Item 2. Management's Discussion and Analysis of Financial Condition and Results of Operations

The following discussion should be read in conjunction with the attached financial statements and notes thereto included in Part I, Item 1 of this Quarterly Report on Form 10-Q, as well as our audited financial statements and related notes thereto and management's discussion and analysis of financial condition and results of operations for the fiscal year ended September 30, 2021 included in our Annual Report on Form 10-K filed with the U.S. Securities and Exchange Commission (the "SEC") on November 18, 2021. This Quarterly Report on Form 10-Q, including the following sections, contains forward-looking statements within the meaning of the U.S. Private Securities Litigation Reform Act of 1995. These statements are subject to risks and uncertainties that could cause actual results and events to differ materially from those expressed or implied by such forward-looking statements. For a detailed discussion of these risks and uncertainties, see "Risk Factors" in our Annual Report on Form 10-K. We caution the reader not to place undue reliance on these forward-looking statements, which reflect management's analysis only as of the date of this Quarterly Report on Form 10-Q. We undertake no obligation to update forward-looking statements to reflect events or circumstances occurring after the date of this Quarterly Report on Form 10-Q. Throughout this discussion, unless the context specifies or implies otherwise, the terms "ESSA," "the Company," "we," "us," and "our" refer to ESSA Pharma Inc. and its subsidiaries.

Overview

ESSA is a clinical stage pharmaceutical company, focused on developing novel and proprietary therapies for the treatment of prostate cancer with an initial focus on patients whose disease is progressing despite treatment with current standard of care therapies, including second-generation antiandrogen drugs such as abiraterone, enzalutamide, apalutamide, and darolutamide. The Company believes its latest series of investigational compounds, including its product candidate EPI-7386, have the potential to significantly expand the interval of time in which patients with castration-resistant prostate cancer ("CRPC") can benefit from anti-hormone-based therapies. Specifically, the compounds are designed to disrupt the androgen receptor ("AR") signaling pathway, the primary pathway that drives prostate cancer growth and prevent AR activation through selective binding to the N-terminal domain ("NTD") of the AR. In this respect, the Company's compounds are designed to mechanistically differ from classical non-steroid antiandrogens. These antiandrogens interfere either with androgen synthesis (i.e., abiraterone), or with the binding of androgens to the ligand-binding domain ("LBD"), located at the opposite end of the receptor from the NTD (i.e., "lutamides"). A functional NTD is essential for the functionality of the AR; blocking the NTD inhibits AR-driven transcription and therefore androgen-driven biology.

The Company believes that the transcription inhibition mechanism of its preclinical compounds is unique and has the potential advantage of bypassing several of the identified mechanisms of resistance to the antiandrogens currently used in the treatment of CRPC. The Company has been granted by the United States Adopted Names ("USAN") Council a unique USAN stem "-aniten" to recognize this new first-in-class mechanistic class. The Company refers to this series of proprietary investigational compounds as the "aniten" series. In preclinical studies, blocking the NTD has demonstrated the capability to prevent AR-driven gene expression. A previously completed Phase 1 clinical trial of ESSA's first-generation agent, ralaniten acetate ("EPI-506") administered to patients with metastatic CRPC ("mCRPC") refractory to current standard of care therapies demonstrated prostate-specific antigen ("PSA") declines, a sign of inhibition of AR-driven biology. This inhibition, however, was neither deep nor sustained enough to confer clinical benefit and the Company made the decision to develop a more potent next generation drug which would also have a longer half-life. The Company has done so and is now in clinical trial with this next generation aniten, EPI-7386.

According to the American Cancer Society, in the United States, prostate cancer is the second most frequently diagnosed cancer among men, behind skin cancer. Approximately one-third of all prostate cancer patients who have been treated for local disease with curative intent will subsequently have rising serum levels of PSA, which is an indication of recurrent disease with or without development of distant metastasis. Patients with recurrent disease as indicated by rising PSA usually undergo initial androgen ablation therapy using analogues of luteinizing hormone releasing hormone or surgical castration; this approach is termed "androgen deprivation therapy" ("ADT"). Most of these patients initially respond to this androgen ablation therapy; however, many experience a recurrence in tumor growth despite the reduction of testosterone to castrate levels, and at that point are considered to have CRPC. Following diagnosis of CRPC, patients have been generally treated with antiandrogens that block the binding of androgens (darolutamide, enzalutamide, apalutamide or bicalutamide) to the AR, or inhibit synthesis of androgens (abiraterone). More recently, significant improvements in progression free survival and overall survival have been achieved by utilizing this latest generation of antiandrogens in combination with ADT earlier in the disease natural history (i.e., HSPC and nmCRPC).

Since the mid-20th century, it has been recognized that the growth of prostate tumors is in large part mediated by an activated AR. Generally, there are three means of activating the AR. First, androgens such as dihydrotestosterone can activate AR by binding to its LBD. Second, CRPC can be driven by variants of AR that lack an LBD, are constitutively activated, and consequently do not require androgen for activation. A third mechanism, of less certain clinical significance, may involve certain signaling pathways that activate AR independent of androgen activity. Generally, current drugs for the treatment of prostate cancer are directed against the first mechanism by either (i) interfering with the production of androgen, or (ii) preventing androgen from binding to the LBD. Over time, these approaches eventually fail due to mechanisms of resistance which involve the LBD end of the receptor, whether at the DNA (AR amplification or LBD mutations) or RNA level (emergence of AR splice variants). With respect to the development of alternative pathway mechanisms of AR activation, tumors might also be insensitive to antiandrogen activity. Finally, in patients who have been treated for years with various antiandrogen therapies, genomic changes may lead to additional, non-AR-related oncogenic drivers, also insensitive to inhibition of AR biology.

The Company believes that through their potential to block androgen-driven gene transcription by using a unique mechanism involving the NTD and thereby bypassing these known mechanisms of resistance to current antiandrogens, the aniten series of compounds hold the potential to be effective in cases where LBD-based mechanisms of resistance to second generation antiandrogens in otherwise AR-driven disease are operating. The results from both extensive preclinical studies and the initial clinical experience support the Company's belief. In preclinical studies, the aniten series of compounds has been observed to shrink AR-dependent prostate cancer xenografts, including tumors both sensitive and resistant to the second-generation antiandrogens such as enzalutamide. Plasma PSA level declines as well as declines in circulating tumor DNA and decrease in radiographic tumor measurements were observed in the initial results of the Phase 1 study of EPI-7386 as described below. Importantly with respect to the potential clinical application of NTD inhibition, recent studies by the Company and its collaborators have also suggested the potential advantage for combinations of the Company's aniten compounds with currently approved antiandrogens to inhibit AR-driven biology more completely than AR inhibition from either end of the receptor alone. This hypothesis is supported by the clinical trial results obtained in recent years of the superior overall survival obtained with initial combination therapy with ADT and latest generation antiandrogens relative to the administration of these two therapies sequentially.

While the potential importance of the NTD as a drug target has been appreciated for more than two decades, for technical reasons this has been a difficult target for therapeutic agent development. The NTD of the AR is flexible with a high degree of intrinsic disorder making it difficult for use in classic crystal structure-based drug design. The Company is not currently aware of any clinical-stage NTD AR inhibitors that are in development by other drug development companies. The nature of the highly specific binding of the aniten compounds to the NTD, and the biological consequences of that binding, have been defined in scientific studies. The selectivity of the binding, based on *in vivo* imaging as well as *in vitro* studies, has been consistent with the favorable toxicological results observed in preclinical studies of the first-generation EPI-506 and the subsequent safety results observed in the Phase 1 trial of EPI-506. Subsequent to this trial and following the decision to pursue EPI-7386 as the Company's lead product candidate, the Company completed a series of similar biophysical and biological studies revealing the interaction and binding of EPI-7386 to the NTD of the AR and presented these findings at several medical conferences in 2021. See "*Completed Phase 1 Clinical Study of EPI-506*" and "*Next generation Aniten molecules*" below.

The incidence of both metastatic and non-metastatic CRPC continues to rise, and using a dynamic progression model, Scher et al.[1] projected a 2020 incidence of 546,955 and prevalence of 3,072,480. The Company believes that the aniten series of compounds could ultimately hold potential benefit for many of those patients. In its early clinical development, the Company intends to initially focus on patients who have failed second-generation antiandrogen therapies (i.e., abiraterone and/or lutamides) for the following reasons:

- CRPC treatment remains a prostate cancer market segment with an apparent and significant unmet therapeutic need and is therefore a potentially large market;
- the Company believes that the unique mechanism of action of its aniten compounds is well suited to treat those patients who have failed AR LBD focused therapies and whose biological characterization reveals that their tumors are still largely driven by AR biology; and
- the Company expects that the relatively large number of patients with an apparent unmet therapeutic need in this area will facilitate timely enrollment in its clinical trials.

Furthermore, the Company believes that a successful Phase 1 clinical trial will facilitate the early study of the combination of EPI-7386 with second-generation antiandrogens. The Company and its collaborators have developed preclinical *in vitro* and *in vivo* evidence supporting further evaluation of the combination of NTD inhibitors together with the LBD inhibiting antiandrogens. The Company believes that the application of two independent, complementary mechanisms of AR transcription inhibition may result in greater suppression of androgen activity and the delay or prevention of drug resistance. Recent progress in the clinical treatment of prostate cancer has resulted from the earlier utilization of antiandrogens in combination with classic ADT, consistent with the premise that more effective androgen suppression may yield clinical benefit. The Company believes that the introduction of NTD inhibitors such as EPI-7386 therefore has the potential to improve androgen suppression, delay the emergence of resistance, and result in improved clinical benefit.

