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Helix BioPharma Corp. (HBP.TO - TSX)

A New Approach to Enhance Standard of Care

Based on our DCF model and a 15% discount rate, Helix is valued at approximately CAD$2.00 per share. Our model applies a 15% probability of ultimate approval and commercialization for L-DOS47 in NSCLC and pancreatic cancer. The model includes contributions from the United States and Europe.

Current Price (1/3/2020)	$1.48
Valuation ($CAD)	**$2.00**

INITIATION

Helix is an immuno-oncology company developing an anti-cancer therapeutic platform which acts by modulating the tumor micro-environment pH with an enzyme conjugated to an antibody. Helix's lead candidate, L-DOS47, is being evaluated in clinical trials for NSCLC and pancreatic cancer in combination with other agents. The antibody targets the CEACAM6 antigenic site in tumor cells allowing the linked urease enzyme to increase adjacent pH by catalyzing urea breakdown. Additional DOS47 compounds are in the preclinical stage for solid tumors. The company is working with ProMab Bio to co-develop a CAR-T therapeutic for hematological cancer which is in the preclinical stage

Lead candidate L-DOS47 is in Ph2 clinical trials for pancreatic cancer & NSCLC in combination with chemotherapy. We expect pivotal trials to generate registrational data in 2025 for both indications and work with a partner will advance the candidate outside North America.

Our valuation assumes a 2026 approval and launch of L-DOS47 in select markets including the US and Europe, the latter of which will be achieved through the efforts of partners.

SUMMARY DATA

52-Week High	**1.50**
52-Week Low	**0.24**
One-Year Return (%)	**179**
Beta	**0.47**
Average Daily Volume (sh)	**5,349**
Shares Outstanding (mil)	**124.9**
Market Capitalization ($mil)	**184.9**
Short Interest Ratio (days)	**2.3**
Institutional Ownership (%)	**N/A**
Insider Ownership (%)	**N/A**
Annual Cash Dividend	**$0.00**
Dividend Yield (%)	**0.00**
5-Yr. Historical Growth Rates	
Sales (%)	**N/A**
Earnings Per Share (%)	**N/A**
Dividend (%)	**N/A**
P/E using TTM EPS	**N/A**
P/E using 2020 Estimate	**N/A**
P/E using 2021 Estimate	**N/A**
Zacks Rank	**N/A**

Risk Level	**Above Average**
Type of Stock	**Small-Growth**
Industry	**Med-Biomed/Gene**

ZACKS ESTIMATES

Revenue

(In millions of CAD)

	Q1 (Oct)	Q2 (Jan)	Q3 (Apr)	Q4 (Jul)	Year (Jul)
2019	$0.0 A	$0.0 A	$0.0 A	$0.0 A	$0.0 A
2020	$0.0 A	$0.0 E	$0.0 E	$0.0 E	$0.0 E
2021					$0.0 E
2022					$0.0 E

Earnings per Share

	Q1	Q2	Q3	Q4	Year
2019	-$0.01 A	-$0.02 A	-$0.02 A	-$0.02 A	-$0.07 A
2020	-$0.02 A	-$0.02 E	-$0.02 E	-$0.02 E	-$0.07 E
2021					-$0.07 E
2021					-$0.08 E

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INITIATING COVERAGE

We are initiating coverage of Helix BioPharma Corp. (TSX: HBP.TO / OTC: HBPCF) with a current valuation of CAD$2.00[1] per share. This present value is based on our estimates for continued development of L-DOS47 in phased trials and a 2026 global launch of L-DOS47 for non-small cell lung cancer (NSCLC) and pancreatic cancer in conjunction with partners. The clinical-stage company is developing its lead candidate, an enzyme conjugated to a monoclonal antibody (mAb) which can increase the pH of the tumor microenvironment (TME), to provide multiple beneficial effects against cancer. The construct is known as an antibody protein conjugate (APC) and is similar in composition to an antibody drug conjugate (ADC). The candidate is in Phase II studies for NSCLC and pancreatic cancer.

L-DOS47 links the enzyme urease to a mAb which can bind to a tumor marker appearing on lung and pancreatic cancer cells. When the mAb is bound to the tumor cell, the action of the linked enzyme is able to alter the pH of the TME by converting nearby urea into ammonia. The ammonia is cytotoxic to the tumor cells and causes a slight rise in the nearby pH potentially enhancing the efficacy of weak base chemotherapeutics. Preclinical work has also shown that the presence of L-DOS47 can reduce expression of the PD-L1 protein, enhancing the natural immune system's ability to recognize cancerous cells. The biologic is being developed as therapy in combination with chemotherapy or other immunotherapy in both indications. This approach aims to act against the tumor from multiple directions, enhancing the tumor fighting effect of chemotherapeutics and the natural immune system. While first line therapy is effective in some cases, most patients require second line, which maintains a sizable market in both settings for the APC if eventually found effective and approved. The possibility also exists that the agent may be appropriate for both first and later line treatments in various circumstances.

Helix is conducting several Phase II trials. A combination chemotherapy trial for European and Asian markets and a monotherapy trial which has completed data collection and is now finalizing reports for non-small cell lung cancer (NSCLC). A Phase Ib/II pancreatic cancer trial was recently launched that is expected to read out in 2021.

On October 31, 2019, Helix held approximately $1.7 million in cash on its balance sheet following a $7.0 million capital raise. The availability of these funds has enabled Helix to launch its Phase Ib/II pancreatic cancer study with L-DOS47. However, additional funds will be required in the near term to continue research and development activities. The company currently holds no debt. We expect Helix to consume ~$600,000 in cash per month in 2020 as it advances its Phase II programs.

Based on our review, we anticipate that pivotal data will be available for indications NSCLC and pancreatic cancer by 2025. We expect a submission of a biologics license application (BLA) to regulatory authorities in the US and Europe and a response from the FDA and EMA over the 2025 to 2027 period with the first submission to the FDA in pancreatic cancer. Approval and commercialization are expected one year after submission based on historical precedents. If data from the trial demonstrate a major advance in treatment, Helix may receive a breakthrough or priority review designation, which would advance the drug more quickly through the application process. Pancreatic cancer is diagnosed in between 50 and 60 thousand persons per year which may qualify L-DOS47 for an Orphan Drug Designation.

Helix' innovative approach to addressing cancer has several synergies with chemotherapeutics, can precisely deliver cancer cell cytotoxicity to target cells and may enhance the body's immune response. We anticipate a near-term readout for the L-DOS47 monotherapy trial followed by interim readouts for the other studies in progress. The company needs a partner and continued financing to further advance L-DOS47 through 2020 and if data is supportive of continued work we anticipate a BLA submission and ultimate commercialization.

[1] Share prices, value references in the text and financial statement items are denominated in Canadian dollars.

INVESTMENT THESIS

A substantial body of research has shown that the tumor microenvironment becomes acidic as cancerous cells favor metabolism via glycolysis. The high metabolic demand of tumor cells' fermentation of glucose to lactic acid creates free H^+ ions that lower the surrounding pH. As a result of low tissue perfusion due to defective vasculature the acidic environment is not thoroughly flushed with oxygenated blood. Cancer cells can adapt to survive in low pH environments through increased glycolytic activity and expression of proton transporters that normalize intracellular pH. However, the extracellular acidic tumor microenvironment has been shown to be immuno-suppressive. The lower pH inhibits T and natural killer (NK) cells and promotes myeloid derived suppressor cells and T regulatory cells. This lower pH not only increases immuno-suppression around the tumor but also can impact the effectiveness of cancer therapies such as checkpoint inhibitors and chemotherapy by producing an acidic shield around the TME.

To address this imbalance, Helix has designed an elegant solution designated L-DOS47 that conjugates a tumor protein specific monoclonal antibody (mAb) with a urease enzyme to convert nearby urea into ammonia and carbon dioxide. The mAb targets carcinoembryonic antigen-related cell adhesion molecule 6 (CEACAM6), which is expressed in numerous cancers, including NSCLC and pancreatic. The enzymatic reaction's ammonia production is toxic to tumor cells and also has the effect of increasing the pH, potentially reversing immuno-suppressive effects and allowing weak-base chemotherapeutics to work better. Helix has initiated two Phase II trials and has just begun a Phase Ib/II in pancreatic cancer which are evaluating lead candidate L-DOS47.

L-DOS47's unique mechanism of action which both raises pH and creates a toxic environment for cancer cells is particularly amenable to combination therapy. Weak base chemotherapeutics such as vinorelbine may show synergistic efficacy with L-DOS47. The candidate may also reduce PD-L1 expression on tumor cells thereby enhancing T cell effectiveness. Studies have shown that raising intratumoral pH can improve responses to checkpoint blockade inhibitor immunotherapy.

Current standard of care for non-small cell lung carcinoma (NSCLC) is dominated by surgery, radiation therapy and chemotherapy; however, targeted therapy and immunotherapy are also appropriate. There are ~228,000 new US cases of lung and bronchus cancer expected in 2019, second in incidence only to breast cancer. NSCLC makes up a large portion of this population and is a particularly attractive indication for Helix as there are many cases that can be addressed. If proven safe and effective, L-DOS47 would be a prime candidate for combination therapy with checkpoint inhibitors in first line therapy or with chemotherapy in second line therapy.

Pancreatic cancer is one of the most deadly cancers in large part due to the difficulty of early detection. Surgery radiation and chemotherapy may be appropriate for the disease when caught in its earlier stages; however, there are few effective treatments for most who are diagnosed with the disease. Pancreatic cancer makes up about 3% of all cancers which is equivalent to ~57,000 new cases per year in the United States. It is a desirable indication to pursue due to the lack of alternative therapies and the severe unmet need. The DOS47 platform may also be appropriate for other cancers.

We adopt a conservative approach and anticipate the drug to have similar pricing as immunotherapies and oncology biologics in the United States. We expect a discount to these levels in other markets such as Europe and Asia. We make reductions for regions ex-US to reflect relative prices in these economic areas.

While our target price is generated based on L-DOS47 success in NSCLC and pancreatic cancer, Helix has several other assets in its portfolio including V-DOS47 and a chimeric antigen receptor (CAR)-T cell candidate. We anticipate adding a valuation component for these programs as they advance to a more mature stage.

Key reasons to own Helix shares:

- **Novel mechanism of action that is synergistic with other therapies**
- **CEACAM6 target is specific to tumor cells, especially lung and pancreatic adenocarcinoma**
- **L-DOS47 may reverse acidic extra-cellular conditions favorable to cancer cell survival**
- **L-DOS47 may improve uptake of weak-base chemotherapeutics**
- **L-DOS47 may reduce PD-1 and PD-L1 expression thereby improving immune response**
- **Favorable drug safety profile with no reported drug-related adverse events**
- **Biologic eligible for 12 years of exclusivity in United States and extended protection in other geographies**
- **North American rights to intellectual property**
- **Pursuing multiple indications**
    - **Non small cell lung cancer**
    - **Pancreatic cancer**

In the following sections we review the oncology space and DOS47's position in it with a discussion of ADCs and their relationship to Helix' platform. A primer on non-small cell lung carcinoma (NSCLC) and pancreatic cancer is also provided as well as a review of market size and current standard of care. Relevant preclinical and clinical data, trial design and drug history for both in-process and pivotal trials required for L-DOS47 approval are also presented. We expect first sales in 2026 following favorable registrational data, the submission of a BLA and regulatory approval. We discuss the assumptions in our appraisal and generate a valuation of $2.00 per share. L-DOS47 may prove to be an excellent complement to chemotherapy and immunotherapy lending significant synergies through the precise mechanism of targeting and reducing the acidity in the tumor microenvironment.

