospitalizations, cumulative hospital days, and incidents of acute chest syndrome. These results were achieved irrespective of hydroxyurea use, which supports the use of Endari® as a monotherapy or in combination with hydroxyurea as a safe and effective treatment options for patients with SCD. Endari®'s safety profile was similar to placebo, as it was well-tolerated in pediatric and adult patients alike, giving SCD patients a non-chemotherapeutic treatment option.

Adakveo® (Crizanlizumab)

Crizanlizumab, marketed under the brand name Adakveo® by Novartis AG, is a **monoclonal antibody** that has been approved by the FDA as a treatment for painful VOC events caused by SCD in patients 16 and older. Crizanlizumab, administered intravenously in two doses two weeks apart and every four weeks thereafter, showed in a Phase 3 trial that it could significantly reduce the annual rate of sickle cell-related pain crisis in adults and children older than 16. Side effects can include nausea, joint pain, back pain, and fever.

However, Adakveo® treatment effectiveness has been put into questions. During its marketing approval in the UK, the National Institute for Health and Care Excellence (NICE) drug appraisal committee pointed to Adakveo®'s Phase 3 study's small sample size and duration of a little over a year, arguing that the long-term effectiveness and cost-effectiveness of Adakveo® were unproven (Source: Fierce Pharma's *NICE backs Novartis' Adakveo via special channel despite 'high uncertainty' about cost, long-term efficacy,* 2021).

Oxbryta™ (Voxelotor)

The FDA approved Oxbryta™ in November 2019 for the treatment of SCD in adults and pediatric patients 12 years of age and older. In December 2021, the FDA granted accelerated approval for Oxbryta™ to treat SCD in pediatric patients aged four to less than 12 years. The drug works by increasing the oxygen affinity for hemoglobin, stabilizing RBCs, and preventing them from becoming sickled. Healthy RBCs, unlike those that are sickled, can maintain normal blood flow and oxygen throughout the body. While voxelotor was shown to reduce hemolysis and anemia in patients with SCD in clinical trials, it did not demonstrate a statistically significant improvement in VOC occurrence. The drug's HOPE Phase 3 study showed an increase in hemoglobin levels and reduced markers of hemolysis. However, these findings have not correlated with reduced episodes of pain crisis and/or organ damage (Source: *Frontiers in Physiology*, Vol. 11: 435, 2020). Overall, Oxbryta™ met the primary end point of a positive hemoglobin response but failed to meet any of the key secondary clinical endpoints that were initially required for drug approval (Source: *American Journal of Hematology Vol. 97(8): E318-E320*, 2022).

In addition, therapeutic agents that shift hemoglobin's oxygen affinity present some concerns of potential negative effects as the bound oxygen cannot be off loaded, resulting in a potential risk for reduced oxygen delivery in tissues with high oxygen requirements, such as the brain and the heart. This is a bigger concern in a disease such as SCD, which is already characterized by decreased oxygen delivery. These concerns apply to voxelotor, despite published safety data from clinical trials, due to the rapid approval with what some deem to be inadequate long-term data (Source*: Therapeutic Advances in Hematology, Vol. 12: 20406207211001136*, 2021). This effect was corroborated by researchers using models to simulate whole-blood oxygen dissociation curves and red cell sickling in the absence and presence of voxelotor. The results indicated that the increase in oxygen delivery from reduced sickling is largely offset by the increase in oxygen affinity, with a net result of an increase in overall oxygen delivery only at the very lowest oxygen pressures (Source: *Blood, Vol.138(13):1172-1181*, 2021).

Oxbryta™'s approval provided the chance to assess its use in real-world scenarios. One such study examined the use of voxelotor in patients at a comprehensive urban sickle cell center. The study included 65 patients prescribed voxelotor from November 2019 to December 2020. Of the 65 patients prescribed voxelotor, 22 never started the medication due to economic and social barriers (including application forms and insurance issues), and 12 discontinued due to side effects, leaving less than half (31) of the patients prescribed voxelotor taking it a year later, and of those, 12 were taking reduced doses. Of note, researchers detected a statistically significant increase in **ALT levels**, signaling possible damage or injury to the liver cells, a side effect not reported in the Hope trial. While none of the patients in this cohort required a dose modification for this, three recently seen patients developed Grade 2 (n=2) and Grade 3 (n=1) ALT abnormalities within two weeks after starting the drug, all

improving after either dose reduction or discontinuation (Source: *American Journal of Hematology, Vol. 97(3): E125-E128*, 2022).

Another journal article described a newly initiated voxelotor patient with SCD being admitted to an emergency department (ED) with acute onset shortness of breath. The patient was found to have multiple acute subsegmental **pulmonary embolisms** as well as acute bilateral lower extremities **deep vein thrombosis (DVTs)**. Voxelotor, which was suspected to have provoked the DVTs, was discontinued indefinitely after a causal relationship between the DVTs and voxelotor was established (Source: *American Journal of Emergency Medicine, Vol. 55: 225.e1-225.e3,* 2022*).*

Treatment Expense

Treatment of sickle cell crises is burdensome and expensive for patients and payors, as it encompasses costs for hospitalization, urgent care and emergency room visits, and prescription pain medication. Lifetime SCD-related medical expenses add up to approximately $1.6 million for women and $1.7 million for men. Notably, participants also spent around $44,000 on out-of-pocket expenses, which can represent up to 10% of their annual income (Source: American Society of Hematology's *The Cost of Living with Sickle Cell Disease*, 2022).

A big part of the expense are the costs associated with the newer therapeutic agents used for treatments, with a study showing that 29.4% of surveyed patients stated that difficulty affording services was a major barrier to accessing SCD treatment (Source: AJMC's *Managing Sickle Cell Disease: Innovations, Limitations Within Evolving Standards of Care*, 2020). Both Adakveo® and Oxbryta™ have annual list prices of over $100,000 ($132,000 and $127,000, respectively). On the other hand, Endari® has annual list price of $40,500, with Figure 7 illustrating the price comparison between these sickle cell therapeutics. (Source: The Institute for Clinical and Economic Review's *Crizanlizumab, Voxelotor, and L-Glutamine for Sickle Cell Disease: Effectiveness and Value,* 2021).

Figure 7
SICKLE CELL THERAPEUTICS COST

	Annual List Price
Adakveo (Crizanlizumab)	$132,000
Oxbryta (Voxelotor)	$127,000
ENDARI (L-glutamine)	$40,500

Source: The Institute for Clinical and Economic Review.

ENDARI®

Endari® (L-glutamine oral powder) is Emmaus' prescription oral treatment approved by the FDA to reduce the acute complications of SCD in adult and pediatric patients five years of age and older. Endari® was approved in July 2017 and, at the time, was the first new treatment for SCD in nearly 20 years shown to reduce the acute complications of SCD in adults, and the first ever treatment for pediatric patients (5 years and older) with SCD. Endari® has received Orphan Drug designation in the U.S., and Orphan Medicinal Product designation in the EU. Endari® comes in a carton that holds 60 individually packaged sachets of Endari® powder (shown in Figure 8). Each sachet contains 5 grams of oral powder that should be mixed with food or drink when taken. A dose of Endari® can be a single sachet, two sachets, or three sachets, depending on the patient's weight.

Figure 8
ENDARI®

Source: Emmaus Life Sciences, Inc.

Endari®'s Mechanism of Action

Oxidative stress plays a very significant role in the pathophysiology of SCD and associated complications. Oxidation is the chemical term that describes removing electrons from an atom, while **reduction** is the opposite, an atom gaining an electron. The human body's daily actions generate byproducts, including **reactive oxygen species (ROS)** free radicals—unstable molecules that require an electron from another molecule to become stable.

Although ROS are needed by the body for important physiological processes, when there are too many free radicals circulating through the body, the imbalance starts a chain reaction that can eventually lead to excess oxidation and tissue damage. Under normal conditions, there is a balance between oxidant and antioxidant systems, referred to as a balanced **oxidation-reduction (redox)** state. This is achieved by, among other mechanisms, the production of antioxidants that reduce oxidative molecules to non- or less-reactive matter. Oxidative stress is the imbalance between the production and accumulation of ROS in cells and tissues and the ability of the body to counteract their negative effects by neutralizing them with antioxidants.

An increase in oxidative stress and an abnormal oxidant/antioxidant balance in the body have been reported to be a contributing factor in the pathophysiology of SCD. In SCD, the sickle red blood cells (RBCs) are a primary source of oxidative stress, as sickle RBC oxidation-reduction (redox) balance state is compromised as a result of a continuous production of ROS. This is due, in part, to an imbalance in the **nicotinamide adenine dinucleotide (NAD)** redox ratio (Source: *Antioxidants, Vol. 10:1608*, 2021).

NAD is a coenzyme that plays a key role in maintaining a balanced metabolism. NAD oxidized form (NAD+) and its reduced form (NADH) play roles in regulating and preventing oxidative damage in RBCs, with NADH acting as a natural antioxidant to maintain RBC redox balance, as seen in Figure 9. However, the higher levels of oxidation experienced by SCD patients tilts the NAD+/NADH equilibrium towards NAD+ production, resulting in increased oxidative stress that adversely effects RBC performance (Source: *Experimental Biology and Medicine, Vol. 245 (2)*, 2020).

Figure 9

NAD EQUILIBRIUM

Source: Emmaus Life Sciences, Inc.

L-glutamine is an amino acid with a myriad of roles in the body, including the synthesis of antioxidants, such as NADH. As such, it plays an important role in the regulation of oxidative stress by normalizing the altered NAD redox ratio in patients with SCD. L-glutamine increases the NADH and NAD redox potential to help to neutralize the oxidative stress in sickle cells (Source: *HemaSphere, Vol. 6 (Suppl):24-25*, 2022). As the oxidative stress in sickle cells increases, the cell requires more antioxidants to try and regain redox balance. This could lead to overutilization and depletion of the required molecules for the synthesis of antioxidants. For example, uptake of L-glutamine is several times greater in sickle RBCs than in normal RBCs. Previous *in vitro* studies also demonstrated that glutamine depletion contributed to RBC membrane damage and adhesion. Uptake of L-glutamine is markedly increased in patients with SCD, primarily to increase the total intracellular NAD level (Source*: Frontiers in Physiology*, *Vol. 11: 435*, 2020).

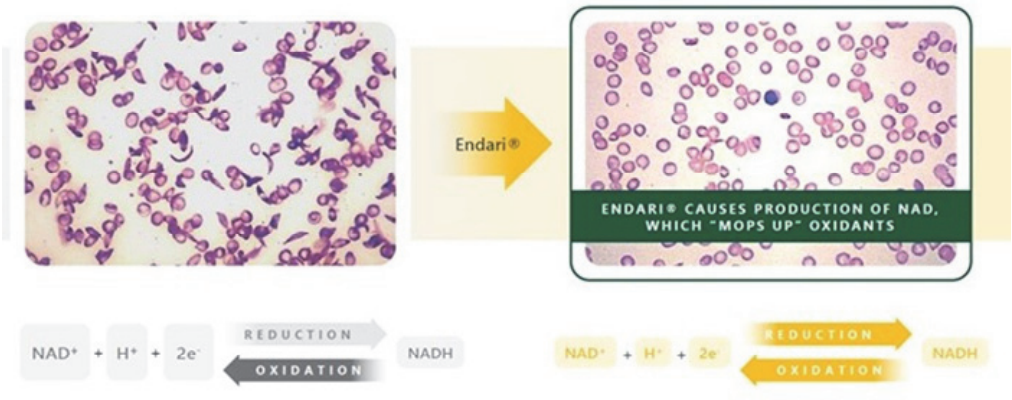
Research conducted by a team led by Dr. Niihara, the Company's founder and Chief Executive Officer (biography on page 10), reported that sickle cells have a higher level of active transport and utilization of glutamine. The team also demonstrated that L-glutamine administration increases the redox potential, which appears to result in a decreased sensitivity of sickle cells to oxidative stress (Source: *Biochemistry, Vol. 57 (5): 470–471*, 2018).

The mechanism of action of the amino acid L-glutamine in treating SCD is not fully understood. Administration of pharmaceutical-grade L-glutamine was shown to raise the NAD redox ratio within sickle cells; thus, higher L-glutamine consumption by oxidation-stressed sickle red cells may be counterbalanced by oral administration of L-glutamine, leading to additional synthesis of NADH and the improvement and restoration of the NAD redox ratio balance (Source: *New England Journal of Medicine, Vol. 379:226-235*, 2019).

Endari®'s administration was found to help restore the NAD redox balance by enhancing NAD synthesis to reduce excessive oxidative stress in sickle red blood cells, as seen in Figure 10. Better management of sickle cells' oxidative stress can prevent much of the damage leading to characteristic symptoms of SCD, which may lead to less obstruction or blockage of small blood vessels, thereby alleviating a major cause of the pain and other problems associated with SCD.

Figure 10

ENDARI® IMPACT



Source: Emmaus Life Sciences, Inc.

Endari® Phase 3 Clinical Trials

The FDA's approval of Endari® was based upon the results of a 48-week randomized, double-blind, placebo-controlled, multi-center Phase 3 clinical trial. The study evaluated the efficacy and safety of Endari® (pharmaceutical-grade L-glutamine) in 230 patients (5 to 58 years of age) with sickle cell anemia or sickle β0-thalassemia who had two or more painful crises within 12 months prior to enrollment. Results of the trial were published in the *New England Journal of Medicine* (Source: *New England Journal of Medicine, Vol. 379:226-235*, 2018).

Patients were randomized using a 2:1 ratio of Endari® to placebo, with participants in the treatment group receiving up to 30 grams of Endari® daily (0.3 g per kilogram of body weight per dose), administered twice daily by oral route. Eligible patients stabilized on hydroxyurea for at least three months before screening continued their therapy throughout the study.

The primary efficacy end point was the number of sickle cell crises experienced by patients in the trial. Secondary efficacy end points included the number of hospitalizations for sickle cell-related pain, the number of visits to an emergency department (ED) or outpatient treatment center for sickle cell–related pain, and changes in hematologic measures.

A total of 156 patients completed the trial: 97 of 152 patients (63.8%) in the L-glutamine group and 59 of 78 patients (75.6%) in the placebo group. The reasons for discontinuation were mainly unrelated to the trial medication. Although the percentage of patients who withdrew was higher in the L-glutamine group than in the placebo group, the reasons for withdrawal were similar in the two groups, with the most common reasons being withdrawal of consent, other reasons (which include pregnancies), and nonadherence. The overall noncompletion rate of 32% was similar to that of a recent trial of crizanlizumab in patients with SCD (35%).

Trial Results

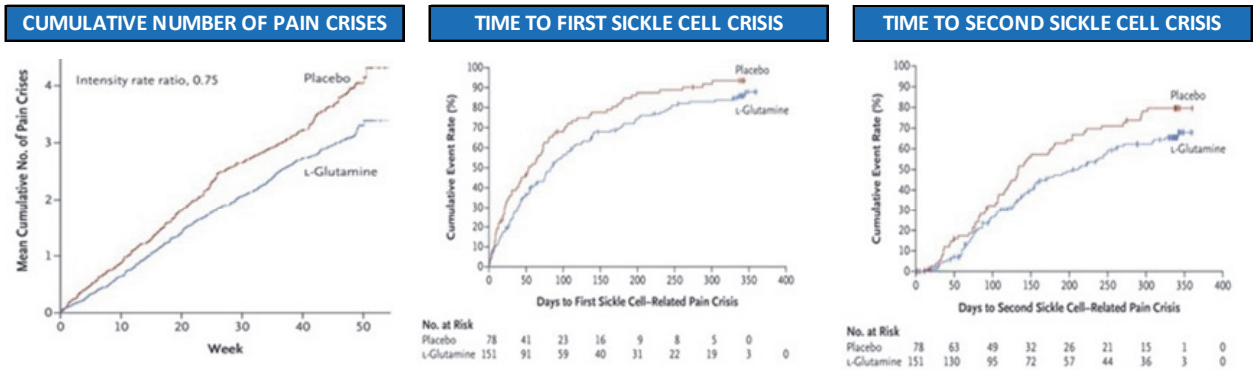
Results of the trial demonstrated a reduction in the number of sickle cell crises among patients that received Endari® compared to patients who received placebo. Treatment with Endari® also resulted in fewer hospitalizations, fewer cumulative days in hospital, longer time until first sickle cell crisis, and a lower incidence of acute chest syndrome.

Endari® reduced the frequency of sickle cell crises by 25%, with a median of 3.0 in the L-glutamine group and 4.0 in the placebo group. An analysis of recurrent sickle cell-related pain crises over time yielded an intensity rate ratio of 0.75, which suggests that the cumulative number of pain crises was 25% lower in the L-glutamine group than in the placebo group over the entire 48-week treatment period (Figure 11).

Furthermore, Endari® also had a positive effect in median time to first and second sickle cell crises, as seen in Figure 11. The median time to the first pain crisis was 84 days (range of 62 to 109) in the L-glutamine group compared to 54 days (range of 31 to 73) in the placebo group, a 56% delay. The median time to the second pain crisis was 212 days (range of 153 to 250) in the L-glutamine group compared to 133 days (range of 115 to 179) in the placebo group.

Figure 11

ENDARI® EFFECT ON SICKLE CELL CRISES



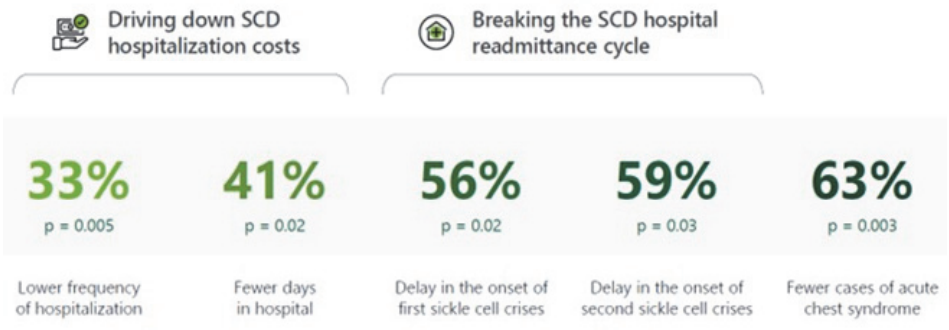
Source: New England Journal of Medicine.

The use of Endari® was also found to result in 63% fewer cases of acute chest syndrome. There were significantly fewer occurrences of acute chest syndrome in the L-glutamine group than in the placebo group; 13 of 152 patients (8.6%) in the L-glutamine group had at least one episode of acute chest syndrome compared to 18 of 78 (23.1%) in the placebo group.

Researchers found that Endari®'s positive effect on sickle cell crises, including acute chest syndrome occurrences, resulted in a decrease of hospitalization by 33% (a median of 2.0 in the L-glutamine group and 3.0 in the placebo group) and a 41% decrease in cumulative hospital days decrease (a median cumulative number of days in the hospital of 6.5 [range of 0 to 94] in the L-glutamine group and 11 [range of 0 to 187] in the placebo group), as illustrated in Figure 12 (page 23).

Figure 12

ENDARI® HOSPITALIZATION EFFECT



Source: Emmaus Life Sciences, Inc.

A subgroup analysis according to hydroxyurea use indicated that the benefits of L-glutamine therapy were consistent regardless of whether the patients were receiving hydroxyurea or not. The FDA has acknowledged that the clinical benefit of Endari® was observed irrespective of hydroxyurea use, which supports the use of Endari® as a monotherapy or in combination with hydroxyurea as safe and effective treatment options for patients with SCD. L-glutamine thus provides an alternative therapy for those who decline treatment with hydroxyurea or who may have unacceptable side effects from hydroxyurea, as well as an additive therapy to lower the incidence of pain crises for those who may have suboptimal response to hydroxyurea.

A summary of Endari®'s Phase 3 clinical trial is provided in Figure 13.

Figure 13

ENDARI® PHASE 3 RESULT SUMMARY

ENDARI WAS SHOWN TO LOWER THE FREQUENCY OF SICKLE CELL CRISES BY 25%
ENDARI: A median number of 3 sickle cell crises per patient
Placebo: A median number of 4 sickle cell crises per patient

ENDARI WAS SHOWN TO INCREASE TIME TO FIRST SICKLE CELL CRISIS BY 30 DAYS
ENDARI: A median number of 84 days until the first sickle cell crisis
Placebo: A median number of 54 days until the first sickle cell crisis

ENDARI WAS SHOWN TO LOWER THE FREQUENCY OF HOSPITALIZATIONS BY 33%
ENDARI: A median number of 2 hospitalizations for sickle cell pain
Placebo: A median number of 3 hospitalizations for sickle cell pain

ENDARI WAS SHOWN TO REDUCE CUMULATIVE DAYS SPENT IN THE HOSPITAL BY 41%
ENDARI: A median number of 6.5 cumulative days spent in the hospital
Placebo: A median number of 11 cumulative days spent in the hospital

ENDARI WAS SHOWN TO REDUCE THE OCCURRENCE OF ACUTE CHEST SYNDROME
ENDARI: 13 out of 152 patients (8.6%) experienced acute chest syndrome
Placebo: 18 out of 78 (23.1%) patients experienced acute chest syndrome

Source: Emmaus Life Sciences, Inc.

