Celsion

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Ticker (Exchange)	(CLSN-NASDAQ)
Recent Price (12/09/2020)	$0.62
52-week Range	$0.43 - 6.50
Shares Outstanding	36.2 million
Market Capitalization	$23 million
Average volume	785,893
Insider Ownership +>5%	~2%
Institutional Ownership	~10%
EPS (Qtr. ended 09/30/2020)	($0.24)
Employees	26

CLSN (NASDAQ) One-year Stock Chart

CELSION PRODUCT PIPELINE				
Product	**Indication**	**Pre-clinical**	**Phase I/II**	**Phase III**
Thermodox®	Primary Liver Cancer			
GEN-1	Ovarian Cancer			
Thermodox®	Bladder Cancer			

COMPANY DESCRIPTION

Celsion Corporation ("Celsion" or "the Company") is a fully integrated biopharmaceutical company focused on developing cancer therapies for difficult-to-treat forms of cancers. Through the application of its two distinct **nanoparticle†**-based technology platforms, Celsion has developed a robust pipeline that includes two clinical programs: (1) GEN-1, a DNA-based **immunotherapy** in a Phase I/II study for the treatment of Stage III/IV ovarian cancer. GEN-1 is a non-viral, synthetic delivery platform that facilitates the localized secretion of **interleukin-12 (IL-12)**—an immune protein that plays a key role in generating an immune response against cancer—into the tumor region; and (2) ThermoDox®, a heat-activated nanoparticle encapsulation of **doxorubicin** (a widely used chemotherapeutic agent) in a Phase III clinical trial for the treatment of **hepatocellular cancer (HCC)**/primary liver cancer. When heated through the application of heat-based treatments, ThermoDox® changes structure, creating openings that release doxorubicin directly into the tumor. Through investigator sponsored studies, Celsion is further supporting clinical studies to expand the application of its ThermoDox® technology platforms into other cancer indications in breast, pancreatic, and bladder cancer.

KEY POINTS

- In clinical trials, GEN-1 has resulted in a marked advantage in **Progression Free Survival (PFS)**—21 months, which was 75% higher than the estimate of 12 months historically seen in this patient population, while circumventing toxicities normally associated with IL-12 administration. GEN-1 is being evaluated in a Phase I/II study (OVATION 2). The Phase II part of the study is in line to complete enrollment by mid-2021, with PFS data expected by Q4 2022.
- Studies have demonstrated ThermoDox®'s ability to deliver a greater volume of doxorubicin to the tumor area—25x more vs. doxorubicin IV infusion—leading to a better clinical outcome. In HCC patients with single lesions that underwent **radiofrequency ablation (RFA)** for at least 45 minutes, the use of ThermoDox® resulted in a 2.1-year improvement in **Overall Survival (OS)**.
- Following completion of the second interim analysis of ThermoDox®'s Phase III study (OPTIMA) by the independent Data Monitoring Committee (DMC), the DMC recommended to consider stopping the study for futility. Celsion plans to continue following patients while it conducts independent statistical analyses of the data, as preliminary evaluation of the unblinded data indicates that this development might be associated with a data maturity issue. The Company expects to report findings from these independent statistical analyses before the end of 2020.
- Celsion's leadership team holds over 150 years of experience within healthcare, including clinical development programs, R&D, pharmaceutical operations, and corporate finance.
- The Company ended Q3 2020 with $18.3 million in cash and cash equivalents. With future planned sales of its New Jersey net operating losses (NOLs), Celsion believes it has sufficient capital resources to fund its operations through the end of 2021.

Celsion

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Executive Overview

Celsion Corporation ("Celsion" or "the Company") is a fully integrated biopharmaceutical company focused on developing a portfolio of innovative cancer treatments through the application of its two distinct and innovative nanoparticle-based technology platforms: TheraPlas™ and Lysolipid Thermally Sensitive Liposomes (LTSL). With the application of these technologies, Celsion is working to develop and commercialize targeted oncology therapies and immunotherapies for difficult-to-treat cancers that aim to maximize the efficacy of proven therapeutic agents and minimize side effects common to cancer treatments.

The use of TheraPlas™ has resulted in product candidate GEN-1, an immunotherapy for the localized treatment of ovarian cancer, which is currently being evaluated in the Phase I/II OVATION 2 Study in combination with chemotherapy, for newly diagnosed advanced ovarian cancer patients. The Company's pipeline also includes ThermoDox®, a heat-mediated nanoparticle delivery platform that uses Celsion's LTSL technology to encapsulate doxorubicin, a proven and commonly used cancer drug, to facilitate its targeted delivery at the tumor site. ThermoDox® is currently being evaluated in the OPTIMA Study, a global Phase III clinical trial for the treatment of hepatocellular cancer (HCC)/primary liver cancer. Through investigator-sponsored studies, Celsion is further supporting clinical studies to expand the application of its ThermoDox® technology platforms into other cancer indications in breast, pancreatic, and bladder cancer (Figure 1).

Figure 1

CELSION PRODUCT PIPELINE

Product	Indication	Pre-clinical	Phase I/II	Phase III
Thermodox®	Primary Liver Cancer			
GEN-1	Ovarian Cancer			
Thermodox®	Bladder Cancer			

Source: Celsion Corporation.

GEN-1 IMMUNO-ONCOLOGY OVERVIEW

GEN-1, the first product designed via the TheraPlas™ platform technology, is an immuno-oncology candidate for the treatment of cancer. GEN-1 is currently under clinical evaluation for the treatment of ovarian cancer (an indication for which it received Orphan Drug Designation in the U.S. and EU).

TheraPlas™ Technology

Celsion's TheraPlas™ is a proprietary technology platform that uses synthetic, non-viral carriers capable of providing cell **transfection** of **plasmids** coded for the expression of specific therapeutic proteins that can promote an effective immune response. Unlike viral carriers that can only be applied once, TheraPlas™ non-viral carriers can skirt the immune system's neutralizing activity and be used for multiple applications—ideal for cancer therapies.

Transfection is the process of artificially introducing nucleic acids (DNA, siRNA, or **messenger RNA [mRNA]**) into cells, by means other than viral infection, in order to produce genetically modified cells. Once transfection complexes, which consist of a transfection reagent combined with a nucleic acid, enters the cell, the process results in the expression of specific immune proteins by the cell, which can elicit a desired immune response.

There are two components of the TheraPlas™ system: a plasmid DNA or mRNA payload encoding a therapeutic protein and a delivery system. The delivery system is designed to protect the DNA/RNA from degradation and promote trafficking into cells and through intracellular compartments. According to the Company, compared to naked DNA, TheraPlas™ is generally safer, more efficient, and more cost effective.

GEN-1 Immunotherapy Program

GEN-1 is an immunotherapy that incorporates a DNA plasmid payload encoding interleukin-12 (IL-12)—a **cytokine** that plays a key role in generating an immune response against cancer—into a unique nanoparticle delivery system polymer. The polymer is condensed together with the plasmid, forming nanoparticles. Following administration, GEN-1 nanoparticle profile enables cell transfection followed by durable local secretion of the IL-12 protein in the vicinity of the tumor that persists for several days after a single treatment. The sustained concentrations of IL-12 may lead to prolonged infiltration of immune cells in the tumor, enhancing the local immune response against cancer.

Despite the IL-12 cytokine playing a key role in generating an effective anti-cancer immune response, when administered intravenously, IL-12 requires frequent, large bolus injections, resulting in serious toxicities that limit its effectiveness and applications. According to the Company, since GEN-1 elicits local secretion of IL-12 around the tumor location, it circumvents toxicity issues typically associated with IL-12 administration.

Clinical Trials–OVATION Studies

GEN-1 is being administered to ovarian cancer patients via a catheter directly to the **peritoneal cavity**, resulting in durable local expression of IL-12 in the affected area. Ovarian cancer is the most lethal gynecological malignancy among women (accounting for 5% of all cancer-related death). Survival rate for ovarian cancer is only 46.2% because most patients (59%) are diagnosed with distant-stage disease, for which survival is 29%. Debulking surgery plus adjuvant platinum-based chemotherapy is the accepted primary treatment for the disease. However, immediate surgery is not advisable for some patients with an initial high disease burden. In these cases, **neoadjuvant chemotherapy (NAC)** followed by **interval debulking surgery (IDS)** is used to shrink the tumor in preparation for surgery. It is to this NAC treatment that Celsion is adding weekly cycles of GEN-1.

- OVATION I Study – GEN-1 added to NAC before IDS
- OVATION 2 Study – GEN-1 added to NAC before IDS + GEN-1 added to Adjuvant Chemotherapy after IDS

The Company is currently evaluating GEN-1 in the Phase I/II OVATION 2 Study, in combination with standard NAC for newly diagnosed ovarian cancer patients. The study follows the successful completion of OVATION 1, a Phase I study of the safety and biological activity of GEN-1. OVATION 1 showed that administration of GEN-1 caused a dose dependent response, with the two lower doses of GEN-1 resulting in an **objective tumor response** (the percentage of patients showing a complete or partial response) of 60% compared to an objective tumor response of 100% at the two higher doses. Furthermore, higher doses of GEN-1 resulted in a significant increase of **R-0** surgical resection events (the surgical removal of all visible tumor) following IDS, from 40% in the two lower doses to 88% (8 out of 9 patients) at the two higher doses.

In addition, Celsion conducted data analysis comparing its OVATION I results to a **synthetic control arm (SCA)**, created by collecting data from control arm patients from other studies who would have otherwise qualified for this trial. Patients in the GEN-1 treated cohort displayed a marked advantage in Progression Free Survival (PFS)—although not statistically significant due to the small numbers, almost doubling the time to progression of the control group. Furthermore, a comparison of GEN-1 patients treated per protocol in the OVATION 1 Phase 1b trial versus the historical PFS found in the literature saw an improvement of almost 75% in the median time to progression. Of significance, the peritoneal plasma barrier seemed to minimize the spillover of IL-12 into the systemic circulation, resulting in normal blood levels of IL-12, showing GEN-1's ability to circumvent toxicities normally associated with IL-12 administration.

The OVATION 2 trial is a Phase I/II study comprised of up to 110 patients. The Phase I portion of the study, which included 15 patients, was completed in Q2 2020. The Phase I portion of the study showed favorable safety data from 15 randomized patients and no dose limiting toxicities, with seven out of nine patients (78%) in the GEN-1 treatment arm having an R-0 surgical resection, against three out of six patients (50%) in the NAC only arm. The Phase II portion of the study, which initiated enrollment in Q3 2020, has enrolled approximately 30 patients and expects to complete enrollment by mid-2021. The Company expects PFS data to be reported in the second half of 2022.

THERMODOX® OVERVIEW

ThermoDox® uses the Company's Lysolipid Thermally Sensitive Liposomes (LTSL) technology to produce heat-sensitive **liposomes** that encapsulate doxorubicin, a widely used and proven chemotherapeutic agent, to facilitate its targeted delivery at the tumor site. ThermoDox® is currently being evaluated in clinical studies for hepatocellular carcinoma (HCC)/primary liver cancer (an indication for which it has received Orphan Drug Designation in the U.S. and EU, as well as Fast Track designation for HCC in the U.S.), and is also being evaluated for breast, pancreatic, and bladder cancer in investigator sponsored studies in Oxford, UK, Utrecht, NL, and by the National Institutes of Health.

Lysolipid Thermally Sensitive Liposomes (LTSL)

LTSL is a proprietary technology that achieves targeted delivery of known chemotherapeutics using heat-sensitive liposomes. LTSL's unique liposomal technology delivers high concentrations of drug—up to 25 times the systemic dose—to the target area with the application of tolerable heat. Celsion licensed the exclusive worldwide rights to the LTSL technology from Duke University. The liposomes are administered intravenously, then circulate throughout the body. Once they come in contact with tissue that has been heated to just above body temperature (40ºC), the liposomes release the drug at the site in extremely high local concentrations.

ThermoDox® Chemotherapy

ThermoDox® uses LTSL to produce heat-sensitive liposomes that encapsulate doxorubicin, a widely used and proven chemotherapeutic agent. The heat-sensitive liposome rapidly changes structure when heated to 40ºC-45ºC, creating openings that release doxorubicin directly into the target area. ThermoDox® is designed to be used in combination with heat-based treatments, such as radiofrequency thermal ablation (RFA) and high intensity-focused ultrasound (HIFU). The goal is to expand the effective treatment zone in order to capture micrometastases, which are responsible for disease recurrence.

RFA directly destroys the tumor tissue through the application of high temperatures administered by a radiofrequency probe inserted into the core of the tumor. The suitability of RFA largely depends on the size of the tumor, with RFA's effectiveness decreasing with increasing tumor size. For small (≤ 3 cm) lesions, RFA can achieve complete eradication of the tumor. However, the rate of recurrence following RFA increases with larger lesions. Implementation of ThermoDox® includes the following steps:

(1) ThermoDox® is infused intravenously ~15 minutes prior to RFA as a single, outpatient procedure;

(2) RFA is applied directly in the tumor, generating a high temperature (up to 90ºC) that kills tumor cells in the immediate vicinity of the probe;

(3) RFA creates a "Thermal Zone" outside the ablation zone (40ºC-50ºC); and

(4) the heat causes the liposomes to release doxorubicin in the "Thermal Zone," killing the metastases outside the ablation zone.

Celsion believes that the use of ThermoDox® in conjunction with RFA could allow RFA to treat larger tumors, increasing the cases where RFA could produce a positive outcome.

Clinical and preclinical studies on the use of ThermoDox® for liver cancer patients have demonstrated the ability of ThermoDox® to deliver a greater volume of doxorubicin to the tumor area—25x more versus doxorubicin IV infusion—when high temperatures were applied, leading to a better clinical outcome than RFA alone. HCC is one of the most common and deadliest forms of cancer worldwide, and is the fifth and seventh most common cause of cancer death among men and women, respectively, in the U.S., where incidence rates have more than tripled since 1980 (Source: American Cancer Society).

Clinical Trials—The HEAT Study

The HEAT Study was a multicenter trial designed to determine whether ThermoDox improves the efficacy of RFA for HCC lesions. While the study showed that adding ThermoDox to RFA was safe, it did not increase PFS or Overall Survival (OS) in the study population. Researchers noted a wide variation in RFA application times between the 66 active centers. In an exploratory post hoc analysis, researchers determined that RFA burn time (the total time during which radiofrequency energy is being applied) may have influenced the outcomes of this study. Although patients in the shortened burn time subset showed no benefit in PFS and OS, outcomes appeared to be improved in the prolonged burn time subset. OS was significantly improved and PFS showed a trend toward improvement (22.7 versus 16.7 months). Remarkably, in patients with single lesions that underwent RFA for at least 45 minutes (n=285), the data showed a 2.1-year improvement in OS.

Independent NIH Analysis

The National Institutes of Health (NIH) evaluated the importance of RFA burn time as it correlates with clinical outcome and OS benefits. The study intended to determine whether burn time per tumor volume (BPV) (min/mL) is correlated with HCC treatment outcomes using RFA and LTLD. The study demonstrated that increased burn time per tumor volume (BPV) improved OS in ThermoDox®+RFA single-lesion patients. For all single-lesion patients being administered ThermoDox®+RFA, one unit increase in RFA duration per tumor volume improved OS by 20%. In contrast, in single-lesion RFA-only patients, burn time per tumor volume did not have a significant effect in OS. More dramatic differences were found in a subgroup of patients with BPV higher than 2.5 minutes/mL (45 minutes burn time for a 3 cm tumor), where over 60% of patients were alive after seven and a half years.

Clinical Trials—The OPTIMA Study

The subgroup analysis of the HEAT Study and the independent NIH analysis of this same data set were used to design the Phase III OPTIMA Study for liver cancer patients with single lesions. The OPTIMA Study, which completed enrollment in Q3 2018, includes 554 patients in approximately 65 sites in 14 countries (North America, Europe, China, and the Asia-Pacific region). The primary endpoint is OS.

The study included two planned interim efficacy analysis: (1) the first at least 118 deaths, with a target **hazard ratio (HR)** of 0.61, which was completed successfully on November 2019 and (2) the second analysis at least 158 deaths, with a target HR of 0.70, which was completed on July 2020; a final analysis at 197 deaths, with a target HR of 0.75 is pending. Following the first interim analysis, the Data Monitoring Committee (DMC) found that the safety, PFS, and OS values met expectations. Median PFS for the OPTIMA Study of 17.3 months compared favorably with 16.8 months median PFS for the 285 patients in the HEAT study.

<u>Data Monitoring Committee (DMC) Recommends to Consider Stopping OPTIMA Study</u>

Following completion of the second interim analysis in July 2020 by the independent DMC, the DMC recommended to consider stopping the study. The second interim analysis indicated that the OPTIMA Study had narrowly crossed the futility boundary of HR=0.90. The reported HR suggested by the Kaplan-Meier analysis was 0.903. However, since the two-sided p-value of 0.524 for this analysis provides uncertainty, the DMC left the final decision of whether or not to stop the OPTIMA Study to Celsion. Following preliminary evaluation of the unblinded data, Celsion plans to continue following patients, noting that the marginally crossed futility boundary may be associated with a data maturity issue.

OPTIMA investigators in China and Vietnam, who enrolled 37% of the subjects, joined the study approximately 12 and 18 months, respectively, after the trial was initiated. The China sites, in particular, show a negative Kaplan-Meier curve, yet with a 56% improvement in the treatment arm in the median time to death. The Vietnamese sites show a marginal Kaplan-Meier benefit, yet with a 45% improvement in the median time to death. The Company further noticed that of the 16 deaths that occurred in five different Asia-Pacific countries between the first and second interim analyses, 15 were in the ThermoDox® treatment arm. For reference, subsequent to the second interim analysis, there were eight patient deaths in a 3:1 ratio of control arm to treatment arm patients. Another factor in the data inconsistency against previous trials might be anomalies in the RFA heating time discovered during a site-by-site evaluation for RFA burn times, which may have contributed to the treatment arm performance.

Due to these factors, in addition to the fact that there were no safety concerns noted, the Company opted to continue following patients while it conducts independent statistical analysis on the data. To this end, Celsion acquired the services of a global biometrics contract research organization (CRO), with particular expertise in evaluating unusual data from clinical trials. The primary objective of the CRO's work is to determine the basis and reasoning behind continuing to follow patients for survival, and if there were outside influences that may have impacted the forecast of futility. In addition, and in parallel with the CRO analysis, the Company has submitted all OPTIMA Study clinical trial data to the NIH, which will focus on a site-by-site evaluation for RFA heating time-based anomalies that may have contributed to the treatment arm performance.

Celsion expects to report findings from these independent statistical analyses by Y/E 2020, either or both of which will determine whether to continue to follow patients to the final analysis at 197 or more deaths—a milestone that should be reached sometime in mid-2021.

The Company has noted that while the trial outcome as predicted by the second interim analysis may not change, and as unlikely as it may be, in the event it sees substantial clinical benefit from the CRO and NIH analyses, Celsion will carefully review its options with the 14 regulatory agencies under which the OPTIMA Study is being conducted

Preclinical and Independent ThermoDox® Programs

Preclinical studies on the use of ThermoDox® for the treatment of bladder cancer have demonstrated that warm water irrigation of the bladder can release high concentrations of doxorubicin throughout all layers of the bladder wall. The Company has also received multiple requests from investigators to include ThermoDox® in their own studies, involving several clinical indications: (1) Oxford University plans to begin enrolling patients in a Phase I pancreatic cancer study, with ThermoDox® in combination with High Intensity Focused Ultrasound (HIFU) in early 2021; (2) Utrecht University in the Netherlands continues to enroll patients in a Phase I breast cancer study to determine the safety, tolerability, and feasibility of ThermoDox® in combination with Magnetic Resonance Guided High Intensity Focused Ultrasound (MR-HIFU) hyperthermia and cyclophosphamide therapy; and (3) the NIH has organized a clinical project to evaluate ThermoDox® plus the chemotherapy drug mitomycin in bladder cancer. Depending on the NIH timelines, this study may commence as early as 2021.

2020 KEY FINANCIAL ACTIVITIES

During 2020, Celsion strengthened its balance sheet position, resulting in a minimal warrant overhang and a cleaner capital structure, through four key financial activities, described below.

(1) In April 2020, the Company received $1.8 million of net cash proceeds from the sale of approximately $1.9 million of its unused New Jersey net operating losses (NOLs). The NOL sales cover the tax years 2017 and 2018 and are administered through the New Jersey Economic Development Authority's (NJEDA) Technology Business Tax Certificate Transfer (NOL) Program. An additional sale of $2.0 million of unused New Jersey NOLs (anticipated in the second half of 2020) will further increase Celsion's cash reserves on a non-dilutive basis.

(2) In June 2020, the Company entered into an underwriting agreement relating to the sale of 2,666,667 shares of its common stock at an offering price of $3.75 per share. The net proceeds from the offering were $9.3 million.

(3) In September 2020, the Company announced a common stock purchase agreement of up to $26 million with Lincoln Park Capital Fund, LLC (LPC). Under the terms of the agreement, and following an initial purchase of $1 million of common stock at $1.00 per share, the Company has the right but not the obligation to sell up to $26 million worth of shares to LPC (including the $1 million initially purchased) over the 36-month term of the agreement.

(4) In September 2020, the Company elected to reduce the outstanding debt under the $10 million loan agreement with Horizon Technology Finance Corporation (HRZN-NASDAQ) by $5 million and restructure the terms of the remaining $5 million loan balance. In conjunction with the amended loan agreement, Celsion issued to Horizon warrants exercisable for 247,525 shares of Celsion's common stock at an exercise price of $1.01 per share. Warrants previously issued to Horizon exercisable for 95,057 shares at an exercise price of $2.63 per share were cancelled.

CORPORATE INFORMATION AND HISTORY

On June 20, 2014, the Company completed the acquisition of substantially all of the assets of EGEN, a private company located in Huntsville, Alabama. Pursuant to the Asset Purchase Agreement, CLSN Laboratories acquired all of EGEN's right, title, and interest in and to substantially all of the assets of EGEN, including cash and cash equivalents, patents, trademarks, and other intellectual property rights, clinical data, certain contracts, licenses, and permits, equipment, furniture, office equipment, furnishings, supplies, and other tangible personal property. A key asset acquired from EGEN was the TheraPlas™ technology platform and the first drug candidate developed from it is GEN-1. Today, Celsion is incorporated in the State of Delaware, has headquarters in Lawrenceville, New Jersey, and has 26 full time employees as of November 2020.

Company Leadership

Celsion's leadership team holds over 150 years of experience within the healthcare industry, including clinical development programs, research and development (R&D), pharmaceutical operations, and corporate finance. Biographies of key individuals are provided in the accompanying section.

Management Team

Michael H. Tardugno, Chairman, President, and Chief Executive Officer

Mr. Tardugno's career has been focused exclusively within healthcare, with 30 years of experience in the pharmaceutical and medical device industries. Mr. Tardugno was appointed President and Chief Executive Officer of Celsion on January 3, 2007, and was elected to the Board of Directors on January 22, 2007. Prior to joining the company, he served as Senior Vice President and General Manager of Mylan Technologies Inc., a subsidiary of Mylan Laboratories, a transdermal drug company. He was a founding member of management of Songbird Hearing, Inc., a privately held startup, and held the positions of Senior Vice President of Technical Operations at Bristol-Myers Squibb Company and Senior Vice President of Technology Development and Manufacturing for Bausch & Lomb. Mr. Tardugno began his career in 1977 with Abbott Laboratories, where he held positions in pharmaceutical operations. Mr. Tardugno holds a BS in Biology from St. Bonaventure University and completed the Harvard Business School executive program.

Khursheed Anwer, PhD, MBA, Executive Vice President and Chief Scientific Officer

Dr. Anwer assumed the title of Executive Vice President and Chief Scientific Officer, EGEN, Inc., upon Celsion's June 2014 acquisition of the Company, where he was President and Chief Scientific Officer, a position he held since 2009. He joined EGEN, Inc. in July, 2002, as Vice President of Research and Development, and directed the company's clinical and research and development functions throughout his tenure at EGEN, Inc. Dr. Anwer has a PhD in Physiology/Pharmacology from Ohio University and received postdoctoral training from the University of Texas Health Science Center at Houston. Before joining EGEN, Inc., Dr. Anwer was Director of Pre-Clinical Development at Valentis, Inc. From 1993 to 1999, he served in several positions at GeneMedicine, Inc., where he led several research projects in the area of nonviral gene therapy. He has authored more than 40 publications in the area of nonviral gene therapy, resulting from his active career in R&D. Dr. Anwer is an adjunct faculty member in the Biology Department at the University of Alabama in Huntsville and a board member of the University of Alabama Business School, STEP.

Nicholas Borys, MD, Executive Vice President and Chief Medical Officer

Dr. Borys joined Celsion in October 2007 as Vice President and Chief Medical Officer. In this position Dr. Borys manages the clinical development program for Celsion. Most recently Chief Medical Officer at Molecular Insight Pharmaceuticals, Inc., Dr. Borys has accumulated extensive experience in all phases of pharmaceutical development, with a focus in oncology. Prior to joining Celsion, he held increasingly senior positions at Cytogen Corporation, Anthra Pharmaceuticals, Inc., Amersham Healthcare, Inc., and Hoffmann La-Roche Inc. Dr. Borys attended Rutgers University and holds an MD degree from American University of the Caribbean School of Medicine.

Jeffrey W. Church, Executive Vice President, Chief Financial Officer, and Corporate Secretary

Mr. Church was appointed Senior Vice President and Chief Financial Officer of Celsion in July 2013. The appointment marked Mr. Church's resumption of the role of Chief Financial Officer, a position he held prior to his promotion to Senior Vice President in July 2011, while also granting him responsibility for corporate investor relations. Mr. Church joined Celsion in July 2010 as Vice President and Chief Financial Officer. He brings more than 30 years of experience in corporate finance, mergers and acquisitions, investor relations, and SEC reporting. Prior to joining Celsion, Mr. Church held senior financial executive positions with several private and public clinical-stage life science companies, including Alba Therapeutics Corporation, Novavax, Inc., GenVec, Inc., and Meridian Medical Technologies, Inc. Mr.

Church started his career in 1979 with the public accounting firm Price Waterhouse. Mr. Church holds a BS degree from the University of Maryland and received Maryland Certified Public Accountant accreditation in 1979.