Antibody Drug Conjugates

Antibody drug conjugates (ADCs) are monoclonal antibodies (mAbs) chemically attached to a biologically active cytotoxic payload or drug. mAbs are very specific in their targeting and allow the linked payload to be delivered to the desired site thereby limiting off target effects. The precise nature of ADCs allows the use of more potent toxins that would be prohibitive if used systemically. An important component of the ADC is the chemical linker that matches the payload with the mAb. The linker is designed to be either cleavable or non-cleavable, which determines the properties of the drug delivery. The linker also controls the distribution and delivery of the payload to the desired cell and can be designed to deliver the drug over an extended period. In most cases, after binding to surface antigens, ADCs are endocytosed into the cell where they undergo lysosomal degradation and release of their concentrated cytotoxic payload. There are a limited number of cytotoxic payloads that are sufficiently stable to make it to the inside of a cell. The most common attachments include microtubule inhibitors, DNA synthesis inhibitors and topoisomerase inhibitors. If the linked drug has the desired effect, it will cause cell apoptosis and eradicate the cancer.

Helix has introduced a variation on the ADC and maintains the epitope specific mAb and chemical linker, but instead of using a toxic payload, attaches a urease enzyme to create toxic ammonia at the surface of the cancer cell. This is known as an antibody protein conjugate (APC) which functions similarly to an ADC. The L-DOS47 unit developed by Helix consists of a camelid antibody employing a non-cleavable chemical linker to a urease enzyme. A feature differentiating the two structures is that the APC is not internalized into the target cell to release its payload while the ADC is taken inside. L-DOS47 is considered an immunotherapy due to its mechanism of action, which reverses immune system suppression due to acidosis.

Immuno-oncology

Immuno-oncology (IO), or cancer immunotherapy is an approach to fighting cancer that uses the body's own immune system to attack the disease. Normally, the body's immune system can eliminate cancer cells, but in some cases, these cells can adapt to hide and proliferate. When IO drugs or biologics are administered, they allow the immune system to recognize harmful cells and destroy them, in many cases with fewer and shorter-lived side effects compared to surgery, chemotherapy and radiotherapy. Immunotherapy is preferred because it is frequently associated with fewer adverse events, maintains its potency, works well in conjunction with other therapies and is also able to better target the disease. Several classes of immunotherapy exist including therapeutic vaccines, checkpoint inhibitors, immune modulators, adoptive cell therapy (CAR-T), antibody drug conjugates and oncolytic viruses among others. Immunotherapy is commonly used and enhanced by other approaches such as chemotherapy and antibody drug conjugates.[2] In recent years, many of the leading checkpoint inhibitors have advanced towards first line treatment of cancer, despite only working in a minority of cases. One of the goals of approved immunotherapies is to increase their effectiveness by combining with other drugs that enhance the ability of immune system to eradicate cancer.

Acidosis and Tumor Progression

Efforts in the laboratory have demonstrated that aerobic glycolysis combined with poor perfusion causes and perpetuates an acidic environment around tumors. Even when oxygen is present, cancerous cells have adapted to favor the fermentation of glucose to lactic acid, or aerobic glycolysis.[3] The byproduct of this process is the generation of an H^+ ion, a decrease in pH and the establishment of an acidic microenvironment. Acidosis affects immune cell function, clonal cell evolution and drug uptake. Research has been conducted that supports a direct, causative link between greater glucose metabolism and tumor invasion and metastases.[4,5] Acidosis is brought about by several factors; including hypoxia, which forces glycolytic metabolism and the build-up of lactic acid. The high metabolic demand of cancer cells also increases acidity through the increase in H^+ ions. As cancer cells stimulate imperfect angiogenesis, insufficient vasculature and blood flow prevents a flush of the ion build up and

[2] https://www.pharmoutsourcing.com/Featured-Articles/358918-The-Evolving-Shape-of-the-ADC-Market-The-Widening-Application-of-ADCs-and-Manufacturing-Improvements-Meeting-Demand/

[3] Aerobic glycolysis is also known as The Warburg effect which refers to a behavior observed in many organisms and cell types including cancer cells, yeast and bacteria. Both the efficient aerobic pathway and the inefficient fermentation pathway are utilized for respiration, despite the presence of sufficient oxygen. The process diverts pyruvate to lactate dehydrogenase, which reduces pyruvate into lactate thereby increasing the acidity of the surrounding area.

[4] Estrella, V.; Chen, T.; et al. Acidity Generated by the Tumor Microenvironment Drives Local Invasion. Cancer Res; 73(5) March 1, 2013

[5] Damgaci, Sultan; et al. Hypoxia and acidosis: immune suppressors and therapeutic targets. Immunology. doi:10.1111/imm.12917

allows the formation of an acidic environment. pH values ranging from 5.7 to 7.0 have been observed in the extracellular environment proximate to many solid tumors including breast cancer, brain tumors, sarcomas, malignant melanoma, squamous cell carcinomas, and adenocarcinomas.

Acidosis encourages malignant behaviors by cancer cells, allowing increased invasion and metastasis, chemoresistance, and inhibition of immune surveillance.[6] Extracellular acidosis can suppress the antitumoral activity of natural killer (NK) cells by inhibiting the release of perforin and granzyme containing granules, the secretion of IFN-γ and TNF-α, and the cytotoxic response against tumor cells.[7] Lactic acid accumulation, which is a byproduct of glycolysis, also has immunosuppressive effects. A study by Husain et al.[8] reported that lactate from cancer cells increases tumor size and inhibits NK cell cytotoxicity, especially at lower pH values in a pancreatic cancer model. Acidification induces an anergic state in both human and mouse tumor□specific CD8+ T lymphocytes thereby impairing cytotoxicity. Neutralization of tumor acidity has also been shown to reverse immune suppression, and a paper by Pilon-Thomas, *et al.* demonstrated in multiple models that increasing pH by using bicarbonate therapy along with checkpoint inhibitors improved antitumor responses.[9]

Therapies based on manipulation of tumor micro□environment acidosis using buffers such as sodium bicarbonate or proton pump inhibitors have shown improved results as monotherapy in a variety of animal cancer models. Preliminary studies have also shown that neutralizing tumor acidosis with buffers in combination with immunotherapy can lead to improved durable outcomes. However, it is difficult to successfully implement these approaches in humans despite the anticipated benefits.

Low pH in extracellular spaces in the TME can stimulate tumor cell survival, migration and invasion.[10] Low pH can also cause drug resistance to weak-base chemotherapeutics and from elevated p-glycoprotein activity. The acidic shield presented by solid tumors creates a barrier that prevents weak-base chemotherapeutics from interacting with tumor cells.[11] When acidity is high in the TME, positively charged weak bases become trapped extracellularly, which limits cellular uptake and efficacy of these therapeutics. This is in contrast to uncharged molecules which can easily diffuse across the cell membrane. If by some mechanism the pH is increased, then there is less charge imbalance and the molecules may more easily pass. Conversely, weak-acid chemotherapeutics such as chlorambucil and 5-fluorouracil will more readily cross the cellular membrane when encountering an acidic environment. As for p-glycoprotein, the transporter removes chemotherapeutic from the cell. When p-glycoprotein activity is increased, the important cytotoxic drugs are removed from the tumor cells more quickly thereby reducing their effect.

L-DOS47

L-DOS47 is Helix' first drug product candidate and has recently completed a Phase I/II monotherapy trial. The candidate is currently in a Phase I combination trial with carboplatin and pemetrexed in the United States and a Phase II combination trial with vinorelbine and cisplatin in Ukraine and Poland. The product was recently cleared by the FDA to launch a Phase Ib/II trial for advanced pancreatic cancer in the United States with enrollment and screening beginning in December 2019.

L-DOS47 is an antibody protein conjugate (APC) which provides benefits as compared to other therapies. The candidate makes use of a camelid single domain antibody designated AFAIKL2 that can identify specific antigenic sites on cancer cells and precisely deliver the enzyme to the desired site. L-DOS47 is a chemical conjugate of a recombinant single domain antibody and Jack bean urease which can link multiple antibodies per urease molecule. The urease enzyme is derived and purified from the jack-bean plant, which produces beans that can be consumed by humans and animals, although it can be toxic if consumed to excess. Urease is extracted from the seeds of the plant by using a complex refining process, then is conjugated with an antibody by a chemical linker. After completion of manufacture and administration, the AFAIKL2 antibody binds with the CEACAM6 antigenic site expressed on certain cancer cells.

[6] Estrella, V; *et al*. Acidity generated by the tumor microenvironment drives local invasion. Cancer Res. 2013 Mar 1;73(5):1524-35. doi: 10.1158/0008-5472.CAN-12-2796. Epub 2013 Jan 3.
[7] Erra Diaz, F.; et al. Unravelling the Interplay between Extracellular Acidosis and Immune Cells. Mediators Inflamm. 2018; 2018: 1218297.
[8] Husain Z., Huang Y., Seth P., Sukhatme V. P. Tumor-derived lactate modifies antitumor immune response: effect on myeloid-derived suppressor cells and NK cells. The Journal of Immunology. 2013;191(3):1486–1495. doi: 10.4049/jimmunol.
[9] Pilon-Thomas, S. et al. Neutralization of Tumor Acidity Improves Antitumor Responses to Immunotherapy. Cancer Res; 76(6); 1381–90. 2015 AACR.
[10] Wojtkowiak JW, Verduzco D, Schramm KJ, Gillies RJ. Drug resistance and cellular adaptation to tumor acidic pH microenvironment. Mol Pharm. 2011 Dec 5;8(6):2032-8. doi: 10.1021/mp200292c. Epub 2011 Oct 26.
[11] Raghunand, N.; et al. Tumor acidity, ion trapping and chemotherapeutics. II. pH-dependent partition coefficients predict importance of ion trapping on pharmacokinetics of weakly basic chemotherapeutic agents. Biochem Pharmacol. 2003 Oct 1;66(7):1219-29.

CEACAM6

CEACAM6, or Carcinoembryonic Antigen Related Cell Adhesion Molecule 6 in long form, refers to a cell surface glycoprotein and antigenic site associated with tumor cells. CEACAM6 is expressed in many solid tumors including breast, pancreatic, ovarian, lung and colon types and is recognized as a tumor marker. The protein itself is a pan-inhibitor of cell differentiation and cell polarization, and causes distortion of tissue structure. If excessively expressed, the protein can alter cancer progression through aberrant cell differentiation, anti-apoptosis, cell growth and resistance to therapeutic agents. It can also promote cell invasion and metastasis.[12] The CEACAM6 marker may preferentially identify those cells most at risk of metastasis.