Furthermore, annualized statistics for the use of Endari® post approval yield a 44% reduction in frequency of SCD crises (median 2.4 vs. median 4.3) and a 38% reduction in hospital days (median 8 vs. median 13).

Endari®'s Safety

The safety of Endari® was based upon data from 298 patients, 187 treated with Endari® and 111 patients treated with placebo, in Phase 2 and Phase 3 studies. Endari®'s safety profile was similar to that of the placebo and Endari® was well-tolerated in pediatric and adult patients alike. The most common adverse reactions, occurring in more than 10% of patients treated with Endari®, were constipation, nausea, headache, abdominal pain, cough, pain in extremity, back pain, and chest pain (non-cardiac). Of these, low-grade nausea, noncardiac chest pain, fatigue, and musculoskeletal pain occurred more frequently in the L-glutamine group than in the placebo group. Treatment discontinuation due to adverse reactions was reported in 2.7% (n=5) of patients receiving Endari®. These adverse reactions included one case each of **hypersplenism**, abdominal pain, **dyspepsia**, burning sensation, and hot flashes. In the Phase 3 trial, the rate of adverse events was higher in the placebo group than in the L-glutamine group (100% vs. 98.0%), as was the rate of serious adverse events (87.1% vs. 78.2%), demonstrating the drug's ability to control SCD's symptoms and complications.

Additional Studies

Additional studies on the safety and efficacy of Endari® were conducted following the approval and marketing of the compound. The highlights of two such studies—one post-hoc analysis of the Phase 3 data and one real-world data on the use of Endari® post approval—are provided in the accompanying section.

The Evaluation of Transfusion Data from the Phase 3 Clinical Study of L-Glutamine in Sickle Cell Disease (Source: Blood, Vol. 138 (1): 3116, 2021)

Post-hoc analyses of the L-glutamine Phase 3 clinical study in SCD were performed to assess the effect of the use of Endari® on the number of units of red blood cells (RBC) transfused and on the number of transfusions that took place during the study. The study found that there was a significant difference in the number of units of RBCs transfused in the L-glutamine treatment arm than in the placebo arm. Of patients requiring RBC transfusions, those assigned to L-glutamine required approximately 43% fewer units of RBCs (2.86 units per patient-year) compared to those assigned to placebo (5.38 units per patient-year) over the 48-week period. There was also a lower trend in the mean cumulative number of RBC transfusion episodes in the L-glutamine arm than the placebo arm; 1.702 RBC transfusion episodes per patient-year in the L-glutamine arm compared to 2.659 RBC transfusion episodes per patient-year in the placebo arm.

Real-world data on the efficacy of pharmaceutical-grade L-glutamine in preventing sickle cell disease-related acute complications and hemolysis in pediatric and adult patients (Source: HemaSphere, Vol. 6 (Suppl):24-25, 2022)

Following the Phase 3 clinical trial results, researchers conducted a follow up study to confirm the efficacy of pharmaceutical-grade L-glutamine in pediatric and adult patients with SCD at follow-up time points of 24, 48, and 72 weeks. In a retrospective study conducted from October 2019 to April 2020, 19 patients aged 8 to 54 years old (4 patients from Qatar and 15 patients from French Guyana) were treated orally with L-glutamine (0.3mg/kg) twice daily. Clinical parameters (number of VOCs, hospitalizations, days hospitalized, ACS events, and blood transfusions) were documented for the year prior to treatment initiation as baseline values. These parameters were also collected at 24, 48, and 72 weeks from treatment initiation.

Compared to baseline, patients had significantly fewer VOCs at 24, 48, and 72 weeks following L-glutamine therapy (median change from 3.0 to 0), fewer hospitalizations (median change from 3.0 to 0), and fewer days in the hospital (median change from 15.0 to 0). Moreover, at 24, 48, and 72 weeks, the number of blood transfusions was considerably lower than at baseline (median change from 3.0 to 0). In the year prior to treatment initiation, two patients reported a single ACS event but no such events were observed during therapy.

SCD-related laboratory measures also improved. Following treatment with L-glutamine, the mean hemoglobin levels (Hg) level increased significantly after 72 weeks (8.2 to 8.8 g/dL) with peak mean increase from baseline of 11.2% at 48 weeks. A similar increasing trend was observed for **hematocrit** proportion (Ht) from baseline to 72 weeks (24% to 27%) with highest mean improvement from baseline of 15.5% at 48 weeks.

This study demonstrated that L-glutamine therapy in SCD patients resulted in significant and sustained improvements in clinical outcomes (number of VOCs, number and duration of hospitalizations, and number of blood transfusions) and an increase in Hg and a reduction of hemolysis.

ENDARI®'S COMMERCIALIZATION

Endari® provides key competitive benefits compared to other therapeutic options for SCD:

- *Broad indication*: Approved for any complication of sickle cell disease.
- *Pediatric usage*: Approved for patients aged 5 and up.
- *Real-world data*: On the market for approximately five years.
- *Significantly lower cost than new competitors*: Annual list price of $40,500 in comparison to list prices of over $100,000 for both Adakveo® (crizanlizumab) and Oxbryta™ (Voxelotor).
- *Positive safety profile*: No warnings, precautions, or drug interaction notices on label.
- *No labs required*: No requirement of blood testing before or during taking the medication.

Figure 14 provides an overview of Endari®'s competitive position.

Figure 14

ENDARI® COMPETITIVE POSITION

	Endari® (L-glutamine)	**Hydroxyurea**	**Siklos** (Hydroxyurea) (Amedica)	**Oxbryta** (Global Blood Therapeutics)	**Adakveo**
Broad indication	YES	NO	NO	NO	NO
Black box warning	NONE	YES	YES	NONE	NONE
Lab tests required	NONE	YES	YES	YES	YES
Patient age range	5+ years old	18+ years old, used off label for pediatrics	2+ years old	4+ years old	16+ years old

Source: Emmaus Life Sciences, I...

International Commercialization Approvals

The Company believes that its international expansion is key to its future growth potential. Currently, Endari® is approved for use in the U.S. (2017), Israel (2020), United Arab Emirates (UAE) (March 2022), Qatar (November 2022), and Kuwait (December 2022). Emmaus is aggressively seeking additional marketing approval for Endari® in geographic regions that account for a significant share of the world's SCD cases: the Middle East and North Africa (MENA), the Mediterranean (Europe), South America, and India.

Middle East and North Africa

Emmaus obtained marketing approval for Endari® in UAE, Qatar, and Kuwait. The process for gaining approval has begun in other Gulf Cooperation Council countries, including submission for approval in Saudi Arabia, Bahrain, and Oman. Emmaus opened an office in Dubai in 2020 and has entered into exclusive distribution agreements with strategic partners to register, commercialize, and distribute Endari® in the Gulf Cooperation Council countries and other countries throughout the MENA region in collaboration with the branch office in Dubai. In November 2022, the Company announced that it received the first major purchase order from its distributor in Saudi Arabia, where Endari® is available on an early access basis only.

Europe

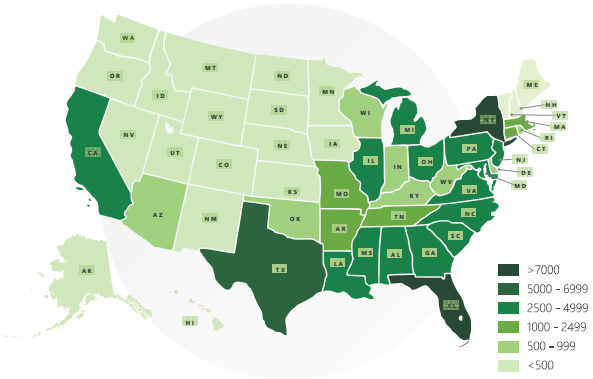
In July 2012, the European Commission granted Orphan Drug Designation status in the European Union (EU) for the Company's prescription grade L-glutamine oral powder, to be known as Xyndari™ in the EU, for the treatment of SCD, resulting in 10 years of Orphan Drug exclusivity starting from approval date.

The Company is working to obtain marketing approval in EU and non-EU countries, with an initial focus on Early Access programs currently underway or planned in the UK, France, and Turkey. Emmaus secured an exclusive early access agreement with a strategic partner in the EU in which its partner distributes Xyndari™ on an early access basis only in France and certain other EU member states. The Company is also in talks with potential strategic partners in other countries to establish similar early access programs while it considers seeking marketing authorization.

In 2019, the European Medicines Agency (EMA)'s Committee for Medicinal Products for Human Use (CHMP) adopted a negative opinion regarding its marketing authorization application (MAA) based upon the position that Xyndari™'s main clinical study did not conclusively support the efficacy of the treatment in SCD patients, although no safety concerns were raised. With Brexit in place, Emmaus plans to update its MAA for both the UK national submission and for either a centralized procedure in the EU or separate national submissions in the EU.

Rest of the World

Figure 15
SCD MARKET DISTRIBUTION



Source: Emmaus Life Sciences, Inc.

Emmaus is actively looking for distribution partners in Africa, Asia (with a focus on India), and Latin America (with a focus on Brazil and Colombia).

Endari®'s U.S. Commercialization and Support

Endari® is marketed and sold in the U.S. by Emmaus' in-house commercial team, encompassing sales, marketing, patient support, and distribution support personnel. Approximately 86% of SCD patients in the U.S. reside in major metropolitan areas in 18 states (Figure 15). This allows Emmaus to have a more targeted sales approach, as a highly concentrated market allows for a more effective and smaller sales force. The Company believes that its current sales force is well deployed to serve this market.

Through the effective use of its sales force, Emmaus is attempting to expand the reach of Endari®. To achieve this objective, its sales team targets pediatric and adult SCD hematologists, physicians, and treatment centers, while also working with local and national sickle cell disease foundations and advocacy groups to increase product awareness of Endari®.

To support its sales and distribution efforts, Emmaus has agreements in place with the nation's leading distributors, as well as physician groups, purchasing organizations, and pharmacy benefits managers. The Company has agreements with three of the largest specialty distributors of prescription drugs in the U.S: AmerisourceBergen Corporation (through AmerisourceBergen Specialty Group and its subsidiaries ASD Healthcare LLC and US Bioservices Corporation), McKesson Corporation (through its subsidiary McKesson Plasma and Biologics LLC), and Cardinal Health Inc. (through its subsidiary Cardinal Health 108, LLC). The result is that Emmaus has a network of over 600 specialty and health system pharmacies distributing Endari®, with prescriptions having been filled in 46 states, Puerto Rico, and Washington D.C.

Emmaus also started two key programs aimed at facilitating patient access: (1) in February 2019, Emmaus established a Commercial Patient Assistance Program (C-PAP) to provide financial assistance to eligible patients who are unable to afford their monthly co-payments for Endari®; and (2) in December 2020, the Company announced the launch of the Endari® Patient Support Program to provide eligible patients access to Endari® where appropriate.

Endari® is well covered by various insurance programs, including Managed Medicare, the Children's Health Insurance Program (CHIP), commercial insurance, and Medicare, while also providing patient assistance where required. Endari® is reimbursable by the Centers for Medicare and Medicaid Services, and every state provides coverage for Endari® for outpatient prescriptions to all eligible Medicaid enrollees within their state Medicaid programs.

An overview of Endari®'s commercialization activities is provided in Figure 16.

Figure 16

ENDARI® COMMERCIALIZATION

Source: Emmaus Life Sciences, Inc.

Direct-to-Consumer Marketing Initiatives

The Company's U.S. marketing efforts include direct-to-consumer programs intended to reach people nationwide who lack information regarding available SCD treatment options, such as Endari®. An example of these initiatives is the collaboration between Emmaus and *The Steve Harvey Morning Show's* cast member Kier (Junior) Spates to share Mr. Spates' personal experience with the use of Endari® to treat his SCD, during the morning show https://bit.ly/3HhQtjS. *The Steve Harvey Morning Show* airs weekdays from 6:00 to 10:00 in the morning on more than 100 radio stations. The program is heard by nearly seven million weekly listeners and is the number one syndicated morning radio show in the U.S.

The Company believes that the collaboration with Mr. Spates can help destigmatize SCD and inform listeners to Mr. Harvey's popular show, including those who with SCD, about Endari®. In addition, Mr. Spates is planning to start a podcast, which the Company hopes to further improve and expand knowledge and uptake of Endari® among the SCD population.

As co-host of the nationally syndicated *The Steve Harvey Morning Show*, Mr. Spates is known for his comedic and high-energy commentary. In 2013, he signed on as the national celebrity ambassador for the Sickle Cell Disease Association of America, Inc. (SCDAA). Together, SCDAA and Spates launched the "Rise Above" initiative, which aims to educate and raise awareness about the blood disease across the nation. Mr. Spates is also the founder of Kier's Hope Foundation (KHF), a non-profit organization benefitting those affected by SCD.

Endari®'s Telehealth Program

In April 2022, Emmaus launched an innovative full-service telehealth solution (https://www.endarirx.com/ask-physician) that provides online access to Endari®. The Company believes that of the approximately 100,000 sickle cell patients in the U.S., up to 75,000 can be accessed through telehealth, substantially more than the 25,000 accessible through traditional channels. The telehealth program, developed and implemented with its strategic partners Asembia LLC, US Bioservices Corporation, and UpScriptHealth, capitalizes on the expansion of telemedicine in the U.S. to provide patients and providers on-line access to Endari®.

Endari®'s telehealth program allows prospective patients to connect to a physician by phone or any device with internet access. The process involves filling out a medical questionnaire prior to the physician online appointment, where patients can discuss their symptoms, treatment options, answer any questions or concerns, and determine if Endari® is appropriate for their case. The program allows for same day physician authorization and prescription, with medication sent to the patient's home within three business days.

The Company believes that Endari®'s safety profile can result in the medication becoming the first choice SCD therapeutic candidate for patients using telemedicine services. In particular, the following factors differentiate Endari® from its competitors, making it an ideal option for telehealth:

- No preliminary bloodwork required to be prescribed or follow-up testing is needed;
- No drug interactions or warnings on label;
- Oral administration; and
- Same-day physician authorization and prescription.

Following authorization by the physician, Endari® can be delivered to the patients' home. Endari®'s powder form makes it easy to deliver and ingest, with patients mixing it with food or drinks. Figure 17 (page 29) provides an overview of Endari®'s advantages in terms of safety and administration against other prescription options, which the Company believes makes Endari® a prime candidate for a telehealth prescription program.

Figure 17

ENDARI® TELEHEALTH PROFILE

Source: Emmaus Life Sciences, Inc.

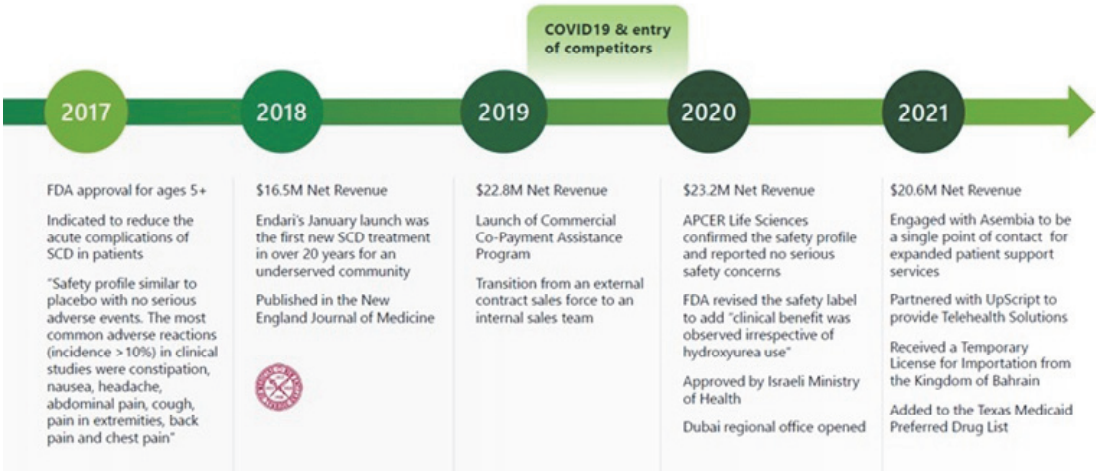
COVID-19 Pandemic Effect on Business Results

The Company launched Endari® in 2018, which resulted in approximately $16.5 million in revenue for the fiscal year. Acceptance of Endari® continued to increase, resulting in revenues of $22.8 million for 2019. According to the Company, the COVID pandemic significantly affected its sales and marketing efforts, resulting in limited growth. However, despite this and the FDA approval of Adakveo® and Oxbryta™ in 2019, revenues in 2020 of $23.2 million were in line with the previous year. Fiscal year 2021 resulted in a slight decrease in revenue ($20.6 million) as a result of distributor overstocking of the medication as they accumulated inventory in line with pre-COVID sales expectations. This effect continued into the early part of 2022.

However, revenue numbers from the second half of 2022 showed steady growth. Weekly sales have continued to increase, reaching steady levels of $500,000 to $600,000 per week during the latter part of the year (equivalent to expected annualized sales of $24 million to $30 million). The Company believes that this growth is due to a post-COVID shutdown recovery to normal business levels, coupled with the initial effects of its direct-to-consumer marketing initiatives, which started in 2022. Emmaus believes that this domestic growth can continue behind the effect of its direct-to-consumer marketing programs, including expansion of its telehealth initiative. Figure 18 provides an overview of Endari®'s business results and key Company initiatives.

Figure 18

ENDARI® HISTORY AND RESULTS



Source: Emmaus Life Sciences, Inc.

In 2021, Emmaus generated over $20 million in revenue from approximately 1,000 patients using Endari®. The Company believes that even a modest increase in patient acquisition over the next few years, for example to 5,000 patients (out of the 100,000 total SCD population), could result in revenues of over $100 million from domestic business. This is in addition to the Company's international efforts, where Endari® has received marketing approval in three Middle Eastern and North African (MENA) countries during 2022, with expectations for additional approvals in this region as well as in Europe and Asia.

Emmaus Manufacturing Operations

Endari® uses prescription grade L-glutamine (PGLG), which differs from non-prescription grade L-glutamine widely available as a nutritional supplement. PGLG is differentiated from ordinary L-glutamine by several factors, including the presence of a Drug Master File, oversight of purity and manufacturing at FDA inspected facilities, and stringent stability tested packaging.

There are limited global suppliers of PGLG. Emmaus does not currently have its own manufacturing capabilities and obtains substantially all of its PGLG needs, both for commercial supplies of Endari® and its product candidates under development, directly or indirectly from a single Japanese supplier: Ajinomoto Health and Nutrition North America, Inc. (Ajinomoto), a subsidiary of Ajinomoto North American Holdings, Inc. Despite the issues with relying on a single supplier, the limited availability of global suppliers of PGLP is one of the biggest barriers to entry for other companies intending to use L-glutamine for the treatment of SCD or other conditions.

Ajinomoto provided PGLG to the Company free of charge for its clinical trials of Endari®, including the Phase 3 study. In return, pursuant to a letter of intent with Ajinomoto, Emmaus agreed to purchase from Ajinomoto substantially all its commercial needs for PGLG, subject to certain exceptions; however, Emmaus has not entered into a long-term supply agreement with Ajinomoto.

Endari® and any other commercial products the Company develops must be manufactured and packaged by facilities that meet FDA requirements for **current Good Manufacturing Practices (cGMP)**. Emmaus believes that Ajinomoto and Packaging Coordinators, Inc., which packages Endari®, meet FDA cGMP regulations.

Purchase of Manufacturing Facility

In December 2019, EJ Holdings, Inc., a Japanese corporation established as a joint venture between Emmaus (40% ownership) and Japan Industrial Partners, Inc. (60% ownership), purchased a phased-out active pharmaceutical ingredient manufacturing facility in Ube, Japan from Kyowa Hakko Bio Co. Ltd, for the manufacture of L-glutamine and other amino acids (Figure 19 [page 31]).

EJ Holdings is in the process of retrofitting the plant to prepare for a regulatory recertification, including obtaining FDA and other regulatory approvals for the manufacture of PGLG in accordance with current cGMP. Emmaus currently anticipates the process to be completed and test production runs to take place during 4Q 2023/1Q 2024, with regulatory approval following shortly thereafter. Once the plant is active, Emmaus plans to enter into a long-term agreement with EJ Holdings for the supply of PGLG.

The joint venture between Emmaus and Japan Industrial Partners was established as a variable interest entity. The agreement established that Emmaus would be the principal source of funding for EJ Holdings' ownership and operation of the plant, including the refurbishment process, and as a result, the ownership interest of Emmaus would increase accordingly. The Company expects to start the ownership transfer process during the 1Q 2024/2Q 2023, resulting in an ownership position by the Company of at least 95%.

