



## **ANNUAL INFORMATION FORM**

October 26, 2018

### **HELIX BIOPHARMA CORP.**

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## **FORWARD-LOOKING STATEMENTS**

This Annual Information Form (“AIF”) contains forward-looking information (collectively, “forward-looking information”) within the meaning of applicable Canadian securities laws. Forward-looking information means disclosure regarding possible events, conditions or financial performance that is based on assumptions about future economic conditions and courses of action and includes financial projections and estimates; statements regarding plans, goals, objectives, intentions and expectations with respect to the Company’s future business, operations, research and development, including the focus of the Company on L-DOS47 which is the Company’s primary drug candidate, Topical Interferon Alpha-2b and other information relating to future periods. Forward-looking information includes, without limitation, statements concerning (i) the Company’s ability to continue to operate on a going concern basis being dependent mainly on obtaining additional financing; (ii) the Company’s growth and future prospects being dependent mainly on the success of L-DOS47; (iii) the Company’s priority continuing to be L-DOS47; (iv) the Company’s development programs, including but not limited to, extension of the current drug candidate(s) to other indications and the identification and development of further tumour-targeting antibodies for DOS47; (v) the anticipated timeline for completion of enrolment and other matters relating to the Company’s European Phase I/II clinical study for L-DOS47 in Poland, including the number of cohorts required to reach Maximum Tolerable Dose (“MTD”) and the Company’s U.S. Phase I clinical study for L-DOS47, (vi) seeking strategic partner support and therapeutic market opportunities; (vii) the nature, design and timing of future clinical trials (including the Company’s anticipated reassessment of the re-design of the LDOS003 study to focus on advanced stage lung cancer patients by combining L-DOS47 with Vinorelbine/Cisplatin (“VIN/CIS”) and commercialization plans; (viii) the Company’s advancement in the area of cell based therapy via its subsidiary Helix Immuno-Oncology S.A. (formerly Helix Immuno-Oncology Sp. z o.o and Helix Polska Sp. z o.o.) (“HIO”) (ix) future expenditures, insufficiency of the Company’s current cash resources and the need for financing and the Company’s possible response for such matters; (x) future financing requirements, the seeking of additional funding (including the possible receipt of grants) and anticipated future operating losses; (xi) changes in the application of accounting standards and interpretations; and (xii) industry performance, competition (including potential developments relating to immunotherapies and the Company’s possible response to such developments), prospects, and general prevailing business and economic conditions. Forward-looking information can further be identified by the use of forward-looking terminology such as “expects”, “plans”, “designed to”, “potential”, “believe”, “intended”, “continues”, “opportunities”, “anticipated”, “2017”, “2020”, “next”, “ongoing”, “seek”, “objective”, “estimate”, “future”, or the negative thereof or any other variations thereon or comparable terminology referring to future events or results, or that events or conditions “will”, “may”, “could”, “would”, or “should” occur or be achieved, or comparable terminology referring to future events or results.

Forward-looking information includes statements about the future and are inherently uncertain, and are necessarily based upon a number of estimates and assumptions that are also uncertain. Although the Company believes that the expectations reflected in such forward-looking information are reasonable, such statements involve risks and uncertainties, and undue reliance should not be placed on such statements. Forward-looking information, including financial outlooks, are intended to provide information about management’s current plans and expectations regarding future operations, including without limitation, future financing requirements, and may not be appropriate for other purposes. The Company’s actual results could differ materially from those anticipated in the forward-looking information contained in this AIF as a result of numerous known and unknown risks and uncertainties, including, but not limited to:

- the Company’s need for additional capital which may not be available in a timely manner or at all (whether from additional issuances of the Company’s securities, grant applications or otherwise) and which, if not obtained, will have a material adverse impact on the Company and its ability to continue as a going concern;
- the risk that the Company may have to suspend or terminate one or more of its clinical trials for lack of funding, as the Company does not have sufficient funds to complete them and will need to raise additional funding, which is not assured;
- uncertainty as to whether the Company’s drug product candidate(s), especially L-DOS47, will be successfully developed and marketed;
- developments in immunotherapies may result in significant changes in the treatment of cancer and may result in a reduction, which may be significant, in the potential patient population and/or treatment protocols available to chemotherapies and other treatments currently in development, such as the Company’s primary drug product L-DOS47;
- the possibility of dilution to current shareholders from future equity financings;
- the impact of the ongoing volatility in the economic environment which has negatively affected the availability and terms of debt and equity financings and may have a negative effect on the Company’s ability to raise further financing and its research and development initiatives;

- risks relating to the difficulty in enrolling patients in clinical trials which may result in delays or cancellation of clinical trials;
- intellectual property risks, including the possibility that patent applications may not result in issued patents, that issued patents may be circumvented or challenged and ultimately struck down, that any expiry of an issued patent, may negatively impact the further development or commercialization of the underlying technology, and that the Company may not be able to protect its trade secrets or other confidential proprietary information;
- research and development risks, including without limitation, the fact that the Company's drug product candidate(s) are complex compounds and the Company faces difficult challenges in connection with the manufacture of clinical batches, and the risk of obtaining negative findings or factors that may become apparent during the course of research or development, any of which may result in the delay or discontinuation of the research or development projects;
- partnership/strategic alliance risks and the need to secure new strategic relationships, which are both not assured;
- the Company's dependence on third parties, including without limitation, contract research organizations, contract manufacturing organizations, clinical trial consultants, collaborative research consultants, regulatory affairs advisors, and others, whose performance and interdependence can critically affect the Company's performance and the achievement of its milestones;
- the Company's dependence on assurances from third parties regarding licensing of proprietary technology owned by others, including the Company's dependence on its license of the L-DOS47 antibody;
- the need for future clinical trials, the occurrence and success of which cannot be assured, and the fact that results seen in earlier clinical trials may not be repeated in later trials;
- manufacturing risks, the need to manufacture to regulatory standards, uncertainty whether the manufacturing process for the Company's drug candidates can be further scaled-up successfully or at all and the risk that clinical batches of the Company's drug candidate may not be able to be produced in a timely manner or at all, which would have a negative effect on the timing and/or occurrence of planned clinical trials and the potential commercialization of the drug candidates;
- uncertainty as to the size and existence of a market opportunity for, and market acceptance of the Company's drug product candidate(s) including as a result of possible changes in the market for the Company's drug candidates resulting from development in immunotherapies or other future cancer treatments;
- uncertainty as to the availability of raw materials that the Company utilizes to manufacture its products, and in particular, Good Manufacturing Practice ("GMP") grade materials, on acceptable terms or at all, and that the Company may not be able to timely obtain alternative suppliers upon commercially viable terms or at all, which could have a material adverse effect on the further development and commercialization of any or all of the Company's drug product candidate(s);
- product liability and insurance risks;
- the risk of lawsuits and other legal proceedings against the Company;
- the effect of competition, especially from the new immunotherapy treatments for non-small cell lung cancer ("NSCLC");
- the risk of unknown side effects arising from the development, manufacture or use of the Company's products;
- uncertainty as to the Company's ability to maintain product liability insurance required by third parties and the risk of corresponding agreements being terminated;
- the risk of misconduct on the part of our employees and consultants, including non-compliance with regulatory standards and requirements;
- the need to attract and retain key personnel and reliance on key personnel;
- that the Company has no sales, marketing and distribution experience;
- government regulation, including drug price regulation, and the need for regulatory approvals for both the development and profitable commercialization of products, which are not assured;
- risks associated with the fact that the U.S. Food and Drug Administration (the "FDA") and any other regulatory agency that the Company has consulted are not bound by their scientific advice, nor are any approvals given by one regulatory body binding on another;
- rapid technological change and competition from pharmaceutical companies, biotechnology companies and universities, which may make the Company's technology or products obsolete or uncompetitive;
- risks associated with claims, or potential claims, of infringement of third-party intellectual property and other proprietary rights;

- the risk of unanticipated expenses;
- the impact on the Company's finances resulting from shifts in foreign exchange rates, credit risk and interest rate risk,
- risks relating to changes in the Company's tax rates;
- risks relating to a failure to maintain an effective system of internal controls;
- risks relating to the requirements of being a public company;

and other risk factors that are discussed above and elsewhere in this AIF or identified in the Company's other public filings under the Company's profile on SEDAR at [www.sedar.com](http://www.sedar.com), (together the "Helix Risk Factors"), any of which could cause actual results to vary materially from current results or the Company's anticipated future results. Certain material factors, estimates or assumptions have been applied in making forward-looking information in this AIF, including, but not limited to, the safety and efficacy of the Company's drug product candidate(s); the Company's cost and timing in connection with the Phase I U.S. clinical trial for L-DOS47; the cost and timing for achieving MTD in the Company's European Phase I/II clinical trial for L-DOS47 in Poland; that additional and sufficient financing will be obtained in a timely manner or at all to allow the Company to continue operations; the timely provision of services and supplies or other performance of contracts by third parties; future costs; the absence of any material changes in business strategy or plans, the timely receipt of required regulatory approvals, strategic partner support; and that the Helix Risk Factors will not cause the Company's actual results or events to differ materially from the forward-looking information.

For all of the reasons set forth above, which do not represent an exhaustive list of factors that may affect the forward-looking information, investors should not place undue reliance on forward looking information. The forward-looking information is based on the beliefs, assumptions, opinions and expectations of the Company's management at the time they are made, and the Company does not assume any obligation to update any forward-looking information should those beliefs, assumptions, opinions or expectations, or other circumstances change, except as required by law.

Data relevant to estimated market sizes in connection with Company's lead products under development are presented in this AIF. These data have been obtained from a variety of published resources, including published scientific literature, websites and information generally available through publicized means. The Company attempts to source reference data from multiple sources whenever possible for confirmatory purposes. Although the Company believes the data is reliable, the Company has not independently verified the accuracy and completeness of this data.

## **CORPORATE STRUCTURE**

### **Name, address and incorporation**

Helix BioPharma Corp. ("**Helix**" or the "**Company**") is a Canadian corporation which was originally formed upon the amalgamation of International Helix Biotechnologies Inc. and Intercon Pharma Inc. on July 31, 1995. On April 30, 2008, the Company further amalgamated by way of short-form vertical amalgamation under the *CBCA* with Helix Product Developments Inc., 6933912 Canada Ltd., Sensium Technologies Inc. and 6965954 Canada Inc.

The Company's principle corporate offices were recently relocated to 9120 Leslie Street, Suite 205, Richmond Hill, Ontario, Canada L4B 3J9. The Company's phone number is (905) 841-2300. The Company's website is [www.helixbiopharma.com](http://www.helixbiopharma.com).

### **Inter-corporate relationships**

The following table summarizes the Company's wholly-owned subsidiaries:

	Date of Incorporation	Jurisdiction	Ownership
Helix BioPharma Inc.	December 4, 2000	USA	100% by Helix BioPharma Corp.
Helix Product Development (Ireland) Limited	March 24, 2004	Ireland	100% by Helix BioPharma Corp.
Helix Immuno-Oncology S.A.	July 6, 2013	Poland	100% by Helix BioPharma Corp.

\* Reflects name change effective September 1, 2017 (formerly Helix Immuno-Oncology Sp. z o.o and Helix Polska Sp. z o.o.)

There were no material amendments to the Company's articles or other constating or established documents in the 2017 fiscal year.

## **GENERAL DEVELOPMENT OF THE BUSINESS**

Helix is an immuno-oncology company primarily focused in cancer drug development. The Company is developing products for the treatment and prevention of cancer based on its proprietary technologies. The Company's product development initiatives are focused primarily on technologies that modulate the tumour microenvironment.

To date, the Company's proprietary technology platform, DOS47 has yielded two new drug product candidates, L-DOS47 and V-DOS47. L-DOS47 is currently under clinical study for the treatment of NSCLC. L-DOS47 has completed extensive preclinical testing and manufacturing development, following which, regulatory approvals to conduct a Phase I/II clinical trial in Poland and a Phase I study in the U.S. were obtained. V-DOS47 has been licensed to the Company's wholly-owned Polish subsidiary for preclinical and clinical development. The V-DOS47 drug candidate uses the Company's proprietary DOS47 technology conjugated to anti-VEGFR2 antibody targeting a wide range of cancers.

The Company continues to actively pursue additional new antibody based technologies for cell-based therapies. In September 2016 the Company announced that it was developing a novel Chimeric Antigen Receptor T-Cell (CAR-T) therapeutic. The Company believes CEACAM6 specific CAR immune cells may have broad applications in a number of cancer types and is working on two camelid single domain antibodies that target CEACAM6.

The Company currently believes that its growth and future prospects are mainly dependent on the success of its DOS47 drug product candidates, and the successful development of cell-based therapies.

On December 23, 2016, the Company announced, it signed an exclusive out-license agreement with Xisle Pharma Ventures Trust ("Xisle") for the Company's late-stage, Biphasix™ technology platform, including the lead product candidate, interferon alpha. Xisle is responsible for the continued clinical development and subsequent commercialization of the product for the treatment of HPV-induced, low-grade, cervical intraepithelial lesions. As part of its asset development strategy, Xisle has initiated collaboration with senior pharmaceutical executives at Altum Pharmaceuticals Inc., who possess regulatory, clinical, and product development expertise. Under the terms of the agreement, Xisle paid an up-front fee of USD125,000 and agreed to pay subsequent milestone payments as they advance the technology to registration and market approvals and royalties. As part of the agreement, Helix retains marketing rights for Belarus, Bulgaria, Czech Republic, former Eastern Germany, Hungary, Moldova, Poland, Romania, Russia, Slovakia and Ukraine. In addition, the Company also retains non-exclusive rights for co-promotion in Canada.

The Company subsequently assigned the foregoing marketing rights which it retained to HIO, its wholly-owned subsidiary in Poland, pursuant to an agreement between the Company and HIO with the agreement being subject to the restrictions and limitations associated with the out-license agreement signed between the Company and Xisle. In addition, HIO will be responsible for commercialization with milestone and royalty payments to be paid back to the Company upon successful product development through to commercialization.

The Company finances its research and development programs primarily from the issuance of its securities. In addition, the Company is also looking at alternative sources of additional financing. On July 21, 2016, the Company announced that its wholly-owned subsidiary in Poland had been awarded a funding grant from the Polish National Centre for Research and Development ("PNCRD") to develop V-DOS47. There can be no assurance that the Company will be successful in qualifying and/or receiving any additional grant money or that it will obtain additional financing or that the V-DOS47 program will be successful.

The Company expects to incur additional losses for the foreseeable future and will require additional financial resources to fund the Company's ongoing research and development activities and overhead costs.

The Company continues to not have sufficient cash reserves to meet anticipated cash needs for working capital and capital expenditures through the next twelve months. The Company's cash reserves as at July 31, 2018 of \$366,000 are not sufficient to see the current research and development initiatives through to completion or properly allocate scarce cash resources efficiently and as such, the Company will require additional financing in the very near term. Securing additional sufficient financing continues to be of critical importance to the Company.

Given the possibility of not being able to secure sufficient additional financing, whether on a timely basis or not at all, the Company may be required to reduce, delay or cancel one or more of its planned research and development initiatives, including clinical trials along with further reductions in overhead, any of which could impair the current and future value of the Company.

## **THREE YEAR HISTORY**

Important events which have occurred in the last three fiscal years and the period subsequent to July 31, 2018 up to the date of filing this AIF under the Company's profile on SEDAR at [www.sedar.com](http://www.sedar.com) include the following:

### **July 31, 2018 to the date of this AIF**

- On October 16, 2018, the Company announced the conditional approval by the TSX to extend the maturity of 4,546,000 outstanding common share purchase warrants, all of which are held by arm's-length parties. Each warrant currently entitles the holder to purchase one common share of the company at an exercise price of \$1.61 at any time until October 31, 2018. Subject to TSX approval, the expiry date of the warrants will be extended by two years to October 31, 2020. The exercise price of the warrants will remain unchanged at \$1.61. If approved by the TSX, the effective date of the amendment will be October 31, 2018.
- On October 10, 2018, the Company announced the extension of its collaboration agreement with the Moffitt Cancer Centre for an additional year.
- On September 13, 2018, the Company announced the initiation of enrollment of the second to last cohort in the U.S. combination treatment study of L-DOS47.
- On September 12, 2018, the Company announced that a scientific research collaborator published a paper describing research and validation work on the antibody that the companies are co-developing for a CAR-T application against multiple myeloma.
- On September 10, 2018, the Company announced the closing of a private placement for gross proceeds of approximately \$0.46 million.
- On August 8, 2018, the Company announced the closing of a private placement for gross proceeds of approximately \$0.82 million.

### **Fiscal year ended July 31, 2018**

- On July 25, 2018, the Company announced the completion of the third dosing cohort and initiated enrollment of the next cohort in the U.S. combination treatment study of L-DOS47.
- On July 9, 2018, the Company announced the closing of a private placement for gross proceeds of approximately \$1.00 million.
- On June 7, 2018, the Company announced the closing of a private placement for gross proceeds of approximately \$0.95 million.
- On May 30, 2018, the Company announced the completion of the third dosing cohort and initiated enrollment of the next cohort in the U.S. combination treatment study of L-DOS47.
- On April 30, 2018, the Company announced the closing of a private placement for gross proceeds of approximately \$0.61 million.
- On April 10, 2018, the Company announced the regulatory approval to commence a Phase II randomized study of L-DOS47 in combination with vinorelbine and cisplatin in Ukraine.
- On March 22, 2018, the Company announced the forming of a new scientific and strategic advisory board comprising of Dr. Daniel Von Hoff, Dr. Kazimierz Roszkowski-Sliz and Dr. Robert Gillies.
- On March 3, 2018, the Company signed a collaboration agreement with ProMab Biotechnologies to develop chimeric antigen receptor T-cell therapy for hematological malignancies and solid tumours.
- On February 2, 2018, the Company retained Deloitte Corporate Finance Inc. as strategic advisor to help explore potential partnering and licensing opportunities.
- On December 22, 2017, the Company announced the closing of a private placement for gross proceeds of approximately \$0.75 million.

- On December 12, 2017, at the Company's annual and special meeting of shareholders, Messrs. Sylwester Cacek, Slawomir Majewski, Marek Orłowski, Heman Chao were elected to the Board by shareholders. In addition, the Company announced the approval by shareholders to reduce the number of board seats to four.
- On December 1, 2018, the Company announced the resignation of the Company's Chief Operating Officer.
- On October 19, 2017, the Company announced the closing of a private placement for gross proceeds of approximately \$3.91 million.
- On September 27, 2017, the Company announced that the U.S. Food and Drug Administration ("FDA") has approved an amendment to the U.S. Phase I study, protocol LDOS001, that will accelerate the dose escalation phase of the study. In order to maximize the number of patients receiving a potentially active dose of L-DOS47, the study will implement an accelerated dose design up to 6µg/kg followed by a standard 3+3 design for the final two dosing cohorts, 9 and 12 µg/kg, respectively.
- On September 1, 2017, the Company's wholly-owned Polish subsidiary was legally transformed from an Sp. z o.o to an S.A. company.
- On August 31, 2017, the Company announced the closing of a private placement for gross proceeds of approximately \$1.31 million.
- On August 22, 2017, the Company announced the publication of a peered-reviewed V-DOS47 manuscript in "Frontiers in Immunology" journal. The article, entitled "Development and Characterization of a Camelid Single Domain Antibody-Urease Conjugate That Targets Vascular Endothelial Growth Factor Receptor 2", describes the design and construction of V-DOS47 for breast cancer and other potential indications.

