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

Form 10-K

(Mark One)

☑ **ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**
For the fiscal year ended December 31, 2022

or

☐ **TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**
For the transition period from to

Commission file number: 001-33221

HERON THERAPEUTICS, INC.

(Exact name of registrant as specified in its charter)

DELAWARE	**94-2875566**
(State or other jurisdiction of incorporation or organization)	*(I.R.S. Employer Identification No.)*
4242 CAMPUS POINT COURT, SUITE 200 **SAN DIEGO, CA** *(Address of principal executive offices)*	**92121** *(Zip Code)*

Registrant's telephone number, including area code:
(858) 251-4400

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	Trading Symbol(s)	Name of each exchange on which registered
Common Stock, par value $0.01 per share	HRTX	The Nasdaq Capital Market

Securities registered pursuant to Section 12(g) of the Act: None

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. Yes ☐ No ☑

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Act. Yes ☐ No ☑

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes ☑ No ☐

Indicate by check mark whether the registrant has submitted electronically every Interactive Data File required to be submitted pursuant to Rule 405 of Regulation S-T (§ 232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit such files). Yes ☑ No ☐

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 pursuant to Section 13(a) of the Exchange Act. ☐

Indicate by check mark whether the registrant has filed a report on and attestation to its management's assessment of the effectiveness of its internal control over financial reporting under Section 404(b) of the Sarbanes-Oxley Act (15 U.S.C. 7262(b)) by the registered public accounting firm that prepared or issued its audit report. ☐

If securities are registered pursuant to Section 12(b) of the Act, indicate by check mark whether the financial statements of the registrant included in the filing reflect the correction of an error to previously issued financial statements. ☐

Indicate by check mark whether any of those error corrections are restatements that required a recovery analysis of incentive-based compensation received by any of the registrant's executive officers during the relevant recovery period pursuant to §240.10D-1(b). ☐

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Exchange Act). Yes ☐ No ☑

The aggregate market value of voting and non-voting common stock held by non-affiliates of the registrant as of June 30, 2022 totaled $285.4 million based on the closing price of $2.79 as reported by The Nasdaq Capital Market. As of March 14, 2023, there were 119,259,315 shares of the Company's common stock ($0.01 par value) outstanding.

Documents Incorporated by Reference

Portions of the registrant's Definitive Proxy Statement related to its 2023 Annual Meeting of Stockholders to be held on or about May 18, 2023 are incorporated by reference into Part III of this Annual Report on Form 10-K. Such Definitive Proxy Statement will be filed with the U.S. Securities and Exchange Commission within 120 days after the end of the fiscal year to which this report relates. Except as expressly incorporated by reference, the registrant's Definitive Proxy Statement shall not be deemed to be part of this report.

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FORWARD-LOOKING STATEMENTS

This Annual Report on Form 10-K contains forward-looking statements within the meaning of the federal securities laws. We make such forward-looking statements pursuant to the safe harbor provisions of the Private Securities Litigation Reform Act of 1995 and other federal securities laws. In some cases, you can identify forward-looking statements by the use of the words "believe," "expect," "anticipate," "intend," "estimate," "project," "will," "would," "could," "should," "may," "might," "plan," "assume" and other expressions that predict or indicate future events and trends and which do not relate to historical matters. All statements other than statements of historical facts contained in this Annual Report on Form 10-K, including statements regarding our future results of operations and financial position, commercialization strategy, products and product candidates, research pipeline, ongoing and planned preclinical studies and clinical trials, regulatory submissions and approvals, addressable patient population, research and development expenses, timing and likelihood of success, as well as plans and objectives of management for future operations, are forward-looking statements. You should not rely on forward-looking statements because they involve known and unknown risks, uncertainties and other factors, some of which are beyond our control. These risks, uncertainties and other factors may cause our actual results, performance or achievements to be materially different from our anticipated future results, performance or achievements expressed or implied by the forward-looking statements.

Factors that might cause these differences include the following:

- our ability to successfully commercialize, market and achieve market acceptance of ZYNRELEF® (bupivacaine and meloxicam) extended-release solution ("ZYNRELEF") in the United States ("U.S."), the European Union ("EU"), the other countries in the European Economic Area ("EEA"), the United Kingdom, Canada and any other countries in which we receive applicable regulatory approvals, and of CINVANTI® (aprepitant) injectable emulsion ("CINVANTI"), SUSTOL® (granisetron) extended-release injection ("SUSTOL") and APONVIE™ (aprepitant) injectable emulsion ("APONVIE") in the U.S. (collectively, our "Products"), and HTX-034, if approved by applicable regulatory authorities, and our positioning relative to products that now or in the future compete with our Products or product candidates;

- the timing of the U.S. Food and Drug Administration's ("FDA") review process, whether and to what degree the FDA approves our currently pending, and any future, supplemental New Drug Application ("sNDA") for ZYNRELEF to further expand the U.S. label, and our ability to capture the potential additional market opportunity for any expanded U.S. label;

- our ability to establish satisfactory pricing and obtain adequate reimbursement from government and third-party payors of our Products and our product candidates that receive regulatory approvals;

- whether study results of our Products and product candidates are indicative of the results in future studies;

- the results of the commercial launch of APONVIE in the U.S.;

- the timing and results of the commercial launch of ZYNRELEF in Europe and Canada;

- the potential regulatory approval for and commercial launch of our product candidates, if approved;

- the potential market opportunities for our Products and our product candidates, if approved;

- our competitors' activities, including decisions as to the timing of competing product launches, generic entrants, pricing and discounting;

- whether safety results of our preclinical studies, safety and efficacy results of our clinical studies and other required tests for expansion of the indications for our Products and approval of our product candidates provide data to warrant progression of clinical trials, potential regulatory approval or further development of any of our Products or product candidates;

- our ability to develop, acquire and advance product candidates into, and successfully complete, clinical studies, and our ability to submit for and obtain regulatory approval for product candidates in our anticipated timing, or at all;

- our ability to meet the postmarketing study requirements within the FDA's mandated timelines and to obtain favorable results and comply with standard postmarketing requirements, including U.S. federal advertising and promotion laws, federal and state anti-fraud and abuse laws, healthcare information privacy and security laws, safety information, safety surveillance and disclosure of payments or other transfers of value to healthcare professionals and entities for Products or any of our product candidates;

- our ability to successfully develop and achieve regulatory approval for HTX-034 and our other future product candidates utilizing our proprietary Biochronomer® drug delivery technology ("Biochronomer Technology");

- our ability to establish key collaborations and vendor relationships for our Products and our product candidates;

- our ability to successfully develop and commercialize any technology that we may in-license or products we may acquire;

- unanticipated delays due to manufacturing difficulties, supply constraints or changes in the regulatory environment;

- our ability to successfully operate in non-U.S. jurisdictions in which we may choose to do business, including compliance with applicable regulatory requirements and laws;

- uncertainties associated with obtaining and enforcing patents and trade secrets to protect our Products, our product candidates, our Biochronomer Technology and our other technology, and our ability to successfully defend ourselves against unforeseen third-party infringement or invalidity claims;

- the extent of the evolving Coronavirus Disease 2019 ("COVID-19") pandemic on our business, including any COVID-19 mutations or variants and any other diseases related to or resulting from COVID-19;

- our estimates regarding our capital requirements;

- the impact of our restructuring activities, including the reduced headcount and external spend; and

- our ability to obtain additional financing and raise capital as necessary to fund operations or pursue business opportunities.

Any forward-looking statements in this Annual Report on Form 10-K reflect our current views with respect to future events or to our future financial performance and involve known and unknown risks, uncertainties and other factors that may cause our actual results, performance or achievements to be materially different from any future results, performance or achievements expressed or implied by these forward-looking statements. Factors that may cause actual results to differ materially from current expectations include, among other things, those listed under the section entitled "Risk Factors" in this Annual Report on Form 10-K. You should carefully review all of these factors. Given these uncertainties, you should not place undue reliance on these forward-looking statements. These forward-looking statements were based on information, plans and estimates as of the date of this Annual Report on Form 10-K, and except as required by law, we assume no obligation to update any forward-looking statements to reflect changes in underlying assumptions or factors, new information, future events or other changes. These risk factors may be updated by our future filings under the Securities Exchange Act of 1934. You should carefully review all information therein.

PART I

In this Annual Report on Form 10-K, all references to "Heron," the "Company," "we," "us," "our" and similar terms refer to Heron Therapeutics, Inc. and its wholly-owned subsidiary, Heron Therapeutics B.V. Heron Therapeutics®, the Heron logo, ZYNRELEF, APONVIE, CINVANTI, SUSTOL and Biochronomer are our trademarks. All other trademarks appearing or incorporated by reference into this Annual Report on Form 10-K are the property of their respective owners.

ITEM 1. BUSINESS.

Overview

We are a commercial-stage biotechnology company focused on improving the lives of patients by developing and commercializing therapeutic innovations that improve medical care. Our advanced science, patented technologies, and innovative approach to drug discovery and development have allowed us to create and commercialize a portfolio of products that aim to advance the standard of care for acute care and oncology patients.

Acute Care Product Portfolio

ZYNRELEF

ZYNRELEF was initially approved by the FDA in May 2021, and we commenced commercial sales in the U.S. in July 2021. In December 2021, the FDA approved our sNDA for ZYNRELEF, which significantly expanded the indication statement. ZYNRELEF is currently indicated for use in adults for soft tissue or periarticular instillation to produce postsurgical analgesia for up to 72 hours after foot and ankle, small-to-medium open abdominal, and lower extremity total joint arthroplasty surgical procedures.

ZYNRELEF is a dual-acting local anesthetic that delivers a fixed-dose combination of the local anesthetic bupivacaine and a low dose of the nonsteroidal anti-inflammatory drug meloxicam. ZYNRELEF is the first and only modified-release local anesthetic to be classified by the FDA as an extended-release product because ZYNRELEF demonstrated in Phase 3 studies significantly reduced pain and significantly increased proportion of patients requiring no opioids through the first 72 hours following surgery compared to bupivacaine solution, the current standard-of-care local anesthetic for postoperative pain control.

In December 2022, we submitted an sNDA to the FDA requesting expansion of the indication statement for ZYNRELEF to broadly cover soft tissue and orthopedic surgical procedures. This sNDA is based on safety and pharmacokinetic data from clinical trials in total shoulder arthroplasty, spinal surgery, abdominoplasty, and C-section showing comparable results to the previously completed pivotal safety and efficacy trials of ZYNRELEF. The FDA accepted the sNDA for filing and set a Prescription Drug User Fee Act goal date of October 23, 2023.

In the fourth quarter of 2022, we validated large-scale manufacturing of our proprietary polymer and ZYNRELEF, which will allow for the manufacturing of millions of doses of ZYNRELEF annually at a significantly reduced cost of product sales.

In March 2022, CMS approved a 3-year transitional pass-through status of ZYNRELEF, which became effective on April 1, 2022, for separate reimbursement outside of the surgical bundle payment in the Hospital Outpatient Department (HOPD) setting of care. In addition, in December 2022, H.R. 2617, the omnibus spending bill was approved by Congress that includes a provision requiring CMS to pay for certain non-opioids outside the existing bundled payment for surgeries for the period January 1, 2025 through December 31, 2027.

ZYNRELEF was granted a marketing authorization by the European Commission ("EC") in September 2020. As of January 1, 2021, ZYNRELEF is approved in 31 European countries including the countries of the EU and EEA and the United Kingdom. ZYNRELEF is indicated in Europe for the treatment of somatic postoperative pain from small- to medium-sized surgical wounds in adults.

Health Canada issued a Notice of Compliance to commercialize ZYNRELEF in March 2022. ZYNRELEF is indicated in Canada for instillation into the surgical wound for postoperative analgesia after bunionectomy, open inguinal herniorrhaphy, and total knee arthroplasty surgical procedures. Based on prior agreements with the FDA, Heron already has clinical studies underway, which we plan to submit to Health Canada to expand the indication statement.

As we build large-scale manufacturing capacity to meet the anticipated commercial demand in the U.S. and the rest of the world, we are developing a coordinated global marketing strategy.

APONVIE (HTX-019)

APONVIE was approved by the FDA in September 2022 and became commercially available in the U.S. in March 2023. APONVIE is indicated for the prevention of postoperative nausea and vomiting ("PONV") in adults. CMS granted pass-through payment status for APONVIE, effective April 1, 2023.

APONVIE is the first and only intravenous (IV) formulation of a substance NK_1 receptor antagonist indicated for PONV. Delivered via single 30-second IV injection, APONVIE has demonstrated rapid achievement of therapeutic drug levels ideally suited for the surgical setting.

HTX-034

HTX-034, our next-generation product candidate for postoperative pain management, is an investigational non-opioid, fixed-dose combination, extended-release solution of the local anesthetic bupivacaine, the nonsteroidal anti-inflammatory drug meloxicam and aprepitant that further potentiates the activity of bupivacaine. HTX-034 is formulated in the same proprietary polymer as ZYNRELEF. By combining two different mechanisms that each enhance the activity of the local anesthetic bupivacaine, HTX-034 is designed to provide superior and prolonged analgesia. Local administration of HTX-034 in a validated preclinical postoperative pain model resulted in sustained analgesia for 7 days.

In May 2020, we initiated a Phase 1b/2 clinical study in patients undergoing bunionectomy of HTX-034. In the Phase 1b portion of this Phase 1b/2 double-blind, randomized, active-controlled, dose-escalation study in 33 patients undergoing bunionectomy, the reduction in pain intensity observed was greater with the lowest dose of HTX-034 evaluated (containing 21.7 mg of bupivacaine plus meloxicam and aprepitant) than with the bupivacaine 50 mg solution through 96 hours. In addition, 45.5% of HTX-034 patients remained opioid-free through Day 15 with median opioid consumption of 2.5 milligram morphine equivalents (same as one 5 mg oxycodone pill) through 72-hours, a 71% reduction compared to bupivacaine solution. We initiated the expanded Phase 2 portion of the study for HTX-034 in the first quarter of 2021. We have temporarily postponed work on HTX-034 to understand the studies needed for a broad indication for ZYNRELEF, which could impact development planning for HTX-034. We are pausing the HTX-034 program to focus on the efficacy supplement to further expand the ZYNRELEF indication to broadly include soft tissue and orthopedic surgical procedures.

Oncology Care Product Portfolio

SUSTOL

SUSTOL was approved by the FDA in August 2016, and we commenced commercial sales in the U.S. in October 2016.

SUSTOL is indicated in combination with other antiemetics in adults for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic chemotherapy (MEC) or anthracycline and cyclophosphamide (AC) combination chemotherapy regimens. SUSTOL is an extended-release, injectable 5-hydroxytryptamine type 3 ("5-HT_3") receptor antagonist that utilizes our Biochronomer Technology to maintain therapeutic levels of granisetron for ≥5 days. The SUSTOL global Phase 3 development program was comprised of two, large, guideline-based clinical studies that evaluated SUSTOL's efficacy and safety in more than 2,000 patients with cancer. SUSTOL's efficacy in preventing nausea and vomiting was evaluated in both the acute phase (0–24 hours following chemotherapy) and the delayed phase (24–120 hours following chemotherapy).

SUSTOL is the first extended-release 5-HT_3 receptor antagonist approved for the prevention of acute and delayed nausea and vomiting associated with both MEC and AC combination chemotherapy regimens. A standard of care in the treatment of breast cancer and other cancer types, AC regimens are among the most commonly prescribed HEC regimens, as defined by both the National Comprehensive Cancer Network ("NCCN") and the American Society of Clinical Oncology ("ASCO").

In February 2017, the NCCN included SUSTOL as a part of its NCCN Clinical Practice Guidelines in Oncology for Antiemesis Version 1.2017. The NCCN has given SUSTOL a Category 1 recommendation, the highest-level category of evidence and consensus, for use in the prevention of acute and delayed nausea and vomiting in patients receiving HEC or MEC regimens. The guidelines now identify SUSTOL as a "preferred" agent for preventing nausea and vomiting following MEC. Further, the guidelines highlight the unique, extended-release formulation of SUSTOL.

In January 2018, a product-specific billing code, or permanent J-code ("J-code"), for SUSTOL became available. The new J-code was assigned by the Centers for Medicare and Medicaid Services ("CMS") and has helped simplify the billing and reimbursement process for prescribers of SUSTOL.

CINVANTI

CINVANTI was approved by the FDA in November 2017, and we commenced commercial sales in the U.S. in January 2018.

CINVANTI, in combination with other antiemetic agents, is indicated in adults for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy (HEC) including high-dose cisplatin as a single-dose regimen, delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (MEC) as a single-dose regimen, and nausea and vomiting associated with initial and repeat courses of MEC as a 3-day regimen.

CINVANTI is an intravenous ("IV") formulation of aprepitant, a substance P/neurokinin-1 ("NK_1") receptor antagonist. CINVANTI is the first IV formulation to directly deliver aprepitant, the active ingredient in EMEND® capsules. Aprepitant (including its prodrug, fosaprepitant) is the only single-agent NK_1 receptor antagonist to significantly reduce nausea and vomiting in both the acute phase (0–24 hours after chemotherapy) and the delayed phase (24–120 hours after chemotherapy). CINVANTI is the first and only IV formulation of an NK_1 receptor antagonist indicated for the prevention of acute and delayed nausea and vomiting associated with HEC and nausea and vomiting associated with MEC that is free of synthetic surfactants, including polysorbate 80.

NK_1 receptor antagonists are typically used in combination with 5-HT_3 receptor antagonists. The only other injectable NK_1 receptor antagonist currently approved in the U.S. for both acute and delayed chemotherapy induced nausea and vomiting ("CINV"), EMEND® IV (fosaprepitant), contains polysorbate 80, a synthetic surfactant, which has been linked to hypersensitivity reactions, including anaphylaxis, and infusion site reactions. The CINVANTI formulation does not contain polysorbate 80 or any other synthetic surfactant. Our CINVANTI data has demonstrated the bioequivalence of CINVANTI to EMEND IV, supporting its efficacy for the prevention of both acute and delayed nausea and vomiting associated with HEC and nausea and vomiting associated with MEC. Results also showed CINVANTI was better tolerated in healthy volunteers than EMEND IV, with significantly fewer adverse events ("AEs") reported with CINVANTI.

In January 2019, a J-code for CINVANTI became available. The new J-code was assigned by CMS and has helped simplify the billing and reimbursement process for prescribers of CINVANTI.

In February 2019, the FDA approved our sNDA for CINVANTI, for IV use, which expanded the administration of CINVANTI beyond the initially approved administration method (a 30-minute IV infusion) to include a 2-minute IV injection.

In October 2019, the FDA approved our sNDA for CINVANTI to expand the indication and recommended dosage to include the 130 mg single-dose regimen for patients receiving MEC.

In the fourth quarter of 2022, we validated larger-scale manufacturing of CINVANTI, which will significantly reduce the cost of product sales.

Biochronomer Technology

Our proprietary Biochronomer Technology is designed to deliver therapeutic levels of a wide range of otherwise short-acting pharmacological agents over a period from days to weeks with a single administration. Our Biochronomer Technology consists of polymers that have been the subject of comprehensive animal and human toxicology studies that have shown evidence of the safety of the polymer. When administered, the polymers undergo controlled hydrolysis, resulting in a controlled, sustained release of the pharmacological agent encapsulated within the Biochronomer-based composition. Furthermore, our Biochronomer Technology is designed to permit more than one pharmacological agent to be incorporated, such that multimodal therapy can be delivered with a single administration.

Sales and Marketing

Our U.S.-based sales and marketing team consists of 117 employees as of December 31, 2022. The sales and marketing infrastructure includes a targeted, acute care and oncology sales force to establish relationships with a focused group of surgeons, oncologists, nurses and pharmacists. Additionally, the commercial team manages relationships with key accounts, such as managed care organizations, group purchasing organizations, hospital systems, oncology group networks, payors and government accounts. The sales force is supported by sales management, internal sales support, an internal marketing group and distribution support.

Customers

Our Products are distributed in the U.S. through a limited number of specialty distributors and full line wholesalers (collectively, "Customers") that resell to healthcare providers and hospitals, the end users of our Products.

Competition

The biotechnology and pharmaceutical industries are extremely competitive. Our potential competitors are many in number and include major and mid-sized pharmaceutical and biotechnology companies. Many of our potential competitors have significantly more financial, technical and other resources than we do, which may give them a competitive advantage. In addition, they may have substantially more experience in effecting strategic combinations, in-licensing technology, developing drugs, obtaining regulatory approvals and manufacturing and marketing products. We cannot give any assurances that we can compete effectively with these other biotechnology and pharmaceutical companies. Our Products compete in, and our product candidates, if approved, will compete in, highly competitive markets. Our potential competitors in these markets may succeed in developing products that could render our Products and our product candidates obsolete or noncompetitive.

In the U.S., ZYNRELEF competes in, and HTX-034, if successfully developed, will compete in, the postoperative pain management market with MARCAINE™ (bupivacaine hydrochloride injection, solution, marketed by Pfizer Inc.) and generic forms of bupivacaine; NAROPIN® (ropivacaine, marketed by Fresenius Kabi USA, LLC) and generic forms of ropivacaine; EXPAREL® (bupivacaine liposome injectable suspension, marketed by Pacira BioSciences, Inc.); XARACOLL® (bupivacaine HCl implant, marketed by Innocoll Pharmaceuticals Limited); POSIMIR® (owned by Durect Corporation and to be marketed in the U.S. by Innocoll Pharmaceuticals Limited); ANJESO® (meloxicam injection, marketed by Baudax Bio, Inc.); OFIRMEV® (acetaminophen injection, marketed by Mallinckrodt Pharmaceuticals); SEGLENTIS® (celecoxib and tramadol hydrochloride, marketed by Kowa Pharmaceuticals America, Inc. in the U.S.); generic forms of IV acetaminophen; and potentially other products in development for postoperative pain management that reach the U.S. market.

In the EU, ZYNRELEF will, and HTX-034, if successfully developed will also, face significant competition. Currently there are numerous generic local anesthetics and other non-opioids for postoperative pain management available in the EU, and other products in development for postoperative pain management may also reach the EU market. For example, in November 2020 the EC granted a marketing authorization for EXPAREL® (bupivacaine liposome injectable suspension, marketed by Pacira BioSciences, Inc. in the U.S.) for postsurgical analgesia, and EXPAREL was launched in the EU in the fourth quarter of 2021.

ZYNRELEF will compete with MARCAINE™ (bupivacaine hydrochloride injection, solution, marketed by Pfizer Inc.); SENSORCAINE® (bupivacaine and epinephrine injection, marketed by Aspen Pharmacare Canada Inc.); NAROPIN® (ropivacaine and hydrochloride, marketed by Aspen Pharmacare Canada Inc.); and potentially other products in development for postoperative pain management that reach the Canadian market.

CINVANTI faces significant competition. NK_1 receptor antagonists are administered for the prevention of CINV, in combination with 5-HT_3 receptor antagonists, to augment the therapeutic effect of the 5-HT_3 receptor antagonist. Currently available NK_1receptor antagonists include: generic versions of EMEND® IV (fosaprepitant); EMEND® IV (fosaprepitant, marketed by Merck & Co., Inc.); EMEND® (aprepitant, marketed by Merck & Co., Inc.); AKYNZEO® (palonosetron, a 5-HT_3 receptor antagonist, combined with netupitant, an NK_1 receptor antagonist, marketed by Helsinn Therapeutics (U.S.), Inc.); VARUBI®(rolapitant, marketed by TerSera Therapeutics LLC) and other products that include an NK_1 receptor antagonist that reach the market for the prevention of CINV.

SUSTOL faces significant competition. Currently available 5-HT_3 receptor antagonists include: AKYNZEO® (palonosetron, a 5-HT_3 receptor antagonist, combined with netupitant, an NK_1 receptor antagonist, marketed by Helsinn Therapeutics (U.S.), Inc.); SANCUSO® (granisetron transdermal patch, marketed by Cumberland Pharmaceuticals Inc.); and generic products including ondansetron (formerly marketed by GlaxoSmithKline plc as ZOFRAN), granisetron (formerly marketed by Hoffman-La Roche, Inc. as KYTRIL) and palonosetron (formerly marketed by Eisai in conjunction with Helsinn Healthcare S.A. as ALOXI). Currently, palonosetron is the only 5-HT_3 receptor antagonist other than SUSTOL that is approved for the prevention of delayed CINV associated with MEC regimens. SUSTOL is indicated in combination with other antiemetics in adults for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic chemotherapy (MEC) or anthracycline and cyclophosphamide (AC) combination chemotherapy regimens, which is considered to be a HEC regimen by the NCCN and ASCO. No other 5-HT_3 receptor antagonist is specifically approved for the prevention of delayed CINV associated with a HEC regimen.

In the U.S., APONVIE will compete in the PONV prevention market with generic ondansetron, the current standard of care, generic aprepitant, and BARHEMSYS® (amisulpride, marketed by Eagle Pharmaceuticals, Inc.); TAK-951 (a peptide agonist under development (PH2) by Takeda Pharmaceutical Company Limited for PONV and not approved anywhere globally for any use); and potentially other products in development for PONV prevention that reach the market.

Manufacturing and Clinical Supplies

We do not own or operate manufacturing facilities for the production of commercial or clinical quantities of any product, including our Products and product candidates. We currently rely on a small number of third-party manufacturers to produce compounds used in our product development and commercial activities and expect to continue to do so to meet the preclinical and clinical requirements of our potential products and for all of our commercial needs. We currently have long-term commercial supply agreements with certain third-party manufacturers. Our manufacturing and processing agreements require that all third-party contract manufacturers and processors produce active pharmaceutical ingredients, excipients and finished products in accordance with the FDA's current Good Manufacturing Practices ("cGMP") and all other applicable laws and regulations. We maintain confidentiality agreements with potential and existing manufacturers in order to protect our proprietary rights related to our Products, our product candidates and our Biochronomer Technology.

Some of the critical materials and components used in manufacturing our Products and our product candidates are sourced from single suppliers. An interruption in the supply of a key material could significantly delay our research and development process or increase our expenses for commercialization or development of our Products or product candidates. Specialized materials must often be manufactured for the first time for use in drug delivery technologies, or materials may be used in the technologies in a manner that is different from their customary commercial uses. The quality of materials can be critical to the performance of a drug delivery technology, so a reliable source that provides a consistent supply of materials is important. Materials or components needed for our drug delivery technologies may be difficult to obtain on commercially reasonable terms, particularly when relatively small quantities are required or if the materials traditionally have not been used in pharmaceutical products.

Intellectual Property

Our success will depend in large part on our ability to:

- obtain and maintain international and domestic patents and other legal protections for the proprietary technology, inventions and improvements we consider important to our business;
- prosecute and defend our patents;
- preserve our trade secrets; and
- operate without infringing the patents and proprietary rights of other parties.

We intend to continue to seek appropriate patent protection for the product candidates in our research and development programs and their uses by filing patent applications in the U.S. and other selected countries. We intend for these patent applications to cover, where possible, claims for composition of matter, medical uses, processes for preparation and formulations.

We have filed a number of U.S. patent applications on inventions relating to the composition of a variety of polymers, specific products, product groups and processing technology. As of December 31, 2022, we had a total of 33 issued U.S. patents and an additional 111 issued (or registered) foreign patents. The patents on the bioerodible technologies expire in March 2026. Currently, CINVANTI is covered by 9 patents issued in the U.S. and by three patents issued (or registered) in foreign countries including Korea and Japan. U.S. patents covering CINVANTI have expiration dates ranging from September 2035 to February 2036; foreign patents covering CINVANTI have expiration dates ranging from September 2035 to February 2036. Currently, SUSTOL is covered by 6 patents issued in the U.S. and by 18 patents issued (or registered) in foreign countries including France, Germany, Hong Kong,

Ireland, Italy, Japan, Spain, Sweden, Switzerland, Taiwan, and the United Kingdom. U.S. patents covering SUSTOL expire in September 2024; foreign patents covering SUSTOL expire in September 2025. Currently, ZYNRELEF is protected by 15 patents issued in the U.S. and by 89 patents issued (or registered) in foreign countries including Albania, Australia, Austria, Belgium, Bulgaria, Canada, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hong Kong, Hungary, Iceland, Ireland, Italy, Japan, Korea, Latvia, Lithuania, Luxembourg, Macedonia, Malta, Mexico, Monaco, Netherlands, Norway, Poland, Portugal, Romania, Serbia, Slovakia, Slovenia, Spain, Sweden, Switzerland, Taiwan, Turkey and the United Kingdom. U.S. patents covering ZYNRELEF have expiration dates ranging from March 2034 to April 2035; foreign patents covering ZYNRELEF have expiration dates ranging from November 2033 to November 2036. APONVIE is covered by 9 patents issued in the U.S. and by three patents issued (or registered) in foreign countries including Korea and Japan. U.S. patents covering APONVIE have expiration dates ranging from September 2035 to February 2036; foreign patents covering APONVIE have expiration dates ranging from September 2035 to February 2036. HTX-034 is protected by 12 patents issued in the U.S. and by 89 patents issued (or registered) in foreign countries including Albania, Australia, Austria, Belgium, Bulgaria, Canada, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hong Kong, Hungary, Iceland, Ireland, Italy, Japan, Korea, Latvia, Lithuania, Luxembourg, Macedonia, Malta, Mexico, Monaco, Netherlands, Norway, Poland, Portugal, Romania, Serbia, Slovakia, Slovenia, Spain, Sweden, Switzerland, Taiwan, Turkey and the United Kingdom. U.S. patents covering HTX-034 have expiration dates ranging from March 2034 to April 2035; foreign patents covering HTX-034 have expiration dates ranging from November 2033 to November 2036. Our policy is to actively seek patent protection in the U.S. and to pursue equivalent patent claims in selected foreign countries, thereby seeking patent coverage for novel technologies and compositions of matter that may be commercially important to the development of our business. Granted patents include claims covering the product composition, methods of use and methods of preparation. Our existing patents may not cover future products, additional patents may not be issued and current patents, or patents issued in the future, may not provide meaningful protection or prove to be of commercial benefit.

Although we believe that our rights under patent applications we own provide a competitive advantage, the patent positions of pharmaceutical and biotechnology companies are highly uncertain and involve complex legal and factual questions. We may not be able to develop patentable products or processes, and may not be able to obtain patents from pending applications. Even if patent claims are allowed, the claims may not issue, or in the event of issuance, may not be sufficient to protect the technology owned by or licensed to us. Any patents or patent rights that we obtain may be circumvented, challenged or invalidated by our competitors.

We also rely on trade secrets, proprietary know-how and continuing innovation to develop and maintain our competitive position. We seek protection of these trade secrets, proprietary know-how and any continuing innovation, in part, through confidentiality and proprietary information agreements. However, these agreements may not provide meaningful protection for, or adequate remedies to protect, our technology in the event of unauthorized use or disclosure of information. Furthermore, our trade secrets may otherwise become known to, or be independently developed by, our competitors.

Government Regulation

Pharmaceutical Regulation

Pharmaceutical products that we market in the U.S. are subject to extensive government regulation. Likewise, if we receive approvals to market and distribute any such products abroad, they would also be subject to extensive foreign government regulation. Compliance with these regulations has not had a material effect on our capital expenditures, earnings, or competitive position to date, but new regulations or amendments to existing regulations to make them more stringent could have such an effect in the future. We cannot estimate the expenses we may incur to comply with potential new laws or changes to existing laws, or the other potential effects these laws may have on our business.

In the U.S., the FDA regulates pharmaceutical products. FDA regulations govern the testing, research and development activities, manufacturing, quality, storage, advertising, promotion, labeling, sale and distribution of pharmaceutical products. Accordingly, there is a rigorous process for the approval of new drugs and ongoing oversight of marketed products. We are also subject to foreign regulatory requirements governing clinical trials and drug products if products are tested or marketed abroad. The approval process outside the U.S. varies from jurisdiction to jurisdiction and the time required may be longer or shorter than that required for FDA approval.

Regulation in the U.S.

The FDA testing and approval process requires substantial time, effort and money. The FDA approval process for new drugs includes, without limitation:

- preclinical studies;
- submission in the U.S. of an Investigational New Drug application ("IND"), for clinical trials conducted in the U.S.;
- adequate and well-controlled human clinical trials to establish safety and efficacy of the product;
- submission and review of an NDA in the U.S.; and
- inspection of the facilities used in the manufacturing of the drug to assess compliance with the FDA's current cGMP regulations.

The FDA monitors the progress of trials conducted in the U.S. under an IND and may, at its discretion, re-evaluate, alter, suspend or terminate testing based on the data accumulated to that point and the FDA's risk/benefit assessment with regard to the patients enrolled in the trial. The FDA may also place a hold on one or more clinical trials conducted under an IND for a drug if it deems warranted. Furthermore, even after regulatory approval of an NDA is obtained, under certain circumstances, such as later discovery of previously unknown problems, the FDA can withdraw approval or subject the drug to additional restrictions.

Preclinical Testing

Preclinical studies include laboratory evaluation of the product and animal studies to assess the potential safety and effectiveness of the product. Most of these studies must be performed according to Good Laboratory Practices ("GLP"), a system of management controls for laboratories and research organizations to ensure the consistency and reliability of results.

An IND is the request for authorization from the FDA to administer an investigational new drug product to humans. The IND includes information regarding the preclinical studies, the investigational product's chemistry and manufacturing, supporting data and literature and the investigational plan and protocol(s). Clinical trials may begin 30 days after an IND is received, unless the FDA raises concerns or questions about the conduct of the clinical trials. If concerns or questions are raised, an IND sponsor and the FDA must resolve any outstanding concerns before clinical trials can proceed. An IND must become effective before human clinical trials begin. We have filed INDs in the U.S. and Clinical Trial Applications ("CTAs") in the EU, and we may file additional INDs and CTAs in the future. We cannot assure that submission of any additional INDs or CTAs for any of our product candidates will result in authorization to commence clinical trials.

Clinical Trials

Clinical trials involve the administration of the product candidate that is the subject of the trial to volunteers or patients under the supervision of a qualified principal investigator and in accordance with a clinical trial protocol, which sets forth details, such as the study objectives, enrollment criteria and the safety and effectiveness criteria to be evaluated. Each clinical trial must be reviewed and approved at each institution at which the study will be conducted by an independent Institutional Review Board in the U.S., referred to as an Ethics Committee in the EU and other markets or Research Ethics Board in Canada. The Institutional Review Board, Ethics Committee or Research Ethics Board (hereafter collectively referred to as "IRB") will consider, among other things, ethical factors, safety of human subjects and the possible liability of the institution arising from the conduct of the proposed clinical trial. In addition, clinical trials in the U.S. and other regions must be performed according to current Good Clinical Practices ("cGCP"), which are enumerated in FDA regulations and guidance documents. Some studies include oversight by an independent group of experts, known as a data safety monitoring board, which authorizes whether a study may move forward based on certain data from the study and may stop the clinical trial if it determines that there is an unacceptable safety risk for subjects or other grounds.

The FDA or other regulatory authorities may order the temporary, or permanent, discontinuation of a clinical trial at any time, or impose other sanctions, if it or they believe that the clinical trial is not being conducted in accordance with regulatory requirements or presents an unacceptable risk to the clinical trial patients. 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 it may impose other conditions.

Clinical trials typically are conducted in sequential phases: Phases 1, 2, 3 and 4. The phases may overlap. The FDA may require that we suspend clinical trials at any time on various grounds, including if the FDA makes a finding that the subjects participating in the trial are being exposed to an unacceptable health risk.

In Phase 1 clinical trials, the investigational product is usually tested on a small number of healthy volunteers to determine safety, any adverse effects, proper dosage, absorption, metabolism, distribution, excretion and other drug effects. Follow-on Phase 1b clinical trials may also evaluate efficacy with respect to trial participants.

In Phase 2 clinical trials, the investigational product is usually tested on a limited number of patients (generally up to several hundred) to preliminarily evaluate the efficacy of the drug for specific, targeted indications, to determine dosage tolerance and optimal dosage, and to identify possible adverse effects and safety risks. Multiple Phase 2 clinical trials may be conducted to obtain information prior to beginning Phase 3 clinical trials.

In Phase 3 clinical trials, the investigational product is administered to an expanded patient population to confirm proof of concept and efficacy claims, provide evidence of clinical efficacy and to further test for safety, generally at multiple clinical sites.