Figure 19

ENDARI® MANUFACTURING SITE

Ube, Yamaguchi Prefecture, Japan

Product: Prescription Grade L-Glutamine (PGLG)

Manufacturing capacity: 2,000 tons/yr

Area: 95.1 acres

Acquired: December 25, 2019 for $10.4 million

Fair market value (appraisal by Marshall and Stevens): $53.5 MM

Projected launch year: 2024

Source: Emmaus Life Sciences, Inc.

EMMAUS' CLINICAL AND PRECLINICAL PROGRAMS

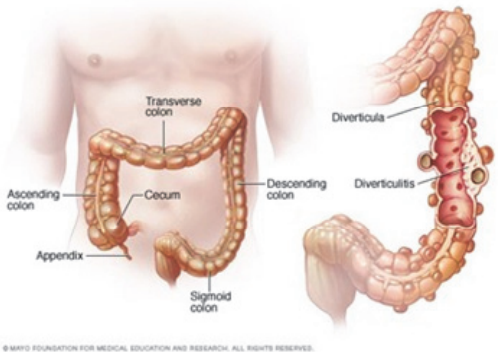
The amino acid L-glutamine that makes up Endari® has also shown promise in combating other conditions. The most promising development involving Endari® beyond SCD is in the treatment of diverticulosis, currently in a pilot trial. In addition, the Company' pipeline includes two pre-clinical programs: (1) a regenerative medicine program based on cell sheet technology; and (2) an oncology program for solid cancers, blood-cancers, and lymphoma.

Diverticulitis Program-ELS004

Diverticulosis is an often-asymptomatic gastrointestinal (GI) condition affecting large populations. Diverticulosis often progresses to a more serious GI disease—diverticulitis—a debilitating disease that typically requires surgical intervention. Limited clinical observations have shown that Endari® may be effective in treating diverticulosis by slowing or stopping the progression of the disease to diverticulitis. Emmaus begun a small pilot trial in the first half of 2019 to study the potential use of L-glutamine as a new treatment for patients with diverticulosis.

Figure 20

DIVERTICULITIS



Source: Mayo Foundation for Medical Educataion and Research.

Diverticulitis Background

Diverticula are small, bulging pouches that can form in the lining of the digestive system (Figure 20). They are found most often in the lower part of the large intestine (colon). The presence of diverticula is known as diverticulosis, a common condition that does not normally cause problems. However, in some cases, the pouches can become inflamed or infected, causing a condition known as diverticulitis.

Diverticulosis is very common in industrialized nations, with its prevalence increasing with age. Over 50% of people over the age of 60 are estimated to have diverticulosis, with as many as 70% of 80 year old's have the condition. Of these individuals, 10% to 25% are expected to develop diverticulitis, resulting in abdominal pain, nausea, vomiting, constipation, diarrhea, fever, and leukocytosis (Source: *Inflammatory Disease Journal, Vol.3 (2)*, 2018). Mild diverticulitis can be treated with rest, changes in diet, and antibiotics. However, severe or recurring diverticulitis may require surgery.

Annually, in the U.S., there are over 2.7 million outpatient visits and 200,000 inpatient admissions for diverticulitis. The incidence of diverticulitis has increased over time and increases with patient age. However, the increase in diverticulitis in recent decades has been greatest in young patients. For example, from 1980 through 2007, the incidence of diverticulitis in individuals 40 to 49 years old increased by 132% (Source: *Reviews and Perspectives Reviews in Basic and Clinical Gastroenterology And Hepatology* Vol. 156 (5): P1282-1298, 2019).

ELSOO4 Development

The pathogenesis of diverticulosis is believed to result from structural abnormalities of the colonic wall, disordered motility, and low fiber diets. The relationships between glutamine and intestinal physiology have been extensively studied in ulcerative colitis, Crohn's disease, short bowel syndrome, and as a nutritional therapy for critical illnesses. Overall, glutamine causes suppression of pro-inflammatory signaling pathways, suppression of intestinal cell apoptosis and cellular stress, and microbiome regulation, among other mechanisms of action. Glutamine also helps to maintain intestinal tissue integrity through various signaling pathways.

Emmaus theorizes that L-glutamine may rejuvenate the mucosa membrane of the large intestine, which support muscle cells, including those surrounding the intestine, helping to prevent diverticula formation. In April 2019, Emmaus initiated a Pilot/Phase 1 study of the safety and efficacy of PGLG oral powder in diverticulosis. The study plans to evaluate the change in the number and size of colonic diverticula and assess safety in a total of up to 10 to 15 patients at multiple study sites. The COVID-19 pandemic interrupted the progress of clinical trials in the pharmaceutical industry, in general, and the Pilot/Phase 1 study was temporarily interrupted.

On August 5, 2020, the Company announced preliminary top-line data for two patients who had most recently completed the first six months of the scheduled twelve months of treatment in the pilot study of diverticulosis. In each of these patients, the investigator noted the appearance of healthier mucosa with pinkish coloration compared to the baseline. Subsequently, Emmaus collected data on two more patients who completed the first six months of treatment, with the patients showing a 100% and 50% reduction in the number of diverticula over six months. There were no safety concerns reported by the patients. The Company owns patents on the use of its L-glutamine product for diverticulosis in the U.S., EU, Australia, China, Russia, Japan, South Korea, Mexico, Indonesia, and India (as described on page 8).

Cell Sheet Technology – ELS002 and ELS003

Emmaus is also conducting pre-clinical studies on its regenerative medicine program based on cell sheet technology. A cell sheet is a composite of cells grown and harvested in an intact sheet, rather than as individual cells. These cell sheets can be used for tissue transplantation or to engineer complex multilayer cell sheets composed of different types of cells. Cell sheets offer several potential advantages over existing treatment options, including reduced chemical toxins needed during cell sheet generation, easier and more convenient cell coverage of the injured tissue, and **allogeneic** (i.e., use of stem cells from one individual in another individual) transplantation.

The Company's technology takes small quantities of progenitor cells and cultures them in a special cell culturing dish. When the cells have grown sufficiently to create a sheet of cells, they are transplanted into the patient. If the transplant is successful, the cells will differentiate to replace the damaged cells and restore the functions that have been lost.

Cultured Autologous Oral Mucosal Epithelial Cell Sheets (CAOMECS)

An Emmaus-led team at The Lundquist Institute (Torrance, CA, USA), a non-profit biomedical research organization academically affiliated with the David Geffen School of Medicine at UCLA, is conducting a pre-clinical study of Cultured Autologous Oral Mucosal Epithelial Cell Sheet, or CAOMECS, technology. Emmaus' lead CAOMECS program is for the treatment of corneal diseases. Using a patient's own oral mucosal epithelial cells, the Company is working toward being able to grow and harvest a cell sheet for directly transplanting onto the cornea of the patient's affected eye to repair the damaged cornea. The development of CAOMECS for treating corneal and other diseases, including limbal stem cell deficiency, has been successful in animal studies.

Chondrocyte Cell Sheet Technology

The Company has developed human cartilage and bone multilayer cell sheets using human adult **mesenchymal** stem cells and is conducting preclinical studies to assess the restorative properties of these cell sheets. Cartilage cell sheet have the potential to treat diseases such as articular cartilage injury and osteoarthritis. Bone cell sheets are potentially useful in treating diseases such as osteoarthritis, **fracture nonunion,** and **Paget's disease**.

This cell sheet technology offers several potential advantages over the existing treatment options. The harvesting does not require any special treatment, such as the use of enzymes, which could be harmful to the treated cells and patients. Current treatments options involve the injection of individual cells to the damaged area, which requires identification of precise injection location and multiple injections due to rapid cells death. In contrast, cell sheet technology allows wider coverage of needed cells to the damaged cartilage and higher cell survival due to the cell sheet structure. Unlike existing cell therapies, Emmaus' cell sheets can be produced from stem cells from one patient for use on other patients, thereby decreasing the risk of immune rejection. The Company believes that these advantages may also lead to lower-cost and more efficient production.

Device Measuring Cell Sheets Transparency

The Company has also developed a device for quality control in the cell-sheet manufacturing process. The device measures the thickness and maturity of biological cell cultures for harvesting of cell sheets, as well as the number and transparency of cells present in one or more cell sheets of the biological cell cultures. The application of this device extends to ophthalmology to assess the transparency of donor's cornea before transplantation. Currently, there is no objective method to assess the donor's cornea to understand readiness or compatibility. The Company believes that the new device can become an essential tool for quality control in the growing field of cell sheet translational medicine. Emmaus may seek a potential partner to develop or commercialize the device.

Oncology Project-ELS005

On October 7, 2021, Emmaus entered into a License Agreement with Kainos Medicine, Inc. (Kainos), a South Korean corporation, under which Kainos granted the Company an exclusive license in the territory encompassing the U.S., the U.K., and the EU to patent rights, know-how, and other intellectual property relating to Kainos's novel **IRAK4 inhibitor**, referred to as KM10544, for the treatment of cancers, including leukemia, lymphoma, and solid tumor cancers. Emmaus' responsibilities include investigation and proof of target disease selection, efficacy, and safety in all targeted indications.

In consideration of the license, the Company paid Kainos a six-figure upfront fee in cash and agreed to make future cash payments upon the achievement of specified milestones totaling in the mid-eight figures, a single-digit percentage royalty based on net sales of the licensed products, and a similar percentage of any sublicensing consideration.

Emmaus is conducting pre-clinical studies to assess KM10544's efficacy in two cancer cell lines, acute myeloid leukemia and **Waldenstrom macroglobulinemia (WM)**. In *in vitro* studies, KM10544 suppressed the proliferation and also induced apoptosis (cell death) in both cancer cell lines. Further *in vitro* studies indicated that KM 10544 had minimal toxic effects on healthy human cell lines, including human dermal fibroblasts and human adipose stromal cells. Based upon the positive pre-clinical results, the Company plans to undertake further *in vivo* testing to evaluate its toxicity and efficacy against targeted cancers, including acute myeloid leukemia and WM.

Leukemia is a cancer of blood-forming tissue causing high variation of its manifestation and therefore requiring many different treatment options. While there has been an increase in the survival rate by seven years from treatment of the younger patient population (i.e., less than 60 years) since 1970, the survival rate has increased by only one year for patients older than 60 years. Waldenstrom macroglobulinemia (WM) is a rare blood cancer that accounts for 1% to 2% of all hematological malignancies. In the U.S., approximately 1,000 to 5,000 new cases are detected each year. Many of the WM patients are asymptomatic, making it difficult to detect and treat WM in its early stages.

External Programs

The Company's technologies are also being investigated by third parties for the use of burn injuries (Phase 3) and pancreatic cancer (Phase 1), with study product provided by Emmaus.

Milestones

Over the last 18 months, Emmaus has achieved significant milestones as it continues to support the commercialization of Endari® in the U.S., expand its international operations through obtaining additional marketing approval in key foreign countries, and move its pipeline of potential candidates closer to FDA approval.

Endari® Commercialization

- November 2021—Entered into an agreement with Asembia to provide expanded patient support services and announced a partnership with UpScript IP Holdings, LLC to provide telehealth solutions to SCD patients.
- December 2021—Announced that data on Endari® had been accepted for a poster presentation at the 63rd American Society of Hematology Annual Meeting and Exhibition.
- April 2022—Launched an innovative full-service telehealth solution that provides online access to Endari®.
- September 2022—Announced a collaboration with *The Steve Harvey Morning Show* cast member Kier (Junior) Spates to share Mr. Spates' personal experience with the use of Endari® to treat his SCD, during the morning show (https://bit.ly/3HhQtjS).

Endari® International Operations

- 2022—Received approval for marketing of Endari® to treat SCD from the United Arab Emirates (March 2022), Qatar (November 2022), and Kuwait (December 2022). Emmaus also submitted request for approval in Saudi Arabia, Bahrain, and Oman.
- November 2022—Received the first major purchase order from its distributor in Saudi Arabia, where Endari® is available on an early access basis only.

Other Programs

- October 2021—Entered into an exclusive license agreement with Kainos Medicine, Inc. for patent rights to Kainos' novel IRAK4 inhibitor in the U.S., the U.K. and the EU, expanding the companies' collaboration for the preclinical development of the compound for potential anti-cancer therapies.
- December 2021—Completed patient enrollment on the Phase 1 sub-study for the development of ELSOO4 (L-glutamine) for the treatment of diverticulosis.

Competition

Emmaus faces intense competition from companies with greater resources. If competitors are successful in marketing or developing alternative treatments, the Company's commercial opportunities may be diminished or eliminated. The pharmaceutical industry is characterized by rapidly advancing technologies, intense competition, and an emphasis on creating proprietary therapeutics. Emmaus faces competition from a number of fronts, some of which may target the same indication as Endari®, such as pharmaceutical companies, as well as generic drug companies, biotechnology companies, drug delivery companies, and academic and research institutions, many of which have greater financial resources, marketing capabilities, as well as established sales forces, manufacturing capabilities, research and development capabilities, and experience in obtaining regulatory approvals for product candidates.

Emmaus' Endari® has a broad indication and is approved for any complication of SCD. The Company believes that its product offers a practical solution for SCD since it is an oral therapy and has shown to have little to no side effects. The drug is taken twice daily, with no requirement for blood testing prior to starting treatment and no required blood testing while taking the medication, which make it idea for telehealth as the drug can be shipped directly to a patient's doorstep. This is in contrast to other medications for SCD, which require blood testing while taking treatment and are not conducive to being monitored via telehealth. The follow companies have approved products, which address the same indication as Endari®.

Approved Products for SCD

Adakveo® (crizanlizumab) from Novartis

The FDA approved a new drug application (NDA) submitted by Novartis in late 2019, permitting the marketing of Adakveo® (crizanlizumab) to reduce the frequency of vaso-occlusive crises in adults and pediatric patients aged 16 years and older with SCD. Adakveo®, which is administered by intravenous infusion every four weeks, is a selectin blocker humanized IgG2 kappa monoclonal antibody that binds to P-selectin.

Emmaus does not believe the Novartis product represents a source of significant competition as they are not currently marketing their product. As a monthly antibody injection, it decreases some of the complications of SCD but does not reduce hospitalizations or acute chest syndrome (which is one of the worst complications of SCD patients). Furthermore, the issue with this monthly antibody injection is that it is almost like a giving chemotherapy every month, with the treatment being very hard on the body (with some patients taking several days to feel better following treatment).

Oxbryta™ (Voxelotor) tablets from Global Blood Therapeutics, Inc. (GBT), now owned by Pfizer, Inc.

In late 2019, Global Blood Therapeutics, Inc. (GBT) announced that the FDA approved its NDA for Oxbryta™ (voxelotor) tablets for the treatment of SCD in adults and is now approved in children 4 years of age and older (as of December 2021). Oxbryta™ is an oral, once-a-day therapy intended to treat SCD by targeting hemoglobin polymerization. On October 5, 2022, Pfizer Inc. announced that it had completed its acquisition of Global Blood Therapeutics, Inc. (GBT), where GBT is now a wholly owned subsidiary of Pfizer.

Cost

The current cost of Endari® is approximately $1,250 per carton, with patients taking one to three cartons per month, depending on their size—with essentially the entire cost covered by Medicare and Medicaid. This compares positively against the newer therapeutic agents approved for SCD. Both Adakveo® and Oxbryta™ have annual list prices of over $100,000 ($132,000 and $127,000, respectively). On the other hand, Endari® annual list price is $40,500 (Source: The Institute for Clinical and Economic Review's *Crizanlizumab, Voxelotor, and L-Glutamine for Sickle Cell Disease: Effectiveness and Value,* 2021).

In addition, the use of Endari® brings a decrease or elimination of the costs associated with hospitalization as well as lab tests due to two key competitive advantages: (1) Endari®'s proven ability to reduce hospitalizations and cumulative days in the hospital; (2) Endari® does not require blood testing before or during administration of the therapeutic, as opposed to the lab tests used to monitor patients taking the other approved SCD therapeutics.

Other Potential Competition

The Company also faces competition from hydroxyurea and non-prescription grade L-glutamine supplements. Non-prescription grade L-glutamine is manufactured in large quantities, primarily by a few large chemical companies, and processed and sold as a nutritional supplement. Hydroxyurea is used to treat cancer of the white blood cells, called chronic myeloid leukemia (CML), and may also be given together with radiation treatment for head and neck cancer (advanced squamous cell cancer). Hydroxyurea interferes with the growth of cancer cells, which are eventually destroyed by the body. The drug is used to prevent painful episodes and reduce the need for blood transfusions in patients with sickle cell anemia as it works by making the red blood cells more flexible.

Treatments in Development

bluebird bio, Inc.

bluebird bio, Inc. (BLUE-NASDAQ) of Somerville, MA is expected to apply for U.S. approval of its gene therapy in 2023. The company's lovotibeglogene autotemcel (lovo-cel) gene therapy is an investigational one-time treatment being studied for sickle cell disease (SCD), that is designed to add functional copies of a modified form of the β-globin gene (βA-T87Q-globin gene) into a patient's own hematopoietic (blood) stem cells (HSCs). Once patients have the βA-T87Q-globin gene, their red blood cells (RBCs) can produce anti-sickling hemoglobin (HbAT87Q) that decreases the proportion of HbS, with the goal of reducing sickled RBCs, hemolysis, and other complications. bluebird bio's clinical development program for lovo-cel includes the completed Phase 1/2 HGB-205 and ongoing Phase 1/2 HGB-206 and Phase 3 HGB-210 studies. bluebird bio is also conducting a long-term safety and efficacy follow-up study (LTF-307) for people who have been treated with lovo-cel in bluebird bio sponsored clinical studies. The Company has completed treatment of all patients in HGB-206 Group C, which will form the primary basis for efficacy in its lovo-cel BLA submission and expects to complete vector and drug product analytical comparability studies for the lovo-cel BLA in the fourth quarter 2022. The FDA previously granted orphan drug designation, fast track designation, regenerative medicine advanced therapy (RMAT) designation, and rare pediatric disease designation for lovo-cel.

Additional Potential Treatments

Other potential treatments for SCD being may include:

- Developing allogenic stem cell transplant procedures that are less debilitating by creating a drug that minimizes the amount of chemotherapy patients undergo to prepare for them;
- Expanding the group of stem cell donors by improving the success of transplants using half-matches through genetic editing so more individuals can experience the curative benefits of the procedure;
- Examining new agents that could improve on hydroxyurea's ability to increase fetal hemoglobin above the current 30% to 50% or even more;
- Exploring more potential drugs in the pipeline that are sickling inhibitors, anti-adhesion agents, and others that ameliorate other downstream effects of SCD;
- Leveraging the four existing pathophysiological strategies for delaying sickling beside fetal hemoglobin induction to search large libraries of drugs that have been tested in humans and could quickly move to clinical testing if they match a strategy.

Investment Highlights

- Emmaus Life Sciences, Inc. ("Emmaus" or "the Company") is a commercial-stage biopharmaceutical company engaged in the development and commercialization of therapies, primarily for rare and orphan diseases, with an initial focus on sickle cell disease (SCD).

    - Emmaus' lead commercial product is Endari® (L-glutamine oral powder), a safe and effective oral treatment indicated to reduce acute complications of SCD in adult and pediatric patients.

- At the time of FDA approval in 2017, Endari® was the first ever FDA-approved treatment for SCD pediatric patients (5+ years old) and first new treatment of SCD in 20 years. Endari® has received Orphan Drug designation from the FDA and Orphan Medicinal designation from the European Commission.

- Results of the Company's Phase 3 trial demonstrated that the use of Endari® led to a significant reduction in the number of sickle cell crises, a delay in median time to sickle cell crises, and a reduction in hospitalizations and cumulative days in hospital.

- The global SCD treatment market was estimated at $3.4 billion in 2020, and is expected to reach $8.5 billion by 2026, behind an increasing prevalence off SCD and new innovative treatments. Currently, only four therapeutic drugs have been approved by the FDA for the treatment of SCD: (1) hydroxyurea; (2) L-glutamine; (3) crizanlizumab; and (4) voxelotor.

    - Concerns about the safety and/or efficacy of some available therapeutic options are on-going. For example, hydroxyurea, approved by the FDA in 1998, contains a black-label warning highlighting the risk of severely low blood cell counts and cancer, the most stringent warning imposed by the FDA.

    - Voxelator's mechanism of action, increasing hemoglobin's oxygen affinity, presents some concerns of potential negative effects, as the bound oxygen cannot be off loaded when needed, resulting in a risk for reduced oxygen delivery in tissues with high oxygen requirements, such as the brain and the heart.

- Endari®'s competitive position relies of the following key marketing advantages against other therapeutic options:

    - Approved for any complication of SCD (broad indication).