Completed Phase 1 Clinical Study of EPI-506

The Company conducted an initial proof-of-concept Phase 1 clinical study utilizing the first-generation aniten compound, EPI-506 from 2015 to 2017. The objective of the EPI-506 Phase 1 clinical trial was to explore the safety, tolerability, maximum tolerated dose and pharmacokinetics of EPI-506, in addition to anti-tumor activity in asymptomatic or minimally symptomatic patients with mCRPC who were no longer responding to either abiraterone or enzalutamide treatments, or both. Efficacy endpoints, such as PSA reduction, and other disease progression criteria were evaluated. Details relating to the design of the Phase 1/2 clinical trial of EPI-506 are available on the U.S. National Institutes of Health clinical trials website (see https://clinicaltrials.gov).

[1] Scher HI, Solo K, Valant J, Todd MB, Mehra M (2015) Prevalence of Prostate Cancer Clinical States and Mortality in the United States: Estimates Using a Dynamic Progression Model. PLoS ONE 10(10): e0139440. doi:10.1371/journal.pone.013944

The Investigational New Drug ("IND") application to the FDA for EPI-506, to begin a Phase 1 clinical trial, was allowed in September 2015, with the first clinical patient enrolled in November 2015. The Company's Clinical Trial Application ("CTA") submission to Health Canada was subsequently also cleared. Based on allometric scaling, an initial dose level of EPI-506 of 80 mg was determined. However, following the enrollment of the initial cohorts, it became apparent that EPI-506 exposure was much lower in humans than projected. EPI-506 dosing was escalated aggressively to allow patients in the clinical study greater exposure to the drug. The highest dose patients ultimately received was 3600 mg of EPI-506, administered in a single dose or split into two doses daily. The initial data from the Phase 1 clinical trial was presented at the European Society of Medical Oncology meeting in September 2017.

Conducted at five sites in the United States and Canada, the open-label, single-arm, dose-escalation study evaluated the safety, pharmacokinetics, maximum-tolerated dose and anti-tumor activity of EPI-506 in men with end-stage mCRPC who had progressed after prior enzalutamide and/or abiraterone treatment and who may have received one prior line of chemotherapy. Twenty-eight patients were available for analysis, with each patient having received four or more prior therapies for prostate cancer at the time of study entry. Patients self-administered oral doses of EPI-506 ranging from 80 mg to 3600 mg, with a mean drug exposure of 85 days (range of eight to 535 days). Four patients underwent prolonged treatment (with a median of 318 days; and a range of 219 to 535 days at data cut-off), following intra-patient dose escalation. PSA declines, a measure of potential efficacy, ranging from 4% to 37% were observed in five patients, which occurred predominantly in the higher dose cohorts (≥1280 mg).

EPI-506 was generally well-tolerated with favorable safety results observed across all doses up to 2400 mg. At a dose of 3600 mg, gastrointestinal adverse events (nausea, vomiting and abdominal pain) were observed in two patients: one patient in the once-daily ("QD") dosing cohort and one patient in the 1800 mg twice-daily dosing cohort, leading to study discontinuation and a dose-limiting toxicity ("DLT") due to more than 25% of doses being missed in the 28-day safety reporting period. A separate patient in the 3600 mg QD cohort experienced a transient Grade 3 increase in liver enzymes (AST/ALT), which also constituted a DLT, and enrollment was consequently concluded in this cohort.

Although the Company believes that the safety results and possible signs of anti-tumor activity observed at higher dose levels support the concept that inhibiting the AR-NTD may provide a clinical benefit to mCRPC patients, the pharmacokinetic and metabolic studies revealed the limitations of the first generation agent EPI-506. Through its discovery research the Company had concluded that it should be feasible to develop a next generation of NTD inhibitor which would demonstrate greater potency, reduced metabolism and other improved pharmaceutical properties. As a result, the Company announced on September 11, 2017 its decision to discontinue the further clinical development of EPI-506 and to implement a corporate restructuring plan to focus research and development resources on its next-generation anitens targeting the AR-NTD. The restructuring included a decrease in headcount and a reduction of operational expenditures related to the clinical program. This next generation aniten compound includes significantly more potent drugs designed to exhibit increased resistance to metabolism and therefore a longer predicted circulating half-life. The Company's lead product candidate EPI-7386 has demonstrated these and other favorable characteristics in extensive preclinical characterization studies which the Company has presented in a series of poster presentations at scientific meetings.

Next generation Aniten molecules

The Company's family of next-generation investigational aniten compounds incorporate multiple chemical scaffold changes to the first-generation drugs which in preclinical studies retain NTD inhibition of the AR. In addition, they have shown improvement in a range of attributes when compared to the first-generation compound, EPI-506, in preclinical studies. In *in vitro* assays measuring inhibition of AR transcriptional activity, these product candidates demonstrated 20 times higher potency than EPI-506 or its active metabolite, EPI-002. In addition, the compounds have demonstrated increased metabolic stability in preclinical studies, suggesting the potential for longer half-lives in humans. Lastly, the compounds have demonstrated more favorable pharmaceutical properties relative to EPI-506. The Company believes that these product candidates, if successfully developed and approved, may offer advancements in ease and cost of large-scale manufacture, drug product stability, and suitability for commercialization globally. Of these next-generation anitens, EPI-7386 was selected for IND filing and Phase 1 clinical trial.

Our Strategy

In developing possible therapeutics that involve binding to the NTD, the Company's strategic approach involves:

- pursuing the clinical development of EPI-7386 as a monotherapy treatment for patients with non-metastatic CRPC ("nmCRPC") and mCRPC resistant to current standard of care, as a safe and effective therapy for those prostate cancer patients whose tumors have progressed on current antiandrogen therapy while remaining prevalently driven by the AR pathway;

- combining aniten compounds with antiandrogens at the earlier stage of the disease as has been shown in preclinical studies. The Company, with industry partners, has been conducting clinical trails of combinations of EPI-7386 and second generation antiandrogens in patients with mCRPC in earlier lines of treatment;

- the strategic importance of continuing preclinical development of aniten and aniten-related compounds with the Company's study of NTD degraders as a new approach to AR pathway inhibition. The Company's first generation of AR ANITen bAsed Chimera ("ANITAC") demonstrate the feasibility of this new approach to AR pathway inhibition for patients with mCRPC; and

- continuing to further explore, preclinically, other potential applications for AR-NTD inhibitors.

The identification and characteristics of EPI-7386

The purpose of the next-generation program has been to identify drug candidates with increased potency, reduced metabolic susceptibility and superior pharmaceutical properties compared to ESSA's first-generation compounds. Structure-activity relation studies conducted on the chemical scaffold of ESSA's first-generation compounds have resulted in the generation of a new series of compounds that have demonstrated higher potency and predicted longer half-lives. Multiple changes in the chemical scaffold have also been incorporated with the goal of improving ADME (absorption, distribution, metabolism, and excretion) and pharmaceutical properties of the chemical class.

Several next-generation aniten molecules met prespecified preclinical target product profile goals regarding potency, stability, selectivity and pharmaceutical properties. On March 26, 2019, the Company announced the nomination of EPI-7386 as its lead clinical candidate for the treatment of mCRPC through inhibition of the NTD of the androgen receptor. In preclinical studies, EPI-7386 has displayed activity *in vitro* in numerous AR-dependent prostate cancer models including models where second-generation antiandrogens are inactive. In addition, EPI-7386 is significantly more potent, metabolically stable and more effective in preclinical studies compared to ESSA's first-generation compound, EPI-506. Lastly, EPI-7386 has demonstrated a favorable tolerability profile in all animal studies of the compound conducted to date.

From this series of next-generation compounds, EPI-7386 was selected as the lead candidate for clinical development in mCRPC and an IND was submitted to the FDA on March 30, 2020 and was allowed by the FDA on April 30, 2020. A CTA was filed with Health Canada in April 2020 and clearance was subsequently received. Clinical testing of EPI-7386 commenced in July 2020, allowing for accommodations to the planned timeline as a result of the impact of COVID-19 at clinical trial sites (see "*Risk Factors - Risks Relating to COVID-19*" in our Annual report on Form 10-K).

Advancing EPI-7386 through clinical development

The Phase 1 clinical trial of EPI-7386 "Oral EPI-7386 in Patients With Castration-Resistant Prostate Cancer (EPI-7386)" is currently actively enrolling nmCRPC patients and mCRPC patients who are refractory to standard of care treatments at clinical sites in the U.S. and Canada (www.clinicaltrials.gov). In September 2021 the Company filed a protocol amendment for its Part 1a study with the FDA to allow for a 800 mg/day and 1200 mg/day dosages, administered as either 400 mg or 600 mg dosed twice daily ("BID"), respectively. In addition, the protocol amendment focused further monotherapy development in less heavily pretreated patients with mCRPC i.e. patients who have received a maximum of three prior approved systemic therapies for mCRPC. The Company filed a further amendment in July 2022 for a Part 1a and Part 1b study. The Part 1a study further focused monotherapy development in less heavily pretreated patients with mCRPC, opening eligibility to patients who have received at least two but not more than three prior lines of therapy for mCRPC including at least one second generation antiandrogen. The Part 1b study contains two components, a Part 1b dose expansion phase evaluated by Cohort A which will further evaluate the safety and tolerability of EPI-7386 in a patient population that has not been previously treated with chemotherapy, and a Part 1b window of opportunity with clinical endpoints phase evaluated by Cohort B, which will evaluate the anti-tumor activity of EPI-7386 for a limited window of time (up to 12 weeks prior to the start of standard of care therapy) in nmCRPC patients unperturbed by previous second generation antiandrogen therapies or chemotherapy.