Board of Directors

Michael H. Tardugno, Chairman, President, and Chief Executive Officer

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Augustine Chow, MSc, PhD, Director since March 2007

Dr. Chow was appointed to the Board of Directors in March 2007. Dr. Chow is the Chairman of Harmony Asset Management Limited in Hong Kong as well as a Director of Medifocus Inc. (TSX Venture: MFS). From 1996-2015, Dr. Chow was the Chief Executive Officer of Harmony Asset Limited, a Hong Kong listed investment company. Between 2008 and 2016, he served as Executive Director of Kaisun Energy Group Limited. From 1990 to 1998, Dr. Chow was the Chief Executive Officer of Allied Group of Companies based in Hong Kong, which included a number of publicly-listed companies spanning various industries. Prior to this, Dr. Chow held a senior position with Brunswick Corporation and Outboard Marine Corporation and was responsible for all business activities in South East Asia and China. Dr. Chow has extensive experience in managing publicly-listed companies that are involved in manufacturing, marketing, and financial services. He specializes in mergers and acquisitions. Dr. Chow's qualifications include a number of Bachelors, Masters, and Doctoral degrees. Among these are a MSc from London Business School, a PhD from the University of South Australia, and an Engineering Doctorate and PhD on Biology from City University of Hong Kong.

Robert W. Hooper, Director since August 2010

Mr. Hooper was appointed to the Board of Directors in August 2010 and currently serves as President of Crows Nest Ventures, Inc., an advisory and consulting services firm to the healthcare industry. From 1997-2001, he served as President, North America, for IMS Health, the global leader in healthcare information and market research. From 1993-1997, Mr. Hooper served as President of Abbott Laboratories Canada, based in Montreal. From 1989-1993, he served as Managing Director, Australia/Asia for Abbott Laboratories. Prior to 1989, Mr. Hooper served as Director of Manufacturing and Plant Manager for Abbott's Nutritional and Hospital Products Divisions. Mr. Hooper began his career with E.R. Squibb and Sterling Winthrop Labs. He received a BA in Biology from Wilkes University.

Alberto Martinez, MD, Director since December 2010

Dr. Martinez has served as a Director of the Company since December 2010. He is currently a consultant to the healthcare industry. From 2007 to 2008, Dr. Martinez served as the President and Chief Executive Officer of Talecris Biotherapeutics, a publicly traded life science company. Prior to that, he was Executive Vice President of Worldwide Commercial Operations for CSL Behring, the company formed by the 2004 acquisition of Aventis Behring by the Australian company CSL. He was Vice President and General Manager for Emerging Markets for Aventis Behring from 1996-2000 and served as President of Aventis BioServices from 2000-2004. Dr. Martinez began his career with Sandoz Ltd. (today known as Novartis). He spent twenty years working with Sandoz in a variety of roles across the world, including Director and Head of Corporate Strategic Planning in the U.S., Head of the Latin America Business Operations in Switzerland, Director of Marketing and Sales in Spain, and Head of Marketing and Clinical Research in Brazil. Dr. Martinez completed his undergraduate and graduate studies at the University of Sao Paulo and received his medical degree from the University of Sao Paulo in 1973. After completing his residency in Pediatrics in 1975, he studied Business and Marketing Administration at the Fundação Getúlio Vargas in Sao Paulo, Brazil.

Frederick J. Fritz, Director since July 2011

Mr. Fritz was appointed to the Board of Directors in July 2011. He is the CEO and Founder of NeuroDx, a development-stage diagnostic device company focused on the neurosurgery market. Mr. Fritz joined NeuroDx from Valeo Medical, a biotech company he founded in 2003, to develop the world's first noninvasive diagnostic test for endometriosis. Prior to that, Mr. Fritz was President and CEO of Songbird Hearing, a medical device company spin-off of Sarnoff Corp. Mr. Fritz began his career in marketing management and new product development. He joined Schering Plough's Wesley Jessen in 1985 as Vice President, Marketing and Sales. He was promoted to general manager of Schering's OTC pharmaceutical business in 1988 and of the podiatric products business in 1990. Additionally, Mr. Fritz was President of Coleman North America from 1995-1997. He holds an Engineering degree from the University of Illinois, from which he was graduated Summa Cum Laude, and an MBA from Harvard Business School.

Donald Braun, PhD, Director since December 2015

Dr. Braun joined Celsion in 2015 and brings over 30 years of research expertise in oncology, with a focus on immunotherapy and effectiveness and impact of chemotherapy protocols on various cancers and tumor types. Prior to his retirement in 2016, Dr. Braun served as Vice President Translational Research and Chief Science Officer at the Cancer Treatment Centers of America (CTCA). Prior to the CTCA, he was the Scientific Director of the Cancer Center and Professor of Medicine and Immunology at Rush Medical College in Chicago, and the Administrative Director of the Cancer Institute and a Professor of Surgery with tenure at the Medical College of Ohio. Dr. Braun has been appointed to and served on more than a dozen federal government and public advisory committees on oncology and immunology. He received his PhD in Immunology and Microbiology from the University of Illinois at the Medical Center in Chicago.

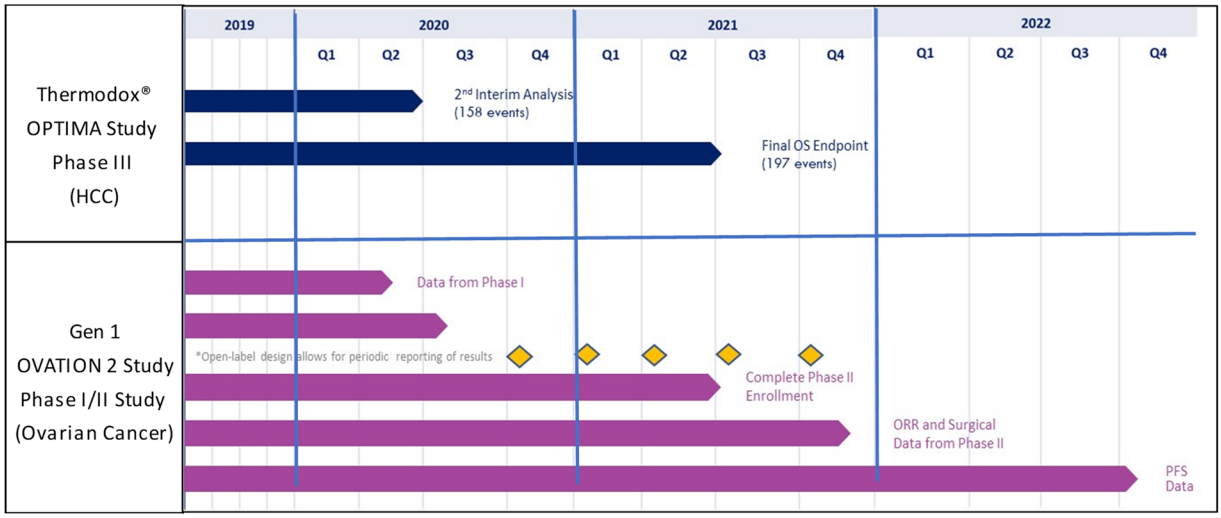
Andreas Voss, MD, Director since December 2015

Dr. Voss joined Celsion in 2015 and currently serves as Vice President of Clinical Affairs in Europe at Caris Life Sciences, a biotechnology company focused on implementing personalized medicine in oncology through its liquid biopsy technology. Prior to joining Caris in 2010, he was responsible for the global clinical development of Avastin® and a member of the Corporate Drug Safety Board at F. Hoffmann-La Roche. Before joining Roche in 2006, he was Medical Director for the Lung Cancer Disease Area at AstraZeneca, and from 2000 to 2003, he was the Medical Director for Anti-invectives and Oncology at Bayer GmbH. From 1996 to 2000, Dr. Voss was Head of Medical Research, Oncology at Asta Medica AG. Dr. Voss received his MD from the University of Hamburg Medical School and was postdoctoral fellow at the University of California at San Diego. He is board certified in internal medicine.

Milestones

Over the last 12 months, Celsion has achieved significant milestones as it continues to advance its clinical programs. An overview of achieved and potential milestones with regard to the Company's ThermoDox® and GEN-1 development efforts is provided in Figure 2. Potential upcoming milestones are outlined thereafter.

Figure 2
MILESTONES



Source: Celsion Corporation.

Completed Milestones

- Completed the Phase I portion of the OVATION 2 study with GEN-1 in advanced ovarian cancer (Q2 2020).
- Initiated the Phase II portion of the OVATION 2 study in Q3 2020, with the randomization of the first two patients in July 2020.
- Received Orphan Drug designation from the European Medicines Agency for its GEN-1 immunotherapy in March 2020.
- Completed first interim efficacy analysis of the OPTIMA Phase III study in November 2019.
- Initiated independent statistical evaluation of the data for the second interim analysis of the OPTIMA study in July 2020.

Potential Milestones

- Complete enrollment of up to 118 patients for the Phase II portion of the OVATION 2 study in Q2/Q3 2021.
- Complete findings from the independent statistical evaluation of the data for the second interim analysis of OPTIMA by Y/E 2020.
- Achieve requirements for the final analysis of OPTIMA (197 or more deaths) by Q3 2021 (assuming the results of the evaluation of the data for the second interim analysis are positive).
- Obtain overall response rate (ORR) and surgical data from GEN-1's OVATION 2 Phase II study.

Intellectual Property

Patents and Proprietary Rights

Celsion holds an exclusive license agreement with Duke University for its temperature-sensitive liposome technology that covers the ThermoDox® formulation. The Company has also issued patents which pertain specifically to methods of storing stabilized, temperature-sensitive liposomal formulations, which will assist in the protection of global rights. These patents will extend the overall term of the ThermoDox® patent portfolio to 2026. These patents are the first in this family, which includes pending applications in the U.S., Europe, and additional key commercial geographies in Asia. This extended patent runway to 2026 allows for the evaluation of future development activities for ThermoDox® and Celsion's heat-sensitive liposome technology platform.

- For the ThermoDox® technology, Celsion either exclusively licenses or owns U.S. and international patents with claims and methods and compositions of matters that cover various aspects of lysolipid thermally sensitive liposomes technology, with expiration dates ranging from 2018 to 2026.

- For the TheraPlas™ technology, the Company owns three U.S. and international patents and related applications with claims and methods and compositions of matters that cover various aspects of TheraPlas™ and GEN-1 technologies, with expiration dates ranging from 2020 to 2028.

Orphan Drug Designation (U.S.)

In 2009, the FDA granted orphan drug designation for ThermoDox® for the treatment of HCC.

In 2005, the FDA granted orphan drug designation for GEN-1 for the treatment of ovarian cancer.

Orphan drug designation does not convey any advantage in, or shorten the duration of, the regulatory review and approval process. However, if a product which has an orphan drug designation subsequently receives the first FDA approval for the indication for which it has such designation, the product is entitled to orphan drug exclusivity, which means the FDA may not approve any other application to market of the same drug for the same indication for a period of seven years, except in limited circumstances, such as a showing of clinical superiority to the product with orphan exclusivity. Orphan drug designation can also provide opportunities for grant funding towards clinical trial costs, tax advantages, and FDA user-fee benefits.

Orphan Drug Designation (Outside the U.S.)

In March 2011, the European Commission (EC) granted orphan drug designation for the Company's lead compound, ThermoDox®, a proprietary heat-activated liposomal encapsulation of doxorubicin, for the treatment of hepatocellular carcinoma (HCC), commonly referred to as primary liver cancer.

In March 2020, the European Medicines Agency (EMA) Committee for Orphan Medicinal Products (COMP) recommended that GEN-1 be designated as an orphan medicinal product for the treatment of ovarian cancer.

As established by the EMA, Orphan Medicinal Product Designation by the European Commission provides for scientific advice and certain regulatory assistance during the product development phase, direct access to centralized marketing authorization, and certain financial incentives for companies developing new therapies intended to treat a life-threatening or chronically debilitating conditions that affect no more than five in 10,000 people in the European Union (EU).

Benefits for the designation are manifold and include:

- 10 years of market exclusivity (in which other industry sponsors are prevented from entering the market with a similar product for the same therapeutic indication);
- EMA protocol assistance for sponsors on the conduct of the tests and trials necessary to demonstrate their quality, safety and efficacy, or regulatory assistance;
- EMA advice will be free or given in return for reduced fees;
- Access to a centralized procedure allowing immediate marketing authorization in all Member States and facilitating the availability of medicines to all patients in the EU; and
- Eligibility for a reduction of regulatory fees associated with pre-authorization inspections, as well as marketing authorization application fees and certain other fees for qualifying companies.

Core Story

Celsion Corporation ("Celsion" or "the Company") is a fully integrated biopharmaceutical company focused on developing a portfolio of innovative cancer treatments through the application of its two distinct and innovative nanoparticle-based technology platforms: TheraPlas™ and Lysolipid Thermally Sensitive Liposomes (LTSL). Celsion's proprietary platform technologies (profiled below) are engineered to enhance the clinical benefits of proven therapeutic agents and provide the basis for developing a range of therapeutics and immunotherapies for difficult-to-treat forms of cancers.

- TheraPlas™ is a novel nonviral vector delivery system for therapeutic plasmids.
- Lysolipid Thermally Sensitive Liposomes (LTSL) is a heat-sensitive liposomal formulation that allows for the targeted delivery of known chemotherapies in the presence of mild heat.

Through the application of these technologies, Celsion is working to develop and commercialize more efficient, effective, and targeted oncology therapies that seek to maximize efficacy and minimize side effects common to cancer treatments. The Company's pipeline (Figure 3) represents a comprehensive, integrated portfolio of therapeutic agents in the areas of chemotherapy, immunotherapy, and RNA-based therapy, largely focused on first-line treatment in combination with the standard of care (SOC).

The use of TheraPlas™ has resulted in product candidate GEN-1, a DNA-based immunotherapy, currently being evaluated in the Phase I/II OVATION 2 Study, in combination with chemotherapy, for the localized treatment of newly diagnosed ovarian cancer. GEN-1 obtained Orphan Drug Designation in the U.S. and EU. The Company's pipeline also includes ThermoDox®, a heat-mediated doxorubicin delivery platform. ThermoDox® uses Celsion's LTSL technology to encapsulate doxorubicin, a proven and commonly used cancer drug, to facilitate its targeted delivery at the tumor site. ThermoDox® is currently being evaluated in the OPTIMA Study, a global Phase III clinical trial for the treatment of hepatocellular cancer (HCC)/primary liver cancer, and has obtained Orphan Drug Designation in the U.S. and EU, as well as Fast Track designation for HCC in the U.S. In addition, Celsion is conducting preclinical studies to expand the application of its technologies to address unmet medical needs in other cancer indications—ThermoDox® in bladder, breast, and pancreatic cancer. Greater details of each of these candidates is provided in the accompanying sections.

Figure 3

CELSION PRODUCT PIPELINE

Product	Indication	Pre-clinical	Phase I/II	Phase III
Thermodox®	Primary Liver Cancer			
GEN-1	Ovarian Cancer			
Thermodox®	Bladder Cancer			

Source: Celsion Corporation.

GEN-1 IMMUNO-ONCOLOGY OVERVIEW

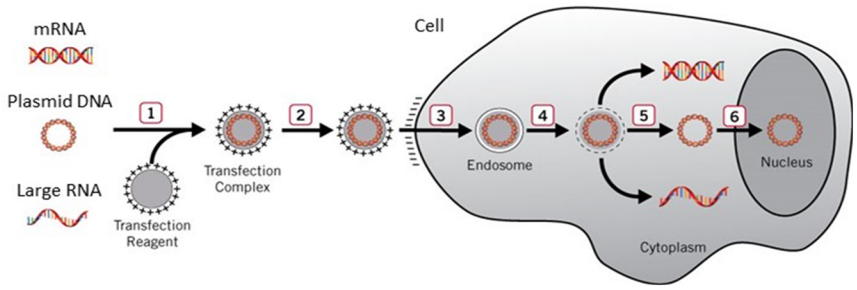
GEN-1, the first product designed from the TheraPlas™ platform technology, is an immuno-oncology candidate that provides localized immunotherapy for the treatment of cancer. GEN-1 is currently under clinical evaluation for the treatment of ovarian cancer (an indication for which it received Orphan Drug Designation in the U.S. and EU).

THERAPLAS™ TECHNOLOGY

Celsion's TheraPlas™ is a proprietary technology platform aimed at improving the safety and efficacy of gene-based immunotherapies. The technology uses synthetic, nonviral carriers capable of providing cell transfection of DNA plasmids and large RNA segments coded for the expression of therapeutic proteins that can promote an effective immune response. Unlike viral carriers that can only be applied once, TheraPlas™ non-viral carriers can skirt the immune system neutralizing activity and can be used for multiple applications, which is ideal for cancer therapies.

Transfection is the process of artificially introducing nucleic acids (DNA, siRNA, or messenger RNA [mRNA]) into cells, by means other than viral infection, in order to produce genetically modified cells. The process, illustrated in Figure 4, starts when a transfection reagent is combined with nucleic acid to form transfection complexes. The complex, which is positively charged, then binds to the negatively charged cell surface, where it is taken up by the cell via **endocytosis** into endosomes. Once inside the cell, the nucleic acid escapes from the endosomes into the cytoplasm. In the case of DNA transfection, the DNA then enters the nucleus of the cell, where it is transcribed into mRNA. Once mRNA is formed, the mRNA molecule will be released into the cytoplasm and be translated into a specific immune protein.

Figure 4
TRANSFECTION



Source: Mirus Bio LLC.

There are two components of the TheraPlas™ system: a plasmid DNA or mRNA payload encoding a therapeutic protein, and a delivery system. The delivery system is designed to protect the DNA/RNA from degradation and promote trafficking into cells and through intracellular compartments. Biocompatibility of the polymers reduces the risk of adverse immune reactions, allowing for repeat administration. Compared to naked DNA, TheraPlas™ is generally safer, more efficient, and more cost effective.

The design of the TheraPlas™ delivery system is based on molecular functionalization of polyethyleneimine (PEI), a cationic delivery polymer with a distinct ability to escape from the endosomes. The transfection activity and toxicity of PEI is proportionally coupled to its molecular weight, limiting its clinical application. Celsion used molecular functionalization strategies to improve the activity of low-molecular-weight PEIs without augmenting their cytotoxicity. In addition, the Company achieved further improvements to PEI activity by crosslinking low-molecular-weight PEIs through degradable linkages to create larger and degradable structures. Two cross-linked polymers have been synthesized with this approach and optimized for transfection activity. Both cross-linked polymers expressed several-fold higher transfection activity than their respective **monomers** and lower cytotoxicity than a commercially available 25 kDa polymer.

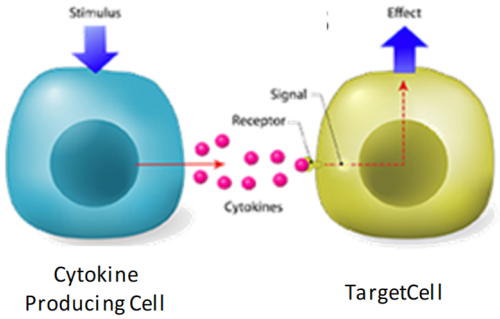
The Company's first product designed using the TheraPlas™ platform technology is GEN-1, which combines TheraPlas™ with the interleukin-12 (IL-12) plasmid. Its nanoparticle profile enables cell transfection of the plasmid followed by persistent, local secretion of the IL-12 protein at therapeutic levels, while avoiding the toxicities associated with recombinant IL-12.

GEN-1 IMMUNO-ONCOLOGY PROGRAM

GEN-1 is gene-mediated immunotherapy that incorporates a DNA plasmid payload encoding IL-12 into a unique nanoparticle delivery system. GEN-1 is currently being evaluated in the Phase I/II OVATION 2 study, in combination with chemotherapy, for newly diagnosed ovarian cancer patients.

TheraPlas™ technology has proven to be an effective immunotherapy for treating various types of tumors when utilized in combination with an IL-12 plasmid. IL-12 is one of the most active cytokines for stimulating an immune response against cancer. Cytokines are protein molecules that help regulate virtually all biological functions. In particular, cytokines play crucial roles in coordinating the activities of the innate and adaptive immune system. In response to pathogen recognition, innate immune cells secrete cytokines that act as messengers, allowing cells of the immune system to communicate with one another and generate a coordinated robust response to a target antigen (Figure 5). They also help to boost anti-cancer activity by sending signals that can help abnormal cells to die and normal cells to live longer (Source: American Cancer Society).

Figure 5
CYTOKINES



Source: Biology Dictionary.

Thus, these messenger molecules can be used as cancer therapeutic agents by trying to harness the biological potency of specific cytokines and exploit their vast signaling networks to elicit novel or strengthen pre-existent tumor-targeting immune responses, as well as to prevent or manage chemotherapy side effects. To accomplish this, specific cytokines are synthesized in the laboratory and injected in larger doses than the body would normally produce, with interleukins and interferons being the two most common cytokines used in cancer therapy.

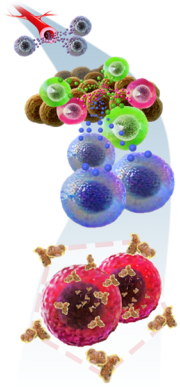
Interleukin-12 (IL-12) Anti-Cancer Modulation

Interleukins (ILs) are a group of cytokines that act as chemical signals between white blood cells. There are more than a dozen interleukins, including IL-12, a pro-inflammatory cytokine that regulates **cytotoxic T-cell (CD-8+)** and **natural killer-cell** responses, induces the production of **interferon-gamma (IFN-γ)**, favors the differentiation of **T-helper cells (CD-4+)**, and is an important link between innate resistance and adaptive immunity (Source: *Cytokine*, Vol.75(2): 249–255, 2015).

Due to the ability of IL-12 to play a key role in coordinating the activities of the innate and adaptive immune system, this cytokine family can also induce anti-cancer immunity actions through multiple mechanisms, as depicted in Figure 6 (page 18). Specifically, IL-12 performs the following immune-related activities: (1) recruits both the adaptive and the innate immune system, stimulating the proliferation of both cytotoxic **T-cells** and natural killer cells; (2) shifts the differentiation of naive T-helper cells towards a **TH-1 immune response**; (3) promotes the creation of interferon-gamma (IFN-γ), which encourages the expression of anti-angiogenic molecules, halting the growth of new blood vessels that supply the tumor; and (4) inhibits regulatory T-cells that suppress the immune response.

Figure 6

INTERLEUKEN-12

Activation Proliferation		Stimulates the proliferation of CD-8 positive T-cells and natural killer (NK) cells and their cytotoxic activity against the tumor.
Maturation/Proliferation		Shifts the differentiation of naive CD-4 positive T-cells toward a TH-1 phenotype, further enhancing the immune response – Turns "cold" tumors into "hot" tumors.
Anti-Angiogenesis		Promotes cellular production of the potent immune mediator IFN-γ and TNF-α. IFN-γ promotes the expression of anti-angiogenic molecules, halting the growth of new blood vessels that supply oxygen to the tumor.
Inhibition of Immune Suppression		IL-12 may inhibit regulatory T-cells that suppress immune responses by "hiding" the tumor from the body's immune system.

Source: Celsion Corporation.

The recruitment of cytotoxic T-cells helps the immune system fight the disease, as these cells can recognize and kill cancerous cells. This effect is augmented by IL-12's ability to drive the immune system towards a TH-1 immune response—an acquired response characterized by high cytotoxic T-cell that is promoted by Th1 helper cells. IL-12 also promotes the generation of IFN-γ. Interferons are immune proteins that help the body resist virus infections and cancers. Interferon gamma drives angiogenic activity, which halts or slows the growth the blood vessels that tumors need to grow. In addition to helping the immune system attack the cells, IL-12 also plays a key role in preventing tumor tolerance, as it inhibits the presence of regulatory T-cells that suppress anti-cancer immune response through tumor tolerance mechanisms. IL-12 leverages T-helper cells, which facilitates the immune system's recognition of cancerous cells, thereby functionally "breaking" tumor tolerance.

However, when administered intravenously as a recombinant protein, IL-12 displays a short half-life, which requires that it be administered by frequent, large bolus injections, resulting in serious toxicities that limit its effectiveness and applications. According to the Company, GEN-1 circumvents toxicity issues typically associated with IL-12 by its targeted administration directly to the tumor location.

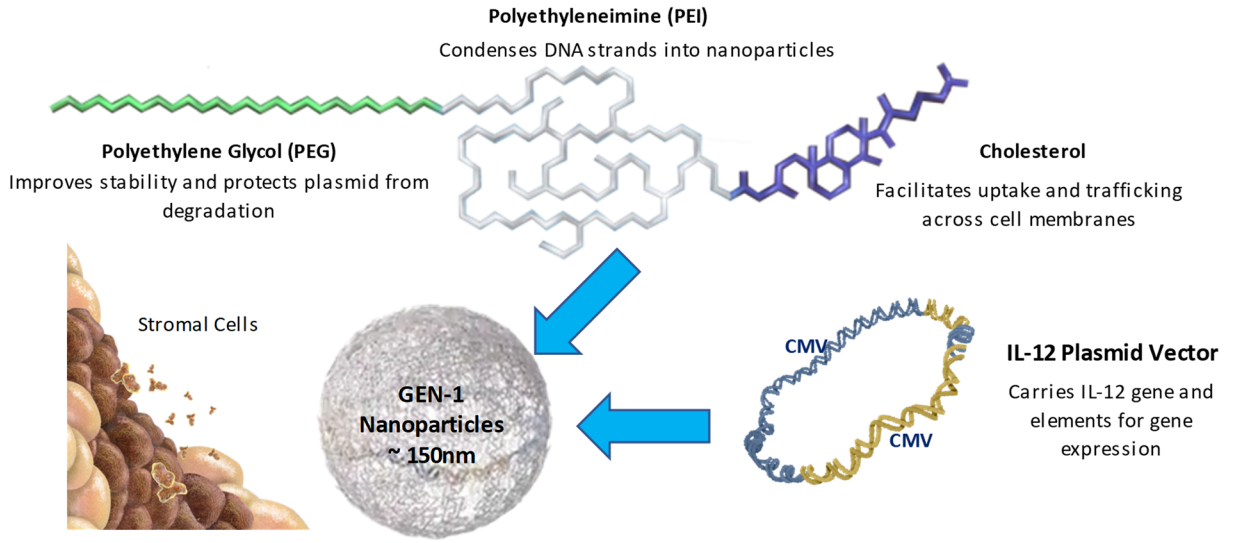
GEN-1 Overview

GEN-1 is a novel immune-gene therapeutic designed with Celsion's proprietary TheraPlas™ technology. When delivered to a tumor site, GEN 1 may activate both innate and acquired immune responses against cancer. The safety, biological activity, and antitumor activity has been demonstrated in animal models as well as Phase I clinical trials in ovarian cancer patients, and in a murine model of glioma. These two cancers display similar characteristics that make it attractive for GEN-1 treatment because: (1) complete surgical resection of tumors is difficult to achieve; (2) recurrences are common; and (3) chemotherapy has not been proven curative in recurrent disease. While traditional chemotherapy kills fast-growing cancer cells, GEN-1 immunotherapy enhances the local and systemic immune response against tumors, potentially offering a more targeted and less toxic approach to cancer treatment.