#### **Fiscal year ended July 31, 2017**

- On July 31, 2017, the Company announced that the poster entitled: "*Immune checkpoint modulation by urease-mediated alkalization*", had been accepted for presentation in the "Checkpoint Blockade Therapy" session at the Third International Cancer Immunotherapy Conference in Mainz Germany on September 6, 2017 at the Rheingoldhalle Congress Center Mainz.
- On July 25, 2017, the Company announced the opening of patient screening in the third dosing cohort of its ongoing U.S. study of L-DOS47 in combination treatment with pemetrexed/carboplatin.
- On July 18, 2017, the Company announced that it had entered into a collaboration agreement with Moffitt Cancer Center to perform basic research studies to further investigate the pharmacodynamics of L-DOS47 and determine the potential benefits of combining L-DOS47 with immune checkpoint inhibitors.
- On July 17, 2017, the Company announced that the Board has accepted Mr. Albert Beraldo's resignation as director of the Company and Audit Committee Chair, effective July 14, 2017.
- On July 11, 2017, the Company announced it has entered into a collaboration agreement with the Moffitt Cancer Center to extract radiomics data using their proprietary HealthMyne platform from CT scans of late stage lung cancer patients treated with L-DOS47.
- On June 7, 2017, the Company announced the closing of a private placement for gross proceeds of approximately \$3.03 million.
- On May 30, 2017, the Company announced that Dr. Heman Chao, Chief Executive Officer, would be presenting at the 3<sup>rd</sup> Annual Immuno-oncology BD&L and Investment Forum on June 2, 2017 in Chicago.
- On April 27, 2017, the Company announced the closing of a private placement for gross proceeds of approximately \$0.82 million.
- On March 21, 2017, the Company announced that results from the Phase I L-DOS47 monotherapy study in Poland would be presented at the upcoming 9<sup>th</sup> International Conference of Contemporary Oncology meeting in Poznan, Poland on March 22, 2017.



- On March 17, 2017, the Company announced the closing of a private placement for gross proceeds of approximately \$1.11 million.
- On March 7, 2017, the Company announced that Dr. Sven Rohmann, Chief Executive Officer and Chairman, would be stepping down as Chief Executive Officer and replaced by Dr. Heman Chao.
- On February 27, 2017, the Company announced the signing of a license agreement with the National Research Council of Canada (“NRC”) for the worldwide rights to anti-CEACAM6 antibody 2A3, for oncology applications.
- On February 22, 2017, the Company announced that its wholly-owned Polish subsidiary, HIO, had signed a non-binding letter of intent with KEN Poland Limited Partnership (“KEN POLAND”) in support of the European Centre for Cancer Immunotherapy (“ECCL”). The common intention of HIO and KEN POLAND of establishing a cooperation and initiating a framework of investment in the ECCL, using the innovative Helix CAR-T and DOS47 technologies. The letter of intent contemplates a proposed investment by KEN POLAND of approximately \$30 million with additional financing for the venture to be sought from both private and public sources. The ECCL is planned to consist of five satellite clinics located in existing Polish hospitals and a planned central clinic providing access to cancer patients requiring immune-based therapies.
- On February 13, 2017, the Company announced that the Company would be attending and/or presenting at the following conferences during the first half of 2017:
  - BIO CEO & Investor conference in New York City on February 13-14, 2017
  - Moffit Cancer Center Business of Biotech Conference in Tampa, Florida on February 24, 2017
  - American Association of Cancer Research (AACR2017) in Washington, D.C., April 1-5, 2017
  - American Society of Clinical Oncology (ASCO2017) in Chicago, Illinois, June 2-7, 2017.
- On February 2, 2017, the Company announced the Helix’s Chief Executive Officer, Dr. Sven Rohmann, would be presenting at the BIO CEO and Investor Conference in New York City on February 14, 2017.
- On January 23, 2017, the Company announced that its poster entitled: *CAR-T cell harboring a camelid single domain antibody as a targeting agent to kill tumours expressing VEGFR2* has been accepted for presentation at the AACR Annual Meeting 2017 on April 4, 2017 in Washington, D.C., USA.
- On January 17, 2017, at the Company’s annual and special meeting of shareholders, Messrs. Sylwester Cacek, Slawomir Majewski, Marek Orłowski, Sven Rohmann, Albert G. Beraldo, Theodore J. Witek Jr. and George Anders were elected to the Board by shareholders.
- On December 30, 2016, the Company announced the closing of an additional private placement for gross proceeds of approximately \$0.24 million.
- On December 29, 2016, the Company announced the receipt of private placement subscriptions totalling \$1.82 million and the closing of \$1.58 million of such subscriptions.
- On December 23, 2016, the Company announced the signing of an exclusive out-license agreement with Xisle Pharma Venture Trust for the Company’s late-stage BiPhasix technology platform, including the Company’s lead drug product candidate, interferon alpha2b.
- On December 22, 2016, the Company announced that it had entered into a non-binding letter of intent with ProMab Biotechnologies to complete due diligence and establish a collaboration to develop chimeric antigen T-cell based therapies for hematological malignancies and solid tumours.
- On December 9, 2016, the Company announced that Dr. Sven Rohmann, Helix’s Chief Executive Officer, would be presenting at the Biotech Showcase Conference which was running in parallel during the Annual JP Morgan Conference week in San Francisco from January 9-12, 2017.
- On December 6, 2016, the Company announced topline L-DOS47 results from its Phase I/II dose escalation study on immunoconjugate at the 17<sup>th</sup> IASCLC World Conference on Lung Cancer in Vienna, Austria.
- On November 30, 2016, the Company announced that after reviewing safety data from the Company’s Phase I/II study of L-DOS47 in non-small cell lung cancer, the U.S. Food and Drug Administration has accepted an

accelerated escalation scheme for L-DOS47 dosing up to 12µg/kg in combination with pemetrexed/ carboplatin.

- On November 17, 2016, the Company announced a poster presentation entitled “Phase I/II dose escalation study of immunoconjugate L-DOS47 as a monotherapy in non-squamous non-small cell lung cancer patients” had been selected for poster presentation at the 17<sup>th</sup> World Conference on Lung Cancer in Vienna, Austria scheduled for December 6, 2017.
- On November 4, 2016, the Company’s wholly-owned subsidiary officially changed its name from Helix Polska Sp. z o.o. to Helix Immuno-Oncology Sp. z o.o (now Helix Immuno-Oncology S.A.).
- On October 27, 2016, the Company announced that Chief Executive Officer Dr. Sven Rohmann would be presenting a corporate overview at the National Investment Banking Association conference on October 27, 2016 in Newport Beach, California.
- On October 19, 2016, the Company announced a CAR-T poster presentation at the AACR Conference of Tumor Immunology and Immunotherapy entitled: *CAR-T Cells Harboring Camelid Single Domain Antibody Targeting Agent to CEACAM6 Antigen in Pancreatic Cancer*.
- On October 6, 2016, the Company announced that Chief Executive Officer Dr. Sven Rohmann would be presenting a corporate overview at the Bio Investor Forum on October 19, 2017 in San Francisco, California.
- On September 9, 2016, the Company announced that Dr. Heman Chao would be presenting at the Precision Lunch Cancer World R&D Summit on September 13-14, 2016 in Boston.
- On September 7, 2016, the Company announced the appointment of Dr. Theodore Witek Jr. to the Board of Directors of the Company.
- On September 1, 2016, the Company announced a poster presentation entitled “*CAR-T Cells Harboring Camelid Single Domain Antibody as Targeting Agent to CEACAM6 Antigen in Pancreatic Cancer*” at the AACR Conference on Tumor Immunology and Immunotherapy from October 20-24, 2016 in Boston.
- On August 19, 2016, the Company announced the closing of a private placement for gross proceeds of approximately \$1.0 million.

#### **Fiscal year ended July 31, 2016**

- On July 29, 2016, the Company announced the closing of a private placement for gross proceeds of approximately \$1.8 million.
- On July 21, 2016, the Company announced that its wholly-owned subsidiary, HIO, had finalized a grant approval with the PNCRD to develop V-DOS47 in breast cancer.
- On July 18, 2016, the Company announced an agreement in principle with the NRC to collaborate on various immuno-oncology initiatives.
- On June 28, 2016, the Company and its wholly-owned subsidiary, HIO, signed the Amended and Restated Licence Agreement for DOS47 and V-DOS47 Technology.
- On June 2, 2016, the Company announced the appointment of Evolution Life Science Partners to act as advisors in any partnering or other collaborative agreements.
- On May 11, 2016, the Company announced that the first patient had been dosed in its Phase II study in non-small cell lung cancer in Poland.
- On May 9, 2016, the Company announced that its wholly-owned subsidiary, HIO, qualified for a \$4.1 million government grant from the PNCRD to develop V-DOS47 in breast cancer.
- On April 29, 2016, the Company announced the closing of a private placement for gross proceeds of approximately \$4.7 million.

- On April 28, 2016, the Company announced first patient enrollment in the Phase II study of L-DOS47 in non-small cell lung cancer, in Poland.
- On April 21, 2016, the Company received approval from the trial steering committee who recommended the initiation of the Phase II study in non-small cell lung cancer in Poland.
- On April 20, 2016, the Company announced the appointments of Dr. Patrick Frankham to Chief Operating Officer and promoted Mr. Steve Demas to Chief Medical Officer.
- On March 29, 2016, the Company announced that Dr. Zbigniew Markowski, was stepping down from his roles as Chief Executive Officer of the Company and Chairman of the Company's wholly-owned subsidiary, HIO. Stepping into both roles, effective immediately was Dr. Sven Rohmann.
- On March 8, 2016, the Company announced the approved amendment by The Registration Office of Medicinal Products, Medical Devices and Biocides in Poland for the Company's Phase I/II study defining the dose and dosing regimen for the Phase II portion of the study. The following changes were approved:
  - No further escalations of L-DOS47 past cohort sixteen. Assuming no further dose-limiting toxicities, the cohort sixteen dose of 13.55 microgram per kilogram would be the dose administered to patients in the Phase II dose.
  - The safety profile supported a more frequent administration of L-DOS47, twice weekly over 14 days (days one, four, eight, 11) followed by a seven-day rest.
  - An increase in the number of patients in the Phase II study to 45 patients. Based on Simon's optimal two-stage design, 17 evaluable patients are to be enrolled in the first stage of the Phase II component of the study. If there is/are greater than or equal to one response(s) out of these initial 17 evaluable patients, 22 additional evaluable patients would need to be enrolled. To obtain 39 patients evaluable for response, enrolment of approximately 45 patients are required.
- On March 3, 2016, the Company announced the completed review safety data and has recommended the opening of patient screening for the sixteenth-dose-level cohort in its continuing Phase I/II clinical safety, tolerability and preliminary efficacy study of L-DOS47 in Poland.
- On February 4, 2016, the Company announced the appointment of Dr. Zbigniew Markowski as Chairman of the Board of Helix Polska Sp. z o.o.
- On January 29, 2016, the Company announced the appointment of Messrs. Albert Beraldo and Dr. George J. Anders to the Board of Directors replacing Messrs. Gary Littlejohn and Yvon Bastien who tendered their resignations.
- On January 21, 2016, the Company announced that it had initiated enrollment in the second dosing cohort of its U.S. Phase I combination study of its L-DOS47 lung cancer drug candidate.
- On January 12, 2016 the Company appointed Dr. Zbigniew Markowski, as Chief Executive Officer, replacing Gary Littlejohn who was serving as Interim Chief Executive Officer.
- On January 6, 2016, the Company announced the granting of a worldwide exclusive licence for v-DOS47, an antibody DOS47 conjugate that targets the vascular endothelial growth factor 2 receptor (VEGFR2), to its wholly-owned subsidiary, Helix Polska.
- On December 23, 2015, the Company announced that it had initiated enrollment in the fifteenth cohort of the Company's Polish Phase I/II clinical study of it L-DOS47 lung cancer drug candidate.
- On December 16, 2015, at the Company's annual general meeting, Messrs. Yvon Bastien, Sylwester Cacek, Gary Littlejohn, Slawomir Majewski, Marek Orłowski and Sven Rohmann, were elected to the Board by shareholders.
- On November 4, 2015, the Company announced that it had initiated enrollment in the fourteenth cohort of the Company's Polish Phase I/II clinical study of it L-DOS47 lung cancer drug candidate.
- On September 30, 2015, the Company announced the appointment of Gary Littlejohn to the Board of Directors, effective September 23, 2015 and as a consultant to the Company, effective September 29, 2015 in order to facilitate a smooth leadership transition while the Company searches for a new permanent president and chief

executive officer. Mr. Littlejohn was subsequently appointed Interim Chief Executive Officer as of November 1, 2015.

- On September 30, 2014, the Company announced the completion of a second interim review of data collected to date in its ongoing European Phase I/II clinical study of L-DOS47 in Poland;
- On September 23, 2015, the Company announced the voluntary resignation of Stacy L. Wills from the Board of Directors, effective September 25, 2015.
- On September 19, 2015, the Company announced the resignation of the Company's President and Chief Executive Officer, effective November 1, 2015 and as a member of the Board of Directors, effective immediately.
- On September 8, 2015, the Company announced the presentation and update of the ongoing clinical study LDOS002 for the Company's drug candidate L-DOS47 during the 16th World Conference on Lung Cancer held in Denver Colorado. The presentation included the following data:
  - forty (40) patients were enrolled in the first twelve dosing cohorts;
  - L-DOS47 was well tolerated at the dose levels up to 4.33 µg/kg;
  - no Dose Limiting Toxicities ("DLT") were reported for Cohorts 1-12;
  - one (1) DLT was reported for Cohort 13;
  - adverse events reported to date were expected for the population under study;
  - twenty-one (21) of forty (40) patients had an overall response of stable disease based on radiological assessment after completing two cycles of L-DOS47;
  - eleven (11) of these 21 patients continued with a response of stable disease based on radiological assessment after completing four cycles of L-DOS47;
  - one patient in cohort 9 was dosed for ten (10) cycles (approximately seven (7) months) without disease progression; and
  - the study was enrolling patients in the thirteen-dosing cohort (5.76 µg/kg).

## **NARRATIVE DESCRIPTION OF THE BUSINESS**

Helix is an immuno-oncology company primarily focused in cancer drug development. The Company is developing products for the treatment and prevention of cancer based on its proprietary technologies. The Company's product development initiatives are focused primarily on technologies that modulate the tumour microenvironment.

To date, the Company's proprietary technology platform, DOS47 has yielded two new drug product candidates, L-DOS47 and V-DOS47. L-DOS47 is currently under clinical study for the treatment of NSCLC. L-DOS47 has completed extensive preclinical testing and manufacturing development, following which, regulatory approvals to conduct a Phase I/II clinical trial in Poland and a Phase I study in the U.S. were obtained. V-DOS47 has been licensed to the Company's wholly owned Polish subsidiary for preclinical and clinical development. The V-DOS47 drug candidate uses the Company's proprietary DOS47 technology conjugated to anti-VEGFR2 antibody targeting a wide range of cancers.

The Company continues to actively pursue additional new antibody-based technologies for cell-based therapies. In September 2016 the Company announced that it was developing a novel Chimeric Antigen Receptor T-Cell (CAR-T) therapeutic. The Company believes CEACAM6 specific CAR immune cells may have broad applications in a number of cancer types and is working on two camelid single domain antibodies that target CEACAM6.

The Company currently believes that its growth and future prospects are mainly dependent on the success of its DOS47 drug product candidates, and the successful development of cell-based therapies.

On December 23, 2016, the Company announced, it signed an exclusive out-license agreement with Xisle Pharma Ventures Trust ("Xisle") for the Company's late-stage, Biphasix™ technology platform, including the lead product candidate, interferon alpha. Xisle is responsible for the continued clinical development and subsequent commercialization of the product for the treatment of HPV-induced, low-grade, cervical intraepithelial lesions. As part of its asset development strategy, Xisle has initiated collaboration with senior pharmaceutical executives at Altum Pharmaceuticals Inc., who possess regulatory, clinical, and product development expertise. Under the terms of the agreement, Xisle paid an up-front fee of \$125,000 USD and agreed to pay subsequent milestone payments as they advance the technology to registration and market approvals and royalties. As part of the agreement, Helix retains marketing rights for Belarus, Bulgaria, Czech Republic, former Eastern Germany, Hungary, Moldova, Poland, Romania, Russia, Slovakia and Ukraine. In addition, the Company also retains non-exclusive rights for co-promotion in Canada.

The Company subsequently assigned the foregoing marketing rights which it retained to HIO, its wholly-owned subsidiary in Poland pursuant to an agreement between the Company and HIO with the agreement being subject to the restrictions and limitations associated with the out-license agreement signed between the Company and Xisle. In addition, HIO will be responsible for commercialization with milestone and royalty payments to be paid back to the Company upon successful product development through to commercialization.

The Company finances its research and development programs primarily from the issuance of its securities. In addition, the Company is also looking at alternative sources of additional financing. On July 21, 2016, the Company announced that its wholly-owned subsidiary in Poland had been awarded a funding grant from the Polish National Centre for Research and Development (“PNCRD”) to develop V-DOS47. There can be no assurance that the Company will be successful in qualifying and/or receiving any additional grant money or that it will obtain additional financing or that the V-DOS47 program will be successful.

The Company expects to incur additional losses for the foreseeable future and will require additional financial resources to fund the Company’s ongoing research and development activities and overhead costs.

The Company continues to not have sufficient cash reserves to meet anticipated cash needs for working capital and capital expenditures through the next twelve months. The Company’s cash reserves as at July 31, 2018 of \$366,000 are not sufficient to see the current research and development initiatives through to completion or properly allocate scarce cash resources efficiently and as such, the Company will require additional financing in the very near term. Securing additional sufficient financing continues to be of critical importance to the Company.

Given the possibility of not being able to secure sufficient additional financing, whether on a timely basis or not at all, the Company may be required to reduce, delay or cancel one or more of its planned research and development initiatives, including clinical trials along with further reductions in overhead, any of which could impair the current and future value of the Company.

## **RESEARCH AND DEVELOPMENT ACTIVITIES**

### **Background**

The immune system utilizes two strategies in attacking different types of pathogens. The humoral immune system uses antibodies as its main weapon. Antibodies are proteins that bind to extracellular foreign invaders, such as bacteria, and lead to their destruction. The cellular immune system utilizes specialized immune cells, called T-cells to identify and bind to abnormal cells and subsequently destroy them.

Cancer cells have adopted and developed several strategies for evading the immune system. In some cases, proteins are expressed on the surface of tumour cells that “turn off” attacking T-cells. By using antibodies to block these interactions (such as anti-PD1), T-cells are reactivated to kill the tumours. Although anti-PD1 and anti-PDL1 therapies (checkpoint inhibitors) have improved outcomes for patients, there are many that do not respond to these treatments. One possible explanation suggests that the unique metabolism of cancer cells creates an acidic tumour microenvironment and this acidity has the effect of interfering with T-cell function. The Company believes it has developed a novel system to raise pH at the tumour site, thus breaking the physiologic barrier that acts to defend against tumour-killing T-cells.

### ***Alkalization using Urease***

Urease is an enzyme that catalyzes the hydrolysis of urea into carbon dioxide and ammonia ( $(\text{NH}_2)_2\text{CO} + \text{H}_2\text{O} \rightarrow \text{CO}_2 + 2\text{NH}_3$ ). The Company has conjugated urease to an antibody that specifically targets lung cancer cells, thus delivering the urease directly to the site of the tumour. L-DOS47, the Company’s first drug product candidate, has recently completed a Phase I/II monotherapy trial in Poland. It 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. By delivering urease to the tumour site, the company expects the pH of the tumour microenvironment to increase and activity of tumour-killing T-cells to be enhanced. The Company believes the urease system can be used with any tumour specific antibody as a general method for modifying the tumour microenvironment, and as such, could be combined with any of the current checkpoint inhibitor products to improve patient outcomes.

### ***CAR-T Cells***

To date, success in Adoptive Cell Transfer (“ACT”) with engineered T-cells such as Chimeric Antigen Receptor T-cells (“CAR-T”) has occurred mainly in the area of hematological malignancies. As of the end of 2016, 220 CAR T cell trials were documented of which approximately 188 are ongoing including nine long-term follow-up studies. Of the

current trials, 133 target hematological malignancies and 78 solid tumors (Hartman et. al, EMBO Mol Med (2017) 9: 1183–1197). Most clinical trials have used autologous, unselected peripheral blood mononuclear cells (“PBMC”) as the starting material and IL-2 for stimulation resulting in a CAR-T cell product consisting of CD4 and CD8 T cells with an activated effector T-cell phenotype. In five trials, more than 85% of treated patients reached complete response (“CR”) as best clinical outcome (Hartman et. al, EMBO Mol Med (2017) 9: 1183–1197).

While CAR-T cell therapy has shown impressive clinical benefit, it is sometimes associated with a variety of toxicities that can be life-threatening. Several death cases have been reported, especially in the last year. These were due to neurotoxicity caused by cerebral edemas in the CD19-CAR trials sponsored by Juno Therapeutics. Whether neurological toxicities are solely restricted to CD19-specific CAR-T cells or generally associated with CAR-T cell therapy remains to be elucidated (Hartman et. al, EMBO Mol Med (2017) 9: 1183–1197).