    - Approved for patients aged 5 and up.

    - Significantly lower cost versus new competitors.

    - No warnings, precautions, or drug interaction notices on label.

    - No requirement of blood testing before or during taking the medication.

- Since FDA approval, yearly revenue has increased despite the effect from COVID-19 and the approval of competitive options. According to the Company, Emmaus has regained its growth position in the second half of 2022, behind the effective use of its in-house sales force and its newly launched direct-to-consumer programs, including an innovative full-service telehealth solution that provides online access to Endari®.

- Through its distribution agreements, the Company has accumulated a network of over 600 specialty and health system pharmacies distributing Endari®, with prescriptions having been filled in 46 states, Puerto Rico, and Washington D.C.

- Emmaus offers significant domestic and expanding global opportunities targeting the underserved SCD patient population and undeveloped therapeutic markets. Currently, Endari® is approved for use in the U.S. (2017), Israel (June 2020), United Arab Emirates (UAE) (March 2022), Qatar (November 2022), and Kuwait (December 2022).

    - The process for gaining approval has started in other Gulf Cooperation Council countries, including submission for approval in Saudi Arabia, Bahrain, and Oman. The Company is also working to obtain marketing approval in EU and non-EU countries, with an initial focus on Early Access programs currently underway or planned in the UK, France, and Turkey.

- Emmaus has secured a source of prescription grade L-glutamine (PGLG), overcoming one of the biggest barriers to entry for other companies intending to use L-glutamine for the treatment of SCD or other conditions due to its limited availability.

    - In December 2019, EJ Holdings, Inc., a Japanese joint venture between Emmaus (40% ownership) and Japan Industrial Partners, Inc. (60% ownership), purchased a pharmaceutical ingredient manufacturing facility in Ube, Japan for the manufacture of L-glutamine and other amino acids. EJ Holdings is in the process of retrofitting the plant to prepare it for a regulatory recertification, with test production runs expected to take place during 4Q 2023/1Q 2024, with regulatory approval expected to following shortly thereafter.

- Emmaus is also involved in assessing L-glutamine as a treatment for diverticulosis, currently in a pilot trial, as well as pre-clinical programs for oncology and regenerative medicine with other compounds. The Company believes that its Endari® commercial activities and its developing pipeline of new products provide a sustainable business model resulting in multiple potential future sources or revenue.

- Emmaus has a highly experienced management team with proven success in pharmaceutical research, development, and commercialization, led by CEO and principal inventor of Endari®, Dr. Yutaka Niihara (biography on page 10).

- The Company has a sustainable business model and is developing pipeline of new products, which is expected to result in potentially multiple potential future sources or revenue.

- As of its most recent quarter, the Company currently held $1.1 million in cash and cash equivalents.

Recent Events

December 20, 2022—Emmaus Life Sciences, Inc. announced that Dr. Yutaka Niihara, Chairman and Chief Executive Officer of the Company, was hosted in Mumbai, India on December 16, 2022 by Bhagat Singh Koshyari, the Governor of the State of Maharashtra, the industrial, financial, and commercial center of India. In remarks on social media (https://t.co/vTrKwVT4if), the Governor cited the more than 20 million people suffering from sickle cell disease (SCD) in his country and spoke of the discovery of Endari® that can help patients with SCD.

December 19, 2022—Announced that Dr. Yutaka Niihara was feted at an event held on December 16, 2022 at the World Trade Center in Mumbai, India by the Minister of State of India, Arun Halder, in recognition of Dr. Niihara's work in developing Endari® to treat sickle cell disease (SCD). The event was hosted by Dr. Aviti Govatikar, a medical doctor and former Mrs. World.

December 7, 2022—Announced that it has received Registration Approval from the Pharmaceutical and Herbal Medicines Registration and Control Administration (Drug and Food Control) of the Kuwaiti Ministry of Health granting marketing authorization for the commercial distribution and sale of Endari® in the country. Kuwait is the latest Gulf Cooperation Council (GCC) country to grant full marketing approval for Endari® following approvals in the United Arab Emirates and the State of Qatar earlier this year.

November 17, 2022—Announced that it has been issued a Registration Certificate from the Registration Committee for Pharmaceutical Companies & their Products of the Qatar Ministry of Public Health granting marketing authorization for the commercial distribution and sale of Endari® in the country. The Company also announced that it received its first major purchase order from its distributor in the Kingdom of Saudi Arabia, where Endari® is available on an early access basis only.

November 14, 2022—Reported on its results of operations and financial condition as of and for the three and nine months ended September 30, 2022 and provided a business update.

September 28, 2022—Announced a collaboration with *The Steve Harvey Morning Show* cast member Kier (Junior) Spates to share Mr. Spates' personal experience with the use of Endari®, Emmaus' prescription L-glutamine oral powder, to treat his sickle cell disease (SCD).

August 15, 2022—Reported financial results for the three and six months ended June 30, 2022, and provided a business update.

July 12, 2022—Announced the recent engagement of Acorn Management Partners, LLC to provided professional relations and consulting services to build investor awareness of Emmaus.

June 21, 2022—Virtual Investor Conferences, the leading proprietary investor conference series, in partnership with Zacks Small-Cap Research, announced the agenda for the upcoming Life Sciences Investor Forum to be held on June 23rd. Individual investors, institutional investors, advisors, and analysts are invited to attend. The program begins at 9:30 AM EDT on Thursday, June 23rd.

May 13, 2022—Reported financial results for the three months ended March 31, 2022 and provided a business update.

April 26, 2022—Announced participation in the following investor conferences in May: May 3-4: Q2 Investor Summit 2022, and May 23-26: H.C Wainwright Global Investment Conference.

April 11, 2022—Announced the launch of an innovative full-service telehealth solution (https://www.endarirx.com/ask-physician) with its strategic partners, including Asembia LLC, US Bioservices Corporation, and UpScriptHealth. The telehealth program capitalizes on the expansion of telemedicine in the U.S. to afford patients and providers on-line access to Endari®, the Company's prescription-grade L-glutamine oral powder, for the treatment of SCD.

April 7, 2022—Announced real-world data on Endari® in preventing acute complications from sickle cell disease (SCD) and hemolysis in pediatric and adult patients in French Guiana and Qatar. The data was introduced by Dr. Mohamed Yassin and his co-authors at the 62nd Annual Meeting of the British Society for Haematology (BSH), which was held April 3-5, 2022 at the Manchester Central in Manchester, England and virtually.

March 31, 2022—Reported financial results for the year ended December 31, 2021 and an update on recent activities.

March 29, 2022—Announced that the Florida Medicaid Pharmaceutical & Therapeutics Committee has approved adding Endari®, the Company's prescription-grade L-glutamine oral powder for the treatment of sickle cell disease, to the Florida Medicaid Preferred Drug List (PDL), effective April 1, 2022. According to the Florida Agency for Health Care Administration (AHCA) website, the PDL is a listing of cost-effective, safe, and clinically efficient medication, which can be prescribed without prior authorization documentation. However, clinicians retain the option of prescribing drugs not on the PDL.

March 23, 2022—Announced the approval of its application for marketing authorization of Endari® from the United Arab Emirates (U.A.E.'s) Ministry of Health after a five-month review of the Company's marketing authorization application. During the review period, Endari® was available in the U.A.E. on a named patient, or early access, basis only.

March 4, 2022—Announced that real world data on Endari® has been accepted for an e-poster at the 62nd Annual Meeting of the British Society for Haematology (BSH) to be held April 3-5, 2022 at the Manchester Central in Manchester, England and virtually.

January 4, 2022—Announced that Yutaka Niihara will present a company overview at the H.C. Wainwright BioConnect Conference, being held virtually, January 10-13, 2021.

December 14, 2021—Announced positive transfusion data from a post-hoc analysis of its Phase 3 clinical study of Endari®, the Company's prescription L-glutamine oral powder, in patients with SCD. The data was introduced in a poster presentation on Monday, December 13, 2021 at the 63rd American Society of Hematology (ASH) Annual Meeting and Exhibition at the Georgia World Congress Center in Atlanta, Georgia, and virtually.

December 9, 2021—Announced that Yutaka Niihara, M.D., M.P.H., Chairman and Chief Executive Officer of Emmaus, will present live at VirtualInvestorConferences.com, at 12:30 pm ET on December 16th.

Historical Financial Results

Figures 21, 22, and 23 (pages 42-44) provide a summary of Emmaus' most recent key financial statements for the quarter ended September 30, 2022.

Figure 21

EMMAUS LIFE SCIENCES, INC.

CONDENSED CONSOLIDATED STATEMENTS OF OPERATIONS AND COMPREHENSIVE INCOME (LOSS)

(In thousands, except share and per share amounts)

(Unaudited)

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2022	2021	2022	2021
REVENUES, NET	$ 4,939	$ 5,766	$ 12,460	$ 17,590
COST OF GOODS SOLD	540	445	1,943	1,311
GROSS PROFIT	4,399	5,321	10,517	16,279
OPERATING EXPENSES				
Research and development	432	470	1,196	3,032
Selling	1,664	1,518	5,076	4,254
General and administrative	2,963	3,364	9,413	10,156
Total operating expenses	5,059	5,352	15,685	17,442
LOSS FROM OPERATIONS	(660)	(31)	(5,168)	(1,163)
OTHER INCOME (EXPENSE)				
Loss on debt extinguishment	(421)	—	(421)	(1,172)
Change in fair value of warrant derivative liabilities	51	(131)	1,341	(322)
Change in fair value of conversion feature derivative, notes payable	3,850	(1,357)	3,235	(1,132)
Realized loss on investment in convertible bond	—	—	(133)	—
Net loss on equity method investment	(431)	(663)	(1,490)	(1,999)
Foreign exchange loss	(1,470)	(246)	(5,131)	(1,421)
Interest and other income	175	192	530	573
Interest expense	(1,520)	(683)	(3,544)	(2,390)
Total other income (expense)	234	(2,888)	(5,613)	(7,863)
LOSS BEFORE INCOME TAXES	(426)	(2,919)	(10,781)	(9,026)
Income tax provision (benefit)	(35)	232	44	58
NET LOSS	(391)	(3,151)	(10,825)	(9,084)
COMPONENTS OF OTHER COMPREHENSIVE LOSS				
Unrealized loss on debt securities available for sale (net of tax)	(3,047)	(2,754)	(7,112)	(2,150)
Reclassification adjustment for loss included in net income	—	—	7	—
Foreign currency translation adjustments	481	86	1,455	243
Other comprehensive loss	(2,566)	(2,668)	(5,650)	(1,907)
COMPREHENSIVE LOSS	$ (2,957)	$ (5,819)	$ (16,475)	$ (10,991)
NET LOSS PER COMMON SHARE - BASIC AND DILUTED	$ (0.01)	$ (0.06)	$ (0.22)	$ (0.18)
WEIGHTED-AVERAGE COMMON SHARES OUTSTANDING	49,558,501	49,311,864	49,397,690	49,233,371

Source: Emmaus Life Sciences, Inc.

Figure 22

EMMAUS LIFE SCIENCES, INC.

CONDENSED CONSOLIDATED BALANCE SHEETS

(In thousands, except share and per share amounts)

(Unaudited)

	As of	
	September 30, 2022	December 31, 2021
ASSETS		
CURRENT ASSETS		
Cash and cash equivalents	$ 1,179	$ 2,279
Accounts receivable, net	1,491	1,040
Inventories, net	2,739	4,392
Prepaid expenses and other current assets	973	1,380
Total current assets	6,382	9,091
Property and equipment, net	79	147
Equity method investment	16,594	17,616
Right of use assets	2,944	3,485
Investment in convertible bond	15,943	26,100
Other assets	259	295
Total assets	$ 42,201	$ 56,734
LIABILITIES AND STOCKHOLDERS' DEFICIT		
CURRENT LIABILITIES		
Accounts payable and accrued expenses	$ 11,134	$ 9,189
Operating lease liabilities, current portion	653	740
Conversion feature derivative, notes payable	4,272	7,507
Other current liabilities	2,270	4,404
Revolving line of credit from related party	400	400
Warrant derivative liabilities	33	1,503
Notes payable, current portion, net of discount	5,635	2,399
Notes payable to related parties	2,780	800
Convertible notes payable, net of discount	14,346	10,158
Total current liabilities	41,523	37,100
Operating lease liabilities, less current portion	2,764	3,261
Other long-term liabilities	32,122	33,173
Notes payable, less current portion	—	1,500
Notes payable to related parties, net	3,381	—
Convertible notes payable	—	3,150
Total liabilities	79,790	78,184
STOCKHOLDERS' DEFICIT		
Preferred stock, par value $0.001 per share, 15,000,000 shares authorized, none issued or outstanding	—	—
Common stock, par value $0.001 per share, 250,000,000 shares authorized, 49,558,501 and 49,311,864 shares issued and outstanding at September 30, 2022 and December 31, 2021, respectively	50	49
Additional paid-in capital	220,803	220,022
Accumulated other comprehensive loss	(5,905)	(255)
Accumulated deficit	(252,537)	(241,266)
Total stockholders' deficit	(37,589)	(21,450)
Total liabilities & stockholders' deficit	$ 42,201	$ 56,734

Source: Emmaus Life Sciences, Inc.

Figure 23

EMMAUS LIFE SCIENCES, INC.

CONDENSED CONSOLIDATED STATEMENTS OF CASH FLOWS

(In thousands)

(Unaudited)

	Nine Months Ended September 30,	
	2022	2021
CASH FLOWS FROM OPERATING ACTIVITIES		
Net loss	$ (10,825)	$ (9,084)
Adjustments to reconcile net loss to net cash flows used in operating activities		
Depreciation and amortization	40	44
Inventory reserve	1,240	423
Amortization of discount of notes payable and convertible notes payable	1,303	1,410
Foreign exchange adjustments	5,072	1,415
Net gain on investment in marketable securities	133	—
Loss on equity method investment	1,490	1,999
Loss on debt extinguishment	421	1,172
Gain on disposal of property and equipment	—	(1)
Loss on leased assets	22	—
Share-based compensation	13	548
Shares issued for services	55	500
Change in fair value of warrant derivative liabilities	(1,341)	322
Change in fair value of conversion feature derivative, notes payable	(3,235)	1,132
Net changes in operating assets and liabilities		
Accounts receivable	(485)	(2,469)
Inventories	390	404
Prepaid expenses and other current assets	148	202
Other non-current assets	446	417
Income tax receivable and payable	28	15
Accounts payable and accrued expenses	1,479	(173)
Other current liabilities	(3,199)	242
Other long-term liabilities	55	(637)
Net cash flows used in operating activities	(6,750)	(2,119)
CASH FLOWS FROM INVESTING ACTIVITIES		
Sale of convertible bond	2,919	—
Purchases of property and equipment	(18)	(11)
Loan to equity method investee	(4,226)	(5,241)
Net cash flows used in investing activities	(1,325)	(5,252)
CASH FLOWS FROM FINANCING ACTIVITIES		
Proceeds from notes payable issued, net of issuance cost	4,283	—
Proceeds from notes payable issued, net of issuance cost, related party	5,469	1,000
Proceeds from convertible notes payable issued, net of issuance cost and discount	—	14,490
Payments of notes payable	(2,689)	(1,079)
Payments of convertible notes	—	(7,200)
Net cash flows provided by financing activities	7,063	7,211
Effect of exchange rate changes on cash	(88)	(6)
Net decrease in cash, cash equivalents and restricted cash	(1,100)	(166)
Cash, cash equivalents and restricted cash, beginning of period	2,279	2,487
Cash, cash equivalents and restricted cash, end of period	$ 1,179	$ 2,321
SUPPLEMENTAL DISCLOSURES OF CASH FLOW ACTIVITIES		
Interest paid	$ 817	$ 840
Income taxes paid	$ 16	$ 43
NON-CASH INVESING AND FINANCING ACTIVITIES		
Debt discount due to embedded derivative	$ 68	$ 5,555
Debt discount due to deferred financing cost	$ 213	$ —
Debt discount due to warrants	70	—

Source: Emmaus Life Sciences, Inc.

Risks and Disclosures

This Executive Informational Overview® (EIO) has been prepared by Emmaus Life Sciences, Inc. ("Emmaus" or "the Company") with the assistance of Crystal Research Associates, LLC ("CRA") based upon information provided by the Company. CRA has not independently verified such information. Some of the information in this EIO relates to future events or future business and financial performance. Such statements constitute forward-looking information within the meaning of the Private Securities Litigation Act of 1995. Such statements can only be predictions and the actual events or results may differ from those discussed due to the risks described in Emmaus' statements on forms filed from time to time.

The content of this report with respect to Emmaus has been compiled primarily from information available to the public released by the Company through news releases and other filings. Emmaus is solely responsible for the accuracy of this information. Information as to other companies has been prepared from publicly available information and has not been independently verified by Emmaus or CRA. Certain summaries of activities and outcomes have been condensed to aid the reader in gaining a general understanding. CRA assumes no responsibility to update the information contained in this report. In addition, for year one of its agreement, CRA has been compensated by the Company in cash of forty-five thousand dollars and five hundred thousand warrants for its services in creating this report and for quarterly updates.

Investors should carefully consider the risks and information about Emmaus' business, as described below. Investors should not interpret the order in which considerations are presented in this or other filings as an indication of their relative importance. In addition, the risks and uncertainties overviewed in the accompanying section are not the only risks that the Company faces. Additional risks and uncertainties not presently known to Emmaus or that it currently believes to be immaterial may also adversely affect the Company's business. If any of such risks and uncertainties develops into an actual event, Emmaus' business, financial condition, and results of operations could be materially and adversely affected.

This report is published solely for information purposes and is not to be construed as an offer to sell or the solicitation of an offer to buy any security in any state. Past performance does not guarantee future performance. For more complete information about the risks involved of investing in the Company, as well as for copies of this report, please contact Emmaus by calling (310) 214-0065.

Risks Related to the Company's Business

Emmaus has operated at a loss and may continue to operate at a loss for the foreseeable future.

The Company realized comprehensive loss of $17.3 million for the year ended December 31, 2021, compared to comprehensive income of $2.6 million for the year ended December 31, 2020, and has historically operated at a loss due to substantial expenditures related to commercialization of Endari®, pursuit of marketing authorization of Endari® outside the U.S., research and development of its other product candidates, interest on outstanding indebtedness, and general and administrative expenses. While Emmaus anticipates increased net revenues as expands its commercialization of Endari® in the U.S. through telehealth and other initiatives, as well as in the MENA region, there is no assurance that the Company will be able to increase Endari® sales or attain sustainable profitability or that it will have sufficient capital resources to fund Company operations until it is able to generate sufficient cash flow from operations.

The Company is dependent on financing to sustain its operations and there is substantial doubt regarding its ability to continue as a going concern.

Unless and until Emmaus becomes profitable, the Company will continue to depend upon proceeds from related-party loans, sales of its debt or equity securities (including the exercise of options and warrants) or other financing arrangements, and to a lesser extent, upon payments from potential strategic partners and licensees, to generate funds needed to finance its business and operations. As of December 31, 2021, Emmaus had cash and cash equivalents of $2.3 million and a working capital deficit of $28 million. Depending upon future results of operations and other factors, the Company will need additional financing to fund its business and operations, including its commitment to provide funding to EJ Holdings, Inc. and will continue to be dependent on future financing until such time, if ever, as the Company can generate sufficient revenues to become profitable.

Emmaus has no current understanding or arrangement to obtain any additional financing.

Accordingly, the Company may not be able to obtain future financing on favorable terms, or at all. If the Company is unable to obtain needed future financing, it may have to curtail some of its business activities or modify its business plans and may be unable to repay the outstanding indebtedness or continue providing funding to EJ Holdings, Inc.

Because Emmaus did not timely file its Annual Report on Form 10-K for the year ended December 31, 2020 and Quarterly Reports for 2021 under the Securities Exchange Act of 1934, as amended (the "Exchange Act"), it is ineligible to utilize the short-form Registration Statement on Form S-3 for the public offer and sale of securities until it has timely filed all required reports under the Exchange Act for the 12 months prior to filing a Registration Statement on Form S-3. The inability to utilize Form S-3 may adversely impact the Company's ability to raise capital in a timely manner and increase transaction costs. In light of the foregoing, there is substantial doubt regarding its ability to continue as a going concern and the report of the Company's independent public accounting firm on its financial statements as of and for the year ended December 31, 2021 contains a going concern qualification.

Emmaus is dependent on the commercial success of its only approved product, Endari®.

