As filed with the Securities and Exchange Commission on December 16, 2022

Registration No.

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

Form S-1

REGISTRATION STATEMENT
UNDER
THE SECURITIES ACT OF 1933

PANBELA THERAPEUTICS, INC.

(Exact name of registrant as specified in its charter)

Delaware	**2834**	**88-2805017**
(State or other jurisdiction of incorporation or organization)	*(Primary Standard Industrial Classification Code Number)*	*(I.R.S. Employer Identification No.)*

712 Vista Blvd, Suite 305
Waconia, Minnesota 55387
(952) 479-1196
(Address, including zip code, and telephone number, including area code, of registrant's principal executive offices)

Jennifer K. Simpson
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(Name, address, including zip code, and telephone number, including area code, of agent for service)

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Approximate date of commencement of proposed sale to the public: As soon as practicable after the effective date of this registration statement.

If any of the securities being registered on this Form are to be offered on a delayed or continuous basis pursuant to Rule 415 under the Securities Act of 1933, as amended, check the following box. ☑

If this Form is filed to register additional securities for an offering pursuant to Rule 462(b) under the Securities Act, please check the following box and list the Securities Act registration statement number of the earlier effective registration statement for the same offering. ☐

If this Form is a post-effective amendment filed pursuant to Rule 462(c) under the Securities Act, check the following box and list the Securities Act registration statement number of the earlier effective registration statement for the same offering. ☐

If this Form is a post-effective amendment filed pursuant to Rule 462(d) under the Securities Act, check the following box and list the Securities Act registration statement number of the earlier effective registration statement for the same offering. ☐

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, a smaller reporting company or an emerging growth company. See the definitions of "large accelerated filer," "accelerated filer," "smaller reporting company," and "emerging growth company" in Rule 12b-2 of the Exchange Act.

Large accelerated filer ☐	Accelerated filer ☐
Non-accelerated filer ☑	Smaller reporting company ☑
	Emerging growth company ☐

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided to Section 7(a)(2)(B) of the Securities Act. ☐

The registrant hereby amends this registration statement on such date or dates as may be necessary to delay its effective date until the registrant shall file a further amendment which specifically states that this registration statement shall thereafter become effective in accordance with Section 8(a) of the Securities Act of 1933, as amended, or until the registration statement shall become effective on such date as the Commission, acting pursuant to said Section 8(a), may determine.

The information in this prospectus is not complete and may be changed. We may not sell these securities until the registration statement filed with the Securities and Exchange Commission is effective. This prospectus is not an offer to sell securities, and we are not soliciting offers to buy these securities, in any state where the offer or sale is not permitted.

PRELIMINARY PROSPECTUS **SUBJECT TO COMPLETION** **DATED DECEMBER 16, 2022**

Up to 4,222,972 Shares of Common Stock

Warrants to purchase up to 6,334,458 Shares of Common Stock

Pre-Funded Warrants to purchase up to 4,222,972 Shares of Common Stock

This is a best efforts public offering of up to 4,222,972 shares of our common stock and common stock purchase warrants (the "common warrants") to purchase an aggregate of up to 6,334,458 shares of our common stock at an assumed combined public offering price of $3.552 per share (assuming a public offering price based on completion of a 1-for 40 reverse stock split and the last sale price of our common stock as reported by the Nasdaq Capital Market on December 12, 2022, which was $0.0888). Each share of our common stock is being sold together with common warrants to purchase 1.5 shares of our common stock. Each common warrant is assumed to have an exercise price of $ per share (100% of the public offering price per share and warrant), will be exercisable upon issuance, and will expire five years from the date of issuance.

We are also offering to those purchasers, if any, whose purchase of common stock in this offering would otherwise result in any such purchaser, together with its affiliates, beneficially owning more than 4.99% (or, at the election of such purchaser, 9.99%) of our outstanding common stock immediately following the consummation of this offering, the opportunity to purchase pre-funded warrants in lieu of shares of our common stock that would otherwise result in such purchaser's beneficial ownership exceeding 4.99% (or, at the election of such purchaser, 9.99%) of our outstanding common stock. The purchase price for each pre-funded warrant will equal the per share public offering price for the common stock in this offering less the $0.001 per share exercise price of each such pre-funded warrant. Each pre-funded warrant will be exercisable upon issuance and will not expire prior to exercise. For each pre-funded warrant we sell, the number of shares of common stock we are offering will be decreased on a one-for-one basis.

For purposes of clarity, each share of common stock or pre-funded warrant to purchase one share of common stock is being sold together with common warrants to purchase 1.5 shares of common stock.

Our common stock is listed on the Nasdaq Capital Market under the symbol "PBLA." On December 12, 2022, the last reported sale price of our common stock on the Nasdaq Capital Market was $0.0888 per share, which does not reflect the pending reverse stock split. None of the common warrants or pre-funded warrants are listed on a national securities exchange. We do not intend to apply to list the common warrants or pre-funded warrants on any national securities exchange. Without an active trading market, the liquidity of the common warrants and pre-funded warrants may be limited.

On November 29, 2022, our stockholders approved a 1-for-40 reverse stock split of our outstanding shares of common stock. Unless specifically provided otherwise herein, the share and per share information that follows in this prospectus, other than in the historical financial statements and related notes included elsewhere in this prospectus, assumes the effect of the reverse stock split, which we intend to effect prior to the offering.

Investing in our securities involves a high degree of risk. You should review carefully the risks and uncertainties described under the heading "Risk Factors" beginning on page 9 of this prospectus, and under similar headings in any amendments or supplements to this prospectus.

We have engaged Roth Capital Partners, LLC as our exclusive placement agent ("Roth" or the "placement agent") to use its reasonable best efforts to solicit offers to purchase our securities in this offering. The placement agent has no obligation to purchase any of the securities from us or to arrange for the purchase or sale of any specific number or dollar amount of the securities. Because there is no minimum offering amount required as a condition to closing in this offering the actual public offering amount, placement agent's fee, and proceeds to us, if any, are not presently determinable and may be substantially less than the total maximum offering amounts set forth above and throughout this prospectus. We have agreed to pay the placement agent the placement agent fees set forth in the table below and to provide certain other compensation to the placement agent. See "Plan of Distribution" beginning on page 69 of this prospectus for more information regarding these arrangements.

Neither the Securities and Exchange Commission nor any state securities commission has approved or disapproved of these securities or passed upon the adequacy or accuracy of this prospectus. Any representation to the contrary is a criminal offense.

	Per Share and Common Warrant	Per Pre-Funded Warrant and Common Warrant	Total
Public offering price	$	$	$
Placement Agent fees	$	$	$
Proceeds to us, before expenses(1)	$	$	$

(1) The above summary of offering proceeds does not give effect to any proceeds from the exercise of the common warrants or pre-funded warrants being issued in this offering.

Delivery of the shares of our common stock and pre-funded warrants to certain of the investors, together with accompanying common warrants, is expected to be made on or about , 2022, subject to customary closing conditions.

Roth Capital Partners

The date of this prospectus is , 2022

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You should rely only on the information contained in this prospectus. We have not, and the placement agent has not, authorized anyone to provide you with any information other than that contained in this prospectus. We take no responsibility for and can provide no assurance as to the reliability of, any other information that others may give you. This prospectus may only be used where it is legal to offer and sell our securities. The information in this prospectus is accurate only as of the date of this prospectus, regardless of the time of delivery of this prospectus or any sale of our securities. Our business, financial condition, results of operations and prospects may have changed since that date. We are not, and the placement agent is not, making an offer of these securities in any jurisdiction where the offer is not permitted.

For investors outside the United States: We have not and the placement agent has not done anything that would permit this offering or possession or distribution of this prospectus in any jurisdiction where action for that purpose is required, other than in the United States. Persons outside the United States must inform themselves about, and observe any restrictions relating to, the offering of securities and the distribution of this prospectus outside the United States.

This prospectus includes statistical and other industry and market data that we obtained from industry publications and research, surveys and studies conducted by third parties. Industry publications and third-party research, surveys and studies generally indicate that their information has been obtained from sources believed to be reliable, although they do not guarantee the accuracy or completeness of such information. We believe that the data obtained from these industry publications and third-party research, surveys and studies are reliable. We are ultimately responsible for all disclosure included in this prospectus.

You should rely only on the information contained in this prospectus, as supplemented and amended. We have not authorized anyone to provide you with information that is different. This prospectus may only be used where it is legal to sell these securities. The information in this prospectus may only be accurate on the date of this prospectus.

We urge you to read carefully this prospectus, as supplemented and amended, before deciding whether to invest in any of the securities being offered.

PROSPECTUS SUMMARY

This summary highlights information contained elsewhere in this prospectus and does not contain all of the information that you should consider in making your investment decision. Before investing in our securities, you should carefully read this entire prospectus, including our financial statements and the related notes and the information set forth under the headings "Risk Factors" and "Management's Discussion and Analysis of Financial Condition and Results of Operations" in each case included elsewhere in this prospectus. Unless otherwise stated or the context requires otherwise, references in this prospectus to "Panbela," the "Company," "we," "us," "our" and similar references refer to Panbela Therapeutics, Inc. and its subsidiaries.

Business Overview

Panbela is a clinical stage biopharmaceutical company developing disruptive therapeutics for the treatment of patients with urgent unmet medical needs. We are currently enrolling patients in our randomized double blind placebo controlled clinical trial for the treatment of pancreatic cancer and we are a regulatory and commercial collaborator in a Phase III clinical trial funded by the National Cancer Institute (the "NCI") for the study of colon cancer risk reduction and colon adenoma therapy ("CAT"), a preventative treatment approach for survivors of colorectal cancer or those who have high-risk colon polyps. In addition, we are working closely with our North American partner One-Two Therapeutics designing a Phase III registration trial for familial adenomatous polyposis ("FAP"), a rare inherited condition that can cause the growth of thousands of colorectal adenomas (i.e., adenomatous polyps), which are recognized as a key risk factor for colon cancer. We also support several investigator initiated trials and company sponsored preclinical trials including: (1) Phase I and Phase II clinical trials for the treatment of neuroblastoma ("neuroblastoma" or "NB"), funded by nonprofit organizations; (2) Phase I and Phase II clinical trial for the treatment of early-onset type 1 diabetes funded by the Juvenile Diabetes Research Foundation; (3) Phase II clinical trial for treatment of gastric cancer funded by the NCI; (4) Phase I/II clinical trial for the treatment of non-small cell lung cancer (NSCLC) possessing the STK11 mutation; and (5) preclinical studies that we have sponsored in the orphan disease and cancer fields.

The company's lead assets are ivospemin (SBP-101), Flynpovi™ (eflornithine (CPP-1X) and sulindac), and eflornithine (CPP-1X) which provide a multi-targeted approach to reset dysregulated biology present in many types of diseases such as cancer and autoimmunity. Many tumors require greatly elevated levels of polyamines to support their growth and survival. These agents target the polyamine pathway at complementary junctions which have been shown to be altered in disease. In particular, our lead assets have the potential to suppress and prevent tumor growth, enhance anti-tumor activity of other anti-cancer agents, and modulate the immune system.

Ivospemin is a proprietary polyamine analogue designed to induce polyamine metabolic inhibition. Ivospemin has demonstrated encouraging activity against metastatic disease in a clinical trial of patients with pancreatic cancer. The efficacy and safety results demonstrated in our completed Phase I clinical trial of ivospemin in combination with gemcitabine and nab-paclitaxel in the first line treatment of metastatic pancreatic cancer provides support for the current randomized, double-blind, placebo-controlled study of ivospemin in combination with gemcitabine and nab-paclitaxel in patients previously untreated for metastatic pancreatic cancer. We believe that ivospemin, if successfully developed, may represent a novel approach that effectively treats patients with pancreatic cancer and could become a dominant product in that market. Only three first-line treatment combinations, a single maintenance treatment for a subset (3-7%) of patients, and one second-line drug have been approved by the US Food and Drug Administration ("FDA") for pancreatic cancer in the last 25 years. ivospemin has received Fast Track status and orphan drug designation status for pancreatic cancer in the United States and we are currently pursuing an orphan drug designation status in Europe.

On June 15, 2022 Panbela acquired Cancer Prevention Pharmaceuticals, Inc. ("CPP"), which added the company's second lead asset, eflornithine in multiple forms. First, an investigational new drug product, Flynpovi is a combination of the polyamine synthesis inhibitor eflornithine and the non-steroidal anti-inflammatory drug sulindac and then eflornithine as a single agent. Eflornithine is an enzyme-activated, irreversible inhibitor of the enzyme ornithine decarboxylase, the first rate-limiting enzyme in the biosynthesis of polyamines. Sulindac, a non-steroidal anti-inflammatory drug (NSAID), facilitates the export and catabolism of polyamines. Flynpovi has a unique dual mechanism of action whereby it suppresses the synthesis of new polyamines and increases the export and catabolism of polyamines from the diet and microbiome. We believe Flynpovi is unique in that it is designed to treat the risk factors (e.g., polyps) that are hypothesized to lead to Familial Adenomatous Polyposis (FAP) surgeries and colon cancer and therefore may have the ability to prevent various types of colon cancer. In the FAP-310 Phase III trial, the efficacy and safety of the combination of Flynpovi (eflornithine CPP-1X) and sulindac, as compared with either drug alone, in adults with FAP was conducted. While the study missed the primary composite endpoint (Burke et al. 2020), a post-hoc analysis showed that none of the patients in the combination arm progressed to a need for lower gastrointestinal (LGI) surgery for up to 48 months compared to 13.2% and 15.7% of patients in the sulindac and eflornithine arms (Balaguer et al. 2022). These data corresponded to risk reductions for the need for LGI surgery approaching 100% between combination and either monotherapy. Given the statistical significance of the LGI group, a new drug application (NDA) was filed with the FDA; however, since this was based on the results of an exploratory analysis, a complete response letter (CRL) was issued. To address the CRL, the Company, together with an existing North American license partner, is designing a Phase III registration trial which is scheduled to begin in the first-half of 2023. There are no currently approved pharmaceutical therapies for FAP.

Additional programs are evaluating a single agent tablet eflornithine or high dose powder eflornithine sachet for several indications including prevention of gastric cancer, treatment of high-risk refractory neuroblastoma, recent onset Type 1 diabetes, and STK-11 mutant NSCLC. Preclinical studies as well as Phase I or Phase II investigator-initiated trials suggest that eflornithine treatment is well tolerated and has potential activity.

Flynpovi has received Fast Track designation in the United States and orphan drug designation status for FAP in the United States and Europe. In addition, we have received orphan drug designation status for eflornithine as a single agent for Neuroblastoma in the United States and Europe and for gastric cancer in the United States.

Holding Company Reorganization

Effective June 15, 2022, Panbela became a successor issuer to Panbela Research, Inc. (formerly known as Panbela Therapeutics, Inc., the "Predecessor") pursuant to a holding company reorganization in which the Predecessor became a direct, wholly-owned subsidiary of Panbela. Panbela became a successor issuer to the Predecessor by operation of Rule 12g-3(a) promulgated under the Securities Exchange Act of 1934, as amended the ("Exchange Act").

CPP Acquisition

On June 15, 2022, Panbela acquired CPP, a private clinical stage company developing therapeutics to reduce the risk and recurrence of cancer and rare diseases, via merger for consideration consisting of (a) 6,587,576 shares of common stock, (b) 731,957 shares of common stock that remained subject to a holdback escrow (as defined in the Merger Agreement), (c) replacement options to purchase up to 1,596,754 shares of common stock at a weighted average exercise price of $0.35 per share, and (d) replacement warrants to purchase up to 338,060 shares of common stock at a weighted average exercise price of $4.145 per share, and post-closing contingent payments up to a maximum of $60 million, subject to satisfaction of milestones.

Clinical Trials

Ivospemin (SBP-101)

In August 2015, the FDA accepted our Investigational New Drug ("IND") application for our ivospemin product candidate. We have completed an initial clinical trial of ivospemin in patients with previously treated locally advanced or metastatic pancreatic cancer. This was a Phase I, first-in-human, dose-escalation, safety study. From January 2016 through September 2017, we enrolled twenty-nine patients into six cohorts, or groups, in the dose-escalation phase of the Phase I trial. No drug-related bone marrow toxicity or peripheral neuropathy was observed at any dose level. In addition to being evaluated for safety, 23 of the 29 patients were evaluable for preliminary signals of efficacy prior to or at the eight-week conclusion of their first cycle of treatment using the Response Evaluation Criteria in Solid Tumors ("RECIST"), the currently accepted standard for evaluating change in the size of tumors.

In 2018, we began enrolling patients in our second clinical trial, a Phase Ia/Ib study of the safety, efficacy, and pharmacokinetics of ivospemin administered in combination with two standard-of-care chemotherapy agents, gemcitabine and nab-paclitaxel. A total of 25 subjects were enrolled in 4 cohorts to evaluate the dosage level and schedule. An additional 25 subjects were enrolled in the expansion phase of the trial. Interim results were presented in January of 2022. Best response in evaluable subjects (cohorts 4 and Ib N=29) was a Complete Response (CR) in 1 (3%), Partial Response (PR) in 13 (45%), Stable Disease (SD) in 10 (34%) and Progressive Disease (PD) in 5 (17%)**.** One subject did not have post baseline scans with RECIST tumor assessments. Median Progression Free Survival ("PFS"), now final at 6.5 months may have been negatively impacted by drug dosing interruptions to evaluate potential toxicity. Median overall survival in Cohort 4 + Phase Ib was 12.0 months when data was presented in January 2022 and is now final at 14.6 months. Two patients from cohort 2 have demonstrated long term survival. One at 30.3 months (final data) and one at 33.0 months and still alive. Seven subjects are still alive at this time, one from cohort 2 and six from cohort 4 plus Ib.

In January of 2022, the Company announced the initiation of a new pancreatic cancer clinical trial. Referred to as ASPIRE, the trial is a randomized double-blind placebo-controlled trial in combination with gemcitabine and nab-paclitaxel, a standard pancreatic cancer treatment regimen, in patients previously untreated for metastatic pancreatic cancer. The trial will be conducted globally at approximately 95 sites in the United States, Europe and Asia - Pacific.

The Aspire trial commenced early this year and, while opening of clinical sites in the US and the rest of the world has been slower than originally anticipated, due in part to resource fatigue in the medical community, the Company expects all countries and sites to be open by early 2023.

The trial was originally designed as a Phase II/III with a smaller sample size (150) to support the events required for interim analysis based on Progression Free Survival (PFS) and a primary endpoint of overall survival. In response to European and FDA regulatory feedback the study was amended to include the total trial sample size (600) and the design modified to utilize overall survival as the primary endpoint to be examined at interim analysis. PFS will also be analyzed to provide additional efficacy evidence. This amendment was supported by the final data from the Phase Ia/b first line metastatic pancreatic cancer trial which completed enrollment in December of 2020. The study will enroll 600 subjects and is anticipated to take 36 months for complete enrollment with the interim analysis available in early 2024**.**

If we can successfully complete all FDA recommended clinical studies, we intend to seek marketing authorization from the FDA, the European Medicines Agency ("EMA") (European Union), Ministry of Health and Welfare (Japan) and TGA (Australia). The submission fees may be waived when ivospemin has been designated an orphan drug in each geographic region.

Additionally, in early April 2022, the Company announced a poster presentation highlighting the results for ivospemin as a polyamine metabolism modulator in ovarian cancer at the American Association for Cancer Research Annual Conference The poster concludes that the ivospemin treatment of C57Bl/6 mice injected with VDID8+ ovarian cancer cells significantly prolonged survival and decreased overall tumor burden. The results suggest that ivospemin may have a role in the clinical management of ovarian cancer, and the Company intends to continue pre-clinical and clinical studies in ovarian cancer.

FLYNPOVI

In December 2009, the FDA accepted our IND application for the combination product, Flynpovi. Flynpovi showed promising results in a NCI supported randomized, placebo-controlled Phase IIb/III clinical trial to prevent recurrent colon adenomas, particularly high-risk pre-cancerous polyps in which 375 subjects who had resected sporadic adenoma were treated for 3 years with eflornithine (500 mg once a day) + sulindac (150 mg once a day [N = 191]) or matched placebo/placebo (N = 184). Results demonstrated a marked risk reduction (70%) in developing metachronous adenomas, 92% risk reduction in developing advanced adenomas, and 95% risk reduction in developing multiple adenomas with the active combination regimen compared to placebo (Meyskens et al. 2008). This combination regimen was generally well tolerated.

Given the similar mechanism of disease in sporadic and FAP-associated adenomatous polyposis, and the mechanism of action of Flynpovi in prevention of progressive polyposis in both the general population with sporadic adenomas and in patients with FAP, a Phase III program in FAP, and a Phase III program to study colon cancer risk reduction in partnership with the Southwest Oncology Group (SWOG) and the NCI were initiated.

In the FAP-310 Phase III study completed in 2019, the efficacy and safety of the combination of eflornithine and sulindac, as compared with either drug alone, in adults with familial adenomatous polyposis was conducted (Burke et al. 2020). The patients were randomly assigned in a 1:1:1 ratio to receive eflornithine, sulindac, or both once daily for up to 48 months. The primary end point, assessed in a time-to-event analysis, was disease progression, defined as a composite of major surgery, endoscopic excision of advanced adenomas, diagnosis of high-grade dysplasia in the rectum or pouch, or progression of duodenal disease. A total of 171 patients underwent randomization. Disease progression occurred in 18 of 56 patients (32%) in the eflornithine-sulindac group, 22 of 58 (38%) in the sulindac group, and 23 of 57 (40%) in the eflornithine group, with a hazard ratio of 0.71 (95% confidence interval [CI], 0.39 to 1.32) for eflornithine-sulindac as compared with sulindac (P = 0.29) and 0.66 (95% CI, 0.36 to 1.23) for eflornithine-sulindac as compared with eflornithine (Burke et al. 2020). Adverse and serious adverse events were similar across the treatment groups. In a post-hoc analysis, none of the patients in the combination arm progressed to a need for LGI surgery for up to 48 months compared with 7 (13.2%) and 8 (15.7%) patients in the sulindac and eflornithine arms (Balaguer et al. 2022). These data corresponded to risk reductions for the need for LGI surgery approaching 100% between combination and either monotherapy with HR = 0.00 (95% CI, 0.00-0.48; p = 0.005) for combination versus sulindac and HR = 0.00 (95% CI, 0.00-0.44; p = 0.003) for combination versus eflornithine. Given the statistical significance of the LGI group, an NDA was filed with the FDA. As the study failed to meet the primary endpoint, and the NDA was based on the results of an exploratory analysis, a complete response letter was issued. To address this deficiency concern, the Company must submit the results of one or more adequate and well-controlled clinical trials which demonstrate an effect on a clinical endpoint.

In collaboration with the NCI, and SWOG, a Phase III clinical trial has been initiated to study the benefits of Flynpovi as a therapeutic treatment for use by colon cancer survivors. The trial is named PACES for "Prevention of Adenomas and Cancer with eflornithine and sulindac." The PACES trial is funded by the NCI and managed by the Southwest Oncology Group ("SWOG"). This is an ongoing double blind placebo-controlled trial of Flynpovi to prevent recurrence of high risk adenomas and second primary colorectal cancers in patients with stage 0-III colon or rectal cancer, Phase III – Preventing Adenomas of the Colon With Eflornithine and Sulindac ("PACES"). The purpose of this study is to assess whether Flynpovi (compared to corresponding placebos) has a reduced rate of cancer or high-risk adenoma recurrence compared to comparator arms after three years of daily dosing. We have exclusive rights to the data that comes from the trial for regulatory and commercial purposes. The Company is evaluating its options for CAT in the European Union and Asia.

On July 16, 2021, CPP entered into a license agreement with One-Two Therapeutics Assets Limited ("One-Two"). Under the license agreement, One-Two has licensed the North American development and commercialization rights for CPP's asset, Flynpovi, a combination pharmaceutical product formulated for oral delivery for the FAP indication in adults, as described in the Company's IND application. As the result of this license agreement, the FAP registration trial is fully funded and is scheduled to begin in the first-half of 2023.

Eflornithine (CPP-1X) and eflornithine sachets (CPP-1X-S)

For the single agent eflornithine, there is a trial ongoing evaluating eflornithine sachets (CPP-1X-S) in relapsed refractory neuroblastoma supported by the Children's' Oncology Group (COG) and NCI. Additionally, a Phase I/II trial in STK11 mutation patients with non-small cell lung cancer and Phase II trial in Recent Onset Type I diabetes with eflornithine are scheduled to begin late this year. Lastly, a Phase II trial evaluating eflornithine for the prevention of gastric cancer was completed in 2021 with data analysis ongoing.

Recent Developments

Reverse Stock Split

On November 29, 2022, at a special meeting of stockholders, our stockholders approved an amendment to our Amended and Restated Certificate of Incorporation to effect a 1-for-40 reverse stock split of our outstanding shares of common stock. We intend to effect the reverse stock split prior to this offering to ensure a sufficient number of shares of authorized common stock is available to complete the offering.

The common stock purchase warrants we issued in October 2022 provide that their exercise price will be reduced to the lowest volume-weighted average price on any trading day during the five-trading day period immediately following the date a reverse stock split is effected. Accordingly, we are unable to estimate the adjustment, if any, to the exercise price of those outstanding warrants that would result from the pending reverse stock split. Although the common stock purchase warrants offered pursuant to this prospectus contain a similar provision, because the reverse stock split will be effected before the offering, no such adjustment will be made to the exercise price of those warrants.

Product Developments

Through December 15, 2022, we had:

- secured an orphan drug designation for ivospemin from the FDA;
- submitted and received acceptance from the FDA for an IND application for ivospemin;
- received Country approvals for the Aspire Trial in Australia, France, Italy and Spain;
- completed a Phase Ia monotherapy safety study of ivospemin in the treatment of patients with metastatic pancreatic ductal adenocarcinoma;
- received "Fast Track" designation from the FDA for ivospemin for metastatic pancreatic cancer;
- completed enrollment and released interim results in our second trial a Phase Ia /Ib clinical study of ivospemin, a first-line study with ivospemin given in combination with a current standard of care in patients with pancreatic ductal adenocarcinoma who were previously untreated for metastatic disease; a total of 50 subjects were enrolled in this study, 25 in the Phase Ia and 25 in the Phase Ib or expansion phase;
- secured a two year research agreement with Johns Hopkins School of Medicine led by Professor Robert Casero, an internationally recognized researcher in polyamine biology;
- completed process improvement measures expected to be scalable for commercial use and received issue notification for a patent covering this new shorter synthesis of ivospemin;
- initiated a randomized, double-blind, placebo controlled study with ivospemin given in combination with gemcitabine and nab-paclitaxel in patients with pancreatic ductal adenocarcinoma who are previously untreated for metastatic disease;
- completed preclinical evaluation of ivospemin for use as neoadjuvant therapy in resectable pancreatic cancer prior to surgery;

- obtained early, preclinical, indication of tumor growth inhibition activity in ovarian cancer and presented the results at ASCO-GI conference;
- received USAN adoption of the nonproprietary name of ivospemin for SBP-101; and
- acquired and integrated CPP, adding a second lead asset in multiple forms and an expansive clinical development program ranging from pre-clinical to registration level clinical trials.

Risks Associated with Our Business

Our business is subject to many significant risks, as more fully described in the section titled "Risk Factors" immediately following this prospectus summary. You should read and carefully consider these risks, together with the risks set forth under the section titled "Risk Factors" and all of the other information in this prospectus, including the financial statements and the related notes included elsewhere in this prospectus, before deciding whether to invest in our securities. If any of the risks discussed in this prospectus actually occur, our business, financial condition or operating results could be materially and adversely affected. In particular, our risks include, but are not limited to, the following:

- our lack of diversification and the corresponding risk of an investment in our Company;
- potential deterioration of our financial condition and results due to failure to diversify;
- our ability to successfully complete acquisitions and integrate operations for new product candidates;
- our ability to obtain additional capital, on acceptable terms or at all, required to implement our business plan;
- final results of our Phase I clinical trials in first line metastatic pancreatic cancer and early onset Type I onset diabetes;
- progress and success of our randomized double-blind placebo controlled clinical trial;
- progress and success of registration trial conducted by our Flynpovi licensing partner;
- our ability to demonstrate safety and effectiveness of our product candidates;
- our ability to obtain regulatory approvals for our product candidates in the United States, the European Union, or other international markets;
- the market acceptance and future sales of our product candidates;
- the cost and delays in product development that may result from changes in regulatory oversight applicable to our product candidates;
- the rate of progress in establishing reimbursement arrangements with third-party payors;
- the effect of competing technological and market developments;
- the costs involved in filing and prosecuting patent applications and enforcing or defending patent claims; and
- other risk factors included under the caption "Risk Factors" starting on page 9 of this prospectus.

Implications of Being a Smaller Reporting Company

We are a "smaller reporting company" as defined in Rule 12b-2 of the Exchange Act and have elected to take advantage of certain scaled disclosure available to smaller reporting companies.

Corporate History

The primary business underlying Panbela Therapeutics, Inc., was originally incorporated under the laws of the State of Delaware under the name "Sun BioPharma, Inc." in September 2011. In 2015, it became a public company by completing a merger transaction with a wholly owned subsidiary of a public company then organized under the laws of the State of Utah. In 2016, it was reincorporated under the laws of the State of Delaware via a merger with our operating subsidiary. That company changed its name to "Panbela Therapeutics, Inc." on December 2, 2020. On June 15, 2022, we became a successor issuer to Panbela Therapeutics, Inc. and adopted its name, pursuant to a holding company reorganization via merger by operation of Rule 12g-3(a) promulgated under the Exchange Act, resulting in our current structure – consisting of two wholly owned subsidiaries: Panbela Research, Inc. and Cancer Prevention Pharmaceuticals, Inc.

Corporate Information

Our corporate mailing address is 712 Vista Blvd, #305, Waconia, MN 55387. Our telephone number is (952) 479-1196, and our website is www.panbela.com. The information on our website is not part of this prospectus. We have included our website address as a factual reference and do not intend it to be an active link to our website. The information contained in or connected to our website is not incorporated by reference into, and should not be considered part of, this prospectus. The trade names, trademarks, and service marks of other companies appearing in this prospectus are the property of the respective holders.

THE OFFERING

Common stock offered by us	4,222,972 shares of our common stock
Common warrants offered by us	Warrants to purchase up to 6,334,458 shares of our common stock, which will be exercisable during the period commencing on the date of their issuance and ending five years from such date at an exercise price of $ per share of common stock.
Pre-funded warrants offered by us	We are also offering to certain purchasers whose purchase of our common stock in this offering would otherwise result in the purchaser, together with its affiliates, beneficially owning more than 4.99% (or, at the election of the purchaser, 9.99%) of our outstanding shares of common stock immediately following the consummation of this offering, the opportunity to purchase pre-funded warrants (together with the common warrants, the "warrants") in lieu of common stock that would otherwise result in any such purchaser's beneficial ownership exceeding 4.99% (or, at the election of the purchaser, 9.99%) of our outstanding shares of common stock. Each pre-funded warrant will be exercisable for one share of common stock. The purchase price of each pre-funded warrant and the accompanying common warrant will equal the price at which the common stock and the accompanying common warrant are being sold to the public in this offering, minus $0.001, and the exercise price of each pre-funded warrant will be $0.001 per share. The pre-funded warrants will be exercisable immediately and may be exercised at any time until exercised in full. For each pre-funded warrant we sell, the number of shares of common stock we are offering will be decreased on a one-for-one basis. Because we will issue common warrants to purchase 1.5 shares of common stock for each share of common stock and for each pre-funded warrant sold in this offering, the number of common warrants sold in this offering will not change as a result of a change in the mix of the shares of our common stock and pre-funded warrants sold.
Public offering price	$3.552 per share of common stock and accompanying common warrant, or $3.551 per pre-funded warrant and accompanying common warrant, as applicable.
Common stock outstanding before this offering	1,022,249 shares
Common stock to be outstanding immediately after this offering	5,245,221 shares (assuming we sell only shares of common stock and no pre-funded warrants, and none of the common warrants issued in this offering are exercised).
Use of proceeds	We estimate that the net proceeds from this offering will be approximately $13.7 million, based on an assumed combined public offering price of $3.552 per share of common stock and accompanying common warrant, after deducting the placement agent fees and estimated offering expenses payable by us. We intend to use the net proceeds from this offering for the continued clinical development of our product candidates ivospemin and eflornithine and for working capital, and other general corporate purposes, which may include repayment of debt. Because this is a best efforts offering with no minimum amount as a condition to closing, we may not sell all or any of the securities offered hereby. As a result, we may receive significantly less in net proceeds than we currently estimate. See "Use of Proceeds" on page 22.

Risk Factors	You should read the "Risk Factors" section of this prospectus beginning on page 9 for a discussion of factors to consider carefully before deciding to invest in our securities.
Nasdaq Capital Market trading symbol	"PBLA"
Reverse Stock Split	We intend to effect a 1-for-40 reverse stock split of our outstanding shares of common stock prior to this offering to ensure a sufficient number of shares of authorized common stock is available to complete the offering.

The number of shares of our common stock outstanding before and after this offering is based on 1,022,249 shares of our common stock outstanding as of December 12, 2022, and excludes:

- all shares issuable upon the exercise of warrants sold in this offering;
- 100,578 shares of common stock issuable upon the exercise of outstanding stock options as of the date of this prospectus at a weighted average exercise price of $145.64 per share;
- 50,494 additional shares of common stock reserved and available for future issuances under our equity plans; and
- 889,911 shares of common stock issuable upon exercise of stock purchase warrants at a weighted average exercise price of $38.05 per share, before any potential adjustments resulting from the pending reverse stock split.

Unless otherwise indicated, all information in this prospectus assumes no exercise of the outstanding options or warrants.

SUMMARY CONSOLIDATED FINANCIAL DATA

The following selected historical financial information is derived from our consolidated financial statements incorporated into this prospectus by reference. Our historical results for any period are not necessarily indicative of results to be expected in any other period, including the full fiscal year ending December 31, 2022. You should read this information together with the sections titled "Capitalization," "Dilution" and "Management's Discussion and Analysis of Financial Condition and Results of Operations" included elsewhere in this prospectus or incorporated by reference herein.

Summary of Consolidated Statements of Operations
(in thousands, except share and per share amounts)

	Three months ended September 30,		Nine months ended September 30,		Year ended December 31,	
	2022	2021	2022	2021	2021	2020
	(unaudited)	(unaudited)	(unaudited)	(unaudited)		
Operating Expenses:						
General and administrative	$ 1,294	$ 924	$ 4,349	$ 3,316	$ 4,587	$ 3,249
Research and development	2,329	1,286	24,563	3,383	5,423	2,505
Total operating expenses	3,623	2,210	28,912	6,699	10,010	5,754
Operating loss	(3,623)	(2,210)	(28,912)	(6,699)	(10,010)	(5,754)
Other (expense) income net	(779)	(68)	(1,286)	102	(125)	986
Net loss	$ (4,402)	$ (2,142)	$ (30,198)	$ (6,597)	$ (10,135)	$ (4,768)
Net loss per share – basic and diluted	(0.21)	$ (0.16)	(1.85)	(0.59)	$ (0.87)	$ (0.62)
Weighted average shares outstanding - basic and diluted	$ 20,780,848	13,285,223	$ 16,313,639	$ 11,122,725	11,709,035	7,732,882

Summary Consolidated Balance Sheet Information
(in thousands)

	September 30,		December 31,	
	2022	2021	2021	2020
	(unaudited)	(unaudited)		
Cash	$ 941	$ 14,072	$ 11,867	$ 9,022
Total assets	$ 4,867	$ 14,802	$ 12,872	$ 9,813
Total current liabilities	$ 7,952	$ 1,339	$ 2,660	$ 1,365
Long-term debt, net	$ 5,194	$ –	$ –	$ –
Stockholders' (deficit) equity	$ (8,279)	$ 13,463	10,212	$ 8,448

RISK FACTORS

Any investment in our securities involves a high degree of risk. Investors should carefully consider the risks described below and all of the information contained in this prospectus before deciding whether to purchase our securities. Our business, financial condition or results of operations could be materially adversely affected by these risks if any of them actually occur. This prospectus also contains forward-looking statements that involve risks and uncertainties. Our actual results could differ materially from those anticipated in these forward-looking statements as a result of certain factors, including the risks we face as described below and elsewhere in this prospectus.

Risks Related to Our Business and Financial Position

We are a pre-revenue company with a history of negative operating cash flow.

We have experienced negative cash flows for our operating activities since inception, primarily due to the investments required to commercialize our primary drug candidates, ivospemin, Flynpovi, and eflornithine. Our financing cash flows historically have been positive due to proceeds from the sale of equity securities and the issuance of promissory notes. Our net cash used in operating activities was $6.7 million and $3.9 million for the years ended December 31, 2021 and 2020, respectively, and we had working capital of $9.6 million and $8.4 million as of the same dates, respectively. Our net cash used in operating activities for the nine months ended September 30, 2022 was 10.3 million. As of September 30, 2022, we had a working capital deficit of $6.2 million. Working capital is defined as current assets less current liabilities.

Our operations are subject to all the risks, difficulties, complications and delays frequently encountered in connection with the development of new products, as well as those risks that are specific to the pharmaceutical and biotechnology industries in which we compete. Investors should evaluate us considering the delays, expenses, problems and uncertainties frequently encountered by companies developing markets for new products, services and technologies. We may never overcome these obstacles.

As a result of our current limited financial liquidity, our auditors have expressed substantial doubt regarding our ability to continue as a "going concern."

As a result of our current limited financial liquidity, our auditors' report for our 2021 financial statements, contains a statement concerning our ability to continue as a "going concern." Our limited liquidity could make it more difficult for us to secure additional financing or enter into strategic relationships on terms acceptable to us, if at all, and may materially and adversely affect the terms of any financing that we may obtain and our public stock price generally.

Our continuation as a "going concern" is dependent upon, among other things, achieving positive cash flow from operations and, if necessary, augmenting such cash flow using external resources to satisfy our cash needs. Our plans to achieve positive cash flow primarily include engaging in offerings of securities. Additional potential sources of funds include negotiating up-front and milestone payments on our current and potential future product candidates or royalties from sales of our products that secure regulatory approval and any milestone payments associated with such approved products. These cash sources could, potentially, be supplemented by financing or other strategic agreements. However, we may be unable to achieve these goals or obtain required funding on commercially reasonable terms, or at all, and therefore may be unable to continue as a going concern.

We may be unable to obtain the additional capital that is required to execute our business plan, which could restrict our ability to grow.

Our current capital and our other existing resources will be sufficient only to provide a limited amount of working capital and will not be sufficient to fund our expected continuing opportunities. While we project that our current capital resources are to fund our operations, including increased clinical trial costs, into early in the first quarter of 2023, we will require additional capital to continue to operate our business and complete our clinical development plans.

Future research and development, including clinical trial cost, capital expenditures and possible acquisitions, and our administrative requirements, such as salaries, insurance expenses and general overhead expenses, as well as legal compliance costs and accounting expenses, will require a substantial amount of additional capital and cash flow. There is no guarantee that we will be able to raise the additional capital required to fund our ongoing business on commercially reasonable terms or at all.

We intend to pursue sources of additional capital through various financing transactions or arrangements, including collaboration arrangements, debt financing, equity financing or other means. We may not be successful in locating suitable financing transactions on commercially reasonable terms, in the time period required or at all, and we may not obtain the capital we require by other means. If we do not succeed in raising additional capital, our resources will not be sufficient to fund our operations going forward.