A direct connection to another frequent side effect, the cytokine-release syndrome (“CRS”), also appears likely. CRS has so far been the most frequently observed adverse drug reaction. On-target, off-tumor recognition has become a relevant concern, since many targeted tumor antigens are also expressed on normal tissue (Hartman et. al, EMBO Mol Med (2017) 9: 1183–1197).

On August 30, 2017, the FDA approved Novartis’ Kymriah (tisagenlecleucel) for certain pediatric and young adult patients with a form of acute lymphoblastic leukemia (“ALL”). Kymriah is a genetically-modified autologous T-cell immunotherapy. Each dose of Kymriah is a customized treatment created using an individual patient’s own T-cells.

Solid tumours have created challenges and as such, it is hypothesized that the failure of CAR-T therapies to date may be the result of the acidic tumour microenvironment surrounding the cancer cell that inhibits CAR T-cell activity. The Company believes it is well positioned to use its proprietary urease-antibody technology to alkalize the tumour microenvironment and improve the ability of CAR-T cells to destroy solid tumours.

### **Check Point Inhibitors**

Dr. Robert J. Gillies of the Moffitt Cancer Center in Tampa Florida demonstrated some interesting results when treating acidic tumours in animal models. Dr. Gillies demonstrated that in alkalized tumour cells, the activity of antibodies that target PD-L1, is enhanced. This would indicate that tumour acidosis may protect tumours from immune check-point inhibitors. Since tumour acidosis is experimentally shown to occur in cancers such as breast, colon, lung and pancreas, the Company believes methodologies that can alkalize the tumour microenvironment, such as the Company’s proprietary DOS47 platform technology, may work beneficially with check-point inhibitors.

### **DOS47 – A broad anti-cancer therapeutic platform**

DOS47 is based upon a naturally occurring enzyme isolated from the jack-bean plant called urease that breaks down a natural substance found in the body, urea, into metabolites that include ammonia and hydroxyl ions. By doing so at the site of cancerous tissues in the body, the Company believes DOS47 can modify the micro environmental conditions of cancerous cells in a manner that leads to apoptosis.

DOS47 stimulates an increase in the pH of the microenvironment surrounding the cancerous cells, effectively reversing the acidic extra-cellular conditions that are believed to act to defend the tumour. This acidic environment can also reduce or negate the effectiveness of some commonly used anti-neoplastic agents. The local production of ammonia at the site of cancerous tissues is thought to readily diffuse into the cancer cells to exert a potent cytotoxic effect by interfering with their critical metabolic functions. Enzymatic action of urease at the site of cancerous cells is potentially repetitive and sustainable due to the plentiful supply of urea.

The Company is pursuing the development of DOS47 as an adjunct therapy in combination with certain chemotherapeutics, immunotherapies and/or radiation regimens, with a view to maximizing the DOS47 commercial potential.

DOS47 candidates are produced by conjugating urease with a targeting antibody or antibody fragment that can specifically direct the urease to the surface of a cancer cell. Once docked to the cell, the urease produces ammonia enzymatically through the conversion of urea found throughout the body. These conjugates of antibodies to urease are called DOS47 candidates. By selecting antibodies that are selective to different tumour cell surface receptors, the Company believes that DOS47 candidates can be used in several types of solid tumours.

In fiscal 2015, the Company entered into a collaborative research agreement with Afflogic to assess proprietary anti-tumour targeting agents in combination with DOS47. The agreement calls for a feasibility study using a targeting agent

in conjugation with DOS47. Continuing development of these new conjugates is subject to a successful feasibility study, execution of a formal development and licensing agreement, and the availability sufficient financial resources.

The Company continues to reach out to third parties in order to identify and test additional tumour-targeting antibodies for conjugation with DOS47. In the event that antibody candidates worthy of further development are identified, the Company will need to discuss development and licensing arrangements, which may not be available on terms acceptable to the Company or at all.

### **L-DOS47**

L-DOS47 is the Company's first targeted therapeutic immune-conjugate under development based on the DOS47 technology.

L-DOS47 is an antibody protein conjugate where the urease component enzymatically converts naturally occurring urea to ammonia. The L-DOS47 drug molecule includes a highly specialized camelid-derived single domain antibody, designed to identify a unique CEACAM6 antigenic site associated with NSCLC cells. By delivering the conjugate in a targeted manner, the Company believes L-DOS47 stimulates an increase in the pH of the microenvironment surrounding the NSCLC cells, reversing the acidic extra-cellular conditions that are shown to be favourable for cancer cell survival.

L-DOS47 is intended to offer an innovative approach to the first-line treatment of inoperable, locally advanced, recurrent or metastatic NSCLC. However, other emerging therapies, including immunotherapy, may alter the treatment paradigm in NSCLC. Therefore, the eventual approval for L-DOS47 as a first-line treatment for NSCLC will depend on both successful clinical trials and on the treatment landscape shaped by these new therapies. The Company continues to monitor developments in this area and to consider their effect on its L-DOS47 program, including its focus on L-DOS47 as a first-line treatment for NSCLC.

In 2005, the Company entered into a worldwide exclusive license with the National Research Council of Canada ("NRC"), through which it obtained the rights to combine this highly specialized camelid-derived single domain antibody with Helix's DOS47 technology. As a result, the Company has certain royalty and milestone payment obligations pursuant to the license agreement. The license agreement with the NRC has been filed under the Company's profile on SEDAR at [www.sedar.com](http://www.sedar.com). The NRC filed patent applications in respect of the antibody in Canada, the United States and other countries. On March 2, 2011, the NRC was issued a U.S. patent in respect of the antibody.

In addition to being a key for cancer progression by promoting invasiveness and metastatic behaviors of cancer cells, the acidic tumour microenvironment protects cancer cells from immunotherapy by suppressing the proliferation and cytotoxic activities of local immune cells. A series of experiments were performed in which L-DOS47 was used to neutralize acidic tissue culture media and the effects on tumor and immune cells in vitro were studied. L-DOS47 treatment reduced PD-L1 expression on the MDA-MB-231 breast cancer cell line and increased IL-2 production from the Jurkat human T cell line. In addition, L-DOS47 reduced PD-1 expression on primary human CD8+ T cells, and increased IL-2 and IFN $\gamma$  production by primary human CD8+ T cells, suggesting that L-DOS47 treatment may improve anti-tumor immune responses.

On July 11 and 18, 2017, the Company announced that it had entered into a collaboration agreement with Moffitt Cancer Center to perform basic research studies to further investigate the pharmacodynamics of L-DOS47 and determine the potential benefits of combining L-DOS47 with immune checkpoint inhibitors. Under the research plan Moffitt Cancer Center will perform in vitro and in vivo research studies to study the pharmacodynamics of L-DOS47 and its effect when combined with check-point blockage agents using their unique tumor models.

### **V-DOS47**

V-DOS47 is an antibody DOS47 conjugate that targets the vascular endothelial growth factor 2 receptor (VEGFR2). V-DOS47 is the second immuno-oncology drug candidate derived from the Company's DOS47 technology platform.

In January 2016, the Company granted a world-wide exclusive license for V-DOS47 to its wholly-owned subsidiary, HIO in Poland. The Company expects that day-to-day development activities in respect of V-DOS47 will be coordinated by HIO with coordination and oversight from some of the Company's scientists in Canada.

In order to advance the V-DOS47 initiative in Poland the Company has established a wet lab facility with the majority of the funding coming from the grant application with the PNCRD.

Based on the Grant Funding Agreement (the "Agreement") with the Polish National Centre for Research and Development ("PNCRD"), certain expenditures made commencing on March 1, 2016 are eligible for reimbursement

with the final reimbursement submission to be made no later than September 30, 2021. Total costs associated with the V-DOS47 development program under the Agreement is PLN19,794,416. Of the total project costs of PLN19,794,416, the PNCRD will reimburse the Company's Polish subsidiary PLN12,506,955 for eligible expenditures, under the program. Under the Agreement, the Company's subsidiary is required to spend PLN4,437,459 towards eligible project expenditures plus an additional PLN2,850,000 for manufacturing and clinical trial documentation costs that are not eligible for subsidies from the PNCRD. Subsidized amounts may be drawn in advance or on a reimbursement basis, with varying criteria and timelines for justification of claims being made by the Company's subsidiary.

The Company had 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 this know-how to develop a V-DOS47 clinical drug product candidate. The Company will assist HIO by sharing its extensive knowledge in GMP manufacturing, preclinical research and clinical experiences. HIO will collaborate with several Polish institutes through the grant to complete the development of the first v-DOS47 clinical drug product candidate. The development of the clinical drug product candidate for Phase I testing is expected to take two to three years. The actual duration of the development process will depend on successful completion of preclinical research favorable for clinical testing and establishment of cGMP manufacturing processes. The Company expects to enter clinical trials in 2019 provided success is achieved during the preclinical and there are sufficient funds.

The Company is also leveraging its know-how in manipulating the tumour 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 ACT for solid and hematological malignancies. The Company has selected CEACAM6 and VEGFR2 specific CARs for solid tumour. For hematological malignancies the Company has selected CD19 and CD22.

As announced by the Company in August of 2017, a peer-review of V-DOS47 was published in the "Frontiers in Immunology" journal. V-DOS47 is Helix's second DOS47 development candidate following L-DOS47, which is currently in clinical testing for the treatment of triple negative breast cancer. The article, entitled "Development and Characterization of a Camelid Single Domain Antibody-Urease Conjugate That Targets Vascular Endothelial Growth Factor Receptor 2", describes the design and construction of V-DOS47 for breast cancer and other potential indications.

### ***CAR-T for solid tumours and hematological malignancies***

#### ***CEACAM6 specific CARs***

Expression of CEACAM6 protein has been reported in a variety of normal human tissues including granulocytes. However, its expression is elevated in many types of solid tumours such as breast, pancreatic, ovarian, lung and colon. CEACAM6 is envisaged as a biomarker and potential therapy target for pancreatic ductal adenocarcinoma and pancreatic intraepithelial neoplasia (Duxbury et al., 2004a, 2004c, 2004d). Recently CEACAM6 is suggested to be check point molecule in multiple myeloma.

The Company believes CEACAM6 specific CAR immune cells may have broad applications in a number of cancer types. The Company is working on two camelid single domain antibodies that target CEACAM6.

2A3 is a camelid single domain antibody isolated from a whole cancer cell immunized llama library. The antibody binds specifically to the CEACAM6 antigen with high affinity and inhibits the proliferation of CEACAM6-expressing cancer cells *in vitro*. The efficacy of CEACAM6-CAR-T cells in xenograft model was examined *in vivo*. The results strongly support that CEACAM6-CAR-T cells can be used as an effective immunotherapy agent against CEACAM6-expressing cancers, and that camelid single domain antibodies can be easily adopted for CAR-T type therapies.

The Company continues to collaborate with ProMab Technologies, Inc. ("ProMab") on CAR-T. Most recently ProMab published a paper describing research and validation work on the antibody that the we are co-developing for a CAR-T application against multiple myeloma. Data described in the paper included in vitro work and proof-of-concept CAR-T animal studies.

#### ***Vascular epithelial growth factor receptor 2 (VEGFR2) CARs***

Most solid tumours and some hematologic malignancies are characterized by an angiogenic phenotype that is an absolute requirement for tumour survival, progression, and metastasis. Therapeutic approaches targeting molecules involved in tumour angiogenesis can inhibit tumour growth. Proliferating endothelial cells in the vessels within solid tumours aberrantly express high levels of angiogenic growth factors, receptors, and adhesion molecules that are absent or barely detectable in established blood vessels, which are normally quiescent. Among these, VEGF and its receptors appear to be the dominant regulators of angiogenesis responsible for the vascularization of normal and neoplastic tissues. Overexpression of VEGF and its receptors is associated with tumour angiogenesis, survival, invasion,



metastasis, recurrence, and prognosis in human cancers. VEGF stimulates angiogenesis mainly through VEGFR-2 (also known as Flk1 in mice and KDR in humans), a tyrosine kinase receptor that is overexpressed in tumour endothelial cells and on some tumour cells. Pharmacologic approaches to inhibit VEGF, using monoclonal antibodies or small molecules, are of value in cancer treatment, though the cytostatic rather than cytotoxic nature of these interventions and the redundancy of angiogenic pathways have limited the curative potential of these treatments). The Company believes VEGFR2 specific CAR immune cells may have broad applications in a number of cancer types. Helix is working on two camelid single domain antibodies that target VEGFR2.

The Company is also leveraging its know-how in manipulating the tumour 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 ACT for solid and hematological malignancies. The Company has selected CEACAM6 and VEGFR2 specific CARs for solid tumour. For hematological malignancies the Company has selected CD19,CD22 and BCMA as potential targets

On March 2018, The Company has entered a collaboration agreement with ProMab Biotechnologies, Inc. ("ProMab") to develop novel antibody and chimeric antigen receptor T-cell therapy ("CAR-T") that targets BCMA to treat multiple myeloma. In this collaboration, the Company retains commercial rights for this CAR-T in Canada and Europe. The Company will be exploiting its cell therapy programs through its Polish subsidiary.

The Company has also approached five Polish hospitals with plans to establish centers of excellence (European Center for Cancer Immunotherapy ("ECCI") that will participate in the development of their proprietary immune therapies. The Company will be seeking investment in the establishment of the ECCI in Poland once a business/strategic plan has been finalized and approved by the Company's Board of Directors.

### **Clinical study initiatives**

Regulatory approvals were granted to conduct a Phase I/II monotherapy (LDOS002) and a Phase I combination study (LDOS001) of L-DOS47 in Poland and the U.S. respectively, for the treatment of NSCLC. The Company was also granted regulatory approvals in Ukraine and Poland for study LDOS003, a clinical trial of L-DOS47 in combination with VIN/CIS in NSCLC patients with metastatic solid tumours. In addition, the Company is actively developing a new Phase I/II study (LDOS006) in the U.S., L-DOS47 in combination with doxorubicin, for the treatment of metastatic pancreatic cancer.

#### *U.S. Phase I clinical study ("LDOS001")*

On February 7, 2011, the Company announced it received approval by the FDA to conduct a U.S. Phase I clinical study with L-DOS47. The Company originally planned to commence the L-DOS47 U.S. Phase I study during fiscal 2012 but, given the Company's limited cash resources, the Company prioritized the LDOS002 European Phase I/II clinical study with L-DOS47 in Poland while deferring the previously planned commencement of the U.S. Phase I clinical study with L-DOS47.

On April 22, 2014, the Company announced an IND approval by the FDA to commence a study for an L-DOS47 Phase I, open label, dose escalation study in combination with standard doublet therapy of pemetrexed/carboplatin in patients with Stage IV recurrent or metastatic non-squamous NSCLC. The Company has initiated three U.S. sites: Dr. Sarina Piha-Paul at the MD Anderson Cancer Center, Dr. Chandra Belani at Penn State University and the Milton S. Hershey Medical Center, and Dr. Afshin Dowlati at University Hospitals Case Medical Center.

On November 30, 2016 the Company announced that after reviewing safety data from the Phase I/II study of L-DOS47 in non-squamous non-small cell lung cancer (LDOS002), the FDA had accepted an accelerated escalation scheme for L-DOS47 dosing in the U.S. Phase I study (LDOS001) up to 12µg/kg in combination with pemetrexed/carboplatin.

The Company provided an update to the LDOS001 study at the Biotech Showcase meeting on January 10, 2017 in San Francisco. Highlights of the presentation included the following:

- No dose limiting toxicities reported at doses up to 0.78µg/kg;
- Partial responses were reported in three (3) of the first six (6) patients dosed;
- Best tumour response reported was a 44% reduction in the sum of target lesions measured; and
- Three (3) patients continued L-DOS47 monotherapy following induction therapy of L-DOS47 in combination with pemetrexed/carboplatin.

On May 26, 2017, the Penn State Cancer Institute (PSCI) announced closure of the site due to limited enrollment activity. The site has subsequently been closed and no longer actively recruiting patients.

On June 29, 2017, the MD Anderson Electronic Protocol Accrual Auditing Committee (ePAAC) met to review the LDOS001 protocol due to slow patient recruitment. The committee decided to keep the protocol open for an additional six months at which time, another review will be conducted.

On July 25, 2017 the Company announced the opening of patient screening in the third dosing cohort. After a review of safety data, the Safety Review Committee ("SRC") recommended that Helix begin enrollment of patients into the third dosing cohort of study LDOS001. Patients enrolled in the third dosing cohort will receive 1.50 µg/kg in combination with pemetrexed/carboplatin.

On September 27, 2017 the Company announced that the FDA had approved an amendment to their U.S. Phase I study, protocol LDOS001, accelerating the dose escalation phase of the study. In order to maximize the number of patients receiving a potentially active dose of L-DOS47, the study implemented an accelerated dose design up to 6µg/kg followed by a standard 3+3 design for the final two dosing cohorts, 9 and 12 µg/kg respectively.

On May 29, 2018 the Company announced the opening of patient screening in the fourth dosing cohort. After a review of safety data, the SRC recommended that Helix begin enrollment into the fourth dosing cohort. Patients enrolled in this cohort will receive LDOS47 at a dose level of 3.0 µg/kg in combination with pemetrexed/carboplatin.

On July 25, 2018 the Company announced the completion of safety review for the fourth dosing cohort and following SRC recommendations, will open patient screening in the fifth dosing cohort. Patients enrolled in this cohort will receive L-DOS47 at a dose level of 6.0 µg/kg in combination with pemetrexed/carboplatin.

On September 13, 2018 the Company announced the opening of patient screening in the sixth cohort, following SRC review of safety data from cohort five. Patients enrolled in the sixth of seven dose escalation cohorts will receive L-DOS47 at a dose level of 9.0 µg/kg in combination with pemetrexed/carboplatin.

To date, twelve (12) patients have been dosed across 5 dose levels: 0.59 µg/kg, 0.78 µg/kg, 1.5 µg/kg, 3.0 and 6.0 µg/kg. Of eleven patients assessed for tumour response, five (5) patients have had a confirmed partial response (as defined by RECIST v1.1) following treatment of L-DOS47 in combination with pemetrexed/carboplatin, remaining progression-free ranging from 5.9 to 12.4 months. One additional patient had stable disease and remained progression-free for 13.3 months. The most recently enrolled patient in cohort 5 awaits assessment post-initiation of L-DOS47 treatment in combination with pemetrex/carboplatin. In addition to the protocol amendment approved by the FDA for an accelerated dose escalation scheme, which reduced the number of patients required to complete the study. On January 25, 2018, the Company entered into contract negotiations and start-up activities with US Oncology Research, to add 6 additional study sites with planned recruitment to begin mid-summer 2018.

With the recent FDA approval of pembrolizumab (Keytruda®) as first line treatment for NSCLC with PD-L1>1%, either as first line or in combination with carboplatin/pemetrexed, there is an urgent need for data to demonstrate safety of LDOS47 in combination with accepted standard chemotherapies, and also in combination with immunotherapies that are being offered with growing frequency.

The Company continues to have insufficient cash resources to see the entire LDOS001 U.S. Phase I clinical study through to completion. Given the Company's limited current cash resources and the possibility of not being able to obtain additional financing on a timely basis, the Company may be required to reduce, delay or cancel one or more of its planned research and development programs, including clinical trials along with further reductions in overhead, any of which could impair the current and future value of the business.

#### *European Phase I/II clinical study in Poland ("LDOS002")*

On July 25, 2011, Helix announced that the Company had received approval from the Central Register of Clinical Trials at the Polish Ministry of Health to perform a European Phase I/II clinical study with L-DOS47 and, on May 14, 2012, announced that clinical site initiation and patient recruitment activities had commenced for its European Phase I/II clinical study of L-DOS47. On October 23, 2012, the Company announced that its first patient had been enrolled and the first dose had been administered in this study.

The study was conducted at five Polish centers under the direction of Dr. Dariusz Kowalski at The Maria Sklodowska-Curie Memorial Cancer Centre & Institute of Oncology as the overall coordinating investigator, together with four other principal investigators: Prof. Cezary Szczylik, MD, PhD at the Military Medical Institute, Prof. Elzbieta Wiatr, MD, PhD at the National Tuberculosis and Lung Diseases Research Institute, Dr. Aleksandra Szczensa, MD, PhD at the Mazovian Center of Pulmonary Diseases and Tuberculosis in Otwock and Prof. Rodryg Ramlau, MD, PhD at Med. Polonia Hospital Poznan.