In Phase 4 clinical trials or other post-approval commitments, additional studies and patient follow-up are conducted to gain experience from the treatment of patients in the intended therapeutic indication. The FDA and other regulatory authorities may require a commitment to conduct post-approval Phase 4 studies as a condition of approval. Additional studies and follow-up may be conducted to document a clinical benefit where drugs are approved under accelerated approval regulations and based on surrogate endpoints. In clinical trials, surrogate endpoints are alternative measurements of the symptoms of a disease or condition that are substituted for measurements of observable clinical symptoms. In the U.S., failure to timely conduct Phase 4 clinical trials and follow-up could result in withdrawal of approval for products approved under accelerated approval regulations.

Clinical Data Review and Approval in the U.S.

The data from the clinical trials, together with preclinical data and other supporting information that establishes a drug candidate's safety, are submitted to the FDA in the form of an NDA, or sNDA (for approval of a new indication if the product candidate is already approved for another indication). Under applicable laws and FDA regulations, the FDA reviews the NDA within 60 days of receipt of the NDA submission to determine whether the application will be accepted for filing based on the FDA's threshold determination that the NDA is sufficiently complete to permit substantive review. If deemed complete, the FDA will "file" the NDA, thereby triggering substantive review of the application. The FDA can refuse to file any NDA that it deems incomplete or not properly reviewable.

The FDA has established internal substantive review goals of 10 months for most NDAs. The FDA has various programs, including Breakthrough Therapy, Fast Track and Priority Review, which are intended to expedite or simplify the process for reviewing drug candidates, and/or provide for approval based on surrogate endpoints. Even if a drug candidate qualifies for one or more of these programs, the FDA may later decide that the drug candidate no longer meets the conditions for qualification or that the period for FDA review or approval will not be shortened. Generally, drug candidates that may be eligible for these programs are those for serious or life-threatening conditions, those with the potential to address unmet medical needs, and those that offer meaningful benefits over existing treatments. For example, Fast Track is a process designed to facilitate the development, and expedite the review, of drugs to treat serious diseases and fill an unmet medical need. The request may be made at the time of IND submission and generally no later than the pre-NDA meeting. The FDA will respond within 60 calendar days of receipt of the request. Priority Review designation, which is requested at the time of an NDA submission, is designed to give drugs that offer major advances in treatment or provide a treatment where no adequate therapy exists, an initial review within 6 months as compared to a standard review time of 10 months. Although Fast Track and Priority Review do not affect the standards for approval, the FDA will attempt to facilitate early and frequent meetings with a sponsor of a Fast Track designated drug and expedite review of the application for a drug designated for Priority Review. Accelerated approval provides an expedited approval of drugs that treat serious diseases and that fill an unmet medical need based on a surrogate endpoint. The FDA, however, is not legally required to complete its review within these periods, and these performance goals may change over time.

If the FDA approves the NDA, it will issue an approval letter authorizing the commercial marketing of the drug with 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. Additionally, the FDA will inspect the facility or the facilities at which the drug is manufactured. 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. In many cases, the outcome of the review, even if generally favorable, is not an actual approval, but a "complete response" that generally outlines the deficiencies in the submission, which may require substantial additional testing or information before the FDA will 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.

Satisfaction of FDA requirements or similar requirements of state, local and foreign regulatory agencies typically takes several years and requires the expenditure of substantial financial resources. Information generated in this process is susceptible to varying interpretations that could delay, limit or prevent regulatory approval at any stage of the process. Accordingly, the actual time and expense required to bring a product to market may vary substantially. Data obtained from clinical activities is not always conclusive and may be susceptible to varying interpretations, which could delay, limit or prevent regulatory approval. Success in early-stage clinical trials does not ensure success in later-stage clinical trials. Even if a product candidate receives regulatory approval, the approval may be significantly limited to specific disease states, patient populations and dosages, or have conditions placed on it that restrict the commercial applications, advertising, promotion or distribution of these products.

Once issued, the FDA may withdraw product approval if ongoing regulatory standards are not met or if safety problems occur after the product reaches the market. In addition, the FDA may require testing and surveillance programs to monitor the safety or effectiveness of approved products which have been commercialized, and the FDA has the power to prevent or limit further marketing of a product based on the results of these postmarketing programs. The FDA may also request or require additional Phase 4 clinical trials after a product is approved. The results of Phase 4 clinical trials can confirm the effectiveness of a product candidate and can provide important safety information to augment the FDA's voluntary adverse drug reaction reporting system. Any products manufactured or distributed by us pursuant to FDA approvals would be subject to continuing regulation by the FDA, including recordkeeping requirements and reporting of adverse experiences with the drug. Drug manufacturers and their subcontractors are required to register their establishments with the FDA and certain state agencies and are subject to periodic unannounced inspections by the FDA and certain state agencies for compliance with cGMPs, which impose certain procedural and documentation requirements on us and our third-party manufacturers.

In addition, both before and after approval is sought, we are required to comply with a number of FDA requirements. For example, we are required to report certain adverse reactions and production problems, if any, to the FDA, and to comply with certain limitations and other requirements concerning advertising and promotion for our products. In addition, quality control and manufacturing procedures must continue to conform to cGMP after approval, and the FDA periodically inspects manufacturing facilities to assess compliance with continuing cGMP. In addition, discovery of problems, such as safety problems, may result in changes in labeling or restrictions on a product manufacturer or NDA holder, including removal of the product from the market.

The FDA closely regulates the marketing and promotion of drugs. Approval may be subject to postmarketing surveillance and other recordkeeping and reporting obligations and involve ongoing requirements. Product approvals may be withdrawn if compliance with regulatory standards is not maintained or if problems occur following initial marketing. A company can make only those claims relating to safety and efficacy that are approved by the FDA. Failure to comply with these requirements can result in adverse publicity, warning letters, corrective advertising and potential civil and criminal penalties.

Clinical Trial Conduct and Product Approval Regulation in Non-U.S. Jurisdictions

In addition to regulations in the U.S., we may be subject to a variety of foreign regulations governing clinical trials and commercial sales and distribution of our products. For example, our clinical trials conducted in the EU must be done under an Investigational Medicinal Product Dossier, and the oversight of an Ethics Committee. If we market our products in foreign countries, we also will be subject to foreign regulatory requirements governing marketing approval for pharmaceutical products. The requirements governing the conduct of clinical trials, product approval, pricing and reimbursement vary widely from country to country. Whether or not FDA approval has been obtained, approval of a product by the comparable regulatory authorities of foreign countries must be obtained before manufacturing or marketing the product in those countries. The approval process varies from country to country and the time required for such approvals may differ substantially from that required for FDA approval. There is no assurance that any future FDA approval of any of our product candidates will result in similar foreign approvals or vice versa. The process for clinical trials in other jurisdictions are similar, and trials are heavily scrutinized by the designated Ethics Committee.

Section 505(b)(2) Applications

Some of our product candidates may be eligible for submission of applications for approval under the FDA's Section 505(b)(2) approval process, which provides an alternate path to FDA approval for new or improved formulations or new uses of previously approved products. Section 505(b)(2) was enacted as part of the Drug Price Competition and Patent Term Restoration Act of 1984, also known as the Hatch-Waxman Act, and allows approval of NDAs that rely, at least in part, on studies that were not conducted by or for the applicant and to which the applicant has not obtained a right of reference. Such studies can be provided by published literature, or the FDA can rely on previous findings of safety and efficacy for a previously approved drug. If the 505(b)(2) applicant can establish that reliance on the FDA's previous approval is scientifically appropriate, it may eliminate the need to conduct certain preclinical studies or clinical trials of the new product. Section 505(b)(2) applications may be submitted for drug products that represent a modification (*e.g.*, a new indication or new dosage form) of an eligible approved drug. In such cases, the additional information in 505(b)(2) applications necessary to support the change from the previously approved drug is frequently provided by new studies submitted by the applicant. Because a Section 505(b)(2) application relies in part on previous studies or previous FDA findings of safety and effectiveness, preparing 505(b)(2) applications is generally less costly and time-consuming than preparing an NDA based entirely on new data and information from a full set of clinical trials. The FDA may approve the new product candidate for all, or some, of the label indications for which the referenced product has been approved, as well as for any new indication sought by the Section 505(b)(2) applicant. The law governing Section 505(b)(2) or FDA's current policies may change in such a way as to adversely affect our applications for approval that seek to utilize the Section 505(b)(2) approach. Such changes could result in additional costs associated with additional studies or clinical trials and delays.

The FDA provides that reviews and/or approvals of applications submitted under Section 505(b)(2) will be delayed in various circumstances. For example, the holder of the NDA for the listed drug may be entitled to a period of market exclusivity during which the FDA will not approve, and may not even review, a Section 505(b)(2) application from other sponsors. If the listed drug is claimed by one or more patents that the NDA holder has listed with the FDA, the Section 505(b)(2) applicant must submit a certification with respect to each such patent. If the 505(b)(2) applicant certifies that a listed patent is invalid, unenforceable or not infringed by the product that is the subject of the Section 505(b)(2) application, it must notify the patent holder and the NDA holder. If, within 45 days of providing this notice, the NDA holder sues the 505(b)(2) applicant for patent infringement, the FDA will not approve the Section 505(b)(2) application until the earlier of a court decision favorable to the Section 505(b)(2) applicant or the expiration of 30 months. The regulations governing marketing exclusivity and patent protection are complex, and it is often unclear how they will be applied in particular circumstances.

Drug Enforcement Agency Regulation

Our research and development processes involve the controlled use of hazardous materials, including chemicals. Some of these hazardous materials are considered to be controlled substances and subject to regulation by the U.S. Drug Enforcement Agency ("DEA"). Controlled substances are those drugs that appear on one of 5 schedules promulgated and administered by the DEA under the Controlled Substances Act ("CSA"). The CSA governs, among other things, the distribution, recordkeeping, handling, security and disposal of controlled substances. We must be registered by the DEA in order to engage in these activities, and we are subject to periodic and ongoing inspections by the DEA and similar state drug enforcement authorities to assess ongoing compliance with the DEA's regulations. Any failure to comply with these regulations could lead to a variety of sanctions, including the revocation, or a denial of renewal, of the DEA registration, injunctions or civil or criminal penalties.

Third-party Payor Coverage and Reimbursement

Commercial success of our Products and our product candidates that are approved or commercialized for any indication will depend, in part, on the availability of coverage and reimbursement from third-party payors at the federal, state and private levels. Government payor programs, including Medicare and Medicaid, private health care insurance companies and managed care plans have attempted to control costs by limiting coverage and the amount of reimbursement for particular procedures or drug treatments. The U.S. Congress and state legislatures, from time to time, propose and adopt initiatives aimed at cost containment. Ongoing federal and state government initiatives directed at lowering the total cost of health care will likely continue to focus on health care reform, the cost of prescription pharmaceuticals and on the reform of the Medicare and Medicaid payment systems. Examples of how limits on drug coverage and reimbursement in the U.S. may cause reduced payments for drugs in the future include:

- changing Medicare reimbursement methodologies;
- fluctuating decisions on which drugs to include in formularies;
- revising drug rebate calculations under the Medicaid program or requiring that new or additional rebates be provided to Medicare, Medicaid and other federal or state healthcare programs; and
- reforming drug importation laws.

Some third-party payors also require pre-approval of coverage for new drug therapies before they will reimburse health care providers that use such therapies. While we cannot predict whether any proposed cost-containment measures will be adopted or otherwise implemented in the future, the announcement or adoption of these proposals could have a material adverse effect on our ability to obtain adequate prices for our current and future products and to operate profitably.

Reimbursement systems in international markets vary significantly by country and, within some countries, by region. Reimbursement approvals must be obtained on a country-by-country basis. In many foreign markets, including markets in which we hope to sell our Products, the pricing of prescription pharmaceuticals is subject to government pricing control. In these markets, once marketing approval is received, pricing negotiations could take significant additional time. As in the U.S., the lack of satisfactory reimbursement or inadequate government pricing of any of our Products would limit widespread use and lower potential Product revenues.

Anti-kickback, Fraud and Abuse and False Claims Regulation

We are subject to health care fraud and abuse regulation and enforcement by both the federal government and the states in which we conduct our business. Healthcare providers, physicians and third-party payors play a primary role in the recommendation and prescription of our Products and any other product candidates for which we obtain marketing approval. Arrangements with third-party payors and customers may expose us to applicable fraud and abuse and other healthcare laws and regulations that may constrain the business or financial arrangements and relationships through which we market, sell and distribute our Products and any other product candidates for which we obtain marketing approval.

Regulations under applicable federal and state healthcare laws and regulations include the federal health care programs' Anti-Kickback Law, which prohibits, among other things, persons from knowingly and willfully soliciting, receiving, offering or paying remuneration, directly or indirectly, in exchange for or to induce either the referral or purchase of any good or service for which payment may be made under federal health care programs such as the Medicare and Medicaid programs. Remuneration has been broadly defined to include anything of value, including cash, improper discounts, and free or reduced-price items and services. Many states have similar laws that apply to their state health care programs as well as private payors. In addition, the False Claims Act ("FCA") imposes liability on persons who, among other things, present or cause to be presented false or fraudulent claims for payment by a federal health care program. The FCA has been used to prosecute persons submitting claims for payment that are inaccurate or fraudulent, that are for services not provided as claimed, or for services that are not medically necessary. Actions under the FCA may be brought by the United States Department of Justice ("DOJ") or as a *qui tam* action by a private individual in the name of the government. Violations of the FCA can result in significant monetary penalties and treble damages. The federal government is using the FCA, and the accompanying threat of significant liability, in its investigation and prosecution of pharmaceutical and biotechnology companies throughout the country, for example, in connection with the promotion of products for unapproved uses and other sales and marketing practices.

The risk of being found in violation of these laws is increased by the fact that many of them have not been fully interpreted by the regulatory authorities or the courts, and their provisions are open to a variety of interpretations. Moreover, recent health care reform legislation has strengthened many of these laws. For example, the Patient Protection and Affordable Care Act ("PPACA"), among other things, amends the intent requirement of the federal anti-kickback and criminal health care fraud statutes to clarify that a person or entity does not need to have actual knowledge of this statute or specific intent to violate it. In addition, PPACA provides 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 false claims statutes.

The continuing interpretation and application of these laws could have a material adverse impact on our business and our ability to compete in a highly competitive market.

Federal and State Sunshine Laws

We must comply with federal and state "sunshine" laws, now known as Open Payments that require transparency regarding financial arrangements with health care providers. This would include the reporting and disclosure requirements imposed by the PPACA on drug manufacturers regarding any "payment or transfer of value" made or distributed to physicians and teaching hospitals. Failure to submit required information can result in civil monetary penalties. A number of states have laws that require the implementation of commercial compliance programs, impose restrictions on drug manufacturer marketing practices and/or require pharmaceutical companies to track and report payments, gifts and other benefits provided to physicians and other health care professionals and entities.

Foreign Corrupt Practices Act

We are subject to the Foreign Corrupt Practices Act of 1997 ("FCPA"). The FCPA and other similar anti-bribery laws in other jurisdictions, such as the U.K. Bribery Act, generally prohibit companies and their intermediaries from providing money or anything of value to officials of foreign governments, foreign political parties, or international organizations with the intent to obtain or retain business or seek a business advantage. Recently, there has been a substantial increase in anti-bribery law enforcement activity by U.S. regulators, with more frequent and aggressive investigations and enforcement proceedings by both the DOJ and the U.S. Securities and Exchange Commission ("SEC"). A determination that our operations or activities are not, or were not, in compliance with U.S. or foreign laws or regulations could result in the imposition of substantial fines, interruptions of business, loss of supplier, vendor or other third-party relationships, termination of necessary licenses and permits and other legal or equitable sanctions. Other internal or government investigations or legal or regulatory proceedings, including lawsuits brought by private litigants, may also follow as a consequence. We have a policy against using Company funds for political purposes, and we incurred no costs in 2021 associated with legal or regulatory fines or settlements associated with violations of bribery, corruption or anti-competitive standards.

Patient Privacy and Data Security

We are required to comply, as applicable, with numerous federal and state laws, including state security breach notification laws, state health and personal information privacy laws and federal and state consumer protection laws, and to govern the collection, use and disclosure of personal information. For example, the California Consumer Privacy Act ("CCPA") became effective on January 1, 2020 and gave California residents expanded rights to access and request deletion of their personal information, opt out of certain personal information sharing and receive detailed information about how their personal information is used. Additionally, the California Privacy Rights Act (the "CPRA"), a ballot measure that was approved by California voters on November 3, 2020 and became operative on January 1, 2023, amends and expands the CCPA and its accompanying obligations, including through yet-to-be-finalized implementing regulations from a new enforcement agency, the California Privacy Protection Agency. Other states, such as Virginia and Colorado, have also passed comprehensive data privacy and security laws, and similar laws are being considered in several other states, as well as the federal and local levels. Other countries also have developed, or are developing, laws governing the collection, use and transmission of personal information, such as the General Data Protection Regulation in the EU that became effective in May 2018 and the Personal Information Protection and Electronic Documents Act that became effective in Canada in April 2000. In addition, most healthcare providers who utilize our Products or who may utilize other products we may sell in the future are subject to privacy and security requirements under the Health Insurance Portability and Accountability Act of 1996, as amended by the Health Information Technology and Clinical Health Act, and its implementing regulations (collectively, "HIPAA"). We are not a HIPAA covered entity, do not intend to become one, and we do not operate as a business associate to any covered entities. Therefore, these privacy and security requirements do not apply to us. However, we could be subject to civil and criminal penalties if we knowingly obtain individually identifiable or protected health information from a covered entity in a manner that is not authorized or permitted by HIPAA or for aiding and abetting the violation of HIPAA. The legislative and regulatory landscape for privacy and data protection continues to evolve, and there has been an increasing amount of focus on privacy and data protection issues with the potential to affect our business, including through affecting our customers. These laws could create liability for us or increase our cost of doing business, and any failure to comply could result in harm to our reputation, and potentially fines and penalties.

In addition, state laws govern the privacy and security of health information in certain circumstances, many of which differ from each other in significant ways and may not have the same effect, thus complicating compliance efforts.

Environmental, Health and Safety Laws

Our operations are subject to complex and increasingly stringent environmental, health and safety laws and regulations. Further, in the future, we may open manufacturing facilities that would likely be subject to environmental and health and safety authorities in the relevant jurisdictions. These authorities typically administer laws which regulate, among other matters, the emission of pollutants into the air (including the workplace), the discharge of pollutants into bodies of water, the storage, use, handling and disposal of hazardous substances, the exposure of persons to hazardous substances, and the general health, safety and welfare of employees and members of the public. Violations of these laws could subject us to strict liability, fines or liability to third parties.

Other Laws

We are subject to a variety of financial disclosure and securities trading regulations as a public company in the U.S., including laws relating to the oversight activities of the SEC and the regulations of The Nasdaq Capital Market, on which our shares are traded. We are also subject to various laws, regulations and recommendations relating to safe working conditions, laboratory practices and the experimental use of animals.

Human Capital Management

Heron Employees

As of December 31, 2022, Heron employed 203 full-time employees, 117 of whom are involved in sales and marketing activities, 63 of whom are involved in research and development activities and 23 of whom are involved in general and administrative activities. In 2022, Heron reduced headcount, across all functions, in order to enable us to decrease costs and focus our resources more on commercial activities to support revenue growth. Our 2022 voluntary turnover rate of 18% was aligned with industry average voluntary turnover but increased from the prior year due to employee concerns of job stability following our restructuring, and still amid an ongoing period of high employee resignations across all industries (commonly referred to as the "Great Resignation"). None of our employees are represented by a labor union or covered by a collective bargaining agreement.

We expect to hire a small number of additional employees in 2023 to backfill critical positions, but do not expect significant headcount growth. We continually evaluate business needs and opportunities in addition to balancing in-house expertise and capacity with that of outsourced resources. Currently, we outsource substantial clinical study work to clinical research organizations and drug manufacturing work to contract manufacturers.

Drug development is a complex endeavor that requires deep expertise and experience across a broad array of disciplines. Pharmaceutical companies both large and small compete for a limited number of qualified applicants to fill specialized positions, which continued in 2022, with heavy competition for talent. To attract qualified applicants, Heron offers a total rewards package consisting of base salary and cash bonus incentive targets aligned with the applicable market norms, equity compensation, and a comprehensive health and welfare benefits package for every employee. Bonus opportunity and equity compensation increase as a percentage of total compensation based on level of responsibility. Actual bonus payouts for all employees except our senior executives are based on a weighting of Company and individual performance, which varies based on level of responsibility. Actual bonus payout for our senior executives is based exclusively on Company performance, as will be more fully described in our Definitive Proxy Statement to be filed with the SEC related to our 2023 Annual Meeting of Stockholders.

Heron supports our employees' further development with individualized development plans, mentoring, coaching, internal development workshops, and certain financial support, including company-paid external conference attendance and tuition reimbursement. Heron sponsors professional society memberships for all employees, as well as memberships for interested female employees in a women's advocacy organization supporting women in Science, Technology, Engineering and Math.

Developing and maintaining a positive corporate culture is a priority for Heron. We collected feedback from employees about their working experience during 2022 through direct employee surveys and many individual discussions to identify opportunities to enhance our corporate culture, especially in a very challenging year. A cross-functional team was established to identify and implement initiatives in response to such employee feedback in order to ensure a positive, productive and inclusive work environment. This work continues as an ongoing effort.

We also monitor employee compliance with applicable laws and regulations through a third party ethics and compliance hotline system that facilitates anonymous internal and external reporting of complaints or concerns. We did not receive any complaints during 2022.

Heron strives for greater diversity and inclusion through our employment and management practices, as evidenced by an annual third-party demographic analysis indicating that the diversity of our employee population generally reflects the ethnicity, race and gender of the overall available workforce at all job levels. Where underutilization is identified, we remain committed to current and future outreach efforts in place to build employee diversity through our hiring efforts. We are also building diversity in our leadership team. In 2022, 40% of our Section 16 officers were female. We believe diversity is a competitive advantage and through initiatives established in our recruiting strategy and documented in our Affirmative Action Plan, we expanded our recruiting efforts in 2022 to reach underrepresented candidates and plan to continue doing so on an ongoing basis. Heron also monitors pay practices and decisions to ensure pay equity for minority and female employees when compared to non-minority and male employees in same or similar positions and when considering objective factors related to position qualifications.

Heron is committed to upholding basic human rights and complies with all laws and practices that prohibit child labor, forced or indentured labor, human trafficking and unfair wages.

Heron's Injury and Illness Prevention Plan documents procedures to reduce work-related injuries and occupational illnesses. In 2022, Heron had two Occupational Safety and Health Administration-reportable work-related injuries and did not experience any work-related deaths.

In response to the COVID-19 pandemic, we continued a remote work arrangement for non-laboratory employees and additional safety measures for employees continuing critical on-site work. In addition, we provided cell phone and home internet stipends to reimburse all employees for additional expenses related to working from home.

Company Information

Our principal executive offices are located at 4242 Campus Point Court, Suite 200, San Diego, California 92121, and our telephone number is (858) 251-4400. Our website address is *www.herontx.com*. We make our periodic and current reports available on our website, free of charge, as soon as reasonably practicable after such material is electronically filed with, or furnished to, the SEC. No portion of our website is incorporated by reference into this Annual Report on Form 10-K. We file our annual, quarterly and special reports, proxy statements and other information with the SEC. Our filings with the SEC are also available to the public on the SEC's website at *http://www.sec.gov*. Additional information regarding us, including our audited financial statements and descriptions of our business, is contained in the documents incorporated by reference in this Annual Report on Form 10-K. Our common stock is traded on The Nasdaq Capital Market, under the symbol "HRTX."

ITEM 1A. RISK FACTORS

Risk Factor Summary

You should carefully consider the following information about risks and uncertainties that may affect us or our business, together with the other information appearing elsewhere in this Annual Report on Form 10-K. If any of the following events, described as risks, actually occur, our business, financial condition, results of operations and future growth prospects could be materially and adversely affected. In these circumstances, the market price of our common stock could decline, and you may lose all or part of your investment in our securities. An investment in our securities is speculative and involves a high degree of risk. You should not invest in our securities if you cannot bear the economic risk of your investment for an indefinite period of time and cannot afford to lose your entire investment.

Below is a summary of material factors that make an investment in our securities speculative or risky. Importantly, this summary does not address all of the risks that we face. Additional discussion of the risks summarized in this risk factor summary, as well as other risks that we face, can be found below.

- We are substantially dependent on the commercial success of our Products and our U.S. product candidates, and if these Products and product candidates do not attain market acceptance by healthcare professionals and patients, our business and results of operations will suffer.

- If we are unable to develop and maintain sales, marketing and distribution capabilities or enter into agreements with third parties to sell and market our Products or our product candidates, our sales may be adversely affected.

- If we cannot establish satisfactory pricing of our Products or product candidates, if approved, that is also acceptable to the U.S. government, insurance companies, managed care organizations and other payors, or arrange for favorable reimbursement policies, our product sales may be adversely affected and our future revenue might suffer.

- If we fail to comply with our reporting and payment obligations under U.S. governmental pricing and contracting programs, we could be subject to additional reimbursement requirements, penalties and fines, which could have a negative impact on our business, financial condition, and results of operations.

- Because the results of preclinical studies and clinical trials are not necessarily predictive of future results, we can provide no assurances that our Products or product candidates will have favorable results in future studies or receive regulatory approval or expansion of approved indications.

- Interim, topline or preliminary data from our clinical trials that we announce or publish may change as more patient data become available and are subject to audit and verification procedures that could result in material changes in the final data.

- Although the FDA might grant Fast Track, Breakthrough Therapy, Priority Review or similar designations to our Products and product candidates, there can be no assurance that any of our Products or product candidates that receive similar designations in the U.S. or in any other regulatory jurisdictions will receive regulatory approval any sooner than other Products or product candidates that do not have such designations, or at all.

- Our product platforms or product development efforts may not produce safe, efficacious or commercially viable products, and, if we are unable to develop new products, our business may suffer.

- We rely on third parties to conduct our preclinical testing and conduct our clinical trials, and their failure to perform their obligations in a timely and competent manner may delay development and commercialization of our Products and product candidates and our business could be substantially harmed.

- If our suppliers or contract manufacturers are unable to manufacture in commercially viable quantities, we could face delays in our ability to commercialize our Products and product candidates, our costs will increase and sales of our Product and product candidates, if approved, may be severely hindered.

- The evolving effects of the COVID-19 pandemic and associated global economic instability could have further adverse effects on our business, including our commercialization efforts, supply chain, regulatory activities, clinical development activities and other business operations.

- We have a history of losses, we expect to generate losses in the near future, and we may never achieve or maintain profitability.

- Additional capital may be needed in the future to enable us to implement our business plan, and we may be unable to raise capital, which would force us to limit or cease our operations and related product development programs.

- Drug development involves a lengthy and expensive process with an uncertain outcome, and results of earlier studies and trials may not be predictive of future trial results.

- Delays in, or suspensions and terminations of, clinical testing could increase our costs and delay our ability to obtain regulatory approval for, and commercialize, our product candidates.

- We may not obtain regulatory approval for our product candidates in development. Regulatory approval may also be delayed or revoked or may impose limitations on the indicated uses of a product candidate. If we are unable to obtain regulatory approval for our product candidates in development, our business will be substantially harmed.

- Even if our product candidates in development receive regulatory approval, they may still face future development and regulatory difficulties. If we fail to comply with continuing federal, state and foreign regulations, we could lose our approvals to market drugs, and our business would be seriously harmed.

- If we are unable to adequately protect or enforce our intellectual property rights, we may lose valuable assets or incur costly litigation to protect our rights.

- The price of our common stock has been and may continue to be volatile.

Risks Related to Our Business

We are substantially dependent on the commercial success of our Products and our U.S. product candidates, and if these Products and product candidates do not attain market acceptance by healthcare professionals and patients, our business and results of operations will suffer.

The success of our business is substantially dependent on our ability to commercialize our Products and our product candidates. Although members of our management team have prior experience launching new drugs, ZYNRELEF, APONVIE, CINVANTI and SUSTOL are the first four products that we have launched and, if HTX-034 is approved in the U.S., it would be the fifth product that we launch in the U.S. ZYNRELEF, approved for commercial sale in the U.S., Canada, EU, the other countries in the EEA, and the United Kingdom, would be our first Product to be made commercially available in Canada or Europe.

Further, even if our sales organization performs as expected, the revenue that we may receive from the sales of our Products and our product candidates, if approved, may be less than anticipated due to factors that are outside of our control. These factors that may affect revenue include:

- the scope of our approved Product labels, including any expanded indication statement of ZYNRELEF in the U.S.;
- the perception of physicians and other members of the health care community of the safety and efficacy and cost-competitiveness relative to that of competing products;
- our ability to maintain successful sales, marketing and educational programs for certain physicians and other health care providers;
- our ability to raise patient and physician awareness of the risks associated with using opioids for postoperative pain management and encourage physicians to consider utilizing a non-opioid alternative;
- our ability to raise patient and physician awareness of CINV associated with AC combination chemotherapy regimens, MEC or HEC and encourage physicians to look for incidence of CINV among patients;
- our ability to raise patient and physician awareness of PONV associated with surgical procedures and encourage physicians to look for incidence of PONV among patients;
- the cost-effectiveness of our Products and our product candidates;
- the timing and scope of acceptance of our Products by institutional formulary committees and the amount of time between such acceptance and the first use of our Products within the applicable setting of care;
- patient and physician satisfaction with our Products and our product candidates;
- the size of the potential market for our Products and our product candidates;
- our ability to obtain adequate reimbursement from government and third-party payors;
- unfavorable publicity concerning our Products, our product candidates or similar products;
- the introduction, availability and acceptance of competing treatments, including competing generic products;
- adverse event information relating to our Products, our product candidates or similar classes of drugs;
- product liability litigation alleging injuries relating to our Products, our product candidates or similar classes of drugs;
- our ability to maintain and defend our patents and trade secrets for our Products, our product candidates and our Biochronomer Technology;
- our ability to continue to have our Products manufactured at commercial production levels successfully and on a timely basis;
- our ability to scale up manufacturing of our Products to meet commercial requirements;

- the availability of raw materials necessary to manufacture our Products and our product candidates;
- our ability to access third parties to manufacture and distribute our Products and our product candidates on acceptable terms or at all and those third parties' ability and/or willingness to fully perform their obligations;
- regulatory developments related to the manufacture or continued use of our Products and our product candidates;
- conduct of post-approval study requirements and the results thereof;
- the extent and effectiveness of sales and marketing and distribution support for our Products and our product candidates;
- the extent of the evolving effects of the COVID-19 pandemic on our business;
- our competitors' activities, including decisions as to the timing of competing product launches, generic entrants, pricing and discounting; and
- any other material adverse developments with respect to the commercialization of our Products and our product candidates.

Our business will be adversely affected if, due to these or other factors, our commercialization of our Products and our product candidates does not achieve the acceptance and demand necessary to sustain revenue growth. If we are unable to successfully commercialize our Products and our product candidates our business and results of operations will suffer.

If we are unable to develop and maintain sales, marketing and distribution capabilities or enter into agreements with third parties to sell and market our Products or our product candidates, our sales may be adversely affected.

We have established an internal commercial organization for the sale, marketing and distribution of our Products in the U.S. In order to successfully commercialize ZYNRELEF and any other Products or product candidates we obtain regulatory approval for in Canada or Europe, we must increase our sales, marketing, distribution and other non-technical capabilities or make arrangements with third parties to perform these services. The development of a sales organization to market our Products and product candidates is expensive and time consuming, and we cannot be certain that we will be able to successfully develop this capacity or that this function will execute as expected. If we are unable to establish and maintain adequate sales, marketing and distribution capabilities, whether independently (including as a result of our recent reduction in force) or with third parties, we may not be able to generate product revenue and our business and results of operations will suffer.

Our internal sales and marketing organization is not currently structured or staffed to launch products on an international level and, therefore, we may not be able to successfully commercialize our Products or product candidates outside of the U.S. In order to commercialize our Products or product candidates in jurisdictions other than the U.S., we would be required to obtain separate marketing approvals and comply with numerous and varying regulatory requirements in each foreign country. If we decide to seek the assistance of third parties with international expertise to help commercialize our Products or product candidates outside of the U.S., we may not be successful in finding willing third parties and, even if we are able to find willing third parties, they might not be able to successfully obtain the approvals and take the steps needed to commercialize our Products or product candidates. If we decide to commercialize our Products or product candidates outside of the U.S. without the assistance of third parties with international expertise, it may take longer than expected to obtain the approvals and take the steps needed to commercialize them. As a result, we may decide to delay or abandon development efforts in certain markets. Any such delay or abandonment may have an adverse effect on the benefits otherwise expected from marketing our Products or product candidates in foreign countries.

If we cannot establish satisfactory pricing of our Products or product candidates, if approved, that is also acceptable to the U.S. government, insurance companies, managed care organizations and other payors, or arrange for favorable reimbursement policies, our product sales may be adversely affected and our future revenue may suffer.

The continuing efforts of the U.S. government, insurance companies, managed care organizations and other payors of health care costs to contain or reduce costs of health care may adversely affect our ability to generate adequate revenues and gross margins to make our Products or product candidates commercially viable. Our ability to commercialize our Products and product candidates successfully will depend in part on the extent to which governmental authorities, private health insurers and other organizations establish appropriate reimbursement levels for the cost of such products and related treatments and for what uses reimbursement will be provided.

Adoption of our Products and product candidates by the medical community may be limited if third-party payors will not offer adequate coverage. In addition, third-party payors often challenge the price and cost-effectiveness of medical products and services and such pressure may increase in the future. In many cases, uncertainty exists as to the adequate reimbursement status of newly approved healthcare products. Accordingly, our Products and product candidates may not be reimbursable by certain third-party payors at the time of commercial launch and potentially for an extended period of time thereafter. In addition, our Products and product candidates may not be considered cost-effective and adequate third-party reimbursement may not be available to enable us to maintain price levels sufficient to realize a profit. Further, coverage policies and third-party payor reimbursement rates may change at any time. Even if favorable coverage and reimbursement status is attained for one or more of our Products or product candidates for which we receive regulatory approval, less favorable coverage policies and reimbursement rates may be implemented in the future.

Legislation and regulations affecting the pricing of pharmaceuticals may change and any such changes could further limit reimbursement. Cost control initiatives may decrease coverage and payment levels for our Products or product candidates and, in turn, the reimbursement that we receive. We are unable to predict all changes to the coverage or reimbursement methodologies that will be applied by private or government payors to our Products or product candidates. If our Products or product candidates do not receive adequate reimbursement, our revenue could be severely limited.

In the U.S., given recent federal and state government initiatives directed at lowering the total cost of health care, the U.S. Congress and state legislatures will likely continue to focus on health care reform, reducing the cost of prescription pharmaceuticals and reforming the Medicare and Medicaid systems. For example, the Patient Protection and Affordable Care Act of 2010, as amended by the Health Care and Education Reconciliation Act of 2010 (collectively, "PPACA") encourages comparative effectiveness research. Any adverse findings for our Products from such research may negatively impact reimbursement available for our Products. Similarly, the SUPPORT Act, which was signed into law on October 24, 2018, encourages the prevention and treatment of opioid addiction and the development of non-opioid pain management treatments. Although it is too early to assess the impact of the SUPPORT Act, it could potentially increase competition for ZYNRELEF and, if approved, HTX-034, and have other negative impacts on our business.

In March 2021, Congress enacted the American Rescue Plan Act of 2021, which removed the statutory cap on rebates that manufacturers pay to state Medicaid programs pursuant to the Medicaid Drug Rebate Program. This provision, which takes effect in 2024, may increase our rebate obligations and have a negative impact on our business. The Infrastructure Investment and Jobs Act, signed into law on November 15, 2021, also included a provision requiring drug manufacturers to pay CMS a refund for certain amounts of Part B drugs that are discarded from a single-dose container or single-use package. Under the law, and a CMS Proposed Rule issued in July 2022, this refund program became effective on January 1, 2023.