Any additional capital raised through the sale of equity may dilute the ownership percentage of our stockholders. This could also result in a decrease in the fair market value of our equity securities because our assets would be owned by a larger pool of outstanding equity. The terms of securities we issue in future capital transactions may be more favorable to our new investors, and may include preferences, superior voting rights and the issuance of warrants or other derivative securities which may have a further dilutive effect.

Our ability to obtain needed financing may be impaired by such factors as the capital markets, both generally and in the pharmaceutical and other drug development industries in particular, the limited diversity of our activities and/or the loss of key personnel. If the amount of capital we are able to raise from financing activities is not sufficient to satisfy our capital needs, even to the extent that we reduce our operations, we may be required to cease our operations.

We may incur substantial costs in pursuing future capital financing, including investment banking fees, legal fees, accounting fees, securities law compliance fees, printing and distribution expenses and other costs, which may adversely impact our financial condition.

Our business is subject to risks arising from epidemic diseases, such as the 2020 outbreak of the COVID-19 illness.

In March of 2020, the World Health Organization declared the spread of a novel strain of coronavirus ("COVID-19") a global pandemic. Early in the pandemic, federal, state and local governmental authorities took actions to combat the spread of COVID-19, including through issuances of "stay-at-home" directives and similar mandates for many individuals to substantially restrict daily activities and for many businesses to curtail or cease normal operations. These measures, while intended to protect human life, led initially to significantly reduced economic activity. Vaccines became available at the end of 2020, and distribution in the United States accelerated during the first quarter of 2021 and then leveled off in the second quarter. In the fall of 2021, infection rates increased in the United States and other parts of the world as the result of the delta variant, and in winter of 2021, infections again increased due to the omicron variant. In the second quarter of 2022, infection rates were decreasing. The development and uncertainty of the situation continues to preclude any prediction as to the ultimate impact COVID-19 will have on the Company's business, financial condition, results of operations and cash flows, which will depend largely on future developments directly or indirectly relating to the duration and scope of the COVID-19 outbreak in the United States, Australia, Europe and the rest of the world. During the spring of 2021, the Company experienced a delay in the manufacturing of the active product substance, which is manufactured in India. There was also a delay in the final manufacturing steps which are completed in the United States, in part related to COVID-19. To date neither one of these delays has caused a disruption in supply for our clinical or preclinical testing. In January of 2022, the Company announced the opening of a global randomized clinical trial, which is expected to be conducted in the United States, Europe and Australia. While opening of clinical sites in the US and the rest of the world has been slower than originally anticipated, due in part to resource fatigue in the medical community, the Company does not expect any serious disruption to the conduct of this new clinical trial associated with COVID-19. The Company's administrative operations have been decentralized since inception so the Company experienced no administrative disruptions or additional costs due to the pandemic or related restrictions.

While we have not to date experienced any significant disruptions as a result of the pandemic, we are unable to estimate the future impact that COVID-19 could have on our operations. The recent trends in reduced infections and deaths, and increased levels of vaccination should help reduce the risk that the pandemic may slow potential enrollment of clinical trials and reduce the number of eligible patients for our clinical trials. While the pandemic could still disrupt the supply chain and the manufacture or shipment of both drug substance and finished drug product for our product candidates for preclinical testing and clinical trials, we believe that product secured in 2021 will be sufficient to complete the conduct of our new clinical trial. We often attend and present clinical updates at various medical and investor conferences throughout the year. The COVID-19 outbreak has caused, and may continue to cause, cancellations or reduced attendance of these conferences and we may need to seek alternate methods to present clinical updates and to engage with the medical and investment communities. The COVID-19 outbreak, including new variants of the virus, and future mitigation measures may also have an adverse impact on global economic conditions which could have an adverse effect on our business and financial condition and our potential to conduct financings on terms acceptable to us, if at all. The extent to which the COVID-19 outbreak impacts our results will depend on future developments that remain uncertain and cannot be predicted, including new information that may emerge concerning the severity of the virus and the actions to contain its impact.

The markets for our product candidates are highly competitive and are subject to rapid scientific change, which could have a material adverse effect on our business, results of operations and financial condition.

The pharmaceutical and biotechnology industries in which we compete are highly competitive and characterized by rapid and significant technological change. We face intense competition from organizations such as pharmaceutical and biotechnology companies, as well as academic and research institutions and government agencies. Some of these organizations are pursuing products based on technologies similar to our technology. Other of these organizations have developed and are marketing products or are pursuing other technological approaches designed to produce products that are competitive with our product candidates in the therapeutic effect these competitive products have on the diseases targeted by our product candidates. Our competitors may discover, develop or commercialize products or other novel technologies that are more effective, safer or less costly than any that we may develop. Our competitors may also obtain FDA or other regulatory approval for their products more rapidly than we may obtain approval for our product candidates.

Many of our competitors are substantially larger than we are and have greater capital resources, research and development staffs and facilities than we have. In addition, many of our competitors are more experienced in drug discovery, development and commercialization, obtaining regulatory approvals and drug manufacturing and marketing.

We anticipate that the competition with our product candidates and technology will be based on a number of factors including product efficacy, safety, availability and price. The timing of market introduction of our planned future product candidates and competitive products will also affect competition among products. We expect the relative speed with which we can develop our product candidates, complete the required clinical trials, establish strategic partners and supply appropriate quantities of the product candidate for late stage trials, if required, to be important competitive factors. Our competitive position will also depend upon our ability to attract and retain qualified personnel, to obtain patent protection in non-U.S. markets, which we currently do not have, or otherwise develop proprietary products or processes and to secure sufficient capital resources for the period between technological conception and commercial sales or out-license to pharmaceutical partners. If we fail to develop and deploy a proposed product candidate in a successful and timely manner, we will in all likelihood not be competitive.

Our lack of diversification increases the risk of an investment in our Company and our financial condition and results of operations may deteriorate if we fail to diversify.

Our Board of Directors has centered our attention on our drug development activities, which are currently focused a limited number of product candidates. Our ability to diversify our investments will depend on our access to additional capital and financing sources and the availability and identification of suitable opportunities.

Larger companies have the ability to manage their risk by diversification. However, we lack and expect to continue to lack diversification, in terms of both the nature and geographic scope of our business. As a result, we will likely be impacted more acutely by factors affecting pharmaceutical and biotechnology industries in which we compete than we would if our business were more diversified, enhancing our risk profile. If we cannot diversify our operations, our financial condition and results of operations could deteriorate.

Our business may suffer if we do not attract and retain talented personnel.

Our success will depend in large measure on the abilities, expertise, judgment, discretion, integrity and good faith of our management and other personnel in conducting our business. We have a small management team, and the loss of a key individual or inability to attract suitably qualified staff could materially adversely impact our business.

Our success depends on the ability of our management, employees, consultants and strategic partners, if any, to interpret market data correctly and to interpret and respond to economic market and other conditions in order to locate and adopt appropriate investment opportunities, monitor such investments, and ultimately, if required, to successfully divest such investments. Further, no assurance can be given that our key personnel will continue their association or employment with us or that replacement personnel with comparable skills can be found. We will seek to ensure that management and any key employees are appropriately compensated; however, their services cannot be guaranteed. If we are unable to attract and retain key personnel, our business may be adversely affected.

We may be required to defend lawsuits or pay damages for product liability claims.

Product liability is a major risk in testing and marketing biotechnology and pharmaceutical products. We may face substantial product liability exposure in human clinical trials and in the sale of products after regulatory approval. Product liability claims, regardless of their merits, could exceed policy limits, divert management's attention and adversely affect our reputation and the demand for our product. In any such event, your investment in our securities could be materially and adversely affected.

Risks Related to Acquisitions and Integrations

We have and expect to incur substantial costs related to the acquisition of CPP and subsequent integration efforts.

We have incurred and expect to incur a number of non-recurring costs associated with acquisition of CPP and related transactions. These costs include legal, financial advisory, accounting, consulting and other advisory fees, retention, severance and employee benefit-related costs, regulatory fees, closing, integration and other related costs.

Although the legal acquisition of CPP has been completed, integration may be more difficult, costly, or time-consuming than expected, and we may not realize the anticipated benefits of the underlying acquisition.

The anticipated benefits of the combined company, including product candidate diversification and growth, may not be realized fully or at all or may take longer to commercialize than expected and integration may result in additional and unforeseen expenses. An inability to realize the full extent of the anticipated benefits, as well as any delays encountered in the integration process, could have an adverse effect upon our operating results.

In addition, we and CPP operated independently prior to the completion of the acquisition. It is possible that the now-active integration process could result in the loss of one or more key employees, including employees of CPP, the disruption of each company's ongoing businesses or inconsistencies in standards, controls, procedures, and policies that adversely affect each company's ability to maintain relationships with clients, customers, depositors, and employees or to achieve the anticipated benefits of the acquisition. Integration efforts between the companies may also divert management attention and resources. These integration matters could have an adverse effect on the Company during this transition period and for an undetermined period.

We may not have discovered certain liabilities or other matters related to CPP, which may adversely affect the future financial performance of the combined company.

In the course of the due diligence review that we conducted prior to the execution of the merger agreement, we may not have discovered, or may have been unable to properly quantify, certain liabilities of CPP or other factors that may have an adverse effect on the business, results of operations, financial condition, and cash flows of the combined company.

Our estimates and judgments related to the acquisition accounting methods used to record the purchase price allocation related to the merger may be inaccurate.

Our management will make significant accounting judgments and estimates related to the application of acquisition accounting of the acquisition under GAAP, as well as the underlying valuation models. Our business, operating results, and financial condition could be materially adversely impacted in future periods if the accounting judgments and estimates prove to be inaccurate.

Risks Related to the Development and Approval of New Drugs

Clinical trials required for our product candidate are expensive and time-consuming, and their outcome is highly uncertain. If any of our drug trials are delayed or yield unfavorable results, we will have to delay or may be unable to obtain regulatory approval for our product candidate.

We must conduct extensive testing of our product candidate before we can obtain regulatory approval to market and sell it. We need to conduct both preclinical animal testing and human clinical trials. Conducting these trials is a lengthy, time-consuming and expensive process. These tests and trials may not achieve favorable results for many reasons, including, among others, failure of the product candidate to demonstrate safety or efficacy, the development of serious or life-threatening adverse events, or side effects, caused by or connected with exposure to the product candidate, difficulty in enrolling and maintaining subjects in the clinical trial, lack of sufficient supplies of the product candidate or comparator drug, and the failure of clinical investigators, trial monitors, contractors, consultants, or trial subjects to comply with the trial protocol. A clinical trial may fail because it did not include a sufficient number of patients to detect the endpoint being measured or reach statistical significance. A clinical trial may also fail because the dose(s) of the investigational drug included in the trial were either too low or too high to determine the optimal effect of the investigational drug in the disease setting. Many clinical trials are conducted under the oversight of Independent Data Monitoring Committees ("IDMCs") also known as DSMB's. These independent oversight bodies are made up of external experts who review the progress of ongoing clinical trials, including available safety and efficacy data, and make recommendations concerning a trial's continuation, modification, or termination based on interim, unblinded data. Any of our ongoing clinical trials may be discontinued or amended in response to recommendations made by responsible IDMCs based on their review of such interim trial results.

We will need to reevaluate our product candidates if they do not test favorably and either conduct new trials, which are expensive and time consuming, or abandon our drug development program(s). Even if we obtain positive results from preclinical or clinical trials, we may not achieve the same success in future trials. Many companies in the biopharmaceutical industry have suffered significant setbacks in clinical trials, even after promising results have been obtained in earlier trials. The failure of clinical trials to demonstrate safety and effectiveness for the desired indication could harm the development of our product candidate and our business, financial condition and results of operations may be materially harmed.

We face significant risks in our product candidate development efforts.

Our business depends on the successful development and commercialization of our product candidates. We are currently focused on developing our product candidates, ivospemin, Flynpovi, and eflornithine and are not permitted to market them in the United States until we receive approval of an NDA from the FDA, or in any foreign jurisdiction until we receive the requisite approvals from such jurisdiction. The process of developing new drugs and/or therapeutic products is inherently complex, unpredictable, time-consuming, expensive and uncertain. We must make long-term investments and commit significant resources before knowing whether our development programs will result in drugs that will receive regulatory approval and achieve market acceptance. A product candidate that appears to be promising at all stages of development may not reach the market for a number of reasons that may not be predictable based on results and data from the clinical program. A product candidate may be found ineffective or may cause harmful side effects during clinical trials, may take longer to progress through clinical trials than had been anticipated, may not be able to achieve the pre-defined clinical endpoints even though clinical benefit may have been achieved, may fail to receive necessary regulatory approvals, may prove impracticable to manufacture in commercial quantities at reasonable cost and with acceptable quality, or may fail to achieve market acceptance.

We cannot predict whether or when we will obtain regulatory approval to commercialize our product candidates and we cannot, therefore, predict the timing of any future revenues from this or other product candidates, if any. The FDA has substantial discretion in the drug approval process, including the ability to delay, limit or deny approval of a product candidate for many reasons. For example, the FDA:

- could determine that the information provided by us was inadequate, contained clinical deficiencies or otherwise failed to demonstrate the safety and effectiveness of any of our product candidates for any indication;
- may not find the data from clinical trials sufficient to support the submission of an NDA or to obtain marketing approval in the United States, including any findings that the clinical and other benefits of our product candidates outweigh their safety risks;
- may disagree with our trial design or our interpretation of data from preclinical studies or clinical trials or may change the requirements for approval even after it has reviewed and commented on the design for our trials;
- may identify deficiencies in the manufacturing processes or facilities of third-party manufacturers with which we enter into agreements for the manufacturing of our product candidates;
- may approve our product candidates for fewer or more limited indications than we request or may grant approval contingent on the performance of costly post-approval clinical trials;
- may change its approval policies or adopt new regulations; or
- may not approve the labeling claims that we believe are necessary or desirable for the successful commercialization of our product candidates.

Any failure to obtain regulatory approval of our initial product candidate or future product candidates we develop, if any, would significantly limit our ability to generate revenues, and any failure to obtain such approval for all of the indications and labeling claims we deem desirable could reduce our potential revenues.

Our product candidates are based on a new formulation of an existing technology which has never been approved for the treatment of any cancer and, consequently, is inherently risky. Concerns about the safety and efficacy of our product candidate could limit our future success.

We are subject to the risks of failure inherent in the development of product candidates based on new technologies. These risks include the possibility that any product candidates we create will not be effective, that our current product candidate will be unsafe, ineffective or otherwise fail to receive the necessary regulatory approvals or that our product candidate will be hard to manufacture on a large scale or will be uneconomical to market.

Many pharmaceutical products cause multiple potential complications and side effects, not all of which can be predicted with accuracy and many of which may vary from patient to patient. Long term follow-up data may reveal additional complications associated with our product candidate. The responses of potential physicians and others to information about complications could materially affect the market acceptance of our product candidate, which in turn would materially harm our business.

Our ability to commence and complete the planned FAP registration trial depends substantially on a third-party and its resources.

In July 2021, CPP licensed the U.S. and Canadian rights to Flynpovi to One-Two Therapeutics Assets Limited ("One-Two"), a private commercial-stage specialty pharma company focused on GI and orphan disease. Under the terms of the license, One-Two is responsible for all costs of development and approval of Flynpovi in North America. Accordingly, our ability to potentially obtain FDA approval of Flynpovi is dependent on One-Two's ability to fund and complete the registration trial. Any failure to obtain regulatory approval of Flynpovi in this context could significantly limit our ability to obtain milestone payments or generate revenues from Flynpovi.

Due to our reliance on third parties to conduct our clinical trials, we are unable to directly control the timing, conduct, expense and quality of our clinical trials, which could adversely affect our clinical data and results and related regulatory approvals.

We extensively outsource our clinical trial activities and expect to directly perform only a small portion of the preparatory stages for planned trials. We rely on independent third-party CROs to perform most of our clinical trials, including document preparation, site identification, screening and preparation, pre-study visits, training, program management and bio-analytical analysis. Many important aspects of the services performed for us by the CROs are out of our direct control. If there is any dispute or disruption in our relationship with our CROs, our clinical trials may be delayed. Moreover, in our regulatory submissions, we rely on the quality and validity of the clinical work performed by third-party CROs. If a CRO's processes, methodologies or results are determined to be invalid or inadequate, our own clinical data and results and related regulatory approvals could be adversely affected or invalidated.

We rely on third-party suppliers and other third parties for production of our product candidates and our dependence on these third parties may impair the advancement of our research and development programs and the development of our product candidates.

We rely on, and expect to continue to rely on, third parties for the supply of raw materials and manufacture of drug supplies necessary to conduct our preclinical studies and clinical trials. During 2021 the Company, in collaboration with our manufacturing partner confirmed a new shorter and less expensive synthesis of the active drug substance for ivospemin. However, delays in production by third parties could delay our clinical trials or have an adverse impact on any commercial activities. In addition, the fact that we are dependent on third parties for the manufacture of and formulation of our product candidates means that we are subject to the risk that the products may have manufacturing defects that we have limited ability to prevent or control. Although we oversee these activities to ensure compliance with our quality standards, budgets and timelines, we have had and will continue to have less control over the manufacturing of our product candidates than potentially would be the case if we were to manufacture our product candidates. Further, the third parties we deal with could have staffing difficulties, might undergo changes in priorities or may become financially distressed, which would adversely affect the manufacturing and production of our product candidates.

The results of pre-clinical studies and completed clinical trials are not necessarily predictive of future results, and our current product candidates may not have favorable results in later studies or trials.

Pre-clinical studies and Phase I clinical trials are not primarily designed to test the efficacy of a product candidate in the general population, but rather to test initial safety, to study pharmacokinetics and pharmacodynamics, to study limited efficacy in a small number of study patients in a selected disease population, and to identify and attempt to understand the product candidate's side effects at various doses and dosing schedules. Success in pre-clinical studies or completed clinical trials does not ensure that later studies or trials, including continuing pre-clinical studies and large-scale clinical trials, will be successful nor does it necessarily predict future results. Favorable results in early studies or trials may not be repeated in later studies or trials, and product candidates in later stage trials may fail to show acceptable safety and efficacy despite having progressed through earlier trials.

Risks Related to the Regulation of our Business

Federal and state pharmaceutical marketing compliance and reporting requirements may expose us to regulatory and legal action by state governments or other government authorities.

The Food and Drug Administration Modernization Act (the "FDMA") established a public registry of open clinical trials involving drugs intended to treat serious or life-threatening diseases or conditions in order to promote public awareness of and access to these clinical trials. Under the FDMA, pharmaceutical manufacturers and other trial sponsors are required to post the general purpose of these trials, as well as the eligibility criteria, location and contact information of the trials. Failure to comply with any clinical trial posting requirements could expose us to negative publicity, fines and other penalties, all of which could materially harm our business.

In recent years, several states, including California, Vermont, Maine, Minnesota, New Mexico and West Virginia have enacted legislation requiring pharmaceutical companies to establish marketing compliance programs and file periodic reports on sales, marketing, pricing and other activities. Similar legislation is being considered in other states. Many of these requirements are new and uncertain, and available guidance is limited. Unless we are in full compliance with these laws, we could face enforcement actions and fines and other penalties and could receive adverse publicity, all of which could harm our business.

If the product candidates we develop becomes subject to unfavorable pricing regulations, third party reimbursement practices or healthcare reform initiatives, our ability to successfully commercialize our product candidates may be impaired.

Our future revenues, profitability and access to capital will be affected by the continuing efforts of governmental and private third-party payors to contain or reduce the costs of health care through various means. We expect several federal, state and foreign proposals to control the cost of drugs through government regulation. We are unsure of the impact recent health care reform legislation may have on our business or what actions federal, state, foreign and private payors may take in response to the recent reforms. Therefore, it is difficult to predict the effect of any implemented reform on our business. Our ability to commercialize our product candidate successfully will depend, in part, on the extent to which reimbursement for the cost of such product candidate and related treatments will be available from government health administration authorities, such as Medicare and Medicaid in the United States, private health insurers and other organizations. Significant uncertainty exists as to the reimbursement status of newly approved health care products, particularly for indications for which there is no current effective treatment or for which medical care typically is not sought. Adequate third-party coverage may not be available to enable us to maintain price levels sufficient to realize an appropriate return on our investment in product research and development. If adequate coverage and reimbursement levels are not provided by the government and third-party payors for the use of our product candidates, our product candidates may fail to achieve market acceptance and our results of operations will be harmed.

Healthcare legislative reform measures may have a material adverse effect on our business and results of operations.

Legislative and regulatory actions affecting government prescription drug procurement and reimbursement programs occur relatively frequently. In the United States, the ACA was enacted in 2010 to expand healthcare coverage. Since then, numerous efforts have been made to repeal, amend or administratively limit the ACA in whole or in part. For example, the Tax Cuts and Jobs Act, signed into law by President Trump in 2017, repealed the individual health insurance mandate, which is considered a key component of the ACA. In December 2018, a Texas federal district court struck down the ACA on the grounds that the individual health insurance mandate is unconstitutional, although this ruling has been stayed pending appeal. The ongoing challenges to the ACA and new legislative proposals have resulted in uncertainty regarding the ACA's future viability and destabilization of the health insurance market. The resulting impact on our business is uncertain and could be material.

Efforts to control prescription drug prices could also have a material adverse effect on our business. For example, in 2018, President Trump and the Secretary of the U.S. Department of Health and Human Services ("HHS") released the "American Patients First Blueprint" and have begun implementing certain portions. The initiative includes proposals to increase generic drug and biosimilar competition, enable the Medicare program to negotiate drug prices more directly and improve transparency regarding drug prices and ways to lower consumers' out-of-pocket costs. The Trump administration also proposed to establish an "international pricing index" that would be used as a benchmark to determine the costs and potentially limit the reimbursement of drugs under Medicare Part B. Among other pharmaceutical manufacturer industry-related proposals, Congress has proposed bills to change the Medicare Part D benefit to impose an inflation-based rebate in Medicare Part D and to alter the benefit structure to increase manufacturer contributions in the catastrophic phase. The volume of drug pricing-related bills has dramatically increased under the current Congress, and the resulting impact on our business is uncertain and could be material.

In addition, many states have proposed or enacted legislation that seeks to regulate pharmaceutical drug pricing indirectly or directly, such as by requiring biopharmaceutical manufacturers to publicly report proprietary pricing information or to place a maximum price ceiling on pharmaceutical products purchased by state agencies. For example, in 2017, California's governor signed a prescription drug price transparency state bill into law, requiring prescription drug manufacturers to provide advance notice and explanation for price increases of certain drugs that exceed a specified threshold. Both Congress and state legislatures are considering various bills that would reform drug purchasing and price negotiations, allow greater use of utilization management tools to limit Medicare Part D coverage, facilitate the import of lower-priced drugs from outside the United States and encourage the use of generic drugs. Such initiatives and legislation may cause added pricing pressures on our products.

Changes to the Medicaid program at the federal or state level could also have a material adverse effect on our business. Proposals that could impact coverage and reimbursement of our products, including giving states more flexibility to manage drugs covered under the Medicaid program and permitting the re-importation of prescription medications from Canada or other countries, could have a material adverse effect by limiting our products' use and coverage. Furthermore, state Medicaid programs could request additional supplemental rebates on our products as a result of an increase in the federal base Medicaid rebate. To the extent that private insurers or managed care programs follow Medicaid coverage and payment developments, they could use the enactment of these increased rebates to exert pricing pressure on our products, and the adverse effects may be magnified by their adoption of lower payment schedules.

Other proposed regulatory actions affecting manufacturers could have a material adverse effect on our business. It is difficult to predict the impact, if any, of any such proposed legislative and regulatory actions or resulting state actions on the use and reimbursement of our products in the United States, but our results of operations may be adversely affected.

Risks Related to our Intellectual Property

If we are unable to obtain, maintain and enforce our proprietary rights, we may not be able to compete effectively or operate profitably.

For ivospemin, we are party to a license agreement with the University of Florida Research Foundation ("UFRF") and for Flynpovi, we are party to a license agreement with the Arizona Board of Regents of the University of Arizona. The patents underlying the licensed intellectual property and those of other biopharmaceutical companies are generally uncertain and involve complex legal, scientific and factual questions.

Our ability to develop and commercialize drugs depends in significant part on our ability to: (i) obtain and/or develop broad, protectable intellectual property; (ii) obtain additional licenses, if required, to the proprietary rights of others on commercially reasonable terms; (iii) operate without infringing upon the proprietary rights of others; (iv) prevent others from infringing on our proprietary rights; and (v) protect our corporate know-how and trade secrets.

Patents that we may acquire and those that might be issued in the future, may be challenged, invalidated or circumvented, and the rights granted thereunder may not provide us with proprietary protection or competitive advantages against competitors with similar technology. Furthermore, our competitors may independently develop similar technologies or duplicate any technology we develop. Because of the extensive time required for development, testing and regulatory review of a potential product candidates, it is possible that, before any of our product candidates can be commercialized, any related patent may expire or remain in force for only a short period following commercialization, thus reducing any advantage of the patent.

Because patent applications in the U.S. and many foreign jurisdictions are typically not published until at least 12 months after filing, or in some cases not at all, and because publications of discoveries in the scientific literature often lag behind actual discoveries, neither we nor our licensors can be certain that either we or our licensors were the first to make the inventions claimed in issued patents or pending patent applications, or that we were the first to file for protection of the inventions set forth in these patent applications.

Additionally, UFRF previously elected to seek protection for certain elements of the licensed technology only in the United States, and the time to file for international patent protection has expired. This limits the strength of the Company's intellectual property position in certain markets and could affect the overall value of the Company to a potential corporate partner.

Obtaining and maintaining our patent protection depends upon compliance with various procedural, document submission, fee payment and other requirements imposed by governmental patent agencies, and our patent protection could be reduced or eliminated for non-compliance with these requirements.

The United States Patent and Trademark Office and various foreign governmental patent agencies require compliance with a number of procedural, documentary, fee payment and other provisions during the patent process. There are situations in which noncompliance can result in abandonment or lapse of a patent or patent application, resulting in partial or complete loss of patent rights in the relevant jurisdiction. In such an event, competitors might be able to enter the market earlier than would otherwise have been the case.

We may be exposed to infringement or misappropriation claims by third parties, which, if determined adversely to us, could cause us to pay significant damage awards.

There has been substantial litigation and other proceedings regarding patent and other intellectual property rights in the pharmaceutical and biotechnology industries. We may become a party to various types of patent litigation or other proceedings regarding intellectual property rights from time to time even under circumstances where we are not using and do not intend to use any of the intellectual property involved in the proceedings.

The cost of any patent litigation or other proceeding, even if resolved in our favor, could be substantial. Some of our competitors may be able to sustain the cost of such litigation or proceedings more effectively than we will be able to because our competitors may have substantially greater financial resources. If any patent litigation or other proceeding is resolved against us, we or our collaborators may be enjoined from developing, manufacturing, selling or importing our drugs without a license from the other party and we may be held liable for significant damages. We may not be able to obtain any required license(s) on commercially acceptable terms or at all.

Uncertainties resulting from the initiation and continuation of patent litigation or other proceedings could have a material adverse effect on our ability to compete in the marketplace. Patent litigation and other proceedings may also absorb significant management time.

Confidentiality agreements with employees and others may not adequately prevent disclosure of our know-how, trade secrets and other proprietary information and may not adequately protect our intellectual property, which could impede our ability to compete.

Because we operate in the highly technical field of medical technology development, we rely in part on trade secret protection in order to protect our proprietary trade secrets and unpatented know-how. However, trade secrets are difficult to protect, and we cannot be certain that others will not develop the same or similar technologies on their own. We have taken steps, including entering into confidentiality agreements with all of our employees, consultants and corporate partners to protect our trade secrets and unpatented know-how. These agreements generally require that the other party keep confidential and not disclose to third parties any confidential information developed by the party or made known to the party by us during the course of the party's relationship with us. We also typically obtain agreements from these parties which provide that inventions conceived by the party in the course of rendering services to us will be our exclusive property. However, these agreements may not be honored and may not effectively assign intellectual property rights to us. Enforcing a claim that a party illegally obtained and is using our trade secrets or know-how is difficult, expensive and time consuming, and the outcome is unpredictable. In addition, courts outside the United States may be less willing to protect trade secrets or know-how. The failure to obtain or maintain trade secret protection could adversely affect our competitive position.

We may be subject to claims that our employees have wrongfully used or disclosed alleged trade secrets of their former employers.

As is common in the biotechnology industry, we employ individuals who were previously employed at other biotechnology companies, including our competitors or potential competitors. Although no claims against us are currently pending, we may be subject to claims that these employees or we have inadvertently or otherwise used or disclosed trade secrets or other proprietary information of their former employers. Litigation may be necessary to defend against these claims. Even if we are successful in defending against these claims, litigation could result in substantial costs and be a distraction to management.

Risks Associated with this Offering and Ownership of Our Common Stock

Raising additional capital may cause dilution to our stockholders or restrict our operations.

To the extent that we raise additional capital through the sale of equity or convertible debt securities, stockholders' ownership interest will be diluted, and the terms may include liquidation or other preferences that adversely affect their rights as stockholders. Debt financing, if available, may involve agreements that include covenants limiting or restricting our ability to take specific actions such as incurring additional debt, making capital expenditures or declaring dividends. Any of these events could adversely affect our ability to achieve our product development and commercialization goals and harm our business. We do not anticipate any adverse effects stemming from the lack of available credit facilities at this time.

Issuances of common stock in offerings or pursuant to the exercise of rights to purchase shares may cause the price of our common stock to decline and cause investors to lose a significant portion of their investment.

If our stockholders sell substantial amounts of our common stock in the public market or upon the expiration of any statutory holding period under Rule 144, or upon expiration of lock-up periods applicable to outstanding shares or issued upon the exercise of outstanding options or warrants, it could create a circumstance commonly referred to as an "overhang" and in anticipation of which the market price of our common stock could fall. The existence of an overhang, whether sales have occurred or are occurring, also could make our ability to raise additional financing through the sale of equity or equity-related securities in the future at a time and price that we deem reasonable or appropriate more difficult. As of September 30, 2022, without taking into account the effect of a 1-for-40 reverse stock split, we had outstanding options to purchase 4,023,119 shares of our common stock at a weighted-average exercise price of $3.64 per share with a remaining contractual life of 6.9 years and outstanding warrants to purchase 5,446,561 shares of common stock at a weighted-average exercise price of $4.56 per share, before any potential adjustments resulting from the pending reverse stock split, and a remaining exercise period of 2.2 years.

Securities analysts may not initiate coverage or continue to cover our common stock, and this may have a negative impact on the market price of our common stock.

Common stock prices are often significantly influenced by the research and reports that securities analysts publish about companies and their business. We do not have any control over these analysts. There is no guarantee that securities analysts will cover, or continue to cover, our common stock. If securities analysts do not cover our common stock, the lack of research coverage may adversely affect the market price of our common stock. If our common stock is covered by securities analysts and our stock is downgraded, our stock price will likely decline. If one or more of these analysts ceases to cover us or fails to publish regular reports on us, we can lose visibility in the financial markets, which can cause our stock price or trading volume to decline.

If you purchase shares of common stock in this offering, you will incur immediate and substantial dilution in the book value of the shares of our common stock.

The proposed public offering price of the shares of our common stock is substantially higher than the net tangible book value per share of our common stock. Investors purchasing shares of common stock in this offering will pay a price per share that substantially exceeds the book value of our tangible assets after subtracting our liabilities. As a result, investors purchasing shares of common stock in this offering will incur immediate dilution of $ per share, based on an assumed combined public offering price of $ per share and accompanying common warrant. Further, investors purchasing shares of common stock in this offering will contribute approximately % of the total amount invested by shareholders since our inception, but will own, as a result of such investment, only approximately % of the shares of common stock outstanding immediately following this offering. As a result of the dilution to investors purchasing shares of common stock in this offering, investors may receive significantly less than the purchase price paid in this offering, if anything, in the event of our liquidation. Further, because we may need to raise additional capital to fund our anticipated level of operations, we may in the future sell substantial amounts of common stock or securities convertible into or exchangeable for common stock. These future issuances of equity or equity-linked securities, together with the exercise of outstanding options and any additional shares issued in connection with acquisitions, if any, may result in further dilution to investors.

Holders of our warrants will have no rights as a common stockholder until they exercise their warrants and acquire our common stock.

Until you acquire shares of our common stock upon exercise of your warrants, you will have no rights with respect to shares of our common stock issuable upon exercise of your warrants. Upon exercise of your warrants, you will be entitled to exercise the rights of a common stockholder only as to matters for which the record date occurs after the exercise date.

The common warrants are speculative in nature.

The common warrants offered pursuant to this prospectus do not confer any rights of common stock ownership on their holders, such as voting rights or the right to receive dividends, but rather merely represent the right to acquire shares of our common stock at a fixed price for a limited period of time. Specifically, commencing on the date of issuance, holders of the common warrants may exercise their right to acquire the common stock and pay an exercise price of $, prior to five years from the date of issuance, after which date any unexercised common warrants will expire and have no further value. Moreover, following this offering, the market value of the common warrants is uncertain and there can be no assurance that the market value of the common warrants will equal or exceed their public offering price. There can be no assurance that the market price of the common stock will ever equal or exceed the exercise price of the common warrants, and, consequently, whether it will ever be profitable for holders of the common warrants to exercise those warrants.

There is no established public trading market for the warrants being offered in this offering.

There is no established public trading market for the common warrants or the pre-funded warrants being offered in this offering. We do not intend to apply to list the common warrants or the pre-funded warrants to be issued in this offering on any national securities exchange or to seek qualification of the common warrants or the pre-funded warrants for quotation on the over-the-counter markets. Without an active trading market, the liquidity of the common warrants and the pre-funded warrants will be limited without first exercising them.

Our charter documents and Delaware law may inhibit a takeover that stockholders consider favorable.

The provisions of our certificate of incorporation and bylaws and applicable provisions of Delaware law may make it more difficult for or prevent a third party from acquiring control of us without the approval of our board of directors. These provisions:

- set limitations on the removal of directors;
- limit who may call a special meeting of stockholders;
- establish advance notice requirements for nominations for election to our board of directors or for proposing matters that can be acted upon at stockholder meetings;
- do not permit cumulative voting in the election of our directors, which would otherwise permit less than a majority of stockholders to elect directors;

- establish a classified board of directors limiting the number of directors that are elected each year; and

- provide our board of directors the ability to designate the terms of and issue preferred stock without stockholder approval.

In addition, Section 203 of the Delaware General Corporation Law generally limits our ability to engage in any business combination with certain persons who own 15% or more of our outstanding voting stock or any of our associates or affiliates who at any time in the past three years have owned 15% or more of our outstanding voting stock unless our board of directors has pre-approved the acquisitions that lead to such ownership. These provisions may have the effect of entrenching our management team and may deprive stockholders of the opportunity to sell their shares to potential acquirers at a premium over prevailing prices. This potential inability to obtain a control premium could reduce the price of our common stock.

If we issue preferred stock, the rights of the holders of our common stock and the value of such common stock could be adversely affected.

Our Board of Directors is authorized to issue classes or series of preferred stock, without any action on the part of the stockholders. The Board of Directors also has the power, without stockholder approval, to set the terms of any such classes or series of preferred stock, including voting rights, dividend rights and preferences over the common stock with respect to dividends or upon the liquidation, dissolution or winding-up of our business and other terms. If we issue preferred stock in the future that has a preference over the common stock with respect to the payment of dividends or upon liquidation, dissolution or winding-up, or if we issue preferred stock with voting rights that dilute the voting power of the common stock, the rights of holders of the common stock or the value of the common stock would be adversely affected.

If we fail to maintain effective internal controls over financial reporting, the price of our common stock may be adversely affected.

We are required to establish and maintain appropriate internal controls over financial reporting. Failure to establish those controls, or any failure of those controls once established, could adversely impact our public disclosures regarding our business, financial condition or results of operations. Any failure of these controls could also prevent us from maintaining accurate accounting records and discovering accounting errors and financial fraud. Management's assessment of internal controls over financial reporting may identify weaknesses that need to be addressed or other potential matters that may raise concerns for investors. Any actual or perceived weaknesses that need to be addressed in our internal control over financial reporting or disclosure of management's assessment of our internal controls over financial reporting may have an adverse impact on the price of our common stock.

Even if this offering is completed, we will need to raise additional capital in the future to finance our operations, which may not be available on acceptable terms, or at all. Failure to obtain this necessary capital when needed may force us to delay, limit or terminate our product development efforts or other operations.

We have had recurring losses from operations, negative operating cash flow and have an accumulated deficit. We must raise additional funds in order to continue financing our operations. If additional capital is not available to us when needed or on acceptable terms, we may not be able to continue to operate our business pursuant to our business plan or we may have to discontinue our operations entirely. Any additional capital raised through the sale of equity or equity-backed securities may dilute our stockholders' ownership percentages and could also result in a decrease in the market value of our equity securities. The terms of any securities issued by us in future capital transactions may be more favorable to new investors, and may include preferences, superior voting rights and the issuance of warrants or other derivative securities, which may have a further dilutive effect on the holders of any of our securities then outstanding.

If we are unable to secure additional funds when needed or on acceptable terms, we may be required to defer, reduce or eliminate significant planned expenditures, restructure, curtail or eliminate some or all of our operations, dispose of technology or assets, pursue an acquisition of our company by a third party at a price that may result in a loss on investment for our stockholders, file for bankruptcy or cease operations altogether. Any of these events could have a material adverse effect on our business, financial condition and results of operations. Moreover, if we are unable to obtain additional funds on a timely basis, there will be substantial doubt about our ability to continue as a going concern and increased risk of insolvency and up to a total loss of investment by our stockholders.

This is a best efforts offering, no minimum amount of securities is required to be sold, and we may not raise the amount of capital we believe is required for our business plans.

The placement agent has agreed to use its reasonable best efforts to solicit offers to purchase the securities being offered in this offering. The placement agent has no obligation to buy any of the securities from us or to arrange for the purchase or sale of any specific number or dollar amount of the securities. There is no required minimum number of securities or amount of proceeds that must be sold as a condition to completion of this offering. Because there is no minimum offering amount required as a condition to the closing of this offering, the actual offering amount, placement agent fees and proceeds to us are not presently determinable and may be substantially less than the maximum amounts set forth above. We may sell fewer than all of the securities offered hereby, which may significantly reduce the amount of proceeds received by us, and investors in this offering will not receive a refund in the event that we do not sell an amount of securities sufficient to fund for our operations as described in the "Use of Proceeds" section herein. Thus, we may not raise the amount of capital we believe is required for our operations in the short-term and may need to raise additional funds, which may not be available or available on terms acceptable to us.