As shown in Figure 7 (page 19), GEN-1 consists of a human IL-12 plasmid, formulated with a non-viral synthetic DNA delivery system: **P**olyethylene Glycol (PEG) **P**olyethyleneimine (PEI) **C**holesterol, denominated PPC. The PPC polymer is condensed together with the plasmid, forming nanoparticles. These lyophilized nanoparticles are simply reconstituted at the patient's bedside, and the solution is infused directly into the local tumor environment via a catheter.

Figure 7

GEN-1 CONSTRUCT



Source: Celsion Corporation.

Following administration, the nanoparticles can become endocytosed by many types of stromal cells in the tumor microenvironment. The three components of PPC play different roles in bringing plasmids to their target cells. The PEI condenses DNA strands into nanoparticles, the PEG improves stability and protects plasmid from degradation, and the cholesterol facilitates uptake and trafficking across cell membranes. Within the cell, PEI also facilitates lysis of the endosome, allowing the naked DNA plasmid to emerge and allowing the IL-12 gene that it encodes to be expressed by the cellular machinery.

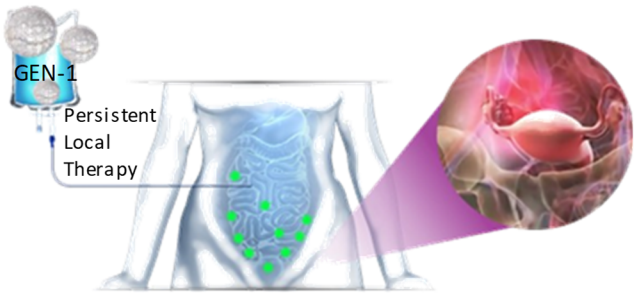
Transfected cells are able to produce sustained concentrations of IL-12 in the vicinity of the tumor. GEN-1 provides for a local and durable elevation of IL-12 at the tumor site, with exposure that persists for several days after a single treatment. The IL-12 minimizes toxicity by avoiding spillover into the systemic circulation. Sustained concentrations of IL-12 may lead to prolonged infiltration of immune cells in the tumor environment, enhancing the local immune response against cancer.

GEN-1 Administration Protocol—Ovarian Cancer

During clinical trials, GEN-1 is being administered to ovarian cancer patients via a catheter directly into the peritoneal cavity, where the GEN-1 nanoparticles transfect into cells that it comes in contact with, as seen in Figure 8. Administration of GEN-1 through this method has shown durable local expression of IL-12 in the affected area. In addition, the peritoneal plasma barrier minimizes the spillover of IL-12 into the systemic circulation, minimizing the toxicity normally associated with IL-12 administration, resulting in a favorable safety profile.

Figure 8

GEN-1 ADMINISTRATION



Intracavity infusion of GEN-1 has demonstrated durable and local expression of IL-12 in the peritoneum

Peritoneal-plasma barrier minimizes systemic exposure of IL-12, thereby giving a favorable safety profile to GEN-1

Source: Celsion Corporation.

Ovarian cancer is the most lethal of gynecological malignancies among women. There will be approximately 21,750 new cases of ovarian cancer in the U.S. in 2020, with an estimated 13,940 deaths. Among women, ovarian cancer is the 11th most common cancer, ranking fifth in cancer mortality, and accounting for 5% of all cancer related death among women (Source: American Cancer Society's *Cancer Facts and Figures 2020*).

Figure 9

OVARIAN CANCER SURVIVAL RATES

	% Diagnosed	5-yr Survival Rate	
All Stages		**46.2%**	
Localized	15%	92%	
Regional	21%	75%	
Distant	59%	29%	→ 39% for Stage III 17% for Stage IV

Source: OCRA: Ovarian Cancer Research Alliance .

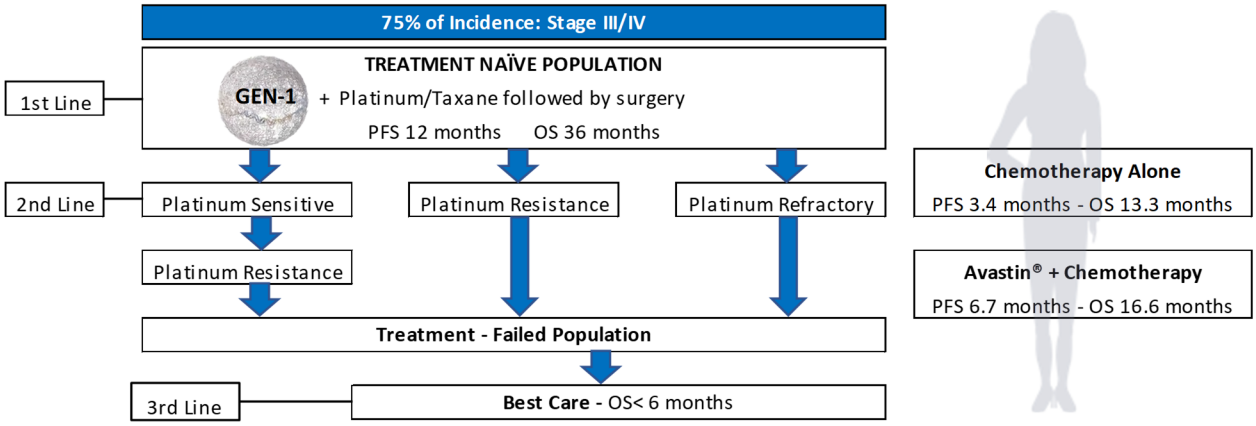
As seen in Figure 9, the 5-year survival rate for ovarian cancer is only 46.2% because most patients (59%) are diagnosed with distant-stage disease, for which survival is 29%. This is mostly due to the lack of detection tests, as there is no early detection test for ovarian cancer. Most women with ovarian cancer are not diagnosed until Stage III or IV, when the disease has spread outside the pelvis to the abdomen and beyond, where 5-year survival rates are 39% and 17%, respectively. For the 15% of patients diagnosed with localized disease, 5-year survival is 92%.

Debulking surgery plus adjuvant platinum-based chemotherapy has become the accepted primary treatment for the disease. However, for some patients in the advance stages, immediate surgery is not advisable, as studies have shown that patients with an initial high disease burden will have a worse prognosis despite optimal resection. In these cases, neoadjuvant chemotherapy (NAC) followed by interval debulking surgery (IDS) was introduced to diminish the initial disease burden and shrink the tumor in preparation for surgery, increasing the likelihood of successful IDS (Source: *Journal of Clinical Medicine*, Vol. 9(4): 1235, 2020). It is to this NAC treatment that Celsion is adding weekly cycles of GEN-1.

First-line chemotherapy regimens are typically platinum-based combination therapies (Figure 10). Although this first line of treatment has an approximate 80% response rate, 55% to 75% of women will develop recurrent ovarian cancer within two years and ultimately will not respond to platinum therapy. First line treatments results in a progression-free survival (PFS)—the length of time during and after the treatment of a disease that a patient lives with the disease but it does not get worse—of 12 months and overall survival of 36 months.

Figure 10

OVARIAN CANCER - TREATMENT PROTOCOL



Source: Celsion Corporation.

Patients whose cancer recurs or progresses after first-line treatments are normally divided into two groups based on the time from completion of therapy to disease recurrence: (1) the platinum-sensitive group, which has a recurrence platinum-free interval of longer than 6 months, generally responds to additional treatment with platinum-based therapies; and (2) the platinum-resistant group, with a platinum-free interval of shorter than 6 months, is resistant to additional platinum-based treatments. Chemotherapy and Avastin® are the only approved

second-line therapies for platinum-resistant ovarian cancer. Of note, patients that undergo secondary surgery following recurrence do not live longer and may fare worse than those who do not (Source: NIH).

GEN-1 Clinical Studies

Preclinical and clinical studies suggest that GEN-1 can be safely and repeatedly administered for the treatment of a variety of tumor types, including ovarian, colorectal, and brain cancers. GEN-1's nanoparticle profile enables cell transfection followed by persistent, local secretion of IL-12 at therapeutic levels, while avoiding the toxicities associated with recombinant IL-12. Targeted administration directly to the tumor location also helps reduce toxicities. Figure 11 lists selected journal articles and presentations relating to the GEN-1 technology, with key studies' results summarized below.

Figure 11

GEN-1 SELECTED JOURNAL ARTICLES AND PRESENTATIONS

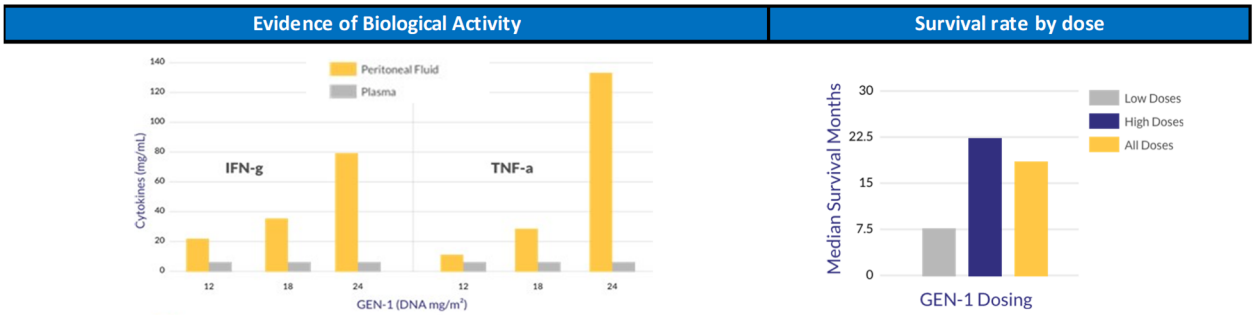
Title	Journal/Location	Year
Synthetic tumor networks for screening drug delivery systems.	Journal of Controlled Release Vol. 201:49-55	2015
A Phase II trial of intraperitoneal EGEN-001, an IL-12 plasmid formulated with PEG-PEI-cholesterol lipopolymer in the treatment of persistent or recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer: a Gynecologic Oncology Group study.	Gynecolic Oncology Vol. 133(3):433-438	2014
Phase I trial of a formulated IL-12 plasmid in combination with carboplatin and docetaxel chemotherapy in the treatment of platinum-sensitive recurrent ovarian cancer.	Gynecolic Oncology Vol. 131(1):169-173	2013
Biocompatible polymers for nucleic acid delivery.	Biodegradable Polymers in Clinical use and Clinical Development Chapter 15: 521-563	2011
Phase I clinical trial of IL-12 plasmid/lipopolymer complexes for the treatment of recurrent ovarian cancer.	Gene Therapy Vol. 17: 360-369	2010
Treatment of disseminated ovarian cancer using nonviral interleukin-12 gene therapy delivered intraperitoneally.	The Journal of Gene Medicine Vol. 11(8):718-728	2009
Functionalized Polymers for gene therapy: Discovery, optimization, and clinical development.	2008 National American Chemical Society Meeting - Presentation Polymer Preprints - Vol. 49(2):423-424	2008
Formulation for DNA delivery via electroporation in vivo.	Methods in Molecular Biology Vol. 423:77-89	2008
A safety and efficacy study of local delivery of interleukin-12 transgene by PPC polymer in a model of experimental glioma.	Anti-cancer Drugs Vol. 19(2):133-142	2008
Synthesis and characterization of low molecular weight linear polyethylenimines for gene delivery.	Journal of Biomedical Nanotechnology Vol. 2(1):53-61	2006

Source: Celsion Corporation.

As seen in Figure 12, biological activity and clinical benefits have been demonstrated in platinum-resistant ovarian cancer in multiple clinical studies, where GEN-1 was administered as a single agent or as a combination agent with chemotherapy.

Figure 12

GEN-1 CLINICAL TRIAL OVERVIEW



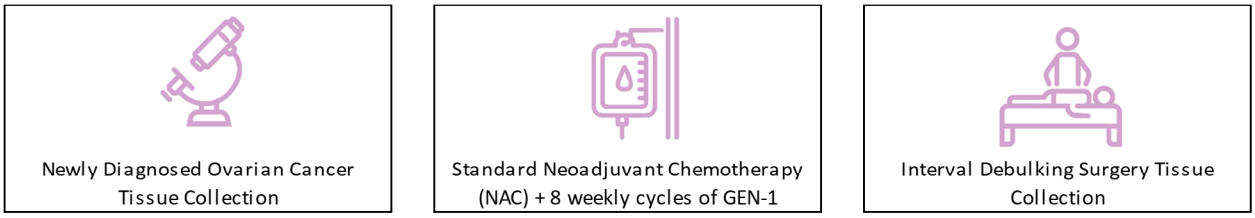
Source: Celsion Corporation.

OVATION I Phase I Study

OVATION I was a Phase I study of the safety and biological activity of intraperitoneal GEN-1 administered in combination with standard neoadjuvant chemotherapy (NAC) in patients newly diagnosed Stage III/IV epithelial ovarian, fallopian tube, or primary peritoneal cancer. The primary endpoint was determination of a recommended Phase II dose of GEN-1 in combination with standard neoadjuvant therapy. The study also evaluated dose-related biological response to IL-12, with secondary endpoints related to clinical and surgical response as well as biological activity. Figure 13 provides an overview of the OVATION I study.

Figure 13

OVATION I STUDY



Ovarian Cancer Patients
(FIGO IIIC & IV)

3+3 Dose Escalation

Starting at 36 mg/m^2
Final Dose at 79 mg/m2

Primary Endpoint

Safety

Optimal Dose

Secondary Endpoints

Clinical Response, PFS, Pathological Response, Surgical Response, Biological Response

Source: Celsion Corporation.

The dose escalating study followed a standard 3+3 design with approximate 30% dose increments between successive cohorts of patients. The study's initial dose was 36 mg/m^2, ending with six patients at 79 mg/m^2. In a 3+3 design, three patients are initially enrolled into a given dose cohort. If there are no dose-limiting toxicity (DLT) events, defined as clinically significant adverse effects, in any of these subjects, the trial proceeds to enroll additional subjects into the next higher dose cohort. If one subject develops a DLT at a specific dose, an additional three subjects are enrolled into that same dose cohort. The dose escalation continues until at least two patients among a cohort of six patients experience dose-limiting toxicities.

The study showed that administration of GEN-1 resulted in a dose dependent response. As seen in Figure 14, lower doses of GEN-1 resulted in an objective tumor response—the percentage of patients showing a complete response (elimination of all signs of cancer) or partial response (reduction of tumor lesion by at least 30%)—of 60%, compared to an objective tumor response of 100% at the highest doses.

Figure 14

GEN-1 DOSE RESPONSE

	GEN-1	
	Low-Dose Cohorts **36 mg/mg² & 47 mg/mg²**	**High-Dose Cohorts** **61 mg/mg² & 79 mg/mg²**
Objective Tumor Response (CR/PR)	**60%**	**100%**
Interval Debulking Status Resection Rate R0	**40%**	**88%**

Source: Celsion Corporation.

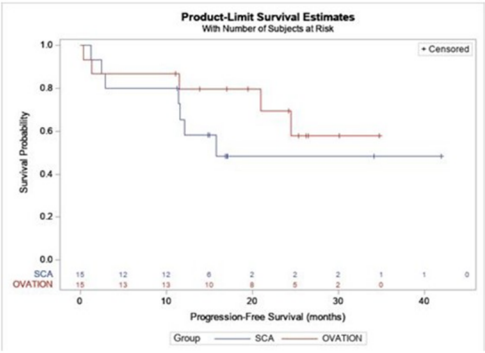
The trial also measured the ability of the surgeon to remove all of the visible tumor following neoadjuvant treatment. The removal of all visible tumor is designated as an R-0 event, a difficult outcome that can be achieved in only 30% to 60% of Stages III/IV ovarian cancers. A recent study of 220 patients showed R-0 levels for primary debulking surgery and IDS following NAC at 32.6% and 43.3%, respectively (Source: *Journal of Ovarian Research*, Vol. 12(85), 2019). Higher doses of GEN-1 resulted in a significant increase of R-0 following IDS, from 40% in lower doses to 88% (8 out of 9 patients) at higher doses.

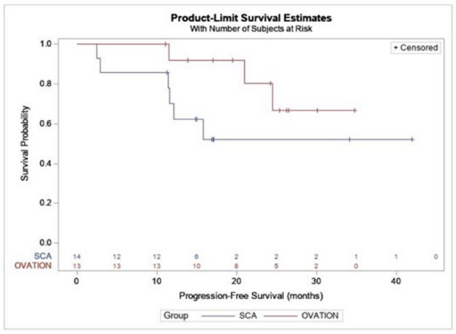
The Company conducted additional data analysis, comparing its OVATION I results to a Synthetic Control Arm (SCA), created by collecting data from control arm patients from other studies who would have otherwise qualified for this trial. Patients in the GEN-1-treated cohort displayed a marked advantage in PFS (time until disease progression), nearly doubling PFS against the control group. Trial patients that followed the OVATION treatment protocol had a PFS of 21 months, 75% higher than the historical estimate of 12 months. Hazard ratio for patients following protocol was 0.33 when compared to the SCA, tripling the median time to progression between the treated patients and the control arm. Figure 15 shows the Kaplan-Meier curves for both the Intent to Treat (ITT) and Per Protocol group, as compared to the SCA. According to Celsion, these findings, although not statistically significant due to the small number of patients, are encouraging and supportive of its current Phase II study.

Figure 15

PROGRESSION FREE SURVIVAL (PFS)

INTENT TO TREAT POPULATION	PER PROTOCOL POPULATION
Hazard Ratio = 0.53	**Hazard Ratio = 0.33**



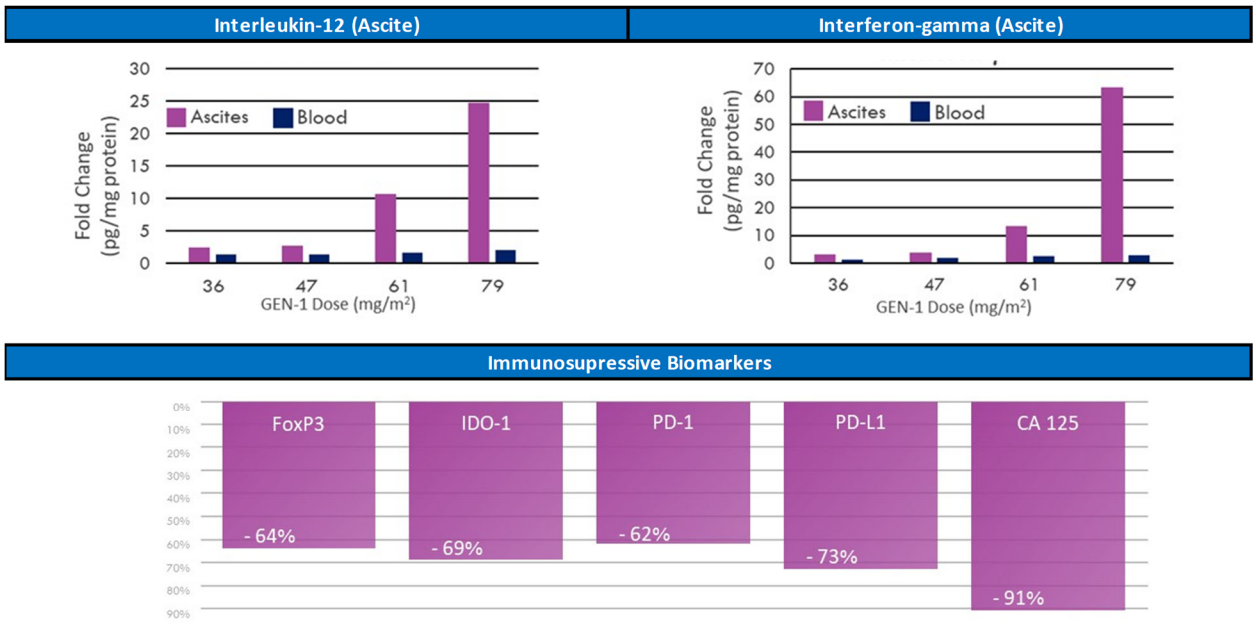


Source: Celsion Corporation.

These results display positive clinical outcomes, surgical response, and PFS, part of secondary endpoint guidelines. The Company also wanted to evaluate GEN-1-mediated biological activity. Celsion conducted independent analysis of tissue samples collected from patients before treatment and after treatment, which are shown in Figure 16. Analysis of **ascites**—the abnormal fluid in the peritoneal cavity normally associated to liver disease and cancer—displayed a dose dependent response on the production of IL-12 and Interferon-gamma. Of significance is that normal blood levels of IL-12 and Interferon-gamma underpin the safety profile of GEN-1, showing its ability to circumvent toxicities normally associated with IL-12 administration. Additional results showed a corresponding increase in dendritic cells and effector memory cells, demonstrating activation of the cellular immune system, as well as a six-fold increase in CD8+/CD4+ cells in the tumor. Furthermore, administration of GEN-1 also resulted in a decrease in immune-suppressant biomarkers, making the tumor visible to the immune system. As shown in the bottom of Figure 16, cancer antigen 125 (CA 125) levels decrease by 91%. CA 125 levels are used to watch for early signs of ovarian cancer in people with an extremely high risk of the disease and may be used to monitor certain cancers during and after treatment. Overall, the decrease in immunosuppressant biomarkers show a shift in tumor microenvironment to immunostimulatory status.

Figure 16

OVATION I BIOLOGICAL ACTIVITY



Source: Celsion Corporation.

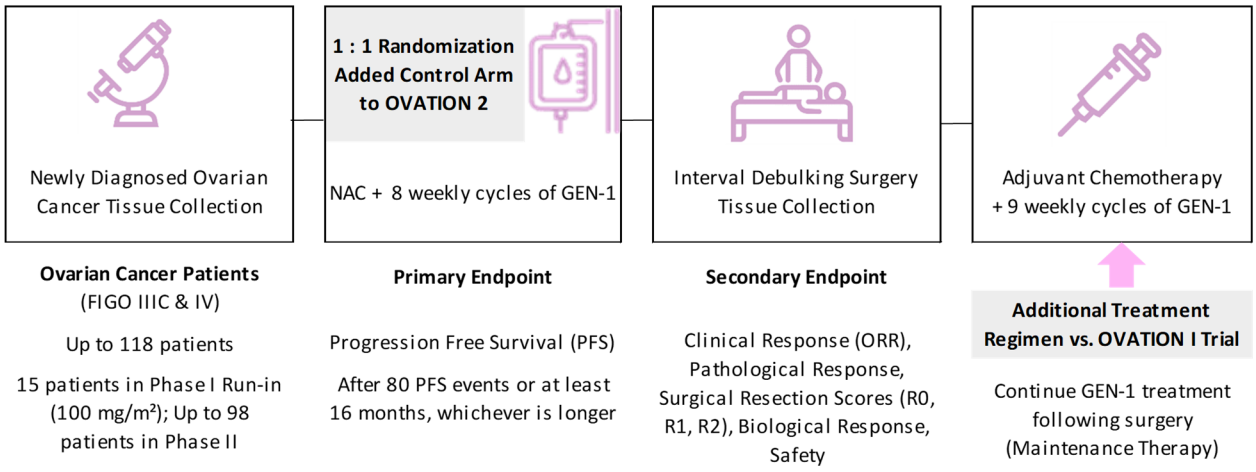
OVATION 2 Phase I/II Study

OVATION 2 is a Phase I/II randomized, open label multicenter study evaluating the dosing, safety, efficacy, and biological activity of intraperitoneal GEN-1 administered in combination with chemotherapy in patients newly diagnosed with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer.

The trial is comprised of up to 110 patients. The Phase I portion of the study, which included 15 patients, was completed in Q2 2020, confirming the dose for the Phase II portion of trial at 100 mg/m² (30% higher than the final dose at OVATION 1). The rest of the eligible subjects are randomly assigned 1:1 to the treatment and control arms. The control arm receives the SOC NAC, followed by surgery (interval debulking surgery), followed by adjuvant therapy. The treatment arm includes SOC plus eight weekly cycles of GEN-1 neoadjuvant treatment. In OVATION 2, the patients continue to receive GEN-1 treatments (in adjuvant capacity) following surgery, with this maintenance therapy lasting up to nine weeks. Celsion believes that GEN-1's ability to elicit an effective immune response can have an impact in destroying cancer cells that remain following chemotherapy and surgery. Figure 17 (page 25) provides an overview of the OVATION 2 study.

Figure 17

OVATION 2 STUDY



Source: Celsion Corporation.

In May 2020, the Company announced the final recommendations of the Data and Safety Monitoring Board (DSMB) to proceed to the Phase II portion of the OVATION 2 study following completion of the Phase I dose-finding and tolerance portion. Based on favorable safety data from 15 randomized patients, the DSMB recommended that the Phase II portion of the OVATION Study proceed with the dose of 100 mg/m², as no dose limiting toxicities were reported. Of the 15 patients treated in the Phase I portion, nine were treated with GEN-1 at a dose of 100 mg/m² plus NACT and six were treated with NACT only. All 15 had successful resections of their tumors, with seven out of nine patients (78%) in the GEN-1 treatment arm having an R-0 resection, while only three out of six patients (50%) in the NACT only treatment arm had an R-0 resection.

The Phase II portion of the study, which initiated enrollment in Q3 2020, has enrolled approximately 30 patients and expects to complete enrollment by mid-2021. The primary objective of the study is to evaluate safety and compare PFS between SOC plus GEN-1 patients versus those receiving SOC alone. Similar to the OVATION I study, the Company plans to continue data and tissue sample collection before and after surgery, to assess the biological and clinical response as well as resection scores. The Company expects PFS data reported in the second half of 2022.