Further, the Inflation Reduction Act of 2022 ("IRA"), signed into law in August 2022, includes various provisions intended to address drug-pricing issues (such as provisions empowering the federal government to negotiate the price of some high-cost, single-source Medicare Part B and Part D drugs (with the new pricing to take effect in January 2026 or thereafter) and requiring rebates for certain Part B and Part D drugs if their price increases outpace inflation). Although it is too early to assess the impact of these provisions on our Products and product candidates, they could impact our product pricing or increase our rebate obligations.

As evidenced by developments such as these, low prices of our Products and product candidates in the U.S. and foreign jurisdictions may have a negative impact on the prices of our Products and product candidates in the U.S. For example, if legislation is passed or regulations are adopted that tie the prices of U.S. pharmaceuticals to the cost of pharmaceuticals in other countries and if ZYNRELEF is subject to pricing regulations in the EU or in other countries in which it is approved that keep its price low in those jurisdictions, then this could lower the potential price of the product in the U.S., thereby limiting the revenue we would be able to generate from it. Additionally, on September 24, 2020, the FDA published the Importation Rule. Although it is too early to assess the impact of the Importation Rule, it could potentially reduce U.S. revenues for any of our Products or product candidates that are also approved in Canada, including ZYNRELEF, and potentially have other negative impacts on our business.

Economic pressure on state budgets may result in states increasingly seeking to achieve budget savings through mechanisms that limit coverage or payment for drugs. State Medicaid programs are increasingly asking manufacturers to pay supplemental rebates and requiring prior authorization by the state program for use of any drug for which supplemental rebates are not being paid. Further, the trend toward managed health care in the U.S., which could significantly influence the purchase of health care services and products, may result in lower prices for our Products and our product candidates, once approved for marketing. While we cannot predict whether any legislative or regulatory proposals affecting our business will be adopted, the announcement or adoption of these proposals could have a material and adverse effect on our potential revenues and gross margins.

If we fail to comply with our reporting and payment obligations under U.S. governmental pricing and contracting programs, we could be subject to additional reimbursement requirements, penalties and fines, which could have a negative impact on our business, financial condition, and results of operations.

The Medicare program and certain government pricing programs, including the Medicaid drug rebate program, the Public Health Services' 340B drug pricing program, and the pricing program under the Veterans Health Care Act of 1992 impact the reimbursement we may receive from sales of our Products, our product candidates or any other products that are approved for marketing in the U.S. Pricing and rebate calculations vary among programs. The calculations are complex and are often subject to interpretation by manufacturers, governmental or regulatory agencies and the courts. We are required to submit a number of different pricing calculations to government agencies on a quarterly basis. Failure to comply with our reporting and payment obligations under U.S. governmental pricing and contracting programs may result in additional payments, penalties and fines due to government agencies, which could negatively impact our business, financial condition and results of operations.

Because the results of preclinical studies and clinical trials are not necessarily predictive of future results, we can provide no assurances that our Products or product candidates will have favorable results in future studies or receive regulatory approval or expansion of approved indications.

Positive results from preclinical studies or clinical trials should not be relied on as evidence that later or larger-scale studies will succeed. Even if our Products or product candidates achieve positive results in early-stage preclinical studies or clinical studies, we will be required to demonstrate that they are safe and effective for use in Phase 3 studies before we can seek expanded indications or regulatory approvals for their commercial sale. Even if our early-stage preclinical studies or clinical studies achieve the specified endpoints, the FDA may determine that these data are not sufficient to allow the commencement of Phase 3 studies. There is an extremely high historical rate of failure of product candidates proceeding through clinical trials in our industry. There is no guarantee that the efficacy of any of our product candidates shown in early patient studies will be replicated or maintained in future studies and/or larger patient populations. Similarly, favorable safety and tolerability data seen in short-term studies might not be replicated in studies of longer duration and/or larger patient populations. If any Product or product candidate demonstrates insufficient safety or efficacy in any preclinical study or clinical trial, we would experience potentially significant delays in, or be required to abandon, development of that Product for an expanded indication, or product candidate for approval. In addition, product candidates in Phase 3 studies may fail to show the desired safety and efficacy despite having progressed through preclinical and earlier stage clinical trials, which could delay, limit or prevent regulatory approval. Further, data obtained from pivotal clinical studies are susceptible to varying interpretations, which could delay, limit or prevent regulatory approval. Regulatory approval may also be delayed, limited or prevented by other factors. If we delay or abandon our efforts to develop any of our Products for expanded indications, or product candidates for approval, we may not be able to generate sufficient revenues to

become profitable, and our reputation in the industry and in the investment community would likely be significantly damaged, each of which would cause our stock price to decrease significantly.

Interim, topline or preliminary data from our clinical trials that we announce or publish may change as more patient data become available and are subject to audit and verification procedures that could result in material changes in the final data.

We may publicly disclose interim, topline, or preliminary data from our clinical trials, which is based on a preliminary analysis of then-available data, and the results and related findings and conclusions are subject to change following a full analyses of all data related to the particular trial. We also make assumptions, estimations, calculations and conclusions as part of our analyses of data, and we may not have received or had the opportunity to fully and carefully evaluate all data. As a result, the interim, topline, or preliminary results that we report may differ from future results of the same trials, or different conclusions or considerations may qualify such results, once additional data have been received and fully evaluated. Topline data also remain subject to audit and verification procedures that may result in the final data being materially different from the preliminary data we previously published. As a result, topline data should be viewed with caution until the final data are available. We may also disclose interim data from our clinical trials. Interim data from clinical trials that we may complete are subject to the risk that one or more of the clinical outcomes may materially change as patient enrollment continues and more patient data become available. Adverse differences between interim, topline or preliminary data and final data could significantly harm our business prospects.

Further, others, including regulatory agencies, may not accept or agree with our assumptions, estimates, calculations, conclusions or analyses or may interpret or weigh the importance of data differently, which could impact the value of the particular program, the approvability or commercialization of the particular product candidate or product and our business in general. In addition, the information we choose to publicly disclose regarding a particular study or clinical trial is based on what is typically extensive information, and you or others may not agree with what we determine is the material or otherwise appropriate information to include in our disclosure, and any information we determine not to disclose may ultimately be deemed significant with respect to future decisions, conclusions, views, activities or otherwise regarding a particular drug, product candidate or our business. If the interim, topline, or preliminary data that we report differ from actual results, or if others, including regulatory authorities, disagree with the conclusions reached, our ability to obtain expanded indications for our Products, or to obtain approvals for and commercialize our product candidates, our business, operating results, prospects or financial condition may be harmed.

Although the FDA might grant Fast Track, Breakthrough Therapy and Priority Review or similar designations to our Products and product candidates, there can be no assurance that any of our Products or product candidates that receive similar designations in the U.S. or in any other regulatory jurisdictions will receive regulatory approval any sooner than other Products or product candidates that do not have such designations, or at all.

Fast Track designation is intended to facilitate the development and expedite the review of new therapies to treat serious conditions with unmet medical needs by providing sponsors with the opportunity for frequent interactions with the FDA. Breakthrough Therapy designation is designed to expedite the development and review of drugs that are intended to treat serious conditions and for which preliminary clinical evidence indicates substantial improvement over available therapies on clinically significant endpoint(s). Priority Review designation is for drugs that, if approved, would be significant improvements in the safety or effectiveness of the treatment or prevention of serious conditions. product candidates that receive Fast Track or Breakthrough Therapy designation may receive more frequent interactions with the FDA regarding the product candidate's development plan and clinical trials and may be eligible for the FDA's Rolling Review and Priority Review. Priority Review designation is intended to direct overall attention and resources of the FDA to the evaluation of such applications and means that the FDA's goal is to take action on such applications within 6 months, compared to 10 months under standard review. We can provide no assurances that any of our Products or product candidates that receive Fast Track, Breakthrough Therapy, Priority Review or similar designations in the U.S. or in any other regulatory jurisdictions will receive regulatory approval any sooner than other Products or product candidates that do not have such designations, or at all. The FDA or any foreign regulatory authorities may also withdraw or revoke Fast Track, Breakthrough Therapy, Priority Review or similar designations, or elect to treat designated candidates in a manner different from what was originally indicated, if they determine that any of our Products or product candidates that receive such designations no longer meet the

relevant criteria. Failure to realize the potential benefits of these designations could materially and adversely affect our business, financial condition, cash flows and results of operations.

Our product platforms or product development efforts may not produce safe, efficacious or commercially viable products, and, if we are unable to develop new products, our business may suffer.

Our long-term viability and growth will depend on the successful development of products through our research and development activities. Product development is very expensive and involves a high degree of risk. Only a small number of research and development programs result in the commercialization of a product. Success in preclinical work or early-stage clinical trials does not ensure that later-stage or larger-scale clinical trials will be successful. Our ability to complete our clinical trials in a timely fashion depends in large part on a number of key factors, including protocol design, regulatory and IRB approval, the rate of patient enrollment in clinical trials and compliance with extensive cGCP.

In addition, because we fund the development of our Products and product candidates, we may not be able to continue to fund all such development efforts to completion or to provide the support necessary to perform the clinical trials, obtain regulatory approvals, or market any approved products. If our drug delivery technologies or product development efforts fail to result in the successful development and commercialization of our Products and product candidates, or if our new Products do not perform as anticipated, such events could materially and adversely affect our business, financial condition, cash flows and results of operations.

We rely on third parties to conduct our preclinical testing and conduct our clinical trials, and their failure to perform their obligations in a timely and competent manner may delay development and commercialization of our Products and product candidates and our business could be substantially harmed.

We have used contract research organizations ("CROs") to oversee or provide selected services for our clinical trials for our Products and our product candidates, and we expect to use the same or similar organizations for our future clinical trials and pipeline programs. There can be no assurance that these CROs will perform their obligations at all times in a competent or timely fashion, and we must rigorously oversee their activities in order to be confident in their conduct of these trials on our behalf. If the CROs fail to commit resources to our Products or product candidates, our clinical programs could be delayed, terminated or unsuccessful, and we may not be able to obtain initial or expanded regulatory approvals for, or successfully commercialize, them. Different cultural and operational issues in foreign countries could cause delays or unexpected problems with patient enrollment or with the data obtained from those locations. If we experience significant delays in the progress of our clinical trials or experience doubts with respect to the quality of data derived from our clinical trials, we could face significant delays in gaining necessary product approvals.

We also rely on third parties to assist in conducting our preclinical studies in accordance with GLP and the Animal Welfare Act requirements. We, our CROs and other third parties are required to comply with cGCP, which are regulations and guidelines enforced by the FDA, the Competent Authorities of the Member States of the EEA and comparable foreign regulatory authorities. Regulatory authorities enforce cGCP through periodic inspections of trial sponsors, principal investigators and trial sites. If we or any of our CROs fail to comply with applicable cGCP, the clinical data generated in the clinical trials may be deemed unreliable, and the FDA or comparable foreign regulatory authorities may require us to perform additional clinical trials before approving our marketing applications. We cannot be certain that on inspection by a given regulatory authority, such regulatory authority will determine that any of our ongoing or future clinical trials comply with cGCP. In addition, all of our clinical trials must be conducted with product produced under cGMP. Failure to comply with these regulations may require us to repeat preclinical and clinical trials, which would increase our related expenses and delay the regulatory approval process.

Our CROs and other third parties we may engage to support our development programs are not our employees, and, except for remedies available to us under our agreements with such CROs, we cannot control whether or not they devote sufficient time and resources to our ongoing clinical, non-clinical and preclinical programs. Outsourcing these functions involves risk that third parties may not perform to our standards, may not produce results in a timely manner, or may fail to perform at all. If CROs do not successfully carry out their contractual duties or obligations or meet expected deadlines or if the quality or accuracy of the preclinical results or clinical data they obtain is

compromised due to the failure to adhere to test requirements, our clinical protocols, regulatory requirements or for other reasons, our clinical trials may be extended, delayed or terminated and we may not be able to obtain regulatory approval for or successfully commercialize our Products and product candidates. As a result, our results of operations and the commercial prospects for our Products and product candidates would be harmed, our costs could increase and our ability to generate revenues could be delayed.

If our suppliers or contract manufacturers are unable to manufacture in commercially viable quantities, we could face delays in our ability to commercialize our Products and product candidates, our costs will increase and sales of our Products and product candidates, if approved, may be severely hindered.

If in the future any of our product candidates are approved for commercial sale, we will need to be able to consistently manufacture such product candidates in larger quantities and be able to show equivalency to the FDA, and foreign regulatory authorities, in the manufacture of such product candidates at commercial scale as compared to development batch size. The commercial success of our Products and our product candidates will be dependent on the ability of our contract manufacturers to produce a product in commercial quantities at competitive costs of manufacture in a process that is validated by the FDA. We have scaled up manufacturing for CINVANTI and ZYNRELEF in order to realize important economies of scale, and these activities took time to implement, required additional capital investment, process development and validation studies and regulatory approval. We cannot guarantee that we will be successful in achieving competitive manufacturing costs through such scaled-up activities or that our contract manufacturers will perform their obligations. In addition, our manufacturing agreements include payment terms that require significant cash payments at specified times, and if we are unable to make the required payments at the required times, we are at risk of default under the agreements, which would severely hinder our ability to procure adequate amounts of our Products or product candidates.

The manufacture of pharmaceutical products is a highly complex process in which a variety of difficulties may arise, including product loss due to material failure, equipment failure, vendor error, operator error, labor shortages, inability to obtain material, equipment or transportation, physical or electronic security breaches and natural or man-made disasters. Problems with manufacturing processes could result in product defects or manufacturing failures, which could require us to delay shipment of products or recall products previously shipped, or could impair our ability to expand into new markets or supply products in existing markets. We may not be able to resolve any such problems in a timely manner, if at all.

We depend on third-party suppliers and contract manufacturers to manufacture our Products and our product candidates, and we expect to do the same for any future products that we develop; if our contract manufacturers do not perform as expected, our business could suffer.

We do not own or operate manufacturing facilities for the production of commercial or clinical quantities of any product, including our Products and our product candidates. Our ability to successfully commercialize our Products and our product candidates depends in part on our ability to arrange for and rely on other parties to manufacture our products at a competitive cost, in accordance with regulatory requirements, and in sufficient quantities for clinical testing and eventual commercialization. We currently rely on a small number of third-party manufacturers to produce compounds used in our product development activities and expect to continue to do so to meet the preclinical and clinical requirements of our potential products and for all of our commercial needs. Certain contract manufacturers are, at the present time (and are expected to be for the foreseeable future), our sole resource to manufacture certain key components of our Products and our product candidates, as well as key components for future product candidates in clinical and preclinical testing in our research and development program. Although we entered into long-term commercial manufacturing agreements for the manufacture of our Products and our product candidates, and we have long-term agreements for the manufacture of our Biochronomer Technology, we might not be able to successfully negotiate long-term agreements with any additional third parties, or we might not receive all required regulatory approvals to utilize such third parties, and, accordingly, we might not be able to reduce or remove our dependence on a single supplier for the commercial manufacturing of our Products or our product candidates. We may have difficulties with these manufacturer relationships, and we may not be able to find replacement contract manufacturers on satisfactory terms or on a timely basis. At times, our contract manufacturers or other third parties might not perform their obligations under long-term commercial manufacturing agreements or other agreements, which could impede the manufacturing of our Products and our product candidates and could require us to incur additional costs, including legal fees, as we seek to enforce our contractual rights. Our reliance on

third-party suppliers and contract manufacturers also subjects our business to risks associated with geographic areas in which those parties reside, which could include natural or man-made disasters, including epidemics, pandemics, acts of war or terrorism, or resource shortages. Due to regulatory and technical requirements, we may have limited ability to shift production to a different third-party should the need arise. We cannot be certain that we could reach agreement on reasonable terms, if at all, with such a manufacturer. Even if we were to reach agreement, the transition of the manufacturing process to a different third-party could take a significant amount of time and money, and may not be successful.

Further, we, along with our contract manufacturers, are required to comply with FDA and foreign regulatory requirements related to product testing, quality assurance, manufacturing and documentation. Our contract manufacturers may not be able to comply with the applicable FDA or foreign regulatory requirements. They may be required to pass an FDA pre-approval inspection for conformity with cGMP before we can obtain approval to manufacture our Products and our product candidates and will be subject to ongoing, periodic, unannounced inspection by the FDA and corresponding state agencies to ensure strict compliance with cGMP, and other applicable government regulations and corresponding foreign standards. If we and our contract manufacturers fail to achieve and maintain high manufacturing standards in compliance with cGMP, or fail to scale up manufacturing processes in a timely manner, we may experience manufacturing errors resulting in defective products that could be harmful to patients, product recalls or withdrawals, delays or interruptions of production or failures in product testing or delivery, delay or prevention of filing or approval of marketing applications for our product candidates, cost overruns or other problems that could seriously harm our business. Not complying with FDA or foreign regulatory requirements could result in an enforcement action, such as a product recall, or prevent commercialization of our product candidates and delay our business development activities. In addition, such failure could be the basis for the FDA or foreign regulators to issue a warning or untitled letter or take other regulatory or legal action, including recall or seizure, total or partial suspension of production, suspension of ongoing clinical trials, refusal to approve pending applications or supplemental applications, and potentially civil and/or criminal penalties depending on the matter.

Our Products and product candidates may be in competition with other products for access to the facilities of third parties and, consequently, could be subject to manufacturing delays if our contractors give other companies' products greater priority than ours. Additionally, our contractors might be required by government regulation or government authority to prioritize production of other products, such as priority-rated orders pursuant to the U.S. Government Department of Defense Operation Warp Speed under the Health Resources Priority and Allocations System regulation. For this and other reasons, our third-party contract manufacturers may not be able to manufacture our Products or product candidates in a cost-effective or timely manner. If not manufactured in a timely manner, the clinical development of any of our Products or product candidates or their submission for regulatory approval could be delayed, and our ability to deliver products to market on a timely basis could be impaired. This could increase our costs, cause us to lose revenue or market share and damage our reputation.

Certain of the components used in the manufacture of our Products and product candidates are, or might be, sourced from a single vendor, and the loss or disruption of this vendor could significantly harm our business.

Some of the critical materials and components used in manufacturing our Products and product candidates are, or might be, sourced from single suppliers. An interruption in the supply of a key material could significantly delay our research and development process or increase our expenses for commercialization or development products. Specialized materials must often be manufactured for the first time for use in drug delivery technologies, or materials may be used in the technologies in a manner different from their customary commercial uses. The quality of materials can be critical to the performance of a drug delivery technology, so a reliable source that provides a consistent supply of materials is important. Materials or components needed for our drug delivery technologies may be difficult to obtain on commercially reasonable terms, particularly when relatively small quantities are required or if the materials traditionally have not been used in pharmaceutical products. Our reliance on a single vendor for certain components used in the manufacturing of our Products and our product candidates also subjects our business to risk associated with the geographic areas in which those single vendors reside, which could include natural or man-made disasters, including pandemics, acts of war or terrorism, armed conflict, geopolitical instability or resource shortages. Such adverse events could cause global supply chain interruptions that could increase our costs and, to the extent such interruptions impair our ability to have sufficient inventory, cause us to lose revenue or market share. We continually evaluate our supply chains to identify potential risks and needs for additional

manufacturers and other suppliers for the manufacturing of our Products and product candidates. Establishing additional or replacement suppliers for certain raw materials in our proprietary polymers, if required, may not be accomplished quickly, or at all, and may involve significant expense. If we are able to find a replacement supplier, we would need to evaluate and qualify such replacement vendor and its ability to meet quality and compliance standards. Any change in suppliers or the manufacturing process could require additional regulatory approval and result in operational delays.

Some of our suppliers may experience disruption to their respective supply chains due to the adverse events or conditions, including the effects of the COVID-19 pandemic, rising geopolitical tensions, armed conflict or other factors, which could delay, prevent or impair our development or commercialization efforts.

We obtain certain critical materials and components used in manufacturing our Products and our product candidates from third-party suppliers whose operations might be directly or indirectly affected by adverse events or conditions, including the effects of the COVID-19 pandemic, rising geopolitical tensions, armed conflict or other factors (including, without limitation, adverse weather conditions, political instability, war, civil unrest, economic instability, outbreaks of disease, or other public health emergencies and the impact of any such U.S. or foreign government response and public fears regarding any of the foregoing). For example, in particular, in recent years, tensions between mainland China and Taiwan have further escalated, with China accelerating the development of military capabilities and threatening the use of military force to gain control over Taiwan in certain circumstances. Similarly, the ongoing armed conflict between Russia and Ukraine remains unpredictable and could escalate into a broader armed conflict and additional economic sanctions by the U.S., the United Nations or other countries against Russia. If we are unable to obtain these critical materials and components in sufficient quantities and in a timely manner, the development, testing and clinical study of our Products and product candidates might be delayed or infeasible, and regulatory approval or commercialization of our Products and product candidates might be delayed, not obtained or hindered, which could significantly harm our business.

We have, or may have, significant inventory levels of drug products, and write-downs related to the impairment of those inventories may adversely impact or delay our profitability.

We have, or may have, significant inventory levels of drug products, and we may increase those inventory levels as we continue to commercialize our Products and our product candidates. We determine inventory levels of drug products based on a variety of estimates, including timing of regulatory approval of our drug products, market demand for our drug products and those of our competitors, entrance of competing drug products, introduction of new, or changes in interpretations of, pharmaceutical regulations, and changes in healthcare provider and insurer reimbursement policies. These estimates are inherently difficult to make and may be inaccurate. We analyze our inventory levels and will write down inventory that has become obsolete. If our initial estimate of the appropriate inventory levels of drug products is or becomes inaccurate, write-downs of inventory may be required, which would be recorded as cost of product sales and thereby adversely impact or delay our profitability.

It is difficult to predict commercial demand for our Products, and, if our estimates of demand are too low, it may adversely impact our ability to generate revenue and profits in the short term and our ability to establish and maintain a competitive position in the relevant markets where our Products are sold, or may be sold, in the future.

Despite our efforts to maintain appropriate inventory levels of our Products, as we continue to commercialize our Products, our estimates of appropriate inventory levels may not be accurate. If we fail to build up sufficient inventory levels to meet commercial demand, our ability to generate revenue and profits in the short term would be adversely impacted. Failure to meet demand may also cause us to lose market share to our competitors, which could materially and adversely affect our business, financial condition, cash flows and results of operations. Given the time required to scale production and replenish inventory, our ability to correct for inaccurate estimates in a timely manner may be limited.

Similarly, if we are unable to ramp up production of prospective product candidates to coincide with the regulatory approval of those product candidates, our ability to generate revenue and profits in the short term would be adversely impacted. If our competitors are able to meet demand with their products before we are able to produce and sell inventory, our ability to gain market share will be adversely impacted, which could materially and adversely

affect our business, financial condition, cash flows and results of operations. In addition, if regulatory approval of any of our product candidates comes earlier than anticipated, as a result of preferential designations designed to hasten the approval process or otherwise, and we have not built up sufficient inventory to meet commercial demand, our ability to generate additional revenue sooner as a result of those early approvals may be diminished.

We face intense competition from other companies developing products for the management of postoperative pain or the prevention of CINV and PONV.

In the U.S., ZYNRELEF competes in, and HTX-034, if successfully developed, will compete in, the postoperative pain management market with MARCAINE™ (bupivacaine hydrochloride injection, solution, marketed by Pfizer Inc.) and generic forms of bupivacaine; NAROPIN® (ropivacaine, marketed by Fresenius Kabi USA, LLC) and generic forms of ropivacaine; EXPAREL® (bupivacaine liposome injectable suspension, marketed by Pacira BioSciences, Inc.); XARACOLL® (bupivacaine HCl implant, marketed by Innocoll Pharmaceuticals Limited); POSIMIR® (owned by Durect Corporation and to be marketed in the U.S. by Innocoll Pharmaceuticals Limited); ANJESO® (meloxicam injection, marketed by Baudax Bio, Inc.); OFIRMEV® (acetaminophen injection, marketed by Mallinckrodt Pharmaceuticals); SEGLENTIS® (celecoxib and tramadol hydrochloride, marketed by Kowa Pharmaceuticals America, Inc. in the U.S.); generic forms of IV acetaminophen; and potentially other products in development for postoperative pain management that reach the U.S. market.

In the EU, ZYNRELEF will, and HTX-034, if successfully developed will also, face significant competition. Currently there are numerous generic local anesthetics and other non-opioids for postoperative pain management available in the EU, and other products in development for postoperative pain management may also reach the EU market. For example, in November 2020 the EC granted a marketing authorization for EXPAREL® (bupivacaine liposome injectable suspension, marketed by Pacira BioSciences, Inc. in the U.S.) for postsurgical analgesia, and EXPAREL was launched in the EU in the fourth quarter of 2021.

ZYNRELEF will compete with MARCAINE™ (bupivacaine hydrochloride injection, solution, marketed by Pfizer Inc.); SENSORCAINE® (bupivacaine and epinephrine injection, marketed by Aspen Pharmacare Canada Inc.); NAROPIN® (ropivacaine and hydrochloride, marketed by Aspen Pharmacare Canada Inc.); and potentially other products in development for postoperative pain management that reach the Canadian market.

CINVANTI faces significant competition. NK_1 receptor antagonists are administered for the prevention of CINV, in combination with 5-HT_3 receptor antagonists, to augment the therapeutic effect of the 5-HT_3 receptor antagonist. Currently available NK_1receptor antagonists include: generic versions of EMEND® IV (fosaprepitant); EMEND® IV (fosaprepitant, marketed by Merck & Co., Inc.); EMEND® (aprepitant, marketed by Merck & Co., Inc.); AKYNZEO® (palonosetron, a 5-HT_3 receptor antagonist, combined with netupitant, an NK_1 receptor antagonist, marketed by Helsinn Therapeutics (U.S.), Inc.); VARUBI® (rolapitant, marketed by TerSera Therapeutics LLC) and other products that include an NK_1 receptor antagonist that reach the market for the prevention of CINV.

SUSTOL faces significant competition. Currently available 5-HT_3 receptor antagonists include: AKYNZEO® (palonosetron, a 5-HT_3 receptor antagonist, combined with netupitant, an NK_1 receptor antagonist, marketed by Helsinn Therapeutics (U.S.), Inc.); SANCUSO® (granisetron transdermal patch, marketed by Cumberland Pharmaceuticals Inc.); and generic products including ondansetron (formerly marketed by GlaxoSmithKline plc as ZOFRAN), granisetron (formerly marketed by Hoffman-La Roche, Inc. as KYTRIL) and palonosetron (formerly marketed by Eisai in conjunction with Helsinn Healthcare S.A. as ALOXI). Currently, palonosetron is the only 5-HT_3 receptor antagonist other than SUSTOL that is approved for the prevention of delayed CINV associated with MEC regimens. SUSTOL is indicated in combination with other antiemetics in adults for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic chemotherapy (MEC) or anthracycline and cyclophosphamide (AC) combination chemotherapy regimens, which is considered to be a HEC regimen by the NCCN and ASCO. No other 5-HT_3 receptor antagonist is specifically approved for the prevention of delayed CINV associated with a HEC regimen.

In the U.S., APONVIE will compete in the PONV prevention market with generic ondansetron, the current standard of care, generic aprepitant, and BARHEMSYS® (amisulpride, marketed by Eagle Pharmaceuticals, Inc.); TAK-951 (a peptide agonist under development (PH2) by Takeda Pharmaceutical Company Limited for PONV and not approved anywhere globally for any use); and potentially other products in development for PONV prevention that

reach the market. Small or early-stage companies and research institutions may also prove to be significant competitors, particularly through collaborative arrangements with large and established pharmaceutical companies. We will also face competition from these parties in recruiting and retaining qualified scientific and management personnel, establishing clinical trial sites and patient registration for clinical trials, and acquiring and in-licensing technologies and products complementary to our programs or potentially advantageous to our business. If any of our competitors succeed in obtaining approval from the FDA or other regulatory authorities for their product candidates sooner than we do for our product candidates that are more effective or less costly than ours, our commercial opportunity could be significantly reduced. Major technological changes can happen quickly in the biotechnology and pharmaceutical industries, and the development of technologically improved or different products or drug delivery technologies may make our product candidates or platform technologies obsolete or noncompetitive.

Our Products and product candidates may face competition from lower-cost generic products offered by our competitors.

Pricing for therapeutics can be extremely competitive, and strict formulary guidelines enforced by payors may create significant challenges in the acceptance and profitability of branded products. The market for generic products can be very lucrative, and it is dominated by companies that may have much larger distribution capabilities than we may have in the future. It can be very difficult to predict the timing of the launch of generic products given the commonality of litigation with manufacturers over anticipated patent expiration. Our inability to accurately foresee and plan for generic product launches that may compete with our Products and our product candidates may significantly impact our potential revenues from such Products and product candidates. On the expiration or loss of patent protection for a branded product, or on the "at-risk" launch (despite pending patent infringement litigation against the generic product) by a manufacturer of a generic version of a drug that may compete with one of our products, we could quickly lose a significant portion of our sales of that Product or product candidate. The inability for a branded Product or product candidate we may sell to successfully compete against generic products could negatively impact sales of our Product or product candidate, reduce our ability to grow our business and significantly harm our business prospects.

For example, generic versions of EMEND® IV (fosaprepitant) launched in September 2019 following the expiration of the EMEND IV patents. As a result, we experienced increased competition for CINVANTI, which reduced CINVANTI sales and harmed and may continue to harm our business prospects. These and other risks related to the entry of generic product competing with CINVANTI are difficult to assess in terms of timing and impact on our operations and prospects.

Additionally, while we had expected that generic versions of ALOXI (palonosetron) would launch in September 2018 following the expiration of the ALOXI patents, a U.S. Court of Appeals for the Federal Circuit decision in May 2017 ruled in favor of a generic drug company challenging the ALOXI patents, thereby potentially accelerating the entry of generic versions of ALOXI (palonosetron). The Supreme Court granted certiorari in June 2018 and affirmed the Federal Circuit decision in January 2019. As a result of this litigation, generic versions of ALOXI (palonosetron) have entered the market and we have experienced increased competition for SUSTOL, which has reduced SUSTOL sales and may continue to negatively affect our future business prospects. These and other risks related to the entry of generic product competing with SUSTOL are difficult to assess in terms of timing and impact on our operations and prospects.

Our business and results of operations may suffer as a result of changes in our pricing or marketing strategies.

In an effort to remain competitive in the marketplace, we can determine, from time to time, to change our pricing or marketing strategies for our approved Products, including by altering the amount or availability of discounts or rebates for any of our approved Products. Any such changes could have short-term or long-term negative impacts on our revenues, which would cause our business and results of operations to suffer. For example, in October 2019, we eliminated the discounts on SUSTOL which reduced revenues. Price increases or changes to our marketing strategies may also negatively affect our reputation and our ability to secure and maintain reimbursement coverage for our approved Products, which could result in decreased demand and cause our business and results of operations to suffer.

Guidelines and recommendations published by various organizations could reduce the demand for or use of our Products.

Government agencies promulgate regulations and guidelines directly applicable to us and to our Products and product candidates. In addition, professional societies, practice management groups, private health and science foundations and other organizations from time to time may publish papers, guidelines or recommendations to the healthcare and patient communities with respect to specific products or classes of products. Recommendations of government agencies or these other groups or organizations may relate to such matters as usage, dosage, route of administration and use of concomitant therapies. Recommendations or guidelines that do not recognize a Product, suggest limitations or inadequacies of a Product or suggest the use of competitive or alternative products as the standard of care to be followed by patients and healthcare providers could result in decreased use or adoption of any of our Products which could have an adverse impact on our business, financial condition and results of operations.

If we are unable to recruit and retain skilled employees, we may not be able to achieve our objectives.

We depend on a small number of key management and personnel, including our Chief Executive Officer. Retaining our current employees and recruiting qualified personnel to perform future research and development and commercialization work will be critical to our success. Competition is always present for highly skilled and experienced personnel, and an inability to recruit or retain sufficient skilled personnel could result in delays in our business growth and development and adversely impact our research and development or commercial activities. If we lose key members of our senior management team, we may not be able to find suitable replacements and our business may be harmed as a result. This competitive situation became exacerbated by the increase in employee resignations that took place throughout the U.S., in part as a result of the COVID-19 pandemic, which was commonly referred to as the "great resignation." In addition, our ability to recruit and retain key skilled employees may be hampered by our recently announced workforce reduction. If we fail to adequately address any of the issues referred to above, it could adversely impact our ability to recruit and retain our skilled employees which may result in a material adverse effect on our business, operating results and financial condition.

We may not realize the expected benefits of our cost-saving initiatives.

In June 2022, in connection with our efforts to decrease costs and maintain a streamlined organization to support our acute care and oncology care franchises, we implemented a workforce reduction that resulted in the termination of approximately 34% of our workforce. If we experience excessive unanticipated inefficiencies or incremental costs in connection with restructuring activities, such as unanticipated inefficiencies caused by our reduced headcount, we may be unable to meaningfully realize cost savings or capitalize on future opportunities and we may incur expenses in excess of what we anticipate. Any of these outcomes could prevent us from meeting our strategic objectives and could adversely impact our results of operations and financial condition.

Our business strategy may include acquisitions of other businesses, products or product licenses. We may not be able to successfully manage such activities.

We may engage in strategic transactions that could cause us to incur contingent liabilities, commitments or significant expense. In the course of pursuing strategic opportunities, we may evaluate potential acquisitions, licenses or investments in strategic technologies, products or businesses. Future acquisitions, licenses or investments could subject us to a number of risks, including, but not limited to:

- our inability to appropriately evaluate and take into consideration the potential uncertainties associated with the other party to such a transaction, including, but not limited to, the prospects of that party and their existing products or product candidates and regulatory approvals;

- difficulties associated with realizing the perceived potential for commercial success with respect to any acquired or licensed technology, product or business;

- our ability to effectively integrate any new technology, product and/or business including personnel, intellectual property or business relationships into our Company;

- our inability to generate revenues from acquired or licensed technology and/or products sufficient to meet our objectives in undertaking the acquisition or license or even to offset the associated acquisition and maintenance costs and/or assumption of liabilities; and

- the distraction of our management from our existing product development programs and initiatives in pursuing an acquisition or license.

In connection with an acquisition or license, we must estimate the value of the transaction by making certain assumptions that may prove to be incorrect, which could cause us to fail to realize the anticipated benefits of a transaction. Any strategic transaction we may pursue may not result in the benefits we initially anticipate, may result in costs that end up outweighing the benefits and may adversely impact our financial condition and be detrimental to our future business prospects.

Our business strategy may include entry into collaborative agreements. We may not be able to enter into collaborative agreements or may not be able to negotiate commercially acceptable terms for these agreements.

Our business strategy may include the entry into collaborative agreements for the development and commercialization of our Products and our product candidates. The negotiation and consummation of these types of agreements typically involve simultaneous discussions with multiple potential collaborators and require significant time and resources from our officers, business development and research and development staff. In addition, in attracting the attention of pharmaceutical and biotechnology company collaborators, we compete with numerous other third parties with product opportunities as well as the collaborators' own internal product opportunities. We may not be able to consummate collaborative agreements, or we may not be able to negotiate commercially acceptable terms for these agreements.

If we do enter into such arrangements, we could be dependent on the subsequent success of these other parties in performing their respective responsibilities and the cooperation of our partners. Our collaborators may not cooperate with us or perform their obligations under our agreements with them. We cannot control the amount and timing of our collaborators' resources that will be devoted to researching our product candidates pursuant to our collaborative agreements with them. Our collaborators may choose to pursue existing or alternative technologies in preference to those being developed in collaboration with us.

Under agreements with any collaborators we may work with in the future, we may rely significantly on them to, among other activities:

- fund or perform research and development activities with us or independently;

- diligently pursue regulatory approvals in certain territories;

- pay us fees on the achievement of milestones; and

- market for or with us any commercial products that result from our collaborations.

If we do not consummate collaborative agreements, we may use our financial resources more rapidly on our product development efforts, continue to defer certain development activities or forego the exploitation of certain geographic territories, any of which could have a negative impact on our business prospects. Further, we may not be successful in overseeing any such collaborative arrangements. If we fail to establish and maintain necessary collaborative relationships, our business prospects could suffer.

The evolving effects of the COVID-19 pandemic and associated global economic instability could have further adverse effects on our business, including our commercialization efforts, supply chain, regulatory activities, clinical development activities and other business operations.