Helix has developed a camelid single chain antibody designated AFAIKL2 which is derived from a llama whole cancer cell. The antibody binds with high affinity to the CEACAM6 antigen and is favored due to its small size and ability to specifically recognize CEACAM6. The antibody is conjugated to the urease enzyme using the linker N-succinimidyl [4-iodoacetyl]-aminobenzoate (SIAB) due to its ability to cross link at different pHs.

Conjugation of Antibody to Urease

Due to the relatively large size of the urease enzyme (544 kDa), several small molecular weight (13 kDa) camelid antibodies (AFAIKL2)[13] are covalently bound to the enzyme. Primary amines on AFAIKL2 and cysteine residues on the urease enzyme are the bases used for the crosslinker. The heterobifunctional crosslinker, SIAB, employs an amine to sulfhydryl conjugation between the two molecules and was selected as the optimal choice due to its ability to conjugate in a variety of pH levels. The SIAB crosslinker is widely used to prepare a variety of conjugate settings providing a 10.6 Å spacer. The urease enzyme can be conjugated with from 8 to 11 AFAIKL2 antibodies.

Exhibit I – Antibodies Linked to Urease Enzyme[14]



As the antibody-urease conjugate ratio increases with more antibodies attached to each urease, a higher binding signal is observed due to multiple bindings from the attached antibodies. The binding affinity was found to be directly proportional to the number of antibodies conjugated to the urease. The specificity and cytotoxicity of L-DOS47 was confirmed by screening in four cell lines including BxPC-3, a pancreatic cell line and A549, a lung cell line. Strong binding was observed for the BxPC-3 and moderate binding for A549, indicating favorable expression of the CEACAM6 antigen on the cell surface. The MCF7 breast cancer cell line was evaluated in preclinical testing; however, no binding was observed between it and L-DOS47.

[12] Rizeq B, Zakaria Z, Ouhtit A; Towards understanding the mechanisms of actions of carcinoembryonic antigen-related cell adhesion molecule 6 in cancer progression. Cancer Sci. 2018 Jan;109(1):33-42. doi: 10.1111/cas.13437. Epub 2018 Jan 2.
[13] AFAIKL2 antibody fragment recognizes CEACAM6 on the surface of certain tumor cells.
[14] Source: Helix BioPharma Tumor Defence Breaker Video. http://www.helixbiopharma.com/

As the molecule binds to the cancer cells, the urease enzyme begins to catalyze normally present urea [$(NH_2)_2CO$] which is prolific in the tumor microenvironment. This function produces carbon dioxide and ammonia. Ammonia that is formed causes the medium to become more alkaline and increases the pH of the tumor microenvironment.

Exhibit II – Catalyzation of Urea to Carbon Dioxide and Ammonia

$$(NH_2)_2CO + H_2O \rightarrow CO_2 + 2NH_3$$

DOS47 Mechanism of Action

DOS47 employs an enzyme to generate metabolites that can raise the pH in the tumor microenvironment. Tumors generate acidic environments (pH below 7.35) that surround their cellular mass. The acidic shield presents a protective barrier to weak-base drugs that are prescribed for cancer and also down-regulates many of the tumor surveillance mechanisms of the immune system, such as T cell function. DOS47 provides a dual benefit to the fight against tumors through the biochemical reaction with urea. The drug is able to produce a cytotoxic substrate, ammonia, and a change in pH that is hazardous to cancer cells while offering favorable conditions to some chemotherapy drugs.

DOS47 is intended to be combined with antibodies that are highly specific for specific tumor markers such as CEACAM6 or VEGFR2. DOS47 can be combined with a variety of antibodies that are specific to the targeted cancer cell. For Helix' lead candidate designated L-DOS47, a urease enzyme is linked to a single domain antibody identified as AFAIKL2. AFAIKL2 binds to CEACAM6, a receptor which appears on the surface of non-small cell lung adenocarcinoma and other tumor cells.

Helix has produced a short video that demonstrates the impact of acidosis on cancer drugs. It illustrates the DOS47 mechanism of action and how it can change the TME to allow other therapies to work. Link to video Tumor Defense Breaker.

V-DOS47

V-DOS47 is the second APC developed by Helix which combines a urease enzyme with another antibody DOS47 conjugate. The antibody targets the vascular endothelial growth factor 2 receptor (VEGFR2) which are expressed in many carcinomas and lymphomas. VEGFR2 is a type V receptor tyrosine kinase mainly known to be expressed in vascular endothelial cells and encoded by the kinase insert domain receptor (KDR) gene.

As tumors grow, their demand for nutrients and oxygen increases. As a result, the cells signal their need for blood supply and trigger angiogenesis through the VEGFR2 ligand–receptor complex. The process begins as cancer cells secrete vascular endothelial growth factor (VEGF); subsequently, VEGF binds to VEGFR2, triggering a tyrosine kinase signaling cascade via the dimerization of VEGFR2. The process stimulates blood vessel permeability, proliferation, survival, migration, and differentiation of mature blood vessels. In cancer, the growth signals sent are irregular leading to tumor blood vessels that are structurally and functionally abnormal and are present at high density. There are a number of anti-angiogenesis drugs including bevacizumab and lenalidomide that interrupt the kinase signaling cascade by blocking the dimerization of VEGFR2 or by inhibiting kinase activity. However, V-DOS47 has a different mechanism of action which exploits the VEGFR2 receptor as landing target to bind to variety of tumors that express this antigen. While the specific indication and setting have not yet been determined for V-DOS47, the VEGFR2 receptor appears with frequency in colorectal, breast, NSCLC and renal cancers as well as for glioblastoma patients.

Helix granted a world-wide exclusive license for V-DOS47 to subsidiary Helix Immuno-Oncology S.A. (HIO), headquartered in Poland. Development of V-DOS47 will be coordinated by HIO with management and oversight from the company's scientists in Canada.

V-DOS47 was awarded a grant by the Polish National Centre for Research and Development (PNCRD). As a condition of the PNCRD grant, Helix established a wet lab facility in Poland. Based on the grant funding agreement, certain expenditures are eligible for reimbursement. Total costs associated with the V-DOS47 development program are $6.8 million and PNCRD will reimburse HIO from 60% to 80% of eligible expenditures and an additional 17% of the government funded portion to cover overhead costs.

HIO previously developed four V-DOS47 research candidates and conducted *in vitro* feasibility studies to establish the potential clinical applications for these molecules. HIO is expected to leverage its experience to develop a V-DOS47 clinical drug product candidate. HIO will collaborate with several Polish institutes through the grant to complete the development of the first V-DOS47 clinical drug product candidate. We anticipate it will take several years before V-DOS47 enters the clinic and merits a valuation component in our discounted cash flow model.

CAR-T for Solid Tumors and Hematological Malignancies

Helix is conducting preclinical work on a chimeric antigen receptor-T cell program in collaboration with ProMab Technologies using a variation of its camelid antibody designated 2A3. The program is targeting CEACAM6 and VEGFR2 in a variety of cancers. Helix and partner ProMab are generating data to submit a BLA for a chimeric antigen receptor T-cell therapy CAR-T candidate against multiple myeloma targeting the B-cell maturation antigen (BCMA). *In vitro* and animal model work have been completed in proof of principle studies. Helix retains commercial rights for the CAR-T program in Canada and Europe.

ProMab recently published a paper entitled "CAR-T Cells Based on Novel BCMA Monoclonal Antibody Block Multiple Myeloma Cell Growth." The paper describes research and validation work on the antibody that it is co-developing for a CAR-T application against multiple myeloma. Data included analysis of *in vitro* work and CAR-T animal studies.

The company is leveraging its experience in manipulating the tumor microenvironment and its expertise in developing unique single domain antibody therapeutics to develop CAR-T novel cell-based treatments. Helix intends to develop CARs for adoptive cellular therapy (ACT) for solid and hematological malignancies. The company has selected CEACAM6 and VEGFR2 specific CARs for solid tumors. For hematological malignancies Helix has selected CD19, CD22 and BCMA as potential targets.

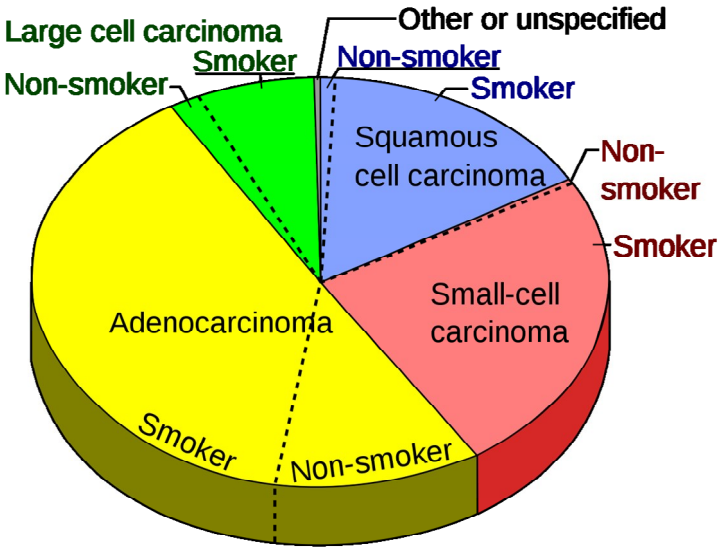
The single domain antibodies being developed bind specifically to the CEACAM6 antigen with high affinity and inhibit the proliferation of CEACAM6-expressing cancer cells *in vitro*. The efficacy of CEACAM6-CAR-T cells in a xenograft model was examined *in vivo*. The results support CEACAM6-CAR-T cells use as an effective immunotherapy agent against CEACAM6-expressing cancers and that camelid single domain antibodies can be easily adopted for CAR-T type therapies.

Non-Small-Cell Lung Cancer (NSCLC)

According to the American Cancer Society, lung cancer is the second most common cancer in the United States with an estimated 228,000 new cases diagnosed in 2019, which represents about 13% of all cancer diagnoses. While the incidence of lung cancer has subsided over the last thirty years due to a decline in smoking habits, it still accounts for one in four cancer deaths, or about 143,000 in 2019. The majority of lung cancer cases are either small cell, which makes up about 13% of the total or non-small cell, which is about 84% of the total. 40% of the non-small cell group are comprised of adenocarcinomas. Globally, there were estimated to have been 2.1 million new lung cancer cases and 1.8 million deaths in 2018.[15] It is a leading cause of death for males in Eastern Europe, Western Asia (especially Russia), Northern Africa and China.

[15] Bray, F; et al. Global Cancer Statistics 2018: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA CANCER J CLIN 2018;68:394–424.

Exhibit III – NSCLC Incidence[16]



First-line treatment for early-stage NSCLC has historically been surgery followed by chemotherapy and radiation therapy. In more advanced stages, a patient will receive chemotherapy with targeted drugs and in recent years more are receiving immunotherapy. Survival for NSCLC in advanced stages is low, with five year survival rates as follows:

- Stage IA ~49%
- Stage IB ~45%
- Stage IIA ~30%
- Stage IIB ~31%
- Stage IIIA ~14%
- Stage IIIB ~5%.
- Metastatic, or stage IV, ~1%.