Part 1a – Safety and tolerability of EPI-7386

The open-label, dose-escalation Phase 1a clinical trial is intended to determine the safety, tolerability, pharmacokinetics, maximum tolerated dose and/or a recommended Phase 2 range of doses ("RP2D") in line with the FDA's Project Optimus, and potential therapeutic benefits of the drug.

The design of the Phase 1 clinical trial includes the standard 3+3 design per dose cohort for the Part 1a dose escalation phase, with subjects receiving a daily oral dose of EPI-7386 until there is objective evidence of clinical disease progression, and or occurrence of an unacceptable toxicity.

Patients for the Part 1a are initially selected clinically, on the basis of having progressive mCRPC as exemplified by rising PSA values and/or radiological disease progression despite latest generation antiandrogen treatment. However, all patients are also retrospectively biologically characterized for underlying tumor genomic characteristics, for evidence of AR pathway activation as well as non-AR oncogenic pathways and during the conduct of the trial, for dose-related biological, pharmacological and pharmacodynamic effects.

Patients are currently being dosed at 1,000 mg QD, and at 800 mg/day, administered as 400 mg dosed twice daily (BID), and at 1,200 mg/day, administered as 600mg BID, to enhance patient drug exposures, with each of these dose levels being cleared as safe and tolerable .The protocol amendments filed with the FDA in September 2021 and July 2022 allow for monotherapy development in less heavily pretreated patients (as described above) in whom the androgen receptor pathway is more likely to be the primary driver of tumor growth. The Company's goal is to establish, one or more doses/schedules to be tested in the expansion Phase 1b study in alignment with the FDA Project Optimus guidance. This recommended dose or range of doses will be based on multiple inputs, including pharmacokinetic and biological observations, in addition to clinical experience.

The Part 1b component of the study, as described above, will have two cohorts enrolling in parallel:

Part 1b Cohort A – Dose Expansion

The primary objective of Cohort A is to further evaluate the safety, tolerability, pharmacokinetics, and preliminary anti-tumor activity (as measured by changes in tumor burden measured by imaging and changes in PSA levels over time) of EPI-7386 at the maximum tolerated dose or RP2D in a patient population enrolled under eligibility criteria similar to the one adopted for the Phase 1a with the exception of prior chemotherapy (not allowed for patients enrolled in this cohort).

Part 1b Cohort B – Window of opportunity with clinical endpoints

The primary objective of Cohort B is to assess the anti-tumor activity (as measured by changes of PSA over time) of EPI-7386 administered at the RP2D for a limited window of time (up to 12 weeks before patients start standard of care therapy) in nmCRPC patients unperturbed by previous second generation antiandrogen therapies or chemotherapy.

Once the Phase 1 clinical trial is complete, the Company plans to review the totality of the data, including the safety, tolerability, evidence of efficacy and pharmacological and biomarker data. This overall experience will inform the final size, design, and timing of a Phase 2 clinical trial, and importantly, the clinical as well as biological characteristics of the patients with mCRPC considered most likely to benefit from this therapeutic approach despite the late stage of their disease. Subsequent Phase 2 and additional clinical trials, including trials of combination aniten/lutamide therapy in earlier lines of treatment, should benefit from this initial clinical trial experience.

Combination studies - developing a new standard of care for the treatment of prostate cancer

An activated AR is required for the growth and survival of most prostate cancer. Unlike current antiandrogen therapies which can only inhibit full-length AR, NTD inhibition of AR-directed biology occurs both in full length AR and splice variant ARs. Therefore, the Company believes that the AR-NTD is an ideal target for next-generation antiandrogen hormone therapy. If ESSA's product candidate is successful in treating CRPC patients, it is reasonable to expect that such clinical candidate may be effective in treating earlier stage patients. Preclinical studies suggest particular value to the use of anitens in combination with the currently widely used antiandrogens.

The Company has announced a number of collaborative studies in line with this strategy. The first collaboration, with Janssen Research & Development, LLC ("Janssen"), to study in clinical trials the safety and potential benefit of combination of EPI-7386 with abiraterone acetate with prednisone as well as the combination of EPI-7386 with apalutamide in patients with mCRPC, was announced on January 13, 2021. Under the collaboration agreement with Janssen, Janssen will pay for and conduct a clinical trial with EPI-7386 and in separate cohorts each of their antiandrogens, apalutamide and abiraterone acetate. This combination trial has been initiated. A second collaboration and supply agreement with Astellas Pharma Inc. ("Astellas") to evaluate EPI-7386 in combination with Astellas and Pfizer Inc.'s androgen receptor inhibitor, enzalutamide, in patients with mCRPC was announced on February 24, 2021. ESSA is paying for and is operationally conducting this trial, with an initial Phase 1 dose equilibration Phase followed by a randomized Phase 2 trial involving a planned 120 patients. The enzalutamide for this trial is supplied by Astellas. The first patient in this Phase 1/2 study was dosed in January 2022 and the safety, tolerability, pharmacokinetics, and initial PSA responses were reported in the June 2022 clinical update. A third collaboration and supply agreement with Bayer Consumer Care AG ("Bayer") to evaluate EPI-7386 in combination with Bayer's androgen receptor inhibitor, darolutamide, in patients with mCRPC was announced on April 28, 2021. Under the collaboration with Bayer, Bayer will pay for and conduct a Phase 1/2 clinical trial with EPI-7386 to evaluate EPI-7386 in combination with darolutamide in earlier line mCRPC patients. ESSA will provide EPI-7386 for the combination trials being conducted by Janssen and Bayer. This clinical trial has not yet been initiated. The Company continues to evaluate potential collaborations that could enhance the value of its prostate cancer program and allow it to leverage the expertise of such strategic collaborators such as those with Janssen,Astellas, and Bayer.

Preclinical Development of Anitens, Degraders, and other indications

As part of the continued preclinical work on Aniten compounds, the Company has studied NTD degraders and presented data for its first generation of AR ANITAC NTD degraders at the AACR annual meeting on April 10, 2022 in a poster titled "Androgen receptor (AR) N-Terminal Domain degraders can degrade AR full length and AR splice variants in CRPC preclinical models". The preclinical data demonstrate the potential of ESSA's ANITAC degraders as a new approach to AR pathway inhibition. The intrinsically disordered nature of the NTD region of the AR has meant it has generally been considered undruggable. The preclinical studies have shown that through their unique ability to bind to the NTD of AR, ANITACs have the ability to inhibit NTD-mediated AR transcription while also degrading AR protein including resistant forms of AR which are commonly associated with castration-resistant prostate cancer.

The preclinical results demonstrate that ANITAC degraders utilize the ubiquitin proteasome system and can degrade many forms of AR including full length, mutant, and splice variants which are often expressed in CRPC patients. Specifically, the ANITAC degraders show robust potency in inhibiting AR transcriptional activity driven by AR-FL, AR-V7, or AR-V567es. In addition, the orally-bioavailable ANITAC degraders exhibit high potency in inhibiting AR-dependent transcription and reducing viability of AR-dependent prostate cancer cells.

The Company continues preclinical work on other emerging potential clinical applications for NTD inhibitors.

Recent Developments

The Company has presented preclinical and clinical scientific data relative to EPI-7386 in a number of presentations at scientific meetings and other forums.

2022

On June 27, 2022, the Company presented, by conference call and webcast, a clinical update on EPI-7386 monotherapy and combination therapy clinical development. The update on the Phase 1a dose escalation study showed initial data from 36 patients that demonstrated that EPI-7386 was well-tolerated, exhibited a favorable pharmacokinetic profile, and demonstrated initial anti-tumor activity in a heavily pretreated group of patients. The Company believes the favorable safety and tolerability profile, good pharmaceutical characteristics together with both antiandrogen biological and anti-tumor activity support the Company's decision to move into earlier lines of therapy and study EPI-7386 in combination with second-generation antiandrogens. The update also noted that ctDNA molecular analysis in the heavily pretreated population has provided a detailed profile of genetic alterations, which reveals the biological complexity of late-stage mCRPC patients and also allows for the continued refinement of the population of prostate cancer patients whose tumors are still primarily driven by the androgen receptor, and therefore most likely to respond to an androgen receptor inhibitor.

The update detailed that in the multi-center, open-label Phase 1a dose escalation study, 31 patients received EPI-7386 as oral tablets once a day (QD) in cohorts with 200 milligram increments from 200 milligrams up to 1000 milligrams. Patients in this QD group were heavily pretreated, with a median of seven lines of prior therapy for prostate cancer and four lines of therapy for mCRPC. Almost 60% of patients had been treated with prior chemotherapy. Patients entered the trial with rapidly progressive disease, as evidenced by a median PSA doubling time of only 2.1 months and a median ctDNA percent of 29%. Almost a third of the patients had lung, liver, or brain metastases, and an overlapping third of patients had overt neuroendocrine differentiation. The ctDNA analysis revealed that tumors in these patients had extensive non-AR associated genomic changes denoting the presence of multiple non-AR oncogenic drivers associated with late-stage prostate cancer. Subsequent to a protocol amendment, the experience was also presented for the five initial patients enrolled in a twice daily dose regimen in 400 mg and 600 mg BID cohorts. The amendment excluded patients who had been treated with more than three prior lines of therapy, excluded patients with visceral metastases, and permitted only one prior line of chemotherapy.