We are subject to risks related to public health crises such as the global pandemic associated with the novel coronavirus and the associated disease. Our business is currently being adversely affected and could in the future be adversely affected by the evolving effects of the COVID-19 pandemic. We may experience disruptions that could severely impact our sales, business, operations, preclinical and clinical studies and corporate culture, such as:

- decreased sales of our Products and our product candidates;
- fewer individuals undertaking or completing cancer treatments and elective surgeries, whether due to contracting COVID-19, self-isolating or quarantining to lower the risk of contracting COVID-19, or being unable to access care as a result of healthcare providers tending to COVID-19 patients;
- our third-party contract manufacturers not being able to maintain adequate (in amount and quality) supply to support the commercial sale of our Products and our product candidates, or the clinical development of our product candidates due to staffing shortages, production slowdowns or stoppages and disruptions in delivery systems;
- delays and difficulties in clinical site initiation, including difficulties in recruiting clinical site investigators and clinical site staff, delays or difficulties in enrolling patients or maintaining enrolled patients in our clinical trials and failure of our CROs to perform all or a part of their obligations;
- interruption or delays in the operations of the FDA and comparable foreign regulatory agencies, which may impact regulatory review and approval timelines;
- limitations on our employee resources, and those of our business partners, that would otherwise be focused on the conduct of our business in all aspects, including because of sickness of employees or members of their families and inherent difficulties involved with maintaining a remote working structure amidst a global pandemic;
- the prolonged and broad-based shift to a remote working environment continues to create inherent productivity, connectivity, and oversight challenges and could affect our ability to market our Products and develop and seek regulatory approvals for our product candidates. In addition, the changed environment under which we are operating could have an effect on our internal controls over financial reporting as well as our ability to meet a number of our compliance requirements in a timely or quality manner. Governmental lockdowns, restrictions or new regulations could significantly impact the ability of our employees and vendors to work productively. Governmental restrictions have been globally inconsistent and it remains unclear whether there could be future worksite or travel restrictions. As a result, we may experience increased costs as we prepare our facilities for a safe work environment and experiment with hybrid work models, in addition to potential effects on our ability to compete effectively and maintain our corporate culture; and
- disruption to global financial markets, which could reduce our ability to access capital and negatively affect our liquidity.

These and other factors arising from the COVID-19 pandemic could result in us not being able to maintain market position or increase market penetration for our Products and our product candidates, and could result in our inability to meet development milestones for our product candidates, each of which would harm our business, financial condition, results of operations and growth. In addition, the COVID-19 pandemic and actions taken in response to it by governments, businesses and individuals may give rise to or amplify the other risks discussed under this section entitled “Risk Factors.”

Natural or man-made disasters, including epidemics, pandemics, acts of war or terrorism, or resource shortages, could disrupt our investigational drug candidate development and approved drug commercialization efforts or have other negative consequences on our business and adversely affect results.

Our ongoing or planned clinical studies and approved drug commercialization efforts could be delayed or disrupted indefinitely on the occurrence of a natural or man-made disaster, including an epidemic, pandemic, cyberattack, or acts of war or terrorism, or resource shortages. For example, COVID-19 has caused a decline in, and suspensions of, elective surgeries, which negatively impacts our ability to conduct our clinical trials and, if it continues, could decrease the potential market opportunities for ZYNRELEF and APONVIE, as well as HTX-034, if approved, in the U.S. or other markets. In addition, COVID-19 has slowed the diagnosis procedures to identify cancer and may reduce the number of new cancer patients seeking treatment which may negatively impact our CINV products. We are also vulnerable to damage from other disasters, such as power losses, fires, earthquakes, floods, hurricanes and similar events. For example, a natural or man-made disaster, including an epidemic, pandemic, cyberattack, or act of war or terrorism, and the resulting damage could negatively impact enrollment and participation in our clinical studies, divert attention and resources at our research sites, cause unanticipated delays in the collection and receipt of data from our clinical studies, cause unanticipated delays in communications with, and any required approvals from, the FDA, European Medicines Agency, United Kingdom's Medicines and Healthcare Products Regulatory Agency, Health Canada, and other regulatory authorities, and cause unanticipated delays in the manufacturing and distribution of our Products and our product candidates. If a significant disaster occurs, our ability to continue our operations could be seriously impaired and we may not have adequate insurance to cover any resulting losses. Any significant unrecoverable losses could seriously impair our operations and financial condition.

Further, the current Russia-Ukraine conflict has created extreme volatility in the global financial markets and is expected to have further global economic consequences, including continued disruptions of the global supply chain and energy markets and heightened volatility of commodity prices. The U.S. government and other nations have imposed significant restrictions on most companies' ability to do business in Russia as a result of the conflict, and it is not possible to predict the broader or longer-term consequences of this conflict, which could include further sanctions, embargoes, regional instability, geopolitical shifts and adverse effects on macroeconomic conditions, security conditions, currency exchange rates and financial markets. Any such instability or disruption may have adverse consequences on us or the third parties on whom we rely, including as a result of a general downturn in global economic conditions, deterioration in the credit or equity markets, or more direct impacts on operational matters. This conflict may also give rise to or amplify the other risks described herein including risks relating to cybersecurity, global economic conditions, and supply chains, which could adversely affect our business, operations and financial condition and results.

Our potential international expansion of our business may expose us to new business, regulatory, political, operational, financial and economic risks associated with such expansion and could adversely affect our business, financial condition, results of operations and growth.

In addition to our operations in the U.S., we are pursuing international expansion to support the planned commercialization of ZYNRELEF through third parties. If ZYNRELEF or our other Products or product candidates are marketed internationally by potential third-party partners, we and such third-party partners could be subject to additional risks related to operating in foreign countries, including:

- general economic conditions and monetary and fiscal policy, including economic weakness or inflation;
- financial risks, such as longer payment cycles, difficulty in collecting from international customers, pricing and insurance regimes, unexpected changes in tariffs, trade barriers, and exposure to foreign currency exchange rate fluctuations and controls, which could result in increased operating expenses and reduced revenue, and the effect of local and regional financial crises;
- conflicting and changing laws and regulations such as export and import restrictions;
- compliance with tax, employment, immigration and labor laws for employees living or traveling abroad;

- foreign taxes, including withholding of payroll taxes;
- difficulties staffing and managing foreign operations;
- workforce uncertainty in countries where labor unrest is more common than in the U.S.;
- potential liability under the FCPA or comparable foreign regulations;
- challenges enforcing contractual and intellectual property rights, especially in those foreign countries that do not respect and protect intellectual property rights to the same extent as the U.S.;
- production shortages resulting from any events affecting raw material supply or manufacturing capabilities abroad, if applicable;
- logistical challenges resulting from distributing our Products and product candidates to foreign countries; and
- economic or business interruptions resulting from civil unrest or social, political, economic, or diplomatic developments, including geo-political actions, such as armed conflict or terrorism.

These and other risks associated with international operations may compromise our ability to earn revenue from arrangements with potential third-party partners for ZYNRELEF or our other Products or product candidates and, therefore, could adversely affect our business, operations and planned international expansion.

Risks Related to Our Financial Condition

We have a history of losses, we expect to generate losses in the near future, and we may never achieve or maintain profitability.

We have incurred significant operating losses and negative cash flows from operations and had an accumulated deficit of $1.8 billion through December 31, 2022. We expect to continue to generate substantial losses in the near future as we:

- expand product development activities with respect to our Products and product candidates;
- conduct preclinical development and clinical trials for our Products and product candidates;
- pursue regulatory approvals for any current or future Products or product candidates; and
- engage in commercialization efforts for any future approved product candidates.

In addition, the amount we spend will impact our profitability. Our spending will depend, in part, on:

- the number of product candidates we pursue;
- the progress of our research and development programs for our product candidates, including clinical trials;
- the time and expense required to pursue FDA and/or non-U.S. regulatory approvals for our product candidates, whether such approvals are obtained and the scope of any approved product label;
- the cost of possible acquisitions of technologies, compounds, product rights or companies;
- the cost of obtaining licenses to use technology owned by others for proprietary products and otherwise;

- the time and expense required to prosecute, enforce and/or challenge patent and other intellectual property rights;

- the costs of potential litigation; and

- the costs associated with recruiting and compensating a highly skilled workforce in an environment where competition for such employees may be intense.

To achieve and sustain profitability, we must, alone or in cooperation with others, successfully develop, obtain regulatory approval for, manufacture, market and sell our Products, including our current work commercializing our Products and our anticipated work commercializing our product candidates. We will incur substantial expenses in our efforts to develop and commercialize our Products and our product candidates and we may never generate sufficient revenue to become profitable or to sustain profitability.

Additional capital may be needed in the future to enable us to implement our business plan, and we may be unable to raise capital, which would force us to limit or cease our operations and related product development programs.

As of December 31, 2022, we had cash, cash equivalents and short-term investments of $84.9 million. Historically, we have financed our operations, including technology and product research and development, primarily through sales of our common stock and debt financings.

Our capital requirements and liquidity going forward will depend on numerous factors, including but not limited to: the costs associated with the U.S. commercial launches of ZYNRELEF, APONVIE and our product candidates, if approved, and making some or all of our Products and our product candidates commercially available outside of the U.S.; the degree of commercial success of our Products and our product candidates, if approved; the scope, rate of progress, results and costs of preclinical testing and clinical trials; the timing and cost to manufacture our Products and our product candidates; the number and characteristics of product development programs we pursue and the pace of each program, including the timing of clinical trials; the time, cost and outcome involved in seeking other regulatory approvals, including an expanded U.S. label for ZYNRELEF; scientific progress in our research and development programs; the magnitude and scope of our research and development programs; our ability to establish and maintain strategic collaborations or partnerships for research, development, clinical testing, manufacturing and marketing of our product candidates; the impact of competitive products; the cost and timing of establishing sales, marketing and distribution capabilities if we commercialize products independently; the cost of establishing clinical and commercial supplies of our product candidates; the impact of our restructuring plans; the extent of the impact of the ongoing COVID-19 pandemic on our business; and general market conditions. Management's view of our liquidity relies on estimates and assumptions about the market opportunity for the expanded U.S. label of ZYNRELEF, which estimates and assumptions are subject to significant uncertainty.

We may not be able to raise additional capital when needed or desired, or we may need to raise additional capital on unfavorable terms, which could result in dilution to existing stockholders.

We may not be able to raise sufficient additional capital when needed on favorable terms, or at all. If we are unable to obtain adequate funds, we may be required to curtail significantly or cease our operations.

The timing and degree of any future capital requirements will depend on many factors, including:

- our ability to successfully commercialize, market and achieve market acceptance of our Products and our product candidates;
- the status of regulatory approval of any pending applications with the FDA, or other regulators, as the case may be, and the costs involved with pursuing regulatory approvals;
- the number and characteristics of product development programs we pursue and the pace of each program;
- the scope, rate of progress, results and costs of preclinical testing and clinical trials;
- our ability to establish and maintain strategic collaborations or partnerships for research, development, clinical testing, manufacturing and marketing of our product candidates;
- the cost and timing of establishing or enlarging sales and marketing capabilities;
- the cost of establishing supply arrangements for clinical and commercial development of our Products and our product candidates; and
- the extent of the evolving effects of the COVID-19 pandemic on our business, or other factors (including the current Russia-Ukraine conflict).

If we issue additional equity securities or securities convertible into equity securities to raise funds, our stockholders will suffer dilution of their investment, and such issuance may adversely affect the market price of our common stock.

Any new debt financing we enter into may involve covenants that restrict our operations. These restrictive covenants may include, among other things, limitations on borrowing and specific restrictions on the use of our assets, as well as prohibitions on our ability to create liens, pay dividends, redeem capital stock or make investments. Our Senior Unsecured Convertible Notes also impose certain negative covenants on the Company, including on the incurrence of certain indebtedness, the creation of certain liens and selling royalty interests in Company assets. In the event that additional funds are obtained through arrangements with collaborative partners, these arrangements may require us to relinquish rights to some of our technologies, product candidates or Products on terms that are not favorable to us or require us to enter into a collaboration arrangement that we would otherwise seek to develop and commercialize ourselves. If adequate funds are not available, we may default on our indebtedness, be required to further delay, reduce the scope of, or eliminate one or more of our product development programs and reduce personnel-related and other costs, which would have a negative impact on our business.

Provisions contained in our debt instruments limit our ability to incur additional indebtedness.

The terms of our Senior Unsecured Convertible Notes require us to seek approval from the holders of such notes before taking certain actions, including incurring certain additional indebtedness, modifying the terms of certain existing indebtedness, creating liens or selling royalty interests in Company assets. The Senior Unsecured Convertible Notes also contain provisions that trigger events of default on any default of our financial obligations under certain material contracts we may enter into. As a result, we may not be able to raise funds through the

issuance of debt or selling of royalty interests in the future, which could impair our ability to finance our business obligations or pursue business expansion initiatives.

We could be exposed to significant product liability claims that could be time-consuming and costly to defend, divert management attention and adversely impact our ability to obtain and maintain insurance coverage.

The administration of drugs in humans, whether in clinical studies or commercially, carries the inherent risk of product liability claims whether or not the drugs are actually the cause of an injury. Our Products, our product candidates and other products that we may commercially market in the future may cause, or may appear to have caused, injury or dangerous drug reactions, and we may not learn about or understand those effects until the Product or product candidate has been administered to patients for a prolonged period of time.

Although we are insured against such risks up to an annual aggregate limit in connection with clinical trials and commercial sales of our Products, our present product liability insurance may be inadequate and may not fully cover the costs of any claim or any ultimate damages we might be required to pay. Product liability claims or other claims related to our Products, regardless of their outcome, could require us to spend significant time and money in litigation or to pay significant damages. Any successful product liability claim may prevent us from obtaining adequate product liability insurance in the future on commercially desirable or reasonable terms. In addition, product liability coverage may cease to be available in sufficient amounts or at an acceptable cost. An inability to obtain sufficient insurance coverage at an acceptable cost or otherwise to protect against potential product liability claims could prevent or inhibit the commercialization of our Products. A product liability claim could also significantly harm our reputation and delay market acceptance of our Products.

If any of our services providers are characterized as employees, we would be subject to employment and tax withholding liabilities and other additional costs.

We rely on independent third parties to provide certain services to us. We structure our relationships with these outside services providers in a manner that we believe results in an independent contractor relationship, not an employee relationship. An independent contractor is generally distinguished from an employee by his or her degree of autonomy and independence in providing services. A high degree of autonomy and independence is generally indicative of an independent contractor relationship, while a high degree of control is generally indicative of an employment relationship. Tax or other regulatory authorities may challenge our characterization of services providers as independent contractors both under existing laws and regulations and under laws and regulations adopted in the future. We are aware of a number of judicial decisions and legislative proposals that could bring about major changes in the way workers are classified, including the California legislature's passage of California Assembly Bill 5, which California Governor Gavin Newsom signed into law in September 2019 ("AB 5") and Assembly Bill 2257, which went into effect in September 2020 and amended certain portions of AB 5 ("AB 2257"). AB 5 and AB 2257 are often referred to collectively simply as AB 5. AB 5 purports to codify the holding of the California Supreme Court's unanimous decision in Dynamex Operations West, Inc. v. Superior Court of Los Angeles, which introduced a new test for determining worker classification that is widely viewed as expanding the scope of employee relationships and narrowing the scope of independent contractor relationships. While AB 5 exempts certain licensed health care professionals, including physicians and psychologists, not all of our independent contractors work in exempt occupations. Given AB 5's relatively recent passage, there is little guidance from the regulatory authorities charged with its enforcement and there is a significant degree of uncertainty regarding its application. In addition, AB 5 has been the subject of widespread national discussion and it is possible that other jurisdictions might enact similar laws. As a result, there is significant uncertainty regarding what the state, federal and foreign worker classification regulatory landscape will look like in future years. The current economic climate indicates that the debate over worker classification will continue for the foreseeable future. If such regulatory authorities or state, federal or foreign courts were to determine that our services providers are employees and not independent contractors, we would, among other things, be required to withhold income taxes, to withhold and pay Social Security, Medicare and similar taxes, to pay unemployment and other related payroll taxes, and to provide certain employee benefits. We could also be liable for unpaid past taxes and other costs and subject to penalties. As a result, any determination that the services providers we characterize as independent contractors are our employees could have a negative impact on our business, financial condition and results of operations.

The investment of our cash is subject to risks, which may cause losses or adversely affect the liquidity of these investments and our results of operations, liquidity and financial condition.

A significant amount of our assets is comprised of cash, cash equivalents and short-term investments. These investments of cash, cash equivalents and short-term investments are subject to general credit, liquidity, market and interest rate risks, which have been and may, in the future, be exacerbated by a U.S. and/or global financial crisis. We may realize losses in the fair value of certain of our investments or a complete loss of these investments if the credit markets tighten, which would have an adverse effect on our results of operations, liquidity and financial condition.

Adverse developments affecting the financial services industry, such as actual events or concerns involving liquidity, defaults or non-performance by financial institutions or transactional counterparties, could adversely affect our current and projected business operations and its financial condition and results of operations.

Actual events involving limited liquidity, defaults, non-performance or other adverse developments that affect financial institutions, transactional counterparties or other companies in the financial services industry or the financial services industry generally, or concerns or rumors about any events of these kinds or other similar risks, have in the past and may in the future lead to market-wide liquidity problems. For example, on March 10, 2023, Silicon Valley Bank ("SVB"), was closed by the California Department of Financial Protection and Innovation, which appointed the Federal Deposit Insurance Corporation, or the FDIC, as receiver. Similarly, on March 12, 2023, Signature Bank and Silvergate Capital Corp. were each swept into receivership. Although a statement by the Department of the Treasury, the Federal Reserve and the FDIC stated that all depositors of SVB would have access to all of their money after only one business day of closure, including funds held in uninsured deposit accounts, borrowers under credit agreements, letters of credit and certain other financial instruments with SVB, Signature Bank or any other financial institution that is placed into receivership by the FDIC may be unable to access undrawn amounts thereunder. If any of our counterparties to any such instruments were to be placed into receivership, we may be unable to access such funds. In addition, if any parties with whom we conduct business are unable to access funds pursuant to such instruments or lending arrangements with such a financial institution, such parties' ability to pay their obligations to us or to enter into new commercial arrangements requiring additional payments to us could be adversely affected. In this regard, counterparties to SVB credit agreements and arrangements, and third parties such as beneficiaries of letters of credit (among others), may experience direct impacts from the closure of SVB and uncertainty remains over liquidity concerns in the broader financial services industry. As of March 10, 2023, we maintained a de minimis amount of cash and cash equivalents, in the low single digit millions of U.S. dollars, with SVB, all of which we were able to successfully recover.

Although we assess our banking relationships as we believe necessary or appropriate, our access to funding sources and other credit arrangements in amounts adequate to finance or capitalize our current and projected future business operations could be significantly impaired by factors that affect us, the financial institutions with which we have arrangements directly, or the financial services industry or economy in general. These factors could include, among others, events such as liquidity constraints or failures, the ability to perform obligations under various types of financial, credit or liquidity agreements or arrangements, disruptions or instability in the financial services industry or financial markets, or concerns or negative expectations about the prospects for companies in the financial services industry. These factors could involve financial institutions or financial services industry companies with which we have financial or business relationships, but could also include factors involving financial markets or the financial services industry generally. The results of events or concerns that involve one or more of these factors could include a variety of material and adverse impacts on our current and projected business operations and our financial condition and results of operations.

In addition, investor concerns regarding the U.S. or international financial systems could result in less favorable commercial financing terms, including higher interest rates or costs and tighter financial and operating covenants, or systemic limitations on access to credit and liquidity sources, thereby making it more difficult for us to acquire financing on acceptable terms or at all. Any decline in available funding or access to our cash and liquidity resources could, among other risks, adversely impact our ability to meet our operating expenses, financial obligations or fulfill our other obligations, result in breaches of our financial and/or contractual obligations or result in violations of federal or state wage and hour laws. Any of these impacts, or any other impacts resulting from the factors described

above or other related or similar factors not described above, could have material adverse impacts on our liquidity and our current and/or projected business operations and financial condition and results of operations.

Further, any further deterioration in the macroeconomic economy or financial services industry could lead to losses or defaults by parties with whom we conduct business, which in turn, could have a material adverse effect on our current and/or projected business operations and results of operations and financial condition. For example, a party with whom we conduct business may fail to make payments when due, default under their agreements with us, become insolvent or declare bankruptcy. Any bankruptcy or insolvency, or the failure to make payments when due, of any counterparty of ours, or the loss of any significant relationships, could result in material losses to us and may material adverse impacts on our business.

Risks Related to Our Industry

Drug development involves a lengthy and expensive process with an uncertain outcome, and results of earlier studies and trials may not be predictive of future trial results.

Conducting clinical trials is a lengthy, time-consuming and expensive process. For example, we incurred significant expenses in developing our Products, with no guarantees that doing so would result in a commercially viable product. Before obtaining regulatory approvals for the commercial sale of any products, we, or our potential partners, must demonstrate through preclinical testing and clinical trials that our product candidates are safe and effective for their intended uses in humans. We have incurred and will continue to incur substantial expense and devote a significant amount of time to preclinical testing and clinical trials.

The outcome of clinical testing is inherently uncertain. Failure can occur at any time during the clinical trial process. The results of preclinical studies and early clinical trials of product candidates may not be predictive of the results of later-stage clinical trials. In addition, regulations are not static, and regulatory agencies, including the FDA, alter their staff, interpretations and practices and may in the future impose more stringent requirements than are currently in effect, which may adversely affect our planned drug development and/or our commercialization efforts. Satisfying regulatory requirements typically takes a significant number of years and can vary substantially based on the type, complexity and novelty of the product candidate. Our business, results of operations and financial condition could be materially and adversely affected by any delays in, or termination of, our clinical trials. Factors that could impede our ability to generate commercially viable products through the conduct of clinical trials include:

- insufficient funds to conduct clinical trials;
- the inability to find partners, if necessary, for support, including research, development, manufacturing or clinical needs;
- the failure of tests or studies necessary to submit an NDA, such as clinical studies, bioequivalence studies in support of a 505(b)(2) regulatory filing, or stability studies;
- the failure of clinical trials to demonstrate the safety and efficacy of our product candidates to the extent necessary to obtain regulatory approvals;
- the failure by us or third-party investigators, CROs, or other third parties involved in the research to adhere to regulatory requirements applicable to the conduct of clinical trials;
- the failure of preclinical testing and early clinical trials to predict results of later clinical trials;
- any delay in completion of clinical trials caused by a regional, national or global disturbance where we or our collaborative partners are enrolling patients in clinical studies, such as a pandemic (including COVID-19), terrorist activities, cyberattack, or war, political unrest, a natural or man-made disaster or any other reason or event, resulting in increased costs;

- any delay in obtaining advice from the FDA or similar regulatory authorities; and

- the inability to obtain regulatory approval of our product candidates following completion of clinical trials, or delays in obtaining such approvals.

There can be no assurance that if our clinical trials are successfully initiated and completed we will be able to obtain approval by the FDA in the U.S. or similar regulatory authorities elsewhere in the world in a timely manner, if at all. If we fail to successfully develop and commercialize one or more of our product candidates, we may be unable to generate sufficient revenues to attain profitability, and our reputation in the industry and in the investment community would likely be significantly damaged, each of which would cause our stock price to significantly decrease.

Delays in, or suspensions and terminations of, clinical testing could increase our costs and delay our ability to obtain regulatory approval for, and commercialize, our product candidates.

Before we can receive regulatory approval for the commercial sale of our product candidates, the FDA and comparable authorities in non-U.S. jurisdictions require extensive preclinical safety testing and clinical trials to demonstrate their safety and efficacy. Significant delays in preclinical and clinical testing could materially impact our product development costs and delay regulatory approval of our product candidates. Our ability to complete clinical trials in a timely manner, or at all, has in the past been, and could in the future be impacted by, among other factors:

- delay or failure in reaching agreement with the FDA or comparable foreign regulatory authority on a trial design that we are able to execute;

- delay or failure in obtaining authorization to commence a trial or inability to comply with conditions imposed by a regulatory authority regarding the scope or design of a clinical study;

- delay or failure in reaching agreement on acceptable terms with prospective CROs and clinical trial sites, the terms of which can be subject to extensive negotiation and may vary significantly among different CROs and trial sites;

- delay or failure in obtaining IRB approval or the approval of other reviewing entities, including comparable foreign entities, to conduct a clinical trial at each site;

- withdrawal of clinical trial sites from our clinical trials as a result of changing standards of care or the ineligibility of a site to participate in our clinical trials;

- delay or failure in obtaining clinical materials;

- delay or failure in recruiting and enrolling suitable subjects to participate in a trial;

- delay or failure of subjects completing a trial or returning for post-treatment follow-up;

- clinical sites and investigators deviating from trial protocol, failing to conduct the trial in accordance with regulatory requirements, or dropping out of a trial;

- inability to identify and maintain a sufficient number of trial sites, many of which may already be engaged in other clinical trial programs, including some that may be for the same indication;

- failure of our third-party clinical trial managers to satisfy their contractual duties or meet expected deadlines;

- delay or failure in adding new clinical trial sites;
- ambiguous or negative interim results or results that are inconsistent with earlier results;
- feedback from the FDA, the IRB, data safety monitoring boards or comparable foreign entities, or results from earlier stage or concurrent preclinical and clinical studies that might require modification to the protocol;
- decisions by the FDA, the IRB, comparable foreign regulatory entities, or recommendations by a data safety monitoring board or comparable foreign regulatory entity to suspend or terminate clinical trials at any time for safety issues or for any other reason;
- unacceptable risk-benefit profiles or unforeseen safety issues or adverse side effects;
- failure to demonstrate a benefit from using a drug;
- manufacturing issues, including problems with manufacturing or obtaining from third parties sufficient quantities of a product candidate for use in clinical trials; and
- changes in governmental regulations or administrative actions or lack of adequate funding to continue the clinical trial.

For example, in 2021 we terminated our GUARDS-1 Study, a Phase 2 clinical study evaluating CINVANTI in early hospitalized patients with COVID-19, early due to slowing enrollment caused by declining numbers in hospitalized patients in the first half of 2021. Patient enrollment, a significant factor in the timing of clinical trials, is affected by many factors including the size and nature of the patient population, the proximity of subjects to clinical sites, the eligibility criteria for the trial, the design of the clinical trial, the ability to obtain and maintain patient consents, whether enrolled subjects drop out before completion, competing clinical trials and clinicians' and patients' perceptions as to the potential advantages of the drug being studied in relation to other available therapies, including any new drugs that may be approved for the indications we investigate. Furthermore, we rely on CROs and clinical trial sites to ensure the proper and timely conduct of our clinical trials and while we have agreements governing their activities, we have limited influence over CROs' actual performance.

Our failure to successfully establish, recruit for, and oversee our clinical trials could delay our product development efforts and negatively impact our business. If we experience delays in the completion of any ongoing study, the commercial prospects of our product candidates or any of our other future product candidates could be harmed, and our ability to generate product revenue will be delayed. Any delays in completing our clinical trials will increase our costs, slow our product candidates' development and approval process and jeopardize our ability to commence product sales and generate revenues. Any of these occurrences may harm our business, financial condition and prospects significantly.

We may not obtain regulatory approval for our product candidates in development. Regulatory approval may also be delayed or revoked or may impose limitations on the indicated uses of a product candidate. If we are unable to obtain regulatory approval for our product candidates in development, our business will be substantially harmed.

The process for obtaining regulatory approval of a new drug is time-consuming, is subject to unanticipated delays and costs and requires the commitment of substantial resources. Any product that we or our potential future collaborative partners develop must receive all necessary regulatory agency approvals or clearances before it may be marketed in the U.S. or other countries. Human pharmaceutical products are subject to rigorous preclinical and clinical testing and other requirements by the FDA in the U.S. and similar health authorities in foreign countries. We may not receive necessary regulatory approvals or clearances to market our product candidates currently in development in the U.S. or in other jurisdictions, as a result of changes in regulatory policies prior to approval or other events. Additionally, data obtained from preclinical and clinical activities, or from stability or bioequivalence studies, are susceptible to varying interpretations that could delay, limit or prevent regulatory agency approvals or clearances.

Our product candidates could fail to receive regulatory approval from the FDA or a comparable foreign regulatory authority for many reasons, including:

- disagreement with the design or implementation of our clinical trials;
- failure to demonstrate that the product candidate is safe and effective for its proposed indication;
- failure of clinical trial results to meet the level of statistical significance required for approval;
- the failure of third parties to manage and conduct the trials or perform necessary oversight to meet expected deadlines or to comply with regulatory requirements;
- failure to demonstrate that the product candidate's clinical and other benefits outweigh its safety risks;
- disagreement with our interpretation of data from preclinical studies or clinical trials;
- the insufficiency of data collected from clinical trials to support the submission and filing of an NDA or other submission or to obtain regulatory approval;
- disapproval of the manufacturing processes or facilities of third-party manufacturers with whom we contract for clinical and commercial supplies; and
- changes in approval policies or regulations that render our preclinical and clinical data insufficient for approval.

The FDA or a comparable non-U.S. regulatory authority may require additional preclinical or clinical data to support approval, such as confirmatory studies and other data or studies to address questions or concerns that may arise during the FDA review process. Regulatory approval may also be delayed, limited or prevented by other factors. For example, in 2013, 2018 and 2019, the U.S. federal government entered shutdowns suspending services deemed non-essential as a result of the failure by Congress to enact regular appropriations. Our development and commercialization activities could be harmed or delayed by a similar shutdown of the U.S. federal government in the future, which may significantly delay the FDA's ability to timely review and process any submissions we have filed or may file or cause other regulatory delays, which could have a negative impact on our business.

Even if granted, regulatory approvals may include significant limitations on the uses for which products may be marketed. Failure to comply with applicable regulatory requirements can, among other things, result in warning letters, imposition of civil penalties or other monetary payments, delay in approving or refusal to approve a product candidate, suspension or withdrawal of regulatory approval, product recall or seizure, operating restrictions, interruption of clinical trials or manufacturing, injunctions and criminal prosecution.

In addition, the marketing and manufacturing of products are subject to continuing FDA review, and later discovery of previously unknown problems with a product, its manufacture or its marketing may result in the FDA requiring further clinical research or restrictions on the product or the manufacturer, including withdrawal of the product from the market.

Failure to obtain regulatory approval in international jurisdictions would prevent our Products and our product candidates from being marketed abroad.

In the event we pursue the right to market and sell our Products or our product candidates in jurisdictions other than the U.S., we or our potential third-party partners would be required to obtain separate marketing approvals and comply with numerous and varying regulatory requirements in each foreign country. The approval procedure varies among countries and can involve additional testing. The time required to obtain approval may differ substantially from that required to obtain FDA approval. The regulatory approval process outside the U.S. generally includes all of the risks associated with obtaining FDA approval. In addition, in many countries outside the U.S., it is required that the product be approved for reimbursement before the product can be approved for sale in that country. In the event we choose to pursue them, we or our potential third-party partners may not obtain approvals from regulatory authorities outside the U.S. on a timely basis, if at all. Approval by the FDA does not ensure approval by regulatory authorities in other countries or jurisdictions, and approval by one regulatory authority outside the U.S. does not ensure approval by regulatory authorities in other countries or jurisdictions or by the FDA. However, failure to obtain approval in one jurisdiction may impact our or our potential third-party partners' ability to obtain approval elsewhere. If we or our potential third-party partners are unable in the future to obtain approval of a product candidate by regulatory authorities in non-U.S. jurisdictions, the commercial prospects of that product candidate may be significantly diminished and our business prospects could decline.

Even if our product candidates in development receive regulatory approval, they may still face future development and regulatory difficulties. If we fail to comply with continuing federal, state and foreign regulations, we could lose our approvals to market drugs, and our business would be seriously harmed.

Even if we obtain regulatory approval for our product candidates in development, they remain subject to ongoing requirements of the FDA and comparable foreign regulatory authorities, including requirements related to manufacturing, quality control, further development, labeling, packaging, storage, distribution, safety surveillance, import, export, advertising, promotion, recordkeeping, and reporting of safety and other postmarket information. Following initial regulatory approval for drugs we develop, including our Products and our product candidates, we remain subject to continuing regulatory review, including review of adverse drug experiences and clinical results that may be reported after drug products become commercially available. This would include results from any postmarketing tests or continued actions required as a condition of approval. The manufacturer and manufacturing facilities we use to make any of our drug candidates will also be subject to periodic review and inspection by the FDA. If a previously unknown problem or problems with a Product or a manufacturing and laboratory facility used by us is discovered, the FDA or foreign regulatory agency may impose restrictions on that Product or on the manufacturing facility, including requiring us to withdraw the Product from the market. Any changes to an approved product, including the way it is manufactured or promoted, often require FDA approval before the product, as modified, can be marketed. We and our contract manufacturers will also be subject to ongoing FDA requirements for submission of safety and other postmarket information. If we and our contract manufacturers fail to comply with applicable regulatory requirements, a regulatory agency may:

- issue warning letters;
- impose civil or criminal penalties;
- suspend or withdraw our regulatory approval;
- suspend or terminate any of our ongoing clinical trials;
- refuse to approve pending applications or supplements to approved applications filed by us;

- impose restrictions on our operations;
- close the facilities of our contract manufacturers; or
- seize or detain products or require a product recall.

The occurrence of any event or penalty described above may inhibit our ability to commercialize our Products and generate revenue.

Additionally, such regulatory review covers a company's activities in the promotion of its drugs, with significant potential penalties and restrictions for promotion of drugs for an unapproved use or other inappropriate sales and marketing activities. Advertising and promotion of any product candidate that obtains approval in the U.S. will be heavily scrutinized by the FDA, the Department of Justice, and the Department of Health and Human Services' Office of Inspector General. Violations of applicable advertising and promotion laws and regulations, including promotion of products for unapproved (or off-label) uses, are subject to enforcement letters, inquiries and investigations and civil and criminal sanctions by the FDA. We are also required to submit information on our open and completed clinical trials to public registries and databases; failure to comply with these requirements could expose us to negative publicity, fines and penalties that could harm our business. We are also required to comply with the requirements to submit to governmental authorities information on payments to physicians and certain other third parties; failure to comply with these requirements could expose us to negative publicity, fines and penalties that could harm our business.

The commercial use of our Products may cause unintended side effects or adverse reactions, or incidents of misuse may occur, which could adversely affect our business.

We cannot predict whether any commercial use of our product candidates, once approved, will produce undesirable or unintended side effects that have not been evident in clinical trials conducted for such product candidates to date. Additionally, incidents of Product misuse may occur. These events, including the reporting of adverse safety events, among others, could result in Product recalls, product liability actions related to our Products or withdrawals or additional regulatory controls (including additional regulatory scrutiny and requirements for additional labeling), all of which could have a negative impact on our business, financial condition, cash flows and results of operations.

The pharmaceutical industry is subject to significant regulation and oversight pursuant to anti-kickback laws, false claims statutes and anti-corruption laws, which may result in significant additional expense and limit our ability to commercialize our Products and our product candidates. In addition, any failure to comply with these regulations could result in substantial fines or penalties.

We are subject to health care fraud and abuse regulations that are enforced by the federal government and the states in which we conduct our business, as well as foreign jurisdictions in which we may conduct business. Healthcare providers, physicians and third-party payors play a primary role in the recommendation and prescription of any drug product with marketing approval. Our future arrangements with third-party payors and customers may expose us to broadly applicable fraud and abuse and other healthcare laws and regulations that may constrain the business or financial arrangements and relationships through which we market, sell and distribute our Products and product candidates with marketing approval. Restrictions under applicable federal, state and foreign healthcare laws and regulations include, but are not limited to, the following:

- the Federal health care programs' Anti-Kickback Law, which prohibits, among other things, persons from knowingly and willfully soliciting, receiving, offering or paying remuneration, directly or indirectly, in exchange for or to induce either the referral of an individual for, or the purchase, lease, order or recommendation of, any good or service for which payment may be made under federal health care programs such as the Medicare and Medicaid programs;

- federal false claims laws, which prohibit, among other things, individuals or entities from knowingly presenting, or causing to be presented, claims for payment from Medicare, Medicaid or other federal health care programs that are false or fraudulent. This false claims liability may attach in the event that a company is found to have knowingly submitted false average sales price, best price or other pricing data to the government or to have unlawfully promoted its drug products;

- the federal Health Insurance Portability and Accountability Act of 1996 ("HIPAA") also prohibits, among other actions, knowingly and willfully executing, or attempting to execute, a scheme to defraud any healthcare benefit program, including private third-party payors, knowingly and willfully embezzling or stealing from a healthcare benefit program, willfully obstructing a criminal investigation of a healthcare offense, and knowingly and willfully falsifying, concealing or covering up 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;

- federal "sunshine" laws, now known as Open Payments, that require transparency regarding financial arrangements with health care providers, such as the reporting and disclosure requirements imposed by the federal Physician Payments Sunshine Act within PPACA on drug manufacturers regarding any "payment or transfer of value" made or distributed to physicians, other healthcare professionals, and teaching hospitals as well as ownership and investment interests held by such physicians and their family; and

- state law equivalents of each of the above federal laws, such as anti-kickback and false claims laws, which may apply to items or services reimbursed by any third-party payor, including commercial insurers; and

- increasingly complex standards for complying with foreign laws and regulations, including those of the EU, that may differ substantially from country to country and may conflict with corresponding U.S. laws and regulations.