Its ability to become profitable will depend upon the commercial success of Endari®. In addition to the risks discussed elsewhere in this section, Emmaus's ability to generate future revenues from Endari® sales will depend on a number of factors, including, but not limited to:

- the efficacy and safety of Endari®;
- the achievement of broad market acceptance and coverage by third-party payors for Endari®;
- the effectiveness of the Company's in-house commercialization team and distribution partners and other efforts in successfully marketing and selling Endari®;
- the Company's ability to effectively work with physicians to ensure that their patients have access to Endari® and fill and refill prescriptions to adhere to their twice daily regimen;
- the Company's ability to compete effectively against competing products, including hydroxyurea, Oxbryta™ (voxelotor) and Adakveo® (crizanlizumab) and potential generic products;
- the Company's contract manufacturers' ability to successfully manufacture commercial quantities of Endari® at acceptable cost levels and in compliance with regulatory requirements;
- the Company's ability to maintain a cost-efficient commercial organization and, to the extent it seeks to do so, successfully partner with third parties; and
- the Company's ability to comply with ongoing regulatory requirements.

Because of the numerous risks and uncertainties associated with Emmaus' commercialization efforts, the Company is unable to predict the extent of revenues that it will generate from Endari® sales or the timing for when or the extent to which it will become and continue to be profitable, if ever. Even if the Company achieves increased net revenues from Endari® sales and becomes profitable, it may not be able to sustain revenues or maintain or increase its profitability on an ongoing basis.

The COVID-19 pandemic may adversely affect the Company's revenues, results of operations, and financial condition and the market price of Emmaus' common stock.

Although the Company believes the COVID-19 pandemic and ongoing epidemic and governmental responses have not had a material adverse effect on its Endari® sales to date, COVID-19 or future official responses may deter or prevent sickle cell disease, or SCD, patients from traveling to see their doctors or filling or refilling their prescriptions for Endari®, which could cause a temporary or prolonged decline in revenues and have a material adverse effect on results of operations and financial condition.

COVID-19 or the governmental response may adversely affect the timing and conduct of clinical studies or the ability of regulatory bodies to consider or grant approvals with respect to Endari® or the Company's prescription grade L-glutamine drug candidates or oversee the development of Emmaus' drug candidates, may further divert the attention and efforts of the medical community to coping with COVID-19, and disrupt the marketplace in which the Company operates. For example, the Company experienced a temporary disruption in 2020 in patient enrollment in its Pilot/Phase I study of its prescription grade L-glutamine oral powder in diverticulosis, but patient enrollment has now been completed.

Emmaus may expend its limited resources to pursue a product candidate or indication and fail to capitalize on product candidates or indications for which there is a greater likelihood of commercial success.

Because Emmaus has limited financial and management resources, the Company focuses on a limited number of research programs and product candidates. As a result, it may forego or delay pursuit of opportunities with other product candidates or for other indications that later prove to have greater commercial potential. The Company's resource allocation decisions may cause it to fail to capitalize on viable product candidates or profitable market opportunities.

The Company's spending on current and future research and development programs and product candidates for the specific indications selected may not yield any commercially viable products. If Emmaus does not accurately evaluate the commercial potential or target market for a particular product candidate, it may relinquish valuable rights to that product candidate through collaboration, licensing, or other arrangements in cases in which it would have been more advantageous for it to retain sole development and commercialization rights.

If Emmaus is unable to achieve and maintain adequate levels of coverage and reimbursement for Endari® on reasonable pricing terms, its commercial success may be severely hindered.

Successful sales of Endari® depend on the availability of adequate coverage and reimbursement from third-party payors and governmental healthcare programs, such as Medicare and Medicaid. Patients who are prescribed medicine for the treatment of their conditions generally rely on third-party payors to reimburse all or a significant portion of the costs associated with their prescription drugs. Coverage determination depends on financial, clinical, and economic outcomes that often disfavors new drug products when more established or lower cost therapeutic alternatives are already available or subsequently become available.

Although Endari® is reimbursable by the Centers for Medicare and Medicaid Services, and every state provides coverage for Endari® for outpatient prescriptions to all eligible Medicaid enrollees within their state Medicaid programs, the reimbursement amounts are subject to change and may not be adequate and may require higher co-payments that patients find unacceptable. Patients are unlikely to use Endari® unless reimbursement is adequate to cover a significant portion of the cost of Endari®. Future coverage and reimbursement will likely be subject to increased pressure in the U.S.

Third-party coverage and reimbursement for Endari® may cease to be available or adequate in the U.S., which could have a material adverse effect on the Company's business, results of operations, financial condition, and prospects. In addition, the market for Endari® will depend significantly on access to third-party payors' drug formularies, which are lists of medications for which third-party payors provide coverage and reimbursement. The competition in the industry to be included in such formularies may lead to downward pricing pressures on the Company. Also, third party payors may refuse to include Endari® in their formularies or otherwise restrict patient access to Endari® if a less costly generic equivalent or other alternative treatment is available.

The majority of Endari® sales are to a few customers and loss of a customer could adversely affect the Company's results of operations.

Emmaus sells Endari® to specialty distributors and specialty pharmacies who, in turn, resell Endari® to pharmacies, hospitals, and other customers. Three of the Company's distributors account for approximately 80% of Endari sales in the year ended December 31, 2021, and the loss of any of these distributors or a material reduction in their Endari® purchases could have a material adverse effect on the Company's business, results of operations, financial condition, and prospects.

In addition, the distribution network for pharmaceutical products in the U.S. has undergone, and may continue to undergo, significant consolidation marked by mergers and acquisitions. As a result, a smaller number of large distributors control a significant share of the market, which has increased, and may continue to increase competitive and pricing pressures on pharmaceutical products. There is no assurance that Emmaus can manage these pricing pressures or that specialty distributor and specialty pharmacy purchases will not fluctuate unexpectedly from period to period.

The market exclusivity for SCD in the U.S. is limited and Endari® will have no market exclusivity in the United Arab Emirates, where it was recently approved for marketing, or other countries in the Middle East North Africa (MENA) region where applications for marketing approval are pending, which lack of exclusivity could adversely affect the commercial success of Endari®.

The exclusivity protections that protect Endari® for use for SCD are limited in ways that may affect the Company's ability to effectively exclude third parties from competing against it. In particular:

- Orphan Drug market exclusivity protection for Endari® for SCD will expire in the U.S. July 7, 2024;

- Orphan Drug designation does not preclude the FDA from granting Orphan Drug designation to another sponsor developing the same drug for the same indication, granting Orphan Drug designation and approving such other drug after Emmaus receives approval, if such drug is considered clinically superior to its product, approving a product that is the same as Emmaus' product for a different indication, or approving a different product intended to treat SCD; in this regard, Global Blood Therapeutics, Inc.'s Oxbryta™ for treating SCD also has been granted Orphan Drug status in the U.S. and in the EU;

- Orphan Medicinal status in the EU is subject to exclusions similar to those in the U.S.; and

- there are many countries, including some key markets for Endari® in the MENA region, in which Emmaus does not have intellectual property protection and where neither orphan drug designation nor data exclusivity is available.

These limitations and any reductions in the Company's expected protection, including other products that could be approved by FDA under the Orphan Drug Act, may subject Endari® to greater competition than the Company expects and could adversely affect its ability to generate revenue from Endari®, perhaps materially. These circumstances may also impair Emmaus' ability to obtain license partners or other international commercialization opportunities on terms acceptable to it, if at all.

A variety of risks associated with marketing Endari® internationally could hurt the Company's business.

Emmaus recently received marketing authorization for Endari in the United Arab Emirates and is seeking regulatory approval for Endari® for SCD in other countries in the MENA region, but may not be successful. For example, in January 2018, the European Medicines Agency, or EMA, provided their agreement on the pediatric investigation plan (PIP) for the Company's prescription grade L-glutamine oral powder in SCD and Emmaus filed with the EMA an application for marketing authorization (MAA) in the EU.

In May 2019, the Company announced that the EMA's Committee for Medicinal Products for Human Use, or CHMP, had adopted a negative opinion regarding the Company's MAA based upon the CHMP's position that Emmaus main clinical study did not conclusively support the efficacy of the treatment in SCD patients. In light of the CHMP's opinion, Emmaus withdrew its MAA in September 2019 to consider pursuing alternative decentralized and centralized regulatory pathways for obtaining marketing authorization in the EU or one or more EU countries. There is no assurance that the Company will be successful in obtaining marketing authorization in the EU or other jurisdictions outside the U.S.

If Emmaus obtains marketing authorization, the Company expects that it will be subject to additional risks related to operating in foreign countries including:

- business interruptions resulting from geopolitical actions, including war such as the recent Russian invasion of Ukraine or terrorism or actual or potential public health emergencies, including the COVID-19 epidemic;
- differing regulatory requirements in foreign countries, such as lack of orphan designation or other market exclusivity;
- the potential for parallel importing (i.e., when a local seller faced with high or higher local prices opts to import goods from a foreign market with low or lower prices rather than buying them locally);
- unexpected changes in tariffs, trade barriers, price and exchange controls and other regulatory requirements;
- economic weakness, including inflation or political instability in particular foreign markets;
- compliance with tax, employment, immigration, and labor laws for employees living or traveling abroad;
- foreign taxes, including withholding of payroll taxes;
- foreign currency fluctuations, which could result in increased operating expenses and reduced revenues, and other obligations related to doing business in another country;
- difficulties staffing and managing foreign operations;
- workforce uncertainty in countries where labor unrest is more common than in the U.S.;
- potential liability under the U.S. Foreign Corrupt Practices Act or comparable foreign regulations;
- challenges enforcing the Company's contractual and intellectual property rights, especially in foreign countries that do not respect and protect intellectual property rights to the same extent as the U.S.; and
- production shortages resulting from any events affecting raw material supply or manufacturing capabilities abroad.

These and other risks associated with international operations may compromise Emmaus' ability to achieve or maintain profitability.

The Company may not be able to anticipate the demand for and appropriate supply of Endari®.

Emmaus monitors its distributors' inventories of Endari® using a combination of methods. However, the Company's estimates of distributor inventories may differ significantly from actual inventory levels. Significant differences between actual and estimated inventory levels may result in excessive production (requiring the Company to hold substantial quantities of unsold inventory, which may result in the establishment of inventory reserves or actual write offs of expired inventory), inadequate supplies of products in distribution channels, insufficient product available at the retail level, and unexpected increases or decreases in orders from the Company's specialty distributors.

For example, as of December 31, 2021, Emmaus established a $2.9 million reserve against possible future inventory write offs. These changes may cause its revenues to fluctuate significantly from quarter to quarter, and in some cases may cause operating results for a quarter to be below expectations. In addition, the Company sometimes offers price discounts to its customers in advance of Endari® price increases, including a price increase implemented as of March 1, 2021, or as an incentive for bulk orders of Endari®. Such discounts may result in specialty distributor purchases in excess of customer demand, resulting in reduced specialty distributor purchases in later periods and substantial fluctuations in the Company's results of operations from period to period. Sales attributable to one-time discounts offered by Emmaus increased in 2021 versus 2020 and may adversely affect sales in subsequent periods. If financial results are below analysts' or investors' expectations, the market price of the Company's common stock may be adversely affected.

If the L-glutamine manufacturer upon which the Company relies fails to produce in the volumes and quality that Emmaus requires on a timely basis or fails to comply with stringent regulations applicable to pharmaceutical manufacturers, Emmaus may face interruptions in the commercialization of or be unable to meet demand for its L-glutamine based products, and may lose any marketing exclusivity and potential revenues.

Emmaus does not currently have its own manufacturing capabilities and depends upon a single Japanese supplier, Ajinomoto Aminoscience, LLC, or Ajinomoto for commercial supplies of Endari® and clinical supplies of PGLG used in its product candidates under development. The Company intends to continue to rely on Ajinomoto to produce its pharmaceutical grade L-glutamine but has not entered into, and may not be able to establish, long-term supply agreements with this key supplier on acceptable terms. Furthermore, pursuant to a letter of intent with Ajinomoto, Emmaus has agreed to purchase from Ajinomoto substantially all of the L-glutamine that it will need for its commercial products. If Ajinomoto were to experience any manufacturing or production difficulties producing prescription grade L-glutamine, or Emmaus was unable to purchase sufficient quantities of PGLG on acceptable terms, it could interrupt sales of Endari® and have a material, adverse effect on Emmaus' financial condition and results of operations.

In addition, all manufacturers, packers, distributors, and suppliers of pharmaceutical products must comply with applicable cGMP regulations for the manufacture of pharmaceutical products, which are enforced by the FDA through its facilities inspection program. If the Company's manufacturers and key suppliers are not in compliance with cGMP requirements, it may result in a delay of approval for products undergoing regulatory review or the inability to meet market demands for any approved products, particularly if these sites are supplying single source ingredients required for the manufacture of any potential product.

Furthermore, each manufacturing facility used to manufacture drug or biological products is subject to FDA inspection and must meet cGMP requirements. As a result, if one of the manufacturers that the Company relies on shifts production from one facility to another, the new facility must undergo a preapproval inspection and, for biological products, must be licensed by regulatory authorities prior to being used for commercial supply. Failure to comply with any applicable manufacturing requirements, including cGMP requirements, could delay or prevent the promotion, marketing, or sale of the Company's products.

If the FDA or any other applicable regulatory authorities do not approve the facilities for the manufacture of Endari® or if they withdraw any such approval in the future, Emmaus may need to find alternative manufacturing facilities, which would significantly impact its ability to commercially supply Endari®. If the safety of any quantities supplied is compromised due to a third-party manufacturer's failure to comply with or adhere to applicable laws or

for other reasons, the Company may be liable for injuries suffered by patients who have taken such products and Emmaus may not be able to obtain regulatory approval for or successfully commercialize its products.

The Company expects to rely on third parties to conduct future clinical trials of its product candidates and those third parties may not perform satisfactorily, including failing to meet deadlines for the conduct of such trials.

Emmaus has engaged a third-party contract research organization (CRO) to conduct its clinical trials for Endari® and expects to engage a CRO to conduct any further required clinical trials of Endari® and any clinical trials with respect to any of its product candidates that may progress to clinical development. The Company expects to continue to rely on third parties, such as CROs, clinical data management organizations, medical institutions, and clinical investigators, to conduct those clinical trials. Agreements with such third parties might terminate for a variety of reasons, including a failure to perform by the third parties.

If Emmaus needs to enter into alternative arrangements, it could delay its product development activities. The Company's reliance on these third parties for research and development activities reduces its control over these activities but does not relieve it of its responsibilities. For example, the Company will remain responsible for ensuring that each of its clinical trials is conducted in accordance with the general investigational plan and protocols for the trial. Moreover, the FDA requires the Company to comply with standards, commonly referred to as GCPs, for conducting, recording and reporting the results of clinical trials to ensure that data and reported results are credible and accurate and that the rights, integrity, and confidentiality of trial participants are protected.

The Company is also required to register ongoing clinical trials and post the results of completed clinical trials on a government-sponsored database (www.ClinicalTrials.gov) within specified timeframes. Failure to do so can result in the FDA refusing to accept a NDA for the product candidate under study, fines, adverse publicity, and civil and criminal sanctions. Furthermore, these third parties may also have relationships with other entities, some of which may be competitors. If these third parties do not successfully carry out their contractual duties, meet expected deadlines, or conduct its clinical trials in accordance with regulatory requirements and the stated protocols, Emmaus will not be able to obtain, or may be delayed in obtaining, marketing approvals for its product candidates and will not be able to, or may be delayed in its efforts to successfully commercialize them as products.

Emmaus also expects to rely on other third parties to store and distribute supplies of its product candidates for clinical trials of them. Any performance failure on the part of the Company's distributors could delay clinical development or marketing approval of its product candidates or commercialization of them as products, producing additional losses, and depriving Emmaus of potential revenue. Delays in the commencement, enrollment, and completion of clinical trials could result in increased costs to the Company and delay in its ability to develop and obtain regulatory approval for product candidates. The commencement, enrollment, and completion of clinical trials can be delayed for a variety of reasons, including delays or difficulties in enrolling patients due to unforeseen natural disasters, public health crises, political crises, and other catastrophic events or other events outside of the Company's control, such as the recent emergence and spread of COVID-19, which may cause participants to not want to participate in these trials or otherwise have any unnecessary contact with the medical community.

Endari® may cause undesirable side effects or have other unexpected properties that could result in post-approval regulatory action.

The most common side effects seen with Endari® included constipation, nausea, headache, pain in the stomach area, cough, pain in the hands or feet, back pain, and chest pain. If Emmaus or others identify previously unknown undesirable side effects, or other previously unknown problems caused by Endari® or other products with the same or related active ingredients, a number of potentially significant negative consequences could result, including:

- regulatory authorities may withdraw their approval of Endari®;
- the Company may need to recall Endari®;
- the Company may need to add warnings or narrow the indication in the product label or to create a Medication Guide outlining the risks of such side effects for distribution to patients;
- the Company may be required to change the way Endari® is administered or modify Endari® in some other way;
- the FDA may require Emmaus to conduct additional clinical trials or costly post-marketing testing and surveillance to monitor the safety or efficacy of the product;
- the Company could be sued and held liable for harm caused to patients; and
- the Company's reputation may suffer.

Any of the above events resulting from undesirable side effects or other previously unknown problems could prevent Emmaus from achieving or maintaining market acceptance of Endari® and could substantially increase the costs of commercializing Endari®.

The Company faces potential product liability exposure relating to Endari® and, if successful claims are brought against it, may incur substantial liability if insurance coverage for those claims is inadequate.

The commercial use of Endari® will expose Emmaus to the risk of product liability claims despite the fact it is approved for commercial sale by the FDA and manufactured in facilities licensed and regulated by the FDA. Any side effects, manufacturing defects, misuse, or abuse associated with Endari® could result in injury to a patient or even death and product liability claims against it. In addition, a liability claim may be brought against the Company even if Endari® merely appears to have caused an injury.

Product liability claims may be brought against Emmaus by consumers, healthcare providers, pharmaceutical companies, or others selling or otherwise coming into contact with Endari® and the Company could incur substantial liabilities. In addition, regardless of merit or eventual outcome, product liability claims may result in:

- decreased demand for Endari®;
- impairment of its business reputation;
- recall or withdrawal of Endari® from the market;
- costs related to litigation;
- distraction of management's attention from the Company's business;
- substantial monetary awards to patients or other claimants; or
- loss of revenues.

Emmaus maintains product liability insurance coverage and carries commercial excess and umbrella coverage, but its insurance coverage may not be sufficient to cover product liability related expenses or losses and may not cover the Company for any consequential expenses or losses Emmaus may suffer. The Company may not be able to continue to maintain insurance coverage at a reasonable cost, in sufficient amounts, or upon adequate terms to protect it against losses due to product liability.

Large judgments have been awarded in class action or individual lawsuits based on drugs that had unanticipated side effects, including side effects that are less severe than those of Endari®. Successful product liability claims against Emmaus could cause the value of the Company's common stock to decline and, if judgments exceed the Company's insurance coverage, reduce its cash and have a material adverse effect business, results of operations, financial condition, and prospects.

The use of any of the Company's product candidates in clinical trials and in the market may expose Emmaus to liability claims.

Emmaus is exposed to potential liability risks inherent in the testing and manufacturing of its product candidates and marketing of any products. While in clinical stage testing, its product candidates could potentially harm people or allegedly harm people and Emmaus may be subject to costly and damaging product liability claims. Informed consent and contractual limitations on payments for subject injury or waivers obtained may not be enforceable and may not protect the Company from liability or the costs of product liability litigation.

While Emmaus carries clinical product liability insurance, it may not be sufficient to cover future claims. In addition, in some cases the contractors on which the Company relies for manufacturing its product candidates may indemnify the Company for third-party claims brought against it arising from matters for which these contractors are responsible. Emmaus could be materially and adversely affected if it were required to pay damages or incur defense costs in connection with a claim outside the scope of indemnity or insurance coverage if the indemnity is not performed or enforced in accordance with its terms, or if Emmaus' liability exceeds the amount of applicable insurance or indemnity. In addition, there can be no assurance that insurance will continue to be available in amounts and on terms acceptable to the Company, if at all, to cover any potential claims or liabilities.

The Company will need to increase the size and complexity of its organization in the future, and may experience difficulties in managing its growth and executing its growth strategy.

Emmaus will need to expand its scientific, sales and marketing, managerial, operational, financial and other resources to support its planned commercialization activities. Continued operations and growth require that the Company manage its commercialization activities for Endari® and product development efforts successfully and in a cost effective manner. The Company will also need to continue to improve its operational, financial, management, and regulatory compliance controls and reporting systems and procedures.

The Company will need to attract and retain sufficient talented employees and scientific collaborators.

Historically it has utilized, and continues to utilize, part-time outside consultants to perform certain tasks, including tasks related to accounting and finance, compliance programs, clinical trial management, regulatory affairs, formulation development, and other drug development functions. The Company's growth strategy related to Endari® may entail expanding its use of consultants to implement these and other tasks going forward. There can be no assurance that Emmaus will be able to manage existing consultants or engage other competent consultants, as needed, on economically reasonable terms.