The key safety results from both QD and BID patients, as of June 1, 2022, showed that EPI-7386 was safe and well-tolerated at all dose levels and schedules tested, with no dose-limiting toxicities, treatment related adverse events were limited to Grade 1 or Grade 2, with one Grade 3 occurrence of anemia ultimately deemed unlikely to be treatment related, and that there was no apparent dose dependency in any of the side effects.

Antiandrogen response was assessed by changes in circulating PSA levels, changes in ctDNA levels, and radiographic changes in disease burden measured by both traditional RECIST criteria as well as by total lesion volumetric quantification using the AIQ Solutions platform.

The key response findings in both QD and BID patients, as of June 1, 2022, demonstrated that tumor volume decreased in five patients out of 10 patients who had measurable disease and were on therapy for more than 12 weeks. PSA decrease or PSA stabilization was observed in a clinical subset of patients with no visceral disease, fewer DNA genomic aberrations in non-AR oncogenic pathways, and fewer than 3 lines of therapy. This provides further information to support refining the monotherapy development program patient population. In 17 patients with measurable ctDNA levels at baseline, ctDNA declines were observed in patients harboring AR point mutations, AR gain/amplification and AR truncations, suggesting EPI-7386's potential activity against these tumors.

The Company expects to initiate the Phase 1b monotherapy expansion study in the third quarter of 2022 and plans to enroll two dose cohorts into this study in line with the FDA Project Optimus recommandations. The study will evaluate a patient population of mCRPC similar to the one treated under the Phase 1a BID cohort but with the additional exclusion of prior chemotherapy. Up to 12 patients per each dose/schedule (600 mg QD and either 400mg or 600 mg BID) will be evaluated to gain additional information about safety, tolerability, exposure and anti-tumor activity of EPI-7386 in a less heavily pretreated patient population.

The update also described the planned window of opportunity cohort as part of the Phase 1b expansion in which a separate group of non-metastatic CRPC will be enrolled into a 12-week study with a clinical endpoint (i.e. PSA changes) to assess the anti-tumor activity of EPI-7386 in a patient population in which the disease is mainly AR-driven and the tumor biology has not been affected by second-generation antiandrogen therapy.

The clinical update also provided the status of the combination studies evaluating EPI-7386 in earlier lines of therapy in Phase 1/2 trials which combine EPI-7386 with approved second-generation antiandrogens. In the Phase 1/2 study being conducted by the Company of EPI-7386 in combination with Astellas Pharma Inc.'s and Pfizer Inc.'s AR inhibitor, enzalutamide, in patients with mCRPC who have not been treated with second-generation antiandrogens, the first cohort had cleared the 28 day DLT period with no safety issues and when reported the trial was currently enrolling the second cohort of patients. The preliminary data from the first cohort in the Phase 1/2 combination trial with enzalutamide suggests that the drugs can be combined safely and based upon clinical and preclinical data predicted to be active. The early data, in addition to preclinical studies, support EPI-7386's potential in combination with second-generation antiandrogens to suppress androgen receptor biology and induce a potent anti-tumor response.

The Company also described the anticipated initiation later in 2022 of a Phase 2 investigator-sponsored neoadjuvant study which will evaluate darolutamide compared to EPI-7386 + darolutamide in patients undergoing prostatectomy for high-risk localized prostate cancer.

At the AACR annual meeting on April 10, 2022, in a poster titled "Androgen receptor (AR) N-Terminal Domain degraders can degrade AR full length and AR splice variants in CRPC preclinical models", the Company presented preclinical data for its first generation of androgen receptor (AR) ANITen bAsed Chimera (ANITAC™) N-terminal domain (NTD) degraders. The preclinical data demonstrate the potential of ESSA's ANITAC degraders as a new approach to AR pathway inhibition. The intrinsically disordered nature of the NTD region of the AR has meant it has generally been considered undruggable. The preclinical studies have shown that through their unique ability to bind to the NTD of AR, ANITACs have the ability to inhibit NTD-mediated AR transcription while also degrading AR protein including resistant forms of AR which are commonly associated with CRPC. The preclinical results demonstrate that ANITAC degraders utilize the ubiquitin proteasome system and can degrade many forms of AR including full length, mutant and splice variant which are often expressed in CRPC patients. Specifically, the ANITAC degraders show robust potency in inhibiting AR transcriptional activity driven by AR-FL, AR-V7, or AR-V567es. In addition, the orally-bioavailable ANITAC degraders exhibit high potency in inhibiting AR-dependent transcription and reducing viability of AR-dependent prostate cancer cells.

On January 19, 2022, the Company announced the first patient dosed in the Company-sponsored Phase 1/2 study to evaluate the safety, tolerability and preliminary efficacy of ESSA's lead product candidate, EPI-7386, a first-in-class N-terminal domain androgen receptor inhibitor, in combination with Astellas and Pfizer Inc.'s ligand-binding domain androgen receptor inhibitor, enzalutamide, in patients with mCRPC. This combination trial investigates the potential clinical benefit of inhibiting the androgen receptor through two independent pathways in the treatment of patients with mCRPC who have not yet received treatment with a second-generation antiandrogen drug. In preclinical models, the combination of EPI-7386 with lutamides by simultaneously targeting both ends of the AR resulted in deeper and broader inhibition of androgen biology.

The Phase 1/2 clinical trial (NCT05075577) is a two part study. The Phase 1 part of the study evaluates the safety and tolerability of the drug combination to establish the recommended Phase 2 range of doses for EPI-7386 and enzalutamide when dosed in combination. This Phase of the study is expected to enroll up to 30 mCRPC patients who have not yet been treated with second-generation antiandrogen therapies. As described below on June 27, 2022 the results of the initial experience with the first cohort was presented, demonstrating the safety and tolerability of the combination in this first cohort, along with the accompany pharmacokinetic and PSA reduction information. In the Phase 2 part of the study single agent enzalutamide is compared to the combination of enzalutamide and EPI-7386 in the same patient population. The goal of the Phase 2 part of the study is to evaluate the safety, tolerability and anti-tumor activity of EPI-7386 in combination with a fixed dose of enzalutamide compared with enzalutamide as a single agent. This part of the study is expected to enroll 120 mCRPC patients who have not yet been treated with second-generation antiandrogen therapies.

2021

In October 2021 the company disclosed the development of a collaboration with Caris Life Sciences, involving the incorporation of Caris' newly developed cNAS ("circulating nucleic acid sequencing") assay in the characterization of patients receiving EPI-7386. The Company believes that the characterization of real time individual patient biology will contribute significantly to understanding the extent to which individual patient's tumors are still AR driven and what mechanisms of resistance exist.

At the October AACR, National Cancer Institute ("NCI"), and European Organisation for Research and Treatment of Cancer ("EORTC") Virtual International Conference on Molecular Targets and Cancer Therapeutics, the Company presented preclinical data characterizing the mechanism of action of EPI-7386, including the results of NMR studies which confirm the binding of the compound to the NTD of the AR, a region not currently targeted by other antiandrogen therapies. The data also demonstrate that the combination of EPI-7386 with enzalutamide results in complete inhibition of genome-wide androgen-induced AR binding, supporting the rationale for Phase 1 / 2 combination trials of EPI-7386 with approved antiandrogens in patients with mCRPC.

On October 7, 2021 at the 2021 AACR-NCI-EORTC Virtual International Conference on Molecular Targets and Cancer Therapeutics the Company presented a virtual poster of preclinical data confirming EPI-7386's target engagement with the NTD of the androgen receptor, the primary driver of prostate cancer growth. The multiple studies showed (i) three separate orthogonal NMR approaches confirm that EPI-7386 binds to the Tau5 region of the NTD; (ii) cellular thermal shift assays (CETSA) confirm engagement of EPI-7386 with both full length AR (AR-FL) and AR-V567es, a splice variant lacking the ligand-binding domain (LBD); (iii) gene expression driven by the AR splice variant, AR-V567es, can be inhibited by EPI-7386 whereas enzalutamide and darolutamide, which bind to the LBD, cannot inhibit AR-V567es-driven gene expression; and (iv) chromatin immunoprecipitation sequencing (ChIP-Seq) data indicate that EPI-7386 inhibits androgen-induced changes at the AR cistrome and when combined with enzalutamide, can completely abrogate genome-wide androgen-induced AR binding.

Additionally, the data demonstrated that the combination of EPI-7386 with enzalutamide results in complete inhibition of genome-wide androgen-induced AR binding, supporting the rationale for the upcoming Phase 1/2 combination trials of EPI-7386 with approved antiandrogens in patients with metastatic castration-resistant prostate cancer.

At the 2021 American Association of Cancer Research ("AACR") Annual Meeting, which took place virtually April 10-15, 2021, ESSA presented an e-poster presentation titled, "Comprehensive *in vitro* characterization of the mechanism of action of EPI-7386, an androgen receptor N-terminal inhibitor." The content of this poster added to previously presented data that EPI-7386 binds to the full-length androgen receptor, inhibits the transcription of AR-regulated genes, and physically interacts with the splice variant form AR-V7, by demonstrating that EPI-7386 can prevent the androgen receptor from binding to genomic DNA and is active against additional androgen receptor splice variants, including AR-v567es. These preclinical data suggest EPI-7386 can potentially inhibit AR related transcription, a key driver of prostate cancer, and further supports the ongoing Phase 1 dose escalation study.