The risk of being found in violation of these laws is increased by the fact that many of them have not been fully interpreted by the regulatory authorities or the courts, and their provisions are open to a variety of interpretations. Moreover, certain health care reform legislation has strengthened many of these laws. For example, the PPACA, among other things, amends the intent requirement of the federal anti-kickback and criminal health care fraud statutes to clarify that a person or entity does not need to have actual knowledge of this statute or specific intent to violate it. In addition, PPACA provides 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 false claims statutes. Finally, some states, such as California, Massachusetts and Vermont, mandate implementation of commercial compliance programs to ensure compliance with these laws.

In addition, a number of states have laws that require pharmaceutical companies to track and report payments, gifts and other benefits provided to physicians and other health care professionals and entities.

We also are subject to the FCPA. In September 2020, ZYNRELEF was granted marketing authorization by the EC, our first such foreign regulatory approval. We are currently assessing the evolving global environment for pharmaceuticals and developing a coordinated global marketing strategy. The FCPA and similar anti-bribery laws in other jurisdictions generally prohibit companies and their intermediaries from providing money or anything of value to officials of foreign governments, foreign political parties, or international organizations with the intent to obtain or retain business or seek a business advantage. Recently, there has been a substantial increase in anti-bribery law enforcement activity by U.S. regulators, with more frequent and aggressive investigations and enforcement proceedings by both the Department of Justice and the SEC. A determination that our operations or activities are not, or were not, in compliance with U.S. or foreign laws or regulations could result in the imposition of substantial fines, interruptions of business, loss of supplier, vendor or other third-party relationships, termination of necessary licenses and permits, and other legal or equitable sanctions. Other internal or government investigations or legal or regulatory proceedings, including lawsuits brought by private litigants, may also follow as a consequence.

Changes in laws affecting the healthcare industry could also adversely affect our revenues and profitability, including new laws, regulations or judicial decisions, or new interpretations of existing laws, regulations or decisions related to patent protection and enforcement, healthcare availability, and drug product pricing and marketing. Changes in FDA regulations and regulations issued by other regulatory agencies inside and outside of the U.S., including new or different approval requirements, timelines and processes, may also delay or prevent the approval of our product candidates, require additional safety monitoring, labeling changes, restrictions on product distribution or other measures that could increase our costs of doing business and adversely affect the market for our Products and our product candidates. The enactment in the U.S. of healthcare reform, new legislation or implementation of existing statutory provisions on importation of lower-cost competing drugs from other jurisdictions and legislation on comparative effectiveness research are examples of previously enacted and possible future changes in laws that could adversely affect our business.

If our operations are found to be in violation of any of the laws described above or any other governmental regulations that apply to us, we may be subject to significant civil, criminal and administrative penalties, damages, fines, exclusion from government-funded healthcare programs, like Medicare and Medicaid, and the curtailment or restructuring of our operations. Any penalties, damages, fines, curtailment or restructuring of our operations could adversely affect our ability to operate our business and our financial results. Although compliance programs can mitigate the risk of investigation and prosecution for violations of these laws, the risks cannot be entirely eliminated. Any action against us for violation of these laws or regulations, even if we successfully defend against it, could cause us to incur significant legal expenses and divert our management's attention from the operation of our business. Moreover, achieving and sustaining compliance with applicable federal, state and foreign privacy, security and fraud laws may prove costly.

We may incur significant liability if it is determined that we are promoting the "off-label" use of drugs or promoting in a non-truthful and misleading way.

We are prohibited from promoting our Products and any product candidates that receive regulatory approval for "off-label" uses or promoting in a non-truthful and misleading way that are not described in its labeling and that differ from the uses approved by the FDA. Physicians may prescribe drug products for off-label uses, and such off-label uses are common across medical specialties. The FDA and other regulatory agencies do not regulate a physician's choice of treatments. However, they do restrict pharmaceutical companies and their sales representatives' dissemination of information concerning off-label use. The FDA and other regulatory agencies actively enforce regulations prohibiting promotion of products for off-label uses and the promotion of products for which marketing authorization has not been obtained. A company that is found to have promoted products for off-label uses may be subject to significant liability, including civil and administrative remedies as well as criminal sanctions. Notwithstanding the regulatory restrictions on off-label promotion, the FDA and other regulatory authorities allow companies to engage in truthful, non-misleading, and non-promotional scientific exchanges concerning their products.

The FDA or other regulatory authorities may conclude that we have violated applicable laws, rules or regulations, and we may therefore be subject to significant liability, including civil and administrative remedies, as well as criminal sanctions. Such enforcement actions could cause us reputational harm and divert the attention of our management from our business operations. Likewise, our distribution and contracting partners and those providing vendor support services may also be the subject of regulatory investigations involving, or remedies or sanctions for, off-label promotion of our Products or product candidates, which may adversely impact sales of our Products or product candidates or trigger indemnification obligations. These consequences, could, in turn, have a negative impact on our business, financial condition and results of operations and could cause the market value of our common shares to decline.

Health care reform could increase our expenses and adversely affect the commercial success of our Products and our product candidates.

The U.S. and some foreign jurisdictions are considering or have enacted a number of reform proposals to change the healthcare system. There is significant interest in promoting changes in healthcare systems with the stated goals of containing healthcare costs, improving quality or expanding access. In the U.S., the pharmaceutical industry has been a particular focus of these efforts and has been significantly affected by federal and state legislative initiatives, including those designed to limit the pricing, coverage, and reimbursement of pharmaceutical and biopharmaceutical products, especially under government-funded healthcare programs, and increased governmental control of drug pricing.

For example, the PPACA includes numerous provisions that affect pharmaceutical companies. The PPACA seeks to expand healthcare coverage to the uninsured through private health insurance reforms and an expansion of Medicaid. The PPACA also imposes substantial costs on pharmaceutical manufacturers, such as an increase in liability for rebates paid to Medicaid, new drug discounts that must be offered to certain enrollees in the Medicare prescription drug benefit and an annual fee imposed on all manufacturers of brand prescription drugs in the U.S. The PPACA also requires increased disclosure obligations—including those required under the "sunshine" laws—and an expansion of an existing program requiring pharmaceutical discounts to certain types of hospitals and federally subsidized clinics and contains cost-containment measures that could reduce reimbursement levels for pharmaceutical products. In addition, the IRA extends enhanced subsidies for individuals purchasing health insurance coverage in PPACA marketplaces through plan year 2025. The IRA also eliminates the "donut hole" under the Medicare Part D program beginning in 2025 by significantly lowering the beneficiary maximum out-of-pocket cost and creating a new manufacturer discount program. These and other aspects of the PPACA, including the regulations that may be imposed in connection with the implementation of the PPACA, could increase our expenses and adversely affect our ability to successfully commercialize our Products and our product candidates.

There have been, and we anticipate that there will be, healthcare reform measures that may be adopted in the future that may result in more rigorous coverage criteria and additional downward pressure on the reimbursement for healthcare products and services. These reform measures may limit the amounts that federal and state governments will pay for healthcare products and services, and also indirectly affect the amounts that private payors are willing to pay. Moreover, in the U.S., there have been several presidential executive orders, congressional inquiries and proposed and enacted federal and state legislation designed to, among other things, bring more transparency to product pricing, review the relationship between pricing and manufacturer patient programs, and reform government program reimbursement methodologies for products.

Our employees may engage in misconduct or other improper activities, including noncompliance with regulatory standards and requirements, which could have a negative impact on our business.

We are exposed to the risk of employee fraud or other misconduct. Misconduct by employees could include intentional failures to comply with FDA regulations or similar regulations of comparable foreign regulatory authorities, provide accurate information to the FDA or comparable foreign regulatory authorities, comply with manufacturing standards we have established, comply with federal and state healthcare fraud and abuse laws and regulations and similar laws and regulations established and enforced by comparable foreign regulatory authorities, report financial information or data accurately, or disclose unauthorized activities to us. In particular, sales, marketing and business arrangements in the healthcare industry are subject to extensive laws and regulations intended to prevent fraud, kickbacks, self-dealing and other abusive practices. These laws and regulations may restrict or prohibit a wide range of pricing, discounting, marketing and promotion, sales commission, customer incentive programs and other business arrangements. Employee misconduct could also involve the improper use of information obtained in the course of clinical trials, which could result in regulatory sanctions and serious harm to our reputation. It is not always possible to identify and deter employee misconduct, and the precautions we take to detect and prevent this activity may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from governmental investigations or other actions or lawsuits stemming from a failure to be in compliance with such laws or regulations. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business and results of operations, including the imposition of significant fines or other sanctions.

We are and may become subject to stringent and evolving laws, regulations, rules, contractual obligations, policies and other obligations related to data privacy and security. Our actual or perceived failure to comply with such obligations could lead to regulatory investigations or actions, litigation, fines and penalties, disruptions of our business operations, reputational harm, loss of revenue or profits, and other adverse business consequences.

In the ordinary course of business, we collect, receive, store, process, generate, use, transfer, disclose, make accessible, protect, secure, dispose of, transmit, and share (collectively, processing) personal data and other sensitive information, including proprietary and confidential business data, trade secrets, intellectual property, sensitive third-party data, business plans, transactions and financial information (collectively, sensitive data). Our data processing activities may subject us to numerous data privacy and security obligations, such as various laws, regulations, guidance, industry standards, external and internal privacy and security policies, contractual requirements, and other obligations relating to data privacy and security.

In the U.S., federal, state, and local governments have enacted numerous data privacy and security laws, including data breach notification laws, personal data privacy laws, consumer protection laws (e.g., Section 5 of the Federal Trade Commission Act), and other similar laws (e.g., wiretapping laws). For example, the CCPA requires businesses to provide specific disclosures in privacy notices and honor requests of California residents to exercise certain privacy rights. The CCPA provides for civil penalties of up to $7,500 per violation and allows private litigants affected by certain data breaches to recover significant statutory damages. In addition, the CPRA, which became operative January 1, 2023, will expand the CCPA's requirements, including applying to personal information of business representatives and employees and establishing a new regulatory agency to implement and enforce the law. Other states, such as Virginia and Colorado, have also passed comprehensive data privacy and security laws, and similar laws are being considered in several other states, as well as at the federal and local levels. These developments may further complicate compliance efforts and may increase legal risk and compliance costs for us and the third parties upon whom we rely.

For example, HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act, imposes specific requirements relating to the privacy, security, and transmission of individually identifiable health information. Healthcare providers who prescribe our products and from whom we may obtain patient health information are subject to privacy and security requirements under HIPAA. We currently are not a HIPAA covered entity, do not intend to become one, and we do not operate as a business associate to any covered entities. We could be subject to criminal penalties if we knowingly obtain individually identifiable health information from a covered entity in a manner that is not authorized or permitted by HIPAA or for aiding and abetting the violation of HIPAA. We are unable to predict whether our actions could be subject to prosecution in the event of an impermissible disclosure of health information to us.

Outside the U.S., an increasing number of laws, regulations, and industry standards may govern data privacy and security. For example, the European Union's General Data Protection Regulation ("EU GDPR"), the United Kingdom's GDPR ("UK GDPR"), Canada's Personal Information Protection and Electronic Documents Act ("PIPEDA") and Canada's Anti-Spam Legislation ("CASL"), impose strict requirements for processing personal data. For example, under the EU GDPR, companies may face temporary or definitive bans on data processing and other corrective actions; fines of up to 20 million Euros or 4% of annual global revenue, whichever is greater; or private litigation related to processing of personal data brought by classes of data subjects or consumer protection organizations authorized at law to represent their interests.

In addition, we may be unable to transfer personal data from Europe and other jurisdictions to the U.S. or other countries due to data localization requirements or limitations on cross-border data flows. Europe and other jurisdictions have enacted laws requiring data to be localized or limiting the transfer of personal data to other countries. In particular, the EEA and the United Kingdom ("UK") have significantly restricted the transfer of personal data to the U.S. and other countries whose data privacy and security laws it believes are inadequate. Other jurisdictions may adopt similarly stringent interpretations of their data localization and cross-border data transfer laws. Although there are currently various mechanisms that may be used to transfer personal data from the EEA and UK to the U.S. in compliance with law, such as the EEA and UK's standard contractual clauses, these mechanisms are subject to legal challenges, and there is no assurance that we can satisfy or rely on these measures to lawfully transfer personal data to the U.S.. If there is no lawful manner for us to transfer personal data from the EEA, the UK, or other jurisdictions to the U.S., or if the requirements for a legally-compliant transfer are too onerous, we could

face significant adverse consequences, including the interruption or degradation of our operations, the need to relocate part of or all of our business or data processing activities to other jurisdictions at significant expense, increased exposure to regulatory actions, substantial fines and penalties, the inability to transfer data and work with partners, vendors and other third parties, and injunctions against our processing or transferring of personal data necessary to operate our business. Some European regulators have prevented companies from transferring personal data out of Europe for allegedly violating the GDPR's cross-border data transfer limitations.

In addition to data privacy and security laws, we may be contractually subject to industry standards adopted by industry groups and may become subject to such obligations in the future. We may also be bound by other contractual obligations related to data privacy and security, and our efforts to comply with such obligations may not be successful. We may publish privacy policies, marketing materials, and other statements, such as compliance with certain certifications or self-regulatory principles, regarding data privacy and security. If these policies, materials or statements are found to be deficient, lacking in transparency, deceptive, unfair, or misrepresentative of our practices, we may be subject to investigation, enforcement actions by regulators, or other adverse consequences.

Obligations related to data privacy and security are quickly changing, becoming increasingly stringent, and creating regulatory uncertainty. Additionally, these obligations may be subject to differing applications and interpretations, which may be inconsistent or conflict among jurisdictions. Preparing for and complying with these obligations requires us to devote significant resources and may necessitate changes to our services, information technologies, systems, and practices and to those of any third parties that process personal data on our behalf. We may at times fail (or be perceived to have failed) in our efforts to comply with our data privacy and security obligations. Moreover, despite our efforts, our personnel or third parties on whom we rely may fail to comply with such obligations, which could negatively impact our business operations. If we or the third parties on which we rely fail, or are perceived to have failed, to address or comply with applicable data privacy and security obligations, we could face significant consequences, including but not limited to: government enforcement actions (e.g., investigations, fines, penalties, audits, inspections, and similar); litigation (including class-action claims); additional reporting requirements and/or oversight; bans on processing personal data; and orders to destroy or not use personal data. Any of these events could have a material adverse effect on our reputation, business, or financial condition, including but not limited to: loss of customers; inability to process personal data or to operate in certain jurisdictions; limited ability to develop or commercialize our products; expenditure of time and resources to defend any claim or inquiry; adverse publicity; or substantial changes to our business model or operations.

Security breaches and other disruptions could compromise our information and expose us to liability, which would cause our business and reputation to suffer.

In the ordinary course of our business, we and the third parties upon which we rely may process sensitive data, and, as a result, we and the third parties upon which we rely face a variety of evolving threats, including but not limited to ransomware attacks, which could cause security incidents. Cyber-attacks, malicious internet-based activity, online and offline fraud, and other similar activities threaten the confidentiality, integrity, and availability of our sensitive data and information technology systems, and those of the third parties upon which we rely. Such threats are prevalent and continue to rise, are increasingly difficult to detect, and come from a variety of sources, including traditional computer "hackers," threat actors, "hacktivists," organized criminal threat actors, personnel (such as through theft or misuse), sophisticated nation states, and nation-state-supported actors.

Some actors now engage and are expected to continue to engage in cyber-attacks, including without limitation nation-state actors for geopolitical reasons and in conjunction with military conflicts and defense activities. During times of war and other major conflicts, we and the third parties upon which we rely may be vulnerable to a heightened risk of these attacks, including retaliatory cyber-attacks, that could materially disrupt our systems and operations, supply chain, and ability to produce, sell and distribute our services. We and the third parties upon which we rely may be subject to a variety of evolving threats, including but not limited to social-engineering attacks (including through phishing attacks), malicious code (such as viruses and worms), malware (including as a result of advanced persistent threat intrusions), denial-of-service attacks (such as credential stuffing), credential harvesting, personnel misconduct or error, ransomware attacks, supply-chain attacks, software bugs, server malfunctions, software or hardware failures, loss of data or other information technology assets, adware, telecommunications failures, earthquakes, fires, floods, and other similar threats. In particular, severe ransomware attacks are becoming increasingly prevalent and can lead to significant interruptions in our operations, loss of sensitive data and income,

reputational harm, and diversion of funds. Extortion payments may alleviate the negative impact of a ransomware attack, but we may be unwilling or unable to make such payments due to, for example, applicable laws or regulations prohibiting such payments.

Remote work has become more common and has increased risks to our information technology systems and data, as more of our employees utilize network connections, computers, and devices outside our premises or network, including working at home, while in transit and in public locations. Additionally, future or past business transactions (such as acquisitions or integrations) could expose us to additional cybersecurity risks and vulnerabilities, as our systems could be negatively affected by vulnerabilities present in acquired or integrated entities' systems and technologies.

Further, our reliance on third-party service providers could introduce new cybersecurity risks and vulnerabilities, including supply-chain attacks, and other threats to our business operations. We may rely on third-party service providers and technologies to operate critical business systems to process sensitive data in a variety of contexts, including, without limitation, cloud-based infrastructure, data center facilities, employee email, and other functions. We may also rely on third-party service providers to provide other products, services, parts, or otherwise to operate our business. Our ability to monitor these third parties' information security practices is limited, and these third parties may not have adequate information security measures in place. If our third-party service providers experience a security incident or other interruption, we could experience adverse consequences. While we may be entitled to damages if our third-party service providers fail to satisfy their data privacy or security-related obligations to us, any award may be insufficient to cover our damages, or we may be unable to recover such award. In addition, supply-chain attacks have increased in frequency and severity, and we cannot guarantee that third parties' infrastructure in our supply chain or our third-party partners' supply chains have not been compromised.

Any of the previously identified or similar threats could cause a security incident or other interruption that could result in unauthorized, unlawful, or accidental acquisition, modification, destruction, loss, alteration, encryption, disclosure of, or access to our sensitive data or our information technology systems, or those of the third parties upon whom we rely. A security incident or other interruption could disrupt our ability (and that of third parties upon whom we rely) to provide our services. We may expend significant resources or modify our business activities to try to protect against security incidents. Additionally, certain data privacy and security obligations may require us to implement and maintain specific security measures or industry-standard or reasonable security measures to protect our information technology systems and sensitive data.

While we have implemented security measures designed to protect against security incidents, there can be no assurance that these measures will be effective. We may be unable in the future to detect vulnerabilities in our information technology systems because such threats and techniques change frequently, are often sophisticated in nature, and may not be detected until after a security incident has occurred. Further, we may experience delays in developing and deploying remedial measures designed to address any such identified vulnerabilities. Applicable data privacy and security obligations may require us to notify relevant stakeholders of security incidents. Such disclosures are costly, and the disclosure or the failure to comply with such requirements could lead to adverse consequences.

If we (or a third party upon whom we rely) experience a security incident or are perceived to have experienced a security incident, we may experience adverse consequences. These consequences may include: government enforcement actions (for example, investigations, fines, penalties, audits, and inspections); additional reporting requirements and/or oversight; restrictions on processing sensitive data (including personal data); litigation (including class claims); indemnification obligations; negative publicity; reputational harm; monetary fund diversions; interruptions in our operations (including availability of data); financial loss; and other similar harms. Security incidents and attendant consequences may cause customers to stop using our services, deter new customers from using our services, and negatively impact our ability to grow and operate our business.

Our contracts may not contain limitations of liability, and even where they do, there can be no assurance that limitations of liability in our contracts are sufficient to protect us from liabilities, damages, or claims related to our data privacy and security obligations. We cannot be sure that our insurance coverage will be adequate or sufficient to protect us from or to mitigate liabilities arising out of our privacy and security practices, that such coverage will continue to be available on commercially reasonable terms or at all, or that such coverage will pay future claims.

In addition to experiencing a security incident, third parties may gather, collect, or infer sensitive information about us from public sources, data brokers, or other means that reveals competitively sensitive details about our organization and could be used to undermine our competitive advantage or market position.

Our use of hazardous materials could subject us to liabilities, fines and sanctions.

Our laboratory and clinical testing sometimes involve use of hazardous, radioactive or otherwise toxic materials. We are subject to federal, state and local laws and regulations governing how we use, manufacture, handle, store and dispose of these materials.

Although we believe that our safety procedures for handling and disposing of such materials comply in all material respects with all federal, state and local regulations and standards, there is always the risk of accidental contamination or injury from these materials. In the event of an accident, we could be held liable for any damages that result, and we could also be subject to fines and penalties and such liability and costs could exceed our financial resources. If we fail to comply with these regulations and standards or with the conditions attached to our operating licenses, the licenses could be revoked, and we could be subjected to criminal sanctions and substantial financial liability or be required to suspend or modify our operations. Compliance with environmental and other laws may be expensive and current or future regulations may impair our product development efforts.

Risks Related to Our Intellectual Property

If we are unable to adequately protect or enforce our intellectual property rights, we may lose valuable assets or incur costly litigation to protect our rights.

Our success will depend in part on our ability to obtain patents and maintain trade secret protection, as well as successfully defending these patents against challenges, while operating without infringing the proprietary rights of others. We have filed a number of U.S. patent applications on inventions relating to the composition of a variety of polymers, specific products, product groups and processing technology. As of December 31, 2022, we had a total of 33 issued U.S. patents and an additional 111 issued (or registered) foreign patents. The patents on the bioerodible technologies expire in March 2026. Currently, CINVANTI is covered by 9 patents issued in the U.S. and by three patents issued (or registered) in foreign countries including Korea and Japan. U.S. patents covering CINVANTI have expiration dates ranging from September 2035 to February 2036; foreign patents covering CINVANTI have expiration dates ranging from September 2035 to February 2036. Currently, SUSTOL is covered by 6 patents issued in the U.S. and by 18 patents issued (or registered) in foreign countries including France, Germany, Hong Kong, Ireland, Italy, Japan, Spain, Sweden, Switzerland, Taiwan, and the United Kingdom. U.S. patents covering SUSTOL expire in September 2024; foreign patents covering SUSTOL expire in September 2025. Currently, ZYNRELEF is protected by 15 patents issued in the U.S. and by 89 patents issued (or registered) in foreign countries including Albania, Australia, Austria, Belgium, Bulgaria, Canada, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hong Kong, Hungary, Iceland, Ireland, Italy, Japan, Korea, Latvia, Lithuania, Luxembourg, Macedonia, Malta, Mexico, Monaco, Netherlands, Norway, Poland, Portugal, Romania, Serbia, Slovakia, Slovenia, Spain, Sweden, Switzerland, Taiwan, Turkey and the United Kingdom. U.S. patents covering ZYNRELEF have expiration dates ranging from March 2034 to April 2035; foreign patents covering ZYNRELEF have expiration dates ranging from November 2033 to November 2036. APONVIE is covered by 9 patents issued in the U.S. and by three patents issued (or registered) in foreign countries including Korea and Japan. U.S. patents covering APONVIE have expiration dates ranging from September 2035 to February 2036; foreign patents covering APONVIE have expiration dates ranging from September 2035 to February 2036. HTX-034 is protected by 12 patents issued in the U.S. and by 89 patents issued (or registered) in foreign countries including Albania, Australia, Austria, Belgium, Bulgaria, Canada, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hong Kong, Hungary, Iceland, Ireland, Italy, Japan, Korea, Latvia, Lithuania, Luxembourg, Macedonia, Malta, Mexico, Monaco, Netherlands, Norway, Poland, Portugal, Romania, Serbia, Slovakia, Slovenia, Spain, Sweden, Switzerland, Taiwan, Turkey and the United Kingdom. U.S. patents covering HTX-034 have expiration dates ranging from March 2034 to April 2035; foreign patents covering HTX-034 have expiration dates ranging from November 2033 to November 2036. Our policy is to actively seek patent protection in the U.S. and to pursue equivalent patent claims in selected foreign countries, thereby seeking patent coverage for novel technologies and compositions of matter that may be commercially important to the development of our business. Granted patents

include claims covering the product composition, methods of use and methods of preparation. Our existing patents may not cover future products, additional patents may not be issued and current patents, or patents issued in the future, may not provide meaningful protection or prove to be of commercial benefit.

The patent positions of pharmaceutical companies, including ours, are uncertain and involve complex legal and factual questions. In addition, the coverage claimed in a patent application can be significantly reduced before the patent is issued. Consequently, our patent applications may not issue into patents, and any issued patents may not provide sufficient protection for our product candidates or provide sufficient protection to afford us a commercial advantage against competitive technologies or may be held invalid if challenged or circumvented. Patent applications in the U.S. are maintained in confidence for at least 18 months after their filing. Consequently, we cannot be certain that the patent applications we are pursuing will lead to the issuance of any patent or be free from infringement or other claims from other parties. Our competitors may also independently develop products similar to ours or design around or otherwise circumvent patents issued to us or licensed by us. In addition, the laws of some foreign countries may not protect our proprietary rights to the same extent as U.S. laws.

We may enter into collaborative agreements that may subject us to obligations that must be fulfilled and require us to manage complex relationships with third parties. In the future, if we are unable to meet our obligations or manage our relationships with our collaborators under these agreements our revenue may decrease. The loss or diminution of our intellectual property rights could result in a decision by our third-party collaborators to terminate their agreements with us. In addition, these agreements are generally complex and contain provisions that could give rise to legal disputes, including potential disputes concerning ownership of intellectual property and data under collaborations. Such disputes can lead to lengthy, expensive litigation or arbitration, requiring us to divert management time and resources to such dispute.

Because the patent positions of pharmaceutical and biotechnology companies involve complex legal and factual questions, enforceability of patents cannot be predicted with certainty. The ultimate degree of patent protection that will be afforded to products and processes, including ours, in the U.S., remains uncertain and is dependent on the scope of protection decided on by the patent offices, courts and lawmakers in these countries. The America Invents Act, which was enacted in 2011 and reformed certain patent laws in the U.S., may create additional uncertainty. Patents, if issued, may be challenged, invalidated or circumvented. As more products are commercialized using our proprietary product platforms, or as any product achieves greater commercial success, our patents become more likely to be subject to challenge by potential competitors.

We also rely on trade secrets, technical know-how and continuing technological innovation to develop and maintain our competitive position. We require our employees, consultants, advisors and collaborators to execute appropriate confidentiality and assignment-of-inventions agreements with us. These agreements typically provide that all materials and confidential information developed or made known to the individual during the course of the individual's relationship with us is to be kept confidential and not disclosed to third parties except in specific circumstances, and that all inventions arising out of the individual's relationship with us shall be our exclusive property. These agreements may be breached, and in some instances, we may not have an appropriate remedy available for breach of the agreements. Furthermore, our competitors may independently develop substantially equivalent proprietary information and techniques, reverse engineer our information and techniques, or otherwise gain access to our proprietary technology. We may be unable to meaningfully protect our rights in trade secrets, technical know-how and other non-patented technology. We may have to resort to litigation to protect our intellectual property rights, or to determine their scope, validity or enforceability. In addition, interference proceedings declared by the U.S. Patent and Trademark Office may be necessary to determine the priority of inventions with respect to our patent applications. Enforcing or defending our proprietary rights is expensive, could cause diversion of our resources and may not prove successful. In addition, courts outside the U.S. may be less willing to protect trade secrets. Costly and time-consuming litigation could be necessary to seek to enforce and determine the scope of our proprietary rights. Any failure to enforce or protect our rights could cause us to lose the ability to exclude others from using our technology to develop or sell competing products.

We may infringe on the intellectual property rights of others, and any litigation could force us to stop developing or selling potential products and could be costly, divert management attention and harm our business.

We must be able to develop products without infringing the proprietary rights of other parties. Because the markets in which we operate involve established competitors with significant patent portfolios, including patents relating to the composition of a variety of polymers, specific products, product groups and processing technology, it could be difficult for us to use our technologies or develop products without infringing the proprietary rights of others. Therefore, there is risk that third parties may make claims of infringement against our Products, our product candidates or our technologies. We may not be able to design around the patented technologies or inventions of others, and we may not be able to obtain licenses to use patented technologies on acceptable terms, or at all. If we cannot operate without infringing the proprietary rights of others, we will not be able to develop or commercialize some or all of our product candidates, and consequently will not be able to earn product revenue.

There is considerable uncertainty within the pharmaceutical industry about the validity, scope and enforceability of many issued patents in the U.S. and elsewhere in the world. We cannot currently determine the ultimate scope and validity of patents that may be granted to third parties in the future or which patents might be asserted to be infringed by any future manufacture, use or sale of our Products and our product candidates. In part as a result of this uncertainty, there has been, and we expect that there may continue to be, significant litigation in the pharmaceutical industry regarding patents and other intellectual property rights. We may have to enforce our intellectual property rights against third parties who infringe our patents and other intellectual property or challenge our patent or trademark applications. For example, in the U.S., putative generics of innovator drug products (including products in which the innovation comprises a new drug delivery method for an existing product, such as the drug delivery market occupied by us) may file Abbreviated New Drug Applications ("ANDA") and, in doing so, certify that their products either do not infringe the innovator's patents or that the innovator's patents are invalid. This often results in litigation between the innovator and the ANDA applicant. This type of litigation is commonly known as "Paragraph IV" litigation in the U.S. On July 27, 2022, we filed a complaint for patent infringement of certain CINVANTI patents against Fresenius Kabi USA, LLC ("Fresenius Kabi") and a related entity in the District of Delaware in response to Fresenius Kabi's ANDA filing seeking approval to manufacture, use or sell a generic version of CINVANTI in the U.S. prior to expiration of the CINVANTI patents. These litigations could result in new or additional generic competition to any of our Products and our product candidates and a potential reduction in product revenue.

If we are required to defend ourselves in a patent-infringement lawsuit, we could incur substantial costs, and the lawsuit could divert management attention, regardless of the lawsuit's merit or outcome. These legal actions could seek damages and seek to enjoin testing, manufacturing and marketing of the accused product or process. In addition to potential liability for significant damages, we could be required to redesign affected products or obtain a license to continue to manufacture or market the accused product or process and any license required under any such patent may not be made available to us on acceptable terms, if at all. Competitors may sue us as a way of delaying the introduction of our Products and our product candidates. Any litigation, including any interference or derivation proceedings to determine priority of inventions, oppositions or other post-grant review proceedings to patents in the U.S. or in countries outside the U.S., or litigation against our partners may be costly and time-consuming and could harm our business. We expect that litigation may be necessary in some instances to determine the validity and scope of certain of our proprietary rights. Litigation may be necessary in other instances to determine the validity, scope and/or non-infringement of certain patent rights claimed by third parties to be pertinent to the manufacture, use or sale of our Products and our product candidates. Ultimately, the outcome of such litigation could adversely affect the validity and scope of our patent or other proprietary rights or hinder our ability to manufacture and market our Products and our product candidates.

Periodically, we review publicly available information regarding the development efforts of others in order to determine whether these efforts may violate our proprietary rights. We occasionally determine that litigation is necessary to enforce our proprietary rights against others. Such litigation can result in substantial expense, regardless of its outcome, and may not be resolved in our favor.

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 and pharmaceutical industries, we employ individuals who were previously employed at other biotechnology and pharmaceutical 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 Related to Our Common Stock

The price of our common stock has been and may continue to be volatile.

The stock markets, in general, and in particular with respect to biotech and life sciences companies, have experienced extreme volatility that has often been unrelated to the operating performance of particular companies. These broad market fluctuations may adversely affect the trading price of our common stock. In addition, the limited trading volume of our stock may contribute to its volatility. Our stock price may be particularly volatile given the stage of our business.

In the past, following periods of volatility in the market price of a particular company's securities, litigation has often been brought against that company. If litigation of this type is brought against us, it could be extremely expensive and divert management's attention and our Company's resources.

Our certificate of incorporation, our bylaws and Delaware law contain provisions that could discourage another company from acquiring us and may prevent attempts by our stockholders to replace or remove our current management.

Provisions of Delaware law, our certificate of incorporation and our bylaws may discourage, delay or prevent a merger or acquisition that stockholders may consider favorable, including transactions in which you might otherwise receive a premium for your shares. In addition, these provisions may frustrate or prevent any attempts by our stockholders to replace or remove our current management by making it more difficult for stockholders to replace or remove our Board of Directors. These provisions include authorizing the issuance of "blank check" preferred stock without any need for action by stockholders.

In addition, Section 203 of Delaware General Corporation Law, which is applicable to us, may discourage, delay or prevent a change in control of our Company by prohibiting stockholders owning in excess of 15% of our outstanding voting stock from merging or combining with us, unless certain approvals are obtained.

Future utilization of net operating loss carryforwards or research and development credit carryforwards may be impaired due to recent changes in ownership.

We believe our net operating loss and research and development credit carryforwards, and certain other tax attributes, may be subject to limitation under Section 382 of the Internal Revenue Code of 1986 ("IRC"). As a result, our deferred tax assets, and related valuation allowance, have been reduced for the estimated impact of the net operating loss and research and development credit carryforwards that we currently estimate may expire, unused. Utilization of our remaining net operating loss and research and development credit carryforwards may still be subject to substantial annual limitations due to ownership change limitations provided by the IRC and similar state provisions for ownership changes after December 31, 2021, including those that may come in conjunction with future equity financings or market trades by our stockholders.

Actions of activist stockholders could impact the pursuit of our business strategies, cause us to incur substantial costs, divert our management's attention and resources, and adversely affect our business, results of operations, liquidity, financial condition, and the trading price of our common stock.

While we value constructive input from investors and regularly engage in dialogue with our stockholders, and we welcome their views and opinions regarding strategy and performance, we may be subject to actions or proposals from activist stockholders that may not align with our business strategies or the interests of our other stockholders, and our Board of Directors and our management are committed to acting in the best interests of all of our stockholders. Accordingly, there is no assurance that the actions taken by our Board of Directors and our management in seeking to maintain constructive engagement with certain stockholders will be successful in preventing the occurrence of stockholder activist campaigns.

As previously reported, in February 2023, we entered into a Cooperation Agreement, dated February 21, 2023, with two of our stockholders, Rubric Capital Management LP and certain of its affiliates and Velan Capital Investment Management LP and certain of its affiliates (collectively, the "Investor Group"), regarding certain changes to the composition of our Board of Directors, including the appointment of three new independent directors, Adam Morgan, Craig Collard, and Kevin Kotler, to our Board of Directors, among other items.

Proxy contests have been waged against many companies in the biopharmaceutical industry over the last few years. If faced with any proxy contest or activist stockholder request or action in the future, we may not be able or willing to respond successfully to the contest, request, or action, which could be significantly disruptive to our business. Even if we are successful, our business, results of operations, liquidity, financial condition, and trading price of our common stock could be adversely affected by any proxy contest or activist stockholder request or action involving us because:

- responding to proxy contests and requests or actions by activist stockholders can be costly and time-consuming, disrupting operations and diverting the attention of management and employees, and can lead to uncertainty;
- perceived uncertainties as to the future direction of the Company and our business may result in the loss of potential acquisitions, collaborations or in-licensing opportunities, and may make it more difficult to attract and retain qualified personnel and business partners;
- if individuals are elected or appointed to our Board of Directors with a specific agenda, it may adversely affect our ability to effectively implement our strategic plan in a timely manner and create additional value for our stockholders; and
- if individuals are elected or appointed to our Board of Directors who do not agree with our strategic plan, the ability of our Board of Directors to function effectively could be adversely affected.