In addition, the Company has scientific and clinical advisors who assist it in commercialization strategies for Endari® and its other product development efforts, including development of new medical indications for L-glutamine-based products. Although the Company has established research collaborations, it cannot provide assurance that its relationships with its research collaborators and scientific and clinical advisors will continue or that Emmaus will be able to attract additional research partners and advisors. Without such scientific relationships to assist in the Company's research and development, Emmaus may not be able to successfully develop its product candidates or expand its product offerings.

Emmaus relies heavily on Yutaka Niihara, M.D., M.P.H., its Chairman and Chief Executive Of icer, and the loss of his services would have a material adverse effect upon the Company's business and prospects.

Emmaus' success depends to a significant extent upon the continued services of Yutaka Niihara, M.D., M.P.H., the Company's founder and Chairman and Chief Executive Officer. The loss of Dr. Niihara's services could materially and adversely affect the Company's business and prospects. Emmaus does not maintain key man life insurance on Dr. Niihara or any of its other executive officers.

Emmaus' business and operations may be adversely affected by information technology (IT) system failures or cybersecurity or data breaches.

Emmaus relies on IT networks and systems, including those of third-party service providers, to collect, process, store and transmit confidential information including, but not limited to, personal information and intellectual property for a variety of functions including, but not limited to, conducting clinical trials, financial reporting, data and inventory management. The Company also outsources certain services, including recruiting services, call center services, contract sales organization services, and other ancillary services relating to the commercial marketing and sale of Endari® in the U.S., as well as significant elements of its IT security systems, and as a result, the Company's service providers have access to Emmaus' confidential information.

Despite the implementation of security measures and recovery plans, the Company's network and information systems and those of third-party service providers may be vulnerable to damage from computer viruses, cyberattacks, physical or electronic break-ins, service disruptions, and security breaches from inadvertent or intentional actions by Company employees or vendors, or from attacks by malicious third parties.

While Emmaus has not experienced any such system failure or security breach to date, if such an event were to occur, its operations may be disrupted, and the Company may suffer from economic loss, reputational harm, regulatory actions or other legal proceedings. Further, such breaches and other inappropriate access can be difficult to detect, and any delay in identifying them may lead to increased risks of the actions described above. The Company expects that risks and exposures related to cybersecurity breaches will remain high for the foreseeable future due to the rapidly evolving nature and sophistication of these threats.

Historical material weaknesses in internal controls over financial reporting have not been fully remediated.

Any material weaknesses in internal control over financial reporting could result in errors in the Company's consolidated financial statements, which could erode market confidence in the Company, adversely affect the market price of its common stock and, in egregious circumstances, result in possible claims based upon such financial information.

The Company's business may be adversely impacted by the consequences of Russia's invasion of Ukraine.

The United States, United Kingdom and European Union governments, among others, have instituted various sanctions and export-control measures in response to the invasion, including comprehensive financial sanctions, targeted at Russia or designated individuals and entities with business interests or government connections to Russia or those involved in Russian military activities. Governments have also enhanced export controls and trade sanctions targeting Russia's imports of goods. The duration and intensity of this conflict and its potential impact on the Company's business or operations is uncertain at this time, but it is possible that the business and operations could be adversely affected.

Risks Related to the Company's Intellectual Property

Emmaus may not be able to obtain and enforce intellectual property rights that cover its commercial activities or are sufficient to prevent third parties from competing against it. The Company's success with respect to Endari® will depend, in part, on its ability to preserve its trade secrets and to prevent third parties from infringing upon its proprietary rights since the Company does not have (and does not expect to be able to obtain) composition of matter patents or methods of use patents that cover Endari®.

In particular, the patent for the use of L-glutamine to treat SCD expired in May 2016 and the Company's license to the patent terminated. This means that its competitors are free to utilize processes, technologies, and methods that were previously protected by the SCD patent to potentially develop competing products. While Emmaus has an Orphan Drug designation for the use of L-glutamine for the treatment of SCD in the U.S., the Company's Orphan Drug exclusivity will expire in July 2024 and may be lost sooner if another L-glutamine product for the same indication demonstrates clinical superiority. If the Company's competitors develop alternative L-glutamine products, it may have a material, adverse effect on Emmaus' business and results of operations.

In addition to seeking patents for its intellectual property, Emmaus also relies on trade secrets, including unpatented know-how, technology, and other proprietary information, in its business. The Company seeks to protect its trade secrets, in part, by entering into non-disclosure and confidentiality agreements with parties who have access to them, such as Company employees, corporate collaborators, outside scientific collaborators, contract manufacturers, consultants, advisors, and other third parties. Despite these efforts, any of these parties may breach the agreements and disclose the Company's proprietary information, including its trade secrets, and remedies thereunder may not be adequate. Enforcing a claim that a party illegally disclosed or misappropriated a trade secret is difficult, expensive, and time consuming, and the outcome is unpredictable. Some courts inside and outside the U.S. are less willing or unwilling to protect trade secrets. In addition, if any of Emmaus' trade secrets were to be lawfully obtained or independently developed by a competitor, the Company would have no right to prevent them, or those to whom they communicate it, from using that technology or information to compete with it.

Although Emmaus expects all its employees to assign their inventions to the Company, and all its employees, consultants, advisors, and any third parties who have access to its proprietary know-how, information, or technology to enter into confidential information and invention agreements, the Company cannot provide any assurances that all such agreements have been duly executed or will be enforceable.

The Company depends on licenses of certain patents for the development of some of its product candidates. If any of these licenses terminate, or if any of the licensed patents is successfully challenged, Emmaus may be unable to continue the development of the affected product candidates.

The Company's ability to develop certain product candidates depends on an exclusive license it has obtained to patents that claim the use of Kainos's KM10544 IRAK4 inhibitor to treat cancers. The license could be terminated if Emmaus fails to satisfy its obligations under it. In the event any claims in the patents that the Company has been licensed are challenged, the court or patent authority could determine that such patent claims are invalid or unenforceable or not sufficiently broad in scope to protect its proprietary rights. As the licensee of such patents, the Company's ability to participate in the defense or enforcement of such patents could be limited.

If Emmaus is unable to protect proprietary technology that it invents and develops, the Company may not be able to compete effectively and its business and financial prospects may be harmed.

Where appropriate, Emmaus seeks patent protection for inventions it conceives and reduces to practice, however, patent protection may be limited or not available for all these inventions. In addition, the Company may need to design around patents held by others. If Emmaus must spend significant time and money protecting its patents, designing around patents held by others, or in-licensing patent or other proprietary rights held by others, potentially for large fees, its business and financial prospects may be harmed.

The patent prosecution process is expensive and time consuming, and the Company may not be able to file and prosecute all necessary or desirable patent applications at a reasonable cost or in a timely manner. It is also possible that Emmaus will fail to identify patentable aspects of its research and development output before it is too late to obtain patent protection. The Company may also have to relinquish to strategic partners or other third parties to whom its license its technology the right to control the preparation, filing, and prosecution of patent applications claiming its inventions and to maintain any resulting patents.

Therefore, patent applications and patents claiming the Company's inventions may not be prosecuted and enforced in a manner consistent with the best interests of its business.

Emmaus' pending and future patent applications may not result in patents being issued that protect its product candidates, in whole or in part, or which effectively prevent others from commercializing competitive product candidates. Changes in either the patent laws or interpretation of the patent laws in the U.S. and other countries may diminish the value of the Company's patents or narrow the scope of its patent protection.

Even if Emmaus' patent applications issue as patents, they may not issue in a form that will prevent competitors from competing with it or otherwise provide the Company with any competitive advantage. Competitors may be able to circumvent the Company's patents by developing similar or alternative treatments in a non-infringing manner.

As well, the issuance of a patent is not conclusive as to its inventorship, scope, validity, or enforceability, and the Company's patents may be challenged in the courts or patent offices in the U.S. and abroad. Such challenges may result in loss of exclusivity, freedom to operate, and/or in patent claims being narrowed, invalidated, or held unenforceable, in whole or in part, which could limit Emmaus' ability to prevent others from commercializing products similar or identical to its product candidates or products, or limit the duration of the patent protection of its product candidates or products. Given the amount of time required for the development, testing, and regulatory review of new therapeutics, patents protecting the Company's product candidates might expire before or shortly after such candidates are commercialized as products. For example, Emmaus' patent protection for Endari® expired in May 2016. As a result, its patent portfolio may not provide sufficient rights to exclude others from commercializing products similar or identical to its products.

Risks Related to Regulatory Oversight of the Company's Business and Compliance with Law

Endari® is subject to ongoing and continued regulatory review, compliance with which may result in significant expense and limit the Company's ability to commercialize Endari®.

Emmaus is subject to ongoing FDA obligations and continued regulatory review with respect to the manufacturing, processing, labeling, packaging, distribution, adverse event reporting, storage, advertising, promotion, and recordkeeping for Endari®. These requirements include submission of safety and other post-marketing information and reports, as well as continued compliance with good clinical practices and good laboratory practices or cGMPs. In addition, its product advertising and promotion are subject to regulatory requirements and continuing regulatory review. The FDA strictly regulates the promotional claims that may be made about prescription drug products. In particular, a drug product may not be promoted for uses that are not approved by the FDA as reflected in the product's approved labeling, although the FDA does not regulate the prescribing practices of physicians.

Manufacturers of drug products and their facilities are subject to continual review and periodic inspections by the FDA and other regulatory authorities for compliance with cGMP regulations. If Emmaus or a regulatory agency discovers previously unknown problems with a product, such as adverse events of unanticipated severity or frequency, or problems with the facility where, or processes by which, the product is manufactured, a regulatory agency may impose restrictions on that product, the manufacturer or the Company, including requiring product recall, notice to physicians, withdrawal of the product from the market, or suspension of manufacturing.

The FDA's regulations, policies, or guidance may change, and new or additional statutes or government regulations may be enacted that could further restrict or regulate post-approval activities relating to the Company's commercialization of Endari®. Emmaus cannot predict the likelihood, nature or extent of adverse government regulation that may arise from future legislation or administrative action. If the Company is unable to achieve and maintain regulatory compliance, it may not be permitted to market Endari®, which would adversely affect its ability to generate revenue and achieve or maintain profitability.

Emmaus may not be able to receive regulatory approval of PGLG treatment for diverticulosis or other indications, which would adversely affect its financial and operating condition.

All the Company's product candidates are still in preclinical or early-stage clinical development. Regulatory approval is required to market its prescription grade L-glutamine treatment for diverticulosis or other indications and for any other product candidates Emmaus may develop. Even if the FDA and other regulatory authorities approve the Company's PGLG treatment for diverticulosis, or any of its other product candidates, the manufacture, packaging, labeling, distribution, marketing, and sale of such products will be subject to strict and ongoing post-approval regulations. Compliance with such regulations will be expensive and consume substantial financial and management resources.

The FDA has the authority to regulate the claims made in marketing the Company's prescription products to ensure that such claims are true, not misleading, supported by scientific evidence, and consistent with the approved labeling of those products. Failure to comply with FDA requirements in this regard could result in, among other things, warning letters, withdrawal of approvals, seizures, recalls, injunctions prohibiting a product's manufacture and distribution, restricting promotional activities, requiring corrective actions regarding sales and marketing activities, other operating restrictions, civil money penalties, disgorgement, and criminal prosecution. As well, if Emmaus makes any marketing claims that are related to a healthcare provider's unlawful submission for reimbursement from government programs, the Company could be subject to potential liability for violations of the False Claims Act, which may lead to disqualification from government programs or criminal prosecution, or both. Any of these government enforcement actions, if taken against it, could negatively impact the Company's product sales and profitability.

Additionally, regulatory approval of any of the Company's prescription products may be conditioned on its agreement to conduct costly post-marketing follow-up studies to monitor the safety or effectiveness of such products or to implement specific risk mitigation strategies. In addition, as clinical experience with any of the Company's products following such approval, if any, expands after approval because the product is used by a greater number and more diverse group of patients than during clinical trials, unknown side effects or other problems may be observed that were not observed or anticipated during pre-approval clinical trials. In any such case, one or more regulatory authorities could require additional risk information be added to the labeling of the product, restrict the indications for which the product may be sold, restrict the distribution channels, or revoke the product's regulatory approval, which could hinder Emmaus' ability to generate revenues from that product. If the Company fails to develop and commercialize its product candidates as planned, financial results and financial conditions will be adversely affected, the Company will have to delay or terminate some or all of its research product development programs, and it may be forced to cease operations.

The development process to obtain FDA approvals for new drugs therapies is very costly and time consuming and if Emmaus cannot complete its clinical trials in a cost effective manner, its operations may be adversely affected.

Prior to obtaining marketing approval from regulatory authorities for the sale of any product candidate, Emmaus or a collaborator must complete preclinical development and then complete one or more extensive clinical trials to demonstrate the safety and effectiveness of the product candidate in humans. Clinical testing is expensive, difficult to design and implement, can take many years to complete and is uncertain as to outcome. Costs of clinical trials may vary significantly over the life of a development project.

- the number of patients that participate in the trials;
- the per patient trial costs;
- the number of sites and clinical investigators involved in the trials;
- the number and types of trials and studies that may need to be performed;
- the length of time required to recruit, screen, and enroll eligible patients;
- the duration of the clinical trials;
- the countries in which the trials are conducted;
- the number of doses that patients receive;
- adverse events experienced by trial participants;
- the drop out or discontinuation rates of patients;
- potential additional safety monitoring or other studies requested by regulatory agencies;
- the extent and duration of patient follow up;
- difficulties that could arise in analyzing and reporting to regulators the results of clinical trials; and
- the efficacy and safety profile of the product candidate.

If Emmaus is unable to control the timing and costs of its clinical trials and conduct its trials and apply for regulatory approvals in a timely and cost-effective manner, the Company's operations may be adversely affected.

The Company's product development costs will also increase if any regulatory agencies impose a clinical hold on any of its clinical studies or if Emmaus experiences delays in obtaining marketing approvals, particularly if it is required to conduct additional clinical studies beyond those that it submits in any NDA. The Company does not know whether any of its preclinical studies or clinical trials will begin as planned, will need to be restructured or will be completed on schedule, or at all. Significant preclinical study or clinical trial delays also could shorten any periods during which the Company may have the exclusive right to commercialize its approved product candidates or allow competitors to bring products to market before it does, and thereby impair Emmaus' ability to successfully commercialize its product candidates.

The Company may not be able to complete clinical trial programs for any of its product candidates successfully within any specific time period or at all, and if such clinical trials take longer to complete than projected, its ability to execute the Company's current business strategy will be adversely affected.

Clinical testing is costly, difficult to design and implement, can take many years to complete, and is uncertain as to outcome. A failure of one or more clinical trials can occur at any stage of development. The outcome of preclinical testing and early clinical trials may not be predictive of the success of later clinical trials, and interim results of a clinical trial do not necessarily predict final results. Moreover, clinical data are often susceptible to varying interpretations and analyses, and many companies that have believed their product candidates performed satisfactorily in preclinical studies and clinical trials have nonetheless failed to obtain marketing approval of them.

Whether Emmaus completes its clinical trials in a timely manner, or at all, for any product candidate is dependent in part upon: (i) the date the applicable investigational new drug, or IND, becomes effective enabling it to commence the applicable clinical studies (which, under U.S. law, occurs no more than 30 days after the FDA receives the IND, unless the FDA places the IND on clinical hold, in which case the FDA may request the Company to provide additional data from completed preclinical studies or undertake additional preclinical studies, the latter of which could materially delay the clinical and regulatory development of the applicable product candidate); (ii) the engagement of clinical trial sites and clinical investigators; (iii) reaching an agreement with clinical investigators on acceptable clinical trial agreement terms, clinical trial protocols or informed consent forms; (iv) obtaining approval from the institutional review boards used by the clinical trial sites Emmaus seeks to engage; (v) the rate of patient enrollment and retention; and (vi) the rate to collect, clean, lock, and analyze the clinical trial database.

Clinical trials required for demonstration of substantial evidence of effectiveness and safety often require the enrollment of large numbers of patients, and suitable patients may be difficult to identify and recruit. The Company's ability to enroll sufficient numbers of patients in its clinical trials, especially when the disease or condition being studied is rare, depends on many factors, including the size of the relevant patient population, the nature and design of the protocol, the proximity of patients to clinical sites, the eligibility and exclusion criteria applicable for the trial, existence of competing clinical trials, and the availability of already approved therapeutics for the indications being studied (whether or not such therapeutics are less safe or less effective than the Company's product candidate under trial). If Emmaus fails to enroll and maintain the number of patients for which the clinical trial was designed, the statistical significance and/or statistical power of that clinical trial may be reduced, which would make it harder to demonstrate that the product candidate being tested in such clinical trial is safe and effective for its intended use.

The Company may be required to suspend, repeat, or terminate its clinical trials if they do not meet regulatory requirements, the results are negative or inconclusive, human subject protections are inadequate, the trials are not well designed, or clinical investigators fail to comply with all requirements for the conduct of trials under the applicable IND—any of which may result in significant negative repercussions on its business and financial condition.

Emmaus cannot market a pharmaceutical product in any jurisdiction until it has completed rigorous preclinical testing and clinical trials for that product, demonstrated the product's safety and substantial evidence of effectiveness for its intended use, obtained the approval of the applicable regulatory authority for its proposed labeling of the product, and met the other requirements of such jurisdiction's extensive regulatory approval process. Preclinical testing and the conduct of clinical trials are long and costly. Data obtained from preclinical and clinical tests can be interpreted in different ways and could ultimately be deemed by regulatory authorities to be insufficient with respect to providing substantial evidence of effectiveness and safety required for regulatory approval, which could delay, limit, or prevent regulatory approval. It may take the Company many years to complete the required testing of its product candidates to support an application for marketing approval and failure can occur at any stage during this process.

Emmaus cannot provide assurance that its preclinical testing and clinical trials will be completed successfully within any time period specified by the Company, or without significant additional resources or expertise provided by third parties to conduct such testing. Emmaus cannot provide assurance that any such testing will demonstrate that its product candidates meet regulatory approval requirements for safety and effectiveness or that any such product will be approved for a specific indication. Results from early clinical trials may not be indicative of the results that will be obtained in later-stage clinical trials or in the population of patients for whom the applicable product is prescribed following any approval. In addition, negative or inconclusive results from the clinical trials conducted or adverse events experienced by the patients in such clinical trials, could cause Emmaus to have to suspend, repeat, or terminate the clinical trials. Clinical trials are subject to continuing oversight by governmental regulatory authorities and institutional review boards and must meet the requirements of these authorities, including but not limited to requirements for informed consent, human subject protection, and good clinical practices. Emmaus cannot guarantee that it will be able to comply or that a regulatory authority will agree that the Company will have complied, with such requirements.

The Company relies on third parties, such as CROs, contract laboratories, regulatory consultants, and data management companies to assist it in overseeing and monitoring clinical trials as well as to process the clinical data and manage test requests, which may result in delays or failure to complete trials if the third parties fail to perform or meet applicable regulatory requirements and standards. Failure by Emmaus or any such third parties to comply with the terms and conditions of the protocol for any clinical study or the regulatory requirements for a product candidate or to complete the clinical trials for a product candidate in the projected time frame could significantly delay or increase the cost of the Company's studies and have a material adverse effect on its business and financial condition.

There are significant requirements imposed on Emmaus and on clinical investigators who conduct clinical trials under an IND. Although the Company is responsible for selecting qualified clinical investigators, providing them with the information they need to properly investigate, ensuring proper monitoring of the investigations, and that the investigations are conducted in accordance with the general investigational plan and protocols contained in the IND, the Company cannot ensure the clinical investigators will maintain compliance with all regulatory requirements at all times. The pharmaceutical industry has experienced cases where clinical investigators have been found to incorrectly record data, omit data, or even falsify data. The Company cannot ensure that the clinical investigators in its trial will not make mistakes or otherwise compromise the integrity or validity of data, any of which would have a significant negative effect on Emmaus' ability to obtain marketing approval.

Changes in regulatory requirements and guidance or unanticipated events during the Company's clinical trials may occur, which may result in necessary changes to clinical trial protocols, informed consents, and clinical trial budgets, any of which changes could result in increased costs to Emmaus, delay its development timeline, or reduce the likelihood of successful completion of the clinical trial.

Changes in regulatory requirements or the FDA's interpretation of those requirements, which may be provided through guidance documents, or the occurrence of unanticipated events during the Company's clinical trials could require Emmaus to amend clinical trial protocols, informed consent forms, and trial budgets. If the Company experiences delays in initiation, conduct or completion of any of its clinical trials, or if Emmaus terminates any of its clinical trials due to changes in regulatory requirements or guidance documents, unexpected and serious adverse events, or other unanticipated events, the Company may incur additional costs and have difficulty enrolling subjects or achieving clinical investigator or institutional review board acceptance of the changes and successfully completing the trial. Any such additional costs and difficulties could materially harm the commercial prospects for its product candidates and delay the Company's ability to generate product revenue.