NSCLC has several subtypes which include adenocarcinoma, squamous cell (epidermoid) carcinoma, and large cell (undifferentiated) carcinoma which together make up 75% to 85% of cases. Adenocarcinoma is the most common type of NSCLC and is found in the outer areas of the lung and comprises 40% of the total. Squamous cell is usually linked to smoking and makes up 30% of NSCLC. The cancer is located in the lung where the larger bronchi join the trachea to the lung, or in one of the main airway branches. Large cell can be found anywhere in the lung and usually grows and spreads quickly.

Lung cancer rates are higher in males than in females, likely attributable to higher rates of smoking and exposure to dangerous workplace substances for men. While lung and bronchus cancer rates are higher in males, the decline in death rate for men has been faster than it has for women over the last 30 years, as shown in the following graphics.

Exhibit IV - Trends in Age-adjusted Cancer Death Rates* by Site, Females, US, 1930-2016[17]

LINK

Exhibit V - Trends in Age-adjusted Cancer Death Rates* by Site, Males, US, 1930-2016[18]

LINK

[16] Häggström, Mikael (2014). "Medical gallery of Mikael Häggström 2014". WikiJournal of Medicine 1 (2). DOI:10.15347/wjm/2014.008. ISSN 2002-4436. Public Domain. https://commons.wikimedia.org/wiki/File:Pie_chart_of_lung_cancers.svg
[17] US Mortality Volumes 1930 to 1959, US Mortality Data 1960 to 2016, National Center for Health Statistics, Centers for Disease Control and Prevention. ©2019, American Cancer Society, Inc., Surveillance Research.
[18] US Mortality Volumes 1930 to 1959, US Mortality Data 1960 to 2016, National Center for Health Statistics, Centers for Disease Control and Prevention. ©2019, American Cancer Society, Inc., Surveillance Research.

Risk Factors & Symptoms

The greatest contributing risk factor for lung cancer is smoking, which is held responsible for 80 to 85% of lung cancers in the US according the American Cancer Society and the Lung Cancer Alliance. Other common risks include exposure to radon, diesel exhaust, asbestos and family history. Carcinogens including industrial chemicals and radioactive agents can also contribute to the incidence of lung cancer. Genetic factors also play a role, especially for the small portion of lung cancers in non-smokers. Symptoms of the disease include a cough that persists, shortness of breath, weight loss and/or coughing up blood.

Treatment

Treatment for NSCLC usually includes surgery to remove the tumor and may be preceded or followed by chemotherapy. Used beforehand, chemotherapy may shrink the tumor to make surgery easier. When chemotherapy is used following surgery, it helps prevent the cancer from returning. Radiotherapy is also used to fight the disease. If the cancer returns after these treatments then alternative therapies are considered.

For patients with inoperable disease, platinum-based chemotherapy in conjunction with radiation therapy is recommended. Chemotherapy by itself is recommended for metastatic NSCLC, as the disease is not localized enough for surgery or radiotherapy to work. Response rates for this group range from 15 to 30%, with average survival of less than a year. A meta-analysis of 52 studies found that chemotherapy treatment increased the chance of one-year survival by 10% and median survival by six weeks, illustrating the need for improved therapies.

Immunotherapy has made substantial headway in the last decade because it frequently has fewer side effects, maintains its potency, works well in conjunction with other therapies and is also able to better target the disease. Several classes of immunotherapy exist including therapeutic vaccines, checkpoint inhibitors, immune modulators, adoptive cell therapy (CAR-T) and oncolytic viruses among others. This success has led to some immuno-therapeutics being advanced to first line treatment. One of the most frequently used immunotherapies is the checkpoint inhibitor class, which produces a durable response in approximately 17% to 20%[19,20] of patients with advanced NSCLC. Checkpoints are particularly effective in patients with “hot” tumors, which have immune cells present. However, a majority of patients do not respond to checkpoint inhibitors, highlighting the need for additional therapies to be used in combination to obtain higher success rates.

Cancer cells have developed methods to escape immune surveillance by downregulating the immune system and converting immune cells into supporters of tumor growth. Furthermore, the variety in tumor composition may allow for progression in certain cancer mutations that are not addressed in treatments with different antigen signatures. Immunotherapy maintains several key benefits relative to other therapies. By allowing the body to fight the tumor itself, there are generally fewer and less severe side effects. Another serious issue in lung and other cancers, is the cancer’s ability to build immunity to the treatment received through mutation and evolution.[21] Helix envisions the benefit of combination therapy to improve the response rate for checkpoint inhibitors.

Checkpoint inhibitors such as Merck’s Keytruda (pembrolizumab) and Bristol-Myers’ Opdivo (nivolumab), are approved in several instances of first and second line NSCLC treatment. Checkpoint inhibitors have shown themselves to be very effective in a certain segment of the population and the search for broader efficacy has prompted efforts using checkpoint inhibitors in combination with other therapies that can potentially provide a synergistic effect.

Competing/Complementary Therapies in Development for NSCLC

NSCLC is a therapeutic area with substantial unmet need. Many research pharmaceutical companies have recognized this and are exploring the use of currently approved drugs for as-yet non-approved indications and working on developing new compounds to address the disease. In the following exhibit we note several of the key therapies that are either approved or in development.

[19] Borghaei H, et al. NEJM 2015;373:1627-39
[20] Nishio M, et al. JCO 2015; 33:15_suppl, 8027-8027
[21] One interesting piece we reviewed evaluated the evolution of NSCLC as tumors were tracked over time. The paper is entitled Tracking the Evolution of Non-Small-Cell Lung Cancer by Jamal-Hanjani, M.; *et al.* Link.

Exhibit VI – Competing Products Approved or in Development for NSCLC

Generic Name	Brand Name	Class
Avastin	Bevacizumab	Antiangiogenic agents
Cyramza	Ramucirumab	Antiangiogenic agents
Ofev	Nintedanib	Antiangiogenic agents
Alimta	Pemetrexed	Antifolate agent
Cyramza	Ramucirumab	VEGFR2 antagonist
Nivolumab	Opdivo	Checkpoint Inhibitor
Pembrolizumab	Keytruda	Checkpoint Inhibitor
Imfinzi	Durvalumab	Checkpoint Inhibitor
Tecentriq	Atezolizumab	Checkpoint Inhibitor
Gemzar	Gemcitabine	Chemotherapy
Paraplatin	Carboplatin	Chemotherapy
Taxol	Paclitaxel	Chemotherapy
Taxotere	Docetaxel	Chemotherapy
Tagrisso	Osimertinib	Kinase Inhibitor
Navelbine	Vinorelbine	Chemotherapy
Tarceva	Erlotinib	EGFR Inhibitor

Many of the checkpoint inhibitors that had been approved for second line in NSCLC have moved to first line for patients without identifiable mutations. The checkpoints are being used in combination with chemotherapy. Pembrolizumab, for example, is being used in combination with carboplatin and either paclitaxel or nab-paclitaxel. Checkpoint inhibitors are particularly effective in combination therapy because the two drugs can act on multiple immune pathways simultaneously. Checkpoints are also being used as monotherapy. NSCLC adenocarcinoma with mutations including EGFR, KRAS, ALK, ROS1 are recommended to have a mutation specific therapy as first line treatment.

The rapid evolution of the space highlights the opportunity for novel approaches to be used in second line treatments, or in combination with checkpoints for first line treatment.

Pancreatic Cancer

Pancreatic cancer comprises approximately 3% of all cancers and is the seventh most common cause of cancer death around the globe.[22] Pancreatic cancer is one of the more feared cancers and one that is most fatal due to the lack of symptoms until the disease is at a late stage. The five year survival rate is only 9%.[23] According to GLOBOCAN estimates for 2018, over 432,000 people died due to the disease and almost 459,000 cases were diagnosed around the world. The age-standardized rate for pancreatic cancer is highest in Europe and North America and the lowest in Africa.

In contrast to most other cancers, pancreatic cancer death rates have actually increased over the last decade. This can be seen in the American Cancer Society links in a previous exhibit which illustrate the trends in the major cancer types in the United States. In Europe, a report by UEG Public Affairs found that death rates have increased by 5% over the 1990 to 2016 period.

There are two main types of pancreatic cancer. The more common type is pancreatic adenocarcinoma, which makes up 85% to 95% of cases and is located in the exocrine glands of the pancreas. The other main type is pancreatic neuroendocrine tumor, which makes up 5% and is located in the endocrine tissue of the pancreas. Five year survival rates for pancreatic adenocarcinoma are:

- Stage IA – 14%
- Stage IB – 12%
- Stage II – 7%
- Stage III – 3%
- Stage IV – 1%

[22] Rawla, P. et al. Epidemiology of Pancreatic Cancer: Global Trends, Etiology and Risk Factors. World J Oncol. 2019 Feb; 10(1): 10–27.
[23] Based on data from SEER 18 2009-2015. https://seer.cancer.gov/statfacts/html/pancreas.html

Risk Factors & Symptoms

Smoking, family history, diet and obesity have all been identified as risk factors for pancreatic cancer. A broad variety of studies have been conducted associating smoke from indoor heating and cooking, alcohol abuse, high consumption of saturated fat and processed meats and reduced physical activity with pancreatic cancer mortality. Even more broadly, exposure to toxic substances can also have an impact on the disease. High fruit, vegetable and nut consumption has been found to be protective.

Pancreatic cancer lacks distinct symptoms in its early stages and is very hard to identify. In later stages non-specific symptoms including jaundice, weight loss, light colored stools, abdominal pain and fatigue are observed. Other signs include itchy skin, a new diagnosis of diabetes or diabetes that is becoming more difficult to control, blood clots and fatigue. Over half of all pancreatic cancers are diagnosed late stage and 90% of all deaths occur after age 55.

Diagnosis & Treatment

Imaging tests such as computerized tomography (CT) scans, magnetic resonance imaging (MRI) and positron emission tomography (PET) scans are used to examine the pancreas and other internal organs. A scope may also be used, which is inserted through the esophagus. Blood test and biopsy are other methods to diagnose pancreatic cancer.

Surgery, chemotherapy and radiotherapy are commonly used to treat patients with earlier stage disease. However, there is no treatment for the more advanced stages of the disease after it has metastasized to nearby organs. Adjuvant chemotherapy or chemoradiation has been shown to prolong survival post resection and is recommended for all patients who are healthy enough to be treated. For a small group of patients with high microsatellite instability (MSI-H) and mismatch repair (MMR) mutations, Keytruda is approved for use in a site agnostic indication. Clinical trials are recommended for pancreatic cancer patients, especially those whose cancer is not resectable. This has opened the space up to many experimental approaches and given the relatively small number of new cases each year, the orphan designation may be a route to approval for some for new treatments.

Competing/Complementary Therapies in Development

Many approaches to addressing pancreatic cancer have failed largely due to the late stage of the disease when diagnosed. The high fatality rate and lack of alternative therapies has made it an open indication for pursuit by a variety of approaches and the possibility of obtaining an orphan designation from regulatory authorities adds additional appeal for sponsor development. Below we provide a selection of novel Phase III trials in pancreatic cancer that have been acknowledged by the FDA.