We could be delisted from Nasdaq, which would seriously harm the liquidity of our stock and our ability to raise capital

As previously disclosed, on September 30, 2022, we received a notice from the Listing Qualifications Department of The Nasdaq Stock Market ("Nasdaq") informing us that because the closing bid price for our Common Stock listed on Nasdaq was below $1.00 per share for 30 consecutive business days, we did not comply with the minimum closing bid price requirement for continued listing on The Nasdaq Capital Market under Nasdaq Listing Rule 5550(a)(2) (the "Minimum Bid Rule"). The Nasdaq notification has no immediate effect on the listing or trading of our Common Stock on The Nasdaq Capital Market. We have been provided an initial compliance period of 180 calendar days, or until March 29, 2023, to regain compliance with the Minimum Bid Rule. During the compliance period, our shares of Common Stock will continue to be listed and traded on The Nasdaq Capital Market. To regain compliance, the closing bid price of our Common Stock must meet or exceed $1.00 per share for a minimum of ten consecutive business days during the 180-calendar day grace period. In the event we are not in compliance with the Minimum Bid Rule by March 29, 2023, we may be afforded a second 180 calendar day grace period. To qualify, we would be required to meet the continued listing requirements for market value of publicly held shares and all other listing standards for The Nasdaq Capital Market, with the exception of the Minimum Bid Rule. In addition, we would be required to provide written notice of our intention to cure the minimum bid price deficiency during this second 180-day compliance period by effecting a reverse stock split, if necessary. If we meet these requirements, Nasdaq will inform us that we have been granted an additional 180 calendar days to regain compliance. However, if it appears to the Listing Qualifications Department that we will not be able to cure the deficiency, or if we are otherwise not eligible, Nasdaq will provide notice that our securities will be subject to delisting. While we intend to continue to actively monitor the bid price for our Common Stock between now and March 29, 2023 and consider available options to resolve the deficiency and regain compliance with the Minimum Bid Rule, including through completion of the 1-for-40 reverse split of our outstanding shares of common stock, there is no assurance that we will be eligible for an additional compliance period or that our Common Stock will not be delisted from Nasdaq for failing to satisfy the Minimum Bid Rule.

In addition, as previously disclosed, on August 19, 2022, we received a second letter from Nasdaq notifying us that we were not in compliance with the minimum stockholders' equity requirement for continued listing on the Nasdaq Capital Market. Nasdaq Listing Rule 5550(b)(1) (the "Minimum Equity Rule") requires companies listed on The Nasdaq Capital Market to maintain stockholders' equity of at least $2,500,000. We reported a stockholders' deficit of $4,838,000 on our consolidated balance sheet for the quarter ended June 30, 2022 and we do not currently satisfy the alternative standards based on market value of listed securities or net income from continuing operations. For the quarter ended September 30, 2022, we reported a stockholders' deficit of $8.64 million. This notice of noncompliance has no immediate impact on the continued listing or trading of our Common Stock on The Nasdaq Capital Market, which will continue to be listed and traded on Nasdaq, subject to our compliance with the other continued listing requirements. We submitted to Nasdaq a plan to regain compliance with the Minimum Equity Rule and Nasdaq has granted an extension through February 15, 2023. We intend to take all reasonable measures available to regain compliance with the Minimum Equity Rule and remain listed on the Nasdaq, including the completion of the offering. However, there can be no assurance that we will ultimately regain compliance with all applicable requirements for continued listing.

If, for any reason, Nasdaq were to delist our securities from trading on The Nasdaq Capital Market and we were unable to obtain listing on another reputable national securities exchange, a reduction in some or all of the following may occur, each of which could materially adversely affect our stockholders:

- the liquidity and marketability of our common stock;
- the market price of our common stock;
- our ability to obtain financing for the continuation of our operations;
- the number of institutional and general investors that will consider investing in our common stock;
- the number of market makers in our common stock;
- the availability of information concerning the trading prices and volume of our common stock; and
- the number of broker-dealers willing to execute trades in shares of our common stock.

In addition, if we cease to be eligible to trade on The Nasdaq Capital Market, we may have to pursue trading on a less recognized or accepted market, such as the over the counter markets, our stock may be traded as a "penny stock" which would make transactions in our stock more difficult and cumbersome, and we may be unable to access capital on favorable terms or at all, as companies trading on alternative markets may be viewed as less attractive investments with higher associated risks, such that existing or prospective institutional investors may be less interested in, or prohibited from, investing in our common stock. This may also cause the market price of our common stock to further decline.

CAUTIONARY NOTE REGARDING FORWARD-LOOKING STATEMENTS

This prospectus contains forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended, and Section 21E of the Securities Exchange Act of 1934, as amended (the "Exchange Act").

In some cases, you can identify forward-looking statements by the following words: "anticipate," "assume," "believe," "continue," "could," "estimate," "expect," "intend," "may," "ongoing," "plan," "potential," "predict," "project," "should," "will," "would," or the negative of these terms or other comparable terminology, although not all forward-looking statements contain these words. Forward-looking statements are not a guarantee of future performance or results and will not necessarily be accurate indications of the times at, or by, which such performance or results will be achieved. Forward-looking statements are based on information available at the time the statements are made and involve known and unknown risks, uncertainties and other factors that may cause our results, levels of activity, performance or achievements to be materially different from the information expressed or implied by the forward-looking statements in this prospectus. These factors include:

- our lack of diversification and the corresponding risk of an investment in our Company;
- potential deterioration of our financial condition and results due to failure to diversify;
- our ability to successfully complete acquisitions;
- our ability to integrate acquired companies and operations for new product candidates
- our ability to obtain additional capital, on acceptable terms or at all, required to implement our business plan;
- final results of our Phase I clinical trial;
- progress and success of our randomized Phase II/III clinical trial;
- our ability to demonstrate safety and effectiveness of our product candidate;
- our ability to obtain regulatory approvals for our product candidate in the United States, the European Union, or other international markets;
- the market acceptance and future sales of our product candidate;
- the cost and delays in product development that may result from changes in regulatory oversight applicable to our product candidate;
- the rate of progress in establishing reimbursement arrangements with third-party payors;
- the effect of competing technological and market developments;
- the costs involved in filing and prosecuting patent applications and enforcing or defending patent claims; and
- the effectuation of a 1-for-40 reverse stock split of our outstanding shares of common stock; and
- other risk factors included under the caption "Risk Factors" starting on page 9 of this prospectus.

You should read the matters described in "Risk Factors" and the other cautionary statements made in this prospectus as being applicable to all related forward-looking statements wherever they appear in this prospectus. We cannot assure you that the forward-looking statements in this prospectus will prove to be accurate and therefore you are encouraged not to place undue reliance on forward-looking statements. You should read this prospectus completely. Other than as required by law, we undertake no obligation to update or revise these forward-looking statements, even though our situation may change in the future.

We caution readers not to place undue reliance on any forward-looking statement that speaks only as of the date made and to recognize that forward-looking statements are predictions of future results, which may not occur as anticipated. Actual results could differ materially from those anticipated in the forward-looking statements and from historical results due to the risks and uncertainties described under the heading "Risk Factors" in this prospectus, as well as others that we may consider immaterial or do not anticipate at this time. Although we believe that the expectations reflected in our forward-looking statements are reasonable, we do not know whether our expectations will prove correct. Our expectations reflected in our forward-looking statements can be affected by inaccurate assumptions that we might make or by known or unknown risks and uncertainties, including those described under the heading "Risk Factors" in this prospectus. The risks and uncertainties described i under the heading "Risk Factors" in this prospectus are not exclusive and further information concerning us and our business, including factors that potentially could materially affect our financial results or condition, may emerge from time to time. We assume no obligation to update forward-looking statements to reflect actual results or changes in factors or assumptions affecting such forward-looking statements. We advise stockholders and investors to consult any further disclosures we may make on related subjects in our subsequent annual reports on Form 10-K, quarterly reports on Form 10-Q, and current reports on Form 8-K that we file with or furnish to the U.S. Securities and Exchange Commission (the "SEC").

USE OF PROCEEDS

We estimate that we will receive net proceeds of approximately $13.7 million from the sale of the securities by us in this offering, based on an assumed combined public offering price of $3.552 per share and accompanying common warrant, which was the last sale price of our common stock as reported by the Nasdaq Capital Market on December 12, 2022, after deducting the placement agent fees and estimated offering expenses payable by us, and excluding the proceeds, if any, received from the exercise of warrants issued in this offering.

We intend to use the net proceeds from the sale of any securities for (i) the continued clinical development of our initial product candidate ivospemin (SBP-101) (ii) cost of drug product for use in clinical development with collaboration partners of CPP assets, (iii general corporate purposes unless otherwise indicated in the applicable prospectus supplement. General corporate purposes may include the repayment of outstanding indebtedness, working capital, general and administrative expenses, and acquisitions. We may also use a portion of the net proceeds to invest in or acquire businesses or technologies that we believe are complementary to our own, although we have no current plans, commitments or agreements with respect to any acquisitions as of the date of this prospectus supplement. We have not yet determined the amount of net proceeds to be used specifically for any of the foregoing purposes. Accordingly, our management will have significant discretion and flexibility in applying the net proceeds from the sale of these securities.

We are party to a guaranty (the "Guaranty") pursuant to which we have agreed to guarantee the payment obligations of CPP, under a promissory note in favor of Sucampo GmbH dated as of September 6, 2017, as amended (the "Note"), which had a principal balance of approximately $6.2 million as of December 12, 2022. CPP is required to make five payments of $1 million, plus accrued but unpaid interest, on January 31st of each of 2023, 2024, 2025, 2026, with the remaining balance due on January 31, 2027. Under the terms of the Note, Panbela is required to pay 10% of cash proceeds from the issuance or offering of any debt, equity, preferred or convertible securities that occurs on or before January 31, 2022, including sales in the Offering, up to a maximum payment totaling $1 million, plus accrued but unpaid interest through the date of payment. The Company completed an equity raise on October 4, 2022 which then gave rise to an obligation to pay 10% of the $6.0 million gross proceeds or $600,000, which was due by November 4, 2022. As the Company has not yet made this payment as of the date of the filing, the note is in default as of the payment date. While the Company is in negotiations with Sucampo GmbH to defer payment of this obligation into the first quarter of 2023 and cure the default, no guarantees can be made regarding their success.

Our expected use of net proceeds from this offering represents our intentions based on our present plans and business conditions, which could change as our plans and business conditions evolve. The amount and timing of our actual expenditures will depend on numerous factors, including the timing and success of clinical studies or clinical studies we may commence in the future, the timing of regulatory submissions and the feedback from regulatory authorities. As a result, our management will have broad discretion over the use of the net proceeds from this offering. Pending our use of the net proceeds from this offering, we may temporarily invest the net proceeds in investment-grade, interest-bearing securities.

We currently estimate the funds will allow us to make significant progress in the conduct of our new randomized double-blind, placebo-controlled clinical trial (known as the ASPIRE trial) for the treatment of pancreatic ductile adenocarcinoma. Continuation of the current trial, if the interim analysis is positive, will be required for FDA or other similar approvals. The cost and timing of additional clinical trials are highly dependent on the number of indications we pursue and the nature and size of the trials. The remaining costs required for clinical trial and approval of Flynpovi in North America will be borne by the Licensing partner. However, it is estimated that the completion of the randomized clinical trial and other steps in the approval process for ivospemin in pancreatic cancer could cost between $60 and $80 million.

Predicting the cost necessary to develop product candidates can be difficult and we anticipate we will need additional funds to complete the development work generally required for obtaining regulatory approval to commercialize a drug. We have based these estimates on assumptions that may prove to be wrong, and we could use our available capital resources sooner than we currently expect.

MARKET INFORMATION

Our common stock is listed on the Nasdaq Capital Market under the symbol "PBLA." As of December 12, 2022, there were 283 holders of record of our common stock.

Equity Compensation Plan Information

The following table provides information as of December 12, 2022 regarding outstanding grants and shares available for grant under our equity compensation plans.

Plan Category	Number of securities to be issued upon exercise of outstanding options, warrants and rights	Weighted-average exercise price of outstanding options, warrants and rights	Number of securities remaining available for future issuance under equity compensation plans
Equity compensation plans approved by security holders	100,578 (1)	$ 145.46	50,494 (2)
Equity compensation plans not approved by security holders	–	–	–
Total	100,578		50,494

(1) Includes 55,503 shares underlying common stock options under the 2016 Plan and 5,600 shares underlying common stock options under the 2011 plan. We ceased issuing awards under the 2011 Plan upon stockholder approval of the 2016 Plan in 2016. Also includes replacement options for the right to acquire a total of 39,475 shares of common stock which were issued with respect to CPP's 2010 Equity Incentive Plan.

(2) The 2016 Plan provides that the number of shares of common stock available for issuance under the plan will increase on January 1 of each year beginning in 2021 and ending on January 1, 2025 in an amount equal to the lesser of (i) the number of shares necessary to increase the total option pool to 20% of the total number of fully diluted shares (as defined in the 2016 Plan) as of December 31 of the immediately preceding calendar year and (ii) such lesser number of shares as may be determined by the Board of Directors or its Compensation Committee prior to January 1 of any calendar year.

2011 Stock Option Plan

Our 2011 Stock Option Plan (the "2011 Plan") was adopted by our Board of Directors in 2011 and subsequently approved by our stockholders in 2012. Upon the initial stockholder approval of the 2016 Plan, our Board of Directors ceased making grants under the 2011 Plan, although awards outstanding under the 2011 Plan will remain outstanding in accordance with and pursuant to the terms thereof. Options granted under the 2011 Plan have a maximum term of ten years and generally vest over zero to two years for employees. As of December 12, 2022, options to purchase 5,600 shares of common stock remained outstanding under the 2011 Plan with a weighted average price of $118.92 per share.

2016 Omnibus Incentive Plan

Our 2016 Omnibus Incentive Plan was initially adopted by our Board of Directors in March 2016 and approved by our stockholders in May 2016. It was amended and restated by our Board of Directors in April 2020 and approved by our stockholders in May 2020 (as amended, the "2016 Plan"). The 2016 Plan permits the granting of incentive and non-statutory stock options, restricted stock, stock appreciation rights and other stock awards to eligible employees, directors and consultants. We grant options to purchase shares of common stock under the 2016 Plan at no less than the fair market value of the underlying common stock as of the date of grant. Options granted under the Plan have a maximum term of ten years. Under the 2016 Plan, a total of 70,000 shares of common stock were initially reserved for issuance and 36,824 shares have been added pursuant to its annual evergreen feature. As of December 12, 2022 options to purchase 55,503 shares of our common stock were outstanding under the 2016 Plan with a weighted average price of $241.63 per share. A total of 50,494 shares of common stock remained available for future grants under the 2016 Plan as of the same date, subject to further adjustment by the evergreen provision described under "Shares Available" below.

Purpose

The purpose of the 2016 Plan is to promote the interests of our Company and our stockholders by providing key personnel of our Company and our affiliates with an opportunity to acquire a proprietary interest in the Company and thereby develop a stronger incentive to put forth maximum effort for the continued success and growth of our Company and our affiliates. In addition, the opportunity to acquire a proprietary interest in our Company will aid in attracting and retaining key personnel of outstanding ability. The 2016 Plan is also intended to provide non-employee directors of the Company with an opportunity to acquire a proprietary interest in the Company, to compensate non-employee directors for their contributions to the Company and to aid in attracting and retaining non-employee directors.

Administration

The 2016 Plan is administered by the Compensation Committee of the Board of Directors (the "Committee"). The Committee has the authority to adopt, revise and waive rules relating to the 2016 Plan and to determine the timing and identity of participants, the amount of any awards and other terms and conditions of awards. The Committee may delegate its responsibilities under the 2016 Plan to one or more of its members or to one or more directors or executive officers of the Company with respect to the selection and grants of awards to employees of the Company who are not deemed to be officers, directors or 10% stockholders of the Company under applicable federal securities laws. The Board of Directors will perform the duties and have the responsibilities of the Committee with respect to awards made to non-employee directors.

Eligibility

All employees of our Company and our affiliates, non-employee directors of our Company and any consultant or advisor who is a natural person and provides services to us or our affiliates are eligible to receive awards under the 2016 Plan at the discretion of the Committee or the Board, as applicable. No awards may be granted under the 2016 Plan in conjunction with a capital-raising transaction or the promotion or maintenance of a market for our securities. Incentive stock options under the 2016 Plan may be awarded to employees of the Company. As of December 12, 2022, there were approximately 14 total employees and non-employee directors. Such employees, directors and others who currently or may in the future provide services to us and our affiliates may be considered for the grant of awards under the 2016 Plan at the discretion of the Committee or the Board, as applicable.

Shares Available

The total number of shares of Company Common Stock available for distribution under the 2016 Plan is 70,000, subject to adjustment for future stock splits, stock dividends and similar changes in the capitalization of the Company. In addition, the 2016 Plan provides that the number of shares of Common Stock available for issuance under the 2016 Plan will increase on January 1 of each year beginning in 2021 and ending on January 1, 2025 in an amount equal to the lesser of (i) the number of the shares necessary to increase the total option pool to 20% of the total number of Fully Diluted Shares (as defined in the 2016 Plan) as of December 31 of the immediately preceding calendar year and (ii) such lesser number of shares as may be determined by the Board of Directors or the Committee prior to January 1st of any calendar year. The shares of our Common Stock covered by the 2016 Plan may be treasury shares or authorized but unissued shares.

Any shares subject to an award under the 2016 Plan that expires, is cancelled or forfeited or is settled for cash shall, to the extent of such expiration, cancellation, forfeiture or cash settlement, remain in the pool of shares available for grant under the 2016 Plan. The following shares will, however, continue to be charged against the foregoing maximum share limitations and will not again become available for grant: (i) shares tendered by the participant or withheld by us in payment of the purchase price of an Option, (ii) shares tendered by the participant or withheld by us to satisfy any tax withholding obligation with respect to an Option of SAR, (iii) shares subject to a SAR that are not issued in connection with the settlement of the SAR upon its exercise and (iv) shares repurchased by us with proceeds received from the exercise of a stock option issued under the 2016 Plan.

Types of Awards

The 2016 Plan allows us to grant stock options, stock appreciation rights ("SARs"), restricted stock, restricted stock units and other stock-based awards. The Committee may provide that the vesting or payment of any award will be subject to the attainment of certain performance objectives established by the Committee, in addition to completion by the plan participant of a specified period of service. The Committee may amend the terms of any award previously granted, but no amendment may materially impair the rights of any participant with respect to an outstanding award without the participant's consent, unless such amendment is necessary to comply with applicable laws or stock exchange rules.

Stock Options

Stock options granted under the 2016 Plan may be either incentive stock options ("ISOs"), which are specifically designated as such for purposes of compliance with Section 422 of the Internal Revenue Code of 1986, as amended (the "Code"), or non-statutory stock options ("NSOs"). Options will vest as determined by the Committee, subject to statutory limitations regarding the maximum term of ISOs and the maximum value of ISOs that by vest in a single year. The exercise price of options may not be less than the fair market value of our Common Stock on the date of grant, which, if our shares or not readily tradable on an established securities market will be determined by the Committee as the result of a reasonable application of a reasonable valuation method that satisfies the requirements of Section 409A of the Code. The exercise price must be paid in full at the time of exercise and may be paid in cash or such other manner as permitted by the Committee, including by withholding shares issuable upon exercise or by delivery of shares already owned by a participant. Although not necessarily indicative of fair market value, the closing price of a share of our common stock on the Nasdaq Capital Market on December 12, 2022 was $0.0888 per share, before giving effect to the pending 1-for-40 reverse stock split.

Stock Appreciation Rights

SARs provide for payment to the participant of all or a portion of the excess of the fair market value of a specified number of shares of our Common Stock on the date of exercise over a specified exercise price, which may not be less than the fair market value of our Common Stock on the date of grant. Payment may be made in cash or shares of our Common Stock or a combination of both, as determined by the Committee.

Restricted Stock

Restricted stock awards are awards of shares of our Common Stock that are subject to vesting conditions, and the corresponding lapse or waiver of forfeiture conditions and other restrictions, based on such factors and occurring over such period of time as the Committee may determine.

Restricted Stock Units

Restricted stock units provide a participant with the right to receive, in cash or shares of our Common Stock or a combination of both, the fair market value of a specified number of shares of our Common Stock and will be subject to such vesting and forfeiture conditions and other restrictions as the Committee determines.

Other Stock-Based Awards

The Committee may grant other awards under the 2016 Plan that are valued by reference to and/or payable in whole or in part in shares of our Common Stock.

Terms of Awards and Plan Provisions

Substitute Awards

Awards may be granted under the 2016 Plan in substitution for awards granted by another entity acquired by our company or with which our company combines. The terms and conditions of these substitute awards will be comparable to the terms of the awards replaced and may therefore differ from the terms and conditions otherwise set forth in the 2016 Plan. Shares subject to substitute awards will not count against the 2016 Plan share reserve.

Repricing of Awards

The Committee may not reduce the exercise price of stock options or SARs granted under the 2016 Plan, exchange outstanding stock options or SARs with new stock options or SARs with a lower exercise price or a new full value award, repurchase underwater stock options or SARs or take any other action that would constitute a "repricing," unless such action is first approved by our stockholders.

Transferability of Awards

Except as noted below, during the lifetime of a person to whom an award is granted, only that person, or that person's legal representative, may exercise an option or SAR, or receive payment with respect to performance units or any other award. No award may be sold, assigned, transferred, exchanged or otherwise encumbered other than to a successor in the event of a participant's death or pursuant to a qualified domestic relations order. However, the Committee may provide that awards, other than incentive stock options, may be transferable to members of the participant's immediate family or to one or more trusts for the benefit of such family members or partnerships in which such family members are the only partners, if the participant does not receive any consideration for the transfer.

Termination of Service

Unless otherwise provided in an award agreement, upon termination of a participant's service with us, all unvested and unexercisable portions of the participant's outstanding awards will immediately be forfeited. If a participant's service with us terminates other than for cause (as defined in the 2016 Plan), death or disability, the vested and exercisable portions of the participant's outstanding stock options and SARs generally will remain exercisable for 90 days after termination. If a participant's service terminates due to death or disability, the vested and exercisable portions of the participant's outstanding stock options and SARs generally will remain exercisable for one year after termination. Upon termination for cause, all unexercised stock options and SARs will be forfeited.

Withholding

The 2016 Plan permits us to withhold from cash awards, and to require a participant receiving Common Stock under the 2016 Plan to pay us in cash, an amount sufficient to cover any required withholding taxes. In lieu of cash, the Committee may permit a participant to cover withholding obligations through a reduction in the number of shares delivered to such participant or a surrender of shares then owned by the participant.

Change in Control

If a change in control (as defined in the 2016 Plan) that involves a corporate transaction (as defined in the 2016 Plan) occurs and any outstanding award is continued, assumed or replaced by our Company or the surviving or successor entity in connection with such change in control, and if within 12 months after the change in control a participant's employment or other service is terminated without cause or with good reason (as defined in the 2016 Plan), then (i) each of the participant's outstanding options and SARs will become exercisable in full, and (ii) each of the participant's unvested full value awards will fully vest. If any outstanding award is not continued, assumed or replaced in connection with such change in control, then the same consequences as specified in the previous sentence with respect to a termination of employment or other service will occur in connection with a change in control unless and to the extent the Committee elects to terminate such award in exchange for a payment in an amount equal to the intrinsic value of the award (or, if there is no intrinsic value, the award may be terminated without payment). The Committee may, in its discretion, take such other action as it deems appropriate with respect to outstanding awards for a change in control not involving a corporate transaction or may generally provide for different circumstances upon any change in control in an individual award agreement.

Adjustment of Awards

In the event of an equity restructuring, such as a stock dividend or stock split, that affects the per share value of our Common Stock, the Committee will make appropriate adjustment to: (i) the number and kind of securities reserved for issuance under the 2016 Plan, (ii) the number and kind of securities subject to outstanding awards under the 2016 Plan, (iii) the exercise price of outstanding options and SARs, and (iv) any maximum limitations prescribed by the 2016 Plan as to grants of certain types of awards. The Committee may also make similar adjustments in the event of any other change in our company's capitalization, including a merger, consolidation, reorganization or liquidation.

Amendment and Termination

The 2016 Plan has a term of ten years from its effective date, or the earlier termination of the 2016 Plan by our Board of Directors. Our Board may amend the 2016 Plan at any time, but no amendment may materially impair the rights of any participant with respect to outstanding awards without the participant's consent. Stockholder approval of any amendment of the 2016 Plan will be obtained if required by applicable law or the rules of any securities exchange on which our Common Stock may then be listed. Awards that are outstanding on the 2016 Plan's termination date will remain in effect in accordance with the terms of the 2016 Plan and the applicable award agreements.

2010 Equity Incentive Plan

We assumed CPP's 2010 Equity Incentive Plan (the "Assumed Plan") in connection with our acquisition of CPP in June 2022. As of December 12, 2022, options to purchase 39,475 shares of common stock remained outstanding under the Assumed Plan with a weighted average exercise price of $14.01 per share.

CAPITALIZATION

The following table presents a summary of our cash and cash equivalents and capitalization as of September 30, 2022:

- on an actual basis; adjusted for the effect of the reverse stock split, which we intend to effect prior to the offering;
- as adjusted for the sale of equity securities on October 4, 2022 to give effect to the sale of 177,175 shares of common stock and the sale and subsequent exercise of 325,325 prefunded warrants for total net proceeds of approximately $5.2 million.
- on an as adjusted basis to give effect to the issuance and sale of 4,222,972 shares of our common stock and common warrants to purchase up to 6,334,458 shares of our common stock in this offering at a combined public offering price of $3.552 per share and accompanying common warrant less placement agent fees and estimated offering expenses payable by us, for total net proceeds of approximately $13.7 (assuming no sale of pre-funded warrants).

The unaudited as adjusted information below is prepared for illustrative purposes only and our capitalization following the completion of this offering will be adjusted based on the actual public offering price and other terms of this offering determined at pricing. You should read the following table in conjunction with "Summary Consolidated Financial Data," "Management's Discussion and Analysis of Financial Condition and Results of Operations" and the historical financial statements and related notes thereto incorporated herein by reference.

(in thousands)	Actual as of September 30, 2022 (unaudited)	As of September 30, 2022 (after reflecting subsequent event)	Offering Adjustment	Pro Forma as Adjusted
Cash	$ 941	$ 6,141	$ 13,657	$ 19,798
Common stock, $0.001 par value, 100,000,000 shares authorized; 1,022,249 shares issued and outstanding, and outstanding, pro forma; 5,245,221 shares issued and outstanding, pro forma as adjusted	0.52	1.02	4.22	5.24
Additional paid-in capital	76,706	81,906	13,653	95,558
Accumulated deficit	(86,359)	(86,359)	-	(86,359)
Accumulated comprehensive income	1,373	1,373	-	1,373
Total stockholders' equity	$ (8,279)	$ (3,079)	$ 13,657	10,577

Each $0.50 (decrease) in the assumed public offering price of $3.552 per share would increase (decrease) each of cash, additional paid-in capital, total shareholders' equity and total capitalization by approximately $2.0 million, assuming the number of shares of common stock and common warrants offered, as set forth on the cover page of this prospectus, remains the same, and after deducting estimated placement agent fees and estimated offering expenses. Similarly, each increase (decrease) of 100,000 shares in the number of shares of common stock and common warrants offered would increase (decrease) cash, additional paid-in capital, total shareholders' equity and total capitalization by approximately $330,000, assuming the assumed public offering price remains the same, and after deducting estimated placement agent fees and estimated offering expenses payable by us. The pro forma as adjusted information discussed above is illustrative only and will be adjusted based on the actual public offering price and other terms of this offering determined at pricing.

The number of shares of our common stock outstanding before and after this offering is based on 519,749 shares of our common stock outstanding as of September 30, 2022, and 177,175 shares sold on October 4, 2022 and 325,325 pre-funded warrants sold on October 4, 2022 and exercised prior to December 12, 2022 and excludes:

- all shares issuable upon the exercise of warrants sold in this offering;
- 100,578 shares of common stock issuable upon the exercise of outstanding stock options at a weighted average exercise price of $145.46 per share;
- 50,494 additional shares of common stock reserved and available for future issuances under our 2016 Plan, as amended and restated;
- 889,911 shares of common stock issuable upon exercise of stock purchase warrants not relating to this offering at a weighted average exercise price of $38.05 per share, before any potential adjustments resulting from the pending reverse stock split;

DILUTION

If you purchase shares of our common stock, your interest will be diluted immediately to the extent of the difference between the offering price per share you will pay in this offering and the as adjusted net tangible book value per share of our common stock after this offering. Net tangible book value per share represents our total tangible assets less total liabilities, divided by the number of shares of our common stock outstanding.

As of September 30, 2022, after giving effect to the sale of equity securities on October 4, 2022, our net tangible book value was negative $3.1 million, or negative $3.01 per share of common stock.

After giving effect to the foregoing pro forma adjustments and the sale by us of 4,222,972 shares of common stock and pre-funded warrants to purchase up to shares of common stock in this offering at an assumed public offering price of $3.552 per share and accompanying common warrant and $ per pre-funded warrant and accompanying common warrant, and after deducting the placement agent fees and estimated offering expenses payable by us, our as adjusted net tangible book value as of September 30, 2022, would have been $10.6 million, or $2.017 per share. This represents an immediate increase in as adjusted net tangible book value of approximately $5.029 per share to our existing stockholders, and an immediate dilution of $1.535 per share to purchasers of shares in this offering, as illustrated in the following table:

Assumed public offering price per share	$	3.552
Pro forma net tangible book value per share as of September 30, 2022	$	(3.012)
Increase per share attributable to new investors	$	5.029
As adjusted net tangible book value per share after this offering	$	2.017
Dilution per share to new investors in the offering	$	1.535

A $0.50 increase or decrease in the assumed public offering price of $3.552 per share would increase or decrease the dilution per share to new investors in the offering by approximately $0.13 per share, assuming that the number of shares offered by us, as set forth on the cover page of this prospectus, remains the same and after deducting the estimated placement agent fees and estimated offering expenses. Similarly, each increase (decrease) of 100,000 shares in the number of shares of common stock offered would increase (decrease) the dilution per share to new investors in the offering by approximately $0.02 per share, assuming the assumed public offering price remains the same, and after deducting estimated placement agent fees and estimated offering expenses payable by us.

The number of shares of our common stock outstanding before and after this offering is based on 519,749 shares of our common stock outstanding as of September 30, 2022, and 177,175 shares sold on October 4, 2022 and 325,325 pre-funded warrants sold on October 4, 2022 and exercised prior to December 12, 2022 and excludes:

- all shares issuable upon the exercise of warrants sold in this offering;
- 100,578 shares of common stock issuable upon the exercise of outstanding stock options at a weighted average exercise price of $145.46 per share;
- 50,494 additional shares of common stock reserved and available for future issuances under our 2016 Stock Option Plan, as amended and restated;
- 889,911 shares of common stock issuable upon exercise of stock purchase warrants not relating to this offering at a weighted average exercise price of $38.05 per share, before any potential adjustments resulting from the pending reverse stock split; and
- with effectuation of a reverse stock split of our common stock.

DIVIDEND POLICY

We have never declared or paid cash dividends on our capital stock. Following the completion of this offering, we intend to retain our future earnings, if any, to finance the further development and expansion of our business and do not expect to pay cash dividends in the foreseeable future. Payment of future cash dividends, if any, will be at the discretion of our Board of Directors after various factors, including our financial condition, operating results, current and anticipated cash needs, outstanding indebtedness, plans for expansion and restrictions imposed by lenders, if any.

MANAGEMENT'S DISCUSSION AND ANALYSIS OF FINANCIAL CONDITION AND RESULTS OF OPERATIONS

The disclosure appearing in Part II, Item 7, of our annual report on Form 10-K for the year ended December 31, 2021, and Part I, Item 2, of each of our quarterly reports on Form 10-Q for the quarters ended March 31, 2022, June 30, 2022, and September 30, 2022 are hereby incorporated by reference in their entirety. The Company is eligible to incorporate this information by reference pursuant to General Instruction VII of Form S-1.

FINANCIAL STATEMENTS

Our audited financial statements for the years ended December 31, 2021 and December 31, 2022, appearing in our annual report on Form 10-K for the year ended December 31, 2021, and our unaudited financial statements for the three and nine months ended September 30, 2021 and September 30, 2022, appearing in quarterly report on Form 10-Q for the quarter ended September 30, 2022 are hereby incorporated by reference in their entirety. The Company is eligible to incorporate this information by reference pursuant to General Instruction VII of Form S-1.

BUSINESS

Panbela Therapeutics, Inc. and its wholly-owned subsidiaries Panbela Research, Inc. and Cancer Prevention Pharmaceuticals, Inc. (collectively "we," "us," "our," and the "Company") exist for the primary purpose of developing disruptive therapeutics for the treatment of patients with urgent unmet medical needs. Panbela Therapeutics Pty Ltd is a wholly owned subsidiary of Panbela Research, Inc. Cancer Prevention Pharmaceuticals, LLC., Cancer Prevention Pharma Limited (Ireland) and Cancer Prevention Pharma Limited (UK and Wales are wholly owned subsidiaries of Cancer Prevention Pharmaceuticals Inc. Panbela Therapeutics, Inc. was originally incorporated under the laws of the State of Delaware in 2011. The term "common stock" refers to our common stock, par value $0.001 per share.

Business Overview

Panbela is a clinical stage biopharmaceutical company developing disruptive therapeutics for the treatment of patients with urgent unmet medical needs. The objective of Panbela's pipeline is the utilization of pharmacotherapies to reduce or normalize increased disease-associated polyamines using complementary pharmacotherapies. Our lead candidates are ivospemin for which we have exclusively licensed the worldwide rights to this compound from the University of Florida Research Foundation, Inc. ("UFRF"). and Flynpovi, for which we have an exclusive license to commercialize from the Arizona Board of Regents of the University of Arizona.

The company's lead assets are ivospemin and Flynpovi™, which provide a multi-targeted approach to reset dysregulated biology present in many types of diseases such as cancer and autoimmunity. Many tumors require greatly elevated levels of polyamines to support their growth and survival. Our lead assets target the polyamine pathway at complementary junctions which have been shown to be altered is disease. In particular, these agents have the potential to suppress and prevent tumor growth, enhance anti-tumor activity of other anti-cancer agents, and modulate the immune system.

Ivospemin is a proprietary polyamine analogue designed to induce polyamine metabolic inhibition, a metabolic pathway of critical importance in multiple tumor types. ivospemin has demonstrated encouraging activity against metastatic disease in a clinical trial of patients with pancreatic cancer. The efficacy and safety results demonstrated in our completed Phase I clinical trial of ivospemin in combination with gemcitabine and nab-paclitaxel in the first line treatment of metastatic pancreatic cancer provides support for the current randomized, double-blind, placebo-controlled study of ivospemin in combination with gemcitabine and nab-paclitaxel in patients previously untreated for metastatic pancreatic cancer. We believe that ivospemin, if successfully developed, may represent a novel approach that effectively treats patients with pancreatic cancer and could become a dominant product in that market. Only three first-line treatment combinations, a single maintenance treatment for a subset (3-7%) of patients, and one second-line drug have been approved by the FDA for pancreatic cancer.

The Company intends to support an investigator led trial in neo adjuvant pancreatic cancer scheduled to begin in the first half of 2023. Pre-clinical evaluations of ivospemin in other cancers has shown some initial favorable results in ovarian cancer. The Company hopes to initiate a Phase I study in ovarian cancer in early 2023.

The Company's second lead asset, acquired via the acquisition of CPP on June 15, 2022 is an investigational new drug product, Flynpovi, which is a combination of the polyamine synthesis inhibitor, eflornithine, and the non-steroidal anti-inflammatory drug, sulindac. Eflornithine is an enzyme-activated, irreversible inhibitor of the enzyme ornithine decarboxylase, the first rate-limiting enzyme in the biosynthesis of polyamines. Sulindac facilitates the export and catabolism of polyamines. Flynpovi has a unique dual mechanism of action whereby it suppresses the synthesis of new polyamines and increases the export and catabolism of polyamines from the diet and microbiome. We believe the investigational drug is unique in that it is designed to treat the risk factors (e.g., polyps) that are hypothesized to lead to Familial Adenomatous Polyposis (FAP) surgeries and colon cancer and therefore may have the ability to prevent various types of colon cancer. Unlike other therapies used to treat FAP and for use with colorectal adenoma therapy, Flynpovi is an oral, non-surgical and non-invasive option that, we believe, has the potential to both improve patients' quality of life and reduce the sizeable expenses associated with current treatment protocols.

Flynpovi showed promising results in a NCI supported randomized, placebo-controlled Phase II/III clinical trial to prevent recurrent colon adenomas, particularly high-risk pre-cancerous polyps (Meyskens et al. 2008). These results led to the FAP-310 Phase III trial in FAP, and the ongoing S0820/PACES Phase III trial to study colon cancer risk reduction in partnership with the Southwest Oncology Group (SWOG) and the NCI.

The FAP-310 Phase III study evaluated the efficacy and safety of the combination of eflornithine and sulindac, as compared with either drug alone, in adults with familial adenomatous polyposis (Burke et al. 2020). This study demonstrated that Flynpovi is safe for up to 4 years of treatment. Additionally, in a post-hoc analysis, none of the patients in the combination arm progressed to a need for lower gastrointestinal (LGI) surgery for up to 48 months. Based on the post-hoc analysis of the FAP-310 trial (Balaguer et al. 2022), the Company is working closely with its North American partners One-Two Therapeutics on the Phase III registration trial for Flynpovi in FAP patients with an intact lower gastrointestinal tract.

Additional programs are evaluating eflornithine as a single agent tablet or high dose powder sachet for several indications including prevention of gastric cancer, treatment of neuroblastoma, STK-11 mutant NSCLC, and recent onset Type 1 diabetes. Preclinical studies as well as Phase I or Phase I investigator-initiated trials suggest that eflornithine treatment is well tolerated and has potential activity.

On July 16, 2021, CPP entered into a license agreement with One-Two Therapeutics Assets Limited ("One-Two"). Under the license agreement, One-Two has licensed the North American development and commercialization rights for Flynpovi, as described in the Company's IND application. The Company transferred the IND for the product to the licensing partner as of the date of the agreement. The agreement provided upfront payments, which were recognized by CPPCPP in the year ended December 31, 2021. The agreement also calls for CPP to receive a milestone payment upon regulatory approval of Flynpovi by the FDA and royalties on net sales of Flynpovi in the licensed territories. Payment of the milestone payment and net sales royalties shall be reduced on a dollar-for-dollar basis by amounts funded by One-Two for One-Twos' direct costs associated with any development activities necessary to secure FDA approval.

Holding Company Reorganization

Effective June 15, 2022, Panbela became a successor issuer to Panbela Research, Inc. (formerly known as Panbela Therapeutics, Inc., the "Predecessor") pursuant to a holding company reorganization pursuant to which the Predecessor became a direct, wholly-owned subsidiary of Panbela. Panbela became a successor issuer to the Predecessor by operation of Rule 12g-3(a) promulgated under the Exchange Act.

CPP Acquisition

On June 15, 2022, Panbela acquired CPP via merger for consideration consisting of (a) 6,587,576 shares of common stock, (b) 731,957 shares of common stock that remained subject to a holdback escrow (as defined in the Merger Agreement), (c) replacement options to purchase up to 1,596,754 shares of common stock at a weighted average exercise price of $0.35 per share, and (d) replacement warrants to purchase up to 338,060 shares of common stock at a weighted average exercise price of $4.145 per share, and post-closing contingent payments up to a maximum of $60 million, subject to satisfaction of milestones.