THERAPLAS™ PRECLINICAL PROGRAM

Preclinical studies on the use of GEN-1 for the treatment of **glioblastoma multiforme (GBM)** have demonstrated that administration of GEN-1 in the brain can lead to an IL-12 expression that lasts for at least one month, producing encouraging survival benefits.

GBM is the most common malignant primary brain tumor and the most aggressive in the central nervous system. The American Cancer Society estimates that 23,890 adults will be diagnosed with brain and other nervous system cancer in 2020, resulting in 18,020 deaths. GBM has an incidence of 2-3 per 100,000 adults per year, and accounts for 52% of all primary brain tumors and 17% of all tumors of the brain (Source: American Association of Neurological Surgeons). These tumors are often aggressive, with a median survival of only three months in untreated patients. Even with treatment, survival from GBM is poor; where only one-third of patients survive for one year and less than 5% live beyond five years following diagnosis. Survival rates for patients with GBM have shown no notable improvement in the last three decades (Source: *Gioblastoma*, Codon Publications; Chapter 8, 2017).

Current treatment strategies that involve surgery, radiation, and chemotherapy address only the tumor cells. Therapies that also target the pro-tumorigenic tumor microenvironment, which is characterized by formation of new blood capillaries and suppression of the immune system, may improve efficacy. Local delivery of IL-12 genes by GEN-1, in combination with the SOC, offers a novel approach to GBM treatment. Local production of IL-12 by GEN-1 is anticipated to modify the tumor microenvironment through activation of tumor-killing lymphocytes, attenuation of immunosuppressive regulatory lymphocytes, and inhibition of tumor angiogenesis. In addition, GEN-1 provides pharmacokinetic and safety advantages over bolus administration of recombinant IL-12.

The clinical development plan for GEN-1 in GBM is supported by preclinical studies in animal models. Encouraging efficacy benefits of GEN-1 added to an approved chemotherapy drug, BCNU (carmustine), have been demonstrated in a mouse glioma model. The addition of a single dose of GEN-1 with BCNU significantly increased survival compared to BCNU treatment alone. The GEN-1 treatment administered alone or in combination with BCNU produced infiltration of CD4+ and CD8+ immune cells in treated tumors, compared to untreated tumors, demonstrating activation of the immune system. The safety and biodistribution studies in normal mice showed GEN-1 plasmid was primarily confined to brain tissue and minimally distributed in other tissues.

THERMODOX® OVERVIEW

ThermoDox® uses the Company's Lysolipid Thermally Sensitive Liposome (LTSL) technology to produce heat sensitive liposomes that encapsulate doxorubicin, a widely used, well characterized and proven chemotherapeutic agent, to facilitate its targeted delivery at the tumor site. ThermoDox® is currently being evaluated in clinical studies for hepatocellular carcinoma (HCC)/primary liver cancer (an indication for which it has received Orphan Drug Designation in the U.S. and EU, as well as Fast Track designation for HCC in the U.S.), and has also demonstrated potential efficacy benefits in bladder cancer in preclinical studies.

LYSOLIPID THERMALLY SENSITIVE LIPOSOME (LTSL)

LTSL is a proprietary technology that achieves targeted delivery of known chemotherapeutics using heat-sensitive liposomes. LTSL is engineered with a unique liposomal technology that delivers locally high concentrations of therapeutic compounds—up to 25 times the systemic dose—in a region targeted with the application of tolerable heat. Celsion licensed the exclusive worldwide rights to the LTSL technology from Duke University.

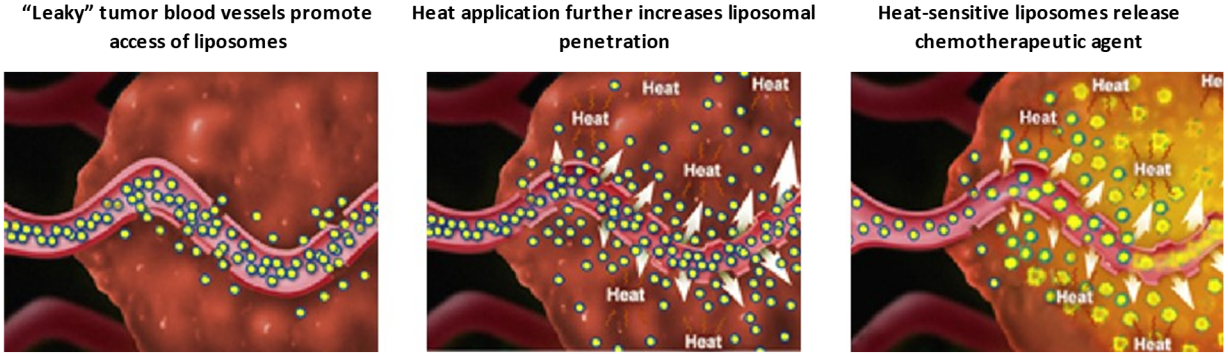
The technology is essentially heat sensitive liposomes that encapsulate a known chemotherapeutic agent. The liposome is administered intravenously, then circulates throughout the body. When it comes in contact with tissue that has been heated to just above body temperature (40ºC), the liposomes release the drug at the site in extremely high local concentrations.

According to the Company, there is general agreement in the medical community that tumor blood vessels are abnormal, manifesting leaky endothelium that influences, among other things, access of therapeutic agents to tumor cells. Administered as a standard intravenous infusion, Celsion's specially designed liposomes circulate throughout the bloodstream and into the tumor through the leaky tumor vasculature, concentrating at the tumor site.

LTSL relies on this physiological abnormality, and further exploits it by applying heat. An external heating device gently heats the tumor tissue to greater than 40ºC. The localized administration of heat accentuates the leakiness of the blood vessels by increasing the porosity of the tumor vasculature, causing more drug-delivering liposomes to be carried into the tumor. Heat application also produces important changes in the liposome. These liposomes are composed of lipid molecules that quickly change structure when heated to a specific temperature, creating channels that allow the encapsulated drug to rapidly disperse into the surrounding tissue. When the tissue reaches a temperature of 40ºC or greater, the heat-sensitive liposome rapidly changes structure and the liposomal membrane selectively dissolves, releasing the chemotherapeutic agent directly into the tumor and surrounding vasculature. As a result, LTSL enables delivery of higher concentrations of proven chemotherapy drugs directly to the tumor, minimizing systemic toxicity and the toxic side-effects normally associated with chemotherapy. This process is depicted in Figure 18.

Figure 18

LTSL



Source: Celsion Corporation.

A key aspect of the LTSL technology is its flexibility when it comes to the type of process used as the means of heating. The technology's flexibility to what heat source is used allows it to be used for the treatment of different types of tumors and cancers. Celsion has shown the LTSL mechanism to be effective whether combined with radiofrequency thermal ablation (RFA) to expand the "treatment zone" for solid tumors, microwave ablation for superficial tumors, or high-intensity focused ultrasound for difficult to reach tumors.

Celsion's first investigational product developed through application of LTSL technology is ThermoDox®, which consists of the liposomal encapsulation of doxorubicin. Furthermore, the LTSL platform has shown its applicability to a variety of drug products, and is being evaluated independently by researchers in bladder cancer, metastatic liver cancer, breast cancer, pancreatic cancer, and at the Children's Hospital in sarcomas.

THERMODOX® CHEMOTHERAPY

ThermoDox® uses LTSL to produce heat sensitive liposomes that encapsulate doxorubicin, a widely used well characterized and proven chemotherapeutic agent. The heat-sensitive liposome rapidly changes structure when heated to 40ºC-45ºC, creating openings in the liposome that release doxorubicin directly into and around the targeted tumor. ThermoDox® leverages two facets of tumor biology: (1) tumors have leaky vasculature, which is permeable to liposomes and enables their accumulation within tumors; and (2) when heated, blood vessels in tumors become even more permeable, further increasing the accumulation of liposomes in tumors before releasing the doxorubicin. In animal models, ThermoDox® has shown to deliver 25 times more doxorubicin into tumors than intravenous (IV) infusion alone, and five times more doxorubicin than standard liposomal formulations of the drug.

One of the first indications in human clinical studies is the use of ThermoDox® for the treatment of HCC/primary liver cancer, where ThermoDox® is currently undergoing a Phase III study. The study—denominated OPTIMA—launched in Q2 2014.

Hepatocellular Carcinoma (HCC)/Primary Liver Cancer

Hepatocellular carcinoma (HCC) is one of the most common and deadliest forms of cancer worldwide. In 2020, an estimated 42,810 new cases of liver and bile duct cancer will be diagnosed in the U.S. and 30,160 people will die from the disease. Liver cancer is the fifth and seventh most common cause of cancer death among men and women, respectively. In the U.S., liver cancer incidence rates have more than tripled since 1980; with the rate increasing by about 2% per year from 2007 to 2016. The death rate for liver cancer has doubled from about 3.0 (per 100,000) during the 1980s to 6.6 during 2013-2017 (Source: American Cancer Society's *Cancer Facts and Figures* 2020).

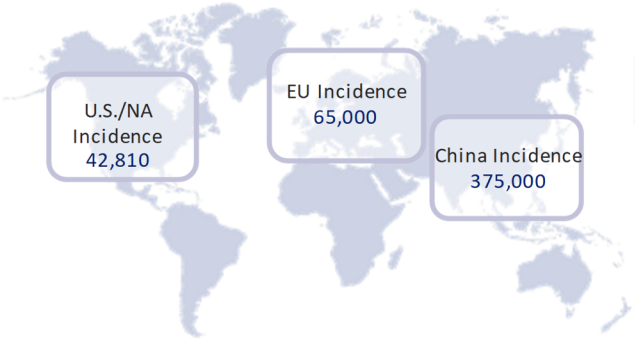
Overall, HCC incidence has been growing on a global scale. Primary liver cancer is the sixth most commonly diagnosed cancer and the fourth leading cause of cancer mortality worldwide, with an estimated 841,000 cases (9.3 cases per 100,000) and 782,000 deaths (8.5 deaths per 100,000) in 2018 (Source: *Frontiers in Oncology*, Vol. 10: 171, 2020). The pattern of HCC occurrence shows a significant geographical imbalance, with the highest incidence rates in East Asia (more than 50% of the cases occurring in China) and sub-Saharan Africa, together accounting for about 85% of all cases. Between 1990 and 2015, newly diagnosed HCC cases increased by 75%, mainly due to changing age structures and population growth. Projections in the U.S. estimate that in 2030, liver cancer will be the third leading cause of cancer-related deaths, surpassing breast, colorectal, and prostate cancers (Source: *Journal of Hepatology*, Vol. 69:182–236,2018). Figure 19 (page 24) provides and overview of HCC's incidence and survival data.

It is often difficult to find liver cancer early because small liver tumors are hard to detect and signs and symptoms—including abdominal pain and/or swelling, weight loss, weakness, loss of appetite, and jaundice—often do not appear until it is in its later stages. At this time, there are no widely recommended screening tests for liver cancer in people who are at average risk. Because of this, less than half (44%) of patients are diagnosed with localized-stage disease, for which 5-year survival is still only 33%, with the 5-year survival rate at regional and distant stages at diagnosis at a dismal 11% and 2%, respectively. Overall, the 5-year relative survival rate is 18%. This is mainly due to the fact that tumor recurrence is common, with the cancer coming back in 70% of the cases within 5 years (Sources: American Cancer Society's *Cancer Facts and Figures 2020* and *Journal of Hepatology*, Vol. 69:182–236,2018).

Figure 19

HEPATOCELLULAR CANCER (HCC)

Global Incidence: 841,000	4th Highest Mortality of all cancers



5-year survival rate	
Overall	18%
Localized	33%
Regional	11%
Distant	2%
Median Survival from time of Diagnosis	<3 years
New patients eligible for curative surgery	< 20%

Addressable Market Oportunity for ThermoDox®: >200K patienst across U.S., Europe, and Asia.

Sources: American Cancer Society, Journal of Hepatology, and Frontiers in Oncology.

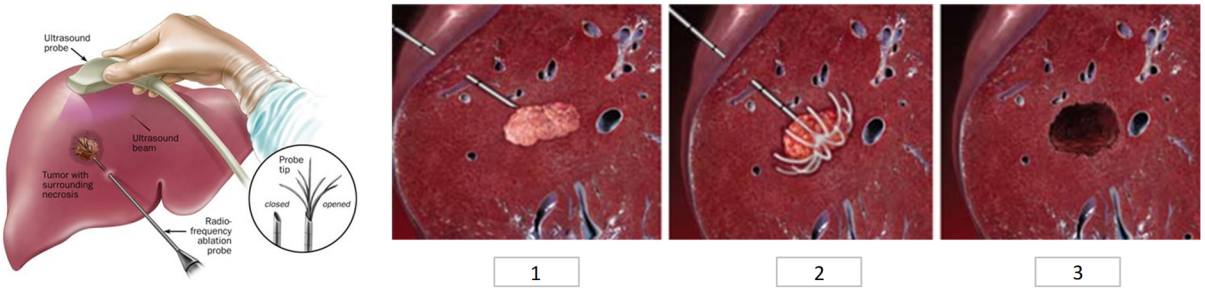
The standard first-line treatment for early stage liver cancer is surgical resection of the tumor. However, surgery may not be an option if the tumor takes up too much of the liver, the liver is too damaged, or the tumor has spread outside the liver. Less than 20% of newly diagnosed patients are eligible for curative surgery or transplantation at time of diagnosis (Source: *Journal of Hepatology*, Vol. 69:182–236,2018). Other treatment options include tumor ablation (destruction), embolization (blocking blood flow), or radiation therapy through the administration of locoregional therapies (LRT). Patients diagnosed at an advanced stage may be offered targeted therapies or immunotherapy. The most widely used LRT are radiofrequency thermal ablation (RFA), transarterial chemoembolization (TAC), microwave ablation, and radiation, with RFA emerging as the standard of care (SOC) for tumors up to 5 cm in diameter.

Radiofrequency Ablation (RFA)

RFA and microwave therapy both use heat to destroy cancer cells. RFA directly destroys the tumor tissue through the application of high temperatures administered by a radiofrequency probe inserted into the core of the tumor. The radiofrequency waves passing through the probe increase the temperature within tumor tissue and results in destruction of the tumor cells, as seen in Figure 20.

Figure 20

RADIO FREQUENCY ABALTION (RFA)



Sources: John Hopkins Medicine and European Society of Radiology.

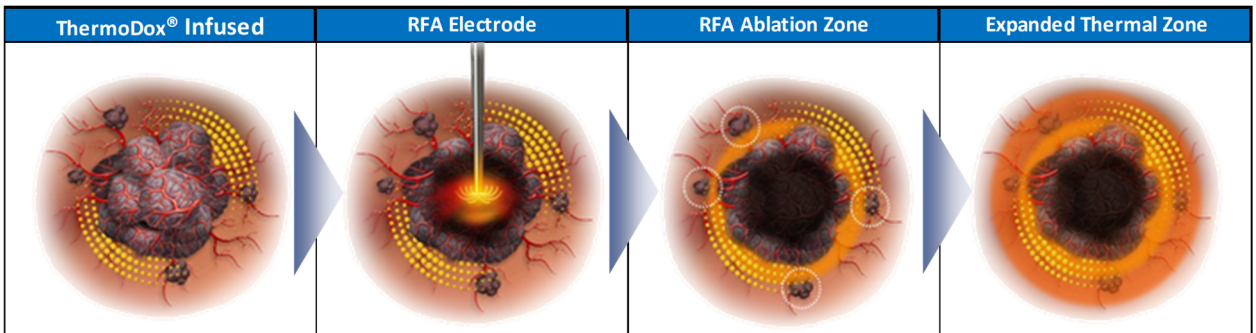
The suitability of RFA largely depends on the size of the tumor, with RFA's effectiveness decreasing with increasing tumor size. For small (≤ 3 cm) HCCs, RFA can achieve complete eradication and is viewed by many as equivalent in efficacy to resection for this scenario (Source: *World Journal of Transplantation*, Vol. 24; 6(2): 306–313, 2016). However, the rates of local tumor recurrence and progression following RFA treatment increase sharply when treating larger lesions; this remains a major problem with the RFA technique. In the current clinical practice, RFA is not recommended for tumors larger than 5 cm (Source: *Cancer Letters*, Vol. 370(1):78-84, 2016).

Thus, in order to take full advantage of RFA in HCC management, recent efforts have focused on multimodal therapeutic strategies, which combine RFA with other anti-cancer approaches, including TAC, nanoparticle-mediated therapy, and immunotherapy. Nanoparticle-mediated drug delivery systems represent one of the hottest research interests in modern medicine. This strategy aims to selectively deliver therapeutic agents to cancer sites using targeted nano-scaled drug carriers, which improves drug efficacy while reducing drug toxicity. Several studies have confirmed that the combined use of nano-drugs with RFA has better efficacy in killing cancer when compared to drug alone or RFA alone, as the delivery of nano-drugs can kill residual tumors and micrometastases in the sub-lethal zone of the RFA area. In the nano-therapeutic treatment of liver cancer, liposomes are one of the most widely investigated nano-drug carriers. A clear example of this technique is the Company's ThermoDox®, which is constructed with a thermal-sensitive liposome delivery system, and has been validated in a recent Phase III clinical trial in the treatment of liver cancer (Source: *Cancer Letters*, Vol. 370(1):78-84, 2016).

ThermoDox® Chemotherapy Process

ThermoDox® uses LTSL to produce heat sensitive liposomes that encapsulate doxorubicin. ThermoDox® is designed to be used in combination with heat-based treatments, such as RFA. The goal is to expand the effective treatment zone in order to capture micrometastases, which are most commonly responsible for post-treatment disease recurrence. Implementation of ThermoDox® includes the following steps, as illustrated in Figure 21: (1) ThermoDox® is infused intravenously ~15 minutes prior to RFA as a single, outpatient procedure. It circulates throughout the body, bathing the tumor and the surrounding areas with a high concentration of doxorubicin; (2) RFA is applied directly in the tumor, generating high temperature (up to 90ºC) and killing tumor cells in the immediate vicinity of the probe; (3) RFA creates a "Thermal Zone" (40ºC-50ºC) in the margin surrounding the tumor, where RFA misses micro-metastases outside the ablation zone; and (4) doxorubicin is released in the "Thermal Zone," expanding the treatment area, killing the metastases outside the ablation zone.

Figure 21
THERMODOX®



Source: Celsion Corporation.

The function of ThermoDox® is based on the structural changes of the liposome when heated to >39°C, which creates openings in the liposome that release doxorubicin directly into and around the targeted tumor. ThermoDox® uses the heat from the RFA procedure to thermally activate the liposomes in the periphery of the tumor, effectively expanding the treatment zone and releasing the encapsulated doxorubicin to kill remaining viable cancer cells throughout the region, including the tumor margins. Trials have demonstrated that ThermoDox® delivers 25x more doxorubicin into tumors versus doxorubicin IV infusion alone (Source: *Plos One*, Vol.10 (10), 2015). Celsion believes that the use of ThermoDox® in conjunction with RFA could allow RFA to treat larger, unresectable tumors, increasing the cases where RFA could produce a positive outcome.

ThermoDox™ Clinical Trials

Clinical and preclinical studies have demonstrated the ability of the heat sensitive ThermoDox® to deliver a greater volume of doxorubicin to the tumor area when high temperatures were applied, as well as the fact that administration of ThermoDox® has resulted in a better clinical outcome than RFA alone. Figure 22 lists selected journal articles and presentations relating to the ThermoDox® technology, with key study results summarized below.

Figure 22

THERMODOX® SELECTED JOURNAL ARTICLES AND PRESENTATIONS

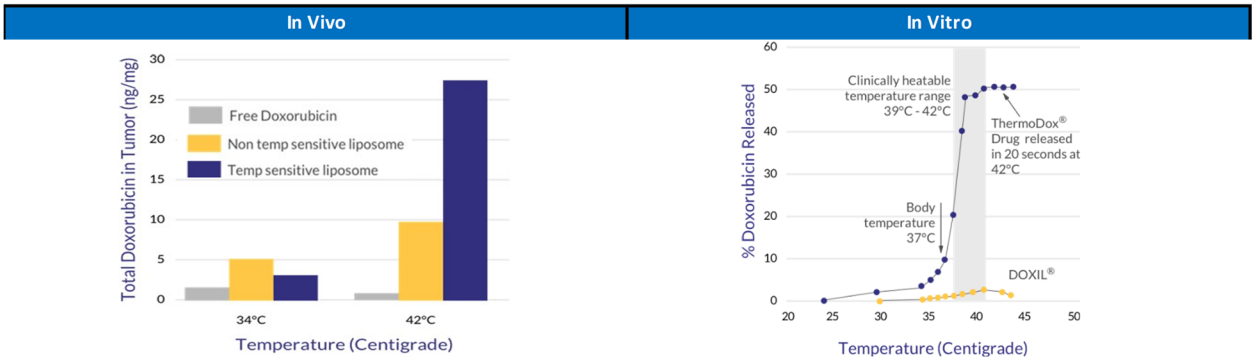
Title	Journal/Location	Year
Thermosensitive liposomal doxorubicin plus radiofrequency ablation increased tumor destruction and improved survival in patients with medium and large hepatocellular carcinoma: A randomized, double-blinded, dummy-controlled clinical trial in a single center	Journal of Cancer Research and Therapeutics Vol. 15(4): 773-783	2019
Real-time fluorescence imaging for visualization and drug uptake prediction during drug delivery by thermosensitive liposomes	International Journal of Hyperthermia Volume 36 (1): 816-825	2019
RFA plus lyso-thermosensitive liposomal doxorubicin: in search of the optimal approach to cure intermediate-size hepatocellular carcinoma.	Hepatic Oncology Vol. 3(3):193-200	2016
Increased Duration of Heating Boosts Local Drug Deposition during Radiofrequency Ablation in Combination with Thermally Sensitive Liposomes (ThermoDox) in a Porcine Model.	PLoS One Vol.10(10):e0139752	2015
Systemic anti-tumour effects of local thermally sensitive liposome therapy.	International Journal of Hyperthermia Vol. 30(6):385-392	2014
Two phase I dose-escalation/pharmacokinetics studies of low temperature liposomal doxorubicin (LTLD) and mild local hyperthermia in heavily pretreated patients with local regionally recurrent breast cancer.	International Journal of Hyperthermia Vol. 30(5):285–294	2014
Standardized radiofrequency ablation (sRFA) ≥ 45 minutes (m) plus lyso-thermosensitive liposomal doxorubicin (LTLD) for solitary hepatocellular carcinoma (HCC) lesions 3-7 cm: a retrospective analysis of phase III HEAT study.	American Society of Clinical Oncology 50th Annual Meeting; Abstract e15143	2014
Novel targeted therapy for breast cancer chest wall recurrence: low temperature liposomal doxorubicin and mild hyperthermia.	San Antonio Breast Cancer Symposium Poster: Abstract P4-15-05.	2013
Breast cancer recurrences at the chest wall (BCRCW) when standard treatments (Tx) have failed: lyso-thermosensitive liposomal doxorubicin (LTLD) + mild local hyperthermia (MLH).	European Society for Medical Oncology 37th Congress Presentation	2012
Lyso-thermosensitive liposomal doxorubicin: an adjuvant to increase the cure rate of radiofrequency ablation in liver cancer.	Future Oncoly Vol. 7(8):937-945.	2011
Nanoscale drug delivery and hyperthermia: the materials design and preclinical and clinical testing of low temperature-sensitive liposomes used in combination with mild hyperthermia in the treatment of local cancer.	The Open Nanomedicine Journal Vol. 3:38-64	2011
Lyso-thermosensitive liposomal doxorubicin: a novel approach to enhance efficacy of thermal ablation of liver cancer.	Expert Opininion on Pharmacotherapy Vol.10(2):333-343	2009
Phase I trial of doxorubicin-containing low temperature sensitive liposomes in spontaneous canine tumors.	Clin Cancer Res. Vol. 12(13):4004-4010	2006

Source: Celsion Corporation.

Preclinical testing, both in vivo and in vitro, confirm the ability of ThermoDox® to deliver a greater volume of doxorubicin to the tumor area when high temperatures were applied, compared to administration of doxorubicin alone or in combination with non-heat sensitive liposomes, as seen in Figure 23 (page 32).

Figure 23

THERMODOX® DRUG DELIVERY



Source: Celsion Corporation.

The HEAT Study
(*Clinical Cancer Research*, Vol. 24 (1): 73-83, 2018)

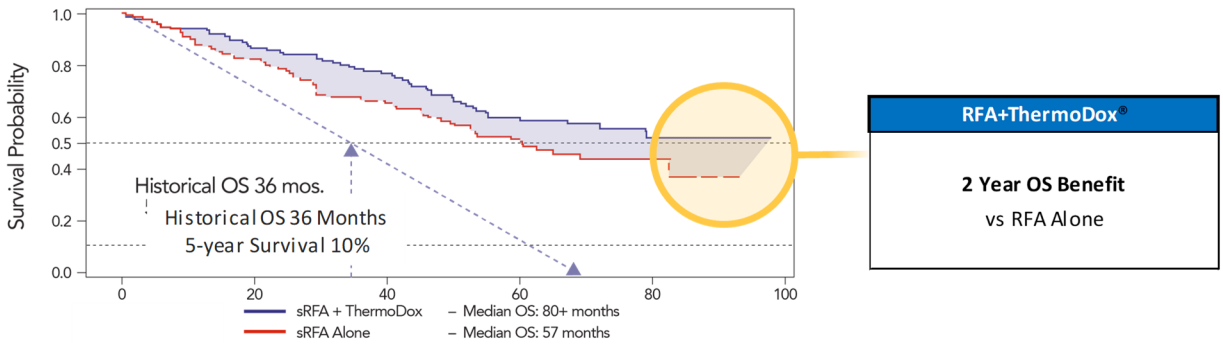
The HEAT Study was a Phase III randomized, double-blind trial designed to determine whether adding lysothermosensitive liposomal doxorubicin (LTLD) improves the efficacy of RFA for HCC lesions. The study included 701 patients that had a maximum of four unresectable HCC lesions with at least one with a maximum diameter (dmax) of 3-7 cm, in 66 total centers. The primary endpoint was progression-free survival (PFS) and a key secondary endpoint was overall survival (OS). Following administration of ThermoDox®, RFA was applied at a minimum of 15 minutes, with the length of the RFA proportional to the size of the tumor(s). There was no pre-specified timing for the RFA procedure in the HEAT Study.