Exhibit VII – Select Phase III Drug Candidates in Development for Pancreatic Cancer

Sponsor	Designation	Class
FibroGen	Pamrevlumab	Connective tissue growth factor inhibitor
AB Science	Masitinib	Tyrosine kinase inhibitor
Tyme, Inc	SM-88	Dysfunctional tyrosine derivative
AstraZeneca	Olaparib	PARP Inhibitor
Rafael Pharmaceutical	CPI-613	Lipoate analog
SynCore Biotechnology	EndoTAG-1	Tumor endothelial targeting agent
National Cancer Institute	Cabozantinib S-malate	Tyrosine kinase inhibitor
Hutchison Medipharma	Surufatinib	VEGF Inhibitor

Research and Development

Preclinical Work

Helix has conducted substantial preclinical work examining the effect of lower pH and L-DOS47 on the tumor microenvironment. Summarized in a poster entitled "Immune Checkpoint Modulation by Urease-Mediated Alkalization,"[24] a study was conducted to evaluate the effect of L-DOS47 and urea on the pH and breast cancer cells in a culture. The cells were first treated with lactic acid, which reduced the pH of the media and increased PD-L1 expression on the breast cancer cells. When treated with L-DOS47 + urea, PD-L1 expression was reduced to levels observed on untreated cells. The same observation was made on ovarian cancer cells. The poster concluded that L-DOS47 is a novel approach to reduce acid-induced immuno-suppressive PD-1/PD-L1 interactions.

In the "Improving Survival in Pancreatic Cancer Using Doxorubicin in Combination with L-DOS" poster, 30 mice were injected with pancreatic cancer cells and then randomized into groups. The groups were administered Doxorubicin, L-DOS47 + Doxorubicin and L-DOS47. Doxorubicin is a type of chemotherapy that slows or stops the growth of cancer cells by blocking an enzyme called topo isomerase 2. The combination of Doxorubicin and L-DOS47 performed better with improved absorbance and activity of Doxorubicin compared to Doxorubicin alone. The combination was also able to reduce the size of tumors in a greater proportion of mice as compared to Doxorubicin alone.

L-DOS47 Phase I Dose Escalation

In April 2014 Helix received clearance to launch LDOS001, its Phase I clinical trial for L-DOS47, an open label dose escalation study in combination with pemetrexed and carboplatin. Patients with Stage IV recurrent or metastatic non-squamous NSCLC were enrolled in two US sites. Dosing escalated from 0.59 µg/kg up to 9.0 µg/kg across six dosing cohorts. Fourteen patients were enrolled across the six cohorts and six of the patients demonstrated a confirmed partial response following treatment with L-DOS47 in combination with pemetrexed and carboplatin. The patients remained progression free for periods ranging from 5.9 months to 12.4 months. One additional patient had stable disease and remained progression-free for 13.3 months. A final clinical study report is expected in the first calendar quarter of 2020.

L-DOS47 Phase I/II Monotherapy and Chemotherapy (Europe)

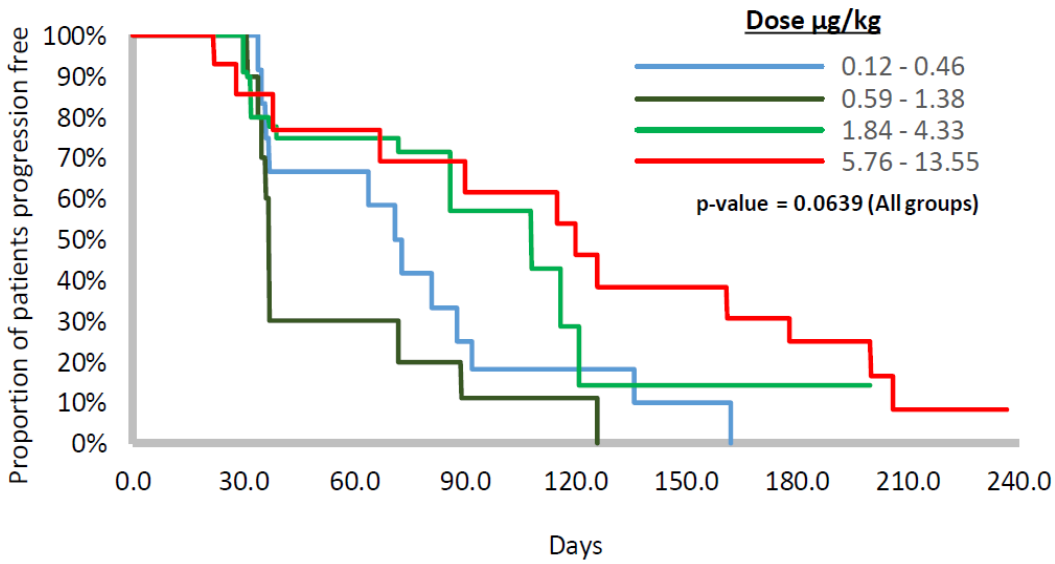
In 2011, Helix received approval from the Central Register of Clinical Trials at the Polish Ministry of Health to conduct a Phase I/II trial using L-DOS47 for NSCLC designated LDOS002. The two part study sought to determine the MTD of L-DOS47 for NSCLC and make a preliminary assessment of L-DOS47 in patients with NSCLC. The first portion of the trial assessed multiple dose levels ranging from 0.12 µg/kg to 13.55 µg/kg. Enrolled patients had inoperable, locally advanced, recurrent or metastatic, histologically confirmed non-squamous stage IIIb/IV NSCLC and were enrolled in five centers located in Poland. Patients were required to have a least one measurable lesion, ECOG[25] performance status of between 0 and 2; life expectancy of more than three months and adequate organ function.

Trial design was open label with weekly doses of L-DOS47 infused in a cycle of two weeks on and one week off. Eligible patients were given esclating doses of L-DOS47 as monotherapy. The first patient was dosed in October 2012 in a 16-cohort study which peaked at 13.55 µg/kg levels of L-DOS47. 90 patients were screened, 55 patients were given a minimum of one dose, 21 patients completed four treatment cycles and 16 patients were administered additional L-DOS47 cycles. A maximum tolerated dose (MTD) was not reached and L-DOS47 was well tolerated across all dose levels. 11 of 14 (79%) of patients in the highest dose cohorts (5.76 to 13.55 µg/kg) had an overall response of stable disease and a reduction in the sum of target lesions and 7 (50%) demonstrated a reduction in the sum of target lesions and 8 (57%) were progression free for more than eight weeks.

[24] Wong, Wah Yau, et al.; Immune Checkpoint Modulation by Urease-Mediated Alkalization
[25] Eastern Cooperative Oncology Group (ECOG) scale available here.

A dose dependent response was observed as indicated in the following Kaplan Meier Plot.

Exhibit VIII – Kaplan Meier Plot Demonstrating Dose Response[26]



In 2016 the Phase II portion of the study was launched which dosed twice weekly for the first two weeks followed by a seven day rest. Target enrollment was 45 patients. After completion of enrollment for the first stage of the Phase II component of the study a steering committee meeting was held. The committee recommended to stop further enrollment due to lack of efficacy as defined by protocol.

Helix conducted four interim data reviews and one final review of the Phase II study for LDOS002. Phase I safety observations found that 80% of patients (44 individuals) had at least one treatment emergent adverse event. It also found that L-DOS47 did not cause a dose-dependent release of cytokines at doses up to 13.55 µg/mg.

Phase II Clinical Study – L-DOS47 + Vinorelbine & Cisplatin

LDOS003 is a study combining L-DOS47 with vinorelbine and cisplatin (VIN/CIS) which plans to enroll 136 participants. LDOS003 was designed to evaluate the potential benefits of L-DOS47 when used in combination with chemotherapeutics. The study will be divided into two parts with the first determining the MTD of L-DOS47 when administered in combination with VIN/CIS and the second will randomize an additional 118 patients between L-DOS47 + VIN/CIS. The study will take place at six sites in Poland and Ukraine and may potentially include Hungary. L-DOS47 will be administered over four 21 day cycles on day 1 and 8 as an intravenous infusion 24 hours before chemotherapy.

Sites were first added in December 2018 and first dosing took place in March 2019. A safety review was completed for the first and second cohort by July 2019 and the Trial Steering committee recommended to advance to the next cohort dose level at 12 µg/kg and two patients were dosed at that level in October 2019. Due to financial constraints the study will delay progress to Part II pending additional financing and/or partner interest. VIN and CIS are commonly used in Europe and Asia and less so in the United States. It is expected that responsibility for this program will be taken over by a partner and ultimately commercialized in Europe and Asia.

L-DOS47 Phase Ib/II Pancreatic Cancer

Following an IND filed in July 2019, the LDOS006 study was cleared by the FDA to pursue a Phase Ib/II study in pancreatic cancer in August 2019. The study, entitled "A Phase Ib/II Study of the Microenvironment Modifier L-DOS47 plus Doxorubicin for the Treatment of Patients with Previously Treated Advanced Pancreatic Cancer" will be conducted in two parts. The Phase Ib will have three dose escalating cohorts enrolling a total of nine patients. Phase II will enroll eleven more patients when the Phase Ib is successfully completed. The study will be conducted at the Scottsdale Hospital in Scottsdale, Arizona USA. Enrollment and screening began in December 2019. Primary outcome measures are the number of complete and partial responders as measured by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 and safety. Secondary endpoints will measure change in tumor

[26] Ramlau, Rodryg; et al. Phase I/II dose escalation study of L-DOS47 as a monotherapy in non-squamous non-small cell lung cancer patients

pH, carbohydrate antigen 19-9 biomarker[27] level and proportion of patients expressing anti-L-DOS47 antibodies. The Phase Ib/II trial will enroll 20 previously treated adult patients with one or more pancreatic metastatic tumors. Based on details provided to the U.S. National Library of Medicine, the trial is anticipated to be complete by October 31, 2021.

Adverse Events

In the monotherapy study the most common adverse event was dyspnea (38%) and gastrointestinal disorders (20%). The only dose limiting toxicity in Phase I was Grade IV bone pain. Bone pain was observed in 5% of patients, mostly in the higher dose levels. L-DOS47 did not elicit a dose-dependent release of cytokines up to 13.55 µg/kg.

Chemistry, Manufacturing and Control (CMC)

Helix outsources all of its manufacturing. Drug substance is manufactured by BioVectra, a Canadian based contract development and manufacturing organization (CDMO). Fill and finish is performed by Emergent Biosolutions (NYSE: EBS), a Baltimore, Maryland-based life sciences company that is both developing and manufacturing drug product. Analytical services are provided by KBI Biopharma, a US-based contract services organization. Helix monitors regulatory agency reviews of each of its manufacturing partners to ensure there are no regulatory violations relating to L-DOS47.

The company requires additional batches of L-DOS47 and production in process. Manufacturing of new drug product can take up to one year to complete and must pass quality assurance requirements.

Product testing is performed both internally (non-GLP, non-GMP development work) and externally (quality control, quality assurance testing) with the majority of this process taking place in-house. Service providers have undergone periodic inspection by a Qualified Person in compliance with the European Medicines Agency rules, which require product used in human clinical trials to meet a similar standard as approved products do. The inspection ensured that the facility was in compliance with cGMP standards and that each batch of investigational product matches requirements of laws in force, product specification file and request for clinical trial authorization.