Clinical Trials

IVOSPEMIN (SBP-101)

In August 2015, the FDA accepted our Investigational New Drug ("IND") application for our ivospemin product candidate. In May of 2022 we were notified that the United States Adopted Names Council (USAN) had adopted ivospemin as a USAN for SBP-101. After August 1, 2022, the USAN information on ivospemin will be scheduled for posting on the USAN Web site (www.ama-assn.org/go/usan). We have completed an initial clinical trial of ivospemin in patients with previously treated locally advanced or metastatic pancreatic cancer. This was a Phase I, first-in-human, dose-escalation, safety study. Between January 2016 and September 2017, we enrolled twenty-nine patients into six cohorts, or groups, in the dose-escalation phase of our Phase I trial. No drug-related serious adverse events occurred during the first four cohorts. In cohort five, serious adverse events (klebsiella sepsis with metabolic acidosis in one patient, renal and hepatic toxicity in one patient, and mesenteric vein thrombosis with metabolic acidosis in one patient) were observed and were determined by the Data Safety Monitoring Board ("DSMB") to be Disease Limiting Toxicities ("DLTs"). Consistent with the study protocol, the DSMB recommended continuation of the study by expansion of cohort 4, one level below that at which DLTs were observed.

In addition to being evaluated for safety, 23 of the 29 patients were evaluable for preliminary signals of efficacy prior to or at the eight-week conclusion of their first cycle of treatment using the RECIST, the current standard for evaluating changes in the size of tumors. Eight of the 23 patients (35%) had Stable Disease ("SD") and 15 of 24 (65%) had Progressive Disease ("PD"). It should be noted that of the 15 patients with PD, six came from cohorts one and two and are considered to have received less than potentially therapeutic doses of ivospemin.

By cohort, stable disease occurred in two patients in cohort 3, two patients in cohort 4 and four patients in cohort 5. The best response outcomes and best median survival were observed in the group of patients who received total cumulative doses of approximately 6 mg/kg (cohort three). Two of four patients (50%) showed SD at week eight. Median survival in this group was 5.9 months, with two patients surviving 8 and 10 months, respectively. By total cumulative dose received, five of twelve patients (42%) who received total cumulative doses between 2.5 mg/kg and 8.0 mg/kg had reductions in the CA19-9 levels, as measured at least once after the baseline assessment. Nine of these patients (67%) exceeded three months of Overall Survival ("OS"), three patients (25%) exceeded nine months of OS and two patients (17%) exceeded one year of OS and were still alive at the end of the study.

We completed enrollment of patients in our second ivospemin clinical trial in December 2020. This second clinical trial was a Phase Ia/Ib study of the safety, efficacy and pharmacokinetics of ivospemin administered in combination with two standard-of-care chemotherapy agents, gemcitabine and nab-paclitaxel. In the Phase Ia portion of this trial, we completed enrollment during the first quarter of 2020 consisting of four cohorts with increased dosage levels of ivospemin administered in the second and third cohorts; the fourth cohort evaluated an alternate dosing schedule. A total of 25 subjects were enrolled in four cohorts of Phase Ia. The demonstration of adequate safety in Phase Ia allowed us to immediately begin enrollment in February 2020 in the Phase Ib exploration of efficacy. By December 2020, an additional 25 subjects in Phase Ib, using the recommended dosage level and schedule determined in Phase Ia, were enrolled.

After Phase Ib enrollment was completed, some patients in the trial were noted to have complaints of serious visual adverse effects. Visual changes were not seen in the ivospemin monotherapy study. We consulted with our DSMB and withheld the administration of ivospemin while all other trial activities continued. In February of 2021, we also conferred with the FDA regarding our plan to withhold dosing of ivospemin. This constituted a "partial clinical hold." In April of 2021, the FDA lifted the partial clinical hold. The Company agreed with the FDA to include in the design of all future studies the exclusion of patients with a history of retinopathy or risk of retinal detachment and scheduled ophthalmologic monitoring for all patients.

Updated, but still not final results, were presented in a poster at the American Society of Clinical Oncology – GI conference ("ASCO-GI") in January 2022. Best response in evaluable subjects (cohorts 4 and Ib N=29) was a Complete Response ("CR") in 1 (3%), Partial Response ("PR") in 13 (45%), SD in 10 (34%) and PD in 5 (17%)**.** One subject did not have post baseline scans with RECIST tumor assessments. Median Progression Free Survival ("PFS"), now final at 6.5 months, may have been negatively impacted by drug dosing interruptions to evaluate potential toxicity. Median overall survival in Cohort 4 + Phase Ib was 12.0 months when data was presented in January 2022 and is now final at 14.6 months. Two patients from cohort 2 have demonstrated long term survival. One at 30.3 months (final data) and one at 33.0 months and still alive. Seven subjects are still alive at this time, one from cohort 2 and six from cohort 4 plus Ib.

The Company announced that the ASPIRE trial, a randomized, double-blind, placebo-controlled study of ivospemin with Gemcitabine and Nab-Paclitaxel versus Gemcitabine, Nab-Paclitaxel and placebo, was initiated in January of 2022. The trial is in patients with first-line metastatic pancreatic ductal adenocarcinoma. The trial was originally designed as a Phase II/III with a smaller sample size (150) to support the events required for interim analysis based on Progression Free Survival (PFS) and a primary endpoint of overall survival. In response to European and FDA regulatory feedback, the study was amended to include the total trial sample size (600) and the design modified to utilize overall survival as the primary endpoint to be examined at interim analysis. PFS will also be analyzed to provide additional efficacy evidence. This amendment was supported by the final data from the Phase Ia/b first line metastatic pancreatic cancer trial which completed enrollment in December of 2020. The study will enroll 600 subjects and is anticipated to take 36 months for complete enrollment with the interim analysis available in early 2024**.**

If we can successfully complete all FDA recommended clinical studies, we intend to seek marketing authorization from the FDA, the European Medicines Agency ("EMA") (European Union), Ministry of Health and Welfare (Japan) and TGA (Australia). The submission fees may be waived when ivospemin has been designated an orphan drug in each geographic region.

Data presented at the American Association for Cancer Research (AACR) in April 2022, demonstrated in an in vitro study evaluating cancer cell lines, ivospemin was toxic in ovarian cancer cell lines with an average IC50 of ~1.5 µM. Efficacy of ivospemin was further assessed in the VDID8+ murine ovarian cancer model. Tumor-bearing mice treated with ivospemin at either 24 mg/kg or 6 mg/kg produced a statistically significant prolongation of survival (24mg/kg p=.0049, 6 mg/kg p=.0042). The prolonged survival was correlated with a delay in the production of ascites, the indication of tumor burden in this model. Given this data, the Company intends to proceed with a clinical development program in ovarian cancer by early 2023.

FLYNPOVI

An NCI-supported study using the Flynpovi combination showed promising results and no overt toxicity in a randomized placebo-controlled Phase II/III clinical trial treating patients with sporadic adenomas for three years of daily dosing (Meyskens et al. 2008). The published results from the trial showed there was a 70% difference in efficacy between the treatment and placebo groups for all adenomas (i.e., both standard risk and high-risk). In measurements of occurrence, 12.3% of all patients treated with Flynpovi showed adenoma occurrence compared to 41.1% in the placebo group. In the subgroups of the study that had high-risk adenomas there was a 92 – 95% difference between the treatment and placebo groups. Compared to placebo, the recurrence of risky adenomas was inhibited by over 90%. The p value for all comparisons in this study was $p < 0.001$ (Meyskens et al. 2008). The results of this study were the basis for the FP and colorectal cancer survivor trials.

In the FAP-310 Phase III study, the efficacy and safety of the combination of eflornithine and sulindac, as compared with either drug alone, in adults with familial adenomatous polyposis was conducted (Burke et al. 2020). The patients were randomly assigned in a 1:1:1 ratio to receive eflornithine, sulindac, or both once daily for up to 48 months. The primary end point, assessed in a time-to-event analysis, was disease progression, defined as a composite of major surgery, endoscopic excision of advanced adenomas, diagnosis of high-grade dysplasia in the rectum or pouch, or progression of duodenal disease. A total of 171 patients underwent randomization. Disease progression occurred in 18 of 56 patients (32%) in the eflornithine-sulindac group, 22 of 58 (38%) in the sulindac group, and 23 of 57 (40%) in the eflornithine group, with a hazard ratio of 0.71 (95% confidence interval [CI], 0.39 to 1.32) for eflornithine-sulindac as compared with sulindac (P = 0.29) and 0.66 (95% CI, 0.36 to 1.23) for eflornithine-sulindac as compared with eflornithine. Adverse and serious adverse events were similar across the treatment groups (Burke et al. 2020). In a post-hoc analysis, none of the patients in the combination arm progressed to a need for lower gastrointestinal (LGI) surgery for up to 48 months compared with 7 (13.2%) and 8 (15.7%) patients in the sulindac and eflornithine arms (Balaguer et al. 2022). These data corresponded to risk reductions for the need for LGI surgery approaching 100% between combination and either monotherapy with HR = 0.00 (95% CI, 0.00-0.48; $p = 0.005$) for combination versus sulindac and HR = 0.00 (95% CI, 0.00-0.44; $p = 0.003$) for combination versus eflornithine. Given the statistical significance of the LGI group, a new drug application (NDA) was filed with the FDA. As the study failed to meet the primary endpoint, and the NDA was based on the results of an exploratory analysis, a complete response letter was issued. To address this deficiency concern, the Company must submit the results of one or more adequate and well-controlled clinical trials which demonstrate an effect on a clinical endpoint. As the result of an existing North American license agreement, the FAP registration trial is fully funded and is scheduled to begin in the first-half of 2023. There are no currently approved pharmaceutical therapies for FAP.

In collaboration with the NCI, and SWOG, a Phase III clinical trial has been initiated to study the benefits of Flynpovi as a therapeutic treatment for use by colon cancer survivors. The trial is named PACES for "Prevention of Adenomas and Cancer with eflornithine and sulindac." The PACES trial is funded by the NCI and managed by the Southwest Oncology Group ("SWOG"). This is an ongoing double-blind placebo-controlled trial of Flynpovi to prevent recurrence of high risk adenomas and second primary colorectal cancers in patients with stage 0-III colon or rectal cancer, Phase III – Preventing Adenomas of the Colon With Eflornithine and Sulindac ("PACES"). The purpose of this study is to assess whether the Flynpovi, combination of eflornithine (CPP-1X) and sulindac, (compared to corresponding placebos) has a reduced rate of cancer or high-risk adenoma recurrence compared to comparator arms after three years of daily dosing. We have exclusive rights to the data that comes from the trial for regulatory and commercial purposes. One-Two Therapeutics has licensed the program for North America and the Company is evaluating its options for CAT in the European Union and Asia.

Eflornithine sachets / eflornithine tablets (CPP-1X-S/CPP-1X)

Additionally, there are several investigator initiated trials evaluating eflornithine sachets including an ongoing Phase II trial in relapsed refractory neuroblastoma a particularly deadly cancer affecting children, supported by the Childrens' Oncology Groups (COG) and NCI and a planned Phase I/II trial STK11 mutation patients with non-small cell lung cancer scheduled to begin this year. For eflornithine tablets, a Phase II trial for the prevention of gastric cancer funded by the NCI has been completed, and an investigator-initiated Phase II trial in Type I onset diabetes is scheduled to begin this year.

Recent Developments

Reverse Stock Split

On November 29, 2022, at a special meeting of stockholders, our stockholders approved an amendment to our Amended and Restated Certificate of Incorporation to effect a 1-for-40 reverse stock split of our outstanding shares of common stock. We intend to effect the reverse stock split prior to this offering to ensure a sufficient number of shares of authorized common stock is available to complete the offering.

The common stock purchase warrants we issued in October 2022 provide that their exercise price will be reduced to the lowest volume-weighted average price on any trading day during the five-trading day period immediately following the date a reverse stock split is effected. Accordingly, we are unable to estimate the adjustment, if any, to the exercise price of those outstanding warrants that would result from the pending reverse stock split. Although the common stock purchase warrants offered pursuant to this prospectus contain a similar provision, because the reverse stock split will be effected before the offering, no such adjustment will be made to the exercise price of those warrants.

Product Developments

The combined entity resulting from Panbela's acquisition of CPP has an expanded pipeline; areas of initial focus include familial adenomatous polyposis (FAP), first-line metastatic pancreatic cancer, neoadjuvant pancreatic cancer, colorectal cancer prevention and ovarian cancer. The combined development programs have a steady cadence of catalysts with programs ranging from pre-clinical to registration studies.

Through December 12, 2022, we had:

- secured an orphan drug designation for ivospemin from the FDA;
- submitted and received acceptance from the FDA for an IND application for ivospemin;
- received Country approvals for the Aspire Trial in Australia, France, Italy and Spain;
- completed a Phase Ia monotherapy safety study of ivospemin in the treatment of patients with metastatic pancreatic ductal adenocarcinoma;
- received "Fast Track" designation from the FDA for ivospemin for metastatic pancreatic cancer;
- completed enrollment and released interim results in our second trial a Phase Ia /Ib clinical study of ivospemin, a first-line study with ivospemin given in combination with a current standard of care in patients with pancreatic ductal adenocarcinoma who were previously untreated for metastatic disease; a total of 50 subjects were enrolled in this study, 25 in the Phase Ia and 25 in the Phase Ib or expansion phase;
- secured a two year research agreement with Johns Hopkins School of Medicine led by Professor Robert Casero, an internationally recognized researcher in polyamine biology;
- completed process improvement measures expected to be scalable for commercial use and received issue notification for a patent covering this new shorter synthesis of ivospemin;
- initiated a randomized, double-blind, placebo controlled study with ivospemin given in combination with gemcitabine and nab-paclitaxel in patients with pancreatic ductal adenocarcinoma who are previously untreated for metastatic disease;
- completed preclinical evaluation of ivospemin for use as neoadjuvant therapy in resectable pancreatic cancer prior to surgery;
- obtained early, preclinical, indication of tumor growth inhibition activity in ovarian cancer and presented the results at ASCO-GI conference;
- received USAN adoption of the nonproprietary name of ivospemin for SBP-101; and
- acquired and integrated CPP, adding a second lead asset in multiple forms and an expansive clinical development program ranging from pre-clinical to registration level clinical trials.

Pancreatic Cancer

Pancreatic cancer afflicts approximately 140,000 people in Europe (GLOBOCAN 2021, Global Cancer Observatory/World Health Organization), approximately 60,000 people in the United States annually, and 293,000 people worldwide – excluding Europe and the United States (GLOBOCAN 2021). It has been identified as the fourth leading cause of death from cancer in Europe (GLOBOCAN 2021) and the third leading cause of death from cancer in the United States (SEER Cancer Statistics Factsheets 2021). On average Pancreatic Ductal Adenocarcinoma ("PDA") represents approximately 95% of all pancreatic cancers diagnosed in any given calendar year. Considering that the median overall survival for previously untreated patients with good performance status is between 8.5 months (Von Hoff 2013) and 11.1 months (Conroy 2011) with the two most commonly available treatment regimens, effective treatment for PDA has remained a major unmet medical need.

Pancreatic cancer is generally not diagnosed early because the initial clinical signs and symptoms are vague and non-specific. The most common presenting symptoms include weight loss, epigastric (upper central region of the abdomen) and/or back pain, and jaundice. The back pain is typically dull, constant, and of visceral origin radiating to the back, in contrast to the epigastric pain which is vague and intermittent. Less common symptoms include nausea, vomiting, diarrhea, anorexia, and new onset diabetes (which can be an early signal) or glucose intolerance (Hidalgo 2010).

Surgery remains the only treatment option with curative intent, although only about 20% of patients are candidates for surgical resection at the time of the diagnosis. Patients who undergo radical surgery still have a limited survival rate, averaging 23 months (Macarulla T, et al Clin Transl Oncol 2017).

For the minority of patients who present with resectable disease, surgery is the treatment of choice. Depending on the location of the tumor the operative procedures may involve cephalic pancreatoduodenectomy, referred to as a "Whipple procedure" distal pancreatectomy or total pancreatectomy. Pancreatic enzyme deficiency and diabetes are frequent complications of both the disease and these surgical procedures. Up to 70% of patients with pancreatic cancer present with biliary obstruction that can be relieved by percutaneous or endoscopic stent placement. However, even if the tumor is fully resected, the outcome in patients with pancreatic cancer has been disappointing (Hidalgo 2010, Seufferlein 2012). Post-operative administration of chemotherapy improved progression-free and overall survival in three large randomized clinical trials (Hidalgo 2010), but median post-surgical survival in patients treated in all three trials was similar, only 20-22 months. Pre-operative (neo-adjuvant) chemotherapy is of increasing interest, with the goal of improved successful resections and long-term outcomes.

For patients who present with unresectable, locally advanced or metastatic disease, which represent a majority of PDA patients, management options range from chemotherapy alone to combined forms of treatment with radiation therapy and chemotherapy. However, due to the increased toxicity of combined treatment, randomized trials of such combined regimens have had low enrollment, precluding a firm conclusion as to any advantage of adding radiation to chemotherapy (Hidalgo 2010).

Gemcitabine was the first chemotherapeutic agent approved for the treatment of patients with PDA in the modern regulatory era, providing a median survival duration of 5.65 months (Burris 1997). Gemcitabine monotherapy was the standard of care for patients with metastatic pancreatic cancer until combination therapy with gemcitabine plus erlotinib (Tarceva®) was shown to increase median survival by two weeks. This modest benefit was tempered by a significant side effect profile and high cost, limiting its adoption as a standard treatment regimen. Subsequently, the multidrug chemotherapy combination FOLFIRINOX, was shown to provide a median survival benefit of 4.3 months (OS = 11.1 months) over gemcitabine alone (6.8 months), but its significant side effect profile limits the regimen to select patients with a good performance status and often requires supplementation with WBC growth factor therapy. Nab-paclitaxel (Abraxane®) received marketing authorization for use in combination with gemcitabine (FDA approved 2013) after showing an increase in overall survival of seven weeks compared to gemcitabine alone (Von Hoff 2013).

Familial adenomatous polyposis

Familial adenomatous polyposis ("FAP") is a rare and potentially life-threatening genetic condition occurring in approximately one in 10,000 individuals in the United States. FAP is caused primarily by mutations in the adenomatous polyposis coli (*APC*) tumor suppressor gene. *APC* mutations are usually inherited as autosomal dominant genetic traits, but as high as 25% of those afflicted with FAP with an identical germline mutation have no family history. Only 1 in 10,000 people will develop FAP. Estimated annual prevalence in the US is approximately 30,000 and in Europe approximately 50,000. If untreated, patients will develop hundreds to thousands of polyps throughout the colon and rectum. FAP often develops in the early teens and result in a nearly 100% lifetime risk of colorectal cancer by age forty if untreated. No approved FAP drug is on the market.

Most patients are asymptomatic for years until the adenomas are large and numerous, and cause rectal bleeding or even anemia, or cancer develops. Generally, cancers start to develop a decade after the appearance of the polyps. Nonspecific symptoms may include constipation or diarrhea, abdominal pain, palpable abdominal masses and weight loss.

Cancer prevention and maintaining a good quality of life are the main goals of management of patients with FAP. By the late teens or early twenties, colorectal cancer prophylactic surgery is advocated. Prophylactic surgery often requires total abdominal colectomy with ileal-rectal anastomoses (IRA) and subsequent frequent endoscopic surveillance, with polypectomy and cautery/laser ablation as needed. Patients with extensive rectal involvement must undergo total proctocolectomy with ileal pouch-anal reconstruction. Despite this, approximately 50% of patients who have had total proctocolectomy with ileal pouch-anal reconstruction will develop adenomatous polyps in the neo-rectum (ileal pouch). Duodenal cancer and desmoids are the two main causes of mortality after total colectomy, they need to be identified early and treated. Upper endoscopy is necessary for surveillance to reduce the risk of ampullary and duodenal cancer. Patients with progressive tumors and unresectable disease may respond or stabilize with a combination of cytotoxic chemotherapy and surgery (when possible, to perform). Individuals with FAP carry a 100% risk of CRC; however, this risk is reduced significantly when patients enter a screening-treatment program.

A major unmet need in the treatment of patients with FAP is a therapeutic means to defer or obviate the need for major surgical interventions, particularly colectomy with IRA or proctocolectomy with an ileal surgical pouch (IPAA). Such interventions often require temporary or permanent ileostomy, and with it, long-term or permanent quality of life (QoL) deficits such as frequent bowel movements (average 6 per day), nocturnal fecal incontinence and, in female patients, reduced reproductive potential. It is critical to find non-surgical alternatives that will delay or obviate the need of repeated endoscopic and surgical procedures to maintain patient QoL. For those patients who have an intact colon in particular, pharmacotherapy offers the opportunity to meaningfully control or delay polyposis progression and offer a greater choice over when or if they undergo prophylactic colectomy/proctocolectomy in order to optimize QoL.

This potential benefit is in fact likely the most powerful potential benefit possible since the long-term course of FAP essentially mandates ultimate colectomy for most patients. The value to a younger patient in safely delaying such a radical procedure by years cannot be overstated.

There are currently no approved and marketed pharmacotherapeutic treatments for patients with FAP. While in 1999 celecoxib was conditionally approved by the FDA for the treatment of FAP based on reductions of polyp number observed in a randomized double-blind placebo-controlled study conducted in patients with FAP, it was subject to the marketing authorization holder, Pfizer, providing additional data. On February 2, 2011, FDA requested that Pfizer voluntarily withdraw the FAP indication for CELEBREX (celecoxib) Capsules from the market because the post-marketing study intended to verify clinical benefit and required as a condition of approval under subpart H was never completed. In a letter dated February 3, 2011, Pfizer requested that FDA withdraw the FAP indication for CELEBREX (celecoxib) Capsules from the market. Effective June 8, 2012 the approval for the FAP indication for CELEBREX (celecoxib) Capsules was withdrawn. Celecoxib was also authorized for FAP treatment centrally by the European Commission after the EMA's scientific review in October 2003 under "exceptional circumstances". Authorization was granted subject to specific obligations during product life-cycle, chiefly to provide further data on its efficacy and safety; however, the applicant/authorization holder could not fulfill this central post-authorization obligation. According to publicly available information, the post- authorization study was initiated in the first quarter of 2004 and the EU Centralized Marketing Authorisation was withdrawn in April 2011 because the holder was unable to provide the data as required.

Ovarian Cancer

Worldwide Ovarian Cancer has an annual incidence of approximately 314,000 and annual deaths of approximately 207,000 (Globocan 2020). In the United States Ovarian cancer represents approximately 1% of all new cancer cases at approximately 21,000 and the five-year survival rate for metastatic disease is approximately 29% (SEER fact sheet Ovarian 2022). According to the American Cancer Society, ovarian cancer is the fifth leading cause of cancer deaths among women, accounting for more deaths than any other cancer of the female reproductive system.

Nearly 70 % of patients are diagnosed with advanced-stage due to the failure of screening methods for detecting early-stage disease (Giornelli. 2016; Partridge et al. 2009; Bast et al. 2007; Gohagan et al. 2000; Chudecka-Glaz 2015). Thus, most patients will relapse within the first two years after diagnosis, even after an optimal primary cytoreductive surgery and six cycles of the standard adjuvant chemotherapy with carboplatin/paclitaxel.

The second line chemotherapy depends mainly on the disease-free interval ("DFI") (time between completion of first line chemotherapy and clinical relapse); or progression-free interval ("PFI") (time between the last chemotherapy given for relapsed disease and progression). There are three classifications: Platinum-refractory/resistant with relapse during platinum treatment (refractory) or with a DFI/PFI <6 months (resistant), Platinum-sensitive relapse occurring >12 m of last platinum-based chemotherapy, or partially sensitive to platinum with disease-free survival ("DFS")/ progression free survival ("PFS") between 6 and 12 months from the last platinum-based chemotherapy.

According to Pignata et al. 2017, in platinum-sensitive patients, treatment with platinum-based combinations is associated with a PFS advantage compared with single agents or non-platinum combinations. For patients with partially sensitive relapse (PFI between 6 and 12 months), two options are available: platinum doublets or non-platinum therapy (single agent or combination). Last, for patients with resistant or refractory relapse (PFI < 6 months) disease there are few options. For these patients, monotherapy with a non-platinum drug or participation in clinical trials is indicated.

Colorectal Cancer

According to United States Cancer Statistics published by the American Cancer Society, in the United States in 2022, it is estimated that CRC will be the third most commonly occurring cancer among males and females and the third leading cause of cancer-related deaths. High-risk adenomatous polyps are considered the key risk factor for CRC. In 2015, the disease will be responsible for an estimated 52,000 deaths in the United States. An even higher rate of incidence occurs in the European Union, where approximately 255,000 people per year die from CRC according to the Globocan 2020 Fact Sheets.

Globally, there are approximately 1,931,000 new diagnoses each year (approximately 180,000 expected in North America in 2020). Rates of presentation are also becoming significant in Asia (China and Japan). Colorectal adenomas (or "polyps") are considered the key risk factor for CRC. The general consensus in the medical and scientific communities is that these polyps are the precursors to more than 90% of all colorectal cancers.

Colon cancer represents nearly three-fourths of all colorectal cancers in the U.S. Despite potentially curative treatment with surgery (with or without adjuvant chemotherapy), local stage and locally-advanced stage colon cancer patients remain at considerable risk for colorectal adenomas, distant recurrence, secondary colonic tumor formation, and colorectal cancer related mortality. Polypectomy appears to be an effective way to decrease mortality from colon cancer but widespread adoption of this approach is limited by both cost and patient acceptability (Newcomb et al. 1992; Selby et al. 1992). Certain types of colorectal polyps have increased risk of progression to colorectal cancer. High-risk polyps (polyps with villous histology, size ≥ 1 cm, high grade dysplasia, or multiple adenomas defined as 3 or more) have become the focus of colorectal tumorigenesis research due to the higher rate of malignant potential for these lesion (Lotfi et al. 1986; Spencer et al. 1984; Winawer et al. 1993; Martinez et al. 2009) . The current standard of care for resected colon cancer patient (beyond surgery, and adjuvant chemotherapy when indicated) is surveillance monitoring with clinical exams, laboratory analyses, and colonoscopic evaluation. However, data suggest that colonoscopy does not predict death from colorectal cancer uniformly throughout the colon – in fact, right-sided colorectal cancers were not observed to gain any mortality benefit from colonoscopy (Baxter et al. 2009). Other potential problems with colonoscopy include (rarely) perforations, infection, bleeding, and non-adherence with current recommendations. Safe and effective chemopreventive interventions, therefore, offer great potential to complement and improve upon the current colon cancer surveillance paradigm. Unlike other therapies used to treat CAT, Flynpovi is a non-surgical and non-invasive option that has the potential to both improve patient quality of life and reduce higher healthcare system-wide expense burdens.

Neuroblastoma

There are approximately 700 to 800 new cases of neuroblastoma each year in the US, with a US prevalence of 5,000 – 6,000 and this disease is found worldwide at similar rates (includes adults that had NB as children). About 50% of cases will be diagnosed as high-risk neuroblastoma (HR-NB) (Maris 2010). These individuals have the poorest survival prognosis. Time to first relapse (TTFR) is associated with overall survival (OS) in HR-NB patients that achieve an objective complete or partial response to initial therapy (London et al. 2011). Approximately 50% of the HR-NB patients will relapse and be eligible for this therapeutic approach.

Proprietary Technology

Function and Characteristics of Polyamines

Polyamines are metabolically distinct entities within human cells that bind to and facilitate DNA replication, RNA transcription and processing, and protein (such as pancreatic enzymes) synthesis. Human cells contain three essential and naturally occurring polyamines - putrescine, spermidine, and spermine. Polyamines perform many functions necessary for cellular proliferation, apoptosis and protein synthesis. The critical balance of polyamines within cells is maintained by several enzymes such as ornithine decarboxylase ("ODC") and spermidine/spermine N1 acetyl transferase ("SSAT"). All of these homeostatic enzymes are short-lived, rapidly inducible intracellular proteins that serve to regulate native polyamine pools tightly and continuously. These enzymes constantly maintain polyamines within a very narrow range of concentration inside the cell.

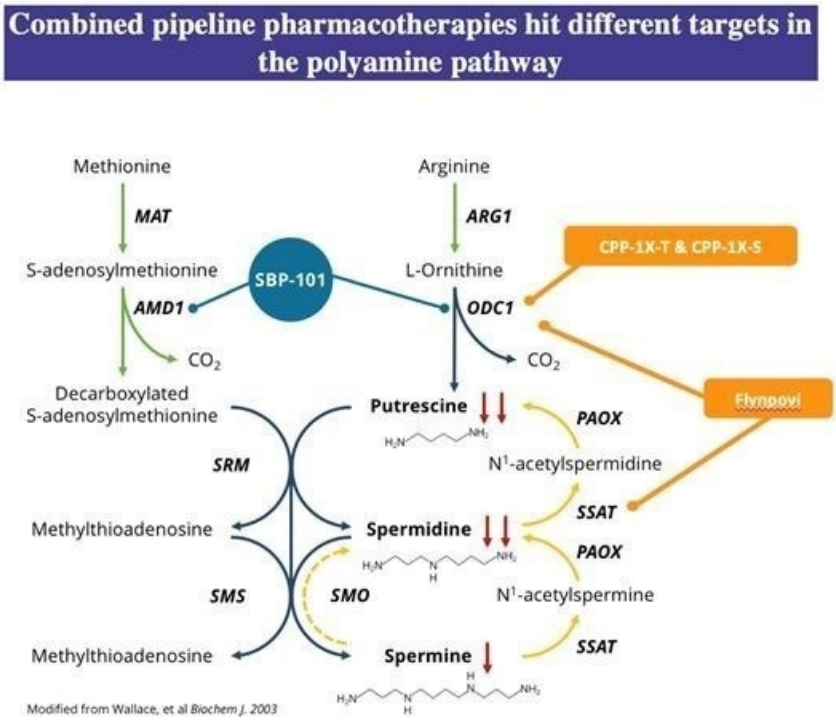
Polyamine metabolism and cancer

Polyamines are required for cell proliferation. It is believed that many cancers, especially oncogene-driven cancers, might be sensitive to interference with polyamine metabolism. The natural polyamines putrescine, spermidine and spermine are intimately involved in growth-related processes, wound healing, and the development of cancer. Under normal conditions, the pool of polyamines is tightly controlled through regulation of synthesis, catabolism, and transport mechanisms (Gerner and Meyskens 2004). The loss of this tight control can result in an excessive accumulation of polyamines, which favors malignant transformation of cells. Consequently, with the loss of growth control in cancer cells, the transformed cells may be more sensitive to polyamine depletion than normal cells. Thus, the polyamine metabolic pathway is a rational target for therapeutic intervention (Casero 2018).

Immune systems require multiple soluble and cellular components, including polyamines, for a normal immune function. As such, polyamines are important modulators of the immune response, particularly in the tumor microenvironment where they are found in high concentrations. High levels of polyamines are present in tumor cells and in autoreactive B- and T-cells in autoimmune diseases. Dysregulation of polyamines can result in tumor immune evasion, elevated cell stress, and increased autoimmunity. By resetting the polyamine pathway through therapeutic interventions, there is the potential to restore normal immune functions.

Pharmacotherapeutic Approaches to Reset the Polyamine Pathway

The company’s lead assets are ivospemin and Flynpovi which provide a multi-targeted approach to reset dysregulated biology present in many types of diseases such as cancer and autoimmunity. For instance, many tumors require greatly elevated levels of polyamines to support their growth and survival. These agents target the polyamine pathway at complementary junctions which have been shown to be altered is disease. In particular, these agents have the potential to suppress and prevent tumor growth, enhance anti-tumor activity of other anti-cancer agents, and modulate the immune system.



Polyamine Analogue- ivospemin (SBP-101)

Many tumors, including pancreatic cancer, display an increased uptake rate of polyamines. Polyamine analogues such as ivospemin are structurally similar to naturally occurring polyamines and are recognized by the cell's polyamine uptake system, allowing these compounds to gain ready entrance to the cell. We believe that pancreatic acinar cells, because of their extraordinary protein synthesis capacity, exhibit enhanced uptake of polyamines and polyamine analogues. Because of this preferential uptake by pancreatic acinar cells, polyamine analogues such as ivospemin disrupt the cell's polyamine balance and biosynthetic network, and induce programmed cell death, or apoptosis, via processes including caspase 3 activation and poly ADP ribose polymerase (PARP) cleavage. Proof of concept has been demonstrated in multiple human pancreatic cancer models, both *in vivo* and *in vitro*, that pancreatic ductal adenocarcinoma exhibits sensitivity to ivospemin.

Ivospemin is a proprietary polyamine analogue, which we believe accumulates in the exocrine pancreas acinar cells due to its unique chemical structure. ivospemin was discovered and extensively studied by Professor Raymond J. Bergeron at the University of Florida College of Pharmacy.

As laboratory studies suggest, the primary mechanism of action for ivospemin has been demonstrated to include the enhanced uptake of the compound in the exocrine pancreas, therefore, pancreatic cancer was logical for the initial development of this compound. Sufficiently high dosing in animal models leads to correspondingly depressed levels of native polyamines, with caspase 3 activation, PARP cleavage and apoptotic destruction (programmed cell death) of the exocrine pancreatic acinar and ductal cells without an inflammatory response. Importantly, pancreatic islet cells, which secrete insulin, are structurally and functionally dissimilar to acinar cells and are not impacted by ivospemin. In animal models at two independent laboratories, ivospemin has demonstrated significant suppression of transplanted human pancreatic cancer cells, including metastatic pancreatic cancer growth.

We believe that ivospemin exploits the natural affinity of the exocrine pancreas, the liver and kidney, and pancreatic ductal adenocarcinoma cells while leaving the insulin-producing islet cells unharmed. Most current cancer therapies, including chemotherapy, radiation, and surgery are associated with significant side effects that further reduce the patient's quality of life. However, based on data evaluated from clinical studies to date, we believe that the adverse effects of ivospemin in causing bone marrow suppression or peripheral neuropathy do not overlap with or exacerbate those seen with typical chemotherapy options. The dose-limiting toxicities observed in cohort five of our first Phase I study, as noted below, were not observed at lower doses and are not expected to overlap with the adverse events of bone marrow suppression and peripheral neuropathy commonly associated with standard chemotherapy. The dose and dosing schedule evaluated in the expansion phase of the recently completed Phase Ia/Ib trial is below the maximum tolerable dose ("MTD") and at this dose level, neither the exocrine nor the endocrine human pancreas is expected to be affected by ivospemin, resulting in no treatment impact on pancreatic enzyme or insulin levels. This dose level and dosing schedule in the new ASPIRE trial will be the same as evaluated in the expansion phase of the Ia/Ib study.

Ornithine Decarboxylase Inhibitor - eflornithine (CPP-1X)

Ornithine decarboxylase is the first and rate-limiting enzyme in the biosynthesis of polyamines which catalyzes the conversion of ornithine to putrescine and regulates the biosynthesis of polyamines in mammalian as well as many other eukaryotic cells. Eflornithine, also known as α-difluoromethylornithine (DFMO) and eflornithine, is an ornithine analogue. Eflornithine irreversibly binds to ODC1 and prevents the natural ODC1 substrate, ornithine, from accessing the active site of the enzyme (Meyskens and Gerner 1999). The administration of eflornithine decreases both ODC activity and polyamine concentrations. In genetic mouse models with an APC gene mutation, the administration of eflornithine reduces intestinal carcinogenesis, decreasing the concentration of polyamines through transport and catabolism and inhibiting tumour development (Babbar et al. 2003).

Treatment of animals with eflornithine results in inhibition of ODC activity, especially in tissues and organs with rapidly dividing cells. Polyamine biosynthesis has been shown to be critical for eukaryotic cellular growth and differentiation, and inhibition of polyamine biosynthesis can stimulate or inhibit cellular differentiation depending on the model studied (Gerner and Meyskens 2004). Accordingly, eflornithine has promoted or inhibited cell differentiation in a variety of models.

Polyamine biosynthesis is also a critical step in experimental chemical-induced carcinogenesis, cell transformation, and tumor cell proliferation, and there is a growing body of evidence that eflornithine's inhibitory effect on cell proliferation and tumorigenesis may involve a complex inter-relationship between oncogenes, polyamine metabolism, and ODC activity. MYC is an oncogene that encodes a transcription factor that is required for the proliferation of normal cells but when overexpressed can lead to aberrant cell growth (Gerner and Meyskens 2004). Additionally, c-Myc is a transcriptional activator of the ODC gene (Pena et al. 1993) (Bello-Fernandez, Packham, and Cleveland 1993). Furthermore, eflornithine has been shown to decrease N-Myc mRNA in neuroblastoma cells and c-Myc mRNA in human colon carcinoma cells (Celano et al. 1988) and spermidine preferentially stimulated transcription and expression of c-Myc, but not c-Fos (Tabib and Bachrach 1999)). Taken together, these results suggest that polyamines play a feedback role in the regulation of expression of certain oncogenes at the level of transcription.

Mice with a mutation of the adenomatous polyposis coli (*Apc*) tumor suppressor gene develop intestinal tumors in numbers similar to those found in patients with FAP. Mutations of the *Apc* gene increases the activity of ODC and leads to increased intestinal polyamine levels. Studies in animal models of FAP indicate that eflornithine alone is effective in reducing the number of intestinal tumors (Erdman et al. 1999b) and colonic tumor burden (Yerushalmi et al. 2006). Eflornithine may lower polyamine levels in colorectal mucosa and skin cells (Gerner and Meyskens 2004).

The major clinical evidence for benefit of eflornithine derives from prospective, randomized, placebo-controlled clinical studies of eflornithine monotherapy in patients with elevated risk for developing certain forms of cancer (prostate and basal cell skin cancer). In a randomized, placebo-controlled, clinical study in subjects with a history of resected colon polyps, eflornithine reduced polyamines in rectal mucosal tissue. This marker study is especially relevant to patients with FAP, in whom target tissues include intestinal and colonic mucosa (Meyskens et al. 1998).

Eflornithine has received regulatory approvals as a high dose, intravenously delivered medication for the treatment of a form of African sleeping sickness, and as a topical agent for the treatment of hirsutism (excess hair growth on body parts where hair growth is usually absent or minimal). No oral dosage form of eflornithine has ever received regulatory approval in any indication.

Activator of Spermidine/Spermine N-Acetyltransferase (SSAT1) – Sulindac

Transport of polyamines is maintained by the peroxisome-proliferator activated receptor-g (PPARg). This receptor positively regulates SSAT transcription facilitating polyamine acetylation and transport of polyamines out of the cell. Under normal conditions, the K-Ras molecule has no activity on PPARg. However, mutation of the K-Ras gene produces a product that inhibits PPARg's effect on SSAT translation resulting in elevated polyamine pools and tumorigenesis. (Babbar et al. 2003). Non-steroidal anti-inflammatory drugs (NSAIDs), such as sulindac, act through PPAR□ to enhance transcriptional of SSAT which increases catabolism and export of polyamines.

Sulindac is a member of the arylalkanoic acid class of NSAIDs and is a non-selective inhibitor of cyclooxygenases involved in prostaglandin synthesis. To understand potential mechanisms of action of sulindac, patterns of gene expression resulting from treatment with sulindac sulfone, a sulindac metabolite lacking cyclooxygenase inhibitory activity, were measured in human colon tumor-derived cells (Babbar et al. 2003). Sulindac sulfone inhibited cell growth, and induced apoptosis and the expression of spermidine/spermine N-acetyltransferase (SSAT1), a polyamine catabolic enzyme implicated in polyamine export (Xie, Gillies, and Gerner 1997). Sulindac sulfone induction of SAT1 expression occurs via a cyclooxygenase-independent transcriptional activation of SAT1 at a specific peroxisomal proliferator activated receptor gamma (PPARγ) responsive element (PPRE) in the SAT1 gene. Treatment of cells with sulindac sulfone induces SAT1 expression and stimulates polyamine export.