The study was conducted in patients with inoperable, locally advanced, recurrent or metastatic, non-squamous stage IIIb/IV NSCLC. The study recruited patients eligible for inclusion into escalating doses of L-DOS47 given as a monotherapy. The study utilized an open-label design, allowing for periodic status updates through its course. The study was intended to demonstrate valuable safety and proof-of-concept efficacy data for L-DOS47.

In the Phase I portion of the study, patients received weekly doses of L-DOS47, administered as an intravenous infusion over 14 days, followed by seven days' rest (one treatment cycle is three weeks), in order to determine the MTD of L-DOS47. The Phase II portion of the study evaluated the preliminary efficacy of L-DOS47.

In the Phase I component of the study, a total of 55 male and female patients, at least 18 years of age, with histologically confirmed non-squamous NSCLC were dosed at 16 L-DOS47 dose levels. Patients were required to have an Eastern Cooperative Oncology Group performance status of 0 – 2 at the screening visit for this study and have at least one site of measurable disease per RECIST v1.1.

The Phase II component enrolled the same patient population as the Phase I at an L-DOS47 dose of 13.55µg/kg. Patients in the study were dosed twice weekly over 14 days (Days 1, 4, 8, 11) followed by a 7-day rest. A total of 21 patients were dosed in the first stage of the Phase II component of the study.

To date, the Company completed four interim data reviews in connection with the LDOS002 Phase I study and one final review of Phase II study.

On October 15, 2013, the Company announced the completion of an interim data review of the first four cohorts for this study. The release stated that L-DOS47 was well tolerated for all patients treated within all cohorts. None of the treatment related adverse events reported to date met the definition of a dose-limiting toxicity. Adverse events reported as of that date were those normally expected for the population under study.

A review of available pharmacokinetic (“PK”) and immunogenicity data showed that these data so far, were consistent with trends seen within pre-clinical animal studies of L-DOS47. Results from these reviews, together with safety data provided guidance on the treatment schedule and dosing for the Phase II portion of the study.

Based on Radiologic Evaluations, patients assigned a status of “Progressive Disease” following any such assessment were withdrawn from the study. At least one patient in each of the four cohorts dosed had a radiological assessment of “Stable Response”. Duration of treatment increased with each dose escalation up to Cohort 4. One patient in Cohort 3 was dosed for 6 cycles without disease progression. None of the patients treated to date had a partial or complete response as defined by RECIST v1.1 definition.

On September 30, 2014, the Company announced the completion of a further interim data review for the first eight cohorts for the LDOS002 study. The review included all available data, including patient demographics, safety assessments, PK data, immunogenicity and radiological tumour assessments. The following observations were made:

- Adverse events reported were expected for investigational product and population under study;
- No Dose Limiting Toxicities (“DLTs”) have been reported;
- Stable disease observed in radiological assessments of 12 of 24 (50%) of patients treated; and
- Two patients completed six cycles of treatment each.

On September 8, 2015, the Company announced the presentation and update of the ongoing clinical study LDOS002 for the Company’s drug candidate L-DOS47 during the 16th World Conference on Lung Cancer held in Denver Colorado. The presentation included the following data:

- 40 patients were enrolled in the first twelve dosing cohorts;
- L-DOS47 was well tolerated at the dose levels up to 4.33 µg/kg;
- No DLTs were reported for Cohorts 1-12;
- One (1) DLT was reported for Cohort 13;
- adverse events reported to date were expected for the population under study;
- 21 of the 40 patients had an overall response of stable disease based on radiological assessment after completing two cycles of L-DOS47;
- 11 of these 21 patients continued with a response of stable disease based on radiological assessment after completing four cycles of L-DOS47;
- one (1) patient in cohort 9 was dosed for 10 cycles (approximately seven (7) months) without disease progression;
- the study is currently enrolling patients in the thirteen-dosing cohort (5.76 µg/kg).

On December 6, 2016, the Company presented the following LDOS002 Phase I data for the Company's drug candidate L-DOS47 during the 17<sup>th</sup> World Conference on Lung Cancer held in Vienna, Austria:

- 90 patients were consented and screened for participation in the study;
- 55 patients were administered at least one dose of L-DOS47 at dose levels ranging from 0.12 to 13.55µg/kg;
- 21 patients completed four treatment cycles and 16 patients were administered additional L-DOS47 cycles;
- Comparatively, patients in cohorts 13 to 16 (5.76 to 13.55µg/kg) were exposed to more L-DOS47 for a longer duration without a significant change to the safety profile of L-DOS47 compared to the other dosing cohorts;
- 44, or 80% of the patients in the safety population had at least one treatment emergent adverse events;
- L-DOS47 did not elicit a dose-dependent release of cytokines at doses up to 13.55µg/kg
- The MTD of L-DOS47 was not reached in the Phase I component of study LDOS002 at doses administered up to 13.55µg/kg;
- L-DOS47 was well tolerated at all dose levels up to 13.55µg/kg.
- A dose response trend was observed when comparing the percentage of patients who were progression free at 16 weeks across dose ranges;
- A similar trend was observed when comparing the percentage of patient who had an overall tumour response of Stable Disease (as defined in RECIST v1.1) and had a reduction in the sum of target lesions;
- 11 of 14 or 79% of patients in the highest dosing cohorts (5.76 to 13.55µg/kg) had an overall tumour response of Stable Disease following the administration of two cycles of L-DOS47;
- Seven (7) of 14 or 50% of patients in the same dosing cohorts had an overall tumour response of Stable Disease and a reduction in the sum of target lesions and 57% of patients were progression free for greater than 16 weeks.

On March 8, 2016, the Company announced the following approved changes by the central ethics committee overseeing the Phase I/II study in Poland as it relates to the Phase II component of the study, which the Company intends to initiate:

- There will be no further escalations of L-DOS47 past cohort 16. If there are no further dose limiting toxicities, the cohort 16 dose, 13.55 µg/kg, will be the dose administered to patients in the Phase II dose.
- The safety profile supports a more frequent administration of L-DOS47. After reviewing safety, pharmacokinetic and immunogenicity data, L-DOS47 will be dosed twice weekly over 14 days (Days 1, 4, 8, 11) followed by a 7-day rest in the Phase II study.
- The number of patients in the Phase II study will be increased to 45 patients. Based on Simon's optimal two-stage design, 17 evaluable patients will be enrolled in the first stage of the Phase II component of the study. If there is/are ≥ 1 response(s) out of these initial 17 evaluable patients, 22 additional evaluable patients will need to be enrolled. To obtain 39 patients evaluable for response, enrolment of approximately 45 patients are needed.

On April 21, 2016, the Company announced the approval by the Trial Steering Committee to initiate the Phase II component of the LDOS002 study. On April 28, 2016, the Company announced the enrolment of the first patient in the Phase II component of the LDOS002 study. The first Phase II patient was dosed on May 10, 2016 and had now completed their first L-DOS47 cycle.

Although the Phase II intensified L-DOS47 regimen was well tolerated by patients enrolled in the first stage of the study, an improvement in potential benefit to patients compared to the Phase I regimen (L-DOS47 dosed once weekly over 14 days (Days 1, 8) followed by a 7-day rest) was not observed. The potential complications associated with more frequent intravenous administrations in LDOS002 did not support the potential benefit to patients, past cycle four. As a result, the LDOS002 protocol was amended to limit the number of dosing cycles to a maximum of 6 cycles.

Following the review of clinical data collected to date, L-DOS47 continues to be well tolerated. The data also suggests that L-DOS47 may provide a clinical benefit for certain patients. After completion of enrolment for the first stage of the Phase II component of study LDOS002 (n=21), a Trial Steering Committee Meeting was held on December 19, 2017 to review safety and efficacy data to determine next steps. A recommendation was made by the committee to stop further enrolment into the second stage of the Phase II component of the study due to lack of efficacy as defined by protocol (≤ 1objective response). Final analyses are complete and final clinical study report is in progress, pending completion of central laboratory reports.

The Company continues to have insufficient cash resources to see the entire LDOS002 European Phase I/II clinical study in Poland through to completion. Given the Company's limited current cash resources and the possibility of not being able to obtain additional financing on a timely basis, the Company may be required to reduce, delay or cancel

one or more of its planned research and development programs, including clinical trials along with further reductions in overhead, any of which could impair the current and future value of the business.

#### *Phase II clinical study (“LDOS003”)*

A potential secondary yet unproven aspect of L-DOS47 action is the observation that an acidic pH microenvironment (< pH 6.8) may limit the effectiveness of weakly basic cytotoxic drugs employed in treatment of lung and other solid tumours. An acidic microenvironment is associated with protonation of these agents and decreased uptake and alkalisation can result in enhanced agent uptake and cytotoxicity. Furthermore, extracellular acidity may also inhibit the active transport of some drugs. This raises the possible application of L-DOS47 to combination cancer therapies with agents which have little or no overlapping toxicities.

This study is designed to determine the possible chemo-enhancing properties of L-DOS47. The possibility of combining L-DOS47 with a weakly basic agent like vinorelbine may improve therapeutic outcomes for cancer patients. The vinorelbine/cisplatin combination is used as a first-line treatment for lung adenocarcinoma.

The Company has initiated a Phase IIb, open-label, randomized study in male and female patients aged  $\geq 18$  years old with metastatic lung adenocarcinoma. The staging will be conducted according to Tumour Node Metastases (TNM), 8<sup>th</sup> Edition. In Part 1 of the study (Dose Escalation), patients will receive eight (8) doses of L-DOS47 over four (4) cycles. On Day 1 and Day 8 of each cycle, L-DOS47 (administered as an intravenous (“IV”) infusion) will be administered 24 hours before vinorelbine/cisplatin. Once the maximum tolerated dose of L-DOS47 as an adjunct to vinorelbine/cisplatin is determined, patients in Part 2 of the study (Randomized Treatment) will be randomly assigned to receive L-DOS47 in combination with vinorelbine/cisplatin or vinorelbine/cisplatin alone. Six (6) sites have been identified in Poland and the Ukraine to participate in Part 1. Initial Competent Authority approval was received for Ukraine in February 2018, and a further amendment approval was received in March 2018. Ethics approvals for three Ukraine sites are already in receipt since end of February 2018. Competent Authority and Ethics Committee approvals for three sites in Poland were received in April 2018. Site selection activities to add a third country, Hungary, to the randomized treatment part of the study were completed in March 2018. However, the Company has placed the LDOS003 study on hold since April 2018, with plans to re-start study activities in the near term.

The Company has insufficient supply of L-DOS47 to complete the LDOS003 study given all the other clinical study initiatives. As a result, the Company has plans to manufacture another batch of drug product in the next fiscal year to support the completion of the study and other planned studies. Completion of the study will depend on the successful release and availability of new drug product.

Due to the rapidly evolving treatment landscape and growing prominence of immunotherapies following the EMA approval of Keytruda®, along with the infrequent use of vinorelbine/cisplatin chemotherapy combination in the US, patient recruitment potential and relevance of data from this study may be limited.

#### *U.S. Phase I clinical study (“LDOS006”)*

Following a June 4, 2018 Scientific and Strategic Advisory Board (“SSAB”), the Company has begun early development of a Phase I/II study, L-DOS47 given in combination with doxorubicin, for the treatment of metastatic pancreatic cancer. Pancreatic cancer accounts for approximately 3% of all cancers in U.S. and for which there are currently few treatment options. Dr. Dan Von Hoff has been identified as Principal Investigator. An initial draft study protocol has been drafted and ongoing development continues.

Given the Company’s limited current cash resources and the possibility of not being able to obtain additional financing on a timely basis, the Company may be required to reduce, delay or cancel one or more of its planned research and development programs, including clinical trials along with further reductions in overhead, any of which could impair the current and future value of the business.

#### **Commercialization**

The Company’s DOS47 commercialization objective is to eventually enter into a strategic partnering alliance with a large pharmaceutical company, on an individual or multiple drug candidate basis, such as L-DOS47 or any potential new DOS47 drug product candidate. The Company has retained Deloitte Corporate Finance as its strategic advisor to explore partnering and licensing Opportunities in February. The intention of Company is to enter a structured process that will include preparing the Company to have discussions with potential partners, engaging in dialogue with a targeted group of qualified partners and licensees, and entering negotiations on a prospective partnership, alliance or licensing transaction. In the meantime, the Company will continue to gather as much value-adding clinical data/findings,

which demonstrate the safety and efficacy of L-DOS47 in patients or any other new potential DOS47 drug candidate so as to maximize value for shareholders when entering into a strategic partnering alliance.

### **Market and Competition**

Based on information published in “Key Statistics for Lung Cancer” by the American Cancer Society ([www.cancer.org](http://www.cancer.org)), lung cancer accounts for about one out of four of all cancer deaths and is by far the leading cause of cancer death among men and women in the U.S. It is estimated that in 2017 there will be over 222,500 new lung cancer cases.

If detected early, surgical removal of the cancerous tissue is currently a patient’s best option. However, in the vast majority of cases, the cancer is not typically identified until it has advanced to a level at which surgical intervention is no longer an option. In the cases of inoperable, locally advanced, recurrent or metastatic NSCLC and with no known targetable mutations, treatment strategies consist of one or more of today’s leading chemotherapeutic drug regimens for lung cancer (e.g. platinum therapy together with certain leading chemotherapeutic drugs). Typically, these regimens relieve symptoms and, at best, delay progression of the disease.

Disease progression, even with targeted therapies, is highly likely to occur, and there are no clear guidelines and/or indications once such therapies fail. Maintenance therapy following the induction of first-line therapy is also a treatment strategy gaining support.

Immunotherapies such as immune checkpoint inhibitors that target Programmed Death 1 (“PD-1”) or its ligands, Programmed Death Ligand 1 or 2 (“PD-L1” and “PD-L2”, respectively) are showing significant clinical successes in NSCLC. On March 4, 2015 the FDA approved Nivolumab, the generic name for the trade drug named Opdivo®, which targets PD-1 for the treatment of metastatic squamous NSCLC with progression on or after platinum-based chemotherapy. On October 2, 2015, the FDA granted accelerated approval for Pembrolizumab, the generic name for the trade drug named Keytruda®, which targets PD-1 to treat patients with advanced metastatic NSCLC whose disease has progressed after other treatments and with tumours that express PD-L1. Anti-PD-L1 drugs such as MPDL3280A from Roche are also advancing rapidly through late stage clinical trials.

In 2015, three randomized Phase III trials found the immune checkpoint inhibitors nivolumab and pembrolizumab to have superior efficacy and less toxicity compared with second-line docetaxel chemotherapy in patients with NSCLC. For the first time, agents blocking a single pathway have shown significant benefit across multiple tumour types, with US Food and Drug Administration (FDA) approval in NSCLC, melanoma, and bladder and renal cell carcinoma. Now more than 1,000 immune checkpoint clinical trials are underway. Many possible treatment avenues are being explored with immune checkpoint inhibitors, including combinations with radiation, chemotherapy, targeted therapy, and other checkpoint inhibitors. Some studies are also investigating checkpoint inhibitors as front-line therapy.

As of March 2017, the FDA had approved five checkpoint inhibitor drugs: ipilimumab (Yervoy®), pembrolizumab (Keytruda®), nivolumab (Opdivo®), atezolizumab (Tecentriq®) and avelumab (Bavencio®).

On May 10, 2017, the FDA granted accelerated approval to pembrolizumab (KEYTRUDA®, Merck and Co., Inc.) in combination with pemetrexed and carboplatin for the treatment of patients with previously untreated metastatic non-squamous non-small cell lung cancer (NSCLC). Approval was based on a cohort (G1) of patients enrolled in an open-label, multicenter, multi-cohort study (KEYNOTE-021). As a result of these developments in the treatment of NSCLC, the Company is currently reassessing its L-DOS47 clinical program given that: (a) its target therapeutic indication, being inoperable, locally-advanced, recurrent or metastatic NSCLC, may be a good candidate to combine with the emerging best-in-class immunotherapies; and (b) leading therapeutics for such oncology applications have commonly been high revenue generators for the pharmaceutical sector. The FDA recently approval pembrolizumab (Keytruda®) as first line treatment for NSCLC with PD-L1 >1%, either as first line or in combination with carboplatin/pemetrexed. Consequently, there is an urgent need for data to demonstrate safety of LDOS47 in combination with accepted standard chemotherapies, and also in combination with immunotherapies that are being offered with growing frequency.

Technological competition from pharmaceutical companies, biotechnology companies and university researchers is intense and is expected to continue to be very intense. Many competitors and potential competitors have substantially greater product development capabilities and financial, scientific, marketing and human resources than the Company, providing them with a competitive advantage over the Company.

### **The Biphaxis™ Topical Formulation System**

The Biphaxis™ Topical Formulation System is a platform technology which the Company acquired and further developed for microencapsulating therapeutic compounds in multilayered, lipid-based microvesicles. These microvesicles have complex structures that include a variety of compartments into which drug molecules can be

integrated. The principal application of the technology is in the preparation of topical dosage forms for the dermal (into the skin) or mucosal (into the mucosal tissues) delivery of large molecular weight drug compounds.

#### *Topical Interferon Alpha-2b*

The Company received investigational new drug (“IND”) approval by the FDA to conduct a U.S. Phase II/III clinical trial of Topical Interferon Alpha-2b in low-grade cervical dysplasia patients, as well as Clinical Trial Application (“CTA”) approval by the Bundesinstitut für Arzneimittel und Medizinprodukte and conditional CTA approval by the Medicines and Healthcare Regulatory Authority to conduct an identical European Phase III confirmatory trial in Germany and/or the United Kingdom, respectively.

Due to a lack of funding, a decision was made by the Company in fiscal 2012 to downsize and eventually close the Saskatoon laboratory which supported the Topical Interferon Alpha-2b drug development program and focus any ongoing activities to sourcing and qualifying alternative interferon alpha-2b raw material samples, and finding suitable strategic partner(s) who would be willing to license or acquire the product and support the remaining development costs through to commercial launch. In 2016, the Company ceased all activities related to Topical Interferon Alpha-2b, other than maintaining existing intellectual property associated with Topical Interferon Alpha-2b.

On December 23, 2016, the Company announced, it signed an exclusive out-license agreement with Xisle for the Company's late-stage, Biphasix™ technology platform, including the lead product candidate, interferon alpha. Xisle is responsible for the continued clinical development and subsequent commercialization of the product for the treatment of HPV-induced, low-grade, cervical intraepithelial lesions. As part of its asset development strategy, Xisle has initiated collaboration with senior pharmaceutical executives at Altum Pharmaceuticals Inc., who possess regulatory, clinical, and product development expertise. Under the terms of the agreement, Xisle paid an up-front fee of \$125,000 USD and agreed to pay subsequent milestone payments as they advance the technology to registration and market approvals and royalties. As part of the agreement, Helix retains marketing rights for Belarus, Bulgaria, Czech Republic, former Eastern Germany, Hungary, Moldova, Poland, Romania, Russia, Slovakia and Ukraine. In addition, the Company also retains non-exclusive rights for co-promotion in Canada.

The Company subsequently assigned the marketing rights which it retained to HIO, its wholly-owned subsidiary in Poland pursuant to an agreement between the Company and HIO with the agreement being subject to the restrictions and limitations associated with the out-license agreement signed between the Company and Xisle. In addition, HIO will be responsible for commercialization with milestone and royalty payments to be paid back to the Company upon successful product development through to commercialization.

### **REVENUE GENERATING ACTIVITIES**

Since the disposition of the Company's distribution business in Canada on January 25, 2013, the Company no longer has any revenue generating activities.

#### ***Royalty and in-licensing commitments***

##### *Agreements with National Research Council*

Helix announced on May 2, 2005 that it had begun to develop its lung cancer-specific drug compound L-DOS47. For this purpose, Helix entered into a worldwide exclusive license with the NRC, through which it obtained the right to combine an antibody that binds to NSCLC cells, and predominantly those of the adenocarcinoma type with minimal cross reactivity to other tissues with Helix's DOS47 technology. Unless earlier terminated pursuant to the license agreement, the license terminates when the last patent right related to the licensed technology expires, on a country-by-country basis. The Company is required to pay a royalty of 3% of net sales, with a minimum royalty of \$10,000 per year. The Company is also required to make certain milestone payments as follows: \$25,000 upon successful completion of Phase I clinical trials; \$50,000 upon successful completion of Phase IIb clinical trials; \$125,000 upon successful completion of Phase III clinical trials; and \$200,000 upon receipt of market approval by a regulatory authority. The license was subsequently amended to include an additional patent application which the Company is no longer pursuing. Patent applications in respect of the antibody originally licensed have been filed in Canada, the United States, and other countries. As announced on March 2, 2011, the NRC was issued a U.S. patent in respect of this antibody.