Results of the study revealed that adding LTLD to RFA was safe but did not increase PFS or OS in the overall study population. However, researchers noted a wide variation in RFA application times between the 66 active centers, as the study did not require minimum RFA length. Since a preclinical study in which healthy pigs received LTLD and RFA demonstrated that doxorubicin concentration increased with RFA duration, researchers conducted an exploratory post hoc analysis to determine whether RFA burn time may have influenced the outcomes of this study. Computational modeling demonstrated not only that doxorubicin concentration increases with heating duration but that the majority of the maximum concentration was delivered in the first 45 minutes. Thus, researchers used the 45-minute cutoff for the sub-analyses of patients in this study.

Although patients in the shortened burn time subset showed no benefit in PFS and OS, outcomes appeared to be improved in the prolonged burn time subset. OS was significantly improved (median not reached after 7 years versus 60.2 months), and PFS showed a trend toward improvement (22.7 versus 16.7 months). Remarkably, in patients with single lesions only that underwent RFA for at least 45 minutes (n=285), the data showed a 2.1-year improvement in OS, as seen in Figure 24.

Figure 24

HEAT STUDY SUBSET ANALYSIS



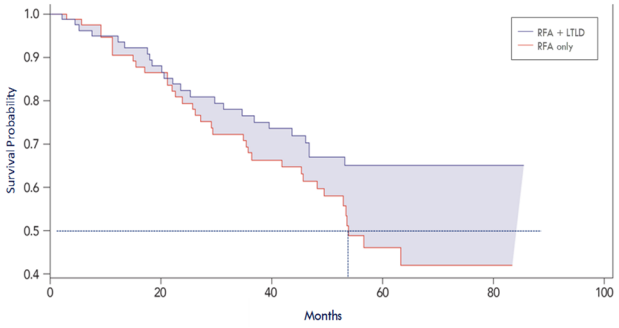
Sources: Clinical Cancer Research and Celsion Corporation.

Independent NIH Analysis
(*Journal of Vascular and Interventional Radiology*, Vol.30(12):1908-1914, 2019)

The NIH also evaluated the importance of RFA burn time as it correlates with clinical outcome and OS benefits. The study intended to determine whether burn time per tumor volume (BPV) (min/mL), where burn time is the total time during which radiofrequency (RF) energy is being applied, is correlated with HCC treatment outcomes using RFA and LTLD.

The study demonstrated that increased BPV improved OS in ThermoDox®+RFA single-lesion patients compared to RFA-only patients. For all single-lesion patients being administered ThermoDox®+RFA, one unit increase in RFA duration per tumor volume improved OS by 20% (n=227). In contrast, in single-lesion RFA-only patients, burn time per tumor volume did not have a significant effect in OS (n=210). More dramatic differences were found in subgroups of patients with BPV higher than 2.5 minutes/mL (45 minutes burn time for a 3 cm tumor), where over 60% of patients were alive after seven and a half years (Figure 25). The study concluded that BPV may be a useful metric for RFA+LTLD combination therapy for solitary HCC. The analysis suggested that the burn time for the tumor needs to be adjusted depending on the tumor volume.

Figure 25
NIH SUBGROUP ANALYSIS



Sources: Journal of Vascular and Interventional Radiology and Celsion Corporation.

OPTIMA Study

The subgroup analysis of the HEAT and NIH studies were used to design the Phase III OPTIMA Study for liver cancer patients with single lesions. The OPTIMA Study, launched in the second half of 2014, is a global clinical study designed to evaluate ThermoDox® in combination with standardized RFA (RFA ≥45 minutes) in primary liver cancer. The study, which completed enrollment in Q3 2018, includes 550 patients in approximately 65 sites in 14 countries (North America, Europe, China, and the Asia-Pacific region). The primary endpoint is OS. The study is powered to demonstrate a 33% improvement in OS. Figure 26 provides an overview of the study design.

Figure 26
OPTIMA STUDY

End Points

Primary
Overall Survival (OS)
Secondary
Progression Free Survival (PFS)

General Eligibility

- Nonresectable HCC
- Single lesions
- Lesion > 3 cm but not > 7 cm
- Treatment naïve
- Child-Pugh A

Study Design

550 Patients
Randomized 1:1

Treatment Group
N = 275
ThermoDox® + sRFA*
Standardized RFA > 45 minutes.

Control Group
N = 275
Dummy Infusion + sRFA*
Standardized RFA > 45 minutes.

Interim efficacy analysis

1st Analysis	2nd Analysis	Final analysis
at least 118 deaths	at least 158 deaths	197 OS deaths
HR < 0.61	HR < 0.70	HR < 0.75
Completed Nov. 2019	Completed July 2020	

Source: Celsion Corporation.

The study included two planned interim efficacy analysis: (1) the first at least 118 deaths, with a target hazard ratio (HR) of 0.61, which was completed successfully on November 2019; (2) the second analysis at least 158 deaths, with a target HR of 0.70, completed on July 2020; and (3) a final analysis at 197 deaths, with a target HR of 0.75.

Hazard ratios (HR) are frequently used to estimate the treatment effect for time-to-event end points, such as overall survival (OS) and progression-free survival (PFS), in oncology randomized clinical trials (RCTs). A simplistic interpretation is that a HR=1 means equal efficacy of the experimental and control treatments. Usually, the HR is presented so that if the experimental treatment is better than the control, then the HR is lower than 1 or if it is worse than the control, then the HR is higher than 1.

Following the first interim analysis, the independent Data Monitoring Committee (DMC) found that the safety, PFS, and OS values met expectations, with the OPTIMA study patient demographics and risk factors consistent with what the Company observed in the HEAT study subgroup of patients treated with RFA >45 minutes. Median PFS for the OPTIMA Study of 17.3 months compared favorably with 16.8 months median PFS for the 285 patients in the HEAT study. In addition, although median OS for the OPTIMA study had not been reached by the time of the analysis; median OS appears to be consistent with the HEAT Study subgroup.

DMC Recommends to Consider Stopping Study

Despite these results, in July 2020, Celsion received a recommendation from the DMC to consider stopping the OPTIMA Study of ThermoDox®. The recommendation was made following the second scheduled interim safety and efficacy analysis by the DMC on July 9, 2020.

The second interim analysis, which covered 80% of the deaths needed for the final analysis, indicated that the OPTIMA Study had narrowly crossed the futility boundary of HR=0.90. The reported HR suggested by the Kaplan-Meier analysis was 0.903. However, since the 2-sided p-value of 0.524 for this analysis provides uncertainty, the DMC has left the final decision of whether or not to stop the OPTIMA Study to Celsion. According to the Company, the news was unexpected, especially since the HR for success at 158 deaths of 0.70, which represents a 30% reduction in the risk of death compared with RFA alone, compares favorably with the HR of 0.65 observed in the HEAT Study subgroup.

Following preliminary evaluation of the unblinded data, Celsion announced it plans to continue following patients, noting that the marginally crossed futility boundary may be associated with a data maturity issue. Celsion noted that OPTIMA investigators in China and Vietnam, who enrolled 37% of the subjects, joined the study approximately 12 and 18 months, respectively, after the trial was initiated. The Kaplan-Meier curves for both geographies demonstrate a potential data maturity issue when compared to the behavior of the HEAT Study subgroup and other OPTIMA Study testing site regions.

The Company further noticed that 26 consecutive patient deaths represented exclusively in the second analysis behave far differently from the balance of the patients who have died as of this date. Specifically, 16 deaths occurred in five different Asia-Pacific countries between the first and second interim analyses, and 15 of these deaths were in the ThermoDox® treatment arm. In addition, subsequent to the second interim analysis, there were eight patient deaths in a 3:1 ratio of control arm to treatment arm patients, which further supports a concern for data maturity. Due to these factors, in addition to the fact that no safety concerns were noted during the interim analysis, the Company decided to continue to follow patients while it conducts independent statistical analysis on the data.

To this end, Celsion acquired the services of a global biometrics contract research organization (CRO), with forensic statistical analysis capability that specializes in data management, statistical consulting, statistical analysis, and data sciences, with particular expertise in evaluating unusual data from clinical trials and experience with associated regulatory issues. The primary objective of the CRO's work is to determine the basis and reasoning behind continuing to follow patients for survival, and if there were outside influences that may have impacted the forecast of futility.

In addition, and in parallel with the CRO analysis, the Company has submitted all OPTIMA Study clinical trial data to the National Institutes of Health (NIH), which will focus on a site-by-site evaluation for RFA heating time-based anomalies that may have contributed to the treatment arm performance. The NIH is expected to conduct a Cox Regression Analysis, including minimum burn time per tumor volume, evaluating similarities to the hypothesis generated from the NIH study in which an increase in RFA heating time per tumor volume significantly improved OS in patients. Celsion expects to report findings from these independent statistical analyses by Q4 2020, either or both of which will determine whether to continue to follow patients to the final analysis at 197 or more deaths—a milestone that should be reached sometime in mid-2021.

THERMODOX® PRECLINICAL PROGRAM

Preclinical studies on the use of ThermoDox® for the treatment of bladder cancer have demonstrated promising results. Bladder cancer is the fourth most common cancer in men and 12th most common cancer in women. The annual incidence continues to increase with an estimated 81,400 new cases expected in 2020 in the U.S., resulting in 19,300 deaths. In about half of all cases, at diagnosis the cancer is limited to the inner wall of the bladder. In the other half, upon presentation it has already invaded the bladder wall, lymph nodes, or other organs. No effective drug for bladder cancer has been approved by the U.S. FDA since BCG (bacillus Calmette-Guerin), which was approved in 1990.

A key difficulty in treating bladder cancer is delivering effective medicine to the bladder wall and muscle. In a recent study of ThermoDox® in bladder models, it was demonstrated that warm water irrigation of the bladder can release high concentrations of doxorubicin throughout all layers of the bladder wall. These data were recently presented at the International Congress of Hyperthermic Oncology (ICHO) and may pave the way for future studies in patients with bladder cancer.

Investigator-Sponsored Studies with ThermoDox®

The Company has received multiple requests from investigators to include ThermoDox® in their own studies, involving several clinical indications.

- Oxford University plans to begin enrolling patients in a Phase I pancreatic cancer study with ThermoDox® in combination with High Intensity Focused Ultrasound (HIFU) in early 2021. The primary objective of this trial, known as the "PanDox Study: Targeted Doxorubicin in Pancreatic Tumors" is to quantify the enhancement in intratumoral doxorubicin concentration when delivered with ThermoDox® and HIFU, versus doxorubicin monotherapy. This study is being undertaken pursuant to promising data in a mouse model of pancreatic cancer, which was published in the International Journal of Hyperthermia in 2018. That preclinical study showed a 23x increase in intratumoral doxorubicin concentration with ThermoDox®+HIFU, compared with a 2x increase in intratumoral doxorubicin concentration with free doxorubicin plus HIFU.

- Utrecht University in the Netherlands continues to enroll patients in a Phase I breast cancer study to determine the safety, tolerability, and feasibility of ThermoDox® in combination with Magnetic Resonance Guided High Intensity Focused Ultrasound (MR-HIFU) hyperthermia and cyclophosphamide therapy for the local treatment of the primary tumor in metastatic breast cancer. This investigator-sponsored study, which is being funded by the Dutch Cancer Society, the Center for Translational Molecular Medicine (a multi-million dollar public-private partnership in the Netherlands), will be conducted at University Medical Center Utrecht and will enroll up to 12 newly diagnosed metastatic breast cancer patients. Celsion will supply ThermoDox® clinical product for the trial.

- As evidence of the ongoing support by Celsion from the NIH, the organization has coordinated a clinical project to evaluate ThermoDox® plus the chemotherapy drug mitomycin in bladder cancer. Depending on the NIH timelines, this study may commence as early as 2021.

Competition

Competition within the oncology therapeutic market is intense. The Company faces competition from pharmaceutical and biotechnology companies, along with academic and research institutions and government agencies both in the U.S. and abroad. This competition is coming from organizations pursuing the same or similar technologies used by Celsion in its drug discovery efforts as well as from organizations developing pharmaceuticals that are competitive to Celsion's product candidates. The summaries presented below are not intended to be an exhaustive collection of potential competitors to Celsion; however they are believed to be a representative of the type of competition the Company may face as it seeks to develop and approve its therapeutic candidates.

GEN-1 Competitive Landscape

Studied indications for GEN-1 include ovarian cancer and glioblastoma multiforme (GBM) brain cancer. In evaluating the competitive landscape for both indications, early stage indications are treated with chemotherapy (temozolomide, BCNU, CCNU for brain cancer; and docetaxel, doxil and cisplatinum for ovarian cancer), while later stage ovarian cancer is treated with Bevacizumab-Avastin®, an anti-angiogenesis inhibitor. Avastin® is also being evaluated for early stage disease. Celsion has conducted clinical studies in combination with chemotherapy for ovarian cancer, and preclinical studies in combination with both temozolomide and Bevacizumab-Avastin®. For the ovarian cancer indications, there currently is no direct immunotherapy competitor for GEN-1, although the Company may face competition with clinical stage plasmid transfection and interleukin-12 (IL-12) delivery technologies that seek to achieve similar results to the Company's TheraPlas™ platform. The following companies may be considered competitors within this respective therapeutic category.

AstraZeneca PLC (AZN-NASDAQ)

AstraZeneca discovers, develops, and commercializes prescription medicines in the areas of oncology, cardiovascular, renal and metabolism, respiratory, autoimmunity, infection, neuroscience, and gastroenterology worldwide. Its marketed products include Imfinzi® (Durvalumab or MEDI4736) approved for the treatment of certain types of cancer in the bladder, urinary tract, and lung. The company is further evaluating Imfinzi® in combination with Lynparza® and bevacizumab in a Phase III study for first line treatment of ovarian cancer. In addition, AztraZeneca is also assessing its product candidate, adavosertib, in a Phase II study for ovarian cancer. AstraZeneca PLC was founded in 1992 and is headquartered in Cambridge, UK.

GlaxoSmithKline plc (GSK-NYSE)

GlaxoSmithKline engages in the creation, discovery, development, manufacture, and marketing of pharmaceutical products, vaccines, over-the-counter (OTC) medicines, and health-related consumer products. It operates through four segments: Pharmaceuticals, Pharmaceuticals R&D, Vaccines, and Consumer Healthcare. Its oncology product portfolio includes ZEJULA® (niraparib), which in April 2020 received FDA approval for the maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer, who are in a complete or partial response to first-line platinum-based chemotherapy. Niraparib is an orally active small molecule PARP inhibitor developed by Tesaro, Inc., which was acquired by GlaxoSmithKline in January 2019. The company is also conducting Phase III trials to assess ZEJULA® as a maintenance therapeutic for ovarian cancer in combination with dostarlimab. GlaxoSmithKline was founded in 1715 and is headquartered in Brentford, UK.

IMV Inc. (IMV-NASDAQ)

IMV is a clinical stage biopharmaceutical company involved in the development of immunotherapies for the treatment of cancer, infectious, and other serious diseases. The company's DPX drug development platform is a formulation that provides a way to deliver active ingredients to the immune system using a novel mechanism of action. IMV's lead candidate is DPX-Survivac, T-cell activating immunotherapy, is in Phase II clinical trials for ovarian cancer and diffuse large B-cell lymphoma. The company was formerly known as Immunovaccine Inc. and changed its name to IMV Inc. in May 2018. IMV Inc. was founded in 2000, with headquarters in Dartmouth, Canada.

OncoSec Medical Incorporated (ONCS-NASDAQ)

OncoSec is a late-stage biotechnology company focused on designing, developing, and commercializing innovative therapies and proprietary medical approaches to stimulate and guide an anti-tumor immune response for the treatment of cancer. Its core platform technology, ImmunoPulse®, is a drug-device therapeutic modality comprised of a proprietary intratumoral electroporation (EP) delivery device. The ImmunoPulse® platform is designed to deliver plasmid DNA-encoded drugs directly into a solid tumor and promote an immunological response against cancer. The ImmunoPulse® device can be adapted to treat different tumor types, and consists of an electrical pulse generator, a reusable handle, and disposable applicators. OncoSec's lead product candidate is a IL-12 DNA plasmid, called tavokinogene telseplasmid (TAVO), being evaluated in multiple cancer indications, including melanoma and Triple Negative Breast Cancer (TNBC). The ImmunoPulse® EP platform is used to deliver TAVO intratumorally, with the aim of reversing the immunosuppressive microenvironment in the treated tumor.

Sunesis Pharmaceuticals, Inc. (SNSS-NASDAQ)

Sunesis, a biopharmaceutical company, focuses on the development and commercialization of targeted inhibitors for the treatment of hematologic and solid cancers. Its lead product candidate is vecabrutinib, a non-covalent inhibitor of Bruton's tyrosine kinase (BTK), which is in Phase Ib/II clinical trial for the treatment of chronic lymphocytic leukemia, mantle cell lymphoma, and other B-cell malignancies. The company is also developing SNS-510, which is in preclinical pharmacology studies for the treatment of solid tumor and hematologic malignancies; various other partnered programs, such as TAK-580, a pan-Raf inhibitor program that is in Phase 1 clinical trial for the treatment of pediatric low-grade glioma; and vosaroxin, an anti-cancer quinolone derivative that intercalates DNA and inhibits topoisomerase II. It has a collaboration agreement with Biogen Idec MA, Inc. to discover, develop, and commercialize small molecule BTK inhibitors; and license agreement with Takeda Pharmaceutical Company Limited to develop and commercialize preclinical inhibitors of PDK1. Sunesis Pharmaceuticals, Inc. was founded in 1998 and is headquartered in South San Francisco, California.

Vascular Biogenics Ltd. (VBL Therapeutic) (VBLT-NASDAQ)

Vascular Biogenics is a clinical-stage biopharmaceutical company focused on the discovery, development, and commercialization of treatments for cancer and immune/inflammatory indications. The company's program is based on its proprietary vascular-targeting system platform technology, which utilizes genetically targeted therapy to destroy newly formed or angiogenic blood vessels. Its lead product candidate is VB-111 (ofranergene obadenovec), an anti-angiogenic gene-therapy biologic designed to address solid tumors by two mechanisms: first, by selectively targeting the blood vessels required for tumor growth, and second, as a viral vector, recruiting immune cells into the tumor. VB-111 has received Orphan Drug designation in both the U.S. and Europe and was granted Fast Track designation by the FDA in patients with recurrent glioblastoma and has also received an Orphan Designation for the treatment of ovarian cancer by the European Medicines Agency (EMA). VB-111 is being studied in the OVAL Phase III study for platinum resistant ovarian cancer. Formerly known as Medicard Ltd., the company changed its name to Vascular Biogenics Ltd. in January 2003. Founded in 2000, Vascular Biogenics has headquarters in Modi'in, Israel.

ZioPharm Oncology, Inc. (ZIOP-NASDAQ)

ZioPharm is a clinical-stage biopharmaceutical company focused on discovering, acquiring, developing, and commercializing a portfolio of immuno-oncology therapies for treating heterogenous solid tumors and unknown antigens. The company develops two immuno-oncology platform technologies, including Sleeping Beauty (SB), which is based on the genetic engineering of immune cells using a non-viral transposon/transposase system to reprogram T-cells outside of the body for infusion; and Controlled IL-12, which delivers IL-12, a master regular of the immune system, in a controlled and safe manner to focus the patient's immune system to attack cancer cells. The company's most advanced candidates are the use of its SB platform, in collaboration with the National Cancer Institute, in a Phase II study for solid tumors, as well as its IL-12 delivery platform plus veledimex, which is in Phase II clinical trial to treat patients with recurrent GBM in adults. ZioPharm is also developing chimeric antigen receptor (CAR) T-cell and T-cell receptor T-cell therapies. ZioPharm was incorporated in 1998 and is headquartered in Boston, Massachusetts.

ThermoDox® Competitive Landscape

In the HCC therapeutic market, the Company may face competition from newly approved therapies, as well as competing therapies currently in development. Until recently, sorafenib (Bayer AG) was the only FDA-approved first-line agent for advanced HCC. However, since 2017, the FDA has approved nine medications for the treatment of advanced HCC. In addition to approved therapeutics, Celsion may also find competition from candidates currently in clinical development. While there are numerous drugs and devices marketed and under development to treat cancer, Celsion is unaware of any other heat-activated drug delivery product either being marketed or in human clinical development. The Company believes that the advantages of its heat-mediated technology platform—LTSL (Lysolipid Thermally Sensitive Liposome)—provide a competitive edge over other existing therapeutics or those currently in development. The following companies may be considered competitors within this respective therapeutic category.

Bayer Aktiengesellschaft (BAYN.DE)

Bayer is a global life science company that operates through pharmaceuticals, consumer health, and crop science segments. The pharmaceuticals segment offers prescription products primarily for cardiology and women's healthcare; specialty therapeutics in the areas of oncology, hematology, and ophthalmology; and diagnostic imaging equipment. Its oncology-related portfolio includes HCC therapeutics Nexavar® (sorafenib) used to treat later stage HCC that cannot be removed by surgery, either as a first-line therapy or for subsequent therapy following disease progression, as well as STIVARGA® (regorafenib), indicated for patients with HCC who have been previously treated with sorafenib. Bayer was founded in 1863 and is based in Leverkusen, Germany.

Bristol-Myers Squibb Company (BMY-NYSE)

Bristol Myers Squibb is a pharmaceutical company that manufactures prescription pharmaceuticals and biologics in several therapeutic areas, including cancer, HIV/AIDS, cardiovascular disease, diabetes, hepatitis, rheumatoid arthritis, and psychiatric disorders. The company's OPDIVO® (nivolumab) is a prescription medicine approved, by itself or in combination with YERVOY® (ipilimumab), to treat people with HCC that have previously received treatment with sorafenib. The company is conducting further evaluation of OPVIDO®'s clinical benefit in HCC, including a Phase III study to study OPDIVO® as a first line therapy or in adjuvant capacity in combination with other agents, as well as a Phase III study for OPDIVO® and YERVOY® for first line treatment. Bristol-Myers Squibb is headquartered in New York City, with its primary R&D sites located in Lawrence, New Jersey, New Brunswick, New Jersey, and Redwood City, California.

Delcath Systems, Inc. (DCTH-NASDAQ)

Delcath, an interventional oncology company, focuses on the treatment of primary and metastatic liver cancers. The company's lead product candidate is the melphalan hydrochloride for injection for use with the Delcath hepatic delivery system to administer high-dose chemotherapy to the liver. Its Phase III clinical trial products include FOCUS Trial for patients with hepatic dominant ocular melanoma; and ALIGN Trial for intrahepatic cholangiocarcinoma. The company also offers melphalan hydrochloride under the Delcath Hepatic CHEMOSAT Delivery System for Melphalan name in Europe. The company was founded in 1988 and is headquartered in New York, New York.

Eisai Co., Ltd (ESALY-OTC)

Eisai is a global pharmaceutical company specializing in the areas of oncology, neurology, and dementia. In the HCC therapeutic arena, Eisai's product portfolio includes Lenvima® (Lenvatinib), an anticancer agent/molecular targeted medicine for the first line treatment in inoperable HCC, thyroid cancer, and renal cell carcinoma in combination with everolimus. In addition, the company is conducting multiple HCC-related trials: LEAP-002, a Phase III study of Levinma® as first line therapy for HCC; LEAP-012, a Phase III study of Levinma® in combination with pembrolizumab and TAC (in collaboration with Merck); and a Phase I study of Levinma® in combination with nivolumab (in collaboration with Ono Pharmaceutical). The company was formerly known as Nihon Eisai Co., Ltd. and changed its name to Eisai Co., Ltd. in 1955. Eisai was founded in 1941 and is headquartered in Tokyo, Japan.

Eli Lilly and Company (LLY-NYSE)

Eli Lilly discovers, develops, manufactures, and markets pharmaceutical products worldwide. It offers endocrinology, neuroscience, immunology, as well as oncology products to treat non-small cell lung, colorectal, head and neck, pancreatic, metastatic breast, ovarian, bladder, and metastatic gastric cancers; among others. The company's product portfolio includes CYRAMZA® (ramucirumab) as a second line treatment of people with HCC who have levels of alphafetoprotein (a protein that may be released into the bloodstream by liver cancer tumor cells) and have been previously treated with sorafenib. The company was founded in 1876 and is headquartered in Indianapolis, Indiana.

Exelixis, Inc. (EXEL-NASDAQ)

Exelixis is an oncology-focused biotechnology company. Exelixis' products include CABOMETYX® for advanced renal cell carcinoma (RCC) and patients with HCC who have been previously treated with sorafenib. In addition, the company's pipeline and collaborations include multiple HCC programs: COSMIC-312, a Phase III study to evaluate the safety and efficacy of cabozantinib in combination with atezolizumab versus the standard of care (SOC) sorafenib as a first line treatment for advanced HCC; CHECKMATE 040, a Bristol-Myers Squibb Phase II study to evaluate efficacy of nivolumab alone or in combination with other agents for the treatment of advanced HCC, where a cohort is evaluating the safety and tolerability of nivolumab in combination with cabozantinib and nivolumab with ipilimumab in combination with cabozantinib; and a Phase I study evaluating cabozantinib and nivolumab as a first line treatment of advanced HCC. Exelixis, Inc. was founded in 1994 and is headquartered in Alameda, California.

Merck & Co., Inc. (MRK-NYSE)

Merck provides health solutions through its prescription medicines, vaccines, biologic therapies, animal health, and consumer care products. It operates through the following segments: Pharmaceutical, Animal Health, Healthcare Services, and Alliances. The Pharmaceutical segment, which includes human health pharmaceutical and vaccine products, provides products to prevent chemotherapy-induced and post-operative nausea and vomiting; as well as to treat HCC, non-small-cell lung, ovarian and breast, esophageal, thyroid, cervical, and brain cancers. Its blockbuster drug, KEYTRUDA® (pembrolizumab), has been approved as a second line treatment for patients with HCC who have been previously treated with sorafenib; and is currently being evaluated in combination with Lenvima® (Lenvatinib) for the first-line treatment of patients with unresectable HCC. The company was founded in 1891 and is headquartered in Kenilworth, New Jersey.