We cannot predict, and no assurances can be given, as to the outcome or timing of any matters relating to the foregoing actions by activist stockholders and our responses thereto or the ultimate impact on our business, results of operations, liquidity, financial condition, and trading price of our common stock. Any such activist stockholder contests, requests or actions, or the mere public presence of activist stockholders among our stockholder base, could cause the market price of our common stock to experience periods of significant volatility or stagnation.

If we identify a material weakness in our internal control over financial reporting, our ability to meet our reporting obligations and the trading price of our common stock could be negatively affected.

A material weakness is a deficiency, or a combination of deficiencies, in internal control over financial reporting, such that there is a reasonable possibility that a material misstatement of our financial statements will not be prevented or detected on a timely basis. Accordingly, a material weakness increases the risk that the financial information we report contains material errors.

We regularly review and update our internal controls, disclosure controls and procedures and corporate governance policies. In addition, we are required under the Sarbanes-Oxley Act of 2002 to report annually on our internal control over financial reporting. Any system of internal controls, however well designed and operated, is based in part on certain assumptions and can provide only reasonable, not absolute, assurances that the objectives of the system are met. If we, or our independent registered public accounting firm, determine that our internal controls over financial reporting are not effective, or we discover areas that need improvement in the future, these shortcomings could have an adverse effect on our business and financial results.

If we cannot conclude that we have effective internal control over our financial reporting, investors could lose confidence in the reliability of our financial statements. Failure to comply with reporting requirements could also subject us to sanctions and/or investigations by the SEC, The Nasdaq Capital Market or other regulatory authorities.

Because we do not anticipate paying any cash dividends on our common stock in the foreseeable future, capital appreciation, if any, will be the source of gain for our stockholders.

We have never declared or paid cash dividends on our common stock. We currently intend to retain all of our current and future earnings to finance the growth and development of our business. As a result, capital appreciation, if any, of our common stock will be the sole source of gain for our stockholders for the foreseeable future.

ITEM 1B. UNRESOLVED STAFF COMMENTS.

None.

ITEM 2. PROPERTIES.

As of December 31, 2022, we had an operating lease for 52,148 square feet of laboratory and office space in San Diego, California, with a lease term that expires on December 31, 2025. In October 2021, we entered into a sublease agreement to sublet 23,873 square feet of laboratory and office space. The space was delivered to the subtenant in March 2022. The sublease agreement expires on December 31, 2025 and is coterminous with the operating lease for the subleased space.

ITEM 3. LEGAL PROCEEDINGS.

On June 14, 2022, the Company received a paragraph IV notice of certification (the "Notice Letter") from Fresenius Kabi advising that Fresenius Kabi had submitted an ANDA to the FDA seeking approval to manufacture, use or sell a generic version of CINVANTI in the U.S. prior to the expiration of U.S. Patent Nos.: 9,561,229, 9,808,465, 9,974,742, 9,974,793, 9,974,794, 10,500,208, 10,624,850, 10,953,018, and 11,173,118 (the "CINVANTI Patents"), which are listed in the FDA's Approved Drug Products with Therapeutic Equivalence Evaluations (the "Orange Book"). The Notice Letter alleges that the CINVANTI Patents are invalid, unenforceable and/or will not be infringed by the commercial manufacture, use or sale of the generic product described in Fresenius Kabi's ANDA.

On July 27, 2022, the Company filed a complaint for patent infringement of the CINVANTI Patents against Fresenius Kabi and a related entity in the District of Delaware in response to Fresenius Kabi's ANDA filing. The complaint seeks, among other relief, equitable relief enjoining Fresenius Kabi from infringing the CINVANTI Patents. The action is currently in fact discovery, and a five-day bench trial is scheduled for June 24, 2024. The Company intends to vigorously enforce its intellectual property rights relating to CINVANTI. As a result of filing our complaint for patent infringement, the FDA may not approve the ANDA until the earlier of December 14, 2024 or resolution of the litigation.

ITEM 4. MINE SAFETY DISCLOSURES.

Not applicable.

PART II

ITEM 5. MARKET FOR REGISTRANT'S COMMON EQUITY, RELATED STOCKHOLDER MATTERS AND ISSUER PURCHASES OF EQUITY SECURITIES.

Information About Our Common Stock

Shares of our common stock are traded on The Nasdaq Capital Market, under the symbol "HRTX."

Stockholders

The number of record holders of our common stock as of March 14, 2023 was 90.

Dividend Policy

We have never paid dividends on our common stock. We currently intend to retain all available funds and any future earnings for use in the operation and expansion of our business, and we do not anticipate paying any cash dividends in the foreseeable future.

Purchases of Equity Securities by the Issuer and Affiliated Purchasers

None.

Unregistered Sales of Equity Securities and Use of Proceeds

None.

ITEM 6. [RESERVED].

ITEM 7. MANAGEMENT'S DISCUSSION AND ANALYSIS OF FINANCIAL CONDITION AND RESULTS OF OPERATIONS.

The following discussion and analysis of our financial condition and results of operations should be read together with our audited financial statements and the related notes and other financial information included elsewhere in this Annual Report on Form 10-K. Some of the information contained in this discussion and analysis or set forth elsewhere in this Annual Report on Form 10-K, including information with respect to our plans and strategy for our business, include forward-looking statements that involve risks and uncertainties. You should review the "Risk Factors" included in Item 1A of this Annual Report on Form 10-K for a discussion of important factors that could cause our actual results to differ materially from the results described in or implied by the forward-looking statements contained in the following discussion and analysis.

Introduction

Management's discussion and analysis of financial condition and results of operations is provided as a supplement to the Consolidated Financial Statements and Notes, included in Item 8 of this Annual Report on Form 10-K, to help provide an understanding of our financial condition, the changes in our financial condition and our results of operations. Our discussion is organized as follows:

- *Overview.* This section provides a general description of our business and operating expenses.

- *Critical accounting policies and estimates.* This section contains a discussion of the accounting policies that we believe are important to our financial condition and results of operations and that require significant judgment and estimates on the part of management in their application. In addition, all of our significant accounting policies, including the critical accounting policies and estimates, are summarized in Note 2 to the Consolidated Financial Statements included in Item 8 of this Annual Report on Form 10-K.

- *Results of operations.* This section provides an analysis of our results of operations presented in the accompanying consolidated statements of operations and comprehensive loss by comparing the results for the year ended December 31, 2022 to the results for the year ended December 31, 2021.

- *Liquidity and capital resources.* This section provides an analysis of our cash flows and a discussion of our outstanding commitments and contingencies that existed as of December 31, 2022. Included in this discussion is our financial capacity to fund our future commitments and a discussion of other financing arrangements.

Overview

We are a commercial-stage biotechnology company focused on improving the lives of patients by developing and commercializing therapeutic innovations that improve medical care. Our advanced science, patented technologies, and innovative approach to drug discovery and development have allowed us to create and commercialize a portfolio of products that aim to advance the standard of care for acute care and oncology patients.

CINVANTI® (aprepitant) injectable emulsion ("CINVANTI") and SUSTOL® (granisetron) extended-release injection ("SUSTOL") are both approved in the United States ("U.S.") for the prevention of chemotherapy-induced nausea and vomiting. ZYNRELEF® (bupivacaine and meloxicam) extended-release solution ("ZYNRELEF") is approved in the U.S., 31 European countries and Canada for the management of postoperative pain.

In September 2022, APONVIE™ (aprepitant) injectable emulsion ("APONVIE") was approved in the U.S. for the prevention of postoperative nausea and vomiting and became commercially available in the U.S. in March 2023. We are also developing HTX-034, an investigational agent, our next generation product candidate for the management of postoperative pain.

Net Product Sales

Net product sales include revenue recognized for sales of CINVANTI, SUSTOL and ZYNRELEF (collectively, our "Products") to a limited number of specialty distributors and full line wholesalers (collectively, "Customers"), less applicable sales allowances. See the "Critical Accounting Policies and Estimates" section of this Annual Report on Form 10-K for further details on our revenue recognition policy.

Cost of Product Sales

Cost of product sales relates to the costs to produce, package and deliver our Products to our Customers. These costs include raw materials, labor, manufacturing and quality control overhead, and depreciation of equipment, as well as shipping and distribution costs. We expect cost of product sales to decrease in 2023, as large-scale manufacturing of ZYNRELEF and CINVANTI were validated in the fourth quarter of 2022. See the "Critical Accounting Policies and Estimates" section of this Annual Report on Form 10-K for further details on our inventory policy.

Research and Development Expense

All costs of research and development are expensed in the period incurred. Research and development expense primarily consists of salaries, stock-based compensation expense and other related costs for personnel in manufacturing, clinical and preclinical development, regulatory, quality and medical affairs. Other research and development expense includes professional fees paid to outside service providers and consultants, facilities costs and materials used in the clinical and preclinical trials and research and development.

At this time, due to the risks inherent in the clinical trial process, we are unable to estimate with any certainty the costs we will incur in the continued development of our product candidates. Other than costs for outsourced services associated with our clinical programs, we generally do not track research and development expense by project; rather, we track such expense by the type of cost incurred.

We expect research and development expense to decrease in 2023 because (i) APONVIE was approved in September 2022, (ii) we received U.S. Food and Drug Administration ("FDA") approval for two manufacturing supplements to the New Drug Application ("NDA") for ZYNRELEF to add a large-scale supplier of our proprietary polymer and to add larger-scale manufacturing of ZYNRELEF, (iii) larger-scale manufacturing of CINVANTI was validated in the fourth quarter of 2022, and (iv) we submitted a supplemental NDA for ZYNRELEF to further expand the indication statement in December 2022.

General and Administrative Expense

General and administrative expense primarily consists of salaries, stock-based compensation expense and other related costs for personnel in executive, finance and accounting, information technology, legal and human resource functions. Other general and administrative expense includes professional fees for legal, investor relations, accounting and other general corporate purposes, facility costs and insurance not otherwise included in research and development expense. We expect general and administrative expense in 2023 to remain comparable with 2022.

Sales and Marketing Expense

Sales and marketing expense primarily consists of salaries and related costs for personnel, stock-based compensation expense and other related costs for sales operations, marketing and market access. Other sales and marketing costs include professional fees and commercialization costs related to launch activities for ZYNRELEF, ongoing costs related to CINVANTI and SUSTOL, and launch preparation activities for APONVIE. We expect sales and marketing expense to decrease in 2023, as 2022 included one-time launch preparation costs for ZYNRELEF and the APONVIE launch will leverage our existing commercial organization in the acute care setting, with no additional field force and limited external spend.

Other Expense, Net

Other expense, net primarily consists of interest expense and the amortization of debt issuance costs related to our convertible notes payable, write-off of property and equipment, and income earned on our cash, cash equivalents and short-term investments.

Critical Accounting Policies and Estimates

A summary of the significant accounting policies is provided in Note 2 to our Consolidated Financial Statements.

The discussion and analysis of our financial condition and results of operations are based on our consolidated financial statements, which have been prepared in accordance with accounting principles generally accepted in the U.S. The preparation of these financial statements requires us to make estimates and judgments that affect the reported amounts of assets, liabilities, revenues and expenses, and related disclosure of contingent assets and liabilities. We evaluate our estimates on an ongoing basis, including those related to revenue recognition, investments, inventory, accrued clinical liabilities, income taxes and stock-based compensation. We base our estimates on historical experience and on assumptions that we believe to be reasonable under the circumstances, the results of which form the basis of making judgments about the carrying values of assets and liabilities that are not readily apparent from other sources. Actual results may differ materially from these estimates under different assumptions or conditions.

Management considers an accounting estimate to be critical if: it requires a significant level of estimation uncertainty, and changes in the estimate are reasonably likely to have a material effect on our financial condition or results of operations.

We believe the following critical accounting policies and estimates describe the most significant judgments and estimates used in the preparation of our consolidated financial statements.

Revenue Recognition

Product Sales

Our Products are distributed in the U.S. through a limited number of Customers that resell to healthcare providers and hospitals, the end users of our Products.

Revenue is recognized in an amount that reflects the consideration we expect to receive in exchange for our Products. To determine revenue recognition for contracts with customers, we perform the following 5 steps: (i) identify the contract(s) with a customer; (ii) identify the performance obligations of the contract(s); (iii) determine the transaction price; (iv) allocate the transaction price to the performance obligations in the contract(s); and (v) recognize revenue when (or as) we satisfy the performance obligations.

Product Sales Allowances

We recognize product sales allowances as a reduction of product sales in the same period the related revenue is recognized. Product sales allowances are based on amounts owed or to be claimed on the related sales. Such variable consideration includes estimates that take into consideration the terms of our agreements with Customers, historical product returns, rebates or discounts taken, the shelf life of the product and specific known market events, such as competitive pricing and new product introductions. If actual future results vary from our estimates, we may need to adjust these estimates, which could have an effect on product sales and earnings in the period of adjustment.

We believe our estimated allowances for distributor fees, group purchasing organization discounts, rebates and administrative fees and Medicaid rebates do not require a high degree of judgment because the amounts are settled within a relatively short period of time.

We believe our estimated allowance for product returns requires a high degree of judgment and is subject to change based on our experience and certain quantitative and qualitative factors. We allow our Customers to return product for credit for up to 12 months after its product expiration date. As such, there may be a significant period of time between the time the product is shipped and the time the credit is issued on returned product. We regularly monitor our estimates and record adjustments when return trends, contract terms or other significant events indicate that a change in estimates is appropriate. To date, our estimates have not differed materially from actual returns. However, subsequent changes in estimates may result in a material change to our product sales allowances, which could materially affect our results of operations and financial position.

Investments

We invest in various types of securities, including U.S. treasury bills and government agency obligations, corporate debt securities and commercial paper. These securities have been initially valued at the transaction price and subsequently valued utilizing a third-party service provider who assesses the fair value using inputs other than quoted prices that are observable either directly or indirectly, such as yield curve, volatility factors, credit spreads, default rates, loss severity, current market and contractual prices for the underlying instruments or debt, broker and dealer quotes, as well as other relevant economic measures. We perform certain procedures to corroborate the fair value of these holdings, and in the process, we apply judgment and estimates that if changed, could significantly affect our statements of financial positions. To date, our estimates have not differed materially from actual values. However, subsequent changes in estimates may result in a material change to the value of our cash equivalents and short-term investments, which could materially affect our results of operations and financial position.

Inventory

Inventory is stated at the lower of cost or estimated net realizable value on a first-in, first-out, or FIFO, basis. We periodically analyze our inventory levels and write down inventory that has become obsolete, inventory that has a cost basis in excess of its estimated realizable value and inventory quantities that are in excess of expected sales requirements as cost of product sales. The determination of whether inventory costs will be realizable requires estimates by management. If actual market conditions are less favorable than projected by management, additional write-downs of inventory may be required. Cost of product sales for the year ended December 31, 2022 included charges of $8.9 million, resulting primarily from the write-off of short-dated ZYNRELEF inventory. In addition, cost of product sales for the year ended December 31, 2021 included charges of $3.8 million, resulting from the write-off of short-dated SUSTOL inventory.

Accrued Research and Development Expenses

We estimate certain costs and expenses and accrue for these liabilities as part of our process of preparing financial statements. Examples of areas in which subjective judgment may be required include, among other things, costs associated with services provided by contract organizations for preclinical and clinical development, and manufacturing of our Products and product candidates. We accrue for costs incurred as the services are being provided by monitoring the status of the services provided, and the invoices received from our external service providers. In the case of clinical trials, we rely on estimates of the progress of the clinical trials and related expenses incurred. Changes to estimates are recorded to research and development expense in the period in which the facts that gave rise to the revision become known. To date, our estimates have not differed materially from the actual costs incurred. However, subsequent changes in estimates may result in a material change to our accruals, which could also materially affect our results of operations and financial position.

Income Taxes

We make certain estimates and judgments in determining income tax expense for financial statement purposes. These estimates and judgments occur in the calculation of certain deferred tax assets and liabilities, which arise from differences in the timing of recognition of revenue and expense for tax and financial statement purposes. As part of the process of preparing our consolidated financial statements, we are required to estimate our income taxes for each of the jurisdictions in which we operate. This process involves estimating our current tax exposure under the most recent tax laws and assessing temporary differences resulting from differing treatment of items for tax and financial statement purposes. At December 31, 2022, we established a valuation allowance to offset our deferred tax assets due to the uncertainty of realizing future tax benefits from our net operating loss carryforwards and other deferred tax assets. To date, our estimates have not materially changed. However, subsequent changes in estimates may result in a significant change to our deferred tax assets and liabilities, which could materially affect our results of operations and financial position.

Stock-based Compensation

We estimate the fair value of stock options granted using the Black-Scholes option pricing model. This fair value is then amortized over the requisite service periods of the awards. The Black-Scholes option pricing model requires the input of subjective assumptions, including each option's expected life and price volatility of the underlying stock. Expected volatility is based on our historical stock price volatility. The expected life of employee stock options represents the average of the contractual term of the options and the weighted-average vesting period, as permitted under the simplified method. To date, our assumptions used in our calculation of stock-based compensation expense has not significantly changed. However, subsequent changes in our assumptions could impact our stock-based compensation expense, which could materially affect our net loss and net loss per share.

Recent Accounting Pronouncements

See Note 2 to the Consolidated Financial Statements included in Item 8 of this Annual Report on Form 10-K.

Results of Operations

Years Ended December 31, 2022 and 2021

Net Product Sales

For the year ended December 31, 2022, net product sales were $107.7 million, compared to $86.3 million for the same period in 2021.

Net Product Sales – Oncology Care

For the year ended December 31, 2022, net product sales of CINVANTI were $87.3 million, compared to $73.5 million for the same period in 2021. For the year ended December 31, 2022, net product sales of SUSTOL were $10.2 million, compared to $9.9 million for the same period in 2021.

Net Product Sales – Acute Care

For the year ended December 31, 2022, net product sales of ZYNRELEF were $10.2 million, which was net of $0.5 million in returns for short-dated product. Short-dated product returns were due to delays in obtaining initial FDA approval of ZYNRELEF. For the year ended December 31, 2021, net product sales of ZYNRELEF were $2.9 million, which was net of $45,000 in returns for short-dated product. We commenced commercial sales of ZYNRELEF in the U.S. in July 2021.

Cost of Product Sales

For the year ended December 31, 2022, cost of product sales was $54.9 million, compared to $46.0 million for the same period in 2021. Cost of product sales primarily included raw materials, labor and overhead related to the manufacturing of our Products, as well as shipping and distribution costs. For the year ended December 31, 2022, cost of product sales also included charges of $8.9 million, resulting primarily from the write-off of short-dated ZYNRELEF inventory. For the year ended December 31, 2021, cost of product sales also included charges of $3.8 million, resulting from the write-off of short-dated SUSTOL inventory.

Prior to FDA approval, $23.6 million of costs to manufacture ZYNRELEF were recorded to research and development expense in prior periods. We began capitalizing raw materials, labor and overhead related to the manufacturing of ZYNRELEF following FDA approval in May 2021.

We began capitalizing raw materials, labor and overhead related to the manufacturing of APONVIE following FDA approval in September 2022. There were no costs incurred prior to FDA approval for the commercial manufacturing of APONVIE.

Research and Development Expense

Research and development expense consisted of the following (in thousands):

	December 31,	
	2022	2021
ZYNRELEF-related costs	$ 46,929	$ 46,804
CINVANTI-related costs	5,594	8,711
APONVIE-related costs	942	6,232
HTX-034-related costs	803	3,260
SUSTOL-related costs	1,902	1,435
Personnel costs and other expenses	33,427	44,897
Stock-based compensation expense	17,909	19,482
Total research and development expense	$ 107,506	$ 130,821

For the year ended December 31, 2022, research and development expense was $107.5 million, compared to $130.8 million for the same period in 2021. This decrease was primarily due to decreases in personnel and related costs of $11.5 million, as well as decreases in costs related to APONVIE, CINVANTI and HTX-034 of $5.3 million, $3.1 million and $2.5 million, respectively.

General and Administrative Expense

For the year ended December 31, 2022, general and administrative expense was $37.4 million, compared to $40.2 million for the same period in 2021. This decrease was primarily due to a reduction in facility-related costs as we subleased a portion of our leased space beginning in March 2022.

Sales and Marketing Expense

For the year ended December 31, 2022, sales and marketing expense was $82.5 million, compared to $87.2 million for the same period in 2021. This decrease was primarily due to a decrease in costs to support the ongoing commercialization of CINVANTI and SUSTOL, partially offset by an increase in costs to support the launch activities for ZYNRELEF.

Other Expense, Net

For the year ended December 31, 2022, other expense, net was $7.4 million, compared to $2.9 million for the same period in 2021. The increase was primarily due to the write-off of property and equipment at a third-party manufacturing site, partially offset by an increase in interest income earned on our short-term investments.

Restructuring Plans

See Note 7 to the Consolidated Financial Statements included in Item 8 of this Annual Report on Form 10-K for discussion of the restructuring plans implemented in October 2021 and June 2022.

Liquidity and Capital Resources

We have incurred significant operating losses and negative cash flows from operations. As of December 31, 2022, we had an accumulated deficit of $1.8 billion and cash, cash equivalents and short-term investments of $84.9 million. In addition, our net loss for the year ended December 31, 2022 was $182.0 million. These factors raise substantial doubt regarding our ability to continue as a going concern for a period of one year after the date that the financial statements are issued, however, based on our current operating plan and projections, management believes that the Company's existing cash, cash equivalents and short-term investments will be sufficient to meet the Company's anticipated cash requirements for at least one year from the date this Annual Report on Form 10-K is filed with the U.S. Securities and Exchange Commission.

In order to meet our cash requirements, we may be required to obtain additional funds and if we are not able to obtain adequate funds, we may be required to delay, reduce the scope of, or eliminate activities to support our Products and reduce personnel and related costs, which could have a material adverse effect on our business.

Our capital requirements and liquidity for the next twelve months will depend on numerous factors, including but not limited to: the degree of commercial success of our Products; the impact of competitive products; the timing and cost to manufacture our Products; the costs associated with the U.S. commercial launch of ZYNRELEF and APONVIE; the time, cost and outcome involved in seeking a further expanded label for ZYNRELEF in the U.S.; our ability to establish and maintain strategic collaborations or partnerships for research, development, clinical testing, manufacturing and marketing of our Products and product candidates; and general market conditions. Management's view of our liquidity relies on estimates and assumptions about the market opportunity for the expanded U.S. label of ZYNRELEF, which estimates and assumptions are subject to significant uncertainty.

We may not be able to raise sufficient additional capital when needed on favorable terms, or at all. If we are unable to obtain adequate funds, we may be required to curtail significantly or cease our operations. If we issue additional equity securities or securities convertible into equity securities to raise funds, our stockholders will suffer dilution of their investment, and such issuance may adversely affect the market price of our common stock.

Any new debt financing we enter into may involve covenants that restrict our operations. These restrictive covenants may include, among other things, limitations on borrowing and specific restrictions on the use of our assets, as well as prohibitions on our ability to create liens, pay dividends, redeem capital stock or make investments. In the event that additional funds are obtained through arrangements with collaborative partners, these arrangements may require us to relinquish rights to some of our technologies, product candidates or Products on terms that are not favorable to us or require us to enter into a collaboration arrangement that we would otherwise seek to develop and commercialize ourselves. If adequate funds are not available, we may default on our indebtedness, which could have a material adverse effect on our business.

Our net loss for the year ended December 31, 2022 was $182.0 million, or $1.67 per share, compared to a net loss of $220.7 million, or $2.24 per share for the same period in 2021.

Our net cash used in operating activities for the year ended December 31, 2022 was $146.9 million, compared to $203.4 million for the same period in 2021. The decrease in net cash used in operating activities was primarily due to changes in working capital, as well as a decrease in net loss.

Our net cash used for investing activities for the year ended December 31, 2022 was $3.3 million, compared to net cash provided by investing activities of $32.7 million for the same period in 2021. The decrease in cash provided by investing activities was primarily due to net purchases of short-term investments of $1.7 million for the year ended December 31, 2022, compared to net maturities of $35.7 million for the same period in 2021.

Our net cash provided by financing activities for the year ended December 31, 2022 was $75.1 million, compared to $156.0 million for the same period in 2021. The decrease in cash provided by financing activities was primarily due to net proceeds of $149.0 million from a convertible note financing received in May 2021, partially offset by net proceeds of $75.1 million received from a private placement in August 2022.

Historically, we have financed our operations, including technology and product research and development, primarily through sales of our common stock and debt financings.

Material Cash Requirements

As of December 31, 2022, we had an operating lease for 52,148 square feet of laboratory and office space in San Diego, California, with a lease term that expires on December 31, 2025. In October 2021, we entered into a sublease agreement to sublet 23,873 square feet of laboratory and office space. The space was delivered to the subtenant in March 2022. The sublease agreement expires on December 31, 2025 and is coterminous with the operating lease for the subleased space. As of December 31, 2022, we had total operating lease obligations of $9.1 million, with $3.0 million due in one year and $6.1 million due within two to three years.

At December 31, 2022, capital expenditures consisted of non-cancellable commitments for equipment at our third-party manufacturers. Total capital expenditures of $0.7 million were not included in our consolidated financial statements for the year ended December 31, 2022 and are due within one year. We intend to use our current financial resources to fund our commitments under the capital expenditure obligations.

At December 31, 2022, purchase obligations primarily consisted of non-cancellable commitments with third-party manufacturers in connection with the manufacturing of our Products. Total purchase obligations of $103.7 million were not included in our consolidated financial statements for the year ended December 31, 2022, with $38.7 million due in one year and $65.0 million due within two to three years. We intend to use our current financial resources to fund our commitments under these purchase obligations.

As of December 31, 2022, $150.0 million aggregate principal amount of the convertible notes were outstanding (see Note 8 to the Consolidated Financial Statements included in this Annual Report on Form 10-K). The convertible notes mature on May 26, 2026, unless earlier converted, redeemed or repurchased.

We enter into agreements with clinical sites and clinical research organizations for the conduct of our clinical trials and contract manufacturing organizations for the manufacture and supply of preclinical, clinical and commercial materials and drug product. We make payments to these clinical sites and clinical research organizations based in part on the number of eligible patients enrolled and the length of their participation in the clinical trials. In some of our agreements with contract manufacturing organizations, we are required to meet minimum purchase obligations. Under certain of these agreements, we may be subject to penalties in the event that we prematurely terminate these agreements. At this time, due to the variability associated with clinical site agreements, contract research organization agreements and contract manufacturing agreements, we are unable to estimate with certainty the future costs we will incur. We intend to use our current financial resources to fund our obligations under these commitments.

ITEM 7A. QUANTITATIVE AND QUALITATIVE DISCLOSURES ABOUT MARKET RISK.

Not required for smaller reporting companies.

ITEM 8. FINANCIAL STATEMENTS AND SUPPLEMENTARY DATA.

REPORT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

To the Stockholders and Board of Directors
Heron Therapeutics, Inc.

Opinion on the Consolidated Financial Statements

We have audited the accompanying consolidated balance sheets of Heron Therapeutics, Inc. and subsidiaries (the "Company") as of December 31, 2022 and 2021, and the related consolidated statements of operations and comprehensive loss, stockholders' equity, and cash flows for each of the two years in the period ended December 31, 2022, and the related notes (collectively referred to as the "consolidated financial statements").

In our opinion, the consolidated financial statements present fairly, in all material respects, the financial position of the Company as of December 31, 2022 and 2021, and the results of its operations and its cash flows for each of the two years in the period ended December 31, 2022, in conformity with accounting principles generally accepted in the United States of America.

Basis for Opinion

These consolidated financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on these consolidated financial statements based on our audits. We are a public accounting firm registered with the Public Company Accounting Oversight Board (United States) ("PCAOB") and are required to be independent with respect to the Company in accordance with the U.S. federal securities laws and the applicable rules and regulations of the Securities and Exchange Commission and the PCAOB.

We conducted our audits in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the consolidated financial statements are free of material misstatement, whether due to error or fraud. The Company is not required to have, nor were we engaged to perform, an audit of its internal control over financial reporting. As part of our audits we are required to obtain an understanding of internal control over financial reporting but not for the purpose of expressing an opinion on the effectiveness of the entity's internal control over financial reporting. Accordingly, we express no such opinion.

Our audits included performing procedures to assess the risks of material misstatement of the consolidated financial statements, whether due to error or fraud, and performing procedures that respond to those risks. Such procedures included examining, on a test basis, evidence regarding the amounts and disclosures in the consolidated financial statements. Our audits also included evaluating the accounting principles used and significant estimates made by management, as well as evaluating the overall presentation of the consolidated financial statements. We believe that our audits provide a reasonable basis for our opinion.

Critical Audit Matters

The critical audit matters communicated below are matters arising from the current period audit of the consolidated financial statements that were communicated or required to be communicated to the audit committee and that: (1) relate to accounts or disclosures that are material to the consolidated financial statements; and (2) involved our especially challenging, subjective, or complex judgments. The communication of critical audit matters does not alter in any way our opinion on the consolidated financial statements, taken as a whole, and we are not, by communicating the critical audit matters below, providing separate opinions on the critical audit matters or on the accounts or disclosures to which they relate.

Allowance for Product Returns

Description of the Matter
As discussed in Note 5 to the consolidated financial statements, the Company earns its revenue through the sale of its products, CINVANTI, SUSTOL and ZYNRELEF, to specialty distributors. Such revenue totaled $107.7 million for the year ended December 31, 2022. The amount of revenue recognized is net of product sales allowances for product returns, distributor fees, group purchase organization fees, discounts and rebates, and Medicare rebates, which totaled $181.1 million for the year ended December 31, 2022. The allowances are recorded in the same period that the related revenue is recognized and create variability in the consideration that the Company expects to receive. Management's estimated allowance for product returns requires a high degree of judgment and is subject to change based on various quantitative and qualitative factors. Accordingly, extensive audit effort and a high degree of auditor judgment were needed to evaluate management's estimates and assumptions used in the determination of product returns. Therefore, we identified management's allowance for product returns as a critical audit matter.

How We Addressed the Matter in Our Audit
We tested the effectiveness of internal control over financial reporting that relate to the Company's processes for estimating product returns.

We evaluated the significant accounting policies relating to product returns, as well as management's application of the policies, for appropriateness and reasonableness.

We selected a sample of customer transactions and performed the following procedures for each selection:

- Obtained and read contract source documents and management's contract analyses.
- Evaluated whether the selected estimates were applied consistently across similar arrangements.
- Tested the reasonableness of management's assumptions by comparing them to historical data, peer group information, and, where available, subsequent product returns.
- Where management used actual shipments and returns to estimate product returns, we tested the third-party reports used by management for completeness and accuracy.

Additionally, we tested the mathematical accuracy of management's calculation of revenue, net of product sales allowances, including product returns, and the associated timing of revenue recognition, in the consolidated financial statements.

Assessment of the Company's Ability to Continue as a Going Concern

Description of the Matter
As discussed in Note 1 to the consolidated financial statements, such financial statements have been prepared on a going concern basis, which contemplates the realization of assets and satisfaction of liabilities in the normal course of business. The Company has identified conditions that raise substantial doubt about its ability to continue as a going concern and has concluded that such substantial doubt is alleviated as a result of consideration of their plans.

We identified management's assessment of their ability to continue as a going concern as a critical audit matter. Significant auditor judgment was required to evaluate certain key assumptions regarding the cash flow projections, including revenue projections, operating expense projections, and the timing of cash flows.

How We Addressed the Matter in Our Audit

The primary procedures we performed to address this critical audit matter included:

- obtaining an understanding of the Company's process for determining their ability to continue as a going concern, which included management's analysis over the inputs and assumptions used to forecast future cash flows in the going concern analysis,
- evaluating the significant assumptions used in developing the financial projections,
- evaluating the sensitivity to change of assumptions used, including revenue projections and operating expense projections, and
- assessing management’s financial projections in the context of other audit evidence obtained during the audit and historical performance to determine whether it was contradictory to the conclusion reached by management.

/s/ WithumSmith+Brown, PC

We have served as the Company's auditor since 2006.

San Francisco, California
March 29, 2023

PCAOB ID Number 100

HERON THERAPEUTICS, INC.

CONSOLIDATED BALANCE SHEETS

(In thousands, except par value amounts)

	December 31, 2022	December 31, 2021
ASSETS		
Current assets:		
Cash and cash equivalents	$ 15,364	$ 90,541
Short-term investments	69,488	67,039
Accounts receivable, net	52,049	35,499
Inventory	54,573	48,382
Prepaid expenses and other current assets	13,961	12,962
Total current assets	205,435	254,423
Property and equipment, net	22,160	23,734
Right-of-use lease assets	7,645	9,829
Other assets	15,711	17,720
Total assets	$ 250,951	$ 305,706
LIABILITIES AND STOCKHOLDERS' EQUITY		
Current liabilities:		
Accounts payable	$ 3,225	$ 3,803
Accrued clinical and manufacturing liabilities	24,468	23,716
Accrued payroll and employee liabilities	13,416	15,263
Other accrued liabilities	38,552	25,859
Current lease liabilities	2,694	2,417
Total current liabilities	82,355	71,058
Non-current lease liabilities	5,499	7,996
Non-current convertible notes payable, net	149,284	149,082
Other non-current liabilities	241	—
Total liabilities	237,379	228,136
Commitments and contingencies (see Note 6)		
Stockholders' equity:		
Preferred stock, $0.01 par value: 2,500 shares authorized; no shares issued or outstanding at December 31, 2022 and 2021	—	—
Common stock, $0.01 par value: 150,000 shares authorized; 119,155 and 102,005 shares issued and outstanding at December 31, 2022 and 2021, respectively	1,191	1,020
Additional paid-in capital	1,807,855	1,689,987
Accumulated other comprehensive loss	(19)	(6)
Accumulated deficit	(1,795,455)	(1,613,431)
Total stockholders' equity	13,572	77,570
Total liabilities and stockholders' equity	$ 250,951	$ 305,706

See accompanying Notes to Consolidated Financial Statements.

HERON THERAPEUTICS, INC.

CONSOLIDATED STATEMENTS OF OPERATIONS AND COMPREHENSIVE LOSS

(In thousands, except per share amounts)

	Years Ended December 31,	
	2022	2021
Revenues:		
Net product sales	$ 107,672	$ 86,346
Operating expenses:		
Cost of product sales	54,874	46,021
Research and development	107,506	130,821
General and administrative	37,437	40,153
Sales and marketing	82,513	87,179
Total operating expenses	282,330	304,174
Loss from operations	(174,658)	(217,828)
Other expense, net:		
Interest income	1,638	433
Interest expense	(2,474)	(2,410)
Other income (expense)	(6,530)	(878)
Total other expense, net	(7,366)	(2,855)
Net loss	(182,024)	(220,683)
Other comprehensive loss:		
Unrealized losses on short-term investments	(13)	(263)
Comprehensive loss	$ (182,037)	$ (220,946)
Basic and diluted net loss per share	$ (1.67)	$ (2.24)
Shares used in computing basic and diluted net loss per share	108,876	98,471

See accompanying Notes to Consolidated Financial Statements.

HERON THERAPEUTICS, INC.

CONSOLIDATED STATEMENTS OF STOCKHOLDERS' EQUITY
(In thousands)

	Common Stock		Additional Paid-In	Accumulated Other Comprehensive	Accumulated	Total Stockholders'
	Shares	Amount	Capital	Income (Loss)	Deficit	Equity
Balance, December 31, 2020	91,310	$ 913	$1,628,070	$ 257	$ (1,392,748)	$ 236,492
Conversion benefit included in Convertible Notes issued	—	—	230	—	—	230
Issuance of common stock under Employee Stock Purchase Plan	175	2	2,137	—	—	2,139
Issuance of common stock under equity incentive plan	476	5	4,921	—	—	4,926
Issuance of common stock on exercise of warrants	195	2	(2)	—	—	—
Issuance of common stock on conversion of Convertible Notes	9,849	98	7,780	—	—	7,878
Stock-based compensation expense	—	—	46,851	—	—	46,851
Net loss	—	—	—	—	(220,683)	(220,683)
Net unrealized loss on short-term investments	—	—	—	(263)	—	(263)
Comprehensive loss	—	—	—	—	—	(220,946)
Balance, December 31, 2021	102,005	$ 1,020	$1,689,987	$ (6)	$ (1,613,431)	$ 77,570
Issuance of common stock under Employee Stock Purchase Plan	407	4	1,440	—	—	1,444
Issuance of common stock under equity incentive plan	614	6	(1,536)	—	—	(1,530)
Issuance of common stock in a private placement	16,129	161	74,984	—	—	75,145
Stock-based compensation expense	—	—	42,980	—	—	42,980
Net loss	—	—	—	—	(182,024)	(182,024)
Net unrealized loss on short-term investments	—	—	—	(13)	—	(13)
Comprehensive loss	—	—	—	—	—	(182,037)
Balance, December 31, 2022	119,155	$ 1,191	$1,807,855	$ (19)	$ (1,795,455)	$ 13,572

See accompanying Notes to Consolidated Financial Statements.