As part of the Company's transformation to an immune-oncology company, the Company has actively pursued additional new antibody based technologies for cell-based therapies. As a result, the Company in-licensed anti-CEACAM6 single domain antibody 2A3 from the NRC. Pursuant to this agreement dated September 22, 2016 with the NRC, the Company is required to pay a royalty of 3% of net sales, with a minimum royalty of \$10,000 per annum generated from the use of a certain antibody to target cancerous tissues of the lung. In addition to the royalty payments,

the Company is also required to make certain milestone payments for the first licensed product: \$25,000 upon successful completion of Phase I clinical trials; \$50,000 upon successful completion of Phase IIb clinical trials; \$150,000 upon successful completion of Phase III clinical trials; \$200,000 upon receipt of first regulatory approval by a regulatory authority; and \$200,000 upon receipt of a second regulatory approval by a regulatory authority. For the development of each subsequent licensed product: \$200,000 upon receipt of first regulatory approval by a regulatory authority; and \$200,000 upon receipt of a second regulatory approval by a regulatory authority. As it relates to sub-licensing arrangement, the Company is required to pay the NRC 33% of any sub-licensing revenues received.

## **PHARMACEUTICAL REGULATORY ENVIRONMENT**

### *New drug development*

Helix conducts drug development within a highly regulated environment. Regional and country-specific laws and regulations define the data required to show safety and efficacy of pharmaceutical products, and govern testing, approval, manufacturing, labeling and marketing of drugs. These regulatory requirements are a major factor in determining whether a marketable product is successfully developed and the amount of time and expense associated with each development process.

A pharmaceutical company launches a new prescription or non-prescription drug, whether innovative (original) or a generic version of a known drug, must demonstrate to the applicable regulatory authority, such as the FDA in the United States and Health Canada in Canada, that the drug is both effective and safe. The regulatory process for new drug approvals in the United States, Canada and Europe are among the most rigorous in the world, and many other jurisdictions follow a similar process. This regulatory process generally comprises the following stages described below.

In general, a potential new drug must first undergo pre-clinical testing in the laboratory (“*in vitro* studies”) and in animal models of the targeted disease or condition (“*in vivo* studies”) before being evaluated in humans (“clinical studies”). Pre-clinical studies primarily involve *in vitro* evaluations of the therapeutic activity of the drug and *in vivo* evaluations of the pharmacokinetic, metabolic and toxic effects of the drug in selected animal models.

Based on data generated during pre-clinical studies, extrapolations will be made to evaluate the potential risks versus the potential benefits of use of the drug candidate in humans under specific conditions of use. Upon successful completion of the pre-clinical studies, the drug candidate will undergo a series of evaluations in humans, including healthy volunteers and/or patients with the targeted disease or condition.

Before undertaking clinical studies, the pharmaceutical company sponsoring the new drug must submit to the Applicable Regulatory Authority an IND submission (in the United States), a CTA (in most European countries) or the equivalent in other jurisdictions. The application must contain specific, specified, information which generally includes the results of the pre-clinical tests completed up to the time of the application. Since the method of manufacture of a particular drug may affect the efficacy and safety of that drug, information on manufacturing methods and standards and the stability of the drug candidate and dosage form must also generally be presented.

The activities which are typically completed prior to obtaining approval for marketing and sale are typically as follows:

- Pre-clinical studies: Conducted using laboratory *in vitro* testing and testing in animal models of the targeted disease or condition to gain data on the efficacy and metabolism of the therapeutic as well as to identify potential safety issues.
- Filing of an IND, CTA or equivalent: The pre-clinical results are submitted to the Applicable Regulatory Authority for approval prior to testing in humans.
- Phase I Trials: Studies are conducted on a small number of human subjects to assess safety and the patterns of drug distribution and metabolism in the body. Normally, the initial human testing is conducted on healthy volunteers. In some cases, Phase I trials will also include patients having the targeted disease or condition: these trials are referred to as Phase I/II trials and may show efficacy results typically obtained in Phase II studies. Upon the completion of Phase I, and every phase thereafter, the drug sponsor must submit the results of such phase to, and obtain approval from, the Applicable Regulatory Authority before proceeding to the next phase of the clinical trial.
- Phase II Trials: Studies are conducted on groups of patients with the targeted disease or condition in order to develop efficacy, dosages and additional safety data. Typically, a Phase IIa trial uses escalating dose groups and a Phase IIb trial uses a specific dosage with a larger number of patients than a Phase IIa trial and adds a placebo arm to the trial.



- Phase III Trials: Large, multi-center, well-controlled studies are conducted on patients having the targeted disease or condition in order to provide statistically relevant proof of efficacy and safety of the therapeutic. Phase II/III trials refer to a combined trial where efficacy and safety are demonstrated.

Following Phase III, the drug sponsor submits a Marketing Authorization Application or equivalent to the Applicable Regulatory Authority for marketing approval. The application typically includes the results of the preclinical and clinical testing, together with manufacturing and controls information. The application is reviewed by the Applicable Regulatory Authority, and if approved, the drug is authorized for sale in the given country or jurisdiction.

#### *Additional government regulation*

In addition to the governmental approvals required in connection with the development of new drugs, governmental regulation in each applicable country or jurisdiction generally regulates research and laboratory procedures (including experimental testing on animals and disposal of potential or actual hazardous materials), clinical studies, manufacturing procedures, marketing, advertising and distribution methods, and industry sponsored scientific and educational activities, all of which significantly increases the level of difficulty and the costs involved in obtaining and maintaining the regulatory approval for marketing new and existing products.

Moreover, once the drug is approved for the market, the Applicable Regulatory Authority may impose restrictions on the marketing and sale of the product, including seizure or recall of the product and suspension or withdrawal of approval, if pre-marketing or post-marketing regulatory standards are not complied with or if there are problems with the product after it reaches the market. The Applicable Regulatory Authority may also require post-marketing studies to monitor the effect of an approved drug, and may impose restrictions on the marketing and sale of such drug based on the results of such studies.

## **INTELLECTUAL PROPERTY**

Patents and other proprietary rights are very valuable to the Company, even though the patent positions of biotechnology companies may be uncertain and involve complex legal and factual issues. The Company has no assurance that any of its patent applications will result in the issuance of any patents. Even issued patents may not provide the Company with a competitive advantage against competitors with similar technologies, or who have designed around the Company's patents. Furthermore, the Company's patents may be struck down if challenged. Intellectual property laws do not protect intellectual property to the same extent from one country to another.

Because of the substantial length of time and expense associated with developing new products, the pharmaceutical, medical device, and biotechnology industries place considerable importance on obtaining patent protection for new technologies, products, and processes. The Company's policy is to file patent applications to protect inventions, technology, and improvements that are important to the development of our business and with respect to the application of our products and technologies to the treatment of a number of disease indications. The Company's policy also includes regular reviews related to the development of each technology and product in light of its intellectual property protection, with the goal of protecting all key research and developments by patent.

The Company seeks intellectual property protection in various jurisdictions around the world and owns patents and patent applications relating to products and technologies in the United States, Canada, Europe and other jurisdictions. The scope and duration of our intellectual property rights vary from country to country depending on the nature and extent of our intellectual property filings, the applicable statutory provisions governing the intellectual property, and the nature and extent of our legal rights. The Company will continue to seek intellectual property protection as appropriate and require our employees, consultants, outside scientific collaborators, and sponsored researchers to enter into confidentiality agreements with us that contain assignment of invention clauses outlining ownership of any intellectual property developed during the course of the individual's relationship with us.

### ***Tumor Defense Breaker™***

On September 29, 2016 the Company filed a Canadian Trade Mark Application for "TUMOR DEFENSE BREAKER". It is planned to expand this trademark in all major markets and territories where will aim to market the products once they receive marketing approval by appropriate regulatory authorities. On May 1, 2017, the Company was notified that the trade mark application had been approved. A similar application was made in Europe which was not accepted and the Company is assessing whether it will appeal this decision.

### ***DOS47, L-DOS47 and V-DOS47***

The Company currently owns two U.S. patents in respect of the DOS47 technology, and also has also licensed patent rights from the NRC for the antibody component of L-DOS47. With respect to non-U.S. patents, the Company owns 52 DOS47 related patents in other jurisdictions with a number of patent applications in countries around the world. The Company has recently filed a joint patent application in the U.S. with Amorfix to cover the antibody-DOS47 conjugates derived from their collaboration. A new U.S. patent application to cover new features of the DOS47 technology was filed by the Company during fiscal 2013. During January 2015, an additional U.S. patent application covering specific L-DOS47 manufacturing and novel features was filed. 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. In addition, two US patents covering anti-VEGFR2 antibodies and their use in DOS47 conjugates (V-DOS4) were filed.

### ***Cell Based Therapy***

The company has recently filed a joint patent application with NRC to protect the use of an antibody for use in cell-based therapies. In addition, the company has also filed new patent application covering the use of anti-VEGFR2 antibodies in cell-based therapy in July 2017. The Company is currently in discussion with third parties to license additional intellectual properties to strengthen the company's portfolio.

### ***Biphaxis™***

The Company, until recently, owned six U.S. Biphaxis™ patents.

On December 23, 2016, the Company announced, it signed an exclusive out-license agreement with Xisle for the Company's late-stage, Biphaxis™ technology platform, including the lead product candidate, interferon alpha. Xisle is responsible for the continued clinical development and subsequent commercialization of the product for the treatment of HPV-induced, low-grade, cervical intraepithelial lesions. As part of its asset development strategy, Xisle has initiated collaboration with senior pharmaceutical executives at Altum Pharmaceuticals Inc., who possess regulatory, clinical, and product development expertise. Under the terms of the agreement, Xisle paid an up-front fee of \$125,000 USD and agreed to pay subsequent milestone payments as they advance the technology to registration and market approvals and royalties. As part of the agreement, Helix retains marketing rights for Belarus, Bulgaria, Czech Republic, former Eastern Germany, Hungary, Moldova, Poland, Romania, Russia, Slovakia and Ukraine. In addition, the Company also retains non-exclusive rights for co-promotion in Canada.

The Company subsequently assigned the foregoing marketing rights which it retained to HIO, its wholly -owned subsidiary in Poland pursuant to an agreement between the Company and HIO with the agreement being subject to the restrictions and limitations associated with the out-license agreement signed between the Company and Xisle. In addition, HIO will be responsible for commercialization with milestone and royalty payments to be paid back to the Company upon successful product development through to commercialization.

## **FACILITIES**

### ***General office space***

The Company's has a head office at 9120 Leslie Street, Suite 205, Richmond Hill, Ontario, Canada. The lease arrangement expires July 31, 2019.

The Company also leases a small office on a month to month basis in Saskatoon, Saskatchewan.

The Company's wholly-owned Polish subsidiary signed an office lease effective August 28, 2018. The 95.36 square meter office is located at Wojskowa Akademia Techniczna, Ul. Urbanowicza 2b, Warsaw, Poland. The lease does not specify any termination date but does provide for a three-month notice period by either party.

### ***Laboratories***

The Company leases approximately 4,155 sq. ft. in Edmonton, Alberta, Canada under a lease arrangement that originally expired on June 30, 2014. The Company successfully amended the lease terms to expire December 2014 and has since renewed the lease on a month-to-month basis. These premises house the Company's oncology research laboratory.

The Company's wholly-owned Polish subsidiary leases a 61.5 square meter laboratory at the Warszawski Uniwersytet Medyczny, Ul. S. Banacha 1b, Warsaw, Poland ("MUW"). The lease was entered into on February 26, 2018. The lease does not specify any termination date but does provide for a three-month notice period by either party.

### **Manufacturing**

The Company has no manufacturing capacity.

### **EMPLOYEES**

The following table depicts the number of full-time equivalent employees as at July 31:

	Canada		Poland	
	2018	2017	2018	2017
Research and development	7.0	8.0	7.5	9.0
Operating, general and administration	2.5	1.5	5.0	4.0
	9.5	9.5	12.5	13.0

None of the Company's employees are covered by collective bargaining agreements.

## **RISK FACTORS**

### **RISKS AND UNCERTAINTIES**

Helix is subject to risks, events and uncertainties, or "risk factors", associated with being both a publicly traded company operating in the biopharmaceutical industry, and as an enterprise with several projects in the research and development stage. As a result of these risk factors, reported information and forward-looking information may not necessarily be indicative of future operating results or of future financial position, and actual results may vary from the forward-looking information or reported information. The Company cannot predict all of the risk factors, nor can it assess the impact, if any, of such risk factors on the Company's business or the extent to which any factor, or combination of factors, may cause future results or financial position to differ materially from either those reported or those projected in any forward-looking information. Accordingly, reported financial information and forward-looking information should not be relied upon as a prediction of future actual results. Some of the risks and uncertainties affecting the Company, its business, operations and results which could cause actual results to differ materially from those reported or from forward-looking information include, either wholly or in part, those described elsewhere in this AIF, as well as the following:

#### ***The Company does not have any source of operating income and is dependent solely on outside sources of financing***

The Company's operations consist of research and development activities, which do not generate any revenue. Accordingly, the Company has no source of revenue, positive operating cash flow or operating earnings to subsidize its ongoing research and development and other operating activities and the ability of the Company to continue as a going concern is dependent upon the Company's ability to rely on cash on hand, and on outside sources of financing to fund its ongoing research and development and other operating activities. Such sources of financing involve risks, including that the Company will not be able to raise such financing on terms satisfactory to the Company or at all, and that any additional equity financing, if secured, would result in dilution to existing shareholders, and that such dilution may be significant. While the Company has been able to raise equity financing in recent years, there can be no assurance that additional funding by way of equity financing will continue to be available. Any additional equity financing, if secured, would result in dilution to the existing shareholders and such dilution may be significant. The Company may also seek additional funding from or through other sources, including technology licensing, co-development collaborations, mergers and acquisitions, joint ventures, and other strategic alliances, which, if obtained, may reduce the Company's interest in its projects or products or result in significant dilution to existing shareholders. The Company may also seek additional funding from government grants. There can be no assurance, however, that any alternative sources of funding will be available. The failure of the Company to obtain additional financing on a timely basis may result in the Company reducing, delaying or cancelling one or more of its planned research, development and/or marketing programs, including clinical trials, further reducing overhead, or monetizing non-core assets, any of which could impair the current and future value of the business or cause the Company to consider ceasing operations and undergoing liquidation. Given the Company's conclusion about the insufficiency of its cash reserves, significant doubt may be cast about the Company's ability to continue operating as a going concern. The continuation of the Company as a going

concern for the foreseeable future depends mainly on raising sufficient capital, and in the interim, reducing, where possible, operating expenses (including making changes to the Company's research and development plans), including the delay of one or more of the Company's research and development programs, further reducing overhead and the possible disposition of assets.

***The Company has a history of losses and expects to continue to incur additional losses for the foreseeable future***

The Company's primary focus continues to be on its research and development of pharmaceutical product candidates. The research and development of pharmaceutical products requires the expenditure of significant amounts of cash over a relatively long-time period. The Company expects to continue to incur losses from continuing operations, for the foreseeable future. The Company's cumulative deficit as at July 31, 2018 is \$164,005,000. There can be no assurance that the Company will record earnings in the future.

***The Company requires additional funding***

The Company's cash reserves will not be sufficient for the Company to fully fund its existing European Phase I/II clinical trial with L-DOS47 in Poland or its U.S. Phase I trial or any of the Company's other ongoing research and development, operating activities, working capital or capital expenditures for the next twelve months.

The Company has no sources of external liquidity, such as a bank loan or line of credit. The Company will therefore continue to rely on equity financing to fund its ongoing research and development activities and other expenses for the foreseeable future.

Equity financing has historically been the Company's primary source of funding; however, the market for equity financings for companies such as the Company is challenging. While the Company has been able to raise equity financing in recent years, there can be no assurance that additional funding by way of equity financing will continue to be available. Any additional equity financing, if secured, would result in dilution to the existing shareholders which may be significant. The Company may also seek additional funding from or through other sources, including grants, technology licensing, co-development collaborations, disposition of assets, mergers and acquisitions, joint ventures, and other strategic alliances, which, if obtained, may reduce the Company's interest in its projects or products or result in significant dilution to existing shareholders. There can be no assurance, however, that any alternative sources of funding will be available.

The failure of the Company to obtain additional financing on a timely basis may result in the Company reducing, delaying or cancelling one or more of its planned research and development, including any clinical trials, further reducing overhead, or monetizing non-core assets, any of which could impair the current and future value of the business or cause the Company to consider ceasing operations and undergoing liquidation.

***The Company faces risks in connection with competition and technological change;***

The biotechnology and pharmaceutical industries are subject to rapid and substantial technological change. Technological competition from pharmaceutical companies, biotechnology companies and university researchers is intense and is expected to continue to be intense.

The rapid advancement of immunotherapies now has the potential to significantly change the treatment of cancer and may result in a reduction, which may be significant, in the potential patient population and/or treatment protocols available to chemotherapies and other treatments currently in development, such as the Company's primary drug product candidate, L-DOS47. Furthermore, developments in immunotherapies may require the Company to reposition its L-DOS47 drug product candidate from a front-line monotherapy to a combination therapy with immunotherapies or other treatment protocols, and any such repositioning, would likely result in additional expenses being incurred by the Company and in delays in the anticipated development timeline for L-DOS47, or in the Company determining that its L-DOS47 drug product candidate is no longer viable.

The Company cell-based therapies initiative may face significant hurdles. The Company's effort is mainly at research proof-of-concept stage. It is possible that the selected targets or choice of antibodies are not optimal. This can delay the initiation of formal preclinical and clinical development significantly. The Company has chosen to develop cell-based therapy for solid tumour. While there are many successful examples of cell-based therapy treatment in hematological malignancies, similar success in solid tumour is less certain.

Many of the Company's competitors have substantially greater financial, technical and human resources and significantly greater experience in conducting preclinical testing and human clinical trials of product candidates, scaling up manufacturing operations and obtaining regulatory approvals of products. Accordingly, the Company's varying competitors may succeed in obtaining regulatory approval for products more rapidly. The Company's ability to compete successfully will largely depend on:

- the efficacy and safety profile of our product candidates relative to marketed products and other product candidates in development;
- our ability to develop and maintain a competitive position in the product categories and technologies on which we focus;
- the time it takes for our product candidates to complete clinical development and receive marketing approval;
- our ability to obtain required regulatory approvals;
- our ability to commercialize any of our product candidates that receive regulatory approval;
- our ability to establish, maintain and protect intellectual property rights related to our product candidates; and
- acceptance of any of our product candidates that receive regulatory approval by physicians and other healthcare providers and payers.

Competitors have developed and may develop technologies that could be the basis for products that challenge the differentiated nature and potential for best-in-class product development programs and discovery research capabilities of the DOS47 platform technology. Some of those products may have an entirely different approach or means of accomplishing the desired therapeutic effect than our product candidates and may be more effective or less costly than our product candidates. The success of our competitors and their products and technologies relative to our technological capabilities and competitiveness could have a material adverse effect on the future preclinical studies and clinical trials of our product candidates, including our ability to obtain the necessary regulatory approvals for the conduct of such clinical trials. This may further negatively impact our ability to generate future product development programs with improved pharmacological properties.

If we are not able to compete effectively against our current and future competitors, our business will not grow and our financial condition and operations will substantially suffer.

***The Company is conducting early stage research and development initiatives for products under development which may not be accepted by the market and may never generate revenue and the Company has limited sales, marketing and distribution experience***

The Company is conducting early stage research and development initiatives and is currently in the process of developing new products that require further time consuming and costly research and development. It will be a number of years, if ever, before its products in development begin to generate revenues, if at all. There can be no assurance that any of the drug product candidates will ever be successfully developed or commercialized.

Even with regulatory approval, the Company may not achieve market acceptance, which depends on a number of factors, including the establishment and demonstration in the medical community of the clinical utility of the Company's products, and their potential advantage over alternative treatment methods. There is also the risk that the actual market size or opportunity for the Company's drug candidates is not certain. Failure to gain market acceptance of either of the Company's products currently under development or an incorrect estimate in the nature and size of their respective markets could have a material adverse effect on the Company.