Experimental findings in human cell and mouse models indicate that sulindac and other NSAIDS activate polyamine catabolism (Gerner and Meyskens 2009). Thus, NSAIDs complement inhibitors of polyamine synthesis, like eflornithine, to reduce tissue polyamine levels. In cell culture, sulindac metabolites reduce cell survival in vitro in a dose-dependent manner at doses above 150 µM at 24-hour exposure times (Lawson et al. 2000).

Experiments in both mouse and rat models of colon cancer have demonstrated a preventative effect for sulindac (Babbar et al. 2003). Sulindac blocked tumor formation in the multiple intestinal neoplasia (Min) mouse, a murine model of APC mutation-associated intestinal carcinogenesis, mimicking FAP. In the Min mouse, tumor-preventing doses of sulindac inhibited tissue levels of prostaglandin-E2 and COX-2 (Boolbol et al. 1996). In other nonclinical studies sulindac had an inhibitory effect on bladder, lung, and forestomach tumor formation in rat and mouse models (Kelloff, Boone, et al. 1994, Kelloff, Crowell, et al. 1994).

Dual Targeting - Flynpovi

The ability to decrease the polyamine pools by a dual mechanism of action, i.e., suppressed synthesis and enhanced catabolism and export, led to the hypothesis that Flynpovi would complement one another in the prevention of tumour development in a patient population where elevated polyamine pools lead to enhanced tumorigenesis. Eflornithine is the irreversible inhibitor of ODC which is responsible for de novo synthesis of polyamines and sulindac regulates SSAT which plays a role in polyamine export and catabolism. Hence the combination, Flynpovi, inhibits the generation of new polyamines and also removes polyamines obtained from the diet and microbiome.

The ability of Flynpovi to reduce polyamines in the GI tract has been demonstrated in both the preclinical and clinical settings. In the study by Igantenko et al, the effect of eflornithine alone and in combination with non-steroidal anti-inflammatory drugs (NSAIDs) sulindac or celecoxib on intestinal tumour number and grade and polyamine content was evaluated in *Apc*Min/+ mice (Ignatenko et al. 2008). Administration of eflornithine in combination with sulindac was superior to each single agent at significantly ($P < 0.05$) decreasing putrescine, spermidine, and total intestinal polyamine concentrations to below baseline levels in the *Apc*Min/+ mice. Additionally, in this study with the exception of the 0.5% eflornithine treatment group, all treatment groups developed significantly ($P<0.05$) fewer tumours/animal than the control group. The combination treatment of 2% eflornithine and sulindac suppressed intestinal tumorigenesis to a level that was not statistically significantly different from that for sulindac alone. Although sulindac alone produced a significant decrease in the number of intestinal tumours in *Apc*Min/+ mice, it did not reduce the percentage of high-grade adenomas. However, the combination of eflornithine and sulindac significantly ($P<0.05$) decreased the number of high-grade adenomas compared to the sulindac alone group.

The ability of the eflornithine and sulindac treatment group to suppress high grade adenomas is a key finding as it is the high grade adenomas in this model which correlate to the high grade adenomas seen in FAP patients that are indicators for excisional and surgical events clinically. These data support the rationale for treatment of FAP patients with eflornithine combined with sulindac to reduce intestinal polyamine contents and the incidence of high-grade intestinal adenomas.

More importantly, combination treatment with Flynpovi dramatically reduces the incidence of metachronous colorectal adenomas in patients with prior sporadic adenomas (Meyskens et al. 2008). Meyskens and colleagues performed a Phase IIb/III, double-blind Pharmacoprevention of Sporadic Colorectal Adenomas Study (PSCA Study) in which 375 subjects who had resected sporadic adenoma were treated for 3 years with eflornithine (500 mg once a day) + sulindac (150 mg once a day [N = 191]) or matched placebo/placebo (N = 184). Results demonstrated a marked risk reduction (70%) in developing metachronous adenomas, 92% risk reduction in developing advanced adenomas, and 95% risk reduction in developing multiple adenomas with the active combination regimen compared to placebo. This combination regimen was generally well tolerated.

The mechanism of disease in sporadic and FAP-associated adenomatous polyposis, and the mechanism of eflornithine and NSAID action in prevention of progressive polyposis in both the general population with sporadic adenomas and in patients with FAP, led to the development of the CPP FAP-310 trial in patients with FAP associated with *APC* germline mutations.

The FAP-310 Phase III study evaluated the efficacy and safety of the combination of eflornithine and sulindac, as compared with either drug alone, in adults with familial adenomatous polyposis was conducted (Burke et al. 2020). The patients were randomly assigned in a 1:1:1 ratio to receive eflornithine, sulindac, or both once daily for up to 48 months. In a post-hoc analysis, none of the patients in the combination arm progressed to a need for lower gastrointestinal (LGI) surgery for up to 48 months compared with 7 (13.2%) and 8 (15.7%) patients in the sulindac and eflornithine arms (Balaguer et al. 2022). These data corresponded to risk reductions for the need for LGI surgery approaching 100% between combination and either monotherapy with HR = 0.00 (95% CI, 0.00-0.48; $p = 0.005$) for combination versus sulindac and HR = 0.00 (95% CI, 0.00-0.44; $p = 0.003$) for combination versus eflornithine.

Development Plan for Ivospemin (SBP-101)

Development of ivospemin for the pancreatic cancer indication has included a pre-clinical and a clinical phase. The pre-clinical phase, which was substantially completed during 2015, consisted of four primary components: chemistry, manufacturing and controls ("CMC"), preclinical (laboratory and animal) pharmacology studies, preclinical toxicology studies, and regulatory submissions in Australia and the United States.

Preparation of the ivospemin IND for pancreatic cancer required collaboration by our manufacturing, preclinical toxicology, pharmacokinetic, and metabolism experts, our regulatory affairs project management, and our in-house clinical expertise. In August 2015, the FDA accepted our application.

In Australia, a Human Research Ethics Committee ("HREC") application was submitted with subsequent Clinical Trial Notification ("CTN") to the Therapeutic Goods Administration ("TGA").

Our initial clinical trial in previously treated patients with locally advanced or metastatic pancreatic cancer was a Phase I, first-in-human, dose-escalation, safety study conducted at clinical sites in both Australia and the United States. We engaged expert clinicians who treat pancreatic cancer at major cancer treatment centers in Melbourne and Adelaide, Australia as well as the Mayo Clinic Scottsdale and HonorHealth in Scottsdale, Arizona. These Key Opinion Leaders, with proven performance in pancreatic cancer studies, agreed to participate as investigators for our Phase I First-in-Human study.

Enrollment in our initial Phase I safety trial of ivospemin in previously treated pancreatic cancer patients commenced in January 2016 and was completed in September 2017. Results from this trial are discussed in *Clinical Development - Pancreatic Cancer, Phase I Clinical Trial Design and Completion (ivospemin Monotherapy)* below.

We completed enrollment of patients in our second clinical trial in December 2020. This second clinical trial was a Phase Ia/Ib study of the safety, efficacy and pharmacokinetics of ivospemin administered in combination with two standard-of-care chemotherapy agents, gemcitabine and nab-paclitaxel. A total of 25 subjects were enrolled in four cohorts of Phase Ia and an additional 25 subjects were enrolled in the expansion Phase Ib by December of 2020. Safety and interim efficacy results from this trial are discussed in *Clinical Development - Pancreatic Cancer, Phase Ia/Ib Clinical Trial Design and Interim Results (First Line Combination Therapy)* below.

In January of 2022 we initiated our third clinical trial. This new trial is a randomized, double blind, placebo controlled study of safety and efficacy of ivospemin administered in combination with two standard-of-care chemotherapy agents, gemcitabine and nab-paclitaxel. Trial design and expected timing are discussed in *Clinical Development - Pancreatic Cancer, Randomized Clinical Trial design and anticipated timing (ASPIRE trial)*.

In addition, we are exploring ivospemin for neoadjuvant treatment in appropriate pancreatic cancer patients. There is also preclinical data to suggest that ivospemin may have potential therapeutic uses for cancers other than pancreatic. In February 2021, we entered into a research agreement with the Johns Hopkins University School of Medicine. The collaboration has focused on the further development of Panbela's investigative agent ivospemin, including activity in cell lines outside of pancreatic cancer, biomarkers informing diagnostics and potential combination with checkpoint inhibitors. In December 2021, the Company announced positive preclinical data supporting the activity of ivospemin in ovarian cancer cell lines. Further data resulting from the ongoing relationship with Johns Hopkins University School of Medicine is expected throughout 2022.

Ivospemin (SBP-101) Clinical Development – Pancreatic Cancer

Our clinical development in Pancreatic Cancer thus far includes:

- a Phase I ivospemin Monotherapy study completed in 2017,
- a Phase Ia/Ib ivospemin First Line Combination Therapy study, which completed enrollment in late 2020, and
- a Randomized, Double Blind Placebo Controlled First Line Combination Therapy study (ASPIRE) was initiated in January of 2022.

Details of these programs follow.

Phase I Clinical Trial Design and Completion (ivospemin Monotherapy)

We have completed an initial clinical trial of ivospemin in patients with previously treated locally advanced or metastatic pancreatic cancer. This was a Phase I, first-in-human, dose-escalation, safety study. From January 2016 through September 2017, we enrolled twenty-nine patients into six cohorts, or groups, in the dose-escalation phase of the Phase I trial. No drug-related bone marrow toxicity or peripheral neuropathy was observed at any dose level. In addition to being evaluated for safety, 23 of the 29 patients were evaluable for preliminary signals of efficacy prior to or at the eight-week conclusion of their first cycle of treatment using the Response Evaluation Criteria in Solid Tumors ("RECIST"), the currently accepted standard for evaluating change in the size of tumors.

The absence of adverse events which could potentially overlap with adverse events typically observed in the use of conventional chemotherapeutic agents, supports the case for combination of ivospemin with conventional chemotherapeutic agents, such as gemcitabine, nab-paclitaxel, or even FOLFIRINOX.

Phase Ia/Ib Clinical Trial Interim Results (First Line Combination Therapy)

In 2018, we began enrolling patients in our second clinical trial, a Phase Ia/Ib study of the safety, efficacy and pharmacokinetics of ivospemin administered in combination with two standard-of-care chemotherapy agents, gemcitabine and nab-paclitaxel. A total of 25 subjects were enrolled in 4 cohorts to evaluate the dosage level and schedule. An additional 25 subjects were enrolled in the expansion phase of the trial. Interim results were presented in January of 2022. Best response in evaluable subjects (cohorts 4 and Ib N=29) was a CR in 1 (3%), PR in 13 (45%), SD in 10 (34%) and PD in 5 (17%). One subject did not have post baseline scans with RECIST tumor assessments. Median Progression Free Survival ("PFS"), now final at 6.5 months may have been negatively impacted by drug dosing interruptions to evaluate potential toxicity. Median overall survival in Cohort 4 + Phase Ib was 12.0 months when data was presented in January 2022 and is now final at 14.6 months. Two patients from cohort 2 have demonstrated long term survival. One at 30.3 months (final data) and one at 33.0 months and still alive. Seven subjects are still alive as of the date of this prospectus, one from cohort 2 and six from cohort 4 plus Ib.

Near Final results:

Figure 4. Evaluation of SBP 101 Phase Ib First-line combo-therapy Safety Trial - Best Overall Response

	BEST OVERALL RESPONSE				Overall Response	Disease Control
	CR	PR	SD	PD		
SBP-101 (0.40 mg/kg) + G/A* (Phla COHORT 2) n=7	0	5 (71%)	2 (29%)	0	**5/7 (71%)**	**5/7 (71%)**
SBP-101 (0.40 mg/kg) + G/A* (Phla COHORT 4 + Ph1b) n=29	1 (3%)	13 (45%)	10 (34%)	5 (17%)	**14/29 (48%)**	**24/29 (83%)**
Gemcitabine + Nab-paclitaxel (G/A*) n=431**	<1%	23%	27%	20%	**23%**	**48%**

Source: Singhal, N., Poster Presentation, ASCO GI 2022

Randomized Clinical Trial design and anticipated timing (ASPIRE trial)

In January of 2022, the Company announced the initiation of a new clinical trial. Referred to as ASPIRE, the trial is a randomized double-blind placebo-controlled trial in combination with gemcitabine and nab-paclitaxel, a standard pancreatic cancer treatment regimen in patients previously untreated for metastatic pancreatic cancer. The trial will be conducted globally at approximately 95 sites in the United States, Europe and Asia - Pacific.

While opening of clinical sites in the US and the rest of the world has been slower than originally anticipated, due in part to resource fatigue in the medical community, the Company expects all countries and sites to be open by early 2023.

The trial was originally designed as a Phase II/III trial with a smaller sample size (150) to support the events required for interim analysis based on Progression Free Survival (PFS) and a primary endpoint of overall survival. In response to European and FDA regulatory feedback the study was amended to include the total trial sample size (600) and the design modified to utilize overall survival as the primary endpoint to be examined at interim analysis. PFS will also be analyzed to provide additional efficacy evidence. This amendment was supported by the final data from the Phase Ia/b first line metastatic pancreatic cancer trial which completed enrollment in December of 2020. The study will enroll 600 subjects and is anticipated to take 36 months for complete enrollment with the interim analysis available in early 2024**.**

If we can successfully complete all FDA recommended clinical studies, we intend to seek marketing authorization from the FDA, the EMA (European Union), Ministry of Health and Welfare (Japan) and TGA (Australia). The submission fees may be waived when ivospemin (SBP-101) has been designated an orphan drug in each geographic region, as described under "Orphan Drug Status."

Development Plan for Flynpovi and Eflornithine (CPP-1X)

In December 2009, the FDA accepted CPP's IND application for the combination product, Flynpovi, product candidate and in November 2009 and August 2018, the FDA accepted IND applications for eflornithine.

The Development plan executed by CPP of Flynpovi for FAP and colon cancer prevention has included both a pre-clinical/non-clinical and a clinical phase. The non-clinical phase consisted of four primary components: CMC, preclinical (laboratory and animal) pharmacology studies, preclinical toxicology studies, and regulatory submissions in the US and Europe. Similarly, the development plan for eflornithine and eflornithine sachets in several different indications included the much of the same primary components and regulatory submission in the US.

Clinical Development –Flynpovi

Our clinical development of Flynpovi thus far includes:

- The FAP-310 Phase III
- The PACES Phase III Trial

FAP-310 Phase III Trial

In the FAP-310 Phase III study, the efficacy and safety of the combination of Flynpovi, as compared with either drug eflornithine or sulindac alone, in adults with FAP was conducted. A total of 171 patients underwent randomization. Disease progression occurred in 18 of 56 patients (32%) in the Flynpovi, 22 of 58 (38%) in the sulindac group, and 23 of 57 (40%) in the eflornithine group, with a hazard ratio of 0.71 (95% CI, 0.39 to 1.32) for Flynpovi as compared with sulindac (P = 0.29) and 0.66 (95% CI, 0.36 to 1.23) for Flynpovi as compared with eflornithine. In a post-hoc analysis, none of the patients in the combination arm progressed to a need for LGI surgery for up to 48 months compared with 7 (13.2%) and 8 (15.7%) patients in the sulindac and eflornithine arms. These data corresponded to risk reductions for the need for LGI surgery approaching 100% between combination and either monotherapy with HR = 0.00 (95% CI, 0.00–0.48; $p = 0.005$) for combination versus sulindac and HR = 0.00 (95% CI, 0.00–0.44; $p = 0.003$) for combination versus eflornithine.

Surgery Events	ES Combo	Eflornithine	Sulindac	Overall
	(N=56)	(N=57)	(N=58)	(N=171)
Need colectomy	0	3	4	7
Need proctectomy	0	1	1	2
Need pouch resection	0	4	1	5
Total Surgical Events	**0**	**8**	**6**	**14**
Event Rate	**0/56 (0%)**	**8/57 (14%)**	**6/58 (10%)**	**14/171 (8%)**

Given the statistical significance of the LGI group, an NDA was filed with the FDA. As the study failed to meet the primary endpoint, and the NDA was based on the results of an exploratory analysis, a complete response letter was issued. To address this deficiency concern, the Company must submit the results of one or more adequate and well-controlled clinical trials which demonstrate an effect on a clinical endpoint. We are working closely with our North American partners One-Two Therapeutics designing a Phase III registration trial for familial adenomatous polyposis ("FAP") to address the CRL. One-Two Therapeutics will manage the trial and the NDA process with the FDA. The Company will be responsible for the approvals in ROW.

Phase III Clinical Trial in Colon Cancer Survivors

In collaboration with the NCI, and SWOG, a Phase III clinical trial has been initiated to study the benefits of Flynpovi as a therapeutic treatment for use by colon cancer survivors. The trial is named PACES for "Prevention of Adenomas and Cancer with eflornithine and sulindac." The PACES trial is funded by the NCI and managed by SWOG. This is an ongoing double blind placebo-controlled trial of Flynpovi to prevent recurrence of high risk adenomas and second primary colorectal cancers in patients with stage 0-III colon or rectal cancer, Phase III PACES. The purpose of this study is to assess whether the Flynpovi, combination of eflornithine and sulindac, (compared to corresponding placebos) has a reduced rate of cancer or high-risk adenoma recurrence compared to comparator arms after three years of daily dosing. We have exclusive rights to the data that comes from the trial for regulatory and commercial purposes. One-Two Therapeutics has licensed the program for North American and the Company is evaluating its options for CAT in the European Union and Asia.

Clinical Development –Eflornithine (CPP – 1X)

Our clinical development of eflornithine thus far includes:

- Phase II Neuroblastoma Trial
- Phase II Gastric Cancer Prevention Trial
- Phase I and Phase II Recent Onset Type 1 Diabetes Trials
- Phase I/II STK-11 Mutant NSCLC Trial

Phase II Neuroblastoma Trial

Neuroblastoma is a form of cancer that occurs in infants and young children, affecting the peripheral nervous system.
Ornithine decarboxylase (ODC1) encodes the first enzyme in polyamine synthesis in mammals and is a direct transcriptional target of *MYC* (Bello-Fernandez, Packham, and Cleveland 1993; Pena et al. 1993). ODC1 and other genes in the polyamine pathway are crucial elements of *MYCN* oncogenesis in neuroblastoma (Hogarty et al. 2008; Rounbehler et al. 2009; Geerts et al. 2010). ODC1 and *MYCN* are also located nearby on chromosome 2, and a subset of *MYCN* amplified tumors have also been shown to co-amplify ODC1 (Hogarty et al. 2008). High ODC1, either in the presence or absence of *MYCN* amplifications, correlates with poor clinical outcome of reduced event free survival (EFS) and overall survival (OS) (Hogarty et al. 2008). Several genes in the polyamine pathway, including ODC1, have been shown to be independent negative prognostic factors for neuroblastoma (Hogarty et al. 2008; Rounbehler et al. 2009; Geerts et al. 2010). The most common genetic alteration in NB is *MYCN* where amplifications occur in approximately 20-25% of all cases and are associated with the high-risk phenotype (Seeger et al. 1985; Brodeur et al. 1984). Additionally, High-Risk-NB that lacks *MYCN* amplifications have MYCN deregulation through other mechanisms. *MYCN* is a well-documented poor prognostic risk factor for children with neuroblastoma (Schwab 1993).

CPP is engaged with leading pediatric oncology research cooperatives in the US and the UK to explore the feasibility of treating neuroblastoma with our CPP-1XS, a high dose powder dosage form of eflornithine. The Children's Oncology Group and the NCI are performing a Phase II study evaluating CPP-1X-S 6.75 g/m2 daily to treat relapsed, refractory, or progressive neuroblastoma in combination with standard of care immunotherapy and chemotherapy. The trial has passed a futility analysis and is ongoing. The Company has received orphan drug designations for the use of eflornithine for the treatment of neuroblastoma in the United States and Europe.

Phase II Gastric Cancer Prevention Trial

H. pylori is the most common bacterial infection in humans and causes gastritis in all individuals. Gastritis progresses along the "Correa cascade" from gastritis to the precancerous stages of atrophic gastritis (loss of specialized gastric epithelium) and intestinal metaplasia (IM), to gastric adenocarcinoma (Correa 1992). In response to *H. pylori* infection the host elicits a robust innate and adaptive immune response, which results in mucosal inflammation but fails to eradicate the organism. Several studies have demonstrated that the failure of the immune response may be related to dysregulated L-arginine metabolism and polyamines including the upregulation of ornithine decarboxylase (ODC) by macrophages (Chaturvedi et al. 2010; Chaturvedi, de Sablet, Coburn, et al. 2012) (Chaturvedi, de Sablet, Peek, et al. 2012), (Chaturvedi et al. 2011) (Xu et al. 2004) (Chaturvedi et al. 2014) (Chaturvedi et al. 2004). Levels of polyamines are increased in *H. pylori*-induced gastritis in mice, and oral DFMO treatment reduces gastric polyamine levels, and severity of both *H. pylori* colonization and gastritis (Chaturvedi et al. 2010). In the gerbil model of *H. pylori*-induced gastric cancer, polyamine levels correlate with levels of gastritis, DNA damage, and progression to dysplasia/carcinoma. In this model, eflornithine reduces polyamine levels and DNA damage, and reduces rates of dysplasia and carcinoma by >50% (Chaturvedi et al. 2014)

In collaboration with investigators at Vanderbilt University and funding by the NCI, the investigator-initiated Phase II trial (IST) performed in Honduras and Puerto Rico was a randomized, double-blinded study comparing once daily eflornithine versus placebo for an up to 18-month treatment period in patients with gastric premalignant lesions. This trial has completed and is undergoing data analysis. The Company has received orphan drug designation for the use of eflornithine for the treatment of gastric cancer in the United States.

Phase I and II Recent Onset Type 1 Diabetes Trials

T1D is an organ-specific autoimmune disease characterized by chronic immune-mediated destruction of pancreatic β-cells, leading to partial, or in most cases, absolute insulin deficiency. The majority of cases result from autoimmune mediated pancreatic β-cell destruction, which occurs at a variable rate. Patients become clinically symptomatic when approximately 90% of pancreatic β-cells are destroyed. Therefore, preserving β-cell function is a target for promising treatments (Couper et al. 2014). The activity of ODC is upregulated in early diabetic kidney disease, contributing to renal hypertrophy and hyperfiltration (Pedersen et al. 1992; Deng et al. 2003). *In vivo* studies in experimental models of recent-onset T1D evaluating eflornithine demonstrate roles in suppressing the development of renal hypertrophy and hyperplasia, decreasing the incidence of diabetes, augmenting the survival and regeneration of β-cell populations, decreasing insulinitis, and maintaining an immune-tolerant balance of T-cell subpopulations.

The Company collaborated with investigators at Indiana University on a JDRF funded Phase I study to evaluate the safety and efficacy of increasing doses of eflornithine in patients with recent onset Type 1 diabetes. The completed Phase I trial demonstrated that a 3-month course of oral eflornithine was well tolerated with a favorable adverse event profile in children and adults with recent-onset T1D. Urinary polyamine data showed that eflornithine treatment inhibited ornithine decarboxylase activity effectively, reflected by a dose dependent reduction in urinary putrescine values. Furthermore, although not powered to detect metabolic efficacy, subjects treated with 750 mg/m2 and 1000 mg/m2/day of eflornithine exhibited higher C-peptide AUC 6 months after treatment indicative of improved β cell function compared to placebo. These data suggest that eflornithine may improve beta cell function alone and in combination regimens to treat or prevent type 1 diabetes that also include immunotherapy. A larger Phase II study fully powered to detect an effect of eflornithine treatment on maintenance of C-peptide is being planned with the goal of initiating by the end of 2022.

Phase I/II STK-11 Mutant NSCLC Trial

STK11 is the fourth-most frequently mutated gene in lung adenocarcinoma, with loss of function occurring in up to 30% of all cases (Laderian et al. 2020). Patients with LKB1 loss have reduced infiltrates of cytotoxic T-cells and respond poorly to anti PD1 or anti-PDL-1 therapies regardless of the PDL-1 status. CheckMate-057 trial lung tumors harboring co-mutations in KRAS and STK11 had an inferior response to PD-1 axis inhibitors (Skoulidis et al. 2018). These results suggest that STK11-mutated tumors were found to have a cold immune microenvironment regardless of KRAS status.

Bioinformatic analyses using two well-annotated lung adenocarcinoma datasets identified upregulation of ornithine decarboxylase (the target for eflornithine). Additionally, LKB1-loss tumors show a significant up-regulation of several solute transporters (*SLC7A2*, *SLC14A2*, and *SLC16A4*). *SLC7A2* is known to be responsible for the membrane transport of cationic amino acids arginine, lysine, and ornithine. Furthermore, LKB1 loss the Arginine pathway in which arginine is converted to ornithine and urea (by arginase) and ornithine is converted to putrescine (by ODC1). Together, the results suggested that ODC1 may be a key metabolic driver in LKB1-loss lung cancer.

In other model systems eflornithine treatment has been shown to modulate the tumor microenvironment. A previously studied cohort revealed that ODC1 may be instrumental to immune suppression (Chamaillard et al. 1997). Since eflornithine is an ODC1 inhibitor, it is hypothesized that inhibiting the metabolic enzyme ODC1 using eflornithine will increase the number of tumor infiltrating lymphocytes (TILs) in LKB1-loss tumors and restore benefit of PD(L)-1 blockade to these patients.

The Company is currently planning a Phase I/II investigator-initiated trial to assess eflornithing in patients with STK-11 mutant NSCLC with the goal of starting by the end of 2022.

Total Development Costs

The development of ivospemin involves a preclinical and a clinical development phase. We have completed our initial preclinical development work for pancreatic cancer as well as two Phase I clinical trials. The Phase II/III trial has just been initiated. Additional clinical trials will likely be required for FDA or other approvals in foreign jurisdictions if the results of the first-line clinical trial of our ivospemin product candidate justify continued development. The cost and timing of additional clinical trials is highly dependent on the nature and size of the trials.

The development of Flynpovi also has involved preclinical and clinical development work for FAP and colon cancer prevention. The company signed a licensing and development agreement giving exclusive rights to commercialize and develop Flynpovi in North America. The licensing and development agreement calls for the cost of development and obtaining approval in North America to be borne by the licensing partner. A registration trial in FAP is expected to begin in mid-2023.

Orphan Drug Status

The Orphan Drug Act ("ODA") provides special status to drugs which are intended for the safe and effective treatment, diagnosis or prevention of rare diseases that affect fewer than 200,000 people in the United States, or that affect more than 200,000 persons but for which a manufacturer is not expected to recover the costs of developing and marketing such a drug. Orphan drug designation has the advantage of reducing drug development costs by: (i) streamlining the FDA's approval process, (ii) providing tax breaks for expenses related to the drug development, (iii) allowing the orphan drug manufacturer to receive assistance from the FDA in funding the clinical testing necessary for approval of an orphan drug, and (iv) facilitating drug development efforts. More significantly, the orphan drug manufacturer's ability to recover its investment in developing the drug is also greatly enhanced by the FDA granting the manufacturer seven years of exclusive US marketing rights upon approval. Designation of a product candidate as an orphan drug therefore may provide its sponsor with the opportunity to adopt a faster and less expensive pathway to commercializing its product.

We obtained US Orphan Drug Status for ivospemin in 2014 and we intend to apply for Orphan Drug Status in Europe, Japan and Australia when we have additional clinical data.

We have obtained orphan drug designation status for Flynpovi and eflornithine for FAP in the United States (2013 and 2011 respectively) and Europe (2013 and 2011 respectively). In addition, we have received orphan drug designation status for eflornithine as a single agent for Neuroblastoma in the United States (2010) and Europe (2011) and for gastric cancer (2015) in the United States.

Fast Track

In June 2020, we received Fast Track Designation from the FDA for development of ivospemin for the treatment of first-line patients with metastatic PDA when administered in combination with gemcitabine and nab-paclitaxel. Additionally, in September 2017, we received Fast Track Designation from the FDA for the development of Flynpovi for the treatment of FAP. With the designation of Fast Track Designation, we, or our North American partners, may engage in more frequent interactions with the FDA, and the FDA may review sections of a New Drug Application ("NDA") before the application is complete. This rolling review is available if the Company provides, and the FDA approves, a schedule for the submission of the remaining information and the applicant pays applicable user fees. However, the FDA's time period goal for reviewing an application does not begin until the last section of the NDA is submitted. Additionally, Fast Track Designation may be withdrawn by the FDA if the FDA believes that the designation is no longer supported by data emerging in the clinical trial process.

Intellectual Property

As the result of efforts at our contract manufacturer Syngene International Ltd to refine the synthetic process, a new shorter synthetic process has been developed on which a patent (US 11,098,005 B2) "METHODS FOR PRODUCING (65,155)-3,8,13,18-TETRAAZAICOSANE-6, 15-DIOL" issued on Aug. 24, 2021 and was assigned to Panbela. The patent claims cover a novel process for the production of ivospemin and reduces the number of synthetic steps from nineteen to six.

For Flynpovi, there is a composition of matter patent for the fixed dose combination of eflornithine and sulindac that is broadly nationalized providing potential protection thru 2037. Additionally, we hold several Method of Use patents or Flynpovi and/or eflornithine for the treatment of Familial Adenomatous Polyposis, Neuroblastoma, and the Treatment of Recent Onset Type 1 Diabetes.

We are evaluating other opportunities to provide additional intellectual property.

Human Capital Management

As of September 30, 2022, we had eight (8) full time employees. None of our employees are represented by a labor union or covered by a collective bargaining agreement. We believe our relationship with our employees is good.

Our human capital resources objectives include, as applicable, identifying, recruiting, retaining, incentivizing, and integrating our existing and new employees, advisors, and consultants. The principal purposes of our equity and cash incentive plans are to attract, retain and reward personnel through the granting of stock-based and cash-based compensation awards, in order to motivate such individuals to perform to the best of their abilities and achieve our objectives and lead to the success of the Company and increase value to our stockholders.

We value diversity of backgrounds and perspectives in our workforce and our policy is that we do not discriminate based on race, religion, creed, color, national origin, ancestry, physical disability, mental disability, medical condition, genetic information, marital status, sex, gender, gender identity, gender expression, age, military and veteran status, sexual orientation or any other protected characteristic as established by federal, state or local laws.

We believe that operational responsibilities can be handled by our current employees, independent consultants and our global CRO. We have historically used the services of independent consultants and contractors to perform various professional services. We believe that this use of third-party service providers enhances our ability to minimize general and administrative expenses. We intend to periodically evaluate our staffing and talent requirements and expect to add employees if that becomes a more appropriate resourcing alternative.

Competition

The development and commercialization of new products to treat cancer is intensely competitive and subject to rapid and significant technological change. While we believe that our knowledge, experience and scientific resources provide us with competitive advantages, we face substantial competition from major pharmaceutical companies, specialty pharmaceutical companies, and biotechnology companies worldwide. Many of our competitors have significantly greater financial, technical, and human resources. Smaller and early-stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies. As a result, our competitors may discover, develop, license or commercialize products before or more successfully than we do.

We face competition with respect to our current product candidates and will face competition with respect to future product candidates, from segments of the pharmaceutical, biotechnology and other related markets that pursue approaches to targeting molecular alterations and signaling pathways associated with cancer. Our competitors may obtain regulatory approval of their products more rapidly than we do or may obtain patent protection or other intellectual property rights that limit our ability to develop or commercialize our product candidates. Our competitors may also develop drugs that are more effective, more convenient, less costly, or possessing better safety profiles than our products, and these competitors may be more successful than us in manufacturing and marketing their products.

In addition, we may need to develop our product candidates in collaboration with diagnostic companies, and we will face competition from other companies in establishing these collaborations. Our competitors will also compete with us in recruiting and retaining qualified scientific, management and commercial personnel, establishing clinical trial sites and patient registration for clinical trials, as well as in acquiring technologies complementary to, or necessary for, our programs.

Furthermore, we also face competition more broadly across the market for cost-effective and reimbursable cancer treatments. The most common methods of treating patients with cancer are surgery, radiation and drug therapy, including chemotherapy, immunotherapy, hormone therapy and targeted drug therapy or a combination of such methods. There are a variety of available drug therapies marketed for cancer. In many cases, these drugs are administered in combination to enhance efficacy. While our product candidates, if any are approved, may compete with these existing drug and other therapies, to the extent they are ultimately used in combination with or as an adjunct to these therapies, our product candidates may be approved as companion treatments and not be competitive with current therapies. Some of these drugs are branded and subject to patent protection, and others are available on a generic basis. Insurers and other third-party payors may also encourage the use of generic products or specific branded products. We expect that if our product candidates are approved, they will be priced at a premium over competitive generic, including branded generic, products. As a result, obtaining market acceptance of, and gaining a significant share of the market for, any of our product candidates that we successfully introduce to the market will pose challenges. In addition, many companies are developing new therapeutics and we cannot predict what the standard of care will be as our product candidate progresses through clinical development.

Commercialization

We have not established a sales, marketing or product distribution infrastructure nor have we devoted significant management resources to planning such an infrastructure because ivospemin is still in clinical development. We currently anticipate that we will partner with a larger pharmaceutical organization having the expertise and capacity to perform these functions.

Flynpovi will be commercialized, if approved, in North America by One-Two

Manufacturing and Suppliers

We do not own or operate, and currently have no plans to establish, any manufacturing facilities. We currently rely, and expect to continue to rely, on third parties for the manufacture of our product candidates for preclinical and clinical testing as well as for commercial manufacture of any products that we may commercialize. If needed, we intend to engage, by entering into a supply agreement or through another arrangement, third party manufacturers to provide us with additional clinical supply. We identified and qualified manufacturers to provide the active pharmaceutical ingredient and fill-and-finish services for our initial product candidate prior to our submission of an NDA to the FDA and expect to continue utilizing this approach for any future product candidates.

Securing the manufacture of Flynpovi for further clinical studies and for commercialization in North America, if the product is approved is the responsibility of One Two, who was granted a non-exclusive license to manufacture for North America

Material Agreements

The Standard Exclusive License Agreement ("License Agreement") dated December 22, 2011, between us and UFRF grants us an exclusive license to the proprietary technology covered by issued United States Patents Nos. US 5,962,533, which expired in February 2016, and US 6,160,022 which expired in July 2020 and Know-How as defined by the License Agreement, with reservations by UFRF for academic or government uses. Under this agreement, we had agreed to pay various royalties, expenses and milestone payments to UFRF. The License Agreement was amended in December 2016 ("First Amendment") and again in October 2019 ("Second Amendment"). Under the Second Amendment all minimum royalty payments and milestone payments defined in the License Agreement were eliminated. In addition, the period for payment of royalties was changed to be the shorter of (i) ten (10) years from first commercial sale or (ii) the period of market exclusivity on a country-by-country basis. UFRF may also terminate this license for standard and similar causes such as material breach of the agreement, bankruptcy, failure to pay royalties and other customary conditions. The agreement allows for UFRF to terminate if the first commercial sale is not made by December 31, 2025.

CPP is party to a license agreement with One-Two dated July 16, 2021. Under the agreement, One-Two has licensed CPP's North American development and commercialization rights for Flynpovi. The agreement also calls for CPP to receive a milestone payment upon regulatory approval of Flynpovi by the FDA and royalties on net sales of Flynpovi in the licensed territories. Payment of the milestone payment and net sales royalties shall be reduced on a dollar-for-dollar basis by amounts funded by One-Two for One-Two's direct employee, clinical and regulatory costs associated with any development activities necessary to secure FDA approval. The Company is not responsible for any costs, as they are incurred, associated with the development and regulatory approval of Flynpovi in North America.

Government Regulation

FDA Approval Process

In the United States, pharmaceutical products are subject to extensive regulation by the FDA. The Federal Food, Drug and Cosmetic Act and other federal and state statutes and regulations govern, among other things, the research, development, testing, manufacture, storage, recordkeeping, approval, labeling, promotion and marketing, distribution, post-approval monitoring and reporting, sampling and import and export of pharmaceutical products. Failure to comply with applicable US requirements may subject a company to a variety of administrative or judicial sanctions, such as FDA refusal to approve pending NDAs, warning or untitled letters, product recalls, product seizures, total or partial suspension of production or distribution, injunctions, fines, civil penalties and criminal prosecution.

Pharmaceutical product development for a new product or certain changes to an approved product in the United States typically involves preclinical laboratory and animal tests, the submission to the FDA of an IND which must become effective before clinical testing may commence, and adequate and well-controlled clinical trials to establish the safety and effectiveness of the drug for each indication for which FDA approval is sought. Satisfaction of FDA pre-market approval requirements typically takes many years and the actual time required may vary substantially based upon the type, complexity and novelty of the product or disease.

Preclinical tests include laboratory evaluation of product chemistry, formulation and toxicity, as well as animal trials to assess the characteristics and potential safety and efficacy of the product. The conduct of the preclinical tests must comply with federal regulations and requirements, including good laboratory practices. The results of preclinical testing are submitted to the FDA as part of an IND along with other information, including the Investigator's Brochure, information about product chemistry, manufacturing and controls, potential perceived side effects and risks, and a proposed clinical trial protocol. Long-term preclinical tests, such as animal tests of reproductive toxicity and carcinogenicity, may continue after the IND is submitted.

A 30-day waiting period after the submission of each IND is required prior to the commencement of clinical testing in humans. If the FDA has neither commented on nor questioned the IND within this 30-day period, the clinical trial proposed in the IND may begin.

Clinical trials involve the administration of the investigational new drug to healthy volunteers or patients under the supervision of a qualified investigator. Clinical trials must be conducted: (i) in compliance with federal regulations; (ii) in compliance with good clinical practice ("GCP"), an international standard meant to protect the rights and health of patients and to define the roles of clinical trial sponsors, administrators and monitors; as well as (iii) under protocols detailing the objectives of the trial, the parameters to be used in monitoring safety and the effectiveness criteria to be evaluated. Each protocol involving testing on US patients and subsequent protocol amendments must be submitted to the FDA as part of the IND.

The FDA may order the temporary, or permanent, discontinuation of a clinical trial at any time, or impose other sanctions, if it believes that the clinical trial either is not being conducted in accordance with FDA requirements or presents an unacceptable risk to the clinical trial patients. The study protocol and informed consent information for patients in clinical trials must also be submitted to an institutional review board ("IRB") for approval. An IRB may also require the clinical trial at the site to be halted, either temporarily or permanently, for failure to comply with the IRB's requirements, or may impose other conditions.

Clinical trials to support NDAs for marketing approval are typically conducted in three sequential phases, but the phases may overlap. In Phase I, the initial introduction of the drug into healthy human subjects/patients, the drug is tested to assess metabolism, pharmacokinetics, pharmacological actions, side effects associated with increasing doses, and, if possible, early evidence of effectiveness. Phase II usually involves trials in a limited patient population to determine the effectiveness of the drug for a particular indication, dosage tolerance and optimum dosage, and to identify common adverse effects and safety risks. If a compound demonstrates evidence of effectiveness and an acceptable safety profile in Phase II evaluations, pivotal, or Phase III trials are undertaken to obtain the additional information about clinical efficacy and safety in a larger number of patients, typically at geographically dispersed clinical trial sites, to permit the FDA to evaluate the overall benefit-risk relationship of the drug and to provide adequate information for the labeling of the drug. In many cases the FDA requires two adequate and well-controlled Phase III clinical trials to demonstrate the efficacy of the drug. A single Phase III trial with other confirmatory evidence may be sufficient in instances where the study 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. After an NDA is approved, a Phase IV trial may be undertaken to evaluate safety over a long period of time, quality of life or cost effectiveness.