Helix maintains policies to ensure that its partner's manufacturing facility is in compliance with EU and US standards at all times. As part of evaluating a BLA, the FDA will review the manufacturing plant's process, controls and procedures prior to approval. Zacks continuously highlights the importance of good practices both internally and with partners who perform manufacturing, testing, packaging, fill and finish and other services. This emphasis is justified given the risk of regulatory agency action highlighting partner oversights and focus on partner compliance in spite of a phamaceutical product that is safe and effective.

Partners & Collaborators

The company's ultimate goal is to enter into a strategic partnering alliance with a large pharmaceutical company that recognizes the value of L-DOS47 and its synergistic potential with chemotherapeutics and immunotherapy. Deloitte Corporate Finance has been retained to explore partnering and licensing activities.

Partner ProMab Biotechnologies, Inc. is working with Helix to advance multiple CAR-T candidates targeting CEACAM6 and VEGFR2.

The company is further seeking to divest of its Polish subsidiary, HIO, in order of obtain additional capital to fund clinical development all the while retaining licensing for futue royalties and milestone payments.

In December 2016, Helix outlicensed its Biphasix technology platform to Xisle, which was subsequently included in a license agreement with the Altum-Avro Pharma Partnership. The product platform including its lead candidate interferon alpha 2-b, will provide milestone and royalty payments to Helix assuming its successful transit through registration, approval and commercialization. Helix maintains some geographical marketing rights which were subsequently assigned to its HIO subsidiary in Poland. Helix will receive milestone and royalty payments from HIO related to platform development on successful advance, regulatory approval and commercialization.

[27] Carbohydrate antigen 19-9 (CA19-9) is a type of antigen released by pancreatic cancer cells. It was derived from a human colorectal cancer cell line targeted by the monoclonal antibody 1116-NS-19-9. It has been widely used in the management of gastrointestinal malignancies, particularly for pancreatic cancer.

In the United States, Helix uses Theradex Oncology for contract research organization (CRO) services. The firm is an oncology-focused provider with clinical data management, clinical monitoring, project management and other services supporting clinical trials. In Europe, the company uses KCR Clinical Development for CRO services. KCR is an international service provider with hubs in Europe and the United States. Helix employs a competitive request for proposal process to identify appropriate CROs. Analytical services are contracted to Charles River Labs and regulatory guidance is provided by Biologics Consulting.

Intellectual Property

Helix has been granted numerous patents worldwide and has other patents pending for the DOS47 platforms. L-DOS47 is a biologic and will be granted 12 years of product exclusivity in the US, 10 years in Europe and eight in Japan assuming approval by the respective regulatory agencies. Below we summarize Helix' key patents.

Exhibit IX – Key Helix Patents

Compound	Title	Patent #	Region	Filed
DOS47	Method and composition for inhibiting cancer cell growth	7,211,250	United States	16-Jul-03
DOS47	Method and composition for inhibiting cancer cell growth	7,264,800	United States	27-Jan-05
DOS47	Anticarcinoma antibodies and uses thereof	7,872,105	United States	25-May-06
DOS47	Antibody urease conjugates	10,316,311	United States	3-Apr-14

The company has been granted multiple U.S. patents for the DOS47 technology and also has also licensed patent rights from the National Research Council of Canada (NRC) for the antibody component of L-DOS47. Helix owns 52 non-US DOS47 related patents in other jurisdictions with a number of patent applications in countries around the world. A joint patent application was filed in the U.S. with Amorfix to cover the antibody-DOS47 conjugates derived from their collaboration. A U.S. patent application to cover new features of the DOS47 technology was filed during fiscal 2013 and an additional U.S. patent application covering specific L-DOS47 manufacturing and novel features was filed in January 2015. During fiscal 2017, a new U.S. patent application protecting the novel use of L-DOS47 in restoring T cell function for therapeutic application was filed. Two US patents covering anti-VEGFR2 antibodies and their use in DOS47 conjugates (V-DOS4) were submitted to the USPTO. The company has filed a joint patent application with NRC to protect the use of an antibody for use in cell-based therapies along with a new patent application covering the use of anti-VEGFR2 antibodies in cell-based therapy in July 2017. Helix is currently in discussion with third parties to license additional intellectual properties to strengthen the company's portfolio.

Corporate Milestones

Helix is conducting multiple Phase II trials and is expected to provide a readout of the L-DOS47 monotherapy study in the first half of 2020. Below we list key milestones that have occurred in the last year and anticipated future events.

- IND clearance by FDA for LDOS006 – August 2019 ($6.4 mm to complete study)
- Final clinical study report for LDOS001 – Calendar 1Q:20 (will cost $627,000)
- Finalized clinical reports for LDOS002 – Calendar 1Q:20
- Completion of first (non-randomized) portion of LDOS003 - Calendar 1Q:20
- Advancement of LDOS003 to Part II – Dependent on partnership
- Anticipated completion of LDOS006 – year-end 2021
- Availability of additional supply of L-DOS47 – Calendar 4Q:20 ($1.64 mm cost)

Helix History

Helix was founded in the mid-1990s as a diagnostic, drug distribution and a small DNA testing company. Over the next decade, the company's founder, Dr. Donald Segal, sharpened the focus to cancer research and shed the other businesses. This move was prompted by a cancer diagnosis in Mr. Segal's wife. After years of researching areas of treatment, the company decided to focus on the role of acidosis on cancer and the impact of pH on the TME. In 2007, the company narrowed its efforts on the DOS47 program, supported by decades of research on the role of acidosis in the disease. Since the early days of research, Helix has expanded its reach to include operations in Poland and the addition of Dr. Robert Gillies of the H. Lee Moffitt Cancer Center and Research Institute to the scientific advisory board.

RISKS

All investments contain an element of risk which reflects the uncertainty of a business and what it will ultimately achieve. Some investments exhibit higher predictability, with current cash flows and established sales. These enterprises will have a lower level of perceived risk while other companies that are developing an undefined, new technology have a much higher level of perceived risk.

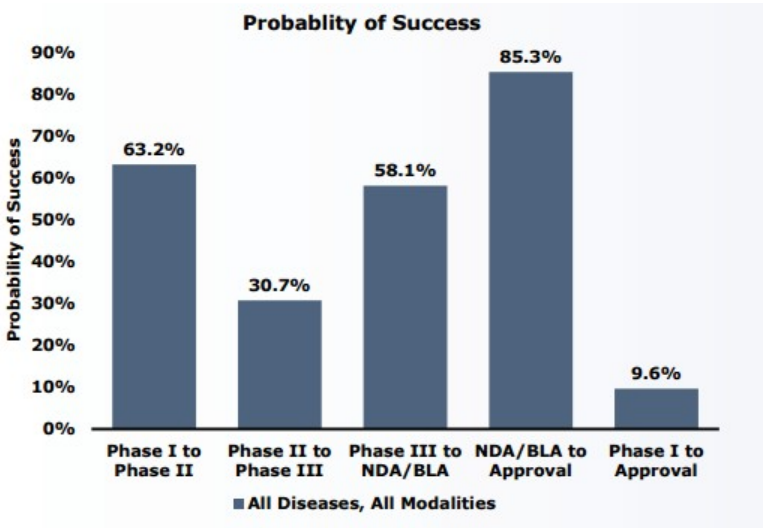
The biotechnology space includes companies at both ends of the spectrum, from mega-cap pharmaceutical powerhouses that have multiple products currently generating revenues, to small operations with a handful of employees conducting pre-clinical studies. Many of the risks faced by the large pharmaceutical companies and smaller biotechnology-focused firms are similar; however, there are some hazards that are particular to smaller companies that have not yet established themselves or their products.

For smaller early-stage companies, investing in drug development is an extended process. The timeframe for conducting pre-clinical research to eventually commercializing a drug can take from 12 to 15 years or even longer given market and company-specific conditions. And with, on average, only one in one thousand compounds eventually making it to the market from the preclinical stage, the risks are substantial.

Even if a company has a strong, experienced team that is developing a therapy with a high likelihood of success and a large addressable market, securing funding may be difficult. Access to financing comes and goes in cycles. During periods of improving confidence, capital may be easy to obtain; however, during a liquidity crisis or a period of heightened risk perception, even companies with bright prospects may be in trouble if they are dependent on the financial markets to fund their work. If capital is needed to sustain operations and it is not readily available, the company may be forced to suspend research and development, sell equity at a substantial discount to previous valuations and dilute earlier shareholders. A lack of funding may leave potentially promising therapies without a viable route to progress or force a company to accept onerous terms.

All drugs must navigate the regulatory approval process in the US, EU and other countries before commercialization in those regions. This effort is a material uncertainty which may take years depending upon the needs and desires of the determining authority. Substantial expense is undertaken to bring a molecule or compound through clinical trials and address all of the regulatory agencies' concerns. Isolating companies that have a long history of research success in drug development, with opinion leaders and experts in the field are important factors that can help mitigate this risk. Companies that have had previous success with the FDA or other regulatory agencies also are more attractive than those who may be new to the process. Some accelerated pathways to approval have been put forth such as those outlined in the Orphan Drug Act and the Breakthrough Therapy designation; however, changes in sentiment or perceived safety for pharmaceuticals drugs could change the regulatory environment to demand a more thorough process and these pathways may be extended or additional requirements may be put in place.

Exhibit X – Success of Phased Trials and Regulatory Approval[28]



[28]Clinical Development Success Rates 2006-2015. David Thomas, Justin Burns, John Audette, Adam Carroll, Corey Dow-Hygelund, Michael Hay.

Helix has steadily advanced its lead candidate L-DOS47 through the difficulties of the drug development process and has conducted several Phase II studies. The company plans to pursue multiple indications in NSCLC and pancreatic cancer, work with partners for regulatory approval around the globe and obtain expedited treatment of L-DOS47 if data are supportive. Despite multiple ongoing Phase II trials, approval is not guaranteed and complete response letters (CRLs) and delays to originally anticipated timelines and issued PDUFA dates are common. Helix has made it clear that they favor working with a partner to commercialize L-DOS47. While a larger partner may have important experience and assets to advance commercialization, their objectives may not be aligned with Helix'. A partner may also demand onerous terms if there are few competitors vying for Helix' assets.

There are many firms competing in the immuno-oncology space and the treatment landscape is rapidly evolving. New approaches and approvals can potentially reduce or eliminate markets that were anticipated earlier in the development process. Checkpoint inhibitors are engaged in numerous monotherapy and combination studies which may dominate treatment in NSCLC or pancreatic cancer prior to approval for L-DOS47. They have also advanced to first line treatment in some settings. The changing landscape can also alter favored therapies in certain regions which may render certain approaches no longer attractive.

Helix maintains insufficient L-DOS47 to complete in-process trials. Despite the recent efforts to secure additional product from a third-party manufacturer, completion of production takes up to a year and requires successful quality assurance release. Current L-DOS47 in inventory is undergoing stability assays and if successful, will be available to use up to April 2020. If the inventory does not pass, then research and development programs will face delays.

Helix relies on an outside partner for manufacturing. Risks of poor manufacturing processes, quality control issues and product delays may postpone ultimate production of a drug if facilities are out of compliance with regulatory agency requirements. Production line availability is also a risk factor and larger customers may dominate capacity resulting in long delays to obtain new product. Helix relies on an internal system to ensure partners' good practices and conformance to guidelines. Despite these efforts, regulatory agencies may identify discrepancies and as a result delay or halt production of a product in the approval process or one that has already been approved.