TRACON Pharmaceuticals, Inc. (TCON-NASDAQ)

TRACON, a clinical stage biopharmaceutical company, focuses on the development and commercialization of therapeutics for cancer. Its lead clinical stage products include envafolimab (KN035), an investigational PD-L1 single-domain antibody in a pivotal Phase III trial for biliary duct cancer and a Phase II trial for gastric cancer (both in China), among other indications. The company's clinical stage products also include TRC102, which is a small molecule that is in a Phase II clinical trial for the treatment of mesothelioma, and Phase I clinical trial to treat solid tumors/lung cancer; TRC253, a small molecule, which is in a Phase II clinical trial for the treatment of metastatic castration-resistant prostate cancer; and TJ004309, a CD73 antibody that is in Phase I clinical development for the treatment of solid tumors. The company was formerly known as Lexington Pharmaceuticals, Inc. and changed its name to TRACON Pharmaceuticals, Inc. in March 2005. TRACON was founded in 2004 and is headquartered in San Diego, California.

Investment Highlights

- Celsion Corporation is a fully integrated biopharmaceutical company focused on developing cancer therapies for difficult-to-treat forms of cancers.

- The Company aims to maximize the efficacy of proven therapeutic agents and minimize side effects common to cancer treatments through the application of its two distinct nanoparticle-based technology platforms—TheraPlas™, a nonviral vector delivery system for therapeutic plasmids and Lysolipid Thermally Sensitive Liposomes (LTSL), a heat-sensitive formulation that allows for the targeted delivery of known chemotherapies.

- Celsion has develop a robust pipeline that includes two clinical programs: GEN-1, an immunotherapy for the localized treatment of ovarian cancer, and ThermoDox®, a heat-mediated delivery platform of chemotherapeutic agent for the treatment of hepatocellular Cancer (HCC)/primary liver cancer. The Company is also conducting preclinical studies to expand the application of its technology platforms in other cancer indications.

- GEN-1, the first product designed via the TheraPlas™ platform technology, is a DNA-based immunotherapy in a Phase I/II study for the treatment of ovarian cancer (an indication for which it received Orphan Drug Designation in the U.S. and EU). GEN-1 is a non-viral delivery platform that facilitates the introduction of a plasmid payload into tumor cells, resulting in a durable localized secretion of interleukin-12 (IL-12)—an immune protein that plays a key role in generating an immune response against cancer.

    - GEN-1 consists of a human IL-12 plasmid formulated with a non-viral synthetic DNA delivery system. Following administration, GEN-1 nanoparticle profile enables cell transfection followed by durable local secretion of the IL-12 protein in the vicinity of the tumor, which may lead to prolonged infiltration of immune cells in the tumor, enhancing the local immune response against cancer.

    - In clinical trials, GEN-1 has resulted in a marked advantage in Progression Free Survival (PFS)—21 months, which was 75% higher than the estimate of 12 months for the control group. Results of its Phase I study OVATION 1 showed that administration of GEN-1 resulted in a dose dependent response, with higher doses of GEN-1 resulting in better objective tumor response (100% versus 60% for lower doses) and an increase in R-0 events (the surgical removal of all visible tumor), from 40% in lower doses to 88% at higher doses.

    - GEN-1 is currently is being evaluated in a Phase I/II study (OVATION 2), in combination with standard neoadjuvant chemotherapy for newly diagnosed ovarian cancer patients. The Phase II portion of the study is in line to complete enrollment in Q2 2021, with the Company expecting progression free survival (PFS) data reported by Q4 2022.

- ThermoDox® uses the Company's LTSL technology to produce heat sensitive liposomes that encapsulate doxorubicin, a widely used chemotherapeutic agent, to facilitate its targeted delivery at the tumor site. When heated, through the application of heat-based treatments (such as radiofrequency thermal ablation [RFA]), the heat-sensitive liposome changes structure, creating openings that release doxorubicin directly into the tumor.

    - The Company has demonstrated the ability of ThermoDox® to deliver a greater volume of doxorubicin to the tumor area—25x more versus doxorubicin IV infusion—leading to a better clinical outcome. In HCC patients with single lesions that underwent RFA for at least 45 minutes, the use of ThermoDox® resulted in a 2.1-year improvement in Overall Survival (OS).

    - ThermoDox® is currently being evaluated in a Phase III clinical trial for the treatment of HCC (the OPTIMA Study). Following completion of the second interim analysis by the independent Data Monitoring Committee (DMC), the DMC recommended to consider stopping the study.

- Celsion is currently conducting independent analysis of its OPTIMA data, as the study crossed a futility boundary on its second scheduled interim analysis. Following preliminary evaluation of the unblinded data, Celsion decided to continue following patients, noting that the crossed futility boundary may be associated with a data maturity issue. Celsion expects to report findings from these independent statistical analyses by Q4 2020.

- Celsion's leadership team incorporates over 150 years of management experience within the healthcare industry, including clinical development program, R&D, pharmaceutical operations, and corporate finance.

- The Company recently strengthened its balance sheet position, resulting in a minimal warrant overhang and cleaner capital structure, through four key financial activities during 2020: (1) a $10 million underwritten offering of common stock (June 2020), (2) the continued sale of New Jersey net operating losses (NOLs) (April 2020), (3) the repayment and restructure of its long-term debt with Horizon Technology Finance Corporation (September 2020), and (4) the Lincoln Park Capital Fund, LLC (LPC) financing (September 2020).

- The Company ended Q3 2020 with $18.3 million in cash and cash equivalents. Coupled with future planned sales of its New Jersey NOL's, the Company believes it has sufficient capital resources to fund its operations through the end of 2021.

Historical Financial Results

Figures 27, 28, and 29 provide Celsion's Condensed Consolidated Statements of Operations, its Condensed Consolidated Balance Sheets, and its Condensed Consolidated Statements of Cash Flows for the three months and nine months ended September 30, 2020.

Figure 27
CONDENSED CONSOLIDATED STATEMENTS OF OPERATIONS
(Unaudited)

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2020	2019	2020	2019
Licensing revenue	$ 125,000	$ 125,000	$ 375,000	$ 375,000
Operating expenses:				
Research and development	2,491,696	3,674,239	8,534,606	9,999,972
General and administrative	1,792,904	1,838,287	5,532,946	6,192,835
Total operating expenses	4,284,600	5,512,526	14,067,552	16,192,807
Loss from operations	(4,159,600)	(5,387,526)	(13,692,552)	(15,817,807)
Other (expense) income:				
(Loss) gain from change in valuation of earn-out milestone liability	(1,099,721)	85,882	(1,397,291)	3,088,821
Impairment of in-process research and development	(2,370,257)	—	(2,370,257)	—
Fair value of warrants issued in connection with amendment to modify GEN-1 earn-out milestone payments	—	—	—	(400,000)
Investment income	10,114	174,439	119,383	432,832
Interest expense	(450,732)	(349,602)	(1,130,699)	(1,049,797)
Other (expense) income	(1,400)	—	7	(2,823)
Total other (expense) income, net	(3,911,996)	(89,281)	(4,778,857)	2,069,033
Net loss	$ (8,071,596)	$ (5,476,807)	$ (18,471,409)	$ (13,748,774)
Net loss per common share				
Basic and diluted	$ (0.24)	$ (0.25)	$ (0.62)	$ (0.67)
Weighted average shares outstanding				
Basic and diluted	34,112,254	21,662,824	29,934,764	20,524,799

Source: Celsion Corporation.

Figure 28
CONDENSED CONSOLIDATED BALANCE SHEETS

	September 30, 2020 (Unaudited)	December 31, 2019
ASSETS		
Current assets:		
Cash and cash equivalents	$ 18,339,728	$ 6,875,273
Investment in debt securities - available for sale, at fair value	—	7,985,886
Accrued interest receivable on investment securities	—	21,369
Advances and deposits on clinical programs and other current assets	1,565,651	1,352,670
Total current assets	**19,905,379**	**16,235,198**
Property and equipment (at cost, less accumulated depreciation of $3,213,681 and $3,096,681, respectively)	**302,281**	**405,363**
Other assets:		
Deferred tax asset	—	1,819,324
In-process research and development, net	13,366,234	15,736,491
Goodwill	1,976,101	1,976,101
Operating lease right-of-use assets, net	1,147,062	1,431,640
Other intangible assets, net	170,489	340,976
Deposits and other assets	407,284	333,274
Total other assets	**17,067,170**	**21,637,806**
Total assets	**$ 37,274,830**	**$ 38,278,367**
LIABILITIES AND STOCKHOLDERS' EQUITY		
Current liabilities:		
Accounts payable — trade	$ 2,168,076	$ 2,862,949
Other accrued liabilities	1,919,779	2,303,547
Notes payable – current portion, net of deferred financing costs	416,476	1,840,228
Operating lease liability - current portion	421,564	387,733
Deferred revenue - current portion	500,000	500,000
Total current liabilities	**5,425,895**	**7,894,457**
Earn-out milestone liability	7,115,000	5,717,709
Notes payable – non-current portion, net of deferred financing costs	4,626,987	7,963,449
Operating lease liability - non-current portion	823,147	1,143,717
Deferred revenue - non-current portion	625,000	1,000,000
Total liabilities	**18,616,029**	**23,719,332**
Commitments and contingencies	—	—
Stockholders' equity:		
Preferred stock - $0.01 par value (100,000 shares authorized, and no shares issued or outstanding at September 30, 2020 and December 31, 2019)	—	—
Common stock - $0.01 par value (112,500,000 shares authorized; 36,160,114 and 23,256,152 shares issued at September 30, 2020 and December 31, 2019, respectively, and 36,159,780 and 23,255,818 shares outstanding at September 30, 2020 and December 31, 2019, respectively)	361,601	232,562
Additional paid-in capital	327,370,577	304,885,663
Accumulated other comprehensive gain	—	42,778
Accumulated deficit	(308,988,189)	(290,516,780)
Total stockholders' equity before treasury stock	**18,743,989**	**14,644,223**
Treasury stock, at cost (334 shares at September 30, 2020 and December 31, 2019)	(85,188)	(85,188)
Total stockholders' equity	**18,658,801**	**14,559,035**
Total liabilities and stockholders' equity	**$ 37,274,830**	**$ 38,278,367**

Source: Celsion Corporation.

Figure 29
CONDENSED CONSOLIDATED STATEMENTS OF CASH FLOWS
(Unaudited)

	Nine Months Ended September 30,	
	2020	**2019**
Cash flows from operating activities:		
Net loss	$ (18,471,409)	$ (13,748,774)
Adjustments to reconcile net loss to net cash from operating activities:		
Depreciation and amortization	572,065	537,211
Change in fair value of earn-out milestone liability	1,397,291	(3,088,821)
Impairment of in-process research and development	2,370,257	—
Fair value of warrants issued in connection with amendment to modify the GEN-1 earn-out milestone payments	—	400,000
Recognition of deferred revenue	(375,000)	(375,000)
Stock-based compensation costs	1,448,202	1,762,172
Shares and warrants issued in exchange for services	44,798	5,350
Deferred income tax asset	1,819,324	—
Amortization of deferred finance charges and debt discount associated with notes payable	439,786	289,182
Net changes in:		
Accrued interest receivable on investment securities	21,369	41,338
Advances and deposits on clinical programs and other current assets	(286,991)	(951,877)
Accounts payable- trade and other accrued liabilities	(866,748)	486,857
Net cash (used in) operating activities:	**(11,887,056)**	**(14,642,362)**
Cash flows from investing activities:		
Purchases of investment securities	(9,956,892)	(19,338,177)
Proceeds from sale and maturity of investment securities	17,900,000	23,310,000
Purchases of property and equipment	(13,918)	(336,445)
Net cash provided by investing activities	**7,929,190**	**3,635,378**
Cash flows from financing activities:		
Proceeds from sale of common stock equity, net of issuance costs	20,250,426	6,175,527
Proceeds from issuance of common stock upon conversion of stock options	371,895	—
Payments on notes payable including end-of-term fees	5,200,000	—
Proceeds from Payroll Protection Program (PPP) loans	1,324,750	—
Repayments on Payroll Protection Program (PPP) loans	(1,324,750)	—
Net cash provided by financing activities	**15,422,321**	**6,175,527**
Increase (decrease) in cash and cash equivalents	**11,464,455**	**(4,831,457)**
Cash and cash equivalents at beginning of period	**6,875,273**	**13,353,543**
Cash and cash equivalents at end of period	**$ 18,339,728**	**$ 8,522,086**

Source: Celsion Corporation.

Recent Events

November 16, 2020—Celsion Corporation announced financial results for the three and nine months ended September 30, 2020, and provided an update on clinical development programs with GEN-1, its DNA-mediated IL-12 immunotherapy currently in Phase II development for the treatment of advanced ovarian cancer, and ThermoDox®, its proprietary heat-activated liposomal encapsulation of doxorubicin currently in Phase III development for the treatment of hepatocellular carcinoma (HCC)/primary liver cancer.

October 12, 2020—Announced that Michael H. Tardugno, the Company's Chairman, President and Chief Executive Officer, issued a letter to stockholders providing an update on the ongoing data analysis from its Phase III OPTIMA Study with ThermoDox® plus radiofrequency ablation (RFA) in patients newly diagnosed with primary liver cancer, or hepatocellular carcinoma (HCC), as well as growing interest among clinical investigators in conducting studies with ThermoDox® as a monotherapy or in combination with other therapies.

September 8, 2020—Provided an update on the OVATION 2 Study with GEN-1 in advanced ovarian cancer patients. Celsion also announced it has entered into a common stock purchase agreement for the issuance and sale of up to $26 million shares of common stock with Lincoln Park Capital Fund, LLC (LPC), a Chicago-based institutional investor. In connection with the execution of the purchase agreement, LPC made an initial purchase of $1 million of common stock at $1.00 per share, representing a significant premium to the current market price.

September 2, 2020—Announced that on August 28, 2020, the Company entered into an amendment to its existing $10 million loan agreement with Horizon Technology Finance Corporation (HRZN-NASDAQ). Consistent with its target to leverage equity capital, Celsion elected to reduce its outstanding debt under the loan by $5 million and restructure the terms of the remaining $5 million loan balance.

August 14, 2020—Announced financial results for the three and six months ended June 30, 2020, and provided an update on clinical development programs with GEN-1, its DNA-mediated IL-12 immunotherapy currently in Phase II development for the treatment of advanced stage ovarian cancer, and ThermoDox®, its proprietary heat-activated liposomal encapsulation of doxorubicin, currently in Phase III development for the treatment of hepatocellular carcinoma, or primary liver cancer.

August 4, 2020—Provided an update on its ongoing review of unblinded data from the second pre-planned interim analysis of the global Phase III OPTIMA Study of ThermoDox® in combination with radiofrequency ablation (RFA) for the treatment of hepatocellular carcinoma (HCC), or primary liver cancer. The Company announced that it will continue following patients for overall survival (OS), noting that the unexpected and marginally crossed futility boundary, suggested by the Kaplan-Meier analysis at the second interim analysis on July 9, 2020, may be associated with a data maturity issue. The Company further notes that 26 consecutive patient deaths represented exclusively in the second analysis behave far differently from the balance of the patients who have died as of this date.

July 13, 2020—Announced that it has received a recommendation from the independent Data Monitoring Committee (DMC) to consider stopping the global Phase III OPTIMA Study of ThermoDox® in combination with radiofrequency ablation (RFA) for the treatment of hepatocellular carcinoma (HCC), or primary liver cancer. The recommendation was made following the second pre-planned interim safety and efficacy analysis by the DMC on July 9, 2020. The DMC analysis found that the pre-specified boundary for stopping the trial for futility of 0.900 was crossed with an actual value of 0.903. However, the 2-sided p-value of 0.524 for this analysis provides uncertainty; subsequently, the DMC has left the final decision of whether or not to stop the OPTIMA Study to Celsion. There were no safety concerns noted during the interim analysis.

June 25, 2020—Affirmed that the DMC is scheduled to meet during the first half of July to conduct the second pre-planned interim safety and efficacy analysis of the Phase III OPTIMA Study with ThermoDox® plus RFA in patients with HCC, or primary liver cancer. Members of the DMC represent the global market for HCC and are based in the U.S., Canada, and Europe, and Celsion believes that any logistical challenges to the Committee's performing its work presented by the global COVID-19 pandemic have been addressed.

June 24, 2020—Announced the entry into an underwriting agreement relating to the sale of 2,666,667 shares of its common stock at an offering price of $3.75 per share, less underwriting discounts and commission. The gross proceeds from the offering will be $10 million, before deducting underwriting discounts and commissions and estimated offering expenses. The shares of common stock are being sold to both existing and new institutional investors of the Company. The offering is expected to close on June 24, 2020, subject to satisfaction of customary closing conditions. Celsion intends to use the net proceeds for clinical development of its product candidates, working capital, and other general corporate purposes.

May 29, 2020—Announced the final recommendations of the Data Safety Monitoring Board (DSMB) following completion of the Phase I dose-finding and tolerance portion of the Phase I/II OVATION 2 Study with GEN-1 in advanced (Stage III/IV) ovarian cancer. Based on favorable safety data from 15 randomized patients, the DSMB has recommended that the Phase II portion of the OVATION Study proceed with the dose of 100 mg/m^2. The DSMB also determined that safety is satisfactory with an acceptable risk/benefit, and that patients tolerate up to 17 doses of GEN-1 during a course of treatment that lasts up to six months. No dose limiting toxicities were reported.

May 15, 2020—Announced financial results for the three months ended March 31, 2020, and provided an update on clinical development programs.

April 23, 2020—Announced it has received $1.82 million of net cash proceeds from the sale of approximately $1.9 million of its unused New Jersey net operating losses (NOLs) and $632,220 in funding under the Paycheck Protection Program (PPP), the federal government's main initiative to help small businesses disrupted by the COVID-19 pandemic. The NOL sales cover the tax years 2017 and 2018 and are administered through the New Jersey Economic Development Authority's (NJEDA) Technology Business Tax Certificate Transfer (NOL) Program. With this new $2.5 million funding, coupled with the $4.4 million in net proceeds from the recent registered direct equity offer completed on March 3, 2020, the Company has strengthened its balance sheet at a time of stock market uncertainty.

April 15, 2020—Announced that the prescribed minimum number of events of 158 patient deaths has been reached for the second pre-specified interim analysis of the OPTIMA Phase III Study with ThermoDox® plus RFA in patients with HCC or primary liver cancer. Following preparation of the data, the DMC is expected to meet in July 2020 to conduct the second interim analysis.

March 26, 2020—Jointly announced with Medidata, a Dassault Systèmes company, that examining matched patient data provided by Medidata in a synthetic control arm (SCA) with results from the Company's completed Phase Ib dose-escalating OVATION I Study with GEN-1 in Stage III/IV ovarian cancer patients showed positive results in progression-free survival (PFS). The hazard ratio (HR) was 0.53 in the intent-to-treat (ITT) group, showing strong signals of efficacy.

March 25, 2020—Announced financial results for the year ended December 31, 2019 and provided an update on clinical development programs.

March 23, 2020—Announced the European Medicines Agency (EMA) Committee for Orphan Medicinal Products (COMP) has recommended that GEN-1 be designated as an orphan medicinal product for the treatment of ovarian cancer. GEN-1 previously received orphan designation from the U.S. Food and Drug Administration and is currently being evaluated in a Phase I/II clinical trial (the OVATION 2 Study) for the treatment of newly diagnosed patients with Stage III and IV ovarian cancer.

March 19, 2020—Announced encouraging initial clinical data from the first 15 patients enrolled in the ongoing Phase I/II OVATION 2 Study for patients newly diagnosed with Stage III and IV ovarian cancer.

March 3, 2020—Announced that Michael H. Tardugno, the company's chairman, president and chief executive officer, issued a letter to stockholders.

February 28, 2020—Announced that Celsion has entered into securities purchase agreements with institutional investors for the purchase and sale of 4,571,428 shares of the Company's common stock, par value $0.01 per share,

pursuant to a registered direct offering. The Company has also agreed to issue to such investors, in a concurrent private placement, warrants to purchase 2,971,428 shares of the Company's common stock. The warrants will be exercisable on the six-month anniversary of the issuance date, will expire on the five-year anniversary of the initial exercise date, and have an exercise price of $1.15 per share. The gross proceeds of the offering will be approximately $4.8 million, before deducting placement agent fees and other estimated offering expenses.

February 6, 2020—Announced that the independent Data Safety Monitoring Board (DSMB) has completed its initial safety review of data from the first fifteen patients treated with the first four neoadjuvant doses of GEN-1 at 100 mg/m² in the ongoing Phase I/II OVATION 2 Study. As requested by the U.S. FDA, a follow-on Phase I review by the DSMB will evaluate the safety of GEN-1 in up to 17 weekly doses before initiating the Phase II portion of the Study. The OVATION 2 Study combines GEN-1, the Company's IL-12 gene-mediated immunotherapy, with neoadjuvant chemotherapy (NACT), a SOC for newly diagnosed patients with Stage III and IV ovarian cancer. Following NACT, patients undergo interval debulking surgery (IDS) followed by three additional cycles of chemotherapy.

February 4, 2020—Announced that Prof. Riccardo Lencioni, M.D., FSIR, EBIR delivered a presentation titled "Thermally-Sensitive Ablation Enhancers: Where Do We Stand?" at the SPECTRUM 2020 Interventional Oncology Conference held in Miami. Dr. Lencioni is a professor in the Department of Radiology at the University of Pisa School of Medicine in Italy and is an Honorary Research Professor of Interventional Oncology at the Miami Cancer Institute. He was the lead principal investigator in Europe for the Company's completed Phase III HEAT Study in hepatocellular carcinoma (HCC), or primary liver cancer, using radiofrequency ablation (RFA) plus ThermoDox®, the Company's lead product.

Risks and Disclosures

This Executive Informational Overview® (EIO) has been prepared by Celsion Corporation ("Celsion" 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 Celsion's statements on Forms 10-K, 10-Q, and 8-K as well as other forms filed from time to time.

The content of this report with respect to Celsion has been compiled primarily from information available to the public released by the Company through news releases, Annual Reports, and U.S. Securities and Exchange Commission (SEC) filings. Celsion 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 Celsion 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 thirty-nine thousand five hundred U.S. dollars and seventy five thousand four year warrants for its services in creating this report and for quarterly updates.

Investors should carefully consider the risks and information about Celsion's 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 Celsion's SEC filings are not the only risks that the Company faces. Additional risks and uncertainties not presently known to Celsion 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, Celsion's business, financial condition, and results of operations could be materially and adversely affected, and the trading price of the Company's shares could decline.

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 full risk factors involved in an investment in the Company as well as for copies of this report, please contact Celsion by calling (609) 896-9100.

RISKS RELATED TO CELSION'S BUSINESS

The Company has a history of significant losses from operations and expects to continue to incur significant losses for the foreseeable future.

Since its inception, Celsion's expenses have substantially exceeded its revenue, resulting in continuing losses and an accumulated deficit of $291 million as of December 31, 2019. For the years ended December 31, 2019 and 2018, the Company incurred net losses of $16.9 million, and $11.9 million, respectively. Celsion currently has no product revenue and does not expect to generate any product revenue for the foreseeable future. Because they are committed to continuing product research, development, clinical trial, and commercialization programs, the Company will continue to incur significant operating losses unless and until it completes the development of ThermoDox®, GEN-1, and other new product candidates and these product candidates have been clinically tested, approved by the United States Food and Drug Administration (FDA), and successfully marketed. The amount of future losses is uncertain.

The Company's ability to achieve profitability, if ever, will depend on, among other things, it or its collaborators successfully developing product candidates, obtaining regulatory approvals to market and commercialize product candidates, manufacturing any approved products on commercially reasonable terms, establishing a sales and marketing organization or suitable third-party alternatives for any approved product, and raising sufficient funds to finance business activities. If Celsion or its collaborators are unable to develop and commercialize one or more of its

product candidates or if sales revenue from any product candidate that receives approval is insufficient, the Company will not achieve profitability, which could have a material adverse effect on its business, financial condition, results of operations, and prospects.

Celsion does not expect to generate revenue for the foreseeable future.

The Company has devoted its resources to developing a new generation of products and will not be able to market these products until it has completed clinical trials and obtains all necessary governmental approvals. The lead product candidate, ThermoDox® and the product candidates it purchased in its acquisition of EGEN, including GEN-1, are still in various stages of development and trials and cannot be marketed until the Company has completed clinical testing and obtains necessary governmental approval.

The Company's delivery technology platforms, TheraPlas™ and TheraSilence™, are in preclinical stages of development. Accordingly, its revenue sources are, and will remain, extremely limited until its product candidates are clinically tested, approved by the FDA or foreign regulatory agencies, and successfully marketed. Celsion cannot guarantee that any of its product candidates will be approved by the FDA or any foreign regulatory agency or marketed, successfully or otherwise, at any time in the foreseeable future or at all.

Drug development is an inherently uncertain process with a high risk of failure at every stage of development.

Preclinical testing and clinical trials are long, expensive, and highly uncertain processes and failure can unexpectedly occur at any stage of clinical development. Drug development is inherently risky and clinical trials take several years to complete. The start or end of a clinical trial is often delayed or halted due to changing regulatory requirements, manufacturing challenges, required clinical trial administrative actions, slower than anticipated patient enrollment, changing standards of care, availability or prevalence of use of a comparator drug or required prior therapy, clinical outcomes including insufficient efficacy, safety concerns, or financial constraints.

The results from preclinical testing or early clinical trials of a product candidate may not predict the results that will be obtained in later phase clinical trials of the product candidate. Celsion, the FDA, or other applicable regulatory authorities may suspend clinical trials of a product candidate at any time for various reasons, including a belief that subjects participating in such trials are being exposed to unacceptable health risks or adverse side effects. Celsion may not have the financial resources to continue development of, or to enter into collaborations for, a product candidate if the Company experiences any problems or other unforeseen events that delay or prevent regulatory approval of, or its ability to commercialize, product candidates. The failure of one or more of the Company's drug candidates or development programs could have a material adverse effect on Celsion's business, financial condition, and results of operations.

The Company will need to raise additional capital to fund its planned future operations, and may be unable to secure such capital without dilutive financing transactions. If Celsion is unable to raise additional capital, the Company may not be able to complete the development, testing, and commercialization of its product candidates.

Celsion has not generated significant revenue and has incurred significant net losses in each year since its inception. The Company has substantial future capital requirements to continue its research and development activities and advance its product candidates through various development stages. To complete the development and commercialization of its product candidates, Celsion will need to raise substantial amounts of additional capital to fund its operations. The future capital requirements will depend upon numerous unpredictable factors, including, without limitation, the cost, timing, progress, and outcomes of clinical studies and regulatory reviews of its proprietary drug candidates, the Company's efforts to implement new collaborations, licenses and strategic transactions, general and administrative expenses, capital expenditures and other unforeseen uses of cash.