After completion of the required clinical testing, an NDA is prepared and submitted to the FDA. FDA approval of the NDA is required before marketing of the product may begin in the United States. The NDA must include the results of all preclinical, clinical and other testing and a compilation of data relating to the product's pharmacology, chemistry, toxicology, manufacture, controls and any proposed labeling. The cost of preparing and submitting an NDA is substantial, and the fees are typically increased annually.

The FDA has 60 days from its receipt of an NDA to determine whether the application will be accepted for filing based on the agency's threshold determination that it is sufficiently complete to permit substantive review. Once the submission is accepted for filing, the FDA begins an in-depth review. The FDA has agreed to certain performance goals in the review of NDAs to encourage timeliness. Most applications for standard review drug products are reviewed within twelve months from submission; most applications for priority review drugs are reviewed within eight months from submission. Priority review can be applied to drugs that the FDA determines offer major advances in treatment or provide a treatment where no adequate therapy exists. If priority review is achieved, the FDA's goal is to act on the application within six months. The review process for both standard and priority review may be extended by the FDA for three additional months to consider certain late-submitted information, or information intended to clarify information already provided in the submission. The FDA may also refer applications for novel drug products, or drug products that present difficult questions of safety or efficacy, to an outside advisory committee-typically a panel that includes clinicians and other experts-for review, evaluation and a recommendation as to whether the application should be approved. The FDA is not bound by the recommendation of an advisory committee, but it generally follows such recommendations.

Before approving an NDA, the FDA will typically inspect one or more clinical sites to assure compliance with GCP. Additionally, the FDA will inspect the facility or the facilities at which the drug is manufactured. The FDA will not approve the product unless compliance with current good manufacturing practice ("cGMP"), a quality system regulating manufacturing, is satisfactory and the NDA contains data that provide substantial evidence that the drug is safe and effective in the indication studied.

After the FDA evaluates the NDA and the manufacturing facilities, it issues either an approval letter or a complete response letter. 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, or 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 six months depending on the type of information included.

An approval letter authorizes commercial marketing of the drug with specific prescribing information for specific indications. As a condition of NDA approval, the FDA may require a risk evaluation and mitigation strategy ("REMS") to help ensure that the benefits of the drug outweigh the potential risks. REMS can include medication guides, communication plans for healthcare professionals, and elements to assure safe use ("ETASU"). ETASU can include, but are not limited to, special training or certification for prescribing or dispensing, dispensing only under certain circumstances, special monitoring and the use of patient registries. The requirement for a REMS can materially affect the potential market and profitability of the drug. Moreover, product approval may require substantial post-approval testing and surveillance to monitor the drug's safety or efficacy. Once granted, product approvals may be withdrawn if compliance with regulatory standards is not maintained or problems are identified following initial marketing.

Changes to some of the conditions established in an approved application, including changes in indications, labeling, or manufacturing processes or facilities, require submission and FDA approval of a new NDA or NDA supplement before the change can be implemented. An NDA supplement for a new indication typically requires clinical data similar to that in the original application, and the FDA uses the same procedures and actions in reviewing NDA supplements as it does in reviewing NDAs.

Fast Track Designation and Accelerated Approval

The FDA is required to facilitate the development, and expedite the review, of drugs that are (1) intended for the treatment of a serious or life-threatening disease or (2) condition for which there is no effective treatment and which demonstrate the potential to address unmet medical needs for the condition. Under the Fast Track program, the sponsor of a new product candidate may request that the FDA designate the product candidate for a specific indication as a Fast Track drug concurrent with, or after, the filing of the IND for the product candidate. The FDA must determine if the product candidate qualifies for Fast Track Designation within 60 days of receipt of the sponsor's request.

Under the Fast Track program and FDA's accelerated approval regulations, the FDA may approve a drug for a serious or life-threatening illness that provides meaningful therapeutic benefit to patients over existing treatments based upon a surrogate endpoint that is reasonably likely to predict clinical benefit, or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality, that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments.

In clinical trials, a surrogate endpoint is a measurement of laboratory or clinical signs of a disease or condition that substitutes for a direct measurement of how a patient feels, functions, or survives. Surrogate endpoints can often be measured more easily or more rapidly than clinical endpoints. A product candidate approved on this basis is subject to rigorous post-marketing compliance requirements, including the completion of Phase IV or post-approval clinical trials to confirm the effect on the clinical endpoint. Failure to conduct required post-approval studies, or confirm a clinical benefit during post-marketing studies, will allow FDA to withdraw the drug from the market on an expedited basis. All promotional materials for product candidates approved under accelerated regulations are subject to priority review by FDA.

If a submission is granted Fast Track Designation, the sponsor may engage in more frequent interactions with the FDA, and the FDA may review sections of the NDA before the application is complete. This rolling review is available if the applicant provides, and the FDA approves, a schedule for the submission of the remaining information and the applicant pays applicable user fees. However, the FDA's time period goal for reviewing an application does not begin until the last section of the NDA is submitted. Additionally, Fast Track Designation may be withdrawn by the FDA if the FDA believes that the designation is no longer supported by data emerging in the clinical trial process.

Breakthrough Therapy Designation

The FDA is also required to expedite the development and review of the application for approval of drugs that are intended to treat a serious or life-threatening disease or condition where preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints. Under the Breakthrough Therapy program, the sponsor of a new product candidate may request that the FDA designate the product candidate for a specific indication as a breakthrough therapy. The FDA must determine if the product candidate qualifies for Breakthrough Therapy designation within 60 days of receipt of the sponsor's request.

Orphan Drug Designation and Exclusivity

The ODA provides incentives for the development of products intended to treat rare diseases or conditions. Under the ODA, the FDA may grant orphan designation to a drug intended to treat a rare disease or condition, which is generally a disease or condition that affects fewer than 200,000 individuals in the United States, or more than 200,000 individuals in the United States and for which there is no reasonable expectation that the cost of developing and making a drug available in the United States for this type of disease or condition will be recovered from sales of the product. If a sponsor demonstrates that a drug is intended to treat a rare disease or condition, the FDA will grant orphan designation for that product for the orphan disease indication, assuming that the same drug has not already been approved for the indication for which the sponsor is seeking orphan designation. If the same drug has already been approved for the indication for which the sponsor is seeking orphan designation, the sponsor must present a plausible hypothesis of clinical superiority in order to obtain orphan designation. Orphan designation must be requested before submitting an NDA. After the FDA grants orphan designation, the FDA discloses the identity of the therapeutic agent and its potential orphan use.

Orphan designation may provide manufacturers with benefits such as research grants, tax credits, Prescription Drug User Fee Act ("PDUFA") application fee waivers and eligibility for orphan drug exclusivity. If a product that has orphan designation subsequently receives the first FDA approval of the active moiety for that disease or condition for which it has such designation, the product is entitled to orphan drug exclusivity, which for seven years prohibits the FDA from approving another product with the same active ingredient for the same indication, except in limited circumstances. Orphan drug exclusivity will not bar approval of another product under certain circumstances, including if a subsequent product with the same active ingredient for the same indication is shown to be clinically superior to the approved product on the basis of greater efficacy or safety, or providing a major contribution to patient care, or if the company with orphan drug exclusivity is not able to meet market demand. Further, the FDA may approve more than one product for the same orphan indication or disease as long as the products contain different active ingredients. Moreover, competitors may receive approval of different products for the indication for which the orphan drug has exclusivity or obtain approval for the same product but for a different indication for which the orphan drug has exclusivity.

In the European Union, orphan drug designation also entitles a party to financial incentives such as reduction of fees or fee waivers and 10 years of market exclusivity is granted following drug or biological product approval. This period may be reduced to 6 years if the orphan drug designation criteria are no longer met, including where it is shown that the product is sufficiently profitable not to justify maintenance of market exclusivity.

Orphan drug designation must be requested before submitting an application for marketing approval. Orphan drug designation does not convey any advantage in, or shorten the duration of, the regulatory review and approval process.

Post-Approval Requirements

Once an NDA is approved, a product will be subject to certain post-approval requirements. For instance, the FDA closely regulates the post-approval marketing and promotion of drugs, including standards and regulations for direct-to-consumer advertising, off-label promotion, industry-sponsored scientific and educational activities and promotional activities involving the internet. Drugs may be marketed only for the approved indications and in accordance with the provisions of the approved labeling.

Adverse event reporting and submission of periodic reports are required following FDA approval of an NDA. The FDA also may require post-marketing testing, known as Phase IV testing, risk evaluation and mitigation strategies, or REMS, and surveillance to monitor the effects of an approved product, or FDA may place conditions on an approval that could restrict the distribution or use of the product. In addition, quality control, drug manufacture, packaging and labeling procedures must continue to conform to current good manufacturing practices, or cGMPs, after approval. Drug manufacturers and certain of their subcontractors are required to register their establishments with the FDA and certain state agencies. Registration with FDA subjects' entities to periodic unannounced inspections by the FDA, during which the Agency inspects manufacturing facilities to assess compliance with cGMPs. Accordingly, manufacturers must continue to expend time, money and effort in the areas of production and quality-control to maintain compliance with cGMPs. Regulatory authorities may withdraw product approvals or request product recalls if a company fails to comply with regulatory standards, if it encounters problems following initial marketing, or if previously unrecognized problems are subsequently discovered.

Additional Regulations and Environmental Matters

In the United States, our activities are potentially subject to regulation by various federal, state and local authorities in addition to the FDA, including but not limited to, the Centers for Medicare and Medicaid Services, or CMS, other divisions of the U.S. Department of Health and Human Services (e.g., the Office of Inspector General), the U.S. Department of Justice, or DOJ, and individual U.S. Attorney offices within the DOJ, and state and local governments. For example, sales, marketing and scientific/educational grant programs must comply with the anti-fraud and abuse provisions of the Social Security Act, the false claims laws, and our activities may implicate the privacy provisions of the Health Insurance Portability and Accountability Act ("HIPAA") and similar state laws, each as amended.

The federal Anti-Kickback Statute prohibits, among other things, any person or entity, from knowingly and willfully offering, paying, soliciting or receiving any remuneration, directly or indirectly, overtly or covertly, in cash or in kind, to induce or in return for purchasing, leasing, ordering or arranging for the purchase, lease or order of any item or service reimbursable under Medicare, Medicaid or other federal healthcare programs. The term remuneration has been interpreted broadly to include anything of value. The Anti-Kickback Statute has been interpreted to apply to arrangements between pharmaceutical manufacturers on one hand and prescribers, purchasers, and formulary managers on the other. There are statutory exceptions and regulatory safe harbors protecting some common activities from prosecution. The exceptions and safe harbors are drawn narrowly and practices that involve remuneration that may be alleged to be intended to induce prescribing, purchasing or recommending may be subject to scrutiny if they do not qualify for an exception or safe harbor. Failure to meet all the requirements of a particular applicable statutory exception or regulatory safe harbor does not make the conduct per se illegal under the Anti-Kickback Statute. Instead, the legality of the arrangement will be evaluated on a case-by-case basis based on a cumulative review of all its facts and circumstances. While we reasonably believe our practices to be in compliance with the Anti-Kickback Statute, our practices may not in all cases meet all the criteria for protection under a statutory exception or regulatory safe harbor.

Additionally, the intent standard under the Anti-Kickback Statute was amended by the Affordable Care Act ("ACA") to a stricter standard such that a person or entity no longer needs to have actual knowledge of the statute or specific intent to violate it to have committed a violation. In addition, the ACA codified case law that a claim including items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the federal False Claims Act (as further discussed below).

The Civil Monetary Penalties statute authorizes the imposition of severe financial penalties against any person or entity who, among other things, is determined to have presented or caused to be presented a claim to a federal health program that the person knows or should know is for an item or service that was not provided as claimed or is false or fraudulent.

The federal False Claims Act prohibits, among other things, any person or entity from knowingly presenting, or causing to be presented, a false claim for payment to, or approval by, the federal government or knowingly making, using, or causing to be made or used, a false record or statement material to a false or fraudulent claim to the federal government. As a result of a modification made by the Fraud Enforcement and Recovery Act of 2009, a claim includes "any request or demand" for money or property presented to the U.S. government. Recently, several pharmaceutical and other healthcare companies have been prosecuted under these laws for allegedly providing free product to customers with the expectation that the customers would bill federal programs for the product. Other companies have been prosecuted for causing false claims to be submitted because of the companies' marketing of the product for unapproved, and thus non-reimbursable, uses.

HIPAA created new federal criminal statutes that prohibit knowingly and willfully executing, or attempting to execute, a scheme to defraud or to obtain, by means of false or fraudulent pretenses, representations or promises, any money or property owned by, or under the control or custody of, any healthcare benefit program, including private third-party payors and knowingly and willfully falsifying, concealing or covering up by trick, scheme or device, a material fact or making any materially false, fictitious or fraudulent statement in connection with the delivery of, or payment for healthcare benefits, items or services.

Also, many states have similar fraud and abuse statutes or regulations that apply to items and services reimbursed under Medicaid and other state programs, or, in several states, apply regardless of the payor.

We may be subject to data privacy and security regulations by both the federal government and the states in which we conduct our business. HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act ("HITECH") and its implementing regulations, imposes requirements relating to the privacy, security and transmission of individually identifiable health information. Among other things, HITECH makes HIPAA's privacy and security standards directly applicable to business associates, independent contractors or agents of covered entities that receive or obtain protected health information in connection with providing a service on behalf of a covered entity. HITECH also created four new tiers of civil monetary penalties, amended HIPAA to make civil and criminal penalties directly applicable to business associates, and gave state attorneys general new authority to file civil actions for damages or injunctions in federal courts to enforce the federal HIPAA laws and seek attorneys' fees and costs associated with pursuing federal civil actions. In addition, state laws govern the privacy and security of health information in specified circumstances, many of which differ from each other in significant ways and may not have the same effect, thus complicating compliance efforts.

Additionally, the federal Physician Payments Sunshine Act within the ACA, and its implementing regulations, require that certain manufacturers of drugs, devices, biological and medical supplies for which payment is available under Medicare, Medicaid or the Children's Health Insurance Program (with certain exceptions) to report information related to certain payments or other transfers of value made or distributed to physicians, other specified health care professionals and teaching hospitals, or to entities or individuals at the request of, or designated on behalf of, the physicians, other specified health care professionals and teaching hospitals and to report annually certain ownership and investment interests held by physicians and other specified health care professionals and their immediate family members. Some states have analogous laws requiring manufacturers to report certain transfers of value to covered individuals and entities. To distribute products commercially, we must comply with state laws that require the registration of manufacturers and wholesale distributors of drug and biological products in a state, including, in certain states, manufacturers and distributors who ship products into the state even if such manufacturers or distributors have no place of business within the state. Some states also impose requirements on manufacturers and distributors to establish the pedigree of product in the chain of distribution, including some states that require manufacturers and others to adopt new technology capable of tracking and tracing product as it moves through the distribution chain. Several states have enacted legislation requiring pharmaceutical and biotechnology companies to establish marketing compliance programs, file periodic reports with the state, make periodic public disclosures on sales, marketing, pricing, clinical trials and other activities, and/or register their sales representatives, as well as to prohibit pharmacies and other healthcare entities from providing certain physician prescribing data to pharmaceutical and biotechnology companies for use in sales and marketing, and to prohibit certain other sales and marketing practices. All our activities are potentially subject to federal and state consumer protection and unfair competition laws.

If our operations are found to be in violation of any of the federal and state healthcare laws described above or any other governmental regulations that apply to us, we may be subject to penalties, including without limitation, civil, criminal and/or administrative penalties, damages, fines, disgorgement, exclusion from participation in government programs, such as Medicare and Medicaid, injunctions, private "qui tam" actions brought by individual whistleblowers in the name of the government, or refusal to allow us to enter into government contracts, contractual damages, reputational harm, administrative burdens, diminished profits and future earnings, and the curtailment or restructuring of our operations, any of which could adversely affect our ability to operate our business and our results of operations.

Coverage and Reimbursement

Significant uncertainty exists as to the coverage and reimbursement status of any product candidates for which we obtain regulatory approval. In the United States and markets in other countries, sales of any products for which we receive regulatory approval for commercial sale will depend, in part, on the extent to which third-party payors provide coverage and establish adequate reimbursement levels for such products. In the United States, third-party payors include federal and state healthcare programs, privately managed care providers, health insurers and other organizations. The process for determining whether a third-party payor will provide coverage for a product may be separate from the process for setting the price of a product or for establishing the reimbursement rate that such a payor will pay for the product. Third-party payors may limit coverage to specific products on an approved list, also known as a formulary, which might not include all the FDA-approved products for a particular indication. Third-party payors are increasingly challenging the price, examining the medical necessity and reviewing the cost-effectiveness of medical products, therapies and services, in addition to questioning their safety and efficacy. We may need to conduct expensive pharmaco-economic studies to demonstrate the medical necessity and cost-effectiveness of our products, in addition to the costs required to obtain the FDA approvals. Our product candidates may not be considered medically necessary or cost-effective. A payor's decision to provide coverage for a product does not imply that an adequate reimbursement rate will be approved. Further, one payor's determination to provide coverage for a product does not assure that other payors will also provide coverage for the product. This is also true of Medicare reimbursement, where different vendors process payments, so that coverage by one vendor does not assure that all other vendors will provide coverage. Adequate third-party reimbursement may not be available to enable us to maintain price levels sufficient to realize an appropriate return on our investment in product development. In addition, the United States federal government position on matters related to drug pricing is evolving and uncertain, and any changes could have a material impact on drug pricing generally in the United States, including for our product candidates if approved.

Different pricing and reimbursement schemes exist in other countries. In the EU, governments influence the price of pharmaceutical products through their pricing and reimbursement rules and control of national health care systems that fund a large part of the cost of those products to consumers. Some jurisdictions operate positive and negative list systems under which products may only be marketed once a reimbursement price has been agreed. To obtain reimbursement or pricing approval, some of these countries may require the completion of clinical trials that compare the cost-effectiveness of a particular product candidate to currently available therapies. Other member states allow companies to fix their own prices for medicines but monitor and control company profits. The National Institute for Health and Care Excellence (NICE) in the United Kingdom also requires consideration of cost-benefit analysis. The downward pressure on health care costs has become very intense. As a result, increasingly high barriers are being erected to the entry of new products. In addition, in some countries, cross-border imports from low-priced markets exert a commercial pressure on pricing within a country.

The marketability of any product candidates for which we receive regulatory approval for commercial sale may suffer if the government and third-party payors fail to provide adequate coverage and reimbursement. In addition, emphasis on managed care in the United States has increased and we expect will continue to increase the pressure on healthcare pricing. Coverage policies and third-party reimbursement rates may change at any time. Even if favorable coverage and reimbursement status is attained for one or more products for which we receive regulatory approval, less favorable coverage policies and reimbursement rates may be implemented in the future.

Properties

Our primary business functions are conducted by our employees and independent contractors on a distributed basis. Accordingly, we do not lease or own any real property and all employees currently work from their homes. We maintain our principal mailing address at Suite 305 at 712 Vista Boulevard in Waconia, Minnesota.

Legal Proceedings

We are not currently party to any material legal proceedings. From time to time, we may be named as a defendant in legal actions arising from our normal business activities. We believe that we have obtained adequate insurance coverage or rights to indemnification in connection with potential legal proceedings that may arise.

Available Information

Our website is located at www.Panbela.com. The information contained on or connected to our website is not a part of this prospectus. We have included our website address as a factual reference and do not intend it to be an active link to our website.

We make available, free of charge, through our website at www.panbela.com, materials we file or furnish to the SEC pursuant to Section 13(a) or 15(d) of the Exchange Act, including our annual report on Form 10-K, our quarterly reports on Form 10-Q, our current reports on Form 8-K and amendments to those reports. These materials are posted to our website as soon as reasonably practicable after we electronically file them with or furnish them to the SEC.

The SEC maintains a website that contains reports, proxy and information statements and other information about us and other issuers that file electronically at www.sec.gov.

MANAGEMENT

Information about our Executive Officers

Jennifer K. Simpson, Ph.D., MSN, CRNP, age 54, has served as President and Chief Executive Officer and as a director of our Company since July 2020. Prior to joining the Company Dr. Simpson served as President and Chief Executive Officer and as a member of the board of directors of Delcath Systems, Inc. (Nasdaq: DCTH) from 2015 to June 2020. She had previously held various other leadership roles at Delcath since 2012. From 2011 to 2012, Dr. Simpson served as Vice President, Global Marketing, Oncology Brand Lead at ImClone Systems, Inc. (a wholly owned subsidiary of Eli Lilly and Company), where she was responsible for all product commercialization activities and launch preparation for one of the late-stage assets. From 2009 to 2011, Dr. Simpson served as Vice President, Product Champion and from 2008 to 2009 as the Associate Vice President, Product Champion for ImClone's product Ramucirumab. From 2006 to 2008, Dr. Simpson served as Product Director, Oncology Therapeutics Marketing at Ortho Biotech (now Janssen Biotech), a Pennsylvania-based biotech company that focuses on innovative solutions in immunology, oncology and nephrology. Earlier in her career, Dr. Simpson spent over a decade as a hematology/oncology nurse practitioner and educator. Dr. Simpson has served on the board of directors and nominating and corporate governance committee of Eagle Pharmaceuticals, Inc. since August 2019 and on the board of Directors of CytRx Corporation since July 2021. Dr. Simpson earned a Ph.D. in Epidemiology from the University of Pittsburgh, an M.S. in Nursing from the University of Rochester, and a B.S. in Nursing from the State University of New York at Buffalo.

Susan Horvath, age 63, has served as our Vice President and Chief Financial Officer since April 2018. Ms. Horvath has held both finance and operating positions within pharmaceutical, healthcare and consumer organizations. In addition to her position with the Company, Ms. Horvath sits on the board of directors and provides financial consulting services for Photonic Pharma, LLC, a privately held company focused on efficiencies in early stage drug discovery. Prior to joining the Panbela team Ms. Horvath served as Chief Financial Officer of Eyebobs, LLC, a private company focused on eyewear for corrective vision, from 2016 to January 2018; Vice President and Chief Financial Officer of Tenacious Holdings, Inc. (d/b/a ergodyne) a privately held, safety products company, from 2014 to 2016; Chief Financial Officer and Vice President of Human Resources at Healthsense, Inc., a next generation technology (SaaS) and remote monitoring company focused on providing safety and improving quality of life while reducing overall costs of healthcare for seniors and fragile adults, from 2011 to 2014; Chief Financial Officer, Vice President of Operations & Human Resources of Hemosphere, Inc., an early commercialization stage medical device company, from 2008 to 2010; and Vice President & Team Leader International of CNS, Inc, a publicly traded consumer health care products company focused on the development and marketing of strong consumer brands, from 2004 to 2007. Ms. Horvath holds a Bachelor of Science degree in Accounting from the University of Illinois, Champaign, and is a Certified Management Accountant and Certified Public Accountant, inactive.

Information about our Board of Directors

Our business is overseen by a Board of Directors divided into three classes as nearly equal in number as possible, and directors typically are elected to a designated class for a term of three years. The following sets forth certain information regarding the current members of our Board of Directors:

Class I Directors -Terms Expiring in 2023

Daniel J. Donovan, age 58, has served as a director since June 2022. He had served as a director and Chief Business Officer, a non-employee position, of CPP from 2011 until immediately before the completion of its acquisition by Panbela in June 2022. He has served as chief executive officer of rareLife Solutions, Inc., a private company since he co-founded it in 2014. Before rareLife, Mr. Donovan founded Envision Pharma in 2001, serving as managing director then president until 2011. Envision Pharma was acquired by United BioSource Corporation in 2008, where Mr. Donovan served as Senior Vice President Strategy and Market Development and was a member of the leadership team. Mr. Donovan began his career at Pfizer serving in a variety of positions of increasing responsibility, ranging from sales to market research and marketing in the U.S. and internationally, culminating in his position as Director and European Team Leader. During his time at Pfizer, he played a pivotal role in the commercialization of some of the pharmaceutical industry's most successful product launches.

Jeffrey E. Jacob, age 61, has served as a director since June 2022. He served as Chief Executive Officer of CPP from 2009 until immediately before the completion of its acquisition by Panbela in June 2022. He is also the principal of Tucson Pharma Ventures LLC, an Arizona-based biopharmaceutical consulting and investment firm, a role he's held since 2004. In 2004, Mr. Jacob founded Systems Medicine Inc., a startup company applying systems biology, predictive pharmacogenomics, and clinical trial design innovations to the development of new cancer drugs and served as its chief executive officer until its sale in 2007, after which he served as a divisional chief executive officer until late 2008. Between 1987 and 2004, Mr. Jacob was employed by Research Corporation Technologies, most recently as Senior Vice President. During that time, he led the transformation of Research Corporation Technologies from a patent development and licensing organization to an early stage-technology incubation and venture deployment firm. He has served as a member of the board of directors of Research Corporation Technologies and currently serves as its chair. He is also a founding board member and previously served as the chief program officer of Critical Path Institute. Mr. Jacob holds a master's degree in engineering and a master's degree in Technology and Policy from the Massachusetts Institute of Technology and a bachelor's degree in engineering from the University of Arizona.

Jennifer K. Simpson Ph.D., MSN, CRNP, has served as our President and Chief Executive Officer and as a director of our Company since July 2020. See "*Information about our Executive Officers*" above for further information regarding Dr. Simpson's background and experience.

Class II Directors - Term Expiring in 2024

Michael T. Cullen, M.D., M.B.A., age 76, has served as Chairman of the Board and a non-employee director of our Company since his retirement as an employee of the Company in May 2021. Dr. Cullen had served as Executive Chairman and as a director of our Company since its co-founding in November 2011. Dr. Cullen brings 33 years of pharmaceutical experience to our Company, including expertise in working with development-stage companies in planning, designing and advancing drug candidates from preclinical through clinical development. Dr. Cullen served as our President and Chief Executive Officer between October 2018 and July 2020. He previously served as our Chief Medical Officer and President from November 2011 to June 2015. Dr. Cullen provided due diligence consulting to the pharmaceutical industry from 2009 to 2011, after one year in transition consulting to Eisai Pharmaceuticals. He developed several oncology drugs as Chief Medical Officer for MGI Pharma Inc. from 2000 to 2008, and previously at G.D. Searle, SunPharm Corporation, and as Vice President for Clinical Consulting at IBAH Inc., the world's fifth largest contract research organization, where he provided consulting services on business strategy, creating development plans, regulatory matters and designing clinical trials for several development stage companies in the pharmaceutical industry. Dr. Cullen was also a co-founder and Chief Executive Officer of IDD Medical, a pharmaceutical start-up company. Dr. Cullen joined 3M Pharmaceuticals in 1988 and contributed to the development of cardiovascular, pulmonary, rheumatology and immune-response modification drugs. Over the course of his career Dr. Cullen has been instrumental in obtaining the approval of ten drugs, including three since 2004: Aloxi®, Dacogen® and Lusedra®. Board-certified in Internal Medicine, Dr. Cullen practiced from 1977 to 1988 at Owatonna Clinic, Owatonna, MN, where he served as president. Dr. Cullen earned his MD and BS degrees from the University of Minnesota and his M.B.A. from the University of St. Thomas and completed his residency and Board certification in Internal Medicine through the University of North Carolina in Chapel Hill and Wilmington, NC.

D. Robert Schemel, age 67, has served as a director since September 2015. Mr. Schemel had previously served as a director of Sun BioPharma Research, Inc. since March 2012. Mr. Schemel has over 39 years' experience in the agriculture industry. From 1973-2005, Mr. Schemel owned and operated a farming operation in Kandiyohi County, Minnesota, building a 5,000-acre operation producing corn, soybeans and sugar beets. Mr. Schemel has extensive experience in serving on boards of directors. From 1992-1996 he served as a board member for ValAdCo and then from 1996-2003 he served as the Chairman of the Board for Phenix Biocomposites.

Class III Directors -Terms Expiring in 2022

Arthur J. Fratamico, age 57, has served as a director of our Company since December of 2019. He is a registered pharmacist with over 30 years of experience in the pharmaceutical industry and has been the Chief Executive Officer of Radiant Biotherapeutics, which is advancing a novel antibody platform that is focused on the development of Multabodies, which are multi-valent and multi-specific antibodies since May 2021. Prior to Radiant, Mr. Fratamico served as Chief Business Officer at Galera Therapeutics, Inc., a biopharmaceutical company dedicated to discovering and developing novel dismutase mimetics with the goal of transforming cancer radiotherapy, since January 2017. Prior to joining Galera, Mr. Fratamico served as Chief Business Officer of Vitae Pharmaceuticals, Inc., a Nasdaq-listed clinical-stage biotechnology company, from May 2014 until its sale to Allergan in December 2016. Prior to Vitae Pharmaceuticals, he held similar executive roles with a number of biotechnology companies leading their business development efforts, including facilitating the sales of Gemin X Pharmaceuticals, Inc. and MGI Pharma, Inc. In addition to being responsible for numerous licensing transactions and acquisitions, he also directed corporate strategy and managed external corporate communications. He also served in several senior marketing, product planning and new product development positions. Mr. Fratamico earned a bachelor's degree in pharmacy from the Philadelphia College of Pharmacy and Science and an M.B.A. from Drexel University.

Jeffrey S. Mathiesen, age 62, has served as a director of our Company since September 2015. Mr. Mathiesen also serves as a director and audit committee chairman of NeuroOne Medical Technologies Corporation, a publicly traded medical device company. Additionally, Mr. Mathiesen serves Chief Financial Officer of Helius Medical Technologies, Inc., a publicly traded medical technology company focused on neurological wellness, where he previously served as a director and audit committee chairman. He also served as a director and audit committee chairman of eNeura, Inc., a privately held medical technology company providing therapy for both acute treatment and prevention of migraine from July 2018 to February 2020. Mr. Mathiesen has served as Advisor to the CEO of Teewinot Life Sciences, a privately held biopharmaceutical company focused on the biosynthetic production of pure pharmaceutical grade cannabinoids from October 2019 to December 2019, and as Chief Financial Officer from March 2019 to October 2019. In August 2020, Teewinot Life Sciences filed a voluntary petition under Chapter 11 of the United States Bankruptcy Code. Previously he served as Chief Financial Officer of Gemphire Therapeutics Inc., a publicly traded biopharmaceutical company from September 2015 to September 2018. From August 2015 to September 2015, he was a consultant to Gemphire. He served as Chief Financial Officer of Sunshine Heart, Inc., a publicly traded medical device company, from March 2011 to January 2015. Mr. Mathiesen has held executive positions with publicly traded companies dating back to 1993, including vice president and chief financial officer positions. Mr. Mathiesen holds a B.S. in Accounting from the University of South Dakota and is also a Certified Public Accountant.

Director Independence

The continued listing rules of The Nasdaq Stock Market, LLC (the "Nasdaq Rules") require that a majority of our Board of Directors be "independent directors" as that term is defined in the Nasdaq Rules. Our Board has determined that each of our non-employee directors, namely Messrs. Donovan, Fratamico, Mathiesen, and Schemel, are "independent directors."

EXECUTIVE COMPENSATION

Compensation of Named Executive Officers

The following disclosure focuses on our named executive officers. For fiscal 2021 our "named executive officers" consisted of: Dr. Simpson, Ms. Horvath, and Dr. Cullen, who retired from employment with the Company in May of 2021.

Base salaries for each of our named executive officers were initially established based on arm's-length negotiations with the applicable executive. The Compensation Committee of our Board of Directors reviews our executive officers' salaries annually. When negotiating or reviewing base salaries, the Compensation Committee considers market competitiveness based on the experience of its members, the executive's expected future contribution to our success and the relative salaries and responsibilities of our other executives.

Summary Compensation Table

The following table provides information regarding the compensation earned by our named executive officers for fiscal 2021 and 2020 (collectively referred to as the "Executives"):

Name and Principal Positions	Year	Salary ($)	Option Awards (a) ($)	Nonequity Incentive Plan Compensation (b) ($)	Total ($)
Jennifer K. Simpson	2021	476,609	537,702	182,422	1,196,733
President and Chief Executive Officer (c)	2020	145,587	1,529,926	78,750	1,754,263
Susan Horvath	2021	302,200	155,258	99,620	557,078
Chief Financial Officer and Vice President of Finance	2020	226,000	98,176	90,000	414,176
Michael T. Cullen	2021	337,147	218,199	–	555,346
Former Executive Chairman (d)	2020	316,000	179,900	141,750	637,650

(a) The values of option awards in this table represent the fair value of such awards granted during the fiscal year, as computed in accordance with Financial Accounting Standards Board Accounting Standards Codification Topic 718. The assumptions used to determine the valuation of the awards are discussed in Note 9 to the consolidated financial statements.

(b) Represents payments made under the Company's 2021 and 2020 Cash Incentive Program as described further below.

(c) Dr. Simpson joined the Company in July 2020.

(d) Dr. Cullen served as the Company's President and Chief Executive Officer from October 2018 until July 2020 and as Executive Chairman until his retirement. After his retirement in May of 2021, Dr. Cullen received non-employee director compensation of $39,375 included in salary in this table and options and RSU's granted after Dr. Cullen's retirement valued at $54,409, which is reflected in option awards in this table; both amounts are also disclosed in the Director Compensation table below.

Outstanding Equity Awards as of December 31, 2021
(Historical equity awards as of December 31, 2021 have not been adjusted for the anticipated reverse split.)

		Option Awards			
Name	Grant Date	Number of securities underlying unexercised options (#) exercisable	Number of securities underlying unexercised options (#) un-exercisable	Option exercise price ($)	Option expiration date
Jennifer K. Simpson	7/17/2020	106,024	106,024 (a)	9.99	7/17/2030
	3/30/2021	–	170,000 (b)	4.09	3/30/2031
	9/13/2021	–	19,125 (c)	2.26	9/13/2031
Susan Horvath	4/17/2018	40,000	–	5.75	4/17/2028
	5/21/2019	45,725	12,075 (d)	2.95	5/21/2029
	9/24/2019	25,000	–	5.00	9/24/2029
	6/24/2020	16,000	16,000 (e)	4.98	6/24/2030
	3/30/2021	–	40,000 (f)	4.09	3/30/2031
	9/13/2021	–	12,135 (g)	2.26	9/13/2031
Michael T. Cullen	3/5/2015	80,000	–	3.18	3/5/2025
	12/12/2016	15,000	–	15.10	12/12/2026
	2/27/2018	100,000	–	8.10	2/27/2028
	5/21/2019	127,900	28,200 (h)	2.95	5/21/2029
	9/24/2019	30,000	–	5.00	9/24/2029
	6/24/2020	25,000	25,000 (i)	4.98	6/24/2030
	3/30/2021	–	55,000 (j)	4.09	3/30/2031
	5/25/2021	9,276	3,092 (k)	4.17	5/25/2021

(a) Scheduled to vest with respect to 53,012 on July 17th in each of 2022 and 2023.
(b) Scheduled to vest with respect to 56,667 on March 30th in each of 2022, 2023 and 2024.
(c) Scheduled to vest with respect to 6,375 on September 13th in each of 2022, 2023 and 2024.
(d) Scheduled to vest with respect to 12,075 on May 21, 2022.
(e) Scheduled to vest with respect to 8,000 on June 24th in each of 2022 and 2023.
(f) Scheduled to vest with respect to 13,333 on March 30th in each of 2022, 2023 and 2024.
(g) Scheduled to vest with respect to 4,045 on September 13th in each of 2022, 2023 and 2024.
(h) Scheduled to vest with respect to 28,200 on May 21, 2022.
(i) Scheduled to vest with respect to 12,500 on June 24th in each of 2022 and 2023.
(j) Scheduled to vest with respect to 18,333 on March 30th in each of 2022, 2023 and 2024.
(k) Scheduled to vest with respect to 3,092 on May 25, 2022.

Cash Incentive Compensation

For 2020 and 2021, the Compensation Committee established performance objectives for each of the Executives based on clinical development and financial milestones. Each Executive's potential payment upon satisfaction of the objectives was equal to the target set forth in the Executive's employment agreement as described further below. In the first quarter of 2021, the Compensation Committee determined that all of 2020 objectives were achieved and approved payment at target for each Executive. In the first quarter of 2022, the Compensation Committee determined that Dr. Simpson's bonus for 2021 was approved for payment at 76.55% of target and Ms. Horvath's bonus was approved for payment at 82.41% of target. The 2021 incentive was paid in the first quarter of 2022. No cash bonus was paid or will be paid to Dr. Cullen in 2022 as the Company's plan requires that employees are employed as of the end of the year to be eligible for a bonus.

Employment Agreements

During 2021, we were party to employment agreements with each of the Executives. In addition to the specific terms summarized below, each Executive is eligible to participate in the other compensation and benefit programs generally available to our employees, including our other executive officers, if any. Each such employment agreement also includes customary non-competition and non-solicitation covenants and a requirement that the Executive carry out a supplemental agreement regarding confidentiality and assignment of intellectual property.

In accordance with the employment agreements, the base salary of each Executive is reviewed annually by the Compensation Committee of our Board of Directors. Pursuant to the employment agreements, the committee may authorize an increase for the applicable year but may not reduce an Executive's base salary below its then-current level other than with the Executive's consent or pursuant to a general wage reduction in respect of substantially all of our executive officers. As discussed above, the Compensation Committee established performance criteria for 2021 and, based upon achievement of those objectives, cash payments were approved and paid in the first quarter of 2022.

President and Chief Executive Officer

Under her employment agreement, Dr. Simpson is eligible to receive an annual performance-based cash bonus with a target amount equal to no less than 50% of her base salary. Payment of the bonus amount is subject to achievement of metrics to be established by our Board of Directors and her continued employment with the Company through the end of the applicable cash bonus period.

Chief Financial Officer

Under her employment agreement, Ms. Horvath is eligible to receive an annual performance-based cash bonus with a target amount equal to no less than 40% of her base salary. Payment of the bonus amount is subject to achievement of metrics to be established by our Board of Directors and her continued employment with the Company through the end of the applicable cash bonus period.

Former Executive Chairman

Dr. Cullen voluntarily retired from his employment with the Company in May of 2021. Under his employment agreement, Dr. Cullen had been eligible to receive an annual performance-based cash bonus with a target amount equal to no less than 45% of his base salary. Payment of the bonus amount was subject to achievement of metrics to be established by our Board of Directors and his continued employment with the Company through the end of the applicable cash bonus period.

Potential Payments Upon Termination or Change-in-Control

Under their respective employment agreements, if any of the Executive's employment is terminated by us for any reason other than for "cause" (as defined in the applicable employment agreement) or by him or her for "good reason" (as defined in the applicable employment agreement), then he or she will be eligible to receive an amount equal to their respective annualized salary plus an amount equal to a prorated portion of their cash bonus target, if any, for the year in which the termination occurred, in addition to other amounts accrued on or before the date of termination. If any such termination occurs within six months prior or two years after a "change of control" (as defined in the applicable employment agreement), then the Executive would instead receive an amount equal to his or her respective annualized salary, plus an amount equal to his or her full cash bonus target for the year in which the termination occurred.