The Company has limited sales, marketing and distribution experience, and there is no assurance that the Company will be able to establish adequate sales, marketing, and distribution capabilities or make arrangements with any collaborators, strategic partners, licensees, or others to perform such activities, or that such efforts will be successful. The Company's objective for its drug candidate products is to enter into strategic alliances with appropriate pharmaceutical partners. There can be no assurance that any such strategic alliance will be maintained or achieved, or if achieved, that it will result in revenue to the Company.

***The timing of the Company's internal goals and projected timelines may not be met***

The Company sets internal goals for and makes public statements regarding its expected timing of meeting the objectives material to its success, including the commencement, duration and completion of clinical trials and anticipated regulatory approvals. The actual timing of these forward-looking events can vary dramatically

due to a number of factors, including, without limitation, delays in scaling-up of drug product candidates, delays or failures in clinical trials, additional data requirements from the regulators, the Company failing to obtain required financing, and other risks referred to herein. Without limiting the generality of the foregoing, it is possible that required regulatory approvals may be delayed or denied, including those related to undertaking or continuing clinical trials, manufacturing of drug products, and marketing such products.

The Company has expressed certain estimated timelines for its European Phase I/II clinical trials for L-DOS47 in Poland, the U.S. Phase I study. The timeline for the European Phase I/II trials and any future timelines are contingent on the Company having adequate financing to complete the trials and the assumption that the trials will be completed according to the current schedules. A failure to obtain necessary financing or a change in the schedule of the trials (which may occur if certain cost-deferral measures are taken, or due to factors beyond the Company's reasonable control, such as scheduling conflicts, the occurrence of serious adverse events, interruption of supplies of study drugs, withdrawals of regulatory approvals, or slow patient recruitment) could delay their commencement or completion, or result in their suspension or early termination, which could have a material adverse effect on the Company.

***The Company faces intellectual property risks, including the loss of patent protection, the potential termination of licences, the inability to protect proprietary property, and possible claims of infringement against the Company or against a third-party from whom the Company licenses intellectual property***

The Company's success depends, in part, on its ability to secure and protect its intellectual property rights and to operate without infringing on the proprietary rights of others or having third parties circumvent the rights owned or licensed by the Company. However, the Company cannot predict the enforceability of its patents or its ability to maintain trade secrets that may not be protected by patents. Patent risks include the fact that patent applications may not result in issued patents, issued patents may be circumvented, challenged, invalidated or insufficiently broad to protect the Company's products and technologies; blocking patents by third parties could prevent the Company from using its patented technology; it may be difficult to enforce patent rights, particularly in countries that do not have adequate legal enforcement mechanisms, and enforcing such rights may divert management attention and may cause the Company to incur significant expenses; and any expiry of an issued patent may negatively impact the underlying technology.

To protect its trade secrets, the Company enters into confidentiality undertakings with parties that have access to them, such as the Company's current and prospective distributors, collaborators, employees and consultants, but a party may breach the undertakings and disclose the Company's confidential information or competitors might learn of the information in some other way, which could have a material adverse effect on the Company.

The Company uses processes, technology, products, or information, the rights to certain of which are owned by others, such as a license from the NRC of the lung antibody used by the Company for L-DOS47. Termination or expiry of any licenses or rights during critical periods, and an inability to obtain them on commercially favourable terms or at all could have a material adverse effect on the Company and its drug candidates' development.

The Company operates in an industry that experiences substantial litigation involving the manufacture, use and sale of new products that are the subject of conflicting proprietary rights. The Company or one or more of its licensors may be subject to a claim of infringement of proprietary rights by a third party. It is possible that the Company's products and technologies do infringe the rights of third parties, and the Company or such licensor could incur significant expenses, and diversion of management attention, in defending allegations of infringement of proprietary rights, even if there is no infringement. Furthermore, the Company or such licensors may be required to modify its products or obtain licenses for intellectual property rights as a result of any alleged proprietary infringement. The inability to modify products or obtain licenses on commercially reasonable terms, in a timely manner or at all, could adversely affect the Company's business.

***The Company faces research and development risks, including the need to prove the Company's drug candidates are safe and effective in clinical trials***

The Company's drug candidates are complex compounds and the Company faces difficult challenges in connection with the manufacture of clinical batches of each of them, which could further delay or otherwise negatively affect the Company's planned clinical trials, or required regulatory approvals.

There is also the risk that the Company could obtain negative findings or factors that may become apparent during the course of research or development. The results from preclinical and clinical trials may not be

predictive of results obtained in any ongoing or future clinical trials. A number of companies in the biotechnology and pharmaceutical industry have suffered significant setbacks in advanced clinical trials, even after achieving promising results in earlier trials and pre-clinical trials.

The timing and success of the Company's clinical trials also depend on a number of other factors, including, but not limited to: (a) obtaining additional financing, which is not assured; (b) sufficient patient enrolment, which may be affected by the incidence of the disease studied, the size of the patient population, the nature of the protocol, the proximity of patients to clinical sites, the eligibility criteria for a patient to participate in the study and the rate of patient drop-out; (c) regulatory agency policies regarding requirements for approval of a drug, including granting permission to undertake proposed human testing; (d) the Company's capacity to produce sufficient quantities and qualities of clinical trial materials to meet the trial schedule; (e) performance by third parties, on whom the Company relies to carry out its clinical trials; and (f) the approval of protocols and/or protocol amendments.

Clinical trials are complex, expensive and uncertain, and have a high risk of failure, which can occur at any stage. Data obtained from pre-clinical and clinical trials may be interpreted in different ways, or be incorrectly reported, which could delay or prevent further development of the drug candidate studied. Failure to complete clinical trials successfully and to obtain successful results on a timely basis could have a material adverse effect on the Company.

Even if the Company's drug candidates successfully complete the clinical trials and receive the regulatory approval necessary to market the drug candidates to the public, there is also the risk of unknown side effects, which may not appear until the drug candidates are on the market and may result in delay or denial of regulatory approval or withdrawal of previous approvals, product recalls or other adverse events, which could materially adversely affect the Company.

While the Company continues to explore opportunities to expand its drug product pipeline with new DOS47-based therapeutics pending the identification of further tumour targeting agents, there can be no assurance that any such tumour targeting agents will be identified or that any new DOS47-based therapeutics will be developed.

***Difficulty in enrolling patients in the Company's clinical trials, could result in delays or cancellation of clinical trials***

As the Company's product candidates advance from preclinical testing to clinical testing, and then through progressively larger and more complex clinical trials, the Company will need to enroll an increasing number of patients that meet various eligibility criteria. There is significant competition for recruiting cancer patients in clinical trials, and the Company may not be unable to enroll the patients it needs to complete clinical trials on a timely basis or at all. The factors that affect the Company's ability to enroll patients is largely uncontrollable and include, but are not limited to, the following:

- size and nature of the patient population;
- eligibility and exclusion criteria for the trial;
- design of the study protocol;
- competition with other companies for clinical sites or patients;
- the perceived risks and benefits of the product candidate under study;
- the patient referral practices of physicians; and
- the number, availability, location and accessibility of clinical trial sites.

***The Company is dependent on a number of third parties and the failure or delay in the performance of one of these third parties' obligations may adversely affect the Company***

The Company is dependent on third parties to varying degrees in virtually all aspects of its business, including without limitation, on contract research organizations, contract manufacturing organizations, clinical trial consultants, raw material suppliers, collaborative research consultants, regulatory affairs advisers, medical and scientific advisors, clinical trial investigators, business service providers and other third parties. Critical supplies may not be available from third parties on acceptable terms, or at all, including GMP grade materials. Service providers may not perform, or continue to perform, as needed, or be available to provide the required services on acceptable terms or at all. Any lack of or interruption in supplies of raw materials or services, or any change in supply or service providers or any inability to secure new supply or service providers, would have an adverse impact on the development and commercialization of the Company's products. For example, the Company has previously experienced delays in the manufacturing of both engineering and clinical batches

of L-DOS47, which have in turn caused delays in the progression of its development program, and there may be further delays. The Company relies on a third party for its supply of urease and if the contract with the third-party urease supplier is terminated early, the Company will have to find a new supplier of urease, as well as a new manufacturer of bulk drug product for future clinical testing programs. There can be no assurance that a new supplier or manufacturer can be contracted in a timely manner or at all, and this could negatively impact the Company's development plans for L-DOS47.

With respect to L-DOS47, the Company is currently dependent on, in addition to third party suppliers, manufacturers and consultants, the NRC and its license to the Company of a lung cancer antibody in order to develop and commercialize L-DOS47. Early termination of the license with NRC would have a material adverse effect on the further development of L-DOS47 and may require the cessation of such development, which would have a material adverse effect on the Company.

Given the Company's lack of financing, expertise, infrastructure and other resources to support a new drug product from clinical development to marketing, the Company also requires strategic partner support to develop and commercialize its drug candidates. There can be no assurance that such strategic partner support will be obtained upon acceptable terms or at all.

The Company relies heavily on contract manufacturers for the production of product required for its clinical trials, product formulation work, scaling-up experiments and commercial production. The Company may not be able to obtain new, or keep its current, contract manufacturers to provide these services. Even if the Company does, contract manufacturers may not be reliable in meeting its requirements for cost, quality, quantity or schedule, or the requirements of any regulatory agencies. The Company may not be able to manufacture products in quantities or qualities that would enable the Company to meet its business objectives, and failure to do so would materially adversely affect the Company's business.

If the Company can successfully develop markets for its products, the Company would have to arrange for their scaled-up manufacture. There can be no assurance that the Company will, on a timely basis, be able to make the transition from manufacturing clinical trial quantities to commercial production quantities successfully or be able to arrange for scaled-up commercial contract manufacturing. Any potential difficulties experienced by the Company in manufacturing scale-up, including recalls or safety alerts, could have a material adverse effect on the Company's business, financial condition, and results of operations.

***The marketability of the Company's products may be affected by delays and the inability to obtain necessary approvals, and following any market approval, the Company's products will be subject to ongoing regulatory review and requirements which may continue to affect their marketability, including but not limited to regulatory review of drug pricing, healthcare reforms or the payment and reimbursement policies for drugs by the various insurers and other payors in the industry***

The research, development, manufacture and marketing of pharmaceutical products are subject to regulation by the FDA, and comparable regulatory authorities in other countries. These agencies and others regulate the testing, manufacture, safety and promotion of the Company's products. The Company must receive applicable regulatory approval of a product candidate before it can be commercialized in any particular jurisdiction. Approval by a regulatory authority of one country does not ensure the approval by regulatory authorities of other countries. Changes in regulatory approval policies or regulations during the development period may cause delays in the approval or rejection of an application. Regulatory authorities have substantial discretion in the approval process and may refuse to accept any application, or may decide that our data are insufficient for approval, or require additional preclinical, clinical or other trials and place the Company's IND submissions on hold for an indeterminate amount of time. The development and regulatory approval process in each jurisdiction takes many years, requires the expenditure of substantial resources, is uncertain and subject to delays, and can adversely affect the successful development and commercialization of our drug candidates.

Even if the Company obtains marketing approval in a particular jurisdiction, there may be limits on the approval and the Company's products likely will be subject to ongoing regulatory review and regulatory requirements in that jurisdiction. Pharmaceutical companies are subject to various government regulations, including without limitation, requirements regarding occupational safety, laboratory practices, environmental protection and hazardous substance control, and may be subject to other present and future regulations.

The availability of reimbursement by governmental and other third-party payors, such as private insurance plans, will affect the market for any pharmaceutical product, and such payors tend to continually attempt to



contain or reduce the costs of healthcare. Significant uncertainty exists with respect to the reimbursement status of newly approved healthcare products.

***The Company operates in an industry that is more susceptible than others to legal proceedings and, in particular, liability claims***

The Company operates in an industry that is more susceptible to legal proceedings than firms in other industries, due to the uncertainty involved in the development of pharmaceuticals. Defense and prosecution of legal claims can be expensive and time consuming, and may adversely affect the Company regardless of the outcome due to the diversion of financial, management and other resources away from the Company's primary operations. Negative judgments against the Company, even if the Company is planning to appeal such a decision, or even a settlement in a case, could negatively affect the cash reserves of the Company, and could have a material negative effect on the development of its drug products.

The Company may be exposed, in particular, to liability claims which are uninsured or not sufficiently insured, and any claims may adversely affect the Company's ability to obtain insurance in the future or result in negative publicity regarding the efficacy of its drug products. Such liability insurance is expensive, its ability is limited and it may not be available on terms that are acceptable to the Company, if at all.

The use of any of the Company's unapproved products under development, the use of its products in clinical trials, and, if regulatory approval is received, the sale of such products, may expose the Company to liability claims which could materially adversely affect the Company's business. The Company may not be able to maintain or obtain commercially reasonable liability insurance for future products, and any claims under any insurance policies may adversely affect its ability to maintain existing policies or to obtain new insurance on existing or future products. Even with adequate insurance coverage, publicity associated with any such claim could adversely affect public opinion regarding the safety or efficacy of the Company's products. As a result, any product liability claim or recall, including in connection with products previously sold by the Company through its former distribution business, could materially adversely affect the Company's business.

***If the Company were unable to maintain product liability insurance required by third parties, the corresponding agreements would be subject to termination, which could have a material adverse impact on our operations.***

Some of our licensing and other agreements with third parties require or might require us to maintain product liability insurance. If the Company cannot maintain acceptable amounts of coverage on commercially reasonable terms in accordance with the terms set forth in these agreements, the corresponding agreements would be subject to termination, which could have a material adverse impact on the Company's operations.

***The Company is dependent upon key personnel; Director residency requirements***

The Company's ability to continue its development of potential products depends on its ability to attract and maintain qualified key individuals to serve in management and on the Board. However, the Company does not currently have a formal succession plan for members of its senior management team or for its Board and, because competition for qualified key individuals with experience relevant to the industry in which the Company operates is intense, the Company may not be able to attract and/or retain such personnel. Additionally, applicable corporate law requires that at least 25% of the Company's directors be resident Canadians, and the Company's articles provide that the Company cannot have fewer than five directors at any time.

Consequently, if the Company is unable to attract and/or loses and is unable to replace key personnel, its business could be negatively affected and, in particular, if the Company loses one or more of its three current resident Canadian directors in the future and is unable to find a sufficient number of resident Canadian directors to fill the resulting vacancy(ies), the Board will be prevented from taking any action other than appointing additional resident Canadian directors until such time as a sufficient number of new resident Canadian directors have been appointed such that at least 25% of the Company's directors are resident Canadians.

In addition, the Company does not carry key-man insurance on any individuals.

***The Company's employees and consultants may engage in misconduct or other improper activities, including non-compliance with regulatory standards and requirements, which could have a material adverse effect on the Company's business.***

The Company is exposed to the risk of employee and consultant fraud or other misconduct. Misconduct by employees and consultants could include, but are not limited to the following: failure to comply with regulators, failure to provide accurate information, failure to comply with manufacturing standards the Company has established, jurisdictional healthcare fraud and abuse of laws and regulations, failure to report financial information or data accurately or disclose unauthorized activities. For example, sales, marketing and business arrangements in the healthcare industry are subject to extensive laws and regulations intended to prevent fraud, kickbacks, self-dealing, and other abusive practices. These laws and regulations may restrict or prohibit a wide range of pricing, discounting, marketing and promotion, sales commission, customer incentive programs and other business arrangements. Employee and consultant misconduct could also involve the improper use of information obtained in the course of clinical trials, which could result in regulatory sanctions and serious harm to the Company's reputation. If any such actions are instituted against the Company, and the Company is not successful in defending itself or asserting its rights, those actions could have a substantial impact on the Company's business and operating results, including the imposition of substantial fines, halt in trading of the Company's common shares, possible delisting and/or other sanctions.

***Indemnification obligations to directors and officers of the Company may adversely affect the Company's finances***

The Company has entered into agreements pursuant to which the Company has agreed to indemnify its directors and senior management in respect of certain claims made against them while acting in their capacity as such. If the Company is called upon to perform its indemnity obligations, its finances may be adversely affected.

***The Company's finances may fluctuate based on foreign currency exchange rates***

The Company operates internationally and is exposed to foreign exchange risks from various currencies, primarily the U.S. dollar, the Euro and the Polish Zloty.

***Unanticipated changes in the Company's tax rates could affect its future results***

Since the Company operates in different countries and is subject to taxation in different jurisdictions, its future effective tax rates could be impacted by changes in such countries' tax laws or their interpretations. Both domestic and international tax laws are subject to change as a result of changes in fiscal policy, changes in legislation, evolution of regulation and court rulings. The application of these tax laws and related regulations is subject to legal and factual interpretation, judgment and uncertainty.

***Shareholders of the Company may face dilution through exercise of stock options, warrants and future equity financings***

To attract and retain key personnel, the Company has granted options to its key employees, directors and consultants to purchase common shares and share awards as non-cash incentives. In addition, the Company has a significant number of warrants to purchase common shares outstanding. The issuance of shares pursuant to share awards and the exercise of a significant number of such options and warrants may result in significant dilution of other shareholders of the Company.

As noted above, the Company needs additional funding and has historically turned to the equity markets to raise this funding. The future sale of equity and warrants may also result in significant dilution to the shareholders of the Company.

***The Company's share price and trading volumes are volatile and the Company may have difficulty maintaining listing requirements***

The price of the Company's common shares, as well as market prices for securities of biopharmaceutical and drug delivery companies generally, have historically been highly volatile, and have from time to time experienced significant price and volume fluctuations that are unrelated to the operating performance of particular companies.

The trading price of the Company's common shares is subject to change and could in the future fluctuate significantly. The fluctuations could be in response to numerous factors beyond the Company's control, including: quarterly variations in results of operations; announcements of technological innovations or new products by the Company, its customers or competitors; changes in securities analysts' recommendations; announcements of acquisitions; changes in earnings estimates made by independent analysts; general fluctuations in the stock market; or revenue and results of operations below the expectations of public market securities analysts or investors. Any of these could result in a sharp decline in the market price of the common shares.

The Internet offers various avenues for the dissemination of information. The Company has no control over the information that is distributed and discussed on electronic bulletin boards and investment chat rooms. The intention of the people or organizations that distribute such information may not be in the Company's best interest and the best interests of its shareholders. This, in addition to other forms of investment information including newsletters and research publications, could result in a sharp decline in the market price of the common shares.

In addition, stock markets have occasionally experienced extreme price and volume fluctuations. The market prices for high-technology companies have been particularly affected by these market fluctuations and such effects have often been unrelated to the operating performance of such companies. These broad market fluctuations may cause a decline in the market price of the common shares.

Sales of substantial numbers of the Company's common shares could cause a decline in the market price of such common shares. There are minimum listing requirements for an issuer to maintain its listing on the Toronto Stock Exchange ("TSX"), and if the Company fails to maintain these listing requirements, it may be involuntarily delisted from the TSX. De-listing the Company or the Company shares from any securities exchange could have a negative effect on the liquidity of the Company shares and/or the ability of a shareholder to trade in shares of the Company, and could have an adverse effect on the Company's ability to raise future equity financings. The Company's common shares trade in a very low volume compared to the number of common shares outstanding. This means a shareholder could have difficulty disposing of common shares, especially if there are other shareholders of the Company trying to sell their shares in the Company at the same time. Volatility in share price and trading volumes could have an adverse effect on the Company's ability to raise future equity financings.

***The requirements of being a public company may strain the Company's resources, divert management's attention and affect its ability to attract and retain qualified board members***

As a public company, the Company is subject to the reporting requirements of Canadian securities regulators, the listing requirements of the Exchange and other applicable securities rules and regulations. Compliance with these rules and regulations may increase the Company's legal and financial compliance costs, may make some activities more difficult, time-consuming or costly and may increase the demand on the Company's systems and resources. Being a public company requires that the Company file continuous disclosure documents, including, among other things, annual and quarterly financial statements. Management's attention may be diverted from other business concerns, which could have a material adverse effect on the Company's business, financial condition and results of operations. The Company may need to hire more employees in the future, which will increase its costs and expenses.

In addition, changing laws, regulations and standards relating to corporate governance and public disclosure create uncertainty for public companies, increasing legal and financial compliance costs and making some activities more time consuming. This could result in continuing uncertainty regarding compliance matters and higher costs necessitated by ongoing revisions to disclosure and governance practices. The Company may invest resources to comply with evolving laws, regulations and standards, and this investment may result in increased general and administrative expenses and a diversion of management's time and attention from revenue-generating activities to compliance activities. If the Company's efforts to comply with new laws, regulations and standards differ from the activities intended by regulatory authorities, legal proceedings may be initiated against the Company and its business may be harmed.