The data also showed that EPI-7386, in combination with enzalutamide, may result in broader and deeper inhibition of the AR pathway, underscoring the potential clinical benefit of combining EPI-7386 with current standard-of-care antiandrogen therapies for prostate cancer patients at earlier stages of the disease.

On February 11, 2021, the Company presented preclinical and clinical pharmacology data from ESSA's Phase 1 clinical trial of EPI-7386 for the treatment of patients with mCRPC at the 2021 American Society of Clinical Oncology Genitourinary ("ASCO GU") Cancers Symposium in an oral poster presentation titled, "Preclinical and clinical pharmacology of EPI-7386, an androgen receptor N-terminal domain inhibitor for castration-resistant prostate cancer." The poster is available on the Company website.

Data on the poster included a comparison of preclinical projections of EPI-7386 clinical pharmacokinetic parameters to the pharmacokinetic, safety and preliminary clinical data from the initial 200 mg cohort of patients enrolled in ESSA's multi-center, open-label, ascending multiple-dose Phase 1 study of EPI-7386 to treat patients with mCRPC who have become resistant to standard of care treatments. Patients participating in this trial have progressed on two or more approved systemic therapies for mCRPC, including at least one second generation antiandrogen therapy not necessarily in the metastatic disease setting. In this initial cohort of patients receiving the 200 mg once-daily dose, EPI-7386 was well-tolerated with no SAEs observed. The results from this cohort support ESSA's preclinical projections regarding the pharmacologic properties of EPI-7386 in humans. EPI-7386 was well-absorbed, demonstrated high exposure levels and was confirmed to have a long half-life of at least 24 hours. The predicted exposures of EPI-7386 in patients at that 200 mg dose level were similar to the Company's modeled projections and were still below optimal target exposures of EPI-7386 associated with anti-tumor activity in animal models. Although the 200 mg dose exposure was suboptimal, one out of three patients who completed 12 weeks of therapy experienced a PSA decline of more than 50 percent after three cycles of EPI-7386 therapy (12 weeks) with ongoing continued PSA declines continuing through seventeen cycles of therapy, despite previously having failed enzalutamide and abiraterone acetate.

2020

At the 32nd EORTC-NCI-AACR Annual Symposium on Molecular Targets and Cancer Therapeutics ("ENA") on October 24, 2020, an oral poster presentation titled, "The preclinical characterization of the N-terminal domain androgen receptor inhibitor, EPI-7386, for the treatment of prostate cancer," presented new information about EPI-7386 including: (i) in an *in vitro* cellular thermal shift assay (CETSA), EPI-7386 was shown to physically interact with the both the full-length and the splice variant (AR-V7) form of the AR (ii) in an *in vitro* full-length AR-driven cellular model (LNCaP), RNAseq data was analyzed by pathway enrichment analysis. EPI-7386 demonstrates largely similar modulation of AR-regulated genes compared to enzalutamide, but with additional unique elements; and (iii) EPI-7386 exhibits superior activity to enzalutamide in the AR-V7-driven cellular models LNCaP95 and 22Rv1 by modulating AR-driven gene expression with or without the addition of an external androgen.

Previously, *in vitro* data had been presented demonstrating that EPI-7386 binds to the full-length AR and can inhibit the transcription of AR-regulated genes. The new data demonstrate that EPI-7386 can also physically interact with the splice variant form, AR-V7, of the androgen receptor and inhibit its activity. The importance of this interaction with AR-V7 is seen through the superior transcriptional inhibition of AR-regulated genes by EPI-7386 compared to enzalutamide in the AR-V7-driven cell models LNCaP95 and 22Rv1. Together, these data provide insights into mechanistic aspects related to the binding and utility of EPI-7386 against AR-V7 splice-variant driven prostate cancer models. The data supports the Company's rationale for studying EPI-7386 in men with prostate cancer resistant to current antiandrogens.

Future Clinical Development Program

Phase 2/3 Clinical Trial Design for treating CRPC patients

Depending on the results of the Phase 1 study, a Phase 2 single arm clinical trial evaluating the activity of EPI-7386 single agent in a larger group of biologically-characterized mCRPC patients might be conducted.

In order to ultimately obtain full single agent regulatory approval, the Company expects that at least one Phase 3 clinical trial will be required, most likely in patients similar to the population of mCRPC patients who will have been enrolled in the planned Phase 1/2 clinical trial. However, the results of the Phase 1/2 clinical trial may also suggest modification of the initial patient population based on anti-tumor response and biomarker assessment. In a Phase 3 clinical trial, the key end-point is expected to be progression-free survival or overall survival relative to patients receiving the standard-of-care. It is expected that such a Phase 3 clinical trial would be conducted at numerous sites around the world.

Competition

The competition in the prostate cancer market is very high, and many of the companies against which we compete or against which we may compete in the future have significantly greater financial resources and expertise in research and development, manufacturing, preclinical testing, conducting clinical trials, obtaining regulatory approvals and marketing approved products than we do. Mergers and acquisitions in the pharmaceutical and biotechnology industries may result in even more resources being concentrated among a smaller number of our competitors. Several pharmaceutical therapies already have approved and many new molecules are being tested for their effect in this patient population. In addition, generic forms of Zytiga (abiraterone acetate) are now approved and commercially available in the U.S.

Currently approved therapies include:

GENERIC/PROGRAM NAME	BRAND NAME	COMPANY NAME(S)	STAGE
Enzalutamide	Xtandi	Astellas and Pfizer	Marketed
Abiraterone acetate	Zytiga	Johnson & Johnson	Marketed
Sipuleucel-T	Provenge	Valeant	Marketed
Docetaxel	n/a	Sanofi and various	Marketed
Cabazitaxel	Jevtana	Sanofi	Marketed
Radium-233	Xofigo	Bayer	Marketed
Apalutamide (ARN-509)	Erleada	Johnson & Johnson	Marketed
Darolutamide	Nubeqa	Bayer	Marketed
Pembrolizumab	Keytruda	Merck	Marketed
Olaparib	Lynparza	AstraZeneca	Marketed
Rucaparib	Rubraca	Clovis Oncology	Marketed

In this market, ESSA believes that its competitive position is strong because its product candidate, if successful, involves a mechanistically unique, differentiated approach to prostate cancer involving the therapeutic modality that has been shown to make the biggest difference to the survival of recurrent prostate cancer patients: blocking AR activation. Since anitens have been shown to directly bind to AR-NTD and prevent AR-mediated transcription, they have the potential to bypass the AR-dependent resistance pathways (discussed above) that may develop as a result of treatment with current hormone-related therapies that target the AR LBD. If successful, ESSA believes this could represent a significant step forward in the treatment of prostate cancer. To ESSA's knowledge, no other antagonist to the AR-NTD is currently undergoing clinical trials for prostate cancer or any other indication. Other approaches to interfering with AR signaling include potentially complementary strategies to degrade the AR such as that being pursued by Arvinas, Inc.

Patents and Proprietary Rights

License Agreement with UBC and the BCCA

ESSA has in-licensed intellectual property embodied in issued patents, pending patents applications and know-how relating to compounds that modulate AR activity. ESSA refers to these intellectual property rights as the "Licensed IP".

The Company is party to a license agreement with the British Columbia Cancer Agency and the University of British Columbia dated December 22, 2010, as amended on February 10, 2011, May 27, 2014, and May 25, 2021 (the "License Agreement"), which provides the Company with exclusive world-wide rights to develop and commercialize products based on the Licensed IP.

ESSA paid a minimum annual royalty of C$85,000 in 2017, 2018, and 2019 and must continue to pay a minimum of C$85,000 for each year thereafter. For a First Compound entering clinical development, an additional C$50,000 and C$900,000 must be paid upon enrollment of a patient in a Phase 2 and Phase 3 clinical trial, respectively.

The Licensors may terminate the License Agreement upon ESSA's insolvency, or the License Agreement may be terminated by either party for certain material breaches by the other party. ESSA has already spent more than C$5,000,000 in connection with the commercialization of products relating directly to the Licensed IP, as required under the License Agreement. ESSA is required to allocate reasonable time to the development and commercialization of the Licensed IP and to use reasonable efforts to promote, market and sell products covered by the Licensed IP. The terms of the License Agreement required ESSA to issue to the Licensors, 1,000,034 pre-Consolidation common shares, in lieu of payment of an initial license fee. If ESSA develops products covered by the Licensed IP in the future, it will be required to pay certain development and regulatory milestone payments up to an aggregate of C$2.4 million for the first drug product developed under the license and up to an aggregate of C$510,000 for each subsequent product. ESSA must also pay the Licensors low single-digit royalties based on aggregate worldwide net sales of products covered by the Licensed IP and a percentage of sublicensing revenue in the low teens. The License Agreement will expire on the later of 20 years after the date of the License Agreement or the expiry of the last issued patent included in the Licensed IP.

ESSA's Intellectual Property Strategy

The Company currently retains all commercial rights for its aniten series drug portfolio and believes it has developed a strong and defensive intellectual property position for aniten structural classes. ESSA has licensed certain patent rights, with respect to some of its compounds that modulate AR activity, from the Licensors. ESSA has the right to acquire ownership of the licensed patents and patent applications upon specified payment to the Licensors, and providing that payments required under the License Agreement continue to be made.