Director Compensation

The following table sets forth certain information regarding compensation of the persons who served as non-employee directors during the most recent completed fiscal year:

Name	Fees Earned or Paid in Cash ($)	Stock Awards(a) ($)	Option Awards(b) ($)	Total ($)
Michael T. Cullen(c)	39,375	17,998	36,411	93,784
Arthur J. Fratamico(d)	43,752	17,998	36,411	98,161
Jeffrey S. Mathiesen(e)	73,752	17,998	36,411	128,161
Paul W. Schaffer(f)	54,996	17,998	36,411	109,405
D. Robert Schemel(g)	52,500	17,998	36,411	106,909

(a) The values of stock awards, or restricted stock units, in this table represent the fair value of such awards granted during the fiscal year, as computed in accordance with Financial Accounting Standards Board Accounting Standards Codification Topic 718. The assumptions used to determine the valuation of the awards are discussed in Note 9 to our consolidated financial statements, included in our annual report on Form 10-K for the fiscal year ended December 31, 2021.

(b) The values of option awards in this table represent the fair value of such awards granted during the fiscal year, as computed in accordance with Financial Accounting Standards Board Accounting Standards Codification Topic 718. The assumptions used to determine the valuation of the awards are discussed in Note 9 to our consolidated financial statements, included in our annual report on Form 10-K for the fiscal year ended December 31, 2021.

(c) Dr. Cullen's non-employee director compensation is also included in the named executive compensation table above. Dr. Cullen held 2,158 unvested restricted stock units and options to purchase an aggregate of 498,468 shares as of December 31, 2021.

(d) Mr. Fratamico held 2,158 unvested restricted stock units and options to purchase an aggregate of 57,668 shares as of December 31, 2021.

(e) Mr. Mathiesen held 2,158 unvested restricted stock units and options to purchase an aggregate of 80,668 shares as of December 31, 2021.

(f) Mr. Shaffer held 2,158 unvested restricted stock units and options to purchase an aggregate of 96,668 shares as of December 31, 2021.
(g) Mr. Schemel held 2,158 unvested restricted stock units and options to purchase an aggregate of 80,668 shares as of December 31, 2021.

Directors who are also our employees or who provide consulting services receive no additional cash compensation for serving on our Board of Directors. Director, Dr. Suzanne Gagnon, was an employee of the Company until her voluntary retirement in July of 2021. At her departure, Dr. Gagnon became a consultant of the company and as such was not entitled to any additional compensation for serving on the Board of Directors. During 2021, our Company reimbursed non-employee directors for out-of-pocket expenses incurred in connection with attending meetings of our Board of Directors and its committees.

In December 2020, the Compensation Committee approved an update to the compensation of our non-employee directors for 2021. The new program provided cash compensation based on the general responsibilities and committee memberships held by each director. The total annual amounts were paid to directors monthly. In addition, on that same date, the Compensation Committee approved the issuance of restricted stock units (RSUs) to each non-employee director. The number of RSUs granted to each director was 2,875 and they vested in 5 equivalent increments beginning January 2021 through May 2021. In May 2021, the Compensation Committee approved the issuance of RSU's to each non-employee director. The number of RSUs granted to each director was 4,316 and they are scheduled to vest in 4 equivalent increments beginning August 2021 through May 2022. Also in May 2021, the Compensation Committee approved the issuance of stock options to each non-employee director. The number of RSUs granted to each director was 12,368 and they are scheduled to vest in 4 equivalent increments beginning August 2021 through May 2022.

In February 2022, the Compensation Committee approved an update to the cash compensation for non-employee directors. The revised annual amounts described below were effective January 1, 2022 and will be paid out monthly.

Annual Retainer (all amounts in $)	General	Audit Committee	Nominating & Governance Committee	Compensation Committee
Nonemployee director	40,000	-	-	-
Chairman	32,500 (a)			
Lead independent director	22,500 (b)	-	-	-
Committee chair	-	15,000	7,500	10,000
Committee member	-	7,500	4,000	5,000

(a) Paid in addition to nonemployee director retainer.
(b) Paid in addition to nonemployee director retainer.

Certain Relationships and Related Party Transactions

The following is a summary of transactions since January 1, 2020 to which our Company has been a party and in which the amount involved exceeded $113,000, which is approximately 1% of the average of our total assets as of the ends of our last two completed fiscal years, and in which any of our directors, executive officers, or beneficial owners of more than 10% of our capital stock had or will have a direct or indirect material interest, other than the compensation arrangements that are described under the heading "*Executive Compensation: Employment Agreements*".

On June 25, 2022, CPP entered into a Separation and Release Agreement (the "Separation Agreement") with Mr. Jacob, now a director of Panbela, whereby he resigned as its Chief Executive Officer, employee, and all other capacities, immediately prior to the closing under the Merger Agreement. In consideration for Mr. Jacob's acknowledgements, representations, warranties, covenants, releases and agreements set forth in the Separation Agreement, CPP has agreed to pay to Mr. Jacob a total of $350,000, representing one times his base salary at the time of his resignation. Such payment will become due upon the earlier of (i) CPP or its parent completing a material financing and (ii) the two-year anniversary of the Closing Date. As further consideration, CPP has also agreed to reimburse Mr. Jacob for the employer's portion of the premium payments for him to continue his current medical insurance coverage for 12 months through the Consolidated Omnibus Budget Reconciliation Act (COBRA).

Dr. Suzanne Gagnon was the Company's Chief Medical Officer until her retirement in July of 2021. Dr. Gagnon remained a member of our Board of Directors until her resignation from the Board on June 15, 2022. We were party to an employment agreement with Dr. Gagnon in substantially the same form as the employment agreements with the Executives described above under the heading "*Executive Compensation: Employment Agreements*." Dr. Gagnon was eligible to participate in the other compensation and benefit programs generally available to our employees. Her employment agreement also included customary confidentiality, non-competition and non-solicitation covenants. Under the employment agreement in effect through her voluntary retirement, Dr. Gagnon was entitled to receive an annualized base salary of $360,000. During 2020 and 2021, Dr. Gagnon received compensation from the Company amounting to $197,800 and $293,500, respectively. In addition, in February 2021, based on the achievement of established metrics for 2020, Dr. Gagnon received a cash bonus of $117,000. No cash bonus was paid or will be paid to Dr. Gagnon in 2022 as the Company's plan requires that employees are employed as of the end of the year to be eligible for a bonus.

In July 2021, after approval by our Audit Committee, we entered into a consulting contract with Dr. Gagnon. The services to be provided by Dr. Gagnon include her professional support to complete the final study report for the Phase Ia/Ib clinical trial and additional support as a medical consultant for the clinical and administrative teams. The contract provides for a monthly retainer of $14,000 representing approximately eight hours per week for the first three months of the agreement; for the remainder of the term Dr. Gagnon shall be paid $400 per hour for all services provided. The contract will expire in July of 2023 but may be terminated early by either party or extended if mutually agreed upon. For the year ended December 31, 2021 Dr. Gagnon was paid approximately $54,600 in professional consulting fees.

Limitation of Liability of Directors and Officers and Indemnification

Our certificate of incorporation limits the liability of the directors to the fullest extent permitted by Delaware law.

Our bylaws provide that we will indemnify and advance expenses to the directors and officers to the fullest extent permitted by law or, if applicable, pursuant to indemnification agreements. They further provide that we may choose to indemnify other employees or agents of our Company from time to time. The Delaware General Corporation Law and the bylaws also permit us to secure insurance on behalf of any officer, director, employee or other agent for any liability arising out of his or her actions in connection with their services to our Company, regardless of whether the bylaws permit indemnification. We maintain a directors' and officers' liability insurance policy.

At present there is no pending litigation or proceeding involving any of the current or former directors or officers as to which indemnification is required or permitted, and we are not aware of any threatened litigation or proceeding that may result in a claim for indemnification.

Insofar as indemnification for liabilities arising under the Securities Act may be permitted to directors, officers and controlling persons of the registrant pursuant to the foregoing provisions, or otherwise, the registrant has been advised that in the opinion of the SEC this indemnification is against public policy as expressed in the Securities Act and is therefore unenforceable.

Related Person Transaction Approval Policy

Our Board of Directors has adopted a written policy regarding transactions with related persons, which we refer to as our related party transaction approval policy. Our related party transaction approval policy requires that any executive officer proposing to enter into a transaction with a "related party" generally must promptly disclose to our Audit Committee the proposed transaction and all material facts with respect thereto. In reviewing a transaction, our Audit Committee will consider all relevant facts and circumstances, including (1) the commercial reasonableness of the terms, (2) the benefit and perceived benefits, or lack thereof, to us, (3) the opportunity costs of alternate transactions and (4) the materiality and character of the related party's interest, and the actual or apparent conflict of interest of the related party.

Our Audit Committee will not approve or ratify a related party transaction unless it determines that, upon consideration of all relevant information, the transaction is beneficial to our Company and stockholders and the terms of the transaction are fair to our Company. No related party transaction will be consummated without the approval or ratification of our Audit Committee. It will be our policy that a director will recuse him- or herself from any vote relating to a proposed or actual related party transaction in which they have an interest. Under our related party transaction approval policy, a "related party" includes any of our directors, director nominees, executive officers, any beneficial owner of more than 5% of our common stock and any immediate family member of any of the foregoing. Related party transactions exempt from our policy include transactions available to all of our employees and stockholders on the same terms and transactions between us and the related party that, when aggregated with the amount of all other transactions between us and the related party or its affiliates, involved less than one percent of the average of our Company's total assets at yearend for the last two completed fiscal years.

SECURITY OWNERSHIP OF CERTAIN BENEFICIAL OWNERS AND MANAGEMENT

The following table sets forth certain information with respect to the beneficial ownership of our outstanding common stock as of December 12, 2022 by (i) each of our named executive officers identified in the Summary Compensation Table below; (ii) each of our directors; (iii) all of our executive officers, directors and director nominees as a group; and (iv) each other beneficial owner of 5% or more of our outstanding common stock. Ownership percentages are based on 1,022,249 shares of common stock outstanding as of the close of business on the same date. Beneficial ownership is determined in accordance with the rules of the SEC. To our knowledge and subject to applicable community property laws, each of the holders of stock listed below has sole voting and investment power as to the stock owned unless otherwise noted. The table below includes the number of shares underlying rights to acquire common stock that are exercisable within 60 days from December 12, 2022. Except as otherwise noted below, the address for each director or officer listed in the table is c/o Panbela Therapeutics, Inc., 712 Vista Blvd #305, Waconia, Minnesota 55387.

Name	Amount and Nature of Beneficial Ownership	Percentage of Outstanding Shares*
Executive Officers and Directors		
Jennifer K. Simpson	4,933(a)	*
Susan Horvath	5,695(b)	*
Michael T. Cullen	33,824(c)	3.2%
Daniel J. Donovan	9,372(d)	*
Arthur J. Fratamico	1,736(e)	*
Jeffrey E. Jacob	19,201(f)	1.9%
Jeffrey S. Mathiesen	2,266(g)	*
D. Robert Schemel	24,285(h)	2.4%
All directors and current executive officers as a group (8 persons)	101,311(i)	9.4%

* Less than 1.0%.

(a) Includes 25 shares held by spouse, 5,550 shares subject to stock options and 60 shares subject to warrants.

(b) Includes 4,103 shares subject to stock options and 496 shares subject to warrants.

(c) Includes 11,231 shares subject to stock options, and shares subject to warrants. Also includes 9,239 shares and shares subject to warrants in each case held by the Cullen Living Trust.

(d) Includes 1,488 shares subject to stock options. Also includes 1,888 shares held by Westport Boys, LLC ("Westport"), 4,081 shares held by GDB Investments, LLP ("GDB"), and 129 shares subject to a warrant held by GDB Investments, LLP. Mr. Donovan is a managing member of Westport and a designated member of GDB. Mr. Donovan disclaims beneficial ownership of the securities owned by Westport and GDB except to the extent of his pecuniary interest therein.

(e) Includes 1,441 shares subject to stock options and 60 shares subject to warrants.

(f) Includes 1,237 shares subject to warrants, 8,663 shares subject to options and 444 shares held jointly with spouse. Also includes 1,359 shares and 129 shares subject to a warrant, in each case held by the Jeffrey and Debora Jacob Family Revocable Trust.

(g) Includes 2,016 shares subject to options.

(h) Includes 2,016 shares subject to stock options, 12,359 shares and 7,500 shares subject to warrants held by spouse, and 293 held by parent's estate over which director holds both voting and depository power but disclaims beneficial ownership.

(i) Includes 36,507 shares subject to stock options and 17,550 shares subject to warrants.

(j) Based solely on shares issued in connection with the acquisition of CPP.

DESCRIPTION OF SECURITIES

The summary of the general terms and provisions of the common stock, par value $0.001 per share ("Common Stock"), of Panbela set forth below does not purport to be complete and is subject to and qualified by reference to the Corporation's Certificate of Incorporation, as amended (the "Certificate"), and Bylaws of the Corporation, as amended (the "Bylaws"). For additional information, please read the Certificate, Bylaws and the applicable provisions of the General Corporation Law of Delaware (the "DGCL").

Authorized Shares

The Corporation is authorized to issue up to 110,000,000 shares of capital stock, of which 100,000,000 constitute shares of Common Stock and 10,000,000 constitute shares of preferred stock, par value $0.001 per share ("Preferred Stock").

Common Stock

No outstanding shares of common stock is entitled to preference over any other share, and each share is equal to any other share in all respects. Holders of shares of common stock are entitled to one vote for each share held of record at each meeting of shareholders. Holders of shares of common stock are not entitled to any preemptive, subscription, conversion, redemption or sinking fund rights. The absence of preemptive rights could result in a dilution of the interest of shareholders should additional common shares be issued.

Subject to any prior rights of any Preferred Stock then outstanding, holders of common stock are entitled to receive dividends in the form of cash, property or shares of capital stock of the Corporation, when and as declared by the board of directors, provided there are sufficient net profits or surplus legally available for that purpose. In any distribution of capital assets, such as liquidation, whether voluntary or involuntary, holders of shares of common stock are entitled to receive pro rata the assets remaining after creditors have been paid in full. All of the issued and outstanding shares of common stock are non-assessable.

Anti-Takeover Provisions

The Charter Documents and the DGCL contain certain provisions that may discourage an unsolicited takeover of the Company or make an unsolicited takeover of the Company more difficult. The following are some of the more significant anti-takeover provisions that are applicable to the Company:

Delaware Anti-Takeover Law

In general, Section 203 of the DGCL prohibits a Delaware corporation with a class of voting stock listed on a national securities exchange or held of record by 2,000 or more stockholders from engaging in a Business Combination (as defined below) with an Interested Stockholder (as defined below) for a three-year period following the time that this stockholder becomes an interested stockholder, unless the Business Combination is approved in a prescribed manner. A "Business Combination" includes, among other things, a merger, asset or stock sale or other transaction resulting in a financial benefit to the Interested Stockholder. An "Interested Stockholder" is a person who, together with affiliates and associates, owns, or did own within three years prior to the determination of Interested Stockholder status, 15% or more of the corporation's voting stock. Under Section 203, a Business Combination between a corporation and an Interested Stockholder is prohibited for three years unless it satisfies one of the following conditions:

- Before the stockholder became an Interested Stockholder, the board of directors approved either the Business Combination or the transaction which resulted in the stockholder becoming an Interested Stockholder;
- Upon consummation of the transaction which resulted in the stockholder becoming an Interested Stockholder, the Interested Stockholder owned at least 85% of the voting stock of the corporation outstanding at the time the transaction commenced, excluding for purposes of determining the voting stock outstanding, shares owned by persons who are directors and also officers, and employee stock plans, in some instances; or
- At or after the time the stockholder became an Interested Stockholder, the Business Combination was approved by the board of directors of the corporation and authorized at an annual or special meeting of the stockholders by the affirmative vote of at least two-thirds of the outstanding voting stock which is not owned by the Interested Stockholder.

Requirements for Advance Notification of Stockholder Nominations and Proposals

The Bylaws establish advance-notice procedures with respect to stockholder proposals to be brought before a stockholder meeting and the nomination of candidates for election as directors, other than nominations made by or at the direction of the board of directors.

Special Meetings of Stockholders

The Certificate and Bylaws provide that a special meeting of stockholders may be called only by the board of directors, the Chairman of the Board or the Chief Executive Officer of the Corporation.

Classified Board of Directors

The Certificate provides that directors are divided into three classes and elected for staggered terms. At each annual meeting, approximately one third of the directors will be elected to serve a three-year term. Directors serving staggered terms can be removed from office only for cause and only by the affirmative vote of the holders of 75% or more of the outstanding shares of stock then entitled to vote at an election of directors.

Authority of the Board of Directors

The board of directors has the power to issue any or all of the shares of the Corporation's capital stock, including the authority to establish one or more series of Preferred Stock and to fix the powers, preferences, rights and limitations of such class or series, without seeking stockholder approval. The board of directors has the authority to adopt and change Bylaws, subject to the right of holders of at least 66.67% of the voting power of all then-outstanding shares entitled to vote generally in the election of directors to adopt, amend or repeal Bylaws.

Preferred Stock

Our Board of Directors has the authority, without first obtaining the approval of our stockholders, to establish one or more series of preferred stock and to fix:

- the number of shares of such series;
- the designations, preferences and relative rights, including voting rights, dividend rights, conversion rights, redemption privileges and liquidation preferences; and
- any qualifications, limitations or restrictions.

We believe that the ability of our Board of Directors to issue one or more series of preferred stock provides flexibility in structuring possible future financings and acquisitions, and in meeting other corporate needs that may arise. The authorized shares of preferred stock, as well as authorized and unissued shares of common stock, are available for issuance without action by the holders of common stock, unless such action is required by applicable law or the rules of any stock exchange or automated quotation system on which our securities may be listed or traded.

Our Board of Directors may authorize, without stockholder approval, the issuance of preferred stock with voting and conversion rights that could adversely affect the voting power and other rights of holders of common stock. Although our Board of Directors has no current intention of doing so, it could issue a series of preferred stock that could, depending on the terms of such series, impede the completion of a merger, tender offer or other takeover attempt of our Company. Our Board of Directors could also issue preferred stock having terms that could discourage an acquisition attempt through which an acquirer may be able to change the composition of our Board of Directors, including a tender offer or other transaction that some, or a majority, of the stockholders might believe to be in their best interests or in which stockholders might receive a premium for their stock over the then-current market price. Any issuance of preferred stock therefore could have the effect of decreasing the market price of our common stock.

Our Board of Directors will make any determination to issue such shares based on its judgment as to the best interests of our Company and stockholders. We have no current plans to issue any preferred stock.

Options

The 2016 Plan initially authorized the issuance of up to 70,000 shares of our common stock pursuant to awards granted thereunder and 36,824 shares have been added pursuant to its annual evergreen feature. As of December 12, 2022, options to purchase 55,503 shares of our common stock were outstanding under the 2016 Plan with a weighted average price of $241.63 per share. A total of 50,494, shares of common stock remained available for future grants under the 2016 Plan as of the same date.

As of December 12, 2022, options to purchase 5,600 shares of our common stock remained outstanding under the 2011 Plan with a weighted average price of $118.92 per share. We ceased making awards under the 2011 Plan upon stockholder approval of the 2016 Plan.

As of December 12, 2022, options to purchase 39,475 shares of our common stock remained outstanding under CPP's 2010 Equity Incentive Plan with a weighted average price of $14.013, all of which were assumed by us in connection with the acquisition of CPP.

Warrants Outstanding

As of December 12, 2022, we had issued and outstanding warrants to purchase 889,911 shares of common stock and no warrants to purchase shares of preferred stock outstanding. As of the same date, the outstanding warrants had a weighted average exercise price of $38.05 per share, before any potential adjustments resulting from the pending reverse stock split, and an average remaining exercise period of 2.0 years.

Pre-Funded Warrants

The following summary of certain terms and provisions of pre-funded warrants that are being offered hereby is not complete and is subject to, and qualified in its entirety by, the provisions of the pre-funded warrant, the form of which is filed as an exhibit to the registration statement of which this prospectus forms a part. Prospective investors should carefully review the terms and provisions of the form of pre-funded warrant for a complete description of the terms and conditions of the pre-funded warrants.

Duration and Exercise Price. Each pre-funded warrant offered hereby will have an initial exercise price per share equal to $0.001. The pre-funded warrants will be immediately exercisable and may be exercised at any time until the pre-funded warrants are exercised in full. The exercise price and number of shares of common stock issuable upon exercise is subject to appropriate adjustment in the event of stock dividends, stock splits, reorganizations or similar events affecting our common stock and the exercise price. The pre-funded warrants will be issued separately from the accompanying common warrants and may be transferred separately immediately thereafter.

Exercisability. The pre-funded warrants will be exercisable, at the option of each holder, in whole or in part, by delivering to us a duly executed exercise notice accompanied by payment in full for the number of shares of our common stock purchased upon such exercise (except in the case of a cashless exercise as discussed below). Purchasers of the pre-funded warrants in this offering may elect to deliver their exercise notice following the pricing of the offering and prior to the issuance of the pre-funded warrants at closing to have their pre-funded warrants exercised immediately upon issuance and receive shares of common stock underlying the pre-funded warrants upon closing of this offering. A holder (together with its affiliates) may not exercise any portion of the pre-funded warrant to the extent that the holder would own more than 4.99% of the outstanding common stock immediately after exercise, except that upon at least 61 days' prior notice from the holder to us, the holder may increase the amount of ownership of outstanding stock after exercising the holder's pre-funded warrants up to 9.99% of the number of shares of our common stock outstanding immediately after giving effect to the exercise, as such percentage ownership is determined in accordance with the terms of the pre-funded warrants. Purchasers of pre-funded warrants in this offering may also elect prior to the issuance of the pre-funded warrants to have the initial exercise limitation set at 9.99% of our outstanding common stock. No fractional shares of common stock will be issued in connection with the exercise of a pre-funded warrant. In lieu of fractional shares, we will round down to the next whole share.

Cashless Exercise. If, at the time a holder exercises its pre-funded warrants, a registration statement registering the issuance of the shares of common stock underlying the pre-funded warrants under the Securities Act is not then effective or available, then in lieu of making the cash payment otherwise contemplated to be made to us upon such exercise in payment of the aggregate exercise price, the holder may elect instead to receive upon such exercise (either in whole or in part) the net number of shares of common stock determined according to a formula set forth in the pre-funded warrants.

Transferability. Subject to applicable laws, a pre-funded warrant may be transferred at the option of the holder upon surrender of the pre-funded warrant to us together with the appropriate instruments of transfer.

Exchange Listing. There is no trading market available for the pre-funded warrants on any securities exchange or nationally recognized trading system. We do not intend to list the pre-funded warrants on any securities exchange or nationally recognized trading system.

Right as a Stockholder. Except as otherwise provided in the pre-funded warrants or by virtue of such holder's ownership of shares of our common stock, the holders of the pre-funded warrants do not have the rights or privileges of holders of our common stock, including any voting rights, until they exercise their pre-funded warrants.

Fundamental Transaction. In the event of a fundamental transaction, as described in the pre-funded warrants and generally including any reorganization, recapitalization or reclassification of our common stock, the sale, transfer or other disposition of all or substantially all of our properties or assets, our consolidation or merger with or into another person, the acquisition of more than 50% of our outstanding common stock, or any person or group becoming the beneficial owner of 50% of the voting power represented by our outstanding common stock, the holders of the pre-funded warrants will be entitled to receive upon exercise of the pre-funded warrants the kind and amount of securities, cash or other property that the holders would have received had they exercised the pre-funded warrants immediately prior to such fundamental transaction.

Common Warrants

The following summary of certain terms and provisions of common warrants that are being offered hereby is not complete and is subject to, and qualified in its entirety by, the provisions of the common warrants, the form of which is filed as an exhibit to the registration statement of which this prospectus forms a part. Prospective investors should carefully review the terms and provisions of the form of common warrants for a complete description of the terms and conditions of the common warrants.

Duration and Exercise Price. Each common warrant offered hereby will have an initial exercise price per share equal to $. The common warrants will be immediately exercisable and will expire on the fifth anniversary of the original issuance date. The exercise price and number of shares of common stock issuable upon exercise is subject to appropriate adjustment in the event of stock dividends, stock splits, reorganizations or similar events affecting our common stock and the exercise price. The exercise price is separately subject to (i) reduction to the lowest volume-weighted average price on any trading day during the five-trading day period immediately following the date any future reverse stock split is effected and (ii) reduction in the event of certain future dilutive issuances of shares of common stock by us, including pursuant to common stock equivalents and convertible or derivative securities. The common warrants will be issued separately from the common stock and will be held separately immediately thereafter. A common warrant to purchase 1.5 shares of our common stock will be issued for every share of common stock or pre-funded warrant to purchase one share purchased in this offering.

Exercisability. The common warrants will be exercisable, at the option of each holder, in whole or in part, by delivering to us a duly executed exercise notice accompanied by payment in full for the number of shares of our common stock purchased upon such exercise (except in the case of a cashless exercise as discussed below). A holder (together with its affiliates) may not exercise any portion of the common warrant to the extent that the holder would own more than 4.99% of the outstanding common stock immediately after exercise, except that upon at least 61 days' prior notice from the holder to us, the holder may increase the amount of ownership of outstanding stock after exercising the holder's common warrants up to 9.99% of the number of shares of our common stock outstanding immediately after giving effect to the exercise, as such percentage ownership is determined in accordance with the terms of the common warrants. No fractional shares of common stock will be issued in connection with the exercise of a common warrant. In lieu of fractional shares, we will round down to the next whole share.

Cashless Exercise. If, at the time a holder exercises its common warrants, a registration statement registering the issuance of the shares of common stock underlying the common warrants under the Securities Act is not then effective or available and an exemption from registration under the Securities Act is not available for the issuance of such shares, then in lieu of making the cash payment otherwise contemplated to be made to us upon such exercise in payment of the aggregate exercise price, the holder may elect instead to receive upon such exercise (either in whole or in part) the net number of shares of common stock determined according to a formula set forth in the common warrants.

Alternative Cashless Exercise. On or after the thirty-day anniversary of their issuance, a holder of common warrants may also provide notice and elect an "alternative cashless exercise" pursuant to which they would receive an aggregate number of shares equal the product of (x) the aggregate number of shares of common stock that would be issuable upon a cash exercise and (y) 0.50.

Transferability. Subject to applicable laws, a common warrant in book entry form may be transferred at the option of the holder through the facilities of the Depository Trust Company and common warrants in physical form may be transferred upon surrender of the common warrant to the warrant agent together with the appropriate instruments of transfer. Pursuant to a warrant agency agreement between us and VStock Transfer, as warrant agent, the common warrants initially will be issued in book-entry form and will be represented by one or more global certificates deposited with The Depository Trust Company ("DTC") and registered in the name of Cede & Co., a nominee of DTC, or as otherwise directed by DTC.

Exchange Listing. There is no established public trading market for the common warrants, and we do not expect a market to develop. In addition, we do not intend to list the common warrants on any securities exchange or nationally recognized trading system. Without an active trading market, the liquidity of the common warrants will be limited.

Right as a Stockholder. Except as otherwise provided in the common warrants or by virtue of such holder's ownership of shares of our common stock, the holders of the common warrants do not have the rights or privileges of holders of our common stock, including any voting rights, until they exercise their common warrants.

Fundamental Transaction. In the event of a fundamental transaction, as described in the form of common warrant, and generally including any reorganization, recapitalization or reclassification of our common stock, the sale, transfer or other disposition of all or substantially all of our properties or assets, our consolidation or merger with or into another person, the acquisition of more than 50% of our outstanding common stock, or any person or group becoming the beneficial owner of 50% of the voting power represented by our outstanding common stock, the holders of the common warrants will be entitled to receive upon exercise of the common warrants the kind and amount of securities, cash or other property that the holders would have received had they exercised the common warrants immediately prior to such fundamental transaction.

Transfer Agent and Registrar

The transfer agent and registrar for our common stock is VStock Transfer, which can be contacted at 18 Lafayette Place, Woodmere, New York, 11598, info@vstocktransfer.com, or +1 (212) 828-8436.

SHARES ELIGIBLE FOR FUTURE SALE

Future sales of substantial amounts of our common stock in the public market, including shares issued upon exercise of outstanding options and warrants, or the anticipation of these sales, could adversely affect prevailing market prices from time to time and could impair our ability to raise equity capital in the future.

Upon the closing of this offering, we will have a total of 5,245,221 shares of our common stock outstanding and a total of 11,579,679 shares of our common stock outstanding if the warrants sold in this offering are exercised in full, based on the 1,022,249 shares of our common stock outstanding as of December 12, 2022. Of these outstanding shares, all of the shares sold in the offering will be freely tradable, except that any shares purchased in this offering by our affiliates, as that term is defined in Rule 144 under the Securities Act, would only be able to be sold in compliance with the limitations described below.

Rule 144

In general, under Rule 144 as currently in effect, once we have been subject to public company reporting requirements for at least 90 days, a person who is not deemed to have been one of our affiliates for purposes of the Securities Act at any time during the 90 days preceding a sale and who has beneficially owned the shares proposed to be sold for at least six months, including the holding period of any prior owner other than our affiliates, is entitled to sell those shares without complying with the manner of sale, volume limitation or notice provisions of Rule 144, subject to compliance with the public information requirements of Rule 144. If such a person has beneficially owned the shares proposed to be sold for at least one year, including the holding period of any prior owner other than our affiliates, then that person would be entitled to sell those shares upon expiration of the lock-up agreements described below, without complying with any of the requirements of Rule 144.

In general, under Rule 144, as currently in effect, our affiliates or persons selling shares on behalf of our affiliates are entitled to sell upon expiration of the lock-up agreements described below, within any three-month period, a number of shares that does not exceed the greater of:

- 1% of the number of shares of our common stock then outstanding, which will equal approximately shares immediately after this offering; or
- if and when our common stock is listed on the Nasdaq Capital Market, the average weekly trading volume of our common stock on such market during the four calendar weeks preceding the filing of a notice on Form 144 with respect to the sale.

Sales under Rule 144 by our affiliates or persons selling shares on behalf of our affiliates are also subject to certain manner of sale provisions and notice requirements and to the availability of current public information about us.

Rule 701

Rule 701 generally allows a stockholder who purchased shares of our common stock pursuant to a written compensatory plan or contract and who is not deemed to have been an affiliate of our company during the immediately preceding 90 days to sell these shares in reliance upon Rule 144, but without being required to comply with the public information or holding period provisions of Rule 144. Rule 701 also permits affiliates of our company to sell their Rule 701 shares under Rule 144 without complying with the holding period requirements of Rule 144. All holders of Rule 701 shares, however, are required by that rule to wait until 90 days after the date of this prospectus before selling those shares pursuant to Rule 701, subject to the market standoff agreements and lock-up agreements described below.

Stock Options and Warrants

See "Description of Securities" above for a discussion of our outstanding and options warrant to purchase shares of common stock.

Lock-Up Agreements

We and our executive officers and directors expect to enter into lock up agreements with the placement agent prior to the commencement of this offering. See "Plan of Distribution – Lock-Up Agreements" below for additional information regarding the terms of these agreements. Following the expiration of the lock-up agreements, covered shares will become eligible for sale, subject to any applicable limitations of Rule 144.

PLAN OF DISTRIBUTION

Pursuant to a placement agency agreement, dated as of , 2022, we have engaged Roth Capital Partners, LLC to act as our exclusive placement agent to solicit offers to purchase the securities offered by this prospectus on a reasonable best efforts basis. The placement agent is not purchasing or selling any securities, nor is it required to arrange for the purchase and sale of any specific number or dollar amount of securities, other than to use its "reasonable best efforts" to arrange for the sale of the securities by us. Therefore, we may not sell the entire amount of securities being offered, or any at all. The placement agent may engage one or more subagents or selected dealers in connection with this offering.

We will enter into a securities purchase agreement directly with the institutional investors, at the investor's option, who purchase our securities in this offering. Investors who do not enter into a securities purchase agreement shall rely solely on this prospectus in connection with the purchase of our securities in this offering.

The placement agency agreement provides that the placement agent's obligations are subject to the conditions contained in the placement agency agreement.

We will deliver the securities being issued to the investors upon receipt of investor funds for the purchase of the securities offered pursuant to this prospectus. We expect to deliver the securities being offered pursuant to this prospectus on or about , 2022. There is no minimum number of securities or amount of proceeds that is a condition to closing of this offering.

Placement Agent Fees, Commissions and Expenses

Upon the closing of this offering, we will pay the placement agent a cash transaction fee equal to 7.0% of the aggregate gross proceeds to us from the sale of the securities in the offering. In addition, we will reimburse the placement agent for its out-of-pocket expenses incurred in connection with this offering, including the fees and expenses of the counsel for the placement agent, up to $100,000.

The following table shows the public offering price, placement agent fees and proceeds, before expenses, to us, assuming the purchase of all the securities we are offering.

	Per Share and Common Warrant	Per Pre-Funded Warrant and Common Warrant
Public offering price	$	$
Placement Agent fees	$	$
Proceeds to us, before expenses	$	$

We estimate that the total expenses of the offering, including registration, filing and listing fees, printing fees and legal and accounting expenses, but excluding placement agent fees, will be approximately $, all of which are payable by us. This figure includes the placement agent's accountable expenses, including, but not limited to, legal fees for placement agent's legal counsel, that we have agreed to pay at the closing of the offering up to an aggregate expense reimbursement of $100,000.

Lock-Up Agreements

We and our executive officers and directors expect to enter into lock up agreements with the representative prior to the commencement of this offering pursuant to which each of these persons or entities, for a period of 90 days from the effective date of the registration statement of which this prospectus forms a part, without the prior consent of the representative, agree not to (a) offer, pledge, sell, contract to sell, sell any option or contract to purchase, purchase any option or contract to sell, grant any option, right or warrant to purchase, lend, or otherwise transfer or dispose of, directly or indirectly, any shares of our capital stock or any securities convertible into or exercisable or exchangeable for shares of our capital stock; (b) file or cause to be filed any registration statement with the SEC relating to the offering of any shares of our capital stock or any securities convertible into or exercisable or exchangeable for shares of our capital stock; or (c) enter into any swap or other arrangement that transfers to another, in whole or in part, any of the economic consequences of ownership of our capital stock, whether any such transaction described in (a), (b) or (c) above is to be settled by delivery of shares of our capital stock or such other securities, in cash or otherwise.

Indemnification

We have agreed to indemnify the placement agent against certain liabilities, including liabilities under the Securities Act, and to contribute to payments that the placement agent may be required to make for these liabilities.

Determination of Offering Price and Warrant Exercise Price

The actual public offering price of the securities we are offering, and the exercise price of the common warrants and pre-funded warrants that we are offering, were negotiated between us, the placement agent and the investors in the offering based on the trading price of our common stock prior to the offering, among other things. Other factors considered in determining the public offering price of the securities we are offering, as well as the exercise price of the common warrants and pre-funded warrants that we are offering include our history and prospects, the stage of development of our business, our business plans for the future and the extent to which they have been implemented, an assessment of our management, the general conditions of the securities markets at the time of the offering and such other factors as were deemed relevant.

Other Compensation

If within six (6) months following the termination or expiration of our engagement with the placement agent, we complete any sale of equity or equity-linked securities for which the placement agent is not acting as underwriter or placement agent (other than the exercise by any person or entity of any options, warrants or other convertible securities) to any of the investors that the placement agent introduced to us or with which the placement agent conducted discussions on our behalf, subject to specified exceptions, then we are required to pay to the placement agent a commission as described in this section, in each case only with respect to the portion of such financing received from such investors.

Right of First Refusal

Provided the placement agent does not terminate the engagement and the offering is consummated during the engagement period for at least $20,000,000 in gross proceeds, then if during the engagement period or within 12 months thereafter, we pursue any offering of equity, equity-linked or debt securities for cash, the placement agent has the right to act as placement agent or underwriter, as applicable, for such offering, and will be entitled to a minimum of thirty five percent (35%) of the aggregate fees paid to the agents or underwriters for such offering.

Regulation M

The placement agent may be deemed to be an underwriter within the meaning of Section 2(a)(11) of the Securities Act, and any commissions received by it and any profit realized on the resale of the securities sold by it while acting as principal might be deemed to be underwriting discounts or commissions under the Securities Act. As an underwriter, the placement agent would be required to comply with the requirements of the Securities Act and the Exchange Act, including, without limitation, Rule 10b-5 and Regulation M under the Exchange Act. These rules and regulations may limit the timing of purchases and sales of our securities by the placement agent acting as principal. Under these rules and regulations, the placement agent (i) may not engage in any stabilization activity in connection with our securities and (ii) may not bid for or purchase any of our securities or attempt to induce any person to purchase any of our securities, other than as permitted under the Exchange Act, until it has completed its participation in the distribution.

Electronic Distribution

A prospectus in electronic format may be made available on a website maintained by the placement agent. In connection with the offering, the placement agent or selected dealers may distribute prospectuses electronically. No forms of electronic prospectus other than prospectuses that are printable as Adobe® PDF will be used in connection with this offering.

Other than the prospectus in electronic format, the information on the placement agent's website and any information contained in any other website maintained by the placement agent is not part of the prospectus or the registration statement of which this prospectus forms a part, has not been approved and/or endorsed by us or the placement agent in its capacity as placement agent and should not be relied upon by investors.

Certain Relationships

The placement agent and its affiliates may in the future provide, from time to time, investment banking and financial advisory services to us in the ordinary course of business, for which they may receive customary fees and commissions.

The Nasdaq Capital Market Listing

Our common stock is listed on The Nasdaq Capital Market under the symbol "PBLA."

Offer Restrictions Outside the United States

European Economic Area

In relation to each member state of the European Economic Area, no offer of securities which are the subject of the offering has been, or will be made to the public in that Member State, other than under the following exemptions under the Prospectus Directive:

(a) to any legal entity which is a qualified investor as defined in the Prospectus Directive;

(b) to fewer than 150 natural or legal persons (other than qualified investors as defined in the Prospectus Directive), subject to obtaining the prior consent of the Representatives for any such offer; or

(c) in any other circumstances falling within Article 3(2) of the Prospectus Directive,

provided that no such offer of securities referred to in (a) to (c) above shall result in a requirement for the Company or the placement agent to publish a prospectus pursuant to Article 3 of the Prospectus Directive, or supplement a prospectus pursuant to Article 16 of the Prospectus Directive.

Each person located in a Member State to whom any offer of securities is made or who receives any communication in respect of an offer of securities, or who initially acquires any shares of our securities will be deemed to have represented, warranted, acknowledged and agreed to and with the placement agent and the Company that (1) it is a "qualified investor" within the meaning of the law in that Member State implementing Article 2(1)(e) of the Prospectus Directive; and (2) in the case of any shares of our securities acquired by it as a financial intermediary as that term is used in Article 3(2) of the Prospectus Directive, the securities acquired by it in the offer have not been acquired on behalf of, nor have they been acquired with a view to their offer or resale to, persons in any Member State other than qualified investors, as that term is defined in the Prospectus Directive, or in circumstances in which the prior consent of the placement agent has been given to the offer or resale; or where our securities have been acquired by it on behalf of persons in any Member State other than qualified investors, the offer of those securities to it is not treated under the Prospectus Directive as having been made to such persons.

The Company, the placement agent and their respective affiliates will rely upon the truth and accuracy of the foregoing representations, acknowledgments and agreements.

This prospectus has been prepared on the basis that any offer of our securities in any Member State will be made pursuant to an exemption under the Prospectus Directive from the requirement to publish a prospectus for offers of shares. Accordingly, any person making or intending to make an offer in that Member State of our securities which are the subject of the offering contemplated in this prospectus may only do so in circumstances in which no obligation arises for the Company or the placement agent to publish a prospectus pursuant to Article 3 of the Prospectus Directive in relation to such offer. Neither the Company nor the placement agent have authorized, nor do they authorize, the making of any offer of securities in circumstances in which an obligation arises for the Company or the placement agent to publish a prospectus for such an offer.