HERON THERAPEUTICS, INC.

CONSOLIDATED STATEMENTS OF CASH FLOWS

(In thousands)

	Years Ended December 31,	
	2022	2021
Operating activities:		
Net loss	$ (182,024)	$ (220,683)
Adjustments to reconcile net loss to net cash used for operating activities:		
Stock-based compensation expense	42,980	46,851
Depreciation and amortization	2,889	3,021
Amortization of debt discount	—	785
Amortization of debt issuance costs	202	119
Amortization of premium (accretion of discount) on short-term investments	(736)	332
Impairment of property and equipment	209	478
Loss on disposal of property and equipment	74	822
Change in operating assets and liabilities:		
Accounts receivable	(16,550)	6,351
Inventory	(6,191)	(6,477)
Prepaid expenses and other assets	1,010	(8,386)
Accounts payable	(578)	3,278
Accrued clinical and manufacturing liabilities	752	(26,246)
Accrued payroll and employee liabilities	(1,847)	1,666
Other accrued liabilities	12,898	(5,265)
Net cash used in operating activities	(146,912)	(203,354)
Investing activities:		
Purchases of short-term investments	(145,683)	(129,221)
Maturities and sales of short-term investments	143,957	164,940
Purchases of property and equipment	(1,825)	(3,022)
Proceeds from the sale of property and equipment	227	32
Net cash provided by (used in) investing activities	(3,324)	32,729
Financing activities:		
Net proceeds from sale of common stock	75,145	—
Net proceeds from convertible notes financing	—	148,963
Proceeds from purchases under the Employee Stock Purchase Plan	1,444	2,139
Proceeds from (payments for) stock issued under the equity incentive plan	(1,530)	4,926
Net cash provided by financing activities	75,059	156,028
Net decrease in cash and cash equivalents	(75,177)	(14,597)
Cash and cash equivalents at beginning of year	90,541	105,138
Cash and cash equivalents at end of year	$ 15,364	$ 90,541
Supplemental disclosure of cash flow information:		
Interest paid	$ 2,250	$ 1,244

See accompanying Notes to Consolidated Financial Statements.

HERON THERAPEUTICS, INC.
NOTES TO CONSOLIDATED FINANCIAL STATEMENTS

1. Organization and Business

We are a commercial-stage biotechnology company focused on improving the lives of patients by developing and commercializing therapeutic innovations that improve medical care. Our advanced science, patented technologies, and innovative approach to drug discovery and development have allowed us to create and commercialize a portfolio of products that aim to advance the standard of care for acute care and oncology patients.

CINVANTI® (aprepitant) injectable emulsion ("CINVANTI") and SUSTOL® (granisetron) extended-release injection ("SUSTOL") are both approved in the United States ("U.S.") for the prevention of chemotherapy-induced nausea and vomiting. ZYNRELEF® (bupivacaine and meloxicam) extended-release solution ("ZYNRELEF") is approved in the U.S., 31 European countries and Canada for the management of postoperative pain.

In September 2022, APONVIE™ (aprepitant) injectable emulsion ("APONVIE") was approved in the U.S. for the prevention of postoperative nausea and vomiting and became commercially available in the U.S. in March 2023. We are also developing HTX-034, an investigational agent, our next-generation product candidate for the management of postoperative pain.

In accordance with Accounting Standards Codification ("ASC") 205-40, *Going Concern*, we evaluated whether there are conditions and events, considered in the aggregate, that raise substantial doubt about our ability to continue as a going concern within one year after the date that the consolidated financial statements are issued. This evaluation initially does not take into consideration the potential mitigating effect of our plans that have not been fully implemented as of the date the financial statements are issued. When substantial doubt exists under this methodology, we evaluate whether the mitigating effect of its plans sufficiently alleviates substantial doubt about our ability to continue as a going concern. The mitigating effect of our plans, however, is only considered if both (1) it is probable that the plans will be effectively implemented within one year after the date that the financial statements are issued, and (2) it is probable that the plans, when implemented, will mitigate the relevant conditions or events that raise substantial doubt about our ability to continue as a going concern within one year after the date that the financial statements are issued.

We have incurred significant operating losses and negative cash flows from operations. As of December 31, 2022, we had an accumulated deficit of $1.8 billion and cash, cash equivalents and short-term investments of $84.9 million. In addition, our net loss for the year ended December 31, 2022 was $182.0 million. These factors raise substantial doubt regarding our ability to continue as a going concern for a period of one year after the date that the financial statements are issued, however, based on our current operating plan and projections, management believes that the Company's existing cash, cash equivalents and short-term investments will be sufficient to meet the Company's anticipated cash requirements for at least one year from the date this Annual Report on Form 10-K is filed with the U.S. Securities and Exchange Commission ("SEC").

In order to meet our cash requirements, we may be required to obtain additional funds and if we are not able to obtain adequate funds, we may be required to delay, reduce the scope of, or eliminate activities to support our Products and reduce personnel and related costs, which could have a material adverse effect on our business.

Our capital requirements and liquidity for the next twelve months will depend on numerous factors, including but not limited to: the degree of commercial success of our Products; the impact of competitive products; the timing and cost to manufacture our Products; the costs associated with the U.S. commercial launch of ZYNRELEF and APONVIE; the time, cost and outcome involved in seeking a further expanded label for ZYNRELEF in the U.S.; our ability to establish and maintain strategic collaborations or partnerships for research, development, clinical testing, manufacturing and marketing of our Products and product candidates; and general market conditions. Management's view of our liquidity relies on estimates and assumptions about the market opportunity for the expanded U.S. label of ZYNRELEF, which estimates and assumptions are subject to significant uncertainty.

We may not be able to raise sufficient additional capital when needed on favorable terms, or at all. If we are unable to obtain adequate funds, we may be required to curtail significantly or cease our operations. If we issue

additional equity securities or securities convertible into equity securities to raise funds, our stockholders will suffer dilution of their investment, and such issuance may adversely affect the market price of our common stock.

Any new debt financing we enter into may involve covenants that restrict our operations. These restrictive covenants may include, among other things, limitations on borrowing and specific restrictions on the use of our assets, as well as prohibitions on our ability to create liens, pay dividends, redeem capital stock or make investments. In the event that additional funds are obtained through arrangements with collaborative partners, these arrangements may require us to relinquish rights to some of our technologies, product candidates or Products on terms that are not favorable to us or require us to enter into a collaboration arrangement that we would otherwise seek to develop and commercialize ourselves. If adequate funds are not available, we may default on our indebtedness, which could have a material adverse effect on our business.

2. Summary of Significant Accounting Policies

Principles of Consolidation

The accompanying consolidated financial statements include the accounts of Heron Therapeutics, Inc. and its wholly-owned subsidiary, Heron Therapeutics B.V., which was organized in the Netherlands in March 2015. Heron Therapeutics B.V. has no operations and no material assets or liabilities, and there have been no significant transactions related to Heron Therapeutics B.V. since its inception.

Use of Estimates

The preparation of financial statements in conformity with accounting principles generally accepted in the U.S. ("GAAP") requires management to make estimates and assumptions that affect the amounts reported in the financial statements and disclosures made in the accompanying notes to the financial statements. Our significant accounting policies that involve significant judgment and estimates include revenue recognition, investments, inventory and the related reserves, accrued clinical liabilities, income taxes and stock-based compensation. Actual results could differ materially from those estimates.

Cash, Cash Equivalents and Short-term Investments

Cash and cash equivalents consist of cash and highly liquid investments with contractual maturities of three months or less from the original purchase date.

Short-term investments consist of securities with contractual maturities of greater than three months from the original purchase date. Securities with contractual maturities greater than one year are classified as short-term investments on the consolidated balance sheets, as we have the ability, if necessary, to liquidate these securities to meet our liquidity needs in the next 12 months. We have classified our short-term investments as available-for-sale securities in the accompanying consolidated financial statements. Available-for-sale securities are stated at fair market value, with net changes in unrealized gains and losses reported in other comprehensive loss and realized gains and losses included in other expense, net. The cost of securities sold is based on the specific identification method. Interest and dividends on securities classified as available-for-sale are included in interest income.

Fair Value of Financial Instruments

A company may elect to use fair value to measure accounts and loans receivable, available-for-sale and held-to-maturity securities, equity method investments, accounts payable, guarantees and issued debt. Other eligible items include firm commitments for financial instruments that otherwise would not be recognized at inception and non-cash warranty obligations where a warrantor is permitted to pay a third party to provide the warranty goods or services. If the use of fair value is elected, any upfront costs and fees related to the item such as debt issuance costs must be recognized in earnings and cannot be deferred. The fair value election is irrevocable and generally made on an instrument-by-instrument basis, even if a company has similar instruments that it elects not to measure based on fair value. Unrealized gains and losses on existing items for which fair value has been elected are reported as a cumulative adjustment to beginning retained earnings and any changes in fair value are recognized in earnings. We have elected to not apply the fair value option to our financial assets and liabilities.

Financial instruments, including cash and cash equivalents, receivables, inventory, prepaid expenses, other current assets, accounts payable and accrued expenses, are carried at cost, which is considered to be representative of their respective fair values because of the short-term maturity of these instruments. Short-term available-for-sale investments are carried at fair value (see Note 3). Our convertible notes outstanding at December 31, 2022 and 2021 do not have a readily available ascertainable market value, however, the carrying value is considered to approximate its fair value.

Concentration of Credit Risk

Cash, cash equivalents and short-term investments are financial instruments that potentially subject us to concentrations of credit risk. We deposit our cash in financial institutions. At times, such deposits may be in excess of insured limits. We have not experienced any losses in such accounts and believe we are not exposed to significant risk on our cash, cash equivalents and short-term investments.

We may also invest our excess cash in money market funds, U.S. government and agencies, corporate debt securities and commercial paper. We have established guidelines relative to our diversification of our cash investments and their maturities in an effort to maintain safety and liquidity. These guidelines are periodically reviewed and modified to take advantage of trends in yields and interest rates.

CINVANTI, SUSTOL and ZYNRELEF (collectively, our "Products") are distributed in the U.S. through a limited number of specialty distributors and full line wholesalers (collectively, "Customers") that resell to healthcare providers and hospitals, the end users of our Products.

The following table includes the percentage of net product sales and accounts receivable balances for our three major Customers, each of which comprised 10% or more of our net product sales:

	Net Product Sales	Accounts Receivable
	Year Ended December 31, 2022	As of December 31, 2022
Customer A	43.5%	51.6%
Customer B	36.4%	32.5%
Customer C	18.8%	15.0%
Total	98.7%	99.1%

Accounts Receivable, Net

Accounts receivable are recorded at the invoice amount, net of an allowance for credit losses. The allowance for credit losses reflects accounts receivable balances that are believed to be uncollectible. In estimating the allowance for credit losses, we consider: (1) our historical experience with collections and write-offs; (2) the credit quality of our Customers and any recent or anticipated changes thereto; (3) the outstanding balances and past due amounts from our Customers; and (4) reasonable and supportable forecast of economic conditions expected to exist throughout the contractual term of the receivable.

We offered extended payment terms to our Customers in connection with our product launch of ZYNRELEF in July 2021. In addition, we offered extended payment terms to our Customers in January 2021 when we reinstated the promotion and contracting of SUSTOL. These extended payment terms were offered in anticipation of the timing of reimbursement by government and commercial payers. Effective October 2021, we shortened payment terms to our ZYNRELEF and SUSTOL Customers.

As of December 31, 2022 and 2021, we determined that an allowance for doubtful accounts was not required. For the years ended December 31, 2022 and 2021, we did not have any material write-offs any accounts receivable balances.

Inventory

Inventory is stated at the lower of cost or estimated net realizable value on a first-in, first-out, or FIFO, basis. We periodically analyze our inventory levels and write down inventory that has become obsolete, inventory that has a cost basis in excess of its estimated realizable value and inventory quantities that are in excess of expected sales requirements as cost of product sales. The determination of whether inventory costs will be realizable requires estimates by management. If actual market conditions are less favorable than projected by management, additional write-downs of inventory may be required, which would be recorded as cost of product sales.

Property and Equipment

Property and equipment is stated at cost less accumulated depreciation and amortization. Depreciation is calculated on a straight-line basis over the estimated useful lives of the assets (generally 5 years). Leasehold improvements are stated at cost and amortized on a straight-line basis over the shorter of the estimated useful life of the asset or the lease term.

Impairment of Long-Lived Assets

If indicators of impairment exist, we assess the recoverability of the affected long-lived assets by determining whether the carrying value of such assets can be recovered through undiscounted future operating cash flows. If impairment is indicated, we measure the amount of such impairment by comparing the carrying value of the asset to the fair value of the asset and record the impairment as a reduction in the carrying value of the related asset with a corresponding charge to operating expenses. Estimating the undiscounted future operating cash flows associated with long-lived assets requires judgment and assumptions that could differ materially from actual results.

Leases

We determine if an arrangement is a lease or contains lease components at inception. Operating leases with an initial term greater than 12 months are recorded as lease liabilities with corresponding right-of-use ("ROU") lease assets on the consolidated balance sheets. ROU lease assets represent our right to use the underlying assets over the lease term, and lease liabilities represent the present value of our obligation to make lease payments arising from the lease. Lease liabilities are recognized at the lease commencement based on the present value of lease payments over the lease term. As most of our leases do not provide an implicit rate, we use our incremental borrowing rate based on the information available at the commencement date in determining the present value of lease payments. We use the implicit rate when readily determinable. The ROU lease assets equal the lease liabilities, less unamortized lease incentives, unamortized initial direct costs and the cumulative difference between rent expense and amounts paid under the lease. The lease term includes any option to extend or terminate the lease when it is reasonably certain that we will exercise that option. Lease expense is recognized on a straight-line basis over the lease term. We have lease agreements with both lease and non-lease components, which are generally accounted for separately.

Revenue Recognition

Revenue is recognized in accordance with the Financial Accounting Standards Board (the "FASB") ASC Topic 606, *Revenue from Contracts with Customers* ("Topic 606"). Topic 606 is based on the principle that revenue should be recognized to depict the transfer of promised goods or services to customers in an amount that reflects the consideration to which the entity expects to be entitled in exchange for those goods or services.

Product Sales

Our Products are distributed in the U.S. through a limited number of Customers that resell to healthcare providers and hospitals, the end users of our Products.

Revenue is recognized in an amount that reflects the consideration we expect to receive in exchange for our Products. To determine revenue recognition for contracts with customers within the scope of Topic 606, we perform the following 5 steps: (i) identify the contract(s) with a customer; (ii) identify the performance obligations of the contract(s); (iii) determine the transaction price; (iv) allocate the transaction price to the performance obligations in the contract(s); and (v) recognize revenue when (or as) we satisfy the performance obligations.

Product Sales Allowances

We recognize product sales allowances as a reduction of product sales in the same period the related revenue is recognized. Product sales allowances are based on amounts owed or to be claimed on the related sales. Such variable consideration includes estimates that take into consideration the terms of our agreements with Customers, historical product returns, rebates or discounts taken, the shelf life of the product and specific known market events, such as competitive pricing and new product introductions. If actual future results vary from our estimates, we may need to adjust these estimates, which could have an effect on product sales and earnings in the period of adjustment. Our product sales allowances include:

- Product Returns—We allow our Customers to return product for credit for up to 12 months after its product expiration date. As such, there may be a significant period of time between the time the product is shipped and the time the credit is issued on returned product.

- Distributor Fees—We pay distribution service fees to our Customers based on a contractually fixed percentage of the wholesale acquisition cost and fees for data. These fees are paid no later than two months after the quarter in which product was shipped.

- Group Purchasing Organization ("GPO") Discounts and Rebates—We offer cash discounts to GPO members. These discounts are taken when the GPO members purchase product from our Customers, who

then charge back to us the discount amount. Additionally, we offer volume and contract-tier rebates to GPO members. Rebates are based on actual purchase levels during the quarterly rebate purchase period.

- GPO Administrative Fees—We pay administrative fees to GPOs for services and access to data. These fees are based on contracted terms and are paid after the quarter in which the product was purchased by the GPOs' members.

- Medicaid Rebates—We participate in Medicaid rebate programs, which provide assistance to certain low-income patients based on each individual state's guidelines regarding eligibility and services. Under the Medicaid rebate programs, we pay a rebate to each participating state, generally within three months after the quarter in which the product was sold.

We believe our estimated allowance for product returns requires a high degree of judgment and is subject to change based on our experience and certain quantitative and qualitative factors. We believe our estimated allowances for distributor fees, GPO discounts, rebates and administrative fees and Medicaid rebates do not require a high degree of judgment because the amounts are settled within a relatively short period of time.

Our product sales allowances and related accruals are evaluated each reporting period and adjusted when trends or significant events indicate that a change in estimate is appropriate. Changes in product sales allowance estimates could materially affect our results of operations and financial position.

Accrued Clinical Liabilities

We accrue clinical costs based on work performed, which relies on estimates of the progress of the trials and the related expenses incurred. Clinical trial related contracts vary significantly in duration, and may be for a fixed amount, based on the achievement of certain contingent events or deliverables, a variable amount based on actual costs incurred, capped at a certain limit or contain a combination of these elements. Revisions are recorded to research and development expense in the period in which the facts that give rise to the revision become known. Historically, revisions have not resulted in material changes to research and development expense; however, a modification in the protocol of a clinical trial or cancellation of a clinical trial could result in a material charge to our results of operations.

Research and Development Expense

All costs of research and development are expensed in the period incurred. Research and development expense primarily consists of personnel and related costs, stock-based compensation expense, fees paid to outside service providers and consultants, facilities costs and materials used in clinical and preclinical trials and research and development.

Patent Costs

We incur outside legal fees in connection with filing and maintaining our various patent applications. All patent costs are expensed as incurred and are included in general and administrative expense in the consolidated statements of operations and comprehensive loss.

Stock-Based Compensation Expense

We estimate the fair value of stock-based payment awards using the Black-Scholes option pricing model. This fair value is then amortized using the straight-line single-option method of attributing the value of stock-based compensation to expense over the requisite service periods of the awards. The Black-Scholes option pricing model requires the input of complex and subjective assumptions, including each option's expected life and price volatility of the underlying stock.

As stock-based compensation expense is based on awards ultimately expected to vest, it has been reduced for estimated forfeitures. Forfeitures are estimated at the time of grant and revised, if necessary, in subsequent periods if actual forfeitures differ from those estimates. Forfeitures are estimated based on historical data.

Warrants

We have issued warrants to purchase shares of our common stock in conjunction with certain equity financings or in exchange for services. The terms of the warrants were evaluated to determine the appropriate classification as equity or a liability.

Income Taxes

We recognize the impact of a tax position in our consolidated financial statements if the position is more likely than not to be sustained on examination and on the technical merits of the position. The total amount of unrecognized tax benefits, if recognized, would affect other tax accounts, primarily deferred taxes in future periods, and would not affect our effective tax rate, since we maintain a full valuation allowance against our deferred tax assets (see Note 12). We recognize interest and penalties related to income tax matters in income tax expense.

Comprehensive Loss

Comprehensive loss is defined as the change in equity during a period from transactions and other events and circumstances from non-owner sources. Net changes in unrealized gains and losses on available-for-sale securities are included in other comprehensive loss and represent the difference between our net loss and comprehensive net loss for both periods presented.

Net Loss per Share

Basic net loss per share is calculated by dividing the net loss by the weighted-average number of common shares outstanding for the period, without consideration of common stock equivalents. Diluted net loss per share is computed by dividing the net loss by the weighted-average number of common shares and common stock equivalents outstanding for the period determined using the treasury stock method. For purposes of this calculation, stock options, restricted stock units, warrants and shares of common stock underlying convertible notes are considered to be common stock equivalents and are included in the calculation of diluted net loss per share only when their effect is dilutive.

Because we have incurred a net loss for both periods presented in the consolidated statements of operations and comprehensive loss, the following common stock equivalents were not included in the computation of net loss per share because their effect would be anti-dilutive (in thousands):

	December 31,	
	2022	2021
Stock options outstanding	20,749	18,944
Restricted stock units outstanding	3,167	2,803
Warrants outstanding	8,548	—
Shares of common stock underlying convertible notes outstanding	9,819	9,819

Recent Accounting Pronouncements

Adopted in 2022

In August 2020, the FASB issued ASU No. 2020-06, *Debt—Debt with Conversion and Other Options (Subtopic 470-20) and Derivatives and Hedging—Contracts in Entity's Own Equity (Subtopic 815-40): Accounting for Convertible Instruments and Contracts in an Entity's Own Equity* ("ASU 2020-06"). ASU 2020-06 simplifies the accounting for convertible instruments primarily by eliminating the existing cash conversion and beneficial conversion models within Subtopic 470-20, which will result in fewer embedded conversion options being accounted for separately from the debt host. ASU 2020-06 also amends and simplifies the calculation of earnings per share relating to convertible instruments. On January 1, 2022, we adopted the provisions of ASU 2020-06 using the modified retrospective approach, which did not have a material impact on our results of operations, cash flows, financial condition and related disclosures (see Note 8 for further details).

3. Fair Value Measurements

Fair value is defined as the exchange price that would be received for an asset or paid to transfer a liability (an exit price) in the principal or most advantageous market for the asset or liability in an orderly transaction between market participants on the measurement date. Valuation techniques used to measure fair value must maximize the use of observable inputs and minimize the use of unobservable inputs. The FASB ASC Topic 820, *Fair Value Measurements & Disclosures*, establishes a fair value hierarchy which prioritizes the inputs used in measuring fair value as follows:

- Level 1—Observable inputs such as quoted prices in active markets for identical assets or liabilities.
- Level 2—Inputs other than Level 1 that are observable, either directly or indirectly, such as quoted prices for similar assets or liabilities; quoted prices in markets that are not active; or other inputs that are observable or can be corroborated by observable market data for substantially the full term of the assets or liabilities.
- Level 3—Unobservable inputs that are supported by little or no market activity and that are significant to the fair value of the assets or liabilities.

We measure cash, cash equivalents and short-term investments at fair value on a recurring basis. The fair values of these such assets were as follows (in thousands):

	Fair Value Measurements at Reporting Date Using			
	Balance at December 31, 2022	Quoted Prices in Active Markets for Identical Assets (Level 1)	Significant Other Observable Inputs (Level 2)	Significant Unobservable Inputs (Level 3)
Cash and money market funds	$ 13,867	$ 13,867	$ —	$ —
U.S. treasury bills and government agency obligations	35,715	35,715	—	—
U.S. corporate debt securities	1,497	—	1,497	—
U.S. commercial paper	5,481	—	5,481	—
Foreign commercial paper	28,292	—	28,292	—
Total	$ 84,852	$ 49,582	$ 35,270	$ —

	Fair Value Measurements at Reporting Date Using			
	Balance at December 31, 2021	Quoted Prices in Active Markets for Identical Assets (Level 1)	Significant Other Observable Inputs (Level 2)	Significant Unobservable Inputs (Level 3)
Cash and money market funds	$ 86,043	$ 86,043	$ —	$ —
U.S. corporate debt securities	15,006	—	15,006	—
Foreign corporate debt securities	10,548	—	10,548	—
U.S. commercial paper	10,496	—	10,496	—
Foreign commercial paper	35,487	—	35,487	—
Total	$ 157,580	$ 86,043	$ 71,537	$ —

We have not transferred any investment securities between the three levels of the fair value hierarchy.

As of December 31, 2022, cash equivalents included $1.5 million of available-for-sale securities with contractual maturities of three months or less and short-term investments included $69.5 million of available-for-sale securities with contractual maturities of three months to one year. As of December 31, 2021, cash equivalents included $4.5 million of available-for-sale securities with contractual maturities of three months or less and short-term investments included $67.0 million of available-for-sale securities with contractual maturities of three months to one year. The money market funds as of December 31, 2022 and 2021 are included in cash and cash equivalents on the consolidated balance sheets.

4. Balance Sheet Details

Short-Term Investments

The following is a summary of our short-term investments (in thousands):

	December 31, 2022			
	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Estimated Fair Value
U.S. treasury bills and government agency obligations	$ 35,734	$ —	$ (19)	$ 35,715
U.S. commercial paper	5,481	—	—	5,481
Foreign commercial paper	28,292	—	—	28,292
Total	$ 69,507	$ —	$ (19)	$ 69,488

	December 31, 2021			
	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Estimated Fair Value
U.S. corporate debt securities	$ 15,009	$ —	$ (3)	$ 15,006
Foreign corporate debt securities	10,551	—	(3)	10,548
U.S. commercial paper	5,998	—	—	5,998
Foreign commercial paper	35,487	—	—	35,487
Total	$ 67,045	$ —	$ (6)	$ 67,039

The amortized cost of debt securities is adjusted for amortization of premiums and accretion of discounts to maturity. We regularly monitor and evaluate the realizable value of our marketable securities. We did not recognize any impairment losses for the years ended December 31, 2022 and 2021.

Unrealized gains and losses associated with our investments are reported in accumulated other comprehensive loss. For the years ended December 31, 2022 and 2021, we recorded $13,000 and $263,000, respectively, in net unrealized losses associated with our short-term investments.

Realized gains and losses associated with our investments, if any, are reported in the statements of operations and comprehensive loss. We did not recognize any realized gains or losses during the years ended December 31, 2022 and 2021.

Inventory

Inventory consists of the following (in thousands):

	December 31,	
	2022	2021
Raw materials	$ 15,137	$ 21,193
Work in process	20,723	20,935
Finished goods	18,713	6,254
Total inventory	$ 54,573	$ 48,382

As of December 31, 2022, total inventory included $30.9 million related to ZYNRELEF, $19.9 million related to CINVANTI, $2.6 million related to SUSTOL and $1.2 million related to APONVIE. As of December 31, 2021, total inventory included $23.6 million related to ZYNRELEF, $23.1 million related to CINVANTI, and $1.7 million related to SUSTOL. Cost of product sales for the year ended December 31, 2022 included charges of $8.9 million, resulting primarily from the write-off of short-dated ZYNRELEF inventory. In addition, cost of product sales for the year ended December 31, 2021 included charges of $3.8 million, resulting from the write-off of short-dated SUSTOL inventory.

Prepaid Expenses and Other Assets

Prepaid expenses and other assets consist of the following (in thousands):

	December 31,	
	2022	2021
Prepaid expenses	$ 21,120	$ 27,945
Other receivables	6,197	103
Prepaid insurance	1,947	2,135
Deposits	254	254
Interest receivable	154	245
Total prepaid expenses and other assets	$ 29,672	$ 30,682

Property and Equipment

Property and equipment, net consists of the following (in thousands):

	December 31,	
	2022	2021
Scientific equipment	$ 33,318	$ 33,403
Leasehold improvements	647	610
Computer equipment and software	1,506	1,497
Furniture, fixtures and office equipment	982	1,467
Property and equipment, gross	36,453	36,977
Less: accumulated depreciation and amortization	(14,293)	(13,243)
Property and equipment, net	$ 22,160	$ 23,734

Depreciation and amortization expense for the years ended December 31, 2022 and 2021 was $2.9 million and $3.0 million, respectively. As of December 31, 2022 and 2021, $5.4 million and $15.9 million of property and equipment, respectively, was in process and not depreciated during the respective years.

Accrued Payroll and Employee Liabilities and Other Accrued Liabilities

Accrued payroll and employee liabilities consist of the following (in thousands):

	December 31,	
	2022	2021
Accrued employee salaries and benefits	$ 2,134	$ 1,784
Accrued bonuses	7,783	9,439
Accrued vacation	3,499	4,040
Total accrued payroll and employee liabilities	$ 13,416	$ 15,263

Other accrued liabilities consist of the following (in thousands):

	December 31,	
	2022	2021
Accrued product sales allowances	$ 33,317	$ 22,560
Accrued consulting and professional fees	4,236	2,666
Accrued accounts payable	363	70
Other accrued liabilities	636	563
Total other accrued liabilities	$ 38,552	$ 25,859

5. Revenue Recognition

The following table provides disaggregated net product sales (in thousands):

	For the Years Ended December 31,	
	2022	2021
CINVANTI net product sales	$ 87,245	$ 73,507
SUSTOL net product sales	10,231	9,915
ZYNRELEF net product sales	10,196	2,924
Total net product sales	$ 107,672	$ 86,346

The following table provides a summary of activity with respect to our product returns, distributor fees and discounts, rebates and administrative fees, which are included in other accrued liabilities on the consolidated balance sheets (in thousands):

	Product Returns	Distributor Fees	Discounts, Rebates and Administrative Fees	Total
Balance at December 31, 2021	$ 2,579	$ 3,466	$ 16,515	$ 22,560
Provision	1,546	21,153	158,384	181,083
Payments/credits	(789)	(20,439)	(149,098)	(170,326)
Balance at December 31, 2022	$ 3,336	$ 4,180	$ 25,801	$ 33,317

6. Commitments and Contingencies

Leases

As of December 31, 2022, we had an operating lease for 52,148 square feet of laboratory and office space in San Diego, California, with a lease term that expires on December 31, 2025. In October 2021, we entered into a sublease agreement to sublet 23,873 square feet of laboratory and office space. The space was delivered to the subtenant in March 2022. As a result of the sublease agreement, our one 5-year option to renew the lease on expiration applies only with respect to our remaining 28,275 square feet of laboratory and office space. During the year ended December 31, 2022, we paid $2.9 million for our operating lease.

Annual future minimum lease payments as of December 31, 2022 are as follows (in thousands):

Year ended December 31:		
2023	$	2,969
2024		3,030
2025		3,097
2026		—
2027		—
Thereafter		—
Total future minimum lease payments		9,096
Less: discount		(903)
Total lease liabilities	$	8,193

Rent expense under all operating leases totaled $2.8 million and $3.7 million for the years ended December 31, 2022 and 2021, respectively.

Development Agreements

We enter into agreements with clinical sites and clinical research organizations for the conduct of our clinical trials and contract manufacturing organizations for the manufacture and supply of preclinical, clinical and commercial materials and drug product. We make payments to these clinical sites and clinical research organizations based in part on the number of eligible patients enrolled and the length of their participation in the clinical trials. In some of our agreements with contract manufacturing organizations, we are required to meet minimum purchase obligations. Under certain of these agreements, we may be subject to penalties in the event that we prematurely terminate these agreements. At this time, due to the variability associated with clinical site agreements, contract research organization agreements and contract manufacturing agreements, we are unable to estimate with certainty the future costs we will incur. We intend to use our current financial resources to fund our obligations under these commitments.

Purchase Obligations

At December 31, 2022, purchase obligations primarily consisted of non-cancellable commitments with third-party manufacturers in connection with the manufacturing of our commercial products. Total purchase obligations of $103.7 million were not included in our consolidated financial statements for the year ended December 31, 2022, with $38.7 million due in one year and $65.0 million due within two to three years.

7. Reorganization

In June 2022, we implemented a restructuring plan under which we provided employees one-time severance payments upon termination, continuation of benefits for a specific period of time, outplacement services and certain stock award modifications. The total amount incurred for these activities is $5.4 million, $5.0 million of which is primarily for severance and $0.4 million of which is for non-cash, stock-based compensation expense related to stock award modifications. For the year ended December 31, 2022, we recognized $5.4 million of the total expense, $4.2 million of which was included in research and development expense, $1.0 million of which was included in sales and marketing expense, and $0.2 million of which was included in general and administrative expense. We anticipate that the cash payments due to terminated employees will be substantially completed in the first quarter of 2023. As of December 31, 2022, we have paid $4.1 million of the total cash severance charges.

In October 2021, we implemented a restructuring plan under which we provided employees one-time severance payments upon termination, continued benefits for a specific period of time, outplacement services and certain stock option modifications. The total expense for these activities was $1.4 million, $1.3 million of which was primarily for severance and $0.1 million of which was for non-cash, stock-based compensation expense related to stock option modifications. The total expense was recognized in the fourth quarter of 2021, with $1.2 million included in research and development expense and $0.2 million included in sales and marketing expense. As of December 31, 2022, we have paid $1.3 million of the total cash severance charges.

We have accounted for these expenses in accordance with the FASB ASC Topic 420, *Exit or Disposal Cost Obligations*.

8. Convertible Notes

Senior Unsecured Convertible Notes

In May 2021, we entered into a note purchase agreement with funds affiliated with Baker Bros. Advisors LP for a private placement of $150.0 million in Senior Unsecured Convertible Notes ("Notes"). We received a total of $149.0 million, net of issuance costs, from the issuance of these Notes.

The Notes were issued at par. The Notes bear interest at a rate of 1.5% per annum, payable in cash semi-annually in arrears on June 15th and December 15th of each year, beginning on December 15, 2021. The Notes mature on May 26, 2026, unless earlier converted, redeemed or repurchased.

The Notes will be subject to redemption at our option, between May 24, 2024 and May 24, 2025, but only if the last reported sale price per share of our common stock exceeds 250% of the conversion price for a specified period of time, or on or after May 24, 2025 if the last reported sale price per share of our common stock exceeds 200% of the conversion price for a specified period of time. The redemption price will be equal to the principal amount of the Notes to be redeemed, plus accrued and unpaid interest.

Upon conversion, we will settle the Notes in shares of our common stock. The initial conversion rate for the Notes is 65.4620 shares per $1,000 principal amount of the Notes (equivalent to an initial conversion price of $15.276 per share of common stock).

If a holder of the Notes converts upon a make-whole fundamental change or company redemption, the holder may be eligible to receive a make-whole premium through an increase to the conversion rate.

In May 2021, we filed a registration statement with the SEC to register for resale 12.4 million shares of our common stock underlying the Notes, including the maximum number of shares of common stock issuable under the make-whole premium.

The Notes were accounted for in accordance with ASC Subtopic 470-20, *Debt with Conversion and Other Options* ("ASC 470-20") and ASC Subtopic 815-40, *Contracts in Entity's Own Equity* ("ASC 815-40"). Under ASC 815-40, to qualify for equity classification (or non-bifurcation, if embedded), the instrument (or embedded feature) must be both (1) indexed to the issuer's stock and (2) meet the requirements of the equity classification guidance. Based upon our analysis, it was determined that the Notes do contain embedded features indexed to our own stock, but do not meet the requirements for bifurcation, and therefore do not need to be separately accounted for as an equity component. Since the embedded conversion feature meets the equity scope exception from derivative accounting, and, also since the embedded conversion option does not need to be separately accounted for as an equity component under ASC 470-20, the proceeds received from the issuance of the Notes were recorded as a liability on the consolidated balance sheets.

We incurred issuance costs related to the Notes of $1.0 million, which we recorded as debt issuance costs and are included as a reduction to the Notes on the consolidated balance sheets. The debt issuance costs are being amortized to interest expense using the effective interest rate method over the term of the Notes, resulting in an effective interest rate of 1.6%. For the year ended December 31, 2022, interest expense related to the Notes was $2.5 million, which included $2.3 million related to the stated interest rate and $0.2 million related to the amortization of debt issuance costs. As of December 31, 2022, the carrying value of the Notes was $149.3 million, which is comprised of the $150.0 million principal amount of the Notes outstanding, less debt issuance costs of $0.7 million.

Senior Secured Convertible Notes

In April 2011, we entered into a securities purchase agreement for a private placement of up to $4.5 million in Senior Secured Convertible Notes ("Convertible Notes") with certain investors, including Tang Capital Partners, LP. We received a total of $4.3 million, net of issuance costs, from the issuance of these Convertible Notes. The Convertible Notes bore interest at 6% per annum, payable quarterly in cash or in additional principal amount of Convertible Notes, at the election of the purchasers. The Convertible Notes matured on May 2, 2021.