If the Company is unable to obtain additional capital on a timely basis or on acceptable terms, or, if current market conditions, including the volatility in the markets resulting from the worldwide Covid-19 pandemic, make capital raising impractical or impossible, Celsion may be required to delay, reduce, or terminate its research and development programs and preclinical studies or clinical trials, if any, limit strategic opportunities or undergo

corporate restructuring activities. The Company also could be required to seek funds through arrangements with collaborators or others that may require it to relinquish rights to some of its technologies, product candidates, or potential markets, or that could impose onerous financial or other terms. Furthermore, if Celsion cannot fund its ongoing development and other operating requirements, particularly those associated with its obligations to conduct clinical trials under its licensing agreements, it will be in breach of these licensing agreements and could lose its license rights, which could have material adverse effects on its business.

If Celsion does not obtain or maintain FDA and foreign regulatory approvals for its drug candidates on a timely basis, or at all, or if the terms of any approval impose significant restrictions or limitations on use, the Company will be unable to sell those products and its business, results of operations, and financial condition will be negatively affected.

To obtain regulatory approvals from the FDA and foreign regulatory agencies, Celsion must conduct clinical trials demonstrating that its products are safe and effective. The Company may need to amend ongoing trials, or the FDA and/or foreign regulatory agencies may require it to perform additional trials beyond those it has planned. The testing and approval process require substantial time, effort, and resources, and generally take a number of years to complete. The time to complete testing and obtaining approvals is uncertain, and the FDA and foreign regulatory agencies have substantial discretion, at any phase of development, to terminate clinical studies, require additional clinical studies or other testing, delay or withhold approval, and mandate product withdrawals, including recalls. In addition, the Company's drug candidates may have undesirable side effects or other unexpected characteristics that could cause it or regulatory authorities to interrupt, delay, or halt clinical trials and could result in a more restricted label or the delay or denial of regulatory approval by regulatory authorities.

Even if Celsion receives regulatory approval of a product, the approval may limit the indicated uses for which the drug may be marketed. The failure to obtain timely regulatory approval of product candidates, the imposition of marketing limitations, or a product withdrawal would negatively impact its business, results of operations, and financial condition. Even if the Company receives approval, it will be subject to ongoing regulatory obligations and continued regulatory review, which may result in significant additional expense and subject Celsion to restrictions, withdrawal from the market, or penalties if they fail to comply with applicable regulatory requirements or if they experience unanticipated problems with its product candidates, when and if approved. Finally, even if Celsion obtains FDA approval of any of its product candidates, the Company may never obtain approval or commercialize such products outside of the U.S., given that it may be subject to additional or different regulatory burdens in other markets. This could limit Celsion's ability to realize their full market potential.

New gene-based products for therapeutic applications are subject to extensive regulation by the FDA and comparable agencies in other countries. The precise regulatory requirements with which Celsion will have to comply, now and in the future, are uncertain due to the novelty of the gene-based products being developed.

The regulatory approval process for novel product candidates, such as that being developed by Celsion, can be significantly more expensive and take longer than for other, better known or more extensively studied product candidates. Limited data exist regarding the safety and efficacy of DNA-based therapeutics compared with conventional therapeutics, and government regulation of DNA-based therapeutics is evolving. Regulatory requirements governing gene and cell therapy products have changed frequently and may continue to change in the future. The FDA has established the Office of Cellular, Tissue and Gene Therapies within its Center for Biologics Evaluation and Research (CBER), to consolidate the review of gene therapy and related products, and has established the Cellular, Tissue and Gene Therapies Advisory Committee to advise CBER in its review. It is difficult to determine how long it will take or how much it will cost to obtain regulatory approvals for the Company's product candidates in either the U.S. or the European Union or how long it will take to commercialize these product candidates.

Adverse events or the perception of adverse events in the field of gene therapy generally, or with respect to Celsion's product candidates specifically, may have a particularly negative impact on public perception of gene therapy and result in greater governmental regulation, including future bans or stricter standards imposed on gene-based therapy clinical trials, stricter labeling requirements, and other regulatory delays in the testing or approval of the Company's potential products. For example, each clinical trial of investigational gene therapies must be reviewed

and approved by the Institutional Biosafety Committee (IBC) for each clinical site. IBCs were established under the National Institutes of Health (NIH) Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules to provide local review and oversight of nearly all forms of research utilizing recombinant or synthetic nucleic acid molecules. The IBC assesses biosafety issues, specifically, safety practices and containment procedures, related to the investigational product and clinical study.

Compliance with the NIH Guidelines is mandatory for investigators at institutions receiving NIH funds for research involving recombinant DNA, however many companies and other institutions not otherwise subject to the NIH Guidelines voluntarily follow them. Such trials remain subject to FDA and other clinical trial regulations, and only after FDA, IBC, and other relevant approvals are in place can these protocols proceed. The FDA can put an investigational new drug (IND) application on a clinical hold even if the IBC has provided a favorable review. Such committee and advisory group reviews and any new guidelines they promulgate may lengthen the regulatory review process, require the Company to perform additional studies, increase development costs, lead to changes in regulatory positions and interpretations, delay or prevent approval and commercialization of Celsion's product candidates, or lead to significant post-approval limitations or restrictions. Any increased scrutiny could delay or increase the costs of the Company's product development efforts or clinical trials. Even if Celsion's products receive regulatory approval, they may still face future development and regulatory difficulties. Government regulators may impose significant restrictions on a product's indicated uses or marketing or impose ongoing requirements for potentially costly post-approval studies. This governmental oversight may be particularly strict with respect to gene-based therapies.

Serious adverse events, undesirable side effects, or other unexpected properties of the Company's product candidates may be identified during development or after approval, which could lead to the discontinuation of Celsion's clinical development programs, refusal by regulatory authorities to approve its product candidates or, if discovered following marketing approval, revocation of marketing authorizations or limitations on the use of its product candidates, thereby limiting the commercial potential of such product candidate.

As the Company continues development of its product candidates and initiates clinical trials of additional product candidates, serious adverse events, undesirable side effects or unexpected characteristics may emerge, causing Celsion to abandon these product candidates or limit their development to more narrow uses or subpopulations in which the serious adverse events, undesirable side effects, or other characteristics are less prevalent, less severe, or more acceptable from a risk-benefit perspective.

Even if the Company's product candidates initially show promise in these early clinical trials, the side effects of drugs are frequently only detectable after they are tested in large, Phase III clinical trials or, in some cases, after they are made available to patients on a commercial scale after approval. Sometimes, it can be difficult to determine if the serious adverse or unexpected side effects were caused by the product candidate or another factor, especially in oncology subjects who may suffer from other medical conditions and be taking other medications. If serious adverse or unexpected side effects are identified during development and are determined to be attributed to Celsion's product candidate, the Company may be required to develop a Risk Evaluation and Mitigation Strategy (REMS) to mitigate those serious safety risks, which could impose significant distribution and use restrictions on its products.

In addition, drug-related side effects could also affect subject recruitment or the ability of enrolled subjects to complete the trial, resulting in potential product liability claims, reputational harm, withdrawal of approvals, a requirement to include additional warnings on the label, or to create a medication guide outlining the risks of such side effects for distribution to patients. It can also result in patient harm, liability lawsuits, and reputational harm. Any of these occurrences could prevent the Company from achieving or maintaining market acceptance and may harm its business, financial condition, and prospects significantly.

If Celsion encounters difficulties enrolling patients in its clinical trials, its clinical development activities could be delayed or otherwise adversely affected.

The Company may experience difficulties in patient enrollment in its clinical trials for a variety of reasons. The timely completion of clinical trials in accordance with their protocols depends, among other things, on its ability to enroll a sufficient number of patients who remain in the trial until its conclusion. The enrollment of patients depends on many factors, including:

- the patient eligibility and exclusion criteria defined in the protocol;
- the size of the patient population required for analysis of the trial's primary endpoints and the process for identifying patients;
- the willingness or availability of patients to participate in the Company's trials (including due to the recent outbreak of COVID-19 coronavirus);
- the proximity of patients to trial sites;
- the design of the trial;
- Celsion's ability to recruit clinical trial investigators with the appropriate competencies and experience;
- clinicians' and patients' perceptions as to the potential advantages and risks of the product candidate being studied in relation to other available therapies, including any new products that may be approved for the indications being investigated;
- the availability of competing commercially available therapies and other competing drug candidates' clinical trials;
- Celsion's ability to obtain and maintain patient informed consents; and
- the risk that patients enrolled in clinical trials will drop out of the trials before completion.

In addition, the Company's clinical trials will compete with other clinical trials for product candidates that are in the same therapeutic areas as its product candidates, and this competition will reduce the number and types of patients available to it because some patients who might have opted to enroll in these trials may instead opt to enroll in a trial being conducted by one of the Company's competitors. Since the number of qualified clinical investigators is limited, Celsion expects to conduct some of its clinical trials at the same clinical trial sites that some of its competitors use, which will reduce the number of patients who are available for the Company's clinical trials in such clinical trial site. Certain of its planned clinical trials may also involve invasive procedures, which may lead some patients to drop out of trials to avoid these follow-up procedures.

Furthermore, timely enrollment in clinical trials is reliant on clinical trial sites, which may be adversely affected by global health matters, including, among other things, pandemics. For example, the Company's clinical trial sites may be located in regions currently being affected by the COVID-19 coronavirus. Some factors from the COVID-19 coronavirus outbreak that may adversely affect enrollment in Celsion's trials include:

- the diversion of healthcare resources away from the conduct of clinical trial matters to focus on pandemic concerns, including the attention of infectious disease physicians serving as its clinical trial investigators, hospitals serving as its clinical trial sites, and hospital staff supporting the conduct of its clinical trials;
- patients who would otherwise be candidates for enrollment in the Company's clinical trials may become infected with the COVID-19 coronavirus, which may kill some patients and render others too ill to participate, limiting the available pool of participants for the Company's trials;

- limitations on travel that interrupt key trial activities, such as clinical trial site initiations and monitoring;
- interruption in global shipping affecting the transport of clinical trial materials, such as investigational drug product and comparator drugs used in Celsion's trials; and
- employee furlough days that delay necessary interactions with local regulators, ethics committees, and other important agencies.

These and other factors arising from the COVID-19 coronavirus could worsen in countries that are already afflicted with the virus or could continue to spread to additional countries, each of which may further adversely impact the Company's clinical trials. The global outbreak of the COVID-19 coronavirus continues to evolve and the conduct of Celsion's trials may continue to be adversely affected, despite efforts to mitigate this impact.

The Company may not successfully engage in future strategic transactions, which could adversely affect its ability to develop and commercialize product candidates, impact its cash position, increase its expenses, and present significant distractions to the Company's management.

In the future, Celsion may consider strategic alternatives intended to further the development of its business, which may include acquiring businesses, technologies, or products, out- or in-licensing product candidates or technologies or entering into a business combination with another company. Any strategic transaction may require it to incur non-recurring or other charges, increase near- and long-term expenditures and pose significant integration or implementation challenges or disrupt its management or business.

These transactions would entail numerous operational and financial risks, including exposure to unknown liabilities, disruption of its business, and diversion of management's time and attention in order to manage a collaboration or develop acquired products, product candidates or technologies, incurrence of substantial debt or dilutive issuances of equity securities to pay transaction consideration or costs, higher than expected collaboration, acquisition or integration costs, write-downs of assets or goodwill or impairment charges, increased amortization expenses, difficulty and cost in facilitating the collaboration or combining the operations and personnel of any acquired business, impairment of relationships with key suppliers, manufacturers or customers of any acquired business due to changes in management and ownership and the inability to retain key employees of any acquired business. Accordingly, although there can be no assurance that Celsion will undertake or successfully complete any transactions of the nature described above, any transactions that it does complete may be subject to the foregoing or other risks and have a material adverse effect on its business, results of operations, financial condition, and prospects. Conversely, any failure to enter any strategic transaction that would be beneficial to the Company could delay the development and potential commercialization of its product candidates and have a negative impact on the competitiveness of any product candidate that reaches market.

Celsion may never realize the perceived benefits of potential future transactions. The Company cannot provide assurance that it will be successful in overcoming problems encountered in connection with any transactions, and its inability to do so could significantly harm its business, results of operations, and financial condition. These transactions could dilute a stockholder's investment and cause Celsion to incur debt, contingent liabilities, and amortization/impairment charges related to intangible assets, all of which could materially and adversely affect the Company's business, results of operations, and financial condition. In addition, Celsion's effective tax rate for future periods could be negatively impacted by the EGEN acquisition or potential future transactions.

Celsion's business depends on license agreements with third parties to permit it to use patented technologies. The loss of any of the Company's rights under these agreements could impair its ability to develop and market its products.

The Company's success will depend, in a substantial part, on its ability to maintain its rights under license agreements granting Celsion rights to use patented technologies. For instance, the Company is party to license agreements with Duke University, under which they have exclusive rights to commercialize medical treatment products and procedures based on Duke's thermo-sensitive liposome technology. The Duke University license agreement contains

a license fee, royalty and/or research support provisions, testing and regulatory milestones, and other performance requirements that it must meet by certain deadlines. If Celsion breaches any provisions of the license and research agreements, it may lose its ability to use the subject technology, as well as compensation for its efforts in developing or exploiting the technology. Any such loss of rights and access to technology could have a material adverse effect on the Company's business.

Further, Celsion cannot guarantee that any patent or other technology rights licensed to it by others will not be challenged or circumvented successfully by third parties, or that the rights granted will provide adequate protection. The Company may be required to alter any of its potential products or processes or enter into a license and pay licensing fees to a third party or cease certain activities. There can be no assurance that Celsion can obtain a license to any technology that it determines it needs on reasonable terms, if at all, or that it could develop or otherwise obtain alternate technology. If a license is not available on commercially reasonable terms or at all, the Company's business, results of operations, and financial condition could be significantly harmed, and they may be prevented from developing and commercializing the product. Litigation, which could result in substantial costs, may also be necessary to enforce any patents issued to or licensed by Celsion or to determine the scope and validity of another claimed proprietary rights.

If any of the Company's pending patent applications do not issue, or are deemed invalid following issuance, Celsion may lose valuable intellectual property protection.

The patent positions of pharmaceutical and biotechnology companies, such as Celsion, are uncertain and involve complex legal and factual issues. The Company owns various U.S. and international patents and has pending U.S. and international patent applications that cover various aspects of its technologies. There can be no assurance that patents that have issued will be held valid and enforceable in a court of law through the entire patent term. Even for patents that are held valid and enforceable, the legal process associated with obtaining such a judgment is time consuming and costly. Additionally, issued patents can be subject to opposition, interferences, or other proceedings that can result in the revocation of the patent or maintenance of the patent in amended form (and potentially in a form that renders the patent without commercially relevant or broad coverage). Further, the Company's competitors may be able to circumvent and otherwise design around Celsion's patents. Even if a patent is issued and enforceable, since development and commercialization of pharmaceutical products can be subject to substantial delays, patents may expire early and provide only a short period of protection, if any, following the commercialization of products encompassed by its patents. Celsion may have to participate in interference proceedings declared by the U.S. Patent and Trademark Office, which could result in a loss of the patent and/or substantial cost to the Company.

Celsion has filed patent applications, and plans to file additional patent applications, covering various aspects of its technologies and its proprietary product candidates. There can be no assurance that the patent applications for which it applies would actually issue as patents or do so with commercially relevant or broad coverage. The coverage claimed in a patent application can be significantly reduced before the patent is issued. The scope of the Company's claim coverage can be critical to Celsion's ability to enter into licensing transactions with third parties and its right to receive royalties from collaboration partnerships. Since publication of discoveries in scientific or patent literature often lags behind the date of such discoveries, the Company cannot be certain that it was the first inventor of inventions covered by its patents or patent applications. In addition, there is no guarantee that the Company will be the first to file a patent application directed to an invention.

An adverse outcome in any judicial proceeding involving intellectual property, including patents, could subject the Company to significant liabilities to third parties, require disputed rights to be licensed from or to third parties or require Celsion to cease using the technology in dispute. In those instances where the Company seeks an intellectual property license from another, they may not be able to obtain the license on a commercially reasonable basis, if at all, thereby raising concerns as to its ability to freely commercialize its technologies or products.

Celsion relies on trade secret protection and other unpatented proprietary rights for important proprietary technologies, and any loss of such rights could harm its business, results of operations, and financial condition.

The Company relies on trade secrets and confidential information that it seeks to protect, in part, by confidentiality agreements with its corporate partners, collaborators, employees, and consultants. Celsion cannot assure investors that these agreements are adequate to protect its trade secrets and confidential information or will not be breached or, if breached, will have adequate remedies. Furthermore, others may independently develop substantially equivalent confidential and proprietary information or otherwise gain access to the Company's trade secrets or disclose such technology. Any loss of trade secret protection or other unpatented proprietary rights could harm Celsion's business, results of operations, and financial condition.

The Company's products may infringe patent rights of others, which may require costly litigation and, if the Company is unsuccessful, could cause Celsion to pay substantial damages or limit its ability to commercialize products.

Celsion's commercial success depends on its ability to operate without infringing the patents and other proprietary rights of third parties. There may be third party patents that relate to its products and technology. The Company may unintentionally infringe upon valid patent rights of third parties. Although it currently is not involved in any material litigation involving patents, a third-party patent holder may assert a claim of patent infringement against it in the future. Alternatively, Celsion may initiate litigation against the third-party patent holder to request that a court declare that it is not infringing the third party's patent and/or that the third party's patent is invalid or unenforceable.

If a claim of infringement is asserted against Celsion and is successful, and therefore the Company is found to infringe, it could be required to pay damages for infringement, including treble damages if it is determined that Celsion knew or became aware of such a patent and failed to exercise due care in determining whether or not it infringed the patent. If the Company has supplied infringing products to third parties or have licensed third parties to manufacture, use or market infringing products, it may be obligated to indemnify these third parties for damages they may be required to pay to the patent holder and for any losses they may sustain.

Celsion can also be prevented from selling or commercializing any of its products that use the infringing technology in the future unless they obtain a license from such third party. A license may not be available from such third party on commercially reasonable terms or may not be available at all. Any modification to include a non-infringing technology may not be possible, or if possible, may be difficult or time-consuming to develop, and require revalidation, which could delay the Company's ability to commercialize its products. Any infringement action asserted against Celsion, even if it is ultimately successful in defending against such action, would likely delay the regulatory approval process of its products, harm its competitive position, be expensive, and require the time and attention of key management and technical personnel.

Celsion relies on third parties to conduct all of its clinical trials. If these third parties are unable to carry out their contractual duties in a manner that is consistent with Company expectations, complies with budgets and other financial obligations, or meets expected deadlines, Celsion may not receive certain development milestone payments or be able to obtain regulatory approval for or commercialize its product candidates in a timely or cost-effective manner.

The Company does not independently conduct clinical trials for its drug candidates. They rely, and expect to continue to rely, on third-party clinical investigators, clinical research organizations (CROs), clinical data management organizations and consultants to design, conduct, supervise, and monitor its clinical trials.

Because Celsion does not conduct its own clinical trials, it must rely on the efforts of others and have reduced control over aspects of these activities, including the timing of such trials, the costs associated with such trials, and the procedures that are followed for such trials. Celsion does not expect to significantly increase its personnel in the foreseeable future and may continue to rely on third parties to conduct all of its future clinical trials. If it cannot contract with acceptable third parties on commercially reasonable terms or at all, if these third parties are unable to carry out their contractual duties or obligations in a manner that is consistent with Company expectations or meet

expected deadlines, if they do not carry out the trials in accordance with budgeted amounts, if the quality or accuracy of the clinical data obtained is compromised due to their failure to adhere to Company clinical protocols (or for other reasons), or if they fail to maintain compliance with applicable government regulations and standards, its clinical trials may be extended, delayed, or terminated or may become significantly more expensive, Celsion may not receive development milestone payments when expected or at all, and may not be able to obtain regulatory approval for or successfully commercialize its product candidates.

Despite the Company's reliance on third parties to conduct its clinical trials, Celsion is ultimately 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 clinical trials to be conducted in accordance with good clinical practices for conducting, recording, and reporting the results of clinical trials to assure that data and reported results are credible and accurate and that the rights, integrity, and confidentiality of clinical trial participants are protected. The Company also is required to register ongoing clinical trials and post the results of completed clinical trials on a government-sponsored database, ***ClinicalTrials.gov***, within certain timeframes. Failure to do so can result in fines, adverse publicity, and civil and criminal sanctions. Celsion's reliance on third parties that it does not control does not relieve it of these responsibilities and requirements. If Celsion or a third party it relies on fails to meet these requirements, the Company may not be able to obtain, or may be delayed in obtaining, marketing authorizations for its drug candidates and will not be able to, or may be delayed in its efforts to successfully commercialize its drug candidates. This could have a material adverse effect on Celsion's business, financial condition, results of operations, and prospects.

Because the Company relies on third party manufacturing and supply partners, its supply of research and development, preclinical, and clinical development materials may become limited or interrupted or may not be of satisfactory quantity or quality.

Celsion relies on third party supply and manufacturing partners to supply the materials and components for, and manufacture, its research and development, preclinical, and clinical trial drug supplies. The Company does not own manufacturing facilities or supply sources for such components and materials. There can be no assurance that its supply of research and development, preclinical, and clinical development drugs and other materials will not be limited, interrupted, restricted in certain geographic regions, or of satisfactory quality or continue to be available at acceptable prices. Suppliers and manufacturers must meet applicable manufacturing requirements and undergo rigorous facility and process validation tests required by FDA and foreign regulatory authorities in order to comply with regulatory standards, such as current Good Manufacturing Practices (cGMPs). In the event that any of the Company's suppliers or manufacturers fails to comply with such requirements or to perform its obligations in relation to quality, timing, or otherwise, or if the Company's supply of components or other materials becomes limited or interrupted for other reasons, Celsion may be forced to manufacture the materials itself, for which it currently does not have the capabilities or resources, or enter into an agreement with another third party, which it may not be able to do on reasonable terms, if at all.

Fast Track designation may not actually lead to a faster development or regulatory review or approval process.

ThermoDox® has received U.S. FDA Fast Track Designation. However, it may not experience a faster development process, review, or approval compared to conventional FDA procedures. The FDA may withdraw the Company's Fast Track designation if the FDA believes that the designation is no longer supported by data from its clinical or pivotal development program. The Company's Fast Track designation does not guarantee that they will qualify for or be able to take advantage of the FDA's expedited review procedures or that any application that it may submit to the FDA for regulatory approval will be accepted for filing or ultimately approved.

Celsion's relationships with healthcare providers and physicians and third-party payors will be subject to applicable anti-kickback, fraud, and abuse and other healthcare laws and regulations, which could expose the Company to criminal sanctions, civil penalties, contractual damages, reputational harm, and diminished profits and future earnings.

Healthcare providers, physicians, and third-party payors in the U.S. and elsewhere play a primary role in the recommendation and prescription of biopharmaceutical products. Arrangements with third-party payors and customers can expose biopharmaceutical manufacturers to broadly applicable fraud and abuse and other healthcare laws and regulations, including, without limitation, the federal Anti-Kickback Statute and the federal False Claims Act, which may constrain the business or financial arrangements and relationships through which such companies sell, market and distribute biopharmaceutical products. In particular, the research of the Company's product candidates, as well as the promotion, sales and marketing of healthcare items and services, as well as certain business arrangements in the healthcare industry, are subject to extensive laws designed to prevent fraud, kickbacks, self-dealing, and other abusive practices. These laws and regulations may restrict or prohibit a wide range of pricing, discounting, marketing and promotion, structuring and commission(s), certain customer incentive programs and other business arrangements generally. Activities subject to these laws also involve the improper use of information obtained in the course of patient recruitment for clinical trials.

The distribution of biopharmaceutical products is subject to additional requirements and regulations, including extensive record-keeping, licensing, storage, and security requirements intended to prevent the unauthorized sale of biopharmaceutical products.

The scope and enforcement of each of these laws is uncertain and subject to rapid change in the current environment of healthcare reform, especially in light of the lack of applicable precedent and regulations. Ensuring business arrangements comply with applicable healthcare laws, as well as responding to possible investigations by government authorities, can be time- and resource-consuming and can divert a company's attention from the business.

It is possible that governmental and enforcement authorities will conclude that Celsion's business practices may not comply with current or future statutes, regulations, or case law interpreting applicable fraud and abuse or other healthcare laws and regulations. If any such actions are instituted against the Company, and it is not successful in defending itself or asserting its rights, those actions could have a significant impact on Celsion's business, including the imposition of significant civil, criminal, and administrative penalties, damages, fines, disgorgement, imprisonment, reputational harm, possible exclusion from participation in federal and state funded healthcare programs, contractual damages and the curtailment or restricting of Company operations, as well as additional reporting obligations and oversight if the Company becomes subject to a corporate integrity agreement or other agreements to resolve allegations of non-compliance with these laws.

Further, if any of the physicians or other healthcare providers or entities with whom Celsion expects to do business is found to be not in compliance with applicable laws, they may be subject to significant criminal, civil, or administrative sanctions, including exclusions from government funded healthcare programs. Any action for violation of these laws, even if successfully defended, could cause a biopharmaceutical manufacturer to incur significant legal expenses and divert management's attention from the operation of the business. Prohibitions or restrictions on sales or withdrawal of future marketed products could materially affect business in an adverse way.

Ongoing legislative and regulatory changes affecting the healthcare industry could have a material adverse effect on the Company's business.

Political, economic, and regulatory influences are subjecting the healthcare industry to potential fundamental changes that could substantially affect results of operations by requiring, for example: (i) changes to the Company's manufacturing arrangements; (ii) additions or modifications to product labeling; (iii) the recall or discontinuation of the Company's products; or (iv) additional record-keeping requirements.

In the U.S., there has been and continues to be a number of legislative initiatives to contain healthcare costs. For example, in March 2010, the ACA was passed, which substantially changed the way healthcare is financed by both governmental and private insurers, and significantly impacted the U.S. biopharmaceutical industry. The ACA, among other things, addressed a new methodology by which rebates owed by manufacturers under the Medicaid Drug Rebate Program are calculated for drugs that are inhaled, infused, instilled, implanted or injected, increased the minimum Medicaid rebates owed by manufacturers under the Medicaid Drug Rebate Program and extended the rebate program to individuals enrolled in Medicaid managed care organizations, established annual fees and taxes on manufacturers of certain branded prescription drugs, and created a new Medicare Part D coverage gap discount program, in which manufacturers must agree to offer 70% (increased pursuant to the Bipartisan Budget Act of 2018, effective as of 2019) 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 Company cannot predict what healthcare reform initiatives may be adopted in the future. Further, federal and state legislative and regulatory developments are likely, and the Company expects ongoing initiatives in the United States to increase pressure on drug pricing. Such reforms could have an adverse effect on anticipated revenues from reloxaliase and any other product candidates that Celsion may successfully develop and for which they may obtain regulatory approval and may affect the Company's overall financial condition and ability to develop product candidates.