As of July 2022, ESSA owns rights to 58 issued patents, including 15 issued U.S. patents, that are in force and cover multiple EPI- and aniten structural classes of compounds with different structural motifs/analogues. As of July 2022, 5 of these issued patents cover the EPI-7386 compound and are expected to provide protection until 2036 to 2041. Patent applications are also pending in the United States and in contracting states to the Patent Cooperation Treaty for the aniten next-generation NTD inhibitors, with expected expiration dates between 2036-2041.

Both ESSA and the broader pharmaceutical industry attach significant importance to patents for the protection of new technologies, products and processes. Accordingly, ESSA's success depends, in part, on its ability to obtain patents or rights thereto, to protect commercial secrets and carry on activities without infringing the rights of third parties. See "*Risk Factors*" in our Annual Report on Form 10-K. Where appropriate, and consistent with management's objectives, ESSA will continue to seek patents in relation to components or concepts of its technology that it perceives to be important.

Regulatory Environment

The production and manufacture of ESSA's product candidate and potential future product candidates and its R&D activities are subject to regulation for safety, efficacy, quality and ethics by various governmental authorities around the world. In the United States, drugs and biological products are subject to regulation by the FDA. In Canada, these activities are regulated by the Food and Drugs Act and the rules and regulations thereunder, which are enforced by the TPD. Drug approval laws require registration of manufacturing facilities, carefully controlled research and testing of product candidates, government review and approval of experimental results prior to giving approval to sell drug products. Regulators also require that rigorous and specific standards such as cGMP, good laboratory practices ("GLP") and current good clinical practices ("GCP") are followed in the manufacture, testing and clinical development respectively of any drug product. See "*Risk Factors*" in our Annual Report on Form 10-K.

The process of obtaining regulatory approvals and the corresponding compliance with appropriate federal, state, local and foreign statutes and regulations requires the expenditure of substantial time and financial resources. Failure to comply with the applicable U.S. requirements at any time during the product development process, approval process or after approval may subject an applicant or sponsor to a variety of administrative or judicial sanctions, including refusal by the FDA to approve pending applications, withdrawal of an approval, imposition of a clinical hold, issuance of warning letters and other types of enforcement letters, product recalls, product seizures, total or partial suspension of production or distribution, injunctions, fines, refusals of government contracts, restitution, disgorgement of profits, or civil or criminal investigations and penalties brought by the FDA and the Department of Justice or other governmental entities.

Drug Products Development Process

An applicant seeking approval to market and distribute a new drug product in the United States must typically undertake the following:

- completion of extensive nonclinical, sometimes referred to as preclinical laboratory tests, and preclinical animal trials in compliance with applicable requirements for the humane use of laboratory animals and formulation studies, including GLPs;
- submission to the FDA of an IND, which must take effect before human clinical trials may begin;
- approval by an institutional review board ("IRB"), representing each clinical site before each clinical trial may be initiated;
- performance of adequate and well-controlled human clinical trials according to the FDA's regulations commonly referred to as GCP regulations and any additional requirements for the protection of human research subjects and their health information, to establish the safety and efficacy of the proposed drug product for its intended use;
- preparation and submission to the FDA of a New Drug Application ("NDA");
- review of the product by an FDA advisory committee, where appropriate or if applicable;
- satisfactory completion of one or more FDA inspections of the manufacturing facility or facilities at which the product, or components thereof, are produced to assess compliance with cGMP requirements and to assure that the facilities, methods and controls are adequate to preserve the product's identity, strength, quality and purity;
- payment of user fees and securing FDA approval of the NDA; and
- compliance with any post-approval requirements, including Risk Evaluation and Mitigation Strategies ("REMS") and post-approval studies required by the FDA.

In addition to regulations in the United States, we will be subject to a variety of regulations in other jurisdictions governing, among other things, clinical studies and any commercial sales and distribution of our products.

Whether or not we obtain FDA approval for a product, we must obtain the requisite approvals from regulatory authorities in foreign countries prior to the commencement of clinical studies or marketing of the product in those countries. Certain countries outside of the United States have a similar process that requires the submission of a clinical study application much like the IND prior to the commencement of human clinical studies. In the European Union, for example, a CTA must be submitted to each country's national health authority and an independent ethics committee, much like the FDA and IRB, respectively. Once the CTA is approved in accordance with a country's requirements, clinical study development may proceed.

The requirements and process governing the conduct of clinical studies, product licensing, coverage, pricing and reimbursement vary from country to country. In all cases, the clinical studies are conducted in accordance with GCP and the applicable regulatory requirements and the ethical principles that have their origin in the Declaration of Helsinki.

Preclinical Studies

Preclinical studies are conducted *in vitro* and in animals to evaluate pharmacokinetics, metabolism and possible toxic effects to provide evidence of the safety of the product candidate prior to its administration to humans in clinical studies and throughout development. The conduct of preclinical studies is subject to federal regulations and requirements, including GLP regulations. The results of the preclinical tests, together with manufacturing information, analytical data, any available clinical data or literature and plans for clinical studies, among other things, are submitted to the FDA as part of an IND. Some long-term preclinical testing, such as animal tests of reproductive adverse events and carcinogenicity, may continue after the IND is submitted.

Initiation of Human Testing

Clinical trials involve the administration of the investigational product to human subjects under the supervision of qualified investigators in accordance with GCP requirements, which include, among other things, the requirement that all research subjects provide their informed consent in writing before their participation in any clinical trial. Clinical trials are conducted under written trial protocols detailing, among other things, the objectives of the trial, the parameters to be used in monitoring safety and the effectiveness criteria to be evaluated. A protocol for each clinical trial and any subsequent protocol amendments must be submitted to the FDA as part of the IND. An IND automatically becomes effective 30 days after receipt by the FDA, unless before that time the FDA raises concerns or questions related to a proposed clinical trial and places the trial on clinical hold. In such a case, the IND sponsor and the FDA must resolve any outstanding concerns before the clinical trial can begin. In Canada, this application is called a CTA. An IND/CTA application must be filed and accepted by the FDA or TPD, as applicable, before human clinical trials may begin. In addition, an IRB representing each institution participating in the clinical trial must review and approve the plan for any clinical trial before it commences at that institution, and the IRB must conduct continuing review and reapprove the trial at least annually. The IRB must review and approve, among other things, the trial protocol and informed consent information to be provided to trial subjects. An IRB must operate in compliance with FDA regulations.

Two key factors influencing the rate of progression of clinical trials are the rate at which patients can be enrolled to participate in the research program and whether effective treatments are currently available for the disease that the drug is intended to treat. Patient enrollment is largely dependent upon the incidence and severity of the disease, the treatments available and the potential side effects of the drug to be tested and any restrictions for enrollment that may be imposed by regulatory agencies.

Phase 1 Clinical Trials

Phase 1 clinical trials for cancer therapeutics are typically conducted on a small number of patients to evaluate safety, dose limiting toxicities, tolerability, pharmacokinetics and to determine the dose for Phase 2 clinical trials in humans.

Phase 2 Clinical Trials

Phase 2 clinical trials typically involve a larger patient population than Phase 1 clinical trials and are conducted to identify possible adverse effects and safety risks, to preliminarily evaluate the efficacy of a product candidate for specific targeted diseases and to determine dosage tolerance, optimal dosage and dosing schedule.

Phase 3 Clinical Trials

Phase 3 clinical trials typically involve testing an experimental drug on a much larger population of patients suffering from the targeted condition or disease – in ESSA's case, CRPC. These studies involve testing the experimental drug in an expanded patient population at geographically dispersed test sites (multi-center trials) to establish clinical safety and effectiveness. These trials also generate information from which the overall risk-benefit relationship relating to the drug can be determined.

In most cases FDA requires two adequate and well controlled Phase 3 clinical trials to demonstrate the efficacy of the drug. A single Phase 3 trial with other confirmatory evidence may be sufficient in rare instances where the trial is a large multicenter trial demonstrating internal consistency and a statistically very persuasive finding of a clinically meaningful effect on mortality, irreversible morbidity or prevention of a disease with a potentially serious outcome and confirmation of the result in a second trial would be practically or ethically impossible.

New Drug Application

Assuming successful completion of required clinical testing and other requirements, the results of the preclinical and clinical studies, together with detailed information relating to the product's chemistry, manufacture, controls and proposed labeling, among other things, are submitted to the FDA as part of an NDA, or the TPD as part of a New Drug Submission ("NDS"), requesting approval to market the drug product for one or more indications. The NDS or NDA is then reviewed by the applicable regulatory body for approval to market the drug.

The FDA conducts a preliminary review of an NDA within 60 days of its receipt and informs the sponsor by the 74th day after the FDA's receipt of the submission to determine whether the application is sufficiently complete to permit substantive review. The FDA may request additional information rather than accept an NDA for filing. In this event, the application must be resubmitted with the additional information. The resubmitted application is also subject to review before the FDA accepts it for filing. Once the submission is accepted for filing, the FDA begins an in-depth substantive review. The FDA has agreed to specified performance goals in the review process of NDAs. Most such applications are meant to be reviewed within ten months from the date of filing, and most applications for "priority review" products are meant to be reviewed within nine months of filing. The review process may be extended by the FDA for three additional months to consider new information or clarification provided by the applicant to address an outstanding deficiency identified by the FDA following the original submission.