The Convertible Notes contained an embedded conversion feature that was in-the-money on the issuance dates. Based on an effective fixed conversion rate of 1,250 shares for every $1,000 of principal and accrued interest due under the Convertible Notes, the total conversion benefit at issuance exceeded the loan proceeds. Therefore, a debt discount was recorded in an amount equal to the face value of the Convertible Notes on the issuance dates, and we amortized the resultant debt discount over the respective 10-year term of the Convertible Notes which ended in May 2021. For the year ended December 31, 2021 interest expense relating to the stated rate was $0.2 million and interest expense relating to the amortization of the debt discount was $0.8 million.

In May 2021, holders of the Convertible Notes exercised their right to convert the outstanding principal and accrued interest into shares, which resulted in the issuance of 9.8 million shares of common stock. Upon issuance of these shares, there were no remaining obligations under the Convertible Notes.

9. Stockholders' Equity

2022 Private Placement

On August 8, 2022, we entered into an agreement to sell 16.1 million shares of our common stock in a private placement at a purchase price of $3.10 per share. In addition, as a component of the private placement, we agreed to sell 8.5 million pre-funded warrants to purchase shares of our common stock at a purchase price of $3.0999 per share. The pre-funded warrants have an exercise price of $0.0001 per share. The total net proceeds from the sale of the common stock and pre-funded warrants is $75.1 million (net of $1.4 million in issuance costs). In October 2022, we filed a registration statement with the SEC to register for resale 24.6 million shares of our common stock. The registration statement was declared effective on October 18, 2022.

Public Offering Warrants

In June 2014, as a component of our public offering, we sold 600,000 pre-funded warrants to purchase shares of our common stock. The pre-funded warrants have an exercise price of $0.01 per share and expire on June 30, 2021. During the year ended December 31, 2019, warrant holders exercised 132,130 warrants, which resulted in the issuance of 132,130 shares for net cash proceeds of $1,321. During the year ended December 31, 2020, warrant holders exercised 267,870 warrants, which resulted in the issuance of 267,870 shares for net cash proceeds of $2,679. In April 2021, warrant holders exercised 195,574 warrants using the cashless exercise provision, which resulted in the issuance of 195,461 shares and no cash proceeds. As of December 31, 2021, no warrants from the June 2014 public offering remain outstanding.

Common Stock Reserved for Future Issuance

Shares of our common stock reserved for future issuance as of December 31, 2022 were as follows:

	Number of Shares
Stock options outstanding	20,749
Restricted stock units outstanding	3,167
Stock options available for grant	985
Employee Stock Purchase Plan	645
Shares of common stock underlying warrants	8,548
Shares of common stock underlying convertible notes outstanding (see Note 8)	9,819
Total shares reserved for future issuance	43,913

10. Equity Incentive Plans

Employee Stock Purchase Plan

In 1997, our stockholders approved our Employee Stock Purchase Plan ("ESPP") at which time a maximum of 10,000 shares of common stock were available for issuance. In December 2007, May 2009, June 2011, May 2014, May 2015, June 2016, June 2017, June 2019, June 2021 and May 2022, our stockholders authorized increases in the number of shares reserved for issuance under the ESPP by 5,000, 10,000, 25,000, 25,000, 100,000, 100,000, 200,000, 300,000, 200,000 and 850,000 shares, respectively, for a total of 1,825,000 shares reserved at December 31, 2022. Under the terms of the ESPP, employees can elect to have up to a maximum of 10% of their base earnings withheld to purchase shares of our common stock. The purchase price of the stock is 85% of the lower of the closing prices for our common stock on either: (i) the first trading day in the enrollment period, as defined in the ESPP, in which the purchase is made, or (ii) the purchase date. The length of the enrollment period is 6 months. Enrollment dates are the first business day of May and November. Under the ESPP, we issued 406,421 and 175,228 shares in 2022 and 2021, respectively. The weighted-average exercise price per share of the purchase rights exercised during 2022 and 2021 was $3.55 and $12.21, respectively. As of December 31, 2022, 1,180,399 shares of common stock have been issued under the ESPP and 644,601 shares of common stock are available for future issuance.

Stock Option Plans

We currently have one stock option plan from which we can grant options and restricted stock awards to employees, officers, directors and consultants. In December 2007, the stockholders approved our 2007 Amended and Restated Equity Incentive Plan ("2007 Plan") at which time a maximum of 150,000 shares of common stock were available for grant. In May 2010, June 2011, May 2014, May 2015, June 2016, June 2017, June 2019, June 2021 and May 2022, our stockholders approved amendments to our 2007 Plan to increase the maximum number of shares of common stock available for grant by 100,000, 4,500,000, 1,750,000, 4,300,000, 3,000,000, 5,000,000, 7,000,000, 2,000,000 and 2,900,000 shares of common stock, respectively, resulting in an aggregate of 30,700,000 shares of common stock authorized for issuance as of December 31, 2022. At December 31, 2022, there were 985,119 shares available for future grant under the 2007 Plan. Any shares that are issuable on exercise of options granted that expire, are cancelled or that we receive pursuant to a net exercise of options are available for future grant and issuance.

In 2014 and 2013, we granted options to certain employees outside of our stockholder approved stock option plans. All options to purchase our common stock were granted with an exercise price that equals fair market value of the underlying common stock on the grant dates and expire no later than 10 years from the date of grant. The options are exercisable in accordance with vesting schedules that generally provide for them to be fully vested and exercisable 4 years after the date of grant, provided, however, that we have also issued stock options awards that are subject to performance vesting requirements. All stock option grants issued outside of our stockholder approved plans have been registered on Form S-8 with the SEC.

In 2020, we began granting restricted stock units ("RSUs") to employees and non-employee directors pursuant to the 2007 Plan. We satisfy such grants through the issuance of new shares upon vesting.

The following table summarizes the stock option plan activity:

	Outstanding Options	
	Number of Shares	Weighted-Average Exercise Price
Balance at December 31, 2021	18,943,937	$ 18.71
Granted	5,296,547	$ 3.11
Exercised	—	$ -
Cancelled	(3,491,135)	$ 19.40
Balance at December 31, 2022	20,749,349	$ 14.61

	Outstanding RSUs	
	Number of Shares	Weighted-Average Grant Date Fair Value
Balance at December 31, 2021	2,803,193	$ 11.51
Granted	1,831,508	$ 2.73
Released	(899,966)	$ 11.45
Forfeited	(567,338)	$ 11.47
Balance at December 31, 2022	3,167,397	$ 6.46

For the year ended December 31, 2022, equity awards cancelled (included in options outstanding) consisted of 1,227,682 options forfeited with a weighted-average exercise price of $15.57 and 2,263,453 options expired with a weighted-average exercise price of $21.47.

As of December 31, 2022, options exercisable have a weighted-average remaining contractual term of 6.4 years. There were no option exercises during the year ended December 31, 2022. The total intrinsic value of stock option exercises, which is the difference between the exercise price and closing price of our common stock on the date of exercise, during the year ended December 31, 2021 was $0.7 million. As of December 31, 2022, there were no options outstanding and exercisable that were in-the-money. As of December 31, 2021, the total intrinsic value of options outstanding and exercisable was $1.7 million.

	Years Ended December 31,			
	2022		2021	
	Options	Weighted-Average Exercise Price	Options	Weighted-Average Exercise Price
Exercisable at end of year	13,650,210	$ 17.86	12,243,887	$ 19.13
Options vested or expected to vest	20,183,769	$ 14.82	18,416,243	$ 18.77

Exercise prices and weighted-average remaining contractual lives for the options outstanding as of December 31, 2022 were:

Outstanding Options	Range of Exercise Prices	Weighted-Average Remaining Contractual Life (in years)	Weighted-Average Exercise Price	Options Exercisable	Weighted-Average Exercise Price of Options Exercisable
1,440,440	$2.49–$2.74	9.88	$ 2.70	2,369	$ 2.74
3,483,035	$2.88–$3.17	9.32	3.17	764,820	3.17
3,758,189	$3.30–$13.00	4.43	9.84	2,922,363	9.94
3,484,856	$13.05–$15.72	6.83	15.33	2,166,837	15.20
3,346,234	$15.75–$23.90	4.72	17.93	3,154,236	17.91
5,236,595	$24.40–$39.00	5.85	26.32	4,639,585	26.49
20,749,349		6.44	14.61	13,650,210	17.86

On December 31, 2022, we had reserved 23,916,746 shares of common stock for future issuance on exercise of outstanding options and vesting of outstanding restricted stock units granted under the 2007 Plan, as well as the non-plan grants.

Stock-Based Compensation

The following table summarizes stock-based compensation expense related to stock-based payment awards pursuant to our equity compensation arrangements (in thousands):

	December 31,	
	2022	2021
Research and development	$ 17,909	$ 19,482
General and administrative	11,688	11,816
Sales and marketing	13,383	15,553
Total stock-based compensation expense	$ 42,980	$ 46,851

As of December 31, 2022, there was $51.9 million of total unrecognized compensation cost related to non-vested, stock-based payment awards granted under all of our equity compensation plans and all non-plan option grants. Total unrecognized compensation cost will be adjusted for future changes in estimated forfeitures. We expect to recognize this compensation cost over a weighted-average period of 1.9 years.

The fair value of RSUs is estimated based on the closing market price of our common stock on the date of the grant. RSUs generally vest quarterly over a four-year period.

We estimated the fair value of each option grant and ESPP purchase right on the date of grant using the Black-Scholes option pricing model with the following weighted-average assumptions:

Options:

	December 31,	
	2022	2021
Risk-free interest rate	3.3%	1.1%
Dividend yield	—%	—%
Volatility	62.0%	62.6%
Expected life (years)	6	6

ESPP:

	December 31,	
	2022	2021
Risk-free interest rate	3.2%	0.1%
Dividend yield	—%	—%
Volatility	83.8%	46.9%
Expected life (months)	6	6

The weighted-average fair value of options granted was $1.71 and $7.10 for the years ended December 31, 2022 and 2021, respectively.

The weighted-average fair value of shares purchased through the ESPP was $1.65 and $3.64 for the years ended December 31, 2022 and 2021, respectively.

The risk-free interest rate assumption is based on observed interest rates on U.S. Treasury debt securities with maturities close to the expected term of our employee and director stock options and ESPP purchases.

The dividend yield assumption is based on our history and expectation of dividend payouts. We have never paid dividends on our common stock, and we do not anticipate paying dividends in the foreseeable future.

We used our historical stock price to estimate volatility.

The expected life of employee and director stock options represents the average of the contractual term of the options and the weighted-average vesting period, as permitted under the simplified method. We have elected to use the simplified method, as we do not have enough historical exercise experience to provide a reasonable basis on which to estimate the expected term. The expected life for the ESPP purchase rights is 6 months, which represents the length of each purchase period.

11. Employee Benefit Plan

We have a defined contribution 401(k) plan (“Plan”) covering substantially all of our employees. In the past three calendar years, we made matching cash contributions equal to 50% of each participant’s contribution during the Plan year up to a maximum amount equal to the lesser of 3% of each participant’s annual compensation or $9,150 and $8,700 for the years ended December 31, 2022 and 2021, respectively. Such amounts were recorded as expense in the corresponding years. We may also contribute additional discretionary amounts to the Plan as we determine. For the years ended December 31, 2022 and 2021, we contributed $1.4 million and $1.3 million, respectively, to the Plan. No discretionary contributions have been made to the Plan since its inception.

12. Income Taxes

For the years ended December 31, 2022 and 2021, we did not record a provision for income taxes due to a full valuation allowance against our deferred tax assets.

The difference between the provision for income taxes and income taxes computed using the effective U.S. federal statutory rate is as follows (in thousands):

	December 31,	
	2022	2021
Tax at statutory federal rate	$ (38,225)	$ (46,343)
State tax, net of federal benefit	(13,898)	(8,683)
Research and development credits	(3,531)	(4,173)
Stock-based compensation expense	5,857	4,584
Non-deductible compensation	2,104	1,970
Employee retention credit adjustment	(1,265)	—
Change in valuation allowance	46,452	51,459
Other	2,506	1,186
Provision for income taxes	$ —	$ —

Deferred income tax assets and liabilities arising from differences between accounting for financial statement purposes and tax purposes, less valuation allowance at year-end are as follows (in thousands):

	December 31,	
	2022	2021
Deferred tax assets:		
Net operating loss carryforward	$ 313,834	$ 294,189
Research and development credits	60,245	55,789
Section 174 capitalized research and development	20,903	—
Stock-based compensation	23,991	23,342
Lease liabilities	2,052	2,564
Other	3,693	3,953
Total gross deferred tax assets	424,718	379,837
Deferred tax liabilities:		
Right-of-use lease assets	(1,914)	(2,420)
Total gross deferred tax liabilities	(1,914)	(2,420)
Valuation allowance	(422,804)	(377,417)
Net deferred tax assets	$ —	$ —

We have established a valuation allowance to offset net deferred tax assets as of December 31, 2022 and 2021 due to the uncertainty of realizing future tax benefits from such assets.

As of December 31, 2022, we had federal and state net operating loss ("NOL") carryforwards of $1.3 billion and $891.7 million, respectively. The federal NOL carryforwards consist of $542.7 million generated before January 1, 2018, which will begin to expire in 2023, and $718.2 million that can be carried forward indefinitely, but are subject to the 80% taxable income limitation. The state NOL carryforwards will begin to expire in 2028.

As of December 31, 2022, we had federal and state research and development credit carryforwards of $49.3 million and $22.2 million, respectively. The federal research and development credit carryforwards will begin to expire in 2023. The state research and development credit carryforwards will be carried forward indefinitely.

Internal Revenue Code ("IRC") Sections 382 and 383 place a limitation on the amount of taxable income that can be offset by NOL and credit carryforwards after a change in control (generally greater than 50% change in ownership within a three-year period) of a loss corporation. Generally, after a change in control, a loss corporation cannot deduct NOL and credit carryforwards in excess of the IRC Sections 382 and 383 limitation. State jurisdictions have similar rules. We have previously performed an analysis of IRC Sections 382 and 383 through 2018 and determined there were ownership changes in 2007, 2011 and 2013. We are currently in the process of updating our IRC Sections 382 and 383 analysis through 2021. The limitation in the federal and state NOL and research and development credit carryforwards that expire unused would reduce the deferred tax assets, which are fully offset by a valuation allowance.

We file U.S. and state income tax returns with varying statutes of limitations. The tax years from 2002 to 2022 remain open to examination due to the carryover of unused NOL carryforwards and tax credits.

A reconciliation of our unrecognized tax benefits is as follows (in thousands):

	Year Ended December 31,	
	2022	2021
Balance at beginning of year	$ 9,631	$ 7,406
Increase (decrease) for tax positions of prior years	(200)	107
Increase based on tax positions related to current year	1,804	2,118
Balance at end of year	$ 11,235	$ 9,631

Due to our valuation allowance, the $11.2 million of unrecognized tax benefits would not affect the effective tax rate, if recognized. It is the Company's practice to recognize interest and penalties related to income tax matters in income tax expense. As of December 31, 2022, we had no accrued interest and penalties related to uncertain tax positions. We do not expect any material changes to the estimated amount of liability associated with our uncertain tax positions within the next 12 months.

On March 27, 2020, the Coronavirus Aid, Relief and Economic Security Act ("CARES Act") was enacted and signed into law in response to the COVID-19 pandemic. The CARES Act includes changes to the tax provisions that benefits business such as the Employee Retention Credit ("ERC"). The ERC provides an eligible employer with a tax credit that is allowed against certain employment taxes. We qualified for federal government assistance through the ERC provisions for the period between January 1, 2021 and September 30, 2021. We recognize government grants when there is reasonable assurance of compliance with grant conditions and receipt of the credits. As of December 31, 2022, we expect one-time refunds totaling $6.0 million, which are included in the consolidated balance sheets as prepaid expenses and other current assets, as well as in the consolidated statements of operations and comprehensive loss as an offset to the related employee expenses within research and development, general and administrative, and sales and marketing expenses.

Beginning January 1, 2022, the Tax Cuts and Jobs Act (the "Tax Act") eliminated the option to deduct research and development expenditures in the current year and requires taxpayers to capitalize such expenses pursuant to IRC Section 174. The capitalized expenses are amortized over a 5-year period for domestic expenses and over a 15-year period for foreign expenses. As a result of this provision of the Tax Act, deferred tax assets related to capitalized research expenses increased by $21 million.

ITEM 9. CHANGES IN AND DISAGREEMENTS WITH ACCOUNTANTS ON ACCOUNTING AND FINANCIAL DISCLOSURE.

None.

ITEM 9A. CONTROLS AND PROCEDURES.

(a) Disclosure Controls and Procedures

Our management, with the participation of our principal executive and principal financial and accounting officers, has evaluated the effectiveness of our disclosure controls and procedures (as defined in Rules 13a-15(e) and 15d-15(e) under the Securities Exchange Act of 1934 ("Exchange Act")) as of December 31, 2022. Based on this evaluation, our principal executive and principal financial and accounting officers concluded that our disclosure controls and procedures were effective as of December 31, 2022.

(b) Management Report on Internal Control Over Financial Reporting

Our management is responsible for establishing and maintaining adequate internal control over financial reporting. Internal control over financial reporting is defined in Rule 13a-15(f) and Rule 15d-15(f) promulgated under the Exchange Act as a process designed by, or under the supervision of, our principal executive and principal financial officers and effected by our Board of Directors, management and other personnel, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with accounting principles generally accepted in the U.S. and includes those policies and procedures that:

- pertain to the maintenance of records that in reasonable detail accurately and fairly reflect the transactions and dispositions of our assets;

- provide reasonable assurance that transactions are recorded as necessary to permit preparation of financial statements in accordance with accounting principles generally accepted in the U.S., and that receipts and expenditures are being made only in accordance with authorizations of our management and directors; and

- provide reasonable assurance regarding prevention or timely detection of unauthorized acquisition, use or disposition of our assets that could have a material effect on our financial statements.

Because of its inherent limitations, internal control over financial reporting may not prevent or detect misstatements. Projections of any evaluation of effectiveness to future periods are subject to the risk that controls may become inadequate because of changes in conditions, or that the degree of compliance with the policies or procedures may deteriorate.

Our management assessed the effectiveness of our internal control over financial reporting as of December 31, 2022. In making this assessment, our management used the criteria set forth by the Committee of Sponsoring Organizations of the Treadway Commission in *Internal Control-Integrated Framework (2013)*.

Based on our assessment, management concluded that, as of December 31, 2022, our internal control over financial reporting was effective based on those criteria.

This Annual Report does not include an attestation report of the Company's registered public accounting firm due to the Company meeting the definition of a smaller reporting company and the established rules of the SEC related to smaller reporting companies.

(c) Changes in Internal Control Over Financial Reporting

There have been no significant changes in our internal control over financial reporting that occurred during the period covered by this Annual Report on Form 10-K that has materially affected, or is reasonably likely to materially affect, our internal control over financial reporting.

ITEM 9B. OTHER INFORMATION.

None.

ITEM 9C. DISCLOSURE REGARDING FOREIGN JURISDICTIONS THAT PREVENT INSPECTIONS.

Not applicable.

PART III

ITEM 10. DIRECTORS, EXECUTIVE OFFICERS AND CORPORATE GOVERNANCE.

Information required by this item will be contained in our Definitive Proxy Statement for our 2023 Annual Meeting of Stockholders, to be filed pursuant to Regulation 14A with the SEC within 120 days of December 31, 2022. Such information is incorporated herein by reference.

We have adopted a Code of Ethics that applies to our Principal Executive Officer, Principal Financial and Accounting Officer, and to all of our other officers, directors and employees. The Code of Ethics is available in the Corporate Governance section of the Investor Resources page on our website at *www.herontx.com*. We intend to disclose future waivers or material amendments to certain provisions of our Code of Ethics on the above-referenced website within four business days following the date of such waiver or amendment.

ITEM 11. EXECUTIVE COMPENSATION.

Information required by this item will be contained in our Definitive Proxy Statement for our 2023 Annual Meeting of Stockholders, to be filed pursuant to Regulation 14A with the SEC within 120 days of December 31, 2022. Such information is incorporated herein by reference.

ITEM 12. SECURITY OWNERSHIP OF CERTAIN BENEFICIAL OWNERS AND MANAGEMENT AND RELATED STOCKHOLDER MATTERS.

Information required by this item will be contained in our Definitive Proxy Statement for our 2023 Annual Meeting of Stockholders, to be filed pursuant to Regulation 14A with the SEC within 120 days of December 31, 2022. Such information is incorporated herein by reference.

ITEM 13. CERTAIN RELATIONSHIPS AND RELATED TRANSACTIONS, AND DIRECTOR INDEPENDENCE.

Information required by this item will be contained in our Definitive Proxy Statement for our 2023 Annual Meeting of Stockholders, to be filed pursuant to Regulation 14A with the SEC within 120 days of December 31, 2022. Such information is incorporated herein by reference.

ITEM 14. PRINCIPAL ACCOUNTANT FEES AND SERVICES.

Information required by this item will be contained in our Definitive Proxy Statement for our 2023 Annual Meeting of Stockholders, to be filed pursuant to Regulation 14A with the SEC within 120 days of December 31, 2022. Such information is incorporated herein by reference.

PART IV

ITEM 15. EXHIBIT AND FINANCIAL STATEMENT SCHEDULES.

1. Consolidated Financial Statements.

   The consolidated financial statements and supplementary data set forth in Part II of the Annual Report on Form 10-K are included herein.

2. Consolidated Financial Statement Schedules.

   These schedules are omitted because they are not required, or are not applicable, or the required information is shown in the consolidated financial statements or notes thereto.

3. Exhibits.

   The exhibits listed in the accompanying Exhibit Index are incorporated by reference herein or filed as part of this Annual Report on Form 10-K.

EXHIBIT INDEX

Exhibit	Document Description
3.1	Certificate of Incorporation, as amended through July 29, 2009 (incorporated by reference to our Quarterly Report on Form 10-Q for the quarter ended June 30, 2009, as Exhibit 3.1, filed on August 4, 2009)
3.2	Certificate of Amendment of Certificate of Incorporation (incorporated by reference to our Current Report on Form 8-K, as Exhibit 3.1, filed on June 30, 2011)
3.3	Certificate of Amendment to the Certificate of Incorporation (incorporated by reference to our Current Report on Form 8-K, as Exhibit 3.1, filed on January 13, 2014)
3.4	Certificate of Amendment to the Certificate of Incorporation (incorporated by reference to our Company's Post-Effective Amendment to its Registration Statement on Form 8-A/A, filed on July 6, 2017)
3.5	Certificate of Amendment of Certificate of Incorporation (incorporated by reference to our Annual Report on Form 10-K for the year ended December 31, 2018, as Exhibit 3.6, filed on February 22, 2019)
3.6	Amended and Restated Bylaws (incorporated by reference to our Current Report on Form 8-K, as Exhibit 3.1, filed on February 8, 2019)
4.1	Common Stock Certificate (incorporated by reference to our Registration on Form S-3 (Registration No. 333-162968), as Exhibit 4.1, filed on November 6, 2009)
4.2	Form of Warrant to Purchase Shares of Common Stock (incorporated by reference to our Current Report on Form 8-K, as Exhibit 4.1, filed on June 27, 2014)
4.3	Form of Warrant to Purchase Shares of Common Stock (incorporated by reference to our Current Report on Form 8-K, as Exhibit 10.3, filed on October 22, 2009)
4.4	Amended and Restated Certificate of Designation, Preferences, and Rights of Series A Preferred Stock (incorporated by reference to our Current Report on Form 8-K, as Exhibit 3.C, filed on December 19, 2006)
4.5	Description of the Registrant's Securities Registered Pursuant to Section 12 of the Securities Exchange Act of 1934 (incorporated by reference to our Annual Report on Form 10-K for the year ended December 31, 2019, as Exhibit 4.5, filed on March 2, 2020)
4.6	Form of Pre-Funded Warrant to Purchase Common Stock (incorporated by reference to our Current Report on Form 8-K, as Exhibit 10.1, filed on August 10, 2022)
10.1*	1997 Employee Stock Purchase Plan, as amended to date (incorporated by reference to our Definitive Proxy Statement on Schedule 14A, as Exhibit B, filed on April 25, 2022)
10.2*	Amended and Restated 2007 Equity Incentive Plan (incorporated by reference to our Definitive Proxy Statement on Schedule 14A, as Exhibit A, filed on April 25, 2022)
10.3*	Form of 2007 Equity Incentive Plan Stock Option Agreement (incorporated by reference to our Registration on Form S-8 (Registration No. 333-148660), as Exhibit 4.3, filed on January 14, 2008)
10.4*	Form of 2007 Equity Incentive Plan Restricted Stock Unit Agreement (incorporated by reference to our Registration on Form S-8 (Registration No. 333-148660), as Exhibit 4.4, filed on January 14, 2008)
10.5*	Form of 2007 Equity Incentive Plan Restricted Stock Award Agreement (incorporated by reference to our Annual Report on Form 10-K for the year ended December 31, 2007, as Exhibit 10-O, filed on March 31, 2008)
10.6*	Form of Indemnification Agreement (incorporated by reference to our Annual Report on Form 10-K for the year ended December 31, 2007, as Exhibit 10-S, filed on March 31, 2008)
10.7*	Executive Employment Agreement, dated May 1, 2013, by and between the Company and Barry D. Quart, Pharm.D. (incorporated by reference to our Quarterly Report on Form 10-Q for the quarter ended March 31, 2013, as Exhibit 10-AI, filed on May 10, 2013)
10.8	Form of Non-Qualified Stock Option Agreement (incorporated by reference to our Quarterly Report on Form 10-Q for the quarter ended June 30, 2013, as Exhibit 10-AL, filed on August 8, 2013)
10.9*	Amendment to Executive Employment Agreement, dated May 1, 2013, as amended on April 22, 2015, by and between the Company and Dr. Barry Quart (incorporated by reference to our Quarterly Report on Form 10-Q for the quarter ended March 31, 2015, as Exhibit 10.1, filed on May 8, 2015)
10.10+	SUSTOL® (granisetron, extended release) Injection Commercial Manufacturing Services Agreement – Finished Final Drug Product, dated May 27, 2015, by and between the Company and Lifecore Biomedical, LLC) (incorporated by reference to our Current Report on Form 8-K, as Exhibit 10.1, filed on May 29, 2015)

10.11+	Commercial Supply Agreement, dated December 8, 2015, by and between the Company and SAFC, Inc. (incorporated by reference to our Annual Report on Form 10-K/A Amendment No. 1 for the year ended December 31, 2015, as Exhibit 10.36, filed on December 23, 2016)
10.12*	Executive Employment Agreement, dated January 28, 2016, by and between the Company and Kimberly Manhard (incorporated by reference to our Quarterly Report on Form 10-Q for the quarter ended March 31, 2016, as Exhibit 10.1, filed on May 5, 2016)
10.13	Lease Agreement, dated October 18, 2016, by and between the Company and AP3-SD1 Campus Point LLC (incorporated by reference to our Quarterly Report on Form 10-Q for the quarter ended September 30, 2016, as Exhibit 10.3, filed on November 8, 2016)
10.14	First Amendment to Lease, dated March 15, 2017, by and between the Company and AP3-SD1 Campus Point LLC (incorporated by reference to our Current Report on Form 8-K, as Exhibit 10.1, filed on March 17, 2017)
10.15	Second Amendment to Lease, dated May 8, 2018, by and between the Company and AP3-SD1 Campus Point LLC (incorporated by reference to our Quarterly Report on Form 10-Q for the quarter ended March 31, 2018, as Exhibit 10.1, filed on May 10, 2018)
10.16	Third Amendment to Lease, dated December 19, 2019, by and between the Company and ARE-SD Region No. 61, LLC (incorporated by reference to our Current Report on Form 8-K, as Exhibit 10.1, filed on December 20, 2019)
10.17	Note Purchase Agreement, dated as of May 24, 2021, by and among Heron Therapeutics, Inc. and funds affiliated with Baker Bros. Advisors, LP (incorporated by reference to our Current Report on Form 8-K, as Exhibit 10.1, filed on May 25, 2021)
10.18	Fourth Amendment to Lease, dated October 13, 2021, by and between the Company and ARE-SD Region No. 61, LLC (incorporated by reference to our Quarterly Report on Form 10-Q for the quarter ended September 30, 2021, as Exhibit 10.1, filed on November 3, 2021)
10.19*	Executive Employment Agreement, dated March 17, 2016, by and between the Company and David Szekeres (incorporated by reference to our Quarterly Report on Form 10-Q for the quarter ended June 30, 2022, as Exhibit 10.1, filed on August 9, 2022)
10.20	Securities Purchase Agreement, dated August 8, 2022, by and among the Company and the Purchasers signatory thereto (incorporated by reference to our Current Report on Form 8-K, as Exhibit 10.1, filed on August 10, 2022)
10.21	Cooperation Agreement, dated February 21, 2023, by and among Heron Therapeutics, Inc., Rubric Capital Management LP, the persons and entities listed on Schedule A thereto, Velan Capital Investment Management LP, and the persons and entities listed on Schedule B thereto (incorporated by reference to our Current Report on Form 8-K, as Exhibit 10.1, filed on February 22, 2023)
23.1	Consent of Independent Registered Public Accounting Firm (WithumSmith+Brown, PC)
24.1	Power of Attorney (included on the signature page hereto)
31.1	Certification Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002
31.2	Certification Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002
32.1#	Certification Pursuant to 18 U.S.C. Section 1350, as Adopted Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002
101.INS	Inline XBRL Instance Document – the instance document does not appear in the Interactive Data File because its XBRL tags are embedded within the Inline XBRL document
101.SCH	Inline XBRL Taxonomy Extension Schema Document
101.CAL	Inline XBRL Taxonomy Extension Calculation Linkbase Document
101.DEF	Inline XBRL Taxonomy Extension Definition Linkbase Document
101.LAB	Inline XBRL Taxonomy Extension Label Linkbase Document
101.PRE	Inline XBRL Taxonomy Extension Presentation Linkbase Document
104	Cover Page Interactive Data File (embedded within the Inline XBRL document and contained in Exhibit 101)

***** Management contract or compensatory plan, contract or arrangement.
+ Confidential treatment has been requested with respect to certain portions of the exhibit, which portions have been omitted and filed separately with the U.S. Securities and Exchange Commission.
#The certifications attached as Exhibit 32.1 accompany this Annual Report on Form 10-K pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, and shall not be deemed "filed" by the Registrant for purposes of Section 18 of the Securities Exchange Act of 1934, as amended.

ITEM 16. FORM 10-K SUMMARY.

None.

SIGNATURES

Pursuant to the requirements of Section 13 or 15(d) of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned, thereunto duly authorized.

HERON THERAPEUTICS, INC.

DATE: March 29, 2023 BY: /s/ BARRY QUART

Barry Quart, Pharm.D.

Chief Executive Officer

POWER OF ATTORNEY

KNOW ALL PERSONS BY THESE PRESENTS that each individual whose signature appears below constitutes and appoints Barry Quart as his or her true and lawful attorney-in-fact and agent, with full power of substitution, for him or her and in his or her name, place and stead, in any and all capacities, with respect to this annual report and any and all amendments thereto, and to file the same, with all exhibits thereto, and other documents in connection therewith, with the Securities and Exchange Commission, granting unto said attorney-in-fact and agent, full power and authority to do and perform each and every act and thing requisite and necessary to be done in and about the premises, as fully to all intents and purposes as he or she might or could do in person, hereby ratifying and confirming all the said attorney-in-fact and agent or his or her substitute or substitutes, may lawfully do or cause to be done by virtue hereof.

Pursuant to the requirements of the Securities Exchange Act of 1934, this report has been signed below by the following persons on behalf of the Registrant in the capacities and on the dates indicated.

Signature	Title	Date
/s/ BARRY QUART Barry Quart, Pharm.D.	Chief Executive Officer and Chairman of the Board of Directors *(Principal Executive Officer)*	March 29, 2023
/s/ LISA PERAZA Lisa Peraza	Vice President, Chief Accounting Officer *(Principal Financial and Accounting Officer)*	March 29 2023
/s/ CRAIG COLLARD Craig Collard	Director	March 29, 2023
/s/ SHARMILA DISSANAIKE Sharmila Dissanaike	Director	March 29, 2023
/s/ CRAIG JOHNSON Craig Johnson	Director	March 29, 2023
/s/ KEVIN KOTLER Kevin Kotler	Director	March 29, 2023
/s/ ADAM MORGAN Adam Morgan	Director	March 29, 2023
/s/ SUSAN RODRIGUEZ Susan Rodriguez	Director	March 29, 2023
/s/ CHRISTIAN WAAGE Christian Waage	Director	March 29, 2023

Exhibit 23.1

CONSENT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

We hereby consent to the incorporation by reference in the Registration Statements on Form S-3 (Nos. 333-256620 and 333-267781) and Form S-8 (Nos. 333-35151, 333-90428, 333-118546, 333-127574, 333-137954, 333-148660, 333-162610, 333-167515, 333-176365, 333-176366, 333-190549, 333-198853, 333-206165, 333-214503, 333-219830, 333-233023, 333-259518 and 333-267352) of Heron Therapeutics, Inc. of our report dated March 29, 2023, relating to the consolidated financial statements, which appears in this Form 10-K.

/s/ WithumSmith+Brown, PC

San Francisco, California
March 29, 2023

Exhibit 31.1

CERTIFICATION PURSUANT TO
RULES 13a-14(a) AND 15d-14(a) UNDER THE SECURITIES EXCHANGE ACT OF 1934,
AS ADOPTED PURSUANT TO SECTION 302 OF THE SARBANES-OXLEY ACT OF 2002

I, Barry Quart, certify that:

1. I have reviewed this Annual Report on Form 10-K of Heron Therapeutics, Inc.;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer(s) and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

   (a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

   (b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

   (c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

   (d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer(s) and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

   (a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

   (b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: March 29, 2023

By: /s/ Barry Quart
Barry Quart, Pharm.D.
Chief Executive Officer
(As Principal Executive Officer)

Exhibit 31.2

CERTIFICATION PURSUANT TO
RULES 13a-14(a) AND 15d-14(a) UNDER THE SECURITIES EXCHANGE ACT OF 1934,
AS ADOPTED PURSUANT TO SECTION 302 OF THE SARBANES-OXLEY ACT OF 2002

I, Lisa Peraza, certify that:

1. I have reviewed this Annual Report on Form 10-K of Heron Therapeutics, Inc.;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer(s) and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

   (a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

   (b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

   (c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

   (d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer(s) and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

   (a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

   (b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: March 29, 2023

By: /s/ Lisa Peraza
Lisa Peraza
Vice President, Chief Accounting Officer
(As Principal Financial and Accounting Officer)

Exhibit 32.1

CERTIFICATION

Pursuant to the requirement set forth in Rule 13a-14(b) of the Securities Exchange Act of 1934, as amended, (the "Exchange Act") and Section 1350 of Chapter 63 of Title 18 of the United States Code (18 U.S.C. §1350), Barry Quart, Pharm.D., Chief Executive Officer of Heron Therapeutics, Inc. (the "Company"), and Lisa Peraza, Vice President, Chief Accounting Officer of the Company, each hereby certifies that, to the best of his or her knowledge:

- the Company's Annual Report on Form 10-K for the fiscal year ended December 31, 2022, to which this Certification is attached as Exhibit 32.1 (the "Annual Report"), fully complies with the requirements of Section 13(a) or 15(d) of the Exchange Act; and

- the information contained in the Annual Report fairly presents, in all material respects, the financial condition and results of operations of the Company.

Dated: March 29, 2023

In Witness Whereof, the undersigned have set their hands hereto as of the 29th day of March, 2023.

/s/ Barry Quart
Barry Quart, Pharm.D.
Chief Executive Officer
(As Principal Executive Officer)

/s/ Lisa Peraza
Lisa Peraza
Vice President, Chief Accounting Officer
(As Principal Financial and Accounting Officer)

This certification accompanies the Form 10-K to which it relates, is not deemed filed with the Securities and Exchange Commission and is not to be incorporated by reference into any filing of Heron Therapeutics, Inc. under the Securities Act of 1933, as amended, or the Securities Exchange Act of 1934, as amended (whether made before or after the date of the Form 10-K), irrespective of any general incorporation language contained in such filing.

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