***Trading in the Company's common shares outside of Canada may be subject to restrictions on trading under foreign securities laws, and purchasers of securities under private placements by the Company will be subject to certain restrictions on trading***

The Company's common shares trade on the TSX and are freely tradeable only in Canada. As such, shareholders trading the Company's common shares outside of Canada may be subject to restrictions

imposed by foreign securities laws that may restrict their ability to transfer shares freely or at all. Certain securities offered by the Company pursuant to its private placements, including the unlisted warrants issued by the Company, are subject to certain initial hold periods and other restrictions on trading imposed by applicable securities laws and, in the case of the warrants, pursuant to the terms of the applicable warrant certificates. These restrictions may affect the liquidity of the investment of certain shareholders in the securities of the Company.

***General economic conditions may have an adverse effect on the Company and its business***

Continuing global economic volatility and uncertainty may have an adverse effect on the Company and its business, including without limitation the ability to raise additional financing, to obtain strategic partner support or commercialization opportunities and alliances for the Company's new drug candidates, and to obtain continued services and supplies.

***The Company's business involves environmental risks that could result in accidental contamination, injury, and significant capital expenditures in order to comply with environmental laws and regulations***

The Company and its commercial collaborators are subject to laws and regulations governing the use, manufacture, storage, handling and disposal of materials and certain waste products. Although the Company believes that its safety procedures comply with the regulations, the risk of accidental contamination or injury from these materials cannot be eliminated. In the event of such an accident, the Company could be held liable for any damages that result and any such liability could exceed the resources of the Company. The Company is not specifically insured with respect to this liability. The Company (or its collaborators) may be required to incur significant costs to comply with environmental laws and regulations in the future; and the operations, business or assets of the Company may be materially adversely affected by current or future environmental laws or regulations.

***Any failure to maintain an effective system of internal controls may result in material misstatements of our consolidated financial statements or cause us to fail to meet our reporting obligations or fail to prevent fraud; and in that case, our shareholders could lose confidence in our financial reporting, which would harm our business, could negatively impact the price of our common shares and prevent the Company from raising additional capital.***

Effective internal controls are necessary for the Company to provide reliable financial reports and prevent fraud. If the Company fails to maintain an effective system of internal controls, the Company may not be able to report its financial results accurately or prevent fraud; and in that case, the Company's shareholders could lose confidence in our financial reporting, which would harm our business, negatively impact the price of the Company's common shares and also prevent the Company from raising additional capital. Even if we were to conclude that our internal control over financial reporting provides reasonable assurance regarding the reliability of financial reporting and the preparation of consolidated financial statements for external purposes in accordance with IFRS as issued by the IASB, because of its inherent limitations, internal control over financial reporting may not prevent or detect fraud or misstatements. Failure to achieve and maintain effective internal control over financial reporting could prevent the Company from complying with its reporting obligations on a timely basis, which could result in the loss of investor confidence in the reliability of the Company's consolidated financial statements, harm our business, negatively impact the trading price of our common shares and prevent the Company from raising additional capital.

## **DIVIDEND POLICY**

To date, the Company has not paid any dividends on the outstanding common shares and has no current intention to declare dividends on its common shares in the foreseeable future. Any decision to pay dividends on the common shares in the future will be dependent upon the financial requirements of the Company to finance future growth, the financial condition of the Company and other factors that the Board may consider appropriate in the circumstances. The Company has no restrictions on the payment of dividends other than those provided under the provisions of the *CBCA* and the policies of the *TSX*.

## **CAPITAL STRUCTURE**

### ***Share capitalization***

The Company's articles authorize the issuance of an unlimited number of common shares and 10,000,000 preferred shares issuable in series. As at July 31, 2018, the Company has 102,809,579 common shares and nil preferred shares issued and outstanding.

### ***Common shares***

The holders of the common shares of the Company are entitled to receive notice of and to attend all meetings of the shareholders of the Company and have one vote for each common share held at all meetings of shareholders.

Subject to the rights, privileges, restrictions and conditions attaching to any other class or series of shares of the Company, the holders of common shares are entitled to receive dividends as and when declared by the Board, in such amount and in such form as the Board may from time to time determine, and subject to the limitations on declaration of dividends prescribed in the *CBCA*. All dividends which the Board may declare on the common shares must be declared and paid in equal amounts per share on all common shares at the time outstanding.

In the event of the dissolution, liquidation or winding-up of the Company, whether voluntary or involuntary, or in the event of any other distribution of the Company's assets among its shareholders for the purpose of winding-up its affairs, the holders of the common shares shall, subject to the rights of the holders of any other class of shares of the Company, be entitled to receive such assets of the Company upon such distribution.

### ***Preferred shares***

The preferred shares of the Company may at any time or from time to time be issued in one or more series. The directors may alter by resolution the articles of the Company, to fix or change the number of shares in, and to determine the designation, rights, privileges, restrictions and conditions attaching to the shares of each series of preferred shares. The directors may also confer on the holders of any series of preferred shares the right to notice of or to be present or to vote, at any general meeting of the shareholders of the Company. Preferred shares shall be entitled to preference over the common shares and any other shares of the Company ranking junior to the preferred shares in the event of any liquidation, dissolution or winding-up of the Company or any distribution of its assets for the purpose of winding-up its affairs, whether voluntary or involuntary. The preferred shares of each series will rank in parity with the preferred shares of every other series with respect to priority in the payment of dividends and in the distribution of assets in the event of liquidation, dissolution or winding-up of the Company.

### ***Warrants***

Warrants have been issued by the Company in connection with the sale of units, with each unit consisting of one common share and one common share purchase warrant (each, a "Warrant"). The Warrants are subject to certain restrictions on transfer as set out in the applicable certificates representing the Warrants. The certificates provide that any rights under such certificates, including any beneficial interest therein, are not transferrable or assignable to any other person by the holder of such certificate without the prior written consent of the Company.

As of July 31, 2018, there were Warrants outstanding to purchase an aggregate of 35,078,975 common shares at exercise prices ranging from \$1.50 per share to \$2.24 per share (subject to adjustment in the event of a subdivision, consolidation or reclassification of the common shares prior to the expiry time for such Warrants). The Warrants expire at various times between October 31, 2018 and July 8, 2023. Warrants issued subsequent to the Company's July 31, 2018 fiscal year-end are set out below.

On August 8, 2018, the Company completed a private placement, issuing a total of 682,000 units at \$1.20 per unit for gross proceeds of approximately \$818,000. Each unit consisted of one common share and one common share purchase warrant. Each common share purchase warrant entitles the holder to purchase one common share at a price of \$1.50 and has an expiry of five years from the date of issuance.

On September 10, 2018, the Company completed a private placement, issuing a total of 380,000 units at \$1.20 per unit for gross proceeds of approximately \$456,000. Each unit consisted of one common share and one common share purchase warrant. Each common share purchase warrant entitles the holder to purchase one common share at a price of \$1.50 and has an expiry of five years from the date of issuance.

On October 16, 2018, the Company announced to extend the exercise period of a total of 4,546,000 outstanding common share purchase warrants (the “Warrants”), all of which are held by arm’s length parties. The Warrants were issued pursuant to a private placement of the Company completed on November 1, 2013 and represent approximately 4.4% of the Company’s issued and outstanding common shares. Each Warrant currently entitles the holder to purchase one common share of the Company at an exercise price of \$1.61 at any time until October 31, 2018. Subject to TSX approval, the expiry date of the Warrants will be extended by two years to October 31, 2020. The exercise price of the Warrants will remain unchanged at \$1.61. If approved by the TSX, the effective date of the amendment will be October 31, 2018.

## **MARKET FOR SECURITIES**

### ***Trading Price and Volume***

The Company’s common shares began trading on the TSX on June 3, 1996. The current stock symbol is “HBP”. The following table sets forth the price ranges and trading volumes of the Company’s common shares on the TSX for the respective period.

<b>2017</b>	<b>High</b>	<b>Low</b>	<b>Volume</b>
August	\$0.90	\$0.81	19,664
September	\$0.90	\$0.81	21,230
October	\$0.90	\$0.81	22,461
November	\$1.05	\$0.79	222,661
December	\$0.94	\$0.73	141,360
<b>2018</b>	<b>High</b>	<b>Low</b>	<b>Volume</b>
January	\$1.00	\$0.75	169,716
February	\$1.10	\$0.70	93,327
March	\$0.95	\$0.78	51,253
April	\$0.88	\$0.75	23,480
May	\$0.82	\$0.72	23,200
June	\$0.93	\$0.76	29,242
July	\$0.87	\$0.65	65,978
August	\$0.80	\$0.60	139,972
September	\$0.92	\$0.69	100,575
October 1-25	\$0.73	\$0.49	172,739

The Company’s common shares are quoted on the Frankfurt, Stuttgart, Munich and Berlin Stock Exchanges, under the trading symbol “HBP”.

## **DIRECTORS AND OFFICERS**

### ***Name, Occupation and Securities Holding***

The directors of the Company are elected at each annual general meeting of the Company and hold office until the next annual general meeting or until their successors are elected.

The directors have appointed an Audit Committee consisting of three directors, namely, Sylwester Cacek (Chair), Slawomir Majewski and Marek Orłowski.

The following is a list of directors and executive officers of the Company, as of the date of this Annual Information Form, along with a brief biography:

- Sylwester Cacek  
Director since March 2014 (independent director)  
Residence: Zurich, Switzerland

Sylwester Cacek is currently President of Sfinks Polska SA, and was the founder of Dominet Capital Group, which includes a nationwide retail bank, Dominet Bank SA. As Chief Executive Officer of the group, Mr. Cacek created a nationwide financial institution with a wide range of products and services dedicated to individual clients and small and medium enterprises. In 2007, Dominet SA was successfully sold to Fortis Group. In his career, Mr.

Cacek has served as a member of supervisory boards of companies including Dominet Bank SA, Impel SA, OrsNet Sp. z o.o., SportLive24 SA and KS Widzew Łódź SA. He is also a shareholder of the Polish professional football club RTS Widzew Łódź.

- Sławomir Majewski  
Director since October 2012 (independent director)  
Residence: Warsaw, Poland

Prof. Majewski has been the Head of the Department of Dermatology and Venereology, Center of Diagnostics and Treatment of STD, Warsaw Medical University, Poland, since 1998, Deputy Rector for Science and International Relations at the Medical University of Warsaw since 2008, Coordinator of the Polish Center of Preclinical Studies and Technology since 2008 and a member of the scientific advisory board at the Polish Ministry of Health. Prof. Majewski is also a member of several national and international societies and scientific institutions including the Polish Academy of Sciences, European Society of Dermatological Research, European Academy of Dermatology and Venereology, European Association for Cancer Research, American Association for Cancer Research, International Advisory Committee of the Archives of Dermatology and the International Editorial Committee of the Journal of American Academy of Dermatology. He was also member of the board of the European Society for Dermatological Research from 2000 to 2004 and from 2003 to 2008, Prof. Majewski was a member of the International Steering Committee of the FUTURE II Study on the quadrivalent HPV vaccine. He is also a former member of the Board, having served from 2008 to 2009.

- Marek Orłowski  
Director since March 2012 (independent director)  
Residence: Warsaw, Poland

Mr. Orłowski is currently a CEO of Adiuvo S.A., an investment holding company domiciled in Poland. Adiuvo invests in biomedicine and medical technologies. Mr. Orłowski previously acted as a consultant for Sanofi-Aventis for portfolio development and globalization of brands, a position he held since 2010. Mr. Orłowski is the co-founder of the Polish pharmaceutical company, Nepentes S.A., which was acquired by Sanofi-Aventis in 2010. Mr. Orłowski's experience at Nepentes S.A., from the time he co-founded it in 1991 until its acquisition in 2010, included extensive experience in all aspects of marketing, supervision of sales, creation of the company's portfolio and development strategy. His responsibilities included the supervision of strategy of product placement on the market and research and development, the sale of a number of significant brands, creation of new products, and involvement in clinical trials of products. He negotiated distribution contracts and coordinated product launches in Eastern Europe, from Russia through to Poland and Romania. He was also a member of the Management Board of Nepentes S.A. until 2010, where he was responsible for marketing, sales, portfolio creation, strategic development and research and development.

Mr. Orłowski also oversaw the listing of Nepentes S.A. on the Warsaw Stock Exchange and negotiated its subsequent acquisition by Sanofi-Aventis. Mr. Orłowski established and co-owned a direct marketing company, Pelargos Sp. z o.o., as well as a pharmacy network company, Mexigem Polska Sp. z o.o., both of which were later acquired. He is a board member and Chief Executive Officer of Airway Medix Sp. z o.o., a Polish-Israeli company that produces ventilation assistance devices for intensive care units. He also is a board member and major shareholder in a Swedish nutraceutical company, Greenleaf Medical AB. Mr. Orłowski holds a MD (Medical Director) degree from the Medical Academy of Warsaw.

- Heman Chao  
Chief Executive Officer and Chief Scientific Officer  
Residence: Aurora, Ontario, Canada

Heman Chao, Ph.D. has been the Chief Executive Officer of the Company 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 Company subsidiary, between November 2004 and April 2008, when it was amalgamated into the Company. Mr. Chao was previously Vice President of Technology and later Vice President of Research for the Company, between June 2002 to 2004. Between 1999 and June 2002, he was Manager of Sensium Technologies Inc. Prior to joining the Company, 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  
Residence: Richmond Hill, Ontario, Canada

Photios (Frank) Michalargias, CPA, CA, has been Chief Financial Officer of the Company 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 tenures 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 functions, 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 the Company.

To the best of the Company's knowledge, the number and percentage of issued common shares of the Company beneficially owned, directly or indirectly, by the Directors and Officers of the Company, as a group and individually, are as set out in the following table. The table excludes and stock options or warrants beneficially owned, directly or indirectly by the Directors and Officers of the Company, as a group and individually.

Name	Number of Common Shares Held	Percentage of Class <sup>(1)</sup>
Sylwester Cacek	6,997,200 <sup>(2)</sup>	6.81%
Slawomir Majewski	1,705,700	1.66%
Marek Orlovski	1,673,500	1.63%
Heman Chao	0	0.00%
Photios (Frank) Michalargias	0	0.00%
<b>Total Common Shares</b>	<b>10,376,400</b>	<b>10.09%</b>

(1) Based on 102,809,579 common shares issued and outstanding as at July 31, 2018.

(2) Includes common shares beneficially owned by the spouse of Mr. Cacek.

#### ***Cease Trade Orders, Bankruptcies, Penalties and Sanctions***

To the knowledge of the directors and officers of the Company:

- a) no director or officer of the Company is, as at the date of this AIF or has been, within the 10 years before the date of the AIF, a director or executive officer of any company (including the Company) that:
  - (i) while such person was acting in such capacity, was the subject of a cease trade or an order similar to a cease trade order or an order that denied the relevant company access to any exemption under securities legislation, that was in effect for a period of more than 30 consecutive days (an "order"); or
  - (ii) was subject to an order that was issued after such person ceased to act in such capacity and which resulted from an event that occurred while such person was acting in such capacity; or
- b) no director or officer of the Company or a shareholder holding a sufficient number of securities of the Company to affect materially the control of the Company is, at the date of this AIF or has been, within the 10 years before the date of the AIF, a director or executive officer of any company (including the Company) that:
  - (i) while such person was acting in such capacity or with a year of such person ceasing to act in such capacity, became bankrupt, made a proposal under any legislation relating to bankruptcy or insolvency or was subject to or instituted any proceedings, arrangement or compromise with creditors or had a receiver, receiver manager or trustee appointed to hold its assets; or
  - (ii) has, within the 10 years before the date of this AIF, become bankrupt, made a proposal under any legislation relating to bankruptcy or insolvency, or become subject to or instituted any proceedings,



arrangement or compromise with creditors, or had a receiver, receiver manager or trustee appointed to hold such person's assets.

To the knowledge of the directors and officers of the Company, no director or officer of the company: (a) has been subject to any penalties or sanctions imposed by a court relating to Canadian securities legislation or by a Canadian securities regulatory authority or has entered into a settlement agreement with a Canadian securities regulatory authority, or (b) has been subject to any other penalties or sanctions imposed by a court or regulatory body that would likely be considered important to a reasonable investor in making an investment decision.

## **INTEREST OF MANAGEMENT AND OTHERS IN MATERIAL TRANSACTIONS**

To the Company's knowledge, none of its directors, executive officers, or other insiders, nor any associate or affiliate of any of them, has any material interest, direct or indirect, in any transaction within the three most recently completed financial years or during the current financial year that has materially affected or will materially affect the Company.

## **TRANSFER AGENT AND REGISTRAR**

The Company's transfer agent and registrar for its common shares is:

Computershare Trust Company of Canada  
100 University Avenue  
Toronto, Ontario, Canada, M5J 2Y1

## **MATERIAL CONTRACTS**

The following are the material contracts outside the ordinary course of business entered into by the Company which are still in effect.

- 1) The Company in-licensed anti-CEACAM6 single domain antibody 2A3 from the NRC. Pursuant to an agreement dated February 20, 2017 with the NRC, the Company is required to pay a royalty of 3% of net sales, with a minimum royalty of \$10,000 per annum generated from the use of a certain antibody to target cancerous tissues of the lung. In addition to the royalty payments, the Company is also required to make certain milestone payments for the first licensed product: \$25,000 upon successful completion of Phase I clinical trials; \$50,000 upon successful completion of Phase IIb clinical trials; \$150,000 upon successful completion of Phase III clinical trials; \$200,000 upon receipt of first regulatory approval by a regulatory authority; and \$200,000 upon receipt of a second regulatory approval by a regulatory authority. For the development of each subsequent licensed product: \$200,000 upon receipt of first regulatory approval by a regulatory authority; and \$200,000 upon receipt of a second regulatory approval by a regulatory authority. As it relates to sub-licensing arrangement, the Company is required to pay the NRC 33% of any sub-licensing revenues received.
- 2) The Company signed an exclusive out-license agreement with Xisle Pharma Ventures Trust ("Xisle") for the Company's late-stage, Biphasix™ technology platform, including the lead product candidate, interferon alpha. Xisle is responsible for the continued clinical development and subsequent commercialization of the product for the treatment of HPV-induced, low-grade, cervical intraepithelial lesions. Under the terms of the agreement dated November 18, 2016, Xisle paid an up-front fee of USD125,000 and agreed to pay subsequent milestone payments as they advance the technology to registration and market approvals and royalties. As part of the agreement, Helix retains marketing rights for Belarus, Bulgaria, Czech Republic, former Eastern Germany, Hungary, Moldova, Poland, Romania, Russia, Slovakia and Ukraine. In addition, the Company also retains non-exclusive rights for co-promotion in Canada
  - a. Milestones as follows:
    - i. USD3,000,000 upon initiation of the first Phase 3 trial anywhere in Xisle's territory;
    - ii. USD5,000,000 upon first submission of New Drug Application or similar for approval in the Xisle territory; and
    - iii. USD10,000,000 upon first commercial sale of a product in the Xisle territory.
  - b. Royalties as follows until the lapse of 10 years from first commercial sale of a product in Xisle's territory:
    - i. 8% on annual net sales up to USD50,000,000,
    - ii. 10% on the next annual net sales of USD25,000,000, and

- iii. 12.50% on the annual net sales above USD75,000,000.
- 3) The Company assigned certain marketing rights for products containing or made using Biphasix™ technology to HIO, its wholly -owned subsidiary in Poland pursuant to an agreement between the Company and HIO dated January 9, 2017 with the agreement being subject to the restrictions and limitations associated with an out-license agreement between the Company and Xisle dated November 18, 2016. In addition, HIO will be responsible for continuing clinical development and subsequent commercialization with milestone and royalty payments to be paid back to the parent Company upon successful product development through to commercialization.
    - a. Milestones as follows:
      - i. USD1,000,000 upon first submission of a New Drug Application or analogous submission anywhere with the Company's reserved territory for, and
      - ii. USD3,000,000 upon the first arms' length sale of a product in a country in the Company's reserved territory to a third party following regulatory approval.
    - b. Royalties as follows until the lapse of 10 years from first commercial sale of a product in the Company's reserved territory:
      - i. 8% on annual net sales up to USD50,000,000,
      - ii. 10% on the next annual net sales of USD25,000,000, and
      - iii. 12.50% on the annual net sales above USD75,000,000.
  - 4) The Company's wholly-owned subsidiary, HIO (formerly Helix Polska Sp z o.o), entered into an agreement with the PNCRD dated July 11, 2016 whereby certain expenditures made commencing on March 1, 2016 are eligible for reimbursement with the final reimbursement submission to be made no later than September 30, 2021. Of the total project costs, the public subsidy portion represents PLN12,506,955 (~CAD4,089,941). Helix Polska Sp z o.o is required to spend PLN4,437,459 (~CAD1,451,108) towards eligible project expenditures. In addition, there is an expected 2,850,000 of manufacturing and clinical trial documentation costs that are ineligible for co-financing by the ERDF. The public subsidy funds may be drawn in advance or on a reimbursement basis, with varying criteria and timelines on justification of claims being made by Helix Polska Sp z o.o. against the PNCRD for funding of the V-DOS47 development program in Poland. The Agreement may be terminated by either party upon one month's written notice and must also state the grounds for which the Agreement is being terminated. In certain cases of termination, the Subsidiary may be obligated to return the received financial support in full within fourteen days of the day notice is served, with interest.
  - 5) The Company entered into a licence agreement dated June 28, 2016 with its wholly-owned subsidiary, HIO (formerly Helix Polska Sp z o.o), which grants the Company's subsidiary, on a worldwide basis:
    - a) a non-exclusive right, license and privilege to use the Technology DOS47 and the Intellectual Property Rights, solely for the Purpose and in accordance with the terms and conditions of this Agreement; and
    - b) an exclusive right, license and privilege to use the Technology v-DOS47 solely for the Purpose and in accordance with the terms and conditions of the Agreement; and
    - c) an exclusive right, license and privilege to commercialize Technology v-DOS47, where commercialization shall be interpreted as activities associated with building a business model of Technology v-DOS47, development of the sales process and implementation of candidates for products resulting from Technology v-DOS47 on the market in order to create capital and generate profit through the transfer of results of vDOS47 on the conditions determined by market transactions.