In recent years, contract research organizations (CROs) have taken on a larger role in the development of drug candidates as the complexity and cost of trials has increased. Finding appropriate populations to participate in clinical trials has become increasingly difficult due to the shift to personalized medicine and orphan indications that address only a small group of patients. This shift has increased the dependence on these specialized CROs for project management and clinical monitoring services which add additional risks and dependence on third parties.

Helix relies on two CROs to conduct its clinical trials: Theradex and KCR. CROs may have multiple competing projects that are vying for limited resources which can limit their success compared to initial expectations. Small drug development companies are extremely reliant on the hard work and professionalism of their CRO partners and many times a sponsor's success or failure can rest on the efforts of this partner.

Drug price inflation has gained increased attention over the last several years and has contributed to the increase in health care costs over the last decades. As new therapies have been approved, drug prices have set new records and increased at a substantial rate. For example, in 1996, new cancer drugs cost roughly $54,000 for each additional year of life they provided. However, by 2013, this amount increased to over $200,000. The inflation rate for established drugs has also been very high. In a Forbes article, an author highlighted Novartis' leukemia drug Gleevec. This drug cost $24,000 in 2001 when it was first approved; and 14 years later, in 2015, had risen to a cost of $90,000. This represents a 10% compound annual growth rate over that period. Other price moves such as the 5,000% price hike for Turing Pharmaceutical's Daraprim and Valeant Pharmaceuticals 500% and 200% price increase for Isuprel and Nitropress combined with similar moves by other companies may create a situation where further increases are unsustainable. We also cite the broad response to Mylan's EpiPen price increases which have pressured the company to offer lower priced alternatives and brought a number of competitors into the market.

We highlight several risks that come from these pricing increases. Health care may become unaffordable for a broad segment of the population, reducing the market size to a level below current expectations. Pharmacy benefit managers and other third party payors may continue to remove drugs from their formularies due to price concerns and sharp price increases will attract the attention of elected officials and regulators who may create legislation and implement regulations that limit drug profitability. Additionally, the government may impose additional non-price related regulation and disclosure requirements that can increase costs for the industry.

While we have discussed a broad variety of risks above, we believe that our forecast parameters, discount rates, success probabilities and valuation metrics address these eventualities and our target price reflects an assumption of these risks faced by all biotechnology companies.

Competitors, Peers and Competing Therapies

There are many participants in the oncology space with a variety of approaches to addressing the disease worldwide. From biologics to small molecule and immunotherapy, the competitive environment includes such well-known approaches as checkpoint inhibitors, CAR-T, oncolytic viruses, antibody drug conjugates and cancer vaccines to name a few. Some categories, such as checkpoint inhibitors, have been expanding their use to more indications, have moved from second line to first line settings and some[29] have even been approved for a type of cancer independent of location.

L-DOS47 is in a unique class as the drug structure is similar to an ADC; however, rather than linking to a cytotoxic drug that is internalized into the target cancer cell, the approach attaches an enzyme to the mAb allowing its catalytic action to create a cytotoxic compound and alter the pH of the TME on the surface of the tumor cell. L-DOS47 is considered an immunotherapy, as the drug's modulation of the acidic environment reverses the suppression of the immune system. The compound is also classified as a biologic from its use of a mAb to target cancer cells. Given the structure of L-DOS47, we see Helix lead candidate employing a mechanism of action most similar to other ADC companies.

Due to appropriate targeting and improved technology, ADCs have been gaining momentum. Eight ADCs have been approved for use in the United States, including two that were granted approval in December 2019 branded Enhertu and Padcev. There are 15 active or recruiting Phase III trials examining ADCs and commercialization is expected in the areas of refractory Hodgkin lymphoma, glioblastoma, small cell lung cancer, breast cancer, and ovarian cancer.

Seattle Genetics, Genentech and Roche are leaders in the antibody drug conjugate market in terms of market share. Until 2017 only two ADCs were commercially available. These included Adcetris by Seattle Genetics and Kadcyla by Roche. Six additional ADCs have been approved since then, including three candidates in 2019. The first ADC approved was Mylotarg (gemtuzumab ozogamicin) in 2000 for acute myeloid leukemia. The prior approval of compounds in this class should create a clearer regulatory pathway forward for other drugs with similar structures.

Companies pursuing a similar mechanism of action include private firm Cybrexa Therapeutics which is developing an approach that targets acidic tissues. Their pH (low) insertion peptides (pHLIPs) platform can sense an acidic environment and the peptides can insert across cellular membranes based on their pH. Cybrexa is currently conducting preclinical work.

Helix is not only a competitor against a broad variety of oncology therapy companies, but is also a potential collaborator. We see collaboration as an important reality for oncology companies given low success rates for existing monotherapies and the temporary duration of efficacy for many cancer therapies. We anticipate that the future of oncology will include the use of multiple agents from a variety of classes to improve survival from the disease.

On the following page, we highlight several of the key companies that are developing products in the cancer space. This list is not exhaustive but rather represents a cross section of the oncology companies contributing to the treatment objective.

[29] There have been three tissue agnostic approvals in the last several years. In 2017, Keytruda was approved for cancers with the microsatellite instability-high (MSI-H) or DNA mismatch repair deficiency (dMMR). In November 2018 Vitrakvi was approved for adult and pediatric patients with solid tumors that have a neurotrophic receptor tyrosine kinase (NTRK) gene fusion without a known acquired resistance mutation. In August 2019 Rozlytrek was approved for patients whose cancers have the specific genetic defect neurotrophic tyrosine receptor kinase (NTRK) gene fusion marker.

Exhibit XI – Peers and Competitors[30]

Ticker	Company	Price	MktCap (MM)	EV (MM)	Therapeutic Area
ADRO	Aduro Biotech	$1.21	$97	($101)	IO: STING, APRIL (Ckpt inhibit), anti-CD27
ADXS	Advaxis	$1.12	$56	$24	IO: Lm delivery platform
AGEN	Agenus Inc	$3.86	$530	$482	IO: vaccine, checkpoints, bispecifics
AZN	AstraZeneca	$50.09	$132,370	$148,470	IO:PD1/PDL1,CTLA4, BTK, EGFR, PARP&MET Inhibit
BAVA	Barvarian Nordic A/S	$8.34	$839	$801	IO: Ab targeting CEA & MUC1, vaccines
BLUE	Bluebird Bio	$86.95	$4,810	$3,830	IO: CAR-T
BMY	Bristol-Myers	$62.78	$147,170	$95,620	IO: CTLA4,PD1/PDL1, LAG3, PEG-IL2, IDO Inhibit
CLDX	Celldex Therapeutics	$2.37	$40	($31)	IO: anti-CD27, Flt3L, CD135, ErbB3
CLRB	Cellectar Biosciences	$2.30	$21.60	$10.00	Oncology: phospholipid drug conjugate
GILD	Gilead Sciences	$65.07	$82,320	$84,610	IO: CAR-T, anti-BCMA, BTK Inhibit, PI3K inhibitor
HTBX	Heat Biologics	$0.47	$16	$1	Oncology: Tcell activation/stimulation
IMGN	ImmunoGen Inc.	$4.63	$693	$516	IO: ADCs
IMMU	Immunomedics	$19.78	$4,200	$3,470	IO: ADCs
IMV	Immunovaccine Inc	$3.23	$161	$163	IO: T-cell therapy
INO	Inovio Pharmaceuticals	$2.98	$298.00	$300.00	Cancer IO/Infectious Disease
MRK	Merck & Co	$91.25	$232,320	$251,500	IO: PD1/PDL1
MRSN	Mersana Therapeutics	$5.25	$238	$148	ADC for cancer
NKTR	Nektar Therapeutics	$20.53	$3,610	$2,520	IO:Topo I inhibit,CD122 agonist,PEGPH20,IL-2
NVS	Novartis AG	$94.79	$214,690	$236,220	IO: PD1/PDL1,CRISPR,Ab drug conjugates (ADC)
OXB.L	Oxford Biomedica plc.	£6.70	£515	£497	Cancer IO
PGNX	Progenics Pharmaceuticals	£4.85	£419	£411	Oncology, small molecule
RHHBY	Roche Holding AG	$40.65	$275,080	$278,390	Broad pharma including ADCs
SGEN	Seattle Genetics	$112.65	$19,310	$18,510	Ab drug conjugate (ADC),sugar engineered Ab (SEA)
SNGX	Soligenix	$1.45	$30	$24	Various cancer indications & vaccine platform
SRNE	Sorrento Therapeutics	$3.34	$549.50	$691.00	IO: CAR-T, ADC; Pain Mgmt
TNG.PA	Transgene	€ 1.61	€ 134	$171	Cancer IO, Oncolytic Viruses
TROV	TrovaGene Oncology	$1.19	$9,210.00	$2,570.00	Oncology: PLK1 Inhibitor
WL6.DE	Heidelberg Pharma	$2.31	$63.00	$52.00	IO: ADCs
pvt	Millennium Pharmaceuticals				IO: ADCs
pvt	Cybrexa Therapeutics				pH low insertion peptides (pHLIP)
pvt	Oxford BioTherapeutics				IO: ADC, mAb, Bispecifics
pvt	INmuneBIO				Oncology: NK Cell/MDSC Inhibition
pvt	Checkmate Pharma				Cancer IO - TLR9 agonist
HBP.TO	Helix BioPharma	CAD 1.48	CAD 185	CAD 183	IO: Multikine/cytokines

[30] Price and market capitalization data is as of January 3, 2020.

MANAGEMENT PROFILES

Heman Chao, Chief Executive Officer and Chief Scientific Officer

Heman Chao, Ph.D. has been the Chief Executive Officer of Helix BioPharma since March 31, 2017 and its Chief Scientific Officer since December 2008. He is a biochemist with expertise in proteomics technologies. Previously, he was President of Sensium Technologies Inc., a subsidiary of Helix, between November 2004 and April 2008, prior to it folding into the parent company. Dr. Chao was previously Vice President of Technology and later Vice President of Research for the company from June 2002 to 2004. Between 1999 and June 2002, he was Manager of Sensium Technologies Inc. Prior to joining Helix, he was a research fellow in the federally funded Protein Engineering Network of Centres of Excellence coordinating multi-center research. Dr. Chao received his Ph.D in Biochemistry from Queen's University, Canada in 1994.

Photios (Frank) Michalargias, Chief Financial Officer

Photios (Frank) Michalargias, CPA, CA, has been Chief Financial Officer of Helix since June 2005. He possesses over 20 years of senior management experience in both public and private industry and is experienced in transition and growth management, strategic planning and the raising of debt and equity financing. From 2004 to mid-2005, he was Chief Financial Officer of AP Plasman Corporation, a tier one North American automotive parts supplier controlled by Schroder Ventures International. From 2002 through to mid-2004, he was Senior Finance Director for CFM Corporation, a public company listed on the TSX. Mr. Michalargias' previous experience include senior financial roles with Trailmobile Corporation, Huhtamaki Oyi and Unilever. He holds a Commerce and Economics degree from the University of Toronto and is a Chartered Professional Accountant, Chartered Accountant. Mr. Michalargias' business responsibilities as Chief Financial Officer include financial administration; responsibility for accounting and financial statements; liaising with auditors, the financial community and shareholders and coordination of expenses/tax activities of Helix.