There are various uncertainties related to the research, development, and commercialization of Kainos's KM10544 IRAK4 inhibitor to treat cancers and the cell sheet engineering regenerative medicine products being developed, which could negatively affect Emmaus' ability to commercialize such products.

The Company has historically focused on the research and development of its PGLG treatment for SCD and has little or no experience in the research, development, or commercialization of potential cancer treatments, such as Kainos's KM10544 IRAK4 inhibitor or cell sheet regenerative medicine products or any other biological product. The Company is not aware of any clinical trials of cell sheet regenerative products in the U.S. or of any biological products based on cell sheet engineering that have been approved by regulatory authorities in any jurisdiction. Such products must be manufactured in conformance with current cGMP requirements as well as Good Tissue Practice (GTP) requirements and demonstrate that they are safe, pure, and potent to be effective for their intended uses to obtain FDA approval. The GTP requirements, which are specifically applicable to all cellular-based products, are intended to prevent communicable disease transmission.

It is uncertain what type and quantity of scientific data would be required to support initiation of clinical studies or to sufficiently demonstrate the safety, purity, and potency of cell sheet regenerative medicine products for their intended uses. Such uncertainties could delay Emmaus' ability to obtain FDA approval for and to commercialize such products. In addition, the research and commercialization of cell sheet regenerative medicine products could be hindered if third-party manufacturers of such products are not compliant with cGMP, GTP, and any other applicable regulations. Any delay in the development of, obtaining FDA approval for, or the occurrence of any

problems with third-party manufacturers of cell sheet regenerative medicine products would negatively affect the Company's ability to commercialize such products.

Emmaus is subject to numerous complex regulations and failure to comply with these regulations, or the cost of compliance with these regulations, may harm its business.

The research, testing, development, manufacturing, quality control, approval, labeling, packaging, storage, recordkeeping, promotion, advertising, marketing, distribution, possession, and use of Endari® are subject to regulation by numerous governmental authorities in the U.S. The FDA regulates drugs under the Federal Food, Drug and Cosmetic Act and implementing regulations. Noncompliance with any applicable regulatory requirements can result in refusal to approve products for marketing, warning letters, product recalls or seizure of products, total or partial suspension of production, prohibitions or limitations on the commercial sale of products, or refusal to allow the entering into of federal and state supply contracts, fines, civil penalties, and/or criminal prosecution. Additionally, the FDA and comparable governmental authorities have the authority to withdraw product approvals that have been previously granted. Furthermore, the regulatory requirements relating to Endari® may change from time to time, and it is impossible to predict what the impact of any such changes will be.

Healthcare reform measures and changes in policies, funding, staffing, and leadership at the FDA and other agencies could hinder or prevent the commercial success of Endari®.

In the U.S., legislative and regulatory changes to the healthcare system could affect the Company's future results of operations and the future results of operations of the Company's potential customers. For example, the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 established a Part D prescription drug benefit, under which Medicare beneficiaries can obtain prescription drug coverage from private sector plans that are permitted to limit the number of prescription drugs that are covered in each therapeutic category and class on their formularies. If Endari® is not widely included on the formularies of these plans, the Company's ability to market Endari® may be adversely affected.

As well, there have been and continue to be initiatives at the federal and state levels that seek to reduce healthcare costs. In March 2010, President Obama signed into law the Patient Protection and Affordable Health Care Act of 2010, as amended by the Health Care and Education Affordability Reconciliation Act of 2010 (jointly, the "PPACA"), which includes measures to significantly change the way healthcare is financed by both governmental and private insurers. Among the provisions of the PPACA of importance to the pharmaceutical industry are the following:

- an annual, nondeductible fee on any entity that manufactures or imports certain branded prescription drugs and biologic agents, apportioned among these entities according to their market share in certain government healthcare programs;

- an increase in the statutory minimum rebates a manufacturer must pay under the Medicaid Drug Rebate Program, retroactive to January 1, 2010, to 23% and 13% of the average manufacturer price for most branded and generic drugs, respectively;

- a new Medicare Part D coverage gap discount program, in which manufacturers must agree to offer 50% point-of-sale discounts off negotiated prices of applicable brand drugs to eligible beneficiaries during their coverage gap period, as a condition for the manufacturer's outpatient drugs to be covered under Medicare Part D (the required discount was increased to 70% on January 1, 2019 pursuant to subsequent legislation);

- extension of manufacturers' Medicaid rebate liability to covered drugs dispensed to individuals who are enrolled in Medicaid managed care organizations;

- expansion of eligibility criteria for Medicaid programs by, among other things, allowing states to offer Medicaid coverage to additional individuals and by adding new mandatory eligibility categories for certain individuals with income at or below 133% of the Federal Poverty Level, thereby potentially increasing both the volume of sales and manufacturers' Medicaid rebate liability;

- expansion of the entities eligible for discounts under the Public Health Service pharmaceutical pricing program;

- new requirements to report certain financial arrangements with physicians and teaching hospitals, as defined in the PPACA and its implementing regulations, including reporting any "transfer of value" made or distributed to teaching hospitals, prescribers, and other healthcare providers and reporting any ownership and investment interests held by physicians and their immediate family members and applicable group purchasing organizations during the preceding calendar year, with data collection required and reporting to the CMS required by the 90th day of each calendar year;

- a new requirement to annually report drug samples that manufacturers and distributors provide to physicians;

- expansion of health care fraud and abuse laws, including the False Claims Act and the Anti-Kickback Statute, new government investigative powers, and enhanced penalties for noncompliance;

- a licensure framework for follow-on biologic products;

- a new Patient-Centered Outcomes Research Institute to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research;

- creation of the Independent Payment Advisory Board which, beginning in 2014, will have authority to recommend certain changes to the Medicare program that could result in reduced payments for prescription drugs and those recommendations could have the effect of law even if Congress does not act on the recommendations; and

- establishment of a Center for Medicare Innovation at the CMS to test innovative payment and service delivery models to lower Medicare and Medicaid spending, potentially including prescription drug spending.

Additionally, individual states have become increasingly aggressive in passing legislation and implementing regulations designed to control pharmaceutical product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access, and marketing cost disclosure and transparency measures, and encourage importation from other countries and bulk purchasing. Legally mandated price controls on payment amounts by third-party payors or other restrictions could harm the Company's business, results of operations, financial condition, and prospects.

As well, regional healthcare authorities and individual hospitals are increasingly using bidding procedures to determine what pharmaceutical products and which suppliers will be included in their prescription drug and other healthcare programs. This may reduce demand for Endari® or put pressure on the Company's product pricing, which could negatively affect Emmaus' business, results of operations, financial condition, and prospects.

The commercial success of Endari® will depend, in part, upon the availability of coverage and reimbursement from third-party payors at the federal, state, and private levels. Third-party payors include governmental programs such as Medicare or Medicaid, private insurance plans and managed care plans. These third-party payors may deny coverage or reimbursement for a product or therapy in whole or in part if they determine that the product or therapy was not medically appropriate or necessary. Additionally, third-party payors have attempted to control costs by limiting coverage through the use of formularies and other cost-containment mechanisms and the amount of reimbursement for particular procedures or drug treatments.

Furthermore, given recent federal and state government initiatives directed at lowering the total cost of healthcare, Congress and state legislatures will likely continue to focus on healthcare reform, the cost of prescription drugs, and the reform of the Medicare and Medicaid programs. While Emmaus cannot predict the full outcome of any such legislation, it may result in decreased reimbursement for prescription drugs, which may further exacerbate industry-wide pressure to reduce prescription drug prices. This could harm the Company's

ability to market Endari® and generate revenues. In addition, legislation has been introduced in Congress (the Affordable and Safe Prescription Drug Importation Act) that, if enacted, would permit more widespread importation or re-importation of pharmaceutical products from foreign countries into the U.S., including from countries where the products are sold at lower prices than in the U.S. Such legislation, or similar regulatory changes, could lead to a decision to decrease prices to better compete, which could adversely affect the Company's business, results of operations, financial condition, and prospects. It is also possible that other legislative proposals having similar effects will be adopted.

Regulatory authorities' assessment of the data and results required to demonstrate safety and efficacy can change over time and can be affected by many factors, such as the emergence of new information, including on other products, changing policies and agency funding, staffing, and leadership. Emmaus cannot be sure whether future changes to the regulatory environment will be unfavorable to its business prospects.

If Emmaus fails to comply with federal and state healthcare laws, including fraud and abuse and health information privacy and security laws, the Company could face substantial penalties and its business, results of operations, financial condition, and prospects could be adversely affected.

As a pharmaceutical company, even though Emmaus does not and will not control referrals of healthcare services or bill directly to Medicare, Medicaid, or other third-party payors, certain federal and state healthcare laws and regulations pertaining to fraud and abuse and patients' rights are and will be applicable to its business. The Company could be subject to healthcare fraud and abuse and patient privacy regulation by both the federal government and the states in which it conducts its business. The laws that may affect its ability to operate include:

- the federal Anti-Kickback Statute, which constrains out marketing practices, educational programs, pricing policies, and relationships with healthcare providers or other entities, by prohibiting, among other things, soliciting, receiving, offering, or paying remuneration, directly or indirectly, to induce, or in return for, either the referral of an individual or the purchase or recommendation of an item or service reimbursable under a federal healthcare program, such as the Medicare and Medicaid programs;

- federal civil and criminal false claims laws and civil monetary penalty laws, which prohibit, among other things, individuals or entities from knowingly presenting, or causing to be presented, false or fraudulent claims for payment from Medicare, Medicaid, or other third-party payors;

- the federal Health Insurance Portability and Accountability Act of 1996 (HIPAA), which created new federal criminal statutes that prohibit executing a scheme to defraud any healthcare benefit program or making false statements relating to healthcare matters;

- HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act of 2009 (HITECH), and its implementing regulations, which imposes certain requirements relating to the privacy, security and transmission of individually identifiable health information; and

- state law equivalents of each of the above federal laws, such as anti-kickback and false claims laws which may apply to items or services reimbursed by any third-party payor, including commercial insurers, and state laws governing the privacy and security of health information in certain circumstances, many of which differ from each other in significant ways and often are not preempted by HIPAA, thus complicating compliance efforts.

Because of the breadth of these laws and the narrowness of the statutory exceptions and safe harbors available under the U.S. federal Anti-Kickback Statute, it is possible that some of the Company's business activities could be subject to challenge under one or more of such laws. If Emmaus or its operations are found to be in violation of any of the laws described above or any other governmental regulations that apply to it, the Company may be subject to penalties, including civil and criminal penalties, damages, fines, exclusion from participation in U.S. federal or state health care programs, and the curtailment or restructuring of its operations. Any penalties, damages, fines, curtailment or restructuring of its operations could materially adversely affect the Company's ability to operate its business and its financial results.

The FDA provides guidelines with respect to appropriate promotion and continuing medical and health education activities. Although Emmaus' endeavor to follow these guidelines, the FDA or the Office of the Inspector General: U.S. Department of Health and Human Services may disagree, and the Company may be subject to significant liability, including civil and administrative remedies as well as criminal sanctions. In addition, management's attention could be diverted, and its reputation could be damaged.

Although compliance programs can mitigate the risk of investigation and prosecution for violations of these laws, the risks cannot be eliminated entirely. Any action against Emmaus for violation of these laws, even if the Company successfully defends against it, could cause Emmaus to incur significant legal expenses and divert its attention from the operation of its business. Moreover, achieving and sustaining compliance with applicable federal and state privacy, security, and fraud laws may prove costly.

Even though Emmaus has obtained Orphan Drug designation for Endari®, the Company may not be able to maintain Orphan Drug marketing exclusivity for Endari® or any of its other product candidates.

Regulatory authorities in some jurisdictions, including the U.S. and the European Union, may designate therapeutic products under development for relatively small patient populations as "orphan drugs". Under the Orphan Drug Act, the FDA may designate a therapeutic product as an Orphan Drug if it is intended to treat a rare disease or condition, which is generally defined as a patient population of fewer than 200,000 individuals in the U.S. The Company has obtained Orphan Drug designation from the FDA, which will expire July 7, 2024, and Orphan Medicinal designation from the EC for L-glutamine treatment for SCD, and it may seek Orphan Drug designation for its other product candidates.

Generally, if a product candidate with an Orphan Drug designation subsequently receives the first marketing approval for the indication for which it has been granted such designation, the drug is entitled to a period of marketing exclusivity, which precludes the FDA or EC, as applicable, from approving another marketing application for the same product candidate prior to the expiration of that time period. The applicable period is seven years in the U.S. and ten years in the EU. The exclusivity period in the EU can be reduced to six years if the product no longer meets the criteria for Orphan Medicinal designation or if its commercialization is sufficiently profitable so that market exclusivity is no longer justified.

Orphan Drug and Orphan Medicinal exclusivity may be lost if the FDA or EC determines that the request for designation was materially defective or if the manufacturer is unable to ensure sufficient quantities of the product to meet the needs of patients with the rare disease or condition. In the U.S., Orphan Drug exclusivity may be lost if another L-glutamine product for the same indication demonstrates clinical superiority, such as a better safety or efficacy profile, in which case the FDA would be permitted to approve the third-party product. Orphan Drug exclusivity does not bar the FDA from approving another L-glutamine product for any other indication. Nor does Orphan Drug designation bar the FDA from granting Orphan Drug designation and approving another product, such as Oxbryta™, from Global Blood Therapeutics, Inc. for treating SCD, for the same orphan disease or condition.

Any product candidate for which Emmaus obtains marketing approval would be subject to post-marketing regulatory requirements and limitations and could be subject to recall or withdrawal from the market, and the Company may be subject to penalties if it fails to comply with such regulatory requirements or if it experiences unanticipated problems in commercializing any of its product candidates, when and if any of them are approved by regulators.

Any product candidate for which the Company obtains marketing approval, along with the collection and reporting of post-approval clinical data, manufacturing processes, labeling, advertising, and promotional activities for the resulting product, will be subject to continual requirements of and review by the FDA and other regulatory authorities. These requirements include submissions of safety and other post-marketing information and reports, establishment registration and product listing requirements, cGMP requirements relating to manufacturing, quality control, quality assurance, and corresponding maintenance of records and documents, requirements regarding the distribution of samples to physicians and recordkeeping. Even if the FDA or other regulators outside the U.S. grant marketing approval to any of Emmaus' product candidates, the approval may be subject to limitations on the indicated uses for which it may be marketed as a product or to the conditions of approval,

including the requirement to implement a risk evaluation and mitigation strategy (REMS). If any of the Company's product candidates receives marketing approval, the labeling (including the package insert) that must accompany distribution as a product may limit its approved use, which could limit the total number of prescriptions written for such products.

In consultation with the FDA, Emmaus is designing clinical studies to generate data in stages to fulfill the post-marketing commitment for the current SCD indication of Endari®. These studies will require additional funding and are designed to include dosing and safety, particularly in those populations not yet given Endari®. On any future products, the FDA may also require additional costly post-marketing studies or clinical trials or surveillance to monitor the safety or effectiveness of any other approved product. The FDA closely regulates the post-approval marketing and promotion of therapeutic products to ensure they are marketed for the approved indications and in accordance with the provisions of the approved labeling, and that any marketing claims or communications by a person or company responsible for the manufacture and distribution of the product regarding off-label use are truthful and not misleading.

If Emmaus markets any of its products for indications that have not been approved in a manner that is considered misleading or not truthful, the Company may be subject to enforcement action for misbranding the product. Violations of the FDC&A relating to the promotion of prescription products may lead to investigations alleging violations of federal and state healthcare fraud and abuse laws, as well as state consumer protection laws. In recent years, several pharmaceutical companies have been or settled lawsuits for fined significant amounts for such violations.

In addition, later discovery of previously unknown adverse events or other problems with any of Emmaus' product candidates that are approved for marketing as products, the contract manufacturers from which the Company obtains supplies of these products, the manufacturing processes they use to manufacture these products, or its or their failure to comply with regulatory requirements, may have negative consequences, including:

- restrictions on the manufacturers or manufacturing processes for such products;
- restrictions on the labeling or marketing of such products;
- restrictions on distribution or use of such products;
- requirements to conduct post marketing studies or clinical trials;
- warning letters;
- recall or withdrawal of such products from the market;
- refusal to approve pending applications or supplements to approved marketing applications that the Company submits;
- clinical holds on clinical studies of such products;
- fines, restitution, or disgorgement of revenue or profit generated by sales of such products;
- suspension or withdrawal of the marketing approvals of such products;
- refusal to permit the import or export of such products;
- seizure of such products;
- injunctions prohibiting the manufacture, marketing, sale, distribution, or related action in respect of such products;

- the imposition of civil or criminal penalties; and/or

- debarment of the Company and any of its officers or other employees responsible for such problems from future dealings with the FDA.

Noncompliance with applicable regulatory requirements regarding safety monitoring, also called pharmacovigilance, and with requirements related to the development of therapeutics for the pediatric population, can also result in significant financial penalties. Similarly, failure to comply with applicable regulatory requirements regarding the protection of personal information can also lead to significant penalties and sanctions.

Recently enacted and future legislation may increase the difficulty and cost for Emmaus to obtain marketing approval of its product candidates and then commercialize them as products and affect the prices the Company may obtain.

In the U.S. and some foreign jurisdictions, there have been a number of legislative and regulatory changes and proposed changes regarding the healthcare system that could prevent or delay marketing approval of the Company's product candidates, restrict, or regulate post-approval activities, and affect Emmaus' ability to profitably sell any product candidates for which the Company obtains marketing approval.

Among policy makers and payors in the U.S. and elsewhere, there is significant interest in promoting changes in healthcare systems with the stated goals of containing healthcare costs, improving quality and expanding access. In the U.S., the pharmaceutical industry has been a particular focus of these efforts and has been significantly affected by major legislative initiatives. In March 2010, President Obama signed into law the Patient Protection and Affordable Care Act (PPACA), which intended to broaden access to health insurance, reduce or constrain the growth of healthcare spending, enhance remedies against fraud and abuse, add new transparency requirements for the healthcare and health insurance industries, impose new taxes and fees on the health industry and impose additional health policy reforms.

Among the provisions of the PPACA of importance to Emmaus are:

- an annual, nondeductible fee on any entity that manufactures or imports specified branded prescription drugs and biologic agents, apportioned among these entities according to their market share in certain government healthcare programs;

- an increase in the statutory minimum rebates a manufacturer must pay under the Medicaid Drug Rebate Program to 23.1% and 13.0% of the average manufacturer price for branded and generic drugs, respectively;

- expansion of healthcare fraud and abuse laws, including the False Claims Act and the Anti-Kickback Statute, new government investigative powers, and enhanced penalties for noncompliance;

- a new Medicare Part D coverage gap discount program, in which manufacturers must agree to offer 50% point of sale discounts off negotiated prices of applicable brand medicines to eligible beneficiaries during their coverage gap period, as a condition for a manufacturer's medicines purchased outside a hospital setting to be covered under Medicare Part D;

- extension of a manufacturer's Medicaid rebate liability to covered medicines dispensed to individuals who are enrolled in Medicaid managed care organizations;

- expansion of eligibility criteria for Medicaid programs by, among other things, allowing states to offer Medicaid coverage to additional individuals and by adding a new eligibility category for certain individuals with income at or below 133% of the federal poverty level beginning in 2014, thereby potentially increasing a manufacturer's Medicaid rebate liability;

- expansion of the entities eligible for discounts under the 340B Public Health Service pharmaceutical pricing program;

- the new requirements under the federal Open Payments program and its implementing regulations;

- a new requirement to annually report samples of medicines that manufacturers and distributors provide to physicians; and

- a new Patient Centered Outcomes Research Institute to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research.

Emmaus expects that the PPACA, as well as other healthcare reform measures that may be adopted in the future, may result in more rigorous coverage criteria and in additional downward pressure on the price that Emmaus receives for any of its products. Any reduction in reimbursement from Medicare or other government-funded programs may result in a similar reduction in payments from private payors. The implementation of cost containment measures or other healthcare reforms may prevent the Company from being able to generate revenue, attain profitability, or commercialize any of its products.

Legislative and regulatory proposals have been made to expand post-approval requirements and restrict sales and promotional activities for prescription medicines. The Company cannot be sure whether additional legislative changes will be enacted, or whether the FDA regulations, guidance, or interpretations will be changed, or what the impact of such changes on the marketing approvals of its product candidates, if any, may be. In addition, increased scrutiny by the U.S. Congress of the FDA's approval process may significantly delay or prevent marketing approval, as well as subject the Company to more stringent product labeling and post-marketing testing and other requirements.

Risks Related to the Company's Investment in EJ Holdings, Inc.

EJ Holdings has no revenues and is dependent on Emmaus to fund its business and operations, and there is no assurance that Emmaus can continue to provide needed funding or that EJ Holdings will be able to continue its activities.