In consideration of the rights and licenses granted to the Company's subsidiary, the subsidiary will pay, or cause to be paid, the Company, provided that any part of Technology v-DOS47 has been commercialized, the following royalties based on the annual aggregate Net Sales of all Products on a worldwide basis, which rate will increase in accordance with the following brackets as total aggregate Net Sales of such products increase over the course of a particular calendar year:

- a) zero percent (0%) for annual aggregate Net Sales up to and including US\$2,000,000;
  - b) six percent (6%) for annual aggregate Net Sales from US\$2,000,000 up to and including US\$250,000,000;
  - c) eight percent (8%) for annual aggregate Net Sales from US\$250,000,000 up to and including US\$500,000,000; and
  - d) twelve percent (12%) for annual aggregate Net Sales above US\$500,000,000.
- 6) The Company entered into an agreement dated effective July 2, 2018 with ACM Alpha Consulting Management AG ("ACMag"). ACMag will provide certain financial advisory services to the Company under the agreement for a fee equal to 12.5% of the gross proceeds on any capital raised until six months after the termination of the

agreement from an ACM introduced investor with residency outside Canada and the USA. The agreement with ACMag may be terminated by either party upon ninety days' notice. Veronika Kandziora, the Company's Secretary, owns ACMag and is its President and director. Andreas Kandziora, Ms. Kandziora's spouse, is an Observer to the Board of Directors of the Company and serves on the Supervisory Board of the Company's wholly-owned Polish subsidiary, Helix Immuno-Oncology S.A.

- 7) The Company entered into an agreement dated effective July 2, 2018 with ACM Alpha Consulting Management Est. ("ACMest") whereby ACMest will provide certain investor relations and strategic partner advisory services to the Company. The agreement may be terminated by either party on ninety days' notice. Andreas Kandziora, an Observer to the Board of Directors of the Company and a member of the Supervisory Board of the Company's wholly-owned Polish subsidiary, owns ACMest and is its President and director. Veronika Kandziora, Mr. Kandziora's spouse, is Secretary of the Company.

The agreement with ACMest provides for:

- a) a 12.5% fee on payments to the Company by an ACMest introduced strategic partner until twelve months after the termination of the agreement, including but not limited to, any cash payments to the Company as an up-front payment, any co-development proceeds, any milestone payments and any royalties associated with the transaction, but excluding private placements and a sale of assets of the Company or any subsidiary; and
  - b) a monthly fee for investor relations services of CHF33,000 and reimbursement of certain expenses.
- 8) The Company signed a collaboration agreement on March 16, 2018 with ProMab Biotechnologies, Inc. ("ProMab") to develop novel antibody and chimeric antigen receptor T-cell therapy ("CAR-T") for particular hematological malignancies. Under the collaboration agreement, Helix retains commercial rights for this CAR-T in Canada and Europe.

In consideration of the rights and licenses granted, the Company will pay, or cause to be paid to ProMab, the following royalties based on the annual aggregate net sales of all products in the jurisdictions:

- a) Five percent (5%) for annual aggregate net sales up to US\$250,000,000; and
- b) Six percent (6%) for annual aggregate net sales above US\$250,000,000.

In addition, the Company will pay the following milestones to ProMab:

- a) US\$1,000,000 upon the completion of Phase I clinical study meeting primary objectives of the trial for each product; and
  - b) US\$5,000,000 upon the first commercial sale of each product.
- 9) Technology License Agreement with the NRC dated April 28, 2005 and amendment dated December 2, 2009.
  - 10) Clinical Supplies Manufacturing Agreement with BioVectra Inc. dated November 1, 2010. The Company relies on BioVectra for its supply of urease and the manufacturer of bulk drug product for future clinical testing programs.

Electronic copies of the contracts set out above may be accessed under the Company's profile on SEDAR at [www.sedar.com](http://www.sedar.com).

## **INTERESTS OF EXPERTS**

The Company's auditors for fiscal 2018 and 2017 were BDO Canada LLP, 60 Columbia Way, Markham, Ontario, Canada, L3R 0C9. BDO Canada LLP is independent of the Company in accordance with the applicable rules of professional conduct/code of ethics of The Chartered Professional Accountants of Ontario.

## **AUDIT COMMITTEE DISCLOSURE**

### ***Audit Committee Responsibilities***

The Company's Audit Committee is responsible for reviewing the Company's financial reporting procedures and internal controls and for the retention and review of the performance of the Company's external auditors, together with reviewing

the scope and results of the Company's audits and managing the professional services furnished by the independent auditors. The Audit Committee is also responsible for reviewing the annual and quarterly financial statements and accompanying Management's Discussion and Analysis prior to their approval by the full Board. The Audit Committee also reviews the Company's financial controls with the auditors of the Company on an annual basis.

The Company's independent auditor is accountable to the Board and to the Audit Committee. The Board, through the Audit Committee, has the ultimate responsibility for evaluating the performance of the independent auditor, and through the shareholders, to appoint, for replacing and compensating the independent auditor.

The Company's Audit Committee has a charter, a copy of which is attached as Schedule "A".

**Composition and relevant education and experience**

The Audit Committee is currently comprised of three members: Sylwester Cacek, Marek Orłowski and Sławomir Majewski, all of whom are independent directors. Mr. Sylwester Cacek was appointed Chair of the Audit Committee on October 24, 2017.

All members of the audit committee are financially literate, meaning they have the ability to read and understand a set of financial statements that present a breadth and level of complexity of accounting issues that are generally comparable to the breadth and complexity of the issues that can reasonably be expected to be raised by the Company's financial statements. A brief description of the education and experience of each of the audit committee members is set under the heading "Directors and Officers", above.

**Exemptions Relied Upon**

None.

**Pre-approval of non-audit services**

It is the Company's policy that all audit and non-audit services performed by its external auditors will continue to be pre-approved by the Company's Audit Committee.

**Auditor fees**

The total fees billed for professional services by BDO Canada LLP for fiscal 2018 and 2017 are as follows:

Item	2018		2017	
	Amount	Percentage	Amount	Percentage
Audit-Fees	\$81,700	100%	\$72,800	93%
Audit-Related Fees	\$0	0%	\$0	0%
Tax Fee	\$0	0%	\$0	0%
All Other Fees	\$0	0%	\$5,510	7%
Total	\$81,700	100%	\$79,310	100%

**ADDITIONAL INFORMATION**

Additional information, including directors' and officers' remuneration and indebtedness, principal holders of the Company's securities, securities authorized for issuance under equity compensation plans, and interests of insiders in material transactions, if applicable, is contained in the Company's Management Proxy Circular for its most recent annual meeting of shareholders that involved the election of directors. Additional financial information is provided in the Company's comparative financial statements, together with the associated management discussion and analysis, for its most recently completed financial year.

Any request for any documents referred to above should be made to the Chief Financial Officer, attention: Frank Michalargias, 9120 Leslie Avenue, Suite 205, Richmond Hill, Ontario, L4V 3J9 Canada or by fax to (905) 841-2244.

Additional information relating to the Company can be found under the Company's profile on SEDAR at [www.sedar.com](http://www.sedar.com) and the Company's website at [www.helixbiopharma.com](http://www.helixbiopharma.com).

## **GLOSSARY**

**Adenocarcinoma:** Cancer that originates in glandular tissue.

**BioVectra:** BioVectra Inc., a cGMP manufacturer of active pharmaceutical ingredients, advanced intermediates, specialty biochemicals, enzymes and biomolecules.

**Biphaxis™ technology:** Helix's proprietary platform technology designed for dermal, mucosal, transdermal and transmucosal delivery of molecules.

**Board:** The board of directors of the Company.

**BCBA:** means the *Canada Business Corporations Act*.

**cGMP:** Is an acronym for Current Good Manufacturing Practices, a term that is recognized worldwide for the control and management of manufacturing and quality control testing of foods and pharmaceutical products.

**Colposcopy:** A medical diagnostic procedure to examine the epithelial cells of the cervix, vagina, and vulva, especially for early signs of cancer.

**CTA:** Clinical Trial Application.

**Dermal:** Pertaining to the region of skin to the epidermis, consisting of a dense bed of vascular connective tissue. Dermal administration refers to the delivery of substances or compounds into the dermal region.

**Dysplasia:** A term used in pathology to refer to an abnormal growth or development of cells, tissue or organs. Dysplasia is often an indicator of early stage neoplasia or the abnormal proliferation of cells.

**Epithelial:** Of, pertaining to, or characterized by the epithelium, which is tissue, consisting of one or more cellular layers separated by very little intercellular substance, that covers most internal and external surfaces of the body.

**FDA:** United States Food and Drug Administration. The regulatory agency that oversees the development, manufacture, sale and use of diagnostic and therapeutic medical products in the United States.

**GMP:** Good Manufacturing Practice.

**Health Canada:** The department of the federal government of Canada that is responsible for all health-related matters in Canada on a national level.

**Histological:** Of, pertaining to, or characterized by histology, which is the branch of biology dealing with the study of tissues, cells and their structure, especially at the microscopic level.

**HPV:** Human Papilloma Virus. One of the most common sexually transmitted infections, causing cervical dysplasia and ano-genital warts as well as being linked to a variety of cancers.

**IFRS:** International Financial Reporting Standards issued by the International Accounting Standards Board, and as adopted by the Chartered Professional Accountants Canada.

**Immunoconjugate:** A molecular complex consisting of one or more antibodies linked to a second compound.

**IND:** Investigational New Drug.

**Intraepithelial:** Occurring in or among cells of the epithelium including the cells of the epithelial layer of the skin.

**Lipid:** Fats or fat-like substances characterized by being water-insoluble.

**Low-grade cervical lesions:** For the purposes of this AIF, this term refers to cervical abnormalities combining an LSIL finding on Pap smear and a CIN1 or CIN2 diagnosis on colposcopy.

**LSIL:** Low-grade Squamous Intraepithelial Lesions.

**Neoplasia:** A pathological process that results in the abnormal and often uncontrolled growth and proliferation of cells, and is usually associated with cancer.

**NRC:** National Research Council of Canada.

**NSCLC:** Non-small cell lung cancer.

**Pharmacokinetic:** The action of drugs in the body over a period of time, including the processes of absorption, distribution, localization in tissues, biotransformation (metabolism) and excretion.

**Phase I clinical trials:** Clinical trials used to assess the potential toxicity of a new drug, primarily involving healthy volunteers, under the regulations of the applicable jurisdiction.

**Phase II clinical trials:** Clinical trials used to assess the effectiveness and most effective dosage of a new drug under the regulations of the applicable jurisdiction.

**Phase III clinical trials:** Late stage clinical trials used to assess a drug for efficacy and safety at several independent sites in a large number of patients under the regulations of the applicable jurisdiction.

**PNCRD:** Polish National Centre for Research and Development.

**RECIST:** Response Evaluation Criteria In Solid Tumors. A set of published rules that define when cancer patients improve, stay the same, or worsen during treatments.

**Therapeutic:** A medical treatment or curative product for a disease.

**Topical Interferon Alpha-2b:** A topical preparation under development by the Company that is intended to be self-applied to HPV-infected tissues, in order to deliver interferon-alpha intradermally. It is based on Helix's proprietary Biphax<sup>TM</sup> drug delivery technology.

**TSX:** The Toronto Stock Exchange.

**Transdermal:** Access to the systemic blood circulation via migratory passage through the multiple layers of skin.

**Transmucosal:** Access to the systemic blood circulation via migratory passage through the multiple layers of mucosa.

# SCHEDULE A

## HELIX BIOPHARMA CORP.

### AUDIT COMMITTEE CHARTER

The Audit Committee of the Board of Directors (the “Board”) of Helix BioPharma Corp. (the “Corporation”) shall have the composition, responsibilities, powers, duties and authority specified in this Charter.

#### I. Purpose

The Audit Committee’s purpose is to:

- a. Assist the Board’s oversight of:
  - i. The integrity of the Corporation’s financial statements;
  - ii. The Corporation’s financial accounting and reporting, the system of internal controls established by management, and the adequacy of internal and independent auditing relative to these activities;
  - iii. The Corporation’s compliance with legal and regulatory requirements; and
  - iv. The qualifications, independence and performance of the independent public accounting firm auditing the Corporation’s financial statements.
- b. Prepare such reports as may be required from time to time by applicable securities laws and by the rules and regulations of applicable regulatory authorities (including any stock exchange on which the Corporation’s securities are listed) (such laws, rules and regulations being hereinafter referred to, collectively, as the “Rules and Regulations”).
- c. Oversee the work of the Corporation’s independent accounting firm, including the resolution of disagreements between management and the independent public accounting firm regarding financial reporting.

#### II. Composition, Appointment and Procedures.

- a. The Audit Committee shall consist of at least three members of the Board, each of whom shall be, subject to such exceptions as may be permitted by the Rules and Regulations, an “independent director” and “financially literate” within the meaning of the Rules and Regulations.
- b. No member of the Audit Committee may concurrently serve on the audit committee of more than two other public companies unless the Board determines that such simultaneous service would not impair the ability of such director to effectively serve on the Audit Committee.
- c. The members of the Audit Committee shall be appointed by the Board and shall continue to act until their successors are appointed. Members shall be subject to removal at any time by the Board.
- d. The Audit Committee shall meet at least four times each year. At such meetings, the Audit Committee shall discuss such audit matters as the Audit Committee deems appropriate with the Corporation’s CFO and independent public accounting firm.

- e. Periodically, the Audit Committee shall meet separately with the independent public accounting firm.

### **III. Duties and Responsibilities with Respect to Audit, Accounting and Financial Disclosure.**

The Audit Committee shall:

- a. Prior to filing with the applicable regulatory authorities or otherwise publicly disclosing the information, review and discuss with the Corporation's management and independent public accounting firm:
  - i. the Corporation's annual audited financial statements, quarterly financial statements, and annual and quarterly financial press release, including the Corporation's disclosures under "Management's Discussion and Analysis"; and,
  - ii. the scope and results of the annual audit, or any interim reporting;
- b. Review and discuss with the Corporation's management and independent public accounting firm:
  - i. major issues regarding accounting principles and financial statement presentations, including any significant changes in the Corporation's selection or application of accounting principles, and major issues as to the adequacy of the Corporation's internal controls and any special audit steps adopted in light of material control deficiencies;
  - ii. analyses prepared by management and/or the independent public accounting firm setting forth significant financial reporting issues and judgments made in connection with the preparation of the financial statements, including analyses of the effects of alternative IFRS methods on the financial statements;
  - iii. the effect of regulatory and accounting initiatives, as well as off-balance-sheet structures, on the Corporation's financial statements; and
  - iv. the type and presentation of information to be included in quarterly and annual financial press releases;
- c. Review with the Corporation's independent public accounting firm any audit problems or difficulties and management's response, including:
  - i. any restrictions on the scope of the activities of the independent public accounting firm;
  - ii. any restriction on the independent public accounting firm's access to requested materials;
  - iii. any significant disagreements with management; and
  - iv. any material audit differences that the independent public accounting firm noted or proposed but for which the Corporation's financial statements were not adjusted;
- d. Resolve any disagreements between the independent public accounting firm and Corporation's management regarding financial reporting;
- e. Discuss with the Corporation's management, independent public accounting firm and Chief Financial Officer the adequacy of the Corporation's internal accounting, financial and operating controls;



- f. Be satisfied that adequate procedures are in place for the review of the Corporation's public disclosure of financial information extracted or derived from the Corporation's financial statements, and periodically assess the adequacy of such procedures; and
- g. Report to the Board with respect to the foregoing.

#### **IV. Specific Responsibilities with Respect to the Corporation's Independent Public Accounting Firm**

The Corporation's independent public accounting firm is ultimately accountable to the Board and shall report directly to the Audit Committee.

- a. The Audit Committee shall recommend to the Board of Directors:
  - i. The independent public accounting firm to be nominated for the purpose of preparing or issuing an auditor's report or performing other audit, review or attest services for the Corporation; and
  - ii. The compensation of the independent public accounting firm.
- b. The Audit Committee shall annually evaluate the qualifications, performance and independence of the independent public accounting firm and the lead partner.
- c. The Audit Committee shall pre-approve all non-audit services to be provided to the Corporation or its subsidiary entities by the Corporation's independent public accounting firm.
- d. The Audit Committee shall review and approve the compensation and terms of engagement of the Corporation's independent public accounting firm before the firm provides any audit, audit-related, tax or permitted non-audit services.
- e. At least annually, the Audit Committee shall obtain and review a report by the independent public accounting firm describing:
  - i. the firm's internal quality control procedures,
  - ii. any material issues raised by the firm's most recent internal quality control review or peer review; and
  - iii. all relationships between the firm and the Corporation.
- f. At least annually, the Audit Committee shall obtain from the independent public accounting firm assurance that they are not aware of any illegal act that has or may have occurred.
- g. The Audit Committee shall report to the Board with respect to the foregoing.

#### **V. Additional Powers, Duties and Authority.**

The Audit Committee shall have additional powers, duties and authority to:

- a. Monitor, review, and, if necessary or advisable, revise and update the Corporation's procedures for:
  - i. the receipt, retention and treatment of complaints received by the Corporation regarding accounting, internal accounting controls and auditing matters; and

- ii. the confidential, anonymous submission by the Corporation's employees of concerns regarding accounting or auditing matters;
- b. Discuss with the Corporation's management the Corporation's guidelines and policies with respect to risk assessment and risk management, including the Corporation's major financial risk exposures and the steps management takes to monitor and control such exposures;
- c. Annually review the Audit Committee's performance and Charter, which shall include evaluating each member's qualifications, attendance, understanding of the Audit Committee's responsibilities and contribution to the functioning of the Audit Committee, and recommend any proposed changes to the Board for approval;
- d. Prepare such reports as are required by the Rules and Regulations;
- e. Review with the Corporation's legal counsel any legal matters that may have a material impact on the financial statements, the Corporation's Code of Business Conduct and Ethics and any material reports or inquiries received from regulators or governmental agencies;
- f. As the Audit Committee may deem appropriate, retain and terminate any legal, accounting or other consultants, who shall report directly to the Audit Committee, on such terms and conditions, including fees, as the Audit Committee in its sole discretion shall approve;
- g. Request that any of the Corporation's officers, employees, outside counsel or independent public accounting firm attend any meeting of the Audit Committee or meet with any of the Audit Committee's members or consultants;
- h. Review and approve the Corporation's hiring policies regarding partners, employees and former partners and employees of the Corporation's present and former independent public accounting firm; and
- i. Report to the Board with respect to the foregoing.

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