Celsion may fail to comply with evolving European and other privacy laws.

Since the Company is conducting clinical trials in the European Economic Area (EEA), they are subject to additional European data-privacy laws. The General Data Protection Regulation, (EU) 2016/679 ("GDPR") became effective on May 25, 2018 and deals with the processing of personal data and on the free movement of such data. The GDPR imposes a broad range of strict requirements on companies subject to the GDPR, including requirements relating to having legal bases for processing personal information relating to identifiable individuals and transferring such information outside the EEA, including to the U.S., providing details to those individuals regarding the processing of their personal information, keeping personal information secure, having data processing agreements with third parties who process personal information, responding to individuals' requests to exercise their rights in respect to their personal information, reporting security breaches involving personal data to the competent national data protection authority and affected individuals, appointing data protection officers, conducting data protection impact assessments, and record-keeping. The GDPR increases substantially the penalties to which the Company could be subject in the event of any non-compliance, including fines of up to 10,000,000 Euros or up to 2% of its total worldwide annual turnover for certain comparatively minor offenses, or up to 20,000,000 Euros or up to 4% of total worldwide annual turnover for more serious offenses. Given the limited enforcement of the GDPR to date, Celsion faces uncertainty as to the exact interpretation of the new requirements on its trials and may be unsuccessful in implementing all measures required by data protection authorities or courts in interpretation of the new law.

In the event Celsion continues to conduct clinical trials in the EEA, the Company must also ensure that it maintains adequate safeguards to enable the transfer of personal data outside of the EEA, in particular to the U.S., in compliance with European data protection laws. Celsion expects that it will continue to face uncertainty as to whether its efforts to comply with obligations under European privacy laws will be sufficient.

If the Company is investigated by a European data protection authority, it may face fines and other penalties. Any such investigation or charges by European data protection authorities could have a negative effect on the Company's existing business and on its ability to attract and retain new clients or pharmaceutical partners. Celsion may also experience hesitancy, reluctance, or refusal by European or multi-national clients or pharmaceutical partners to continue to use its products and solutions due to the potential risk exposure as a result of the current (and, in particular, future) data protection obligations imposed on them by certain data protection authorities in interpretation of current law, including the GDPR. Such clients or pharmaceutical partners may also view any alternative approaches to compliance as being too costly, too burdensome, too legally uncertain, or otherwise objectionable and therefore decide not to do business with Celsion. Any of the foregoing could materially harm the Company's business, prospects, financial condition, and results of operations

The success of Celsion's products may be harmed if the government, private health insurers, and other third-party payers do not provide sufficient coverage or reimbursement.

The Company's ability to commercialize its new cancer treatment systems successfully will depend, in part, on the extent to which reimbursement for the costs of such products and related treatments will be available from third-party payors, which include government authorities, such as Medicare, Medicaid, TRICARE, and the Veterans Administration, managed care providers, private health insurers, and other organizations. Patients who are provided medical treatment for their conditions generally rely on third-party payors to reimburse all or part of the costs associated with their treatment. Coverage and adequate reimbursement from governmental healthcare programs, such as Medicare and Medicaid, and commercial payors is critical to new product acceptance. Patients are unlikely to use Celsion's product candidates unless coverage is provided and reimbursement is adequate to cover a significant portion of the cost. The reimbursement status of newly approved medical products is subject to significant uncertainty The Company cannot be sure that coverage and reimbursement will be available for, or accurately estimate the potential revenue from, its product candidates or assure that coverage and reimbursement will be available for any product that Celsion may develop.

In order to secure coverage and reimbursement for any product that might be approved for sale, a company may need to conduct expensive pharmacoeconomic studies in order to demonstrate the medical necessity and cost-effectiveness of the product, in addition to the costs required to obtain FDA or other comparable regulatory approvals. Additionally, companies may also need to provide discounts to purchasers, private health plans or government healthcare programs. Nonetheless, product candidates may not be considered medically necessary or cost effective. A decision by a third-party payor not to cover a product could reduce physician utilization once the product is approved and have a material adverse effect on sales, the Company's operations and financial condition.

Celsion's products may not achieve sufficient acceptance by the medical community to sustain its business.

The commercial success of the Company's products will depend upon their acceptance by the medical community and third-party payors as clinically useful, cost effective, and safe. Any of its drug candidates or similar product candidates being investigated by the Company's competitors may prove not to be effective in trial or in practice, cause adverse events, or other undesirable side effects. Celsion's testing and clinical practice may not confirm the safety and efficacy of its product candidates or even if further testing and clinical practice produce positive results, the medical community may view these new forms of treatment as effective and desirable or its efforts to market its new products may fail. Market acceptance depends upon physicians and hospitals obtaining adequate reimbursement rates from third-party payors to make its products commercially viable. Any of these factors could have an adverse effect on Celsion's business, financial condition, and results of operations.

Several of the Company's current clinical trials are being conducted outside the U.S., and the FDA may not accept data from trials conducted in foreign locations.

Several of Celsion's current clinical trials are being conducted outside the U.S. Although the FDA may accept data from clinical trials conducted outside the U.S., acceptance of these data is subject to certain conditions imposed by the FDA. For example, the clinical trial must be well designed and conducted and performed by qualified investigators in accordance with ethical principles. The trial population must also adequately represent the U.S. population, and the data must be applicable to the U.S. population and U.S. medical practice in ways that the FDA deems clinically meaningful. In general, the patient population for any clinical trials conducted outside of the U.S. must be representative of the population for whom the Company intends to label the product in the U.S. In addition, while these clinical trials are subject to the applicable local laws, FDA acceptance of the data will be dependent upon its determination that the trials also complied with all applicable U.S. laws and regulations. Celsion cannot assure investors that the FDA will accept data from trials conducted outside of the U.S If the FDA does not accept the data from such clinical trials, it would likely result in the need for additional trials, which would be costly and time-consuming and delay or permanently halt the development of Company's product candidates.

Celsion has no internal sales or marketing capability. If they are unable to create sales, marketing, and distribution capabilities or enter into alliances with others possessing such capabilities to perform these functions, the Company will not be able to commercialize its products successfully.

Celsion currently have no sales, marketing, or distribution capabilities. The Company intends to market its products, if and when such products are approved for commercialization by the FDA and foreign regulatory agencies, either directly or through other strategic alliances and distribution arrangements with third parties. If Celsion decides to market its products directly, the Company will need to commit significant financial and managerial resources to develop a marketing and sales force with technical expertise and with supporting distribution, administration, and compliance capabilities. If Celsion relies on third parties with such capabilities to market its products, it will need to establish and maintain partnership arrangements, and there can be no assurance that the Company will be able to enter into third-party marketing or distribution arrangements on acceptable terms or at all. To the extent that Celsion does enter into such arrangements, the Company will be dependent on its marketing and distribution partners. In entering into third-party marketing or distribution arrangements, Celsion expects to incur significant additional expenses and there can be no assurance that such third parties will establish adequate sales and distribution capabilities or be successful in gaining market acceptance for its products and services.

Technologies for the treatment of cancer are subject to rapid change, and the development of treatment strategies that are more effective than Celsion's technologies could render its technologies obsolete.

Various methods for treating cancer currently are, and in the future, are expected to be, the subject of extensive research and development. Many possible treatments that are being researched, if successfully developed, may not require, or may supplant, the use of Celsion's technologies. The successful development and acceptance of any one or more of these alternative forms of treatment could render the Company's technology obsolete as a cancer treatment method.

Celsion may not be able to hire or retain key officers or employees needed to implement its business strategy and develop its product candidates and business.

The Company's success depends significantly on the continued contributions of its executive officers, scientific and technical personnel, and consultants and on its ability to attract additional personnel as the Company seeks to implement its business strategy and develop its product candidates and businesses.

The Company cannot guarantee that it will retain key employees to the same extent that it has retained its employees in the past, which could have a negative impact on its business, results of operations, and financial condition. Additionally, during the Company's operating history, Celsion has assigned many essential responsibilities to a relatively small number of individuals. However, as its business and the demands on key employees expand, the Company has been, and will continue to be required to recruit additional qualified employees. The competition for such qualified personnel is intense, and the loss of services of certain key personnel or the Company's inability to attract additional personnel to fill critical positions could adversely affect its business. Further, Celsion does not carry "key man" insurance on any of its personnel. Therefore, loss of the services of key personnel would not be ameliorated by the receipt of the proceeds from such insurance.

Celsion's success will depend in part on its ability to grow and diversify, which in turn will require that the Company manage and control its growth effectively.

The Company's business strategy contemplates growth and diversification. Its ability to manage growth effectively will require it to continue to expend funds to improve operational, financial and management controls, reporting systems, and procedures. In addition, the Company must effectively expand, train, and manage its employees. Celsion will be unable to manage its business effectively if they are unable to alleviate the strain on resources caused by growth in a timely and successful manner. There can be no assurance that the Company will be able to manage growth and a failure to do so could have a material adverse effect on its business.

Celsion faces intense competition and the failure to compete effectively could adversely affect its ability to develop and market its products.

There are many companies and other institutions engaged in research and development of various technologies for cancer treatment products that seek treatment outcomes similar to those that Celsion is pursuing. The Company believes that the level of interest by others in investigating the potential of possible competitive treatments and alternative technologies will continue and may increase. Potential competitors engaged in all areas of cancer treatment research in the U.S. and other countries include, among others, major pharmaceutical, specialized technology companies, and universities and other research institutions. Most of the Company's current and potential competitors have substantially greater financial, technical, human and other resources, and may also have far greater experience than Celsion, both in pre-clinical testing and human clinical trials of new products and in obtaining FDA and other regulatory approvals. One or more of these companies or institutions could succeed in developing products or other technologies that are more effective than the products and technologies that the Company has been or is developing, or which would render Celsion's technology and products obsolete and non-competitive. Furthermore, if the Company is permitted to commence commercial sales of any of its products, it will also be competing, with respect to manufacturing efficiency and marketing, with companies having substantially greater resources and experience in these areas.

Celsion may be subject to significant product liability claims and litigation.

The Company's business exposes it to potential product liability risks inherent in the testing, manufacturing, and marketing of human therapeutic products. Celsion presently has product liability insurance limited to $10 million per incident and $10 million annually. If the Company were to be subject to a claim in excess of this coverage or to a claim not covered by its insurance and the claim succeeded, it would be required to pay the claim with its own limited resources, which could have a severe adverse effect on its business. Whether or not Celsion is ultimately successful in any product liability litigation, such litigation would harm the business by diverting the attention and resources of the Company's management, consuming substantial amounts of its financial resources, and by damaging its reputation. Additionally, Celsion may not be able to maintain its product liability insurance at an acceptable cost, if at all.

Celsion or the third parties upon whom the Company depends may be adversely affected by earthquakes, global pandemics, or other natural disasters and its business continuity and disaster recovery plans may not adequately protect it from a serious disaster, including earthquakes, outbreak of disease, or other natural disasters.

The Company's current operations are located in its facilities in Lawrenceville, New Jersey. Any unplanned event, such as flood, fire, explosion, earthquake, extreme weather condition, medical epidemics, power shortage, telecommunication failure or other natural or manmade accidents or incidents that result in the Company being unable to fully utilize its facilities, or the manufacturing facilities of its third-party contract manufacturers, may have a material and adverse effect on the ability to operate its business, particularly on a daily basis, and have significant negative consequences on its financial and operating conditions. Loss of access to these facilities may result in increased costs, delays in the development of the Company's product candidates, or interruption of its business operations. Earthquakes or other natural disasters could further disrupt the Company's operations and have a material and adverse effect on its business, financial condition, results of operations, and prospects. If a natural disaster, power outage, or other event occurred that prevented Celsion from using all or a significant portion of its headquarters, that damaged critical infrastructure, such as its research facilities or the manufacturing facilities of the Company's third-party contract manufacturers, or that otherwise disrupted operations, it may be difficult or, in certain cases, impossible, for Celsion to continue its business for a substantial period of time.

For example, in December 2019, an outbreak of a novel strain of coronavirus, or the COVID-19 coronavirus, originated in Wuhan, China. To date, this outbreak has already resulted in extended shutdowns of certain businesses in the Wuhan region and has had ripple effects to businesses around the world. An outbreak of communicable diseases in China or elsewhere, or the perception that such an outbreak could occur, and the measures taken by the governments of countries affected, could adversely affect Celsion's business, financial condition, or results of operations by limiting its ability to manufacture products within or outside China, forcing temporary closure of

facilities that the Company relies upon or increasing the costs associated with obtaining clinical supplies of its product candidates. The extent to which the COVID-19 coronavirus impacts the Company's results will depend on future developments, which are highly uncertain and cannot be accurately predicted, including new information which may emerge concerning the severity of the COVID-19 coronavirus and the actions to contain the COVID-19 coronavirus or treat its impact, among others. Global health concerns, such as the COVID-19 coronavirus, could also result in social, economic, and labor instability in the countries in which Celsion or the third parties with whom the Company operates.

The disaster recovery and business continuity plans in place may prove inadequate in the event of a serious disaster or similar event. The Company may incur substantial expenses as a result of the limited nature of its disaster recovery and business continuity plans, which, could have a material adverse effect on its business. As part of its risk management policy, Celsion maintains insurance coverage at levels it believes are appropriate for its business. However, in the event of an accident or incident at these facilities, the Company cannot assure investors that the amounts of insurance will be sufficient to satisfy any damages and losses. If its facilities, or the manufacturing facilities of the Company's third-party contract manufacturers, are unable to operate because of an accident or incident or for any other reason, even for a short period of time, any or all of its research and development programs may be harmed.

Celsion's internal computer systems, or those of its CROs or other contractors or consultants, may fail or suffer security breaches, which could result in a material disruption to the Company's product development programs.

Despite the implementation of security measures, the Company's internal computer systems and those of its CROs and other contractors and consultants are vulnerable to damage from computer viruses, unauthorized access, natural disasters, terrorism, war, and telecommunication and electrical failures. Such events could cause interruptions of the Company's operations. For instance, the loss of preclinical data or data from any clinical trial involving Celsion's product candidates could result in delays in the Company's development and regulatory filing efforts and significantly increase its costs. To the extent that any disruption or privacy or security breach were to result in a loss of, or damage to, Celsion's data, or inappropriate disclosure of confidential or proprietary information, the Company could be subject to reputational harm, monetary fines, civil suits, civil penalties or criminal sanctions, and requirements to disclose the breach, and other forms of liability and the development of its product candidates could be delayed.

Pandemics, such as the COVID-19 coronavirus, could have an adverse impact on the Company's developmental programs and its financial condition.

In December 2019, a novel strain of the COVID-19 coronavirus was first identified in Wuhan, Hubei Province, China. Any outbreak of contagious diseases, or other adverse public health developments, could have a material and adverse effect on the Company's business operations. These could include disruptions or restrictions on Celsion's ability to travel, pursue partnerships and other business transactions, conduct clinical trials, make shipments of biologic materials, as well as be impacted by the temporary closure of the facilities of suppliers and clinical trial sites. Any disruption of suppliers, clinical trial sites, or access to patients would likely impact the Company's clinical trial enrollment progress and rates as well as its ability to access capital through the financial markets. The extent to which the COVID-19 coronavirus impacts Celsion's business will depend on future developments, which are highly uncertain and cannot be predicted, including new information which may emerge concerning the severity of the COVID-19 coronavirus and the actions to contain the COVID-19 coronavirus or treat its impact, among others.

RISKS RELATED TO CELSION'S SECURITIES

The market price of the Company's common stock has been, and may continue to be volatile and fluctuate significantly, which could result in substantial losses for investors and subject the Company to securities class action litigation.

The trading price for Celsion's common stock has been, and is expected to continue to be, volatile. The price at which the Company's common stock trades depends upon a number of factors, including its historical and anticipated operating results, its financial situation, announcements of technological innovations or new products by Celsion or its competitors, the Company's ability or inability to raise the additional capital it may need and the terms on which it raises it, and general market and economic conditions. Some of these factors are beyond the Company's control. Broad market fluctuations may lower the market price of the Company's common stock and affect the volume of trading in its stock, regardless of the Company's financial condition, results of operations, business, or prospect.

In addition, the stock markets, in general, The Nasdaq Capital Market, and the market for pharmaceutical companies in particular, may experience a loss of investor confidence. Such loss of investor confidence may result in extreme price and volume fluctuations in the Company's common stock that are unrelated or disproportionate to the operating performance of its business, financial condition, or results of operations. These broad market and industry factors may materially harm the market price of Celsion's common stock and expose the Company to securities class action litigation. Such litigation, even if unsuccessful, could be costly to defend and divert management's attention and resources, which could further materially harm its financial condition and results of operations.

Future sales of the Company's common stock in the public market could cause its stock price to fall.

Sales of a substantial number of shares of the Company's common stock in the public market, or the perception that these sales might occur, could depress the market price of Celsion's common stock and could impair its ability to raise capital through the sale of additional equity securities.

Celsion's stockholders may experience significant dilution as a result of future equity offerings or issuances and exercise of outstanding options and warrants.

In order to raise additional capital or pursue strategic transactions, Celsion may in the future offer, issue or sell additional shares of its common stock or other securities convertible into or exchangeable for its common stock, including the issuance of common stock in relation to the achievement, if any, of milestones triggering the Company's payment of earn-out consideration in connection with the EGEN acquisition. The Company's stockholders may experience significant dilution as a result of future equity offerings or issuances. Investors purchasing shares or other securities in the future could have rights superior to existing stockholders.

The adverse capital and credit market conditions could affect Celsion's liquidity.

Adverse capital and credit market conditions could affect the Company's ability to meet liquidity needs, as well as its access to capital and cost of capital. The capital and credit markets have experienced extreme volatility and disruption in recent years. Results of operations, financial condition, cash flows, and capital position could be materially adversely affected by continued disruptions in the capital and credit markets.

Celsion's ability to use net operating losses to offset future taxable income are subject to certain limitations.

On December 22, 2017, the President signed into law the Tax Reform Act. The Tax Reform Act significantly changes U.S. tax law by, among other things, lowering corporate income tax rates, implementing a quasi-territorial tax system, providing a one-time transition toll charge on foreign earnings, creating a new limitation on the deductibility of interest expenses and modifying the limitation on officer compensation. The Tax Reform Act permanently reduces the U.S. corporate income tax rate from a maximum of 35% to a flat 21% rate, effective January 1, 2018.

Celsion currently has significant net operating losses (NOLs) that may be used to offset future taxable income. In general, under Section 382 of the Internal Revenue Code of 1986, as amended (the Code), a corporation that undergoes an "ownership change" is subject to limitations on its ability to utilize its pre-change NOLs to offset future taxable income. During 2019, 2018, and years prior, the Company performed analyses to determine if there were changes in ownership, as defined by Section 382 of the Internal Revenue Code that would limit its ability to utilize certain net operating loss and tax credit carry forwards. Celsion determined that it experienced ownership changes, as defined by Section 382, in connection with certain common stock offerings in 2011, 2013, 2015, 2017, and 2018. As a result, the utilization of the Company's federal tax net operating loss carry-forwards generated prior to the ownership changes is limited. Future changes in the Company's stock ownership, some of which are outside of its control, could result in an ownership change under Section 382 of the Code, which would significantly limit Celsion's ability to utilize NOLs to offset future taxable income.

Anti-takeover provisions in Celsion's charter documents and Delaware law could prevent or delay a change in control.

The Company's certificate of incorporation and bylaws may discourage, delay, or prevent a merger or acquisition that a stockholder may consider favorable by authorizing the issuance of "blank check" preferred stock. This preferred stock may be issued by the Company's Board of Directors on such terms as it determines, without further stockholder approval. Therefore, Celsion's Board of Directors may issue such preferred stock on terms unfavorable to a potential bidder in the event that its Board of Directors opposes a merger or acquisition. In addition, Celsion's Board of Directors may discourage such transactions by increasing the amount of time necessary to obtain majority representation on its Board of Directors. Certain other provisions of the Company's bylaws and of Delaware law may also discourage, delay, or prevent a third party from acquiring or merging with Celsion, even if such action were beneficial to some, or even a majority, of the Company's stockholders.

Glossary

Ascites—The abnormal accumulation of fluid in the peritoneal cavity (abdomen), causing swelling.

Cytokine—Small proteins released by cells that have a specific effect on cell interactions, communications, and behavior. Cytokines include interleukins, lymphokines, and cell signal molecules, such as tumor necrosis factor (TNF) and interferons, which trigger inflammation and respond to infections.

Cytotoxic T-cells (CD 8+)—Also called T-lymphocytes or CD-8+ cells, these are immune cells that can recognize and kill cancerous cells and those infected by intracellular pathogens (e.g., bacteria, viruses, and mycoplasma).

Doxorubicin—A bacterial antibiotic that is widely used to treat leukemia and various other forms of cancer.

Endocytosis—A cellular process in which substances or molecules are transported into the cell by engulfing it with its membrane.

Glioblastoma Multiforme (GBM)—A highly malignant fast-growing type of central nervous system tumor that forms from glial (supportive) tissue of the brain and spinal cord**.**

Hazard Ratio (HR)—A measure of how often a particular event happens in one group compared to how often it happens in another group, over time. In cancer research, hazard ratios (HRs) are often used in clinical trials to measure survival at any point in time in a group of patients compared to a control group. A value of HR of 1 means equal efficacy of the experimental and control treatments. If the experimental treatment is better than the control then the HR <1, if it is worse than the control then the HR >1.

Hepatocellular Carcinoma (HCC)—The most common type of primary liver cancer. Hepatocellular carcinoma occurs most often in people with chronic liver diseases, such as cirrhosis caused by hepatitis B or hepatitis C infection.

Immunotherapy—Also called biologic therapy, immunotherapy is a type of cancer treatment that boosts the body's natural defenses to fight cancer. It uses substances made by the body or in a laboratory to improve or restore immune system functions.

Interferon Gamma (IFN-γ)—A cytokine that is critical to both innate and adaptive immunity. IFN-γ stimulates natural killer cells and is involved in the immune infection response as well as tumor killing activities.

Interleukin-12 (IL-12)—A member of a group of naturally occurring proteins (*cytokines*) that mediate communication between cells. Interleukins regulate cell growth, differentiation, and motility. They are particularly important in stimulating immune responses, such as inflammation.

Interval Debulking Surgery (IDS)—A surgery performed in patients whose cancer was not adequately debulked at the time of initial surgery, or in those patients in whom an initial debulking surgery was not attempted. IDS is performed after two to four cycles of neoadjuvant chemotherapy (NAC) or induction chemotherapy, to remove the bulk of the tumor, and followed by adjuvant chemotherapy of the same type.

Liposomes—A spherical-shaped vesicle that is composed of one or more phospholipid bilayers, which closely resembles the structure of cell membranes. The ability of liposomes to encapsulate hydrophilic or lipophilic drugs have allowed these vesicles to become useful drug delivery systems.

Messenger RNA (mRNA)—A single-stranded molecule of RNA that corresponds to the genetic sequence of a gene and is involved in the process of synthesizing a protein. mRNA is an RNA version of the gene that leaves the cell nucleus and moves to the cytoplasm where proteins are made.

Monomers—A molecule that can be bonded to other identical molecules to form a polymer.

Nanoparticle—A particle of matter that is between 1 and 100 nanometers (nm) in diameter.

Natural Killer Cells—Lymphocytes (white blood cells) of the innate immune system that control several types of tumors and microbial infections by limiting their spread and subsequent tissue damage.

Neoadjuvant Chemotherapy (NAC)—Chemotherapy given before the primary (first line) treatment.

Objective Tumor Response—A measure of the proportion of patients with reduction in tumor burden of a predefined amount, used to evaluate the therapeutic effectiveness of an anticancer agent in clinical trials.

Overall Survival (OS)—The time from randomization in a clinical trial to death from any cause, OS is a direct measure of clinical benefit to a patient. OS offers the greatest clinical gain, provided that quality of life is not compromised.

Peritoneal Cavity—The space defined by the diaphragm, walls of the abdominal and pelvic cavities, and abdominal organs.

Plasmid—A small, circular piece of DNA normally found in bacterial cells that is different than the chromosomal DNA. Plasmids usually carry at least one gene, and many of the genes that plasmids carry are beneficial to their host organisms. Plasmids utilized in the lab are usually artificial and designed to introduce foreign DNA into another cell.

Progression Free Survival (PFS)—The length of time during and after the treatment of a disease, such as cancer, that a patient lives with the disease but it does not get worse.

R-0—A microscopically margin-negative resection, in which no gross or microscopic tumor remains in the primary tumor bed.

Radiofrequency Thermal Ablation (RFA)—A procedure that uses radio waves to heat and destroy abnormal cells, used to treat cancer and other conditions. Heat is generated by a high frequency, alternating current that flows from the electrodes. A probe is inserted into the center of the tumor and the local heat that is generated kills (abaltes) the tissue that is adjacent to the probe.

Synthetic Control Arm (SCA)—Statistical methods that are used in clinical trials to evaluate the comparative effectiveness of an therapeutic regimen using external historical clinical trial or real-world information created by collecting data from control arm patients from other studies who would have otherwise qualified for that particular trial.

T-cell—A lymphocyte of a type produced or processed by the thymus gland and actively participating in the immune response. There are 3 main types of T cells: cytotoxic (CD-8), helper (CD-4), and regulatory. Each of them has a different role in the immune response.

T-helper Cells (CD-4+)—Immune cells involved in cell-mediated immunity and function as “helpers” by regulating the overall immune response to antigen presence. Also known as CD4+ cells, Th cells help the activity of other immune cells by releasing cytokines, regulating the immune responses.

TH-1 Immune Response—An acquired immune response characterized by high cytotoxic T-cell activity relative to the amount of antibody production. The Th1 response is promoted by Th1 helper T-cells.

Transfection—The process of artificially introducing nucleic acids (DNA or RNA) into cells, utilizing means other than viral infection, typically with the intention of altering the properties of the cell. Transfection can lead to the expression of specific proteins by the cell.

Intentionally Blank

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