EJ Holdings, Inc., or EJ Holdings, a Japanese corporation 40% owned by Emmaus, is engaged in phasing in its amino acid manufacturing plant in Ube, Japan and obtaining regulatory clearances for the manufacture of PGLG in accordance with cGMP. EJ Holdings has had no revenues since its inception, has depended on loans from Emmaus to acquire the Ube plant and fund its operations and will continue to be dependent on loans from Emmaus or other financing unless and until its plant is activated and it can secure customers, including Emmaus, for its products. There is no assurance that the Company can continue to provide needed funding to EJ Holdings, or that needed funding will be available from other sources. EJ Holdings has no commitments or understandings regarding any additional funding. If EJ Holdings fails to obtain needed funding, it may need to suspend activities at the Ube plant. Under the asset purchase agreement by which EJ Holdings purchased the Ube plant, the seller has the right to repurchase the plant at the purchase price, plus certain taxes, paid by EJ Holdings if the plant does not become operational within a reasonable period of time (not to exceed five years). In that event, it is likely that Emmaus would lose some or all of the Company's investment in EJ Holdings.

EJ Holdings may not be able to obtain needed financing or repay its loans and its ownership interest in EJ Holdings may be diluted by additional financing.

As of December 31, 2021, Emmaus had loaned EJ Holdings a total of $22.6 million, and EJ Holdings will continue to be reliant upon loans from the Company to fund its planned activities at the Ube plant unless and until it is able to secure additional debt or equity financing to fund such activities. EJ Holdings also will need to raise substantial debt or equity financing to fund the plant's operations if the phase-in of the plant is completed, including, but not limited to, maintaining the physical plant and maintaining regulatory approvals for the manufacture of its products. To the extent EJ Holdings raises additional debt or equity financing from sources other than Emmaus, its ability to repay its loans may be adversely affected or Emmaus' ownership interest may be diluted.

If EJ Holdings fails to reactivate its plant and obtain customers, it may not be able to sell its plant and property and Emmaus may lose its investment.

If EJ Holdings fails to reactivate the Ube plant or to secure customers for its products, it may need to sell its plant and property. There is no assurance that it will be able to do so at an attractive price or at all. Emmaus' loans to EJ Holdings are general unsecured obligations of EJ Holdings and the Company has no mortgage or other security interest in the plant or other property of EJ Holdings. Depending on the price at which the plant and property can be sold if it becomes necessary, EJ Holdings may be unable to repay its loans and its other secured or unsecured obligations, and may lose some or all of its investment in EJ Holdings.

EJ Holdings is subject to risks inherent in a new business and may not be successful.

EJ Holdings was formed in February 2017 for the purpose of acquiring, owning, and operating Kyowa's phased-out amino acid manufacturing plant in Ube, Japan. EJ Holdings is engaged in phasing in the plant and obtaining regulatory clearances to reactivate the plant, including FDA and other regulatory approvals for the manufacture of PGLG in accordance with cGMP. EJ Holdings has no operating history, and there is no assurance that it will be successful in bringing the plant online on a timely basis, or at all, or if it does so that it will be able to secure customers for its products or successfully implement its business plan.

Emmaus does not control EJ Holdings, and EJ Holdings may engage in activities contrary to its best interests.

JIP owns 60% of EJ Holdings and is entitled to designate a majority of EJ Holdings' board of directors, its Chief Executive Officer and outside auditors, and, as such, controls the management, business, and operations of EJ Holdings. It is possible that EJ Holdings will engage in actions or business activities that Emmaus believes are inconsistent with the MOU and not in the Company's best interests and that may have an adverse effect on the economic or strategic value of its ownership interest in EJ Holdings.

EJ Holdings retains discretion over its use of any funds that Emmaus provides to it.

Emmaus does not control EJ Holdings' day-to-day operations. Accordingly, funds provided by Emmaus to EJ Holdings may be used by it in any manner its management deems appropriate, including making capital expenditures and paying of salaries and other compensation of its officers and other employees. There is no assurance that EJ Holdings will use Emmaus' funds in a manner that will enhance the value of its ownership interest in EJ Holdings.

Risks Related to the Company's Securities

Emmaus has been delinquent in its past SEC reporting obligations and if the Company fails to timely file its future SEC reports, its security holders and prospective investors will not have current information regarding the Company's financial statements and status of its business and operations and its common stock may no longer be eligible for quotation on the OTC Markets Group, Inc.

The Company was unable to timely file with the SEC its Annual Reports on Form 10-K for the years ended December 31, 2019 and December 31, 2020 and its Quarterly Reports on Form 10-Q for 2020 or its Quarterly Report for the quarter ended March 31, 2021. The Company's failure to timely file its periodic SEC reports adversely affects the ability of Emmaus security holders and prospective investors to have current information regarding its financial statements and status of the Company's business and operations and is likely to have adversely affected the liquidity and trading prices of the Company's common stock. Under applicable rules of the Financial Industry Regulatory Authority, or FINRA, the Company's failure to timely file periodic reports with the SEC may result in the disqualification of the Company's common stock for quotation on the OTC Markets Group, Inc. In such event, there may be no established trading market for the Company's common stock unless and until Emmaus follows its SEC reporting obligations and its common stock once again becomes eligible for quotation on the OTC Markets Group, Inc. or is listed on a national securities exchange.

Emmaus has experienced, and may continue to experience, significant volatility in its stock price.

The trading price for the Company's common stock has historically been volatile and traded at higher or lower prices that are seemingly uncorrelated with Emmaus results of operations, financial condition, or prospects. Between January 1, 2021 and December 31, 2021, the closing sale price of the Company's common stock as reported on the OTC Markets Group, Inc. ranged from a low of $0.72 to a high of $2.16 and may continue to exhibit volatility. Factors such as the following may affect the volatility in the Company's stock price:

- the Company's quarterly operating results;
- marketing approvals or other developments regarding Endari® or competing products;
- announcements of regulatory developments or technological innovations by Emmaus or its competitors;
- changes in the Company's relationship with its vendors, distributors, or other strategic partners;
- government regulation of drug pricing; and
- developments in patent or other intellectual property rights.

Other factors which may affect Emmaus' stock price include general economic conditions or changes in the economy, the financial markets or the pharmaceutical or biotechnology industries driven by extraordinary events such as the COVID-19 pandemic. The Company may be particularly vulnerable to volatility caused by these conditions or events, as it has only a single approved product and has relatively thin trading volume in its common stock.

Trading on the OTC Markets is volatile and sporadic, which could depress the market price of the Company's common stock and make it difficult for its stockholders to resell their common stock.

Until July 31, 2020, the Company's common stock was quoted on the OTCQB tier of the OTC Markets Group, Inc., or OTC Markets. On August 3, 2020, its common stock was relegated to the OTC Pink tier of the OTC Markets. pending the filing of the Company's delinquent SEC reports and posting of its OTCQB Certification and verification of the Company profile through OTCIQ.com. On or about September 13, 2021, public quotations for its common stock became available on the OTCQX tier of the OTC Markets. Trading in securities quoted on the OTC Markets is often thin and characterized by wide fluctuations in trading prices due to many factors, some of which may have little to do with Company operations or business prospects. This volatility could depress the market price of Emmaus' common stock for reasons unrelated to its business or operating performance. Moreover, the OTC Markets is not a stock exchange and trading of securities on the OTC Markets is often more sporadic than the trading of securities listed on a quotation system, such as The Nasdaq Capital Market or a stock exchange like the NYSE American Stock Exchange. These factors may result in investors having difficulty purchasing and reselling shares of the Company's common stock.

Emmaus' outstanding warrants and convertible promissory notes may result in further dilution to its stockholders.

Certain of the Company's outstanding warrants to purchase a total of up to approximately 3,607,200 shares of its common stock provided for so-called full-ratchet antidilution adjustments in the event Emmaus sells or issue shares of common stock or common stock equivalents at an effective price less than the exercise price of such warrants, subject to certain exceptions. These anti-dilution adjustments resulted in a reduction in the exercise price of such warrants to $1.54 per share in February 2021. The Company also has outstanding approximately $14.5 million principal amount of convertible promissory notes, which are convertible into shares of its common stock at a conversion price of $1.48 per share that is subject to possible future reductions on a quarterly basis in the event the prevailing trading price of its common stock is less than the then-conversion price. The anti-dilution adjustments of Emmaus' outstanding warrants would be triggered by future issuances by the Company of shares of its common stock upon conversion of the convertible promissory notes, or otherwise, at a price per share below

the then-exercise price of such warrants, which adjustments would have a further dilutive effect on Company stockholders.

Stockholders may experience future dilution from future equity offerings.

To raise additional capital in the future, Emmaus may sell and issue additional shares of its common stock or securities convertible into or exchangeable for its common stock, which sales would have a dilutive effect on the percentage ownership of its existing stockholders.

A substantial number of shares of common stock may be sold in the market, which may depress the market price for Emmaus' common stock.

Sales of a substantial number of shares of Company common stock in the public market, or the possibility such sales upon the exercise or conversion of its outstanding warrants or convertible promissory notes, could cause the market price of Emmaus' common stock to decline or serve to depress the market price of the Company's common stock. A substantial majority of the outstanding shares of Emmaus' common stock are, and the shares of common stock issuable upon the exercise of its outstanding warrants and other convertible securities or shares which may be sold in future offerings by Emmaus will be, freely tradable without restriction or further registration under the Securities Act.

The Company's common stock is not traded on a national securities exchange, which may adversely affect its ability to raise needed financing.

The OTC Markets is not a national securities exchange within the meaning of federal and state securities laws, so Emmaus' common stock is not eligible for the exemption from state securities, or "blue sky," laws for "covered securities" within the meaning of the National Securities Markets Improvement Act of 1996, which may adversely affect its ability to sell its securities to raise needed financing and increase transactions costs of such financing.

As long as the Company's common stock is quoted on the OTC Markets, its stockholders may face significant restrictions on the resale of common stock due to state "blue sky" laws.

Each state has its own securities laws, often called "blue sky" laws, which limit sales of securities to a state's residents, unless the securities are registered in that state or qualify for an exemption from registration and govern the reporting requirements for broker-dealers doing business directly or indirectly in the state. Before a security is sold in a state, there must be a registration in place to cover the transaction, or the transaction must be exempt from registration. The applicable broker must also be registered in that state. As long as the Company's common stock is quoted on the OTCQX, a determination regarding registration will be made by those broker-dealers, if any, who agree to serve as market-makers for its common stock. There may be significant state blue sky law restrictions on the ability of investors to sell, and on purchasers to buy, Company common stock. Investors should therefore consider the resale market for its common stock warrants to be limited, as the resale of common stock may be unavailable without the significant expense of state registration or qualification.

Emmaus may effect a reverse stock split of its common stock, but it may not result in the intended benefits.

At the Annual Meeting of stockholders held on November 23, 2021, Company stockholders approved an amendment to its restated certificate of incorporation to authorize its board of directors in its discretion to effect a reverse stock split of the outstanding shares of Emmaus' common stock within one year following the Annual Meeting at a ratio of not less than 1-for-3 nor greater than 1-for-6. The Company may choose to effect a reverse stock split for the purpose of facilitating the uplisting of its common stock to a national securities exchange, such as the NYSE American. Absent other factors, reducing the number of outstanding shares of the Company's common stock through a reverse stock split would tend to increase the per share market price of its common stock. However, other factors, such as Company financial results, market conditions, and the market perception of its business may adversely affect the market price of Emmaus' common stock and there can be no assurance that a reverse stock split, if completed, will result in the intended benefits, that the market price of its common stock will

increase in proportion to the reduction in the number of shares of its common stock outstanding before the reverse stock split or that the market price of Emmaus' common stock will not decrease in the future.

Emmaus may issue preferred stock in the future, and the terms of the preferred stock may reduce the value of its common stock.

The Company is authorized to issue up to 15,000,000 shares of preferred stock in one or more series. Its board of directors may determine the terms of future preferred stock offerings without further action by its stockholders. If Emmaus issues preferred stock, it could affect investors' rights or reduce the value of the Company's outstanding common stock. In particular, specific rights granted to future holders of preferred stock may include voting rights, preferences as to dividends and liquidation, conversion and redemption rights, sinking fund provisions, and restrictions on its ability to merge with or sell Company assets to a third party.

Glossary

Acute Chest Syndrome—A severe lung-related complication of sickle cell disease that affects both children and adults. Acute chest syndrome occurs when sickle red blood cells block blood vessels in the lungs. It creates a pneumonia-like illness and is one of the leading causes of morbidity, hospitalizations, and death in children and adults living with sickle cell disease. This is considered an emergency and may be life threatening.

Allogeneic—Taken from different individuals of the same species.

Alt (Alanine Transaminase) Levels—An ALT test measures the amount of ALT (an enzyme found mostly in the liver) in the blood. When liver cells are damaged, they release ALT into the bloodstream. High levels of ALT in the blood may be a sign of a liver injury or disease.

Antioxidant—A substance that inhibits oxidation, especially one used to counteract potentially damaging oxidizing agents in a living organism.

Black-Label Warning—Boxed warnings (formerly known as Black Box Warnings) are the highest safety-related warning that medications can have assigned by the U.S. Food and Drug Administration (FDA). These warnings are intended to bring the consumer's attention to the major risks of the drug.

Bone Marrow Transplantation (BMT)—Also called hematopoietic stem cell transplantation (HSCT), the transplantation of multipotent hematopoietic stem cells, usually derived from bone marrow, in order to replicate inside of a patient to produce normal blood cells.

Cell Sheet Technology—A novel technology used to regenerate injured or damaged tissues that creates composite layer of cells grown and harvested in an intact sheet, rather than as individual cells. A number of cell sheet can be stacked on top of one another according to the thickness needed for the specific tissue regeneration application. Cell sheets can be used for tissue transplantation or to engineer complex multilayer cell sheets composed of different types of cells.

Chondrocyte—Cartilage cell that make the structural components of cartilage. Chondrocytes produce and maintain the cartilaginous matrix.

current Good Manufacturing Practices (cGMP)—Regulations established by the FDA for all domestic and foreign manufacturers requiring the establishment of a quality system that includes requirements related to the methods, controls, and facilities used for designing, manufacturing, packaging, labeling, storing, installing, and servicing products and medical devices intended for human use.

Deep Vein Thrombosis (DVTs)—A blood clot (thrombus) in a deep vein in the thigh or leg. The clot can break off and make its way to the lung, where it can cause respiratory distress and respiratory failure.

Diverticulosis—A condition in which small, bulging pouches (diverticuli) develop in the digestive tract.

Dyspepsia—Indigestion.

Early Access Programs— A program that allows patients and physicians to use investigational (pre-approval) drugs outside the clinical trial setting. These investigational therapies are made available, in certain circumstances, to treat patients with serious diseases who are unable to participate in an ongoing clinical trial or whose treatment options are otherwise limited.

Fracture Nonunion—A condition that occurs when a fractured bone heals in an abnormal position, which can lead to impaired function of the bone or limb. Similarly, a nonunion is the result of a fractured bone failing to heal after an extended period of time, in some cases over a period of 9 to 12 months.

Gulf Cooperation Council—A political and economic alliance of six Middle Eastern countries—Saudi Arabia, Kuwait, the United Arab Emirates, Qatar, Bahrain, and Oman.

HbA1C—A test that measures the amount of glycosylated hemoglobin in the blood. The test gives a good estimate of how well diabetes is being managed over time.

Hematocrit—A test measuring the ratio of red blood cells in a sample of whole blood, used to test for anemia.

Hemoglobin—A protein produced in the bone marrow that enables red blood cells to transport oxygen throughout the body. Hemoglobin, when in contact with oxygen, also gives red blood cells their color.

Hemolysis—The destruction of red blood cells, which leads to the release of hemoglobin from within the red blood cells into the blood plasma.

Hypertriglyceridemia—A high level of a certain type of fat (triglycerides) in the blood.

Hypersplenism—A condition in which the spleen is overactive and removes too many blood cells from the bloodstream.

IRAK4 inhibitor—Interleukin-1 receptor-associated kinase 4 (IRAK-4) inhibitors are novel agents designed to suppress immune signaling pathways involved in inflammation. IRAK-4 is a signaling molecules involved at the nexus of multiple inflammatory pathways implicated in the hematologic malignancies and solid tissue tumors. Preclinical investigations nominate the IRAK kinases as targetable molecular dependencies in diverse cancers.

L-Glutamine—Glutamine, the most abundant amino acid found in the body, is a key component in the biosynthesis of proteins. L-glutamine (the form of glutamine more involved in the production of proteins) is a nonessential amino acid, meaning the human body is able to produce it. However, L-glutamine is also found in many dietary sources and supplements.

Mesenchymal—Refers to cells that develop into connective tissue, blood vessels, and lymphatic tissue.

Monoclonal Antibody—Any of a class of artificial antibodies produced in the laboratory. This type of antibody recognizes only one type of antigen and is sometimes used as an immunotherapy to treat diseases such as cancer.

Morbidity—The condition of suffering from a disease or medical condition.

Nicotinamide Adenine Dinucleotide (NAD)—A coenzyme central to metabolism and a number of critical cellular processes found in all living cells, including several oxidation-reduction reactions in all forms of cellular life. NAD+, the oxidize form of NAD, acts as an oxidizing agent in cellular metabolism. Conversely, NADH, the reduced form of NAD, acts as a metabolic reducing agent (antioxidant).

Orphan Medicinal Designation—A status given by the European Medicines Agency (EMA) assigned to a medicine intended for use against a rare condition. The medicine must fulfil certain criteria for designation as an orphan medicine so that it can benefit from incentives such as protection from competition once on the market. It is the European equivalent to the FDA's *Orphan Drug Designation*.

Orphan Diseases—Designation given to either a rare disease that affects fewer than 200,000 people, or a common disease that has been ignored because it is less prominent in the U.S., compared with developing nations. According to the NIH, there are approximately 6,000 of these diseases.

Orphan Drug Designation—A status given by the U.S. FDA to drugs and biologics that show promise in the treatment, prevention, or diagnosis of orphan diseases. The Orphan Drug Designation provided financial incentives to attract industry's interest, including seven years of market exclusivity after approval, reduced fees for regulatory activities, and tax credits of up to 50 percent for research and development expenses.

Oxidation-Reduction (Redox)—A process in which one substance or molecule is reduced (gains an electron) and another oxidized (loses an electron); oxidation and reduction are considered together as complimentary processes.

Oxidative Stress—An imbalance of potentially toxic free radicals in cells and tissues and the antioxidants that can neutralize them. While some level of oxidative stress is normal and even beneficial, too much of it can contribute to several different health conditions.

Paget's Disease—A chronic bone disorder that is due to irregular breakdown and formation of bone tissue. Paget's disease can cause bones to expand and weaken and may result in bone pain, arthritis, bone deformity, and fractures.

Pulmonary Embolisms—The lodgment of a blood clot in the lumen of a pulmonary artery, causing a severe dysfunction in respiratory function.

Reactive Oxygen Species (ROS)—Free radicals (unstable molecules that require an electron from another molecule to become stable) that contain oxygen and that easily react with other molecules in a cell. Although ROS are needed by the body for important physiological processes, a buildup of ROS in cells may cause damage to DNA and proteins and may cause cell death.

Reduction—A reaction in which electrons are added to a compound.

Regenerative Medicine—Regenerative medicine is an emerging field that approaches the repair or replacement of tissues and organs by incorporating the use of cells, genes, or other biological building blocks along with bioengineered materials and technologies.

Sickle Cell Crises—Also known as acute pain crises, is a broad term covering a range of sickle cell diseases complications. Sickle cell crisis occurs when the sickle-shaped RBCs occlude blood vessels, blocking blood flow and causing excruciating musculoskeletal and visceral pain, increased risk of heart attacks and strokes, and frequent infections.

Sickle Cell Disease (SCD)—A term that defines a group of rare hereditary blood disorder characterized by the production of an altered form of hemoglobin. The abnormal hemoglobin cause red blood cells (RBC) to become sickle-shaped (crescent shaped), rigid, and adhesive. These abnormal RBCs have difficulty passing through small blood vessels, causing blockages and reduced blood flow. The blocked blood flow through the body can lead to serious problems, including stroke, infections, and episodes of pain, called pain crises. It is most common among people whose ancestors come from Africa, the Mediterranean, the Arabian Peninsula, India, and regions in South America, Central America, and parts of the Caribbean.

Telehealth—The delivery and facilitation of health and health-related services, including medical care, physician appointments and diagnosis, health information services, and prescriptions, via telecommunications and digital communication technologies.

Vascular Occlusion Crises (VOCs)—A common and painful complication of sickle cell anemia, it occurs when sickled red blood cells block blood flow to bones and organs such as the liver, kidneys, eyes, or the central nervous system. The blockage can cause ischemic injuries and may cause irreversible organ damage.

Waldenstrom Macroglobulinemia (WM)—A rare blood cell cancer characterized by an excess of abnormal white blood cells in the bone marrow.

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