Before approving an NDA, the FDA typically will inspect the facility or facilities where the product is or will be manufactured. These pre-approval inspections cover all facilities associated with an NDA submission, including drug component manufacturing (such as Active Pharmaceutical Ingredients), finished drug product manufacturing, and control testing laboratories. The FDA will not approve an application unless it determines that the manufacturing processes and facilities are in compliance with cGMP requirements and adequate to assure consistent production of the product within required specifications. Additionally, before approving an NDA, the FDA will typically inspect one or more clinical sites to assure compliance with GCP.

The cost of preparing and submitting an NDA is substantial. The submission of most NDAs is additionally subject to a substantial application user fee, currently exceeding $2,500,000 and the manufacturer or sponsor under an approved new drug application are also subject to significant annual program and establishment user fees. These fees are typically increased annually.

On the basis of the FDA's evaluation of the NDA and accompanying information, including the results of the inspection of the manufacturing facilities, the FDA may issue an approval letter or a complete response letter. An approval letter authorizes commercial marketing of the product with specific prescribing information for specific indications. A complete response letter generally outlines the deficiencies in the submission and may require substantial additional testing or information in order for the FDA to reconsider the application. If and when those deficiencies have been addressed to the FDA's satisfaction in a resubmission of the NDA, the FDA will issue an approval letter. The FDA has committed to reviewing such resubmissions in two or nine months depending on the type of information included. Even with submission of this additional information, the FDA ultimately may decide that the application does not satisfy the regulatory criteria for approval.

If the FDA approves a product, it may limit the approved indications for use for the product, require that contraindications, warnings or precautions be included in the product labeling, require that post-approval studies, including Phase 4 clinical trials, be conducted to further assess the drug's safety after approval, require testing and surveillance programs to monitor the product after commercialization, or impose other conditions, including distribution restrictions or other risk management mechanisms which can materially affect the potential market and profitability of the product. The FDA may prevent or limit further marketing of a product based on the results of post-market studies or surveillance programs. After approval, many types of changes to the approved product, such as adding new indications, manufacturing changes and additional labeling claims, are subject to further testing requirements and FDA review and approval.

Post-Approval Requirements

Drugs manufactured or distributed pursuant to FDA approvals are subject to pervasive and continuing regulation by the FDA, including, among other things, requirements relating to recordkeeping, periodic reporting, product sampling and distribution, advertising and promotion and reporting of adverse experiences with the product. After approval, significant changes to the approved product, such as adding new indications or other labeling claims, are subject to prior FDA review and approval. There also are continuing, annual user fee requirements for any marketed products and the establishments at which such products are manufactured, as well as new application fees for supplemental applications with clinical data.

In addition, drug manufacturers and other entities involved in the manufacture and distribution of approved drugs are required to register their establishments with the FDA and state agencies, and are subject to periodic unannounced inspections by the FDA and these state agencies for compliance with cGMP requirements. Changes to the manufacturing process are strictly regulated and often require prior FDA approval before being implemented. FDA regulations also require investigation and correction of any deviations from cGMP and impose reporting and documentation requirements upon the sponsor and any third-party manufacturers that the sponsor may decide to use. Accordingly, manufacturers must continue to expend time, money, and effort in the area of production and quality control to maintain cGMP compliance.

Once an approval is granted, the FDA may withdraw the approval if compliance with regulatory requirements and standards is not maintained or if problems occur after the product reaches the market. Later discovery of previously unknown problems with a product, including adverse events of unanticipated severity or frequency, or with manufacturing processes, or failure to comply with regulatory requirements, may result in revisions to the approved labeling to add new safety information; imposition of post-market studies or clinical trials to assess new safety risks; or imposition of distribution or other restrictions under a REMS program. Other potential consequences include, among other things:

- restrictions on the marketing or manufacturing of the product, complete withdrawal of the product from the market or product recalls;
- fines, warning letters or holds on post-approval clinical trials;
- refusal of the FDA to approve pending NDAs or supplements to approved NDAs, or suspension or revocation of product license approvals;
- product seizure or detention, or refusal to permit the import or export of products; or
- injunctions or the imposition of civil or criminal penalties.

The FDA strictly regulates marketing, labeling, advertising and promotion of products that are placed on the market. Drugs may be promoted only for the approved indications and in accordance with the provisions of the approved label. The FDA and other agencies actively enforce the laws and regulations prohibiting the promotion of off-label uses, and a company that is found to have improperly promoted off-label uses may be subject to significant liability.

In addition, the distribution of prescription pharmaceutical products is subject to the Prescription Drug Marketing Act, or PDMA, which regulates the distribution of drugs and drug samples at the federal level, and sets minimum standards for the registration and regulation of drug distributors by the states. Both the PDMA and state laws limit the distribution of prescription pharmaceutical product samples and impose requirements to ensure accountability in distribution.

Orphan Designation and Exclusivity

ESSA may, in the future, seek orphan drug designation for its product candidates. Under the Orphan Drug Act, the FDA may designate a drug product as an "orphan drug" if it is intended to treat a rare disease or condition (generally meaning that it affects fewer than 200,000 individuals in the United States, or more in cases in which there is no reasonable expectation that the cost of developing and making a drug product available in the United States for treatment of the disease or condition will be recovered from sales of the product). A company must request orphan product designation before submitting an NDA. If the request is granted, the FDA will disclose the identity of the therapeutic agent and its potential use. Orphan product designation does not convey any advantage in or shorten the duration of the regulatory review and approval process.

If a product with orphan status receives the first FDA approval for the disease or condition for which it has such designation, the product generally will receive orphan product exclusivity. Orphan product exclusivity means that the FDA may not approve any other applications for the same product for the same indication for seven years, except in certain limited circumstances. Competitors may receive approval of different products for the indication for which the orphan product has exclusivity and may obtain approval for the same product but for a different indication. If a drug or drug product designated as an orphan product ultimately receives marketing approval for an indication broader than what was designated in its orphan product application, it may not be entitled to exclusivity.

Selected Quarterly Financial Information

The following table sets forth ESSA's unaudited consolidated financial data for each of the last eight quarters, prepared in accordance with U.S. GAAP. The Company has not earned any revenues or declared dividends as of June 30, 2022:

	For the Quarters Ended			
	June 30, 2022	March 31, 2022	December 31, 2021	September 30, 2021
Research and development expense	$ 6,394,534	$ 7,649,459	$ 6,019,759	$ 6,273,052
General and administration	2,895,542	3,817,370	3,062,170	2,942,432
Comprehensive income (loss)	(8,829,694)	(10,903,335)	(9,097,919)	(8,559,499)
Basic and diluted earnings (loss) per share	(0.20)	(0.25)	(0.21)	(0.19)
Cash and cash equivalents	67,868,096	86,235,830	121,058,121	137,825,024
Short-term investments	106,727,807	94,782,609	68,141,166	57,102,159
Total assets	175,660,846	182,609,005	191,486,181	198,165,818
Long-term liabilities	111,273	145,268	288,971	230,603
Working capital	171,150,678	178,353,354	187,291,085	193,668,414

	For the Quarters Ended			
	June 30, 2021	March 31, 2021	December 31, 2020	September 30, 2020
Research and development expense	$ 6,231,908	$ 7,268,257	$ 4,485,772	$ 2,236,680
General and administration	3,117,900	4,615,332	2,208,917	2,200,159
Comprehensive income (loss)	(8,752,011)	(12,965,247)	(6,528,704)	(4,553,342)
Basic and diluted earnings (loss) per share	(0.21)	(0.36)	(0.20)	(0.17)
Cash and cash equivalents	145,194,181	151,562,303	52,484,512	56,320,763
Short-term investments	57,068,822	57,034,921	22,016,344	22,011,337
Total assets	203,524,045	210,001,054	76,174,988	80,574,565
Long-term liabilities	817,735	1,413,292	38,246	127,376
Working capital	199,949,211	206,202,601	73,861,974	79,038,442

ESSA has never been profitable and has incurred net losses since inception. ESSA's comprehensive losses were $28,830,948 and $28,245,962 for the nine months ended June 30, 2022, and 2021 respectively. ESSA expects to incur losses for the foreseeable future, and it expects these losses to increase as it continues the development of, and seek regulatory approvals for, its product candidate. Because of the numerous risks and uncertainties associated with product development, ESSA is unable to predict the timing or amount of increased expenses or when, or if, it will be able to achieve or maintain profitability.

Results of Operations for the Nine Months Ended June 30, 2022 and 2021

There was no revenue in any of the periods ended as reported. The Company incurred a comprehensive loss of $28,830,948 for the nine months ended June 30, 2022 compared to a comprehensive loss of $28,245,962 for the nine months ended June 30, 2021. Variations in ESSA's expenses and net loss for the periods resulted primarily from the following factors:

Research and Development Expenditures

R&D expense included the following major expenses by nature:

	Three months ended		Nine months ended	
	June 30, 2022	June 30, 2021	June 30, 2022	June 30, 2021
Clinical	$ 1,756,983	$ 1,156,860	$ 3,731,044	$ 4,213,305
Consulting	66,358	225,180	418,740	519,286
Legal patents and license fees	344,118	346,366	853,700	663,219
Manufacturing	991,201	1,409,283	3,970,564	5,516,377
Other	17,848	35,904	73,618	82,235
Preclinical and data analysis	1,869,023	1,268,068	6,045,555	3,231,017
Research grants and administration	-	-	-	157,080
Royalties	-	-	82,485	66,759
Salaries and benefits	369,690	546,455	1,516,507	1,209,060
Share-based payments	872,531	1,243,792	3,253,741	2,323,185
Travel and other	106,782	-	117,798	4,414
Total	$ 6,394,534	$ 6,231,908	$ 20,063,752	$ 17,985,937

The overall R&D expense for the nine months ended June 30, 2022 was $20,063,752 compared to $17,985,937 for the nine months ended June 30, 2021 and includes non-cash expense related to share-based payments expense of $3,253,741 (2021 - $2,323,185). R&D expense in the nine month periods ended June 30, 2022 and 2021 reflects the ongoing clinical trial of EPI-7386 which commenced in July 2020.