For the purposes of this provision, the expression an "offer of our securities to the public" in relation to any of our securities in any Member State means the communication in any form and by any means of sufficient information on the terms of the offer and the securities to be offered so as to enable an investor to decide to purchase or subscribe for the securities, as the same may be varied in that Member State by any measure implementing the Prospectus Directive in that Member State, the expression "Prospectus Directive" means Directive 2003/71/EC (as amended) and includes any relevant implementing measure in each Member State. The above selling restriction is in addition to any other selling restrictions set out below.

Notice to Prospective Investors in the United Kingdom

In addition, in the United Kingdom, this document is being distributed only to, and is directed only at, and any offer subsequently made may only be directed at persons who are "qualified investors" (as defined in the Prospectus Directive) (i) who have professional experience in matters relating to investments falling within Article 19 (5) of the Financial Services and Markets Act 2000 (Financial Promotion) Order 2005, as amended (the "Order") and/or (ii) who are high net worth companies (or persons to whom it may otherwise be lawfully communicated) falling within Article 49(2)(a) to (d) of the Order (all such persons together being referred to as "relevant persons"). This document must not be acted on or relied on in the United Kingdom by persons who are not relevant persons. In the United Kingdom, any investment or investment activity to which this document relates is only available to, and will be engaged in with, relevant persons.

Notice to Prospective Investors in Switzerland

The securities may not be publicly offered in Switzerland and will not be listed on the SIX Swiss Exchange ("SIX") or on any other stock exchange or regulated trading facility in Switzerland. This document has been prepared without regard to the disclosure standards for issuance prospectuses under art. 652a or art. 1156 of the Swiss Code of Obligations or the disclosure standards for listing prospectuses under art. 27 ff. of the SIX Listing Rules or the listing rules of any other stock exchange or regulated trading facility in Switzerland. Neither this document nor any other offering or marketing material relating to our securities or the offering may be publicly distributed or otherwise made publicly available in Switzerland.

Neither this document nor any other offering or marketing material relating to the offering, the Company or our securities have been or will be filed with or approved by any Swiss regulatory authority. In particular, this document will not be filed with, and the offer of our securities will not be supervised by, the Swiss Financial Market Supervisory Authority FINMA (FINMA), and the offer of our securities has not been and will not be authorized under the Swiss Federal Act on Collective Investment Schemes ("CISA"). The investor protection afforded to acquirers of interests in collective investment schemes under the CISA does not extend to acquirers of our securities.

Notice to Prospective Investors in the Dubai International Financial Centre

This prospectus relates to an Exempt Offer in accordance with the Offered Securities Rules of the Dubai Financial Services Authority ("DFSA"). This prospectus is intended for distribution only to persons of a type specified in the Offered Securities Rules of the DFSA. It must not be delivered to, or relied on by, any other person. The DFSA has no responsibility for reviewing or verifying any documents in connection with Exempt Offers. The DFSA has not approved this prospectus nor taken steps to verify the information set forth herein and has no responsibility for the prospectus. The securities to which this prospectus relates may be illiquid and/or subject to restrictions on their resale. Prospective purchasers of the securities offered should conduct their own due diligence on the securities. If you do not understand the contents of this prospectus you should consult an authorized financial advisor.

Notice to Prospective Investors in Australia

No placement document, prospectus, product disclosure statement or other disclosure document has been lodged with the Australian Securities and Investments Commission ("ASIC"), in relation to the offering. This prospectus does not constitute a prospectus, product disclosure statement or other disclosure document under the Corporations Act 2001 (the "Corporations Act") and does not purport to include the information required for a prospectus, product disclosure statement or other disclosure document under the Corporations Act.

Any offer in Australia of our securities may only be made to persons (the "Exempt Investors") who are "sophisticated investors" (within the meaning of section 708(8) of the Corporations Act), "professional investors" (within the meaning of section 708(11) of the Corporations Act) or otherwise pursuant to one or more exemptions contained in section 708 of the Corporations Act so that it is lawful to offer the securities without disclosure to investors under Chapter 6D of the Corporations Act.

The securities applied for by Exempt Investors in Australia must not be offered for sale in Australia in the period of 12 months after the date of allotment under the offering, except in circumstances where disclosure to investors under Chapter 6D of the Corporations Act would not be required pursuant to an exemption under section 708 of the Corporations Act or otherwise or where the offer is pursuant to a disclosure document which complies with Chapter 6D of the Corporations Act. Any person acquiring our securities must observe such Australian on-sale restrictions.

This prospectus contains general information only and does not take account of the investment objectives, financial situation or particular needs of any particular person. It does not contain any securities recommendations or financial product advice. Before making an investment decision, investors need to consider whether the information in this prospectus is appropriate to their needs, objectives and circumstances, and, if necessary, seek expert advice on those matters.

Notice to Prospective Investors in Hong Kong

The securities have not been offered or sold and will not be offered or sold in Hong Kong, by means of any document, other than (a) to "professional investors" as defined in the Securities and Futures Ordinance (Cap. 571) of Hong Kong and any rules made under that Ordinance; or (b) in other circumstances which do not result in the document being a "prospectus" as defined in the Companies Ordinance (Cap. 32) of Hong Kong or which do not constitute an offer to the public within the meaning of that Ordinance. No advertisement, invitation or document relating to the securities has been or may be issued or has been or may be in the possession of any person for the purposes of issue, whether in Hong Kong or elsewhere, which is directed at, or the contents of which are likely to be accessed or read by, the public of Hong Kong (except if permitted to do so under the securities laws of Hong Kong) other than with respect to securities which are or are intended to be disposed of only to persons outside Hong Kong or only to "professional investors" as defined in the Securities and Futures Ordinance and any rules made under that Ordinance.

Notice to Prospective Investors in Japan

The securities have not been and will not be registered under the Financial Instruments and Exchange Law of Japan (Law No. 25 of 1948, as amended) and, accordingly, will not be offered or sold, directly or indirectly, in Japan, or for the benefit of any Japanese Person or to others for re-offering or resale, directly or indirectly, in Japan or to any Japanese Person, except in compliance with all applicable laws, regulations and ministerial guidelines promulgated by relevant Japanese governmental or regulatory authorities in effect at the relevant time. For the purposes of this paragraph, "Japanese Person" shall mean any person resident in Japan, including any corporation or other entity organized under the laws of Japan.

Notice to Prospective Investors in Singapore

This prospectus has not been registered as a prospectus with the Monetary Authority of Singapore. Accordingly, this prospectus and any other document or material in connection with the offer or sale, or invitation for subscription or purchase, of securities may not be circulated or distributed, nor may the securities be offered or sold, or be made the subject of an invitation for subscription or purchase, whether directly or indirectly, to persons in Singapore other than (i) to an institutional investor under Section 274 of the Securities and Futures Act, Chapter 289 of Singapore (the "SFA"), (ii) to a relevant person pursuant to Section 275(1), or any person pursuant to Section 275(1A), and in accordance with the conditions specified in Section 275, of the SFA, or (iii) otherwise pursuant to, and in accordance with the conditions of, any other applicable provision of the SFA.

Where the securities are subscribed or purchased under Section 275 of the SFA by a relevant person which is:

(a) a corporation (which is not an accredited investor (as defined in Section 4A of the SFA)) the sole business of which is to hold investments and the entire share capital of which is owned by one or more individuals, each of whom is an accredited investor; or

(b) a trust (where the trustee is not an accredited investor) whose sole purpose is to hold investments and each beneficiary of the trust is an individual who is an accredited investor,

securities (as defined in Section 239(1) of the SFA) of that corporation or the beneficiaries' rights and interest (howsoever described) in that trust shall not be transferred within six months after that corporation or that trust has acquired the securities pursuant to an offer made under Section 275 of the SFA except:

(a) to an institutional investor or to a relevant person defined in Section 275(2) of the SFA, or to any person arising from an offer referred to in Section 275(1A) or Section 276(4)(i)(B) of the SFA;

(b) where no consideration is or will be given for the transfer;

(c) where the transfer is by operation of law;

(d) as specified in Section 276(7) of the SFA; or

(e) as specified in Regulation 32 of the Securities and Futures (Offers of Investments) (Shares and Debentures) Regulations 2005 of Singapore.

Notice to Prospective Investors in Canada

The securities may be sold only to purchasers purchasing, or deemed to be purchasing, as principal that are accredited investors, as defined in National Instrument 45-106 *Prospectus Exemptions* or subsection 73.3(1) of the *Securities Act* (Ontario), and are permitted clients, as defined in National Instrument 31-103 *Registration Requirements, Exemptions and Ongoing Registrant Obligations*. Any resale of the securities must be made in accordance with an exemption from, or in a transaction not subject to, the prospectus requirements of applicable securities laws.

Securities legislation in certain provinces or territories of Canada may provide a purchaser with remedies for rescission or damages if this prospectus (including any amendment thereto) contains a misrepresentation, provided that the remedies for rescission or damages are exercised by the purchaser within the time limit prescribed by the securities legislation of the purchaser's province or territory. The purchaser should refer to any applicable provisions of the securities legislation of the purchaser's province or territory for particulars of these rights or consult with a legal advisor.

Pursuant to section 3A.3 (or, in the case of securities issued or guaranteed by the government of a non-Canadian jurisdiction, section 3A.4) of National Instrument 33-105 *Underwriting Conflicts* (**NI 33-105**), the placement agent is not required to comply with the disclosure requirements of NI 33-105 regarding underwriter conflicts of interest in connection with this offering.

LEGAL MATTERS

The validity of the securities offered by this prospectus will be passed upon for us by Faegre Drinker Biddle & Reath LLP. Pryor Cashman LLP is acting as counsel for the placement agent in connection with certain legal matters related to this offering.

EXPERTS

The financial statements of Panbela as of December 31, 2021 and 2020 and for the two years in the period ended December 31, 2021 incorporated in this prospectus by reference from the Company's Annual Report on Form 10-K have been audited by Cherry Bekaert LLP, an independent registered public accounting firm, as stated in their report, which is incorporated herein by reference. Such financial statements have been so incorporated in reliance upon the report of such firm given upon their authority as experts in accounting and auditing.

The financial statements of CPP as of December 31, 2021 and 2020 and for the two years in the period ended December 31, 2021, incorporated in this prospectus by reference from the Company's Current Report on Form 8-K have been audited by Mayer Hoffman McCann P.C., an independent public accounting firm, as stated in their report, which is incorporated herein by reference. Such financial statements have been so incorporated in reliance upon the report of such firm given upon their authority as experts in accounting and auditing.

WHERE YOU CAN FIND MORE INFORMATION

We have filed with the SEC a registration statement on Form S-1 under the Securities Act that registers the distribution of the securities offered under this prospectus. The registration statement, including the attached exhibits and schedules, contains additional relevant information about us and the securities. The rules and regulations of the SEC allow us to omit from this prospectus certain information included in the registration statement.

We are subject to the informational requirements of the Securities Exchange Act and are required to file annual, quarterly and current reports, proxy statements and other information with the SEC. Any information we file with the SEC, including the documents incorporated by reference into this prospectus, is also available on the SEC's website at www.sec.gov. We also make these documents publicly available, free of charge, on our website at www.panbela.com as soon as reasonably practicable after filing such documents with the SEC. The information contained in, or that can be accessed through, our website is not part of this prospectus.

INCORPORATION OF DOCUMENTS BY REFERENCE

We have elected to incorporate by reference certain information in this prospectus pursuant to General Instruction VII of Form S-1. We have previously filed the following documents with the SEC and are incorporating them by reference into this prospectus, except for information furnished under Item 2.02 or Item 7.01 of Form 8-K, and any exhibits relating to such information, which is neither deemed filed nor incorporated by reference herein:

- Annual Report on Form 10-K for the year ended December 31, 2021, filed with the SEC on March 24, 2022;
- Quarterly Reports on Form 10-Q for the quarters ended March 31, 2022 , June 30, 2022 , and September 30, 2022 filed with the SEC on May 12, 2022, August 15, 2022, and November 10, 2022 respectively;
- Current Reports on Form 8-K filed with the SEC on February 22, 2022, June 8, 2022, June 16, 2022, July 20, 2022, August 25, 2022, October 3, 2022, October 4, 2022 and November 30, 2022.
- The portions of our Definitive Proxy Statement on Schedule 14A that are deemed "filed" with the SEC under the Exchange Act, filed on April 29, 2022; and
- Description of our common stock contained in Exhibit 4.1 to the Annual Report on Form 10-K for the year ended December 31, 2021, filed with the SEC on March 24, 2022.

As a smaller reporting company, we also are incorporating by reference any future information filed (rather than furnished) by us with the SEC under Section 13(a), 13(c), 14 or 15(d) of the Securities Exchange Act of 1934, as amended, after the date of the initial filing of the registration statement of which this prospectus is a part and before the effective date of the registration statement and after the date of this prospectus until the termination of the offering. Any statements contained in a previously filed document incorporated by reference into this prospectus is deemed to be modified or superseded for purposes of this prospectus to the extent that a statement contained in this prospectus, or in a subsequently filed document also incorporated by reference herein, modifies or supersedes that statement

Our internet address is www.panbela.com. We make available free of charge, on or through the investor relations section of our website, annual reports on Form 10-K, quarterly reports on Form 10-Q, current reports on Form 8-K and amendments to those reports filed or furnished pursuant to Section 13(a) or 15(d) of the Exchange Act as soon as reasonably practicable after we electronically file such material with, or furnish it to, the SEC. You may access the documents incorporated by reference in this prospectus through our website at www.neurometrix.com. Except for the specific incorporated documents listed above, no information available on or through our website shall be deemed to be incorporated by reference in this prospectus or the registration statement of which it forms a part.

We hereby undertake to provide without charge to each person, including any beneficial owner, to whom a prospectus is delivered, upon written or oral request of any such person, a copy of any and all of the information that has been incorporated by reference in this prospectus, but not delivered with the prospectus. Requests for such copies should be sent to us at the following address:

Panbela Therapeutics, Inc.
712 Vista Blvd #305
Waconia, MN 55387
Attention: Investor Relations
(952) 479-1196

Up to 4,222,972 Shares of Common Stock
Warrants to purchase 6,334,458 Shares of Common Stock
Pre-Funded Warrants to purchase 4,222,972 Shares of Common Stock

Panbela Therapeutics, Inc.

PROSPECTUS

Roth Capital Partners

, 2022

PART II

INFORMATION NOT REQUIRED IN PROSPECTUS

Item 13. Other Expenses of Issuance and Distribution.

The following table sets forth the costs and expenses payable by Panbela Therapeutics, Inc. (the "Company") in connection with the offering and sale of the common stock being registered. All amounts shown are estimates, except the Securities and Exchange Commission (the "Commission") registration fee.

U.S. Securities and Exchange Commission registration fee	$	4,133
FINRA filing fee	$	3,500
Accounting fees and expenses	$	40,000
Legal fees and expenses	$	200,000
Transfer agent and registrar fees	$	20,000
Printing expenses	$	10,000
Miscellaneous	$	16,419
Total	$	293,500

Item 14. Indemnification of Directors and Officers.

Section 145 of the Delaware General Corporation Law provides that a corporation may indemnify any person made a party to an action by reason of the fact that he or she was a director, executive officer, employee or agent of the corporation or is or was serving at the request of the corporation against expenses (including attorneys' fees), judgments, fines and amounts paid in settlement actually and reasonably incurred by him or her in connection with such action if he or she acted in good faith and in a manner he or she reasonably believed to be in, or not opposed to, the best interests of the corporation and, with respect to any criminal action or proceeding, had no reasonable cause to believe his or her conduct was unlawful, except that, in the case of an action by or in right of the corporation, no indemnification may generally be made in respect of any claim as to which such person is adjudged to be liable to the corporation.

The Company's certificate of incorporation and amended and restated bylaws limit the liability of its directors to the fullest extent permitted by Delaware law. Delaware law provides that directors of a corporation will not be personally liable for monetary damages for breach of their fiduciary duties as directors, except for liability for any:

- breach of their duty of loyalty to the Company or its stockholders;
- act or omission not in good faith or that involves intentional misconduct or a knowing violation of law;
- unlawful payment of dividends or redemption of shares as provided in Section 174 of the Delaware General Corporation Law; or
- transaction from which the directors derived an improper personal benefit.

These limitations of liability do not apply to liabilities arising under federal securities laws and do not affect the availability of equitable remedies such as injunctive relief or rescission. The Company's amended and restated bylaws provide that it will indemnify its directors and executive officers, and may indemnify other officers, employees and other agents, to the fullest extent permitted by law.

As permitted by the Delaware General Corporation Law, the Company has entered into indemnification agreements with each of the Company's directors and executive officers that require the Company to indemnify such persons against expenses, judgments, penalties, fines, settlements and other amounts actually and reasonably incurred, including expenses of a derivative action, in connection with an actual or threatened proceeding if any of the Company's directors or executive officers may be made a party because he or she is or was one of the Company's directors. The Company will be obligated to pay such amounts only if the director acted in good faith and in a manner that he or she reasonably believed to be in or not opposed to the Company's best interests. With respect to any criminal proceeding, the Company will be obligated to pay such amounts only if the director had no reasonable cause to believe his or her conduct was unlawful. The indemnification agreements also set forth certain procedures that will apply in the event of a claim for indemnification.

Section 145(g) of the Delaware General Corporation Law permits a corporation to purchase and maintain insurance on behalf of any person who is or was a director, officer, employee, or agent of the corporation arising out of his or her actions in connection with their services to the Company, regardless of whether its amended and restated bylaws permit indemnification. The Company has purchased and intends to maintain insurance on behalf of any person who is or was a director or officer against any loss arising from any claim asserted against him or her and incurred by him or her in any such capacity, subject to certain exclusions.

Item 15. Recent Sales of Unregistered Securities.

On August 23, August 30, September 20 and October 10, 2019, the Company entered into securities purchase agreements and sold an aggregate of (i) 909,209 shares of its common stock (the "Shares") and (ii) warrants to purchase up to 909,209 additional shares of common stock for total gross proceeds of approximately $3.2 million. The warrants are exercisable for a period of five years from the date of issuance at an initial exercise price of $4.00 per share.

On February 21, 2020, the Company issued to the placement agent in the public offering a five-year warrant to purchase 75,000 shares at an exercise price of $6.49 per share.

In closings on May 22, June 5, June 15, and June 22, 2020, the Company sold an aggregate of 437,000 shares of its common stock and warrants to purchase up to 437,000 additional shares of common stock for aggregate gross proceeds of approximately $1.7 million, of which approximately $90,000 was received from officers and directors of the Company. The warrants are exercisable for a period of five years from the date of issuance at an initial exercise price of $6.00 per share.

On September 1, 2020, the Company issued 35,665 shares of common stock as a result of the exercise of outstanding warrants that were set to expire as a result of the public offering. All of the warrants were exercised at $1.875 per share. Of the shares issued, 27,500 were issued for approximately $52,000 cash. One warrant to purchase 15,000 shares of common stock was exercised on a net, cashless basis, resulting in the issuance of the remaining 8,165 shares.

During the three months ended March 31, 2021, the Company issued 193,607 shares of common stock as a result of exercises of outstanding warrants. Of the shares of common stock issued, 188,607 shares were issued pursuant to net, cashless, exercises of warrants to purchase 531,140 shares and the remaining 5,000 shares were issued for $25,000 cash.

The net cash proceeds for each of the foregoing sales of securities were used for the continued clinical development of our initial product candidate ivospemin (SBP-101) and for working capital and other general corporate purposes.

On June 15, 2022, pursuant to the Merger Agreement, Panbela sold and issued the following securities to the holders of CPP securities: (a) 6,587,576 shares of Panbela Common Stock, (b) 731,957 shares of Panbela Common Stock that remained subject to the Holdback Escrow (as defined in the Merger Agreement), (iv) replacement options to purchase up to 1,596,754 shares of Panbela Common Stock at a weighted average purchase price of $0.35 per share, and (v) replacement warrants to purchase up to 338,060 shares of Panbela Common Stock at a weighted average purchase price of $4.145 per share.

Unless otherwise indicated, for all of the foregoing transactions, we relied on exemptions from registration set forth in Section 4(a)(2) of the Securities Act, without the use of any general solicitations or advertising to market or otherwise offer the securities for sale and all participants were "accredited investors," as defined in Rule 501 of Regulation D as promulgated by the SEC under the Securities Act.

Item 16. Exhibits and Financial Statement Schedules.

(a) Exhibits

Exhibit No.	Description
2.1	Agreement and Plan of Merger, dated February 21, 2022, by and among Panbela Therapeutics, Inc., Canary Merger Holdings, Inc., Canary Merger Subsidiary I, Inc., Canary Merger Subsidiary II, Inc., CPP Pharmaceuticals, Inc., and Fortis Advisors LLC, as Stockholder Representative (incorporated by reference to Exhibit 2.1 to current report on Form 8-K filed February 22, 2022)
3.1	Amended and Restated Certificate of Incorporation (incorporated by reference to Exhibit 3.1 to current report on Form 8-K filed June 16, 2022)
3.2	Bylaws (incorporated by reference to Exhibit 3.1 to current report on Form 8-K filed June 16, 2022)
4.1	Description of Securities (incorporated by reference to Exhibit 4.1 to annual report on Form 10-K for fiscal year ended December 31, 2020)

Exhibit No.	Description
4.2	Form of Common Stock Warrant issued December 2018 and January 2019 (incorporated by reference to Exhibit 10.3 to current report on Form 8-K filed December 28, 2018)
4.3	Common Stock Warrant issued April 2, 2019 (incorporated by reference to Exhibit 10.3 to quarterly report on Form 10-Q for quarter ended March 31, 2019)
4.4	Form of Common Stock Warrant issued August through October 2019 (incorporated by reference to Exhibit 10.2 to current report on Form 8-K filed August 29, 2019)
4.5	Form of Warrants issued May 22, June 5, June 15, and June 22, 2020 (incorporated by reference to Exhibit 10.2 to current report on Form 8-K filed June 11, 2020)
4.6	Warrant Agency Agreement with VStock Transfer, LLC dated September 1, 2020 (incorporated by reference to Exhibit 4.1 to current report on Form 8-K filed September 1, 2020)
4.7	Form of Common Stock Purchase Warrant (included in Exhibit 4.8)
4.8	Warrant Agency Agreement with VStock Transfer, LLC dated as of October 4, 2022 (incorporated by reference to Exhibit 4.1 to current report on Form 8-K filed on October 4, 2022)
4.9	Form of Common Stock Purchase Warrant (incorporated by reference to Exhibit 4.3 to current report on Form 8-K filed October 4, 2022)
4.10	Form of Pre-Funded Warrant (incorporated by reference to Exhibit 4.2 to current report on Form 8-K filed on October 4, 2022)
4.11++	Form of Warrant Agency Agreement
4.12++	Form of Common Stock Purchase Warrant
4.13++	Form of Pre-Funded Warrant
5.1++	Opinion of Faegre Drinker Biddle & Reath LLP
10.1*	2011 Stock Option Plan, as amended through January 1, 2015 (incorporated by reference to Exhibit 10.1 to current report on Form 8-K filed September 11, 2015)
10.2*	Form of Incentive Stock Option Agreement for awards under 2011 Plan (incorporated by reference to Exhibit 10.2 to current report on Form 8-K filed September 11, 2015)
10.3*	Form of Non-Qualified Stock Option Agreement for awards under 2011 Plan (incorporated by reference to Exhibit 10.3 to current report on Form 8-K filed September 11, 2015)
10.4*	Sun BioPharma, Inc. 2016 Omnibus Incentive Plan as amended and restated through April 9, 2020 (incorporated by reference to Exhibit 99.1 to current report on Form 8-K filed May 26, 2020)
10.5*	Form of Incentive Stock Option Agreement for awards under 2016 Plan (incorporated by reference to Exhibit 10.4 to quarterly report on Form 10-Q for quarter ended June 30, 2016)
10.6*	Form of Non-Qualified Stock Option Agreement for awards under 2016 Omnibus Incentive Plan (incorporated by reference to Exhibit 10.5 to quarterly report on Form 10-Q for quarter ended June 30, 2016)
10.7*	Form of Performance-Based Stock Option Agreement for awards under 2016 Omnibus Incentive Plan (incorporated by reference to Exhibit 10.7 to annual report on Form 10-K for fiscal year ended December 31, 2016)
10.8*	Form of Indemnification Agreement with non-employee directors (incorporated by reference to Exhibit 10.4 to current report on Form 8-K filed September 11, 2015)
10.9**	Standard Exclusive License Agreement with University of Florida Research Foundation, Inc., dated December 22, 2011 (incorporated by reference to Exhibit 10.5 to current report on Form 8-K filed September 11, 2015)
10.10	Form of First Amendment to License Agreement with University of Florida Research Foundation, Inc. dated December 12, 2016 (incorporated by reference to Exhibit 10.10 to annual report on Form 10-K for fiscal year ended December 31, 2019)
10.11	Second Amendment to License Agreement with University of Florida Research Foundation, Inc., dated October 3, 2019 (incorporated by reference to Exhibit 10.1 to current report on Form 8-K filed October 9, 2019)
10.12*	Employment Agreement with Michael T. Cullen, dated December 2, 2015 (incorporated by reference to Exhibit 10.1 to current report on Form 8-K filed December 4, 2015)
10.13*	First Amendment to Employment Agreement with Michael T. Cullen, dated September 12, 2016 (incorporated by reference to Exhibit 10.17 to registration statement on Form S-1filed September 16, 2016)
10.14*	Second Amendment to Employment Agreement with Michael T. Cullen, dated October 1, 2017 (incorporated by reference to Exhibit 10.1 to current report on Form 8-K filed October 13, 2017)
10.15*	Waiver and Third Amendment to Employment Agreement with Michael T. Cullen, effective as of February 27, 2018 (incorporated by reference to Exhibit 10.1 to current report on Form 8-K filed March 5, 2018)
10.16*	Employment Agreement with Susan Horvath, dated April 17, 2018 (incorporated by reference to Exhibit 10.4 to quarterly report on Form 10-Q for quarter ended March 31, 2018)
10.17*	Employment agreement with Jennifer K Simpson dated July 15, 2020 (incorporated by reference to Exhibit 10.1 to current report on Form 8-K filed July 16, 2020)

Exhibit No.	Description
10.18	Seed Capital Accelerator Loan Agreement and Seed Capital Loan Note dated October 26, 2012 (incorporated by reference to Exhibit 10.22 to annual report on Form 10-K for fiscal year ended December 31, 2019)
10.19	First Amendment to Seed Capital Accelerator Loan Agreement and Seed Capital Loan Note dated October 13, 2017 (incorporated by reference to Exhibit 10.1 to quarterly report on Form 10-Q for quarter ended March 31, 2019)
10.20	Second Amendment to Seed Capital Accelerator Loan Agreement and Seed Capital Loan Note dated April 5, 2019 (incorporated by reference to Exhibit 10.2 to quarterly report on Form 10-Q for quarter ended March 31, 2019
10.21	Third Amendment to Seed Capital Accelerator Loan Agreement and Seed Capital Loan Noted dated December 31,2019 (incorporated by reference to Exhibit 10.25 to annual report on Form 10-K for fiscal year ended December 31, 2019)
10.22	Form of Securities Purchase Agreement, dated December 21 and 31, 2018, January 14, 25, and 31, 2019 (incorporated by reference to Exhibit 10.1 to current report on Form 8-K filed December 28, 2018)
10.23	Healthcare Professional Services Agreement with Suzanne Gagnon dated July 19, 2021 (incorporated by reference to Exhibit 10.27 to annual report on Form 10-K for fiscal year ended December 31, 2021)
10.24*	CPP Pharmaceuticals, Inc. 2010 Equity Incentive Plan, as amended (incorporated by reference to Exhibit 10.1 to current report on Form 8-K filed June 16, 2022)
10.25*	Form of Stock Option Assumption Notice (incorporated by reference to Exhibit 10.2 to current report on Form 8-K filed June 16, 2022)
10.26	Form of Replacement Warrant (incorporated by reference to Exhibit 10.3 to current report on Form 8-K filed June 16, 2022)
10.27	Convertible Promissory Note in favor of Sucampo GmbH (f/k/a Sucampo AG), dated as of September 6, 2017, as amended through April 7, 2022 (incorporated by reference to Exhibit 10.4 to current report on Form 8-K filed June 16, 2022)
10.28	Guaranty in favor of Sucampo GmbH (f/k/a Sucampo AG), dated June 15, 2022 (incorporated by reference to Exhibit 10.5 to current report on Form 8-K filed June 16, 2022)
10.29	Separation and Release Agreement with Jeffrey E. Jacobs, dated June 15, 2022 (incorporated by reference to Exhibit 10.6 to current report on Form 8-K filed Jun 16, 2022)
10.30	License Agreement, dated June 16, 2021 between CPP Pharmaceuticals, Inc. and One-Two Therapeutic Assets Limited
10.31	Form of Securities Purchase Agreement (incorporated by reference to Exhibit 10.2 to current report on Form 8-K filed on October 4, 2022)
10.32	Placement Agency Agreement with Roth Capital Partners, LLC dated as of September 29, 2022 (incorporated by reference to Exhibit 10.1 to current report on Form 8-K filed on October 4, 2022)
10.33++	Form of Securities Purchase Agreement
10.34++	Form of Placement Agency Agreement
21.1	List of Subsidiaries (incorporated by reference to Exhibit 21.1 to Form POS AM filed June 22, 2022)
23.1+	Consent of Independent Registered Public Accounting Firm
23.2+	Consent of Independent Public Accounting Firm
23.3++	Consent of Faegre Drinker Biddle & Reath LLP (included in Exhibit 5.1)
24.1+	Powers of Attorney (see signature page)
107	Filing Fee Table

\+ Filed herewith
++ To be filed by amendment.
* Management compensatory plan or arrangement required to be filed as an exhibit to this prospectus.
** Portions of exhibit omitted pursuant to order granting confidential treatment issued by the Securities and Exchange Commission.

(b) Financial Statement Schedules.

All schedules are omitted as the required information is inapplicable or the information is presented in the financial statements or related notes.

Schedule II. Valuation and Qualifying Accounts

All other schedules are omitted as the required information is inapplicable or the information is presented in the financial statements or related notes.

Item 17. Undertakings.

The registrant hereby undertakes:

(1) To file, during any period in which offers or sales are being made, a post-effective amendment to this registration statement:

(i) To include any prospectus required by Section 10(a)(3) of the Securities Act;

(ii) To reflect in the prospectus any facts or events arising after the effective date of the registration statement (or the most recent post-effective amendment thereof) which, individually or in the aggregate, represent a fundamental change in the information set forth in the registration statement. Notwithstanding the foregoing, any increase or decrease in volume of securities offered (if the total dollar value of securities offered would not exceed that which was registered) and any deviation from the low or high end of the estimated maximum offering range may be reflected in the form of prospectus filed with the Commission pursuant to Rule 424(b) if, in the aggregate, the changes in volume and price represent no more than a 20% change in the maximum aggregate offering price set forth in the "Calculation of Registration Fee" table in the effective registration statement; and

(iii) To include any material information with respect to the plan of distribution not previously disclosed in the registration statement or any material change to such information in this registration statement;

provided, however, that paragraphs (a)(1)(i), (ii) and (iii) do not apply if the information required to be included in a post-effective amendment by those paragraphs is contained in reports filed with or furnished to the Commission by the Registrant pursuant to Section 13 or Section 15(d) of the Exchange Act, that are incorporated by reference in the registration statement.

(2) That, for the purpose of determining any liability under the Securities Act, each such post-effective amendment shall be deemed to be a new registration statement relating to the securities offered herein, and the offering of such securities at that time shall be deemed to be the initial bona fide offering thereof.

(3) To remove from registration by means of a post-effective amendment any of the securities being registered which remain unsold at the termination of the offering.

(4) That, for the purpose of determining liability under the Securities Act to any purchaser: each prospectus filed pursuant to Rule 424(b) as part of a registration statement relating to an offering, other than registration statements relying on Rule 430B or other than prospectuses filed in reliance on Rule 430A, shall be deemed to be part of and included in the registration statement as of the date it is first used after effectiveness; *provided, however*, that no statement made in a registration statement or prospectus that is part of the registration statement or made in a document incorporated or deemed incorporated by reference into the registration statement or prospectus that is part of the registration statement will, as to a purchaser with a time of contract of sale prior to such first use, supersede or modify any statement that was made in the registration statement or prospectus that was part of the registration statement or made in any such document immediately prior to such date of first use.

(5) That, for the purpose of determining liability under the Securities Act to any purchaser the information omitted from the form of prospectus filed as part of this Registration Statement in reliance upon Rule 430A and contained in a form of prospectus filed by the Registrant pursuant to Rule 424(b)(1) or (4) or 497(h) under the Securities Act shall be deemed to be part of this Registration Statement as of the time it was declared effective; and for the purpose of determining any liability under the Securities Act, each post-effective amendment that contains a form of prospectus shall be deemed to be a new registration statement relating to the securities offered therein, and the offering of such securities at that time shall be deemed to be the initial *bona fide* offering thereof.

(6) Insofar as indemnification for liabilities arising under the Securities Act may be permitted to directors, officers and controlling persons of the registrant pursuant to the foregoing provisions, or otherwise, the registrant has been advised that, in the opinion of the Securities and Exchange Commission, such indemnification is against public policy as expressed in the Securities Act and is, therefore, unenforceable. In the event that a claim for indemnification against such liabilities (other than the payment by the registrant of expenses incurred or paid by a director, officer or controlling person of the registrant in the successful defense of any action, suit or proceeding) is asserted by such director, officer or controlling person in connection with the securities being registered, the registrant will, unless in the opinion of its counsel the matter has been settled by controlling precedent, submit to a court of appropriate jurisdiction the question whether such indemnification by it is against public policy as expressed in the Securities Act and will be governed by the final adjudication of such issue.

SIGNATURES

Pursuant to the requirements of the Securities Act of 1933, as amended, the registrant has duly caused this registration statement to be signed on its behalf by the undersigned, thereunto duly authorized, in the City of Minneapolis, State of Minnesota on December 16, 2022.

PANBELA THERAPEUTICS, INC.

By: /s/ Jennifer K. Simpson
Jennifer K. Simpson
President and Chief Executive Officer

Power of Attorney

Each person whose signature appears below hereby constitutes and appoints Jennifer K. Simpson and Susan Horvath, and each of them acting individually, as his true and lawful attorneys-in-fact and agents, with full power of each to act alone, with full powers of substitution and resubstitution, for him and in his name, place and stead, in any and all capacities, to sign the Registration Statement filed herewith and any and all amendments to said Registration Statement (including post-effective amendments and any related registration statements thereto filed pursuant to Rule 461 and otherwise), and file the same, with all exhibits thereto, and other documents in connection therewith, with the Securities and Exchange Commission, granting unto said attorneys-in-fact and agents, with full power of each to act alone, full power and authority to do and perform each and every act and thing requisite and necessary to be done in connection therewith, as fully for all intents and purposes as he might or could do in person, hereby ratifying and confirming all that said attorneys-in-fact and agents, or his or their substitutes, may lawfully do or cause to be done by virtue hereof.

Pursuant to the requirements of the Securities Act of 1933, this registration statement has been signed by the following persons in the capacities and on the dates indicated.

Signature	Title	Date
/s/ Jennifer K. Simpson Jennifer K. Simpson	*President and Chief Executive Officer (Principal Executive Officer), and Director*	December 16, 2022
/s/ Susan Horvath Susan Horvath	*Vice President of Finance, Chief Financial Officer, Treasurer and Secretary (Principal Financial and Accounting Officer)*	December 16, 2022
/s/ Michael T. Cullen Michael T. Cullen	*Chair of the Board and Director*	December 16, 2022
/s/ Daniel J. Donovan Daniel J. Donovan	*Director*	December 16, 2022
/s/ Arthur J. Fratamico Arthur J. Fratamico	*Director*	December 16, 2022
/s/ Jeffrey E. Jacob Jeffrey E. Jacob	*Director*	December 16, 2022
/s/ Jeffrey S. Mathiesen Jeffrey S. Mathiesen	*Director*	December 16, 2022
/s/ D. Robert Schemel D. Robert Schemel	*Director*	December 16, 2022

Exhibit 23.1

CONSENT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

We hereby consent to the incorporation in this Registration Statement on Form S-1 of our report dated March 24, 2022, relating to the consolidated financial statements of Panbela Therapeutics, Inc. and Subsidiary (the "Company") appearing in the Annual Report on Form 10-K of the Company for the years ended December 31, 2021 and 2020, and to the reference to us under the header "Experts" in this Registration Statement.

/s/ Cherry Bekaert LLP

Tampa, Florida
December 16, 2022

Exhibit 23.2

CONSENT OF INDEPENDENT PUBLIC ACCOUNTING FIRM

We consent to the incorporation by reference in this Registration Statement on Form S-1 and related prospectus of our report dated March 22, 2022, with respect to the consolidated financial statements of CPP Pharmaceuticals, Inc. (the "Company") as of December 31, 2021 and 2020 and for the two years then ended (which report includes an explanatory paragraph regarding the existence of substantial doubt about the Company's ability to continue as a going concern), and to the reference to us under the heading "Experts" in the prospectus which is part of this Registration Statement.

/s/ Mayer Hoffman McCann P.C.

San Diego, CA
December 16, 2022

Exhibit 107

Calculation of Filing Fee Tables

Form S-1
(Form Type)

Panbela Therapeutics, Inc.
(Exact Name of Registrant as Specified in its Charter)

Table 1: Newly Registered and Carry Forward Securities

	Security Type	Security Class Title	Fee Calculation Rule	Amount Registered	Proposed Maximum Offering Price Per Unit	Maximum Aggregate Offering Price(1)	Fee Rate	Amount of Registration Fee
Fees to be Paid	Equity	Common stock, $0.001 par value per share(2)	Rule 457(o)			$15,000,000(3)	0.00011020	$1,653
	Equity	Common warrants(4)	Other				–	
	Equity	Common stock, $0.001 par value per share, underlying common warrants	Rule 457(o)			$22,500,000	0.00011020	$2,480
	Equity	Pre-funded warrants(4)	Other				–	
	Equity	Common stock, $0.001 par value per share, underlying pre-funded warrants	Rule 457(o)				–	
	Total Offering Amounts					$37,500,000		$4,133
	Total Fees Previously Paid							–
	Total Fee Offsets							–
	Net Fee Due							$4,133

(1) Estimated solely for the purpose of calculating the registration fee pursuant to Rule 457(o) of the Securities Act of 1933, as amended (the "Securities Act"). Includes offering price of shares that the underwriters have the option to purchase to cover over-allotments, if any.
(2) Pursuant to Rule 416 under the Securities Act, the shares of common stock registered hereby also include an indeterminate number of additional shares of common stock as may from time to time become issuable by reason of stock split, stock dividends, recapitalizations, or other similar transactions.
(3) The proposed maximum aggregate offering price of the common stock will be reduced on a dollar-for-dollar basis based on the offering price of any pre-funded warrants issued in the offering, and the proposed maximum aggregate offering price of the pre-funded warrants to be issued in the offering will be reduced on a dollar-for-dollar basis based on the offering price of any common stock issued in the offering. Accordingly, the proposed maximum aggregate offering price of the common stock, common warrants and pre-funded warrants (including the common stock issuable upon exercise of the pre-funded warrants), if any, is $15,000,000.
(4) No fee pursuant to Rule 457(g) of the Securities Act.