Paweł Wiśniewski, Ph.D, Chief Executive Officer, Poland

Dr. Wiśniewski is currently the Chief Executive Officer at Helix Immuno-Oncology, a wholly owned subsidiary of Helix Biopharma. He has over seven years of experience in biotech business development, drug discovery and technical due diligence. Dr. Wiśniewski has also held roles as Associate Member of the Helix BioPharma Management Board, Advisor to the Management Board of the Eastern European Investment Management Venture Capital Fund, founder and CEO of the Institute of Genetic Analyses (INAGEN) Ltd., and co-founder, inventor and general manager at Glia, Ltd.

Financial Results

Helix announced fiscal first quarter 2020 results on December 13, 2019 along with SEDAR filings of their financials and management discussion & analysis reports. The company began their fiscal year closing a private placement for $7.0 million and the launch of the LDOS006 program for treating advanced pancreatic cancer.

The development stage company declared no revenue for the fiscal first quarter and recognized operational expenses of $2.2 million. This compares to zero revenue and operational expenses of $1.4 million in the prior year three month period ending October 31, 2018.

Research and development expenses were $1.5 million and up 49% on greater expenditures for L-DOS47 as efforts for the L-DOS47 programs advanced in both the US and Europe. V-DOS47 expenditures fell slightly on lack of sufficient financial resources to continue at expected levels. The V-DOS47 program receives financial support from a Polish government grant subsidy. Other research and development items were relatively flat such as corporate R&D expenses or they had increased such as trademark and patent related expenses of $153,000 and stock based compensation expense of $39,000.

General and administrative expenses rose 90% in 1Q:20 to $709,000 compared to the same prior year period. Segments that observed material increases included wages and benefits at $174,000, third party advisors at $365,000, other general and administrative expenses of $92,000 and stock based compensation of $33,000. Other segment expenditures such as director fees and depreciation were similar to prior year levels.

The balance sheet held $1.7 million in cash and equivalents and no debt as of October 31, 2019 reflecting a capital raise from a private placement in the fiscal first quarter. Cash burn for 1Q:20 was ($4.6) million compared to ($0.8) million in 1Q:19. Net cash generated from financing was $5.4 million for the three month period.

VALUATION

Helix' lead candidate, L-DOS47, is a cancer therapy that employs a monoclonal antibody to identify cancer cells and deliver a urease enzyme able to convert nearby urea into ammonia and carbon dioxide. The effect of this conversion is expected to create a toxic environment for the cancer cells and increase the pH to a more normal range. The change in pH is expected to have several beneficial effects including improved efficacy for weak-base chemotherapeutics and improved immune response due to downregulation of the checkpoint pathway.

L-DOS47 is in Phase II trials for two indications including specific settings in NSCLC and pancreatic cancer. NSCLC is represented in a large population and is the second most common cancer. Pancreatic cancer has a much lower incidence but is more fatal and may be considered an orphan disease. Most patients in both indications move from first line therapy to second line and later therapies, providing an opportunity for innovative approaches such as L-DOS47 to contribute to a cure, most likely as part of a combination approach with checkpoint inhibitors or chemotherapy. Our development and commercialization estimates are based on the following timeline:

Exhibit XII – Development Timeline

L-DOS47	2024	2025	2026	2027
NSCLC, US	Pivotal	Pivotal	BLA	First Sales
Pancreatic, US	Pivotal	BLA	First Sales	Sales
NSCLC, EU	Pivotal	BLA	First Sales	Sales
Pancreatic, EU	Pivotal	BLA	First Sales	Sales

Our forecasts do not attach any value for commercialization outside of the US and Europe, nor do they attribute any value to the other programs in Helix' portfolio. For our defined markets of NSCLC adenocarcinoma excluding patients with gene mutations, we are left with an addressable market of approximately 64,000 in the United States and 87,000 in Europe. L-DOS47 can be used in either first line with checkpoint inhibitors or second line treatment with chemotherapy. Due to a decline in smoking and a long term trend of fewer cases of NSCLC, we anticipate a 1% annual decline in market size for the lung indication. Initial penetration is anticipated to be 3.5% rising to a peak of 5.0% by year three. Pricing is expected to be USD$150,000 in the United States and USD$75,000 in Europe, in line with other biologics with inflation of 3% *per annum*. We anticipate that Helix will commercialize the product in North America and a partner will commercialize it in Europe. Royalties from European product revenues, which include anticipated milestones and other representations of value in our approach, are expected to be 30%.

For the pancreatic adenocarcinoma cancer market, we anticipate an addressable market size of approximately 52,000 in the US and 92,000 in Europe. Pancreatic cancer is one of the few cancer indications which is increasing in incidence and we forecast a 1% per annum growth in the addressable market. Due to the lack of alternatives for pancreatic cancer, especially when it is in its later stages, if L-DOS47 is found to be effective, we anticipate 6% penetration into the addressable market growing to 7% by year three. Pricing will match the lung cancer indication.

Gross margin is expected to be 90% and sales and marketing expense is expected to be 15% of product sales. Research and development is forecast to be $6.3 million in 2020, rising to a peak of $16.5 million in 2025, then declining to zero by 2028. General and administrative expenses are forecast to be $3.0 million in 2020, rising to $4.0 million by 2025, then increasing at 3% per annum afterwards. We anticipate a Canadian tax rate of 25%.

Our valuation approach employs a discounted cash flow model. Assumptions include a discount rate of 15% and a terminal growth rate of -10%. To our net present value (NPV) we attach a 15% probability of FDA approval and ultimate commercialization based on the guidance provided in the Biomedtracker analysis.[31]

Despite the conservative stance of our assumptions, penetration into addressable markets can potentially be higher in both indications if L-DOS47 demonstrates strong efficacy and safety. We note that the determinant for many of the variables in our model will be the ultimate safety and efficacy profile as demonstrated in pivotal trials. If outcomes are materially stronger than other alternatives there will be greater pricing power, higher penetration and greater demand from a potential acquisitor. We will update our model accordingly as data is made available.

Based on the assumptions identified in our discounted cash flow model and after adjusting for anticipated share issuance, restricted stock and options outstanding, we generate a current valuation of $2.00 per share.

[31] Clinical Development Success Rates 2006-2015. David W. Thomas, Justin Burns, John Audette, Adam Carroll, Corey Dow-Hygelund, Michael Hay.

CONCLUSION

L-DOS47 has shown safety and efficacy in early stage trials and with sufficient funding will continue to progress through clinical trials and yield additional data. The DOS47 platform's innovative approach can potentially address tumor acidosis by generating a byproduct that is toxic to cancer cells and alter the pH of the TME. The increase in pH may allow chemotherapeutics and the body's own immune system to work better.

A large body of research, which we cite in this report, demonstrates the immunosuppressive effect of an acidic TME. Acidosis is a hallmark of tumor development, progression and promotes tumor growth. Cancer cells have adapted to survive and proliferate in acidic environments. The acidic environment that forms on the extracellular surface of tumors acts as a shield that prevents normal immune function from taking place and blocks the uptake of cancer therapies. With the addition of L-DOS47, the acidic environment can be reversed through the production of ammonia by the catalyzation of urea, which is also toxic to cancer cells.

The treatment paradigm is evolving rapidly in oncology. Immunotherapies have moved from second and later line treatments to first line. However, despite having improved safety and efficacy, they fail to work in a majority of cases. This has opened the doors for L-DOS47 to be used in combination with both immunotherapies and chemotherapies to treat some of the most difficult cancers. We anticipate that L-DOS47 will be used in conjunction with current standard of care.

Helix' lead candidate is currently being examined in multiple Phase II trials for both NSCLC and pancreatic cancer. Survival rates are relatively low for advanced stages of both indications. L-DOS47 may represent a new and effective approach that can improve treatment success rates especially when used in combination with other standard of care therapies.

Key reasons to own Helix shares:

- **Novel mechanism of action that is synergistic with other therapies**
- **CEACAM6 target is specific to tumor cells, especially lung and pancreatic adenocarcinoma**
- **L-DOS47 may reverse acidic extra-cellular conditions favorable to cancer cell survival**
- **L-DOS47 may improve uptake of weak-base chemotherapeutics**
- **L-DOS47 may reduce PD-1 and PD-L1 expression thereby improving immune response**
- **Favorable drug safety profile with no reported drug-related adverse events**
- **Biologic eligible for 12 years of exclusivity in United States and extended protection in other geographies**
- **North American rights to intellectual property**
- **Pursuing multiple indications**
    - **Non small cell lung cancer**
    - **Pancreatic cancer**

Based on our analysis of L-DOS47 and its impact on the TME we see a pathway forward in NSCLC and pancreatic cancer. Our valuation work takes into account commercialization of L-DOS47 in both the United States and Europe assuming a 15% probability of ultimate success. The opportunity for L-DOS47 extends beyond the US and Europe and the company has other programs in development that may ultimately generate value. We will add them to our model when they have advanced further through the pipeline. As we initate on Helix Biopharma, our analysis and forecasts generate a valuation of $2.00 per share.

PROJECTED FINANCIALS

Helix BioPharma Corporation - Income Statement

Helix BioPharma Corp	2019 A	Q1 A	Q2 E	Q3 E	Q4 E	2020 E	2021 E	2022 E
Total Revenues ($CAD)	**$0.0**	**$0.0**	**$0.0**	**$0.0**	**$0.0**	**$0.0**	**$0.0**	**$0.0**
Research & Development	$5,006	$1,511	$1,600	$1,600	$1,600	$6,311	$8,000	$10,000
Operating, General & Admin	$2,486	$709	$750	$750	$750	$2,959	$3,000	$3,500
Income from operations	($7,492)	($2,220)	($2,350)	($2,350)	($2,350)	($9,270)	($11,000)	($13,500)
Other Income	($33)	$15	$0	$0	$0	$15	$0	$0
Interest Expense	($1)	($6)	$0	$0	$0	($6)	$0	$0
Pre-Tax Income	($7,526)	($2,211)	($2,350)	($2,350)	($2,350)	($9,261)	($11,000)	($13,500)
Provision for Income Tax	$0	$0	$0	$0	$0	$0	$0	$0
Tax Rate	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*
Net Income	**($7,526)**	**($2,211)**	**($2,350)**	**($2,350)**	**($2,350)**	**($9,261)**	**($11,000)**	**($13,500)**
Net Margin								
Reported EPS	**($0.07)**	**($0.02)**	**($0.02)**	**($0.02)**	**($0.02)**	**($0.07)**	**($0.07)**	**($0.08)**
YOY Growth								
Basic Shares Outstanding	106,646	121,818	130,000	131,000	132,000	128,705	150,000	180,000

Source: Company Filing // Zacks Investment Research, Inc. Estimates

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HISTORICAL STOCK PRICE

Helix BioPharma Corporation – Share Price Chart[32]



[32] Source: Zacks Research System

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