The share-based payments expense of $3,253,741 (2021 - $2,323,185), which is a non-cash expense, relates to the value assigned to stock options and employee share purchase rights granted to key management and consultants of the Company. The expense is recognized in relation to the grant and vesting of these equity instruments, net of expiries and forfeitures, and allocated to research and development, general and administration and financing expenditures relative to the activity of the underlying optionee.

Clinical costs of $3,731,044 (2021 - $4,213,305) were generated in relation to expenditures with the Company's clinical research organizations conducting the Phase 1 clinical trial of EPI-7386.

Preclinical and data analysis costs of $6,045,555 (2021 – $3,231,017) were generated in relation to expenditures for pharmacokinetic data analysis on data from the clinical trial related to the Phase 1 study.

CMC costs of $3,970,564 (2021 - $5,516,377) included costs incurred in formulation and chemistry work around the Company's pharmaceutical characteristics of EPI-7386. CMC costs include cGMP manufacturing of EPI 7386 drug supply to support the ongoing clinical trial.

Consulting costs were $418,740 for the nine months ended June 30, 2022 (2021 - $519,286) relating to contract project management services and collaborations.

Legal patents and license fees for the period totaled $853,700 (2021 - $663,219). The Company has adopted a tiered patent strategy to protect its intellectual property as the pharmaceutical industry places significant importance on patents for the protection of new technologies, products and processes. The costs reflect that ongoing investment and timing of associated maintenance costs. The Company anticipates that there will be continued investment into patent applications.

General and Administration Expenditures

General and administrative expenses include the following major expenses by nature:

	Three months ended		Nine months ended	
	June 30, 2022	June 30, 2021	June 30, 2022	June 30, 2021
Amortization	$ 135,719	$ 25,503	$ 261,671	$ 80,665
Consulting and subcontractor fees	41,235	73,478	185,292	157,274
Director fees	84,750	84,750	254,250	271,055
Insurance	482,080	242,323	1,448,983	698,158
Investor relations	117,960	115,191	454,646	491,409
Office, insurance, IT and communications	117,087	141,919	414,620	271,293
Professional fees	198,411	246,480	724,153	925,174
Regulatory fees and transfer agent	53,211	16,947	192,363	95,410
Rent	1,120	7,703	8,027	42,274
Salaries and benefits	872,863	617,119	3,021,159	2,567,566
Share-based payments	718,469	1,540,150	2,700,703	4,329,428
Travel and other	72,637	6,337	109,215	12,443
Total	$ 2,895,542	$ 3,117,900	$ 9,775,082	$ 9,942,149

General and administration expenses increased to $9,775,082 for the nine months ended June 30, 2022 from $9,942,149 in the nine months ended June 30, 2021 and includes non-cash expense related to share-based payments of $2,700,703 (2021 - $4,329,428). This non-cash expense relates to the value assigned to stock options and employees share purchase rights granted to key management and consultants of the Company. The expense is recognized in relation to the grant and vesting of these equity instruments, net of expiries and forfeitures, and allocated to research and development, general and administration and financing expenditures relative to the activity of the underlying optionee.

Director fees of $254,250 (2021 - $271,055) were incurred for remuneration paid to directors for their membership on the Board of Directors and for Board committee membership based on an annual fee structure.

Insurance expense of $1,448,983 (2021 - $698,158) relates to increased cost of insurance coverage for directors and officers of the Company as a reporting issuer and publicly listed company in the United States, as well as general liability insurance. The Company has realized an increase in premiums which is in line with market trends.

Professional fees of $724,153 (2021 - $925,174) were incurred for legal and accounting services relative to variations in corporate activities. In the prior period, the Company implemented changes with respect to its transition to a domestic issuer from foreign private issuer, including transition of financial statements to U.S. GAAP. The Company is now a U.S. domestic issuer and has ongoing costs to support compliance and contracts.

Three months ended June 30, 2022 and 2021

The Company incurred a comprehensive loss of $8,829,694 for the three months ended June 30, 2022 compared to a comprehensive loss of $8,752,011 for the three months ended June 30, 2021. The detailed changes in R&D and G&A expenses for the three months ended June 30, 2022 and 2021 are included in the tables above.

For the three months ended June 30, 2022, the Company's R&D investment continued with the ongoing clinical trial of EPI-7386. Clinical costs of $1,756,983 (2021 - $1,156,860) and ongoing preclinical costs and data analysis costs of $1,869,023 (2021 - $1,268,068) support the clinical trial and associated analysis. Manufacturing costs of $991,201 (2021 - $1,409,283) reflect the ongoing production of drug and has decreased following initial production loads and narrowing of dosage parameters.

G&A expenses were $2,895,542 (2021 - $3,117,900) for the three months ended June 30, 2022. Professional fees of $198,411 (2021 - $246,480) have decreased as there were collaboration contracts in the prior period. Salaries and benefits of $872,863 (2021 - $617,119) for the three months ended June 30, 2022 include annual bonuses paid to senior management and employees during the period. Directors' fees of $84,750 (2021 - $84,750) are paid to directors for their membership on the Board of Directors and for Board committee membership based on an annual fee structure. Insurance expense of $482,080 (2021 - $242,323) has increased relative to the Company's overall activity level and a market-wide increase in insurance costs.

Share-based payments for research and development team members were $872,531 (2021 - $1,243,792) and $718,469 (2021 – $1,540,150) for key management and personnel allocated to general and administrative costs. Share-based payments expense is non-cash and is estimated under the Black-Scholes method and expensed relative to vesting conditions for the underlying stock options.

Liquidity and Capital Resources

ESSA is a clinical stage company and does not currently generate revenue.

As of June 30, 2022, the Company has working capital of $171,150,678 (September 30, 2021 - $193,668,414). Operational activities during the three months ended June 30, 2022 were financed mainly by proceeds from the financings completed in July 2020 and February 2021. At June 30, 2022, the Company had available cash reserves and short-term investments of $174,595,903 (September 30, 2021 - $194,927,183) to settle current liabilities of $4,033,767 (September 30, 2021 - $3,929,663). At June 30, 2022, the Company believed that it had sufficient capital to satisfy its obligations as they became due and execute its planned expenditures for more than twelve months.

ESSA's future cash requirements may vary materially from those now expected due to a number of factors, including the costs associated with future preclinical work and to take advantage of strategic opportunities, such as partnering collaborations or mergers and acquisitions activities. In the future, it may be necessary to raise additional funds. These funds may come from sources such as entering into strategic collaboration arrangements, the issuance of shares from treasury, or alternative sources of financing. However, there can be no assurance that ESSA will successfully raise funds to continue its operational activities. See "*Risk Factors*" in our Annual Report on Form 10-K.

Critical Accounting Policies and Estimates

The Company makes estimates and assumptions about the future that affect the reported amounts of assets and liabilities. Estimates and judgments are continually evaluated based on historical experience and other factors, including expectations of future events that are believed to be reasonable under the circumstances. In the future, actual experience may differ from these estimates and assumptions.

The effect of a change in an accounting estimate is recognized prospectively by including it in comprehensive income in the period of the change, if the change affects that period only, or in the period of the change and future periods, if the change affects both.

The critical accounting policies are those polices that require the most significant judgments and estimates in the preparation of our condensed consolidated interim financial statements. A summary of the critical accounting policies is presented in Note 2 of the annual consolidated financial statements for the year ended September 30, 2021 filed with the SEC and with the securities commissions in Alberta and Ontario on November 18, 2021.

Trend Information

ESSA is a clinical development stage company and does not currently generate revenue. The Company is focused on the development of small molecule drugs for the treatment of prostate cancer. The Company has acquired a license to certain Licensed IP. As of the date of this Quarterly Report on Form 10-Q, no products are in commercial production or use. The Company's financial success will be dependent upon its ability to continue development of its compounds through preclinical and clinical stages to commercialization.

Off-Balance Sheet Arrangement

ESSA has no material undisclosed off-balance sheet arrangements that have, or are reasonably likely to have, a current or future effect on its results of operations, financial condition, revenues or expenses, liquidity, capital expenditures or capital resources that is material to investors.

Outstanding Share Data

As of August 4, 2022, our authorized share capital consisted of an unlimited number of common shares, each without par value, of which 44,073,076 were issued and outstanding, and an unlimited number of preferred shares, each without par value, none of which were issued and outstanding. As of August 4, 2022, we had 3,234,750 common shares issuable pursuant to 3,234,750 common share purchase warrants pursuant to full cash exercise, 4,435,985 common shares issuable pursuant to 4,435,985 exercisable outstanding stock options, 3,416,076 common shares issuable pursuant to 3,416,076 outstanding options that were not exercisable at that date, and no outstanding restricted stock units.

Safe Harbor

See "*Cautionary Note Regarding Forward-Looking Statements*" in the introduction to this Quarterly Report.